Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

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Herausgegeben von der Kommission Mamma
(vertreten durch: Wolfgang Janni)
der Arbeitsgemeinschaft Gynäkologische Onkologie e.V.
in der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe e.V.
sowie der Deutschen Krebsgesellschaft e.V.

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Empfehlungen der AGO Kommission Mamma

1) Optionen der primären Prävention: Veränderbare Lifestyle-Faktoren
2) Brustkrebsrisiko, Genetik und Prävention
3) Früherkennung und Diagnostik
4) Pathologie
5) Prognostische und prädiktive Faktoren
6) Läsionen mit unsicherem Potential (B3) – ADH, LIN, FEA, Papillom, Radiäre Narbe
7) Duktales Carcinoma in situ (DCIS)
8) Operative Therapie des Mammakarzinoms unter onkologischen Aspekten
9) Onkoplastische und rekonstruktive Mammachirurgie
10) Adjuvante endokrin-basierte Therapie bei Prä- und postmenopausalen Patientinnen
11) Adjuvante zytostatische und zielgerichtete Therapien
12) Neoadjuvante (Primäre) systemische Therapie
13) Adjuvante Strahlentherapie
14) Supportive Therapie und Nebenwirkungsmanagement
15) Brustkrebs: Spezielle Situationen
16) Brustkrebs Nachsorge
17) Lokoregionäres Rezidiv
18) Endokrin-basierte und zielgerichtete Therapie des metastasierten Mammakarzinoms
19) Chemotherapie mit oder ohne zielgerichtete Substanzen beim metastasierten Mammakarzinom
20) Osteoonkologie und Knochengesundheit
21) Behandlung in Abhängigkeit der Lokalisation der Metastasierung
22) ZNS-Metastasen beim Mammakarzinom
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Oxford Levels of Evidence (LoE)

LoE	Therapy/Prevention, Aetiology/Harm	Prognosis
1a	Systematic review (with homogeneity) of randomised controlled trials	Systematic review (with homogeneity) of inception cohort studies; clinical decision rule validated in different populations
1b	Individual randomised controlled trials (with narrow Confidence Interval)	Individual inception cohort study with ≥ 80% follow-up; clinical decision rule validated in a single population
1c	All or none	All or none case-series
2a	Systematic review (with homogeneity) of cohort studies	Systematic review (with homogeneity) of either retrospective cohort studies or untreated control groups in randomised controlled trials
2b	Individual cohort study (including low quality randomised controlled trials; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in a randomised controlled trials; Derivation of clinical decision rule or validated on split-sample only
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research
3a	Systematic review (with homogeneity) of case-control studies	
3b	Individual Case-Control Study	
4	Case-series (and poor quality cohort and case-control studies)	Case-series (and poor quality prognostic cohort studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

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Oxford Grades of Recommendation (GR)

A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** **extrapolations from level 1 studies**
C	level 4 studies ***or*** **extrapolations from level 2 or 3 studies**
D	level 5 evidence ***or*** **troublingly inconsistent or inconclusive studies of any level**

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AGO Grades of Recommendation

++	This investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restriction, and should be performed.
+	This investigation or therapeutic intervention is of limited benefit for patients and can be performed.
+/-	This investigation or therapeutic intervention has not shown benefit for patients and may be performed only in individual cases. According to current knowledge a general recommendation cannot be given.
-	This investigation or therapeutic intervention can be of disadvantage for patients and might not be performed.
--	This investigation or therapeutic intervention is of clear disadvantage for patients and should be avoided or omitted in any case.

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Abbreviations – I

A	Doxorubicin
ACC	Adenoid-zystisches Karzinom (adenoid cystic carcinoma)
ADH	Atypische duktale Hyperplasie
ADL	Aktivitäten des täglichen Lebens (activities of daily life)
ADM	Azelluläre dermale Matrix
ADP	atypische epitheliale Proliferation vom duktalen Typ
AHT	Arterielle Hypertonie
AI	Aromataseinhibitor
AK	Antikörper
ALH	Atypische lobuläre Hyperplasie
A_{lip}	Liposomales Doxorubicin
ALND	Axilläre Lymphknotendissektion
AML	akute myeloische Leukämie
ANC	Absolute Neutrophilenzahl
APBI	Akzelerierte Teilbrustbestrahlung
APR	Aprepitant
AR	Androgenrezeptor
ARDS	Acute Respiratory Distress Syndrome
ASS	Acetylsalicylsäure
AT	Anthrazyklin/Taxan
AZ	Allgemeinzustand
BAL	Bronchoalveoläre Lavage
BC	Mammakarzinom (breast cancer)
BCFI	Brustkrebs-freies Intervall

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Abbreviations – II

BCI	Breast Cancer Index
BCS	Brusterhaltende Operation (breast-conserving surgery)
BCT	Brusterhaltende Therapie (breast-conserving therapy)
BEO	Brusterhaltende Operation
BET	Brusterhaltende Therapie
Bev	Bevacizumab
BfARM	Bundesinstitut für Arzneimittel und Medizinprodukte
BIA-ALCL	Brustimplantat-assoziiertes anaplastisches großzelliges Lymphom
BMI	Body Mass Index
BP	Bisphosphonat
BR	Brustrekonstruktion
BSE	Selbstuntersuchung (breast self-examination)
BZ	Brustkrebszentrum
C	Cyclophosphamid
Ca.	Karzinom
CAM	Komplementäre und alternative Medizin
Cap	Capecitabin
CBE	klinische Brustuntersuchung (clinical breast examination)
CDK4/6i	Cyklin-abhängige Kinase 4/6-Inhibitor
CESM	Kontrastmittel-verstärkte spektrale Mammographie (contrast enhanced spectral Mammography)
CEUS	Kontrastmittel-Sonographie (contrast enhanced ultrasound)
cfDNA	zellfreie DNA
CGA	Umfassende geriatrische Einschätzung (Comprehensive Geriatric Assessment)
CHF	Kardiomyopathie (congestive heart failure)

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Abbreviations – III

CHOP	Cyclophosphamid, Doxorubicin, Vincristin, Prednison
CI	Konfidenzintervall (Confidence interval)
CIA	Chemotherapie-induzierte Amenorrhoe
CIPN	Chemotherapie-induzierte periphere Neuropathie
CISH	Chromogene in situ-Hybridisierung
CMF	Cyclophosphamid, Methotrexat, 5-Fluorouracil
CNB	Stanzbiopsie (core needle biopsy)
COX2	Cyclooxygenase-2
CPS	Combined positive score
CRA	Chemotherapie-induzierte Amenorrhoe (chemotherapy-related amenorrhea)
CSL	Komplexe sklerosierende Läsion
CT	Computertomographie
CTC	Zirkulierende Tumorzellen
CTS	Category of tumor marker study
CTS5	Clinical Treatment Score 5
CTx	Chemotherapie
CUP	Cancer of unknown primary
D	Docetaxel
DAC	Docetaxel, Doxorubicin, Cyclophosphamid
DBT	Digitale Brust-Tomosynthese
DCIS	Duktales Carcinoma in situ
DDFS	Distant disease free survival
DDT	Dichlordiphenyltrichlorethan
DES	Diethylstilbestrol

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Abbreviations – IV

DEX	Dexamethason
DFS	Krankheitsfreies Überleben
DHEA	Dehydroepiandrosteron
DIEP	Deep Inferior Epigastric Perforator (Lappen)
DK-FBEK	Deutsches Konsortium für Familiären Brust- und Eierstockkrebs
DM	Digitale Mammographie
DM	Fernmetastasierung
Dmab	Denosumab
DMSO	Dimethylsulfoxid
DOP	Dopaminrezeptor-Antagonist
DPD	Dihydropyrimidin-Dehydrogenase
DS-GPA	Diagnosis-specific Graded Prognostic Assessment
DTC	Disseminierte Tumorzellen
DXA	Dual-Röntgen-Absorptiometrie
E	Epirubicin
E2	Estradiol
EAT	Erweiterte adjuvante endokrine Therapie
eBC	Frühes Mammakarzinom
EBUS	Endobronchialer Ultraschall
ECS	Extrakapsuläres Tumorwachstum
EFS	Event-freies Überleben
EGFR	Epidermaler Wachstumsfaktorrezeptor
EIC	Extensive intraduktale Komponente
EK	Einschlusskriterien

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Abbreviations – V

ELEE	Geschätzte lebenslange Estrogen-Exposition (Estimated lifetime estrogen exposure)
EM Ca	Endometriumkarzinom
EMA	European Medicines Agency
ER	Estrogenrezeptor
ESF	Erythropoese-stimulierender Faktor
ETx	Endokrine Therapie
F	5-Fluorouracil
F/U	Follow up
FBC	Blutbild (full blood count)
FCI	Fasciocutaneous Infragluteal Flap
FDA	Food and Drug Administration
FDG-PET	^{18}F-2-Fluor-2-Desoxyglucose-Positronen-Emissions-Tomographie
FEA	Flache epitheliale Atypie
FED	Funktioneller Eisenmangel
FFPE	Formalin-fixiertes Paraffin-eingebettetes Gewebe
FISH	Fluoreszenz-in-situ-Hybridisierung
FN	Febrile Neutropenie
FSH	Follikelstimulierendes Hormon
FSRT	Fraktionierte stereotaktische Radiotherapie
Ful	Fulvestrant
G-CSF	Granulozyten-Kolonie-stimulierender Faktor
GC-HBOC	German Consortium for Hereditary Breast and Ovarian Cancer
GCP	Gute klinische Praxis (Good Clinical Practice)

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Abbreviations – VI

GEP	Gexexpressionsprofil
GI	Gastrointestinal
GJG	Goshajinkigan
GKP	Gute klinische Praxis
GKV	Gesetzliche Krankenversicherung
GnRH	Gonadotropin-Releasing-Hormon
GnRHa	Gonadotropin-Releasing-Hormon-Agonist
GR	Oxford Grade of Recommendation
HER2	Human epidermal growth factor receptor 2
HFS	Hand-Fuß-Syndrom
HR	Hazard Ratio
HR	Hormonrezeptor
HRQoL	Gesundheitsbezogene Lebensqualität (Health-related quality of life)
HRT	Hormonersatztherapie
HT	Hormontherapie
IADL	The Lawton Instrumental Activities of Daily Living Scale
IBC	Inflammatorisches Mammakarzinom
IBR	Sofortrekonstruktion (immediate breast reconstruction)
IBTR	Ipsilaterales Brustrezidiv (Ipsilateral Breast Tumor Recurrence)
IC	Immunzellen
ICG	Indocyaningrün
ICG	Infraklavikulärgrube
ICPi	Immuncheckpointinhibitor

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Abbreviations – VII

iddETC	Epirubicin, Paclitaxel, Cyclophosphamid, dosis-dicht, dosis-intensiviert
iDFS	invasives krankheitsfreies Überleben
IGAP	Inferior gluteal artery perforator
IHC	Immunhistochemie
ILC	Invasives lobuläres Karzinom
ILRR	Ipsilaterales lokoregionäres Rezidiv
IMC	Mammaria interna Region (internal mammary lymph node chain)
IMRT	Intensitätsmodulierte Radiotherapie
IOERT	Intraoperative Elektronen-Radiotherapie
IORT	Intraoperative Radiotherapie
IR	Implantat-Rekonstruktion
irAE	Immunbezogenes unerwünschtes Ereignis (Immune-related adverse event)
ISH	In-situ-Hybridisierung
ITC	Isolierte Tumorzellen
IUD	Intrauterine device
KFU	Krebsfrüherkennungsuntersuchung
Lap	Lapatinib
LCIS	Lobuläres Carcinoma in situ
LH	Luteinisierendes Hormon
LHRH	Luteinisierendes-Hormon-Releasing-Hormon
LIN	Lobuläre intraepitheliale Neoplasie
LITT	Laser-induzierte Tumortherapie
LK	Lymphknoten

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Abbreviations – VIII

LN	Lobuläre Neoplasie
LoE	Evidenzlevel (level of evidence)
LR	Lokalrezidiv
LRFI	Lokalrezidiv-freies Intervall
LVEF	Links-ventrikuläre Ejektionsfraktion
LVI	Lymphovaskuläre Invasion
MaCa	Mammakarzinom
MAK	Mamillen-Areola-Komplex
mBC	metastasierter Brustkrebs
MBSR	Mindfulness-Based Stress Reduction
MCP	Metoclopramid
MDS	Myelodysplastisches Syndrom
ME	Mastektomie
MedDRA	Medical Dictionary for Regulatory Activities
MF	Multifokalität
MG	Mammographie
MMF	Mycophenolate mofetil
MPA	Medroxyprogesteronacetat
MPE	Maligner Pleuraerguss
MRI	Magnetresonanztomographie (magnetic resonance imaging)
MRM	Modifiziert radikale Mastektomie
MRT/MR	Magnetresonanztomographie
MS	Mammasonographie
MSI	Mikrosatelliteninstabilität

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Abbreviations – IX

MTX	Methotrexat
MUGA	Multigated acquisition
MZ	Multizentrizität
n.a.	nicht verfügbar (not available)
n.r.	nicht berichtet (not reported)
n.s.	Nicht signifikant
NabPac	Nab-Paclitaxel
NACT	Neoadjuvante Chemotherapie
NEPA	Netupitant / Palonosetron
NET	Neoadjuvante endokrine Therapie
NGS	Next-Generation-Sequencing
NK1	Neurokinin-1
NNT	Number needed to treat
NSAID	Nicht-steroidale Antiphlogistika (non-steroidal anti-inflammatory drug)
NSM	Mamillensparende Mastektomie (nipple-sparing mastectomy)
NST	Kein spezieller Typ (no special type)
NW	Nebenwirkung
NX	Vinorelbin, Capecitabin
OC	Ovarialkarzinom
OFS	Ovarialfunktions-Suppression
OLZ	Olanzapin
OM	Orale Mukositis
ONJ	Kieferosteonekrose (osteonecrosis of the jaw)

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Abbreviations – X

OP	Operation
OPS	Onkoplastische brusterhaltende Operation
OR	Odds Ratio
OS	Gesamtüberleben (overall survival)
OSNA	One Step Nucleic Acid Amplification
Pac	Paclitaxel
PAF	Population attributable fractions
PAI-1	Plasminogen-Aktivator-Inhibitor Typ 1
PARP	Poly-ADP-Ribose-Polymerase
PARPi	PARP-Inhibitor
PBI	Partielle Brustbestrahlung (partial breast irradiation)
PCO	Polycystic Ovarian Syndrome
pCR	pathologische Komplettremission
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death 1 ligand 1
PE	Probeentnahme
PEA	Palmitoylethanolamid
PET-CT	Positronen-Emissions-Tomographie-Computertomographie
PFS	Progressionsfreies Überleben
PJP	Pneumocystis jiroveci-Pneumonie
PLAC	Placebo
PMMA	Polymethylmethacrylat
PMRT	Post-Mastektomie Radiotherapie
POI	Prämature Ovarialinsuffizienz

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Abbreviations – XI

PPE	Palmares und plantares Erythem
PPV	Positiver prädiktiver Wert
PR	Progesteronrezeptor
PROM	Patient-reported outcome measures
PT	Phylloides-Tumor
PTV	Zielvolumen (Planning Target Volume)
PVP	Povidon
Pw	Paclitaxel weekly
Pz	Pertuzumab
QA	Quality assurance
QoL	Lebensqualität (quality of life)
RFA	Radiofrequenzablation
RFID	Radiofrequenz-Identifikation
RFS	Rezidivfreies Überleben
RR	Relatives Risiko
RRBM	Risiko-reduzierende bilaterale Mastektomie
RRCM	Risikoreduzierende kontralaterale Mastektomie
RRSO	Risiko-reduzierende bilaterale Salpingo-Oophorektomie
RS	Recurrence Score
RT	Radiotherapie
RT-PCR	Reverse-Transkriptase-Polymerase-Kettenreaktion
SAE	Schwerwiegendes unerwünschtes Ereignis

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Abbreviations – XII

SAPV	Spezialisierte ambulante Palliativversorgung
SCC	Plattenepithelkarzinom (squamous cell carcinoma)
SCG	Supraklavikulärgrube
SD	Standardabweichung (Standard deviation)
SGAP	Superior gluteal artery perforator (Lappen)
SIEA	Superficial inferior epigastric artery (Lappen)
SIR	Standardized incidence ratio
SIRT	Selektive interne Radiotherapie
SLN	Sentinel-Lymphknoten
SLNE	Sentinel-Lymphknoten-Exzision
SM	Synthetische Mammographie
SNP	Single Nucleotide Polymorphism
SNRI	Serotonin-Noradrenalin-Wiederaufnahmehemmer
SPIO	Superparamagnetic Iron Oxide
SRE	Skeletal-related events
SRS	Stereotactic radiosurgery
SRS-VMAT	Stereotactic radiosurgery with volumetric modulated arc therapy
SSE	Symptomatic skeletal events
SSI	Wundinfektion (surgical site infection)
SSM	Hautsparende Mastektomie (Skin sparing mastectomy)
SSRI	Selektive Serotonin-Wiederaufnahmehemmer
TAD	Targeted Axillary Dissection
Tam	Tamoxifen
TB	Tuberkulose

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Abbreviations – XIII

TBP	Treatment beyond progression
TCHP	Docetaxel, Carboplatin, Trastuzumab, Pertuzumab
TDLU	Terminale duktulolobuläre Einheit
TdP	Torsade de Pointes
TENS	Transkutane elektrische Nervenstimulation
TFI	Therapiefreies Intervall
TFT	Schilddrüsenfunktionstest
TIA	Therapie-induzierte Amenorrhoe
TIL	Tumor-infiltrierende Lymphozyten
TLNE	Targeted Lymph Node Excision
TMG	Transverse Musculocutanaeus Gracilis (Lappen)
TN	triple-negativ
TNBC	triple-negatives Mammakarzinom
TRAM	Transverser Rectus abdominus Muskel (Lappen)
TTR	Zeit zum Rezidiv (time to recurrence)
TxCHP	Paclitaxel, Carboplatin, Trastuzumab, Pertuzumab
Tz	Trastuzumab
UCT	Unkonventionelle Therapie
UE	Unerwünschtes Ereignis
ÜL	Überleben
uPA	Urokinase-Typ Plasminogen Aktivator
uPCR	Urin-Protein:Kreatinin-Ratio
VAB	Vakuumbiopsie (vacuum-assisted breast biopsy)

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Abbreviations – XIV

VAB	Vakuumbiopsie (vacuum-assisted breast biopsy)
VATS	Videoassistierte Thorakoskopie
VUS	Variante unklarer Signifikanz (variant of unknown significance)
WBI	Ganzbrustbestrahlung (whole breast irradiation)
WBRT	Ganzhirnradiatio (whole brain radiotherapy)
ZNS	Zentrales Nervensystem

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- **Prof. Dr. Anton Scharl, Amberg**
- **Prof. Dr. Rita Schmutzler, Köln**
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- **Prof. Dr. Frederik Wenz, Freiburg**

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- **The members of the editing committee of these guidelines are specialists in diagnosis, treatment, and research in breast cancer. Most of the members therefore have cooperations with industry. Thus, potential conflict of interest cannot be excluded.**
- **In order to minimize potential bias within the statements we followed the pre-defined rules:**
  - **These guidelines are strictly based on available evidence from the scientific literature.**
  - **The chapters of each edition were prepared by annually alternating teams of authors.**
  - **Each statement and the correspondent AGO-recommendations were thoroughly discussed within the entire group and accepted by majority decisions.**
  - **Each member of the editing committee is required to submit a written declaration of his/her conflicts of interests to an elected internal COI committee on an annual basis.**
  - **Members who do not submit a COI declaration may not participate in the guideline preparation.**

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Kommission „Mamma“ der
Arbeitsgemeinschaft für gynäkologische
Onkologie
(AGO)
www.ago-online.de

Address for correspondence:

Univ.-Prof. Dr. med. Wolfgang Janni
Frauenklinik, Dpt. Obst&Gyn
Universitätsklinikum Ulm
Prittwitzstr. 43 | D-89075 Ulm
P +49 731 500 58500 | F +49 731 500 58502
direktion.frauenklinik@uniklinik-ulm.de

Prof. Dr. Volkmar Müller
Universitätsklinikum Hamburg-Eppendorf
Martinistr. 52 | 20246 Hamburg
P +49 40 7410-52510 | F +49 40 7410-54355
v.mueller@uke.de

Editorial Assistance: **Dr. Kristina Veselinovic**

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Options for Primary Prevention: Modifiable Lifestyle Factors

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Prevention

- **Versions 2011–2021:**
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- **Version 2022:**
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Risk Factors for Breast Cancer 1

- Older age
- Genetics
- Family history of cancer
- Personal history of breast lesions
  - Non-proliferative lesions
  - Proliferative lesions w/o atypia
  - High risk lesions (ADH, LIN)
  - Breast cancer (DCIS, Inv. BC)
- Breast density
- Chest irradiation
- Type II Diabetes mellitus
- Hyperthyreoidism
- Lifetime number of menstrual cycles
  - Early menarche, late menopause
- Maternal pregnancy factors (e.g. pre-eclampsia) (risk reduction), and low physical activity during pregnancy (risk increase)

Social risk factors

- Lower number of births or no pregnancy
- Advanced age at first full term delivery

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Risk Factors for Breast Cancer 2

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- Short duration or absence of breast feeding
- Postmenopausal BMI < 18.5 and > 25 and especially > 40 (obesity)
- Food content
- Steroid hormone therapy
  - Recent oral contraceptive use
  - Hormone therapy (estrogen / gestagen combination) in postmenopausal women
- Alcohol intake
- Nicotine
- Light exposure at night (night shifts) *contradictory*
- Low physical activity
- Endocrine disruptors in fetal and early childhood development (e.g. DES, bisphenol-A, DDT)
- Effect of carcinogenic substances / working materials
- Exposition to ionizing radiation

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Deodorant-use and risk

Breast Cancer and Deodorants/Antiperspirants: a Systematic Review.

Allam MF[1]: Cent Eur J Public Health. 2016 Sep;24(3):245-247. doi: 10.21101/cejph.a4475.

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So far there is no evidence of a correlation between aluminum containing deodorants and breast cancer risk

- **All observational studies that evaluated the association between breast cancer risk and deodorants / antiperspirants use were reviewed. We have only identified two case-control studies, carried out between 2002 and 2006.**
- **There was no risk of antiperspirants use in the pooled risk (odds ratio 0.40, 95 % confidence interval 0.35-0.46).**

- **Our comprehensive search has identified an insufficient number of studies to conduct a quantitative review and obtain reliable results. Further prospective studies are strongly needed.**

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High Proportion of Postmenopausal Breast Cancer Attributable to Lifestyle Factors

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population attributable fractions (PAFs) of modifiable risk factors

Risk factors: obesity, physical inactivity, alcohol, low-fiber intake, smoking

Results: retrospective cohort study (Netherlands Cancer Registry)

2000: subpopulations of obese women, inactive women, alcohol drinkers, smokers etc.
2010: breast cancer incidence as compared to background incidence in these subgroups

25.7 %	of postmenopausal breast cancer cases in the Netherlands in 2010 were attributable to lifestyle factors
8.8 %	attributed to obesity
6.6 %	attributed to alcohol
5.5 %	attributed to physical inactivity
3.2 %	attributed to low fiber intake
4.6 %	attributed to smoking

Update 2019: Tamimi et al, 2016
USA: more than a third of postmenopausal breast cancers are preventable through changes in modifiable risk factors

van Germert et al., Int J Cancer 2015; 152: 155-162

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Pregnancy Related Factors

	Oxford LoE	Oxford GR
Prevention		
▪ Any full-term pregnancy	2b	B
▪ High number of pregnancies	2b	B
▪ First full-term pregnancy before age of 30 years	2b	B
▪ Breast feeding (protective if total breast-feeding time exceeds 1.5-2 years)	3a	B
▪ Lower birth weight of the first born (3000-3500 vs. > 4500g RR = 1.53)	2b	B
▪ Lower length of pregnancy first born (26-31. WOP vs. 40-41. WOP; HR = 2.38, p = 0.03)	2b	B
No influence		
▪ Polycystic Ovarian Syndrome PCO	3b	C
▪ Assisted reproduction	2b	B
▪ Abortion	2b	B

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Medical Primary Prevention*

	Oxford		
	LoE	GR	AGO
▪ ASS	2a	B	+/-
▪ COX2-Inhibitoren	2a	B	+/-
▪ Bisphosphonates	2b	B	+/-
▪ Vitamin D	2b	B	+/-
▪ Statins	2b	B	-

* No approval, consider side effects

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Medical Prevention

Kehm RD et al., Regular use of aspirin and other non-steroidal anti-inflammatory drugs and breast cancer risk for women at familial or Genetic risk: a cohort study, Breast Cancer Res. 2019 Apr. 18;21(1):52

Prospective multinational cohort study, n = 5606, healthy women questionaire, regular intake of ASS, NSAID, COX2-inhibitors

Regular ASS-intake: HR 0.61, CI 0.33-1.14, breast cancer incidence
Regular COX2-inhibitors : HR 0.39, CI 0.15-0.97, breast cancer incidence other NSAIDs: n.s.
[independent of BRCA-status]

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Prevention by Changing Lifestyle Factors: Body Mass Index / Diet

	Oxford		
	LoE	GR	AGO
▪ **Maintaining normal weight (BMI at 18.5-25 kg/m²)***	2a	B	++
▪ **Premenopausal**	3a	B	+/-
▪ **Postmenopausal**	2a	B	++
▪ **Prevention / screening and treatment of diabetes mellitus type II (reduction of breast cancer incidence and mortality)**	2b	B	++

* **Amount of body fat can be increased in people with normal BMI and correlates with breast cancer risk**

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The risk of breast, ovarian and endometrial cancer in obese women submitted to bariatric surgery: a meta-analysis

B Ishihara, D Farah, M Fonseca and A Nazário, Surg Obes Relat Dis 2020;16(10):1596-1602

- **Meta-analysis, of a total of 150,537 patients in the bariatric surgery arm and 1,461,938 women in the control arm.**
- **The risk of breast cancer was reduced by 49 % [RR: 0.39 (95 % CI [0.31 to 0.56]; I^2 = 90 %; 7 studies).**
- **The risk of ovarian cancer was reduced by 53 % [RR: 0.47 (95 % CI [0.27 to 0.81]; I^2 = 0 %; 3 studies).**
- **The risk of endometrial cancer was reduced by 67 % [RR: 0.33 (95 % CI [0.21 to 0.51]; I^2 = 88 %; 7 studies).**

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Association of Body Fat and Risk of Breast Cancer in Postmenopausal Women With Normal Body Mass Index: A Secondary Analysis of a Randomized Clinical Trial and Observational Study.

Iyengar NM et al.: JAMA Oncol. 2019 Feb 1;5(2):155-163

- **WHI substudy**
- **Among the 3460 women included in the analysis (mean [SD] age, 63.6 [7.6] years), multivariable-adjusted hazard ratios for the risk of invasive breast cancer were 1.89 (95 % CI, 1.21-2.95) for the highest quartile of whole-body fat and 1.88 (95 % CI, 1.18-2.98) for the highest quartile of trunk fat mass.**
- **The corresponding adjusted hazard ratios for ER-positive breast cancer were 2.21 (95 % CI, 1.23-3.67) and 1.98 (95 % CI, 1.18-3.31), respectively.**

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Prevention by Changing Lifestyle Factors: Diet

	Oxford LoE	GR	AGO
▪ **Preference of a balanced diet***	2b	B	+
▪ **Mediterranean Diet**	2a	B	+
▪ **Dietary components**			
▪ Olive oil (extra virgin olive oil), as part of mediterranean diet	2b	B	+
▪ Fat reduced food	2a	B	+
▪ Reduced consumption of red meat	2b	C	+
▪ Nuts / peanuts (> 10g/d) (peanut butter without effect)	2b	B	+
▪ Fiber containing food	2a	B	+
▪ Vitamin D substitution for prevention (MaCa HR1,02)	1b	B	+/-
▪ Vegetables / fruits **	2a	B	+/-
▪ Phytoestrogens / soy	2a	B	+/-
▪ Vegetarian / vegan diet (no significant risk reduction)	2b	C	+/-
▪ Coffee (no significant reduction)	2a	B	+/-
▪ Supplementation of vitamins, minerals, trace elements	2a	B	-

* As recommended by German Society of Nutrition (DGE)

** Recommended as a part of healthy nutrition

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Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

N Engl J Med. 2019 Jan 3;380(1):33-44. doi: 10.1056/NEJMoa1809944. Epub 2018 Nov 10.

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Randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D_3 (cholecalciferol) at a dose of 2000 IU per day and marine n-3 (also called omega-3) fatty acids at a dose of 1 g per day

Primary end points were invasive cancer of any type and major cardiovascular events

25,871 participants

median follow-up of 5.3 years

124 breast cancers (Vit D group) vs. 122 (placebo group) Hazard Ratio: 1,02

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Prevention by Modifying Lifestyle Risk Factors: Alcohol

	Oxford		
	LoE	GR	AGO
▪ **Reduction of alcohol intace reduces risk of breast cancer (ideal < 10g/d, class II evidence)**	2a	B	+
Particularly for			
▪ **ER+ / PR+ tumors**	2a	B	
▪ **Invasive lobular tumors**	2a	B	

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Nature, Nurture and cancer risks: Genetic and nutritional contributions to cancer

Theodoratou, E.: Annu Rev Nutr. 2017 August 21; 37: 293–320.
doi:10.1146/annurev-nutr-071715-051004

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No association was classified as convincing (class I). The association between alcohol intake and ER+ breast cancer was classified as highly suggestive (Class II)

based on a meta-analysis of 20 prospective studies (≥ 30 g/d of alcohol consumption versus non-drinkers

RR (95 % CI): 1.35 (1.23, 1.48, p-value = 5.2×10^{-10}, $I^2 = 26$ %,

$P_{\text{small effect bias}} = 0.184$, $P_{\text{excess significance bias}} = 4 \times 10^{-8}$)

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Prevention by Modifying Lifestyle Risk Factors: Smoking

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Oxford		
LoE	GR	AGO
2a	B	++

- **Never smoking reduces risk of breast cancer ~ 15-24 % reduction of lifetime risk)**

- **Young women smoking have a 60 % increased risk of BC, when smoking > 10 years before the first childbirth (vs. never smokers)**

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Smoking and Risk of Breast Cancer in the Generations Study Cohort

Jones, M.E.:Breast Cancer Res. 2017 Nov 22;19(1):118. doi: 10.1186/s13058-017-0908-4.

102,927 women recruited 2003–2013

average of 7.7 years of follow-up

The HR (reference group was never smokers) was
1.14 (95 % CI 1.03–1.25; *P* = 0.010) for ever smokers,
1.24 (95 % CI 1.08–1.43; *P* = 0.002) for starting smoking at ages < 17 years
1.23 (1.07–1.41; *P* = 0.004) for starting smoking 1–4 years after menarche

Women with a family history of breast cancer (ever vs never smokers HR 1.35; 95 % CI 1.12–1.62; *P* = 0.002) had a significantly larger HR … than women without (ever smoker vs never smoker HR 1.07; 95 % CI 0.96–1.20; *P* = 0.22).

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Prevention by Modifying Lifestyle Risk Factors: Physical Activity

Oxford		
LoE	GR	AGO
2a	B	++

- **Physical exercise**

  (Metabolic equivalents to 3–5 hrs moderate pace walking per week)

These effects also apply to *BRCA1/2* mutation carriers and for women with an increased family risk.

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Recreational Physical Activity Is Associated with Reduced Breast Cancer Risk in Adult Women at High Risk for Breast Cancer: A Cohort Study of Women Selected for Familial and Genetic Risk.

Kehm RD et al.: Cancer Res. 2020 Jan 1;80(1):116-125. doi: 10.1158/0008-5472.CAN-19-1847. Epub 2019 Oct 2.

- **Prospective cohort study**
- **N = 15550, women with fam. Hx of breast cancer**
- **multiplicative interactions of physical activity with predicted absolute breast cancer familial risk based on pedigree data and with BRCA1 and BRCA2 mutation status**
- **Higher physical activity → 20 % reduction of breast cancer incidence**
- **(HR0.80, CI 0.68-0.93), independent of BRCA-status or pedigree risk**

Prevention by Modifying Lifestyle Risk Factors: Hormone Therapy in Postmenopausal Women

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	Oxford LoE	Oxford GR	AGO
Avoiding hormonal therapy in postmenopausal women			
Avoiding estrogen / progestin combinations	1b	A	+
Avoiding estrogens only (no increased, possibly reduced breast cancer risk, but increased risk for endometrial cancer, if not hysterectomized)	1b	A	+/-

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Epigenome-wide association study for lifetime estrogen exposure identifies an epigenetic signature associated with breast cancer risk.

Johansson A et al.: Clin Epigenetics. 2019 Apr 30;11(1):66.

Epidemiological data from EPIC-Italy (n = 31,864)
Study: estimated lifetime estrogen exposure

Method: epigenome-wide association study, blood DNA samples, N = 216 , and 440 healthy controls

Results: an estimated 5 % increase in breast cancer risk per 1-year longer ELEE (OR = 1.05, 95 % CI 1.04-1.07, P = $3x10^{-12}$) in EPIC-Italy.
694 CpG sites were associated with ELEE (FDR Q < 0.05)

Prevention of Hormones in Postmenopausal Patients

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	N	MC-RR (95%CI)	Further information
WHI WHI: JAMA 2002, JAMA 2017	~ 27 000	1.3 (1,0-1,6)	1.3 (1.1-1,6) coronary events 1.4 (1,1-1,9) insults 2.1 (1,4-3,3) pulmonary embolism 2.1 (1,5-2,9) deep vein thrombosis
HERS Hulley S: JAMA 2002	I 2763 RCT, med. 4.1 yrs. II 2321 open-label, 2.7 yrs.	1.2 (0.95-1.5)	med. age 67 yrs. no secondary prevention side effects as comp. to WHI + cholcystectomy↗
Million Women Beral V: Lancet 2003	1.084 110 ~ 50 % HRT 4.1 J. follow-up	1.66 (1.6-1.8)	EPC > E mode of applic. not relevant duration > 5 yrs. Tibolon RR 1.45 (1.2-1.7)
EPIC Int J Cancer 2010	1.153 747 person-years	1.4 (1.2-1.6) 1.8 (1.4-2.2)	E-Mono EPC > E
Metaanalyse Nelson HD: JAMA 2002	16 Studies	1.21-1.40	side effects as compared to WHI +

Chlebowski et al., Climacteric 2015, 18:336-8
Chlebowski et al., J Natl Compr Canc Netw 2015, 13:917-24
Manson JE et al., JAMA 2017; 318: 927-938

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Prevention of Hormones (EGC) in Postmenopausal Patients

	N	MC-RR (95% CI)	Further statements
CLEAR-study (NSW) **Case-Control-Study, retrospect. Australia**	**1236 BC cases**	2.09 (1.57-2.78) 1.03 (0.82-1.28) 2.62 (1.56-4.38) 1.80 (1.21-2.68)	current user past user E/P combination E only

Salagame et al., Int J Cancer. 2016;138(8):1905-14

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Prevention by Modifying Lifestyle Risk Factors: Oral Contraception (OC)

	Oxford LoE
▪ OC does <u>not</u> increase the risk of mortality from breast cancer	1a
▪ <u>Risk</u> of breast cancer slightly increased, risk of ovarian, endometrial cancer is decreased	1a(-)

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Risk Reduction for Ipsi- and Contralateral Breast Cancer

Rationale: Women with breast cancer have an increased risk for a second primary

	Oxford		
	LoE	GR	AGO
▪ Tamoxifen*	1a	A	+
▪ Aromatase inhibitors*	1a	A	+
▪ Suppression of ovarian function* + Tamoxifen	1b	B	+

* Only proven for ER / PgR-positive primary sporadic BC

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Breast Cancer Risk, Genetics and Prevention

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Breast Cancer Risk and Prevention

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Principles of Prevention

- **Women at increased risk for breast cancer are not considered *patients* but *healthy women* or *counselees.***
- **A comprehensive informed consent taking into consideration all potential side effects and risks is warranted prior to offering preventive measures.**
- **Highest priority: „First, do no harm!“**

(Primum nil nocere)

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Indication for Genetic Testing of *BRCA1/2* Genes and Possibly Further Risk Genes?

(Part 1 of 2 – testing according to family history)

Oxford LoE: 2b GR: B AGO: ++

Families with (each from one family branch) at least*

- three women with breast cancer independent of age or
- two women with breast cancer, one < 50 yrs. (before the 51st birthday) or
- one woman affected by breast and one by ovarian cancer or
- one woman affected by breast and ovarian cancer or
- two women affected by ovarian cancer or
- one woman affected by bilateral breast cancer, first before the 51st birthday
- one woman affected by breast cancer < 35 yrs. (before the 36th birthday) or
- one man affected by breast cancer and one additional relative affected by breast or ovarian cancer

* Inclusion criteria of the German Consortium of Hereditary Breast and Ovarian Cancer (GCHBOC) based on a *BRCA1/2* mutation prevalence ≥ 10 % tested in 21,401 families. All mutation carriers should be registered in scientific databases, to validate the inclusion and exclusion criteria (including population-based studies).

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Indication for Genetic Testing of *BRCA1/2* Genes and Possibly Further Risk Genes?

(Part 2 of 2 - testing according to disease)

Oxford LoE: 2b GR: B AGO: ++

- **Other recommended criteria:**
  - **own disease of triple negative breast cancer ≤ 60 yrs. of age**
  - **own disease of ovarian cancer**
  - **if therapeutically relevant (e.g. PARPi)**

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Checklist for Recording a Possible Hereditary Burden of Breast and / or Ovarian Cancer

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Name Patientin/Patient: **Geburtsdatum:**

DKG KREBSGESELLSCHAFT Zertifizierung

A. Patient/in und deren Geschwister / Kinder

Auftreten bei Patientin/Patient	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei der Patientin **vor** dem 36. Geburtstag		3	0
eines triple-negativen Mammakarzinoms bei der Patientin vor dem 60. Geburtstag*		3	0
eines unilateralen Mammakarzinoms bei der Patientin **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei der Patientin, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei der Patientin **nach** dem 51. Geburtstag		1	0
eines uni- oder bilateralen Mammakarzinoms bei dem Patienten (männlich)		2	0
eines Ovarialkarzinoms bei der Patientin vor dem 80. Geburtstag*		3	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei der Patientin		2	0
Auftreten bei Kindern, Geschwistern und deren Kindern			
eines Mammakarzinoms bei Schwestern/Töchtern/Nichten **vor** dem 36. Geburtstag		3	0
eines unilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten **nach** dem 51. Geburtstag		1	0
eines uni- oder bilateralen Mammakarzinoms bei Brüdern/Söhnen/Neffen		2	0
eeines Ovarial-/Tuben-/primären Peritonealkarzinoms bei Schwestern/Töchtern/Nichten		2	0
		A	0

B. Mütterliche Linie (incl. Mutter)

Auftreten	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei einer Angehörigen **vor** dem 36. Geburtstag		3	0
eines unilateralen Mammakarzinoms bei einer Angehörigen **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei einer Angehörigen, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei einer Angehörigen **nach** dem 51. Geburtstag		1	0
eines Mammakarzinoms bei einem angehörigen Mann		2	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei einer Angehörigen		2	0
Summe weitere mütterliche Linie			
		B	0

C. Väterliche Linie (incl. Vater)

Auftreten	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei einer Angehörigen **vor** dem 36. Geburtstag		3	0
eines unilateralen Mammakarzinoms bei einer Angehörigen **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei einer Angehörigen, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei einer Angehörigen **nach** dem 51. Geburtstag		1	0
eines Mammakarzinoms bei einem angehörigen Mann		2	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei einer Angehörigen		2	0
Summe väterliche Linie			
		C	0

D. Der höhere Wert aus B und C — D: 0

E. Summe aus A und D = Risiko-Score — A+D: 0

Ausfüllhinweis

Zunächst wird die Anzahl bekannter Erkrankungsfälle bei den Geschwistern und Kindern, einschließlich der aktuellen Erkrankung der Patientin sowie in der mütterlichen und väterlichen Linie erfragt.

Diese Zahlen werden mit den jeweiligen Gewichtungen multipliziert. Dann wird die Summe aus diesen Ergebnissen errechnet und in die Felder A und B und C eingetragen.

Der höhere der beiden Werte aus den Feldern B und C wird in Feld D eingetragen.

Der Gesamtscore errechnet sich dann aus der Summe der Felder A und D.
Eine Risikoberatung in den ausgewiesenen Zentren ist bei Scores ≥ 3 Punkten zu empfehlen
***Diese Einschlusskriterien gelten nur in Kooperation mit den Zentren des Deutschen Konsortiums Familiärer Brust- und Eierstockkrebs bzw. mit den zertifizierten FBREK-Zentren , die diese im Rahmen der Wissen generierenden Versorgung validieren. Die anderen Einschlusskriterien entsprechen den Vorgabe des EBM.**

Version: 11. Januar 2022 (C)
Ärztekammer Westfalen-Lippe,
Deutsche Krebsgesellschaft,
Deutsche Gesellschaft für Senologie,
Deutsches Konsortium für Erblichen Brust- und Eierstockkrebs

https:///
checkliste_erbliche_belastung_brust_gyn-210212

online tool provided by the GC-HBOC, https://familiaerer-brust-und-eierstockkrebs.uk-koeln.de/informationen/downloads/

State of Research: Relevance of Genetic and non-Genetic Risk Factors

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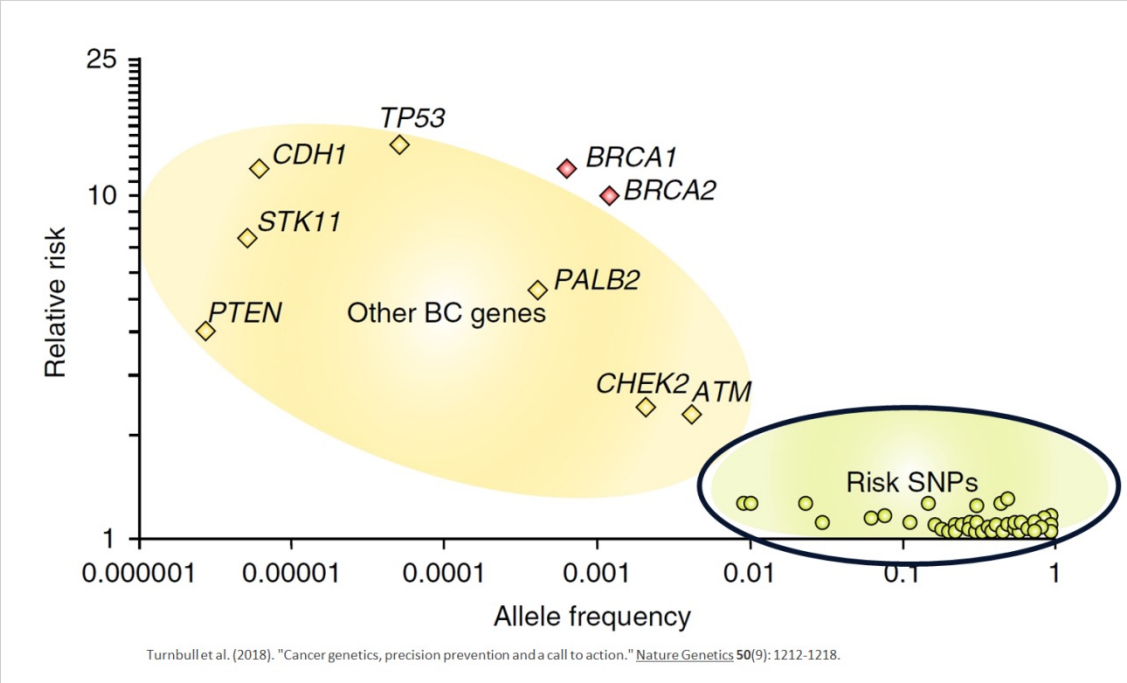
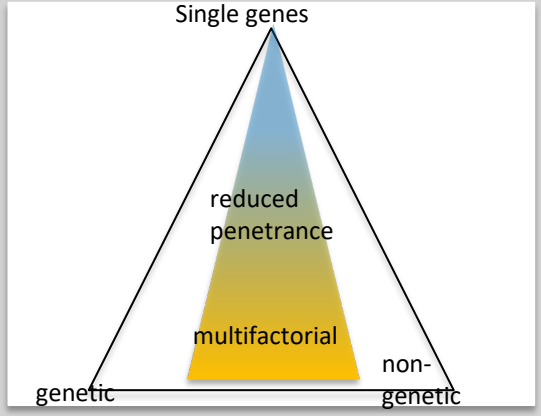
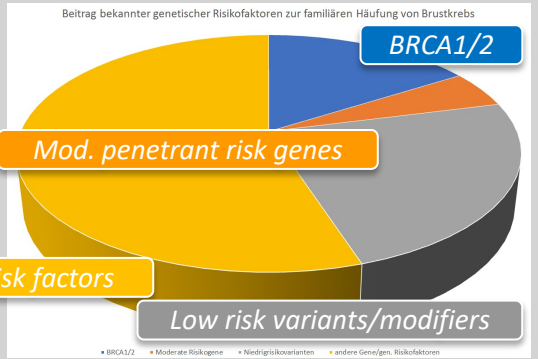


Turnbull et al. (2018). "Cancer genetics, precision prevention and a call to action." Nature Genetics 50(9): 1212-1218.





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Pathogenic Variants with Moderate to High Lifetime Risk for Breast Cancer

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	Oxford		
	LoE	GR	AGO
Age-related risks for breast cancer			
▪ high: ***BRCA1, BRCA2, PALB2***			
▪ high: ***CDH1, PTEN, TP53; STK11#***			
▪ moderate: ***ATM, CHEK2***			
▪ moderate: B***ARD1, RAD51C, RAD51D***			
Clinical benefit* of a genetic test			
▪ ***BRCA1, BRCA2***	1b	A	++°
▪ ***PALB2***	3a	B	+°
▪ ***CDH1, PTEN, TP53, STK11***	3b	B	+°
▪ ***ATM, BARD1, CHEK2, RAD51C, RAD51D***	3a	B	+/- °

* Take into account the effectiveness of preventive measures and competing risks when making clinical decisions.

° Participation in prospective registries or studies is highly recommended.

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Breast Cancer Risk Category

Breast cancer risk category

	Near population risk of breast cancer	Moderate risk of breast cancer	High risk of breast cancer
Lifetime risk from age 20	Less than 17%	Greater than 17% but less than 30%	30% or greater
Risk between ages 40 and 50	Less than 3%	3 to 8%	Greater than 8%

NICE (National Institute for Health and Care Excellence) guidance: Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer
Clinical guideline [CG164] Published: 25 June 2013 Last updated: 20 November 2019

Estimated Cumulative Risk of Breast Cancer with Protein-Truncating Variants in 8 Genes

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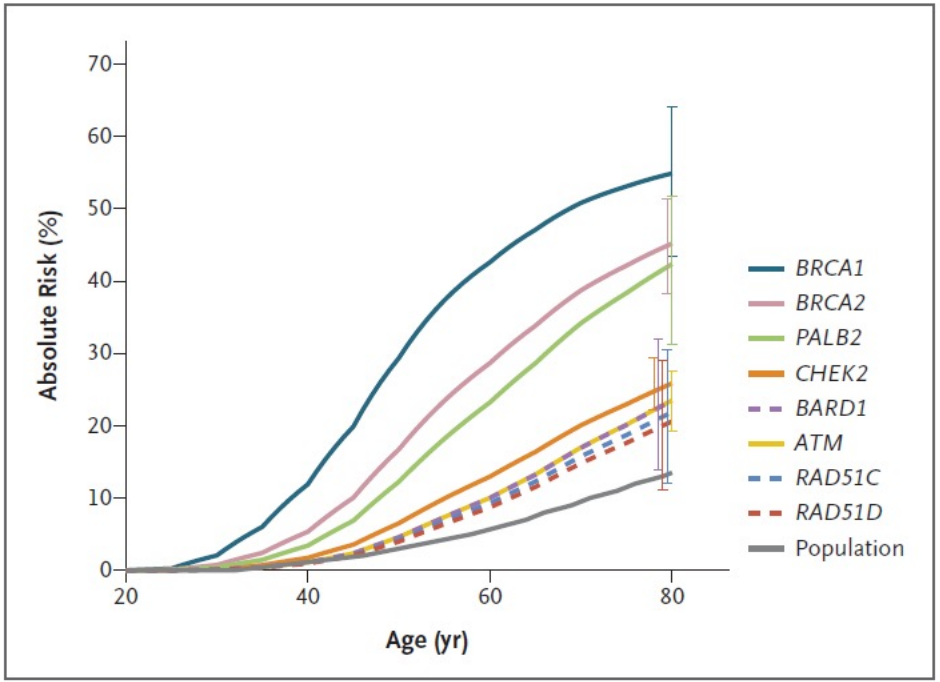

Shown are cumulative risks of breast cancer through 80 years of age for protein-truncating variants in 8 genes that had significant evidence of an association with breast cancer overall, on the basis of estimated odds ratios from population-based studies. Baseline absolute risks were derived from population incidences in the United Kingdom in 2016. The I bars indicate 95 % confidence intervals.

Dorling L, Carvalho S, Allen J et al. Breast-Cancer Risk Genes — Association Analysis in More than 113,000 Women. January 20, 2021 DOI: 10.1056/NEJMoa1913948

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Management of Individuals with Germline Variants in PALB2: A Clinical Practice Resource of the American College of Medical Genetics and Genomics (ACMG)

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Conclusion:
The recommendations made here have been based on expert opinion using comprehensive literature ascertainment approach, but not systematic review. There is strong evidence that P/LP *PALB2* variants confer a range of breast cancer risks across what is considered moderate to high; consequently, enhanced surveillance and the option of risk-reducing interventions are warranted.

The risk range for this gene underlies the need to move away from compartmentalizing PALB2 and consider risk to be a continuous variable from high to moderate, influenced by family history, polygenic risk score, and other factors. The same applies to other breast cancer genes.
Changing this paradigm will allow us **to move to personalized risk estimates by placing the risk from the P/LP variant in the context of other risk factors and develop strategies to translate this information to enhance medical management.**
There is reasonable evidence that **PALB2** P/LP variants confer a small to moderately increased risk for ovarian cancer that may warrant risk-reducing interventions, albeit their clinical benefit is not sufficiently proven yet with respect to the efficacy of preventive measures to reduce morbidity and mortality. …

Given the many uncertainties, those at risk for *PALB2*-related cancers, and the health professionals who care for them are encouraged to contribute follow-up data to long term studies, thereby facilitating the generation of prospective cancer risk estimates and the evaluation of prevention measures…

Tischkowitz M, Balmaña J, Foulkes WD, et al. Management of individuals with germline variants in PALB2: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(8):1416-1423. doi:10.1038/s41436-021-01151-8

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Current Clinical Impact of Further Risk Genes

- **Further moderate and low-risk gene variants are most likely transmitted by an oligo- or polygenic trait.**
- **The penetrance of such genes depends on the own and family cancer history.**
- **Individual low-risk variants increase the risk of disease only insignificantly. They have a multiplicative effect, so that the analysis of multiple gene regions (polygenic risk score, PRS) will be of clinical relevance in the future.**

	Oxford		
	LoE	GR	AGO
▪ Clinical genetic testing of moderate-risk genes, e.g. gene panels	1b	B	+
▪ Clinical genetic testing for low-risk variants (polygenic risk score)	2b	B	+/-*
▪ Referral to centers of the GC-HBOC or cooperating centers	5	D	+

* **Currently, moderately penetrant genes and low-risk variants should only be examined in the context of prospective cohort studies, such as that of the German consortium, in order to assess the clinical benefit.**

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Non BRCA-Associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer

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Syndrome	Gene	Risk for malignancy
Li Fraumeni	*TP53*	Breast, endometrium, colorectal, small intestine, stomach, hepato biliary, skin, osteosarcoma, soft tissue sarcoma, urogenital, CNS, ACC, leukemia, lymphoma, lung
Cowden	*PTEN*	Breast, endometrium, thyroid, colorectal, kidney, melanoma
Hereditary diffuse gastric cancer syndrome	*CDH1*	Hereditary diffuse gastric cancer, lobular invasive breast cancer
Peutz-Jeghers Syndrome	*STK11/ LKB1*	Colorectal, small intestine, stomach, pancreas, testicle, endometrium
Lynch	*MLH1, MSH2, MSH6, PMS2, EPCAM*	Endometrium, ovary, colorectal, small intestine, stomach, hepato biliary, pancreas, kidney, urogenital, CNS
Ataxia telangiectasia (AT-Syndrome)	*ATM*	Breast cancer, leukemia, stomach, melanoma, sarcoma
Franconi Anämie	*BRCA2, BRIP1, RAD51C, PALB2*	AML, MDS, SCC, medulloblastoma, nephroblastoma, breast, pancreas, ovary

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Current Version of the TruRisk® BC / OC* Gene Panel by the German Consortium (GC-HBOC)

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ATM	BARD1	BRCA1	BRCA2	BRIP1	CDH1	CHEK2	PALB2
RAD51C	RAD51D	TP53	EPCAM	MLH1	MSH2	MSH6	PMS2
PTEN	SMARCA4	STK11	APC	FAM175A	FANCC	FANCM	HOXB13
MEN1	MRE11A	MUTYH	NBN	NF1	POLD1	POLE	RAD50
RECQL	XRCC2						

Selection of genes:	**11 BC (breast cancer) / OC (ovarian cancer) 'core genes'** (Data on risk increase) **7** other s**yndrome-associated genes** (Lynch, Cowden, Peutz-Jeghers) with suspected BC/OC association **16 BC / OC** candidate genes from scientific projects (validation in the GC-HBOC)
Strategy: Validation in prospective cohort, continuous expansion and improvement	

TruRisk® V3.1.1.

*** BC = breast cancer, OC = ovarian cancer**

Distinct Genetically Subtypes Defines Distinct Tumor Entities

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Distinct genetic subtypes of breast cancer may show distinct clinical features. Prior to the offer risk reducing clinical procedures the following facts and data should be addressed:

- Age related disease penetrance?
- Typical histopathological features?
- Sensitivity to current screening modalities?
- Better survival of early detected tumors?
- Natural disease course?
- Response to anti-tumor therapy?

→ **Genotype-phenotype-correlations must be known before performing preventive clinical measures**

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VUS: Problems and Questions

- „A Variant of Unknown Significance (VUS IARC class 3) is a genetic variant with unknown clinical relevance.“ (Plon et al. Hum Mutat 2008)
- Most VUS are extremely rare (≤ 3 variants in > 80 % of families)
- Classification of sequence variants should be performed according to the IARC classification system
- Frequency of VUS (IARC class 3) increases with numbers of tested genes
- Clinical interpretation and decision making depending on the IARC classification system is not standardized yet
- In silico prediction tools (PolyPhen2, SIFT) are not adequate or sufficient for clinical decision making
- Additional analyses are required, e.g. in vitro splicing assay, functional assay, segregation analysis, co-occurence analysis, large case / control studies

Variant Classification Proposed by IARC

(Plon et al., Human Mutation, 2008)

Proposed Classification System for Sequence Variants Identified by Genetic Testing		
Class	**Discription**	**Probabilty of being pathogenic**
5	Definitly pathogenic	> 0.99
4	Likely pathogenic	0.95 – 0.99
3	Uncertain	0.05 – 0.949
2	Likely not pathogenic or of little clinical significance	0.001 – 0.049
1	Not pathogenic or of no clinical significance	< 0.001

Only class 4 and 5 variants are considered clinically relevant.

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Classification of IARC Class 3 Variants

Requires additional information and analyses, e.g.

- **Co-occurence data from large data banks**
- **Segregation analysis**
- **Functional analysis etc.**
- **Data should be pooled in large study groups (e.g. ENIGMA)**

* **Most class 3 variants can be downgraded to clinically irrelevant classes 1 or 2 by these analyses. Few are upgraded to the clinically relevant classes 4 or 5. Any re-evaluation of the IARC class should be communicated to the tested persons (see for example the concept of supervision in centres of the German Consortium/GC-HBOC).**

Requirements for the Introduction of New Diagnostic or Predictive Genetic Testing*

- **The risk collective is clearly defined by risk criteria.**
- **The positive predictive value of risk critiera with respect to the identification of the genetic risk factor is known.**
- **The cut-off values for genetic testing evolved through a transparent consensus process.**
- **The genetic test is valide and reliable.**
- **A spectrum bias is excluded or defined.**
- **A clinical prevention strategy exists that leads to early detection or prevention and mortality reduction of the genetically defined subset of the disease.**

* **Acc. to the position paper on risk-adjusted early detection of cancer of the German National Cancer Plan developed under the Federal Ministry of Health, e.g.** "Präventive Gendiagnostik - Hoffnung und Fluch der Genanalyse", Heft 26 des Deutschen Ärzteblattes vom 29.06.2012; Dtsch. Ärztebl. 2012; 109(26): A-1371 / B-1183 / C-1163)

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Non-Directive Counseling Regarding Preventive Measures

AGO ++

According to:

- **The Genetic Diagnostic Law**
- **The Medical Devices Act (e.g. risk assessment)**
- **Application of software for risk calculation requires professional training and experience**

Communicate:

- **Absolute cancer risks within a manageable timeframe**
- **Risk and benefit of a multimodal intensive surveillance program**
- **Risk and benefit of preventive clinical methods**
- **Competing risks, e.g. risk of disease progression in relation to risk of a secondary primary in case women already affected by primary breast cancer**

Allow appropriate time for consideration

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Multimodal Intensive Surveillance Program*

		Oxford LoE	Oxford GR	Oxford AGO
▪ Program for BRCA-mutation carriers without BC				
▪ For the detection of early stage cancers		2b	B	++
▪ Clinical breast exam	≥ 25 years	Semi-annually		
▪ Sonographie	≥ 25 years	Semi-annually		
▪ Mammogram	≥ 40 years	Bi-annually		
▪ Breast MRI	≥ 25 years	Annually		
▪ For improvement of metastasis-free interval		2b	B	+
▪ Survivors after tumors in childhood and radiotherapy of thoracic wall (e.g. M. Hodgkin)		2a	B	++

* The multimodal early detection program should be carried out for women with a pathogenic mutation in risk genes and those with an increased calculated risk without a mutation within the framework of transparent quality assurance and appropriate evaluation

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High-Risk Breast Cancer Surveillance with MRI

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	30-39 years		40-49 years		≥ 50 years	
	Detection rate (‰)	PPV (%)	Detection rate (‰)	PPV (%)	Detection rate (‰)	PPV (%)
BRCA1	43.2	29.4	21.8	25.5	30.5	33.3
BRCA2	22.7	23.3	24.3	27.5	16.3	23.5
BRCA1/2-non carriers with high risk	2.9	2.8	7.4	6.8	10.9	13.8

PPV: Positive predictive value

Detection performance of annual multimodality screening rounds with MRI by risk group and age

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Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. *Breast Cancer Res Treat*. 2019;175(1):217–228. doi:10.1007/s10549-019-05152-9

Multimodal Surveillance Program for Female Carriers of Pathogenic BRCA Mutations after Primary Unilateral Breast Cancer

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		Oxford LoE	Oxford GR	Oxford AGO
▪ **Multimodal intensive surveillance program°**				
▪ **For detection of early stage breast cancers**		2a	B	++
▪ Clinical breast exam	≥ 25 years*	Semi-annually		
▪ Sonographie	≥ 25 years*	Semi-annually		
▪ Mammogram	≥ 40 years*	Biannually		
▪ Breast MRI (until ACR1)	≥ 25 years*	Annually		
▪ **For mortality reduction (10-year survival)**		3a	C	+/-*

° **Aftercare should be carried out within the framework of transparent quality assurance and corresponding evaluation.**
* **or from age at initial diagnosis**

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Surveillance for Male Carriers of Pathogenic BRCA Mutations*

The lifetime risk of breast cancer in the general male population is 0.1 %. *BRCA1* mutation carriers have a risk of breast cancer of about 1 % and an up to 1.8 to 3.75 times higher risk for prostatic cancer ≤ 65y.
***BRCA 2* mutation carriers have an up to 5–7 % lifetime risk for breast cancer and an up to 2.5 to 8.6 times higher risk for prostatic cancer ≤ 65y.**

	Oxford		
	LoE	GR	AGO
Currently, no specific surveillance is recommended → Early detection of cancer as part of standard care			
▪ **For breast cancer: self examination**	**5**	**D**	**+**
▪ **For prostate cancer: Compare German Guideline program**	**5**	**D**	**+**

* **Follow-up care / surveillance should be carried out as part of transparent quality assurance and appropriate evaluation.**

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Modified Surveillance Program for *BRCA*-neg. Women at Moderate to High Risk or Survivors of Hodgkin Disease

Rationale:

- **Increased risk of breast cancer after chest irradiation because of Hodgkin lymphoma in childhood (9–18 years).**
- **Increased risk of breast or ovarian cancer in women from BRCA1/2 negative families at risk that is, however, lower than in women from BRCA1/2 positive families.**
- **Referral to centres of the GC-HBOC or cooperating centres for the evaluation of structured surveillance and follow-up.**

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Surgical Prevention

Oxford		
LoE	GR	AGO
2a	B	+*

- **A secondary risk-reducing unilateral or bilateral mastectomy is not indicated without the presence of clearly defined genetic risk factors because it does not lead to a reduction in mortality.**

* **study participation recommended**

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Surgical Prevention for Healthy Female *BRCA1/2* Mutation Carriers

	Oxford LoE	Oxford GR	AGO
▪ **Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)****	2a	B	
▪ **Reduces OvCa incidence and mortality**			++*
▪ **Reduces overall mortality**			++*
▪ **Risk-reducing bilateral mastectomy (RR-BM)**			
▪ **Reduces BC incidence**	2b	B	+*
▪ **Reduces BC mortality in *BRCA1* mutation carriers*****	2b	B	+*

* **Study participation recommended**

** **The RRSO is recommended from about 35 years for *BRCA1* and from about 40 years for *BRCA2* mutation carriers, taking into account the age of ovarian cancer diagnosis in the family and the family planning status.**

*** **No reduction in mortality could be shown for BRCA2 mutation carriers. RRM counselling should be individualised.**

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Risk-reducing Interventions for BRCA1/2 Female Mutation Carriers Affected by Breast Cancer

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	Oxford		
	LoE	GR	AGO
▪ Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)	2b	B	+*
▪ Reduces OvCa incidence and mortality			
▪ Reduces overall mortality (contradictory results for reduction of cl BC incidence)			
▪ Prophylactic contralateral mastectomy (RR-CM)*	2b	B	+*
▪ Reduces BC incidence and mortality			
▪ Tamoxifen (reduces contralateral BC incidence)	2b	B	+/-*
▪ Indication for RR-CM should consider age at onset of first breast cancer in affected gene	2a	B	++*
▪ RR-BM after ovarian cancer	4	C	+/-**

* Study participation recommended

** Depends on tumor stage (FIGO I/II), recurrence free interval (≥ 5 yrs.), age

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Improved Overall Survival After Contralateral Risk-reducing Mastectomy in *BRCA1/2* Mutation Carriers with a History of Unilateral Breast Cancer: A Prospective Analysis

Analysis[a]	Group	Person years of observation	Deaths	Mortality[b] (95 % CI)	HR (95 % CI)
(a)	Surveillance	3007	65	21.6 (16.9-27.6)	Ref
	CRRM	1975	19	9.6 (6.1-15.1)	0.43 (0.26-0.72) [c] 0.49 (0.29-0.82) [d]
(b)	Surveillance	2673	56	21.0 (16.1-27.2)	Ref.
	CRRM	1837	18	9.8 (6.2-15.5)	0.46 (0.27-0.79) [c] 0.55 (0.32-0.95) [d]

[a] Analysis (a) is the main analysis with start of observation being either the date of primary breast cancer (PBC) diagnosis or the date of DNA diagnosis, whichever came first. In the additional analysis (b), the observation starts either 2 years after PBC or at the date of DNA diagnosis, whichever came first, to exclude patients who presented with distant metastases or died within 2 years after PBC diagnosis (*n* = 17).

[b] Per 1000 person years of observation.

[c] Univariate analysis.

[d] Multivariate analysis, adjusted for risk-reducing salpingo-oophorectomy. The following variables did not meet the criteria for incorporation in the multivariate Cox model as described in the Methods section, and were therefore not included in the multivariate analysis: type of mutation, year of birth, age at DNA diagnosis, age at PBC diagnosis, T-status, presence of positive lymph nodes, differentiation grade, hormone receptor status, HER2 status and treatments administered for PBC.

Abbreviations: CRRM, contralateral risk-reducing mastectomy; HR, Hazard ratio; CI, confidence interval.

We conclude that CRRM is associated with improved overall survival in BRCA1/2 mutation carriers with a history of PBC. Further research is warranted to develop a model based on age at diagnosis and tumour and treatment characteristics that can predict survival benefit for specific subgroups of patients, aiming at further personalized counselling and improved decision making.

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Therapy of Germline Mutation-Associated Breast Cancer

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	Oxford		
Limited prospective cohort studies with short follow-up time	**LoE**	**GR**	**AGO**
▪ Breast conserving surgery: adequate local tumor control (~ 10 years observation)	2a	B	+
▪ Systemic therapy according to sporadic breast cancer	3a	B	+
▪ gBRCA mutation status is predictive for chemotherapy response in TNBC	2b	B	+
▪ Carboplatin (vs. Docetaxel) in metastatic breast cancer	2b	B	+
PARP inhibitor (Her2-negative carcinomas):			
▪ EBC: Olaparib (in case of *gBRCA1/2* mutation)*	1b	B	+
▪ MBC:			
gBRCA1/2 mutation			
Olaparib	1b	A	++
Talazoparib	1b	A	++
• Somatic *BRCA1/2* mutation (germline testing is standard)			
Olaparib	2b	B	+/-
• *gPALB2*			
Olaparib	2b	B	+/-

EBC: Early Breast Cancer; MBC: Metastatic Breast Cancer; * Use according to study inclusion criteria and approval

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Medical Prevention for Women at Increased Risk

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	Oxford		
	LoE	GR	AGO
▪ Tamoxifen for women > 35 years: reduction of invasive BC, DCIS and LN	1a	A	+*
▪ Raloxifen for postmenopausal women: reduction of invasive BC only	1b	A	+*
▪ AI for postmenopausal women	1b	A	+**

* Risk situation as defined in NSABP P1-trial (1.66 % in 5 years) or according to #Tyrer-Cuzick model (IBIS-II)

** Significant risk reduction was seen for anastrozole for ovarian and endometrial cancer, as well as skin, colorectal, hematologic, thyroid and urinary tract cancers. Chemopreventive regimes should only be offered after individual and comprehensive counseling. The net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.

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Cooperation of Certified Breast Cancer (BC) Centres (Ctr) with Certified Familial BC Ctr of the GC-HBOC*

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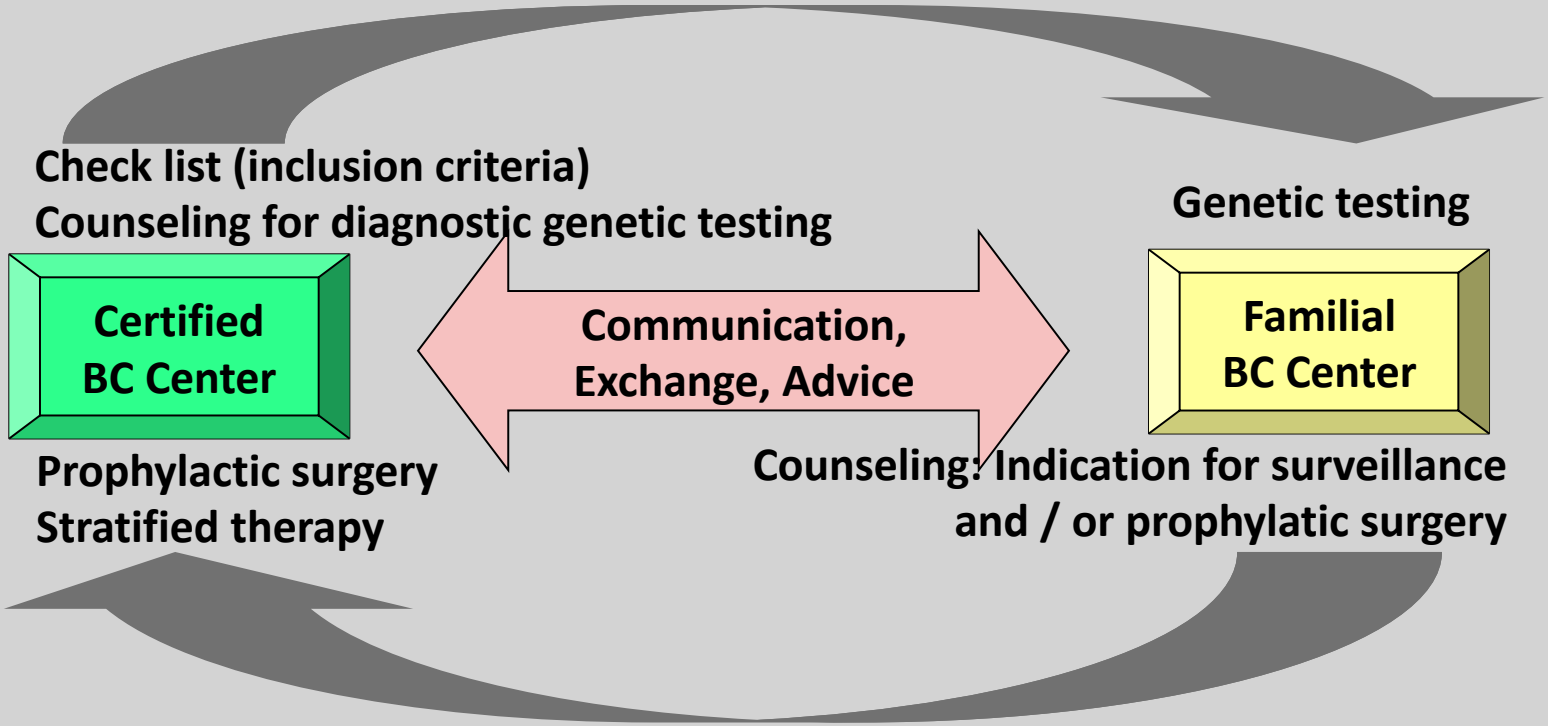

* trans-sectoral contract for integrated care, acc. to code of social law § 140a since 2015

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Early Detection and Diagnosis

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Early Detection and Diagnosis

- **Versions 2005–2021:**
  Albert / Blohmer / Fallenberg / Fersis / Gerber / Junkermann / Maass / Müller-Schimpfle / Scharl / Schreer

- **Version 2022:**
  Fallenberg / Wöckel

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Early Detection with Mammography

Age	Interval	Oxford LOE	Oxford GR	Oxford AGO
< 40	na	-	-	--
40-44	na	1b	B	-
45–49	24-36	1a	B	+#
50–69*	24	1a	A	++
70–74	24	1a	A	+#
> 75**	24	4	C	+/-#

* National Mammography-Screening-Program
** health status + life expectancy more than 10 years
# clear indication necessary

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Early Detection in Asymptomatic Women
Digital Breast Tomosynthesis

	Oxford		
	LOE	GR	AGO
Digital Breast Tomosynthesis (DBT ± SM)*	1a	B	+
Replacing FFDM by synthetic MG in addition to DBT**	1a	B	++

The complete DBT dataset of images has to be available for judgment / reporting, the synthetic mammography only is not sufficient.

* Sign. higher sensitivity, heterogeneous specificity, and higher costs [machine, evaluation, archiving] of DBT in comparison to Full-Field Digital Mammography (FFDM)
Dose reduction due to calculated synthetic 2D mammography (SM) instead of FFDM

** Evaluation for Germany in a randomized prospective trial (TOSYMA)

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Brustkrebs Mortalitätsreduktion

Metaanalyses	RR 95% CI
Independent UK Panel, 2012 13-year metaanalysis	0.80 (0.73–0.89)
Cochrane Review, 2011 Fixed-effect metaanalysis of 9 RCT-trials	0.81 (0.74–0.87)
As above, but excluding women <50 years	0.77 (0.69–0.86)
Canadian Task Force, 2011 Women aged 50–69 years	0.79 (0.68–0.90)
Duffy et al, 2012 Review of all trials and age groups	0.79 (0.73–0.86)
Duffy et al, 2020 Review of 549,091 Women (30% eligible Swedish screening population)	0.59 (0.51-0.68) mortality 0.75 (0.66-0.84) advanced BC

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Brustkrebs Mortalitätsreduktion

Metaanalyses		RR 95% CI
Case-Control Studies		
Broeders et al	Screening Mx Corr. for self selection Invited for screening	0.46 (0.4 – 0.54) 0.52 (0.42–0.65) 0.69 (0.57–0.83)
Incidence-based Mortality Studies		
Broeders et al	Screening Mx Invited to screening	0.62 (0.56–0.69) 0.75 (0.69–0.81)
Randomized Clinical Trials		
Gotsche and Jorgenson	Screening Mx	0.81 (0.74–0.87)
ECIBC	**Screening MX**	
	45-49	0.88 (0.76 - 1.02)
	50-69	0.77 (0.66 - 0.90)
	70-75	0.77 (0.54 - 1.09)

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Breastcancer: incidence and mortality

- **Annual incidence of breast cancer and mortality in the EU (GLOBOCAN 2012)**

Age	Incidence / 1000	Mortality / 1000
40 to 44	1.2	0.1
45 to 49	1.7	0.2
50 to 69	2.7	0.5
70 to 74	3.0	0.8

From: http://gco.iarc.fr/

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Mammography-Screening Benefit and Harm

Data background: Breast Cancer Surveillance Consortium Registry Data per 10.000 Women screened over 10 years

Age	40-49	50-59	60-69	70-74
Breast cancer death avoided (CI 95%)	3 (0-9)	8 (2-17)	21 (11-32)	13 (0-32)
False-positive (n)	1212	932	808	696
Breast biopsies (n)	164	159	165	175
False-negative (n)	10	11	12	13

Siu Al on behalf of the USPSTF 2016, 164:279–296

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Early Detection (normal risk) Sonography / MRI

	Oxford LoE	Oxford GR	AGO
▪ Screening-Breast sonography allone	5	D	--
▪ Automated 3D-sonography	3a	C	--
▪ Breast sonography as an adjunct:			
▪ Dense mammogram (heterogeneously dense, extremely dense)	2a	B	++
▪ Elevated risk	1b	C	++
▪ Mammographic lesion	2b	B	++
▪ Second-look US (MRI-only detected lesions)	2b	C	++
▪ MRI if screening MG is negative and breast composition: extremely dense* 50–75 LJ	1b	B	+

* Definition of extremely dense corresponds to BIRADS-density category D, heterogeneously dense to BIRADS-category C according to ACR BI-RADS-Atlas 5th ed. 2013

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Early Detection (normal risk)
Clinical Breast Examination (CBE)

	Oxford LoE	Oxford GR	AGO
As stand alone procedure			
▪ Self-examination	1a	A	-*
▪ Clinical breast examination (CBE) by health professionals outside checkup for cancer	1a	C	-*
▪ Clinical breast examination (CBE) by health professionals during checkup for cancer	1a	B	++
▪ Medical palpation by blind / visually impaired persons	3b	C	-
CBE because of mammographic / sonographic lesion	5	D	++
CBE in combination with imaging	1a	A	++

* **May increase breast awareness**

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Assessment of Breast Symptoms or Lesions

	Oxford LoE	Oxford GR	Oxford AGO
▪ Clinical examination	3b	B	++
▪ Mammography	1b	A	++
▪ Tomosynthesis***	2a	B	+
▪ Contrast-enhanced mammography (alone or as adjunct)	2a	B	+
▪ Sonography	2b	B	++
▪ Elastography (shear-wave) *	2b	B	+
▪ Automated 3D-sonography	3b	B	+/-
▪ Minimally invasive biopsy	1b	A	++
▪ MRI**	3a	B	+

* Adjunct assessment

** If clinical examination, mammography and sonography incl. needle biopsy do not allow a definite diagnosis

*** Replacement of FFDM with SM

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Pre-therapeutic Assessment of Breast and Axilla

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	Oxford LoE	GR	AGO
▪ Clinical examination	5	D	++
▪ Mammography	2b	B	++
▪ + Tomosynthesis (DBT)***	2b	B	+
▪ Contrast-enhanced mammography (alone or as adjunct)	2a	B	+
▪ Sonography (breast/axilla*)	2b/2a*	B	++
▪ MRI*	1b	B	+
▪ Minimally invasive biopsy**	1b	A	++
▪ Axilla CNB, if lymph node is suspect	2b	B	++
▪ Breast-CT	5	D	-
▪ Axillary PET	2b	B	-

* MRI-guided vacuum biopsy is mandatory in case of MRI-detected additional lesions (in house or with cooperations).
Individual decision for patients at high familiar risk, with dense breast (density C / D), lobular invasive tumors, suspicion of multilocular disease.
No reduction in re-excision rate.

** Histopathology of additional lesions if relevant for treatment

*** Replacement of FFDM with SM

Sensitivities CESM

Author	n	MG	CESM	MRI	US	Analyse
Dromain 2011	110	78	92			Per patient
Fallenberg 2014	118	77.9	94.7			Per patient
Mokhtar 2014	60	93.2	97.7			Per patient
Lobbes 2014*	113	96.9	100			Per patient
Perez 2015 ECR	98		78		66	Per lesion
Luczinska 2014	152	91	100			
Jochelson 2012	52	81 59	96 83	96 93		Per patient Per lesion
Fallenberg 2013	80	81	100	97		Per patient
Fallenberg 2016	155	81 55	94 72	95 76		Index Per Lesion
Lalji 2016*	199	93	96,9			Per patient 10 reader
Tennant 2016	100	84	95			
Luczynska 2016	116	90	100		92	
Xing 2019	235		91,5	91,5		Per lesion

CESM is comparable to MRI regarding index, a bit inferior for additional lesions

* Recall from Screening

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Pre-therapeutic Staging

	Oxford LoE	Oxford GR	AGO
▪ History and clinical examination	5	D	++

Only in case of high metastatic potential and/or symptoms and/or indication for (neo-) adjuvant chemotherapy and/or antibody-therapy:

▪ CT scan of thorax / abdomen	2a	B	+
▪ Bone scan	2b	B	+
▪ Chest X-ray	5	C	+/-
▪ Liver ultrasound	5	D	+/-
▪ Further investigation in case of additonal suspicious lesions (e.g. liver-MRI, CEUS*, biopsy etc.)	2a	B	+
▪ FDG-PET or FDG-PET / CT**	2b	B	+/-
▪ Whole body MRI	4	C	+/-

* Contrast enhanced ultrasound

** especially in patients with high tumor stage (III) if available

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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Pathology

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Pathology

- **Versions 2004–2021:**
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- **Version 2022:**
  Sinn / Huober / Kreipe

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Preanalytics: Fixation

	Oxford		
	LoE	GR	AGO
▪ Minimize time to fixation (cold ischemia time)	5	D	++
▪ Minimal fixation time of 6 hours for optimal antigen preservation	5	D	++
▪ Optimal fixation time 6 - 72 h for core biopsies	5	D	++
▪ Optimal fixation time for resection specimens: 12 - 72 h	5	D	++
▪ Use of neutral buffered formalin	5	D	++

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Use of Breast Cytology*

	Oxford		
	LoE	GR	AGO
▪ Nipple secretion	5	D	+
▪ Tumor*	5	D	-
▪ Cyst	5	D	+/-
▪ Lymph node	5	D	+/-

* Ultrasound-guided core biopsy recommended

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Workup: Core Needle Biopsies (US-Guided or Stereotactic)

	Oxford		
	LoE	GR	AGO
▪ Routine workup in step sections (14G: 1–3 step sections / 11G, 8G: 6–8 step sections)	5	D	++
▪ Correlation with imaging (density, calcifications), use of B-classification	1b	B	++
▪ Frozen section diagnosis on core biopsies	5	D	--
▪ Routine evaluation of ER / PR and HER2 status	3b	C	++
▪ Turn-around time < 24 h (histology)	5	D	+

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Workup: Breast-Conserving Specimens

	Oxford		
	LoE	GR	AGO
▪ Slicing perpendicular to the longitudinal axis (or perpendicular to the nipple-peripheral axis in case of spherical specimens)	5	D	++
▪ Systematic sampling, at least 1 tissue block every 1 cm	5	D	++
▪ Inking of resection margins. Sampling of resection margins	5	D	++
▪ Documentation after slicing using specimen radiography, photo documentation or diagram	5	D	+

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Workup: Mastectomy Specimens

	Oxford		
	LoE	GR	AGO
▪ Margins always to be sampled ▪ Skin close to tumor ▪ Deep margin ▪ Other margins, if close (< 1 cm)	5	D	++
▪ Attention to soft tissue margins in skin sparing mastectomy	5	D	++
▪ Routine sampling of uninvolved quadrants, skin above tumor and retroareolar region	5	D	++
▪ Systematic sampling in prophylactic mastectomies (patients with BRCA-1/2 mutation)	5	D	++

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Workup: Sentinel Node Biopsy

	Oxford		
	LoE	GR	AGO
▪ Full workup using step sections of ≤ 500 µm on paraffin embedded tissue	5	D	++
▪ Cytokeratin immunohistochemistry			
▪ If suspicious, to detect micrometastases	2b	B	+
▪ For micrometastasis detection after NACT	2b	B	+
▪ As a routine procedure	5	D	+/-
▪ Frozen section (compromises paraffin histomorphology)			
▪ If clinical consequences	5	D	+
▪ If no clinical consequences from frozen section (e.g. cT1 or cT2 and cN0 and BCT)	5	D	-
▪ Imprint cytology instead of, or in addition to frozen section	3b	C	+/-
▪ RT-PCR for epithelial genes	4	D	-
▪ OSNA	3b	B	-

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Workup: Intraoperative Pathological Evaluation and Frozen Sections

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	Oxford		
	LoE	GR	AGO
▪ **Sentinel node biopsy for invasive cancer (compromises final paraffin histomorphology)**			
▪ If clinical consequences	5	D	+
▪ No clinical consequences	5	D	-
▪ **Closest margin of resection**			
▪ If macroscopically < 1 cm	5	D	+
▪ If macroscopically > 1 cm	5	D	-
▪ **Lesions ≥ 1 cm, without core biopsy**	5	D	+
▪ **Non-palpable lesions or lesions < 1 cm**	5	D	--
▪ **Conservation of fresh tissue (tumor banking)**	5	D	+

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Reporting: Histologic Tumor Type

Oxford		
LoE	GR	AGO
3b	C	++

- **Histologic tumor typing according to WHO-Classification, (5th ed., 2019)**
  - **Partial special differentiation:**
    > 50 % NST component
    and < 50 % special tumor type (minor component)
  - **Mixed differentiation:**
    > 50 % special tumor type
    and < 50 % NST component
    Example: mucinous breast cancer, mixed type
  - **Pure types:**
    > 90 % special tumor type
    Examples: tubular or cribriform Ca.

Ductal TNBC: Comparable Survival Rates and Similar Response Rates to Chemotherapy for ER = 0 % Compared to ER 1 % - < 10 %

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Reference	Patients	Results
Villegas, S. L. *Eur J Cancer* **148**, 159–170 (2021) DOI: 10.1016/j.ejca.2021.02.020	Neoadjuvant clinical trial cohorts (n = 2765) comparing neg. ER/PR (< 1%) vs. ER/PR low pos. (ER and/or PR < 9%) vs. strong-pos. (ER or PR >= 10%) HR expression.	Low HR-positive, HER2-negative tumours had a similar clinical behavior compared to TNBC, showing high pCR rates and poor survival and also a basal-like gene expression signature. Patients with low HR-positive tumours should be regarded as candidates for therapy strategies targeting TNBC.
Dieci, M. V. et al. Npj Breast Cancer 7, 101 (2021) DOI: 10.1038/s41523-021-00308-7	406 patients with ER < 10% HER2-negative BC. Pat. Were categorized in ER-negative (ER < 1%; N = 364) and ER-low positive (1–9%, N = 42).	No difference was observed in overall survival (OS) according to ER expression levels (5-years OAS 82.3% vs. 76.7% for ER-negative and ER-low positive BC, respectively, p = 0.8). Our results suggest the use of a 10% cut-off, rather than <1%, to define triple-negative BC (TNBC).
Reddy, S. M. *et al.* *British Journal of Cancer* **118**, 17–23 (2018) DOI: 10.1038/bjc.2017.379	Stage I-III TNBC pat. (n = 873) who were disease free at 5 years from diagnosis. Recurrence-free interval (RFI), r.f. survival (RFS), and distant r.f. survival (DRFS) rates were calculated.	After a disease-free interval of 5 years, patients with low hormone receptor-pos. cancers had a higher risk of late events as measured by RFS, and similar risk by RFI or DRFS, compared to TNBC survivors.

Rare Histological TNBC Subtypes Show Divergent Tumor Differentiation Patterns and Clinical Behavior

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Apocrine TNBC

- Luminal phenotype (no basal markers)
- High expression of the androgen receptor
- Low tumor proliferation
- Poor response to chemotherapy
- Better prognosis than ductal TNBC

Metaplastic TNBC

- See chapter 15 Special Situations

Rare and salivary-type TNBC

- Tumors with divergent clinical behavior and specific genetic alterations
- Mostly low tumor proliferation
- Poor response to conventional chemotherapy
- Experimental treatment according to the molecular pathology (e.g. NTREK for secretory ca.)

Apocrine TNBC: More Favorable Survival and Poor Response to Adjuvant Chemotherapy

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Reference	Patients	Results
Saridakis, A. *et al.* *Ann Surg Oncol* **28**, 5610–5616 (2021). DOI: 10.1245/s10434-021-10518-9	Women with invasive apocrine cancer were retrospectively identified from the Surveillance, Epidemiology, and End Results (SEER) database. N = 533 triple-negative apocrine cancers were identified.	Half of apocrine tumors are triple negative, but these have more favorable features and much better survival than non-apocrine triple-negative cancers. Compared with non-apocrine triple-negative, apocrine triple-negative patients were much older, with smaller, lower-grade tumors and much better survival (86% vs. 74%).
Montagna, E. et al. *Breast* **53**, 138–142 (2020). DOI: 10.1038/s41523-021-00308-7	406 patients with ER < 10% HER2-negative BC. Pat. Were categorized in ER-negative (ER < 1%; N = 364) and ER-low positive (1–9%, N = 42).	The outcome of selected apocrine triple negative breast cancer patients who did not received adjuvant chemotherapy is excellent and supports a treatment de-escalation.
Mills, A. M., et al. *Am J Surg Pathol* **40**, 1109–1116 (2016). DOI: 10.1097/pas.0000000000000671	All pure apocrine carcinomas diagnosed during a 10-year period were reviewed, and clinicopathologic characteristics were compared with a control group of 26 non-apocrine TNBC cases. Twenty apocrine carcinomas were identified (~ 0.8% of all breast cancers).	Apocrine TNBC had a favorable clinical prognosis, with 80% of patients showing no evidence of disease-related morbidity or mortality (mean follow-up: 45.2 mo). Pure apocrine carcinomas represent a clinicopathologically distinct subgroup of triple-negative breast cancer characterized by AR positivity.

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Rare and Salivary-Type TNBC: Tumors with Divergent Clinical Behavior and Specific Genetic Alterations

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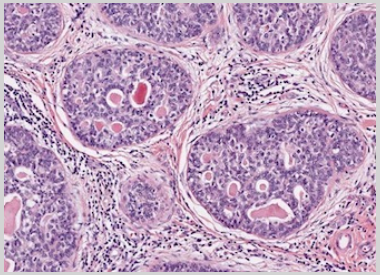
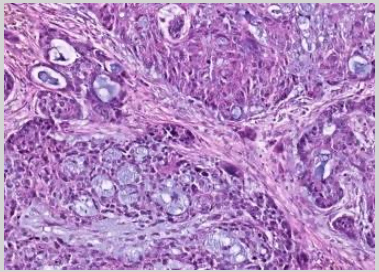
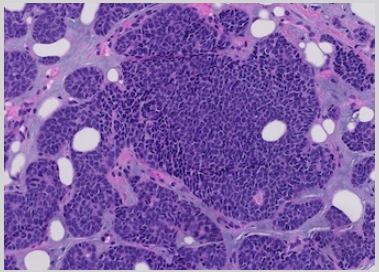
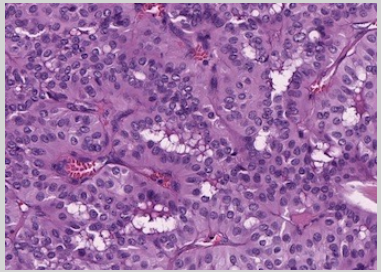
Adenoid-cystic carcinoma	Secretory carcinoma	Polymorphous carcinoma	Tall cell carcinoma with reversed polarity
			
MYB-NFIB ***MYBL1 rearrangements*** ***MYB gene amplification***	***ETV6-NTRK3*** ***gene fusions***	***PRKD1 E710D*** ***PRKD1 / PRKOZ / PRKD3*** ***rearrangements***	***IDH2 hotspot mutations***

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Reporting: Grade of Malignancy

	Oxford		
	LoE	GR	AGO
▪ Use of Nottingham grading system (Elston & Ellis 1991) for all types of invasive breast cancer (incl. status post neoadjuvant systemic therapy)	5	D	++
▪ In case of very little tumor tissue, pure nuclear grading or additional criteria, such as Ki-67 proliferation fraction, may be used	5	D	++
▪ Grading of DCIS, e.g. according to WHO-Classification, (5th ed., 2019)	5	D	++
▪ Reporting of tumor grade in numeric form (e.g. G3)	5	D	++

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Reporting: Tumor Size and Total Extent of Tumor

	Oxford		
	LoE	GR	AGO
▪ Reporting of invasive tumor size taking into account macroscopic and histologic findings and clinical imaging results	5	D	++
▪ Additional reporting of total extent of invasive carcinoma in case of satellite nodules or multifocality	5	D	++
▪ Reporting of size of non-invasive component (DCIS or LCIS) when DCIS or LCIS component is extensive (more than 2 x invasive Ca)	5	D	++

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Reporting: pTNM

Oxford		
LoE	GR	AGO
5	D	++

- **Use of current UICC classification (8th ed.)**

  pT 1-3: Invasive tumor size (largest focus in case of multifocality or multicentricity)

  pT4: Invasion of dermis alone does not qualify as pT4. Criteria for pT4a/b/c/d must be met.

  pT4d: Negative skin biopsy does not rule out pT4d (inflammatory carcinoma).

  pM: pM1 indicates any non-regional disease, except 2nd primary contralateral. Use of MX is not recommended.

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Reporting: Margins of Resection and R-Classification

	Oxford LoE	Oxford GR	Oxford AGO
▪ Evaluation of distance to all resection margins macroscopically and close margins histologically (< 1 cm)	5	D	++
▪ Reporting of minimal distance to resection margin and its topography	5	D	++
▪ R-Classification	5	D	++

R0: No residual tumor

R1: Microscopic invasive or noninvasive carcinoma involving resection margin

RX: Presence of residual tumor cannot be assessed (e.g. tumor in multiple specimens)

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Reporting: Lymphovascular Invasion

	Oxford		
	LoE	GR	AGO
▪ L1: Lymphovascular invasion L0: No lymphovascular invasion	5	D	++
▪ IHC for evaluation of lymphovascular invasion	3b	C	-
▪ Differentiation of peritumoral and extensive lymphovascular invasion	3b	C	++
▪ Reporting of venous invasion (V0/V1) optional, prognostic significance not established	5	D	+

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Reporting: Evaluation of Tumor-Infiltrating Lymphocytes (TIL)

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Oxford		
LoE	GR	AGO
5	D	+/-

- **Identification of tumors with predominant lymphocytic infiltrate (> 50 %) in tumor stroma (according to Salgado et al.*)**

  Consider only lymphocytic infiltrate in tumor stroma and not at the invasion front

  Do not consider central fibrosis and necrotic areas

  Report average of lymphocytic infiltrate as percentage

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* Salgado, R., Denkert, C., Demaria, S., Sirtaine, N., Klauschen, F., Pruneri, G., et al. (2014). The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Annals of Oncology

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Reporting: Evaluation after Neoadjuvant Chemotherapy

	Oxford		
	LoE	GR	AGO
▪ Identification of tumor bed, otherwise ypTX	4	D	++
▪ Reporting of tumor size as total extent of tumor bed area involved by infiltrates of residual vital invasive carcinoma	4	D	++
▪ pCR when absence of invasive Ca. and absence of angioinvasion or LN metastases. Presence of ypTis should be recorded	2b	D	+
▪ Use of IHC to identify tumor residues (lymphnodes)	2b	B	+/-
▪ Reporting of ypTN after neoadjuvant systemic therapy	5	D	++
▪ Repeat IHC for ER, PR, and HER2	5	D	+/-
▪ Intraoperative frozen section (reduced sensitivity)	5	D	-
▪ Tumorregression-Scores: RCB-Score or Sataloff-Score	4	D	+/-

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Special Studies: ER-Testing by IHC

	Oxford		
	LoE	GR	AGO
▪ Immunohistochemical detection on paraffin embedded (FFPE) tissue	1a	A	++
▪ Reporting percentage of pos. tumor nuclei (pos. if ≥ 10 %, low pos. if ≥ 1 %–10 %)	1a	A	++
▪ Staining intensity	4	D	+
▪ Only Allred Score (0–8) or Remmele Score (0–12)	4	D	-
▪ Re-evaluation on excision specimen if uncertain or triple-negative on core biopsy	5	D	+

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Low ER+ (1–10 %)

Reference	Patients	Results
Sanford, R. A. *et al.* *Cancer* **121**, 3422–3427 (2015). DOI: 10.1002/cncr.29572	314 Pat. 1–9% ER, Anteil BRCA mutierter Fälle wie bei ER -	High Incidence of Germline BRCA Mutation in Patients with ER Low-Positive / PR Low-Positive / HER-2 neu Negative Tumors
Deyarmin, B. *et al.* *Ann Surg Oncol* **20**, 87–93 (2013). DOI: 10.1245/s10434-012-2588-8	26 Pat. 1–10% ER, Genexpression eher wie TN oder HER2 enr	Effect of ASCO / CAP Guidelines for Determining ER Status on Molecular Subtype
Prabhu, J. S. *et al.* *J Cancer* **5**, 156–165 (2014) DOI: 10.7150/jca.7668	21 Pat. 1–10% ER, Genexpression wie ER-, Überleben < ER+	A Majority of Low (1–10%) ER Positive Breast Cancers Behave Like Hormone Receptor Negative Tumors
Yi, M. *et al.* *Annals of Oncology* **25**, 1004–1011 (2014). DOI: 10.1093/annonc/mdu053	251 Pat. 1–9% ER Überleben = ER-	Which threshold for ER positivity? A retrospective study based on 9639 patients

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Special Studies: PR-Testing by IHC

	Oxford		
	LoE	GR	AGO
▪ Immunohistochemical detection on paraffin embedded (FFPE) tissue	1a	A	++
▪ Reporting percentage of pos. tumor nuclei (pos. if ≥ 10 %)	1a	A	++
▪ Only Allred Score (0 - 8) or Remmele Score (0 - 12)	4	D	-

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Additional Special Studies: Molecular Analysis of ER / PR Status

	Oxford		
	LoE	GR	AGO
▪ Evaluation of hormone receptors using validated gene expression test kits	3b	A	+/-
▪ Exclusive evaluation of hormone receptor by RNA-quantification	5	D	-
▪ Use of molecular receptor analysis for subtyping	3b	A	+/-

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HER2-Analysis by IHC

	Oxford		
	LoE	GR	AGO
▪ **Reporting of immunohistochemistry (IHC):**	1a	A	++
▪ **3+ staining pattern: HER2+ if strong complete circular membrane staining of > 10 % invasive cells**			
▪ **2+ staining pattern: If > 10 % circular but moderate / weak membrane staining or ≤ 10 % strong staining, U-shaped staining in micropapillary carcinoma: ISH required (CISH, SISH, FISH)**	1a	A	++

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HER2-Analysis by ISH when IHC 2+

	Oxford		
	LoE	GR	AGO
▪ **Single-Color In-Situ-Hybridisation (ISH):**	3a	C	++
▪ HER2+ if signal counts ≥ 6 in at least 20 cohesive cells			
▪ negative if signal counts < 4 signals/nucleus			
▪ 2-Color ISH recommended for ≥ 4 and < 6 signals/nucleus			
▪ **Two-Color In-Situ-Hybridisation (ISH):**	3a	D	++
▪ Group 1: Ratio ≥ 2.0 and signals/nucleus ≥ 4.0 → HER2+			
▪ Group 2: Ratio ≥ 2.0 and signals/nucleus < 4.0 → HER2- (no benefit of anti-HER2 therapy)			
▪ Group 3: Ratio < 2.0 and signals/nucleus ≥ 6.0 → HER2+ (but benefit of anti-HER2 therapy not certain)			
▪ Group 4: Ratio < 2.0 and signals/nucleus ≥ 4.0 und < 6 → HER2- (no benefit of anti-HER2 therapy)			
▪ Group 5: Ratio < 2.0 und signals/nucleus < 4.0 → HER2-			

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HER2 Testing by Validated Dual-Probe ISH Assay when IHC = 2+

Batch controls and on-slide controls show appropriate hybridization

- HER2/CEP17 ratio ≥ 2.0
  - Group 1: Average *HER2* copy number ≥ 4.0 signals/cell → HER2 positive
  - Group 2: Average *HER2* copy number < 4.0 signals/cell → mostly → HER2 negative
- HER2/CEP17 ratio < 2.0
  - Group 3: Average *HER2* copy number ≥ 6.0 signals/cell → mostly → HER2 positive
  - Group 4: Average *HER2* copy number ≥ 4.0 - < 6.0 signals/cell → mostly → HER2 negative
  - Group 5: Average *HER2* copy number <4.0 signals/cell → HER2 negative

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HER2 Testing on Core Biopsies

False positive immunohistochemical labeling may occur in core biopsies. Therefore, methods of individual laboratories should be validated by comparison of core biopsies and resection specimens. Background staining should be evaluated by comparison with normal duct epithelium.

Alternatively, all G1 and G2 cases with HER2 3+ in core biopsies may be analyzed by ISH or may be re-evaluated in the resection specimen.

False positivity is likely when HER+ was reported in G1 tumors of the following types: Infiltrating ductal or lobular carcinoma, ER and PR positive, Tubular (at least 90 % pure), Mucinous (at least 90 % pure) Cribriform (at least 90 % pure), Adenoid cystic carcinoma (90 % pure).

In case of discrepancy between core biopsy and specimen, the HER2 overexpressing sample should be re-evaluated by a different method. If still discrepancy – anti-HER2-treatment if amplified in one of both samples. Expected rate of HER2-overexpression: 15 % HER2 positive.

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Additional Special Studies: Molecular Analysis of HER2 Status

	Oxford		
	LoE	GR	AGO
▪ Therapy decisions should only be based on IHC and ISH	1a	A	++
▪ Evaluation of HER2 using validated gene expression test kits	3b	B	-
▪ Evaluation of HER2-amplification by RNA-sequencing	5	D	-
▪ Use of molecular HER2-testing for subtyping	3b	B	+/-

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Special Studies: Evaluation of Ki-67 Score

	Oxford		
	LoE	GR	AGO
▪ Counting of tumor nuclei at the invasion front	5	D	++
▪ Semiquantitative eyeballing or counting of labelled cells in core needle biopsies	2	A	++
▪ Consideration of weakly stained tumor nuclei	5	D	++
▪ Reporting of Ki-67 positive nuclei as percentage	5	D	++
▪ Establishing of laboratory standards and cut-off values	5	D	++
▪ Use of image analysis for objective Ki-67 evaluation	5	D	+
▪ Determination of Ki-67 dynamics after short term (2-4 weeks) endocrine therapy*	1b	B	+

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* See chapter Neoadjuvant Systemic Therapy

Reproducibility – Quality Assurance is Key for Clinical Decision Making

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- ER / PR: concordance central vs local is high (97 %; Plan B, SABCS 2014)
- Grade: concordance central vs local is 68 % (PlanB, JCO 2016)
- HER2: frequency of false-positive test results 6 % (ASCO /CAP JCO 2013)
- Impact of routine pathologic review in N0 BC: 20 % changes: grade 40 %, LVI 26 %, N 15 %, margin 12 % (JCO 2012)
- pN0 from MIRROR study: pN0 was upstaged in 22 %, in central pathology review (Ann Oncol 2012)
- Ki-67:
  - Inter- and intraobserver variability in measurement of Ki-67 is high (J Nat. Cancer Institute 2011)
  - High reproducibility for low and high Ki-67 levels (J Pathol 2002)
  - Standardized methodology improves analytical validity (JNCI 2020)

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Predictive PD-L1 Assay

Immunohistochemical assay	Oxford LoE	GR	AGO
Immune Score (IC): Cytoplasmic staining of at least 1 % of the leucocyte stromal infiltrate (lymphocytes, macrophages, plasma cells, granulocytes outside of abscesses) for prediction of atezolizumab efficacy in triple-negative metastatic breast cancer.	2	A	++
Metastatic or primary tumor tissue	2	A	++
Detection with antibodies equivalent to Impassion 130 study reagents	3	B	+
Combined positive score (CPS): positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells multiplied by 100; ≥ 10 = positive) for prediction of pembrolizumab efficacy in metastatic triple-negative breast cancer (FDA approval, EMA pending)	3	B	+/-

Mutation Diagnostics* in mBC: „Precision Medicine“ for Targeted Therapies

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Altered genes	Therapeutic relevance	Gene region	Material	Oxford LOE	Oxford GR	Oxford AGO
BRCA1, BRCA2	PARP-Inhibitors	All exons	Germline: Blood cells Somatic: Tissue	1b 2b	A B	++ +/-
PALB2	PARP-Inhibitors		Germline: Blood cells	2b	B	+
PIK3CA	Alpelisib	Exons 7,9 and 20	Primary tumor, metastases, plasma	1b	A	++
HER2-mutation (independent of HER2-status)	Neratinib, lapatinib	Kinase- and extracellular domains; S310, L755, V777, Y772_A775dup	Primary tumor, metastases, plasma particul. lobular BC	4	C	+/-
ESR1	Resistance against AI	Exons 4,7 und 8	Metastases, plasma	2b	B	+/-
NTRK gene fusion	Larotrectinib, entrectinib	Fusion- and splice variants	Tumor tissue, particul. secretory breast cancer	2a	B	+
MSI	Pembrolizumab	Microsatellite-instability	Tissue	2a	B	+

* Ideally panel diagnostics

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Prognostic and Predictive Factors

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Prognostic and Predictive Factors

- **Versions 2002–2021:**
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- **Version 2022:**
  Jackisch / Nitz / Kreipe

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Definition

A **Prognostic Factors** is associated with the probability of the course of the disease (e.g. disease-free or progression-free survival, overall survival). The probability can be influenced by therapy.

A **Predictive Factor** is associated with the probability of the effect of a given therapy.

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“Low absolute risk implies low absolute benefit”

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 379: 432-444, 2012

Prognostic and Predictive Factors

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Quality Criteria

- **Biological hypothesis**
- **Simple and standardized assessment method, quality assurance (QA) of the test**
- **Prospectively planned statistical evaluation (primary goal)**
- **Validation of clinical significance according to**
  - **„Oxford Level of Evidence (LoEOx2001)“ criteria and „Grades of Recommendation (GR)“**
  - **„Grades of Recommendation (GR)“ as well as modified LoE criteria for the use in archived specimen (LoE2009) and category of tumor marker study (CTS)**
- **Clinical relevance for treatment decisions**

[1] Simon et al, J Natl Cancer Inst 101: 1446-1452, 2009
[2] Febbo et al, J Natl Compr Canc Netw 9 Suppl 5: S1-32, 2011
[3] McShane, Hayes, J Clin Oncol 30: 4223 – 4232, 2012

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Early Breast Cancer (M0) – eBC
Prognostic Factors I

Factor	Oxford LoE_{Ox2001}	Oxford GR	AGO
▪ Tumor size - pT	1a	A	++
▪ Axillary lymph node status - pN	1a	A	++
▪ Histological tumor type (mucinous, tubular etc.)	2b	B	++
▪ Grade (Elston & Ellis) - G	2a	B	++
▪ Age	2a	B	++
▪ Histologically proven peritumoral lymphatic vessel and vascular invasion (L1 V1)	1b	B	++
▪ pCR after NACT* in (luminal-B-like, HER2+, TN)	1a	A	++
▪ Increased risk of recurrence in invasive-lobular BC, cT3/4, N+	2a	B	+/-
▪ Obesity (BMI > 30 kg/m²)	1b	B	+
▪ Margins (resection status) - R0 / R1	1a	A	+

* NACT = Neoadjuvant Chemotherapy

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Early Breast Cancer (M0) - eBC
Prognostic Factors II

Factor	Oxford LoE	Oxford GR	AGO
▪ ER / PR	1a	A	++
▪ HER2 (IHC, ISH)	1a	A	++
▪ ER / PR / HER2/ Ki-67 to assess the intrinsic type with regards to tumor histology and biology	2b	B	++
▪ uPA / PAI-1 (Femtelle® ELISA) in N0	1a	A	+
▪ Proliferation markers			
▪ Ki-67 before, during, or after treatment	1a	B	+
▪ Ki-67 Re-Evaluation after short term preoperative endocrine therapy (2-4 weeks) (ypT and ypN)*	1a	B	+

* Biomarker and Multi Gene Expression test should be evaluated on core needle biopsy prior endocrine therapy

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Reproducibility – Quality Assurance is Key for Clinical Decision Making

- **ER / PR: concordance central vs local is high (97%; Plan B, SABCS 2014)**
- **Grade: concordance central vs local is 68% (PlanB, JCO 2016)**
- **HER2: frequency of false-positive test results 6% (ASCO /CAP JCO 2013)**
- **Impact of routine pathologic review in N0 BC: 20% changes: grade 40%, LVI 26%, N 15%, margin 12% (JCO 2012)**
- **pN0 from MIRROR study: pN0 was upstaged in 22%, in central pathology review (Ann Oncol 2012)**
- **Ki67:**
  - **Inter- and intraobserver variability in measurement of Ki-67 is high (J Nat. Cancer Institute 2011)**
  - **High reproducibility for low and high Ki67 levels (J Pathol 2002)**
  - **Standardized methodology improves analytical validity (JNCI 2020)**

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Early Breast Cancer (M0) - eBC
Prognostic Factors III

Factor	Oxford LoE	Oxford GR	AGO
▪ Gene expression profiles (GEP, multigene assays, gene signatures)			
▪ MammaPrint® (N0-1)	1b	A	+*
▪ Oncotype DX® (N0-1, HR+ HER2-)	1b	A	+*
▪ EndoPredict® (N0-1, HR+, HER2 -)	2b	B	+*
▪ Prosigna® (N0-1, HR+, HER2 -)	2b	B	+*
▪ Breast Cancer Index^{SM} (N0-1, HR+ HER2-)**	2b	B	+/-*
▪ IHC4 (ER / PR / HER2 / Ki-67)	2b	B	+/-
▪ PREDICT® algorithm (https://breast.predict.nhs.uk/)	1b	A	+
▪ Clinical-pathological score for lobular breast cancer (nodal status, tumor size, lymphovascular invasion LVI)	2b	B	+/-
▪ CTS5 Clinical Treatment Score**	2b	B	+
▪ CPS-EG Score	2b	B	+

* Should only be used in the context of clinical-pathological criteria (tumor size, nodal involvement, grade, Ki-67, ER, PR, HER2)
** Estimation of late recurrence

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Early Breast Cancer (M0) - eBC
Prognostic Factors IV

Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Disseminated tumor cells (DTC, in bone marrow)	1a	A	+/-
▪ Circulating tumor cells (CTC, in blood, Cell Search®)*	1b	A	+/-
▪ CTC before NACT (regarding OS, DDFS, LRFI)	1b	B	+/-
▪ Therapy decisions based on CTC phenotypes	3a	C	-
▪ Cell-free DNA (cfDNA, in blood, for DFS, PFS, OS)	2b[a]	B	+/-

* Validated clinical data only available for this assay

Commercially Available Molecular Tests

	70 gene signature (MammaPrint®) $	21 gene Recurrence score (Oncotype DX®) $	8 gene signature (Endopredict®) $	PAM 50 (Prosigna®) $	Breast Cancer Index® (BCI) $
Provider	Agendia	Genomic Health	Sividon (Myrirads)	NanoString	Biotheranostics
Type of assay	70-gene assay	21-gene recurrence score	11-gene assay	50-gene assay	5 + 2 (MGI+H/I)
Type of tissue	fresh frozen (technical validation for FFPE available)	FFPE	FFPE	FFPE	FFPE
Technique	Microarrays for RNA	qRT-PCR	q-RT-PCR	Direct hybridization (nCounter®)	q-RT-PCR
Central lab	yes	yes	no	no	yes
Indication and population studied	prognostic N-/+, < 70 Jahre	prognostic N-/+, ER+ endocrine treated	prognostic (pre-) postmenopausal N-/+, ER+ HER2- endocrine treated	prognostic postmenopausal N-/+, ER+ HER2- endocrine treated	Prognostic pT1-3pNo – pN1 ER+ / HER2– Endocrine treated
Risk classes	Low – high	RS (Low – intermediate – high)	Low – high	ROR (Low – inter-mediate – high), molecular types	Low - high
Clinical Validation	Yes	yes	yes	yes	Yes
Registration	FDA clearance as "In Vitro Diagnostic Multivariate Index Assay (IVDMIA)« CE-Mark (fresh tissue and FFPE)	Clinical Laboratory Improvement Amendments (CLIA) + College of American Pathologists (CAP)-accredited ref lab	CE-Mark	CE-Mark FDA 510(k) Clearance	Service Mark (SM)

$ **Validated clinical data only available for this assay**

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	70 gene signature (MammaPrint®) $	21 gene Recurrence score (Oncotype DX®) $	8 gene signature (Endopredict®) $	PAM 50 (Prosigna®) $	Breast Cancer Index® (BCI)
Prognosis after 5 yrs (late recurrences)	not separately shown	yes	yes	yes	yes
Predictive impact (chemotherapy benefit)	poorly validated	yes	not shown	not shown	EAT after 5 yrs
Prospective-retrospective evidence (% of recruited patients)	Multicenter validation	NSABP B-14 **(14%)** NSABP B-20 **(28%)** ECOG 9127 SWOG 8814 **(40%)** ATAC **(30%)**	ABCSG 6 **(19%)** ABCSG 8 **(36%)** GEICAM-9906 **(45%)** ATAC **(10%)**	MA.12 **(59%)** MA.5 **(66%)** ABCSG 8 **(44%)** ATAC **(16%)**	TransATTOM **(11%)**
Prospective evidence	MINDACT (N0, N1) (8y DFS, OS)	TAILORx (9y DFS, OS), N0, RS≤25 vs. ≥ 26) PlanB (N0 highrisk/N+) (5y DFS, OS) RxPONDER (5y DFS, OS), N1, RS≤25 vs. ≥26) ADAPT (5y DFS, OS), N0-1, RS 0-11; RS12-25/Ki67 response	–	–	--

$ **Validated clinical data only available for this assay**

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Prospective Clinical Trials (Oncotype DX® [TAILORx, PlanB, RxPONDER, ADAPT], MammaPrint® [MINDACT])

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Prognosis in low-risk groups excellent for both tests: ~ 94% 5 J. DFS with only adjuvant endocrine therapy (ET)

	TailorX	RxPONDER	PlanB	ADAPT	MINDACT
Follow-up	Median 90 months	Median 5.1 years	5-J-DFS	Median 60 months	Median 8.7 years (ASCO 2020)
Trial design (biomarker question)	pN0; Randomization RS 11-25 (+/- CTX)	pN1; Randomization RS0-25 (+/- CTX)	Prospective ODX testing: ET alone in RS 0-11 pN0-1	Non-inferiority (iDFS) ET alone: RS 0-11 vs RS12-25/ET response	Prospectively defined 5y-DMFS threshold for ET alone
Percentage clinically defined low-risk group	6615/9427 (70.2%, adj-online)	all 1-3 involved lymph nodes	all clincial CTX indication (pN0-1)	all clincial chemotherapy (CTX) indication (c/pN0-1)	3336/ 6693 (49.8%, adj-online)
Percentage high clinical risk and low genomic risk (clinical CTX indication)	16.7% (RS 0–10)	42.8% (RS 0-13)	15.3% (RS 0–11)	ET-trial (pN0-1): all RS 0-25, i.e. low genomic risk with ET alone	23.2% (high clinical/low genomic risk)
Test failure rate	n.r.	n.r.	2.9%	n.r.	26% (fresh frozen)
Percentage genomically intermediate-risk group (only for Oncotype DX, ODX)	69.1% (RS 11–25)	57.2% (RS 14-24)	60.4% (RS 12–25)	Included only RS 0-11 (37.9%) or RS 12-25/ET response (62.1%)	n.a.
Percentage genomically high-risk group (only for Oncotype DX)	14.3% (RS ≥ 26)	n.a.	24.3% (RS ≥ 26)	n.a.	27.0% (high clinical and high genomic risk)
10-year follow-up	n.r.	n.r.	n.r.	n.r.	n.r.

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Adjuvant Endocrine Therapy
Predictive Factors for DFS

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Therapy	Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Endocrine therapy	▪ ER / PR status [%]	1a	A	++
	▪ IHC staining intensity (ER/PR)	1a	A	-
	▪ Ki-67 Re-Evaluation after short preoperative endocrine therapy (2-4 weeks) (ypT and ypN)*	1b	A	+
▪ Extended endocrine therapy (EAT)	▪ Breast Cancer Index^{SM} (5 yrs. Let (MA.17) or 5 yrs. Tam (aTTOM), resp., after 5 yrs. Tam)	2b	B	+
▪ Tamoxifen	▪ CYP2D6-polymorphism	2b	B	-
▪ Ovarian ablation or suppression	▪ Menopausal status	1c	A	++
▪ Aromatase inhibitors vs. tamoxifen	▪ Menopausal status	1c	A	++
	▪ ER / PR / HER2 as single factors	1c	A	-
	▪ Invasiv-lobular breast cancer	2b	B	+
	▪ Ki-67 high	2b	B	+/-
	▪ Obesity (BMI > 30 kg/m²)	2b	B	+/-

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Adjuvant Chemotherapy and Targeted Therapy Predictive Factors for DFS

Therapy	Factor	Oxford LoE	Oxford GR	AGO
▪ Adjuvant Chemotherapy	uPA / PAI-1 (ELISA, Femtelle®)	1a	A	+/-
	70-Gene-signature (Mammaprint®)	1b	A	+
	21-Gene-signature (Oncotype DX RS®)	1b	A	+
	EPclin (Endopredict®)	2b	B	+
	PAM-50 (Prosigna®)	2b	B	+
	Histological type (lobular vs. NST)	2b	B	-
	TIL´s in TNBC	2b	B	+/-
▪ Anti-HER2-Therapy	HER2 (IHC, ISH)	1a	A	++
▪ PARP-Inhibitors	gBRCA1/Mutation (HER2 neg.)	1a	A	+

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Entscheidungshilfe prospektiv evaluierter Biomarker (LOE1a) und Therapieoptionen (eBC)

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Biomarker/ Signatur	**Subtyp/ Population**	**Therapieoption**
Mammaprint (MINDACT)	HR+ / HER2- N0 N1	Postmenopausal, HR+: Bei low risk Mammaprint keine adjuvante CHT Indikation
Oncotype DX (TAILORx, RxPonder)	HR+ / HER2- N0 N1	Bei N0 / RS ≤ 25 keine adjuvante CHT Indikation Bei N1 / RS ≤ 25 keine adjuvante CHT Indikation (Postmenopause)
RS + postendokrines Ki – 67 (ADAPT)	HR+ / HER2- N0 N1	Identisch zu TAILORx/RxPOnder Endokrine Monotherapie: - Prämenopause bei RS ≤11 - RS 12-25/niedriges klinisches Risiko/Ki 67 post < 10 %
gBRCA1/2 Mutation (OlympiA)	HER2- Stad II/III TN ≥ pT2 oder ≥ HR+, > 4 + LK	1 Jahr Olaparib 300 mg 2 x tägl.

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Neoadjuvant Systemic Chemotherapy (NACT)
Predictive Factors for pCR I

Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Young age	↑	1a	A	+
▪ Obesity	↓	2a	B	+
▪ cT1 / cT2 tumors o. N0 o. G3	↑↑	1a	A	++
▪ Negative hormone receptor status	↑↑	1a	A	++
▪ Triple negative breast cancer	↑↑	1a	A	++
▪ Positive HER2-status	↑↑	1a	A	++
▪ Early clinical response	↑	1b	A	+
▪ Lobular tumor type	↓	1a	A	+
▪ Metaplastic tumor type	↓↓	4	C	+

* High (↑) or very high (↑↑) probability to reach pCR, low (↓) or very low (↓↓) probability to reach pCR
See aso chapter „Prognostic and predictive factors“

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Neoadjuvant Systemic Chemotherapy (NACT) Predictive Factors for pCR II

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Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Gene expression profiles (gene signatures) (Mammaprint®, Endopredict® Oncotype DX®, Prosigna®, Breast Cancer Index^{SM})	↑	2b	B	+/-
▪ Ki-67	↑	2b	B	+
▪ Tumor infiltrating lymphocytes**	↑	2a	B	+
▪ *PIK3CA* mutation (for HER2-positive BC)	↑	2a	B	+/-
▪ gBRCA-mutation (for the effect of chemotherapy)	↑	2b	B	+
▪ gBRCA-mutation (for the effect of platinum)	↔	2b	B	+/-

* High (↑) or very high (↑↑) probabililty of pCR, low (↓) or very low (↓↓) probabililty of pCR

** Defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (lymphocytes make up > 50% of stroma area)

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Metastatic Breast Cancer (mBC)
Prognostic Factors

Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Circulating tumor cells (CTC in blood, Cell Search®)			
▪ Prognosis	1a	A	+
▪ Early response assessment (3w)	1b	B	+
▪ Therapy decision solely based on dynamics of CTC numbers over time or CTC phenotype	1b	A	-*
▪ Cell-free DNA (cfDNA in blood)	2a	A	+/-

* Study participation recommended

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Treatment of Metastatic Breast Cancer
Predictive Factors for response

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Therapy	Factor	Oxford LoE	Oxford GR	AGO
▪ Endocrine therapy	ER / PR (prim. tumor, better: metastasis)	1a	A	++
	Response to prior therapy	2b	B	++
	Autocrine receptor mutation (ESR1)	2b	B	+
▪ Alpelisib	PIK3CA mutation (prim. tumor, metastases, plasma)	1b	A	++
▪ Chemotherapy	Response to prior therapy	1b	A	++
▪ Anti-HER2-therapy	HER2 (prim. tumor, better: metastasis)	1a	A	++
▪ Checkpoint-Inhibitors	PD-L1 positivity# (PD-L1ic, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
▪ PARP-Inhibitors	gBRCA1/2-mutation	1a	A	++
▪ Bone modifying drugs	Bone metastasis	1a	A	++
▪ Further therapies	CTC monitoring	1b	A	+*

* In clinical trials; # see chapter „pathology“

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Mutation Diagnostics* in mBC: „Precision Medicine“ for Targeted Therapies

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Altered genes	Therapeutic relevance	Gene region	Material	Oxford LOE	Oxford GR	Oxford AGO
BRCA1, BRCA2	PARP-Inhibitors	All exons	Germline: Blood cells Somatic: Tissue	1b 2b	A B	++ +/-
PALB2	PARP-Inhibitors		Germline: Blood cells	2b	B	+
PIK3CA	Alpelisib	Exons 7, 9 and 20	Primary tumor, metastases, plasma	1b	A	++
HER2-mutation (independent of HER2-status)	Neratinib, lapatinib	Kinase- and extracellular domains; S310, L755, V777, Y772_A775dup	Primary tumor, metastases, plasma particul. lobular BC	4	C	+/-
ESR1	Resistance against AI	Exons 4, 7 and 8	Metastases, plasma	2b	B	+/-
NTRK gene fusion	Larotrectinib, entrectinib	Fusion- and splice variants	Tumor tissue, particul. secretory breast cancer	2a	B	+
MSI	Pembrolizumab	Microsatellite-instability	Tissue	2a	B	+

* Ideally panel diagnostics

Decision guidance prosepectively evaluated biomarkers (LOE1a) and therapy options (mBC)

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Biomarker / Signature-therapy option	**Subtyp / Population**	**Therapy option**
PDL-L1 ≥ 1%	TN	Firtst line Atezolizumab + nab Paclitaxel
CPS > 10	TN	First line Pembro + chemotherapy
PIK3CA mutation	HR+ / HER2-	Fulvestrant + Alplisib after failure offirst line ET
BRCA1/2 mutation (OlympiAD)	HER2 –	Olaparib, Talazoparib

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Therapy-Relevant Mutational Analysis for „Actionable“ Genomic Alterations in BC

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Diagnostic Tool*	Outcome	Oxford LoE	Oxford GR	AGO
Evidence from studies with other cancer patients („tumor-agnostic testing“)				
▪ Companion Diagnostics for therapies of other tumor entities (e.g. BRAF, FGFR1, …)	Efficacy of diverse therapies	4	D	+/-**
▪ Large Panel Gene Analysis (e.g. FoundationOne, GPS Cancer, NeoSelect, Molecular Health Guide, local „hand-selected„ panels)	Efficacy of diverse therapies, prognosis	3a	C	+/-**
▪ Next Generation Sequencing (NGS) (recommended only in Tier 1 + 2)	Efficacy of evaluated drugs	1b	B	+/-**

* Assessment method for somatic mutations (tumor tissue, cf-DNA) is not taken into consideration for LoE

** Participation in clinical trials or structured registries recommended

Joint Consensus Recommendations of AMP, ACMG, ASCO and CAP for Reporting Genetic Variants in Cancer

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Tier	LoE		Explanation
Tier 1	A.1	Biomarkers that predict response or resistance to FDA-approved therapies for a specific type of cancer	Variants of strong clinical significance
	A.2	Biomarkers included in professional guidelines that predict response to therapies for a specific type of tumor	
	B	Biomarkers that predict response or resistance to therapies for a specific type of tumor based on well-powered studies with consensus from experts in the field	
Tier 2	C.1	Biomarkers that predict response or resistance to therapies approved by the FDA or professional societies for a different type of tumor	Variants of potential clinical significance
	C.2	Biomarkers that serve as inclusion criteria for clinical trials	
	D	Biomarkers that show plausible therapeutic significance based on preclinical studies	
Tier 3		Not observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databasis. No convincing publised evidence or cancer association	Variants of unknown clinical significance
Tier 4		Observed at significant allele frequency in the general or specific subpopulation Databases. No existing published evidence of cancer association	Benign or likely benign variants

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Lesions of Uncertain Malignant Potential (B3)

(ADH, LIN, FEA, Papilloma, Radial Scar)

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Lesions of Uncertain Malignant Potential (B3) (including “Precursor Lesions”)

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Pathology Reporting for Minimal Invasive Biopsies

B-Classification*

B1 = Unsatisfactory or normal tissue only

B2 = Benign lesion

B3 = Lesion of uncertain malignant potential

B4 = Suspicion of malignancy

B5 = Malignant

- **B5a = Non-invasive**
- **B5b = Invasive**
- **B5c = In situ / invasion not assessable**
- **B5d = Non epithelial, metastatic**

* **National Coordinating Group for Breast Screening Pathology (NHSBSP), E.C. Working Group on Breast Screening Pathology, S3-Leitlinie Mammakarzinom der DKG**

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B3-Lesions

1. **Lesions with increased risk of associated DCIS or invasive carcinoma**
   - Atypical ductal hyperplasia (ADH) or atypical epithelial proliferation of ductal type (classification possibly as B4, depending on extent of lesion)
   - Flat epithelial atypia (FEA)
   - Lobular neoplasia (LIN; LN; now subdivided into ALH and LCIS, no differentiation according to older nomenclature) classical and non-classical type
   - Atypical apocrine adenosis
2. **Potentially heterogeneous lesions with risk of incomplete sampling**
   - Cellular fibroepithelial lesion or phyllodes tumour without evidence of malignancy
   - Intraductal papilloma with / without atypia (possibly also B4, depending on the extent of the lesion)
   - Radial scar or complex sclerosing lesion (unless the radial scar only microscopically, not radiologically detected: B2)
   - Hemangioma
3. **Rare Lesions**
   - Adenomyoepithelioma, microglandular adenosis, mucocele-like lesion, nodular fasciitis, desmoid-type fibromatosis, spindle cell lesion of unknown significance

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Management after Minimally Invasive Biopsy

	Oxford		
	LoE	GR	AGO
▪ **Interdisciplinary conference: Concordant findings in pathology and imaging?**			
▪ yes: proceed according to histologic type	3a	C	++
▪ no: open biopsy	3a	C	++
Vacuum-assisted biopsy (after core biopsy)	5	D	+

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Atypical ductal Hyperplasia (ADH)

- **Synonyms:** Atypical intraductal epithelial proliferation (AIDEP), atypical epithelial proliferation of ductal type
- **Definition:** Atypical intraductal proliferations with cytological and structural features of well differentiated DCIS, such as rigid bridging or micropapillae, well demarcated cell borders and occupy less than two separate duct spaces. The extension of all involved lumens within one ductulo-lobular unit is less than 2 mm. Atypical ductal proliferations larger than 2 mm or in at least two ductules are classified as DCIS (low-grade).
- **Indicator / Precursor lesion:** Ipsi- and contralateral breast cancer risk: RR 3 - 5 x after 3 - 5 years.
- Particularly high risk for breast cancer when combined with BIRADS IV / V and high breast volume.

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Strategy after Diagnosis of ADH in Biopsy Sypecimen

	Oxford LoE	Oxford GR	AGO
ADH in core- / vacuum-assisted biopsy:			
▪ Open excisional biopsy	3a	C	++
▪ Open excisional biopsy may be omitted, if:	5a	C	+/-
a) No mass-lesion radiologically, and			
b) a small lesion (≤ 2 TDLU*) in vacuum biopsy, and			
c) complete removal of imaging abnormality			
ADH at margins in open biopsy specimen:			
▪ No further surgery, if incidental finding accompanies invasive or intraductal carcinoma	3a	C	++

* Terminal ductal-lobular unit

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Lobular Intraepithelial Neoplasia (LIN)

- Includes:
  - Atypical lobular hyperplasia
  - Classical lobular carcinoma in situ (LIN, classical variant)
  - Non-Classical lobular carcinoma in situ (LIN, classical variant)
- LIN 1–3 classification is not sufficiently validated prognostically
- Non-Classical LIN (pleomorphic LIN, florid LIN) are classified as premalignant → **B5a**
- Indicator / precursor lesion:
  Ipsi- and contralaterally increased breast cancer risk:
  7 x after 10 years

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Classical LIN and Variants of LIN (non-classical LCIS)

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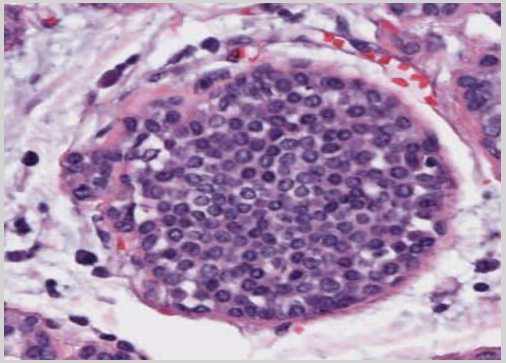
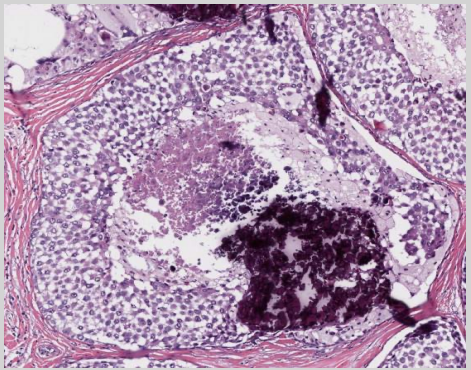
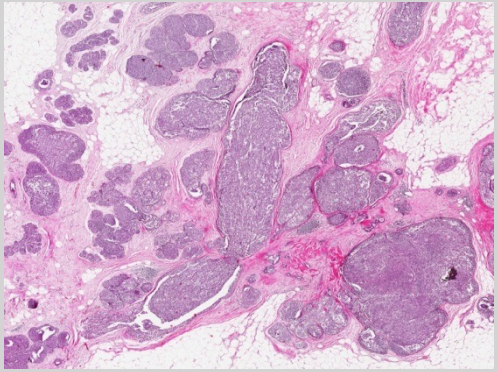


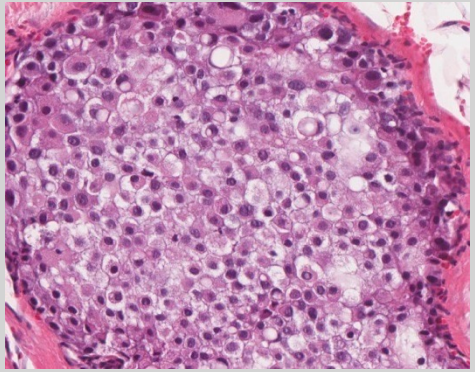
Classical LIN



LIN with comedo type necrosis



Florid LIN



Pleomorphic LIN

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LIN with High Risk

- **Non-Classical LCIS:**
  - **Pleomorphic LCIS: high grade cellular atypia, frequent involvement of ductules, comedo-type necrosis, microcalcifications**
  - **Florid LCIS: Involvement of numerous lobuli with distension and near confluence, extension to ductules and neighboring TDLU**
- **LCIS with microinvasion*:**
  - **classical LCIS: n = 11**
  - **florid LCIS: n = 4**
  - **pleomorphic LCIS: n = 1**

* **Ross DS. Am J Surg Pathol 2011 35: 750–6.**

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Strategy after Diagnosis of LIN

	Oxford LoE	GR	AGO
LIN in core- / vacuum-assisted biopsy:			
No further measures if LIN (LCIS, classical variant) with involvement of ≤ 3 TDLU (terminal ductulo-lobular unit) in vacuum biopsy and concordant with imaging.	2b	C	++
Open excisional biopsy, with pleomorphic LIN, florid LIN (LIN 3), or LIN with comedo type necrosis or if not concordant with imaging findings.	2b	C	++
LIN at margins of resection specimen (BCT):			
No further surgery.	2a	C	++

Exceptions:

a) Pleomorphic LIN, florid LIN, or LIN with necrosis

b) Imaging abnormality is not removed

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Flat Epithelial Atypia (FEA)

- **Synonyms:** Columnar cell hyperplasia with atypia,
  columnar cell metaplasia with atypia,
  ductal intraepithelial neoplasia grade 1A (DIN 1A)
- **Differential diagnosis:**
  - ADH is discriminated by architectural features (micropapillary, cribriform) → **B3**
  - Clinging carcinoma is discriminated by high grade nuclear atypia (G2/G3) and classified as ductal carcinoma in situ → **B5a**
- **Marker lesion:**
  FEA frequently is associated with calcifications and may be associated with low-grade intraductal carcinoma. Frequent occurrence in combination with high density of the breast (OR1.3). High risk for associated breast cancer in the presence of extensive calcifications (also when 75% of calcification remained after biopsy), age ≥ 57 yrs., > 1 cm in imaging, ≥ 4 foci.

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Strategy after Diagnosis of FEA

	Oxford LoE	Oxford GR	AGO
FEA in core biopsy / vacuum-assisted biopsy:			
Open excisional biopsy	2b	B	+
Open excisional biopsy may be omitted under the following circumstances:	2b	B	+
a. a small lesion (≤ 2 TDLU* in vacuum biopsy) and			
b. Complete or near complete removal of imaging abnormality			
FEA at margins in resection specimen:			
No further surgery, unless calcifications have not been completely removed	3b	C	++

* TDLU = Terminal ductal-lobular unit

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Papilloma

- **Includes:** Central and peripheral papilloma > 2 mm, atypical intraductal papilloma (B3)
- To be **distinguished from** peripheral micropapilloma arising in the TDLU, size ≤ 2 mm, may be multiple
- To be distinguished from papilloma with DCIS, from intraductal papillary carcinoma, and from encapsulated papillary carcinoma
- **Precursor lesion:**
  May be associated with in-situ or invasive cancer (up to 6% without atypia if concordant imaging, up to 30% with atypia), increased ipsilateral risk for cancer (up to 4.6% and up to 13% in case of atypical papilloma) .

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Strategy after Diagnosis of Papilloma

	Oxford LoE	Oxford GR	AGO
▪ **Papilloma without atypia in core needle or vacuum biopsy:**			
→ **no further therapy, if biopsy sufficiently representative (100 mm²) and concordant with imaging**	2b	C	+
▪ **Multiple papillomas**			
→ **open biopsy**	3a	C	++
▪ **Papilloma with atypia in core needle or vacuum biopsies:**			
→ **open biopsy**	3a	C	++
▪ **Papilloma at resection margin:**			
→ **no published data available**			

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Radially Sclerosing Lesion

- **Benign pseudoinfiltrative lesion with central fibroelastic core and radical configuration.**
- **Includes:**
  - **radial scar**
  - **complex sclerosing lesion (> 1 cm)**
- **Additional risk factor in patients with benign epithelial hyperplasia (proliferating breast disease)**
- **Risk for upgrade in open biopsy after diagnosis of a radial sclerosing lesion, depending on the size of the needle (CNB) or method (VAB) and additional atypia: 1–18%**

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Strategy after Diagnosis of Radial Scar, Complex Sclerosing Lesion (CSL)

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	Oxford		
	LoE	GR	AGO
▪ **Radial scar / CSL in core- / vacuum-assisted biopsy:**			
→ Open excisional biopsy may be omitted with a small (< 5mm) lesion or complete removal or near complete removal of imaging abnormality	5a	C	+
▪ **Radial scar / CSL at margins in resection specimen:**			
→ No further surgery	3b	C	++

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Management Radial Scar

- "When RS (radial scar) is associated to atypia (such as flat epithelial atypia (FEA), atypical ductal (ADH), or lobular neoplasia (classical LN)), management can the same as recommended in cases of atypia alone."

Rageth CJ, O`Flynn EAM, Pinker K et al.: Second International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions). Review, Breast Cancer Res Treat, 2018, doi: 10.1007/s10549-018-05071-1

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Follow-up Imaging for Women Age 50–69 Years with B3-Lesions

	Oxford		
	LoE	GR	AGO
▪ **FEA, non-atypical papilloma**			
▪ Screening mammography	5	C	++
▪ **LIN**			
▪ Mammography (12 months)	3a	C	++
▪ **ADH**			
▪ Mammography (12 months)	3a	C	++
▪ Women with LIN and ADH should be informed about their elevated risk of breast cancer	3a	C	++

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Medical Prevention for B3-Lesions With Increased Risk of Associated DCIS or Invasive Carcinoma

	Oxford		
	LoE	GR	AGO
▪ Tamoxifen 20 mg for women > 35 years	1a	A	+/-
▪ Low-dose Tamoxifen 5 mg (3 years) independent of menopausal status	2b	B	+/-
▪ Aromatase inhibitors (Exemestane, Anastrozole) for postmenopausal women	1b	A	+/-
▪ Raloxifen for postmenopausal women: Risk reduction of invasive BC only	1b	A	+/-*

Medical prevention should only be offered after individual and comprehensive counseling; overall benefit depends on classification, age, and pre-existing conditions that may influence occurrence of side effects.

* **Risk situation as defined in NSABP P1-trial (1.66% in 5 years)**

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Ductal Carcinoma in Situ (DCIS)

Ductal Carcinoma In Situ (DCIS)

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- **Versions 2002–2021:**

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- **Version 2022:**

  Ditsch / Kühn

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DCIS - Pretherapeutic Assessment

	Oxford		
	LoE	GR	AGO
▪ **Mammography**	1b	B	++
▪ Magnification view of microcalcifications	4	C	++
▪ Increased detection rate of G1 / G2 DCIS by full-field digital mammography (versus screen-film)	2b	B	+
▪ **Ultrasound (to rule out an accompanying invasive component)**	4	C	++
▪ For tumors with a solid part	4	C	++
MRI to determine the extension and planning of surgery	1a	B	+/-
▪ **Clinical examination**	5	D	++
▪ **Stereotactic core needle / vacuum biopsy (VAB)**	2b	B	++
▪ Specimen radiography	2b	B	++
▪ Marker (clip) left at biopsy site for localization if lesion is completely removed	5	D	++
▪ **Interdisciplinary board presentation**	5	D	++

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DCIS – Upstaging, ipsi- / Contralateral Events und Mortality

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Upstaging to BC %	Ipsilateral events (cum. incidence) %	Contralateral events (cum. incidence) %	BC-specific mortality % (95% CI)
5-25.9	*10 years*: BCS: 24.6 BCS and radiotherapy: 9.6 *20 years:* BCS: 30.6 BCS and radiotherapy: 18.2	*10 years:* 4.8-6.4 *15 years*: 6.4-~11	*10 years*: 0.9 (0.7-1.1) (BCS) 0.8 (0.7-1.0) (BCS and radiotherapy) 1.3 (1.1-1.5) (unilateral mastectomy)

~ 50% of all ipsilateral events are invasive.
Breast cancer specific mortality is 3,3%.
Women with DCIS have a 1.8-3-fold increased risk of death compared to normal population/women without DCIS. Risk is greater for young and black women.

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Association of a Diagnosis of Ductal Carcinoma In Situ With Death From Breast Cancer

Giannakeas V, Sopik V, Narod SA. JAMA Netw Open. 2020 Sep 1;3(9):e2017124

- 144,524 women treated for DCIS, 1,540 women died of breast cancer,
- cohort study included data for women who had first primary DCIS diagnosed between 1995 and 2014 from the SEER registries database (use of ET is not reported),
- retrospective analysis,
- results:
  - standardized mortality ratio for death from breast cancer among women with DCIS was 3.36 (95% CI, 3.20-3.53),
  - risk is greater for young and black women,
  - 4,502 (3.1%) ipsilateral invasive recurrences, resulting in a 20-year actuarial risk of 13.9%,
  - 5,527 (3.8%) contralateral invasive breast cancers, resulting in a 20-year actuarial risk of 11.3%,
  - women with DCIS had a 3-fold increased risk of death from breast cancer compared to women without DCIS.

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Risk Factors for Upstaging from DCIS to Invasive Cancer in Final Surgical Specimen

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	Oxford LoE
Higher risk	
▪ DCIS without microcalcification in core needle or vaccum biopsy	3b
▪ Microcalcification ≥ 11,5 mm	3b
▪ Presentation as tumor in MRI	3b
▪ Increased Ki-67 (≥ 20%)	3b
▪ PR negative	3b
▪ High peak contrast enhancement on MRI	3b
▪ Irregularly shaped, non-circumscribed, heterogeneous or margin-enhancing tumors with intratumoral high signal intensity or peritumoral edema on MRI	3b
▪ Biopsy technique: diagnosis by core needle biopsy versus vacuum biopsy (smaler sampling volume)	3b
▪ High platelet-lymphocyte ratio	3b
Lower risk	
▪ Removal ≥ 90% of the microcalcifications by vacuum biopsy	3b

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Good Clinical Practice (GCP)

Surgical excision (BCS or mastectomy) is the standard treatment for DCIS.

Adjuvant treatment (radiotherapy, endocrine treatment) must be discussed with the patient individually. Adverse effects should be weighted against risk reduction.

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Surgical Treatment for Histologically Proven DCIS I

	Oxford		
	LoE	GR	AGO
▪ Excisional biopsy (wire guided)	2b	B	++
▪ Localization with wire-free procedure	3b	C	+/-
▪ Bracketing wire localization in large lesions	3a	C	+
▪ Specimen radiography	2b	B	++
▪ Intraoperative ultrasound (pre-op visible lesion)	3a	C	+/-
▪ Immediate re-excision in case of incomplete resection (specimen radiography)	1c	B	++
▪ Intraoperative frozen section (in individual cases for margin assessment)	3a	D	+/-
▪ Interdisciplinary board presentation	2b	C	++

Open biopsy in suspicious lesions (mammographic microcalcifications, suspicious US, MRI etc.) without preoperative needle biopsy should be avoided

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Surgical Treatment for Histologically Proven DCIS II

	Oxford		
	LoE	GR	AGO
▪ Histologically clear margins (Ris0)	1a	A	++
▪ Multifocal DCIS: BCS if feasible	2b	B	+
▪ Re-excision required for close margin in case of BCS and radiotherapy (≤ 2 mm in paraffin section)*	2b	C	+
▪ Mastectomy**			
▪ Large lesions confirmed by multiple biopsies; no clear margins after re-excision	2a	B	++
▪ SLNE			
▪ Mastectomy	3b	B	+
▪ BCS	3b	B	--
▪ In case of DCIS in the male breast	5	D	+/-
▪ ALND	2b	B	--

* Individual approach taking into account age, tumor size, grading and implementation of radiation, especially in case of no subsequent radiation

** Patients who present with a palpable mass have a significantly higher potential for occult invasion (26%), multicentricity and local recurrence

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Prognostic Factors for an Ipsilateral Recurrence after DCIS I

	LoE
▪ Resection margins	1a
▪ Age	1a
▪ Size	1a
▪ Grade	1a
▪ Comedo necrosis	1a
▪ Method of diagnosis	1a
▪ Focality	1a
▪ HER2-overexpression	1a
▪ ER / PR (positive vs. negative)	1a

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Prognostic Factors for an Ipsilateral Recurrence after DCIS II

	LoE
▪ Growth pattern (cribriform / solid versus „clinging“ / micro-papillary)	2b
▪ Residual tumor-associated microcalcifications	2b
▪ Architecture	2b
▪ (modified) Van Nuys Prognostic Index/ mitotic rate	2b
▪ Palpable DCIS	2b
▪ ER-, HER2+, Ki-67+	2b
▪ Scores: DCIS, Oncotype DX Breast DCIS Score (12 genes); CCP (23 genes)	2b
▪ MSKCC Nomogram	2b
▪ DCISionRT	2b
▪ Intrinsic subtypes (luminal A, B, HER2+, triple negative)	2b
▪ Hereditary breast cancer risk	2a
▪ Premenopausal at time of DCIS diagnosis	2a
▪ High BMI	2a
▪ High breast density	2a
▪ DCIS compared to invasive carcinoma with higher risk of contralateral BC	2b

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DCIS Radiotherapy Statements

- **Radiotherapy has no impact on survival** **LoE 1a**
- **Radiotherapy reduces the risk of ipsilateral (invasive and non invasive) recurrences by 50 %** **LoE 1a**
- **The number needed to treat (for ipsilateral breast recurrence) is 9 (over all risk groups).**

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DCIS
Adjuvant Radiotherapy

	Oxford LoE	Oxford GR	Oxford AGO
Radiotherapy after:			
▪ Breast conserving surgery (BCS)	1a	A	++
▪ Mastectomy	2b	B	--
Radiotherapy procedure:			
▪ Conventionally fractionated radiotherapy (50 Gy in 25 fract.)	1a	A	+
▪ Hypofractionated radiotherapy (40-42,5 Gy in 15-16 fract.)	1a	A	+
▪ Radiotherapy boost of the tumor bed	1b	B	+/-
▪ in case of risk factors* (absolute benefit 5-y-RFS 4 %, rate of fibrosis significant increased)	1b[a]	B	+/-
▪ without risk factors	2b	B	-
▪ Partial breast irradiation [age ≥ 50y, DCIS ≤ 3 cm, G1-2, R0 (≥ 5 mm), unifocal / unicentric]	1b	B	+

Side effects and disadvantages must be weighed against risk reduction. Omitting radiotherapy implies elevated risk for local recurrence without effect for overall survival even in the subset of „good risk" patients. Lack of level-1 evidence supporting the omission of adjuvant radiotherapy in selected low-risk cases: < 2.5 cm, low and intermediate nuclear grade, mammographically detected.

*** < 50 years or ≥ 50 years and diagnosis based on symptoms, ≥ 15 mm, multifocality, palpable tumor, resection margins < 10 mm, G2 / 3, central necrosis, comedo type**

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DCIS – Adjuvant Systemic Treatment

- **Adjuvant endocrine treatment has no impact on survival** — **LoE 1a**
- **Endocrine treatment may have a small effect on ipsilateral invasive and DCIS recurrences** — **LoE 1a**
- **Endocrine treatment for DCIS has an effect on contralateral invasive and non-invasive cancer** — **LoE 1a**
- **The number needed to treat for any ipsilateral breast event is 15** — **LoE 1a**
- **The number needed to treat to prevent invasive breast cancer is 29 for anastrozole vs. 59 for tamoxifen*** — **LoE 1b**

*** within 12 years; according to IBIS II-trial**

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DCIS – Adjuvant Systemic Treatment

	Oxford		
	LoE	GR	AGO
▪ Tamoxifen (only ER+) 20 mg	1a	A	+/-*
▪ Tamoxifen (only ER+) 5 mg (long-term data missing)	2b[a]	B	+/-*
▪ Aromatase inhibitor (only ER+) in postmenopausal women only	1b	A	+/-*#
▪ Trastuzumab (only HER2+)	5	D	--

* Indication for treatment depends on risk factors, side effects and patient preference

\# Anastrozole versus Tamoxifen: Anastrozole higher fracture rate (OR 1.34), Tamoxifen higher rate of stroke (OR 3.10) and TIA (OR 3.10)

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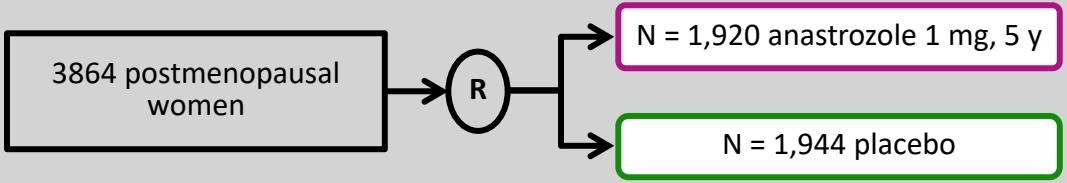
Use of Anastrozole for Breast Cancer Prevention (IBIS-II): Long-Term Results of a Randomised Controlled Trial

Cuzick J et al, Lancet 2020



- N = 3,864 postmenopausal women at inceased risk for breast cancer,
- median follow-up of 131 months,
- results:
  - 49% reduction of all breast cancers with anastrozole (HR 0.51, 95% CI 0.39–0.66, p < 0.0001),
  - significant reduction in incidence for anastrozole for ductal carcinoma in situ (HR 0.41, 0.22–0.79, p = 0.0081), especially for oestrogen-positive (HR 0.22, 0.07–0.65, p = 0.0062),
  - 5-year adherence anastrozole 74.6% vs. 77.0% for placebo,
  - no difference in major side effects (fractures, mycardial infarctions, deep vein thrombosis, pulmonary embolism),
  - NNT to prevent one breast cancer during 12 years: 29 (anastrozole) vs. 59 (tamoxifen).

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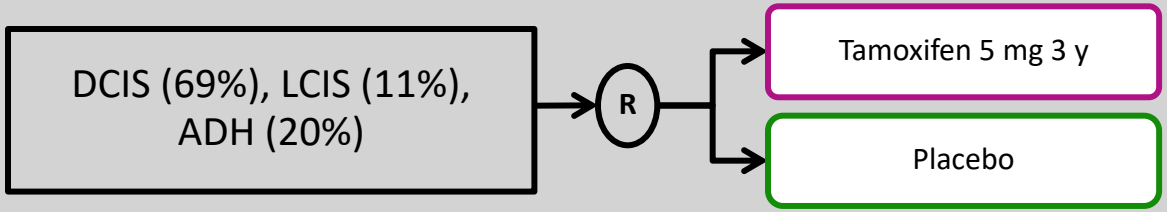
Low Dose Tamoxifen (5 mg) in Premalignant Lesions

Lazzeroni M et al: Breast 2019



- **N = 500,**
- **follow-up 5.69 years,**
- **results:**
  - **EFS: Tam 5.5% (14/253) vs. Pacebo 11.3% (28/247),**
  - **severe adverse event with same incidence (endometrial cancer Tam 1 vs. PLAC 0, thrombo-embolic event Tam 1 vs. PLAC 1)**
  - **adherence Tam 65% vs. PLAC 61%.**

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Therapy of Local DCIS Recurrence after Tumorectomy

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	Oxford		
	LoE	GR	AGO
After Radiation:			
▪ Simple Mastectomy	3a	C	+
+ SLNE	5	D	+
▪ Secondary breast conserving surgery	4	C	+/-
Without radiation after first tumorectomy			
▪ Treatment like primary disease	3	C	++

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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Breast Cancer Surgery
Oncological Aspects

Breast Cancer Surgery
Oncological Aspects

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In collaboration with:

AGO: ++

Surgery is one sub-step out of multiple steps in breast cancer treatment. Thus, both diagnostic and oncological expertise are an essential requirement for every breast surgeon.

AGO: +

Avoidance of a significant delay in cancer treatment

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Pre-therapeutic Assessment of Breast and Axilla

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In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Clinical examination	5	D	++
▪ Mammography	2b	B	++
▪ + Tomosynthesis (DBT)***	2b	B	+
▪ Contrast-enhanced mammography (alone or as adjunct)	2a	B	+
▪ Sonography (breast and axilla)	2a	B	++
▪ MRI*	1b	B	+
▪ Minimally invasive biopsy** (CNB, VAB)	1b	A	++
▪ Axilla CNB, if lymph node is suspect	2b	B	++
▪ Breast-CT	5	D	-
▪ Axillary PET / CT	2b	B	-

* MRI-guided vacuum biopsy is mandatory in case of MRI-detected additional lesions (in house or with cooperations). Individual decision for patients at high familiar risk, with dense breast (density C/D), lobular invasive tumors, suspicion of multilocular disease. No reduction in re-excision rate.

** Histopathology of additional lesions if relevant for treatment

*** Replacement of FFDM with SM

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In collaboration with:

Pre-therapeutic Staging

	Oxford LoE	Oxford GR	AGO
▪ History and clinical examination	5	D	++
Only in case of high metastatic potential and / or symptoms and / or indication for (neo-) adjuvant chemotherapy and / or antibody-therapy:			
▪ CT scan of thorax / abdomen	2a	B	+
▪ Bone scan	2b	B	+
▪ Chest X-ray	5	C	+/-
▪ Liver ultrasound	5	D	+/-
▪ Further investigation in case of suspicious lesions (e.g. liver-MRI, CEUS*, biopsy etc.)	2a	B	+
▪ FDG-PET or FDG-PET / CT**	2b	B	+/-
▪ Whole body MRI	4	C	+/-

* Contrast enhanced ultrasound

** Especially in patients with high tumor stage (III) if available

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Evidence of Surgical Procedure

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In collaboration with:

	Oxford LoE	Oxford GR
▪ Survival rates after lumpectomy + RT are at least equivalent to those after (modified) radical mastectomy	1a	A
▪ Local recurrence rates after skin sparing mastectomy are equivalent to those after mastectomy	2b	B
▪ Conservation of the NAC (nipple areola complex) is an adequate surgical procedure, if R0 resection is achieved	2b	C

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Breast-Conserving Surgery (BCS): Non-Palpable Lesions

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In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Wire-guided localization	1a	A	++
▪ Wireless intraoperative ultrasound-guided localization*	1a	A	++
▪ Other procedures:**			
Radar reflectors	2b	B	+/-
Magnetic Seeds***	2b	B	+/-
Radiofrequency-based markers (RFID)	2b	B	+/-
Radionuclide-guided localization (ROLL)	1a	A	+/-
Radioactive seeds****	1a	A	+/-

* The lesion must be sonographically visualized by the same examiner pre- and intraoperatively in its whole extension. Adequate equipment and training of the surgeon are mandatory.

** according to approval

*** not suitable for MRI-based response assessment under NACT

**** not approved in Germany

Localization Methods for non-Palpable Breast Cancer: a Meta-Analysis

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In collaboration with:

Athanasiou et al. Eur J Surg Onc 2021:

- Meta-analysis of RCTs
- 18 studies with 3112 patients
- Pairwise and network meta-analysis

Ultrasound-guided surgery vs. wire-guided surgery:

- decreased positive margin both in the pairwise [OR = 0.19 (0.11, 0.35); P < 0.01] and network meta-analysis [OR = 0.19 (0.11, 0.60)]
- a statistically significant reduction in re-operation rate [OR = 0.19 (0.11, 0.36); P < 0.01] and operative time [MD = -4.24 (-7.85, -0.63); P = 0.02]

Ultrasound-guided surgery vs. ROLL / RSL:

- a statistically significant reduction in positive margin compared to ROLL [OR = 0.19 (0.11,0.6)] and RSL [OR = 0.26 (0.13, 0.52)]

„Ultrasound-guided surgery has potential benefits in reduction of positive surgical margin, the rest of the techniques seem to have equivalent efficacy."

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Breast-Conserving Surgery (BCS): Resection Margins

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In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ **Invasive breast cancer without extensive intraductal component (EIC)***			
▪ **Aim: tumor-free margins ("no ink on tumor" is sufficient even in case of unfavorable tumor biology)**	2a	A	++
▪ **Re-excision for invasive or non-invasive tumor cells reaching margin (final histology)**	2a	B	++
▪ **Invasive breast cancer with EIC***			
▪ **Re-excision for invasive or non-invasive tumor cells reaching margin (final histology)**	2a	B	++
▪ **Re-excision in case of a close margin of the intraductal component (< 2 mm on final histology)****	2a	B	-

* **No clear definition of EIC in the literature. Increased risk of local recurrence in case of EIC with at least twice the greatest dimension of the invasive tumor component (definition according to the German S3 guideline).**

** **Individual approach with consideration of patient's age and tumor extent**

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Breast-Conserving Surgery (BCS): Surgical and Technical Aspects

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In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Therapeutic stereotactic excision alone	4	D	--
▪ Intraoperative ultrasound to increase negative margin rates in non-palpable lesions	1a	A	+
▪ Intraoperative ultrasound to increase negative margins rates in palpable lesions (with smaller resection volumes)	1b	B	+
▪ Intraoperative margin evaluation (with Margin Probe®)	1b	A	+/-
▪ Specimen radiography and / or -sonography in non-palpable lesions and / or tumor-associated microcalcifications*	2b	B	++

* Mandatory also for probe-guided detection systems (magnetic seeds, radar reflectors, RFID, radioactive seeds, ROLL)

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Breast-Conserving Surgery (BCS) without Neoadjuvant Therapy

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In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Multifocality / Multicentricity (R0 resection of all lesions required)	2b	B	+
▪ Positive microscopic margins after repeated excision	2b	B	--
▪ Inflammatory breast cancer	2b	B	--

For surgery after neoadjuvant chemotherapy see chapter „Neoadjuvant chemotherapy“

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Axillary Lymph Node Dissection (ALND) without Neoadjuvant Chemotherapy

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In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Endpoint: Survival (if patient receives adequate multimodal therapy)	3	D	-
▪ Endpoint: Staging	3	A	-
▪ Endpoint: Locoregional control	2a	A	+/-
▪ pN+ (histologically confirmed pre-surgery)	2a	B	+
▪ cN0 pN0 (i+) (sn)	1b	A	--
▪ cN0 pN1mi (sn)	2b	B	--
▪ cN0 pN1 (sn) (T1/2 , < 3 SN+, BCS + RT + adequate systemic therapy)	1b	A	-
▪ cN0 pN1 (sn) and mastectomy (no chestwall radiotherapy)	1b	B	+*
▪ cN0 pN1 (sn) and mastectomy (T1/2, < 3 SN+, chestwall radiotherapy)	5	D	+/-*
▪ ALND indicated, but not feasible			
▪ Radiotherapy according to AMAROS trial (validated for cN0 pN1sn)	1b	B	+

* Study participation recommended

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Axillary Surgery and NACT

cN status (before NACT)	pN status (before NACT)	ycN status (after NACT)	Axillary surgery (after NACT)	AGO	ypN status (after NACT and surgery)	Surgical consequence based on histopathology	Oxford LoE	Oxford GR	AGO
cN0*	No surgery before NACT	ycN0	SLNE	++	ypN0 (sn)	none	2b	B	++
					ypN0 (i+) (sn)	ALND	2b	C	+/-
					ypN1mi (sn)	ALND	2b	C	+
					ypN1 (sn)	ALND	2b	C	++
cN+**	$pN+_{CNB}$	ycN0	ALND	+	ypN0 / ypN+	none	2b	B	++
			TAD	+	ypN0	none	2b	B	+
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ incl. ypN1mi	ALND	2b	B	+
			SLNE	+/-	ypN0	none	2b	B	+/-
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ incl. ypN1mi	ALND	2b	B	+
		ycN+	ALND	++	ypN0 / ypN+	none	2b	B	++

* Study participation in EUBREAST-01 recommended; ** Study participation in AXSANA recommended

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Targeted Axillary Dissection (TAD)
= TLNE + SLNE

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In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Core needle biopsy and marking of suspicious lymph nodes (LN)	2b	B	++
▪ Marking of multiple LN if more than one LN is suspicious	2b	B	+/-
▪ Evidence for comparison of different markers (clip / coil, carbon, magnetic seed, radar reflector, radiofrequency-based marker etc.) is insufficient *	2b	B	
▪ TAD in case of 1-3 suspicious LN before NACT	2b	B	+
▪ TAD in case of ≥ 4 suspicious LN before NACT	5	D	+/-
▪ Full workup using step sections of ≤ 500 µm on paraffin embedded tissue	5	D	++
▪ Immunohistochemistry for ITC detection	5	D	+/-
▪ ALND in case of pre- or intraoperatively undetectable marker	5	D	+
▪ Further intervention to retrieve lost marker (incl. after ALND)	5	D	-
▪ TLNE only without SLNE	2B	B	+/-

* Study participation in AXSANA recommended

Factors Predicting Conversion from cN+ (before NACT) to ypN0

- Young age
- Intrinsic subtype (TNBC, HER2 pos)
- Grade 3
- Ductal histology
- cN1 (vs. cN2)
- pCR (breast)

Kantor et al. Ann Surg Oncol 2018

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Sentinel Lymph Node Excision (SLNE) Indications I

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	Oxford		
	LoE	GR	AGO
▪ Clinically / sonographically negative axilla (cN0)	1b	A	++
▪ cT 1–2	2b	A	++
▪ cT 3–4c	3b	B	+
▪ Multifocal / multicentric breast cancer	2b	B	+
▪ DCIS			
▪ Mastectomy	3b	B	+
▪ BCT	3b	B	-
▪ DCIS in male	5	D	+/-
▪ Male breast cancer	2b	B	+
▪ Omission of axillary intervention in elderly patients (≥ 70 yrs., co-morbidities, pT1, HR+)	3b	B	+/-

Sentinel Lymph Node Excision (SLNE) Indications II

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In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ During pregnancy and / or breast feeding (only ^{99m}Tc-colloid, no blue dye)	3	C	++
▪ After prior tumor excision	2b	B	+
▪ After prior major breast surgery (e.g. reduction mammoplasty)	3b	C	+/-
▪ Ipsilateral breast recurrence after prior BCS and prior SLNE	4	D	-
▪ SLNE in the mammary internal chain	2b	B	-
▪ After axillary surgery	3b	B	+/-
▪ Prophylactic bilateral / contralateral mastectomy	3b	B	--
▪ Inflammatory breast cancer	3b	C	-

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Sentinel Lymph Node Excision (SLNE) Marking

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In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ ^{99m}Tc Kolloid	1a	A	++
▪ Preoperative lymphoscintigraphy (added infomation limited, but mandatory by legal regulations)*	1b	A	+
▪ Patent blue dye	1a	A	+/-
▪ Indocyanin green (ICG)	2a	B	+/-
▪ SPIO#	2a	B	+/-
▪ Methylene blue	4	D	-

* In Germany required for quality assurance of nuclear medicine

\# SPIO: Superparamagnetic Iron Oxide (Caveat: impaired MRI-sensitivity during follow-up)

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Surgical Approach in the Neoadjuvant Setting

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	Oxford		
	LoE	GR	AGO
▪ Early marking of tumor (incl. detailed topographic documentation)	5	D	++
▪ Surgical removal of tumor / representative excicion of post-therapeutic, marked tumor area	2b	C	++
▪ Tumor resection in new margins	2b	C	++
▪ Microscopically clear margins	2a	B	++

For „Surgery after neoadjuvant chemotherapy“ see chapter „Neoadjuvant chemotherapy“

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Begin of Adjuvant Therapy after Primary Surgery

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▪ Start adjuvant systemic therapy and radiotherapy (RT) as soon as possible (asap) after surgery	1b	A	++
▪ Start of adjuvant chemotherapy +/- HER2 therapy asap after surgery, prior to RT	1b	A	++
▪ Without cytotoxic therapy +/- anti-HER2 therapy:			
▪ Start adjuvant RT within 6–8 weeks after surgery	2b	B	++
▪ Start endocrine therapy after surgery asap	5	D	++
▪ Endocrine therapy concurrent with RT	2b	B	+

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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Oncoplastic and Reconstructive Surgery

Plastic-Reconstructive Aspects after Mastectomy

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- **Versions 2002–2021:**
  Audretsch / Bauerfeind / Blohmer / Brunnert / Dall / Ditsch / Fersis / Friedrich/ Gerber / Hanf/ Heil / Kühn / Kümmel / Lux / Nitz / Rezai / Rody / Scharl / Solbach / Thill / Thomssen

- **Version 2022:**
  Kümmel / Wöckel

Definition of Oncoplastic Surgical Procedures

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In collaboration with:

Use of plastic surgical techniques at the time of tumor removal to enable safe resection margins and to preserve aesthetic breast contour.

Focus on favorable scar placement, adequate soft tissue formation, choice of proper reconstruction procedure (including in the context of radiation) and reconstruction of the contralateral side to achieve symmetric results.

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Classifications

1. By Hoffmann / Wallwiener:

Classification by reconstructive surgery complexity with respect to breast conservation and mastectomy: PubMed Central, Figure 1: BMC Cancer. 2009; 9: 108. Published online 2009 Apr 8. doi: 10.1186/1471-2407-9-108 (nih.gov)

2. By Clough:

Oncoplastic classifcation for breast conservation according to relative resection volume: Level 1: < 20 % of breast volume resection („simple oncoplastic surgery“) and Level 2 > 20 % of breast volume resection with quadrant per quadrant techniques of mastopexy.

Hoffmann D et al., BMC 2009; Clough KB et al., Ann Surg Oncol 2010

Oncoplastic Breast Conserving Surgery (OPS)

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	Oxford		
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▪ OPS may replace mastectomy in selected patients	2b	B	+
▪ OPS and BCS are oncologically similiar	2b	B	+
▪ Complication rates of OPS and BCS are similiar	3b	C	+

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Algorithm of Breast Reconstruction

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In collaboration with:

Patient wishes to undergo breast reconstruction
N.B.: Habitus, breast volume, wishes, previous surgery

No postmastectomy radiotherapy

SSM / NSM and implantation
or
MRM + tissue expander → Implant
or
not suitable for alloplastic reconstruction or wish of patient → autologous reconstruction

Postmastectomy radiotherapy indicated

Mastectomy
à **Radiotherapy**
à **Delayed autologous reconstruction**

To be discussed in individual cases:
Immediate autologous reconstruction
N.B.: Increased fibrosis rate

Delayed prothesis reconstruction
N.B.: Increased complication rate

Not suitable for autologous reconstruction
E.g. too little subcutaneous fat, wishes of patient

Direct prosthesis reconstruction or two-staged implant-based reconstruction:
MRM→ Tissue expander → Implant + Radiotherapy
N.B.: Increased complication rate, particularly capsular fibrosis

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Breast Reconstruction Principles
Good Clinical Practise

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In collaboration with:

AGO: ++

- Planning of reconstructive procedure by interdisciplinary tumor board before mastectomy
- Counseling regarding all surgical techniques, including advantages and disadvantages
- Preference for autologous reconstruction after radiotherapy or if radiotherapy is planned
- Offer second opinion
- Discussion of neoadjuvant treatment if unfavorable tumor-breast-relation
- Consideration of contralateral breast;
  - discuss possible alignment / sequencing surgical procedures to produce symmetry; usually after at least 3-6 months (Caveat: need for post-resections, consider effects of radiotherapy for affected side)
- Preference for less stressful surgical technique with stable long-term esthetic result (prefer BCS / OPS over mastectomy)
- Avoid delay of adjuvant therapy due to reconstruction
- Assessment of outcome, e.g. Patient Reported Outcome (PRO)
- Oncologic safety is not impaired

Postmastectomy Reconstruction

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In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ Use of silicone gel filled breast implants one step or two steps after expander	2a	B	+
▪ Safety comparable to saline implants	2b	B	
▪ Autologous tissue reconstruction	2a	B	+
▪ Pedicled tissue reconstruction	2a	B	+
▪ Free tissue reconstruction (including vascular anastomoses)	2a	B	+
▪ Autologous tissue procedure plus implants	3a	C	+/-

Caveat: BMI > 30, smoking status, diabetes, radiotherapy, age, bilateral mastectomy

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In collaboration with:

Timing of Reconstruction

	Oxford LoE	Oxford GR	Oxford AGO
▪ **Immediate breast reconstruction**	3b	B	++
▪ **Mandatory: SSM / NSM**			
▪ **Avoidance of a postmastectomy syndrome**			
▪ **Delayed breast reconstruction (2-step)**	3b	B	++
▪ **No interference with adjuvant procedures (CHT, RT)**			
▪ **Disadvantage: loss of skin envelope**			
▪ **„Delayed-immediate“ breast reconstruction (placeholder before definitive reconstruction)**	3b	B	+

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Timing of implant Based Reconstruction and Radiotherapy

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	Oxford		
	LoE	GR	AGO
▪ **Implant reconstruction (IR)**	2a	B	+
▪ IR without radiotherapy	2a	B	++
▪ IR prior to radiotherapy	2a	B	+
▪ IR following radiotherapy	2b	B	+/-
▪ IR following secondary mastectomy (after BCS* with radiotherapy)	2a	B	+/-
▪ Perioperative antibiotic prophylaxis (max. 24 hours)	2a	B	+

* BCS: Breast Conserving Surgery

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In collaboration with:

Metaanalysis of Prophylactic Antibiotics > 24 h in Implant-based Immediate Breast Reconstruction (IBR)

- **11 studies (15,966 mastectomy procedures)**
- **Three studies comparing topical antibiotics with no topical antibiotics demonstrated statistical significance (RR = 0.26, 95% CI: 0.12–0.60, *P* = 0.001)**
- **8 studies comparing extended systemic antibiotics with standard of care found no statistical significance (RR = 0.80, 95% CI: 0.60–1.08, *P* = 0.13).**

LoE 2a B

In the setting of immediate breast reconstruction (IBR) following mastectomy, there is insufficient evidence for the use of extended prophylactic antibiotics to reduce surgical site infection (SSI) rates. Welldesigned randomized controlled trials in patients undergoing IBR should be conducted to determine the appropriate regimen and/or duration of prophylactic antibiotics on SSI outcomes.

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Hai Y et al. Plast Reconstr Surg Glob Open 2020;8:e2613; doi: 10.1097/GOX.0000000000002613,
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Radiotherapy and Implant-Based Reconstruction

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In collaboration with:

Cave: High complication rate in combination with radiotherapy (capsular contracture, revision surgery, reconstruction failure, reduced cosmetic outcome and patient satisfaction)

Cave: Lower patient satisfaction with implant-based reconstruction plus radiotherapy compared to autologous reconstruction plus radiotherapy

LoE 2b B

Possible Associations between Implants and Rare Diseases

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In collaboration with:

- **US FDA Breast Implant Postapproval Studies (LPAS)**
  Long-term Outcomes in 99,993 Patients
  (Primary Augmentation: N = 71.937 / Primary Reconstruction: N = 9942)
  - 56% of implants were silicone implants
- **Possible Associations:**
  - **Sjogren syndrome: (SIR* 8.14)**
  - **scleroderma: (SIR 7.00)**
  - **rheumatoid arthritis: (SIR 5.96)**
  - **stillbirth: (SIR 4.50)**
  - **melanoma: (SIR 3.71)**
- **At 7 years, reoperation rate is 11.7% for primary augmentation, and 25% for primary / revision reconstruction.**
- **One case of BIA-ALCL**

Associations need to be further analyzed with patient-level data to provide conclusive evidence!

*** Standardized incidence ratio**

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Possible Associations between Implants and Rare Diseases

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Rare Systemic Harms Compared With the General Population:

	Manufacturer	Study Events	Study Event Rate (Per 10,000 Person Yr)	General Population Event Rate (Per 10,000 Person Yr)	SIR	SIR 95% CI	P Value
Fibromyalgia	Allergan	9	1.8	112.8	0.02	0.01–0.03	< 0.001
	Mentor	307	28.4	112.8	0.25	0.22–0.28	< 0.001
Rheumatoid arthritis	Allergan	4	0.8	5.4	0.15	0.04–0.38	< 0.001
	Mentor	349	32.2	5.4	5.96	5.35–6.62	< 0.001
Scleroderma	Mentor	46	4.2	0.6	7.00	5.12–9.34	< 0.001
Sjogren syndrome	Mentor	62	5.7	0.7	8.14	6.24–10.44	< 0.001
Systemic lupus erythematosus	Allergan	3	0.6	5.4	0.11	0.02–0.32	< 0.001
	Mentor	66	6.0	5.4	1.11	0.86–1.41	0.398
Cancer	Allergan	80	16.0	41.3	0.39	0.31–0.48	< 0.001
	Mentor	532	63.8	41.3	1.54	1.42–1.68	< 0.001
Breast cancer	Mentor	116	13.9	12.5	1.11	0.92–1.33	0.26
Lung cancer	Mentor	5	0.6	5.2	0.12	0.04–0.27	< 0.001
Brain cancer	Mentor	3	0.4	0.6	0.67	0.14–1.95	0.639
Melanoma	Mentor	65	7.8	2.1	3.71	2.87–4.73	< 0.001
Neurological disorder	Allergan	18	3.6	22.5	0.16	0.09–0.25	< 0.001
	Mentor	394	35.8	22.5	1.59	1.44–1.76	< 0.001
Multiple sclerosis	Mentor	47	4.3	2.5	1.72	1.26–2.29	0.001
Myositis	Mentor	17	1.5	0.8	1.88	1.09–3.00	0.018

Allergan follow-up 2 years
Mentor follow-up 7 years

Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

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In collaboration with:

- Approximately 10.000.000 implant carrier
- Rare disease, 3% of Non-Hodgkin Lymphomas, 0.04-0.5% of all malignant breast diseases
- 1:3.000–30.000 in women with textured implants (caveat: underreporting!)
- Estimated incidence 0.6-1.2 / 100.000 women with implants (median age: 54 y)
- Mainly associated with textured implants
- Interval to diagnosis: 8 years (median)
- Clinical symptoms
  - Swelling and seroma. (60%)
  - Solid tumor (17%)
  - Seroma and solid tumor (20%)
- Histology: CD30+ / ALK-T-Cell Lymphoma
- Compulsory registration as SAE (§3 MPSV to BfArM)

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In collaboration with:

BIA-ALCL - Surfaces of Breast Implants

- The cause of BIA-ALCL is not established; however, it has been proposed that lymphomagenesis may be driven by a chronic inflammatory reaction induced by capsule contents or surface. **The risk for BIA-ALCL has been shown to be significantly higher for implants with grade 3 and 4 surfaces.**

Process	Polyurethane foam	Salt Loss (Biocell/ Eurosilicone)	Gas Diffusion	Salt Loss (Nagotex)	Imprinting	Smooth/ Nano
Surface Area	high	intermediate	intermediate	low	low	minimal
Roughness	high	intermediate	low	low	low	minimal
SURFACE TYPE	4	3	3	2	2	1

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BIA-ALCL– Diagnosis

	Oxford		
	LoE	GR	AGO
▪ **Breast US (assessment of new seromas > 1 year after implant insert, solid lesion (sensitivity: 84%, specificity: 75%)**	3a	D	++
▪ **Mamma-MRT in confirmed cases**	3a	D	++
▪ **Staging (Imaging, e.g. CT, PET-CT)**	3a	D	++
▪ **Cytology of late seromas** ▪ **> 50 ml** ▪ **Complete assessment** ▪ **flow-cytology (T-cell clone)** ▪ **BIA-ALCL specific cytologic diagnostic (CD 30+)**	3a	D	++
▪ **Core needle biopsy in solid lesions** ▪ **Lymphoma assessment of resected tissue and histologic staging**	3a	D	++
▪ **Documentation of the implant** (manufacturer, size, volume, surface, Batch-number) **and enter in registry**	5	D	++

BIA-ALCL – Therapy

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	Oxford		
	LoE	GR	AGO
▪ Implant resection and complete capsulectomy including tumorectomy	3a	C	++
▪ Resection of suspicious lymph nodes, no routine use of sentinel-node-biopsy, no axillary dissection	4	D	++
▪ Polychemotherapy (e.g. CHOP) in cases of extra capsular extension	4	D	+
▪ Radiotherapy in unresectable tumors	5	D	+/-
▪ Case discussion in an interdisciplinary tumor board in the presence of a specialist for lymphomas	5	D	++

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Diagnostic Pathways and Assessment

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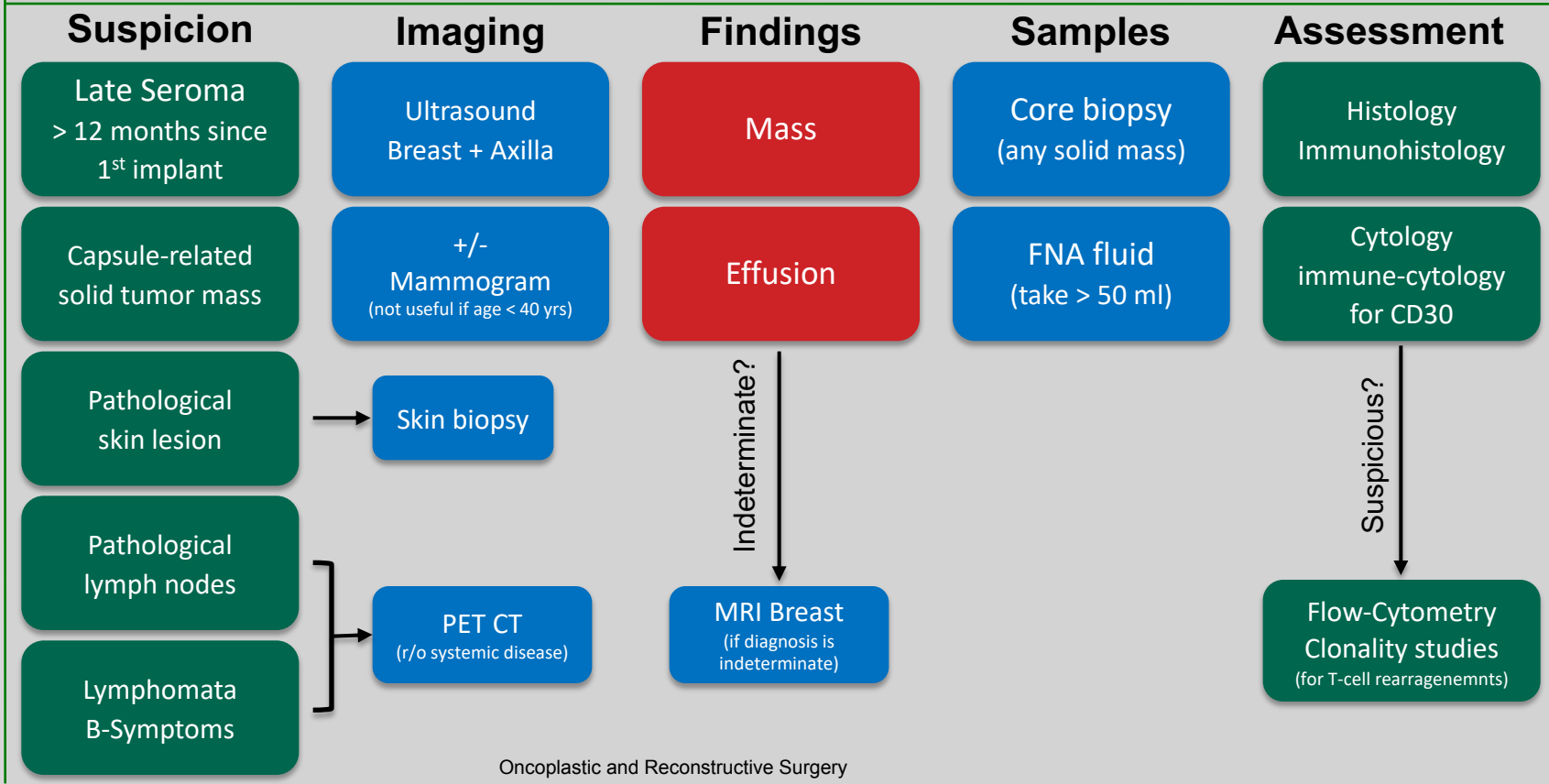

BIA-ALCL Treatment Pathways

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Outcome

- BIA-ALCL confirmed
- Indeterminate
  - Options: Further imaging US / MRI / Repeat FNAC , Tertiary referral
- Negative for BIA-ALCL
  - Treatment of infection / benign seroma (serial aspiration, implant exchange with capsulectomy)

Workup

- Referral to experienced breast cancer center
- PET-CT & breast MRI
- Routine bloods (+/- bone marrow bx)
- MTD Discussion
- Clinical suspicion remains
  - Consider diagnostic capsulectomy

Surgery

- En-bloc capsulectomy and complete excision (mass)
- +/- other breast +/- axilla biopsy (SNB not recommended)
- Histological Staging (Clemens et al. 2016)
- MTD Discussion
- Reports to BfArM, manufacturer, DGPRÄC, PROFILE database (FDA)

Adjuvant Therapy

- Stage I : No further treatment
- Stage II - IV: Consider adjuvant treatment
- Chemo-immunotherapy
- Radiotherapy for positive margins / irresectable thoracic wall infiltration but N0/M0

Follow-up

- Clinical follow-up (ultrasound / CT scan) 3–6 m for 2 y, afterwards for 5 y
- PET-CT if symptomatic

Treatment as per systemic ALCL regimes

24-36 Gy in 15 fractions

TNM Staging of BIA-ALCL

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	TNM-Kategorie	Definition
Tumor extent (cT/pT)	T1	Confined to seroma or a layer on luminal side of capsule
	T2	Early capsule infiltration
	T3	Cell aggregates or sheets infiltrating the capsule
	T4	Lymphoma infiltrates beyond the capsule
Regional lymph nodes (cN/pN)	N0	No lymph node involvement
	N1	One regional lymph node positive
	N2	Multiple regional lymph nodes positive
Metastasis (cM/pM)	M0	No distant spread
	M1	Spread to other organs or distant sites

Stage	Definition
IA	T1 N0 M0
TB	T2 N0 M0
TC	T3 N0 M0
IIA	T4 N0 M0
IIB	T1-3 N1 M0
III	T4 N1-2 M0
IV	T any N any M1

BIA-ALCL – EUSOMA-Recommendation

- **Despite an increase of BIA-ALCL in association with texture implants the use of textured implants is still permitted!**

„For the moment, textured implants can safely continue to be used with patient's fully informed consent, and that women that have these type of implants already in place don't need to remove or substitute them, which would undoubtedly cause harm to many tens of thousands of women, to prevent an exceptionally rare, largely curable and currently poorly understood disease."

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Tissue Replacement Techniques and Meshes (Details of Implant Reconstruction)

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In collaboration with:

	Oxford		
	LoE	GR	AGO
▪ The prepectoral lodge is superior to the subpectoral lodge	3b	C	+/-
▪ Acellular dermal matrix (ADM)			
▪ subpectoral	1b	A	+/-*
▪ prepectoral	2b	B	+/-*
▪ Synthetic meshes			
▪ subpectoral	2b	B	+/-*
▪ prepectoral	2b	B	+/-*

* Participation in registry studies recommended

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In collaboration with:

Lipotransfer

	Oxford		
	LoE	GR	AGO
▪ Lipotransfer following mastectomy and reconstruction	2a	B	+
▪ Lipotransfer after BCS*	2a	B	+
▪ Autologous adipose derived stem cells (ASCs)-enriched fat grafting vs. without stem cells	2a	B	-

* BCS: Breast Conserving Surgery

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In collaboration with:

Postmastectomy Pedicled Reconstruction

	Oxford		
	LoE	GR	AGO
Breast reconstruction (BR) with autologous tissue			
▪ TRAM, latissimus-dorsi-flap (both can be performed as a muscle-sparing technique)	2a	C	+
▪ Delayed TRAM in patients at high-risk	3a	B	+
▪ Ipsilateral pedicled TRAM	2a	B	+
▪ Radiotherapy:			
▪ BR following radiotherapy	2a	B	+
▪ BR prior to radiotherapy	2a	B	+/-
▪ (higher rates of fibrosis, wound healing problems, liponecrosis and reduced aesthetic outcome)			

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In collaboration with:

Free Flaps for Reconstruction

	Oxford LoE	Oxford GR	Oxford AGO
Type of free flap			
▪ DIEP	2a	B	+
▪ Free TRAM	2a	B	+
▪ SIEA	3a	C	+/-
▪ Glutealis flaps (SGAP- / IGAP, FCI)	4	C	+/-
▪ Free gracilis flap (TMG)	4	C	+/-
▪ Use of ICG* to assess flap perfusion	2a	B	+

Advantages

- DIEP and free TRAM are potentially muscle-sparing procedures. DIEP has a lower rate of abdominal hernias, especially in obesity

Disadvantages

- Time- and personnel consuming microsurgical procedures
- Intensified postoperative monitoring
- Pre-reconstruction radiotherapy increases rate of vascular complications

* ICG: indocyanin green

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In collaboration with:

Pedicled versus Free Tissue Transfer

Oxford		
LoE	GR	AGO
3a	A	++

- **Muscle-sparing techniques and accuracy of abdominal wall closure lead to low rates of late donor site complications independent of method used**
- **Autologous abdominal-based reconstructions have highest satisfaction rates (PROM)**
- **Donor site morbidity (e.g. impaired muscle function) has to be taken into consideration with all flap techniques**

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Skin-/ Nipple-Sparing Mastectomy (SSM / NSM) and Reconstruction

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In collaboration with:

	Oxford LoE	Oxford GR	AGO
Skin-/nipple-sparing Mastectomy (SSM / NSM)			
Safe (same recurrence rate as MX)	2b	B	++
Higher QoL for patients	2b	B	++
NAC can be preserved under special conditions	2b	B	++
Feasible after mastopexy / reduction mammoplasty	4	C	++
Use of ICG* to predict necrosis of the skin	1b	B	+
Skin incisions - different possibilities:			
Periareolar			
Hemi-periareolar with / without medial / lateral extension			
Reduction pattern: „inverted-T“ or vertical			
Inferior lateral approach, inframammary fold			
Lowest incidence of complications	2b	B	+

* ICG = Indocyanine Green

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Prevention and Therapy of Capsular Contracture

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▪ **Prevention**			
▪ Textured implantats (Caveat: BIA-ALCL)	1a	A	+
▪ Acellular Dermal Matrix (ADM) vs. nil	2a	B	+
▪ Synthetic mesh vs. nil	3a	C	+
▪ Topical antibiotics / antiseptics	2a	B	+
▪ PVP (Povidone-Iodine)	2a	B	+/-
▪ Leukotriene-antagonists	2a	B	+/-
▪ Breast massage	3a	C	-
▪ **Surgical interventions**			
▪ Capsulectomy	3b	C	+
▪ Capsulotomy (Caveat: exclusion of BIA-ALCL)	3b	C	+

Serome nach Implantatrekonstruktion I

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	Oxford	
	LoE	GR
▪ **Inzidenz: ca. 5-10 % (2-50 %)**	2a	B
Einflussfaktoren:		
▪ **Z. n. Radiatio erhöht Risiko (RR ca. 3)**	2a	B
▪ **Adipositas erhöht Risiko (z. B. BMI > 30 vs. < 30; RR ca. 3)**	2a	B
▪ **Einsatz von ADM erhöht Risiko (RR ca. 3)**	2a	B
▪ **Glatte Expander erhöhen Risiko (RR ca. 5)**	3b	C
▪ **Z. n. neoadjuvanter Chemotherapie erhöht Risiko eher nicht**	2a	B
▪ **Subcutane Loge erhöht Risiko eher nicht**	2b	B

Seroma after Implant-Based Reconstruction II

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	Oxford		
	LoE	GR	AGO
Prevention			
▪ Drain with no, little and much suction	3b	C	+
▪ Drain removal at < 30ml per 24 hours	2b	B	+
Therapy			
▪ Evacuation of serma by FNA or re-insertion of drain	4	C	+
▪ Dressings	5	D	+/-
▪ Revision surgery with capsulectcomy (ultima ratio)	5	D	+
▪ Revision surgery with implant removal (ultima ratio)	5	D	+

Risk-Reducing Bilateral Mastectomy for Healthy Women (RRBM)

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	LoE	GR	AGO
▪ RRBM reduces breast cancer incidence	2b	B	++
▪ RRBM in deleterious BRCA1/2 mutation	2a	B	+*
▪ RRBM in high-risk situation without BRCA 1/2 mutation (individual decision depending on personal- family history and mutational status – e.g. high and moderate-risk genes, Hodgkin lymphoma)	4	D	+/-*
▪ High risk and no BRCA counselling in specialized centre*	5	D	--
▪ Non-directive counselling prior to RR-BM	2b	B	++*
▪ RR-BM should be considered with other risk-reducing surgical options incl. bilateral salpingoophorectomy (BSO) and in the context of pre-existing diseases	2a	A	++*
▪ Further need for education of physicians regarding possibilities and advantages of RRBM	1b	A	++

* Counselling, risk prediction, and follow-up in specialized centers recommended

Surgical Prevention for Healthy Female *BRCA1/2* Mutation Carriers

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	Oxford LoE	Oxford GR	AGO
▪ **Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)****	2a	B	
▪ Reduces OvCa incidence and mortality			++*
▪ Reduces overall mortality			++*
▪ **Risk-reducing bilateral mastectomy (RR-BM)**			
▪ Reduces BC incidence	2b	B	+*
▪ Reduces BC mortality in *BRCA1* mutation carriers***	2b	B	+*

* Study participation recommended

** The RRSO is recommended from about 35 years for *BRCA1* and from about 40 years for *BRCA2* mutation carriers, considering the age of ovarian cancer diagnosis in the family and the family planning status.

*** No reduction in mortality could be shown for BRCA2 mutation carriers. RRM counselling should be individualised.

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Risk-reducing Interventions for BRCA1/2 Female Mutation Carriers Affected by Breast Cancer

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Synchronisierung zum Kapitel Brustkrebsrisiko

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	Oxford		
	LoE	GR	AGO
▪ Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)	2b	B	+*
▪ Reduces OvCa incidence and mortality			
▪ Reduces overall mortality (contradictory results for reduction of cl BC incidence)			
▪ Prophylactic contralateral mastectomy (RR-CM) reduces BC incidence and mortality	2b	B	+*
▪ Tamoxifen (reduces contralateral BC incidence)	2b	B	+/-*
▪ Indication for RR-CM should consider age at onset of first breast cancer in affected gene	2a	B	++*
▪ RR-BM after ovarian cancer	4	C	+/-**

* Study participation recommended

** Depends on tumor stage (FIGO I/II), recurrence free interval (≥ 5 yrs.), age

Forms of Risk-Reducing (Bilateral) Mastectomy (RR-BM)

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	Oxford		
	LoE	GR	AGO
RR-BM reduces breast cancer incidence;* BC-specific mortality also likely reduced			
▪ Simple mastectomy	2b	B	+
▪ RR-BM by SSM**	2b	C	+
▪ RR-BM by NSM** (NAC*** sparing)	2b	C	+
▪ Contralateral prophylactic mastectomy	4	C	+/-

* Depending on prior illnesses, e.g. pre-existing ovarian cancer 1-2% (stage III-IV)
** SSM / NSM: skin-/nipple-Sparing Mastectomy
*** NAC: nipple-areola complex

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Adjuvant Endocrine-based Therapy in pre- and postmenopausal Patients

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Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

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Assessment of Steroid Hormone Receptor Status

Oxford LoE: 1 GR: A AGO: ++

Endocrine responsive – hormone receptor positive
Immunhistology (ER and/or PgR)

0%	**pos. cells:**	**endocrine resistant**
1–10%	**pos. cells:**	**possibly endocrine sensitive**
> 10%	**pos. cells:**	**endocrine sensitive**
Unknown hormone receptor status:		**endocrine sensitive**

If ER negative / PR positive (> 10% positive cells): reassess IHC status

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Adjuvant Endocrine Therapy
Assessment of Menopausal Status

	Oxford		
	LoE	GR	AGO
Assessment of menopausal status:			
▪ **Menstruation history**			++
▪ **FSH, E2**			++

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Adjuvant Endocrine Therapy

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	LoE	GR	AGO
Endocrine therapy:			
▪ Endocrine responsive	1a	A	++
▪ endocrine doubtful responsiveness	3b	D	+
▪ Endocrine therapy sequentially after CT	2a	B	+
▪ Endocrine therapy simultaneous to T-DM1 / anti-HER2 therapy (w/o chemotherapy)	2b	B	+
▪ Non-responsive: No endocrine therapy	1a	A	++

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General Principles in Adjuvant Endocrine Therapy AGO ++

- **Adjuvant endocrine therapy is divided into initial therapy (years 1-5) and extended adjuvant therapy (EAT, years 6-10+).**
- **Standard treatment duration is 5 years.**
- **Extended therapy should be considered based on individual risks and benefits.**
- **Duration, choice & sequence of AI or Tam mainly depend on menopausal status, tolerability, and risk of recurrence.**
- **Switch to another better tolerated endocrine treatment (Tam or AI) is better than stopping endocrine therapy altogether.**
- **AI should be used as first treatment in patients, especially in case of lobular cancers and / or high risk of recurrence.**
- **To date, there is no sufficiently validated biomarker for identification of patients at risk for early versus late recurrence.**

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Premenopausal Patients
Initial Adjuvant Endocrine Therapy (Year 1-5)

	Oxford		
	LoE	GR	AGO
▪ **Low recurrence risk:**			
▪ **Tamoxifen for 5 years**	1a	A	++
▪ **Increased recurrence risk:**			
▪ **OFS 2-5 years* + tamoxifen for 5 years**	1a	A	++
▪ **OFS# + AI for 5 years**	1a	A	++
▪ **GnRHa monotherapie** (Bei relevanten Kontraindikationen für Tam, gegenüber keiner Therapie)	1a	B	+

OFS: ovarian function suppression;

* as long as tolerated and the patient is clearly premenopausal
after chemotherapy if ovarian function resumes within 24 months
The application of chemotherapy in the trials served as surrogate for high recurrence risk

\# in premopausal women AI only in combination with OFS

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TEXT / SOFT Joint Analysis

TEXT
Premenopausal
Patients with HR+ BC
≤ 12 wks after surgery
(N = 2672)

SOFT
Premenopausal patients with HR+ BC
≤ 12 wks after surgery
(if no chemo) *or*
≤ 8 mos after chemo
(N = 3066)

5 yrs

- **Tamoxifen 20 mg/day + OFS*** (n = 1328)
- **Exemestane 25 mg/day + OFS*** (n = 1332)
- **Tamoxifen 20 mg/day + OFS*** (n = 1016)
- **Exemestane 25 mg/day + OFS*** (n = 1014)
- **Tamoxifen 20 mg/day**

Median follow-up: 5.7 yrs

Joint Analysis

- **Tamoxifen + OFS*** (n = 2344)
- **Exemestane + OFS*** (n = 2346)

*OFS
- TEXT: triptorelin 3.75 mg IM every 28 days for 6 mos, then optional bilateral oophorectomy or irradiation
- SOFT: choice of method

Nach Pagani O, et al. N Eng J Med, 371(2) 2014

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Adjuvante Endocrine Therapy in Premenopausal Patients

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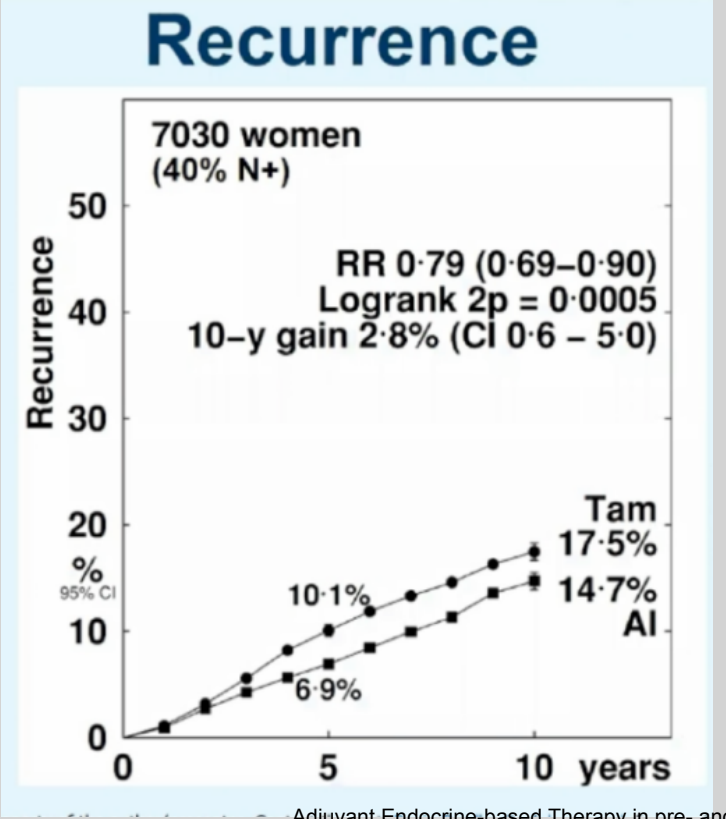

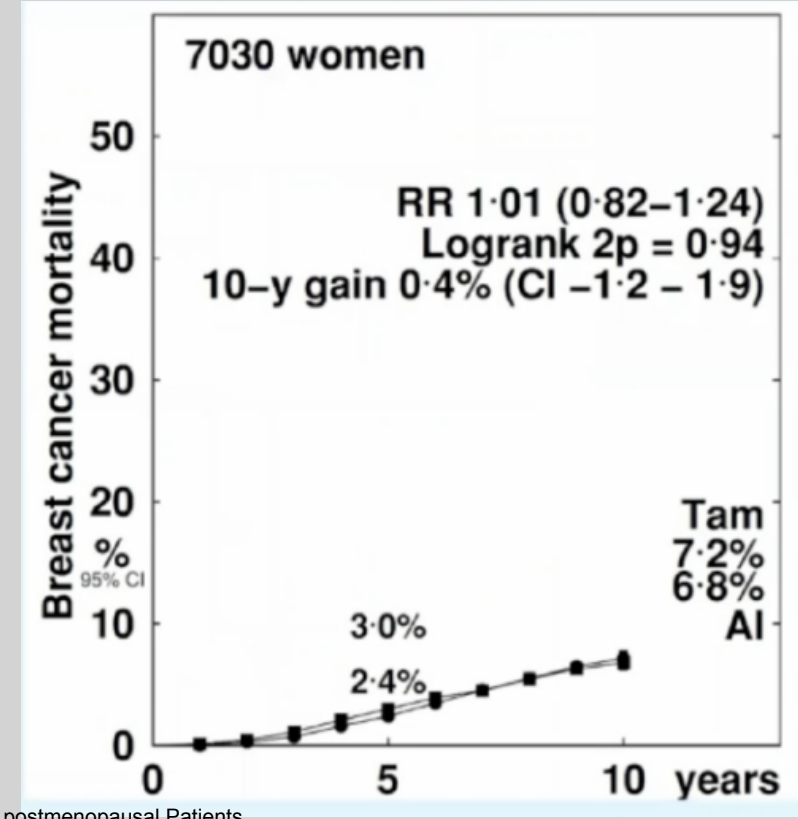

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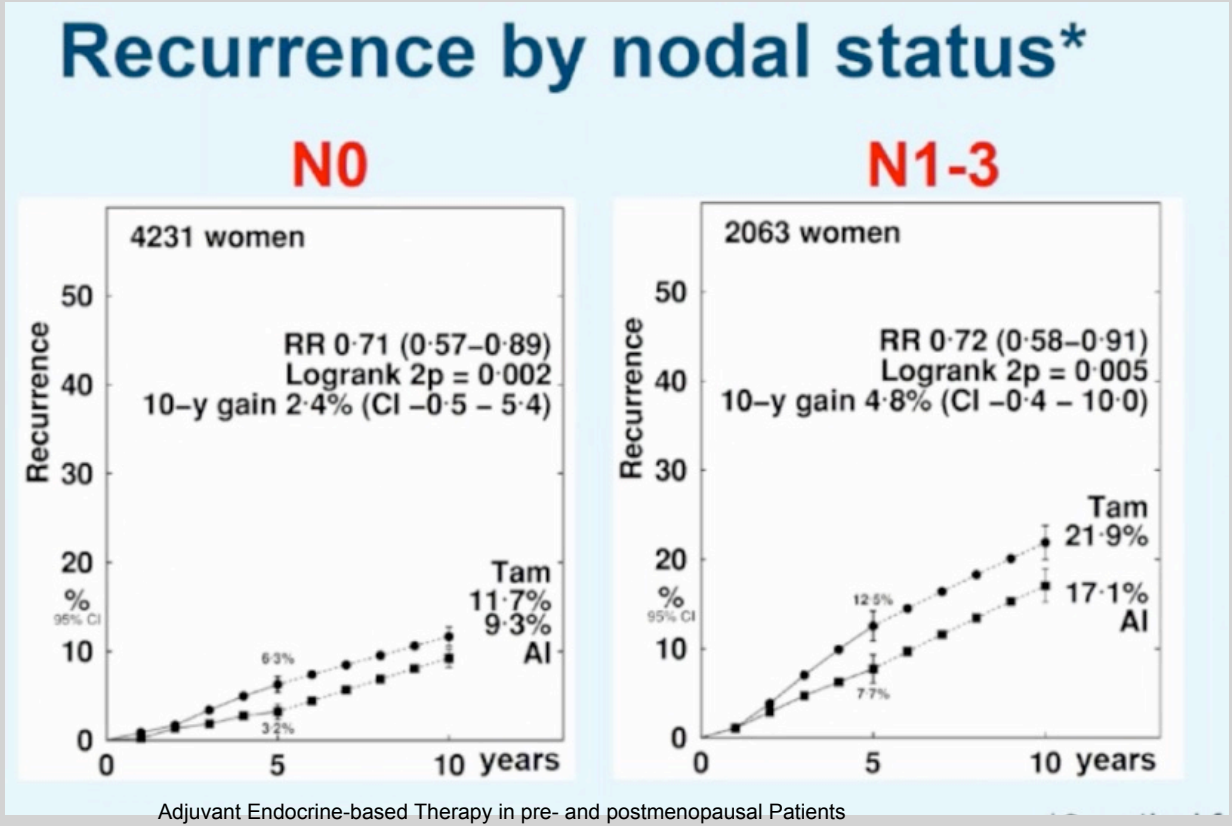

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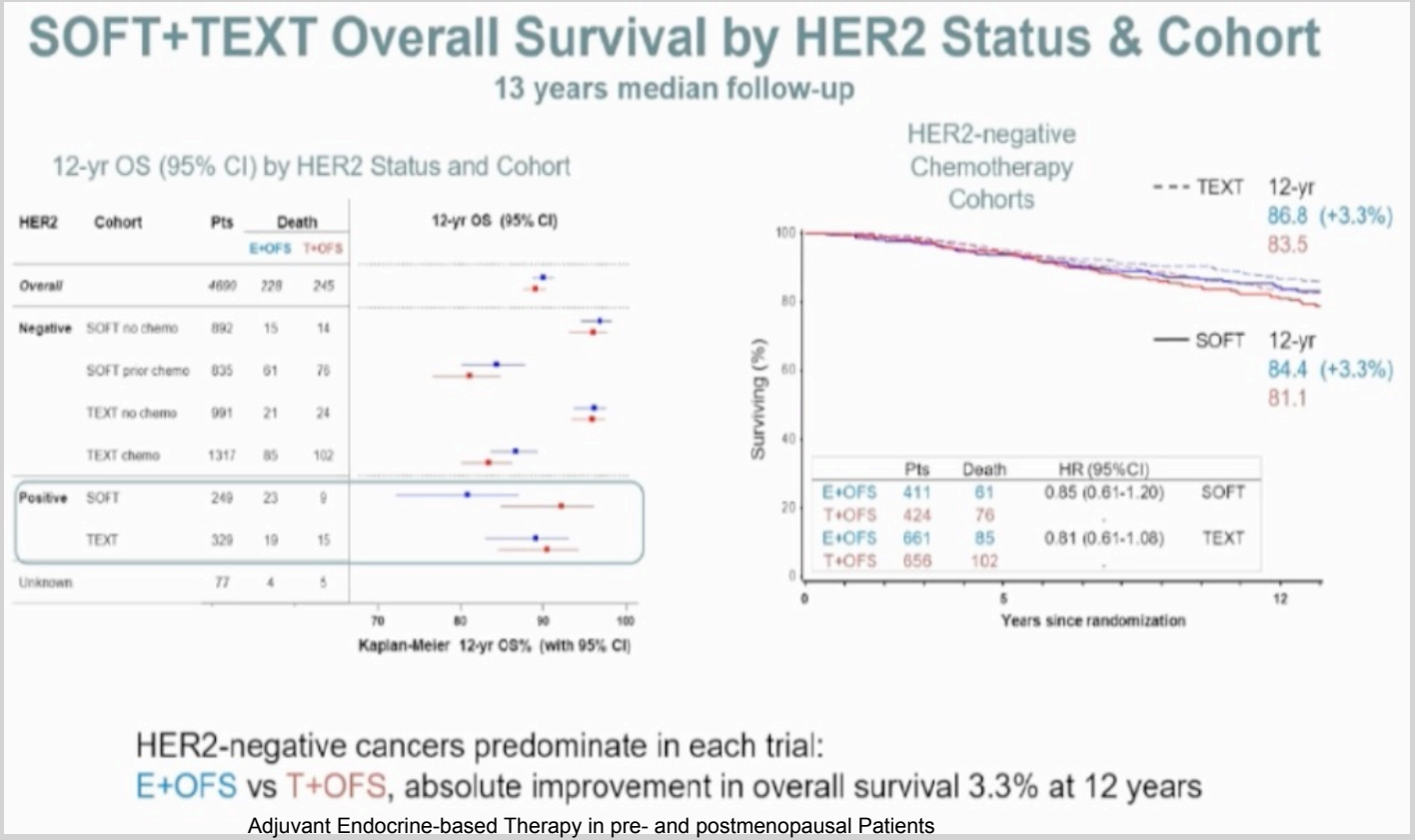

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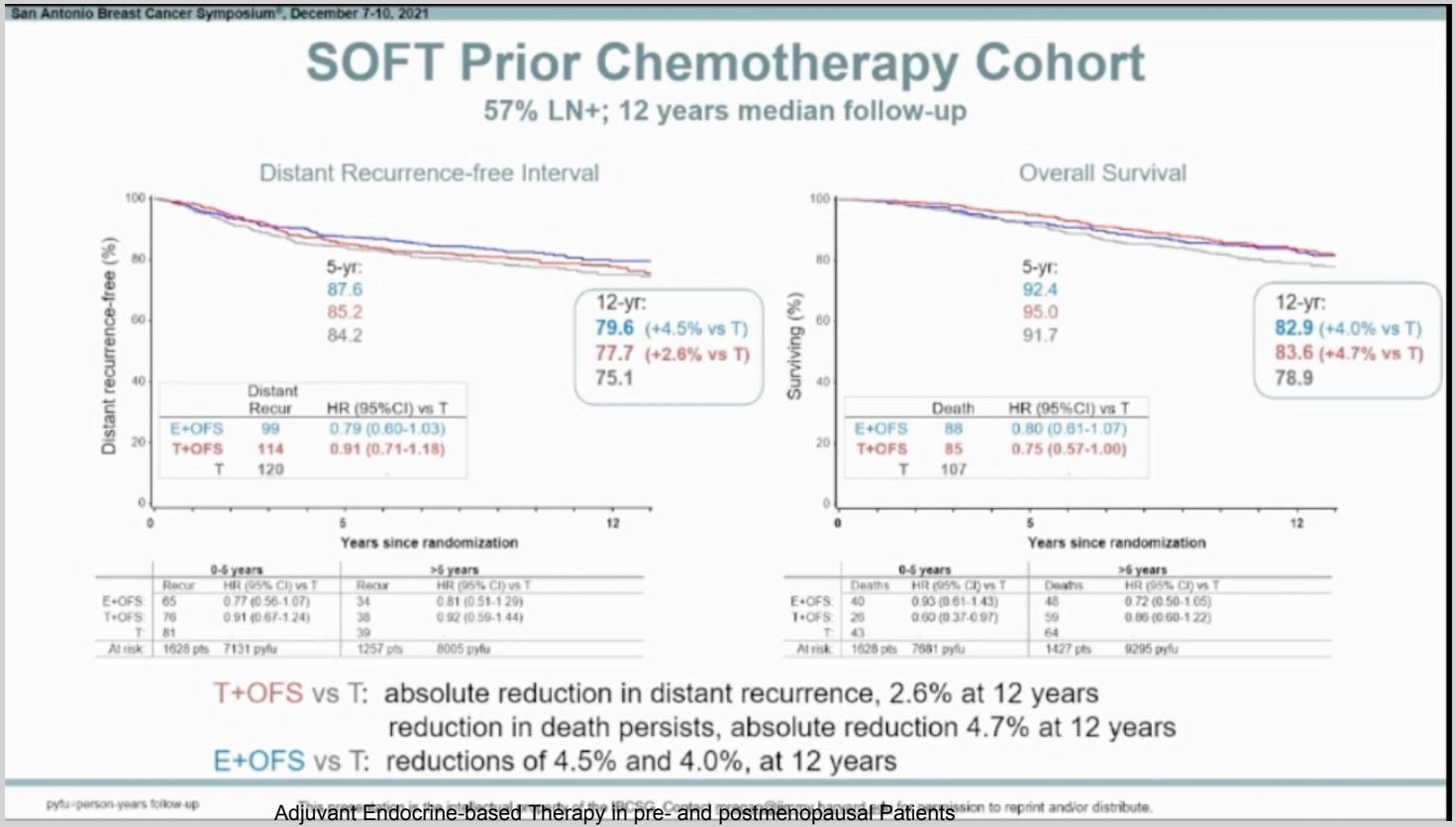

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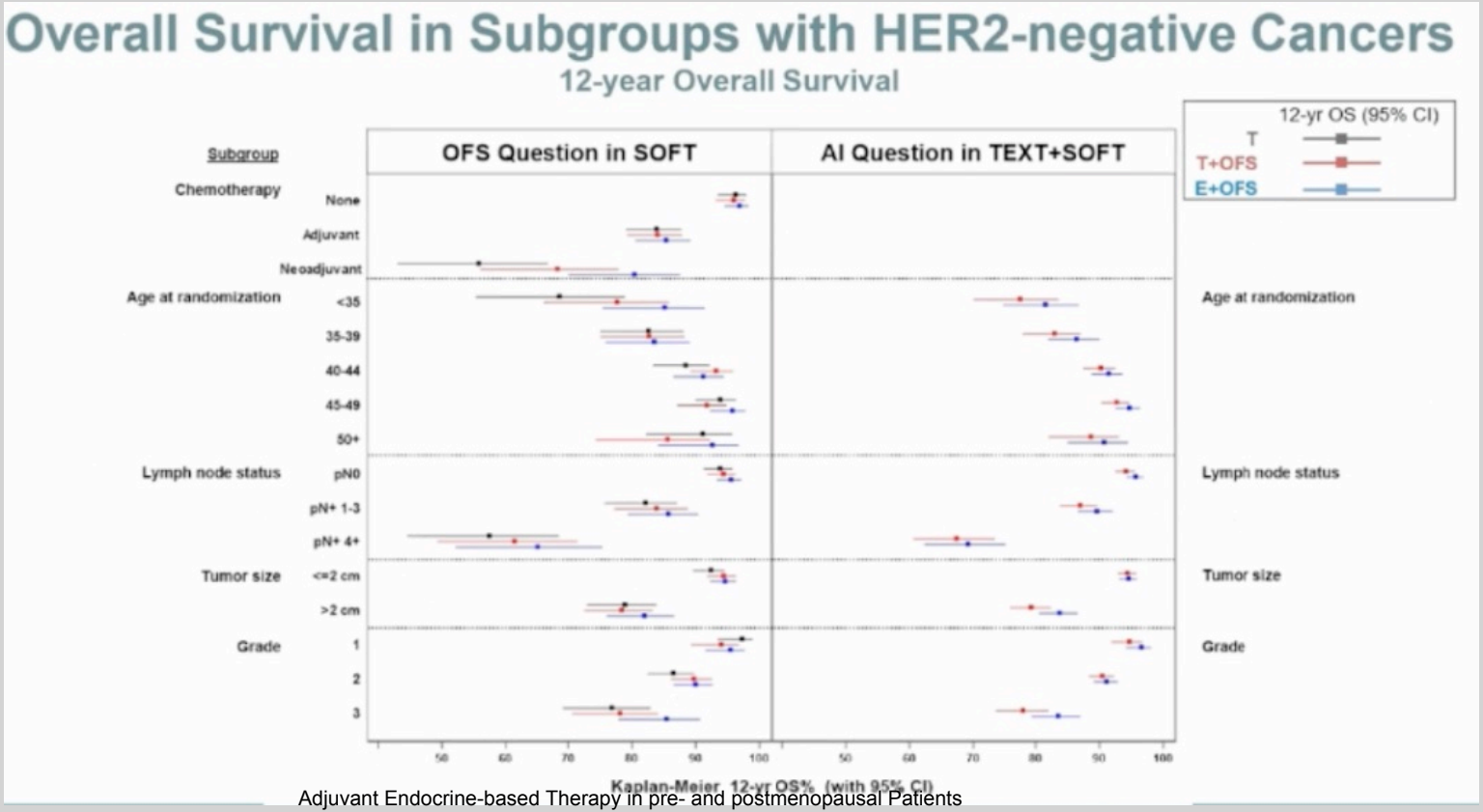

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GnRH Analogue every 3 Months

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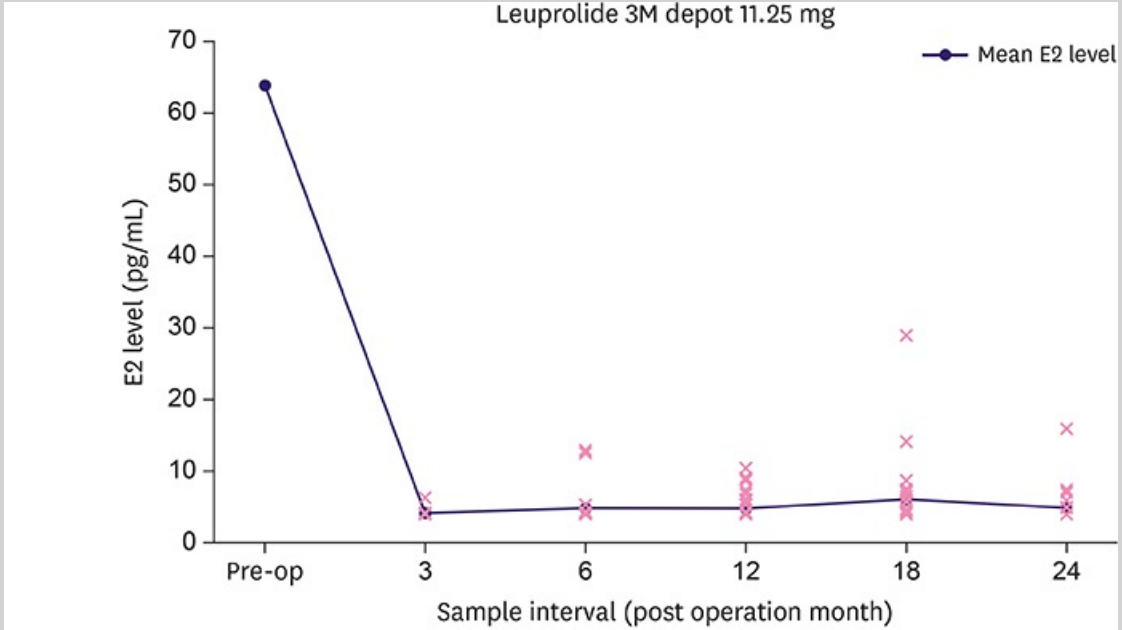

Mean pg/mL (SD)	63.7 (93.8)	4.1 (0.5)	4.8 (2.5)	4.8 (1.7)	6.1 (5.1)	4.9 (2.3)
Number	318	19	23	35	27	30

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Postmenopausal Patients
Initial Adjuvant Endocrine Therapy (Years 1-5)

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	Oxford		
	LoE	GR	AGO
▪ Aromatase inhibitor (AI) for first 5 years	1a	A	++
▪ Non steroidal-AI in lobular cancer	2b	B	+
▪ High risk of recurrence	2b	B	+
▪ Sequential therapy for first 5 years *	1a	A	++
▪ Tam (2-3 yrs.) followed by AI to complete 5 years	1a	A	++
▪ AI (2-3 yrs.) followed by tamoxifen to complete 5 years	1b	C	++
▪ Tamoxifen 20 mg/d for 5 years**	1a	A	+

* in postmenopausal patients, AI should be integrated in the first five years

** Tamoxifen may be offered to individual patients with very low risk of recurrence or if contraindications for AI are present

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Aromatase Inhibitor vs. Tamoxifen vs. Sequentieller Therapie - 5 Jahre Upfront Therapie

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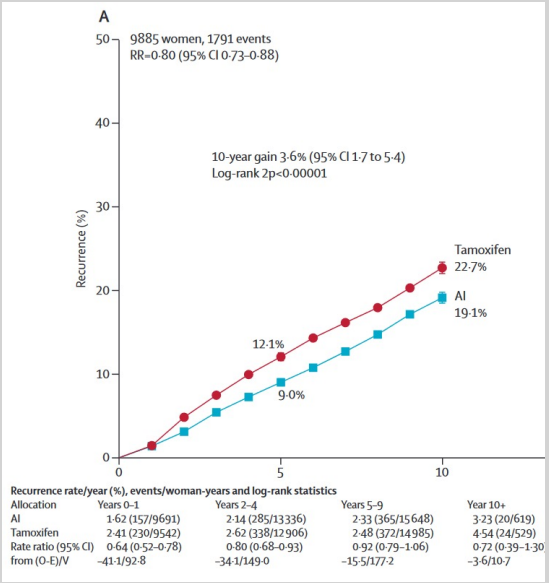
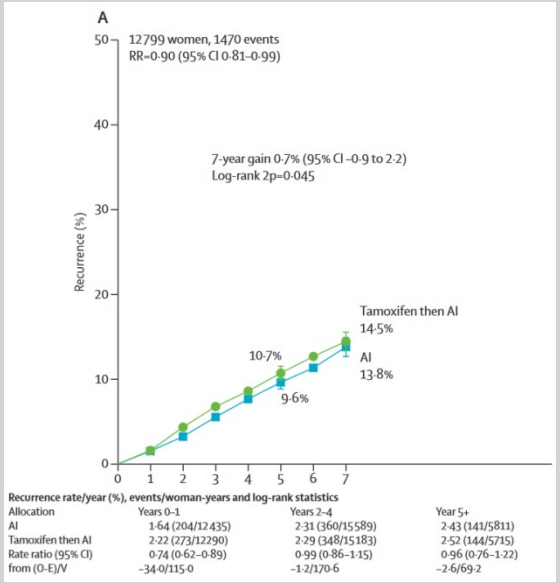


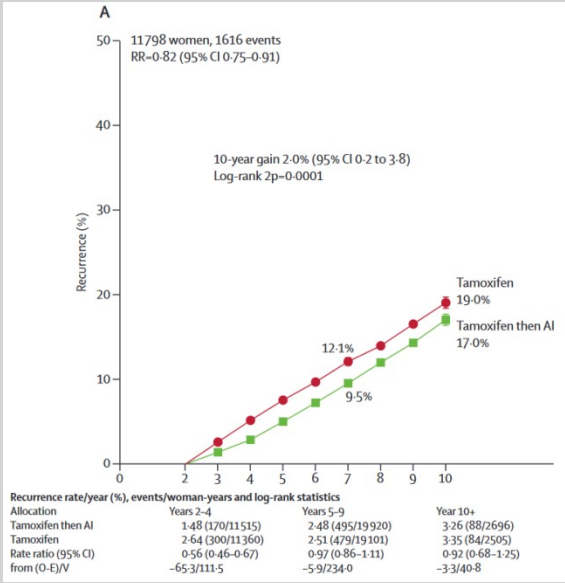
Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	1·62 (157/9691)	2·14 (285/13336)	2·33 (365/15648)	3·23 (20/619)
Tamoxifen	2·41 (230/9542)	2·62 (338/12906)	2·48 (372/14985)	4·54 (24/529)
Rate ratio (95% CI)	0·64 (0·52–0·78)	0·80 (0·68–0·93)	0·92 (0·79–1·06)	0·72 (0·39–1·30)
from (O-E)/V	−41·1/92·8	−34·1/149·0	−15·5/177·2	−3·6/10·7



Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Year 5+
AI	1·64 (204/12435)	2·31 (360/15589)	2·43 (141/5811)
Tamoxifen then AI	2·22 (273/12290)	2·29 (348/15183)	2·52 (144/5715)
Rate ratio (95% CI)	0·74 (0·62–0·89)	0·99 (0·86–1·15)	0·96 (0·76–1·22)
from (O-E)/V	−34·0/115·0	−1·2/170·6	−2·6/69·2



Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 2–4	Years 5–9	Year 10+
Tamoxifen then AI	1·48 (170/11515)	2·48 (495/19920)	3·26 (88/2696)
Tamoxifen	2·64 (300/11360)	2·51 (479/19101)	3·35 (84/2505)
Rate ratio (95% CI)	0·56 (0·46–0·67)	0·97 (0·86–1·11)	0·92 (0·68–1·25)
from (O-E)/V	−65·3/111·5	−5·9/234·0	−3·3/40·8

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet. 2015 Oct 3;386(10001):1341-52.

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Adjuvante Endocrine-Based Therapy with CDK4/6 Inhibitors and PARP Inhibitors

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	LoE	GR	AGO
In patients with increased risk of recurrence and characteristics corresponding to study criteria			
▪ **Abemaciclib for 2 years***	1b	B	+
▪ **Olaparib for 1 year in patients with *gBRCA1/2* mutations****	1b	B	+
▪ **Palbociclib for 1-2 years**	1b	B	-

* corresponding to MonarchE-Study
** corresponding to OlympiA-Study

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How to calculate CPS+EG Score?

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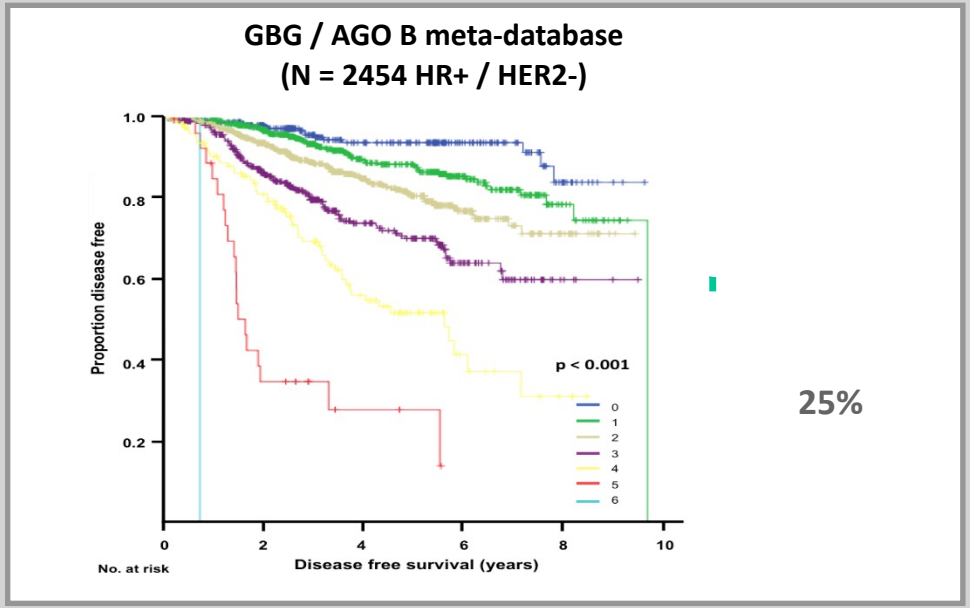
Point assignment for CPS+EG score

Clinical Stage		
I	0	T1N0; T0N1mi, T1N1mi
IIA	0	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2N2
IIIB	2	T4N0-2
IIIC	2	Any T N3
Pathologic Stage		
0	0	T0/isN0
I	0	T1N0; T0N1mi, T1N1mi
IIA	1	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2 N2
IIIB	1	T4 N0-N2
IIIC	2	Any T N3
Tumor Biologic Factors		
ER negative	1	
Nuclear grade 3	1	



25%

Mittendorf EA, J Clin Oncol 2011;
Marmé F, et al. Eur J Cancer 2016

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PARP-Inhibitors in Addition to Standard Endocrine Therapy in the Adjuvant / Post-Neoadjuvant Situation

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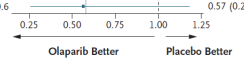
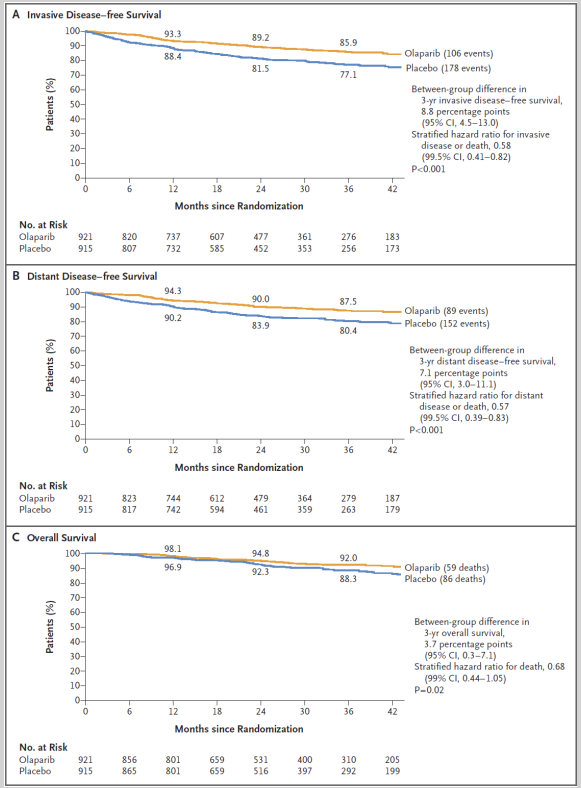
Subgroup	Olaparib	Placebo	3-Yr Invasive Disease–free Survival		Stratified Hazard Ratio for Invasive Disease or Death (95% CI)
	no. of patients with an event/total no.		Olaparib %	Placebo %	
All patients	106/921	178/915	85.9	77.1	0.58 (0.46–0.74)
Timing of previous chemotherapy					
Neoadjuvant	70/460	117/460	82.5	68.0	0.56 (0.41–0.75)
Adjuvant	36/461	61/455	89.3	85.4	0.60 (0.39–0.90)
Previous platinum-based chemotherapy					
Yes	34/247	43/239	82.0	77.0	0.77 (0.49–1.21)
No	72/674	135/676	87.3	77.1	0.52 (0.39–0.69)
Hormone-receptor status					
HR+ and HER2–	19/168	25/157	83.5	77.2	0.70 (0.38–1.27)
TNBC	87/751	153/758	86.1	76.9	0.56 (0.43–0.73)
Germline *BRCA* mutation					
BRCA1	70/558	126/558	85.0	73.4	0.52 (0.39–0.70)
BRCA2	22/230	38/209	88.6	78.0	0.52 (0.30–0.86)
BRCA1 and *BRCA2*	0/1	0/3	NC	NC	NC
Hormone-receptor status and timing of previous chemotherapy					
HR+ and HER2–, NACT	13/104	20/92	86.0	67.0	0.52 (0.25–1.04)
HR+ and HER2–, ACT	6/64	5/65	76.4	89.3	1.36 (0.41–4.71)
TNBC, NACT	57/354	97/368	81.4	67.7	0.57 (0.41–0.79)
TNBC, ACT	30/397	56/390	90.3	84.8	0.54 (0.34–0.83)
Previous platinum-based chemotherapy and timing of previous chemotherapy					
Yes, NACT	26/169	39/169	81.8	70.1	0.66 (0.40–1.07)
Yes, ACT	8/78	4/70	NC	NC	NC
No, NACT	44/291	78/291	83.1	66.8	0.51 (0.35–0.73)
No, ACT	28/383	57/385	90.4	84.2	0.51 (0.32–0.79)
CPS+EG score in patients with previous NACT					
Score of 2, 3, or 4	55/398	96/387	84.3	68.9	0.51 (0.37–0.71)
Score of 5 or 6	11/22	10/15	50.0	17.9	0.44 (0.19–1.06)
Primary database					
Breast International Group	95/810	160/806	86.0	76.7	0.58 (0.45–0.75)
NRG Oncology (United States)	11/111	18/109	85.0	80.6	0.57 (0.26–1.18)





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CDK4/6 Inhibitors in Addition to Standard Endocrine Therapy in the Adjuvant / Post-Neoadjuvant Situation

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	monarchE	PALLAS	PENELOPE[B]
N	5,637	5,600	1,250
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib
% of pts. with NACT	37%	n.r.	100%
Duration of CDK4/6i treatment	24 mths	24 mths	12 mths
Follow-up	27.1 mths	24 mths	43 mths
Discontinuation rate	28%	42%	20%
Discontinuation rate due to AE_{CDKi}	17%	27%	5%
IDFS-HR (95%-CI)	0.70 (0.58-0.82) p<0.0001	0.96 (0.81-1.14) p=0.65	0.93 (0.74-1.16) p=0.525
2-yrs IDFS	92.7% vs. 90.0%	n.r.	88% vs. 78%
3-yrs IDFS	88.8% vs. 83.4%	88% vs. 89%	81% vs. 78%
4-yrs IDFS	n.r.	84.2% vs. 84.5%	73% vs. 72%

IDFS: invasive disease-free survival

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Premenopausal Patients
Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)

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	Oxford		
	LoE	GR	AGO
In case of high risk of recurrence			
▪ 5 years tamoxifen after 5 years tamoxifen	1a	A	++
▪ 2–5 years AI after 5 years tamoxifen in initially premenopausal patients who obtain validated postmenopausal status during course of therapy	1b	B	+
▪ 5 years tamoxifen after 5 years of endocrine therapy + OFS	5	D	+

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Postmenopausal Patients
Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)

	Oxford		
	LoE	GR	AGO
In case of high risk of recurrence			
▪ 5 years tamoxifen after 5 years tamoxifen	1a	A	+
▪ 2–5 years AI after 5 years tamoxifen	1a	A	++
▪ After initial AI-containing therapy (upfront or switch), prolongation of endocrine therapy with AI for 2–5 years*			
▪ High-risk and good tolerabilty of AI	1a	A	+
▪ Low-risk, poor tolerabilty of AI	1a	A	-
▪ Interruption of endocrine treatment up to 3 months during EAT with AI	1b	B	+/-

* Up to date, no impact on OS

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Extended Aromatase Inhibitor Treatment following 5 or more Years of Endocrine Therapy: A Metaanalysis of 22192 Women in 11 Randomised Trials (EBCTCG)

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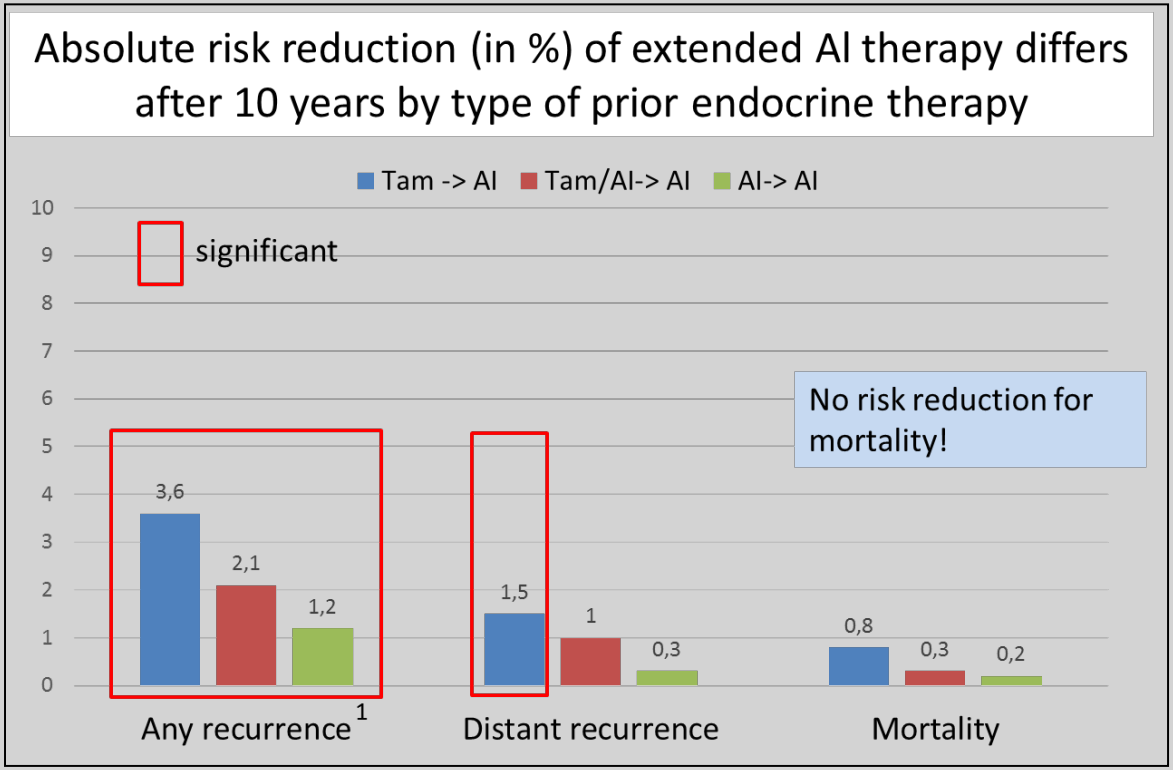

[1] *(new primary breast cancer, local and distant recurrence)*

Gray R et al. SABCS 2018 (GS3-03)

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Extended Adjuvant Treatment, Overiew

Studie	Therapien											De-facto-Vergleiche (Jahre)	HR für DFS	AI-Therapie Jahre 0-5 (%)
Jahre nach Diagnose	1	2	3	4	5	6	7	8	9	10	15			
Studien mit Tamoxifen nach 5 Jahren Tamoxifen														
ATLAS					*							5 vs 10	0,75 – 0,99	0
ATTOM					*							5 vs 10	0,75 – 0,99	0
Studien mit AI nach 5 Jahren Tamoxifen														
MA. 17					*							5 vs 10	0,57	0
NSAPB B-33					*							5 vs 10	0,68	0
ABCSG 6a					*							5 vs 8	0,62	0
Studien mit erweiterter AI-Th. Nach 5 Jahren endokrin inkl. AI														
DATA			*									6 vs 9	0,79	100
NSABP B-42					*							5 vs 10	0,85	100
GIM 4												5 vs 7	0,78	100
MA. 17R										§		10 vs 15	0,66	100
Studien bzgl. optimaler Dauer in Jahr 5-10														
BOOG 2006-05 IDEAL					*							7,5 vs 10	0,92	88
ABCSG 16					*							7 vs 10	1,007	49
SOLE												Cont vs unterbr	1,08	81

Braun: Tamoxifen

Grün: Tamoxifen oder AI

Blau: AI

Gestreift: Zeit der randomisierten Intervention vs keine Therapie od. Plazebo

*: Rando-misierungs-zeitpunkt

§ : MA17R nach 5 Jahren AI mit /ohne Tam zuvor

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Decision Criteria for Extended Adjuvant Therapy

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Factors indicating a clinical benefit from EAT:

- Adjuvant tamoxifen therapy only
- Condition after chemotherapy (indicating high risk)
- Positive lymph node status and / or T2 / T3 tumors
- Elevated risk of recurrence based on immunohistochemical criteria or based on multi-gene expression assays
- High CTS5-score
- BCI (H/I) (Breast Cancer Index)

Further decision criteria:

- Wish of patient
- up to now well tolerated AI therapy,
- good bone health
- younger age
- adherence

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Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)

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	Oxford LoE	Oxford GR	AGO
▪ **Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists (further information *https://fertiprotekt.com/english*)**			++
▪ **CTx + GnRHa (preservation of ovarian function) (GnRHa application > 2 weeks prior to chemo-therapy, independent of hormone receptor status)**	1a	A	+
▪ **CTx + GnRHa (preservation of fertility)**	2a	B	+/-

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Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient–Level Data

N = 837 patients from 5 trial, median follow-up time 5.0 years (IQR, 3.0-6.3 years)

	Control	GnRH	HR (95%-CI)	P-value
POI[1,2]	30.9%	14.1%	0.38; 0.26 to 0.57	< 0.001

1 *premature ovarian insufficiency*
2 *different definitions and time points were used*
3 *i n most trials POI and not pregnancy was defined as the primary endpoint*

No significant differences in disease-free survival and overall survival were observed between groups.

Lambertini M et al. J Clin Oncol 2018

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Adjuvant Cytotoxic and Targeted Therapy

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Adjuvant Cytotoxic and Targeted Therapy

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- **Version 2022:**
  Fasching / Rody

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Strategies for Differentiated Systemic Treatment in the Curative Situation

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	AGO
If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred; study participation recommended	
„Low absolute risk implies low absolute benefit“	
▪ **HR+ / HER2- and „low-risk”**	
▪ **Endocrine therapy without chemotherapy**	++
▪ **HR+ / HER2- and „high-risk”**	
▪ **Conventionally dosed AT-based chemotherapy (q3w)**	+
▪ **Dose dense chemotherapy (including weekly schedule)**	++
▪ **Followed by endocrine endocrine-based therapy**	++
▪ **Triple-negative (TNBC)**	
▪ **Conventional dosed AT-based chemotherapy (q3w)**	+
▪ **Sequential AT-based chemotherapy (incl. weekly schedule)**	++
▪ **Neoadjuvant Neo-/adjuvant platinum-containing chemotherapy**	+
▪ **Neoadjuvant platinum-containing chemotherapy with ICPI (Pembrolizumab)**	+
▪ **HER2 negative, gBRCA1/2mut (ER pos. and TNBC respectively[1])**	
▪ **Olaparib postneoadjuvant**	+
▪ **HER2+**	
▪ **Trastuzumab (plus Pertuzumab in N+ or NACT)**	++
▪ **Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy**	+
▪ **Anthracycline-free, chemotherapy + anti-HER2 therapy**	++

[1] **According to approval or study population (if not approved)**

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Adjuvant Chemotherapy: TNBC

	Oxford		
	LoE	GR	AGO
▪ **Indication for chemotherapy in <u>node-negative disease</u>**			
▪ **> 10 mm**	2b	B	++
▪ **> 5–10 mm**	2b	B	+
▪ **≤ 5 mm**	2b	B	-

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Adjuvant Chemotherapy without Trastuzumab: Overview

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	Oxford		
	LoE	GR	AGO
▪ Dose-dense anthracycline / taxane based (incl. weekly) chemotherapy	1a	A	++
▪ Conventional anthracycline / taxane based (q3w)	1a	A	+
▪ „Tailored“ anthracycline-/ taxane based	1b	B	+/-
▪ If anthracyclines are not a preferred option			
▪ Docetaxel plus cyclophosphamide	1b	B	+
▪ Paclitaxel mono weekly	1b	B	+/-
▪ CMF	1a	A	+/-
▪ Low-dose maintenance chemo	1b	B	-

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Gray R et al., Lancet 2019

Early Breast Cancer Trialists' Cooperative Group (EBCTCG)
Increasing the dose-density of adjuvant chemotherapy: an EBCTCG meta-analysis

Same chemotherapy drugs and doses **(n = 10,004)**

Recurrence-free survival: 10-y Gain 4.3% (95%-C.I. 2.2 – 6.5)
(RR = 0.83; 95%-C.I. 0.76 – 0.91; p < 0.0001)
Overall survival: 10-y Gain 2.8% (95%-C.I. 0.8 – 4.8)
(RR = 0.86; 95%-C.I. 0.77 – 0.96; p = 0.0054)

ER negative: **10-y Gain 4.7%** (95%-C.I. 2.3 – 7.1)
ER positive: **10-y Gain 3.1%** (95%-C.I. 1.5 – 4.7)

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Recommended Dose-dense and / or Dose-escalated, Sequential Adjuvant Chemotherapy

	Oxford LoE	Oxford GR	AGO
Dose-dense regimen			
▪ A_{60} x 4 → Pac_{175} x 4 → C_{600} x 4 q2w	1b	A	++
▪ A_{60}C q2w x 4 → Pac_{175} q2w x 4	1b	B	++
▪ E_{90}C q2w x 4 → Pac_{175} q2w x 4	1b	A	++
▪ E_{90}C q2w x 4 → Pac_{80} q1w x 12	1b	B	++
▪ $NabPac_{125}$ x 8-12 → E_{90}C q2(3)w x 4	1b	B	+
Dose-dense and dose-escalated regimen (N ≥ 4+)			
▪ E_{150} → Pac_{225} → C2000 q2w	1b	A	++

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Recommended Conventional Regimens for Adjuvant Chemotherapy

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		Oxford LoE	Oxford GR	AGO
Anthrazyklin-/ taxan-based regimen				
▪ *EC q3w x 4 → Pac q1w x 12		2b	B	++
▪ AC q3w x 4 → Pac q1w x 12		1b	A	++
▪ AC → D qw3	$A_{60}C$ q3w x 4 → D_{100} x 4	1b	A	+
▪ *EC → D qw3	$E_{90}C$ q3w x 4 → D_{100} x 4	1b	B	+
▪ DAC	$D_{75}A_{50}C$ q3w x 6	1b	A	+[a]
Anthrazyklin-free regimen				
▪ 6 x DC corresponds to EC → D	D_{75} C_{600} x 6	1b	B	+
▪ 4 x DC >> 4 x AC	D_{75} C_{600} x 4	1b	B	+
▪ Pac mono	P_{80} q1w x 12	1b	B	+/-
▪ CMF		1a	A	+/-
Taxan-free regimen (if pN0)				
▪ $FE_{100}C$ x 6	$F_{500}E_{100}C_{500}$ x 6	2b[(a)]	B	+

* Extrapolation from doxorubicin trials

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Adjuvant Chemotherapy
Other Drugs

	Oxford LoE	Oxford GR	Oxford AGO
Capecitabine-containing regimen in TNBC*			
adjuvant / neoadjuvant	1a	A	+/-
postneoadjuvant in non-pCR patients**	1a	A	+
Platinum-containing regimen			
Anthracycline-free adjuvant therapy in TNBC (combination with taxan)	1b	B	+
Anthracycline-based adjuvant therapy in TNBC	5	D	+/-
5- fluorouracile added to EC / AC	1b	A	--

* DPYD genotyping for the identification of a DPD Deficiency

** No platinum pretreatment

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Van Mackelenbergh M et al., SABCS 2019, abstr. GS1-07

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Effects of capecitabine as part of neo-/adjuvant chemotherapy

Meta-analysis of individual patient data from 12 randomized trials (n = 15,457)

HR for DFS overall 0.952 (95%-C.I. 0.895-1.012, p = 0.115)
X add. 0.888 (95%-C.I. 0.817-0.965, p = 0.005)
X instead 1.035 (95%-C.I. 0.945-1.134, p = 0.455)

HR for OS overall 0.892 (95%-C.I. 0.824-0.965, p = 0.005)
X add. 0.837 (95%-C.I. 0.751-0.933, p = 0.001)
X instead 0.957 (95%-C.I. 0.853-1.073, p = 0.450)

Significance only for TNBC overall DFS 0.886 (95%-C.I. 0.789-0.994, p = 0.040)
OS 0.828 (95%-C.I. 0.720-0.952, p = 0.008)
X add.: DFS 0.818 (95%-C.I. 0.713-0.938, p = 0.004)
OS 0.778 (95%-C.I. 0.657-0.921, p = 0.004)

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Adjuvant Treatment with Trastuzumab +/- Pertuzumab

	Oxford LoE	Oxford GR	AGO
Trastuzumab + Pertuzumab			
pN+	1b[a]	B	+
pN-	1b[a]	B	+/-
Trastuzumab in node-negative disease (if chemotherapy is indicated)			
> 10 mm	1a	A	++
> 5–10 mm	2b	B	+
≤ 5 mm	2b	B	+/-

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Adjuvant Treatment with Trastuzumab / Pertuzumab

	Oxford		
	LoE	GR	AGO
Start of treatment			
▪ Simultaneously with taxanes	1a	A	++
▪ Sequentially up to 3 months after chemotherapy	1b	B	+
▪ s.c. = i.v.	1a	A	++
Duration			
▪ For 1 year	1a	A	++
▪ For 0.5 years (Trastuzumab)	1a	A	+
▪ For 2 years	1b	A	-

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Adjuvant Treatment with Trastuzumab +/- Pertuzumab: Chemotherapy regimen

	Oxford		
	LoE	GR	AGO
Trastuzumab simultaneously with			
▪ paclitaxel / docetaxel after AC / EC	1a	A	++
▪ P q1w 12 x in pT < 2 cm, pN0	2b	B	+
▪ docetaxel and carboplatin	1b	A	+
Trastuzumab + Pertuzumab simultaneously with			
▪ paclitaxel q1w (or docetaxel q3w) after EC / AC	1b	B	++
▪ docetaxel+ carboplatin	1b	B	+
▪ taxanes dose-dense	2b	B	+
Radiotherapy concurrently with Trastuzumab / Pertuzumab	2b	B	+

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Adjuvant Therapy With Other Targeted Agents

	Oxford		
	LoE	GR	AGO
▪ Lapatinib	1b[a]	B	-
▪ (delayed adjuvant treatment)	1b	B	-
▪ Lapatinib + Trastuzumab	1b[a]	B	-
▪ Neratinib* (one year) after completing a year of adjuvant trastuzumab (if HR-positive)	1b	B	+
▪ Bevacizumab	1b	B	--

* In addition to standard endocrine treatment

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Postneoadjuvant Therapy HR+ / HER2-

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	Oxford		
	LoE	GR	AGO
HR positive (pCR and non-pCR)			
▪ Endocrine therapy according to menopausal state (s. chap. 10)	1a	A	++
▪ Abemaciclib for 2 yrs + endocrine therapy if high risk of recurrence[1]	1b	B	+
▪ Palbociclib for 1-2 yrs + endocrine therapy	1b	B	-
▪ Olaparib for 1 yr + endocrine therapy (g*BRCA1/2*^{MUT}, if non-pCR and CPS-EG Score ≥ 3)[2]	1b	B	+
▪ Capecitabine (non-pCR)	3b	C	+/-

1 According inclusion criteria monarchE-study,
2 According inclusion criteria OlympiA-study

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How to calculate CPS+EG Score?

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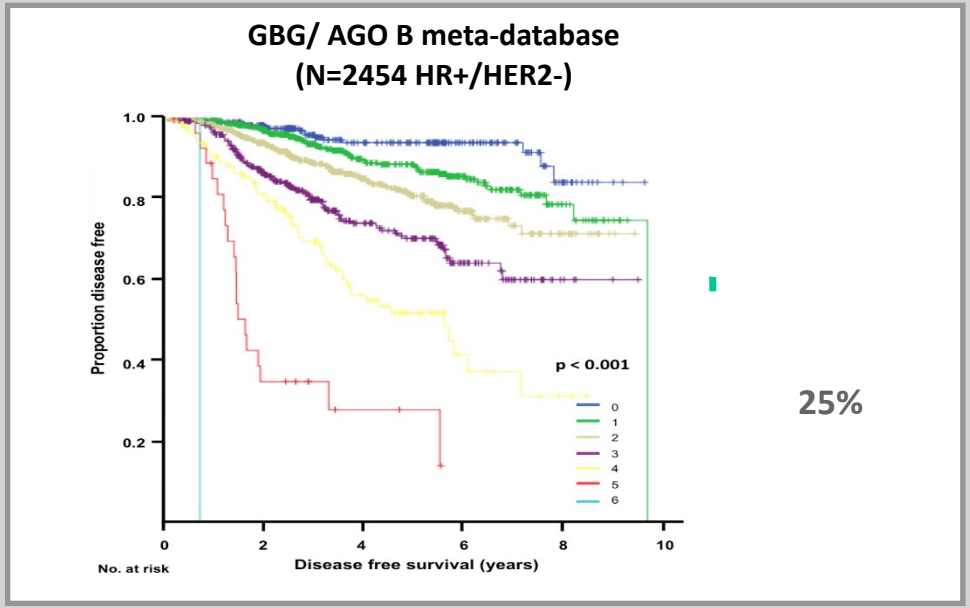
Point assignment for CPS+EG score

Clinical Stage		
I	0	T1N0; T0N1mi, T1N1mi
IIA	0	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2N2
IIIB	2	T4N0-2
IIIC	2	Any T N3
Pathologic Stage		
0	0	T0/isN0
I	0	T1N0; T0N1mi, T1N1mi
IIA	1	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2 N2
IIIB	1	T4 N0-N2
IIIC	2	Any T N3
Tumor Biologic Factors		
ER negative	1	
Nuclear grade 3	1	



Mittendorf EA, J Clin Oncol 2011;
Marmé F, et al. Eur J Cancer 2016

Adjuvant / Post-Neoadjuvant Treatment with CDK4/6i

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	monarchE	PALLAS	PENELOPE[B]
N	5,637	5,600	1,250
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib
% of pts. with NACT	37%	n.r.	100%
Duration of CDK4/6i treatment	24 mths	24 mths	12 mths
Follow-up	27.1 mths	24 mths	43 mths
Discontinuation rate	28%	42%	20%
Discontinuation rate due to AE_{CDKi}	17%	27%	5%
IDFS-HR (95%-CI)	0.70 (0.59-0.82) p < 0.0001	0.96 (0.81-1.14) p = 0.65	0.93 (0.74-1.16) p = 0.525
2-yrs IDFS	92.7% vs. 90.0%	n.r.	88% vs. 78%
3-yrs IDFS	88.8% vs. 83.4%	88% vs. 89%	81% vs. 78%
4-yrs IDFS	n.r.	84.2% vs. 84.5%	73% vs. 72%

IDFS: invasive disease-free survival

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Postneoadjuvant Therapy TNBC

	Oxford LoE	Oxford GR	Oxford AGO
pCR			
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	+
Non-pCR			
▪ Capecitabine (q3w up to 8 courses)*	1a	A	+
▪ Olaparib (*gBRCAm^{MUT}*)[1]	1b	B	+
▪ Continuation of Pembrolizumab, if started with neoadj. therapy (q3w up to 9 courses)	1b	B	++

[1] according inclusion criteria of OlympiA trial
* without platin based previous therapy

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Postneoadjuvant Therapy: HER2-positive

	Oxford		
	LoE	GR	AGO
pCR			
▪ Low risk: Trastuzumab (to complete 12 mths)	2a	C	++
▪ High risk (cN+): Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+
▪ Neratinib after 1 year Trastuzumab (HR-positive)*	2b	B	-
non-pCR			
▪ T-DM1	1b	B	+
▪ Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+/-
▪ Additional HER2-directed therapy after 1 yr (extended adjuvant th.)			
▪ Neratinib after Trastuzumab (HR-positive)*	2b	B	+
▪ Neratinib after other HER2-directed therapies (HR-positive*)	5	D	+/-

* In combination with standard endocrine treatment

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Neoadjuvant
(Primary) Systemic Therapy

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Neoadjuvant Systemic Therapy

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Strategies for Differentiated Systemic Treatment in the Curative Situation

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	AGO
If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred; study participation recommended	
„Low absolute risk implies low absolute benefit“	
▪ **HR+ / HER2- and „low-risk”**	
▪ **Endocrine therapy without chemotherapy**	++
▪ **HR+ / HER2- and „high-risk”**	
▪ **Conventionally dosed AT-based chemotherapy (q3w)**	+
▪ **Dose dense chemotherapy (including weekly schedule)**	++
▪ **Followed by endocrine endocrine-based therapy**	++
▪ **Triple-negative (TNBC)**	
▪ **Conventional dosed AT-based chemotherapy (q3w)**	+
▪ **Sequential AT-based chemotherapy (incl. weekly schedule)**	++
▪ **Neoadjuvant Neo-/adjuvant platinum-containing chemotherapy**	+
▪ **Neoadjuvant platinum-containing chemotherapy with ICPI (Pembrolizumab)**	+
▪ **HER2 negative, gBRCA1/2mut (ER pos. and TNBC respectively[1])**	
▪ **Olaparib postneoadjuvant**	+
▪ **HER2+**	
▪ **Trastuzumab (plus Pertuzumab in N+ or NACT)**	++
▪ **Sequential AT-based chemotherapy with concurrent T + anti-HER2 therapy**	+
▪ **Anthracycline-free, chemotherapy + anti-HER2 therapy**	++

[1] **According to approval or study population (if not approved)**

Anthracycline-free Taxan / Carboplatin based Regimen for HER2+

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Regimen	Ppts. (n)	pCR rate (%)	OUTCOME
6 x TCH (TRIO B07)	34	47	Not published
6 x TCHP (TRYPHAENA)	75	64	3-yr-DFS: 90%
6 x TCHP (KRISTINE - TRIO - 021)	221	56	3-yr-EFS: 94.2
4 x TCHP (NSABP- B52; nur HR+)	155	41	Not published
9 x TxCHP (TRAIN-2)	206	68	3-yr-EFS: 93.5%

T Docetaxel, Tx Paclitaxel, C Carboplatin, H Trastuzumab, P Pertuzumab

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Neoadjuvant Systemic Chemotherapy
Clinical Benefit

	Oxford	
	LoE	GR
▪ Leads to improvement of prognosis by individualization of neoadjuvant and post-neoadjuvant therapy	1b	A
▪ Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and number of cycles), if the postneoadjuvant therapy is not stratified according to pathologic response	1a	A
▪ Pathological complete response is associated with improved survival	1b	A
▪ Can achieve operability in primary inoperable tumors	1b	A
▪ Improved options for breast conserving surgery	1b	A
▪ Decreases rate of axillary lymphadenectomies lymphonodectomies	2b	B
▪ Allows individualization of therapy according to mid-course treatment effect	1b	B

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Neoadjuvant Systemic Chemotherapy - Indications

	Oxford		
	LoE	GR	AGO
▪ If similar postoperative adjuvant chemotherapy is indicated	1b	A	++
▪ To allow a risk adapted postoperative therapy	1b	A	++
▪ Inflammatory breast cancer	2b	B	++
▪ Inoperable breast cancer	1c	A	++
▪ Large operable breast cancer requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation	1b	B	++

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Neoadjuvant Systemic Chemotherapy (NACT)
Predictive Factors for pCR I

Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Young age	↑	1a	A	+
▪ Obesity	↓	2a	B	+
▪ cT1 / cT2 tumors o. N0 o. G3	↑↑	1a	A	++
▪ Negative hormone receptor status	↑↑	1a	A	++
▪ Triple negative breast cancer	↑↑	1a	A	++
▪ Positive HER2-status	↑↑	1a	A	++
▪ Early clinical response	↑	1b	A	+
▪ Lobular tumor type	↓	1a	A	+
▪ Metaplastic tumor type	↓↓	4	C	+

* High (↑) or very high (↑↑) probability to reach pCR, low (↓) or very low(↓↓) probability to reach pCR; See aso chapter „Prognostic and predictive factors“

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Neoadjuvant Systemic Chemotherapy (NACT) Predictive Factors for pCR II

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Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Gene expression profiles (gene signatures) (Mammaprint®, Endopredict® Oncotype DX®, Prosigna®, Breast Cancer Index^{SM})	↑	2b	B	+/-
▪ Ki-67	↑	2b	B	+
▪ Tumor infiltrating lymphocytes**	↑	2a	B	+
▪ *PIK3CA* mutation (for HER2-positive BC)	↑	2a	B	+/-
▪ gBRCA-mutation (for the effect of chemotherapy)	↑	2b	B	+
▪ gBRCA-mutation (for the effect of platinum)	↔	2b	B	+/-

* High (↑) or very high (↑↑) probabililty of pCR, low (↓) or very low (↓↓) probabililty of pCR

** Defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (lymphocytes make up > 50 % of stroma area)

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Neoadjuvant Systemic Chemotherapy Recommended Regimens

	Oxford		
	LoE	GR	AGO
▪ Use of adjuvant standard regimens for NACT*	1a	A	++
▪ Taxane mono followed by anthracycline (reverse order)	4	D	+/-
▪ Platinum in TNBC (cT1 / cN+ or cT2) (irrespective of BRCA status)	1b	A	+
▪ Platinum in TNBC (from cT1 / cN+ or cT2) (irrespective of BRCA status)	1a	A	+
▪ Nab-paclitaxel weekly instead of paclitaxel qw1 (in TNBC)	1a	A	+
▪ Pembrolizumab in combination with carbo / paclitaxel → 4x EC q3w (TNBC**)	1b	B	+

* See chapter Adjuvant Chemotherapy;
** ≥ 2 cm or cN+, PD-L1 independent

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Recommended Regimen in Triple Negative Breast Cancer

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	Oxford LoE	Oxford GR	AGO
Non-platinum-containing regimen			
ddEC x 4 → $pacli_{80}$ q1w x 12	1b	B	++
$NabPac_{125}$ q1w x 12 → $E_{90}C$ q(2)3w x 4	1b	B	+/-
Platinum-containing regimen			
$NabPac_{125}$ / $carbo_{AUC\ 2}$ q1w x 8 → ddEC x 4	1b	B	+
$Pacli_{80}$ q1w x 12 / $carbo_{AUC\ 6}$ q3w x 4 → ddAC / ddEC x 4	1b	B	+
Docetaxel / $carbo_{AUC6}$ q3w x 6 or paclitaxel/$carbo_{AUC1,5}$ q1w x18	2b	B	+
$NabPac_{1oo}$ / $carbo_{AUC\ 6}$ q4w x 4	2b	C	+
Checkpoint inhibitors			
$Pembro_{200}$ q3w + Pac_{80} / $carbo_{AUC\ 1,5}$ q1w x 12 → $E_{90}C$ q3w x 4	1b	B	+
$Pembro_{200}$ q3w + Pac_{80} q1w x 12 / $carbo_{AUC\ 5}$ q3w → $E_{90}C$ q3w x 4	1b	B	+

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ICPi plus Neoadjuvant Chemotherapy for Triple Negative Breast Cancer Patients

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	GeparNuevo	IMpassion031	Keynote 522	neoTRIP
Phase	II	III	III	II
N	174	333	602 (pCR) 1174 (EFS)	280
Prim. endpoint	pCR	pCR	pCR + EFS	EFS
CPi	Durvalumab (24-26 weeks)	Atezolizumab (1y)	Pembrolizumab (1y)	Atezolizumab (24 weeks)
Chemo	$NabPac_{125}$ q1w x12 → EC q2w x4	$NabPac_{125}$q1w x12 → EC q2w x4	Pac q1w x12 + carbo q3w AUC 5 or q1w AUC 1,5 -> AC/EC q3w x4	$NabPac_{125}$ + carbo AUC 2 q1w d1 and d8
Inclusion criteria	cT1b-cT4a-d	cT2-cT4, cN0-cN3	cT1cN1-2 or cT2 N0-2	cT1cN1; cT2cN1; cT3cN0
PD-L1 positive	87%	46%	83%	56%
pCR ITT	53.4% vs. 44.2% Δ 10.8% (n.s.)	57.6% vs. 41.2% Δ 16.5% ($p < 0.01$)	64.8% vs. 51.2% Δ 13.6% ($p < 0.00055$)	43.5% vs. 40.8% Δ 2.6% (n.s.)
pCR PD-L1 positive	58% vs. 50%	69% vs. 49%	69% vs. 55%	52% 48%
pCR PD-L1 negative	44% vs. 18%	48% vs. 34%	45% vs. 30%	32% vs. 32%
Follow up/EFS/iDFS (months)/HR EFS/iDFS	43.7 months iDFS: 0.48 ($p = 0.0389$)	20 months EFS: 0.76 (n.s.)	39.1 months EFS: 15.7 vs. 23.8 m 0.63 ($p = 0.00031$)	---
EFS/iDFS adjusted to pCR/non-pCR	pCR 95.5% vs. 86.1% npCR 76.3% vs. 69.7%	---	pCR 94.4% vs. 92.5% npCR 67.4% vs. 56.8%	---

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Neoadjuvant Systemic Therapy
Recommended Methods of Monitoring of Response

	Oxford		
	LoE	GR	AGO
▪ Breast ultrasound	2b	B	++
▪ Palpation	2b	B	++
▪ Mammography	2b	B	++
▪ MRI	2b	B	+
▪ PET(-CT)	2b	B	+/-
▪ Pretherapeutical marking of tumor region	5	D	++
▪ Pretherapeutical marking of pN+	2a	B	+*

*study participation recommended (AXSANA /Eubreast 3 Trial)

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Neoadjuvant Targeted Therapy in HER2 Positive Tumors

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	Oxford		
	LoE	GR	AGO
▪ Pertuzumab + trastuzumab in combination with chemotherapy (high-risk defined as cT2-4 and / or cN+)	2b	B	++
▪ Trastuzumab in combination with stand polychemotherapy (low-risk)*	1b	A	+
▪ Anti-HER2 agents without chemotherapy	2b	B	+/-

* Single agent chemotherapy combined with trastuzumub should preferably be used in the adjuvant setting

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Neoadjuvant Chemotherapy
Treatment Strategies Based on Clinical Response

	Oxford		
	LoE	GR	AGO
In case of early response			
▪ Completion of neoadjuvant chemotherapy	1b	A	++
In case of no change:			
▪ Completion of neoadjuvant chemotherapy (NACT) followed by surgery	2b	C	++
▪ Continuation of NACT with non cross-resistant regimen	2b	B	+
▪ AC or EC x 4 → D x 4 or Pw x 12	2b	B	+
▪ DAC x 2 → NX x 4	1b	B	+
In case of disease progression			
▪ Re-evaluation of tumorbiological factors	5	D	+/-
▪ Stop NACT and proceed to surgery or radiotherapy	4	D	++
▪ Additional adjuvant chemotherapy with non cross-resistant regimen	4	D	+/-

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Axillary surgery and NACT

cN status (before NACT)	pN status (before NACT)	ycN status (after NACT)	Axillary surgery (after NACT)	AGO	ypN status (after NACT and surgery)	Surgical consequence based on histopathology	Oxford LoE	Oxford GR	AGO
cN0 *	No surgery before NACT	ycN0	SLNE	++	ypN0 (sn)	none	2b	B	++
					ypN0 (i+) (sn)	ALND	2b	C	+/-
					ypN1mi (sn)	ALND	2b	C	+
					ypN1 (sn)	ALND	2b	C	++
cN+ **	$pN+_{CNB}$	ycN0	ALND	+	ypN0 / ypN+	none	2b	B	++
			TAD	+	ypN0	none	2b	B	+
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ incl. ypN1mi	ALND	2b	B	+
			SLNE	+/-	ypN0	none	2b	B	+/-
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ incl. ypN1mi	ALND	2b	B	+
		ycN+	ALND	++	ypN0 / ypN+	none	2b	B	++

* Study participation in EUBREAST-01 recommended; ** Study participation in AXSANA recommended

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Neoadjuvant Systemic Therapy
Loco-regional Surgery (Breast)

	Oxford		
	LoE	GR	AGO
▪ Pretherapeutic discussion in a multidisciplinary tumor board (e.g. to define the surgical procedure)	1a	B	++
▪ Early marking of tumor (incl. detailed topographic documentation)	5	D	++
▪ Surgical removal of tumor / representative excicion of posttherapeutic, marked tumorareal	2b	C	++
▪ Tumor resection in new margins	2b	C	++
▪ Microscopically clear margins	2a	B	++

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Neoadjuvant Systemic Therapy
Indications for Mastectomy

	Oxford		
	LoE	GR	AGO
▪ Positive margins after repeated excisions	3b	C	++
▪ Radiotherapy not feasible	5	D	++
▪ In case of clinical complete response			
▪ Inflammatory breast cancer (in case of pCR)	2b	C	+/-
▪ Multicentric lesions	2b	C	+/-
▪ cT4a-c breast cancer	2b	B	+/-

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Neoadjuvant Systemic Therapy
Timing of Diagnosis, Surgery and Radiotherapy

	Oxford		
	LoE	GR	AGO
Initiation of therapy Delay of therapy (> 60 days) associated with worse prognosis	2b	B	
Timing of surgery 4-8 weeks after last course of chemotherapy	2a	B	++
Radiotherapy within 2 months after surgery	2b	B	++

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Neoadjuvant endocrine Therapy (NET)
- Good clinical practice -

- **Suitable for patients who are**
  - **inoperable**
  - **not able or willing to undergo chemotherapy**
- **Data for premenopausal in contrast to postmenopausal patients is limited**
- **Optimale duration of NET is at least 4-6 months or until best repsonse or progression**
- **Choice of endocrine therapy is based on the menopausal status**
- **Ki-67 analysis after preoperative short term endocrine therapy for 2 to 4 weeks may predict response to endocrine treatment (prognostic / predictive evaluation)**

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Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer

	Oxford LoE	GR	AGO
Postmenopausal patients:			
Optimizes the option for breast conserving therapy	1b	A	+
Aromatase inhibitors (at least 6 months)	1a[a]	B	+
Aromatase inhibitor + lapatinib (HER2+ BC)	2b	B	+/-
Premenopausal patients			
Tamoxifen	2b	C	+
Aromatase inhibitors + LHRHa	1b	C	+/-
Concurrent chemo-endocrine therapy	1b	A	-
Ki-67 analysis after preoperative short term endocrine therapy for 2 to 4 weeks (Tam / AI ± GnRha) (prognostic / predictive evaluation information)	1b	B	+
Prognostic score:			
PEPI: pTN-Stage, ER expression and Ki-67 expression after neoadjuvant endocrine therapy	1b	B	+

[a] Optimal duration of neoadjuvant endocrine therapy is unknown.
No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)

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Postneoadjuvant Therapy HR+ / HER2-

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	Oxford		
	LoE	GR	AGO
HR positive (pCR and non-pCR)			
▪ Endocrine therapy according to menopausal state (s. chap. 10)	1a	A	++
▪ Abemaciclib for 2 yrs + endocrine therapy if high risk of recurrence[1]	1b	B	+
▪ Palbociclib for 1-2 yrs + endocrine therapy	1b	B	-
▪ Olaparib for 1 yr + endocrine therapy (g*BRCA1/2*^{MUT}, if non-pCR and CPS-EG Score ≥ 3)[2]	1b	B	+
▪ Capecitabine (non-pCR)	3b	C	+/-

1 According inclusion criteria monarchE-study
2 According inclusion criteria OlympiA-study

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How to Calculate CPS+EG Score?

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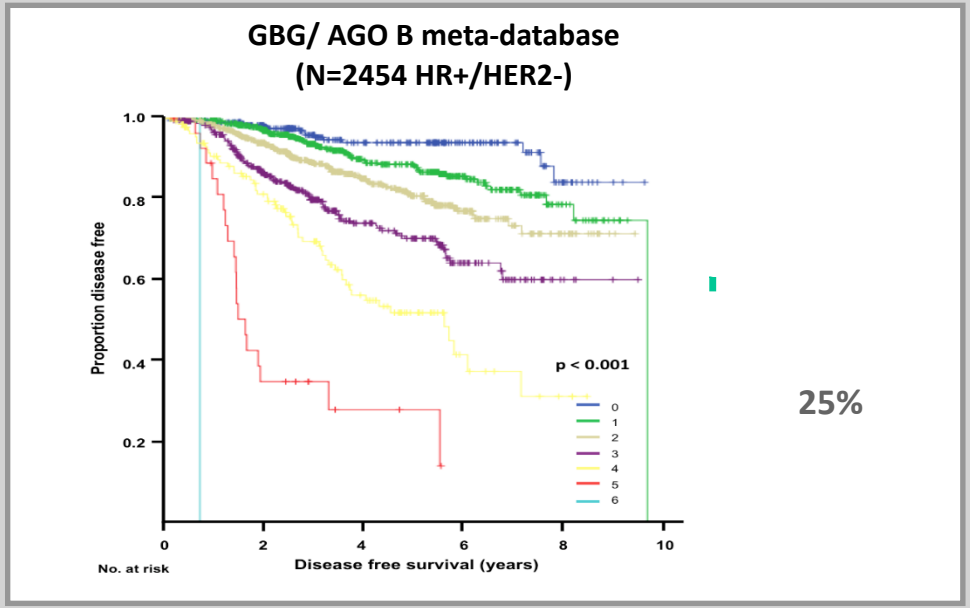
Point assignment for CPS+EG score

Clinical Stage		
I	0	T1N0; T0N1mi, T1N1mi
IIA	0	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2N2
IIIB	2	T4N0-2
IIIC	2	Any T N3
Pathologic Stage		
0	0	T0/isN0
I	0	T1N0; T0N1mi, T1N1mi
IIA	1	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2 N2
IIIB	1	T4 N0-N2
IIIC	2	Any T N3
Tumor Biologic Factors		
ER negative	1	
Nuclear grade 3	1	



Mittendorf EA, J Clin Oncol 2011;
Marmé F, et al. Eur J Cancer 2016

Adjuvant / Post-Neoadjuvant Treatment with CDK4/6i

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	monarchE	PALLAS	PENELOPE[B]
N	5,637	5,600	1,250
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib
% of pts. with NACT	37%	n.r.	100%
Duration of CDK4/6i treatment	24 mths	24 mths	12 mths
Follow-up	27.1 mths	24 mths	43 mths
Discontinuation rate	28%	42%	20%
Discontinuation rate due to AE_{CDKi}	17%	27%	5%
IDFS-HR (95%-CI)	0.70 (0.59-0.82) p < 0.0001	0.96 (0.81-1.14) p = 0.65	0.93 (0.74-1.16) p = 0.525
2-yrs IDFS	92.7% vs. 90.0%	n.r.	88% vs. 78%
3-yrs IDFS	88.8% vs. 83.4%	88% vs. 89%	81% vs. 78%
4-yrs IDFS	n.r.	84.2% vs. 84.5%	73% vs. 72%

IDFS: invasive disease-free survival

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Postneoadjuvant Therapy TNBC

	Oxford LoE	Oxford GR	Oxford AGO
pCR			
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w for 9 courses)	1b	B	+
Non-pCR			
▪ Capecitabine (q3w up to 8 courses)*	1a	A	+
▪ Olaparib (*gBRCAm*^{MUT})[1]	1b	B	+
▪ Continuation of pembrolizumab, if started with neoadj. therapy (q3w up to 9 courses)	1b	B	++

[1] According inclusion criteria of OlympiA trial
* without platin based previous therapy

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Postneoadjuvant Therapy: HER2-positive

	Oxford LoE	Oxford GR	Oxford AGO
pCR			
▪ Low risk: Trastuzumab (to complete 12 mths)	2a	C	++
▪ High risk (cN+): Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+
▪ Neratinib after 1 year Trastuzumab (HR-positive)*	2b	B	-
non-pCR			
▪ T-DM1	1b	B	+
▪ Trastuzumab + Pertuzumab (to complete 12 mths)	2b	C	+/-
▪ Additional HER2-directed therapy after 1 yr (extended adjuvant th.)			
▪ Neratinib after Trastuzumab (HR-positive)*	2b	B	+
▪ Neratinib after other HER2-directed therapies (HR-positive*)	5	D	+/-

* In combination with standard endocrine treatment

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Adjuvant Radiotherapy

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Adjuvant Radiotherapy (RT)

- **Versions 2002 – 2021:**

  Blohmer / Budach / Friedrich / Friedrichs / Göhring / Huober / Janni / Krug / Kühn / Möbus / Rody / Scharl / Seegenschmiedt / Souchon / Thomssen / Untch / Wenz

- **Version 2022:**

  Budach / Krug / Kühn / Schmidt

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Preliminary Note

- **The recommendations on adjuvant radiotherapy for breast cancer are based on a consensus discussion between AGO and DEGRO experts.**
- **For technical radiotherapy details, we refer to the corresponding updated DEGRO practical guidelines.**

Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer): Whole Breast Irradiation

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	Oxford		
	LoE	GR	AGO
▪ Radiotherapy of the affected breast	1a	A	++
▪ Moderately hypofractionated radiotherapy (total dose approx. 40 Gy in 15-16 fractions within 3-5 weeks	1a	A	++
▪ Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in 5-6 weeks)	1a	B	+
▪ Ultra-hypofractionated RT (total dose 26 or 28,5 Gy in 5 fractions in 1 or 5 weeks)	1b	B	+/-
▪ In case of life expectancy < 10 years and pT1, pN0, R0, ER / PR-positive, HER2-negative, endocrine therapy (all criteria), radiotherapy can be omitted after individual counseling, resulting in an increased risk for in-breast recurrence.	1a	B	+

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FAST / FAST-Forward

	FAST	FAST Forward
Timeframe	2004-2007	2011-2014
Sample size	915	4096
Dosse / Fractionation	50 Gy / 2 Gy / 5 weeks 30 Gy / 6 Gy / 5 weeks 28,5 Gy / 5,7 Gy / 5 weeks	40 Gy / 2,67 Gy / 3 weeks 27 Gy / 5,4 Gy / 1 weeks 26 Gy / 5,2 Gy / 1 weeks
Median follow-up	119.8 months	71.5 months
Primary endpoint	change in photographic breast appearance	Ipsilateral breast tumor recurrence (non-inferiority margin 1,6%)
Inclusion criteria	pT1-2 (< 3 cm) pN0 Age ≥ 50 years Breast conserving surgery No chemotherapy	pT1-3 pN0-1 Age ≥ 18 years Breast-conserving surgery or mastectomy Approx. 25% adj. chemotherapy
Boost	No	Approx. 25%, 5-8x 2 Gy

Brunt AM et al. J Clin Oncol. 2020 Oct 1;38(28):3261-3272. Brunt AM et al. Lancet. 2020 May 23;395(10237):1613-1626.

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FAST / FAST-Forward

	FAST (10 year-data)			FAST Forward (5 year-data)		
	Dose	Frequency	Hazard ratio (95%-CI)	Dose	Frequency	Hazard ratio (95%-CI)
Ipsilateral in-breast recurrence	50 Gy	0.7%	-	40 Gy	2.1%	-
	30 Gy	1.4%	HR 1.36 (0.3-6.06)	27 Gy	1.7%	HR 0.86 (0.51-1.44)
	28.5 Gy	1.7%	HR 1.35 (0.3-6.05)	26 Gy	1.4%	HR 0.67 (0.38-1.16)
Moderate / marked normal tissue effects breast / chestwall	50 Gy	33.6%	-	40 Gy	26.8%	-
	30 Gy	50.4%	**HR 1.79 (1.37-2.34)**	27 Gy	35.1%	**HR 1.41 (1.23-1.61)**
	28.5 Gy	47.6%	**HR 1.45 (1.10-1.91)**	26 Gy	28.5%	HR 1.09 (0.95-1.27)

Brunt AM et al. J Clin Oncol. 2020 Oct 1;38(28):3261-3272. Brunt AM et al. Lancet. 2020 May 23;395(10237):1613-1626.

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BCS >= 70 y < 4 cm cN0 : Tamoxifen vs. Tamoxifen + RT

Time:1994-1999, since 8/1996 only pT1cN0 ER / PR+ or unknown allowed

@10 yrs (95% C.I.)	Tamoxifen	Tamoxifen plus Radiotherapy	Hazard Ratio
Local recurrence-free (Δ = 8%)	90% (85%-93%)	98% (96%-99%)	HR = 0.18 (95% CI, 0.07 to 0.42; P < .001)
Mastectomy-free	96% (93% - 98%)	98% (96% - 99%)	HR = 0.50 (95% CI, 0.17 to 1.48; n.s.)
Distant metastasis-free	95% (91% - 97%)	95% (92% - 97%)	HR = 1.20 (95% CI, 0.63 to 2.32; n.s)
Overall survival	66% (61% - 71%)	67% (62% - 72%)	HR = 0.95 (95% CI, 0.77 to 1.18; n.s.)

Hughes KE et al J Clin Oncol 2013; 31:2382-2387

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Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) – Boost Irradiation

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	Oxford		
	LoE	GR	AGO
Boost-RT (improves local control, no survival benefit)			
Premenopausal	1b	B	++
Postmenopausal, if > T1*, G3, HER2-positive, triple negative, EIC (at least 1 factor)	2b	B	+
Techniques			
Percutaneous boost (photons, electrons) as sequential boost	1a	A	++
Multicatheter brachytherapy-boost	1a	A	++
Percutaneous boost as simultaneous integrated boost (with conventionally fractionated whole-breast irradiation)	1b	B	+
Percutaneous boost as simultaneous integrated boost (with hypofractionated whole-breast irradiation)	2b	B	+/-
Intraoperative boost irradiation (followed by whole-breast irradiation)	2b	B	+

* continuous parameter with regard to risk of relapse

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EORTC 22881-10882: Boost vs no Boost (Endpoint: Ipsilateral Breast Recurrence)

@20 yrs (95% C.I.)	Boost (n = 2.661)	No boost (n = 2.657)	Hazard Ratio (95% C.I.)
Overall Survival (Δ = -1.4%)	59.7% (56.3–63.0)	61.1% (57.6–64.3)	HR 1.05 (0.92–1.19) n.s.
Cumulative Risk of Ipsilateral Breast Tumour Recurrence			
All patients	12.0% (9.8–14.4)	16.4% (14.1–18.8)	HR=0.65 (0.52–0.81); p < 0.0001
≤ 40 years (Δ = 11.6%)	24.4% (14.9–33.8)	36.0% (25.8–46.2)	HR=0.56 (0.34–0.92); p = 0.003
41–50 years (Δ = 5.9%)	13.5% (9.5–17.5)	19.4% (14.7–24.1%)	HR=0.66 (0.45–0.98); p = 0.007
51–60 years (Δ = 2.96%)	10.3% (6.3–14.3)	13.2% (9.8–16.7)	HR=0.69 (0.46–1.04); p = 0.020
> 60 years (Δ = 3.0%)	9.7% (5.0–14.4)	12.7% (7.4–18.0)	HR=0.66 (0.42–1.04); p = 0.019

(Median F/U 17.2 y)

acc. to: Bartelink et al. Lancet Oncol 2015; 16: 47–56

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EORTC 22881-10882: Boost vs. no Boost (Endpoint: Any First Recurrence)

@15 yrs/20 yrs (95% C.I.)	Boost (n = 2.661)		No boost (n = 2.657)	Hazard Ratio (95% C.I.)
Overall Survival (Δ = - 1.4%)	59.7% (56.3–63.0)		61.1% (57.6–64.3)	HR 1.05 (0.92–1.19) n.s.
Cumulative Risk of Any First Recurrence				
All patients (Δ ≥ 4%)	@15y @20y	28.1% 32,8%	32.1% 38.7%	HR = 0.92 (0.81-1.04), n.s.
≤ 40 years (Δ > 6%)	@15y @20y	41.5% 49.5%	48.1% 56.8%	HR = 0.80 (0.56-1.15) , n.s.
41–50 years	@15y @20y	34.0% 38.6%	35.6% 44.2%	HR = 0.91 (0.71-1.16), n.s.
51–60 years	@15y @20y	28.5% 34.7%	28.7% 36.2%	HR = 0.96 (0.76-1.21), n.s.
> 60 years	@15y @20y	27.4% 32.1%	29.1% 32.8%	HR = 0.94 (0.74-1.19), n.s.

(Median F/U 17.2 y)

acc. Bartelink et al. Lancet Oncol 2015; 16: 47–56. Suppl.

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Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) – Partial Breast Irradiation (PBI)

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	Oxford		
	LoE	GR	AGO
Intraoperative Radiotherapy (low-risk)*			
As sole radiotherapy, during first breast surgery (IORT 50 kV, IOERT)			
> 50 years	1b	A	+/-
> 70 years	1b	A	+
Postoperative partial breast irradiation (low-risk)*			
Interstitial Multicatheter-Brachytherapy	1b	A	+
Intracavitary balloon-technique	2b	B	-
Intensity-modulated radiotherapy (IMRT) (5 x 6 Gy in 2 weeks)	1b	A	+
3D-conformal radiotherapy (15 x 2.67 Gy in 3 weeks)	1b	A	+
3D-conformal radiotherapy (10 x 3.8 Gy in 2 weeks)	2b	B	+/-
3D-conformal radiotherapy (10 x 3.85 Gy in 1 week)	1b	A	+/-

For definition of target volume and practical conduct see DEGRO practical guidelines

* only for pT1 pN0 R0 G1-2, HR+, non-lobular, > 50 years, no extensive DCIS

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Data on Partial Breast Irradiation

NSABP B-39 / RTOG 0413 (Vicini FA et al. Lancet. 2019 Dec 14;394(10215):2155-2164.)

- Randomised phase III equivalence trial, 4216 pat., 2005-2013, DCIS or invasive carcinoma ≤ 3 cm, 0-3 involved lymph nodes, age > 18 y
- 50 Gy / 25 fr. +/- boost vs. APBI with
  - 38.5 Gy / 10 fr. in one week (external beam irradiation)
  - 34 Gy / 10 fr. in one week (Multicatheter- or Single lumen-Brachytherapy)
- "**We observed an HR of 1.22 with a 90% CI of 0.94–1.58, which did not meet the equivalence criteria** and favoured whole-breast irradiation. The 10-year cumulative incidence of IBTR was 3.9% (95% CI 3.1–5.0) in the whole-breast irradiation group and 4.6% (3.7–5.7) in the APBI group for an absolute difference of 0.7%."
- "**Significantly more evaluable patients in the APBI group had recurrence-free interval events than patients in the whole-breast irradiation group** (figure 3). The 10-year point estimate of recurrence-free interval for the whole breast irradiation group was 93·4% (95% CI 92·1–94·6), and in the APBI group it was 91·8% (90·4–93·0; figure 3)".
- "**Our findings support whole-breast irradiation** but the absolute outcome difference compared with APBI is small, so **partial breast irradiation might also be an acceptable treatment for some patients**. "

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Data on Partial Breast Irradiation

RAPID (Whelan TJ et al. Lancet. 2019 Dec 14;394(10215):2165-2172.)

- Randomised phase III non-inferiority trial, 2135 pat., 2006-2011, DCIS or invasive carcinoma ≤ 3 cm, pN0, age ≥ 40 y., no ILC
- 42.56 / 16 fr. or 50 Gy / 25 fr. +/- Boost vs. APBI 38.5 Gy / 10 fr. in one week (external beam irradiation)
- "In patients treated with **APBI, the 5 year cumulative rate of IBTR was 2·3%** (95% CI 1·4–3·2) and the **8 year cumulative rate was 3·0%** (1·9–4·0). In patients treated with **whole breast irradiation, the 5 year cumulative rate of IBTR was 1·7%** (0·9–2·5) and the **8 year cumulative rate was 2·8%** (1·8–3·9; figure 2). The HR for APBI versus whole breast irradiation was 1·27 (90% CI 0·84–1·91). Thus, **the upper bound of the estimated 90% CI did not exceed the non-inferiority margin** of 2·02."
- "**Late radiation toxicity (grade ≥2 […]) was more common in patients treated with APBI** (346 [32%] of 1070 patients) than whole breast irradiation (142 [13%] of 1065 patients; p < 0·0001). **Adverse cosmesis […] was more common in patients treated with APBI** than in those treated by whole breast irradiation at 3 years (absolute difference, 11·3%, 95% CI 7·5–15·0), 5 years (16·5%, 12·5–20·4), and 7 years (17·7%, 12·9–22·3)."

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Postmastectomy Radiotherapy (PMRT)* to the Chest Wall

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	Oxford		
	LoE	GR	AGO
▪ > 3 tumor infiltrated lymph nodes (LN)	1a	A	++
▪ 1–3 tumor infiltrated LN (high-risk)	1a	A	+
▪ 1–3 tumor infiltrated LN (low-risk*)	5	D	+/-
▪ T3 / T4	1a	A	++
▪ pT3 pN0 R0 (and no additional risk factors)	2b	B	+/-
▪ If R0 is impossible to reach (for invasive tumor)	1a	A	++
▪ In young pts with high-risk features	2b	B	++
The indications for PMRT and regional RT are independent of adjuvant systemic treatment	1a	A	
Inflammatory breast cancer: PMRT and regional nodal irradiation	2c	B	++

* For definition of low-risk, see next slide Radiotherapy of the Chest Wall After Mastectomy (PMRT)

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Radiotherapy of the Chest Wall After Mastectomy (PMRT) in Case of 1-3 Axillary Lymph Node Metastases

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PMRT can be omitted **LoE 3b B AGO +**	PMRT to be discussed **LoE 3b B AGO +/-**	PMRT recommended **LoE 3b B AGO +**
ER pos, G1, HER2 neg, pT1 (at least 3 criteria present)	Patients, who don't fulfill the mentioned criteria for high or low risk	≥ 45 y. AND > 25% pos. ax. Lnn in case of axillary dissection OR <45 y. AND (ER neg. OR>25% pos. ax. Lnn in case of axillary dissection OR medial tumor location)
Kyndi et al. 2009		Truong et al. 2005
		< 40 y. OR HER2 pos. OR lymphovascular invasion
		Shen H et al. 2015
		G3 OR lymphovascular invasion OR triple negative
		Different publications

Comment: In case of an indication for radiotherapy of regional lymph nodes, radiotherapy of the chest wall should also be administered

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Boost in PMRT

	Oxford		
	LoE	GR	AGO
▪ An additional boost irradiation to a part of the chest wall has not been shown to improve DSS and overall survival	2a	B	
▪ An additional boost irradiation to a part of the chest wall should be given in case of of R1 / R2-resection, if secondary resection is not feasible	5	D	++
▪ In case of tumor extention to the pectoral resection margin, but no clinical signs of extention beyond the fascia, the resection margin should be regarded as R0 (provided, that the pectoral fascia was resected). A boost radiotherapy is not required in this situation	5	D	++

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Radiotherapy of Axillary Lymph Nodes in Patients with Positive Sentinel-Lymph Nodes**, Who Did not Undergo Axillary Dissection

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	Oxford		
	LoE	GR	AGO
BCS and ACOSOG Z0011-criteria^{+} met	2b	B	+*
▪ Radiotherapy of the breast including LN level 1 + 2 to 5 mm below the axillary vein (PTV)			
BCS and ACOSOG Z0011-criteria^{+} <u>not</u> met	1b	B	++*
▪ Radiotherapy of the axillary lymph nodes (analog AMAROS)			
ME and chest wall RT indicated and ACOSOG Z011-criteria^{+} <u>not</u> met or ME and chest wall RT <u>not planned</u>			
▪ Radiotherapy of the axillary lymph nodes (analog AMAROS)	1b	B	++
<u>≥ 3 pos. SLN</u>			
▪ Radiotherapy of the axillary lymph nodes (analog AMAROS)	1b	B	+

* Study participation recommended
** Macrometastases
$^{+}$ < T3, no palpable LN, R0, 1-2 positive SN, no extracapsular extention, no NACT

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Additional RT of the Axilla after Primary Surgery

(in case of an indication for RT of the breast/chest wall[1] +/- supra-/infraclavicular and internal mammary node RT[2]) Expansion of the PTV (planning target volume) to level I-II[3]	Oxford		
	LoE	GR	AGO
pN-status			
pN0(sn) / pN1mic(sn)	1b	B	--
pN0/+ after ALND	1a	A	--
pN+(sn) in analogy to ACOSOG Z0011 (no ALND)	2b	B	+
pN+(sn) not fitting ACOSOG Z0011-criteria → RT in analogy to AMAROS[4] (no ALND)	1b	B	++
R2-situation in the axilla	5	D	++

[1]Incidental dose to parts of level i/II is inevitable. [2]The indication for supra-/infraclavicular and internal mammary node RT has to be assessed separately. [3]Cranial border 5 mm below the axillary vein. [4] ≤ T3, cN0, no NACT, always in conjunction with supra-/infraclavicular RT

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Additional RT of the Axilla after Neoadjuvant Therapy

(in case of an indication for RT of the breast/chest wall[1] +/- supra- / infraclavicular and internal mammary node RT[2])

Expansion of the PTV (planning target volume) to level I-II[3]

N-status pre/post NACT	pN-status	Oxford LoE	Oxford GR	AGO
cN0 / ycN0	ypN0(sn)	5	D	-
cN0 / ycN0	ypN1mic(sn) / ypN+(sn) (no ALND)	5	D	+[4]
$pN+_{CNB}$ / ycN0	ypN0(sn/TAD)	5	D	+/-[4]
$pN+_{CNB}$/ ycN0	ypN1mic(sn/TAD) / ypN+(sn/TAD) (no ALND)	5	D	+[4]
cN0/cN+	ypN0/+ after ALND	2b	B	-
	R2-situation in the axilla	5	D	++

[1]Incidental dose to parts of level i/II is inevitable. [2]The indication for supra-/infraclavicular and internal mammary node RT has to be assessed separately. [3]Cranial border 5 mm below the axillary vein. [4]Study participation recommended.

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Dose in the Axillary LN-levels I + II Using Different RT-Techniques

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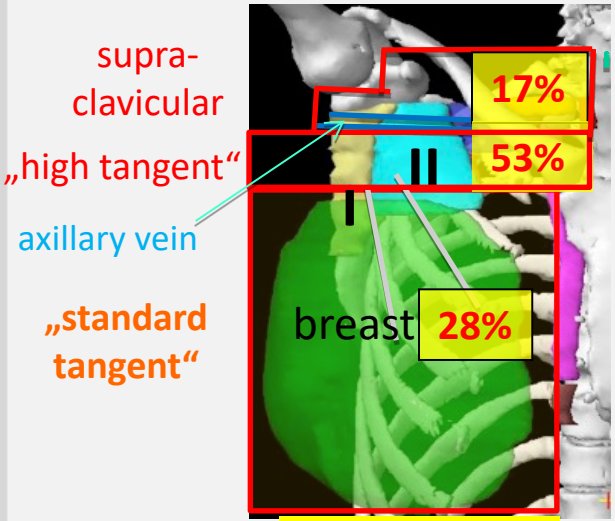
ACOSOG Z0011 Trial
45% micrometast. in the exp. arm

RT-volume
% of patients



AMAROS

LN level 1	mean dose*	encompassed volume**
AMAROS	> 95%	> 95%
high tangent	86%	79%
standard tangent	66%	51%
IMRT+	29%	1%
LN-level 2		
AMAROS	> 95%	> 95%
high tangent	71%	51%
standard tangent	44%	26%
IMRT+	7%	0%

* in relation to the prescribed dose in the breast
** % volume receiving the prescribed dose
\+ Lee et al. Medicine 2016 (3)

Data from 228/856 pat.

Jagsi (2): “The results of Z0011 should not be extrapolated to patients who receive RT using partial-breast or prone techniques, in which substantially less of the axilla is included”

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Radiotherapy (RT) of Other Locoregional Lymph Node Areas (SCG / ICG)

	Oxford		
	LoE	GR	AGO
RT to supra- / infraclavicular lymphatic regions			
▪ ≥ 4 positive axillary lymph nodes (LN) or involved LN in level III or in supra- / infraclavicular LN	1b	A	++
▪ 1–3 positive axillary lymph nodes[1] in case of - central or medial tumor and G2-3 or ER / PR-negative - premenopausal patient and G2-3 or ER / PR-negative	2a	B	+
▪ pN0 with central or medial tumors, if premenopausal and G2-3 and ER / PR-negative	2a	B	+/-

[1] not applicable for micrometastases

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Radiotherapy (RT) of Other Locoregional Lymph Node Areas (IMN)

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	Oxford		
	LoE	GR	AGO
Internal mammary lymph node region (IMN)			
▪ pN0 high-risk with central or medial tumor and premenopausal and G2-3 and ER/PR-negative	1b	B	+/-
▪ 1–3 positive axillary lymph nodes[1] in case of - central or medial tumor and G2-3 or ER / PR-negative - premenopausal patient and G2-3 or ER / PR-negative	2a	B	+
▪ ≥ 4 positive axillary lymph nodes	2a	B	+
▪ involved internal mammary lymph nodes	2a	B	+
▪ In case of cardiac risk factors or if trastuzumab is given	2b	A	--

1 not applicable for micrometastases

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Fractionation of Radiotherapy in Case of Regional Nodal Irradiation

	Oxford		
	LoE	GR	AGO
▪ Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions within 5–6 weeks)	1a	A	++
▪ Moderately hypofractionated radiotherapy (total dose approx. 40–43.5 Gy in 15-16 fractions within 3–5 weeks)	2b	B	+/-

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Hypofractionated Post-Mastectomy Radiotherapy and Regional Nodal Irradiation

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Wang et al. Lancet Oncol. 2019 Mar;20(3):352-360.

- Randomised phase III non-inferiority trial, 820 pat., 2008-2016, T3/4 and / or ≥ 4 involved lymph nodes, 50 Gy / 25 fr. vs. 43.5 Gy / 15 fr.
- 98% 2D-planned radiotherapy, no treatment of the internal mammary lymph nodes
- "The 5-year cumulative incidence of locoregional recurrence was 8.3% (90% CI 5.8–10.7) in the hypo- fractionated radiotherapy group compared with 8·1% (90% CI 5.4–10.6) in the conventional fractionated radiotherapy group (absolute difference 0.2%, 90% CI –3.0 to 2.6; HR 1.10, 90% CI 0.72 to 1.69; figure 2).
- "In conclusion, this study provides high-level evidence for the clinical use of hypofractionated postmastectomy radiotherapy for patients with high-risk breast cancer. It can be recommended in clinical practice to patients who do not plan breast reconstruction and will not receive internal mammary node irradiation."

Multivariate Analysis of Overall Survival: Effect of Radiotherapy of the Internal Mammaria Lymph Nodes

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(median follow-up 10.9 yrs)

Adjuvant treatment	n*	Hazard ratio (95% CI)
No adjuvant reported	625	0.91 (0.59 - 1.39)
Chemotherapy	954	1.05 (0.84 - 1.32)
Endocrine therapy	1185	0.82 (0.63 - 1.06)
Both (endocrine th. and chemotherapy)	1200	0.72 (0.55 – 0.94)
Total	**4004**	**0.88** **(0.76 – 1.01)**

* missing data on 40 patients

Poortmans et al. ECCO Amsterdam 2013

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Radiotherapy following NACT

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Pretreatment	Posttreatment	RT-BCS	PMRT	RT-RN
Locally advanced	pCR / no pCR	yes	yes	yes
cT1/2 cN1+*	ypT1+ or ypN1 + (no pCR)	yes	yes	yes
cT1/2 cN1+*	ypT0/is ypN0	yes	Increased risk of relapse[1]	
cT1/2 cN0 (Sonogr. obligat)	ypN+ or ypT3/4	yes	yes	yes
cT1/2 cN0 (Sonogr. obligat)	ypT0/is ypN0	Yes	no	no

Oxford		
LoE	GR	AGO
1a/1a/1a	A/A/A	++/++/++
1a/2b/2b	A/B/B	++/+/+
2b/2b/2b	B/B/B	+/+/+
2b/2b/2b	B/B/B	+/+/+
2b/2b/2b	A/B/B	+/-/-

Locally advanced: T3-4 or cN2-N3

[1] **Criteria for increased risk of relapse:**
- **pN0 premenopausal high risk: central or medium tumor localization, and (G2-3 and ER/PR-neg.)**
- **pretreatment pN1a/ cN+* high risk: central or medium tumor localization and (G2-3 or ER/PR-neg.) or premenopausal, lateral tumor localization and (G2-3 or ER/PR-neg.)**

* **Regarding coverage of axilla level I/II please also see slides „Additional RT of the axilla after primary surgery“ and „Additional RT of the axilla after neoadjuvant therapy“. ** = confirmed by core biopsy**

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Molecular Predictors and Use of Radiotherapy

- **Results of gene expression profiling should not be used for indication of radiotherapy**

Oxford		
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2b	B	++

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Use of Concomitant Systemic Therapy with Adjuvant Locoregional Radiotherapy

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	Oxford		
	LoE	GR	AGO
▪ Trastuzumab / Pertuzumab*	1a	A	++
▪ T-DM1	1b	A	+
▪ Tamoxifen	2b	B	+
▪ Aromatase inhibitors	2b	B	+
▪ Checkpoint inhibitors	2b	C	+
▪ Capecitabine**	2b	B	+
▪ CDK4/6-inhibitors***	4	C	+/-
▪ Olaparib****	2b	C	+/-

* Concurrent Trastuzumab / Pertuzumab and parasternal radiotherapy should be avoided

** With hypofractionated RT approx. 40 Gy, consider dose reduction of Capecitabine, Pat. with high risk for locoregional recurrence

*** In currently available phase III-trials (monarchE, PALLAS, Penelope-B) RT was given before initiation of CDK4/6-inhibitors. No definitive signs of significantly increased toxicity with concomitant RT in the palliative setting.

**** In currently available phase III-trials, RT was given before initiation of Olaparib.

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Simultaneous Capecitabine with Locoregional Radiotherapy

Woodward et al. Int J Radiat Oncol Biol Phys. 2017 Nov 15;99(4):777-783

- Prospective phase trial, 32 pat. with LABC, sim. def. / neoadj. chemoradiotherapy, median total dose 66 Gy
- "The first 9 patients analyzed […] received CAP 825 mg/m^2 twice daily continuously beginning on the first day of RT. **Because of observed excess grade 3 toxicity the protocol was amended,** and subsequent patients received CAP only on RT days (5 days per week)."
- "Noncontinuous CAP dosing was much better tolerated than continuous dosing. **Thirteen of 26 patients (50%) had grade ≥ 3 and higher treatment-related dermatologic toxicity**. "

Alhanafy et al. Menoufia Medical Journal 2015, 28:325-332

- Randomised phase II-trial, 100 pat., adj. Radiotherapy 40 Gy / 15 fr. +/- CAP 825 mg/m2 Mo-Fr, LABC
- " […] **concurrent capecitabine was feasible with a high percent of patients (96%),** […] only two out of 50 (4%) patients had capecitabine dose modification …".
- "**All early toxicities were GI/GII.** Radiation dermatitis had a peak incidence in the last few fractions of the radiation therapy and the week after radiotherapy; no treatment interruption was needed and the incidence was close in both groups".
- Radiation dermatitis grade I 14% vs. 18%; grade 2 4% vs. 4%

Smoking and Risk of Secondary Lung Cancer

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	Oxford		
	LoE	GR	AGO
▪ Increased risk of lung cancer secondary to breast cancer radiotherapy in smokers	1a	A	
▪ Inform patients about risk			++
▪ Recommend smoking cessation			++

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Supportive Care and Management of Side Effects

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Supportive Care and Management of Side Effects

- **Versions 2002–2021:**

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Guidelines - Evidence

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Guidelines – Evidence

Specific national and international guidelines deal with various aspects of evidence-based supportive therapy of cancer patients.

Without claiming completeness, such guidelines will be quoted, with an emphasis on German guidelines.

Aspects concerning breast cancer patients will especially be highlighted.

The „Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin der DKG“ should especially be highlighted (http://www.onkosupport.de).

<u>Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL):</u>

- **S3-Leitlinie: Supportive Therapie bei onkologischen Patientinnen Langversion 1.3 – Februar 2020 AWMF-Registernummer: 032/054OL**

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Toxicity Assessment

- **Acute toxicity (NCI-CTCAE)**
- **Long term toxicity (ICPC, ICD-GM)**

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Toxicity Assessment

Acute Toxicity (according to WHO[1] or NCI-CTC[2])

Acute toxicities should be asked for and documented after every treatment course **LoE 5 D AGO ++**

Grade		Information required
0	none	organs involved
1	mild	type of toxicity
2	moderate	time interval after treatment
3	severe	effect on general health status
4	life threatening	treatment required
5	death	recovery achieved

Long term toxicity (= secondary diseases after tumour therapy)

Long term surveillance and documentation in regular intervals **LoE 5 D AGO ++**
(acc. ICPC[3] following symptoms or acc. ICD-10-GM[4] following diagnoses)

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Acute Toxicity (NCI CTCAE v 5.0, 2017)

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- **Grade 1**
  Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2**
  Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- **Grade 3**
  Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.**
- **Grade 4**
  Life-threatening consequences; urgent intervention indicated.
- **Grade 5**
  Death related to AE.

Activities of Daily Living (ADL)

*** Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.**

**** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.**

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Incidence of Side Effects

- **According to product information by MedDRA* classification**

* **MedDRA - Medical Dictionary for Regulatory Activities**

Chemotherapy – Acute Toxicities I

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DRUGS	SYSTEM ORGAN CLASS: INFECTIONS AND INFESTATIONS	NEOPLASMS BEN., ALIGNANT AND NSPECIFIED (INCL CYSTS & POLYPS)	BLOOD & YMPH. SYST. ISORDERS	IMMUNE YSTEM DISORDERS (ALLERGIES)	ENDOCRINE DISORDERS	METABOLISM AND NUTRITION DISORDERS	PSYCHIATRIC DISORDERS	NERVOUS SYSTEM DISORDERS	EYE DISORDERS.	EAR AND LABYRINTH DISORDERS	CARDIAC DISORDERS	VASCULAR DISOR. INCL HOT FLUSHES
Alkylating antineoplastic agent												
Cyclophosphamide	4	2	5	5	1	-	1	3	2	3	3	3
Anti-Metabolites												
Methotrexate	1	-	4	3	3	-	3	4	2	-	1	2
5-Fluorouracil*	5	-	5	2	2	5	-	3	3	-	5	3
Capecitabine	4	3 (Lipoma)	4	3	-	5	4	4	4	3	3	4
Gemcitabine	4	-	5	1	-	4	-:	4	-	-	2	2
Platinum-complexes												
Cisplatinum	4	2	5	3	2	5	-	4	2	5	4	4
Carboplatin	4	-	5	4	-	-	-	4	4	4	4	-
Anthracyclines / Anthrachinones												
Epi-/Doxorubicin	5	3	5	1-2	-	1-5	-	-	4	-	4	5
Liposom. Doxorubicin	5	-	5	-	-	5	3	4	(4)	-	4	4
PEG-lipos. Doxorubicin	4	-	4	-	-	5	-	4	4	-	4	-
Mitoxanthrone	5	3	5	3	-	4	-	4	3	3	4	3
Taxanes												
Paclitaxel	5	1	5	5	-	1	1	5	1	1	4	5
nab-Paclitaxel	4	-	5	3	-	5	4	5	4	4	4	4
Docetaxel	5	-	5	5	-	5	-	5	-	-	4	4
Further tubulin-targeting drugs												
Vinorelbine IV (PO)	5(5)	-	-(5)	2(-)	-	-	-(5)	-(5)	-(4)	-	2(3)	3(4)
Eribulin	4	-	4	-	-:	5	4	5	4	4	4	4

Listing and grading of side effects was performed according the MedDRA-classification with the following categories of frequency: 1. Very rarely (<1/10,000); 2. rarely (≥ 1/1,000 to < 1/10,000); 3. occasionally (≥ 1/1,000 to < 1/100); 4. frequently (≥ 1/100 to < 1/10); 5. very frequently (≥ 1/10). - unknown (based on available data incidence not assessable)

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Chemotherapy – Acute Toxicities II

	SYSTEM ORGAN CLASS										
DRUG	RESPIRAT., HORAC. & MEDIA-STINAL DIS.	GASTROINT.DISORD. (NAUSEA, EMESIS)	HEPATOBILIARY DISORDERS	SKIN & SUBCUT. TIS. DISORD. (ALOPECIA)	MUSCULOSKELETAL & CONNECTIVE TISSUE DISORDERS	RENAL& URINARY DISORDERS	PREGN., PUERPER. & PERINATAL CONDIT.	REPRODUCT. SYS. & BREAST DISORDERS	GENERAL DISORD. & ADMINI-STRATION SITE CONDITIONS	CONGEN., FAMILIAL GENET. DISORDERS	SPECIAL FEATURES
Alkylating antineoplastic agent											
Cyclophosphamide	2	4	4	5	-	5	-	4	5	-	Hyponatriaemia
Anti-Metabolitee											
Methotrexate	4	5	5	4	3	3	-	3	1	-	Mucositis, risk of "third space"-toxicity
5-Fluorouracil	5	5	3	5	-	-	-	-	5	-	Risk DPD-deficiency: light 5%, severe 0,1%; diarrhea, heart
Capecitabine	4	5	4	5	4	3	-	3	5	-	Hand-foot-syndrome (HFS), risk of DPD-deficiency; heart
Gemcitabine	5	5	5	5	4	5	-	-	5	-	Flu-like symptoms, edema, heart
Platinum-complexes											
Cisplatinum	4	5	4	4	-	5	-	3	5	-	Nephrotoxicity, ototoxicity, CIPN
Carboplatin	4	5	-	4	4	4	-	-	4	-	Colitis (nephrotoxicity)
Anthracyclines / Anthrachinones											
Epi-/Doxorubicin	2	5	-	5	1	4		1	5	-	Cardiotoxicity (CHF), sec. malign. diseases, extravasation
Lipo. Doxorubicin	4	5	4	5	4	3	-	(4)	5	-	
PEG-lipo. Doxo.	4	5	-	5	4	-	-	4	5	-	Palmar and plantar erythema (PPE)
Mitoxanthrone	4	5	3	5	-	3	-	3	4	-	Sec. AML, cardiomyopathy
Taxanes											
Paclitaxel	2	5	1	5	5	-	-	-	5	-	Peripheral neuropathy (CIPN); hypersensitivity, myalgia
nab-Paclitaxel	4	5	3	5	5	3	-	3	5	-	Peripheral neuropathy (CIPN)
Docetaxel	5	5	-	5	5	-	-	-	5	-	Fluid retention, paronychia, colitis, myalgie
Further tubulin-targeting drugs											
Vinorelbine IV (PO)	3(4)	2 (5)	5(4)	2(5)	-(4)	2(4)	-	-	-	-	Phlebitis, GI-Tox (PO), CIPN
Eribulin	5	5	4	5	5	4	-	-	5	-	Constipation, CIPN

- unknown (based on available data incidence not assessable)

Listing and grading of side effects was performed according the MedDRA-classification with the following categories of frequency: 1. Very rarely (<1/10,000); 2. rarely (≥ 1/1,000 to < 1/10,000); 3. occasionally (≥ 1/1,000 to < 1/100); 4. frequently (≥ 1/100 to < 1/10); 5. very frequently (≥ 1/10).

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Diagnostics* before Start of 5-FU (i.v.) / Capecitabine-Therapy

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Oxford		
LoE	GR	AGO
1a	A	++

- **DPD (Dihydropyrimidin-Dehydrogenase) - Deficiency** Testing (*DPYD*-Genotype or Phenotype)

Phenotype determination (e.g. uracil in plasma / urine, determination of DPD-activity) are less standardized assays

Systematic review (cancer patients under 5-FU therapy):**

- **DPYD-variants (heterozygous or homozygous) 4.1%**
- **Therapy-associated mortality 2.3% (vs. 0.1% w/o DPYD-variants) – risk for therapy-associated death 25.6-fold increase**

* **Recommendation according to Medical Alert (Rote-Hand-Brief) 4.6.2020**

** **Sharma et al, Oncologist 2021**

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Endocrine Therapy – Toxicities

DRUG	INFECTIONS AND INFESTATIONS	NEOPLASMS BEN., MALIGNANT AND UNSPECIFIED (INCL CYSTS & POLYPS)	BLOOD & LYMPH. SYST. DISORDERS	IMMUNE SYSTEM DISORDERS (ALLERGIES)	ENDOCRINE DISORDERS	METABOLISM AND NUTRITION DISORDERS	PSYCHIATRIC DISORDERS	NERVOUS SYSTEM DISORDERS	EYE DISORDERS.	EAR AND LABYRINTH DISORDERS	CARDIAC DISORDERS	VASCULAR DISOR. INCL HOT FLUSHES
SERM												
Tamoxifen	-	3	4	-	3	5	-	4	4	-	-	4
AI												
Anastrozole	-	-	-	-	-	4	5	5	4	-	4	5
Exemestane			4			4	5	4				5
Letrozole	3	-	3	-	-	5	4	4	3	-	3	5
SERD												
Fulvestrant	4	-	3	4	-	4	-	4	-	-	-	4

DRUG	RESPIR.., THORAC. & MEDIASTIN. DIS.	GASTROINT. DIS.. (NAUSEA, EMESIS)	HEPATOBILIARY DISORDERS	SKIN & SUBCUT.TIS. DIS. (ALOPECIA)	MUSCULOSKEL ETAL & CONNECTIVE TISSUE DISORDERS	RENAL& URINARY DISORDERS	PREGN., PUERPER. & PERINAT. COND.	REPRODUCT. SYS. & BREAST DISORDERS	GENERAL DIS. & ADMINISTRATIO N SITE CONDITIONS	CONGEN., FAMIL. &GENET. DISORD.	SPECIAL FEATURES
SERM											
Tamoxifen	3	5	4	5	4	-	-	5	5	1	Hot flushes; rarely: endometrial Ca (>55y); thrombosis
AI											
Anastrozole	-	5	4	5	5	-	-	5	5	-	Hot flushes, arthralgia, osteoporosis; cognition
Exemestane		5		5	5				5	-	Hot flushes, arthralgia, osteoporosis; cognition
Letrozole	3	4	3	5	5	3	-	4	5	-	Hot flushes, arthralgia, osteoporosis; cognition
SERD											
Fulvestrant	-	5	5	4	4	4	-	3	5	-	Hitzewallungen

Listing and grading of side effects was performed according the MedDRA-classification with the following categories of frequency:

1. Very rarely (< 1/10,000); 2. rarely (≥ 1/1,000 to < 1/10,000); 3. occasionally (≥ 1/1,000 to < 1/100); 4. frequently (≥ 1/100 to < 1/10); 5. very frequently (≥ 1/10).
- unknown (based on available data incidence not assessable)

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Key-Toxicities – Antibodies and Antibody-Drug-Conjugates (HER2+)

	Oxford LoE	Oxford GR
Trastuzumab		
▪ Cardiotoxicity in the adjuvant setting (1.0–2.0%)	1b	A
▪ Troponin I may identify patients at risk for cardiotoxicity	2b	B
Pertuzumab		
▪ Skin rash, diarrhea, mucositis	1b	A
Trastuzumab-Emtansine (T-DM1)		
▪ Thrombocytopenia, hepatotoxicity, pyrexia, headache, pneumonitis, neuropathy	1b	A
Trastuzumab-Deruxtecan		
▪ Interstitial lung disease, neuropenia, nausea, alopecia	1b	A

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Toxicities of New Compounds: anti-HER2-TKI – Neratinib, Lapatinib –

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Lapatinib

AE, %	All grades	Grade >/=3
Diarrhea	61%	6%
Nausea	18%	4%
Rash	60%	6%
Fatigue	16%	4%
Cardiac	3%	< 1% SAE
Hepatobiliary	8%	
All AE %	92%	SAE 6%

Neratinib

AE, %	Alle Grade	Grad >/=3
Diarrhea	90	40,1
Nausea	43	2
Abdominal pain	36	2
Fatigue	27	2
Emesis	26	3
Exanthema	18	0,6
Stomatitis	14	0,6
Appetite loss	12	0,2
Dyspepsia	10	0,4
ALAT elevated	9	1,2
ASAT elevated	7	0,7
Nail disorders	8	0,3
Dry skin	6	0

	LoE	GR	AGO
Primary prophylaxis with loperamide	2b	B	++

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Common Toxicities with anti-HER2-TKI: Tucatinib + Trastuzumab + Capecitabine

Event	Capecitabine + Tucatinib + Trastuzumab	
	Any grade (%)	**≥ 3 grade (%)**
Any adverse event	99.3	55.2
Diarrhea	80.9	12.9
PPE syndrome	63.4	13.1
Nausea	58.4	3.7
Fatigue	45.0	4.7
Vomiting	35.9	3.0
Stomatitis	25.5	2.5
Reduced appetite	24.8	0.5
Headache	21.5	0.5

Key-Toxicities – Antibodies and Antibody-Drug-Conjugates (HER2-)

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	Oxford LoE	Oxford GR
Bevacizumab		
▪ Hypertonus, proteinuria, bleeding, left ventricular dysfunction	2b	B
Sacituzumab Govitecan		
▪ (Febrile) neutropenia, leukopenia, anemia, diarrhea, nausea, alopecia	1b	A

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Toxicities of CDK 4/6 Inhibitors (Palbociclib / Ribociclib / Abemaciclib)

UE, %	All Grades	Grade 3	Grade 4
Neutropenia	79,5/74,3/41,3	56,1/49,7/19,6	10,4/9,6/1,5
Leukopenia	39,0/32,9/20,8	24,1/19,8/7,3	0,7/1,2/0,3
Anemia	24,1/18,6/28,4	5,2/0,9/5,8	0,2/0,3/0
Thrombocytopenia	15,5/5,7/10,0	1,4/0,6/2,0	0,2/0/< 1,0
Fatigue	37,4/36,5/40,1	1,8/2,1/1,8	0/0,3/0
Nausea	35,1/51,5/38,5	0,2/2,4/0,9	0/0/0
Vomiting	15,5/29,3/28,4	0,5/3,6/1,2	0/0/0
Diarrhea	26,1/35,0/81,3	1,4/1,2/9,5	0/0/0
Alopecia	32,9/33,2/26,6	-	-
Exantheme	17,8/17,1/14,0	0,9/0,6/< 1,0	0/0/0
ALT elevated	9,9/15,6/15,6	1,7/7,5/5,8	0,1/1,8/0,3
AST elevated	9,7/15,0/15,0	2,5/4,8/3,0	0/0,9/0
Infections	60/50,3/39,1	6,0/3,6/4,0	1/0,6/0,9
QT-prolongation	N.A./7,5/N.A.	N.A./3,0/N.A.	N.A./0/N.A.
Palbociclib/Ribociclib/Abemaciclib			

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Interstitial Lung Disease (ILD) and CDK 4/6 Inhibitors

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Pulmonary toxicity of cyclin-dependent kinase (CDK) 4/6 inhibitors from the publicly available FDA Adverse Event Reporting System (FAERS):

- 2.1% of all reports for abemaciclib; 0.3% of all reports palbociclib / ribociclib
- Increased reporting found for
  - CDK4/6 inhibitors vs. other drugs (ROR = 1.50; 95% CI = 1.28–1.74)
  - Abemaciclib vs other anticancer agents (4.70; 3.62–5.98).

Overall incidence:

Systematic review of published data:

CDK 4/6i: Any grade 1.64% (0.68% control). Pooled RR 2.26, 95% CI: 1.60-3.19, $p < 0.00001$

CDK 4/6i: Grade 3/4 0.28% (0.06% control). Pooled RR 2.35, 95% CI: 0.37-15.08, $p = 0.37$

Monarch-E:

Abemaciclib any grade 2.9% ($\geq$ G3 0.4% - 1 G5 event); control 1.2% ($\geq$ G3 n = 1; 0%)

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Venous Thromboembolic Events: Adjuvant Abemaciclib (Monarch-E trial)

Abemaciclib : All grade 2.3% (grade 3/4 1.2%)
Control arm: All grade 0.5% (grade 3/4 0.1%)

<u>Characterization of VTE (DVT or PE)*</u>

- VTE by first ET = AI
  - Abemaciclib: any grade 1.7% (G3/4 0.9%)
  - Control arm: any grade 0.5% (G3/4 0.2%)
- VTE by first ET = tamoxifen
  - Abemaciclib: any grade 4.1% (G3/4 2.2%)
  - Control arm: any grade 0.7% (G3/4 0.4%)

* *DVT* is a composite term for several forms of venous thrombosis; *PE* is a composite term including embolism and pulmonary embolism

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QT Interval Prolongation: Ribociclib vs. Placebo

- **Post-baseline QT interval prolongation > 480 msec: 6.9% vs. 1.2% (incidence Ribo vs Placebo)**
- **Post-baseline QT interval prolongation > 500 msec: 1.5% vs. 0.3%**
- **Therapy discontinuation for QT interval prolongation: 0.3% vs. 0.6%**
- **QT interval prolongation is not associated with symptoms; however, QT interval prolongation stands for an elevated risk of life-threatening arrhythmia *"torsades de pointes"* (TdP)**

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Toxicities of mTOR-Inhibitor (Everolimus)

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UE, %	All grades (%)	grade >/=3 (%)
Stomatitis	11,6	1,6
Exanthema	7,4	0,02
Anemia	3,3	1,3
Fatigue	6,8	0,8
Nausea	5,6	0
Emesis / Vomiting	2,9	0
Diarrhea	6,2	0,02
Loss of appetite	6,0	0,02
Headache	3,9	0
Weight loss	3,9	0
Dyspnea	3,8	0,08
Arthralgia	3,3	0
Epistaxis	3,1	0
Edema	2,9	0
Constipation	2,6	
Pyrexia	2,9	0
Cough	4,5	0
ALT Elevated	2,6	0
Pneumonitis	0,2	0
Asthenia	2,4	0,04
Dysgeusia	4,3	0

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Toxicities of PI3K Inhibitor Alpelisib in Combination with Endocrine Therapy

Alpelisib + Fulvestrant

UE, %	All Grade	Grad >/=3
Hypergycemia	63,7%	32,7%
Diarrhea	57,7%	6,7%
Nausea	44,7%	2,5%
Decreased appetite	35,6%	< 1% SAE
Rush	35,5%	9,9%
Vomiting	27,1%	< 1% SAE
Weight loss	26,8%	3,9%
Stomatitis	24,6%	2,5%
Fatique	24,3%	3,5
Asthenia	20,4%	1,8
Alopecia	19,7%	0
Mucositis	18,3%	2,1

Regard recommendations for management of side effects (Diabetes mellitus, hyperglycemia, Insulin resistance und metabolic syndrom)

LoE	GR	AGO
2b	B	++

Andre F, et al N Engl J Med 2019;380:1929-1940

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Toxicities of PARP-Inhibitors – Olaparib, Talazoparib

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Olaparib

AE. %	all grades (%)	grade >/=3 (%)
AE, overall	97.1	36.6
Neutropenia	27.3	9.3
Anemia	40.0	16.1
Fatigue	28.8	2.9
Nausea	58.0	0
Emesis	29.8	0
Diarrhea	20.5	0.5
Appetite loss	16.1	0
Headache	20.0	1
Pyrexia	14.1	0
Cough	17.1	0
ALT elevated	11.2	1.5
AST elevated	9.3	2.4
PPE	0.5	
Treatm. discontinuation	4.9	

Talazoparib

AE. %	all grades (%)	grade >/=3 (%)
AE, overall	98,6	31,8
neutropenia	34,6	20.9
Anemia	52.8	39,2
Fatigue	50,3	1,7
Nuasea	48,6	0,3
Emesis	24,8	2,4
Diarrhea	22,0	0,7
Appetite loss	21,3	0,3
Headache	32,5	1,7
Back pain	21,0	2,4
Dyspnea	17,5	2,4
Pleural effusion	2,1	1,7
PPE	1,4	0,3

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Immune Checkpoint Inhibitors

- **Therapeutic approaches (antibodies)**
  - **PD-1 / PD-L1**

    PD-1
    - **Nivolumab**
    - **Pembrolizumab**

    PD-L1
    - **Atezolizumab**
    - **Durvalumab**
    - **Avelumab**

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Immune Checkpoint Inhibitors
Time Course of Adverse Events, e.g. Ipilimumab

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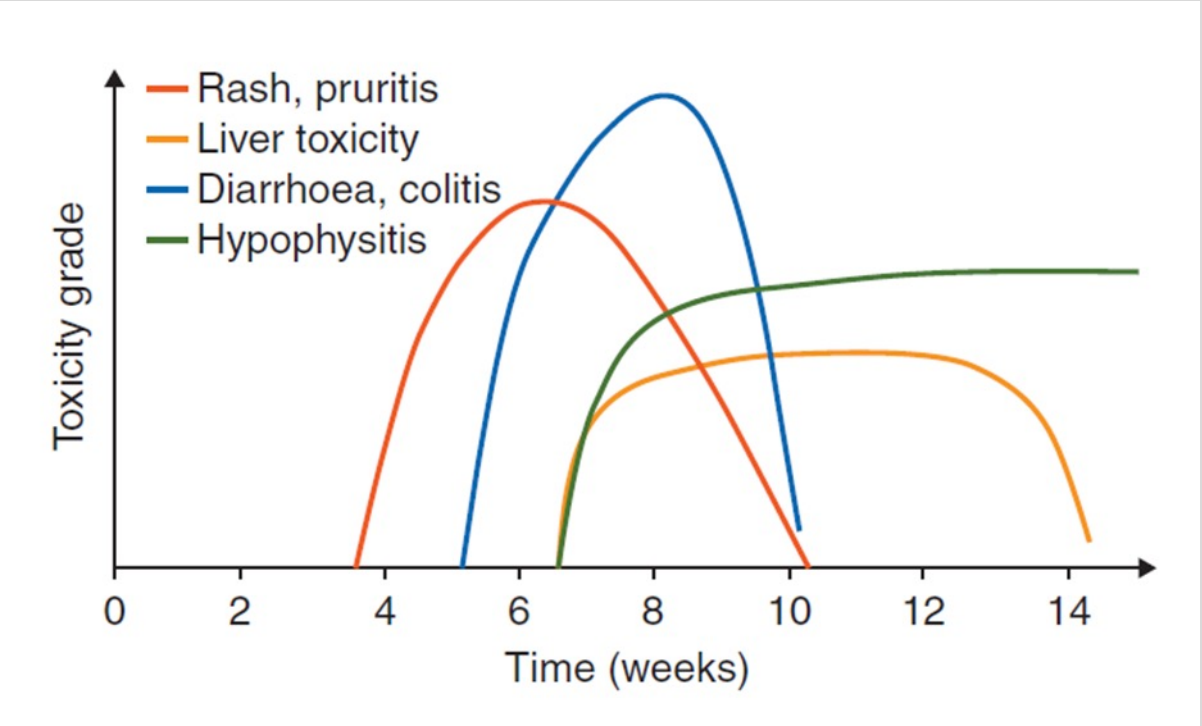

Haanen J et al. Ann Oncol 2017; 28 (suppl 4): 119-142

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Immune Checkpoint Inhibitors
– Side Effects –

- **Adverse events ≥ grade 3**
  - **diarrhea**
  - **fatigue**
  - **skin lesions (maculopapular exanthema, vitiligo, epidermolysis)**
  - **pneumonitis**
  - **colitis**
  - **hypophysitis**
  - **hepatitis**
  - **nephritis**
  - **thyreoiditis (hyper- / hypothyroidism)**
  - **Guillain-Barré syndrome**
  - **cardiomyopathy**
  - **myopathy – myalgia – rhabdomyolysis**
  - **uveitis**

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Immune Checkpoint Inhibitors Toxicities (Total in %)

	atezolizumab	nivolumab	pembrolizumab
diarrhea	18.6%	13%	18%
colitis	1.1%	2%	1%
exanthema	18.6%	15%	< 1%
hepatoxicity	0.3%	1%	0.5%
hypophysitis	< 0.1%	< 1%	0.5%
pneumonitis	3.1%	3%	2.9%
thyroid dysfunction	hyper- 1.7% hypo- 4.7%	hyper -1% hypo- 4%	hyper- 1.2% hypo- 8.3%
nephritis	< 1%	1%	0.7%
neuropathy	0.2%	< 1%	< 1%

Atezolizumab technical product information 2018; Nivolumab, safety management BMS 2014; Pembrolizumab PI 2014

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Immune Checkpoint Inhibitors
Principles of Adverse Event Management

CTC AE-Grade	Management
1	▪ supportive therapy ▪ close examination ▪ exclusion of infective complications ▪ patient information
2	Like grade 1 but ▪ intermission of therapy until recovery of all irAE to grades 0-1 ▪ consider corticosteroids
3	▪ supportive therapy ▪ IV steroids (e.g. 1-2 mg/kg prednisolone) In case of no improvement within 48 h: ▪ consider additional immunosuppressive therapy (infliximab, MMF) ▪ consider further organ specific diagnostics (eg. colonoscopy) ▪ consider specialists consultations ▪ exclusion or treatment of infection ▪ stop of treatment, re-initiation after recovery to CTC AE grades 0, 1 ▪ slow reduction of steroids (3-6 weeks)
4	Like grade 3 but persistent withdrawal of therapy

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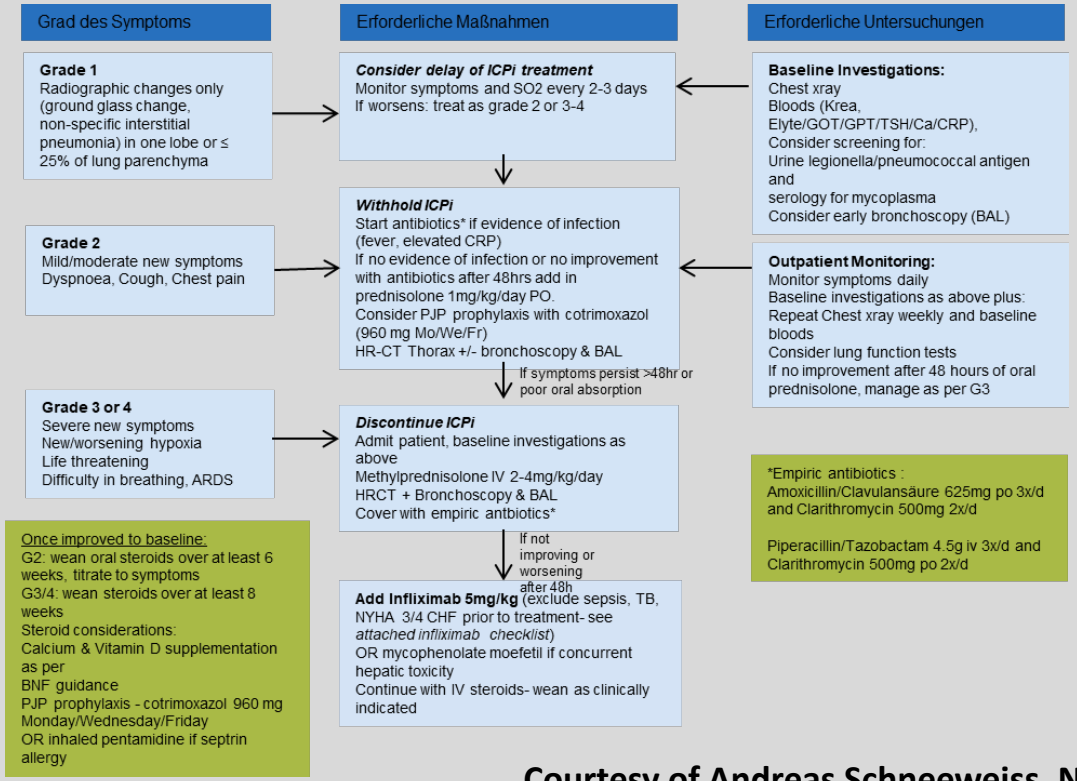
Pneumonitis



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Renal toxicity

Symptom	Erforderliche Maßnahmen	Erforderliche Untersuchungen
Grade 1: Creatinine 1.5x baseline or >ULN-1.5xULN	**Continue ICPi** Repeat creatinine weekly – if worsens, manage as per criteria below	Review hydration status, medications, urine stick and urine culture if urinary symptoms Dipstick urine: protein:creatinine ratio (uPCR) If obstruction suspected: Renal ultrasound +/- doppler to exclude obstruction/clot
Grade 2: Creatinine >1.5-3.0x baseline or >1.5-3.0x ULN	**Withhold ICPi** Hydration and review creatinine in 48-72 hours; if not improving, discuss with Nephrologist and need for biopsy and if attributed to irAE, initiate steroids (oral prednisolone 0.5-1mg/kg) Repeat creatinine/K+ every 48 hours If returns to G1/baseline – recommence ICPi (if on steroids, only once <10mg pred) If not attributed to irAE - may continue ICPi	As above Renal ultrasound +/- doppler to exclude obstruction/clot If proteinuria: for 24 hour collection or urine stick for protein:creatinine ratio (uPCR) If blood: phase contrast microscopy & GN screen* if nephrologist recommends Advise patient to notify if oliguric
Grade 3: Creatinine >3.0x baseline or >3.0-6.0 x ULN	**Withhold ICPi** Admit patient for monitoring and fluid balance; repeat creatinine every 24 hours; Early discussion with Nephrologist and need for biopsy. If worsening, initiate IV methylprednisolone 1-2mg/kg.	As above for G2
Grade 4: Creatinine >6.0x ULN	As per G3; patient should be managed in hospital where renal replacement therapy is available	As above for G2

Renal injury occurs in around 1-4% of patients treated with ICPi's, usually in a pattern of acute tubulo-interstitial nephritis with a lymphocytic infiltrate (Cortazar et al 2016 Kid Int)
Attention needs to be paid to the *patient's baseline creatinine* & not just abnormal results per biochemistry ULN
Confounding diagnoses include dehydration, recent IV contrast, urinary tract infection, medications, hypotension or hypertension
Early consideration for renal biopsy is helpful which may negate the need for steroids and determine if renal deterioration related to ICPi or other pathology
Oliguria should prompt inpatient admission for careful fluid balance and plan for access to renal replacement therapy
Steroid wean: begin to wean once creatinine G1; G2 severity episode– wean steroids over 2-4 weeks; G3/4 episode- wean over ≥4 weeks
If on steroids for >4 weeks – PJP prophylaxis, calcium/Vitamin D supplementation, gastric protection and check afternoon glucose for hyperglycemia
*Glomerulonephritis screen: ANA, Complement C3,C4, ANCA, anti-GBM, Hepatitis B and C, HIV, Immunoglobulins and protein electrophoresis

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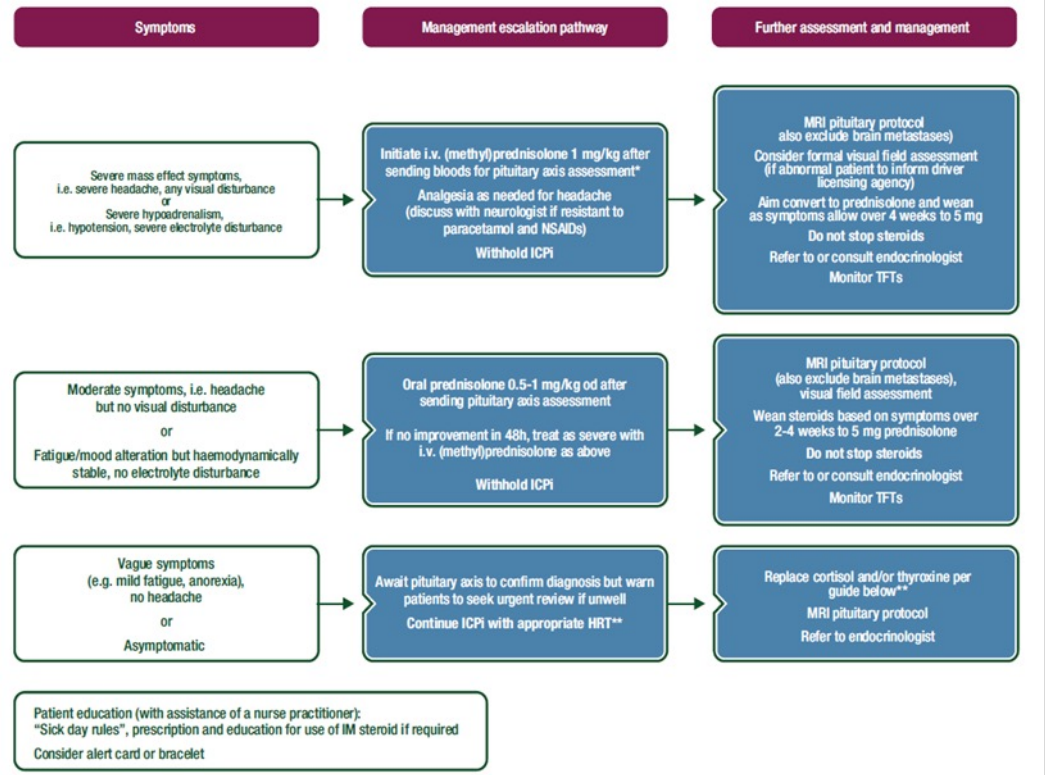
Hypophysitis



Haanen et al.: ESMO guideline. Ann Oncol 2017

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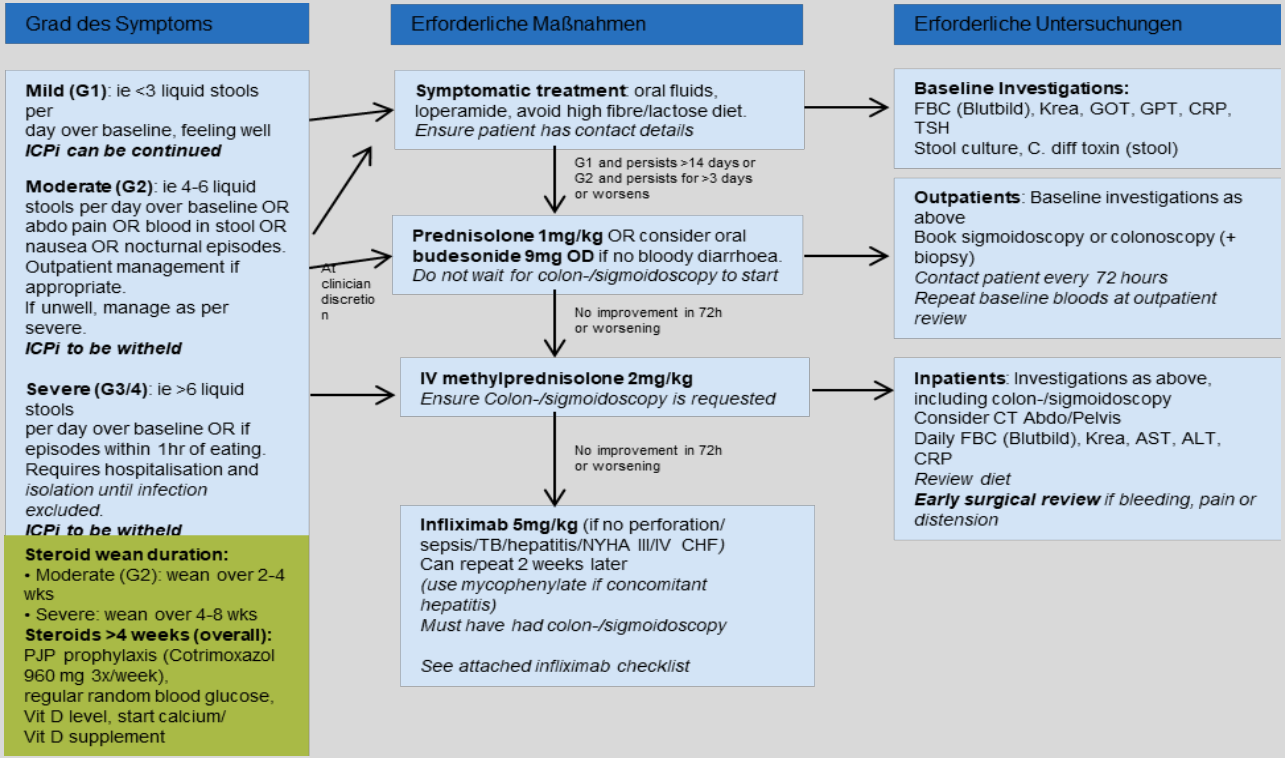
Diarrhea and Colitis



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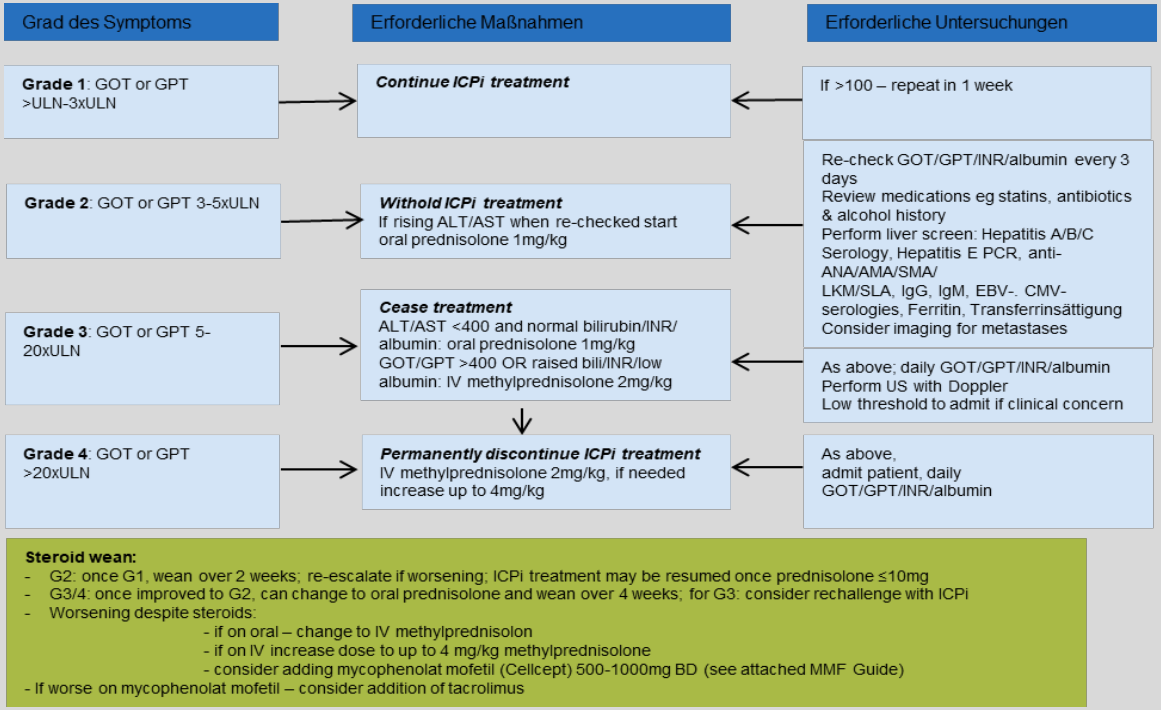
Hepatitis



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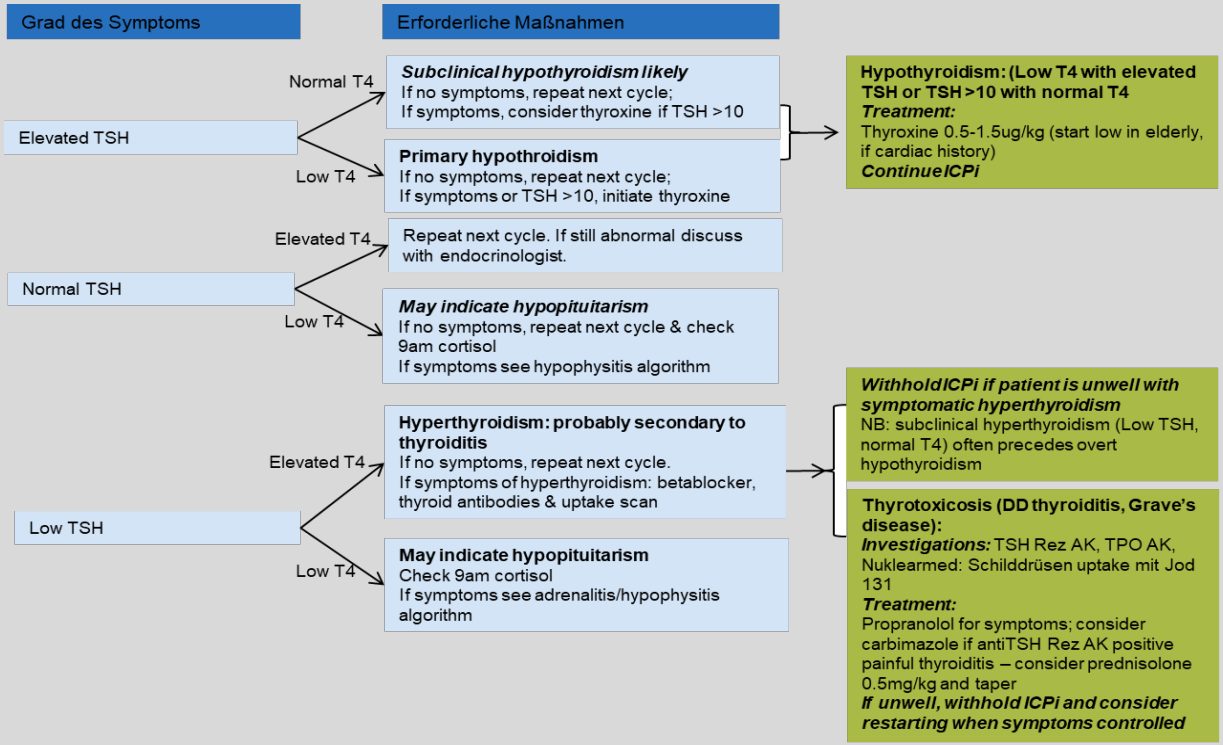
Thyreoiditis



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Side Effects According Organ Systems
Incidence, Prevention, Therapy

1. **Infections**
   - **General prophylaxis for infections**
   - **Hepatitis B virus screening**
   - **Covid-19 (see joint guidelines with DGHO)**

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Prophylaxis of Infections
rarely Applicable to Patients with Solid Tumors (e.g. BC)
ASCO Practice Guideline „Antimicrobial Prophylaxis...“ 2018

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	Oxford		
	LoE	GR	AGO
▪ Avoidance of highly infection-risking behavior or situations	5	D	+
▪ Prophylactic treatment in low-risk patients	1a	B	-
▪ Prophylactic treatment in high-risk* patients (e.g. according to NCCN Guidelines) with			
▪ Antibiotics	1a	A	++
▪ Anti-fungal agents (triazole)	1a	B	+/-
▪ Virostatics in solid tumors	5	D	-
▪ Granulocyte colony-stimulating factors	1a	A	++

* High risk: estimated duration of neutropenia < 100/µl > 7d

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Hepatitis B Virus Screening before Chemotherapy

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	Oxford		
	LoE	GR	AGO
▪ Hepatitis B virus screening before adjuvant chemotherapy (HBsAG, anti-HBC, anti-HBs)	2c	B	+
In case of positive serology or reactivation:			
▪ Prophylactic therapy with virustatic drugs if HBV-DNA detected (according AGIHO / DGHO – recommendations)	1b	A	++
▪ Hepatitis C virus screening before chemotherapy	5	D	+/-

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AGIHO / DGHO – Recommendations on Hepatitis B Virus Screening in Oncology

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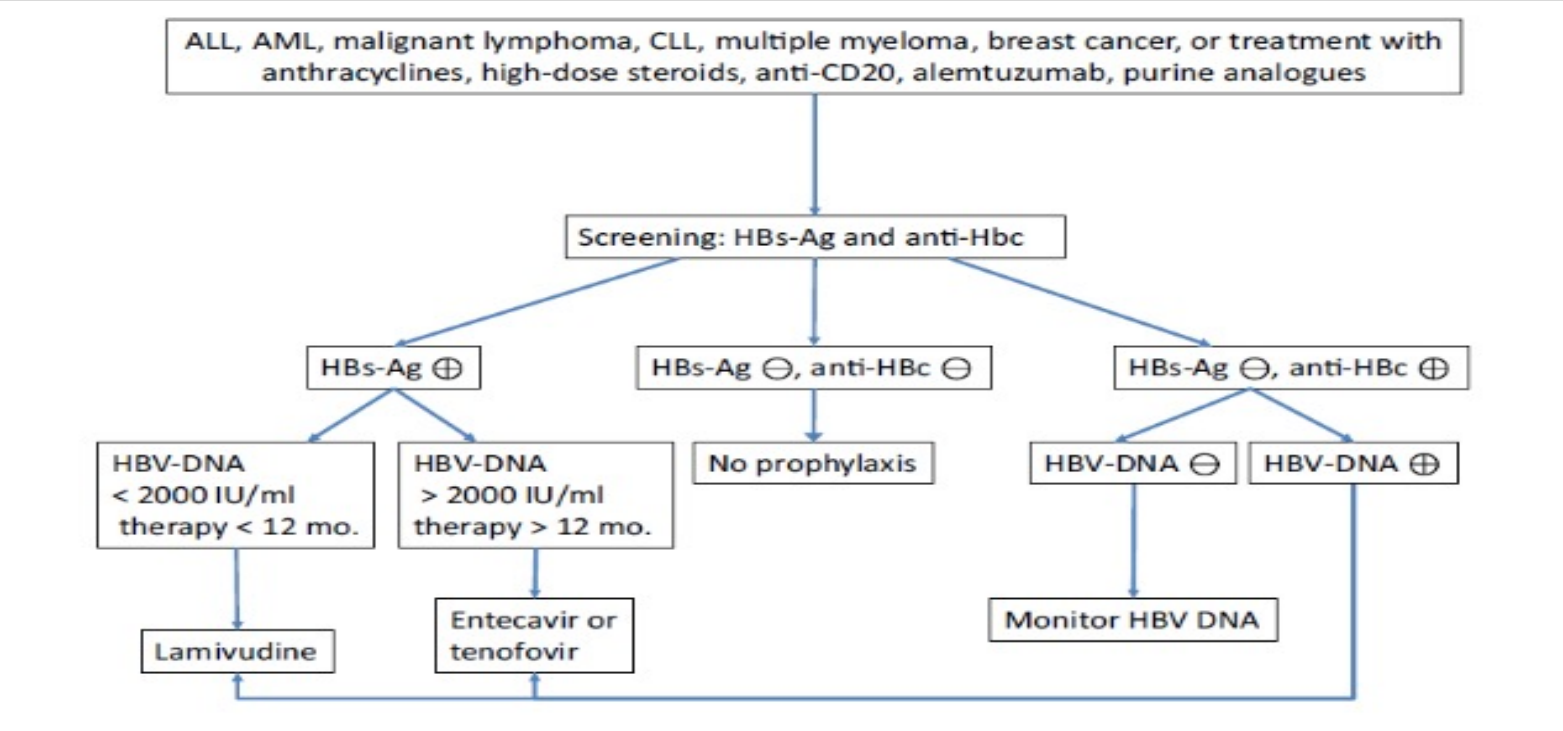

Sandherr M et al. Ann Hematol. 2015 Sep;94(9):1441-50

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2. Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

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Secondary Malignancies I

	Oxford LoE	Oxford GR
▪ With regard to solid tumors, chemotherapy induced secondary malignancies are rare events		2a
▪ Alkylating agents increase the risk of leukemia dose- dependently to a total of 0.2–0.4% within 10–15 years		2a
▪ Anthracycline-containing regimens increase the risk of MDS and leukemia to 0.2–1.7% within 8 to 10 years		2a
▪ PARP-inhibitors are associated with an increased risk of AML and MDS to 0.5–1%		2b
▪ Radiotherapy increases the risk of leukemia by 0.2–0.4% in patients treated with anthracycline-containing chemotherapy		2b
▪ Tamoxifen approximately doubles the risk for developing endometrial cancer (in pts. older than 55 yrs. at start of therapy)		2b

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Secondary Malignancies II (After Radiotherapy)

	Oxford LoE
▪ Radiotherapy (PMRT, BET) may moderately enhance the risk of ipsilateral lung cancer and angiosarcoma (10-15/10.000) 5–10 years after treatment	1a
▪ Enhanced risk especially among ever smokers	2b
▪ No difference of secondary malignancy between PBI und WBI	2c

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Side Effects According Organ Systems
Incidence, Prevention, Therapy

3. *Blood and Lymphatic System Disorders*

- **Anemia**
- **Neutropenia**
- **Febrile Neutropenia (FN)**

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Anemia – Indications for Therapy with Erythropoiesis-stimulating Agents (ESAs)

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	Oxford		
	LoE	GR	AGO
▪ Indicated in asymptomatic anemia	1a	B	-
▪ Therapy and secondary prophylaxis in CTx-induced anemia	1a	A	+
▪ Adjuvant setting	1b	A	+
▪ Neoadjuvant / metastatic setting	1a	A	+/-
▪ In dose-dense / dose-escalated CTx (iddETC)	1b	A	+
▪ Treatment start at Hb-levels < 10 g/dL	1a	A	+
▪ Target Hb 11–12 g/dL	1a	A	+
▪ Improvement of outcome (DFS, OS)	1a	B	--
▪ Risk of thromboembolic events is increased by use of ESAs	1a	A	

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Practical Use of ESAs

- **Epoetin α and Darbepoetin are equieffective**
- **Dosage:**
  - **Epoetin α: 150 IU/kg 3 x weekly s.c. or**
    40.000 IU 1 x /week s.c. or
    80.000 IU q2w s.c. or
    120.000 IU q3w s.c.
  - **Epoetin ß: 30.000 IE weekly s.c.**
  - **Darbepoetin: 2,25 µg/kg s.c. weekly or 500 µg s.c. q3w**
- **Weekly hematologic blood controls**
  - **Dose reduction if Hb-increase > 1g/dl within 2 weeks**
  - **Dose increase if Hb-increase < 1g/dl within 4-6 weeks**
- **In case of FID ("functional iron deficiency") iron supplementation, preferably i.v.**
- **Stop ESA-treatment if there is no Hb increase after 9 weeks**

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Granulocyte Colony-Stimulating Factors

	Oxford LoE	Oxford GR	Oxford AGO
Primary prophylaxis for expected febrile neutropenia (FN)			
If expected risk for FN 10–20%	1b	B	+/-
In case of individual risk factors	3b	C	+
If expected risk for FN > 20% (e.g. DAC, dose-dense CT)	1a	A	++
Secondary prophylaxis during chemotherapy (previous FN or neutropenia grade IV > 7 days)	1b	A	++
Therapeutic use for FN	1a	A	+/-
Start related to chemotherapy and duration			
Pegfilgrastim day 2	1b	A	++
Lipegfilgrastim day 2	1b	A	++
Filgrastim / Lenograstim from day 2–3 until ANC > 2–3 x 10^9	1b	A	++

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Management of Febrile Neutropenia

c.f. Recommendations by Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de

Definition (oral temperature of > 38.5°C or two consecutive readings of > 38°C for 2 h in a patient with an ANC of < 500 cells/mm³ or expected to fall to <500 cells/mm³)

	Oxford		
	LoE	GR	AGO
▪ Clinical examination	5	D	++
▪ Daily evaluation	5	D	++
▪ Hospitalization of high-risk patients	1b	A	++
▪ Homecare in low-risk patients	1b	A	+
▪ Differential blood count	5	D	++
▪ Blood cultures	5	D	++
▪ Imaging of lungs	3	C	++
▪ Immediate initially empiric antibiotic therapy	1a	A	++
▪ Empiric antifungal therapy 4–7 d in case of failure of antibiotic therapy	1b	A	++
▪ G-CSF for treatment (not prophylactic)	2b	B	+/-

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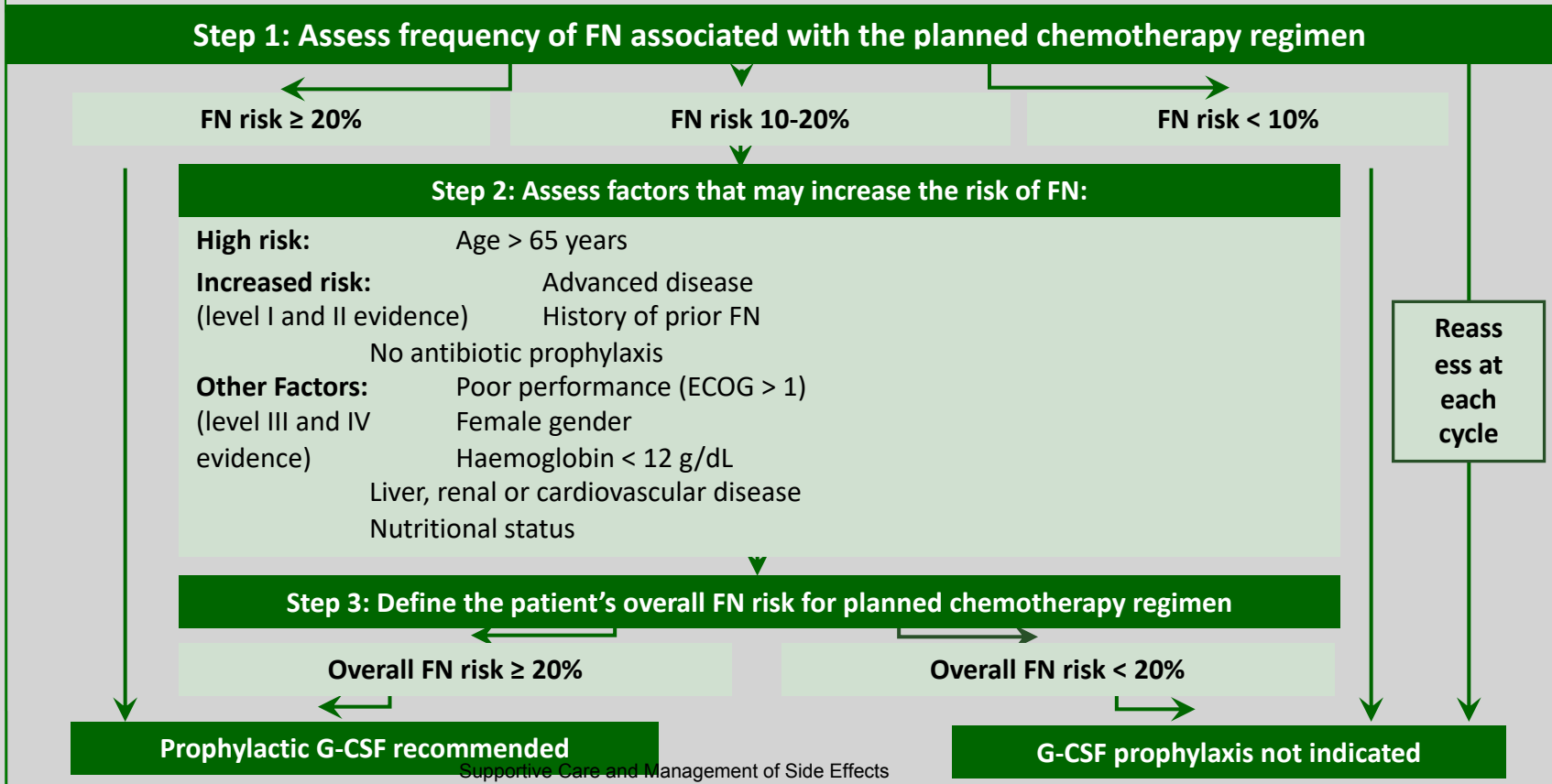
EORTC and ASCO G-CSF Guideline-Based FN Risk Assessment



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4. Toxicities / Ovaries

Therapy-associated amenorrhea (CRA, CIA, TIA)

	Oxford LoE
▪ CRA may be permanent or temporary (depending on age of the patient and type of chemotherapy)	2b
▪ The risk of CRA increases with patient‘s age and duration of the chemotherapy	2b
▪ CRA is an imperfect surrogate for menopause and fertility	5
▪ Adjuvant endocrine therapy with GnRHa induces reversible amenorrhea, but delays conception to a less fertile period	5
▪ Ovarian reserve of women who remain premenopausal after CTX is reduced	2b
▪ CRA is associated with improved outcome (DFS / OS)	1b

Synonym: Chemotherapy related or induced / Treatment induced Amenorrhea (CRA, CIA, TIA)

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5. Psychiatric Disorders

- Depression
- Fatigue
- Cognitive impairment
- Sleep disturbances

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(Therapy-associated) Depression

	Oxford		
	LoE	GR	AGO
▪ Depression is an often reported adverse event in breast cancer patients (20–30%)	2a	B	
▪ Psychological interventions are effective to improve mood, but not survival in distressed and depressed patients	1b	A	
▪ Antidepressants have shown to improve depression in breast cancer patients	1b	A	
▪ Regular exercise participation can prevent depression in breast cancer survivors	2b	B	+

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(Therapy-related) Fatigue

	Oxford		
	LoE	GR	AGO
▪ Fatigue frequent in breast cancer patients (30–60%)	2a	B	
▪ Exclusion of somatic reasons (anemia, tumor burden, co-morbidity, medication) for fatigue	1a	A	++
▪ Psycho-social interventions specifically addressing fatigue efficient in reducing fatigue	1a	A	++
▪ Physical exercise can improve fatigue	1b	D	+
▪ Yoga can improve fatigue	2b	B	+
▪ Methylphenidate or corticosteroids (short-term) can improve fatigue	1a	D	+

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(Therapy-associated) Cognitive Impairment

	Oxford LoE	Oxford GR
▪ Therapy-related cognitive deficits (“chemobrain”) frequently described (16–75%)	2a	B
▪ Cognitive-behavioral therapy beneficial for cognitive function	2b	B
▪ Methylphenidate may improve cognitive function in cancer patients	3a	C
▪ Under therapy with aromatase inhibitors, deterioriation of cognitive performance was observed (espec. verbal memory)	1a	B

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(Therapy-associated) Sleep Disturbances

	Oxford		
	LoE	GR	AGO
▪ Sleep disturbances are a common problem in breast cancer patients during and after therapy (20–70%)	2a	B	
▪ Behavioral therapies demonstrated efficacy in treatment of insomnia and improved quality of life	1b	A	++

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6. Nervous system disorders

- **Chemotherapy-Induced Peripheral Neuropathy (CIPN)**

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Chemotherapy-Induced Peripheral Neuropathy (CIPN)

- **Incidence with taxanes:**
  - **Grade 1–2: 20–50%**
  - **Grade 3–4: 6–20%**
- **Risk factors: type and dose of chemotherapy, BMI, reduced physical activity**
- **Individual risk factors**
  - **Diabetes mellitus**
  - **Nutritive-toxic compounds part. alcohol**
  - **Renal failure**
  - **Hypothyreosis**
  - **Collagenoses / vasculitis**
  - **Vitamine deficiency**
  - **HIV-Infection**
  - **CMT-Gen mutations**

Unclear:

- **Other genetic factors (SNPs, mutations)**

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Chemotherapy-induced Peripheral Neuropathy – Prevention –

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	Oxford		
	LoE	GR	AGO
Non drug-based prevention			
▪ Functional training (physical fitness, sensomotoric stimulation training etc.)	5	D	+
▪ Compression treatment (tight surgical gloves, compression stockings)	2b	B	+
▪ Cooling gloves and stockings	2b[a]	B	+
▪ Elektro-acupuncture	1b	B	-
Drug-based prevention			
There is no drug-based prophylaxis available			
▪ Venlafaxine	2a	C	+/-
▪ Palmitoylethanolamine (PEA) topically or PO	5	D	+/-
▪ A-lipoic-acid (thioctic acid), amifostine, amitriptyline, acetyl-L-car-nitine, carbamazepine, electrolyte solutions, glutathione, Goshajinkigan (GJG), oxcarbazepine, vitamine B, vitamine E, or other compounds[1]	1b	A	-

[1] For list of not recommended drugs, see Hershman et al. 2014

Chemotherapy-induced Peripheral Neuropathy – Therapy –

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	Oxford LoE	GR	AGO
Non drug-based therapy			
▪ Functional training (physical fitness, sensomotoric stimulation training etc.)	2a	C	+
▪ Physiotherapy / physical treatment	5	D	+
▪ acupuncture	2b	B	+
Drug-based therapy			
▪ Menthol locally (1%), capsaicin / lidocain locally	5	D	+
▪ Baclofen / amitryptiline / ketamin-gel	2b	B	+
▪ Duloxetine for therapy of CIPN-induced pain	1b	B	+
▪ Opioids for therapy of CIPN-induced pain	5	D	+
▪ Palmitoylethanolamine (PEA) topically or PO.	5	D	+/-
▪ Venlafaxine	5	D	+/-
▪ Gabapentin, pregabaline	1b	B	+/-
▪ Amitryptiline / nortripyline, imipramine / desipramine	1b	B	+/-
▪ Acetyl-L-carnitine, lamotrigine, or other compounds[1]	1b	B	-

[1] For list of not recommended drugs, see Hershman et al. 2014

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7. Cardiac Disorders

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Cardiotoxicity as Long-term Side Effect

	Oxford		
	LoE	GR	AGO
▪ Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)	2b	B	
▪ Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity	1b	B	
▪ Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently:	2b	B	
▪ Elderly patients, obesity, hypertension, hypercholesterinemia, üre-existing cardiac disease (incl. borderline LVEF), diabetes mellitus			
▪ Monitoring of cardiac function:			
▪ Standardized echocardiography (LVEF or SF in %)	3b	C	+
▪ ECG (QT-interval)	1a	A	+
▪ Troponin I as marker of cardiac toxicicty	2b	B	+/-
▪ Betablocker-prohylaxis during anthracycline therapy	2a	B	+/-

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Adjuvant Trastuzumab
Cardiac Monitoring for CHF

Oxford LoE: 5 **GR: D** **AGO: ++**

Before start of trastuzumab

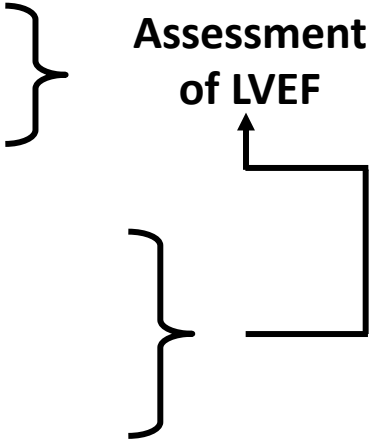
- History, physical examination (edema, hepatomegaly)
- Echocardiography (alternative to MUGA)

During trastuzumab

Regular assessment of

- Heart rate increase > 15% above individual base level
- Body weight increase ≥ 2 kg/week
- Cardiac signs and symptoms

3 monthly assessment of LVEF



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Feasibility of Treatment Combinations Considering Toxicities

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	Oxford		
	LoE	GR	AGO
Regarding cardiac toxicity			
▪ Trastuzumab simultaneous to radiotherapy	2b	B	+
▪ Trastuzumab simultaneous to epirubicin	2b	B	+/-
▪ Trastuzumab simultaneous to doxorubicin	2b	B	-
▪ Anthracycline simultaneous to radiotherapy	2c	C	-
Regarding lung and breast fibrosis			
▪ Tamoxifen simultaneous to radiotherapy	3	C	+/-
▪ Chemotherapy simultaneous to radiotherapy	1b	B	-

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Side Effects of Trastuzumab / Pertuzumab: Algorithm in Case of Cardiac Toxicity

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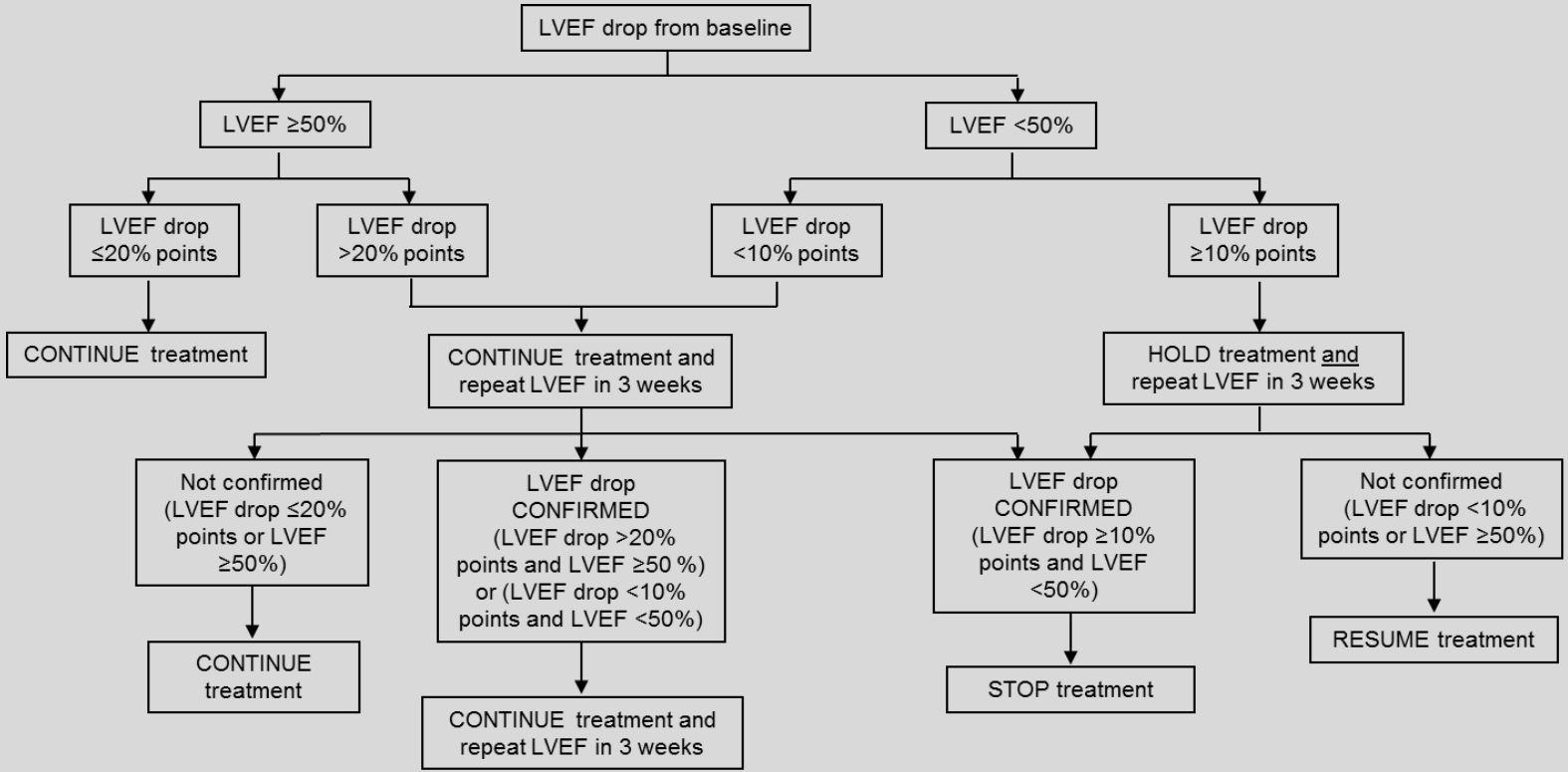

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8. Gastrointestinal Disorders

- Nausea, Emesis
- Mucositis
  - Stomatitis (Everolimus)
- Diarrhea
- Constipation

Antiemetic Therapy

http://www.mascc.org/antiemetic-guidelines
www.onkosupport.de

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	Oxford		
	LoE	GR	AGO
▪ After assessment of emetic potential of chemotherapy protocol	5	D	++
▪ Neurokinin-1-receptor-antagonists	1b	A	++
▪ Dexamethasone (also in chemotherapy combinations with ICPi)	1a	A	++
▪ 5-HT_3-antagonists	1b	A	++
▪ Fixed antiemetic combination therapy	1b	A	++
▪ Rescue Medication			
▪ Olanzapine	1b	A	+
▪ Levomepromazine, benzodiazepines	3b	C	+
▪ Cannabinoids, ginger	3b	C	+/-

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ICPi=Immune Checkpoint inhibitor

Antiemetic Therapy
https://www.mascc.org/antiemetic-guidelines

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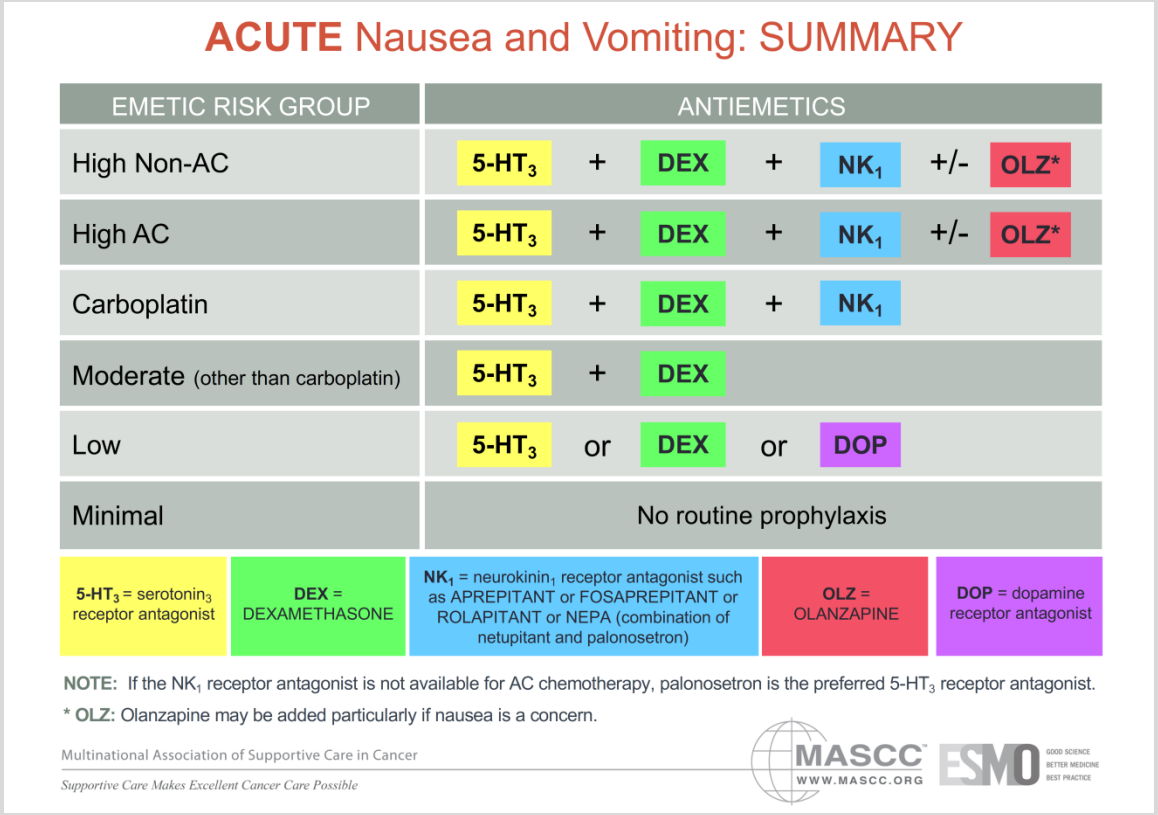

ACUTE Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	5-HT$_3$ + DEX + NK$_1$ +/- OLZ*
High AC	5-HT$_3$ + DEX + NK$_1$ +/- OLZ*
Carboplatin	5-HT$_3$ + DEX + NK$_1$
Moderate (other than carboplatin)	5-HT$_3$ + DEX
Low	5-HT$_3$ or DEX or DOP
Minimal	No routine prophylaxis

5-HT$_3$ = serotonin$_3$ receptor antagonist

DEX = DEXAMETHASONE

NK$_1$ = neurokinin$_1$ receptor antagonist such as APREPITANT or FOSAPREPITANT or ROLAPITANT or NEPA (combination of netupitant and palonosetron)

OLZ = OLANZAPINE

DOP = dopamine receptor antagonist

NOTE: If the NK$_1$ receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT$_3$ receptor antagonist.

* **OLZ:** Olanzapine may be added particularly if nausea is a concern.

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Antiemetic Therapy
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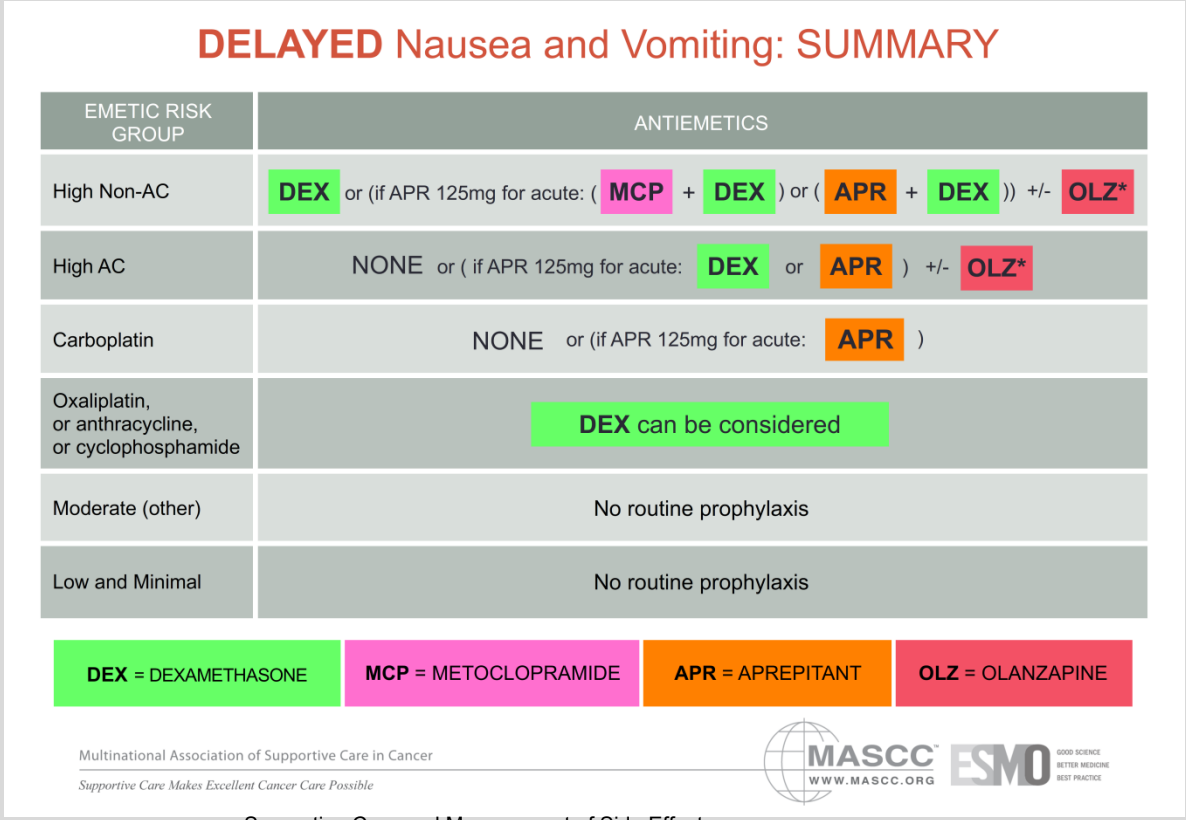

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Supportive Therapy
Antiemetics

Wirkstoffgruppe	Substanz	Dosierung	Nebenwirkungen	Potenzial
Serotonin-antagonisten	Ondansetron Tropisetron Granisetron Palonosetron	8 mg i.v., 2 x 4-8 mg p.o 5 mg i.v., 5 mg p.o. 1-3 mg i.v. 0, 25 mg i.v.	Kopfschmerzen, Diarrhoe, Flushsymptomatik Transaminasenanstieg Darmatonie in hoher Dosierung	sehr hoch
NK1-Antagonisten	Aprepitant Fosaprepitant Rolapitant	125 mg d1, 80 mg d 2-3 p.o. 150 mg d1 i.v. 180 mg d1 p.o.	Cytochrom-P-450- Aktivierung mit Dosis-reduktion von Dexamethason (2 x 8 mg). Keine Kombination mit Astemizol, Terfenadin, Cisaprid	sehr hoch
Dopamin-antagonisten/ substituierte Benzamide	Metoclopramid Alizaprid	bis zu 120 mg/24h als Dauerinfusion od. als Tropfen bis zu 300 mg i.v. oder p.o./24 h (6 Amp. od. 6 Tbl.)	Dyskinesien (Antidot:Biperiden) Angstreaktion, Depressionen, Diarrhoe	hoch
Oxazapine	Olanzepin	10mg/d for d1-4 Ggf. 5mg/d for d1-4	Sedation, weight gain	hoch
Phenothiazine/ Butyrophenone	Haloperidol	1-3 mg 4 x/d	Sedation, Senkung der Krampfschwelle, transiente Leberwerterhöhung	mäßig
Corticosteroide	Dexamethason Prednisolon	8-20 mg i.v. 1-3 x/d 100-250 mg i.v. 1-3 x/d	Blutzuckerentgleisung, psychotische Reaktionen, Flush, Blutdruckanstieg	mäßig
Benzodiazepine	Diazepam Lorazepam	bis zu 20 mg/d 0,5-1,0 mg/d	Sedation, Atemdepression	gering
NEPA (Netupitant and Palonosetron)	fixe Kombinations partner (oral)	NE 300 mg PA 0,5 mg		sehr hoch

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Mucositis Prevention

https://www.mascc.org/mascc-guidelines

Multidisciplinary S3 guidelines of the AWMF (Reg.-Nr. 032-054OL): „Supportive Therapie bei onkologischen Patientinnen – interdisziplinäre Querschnittsleitlinie“

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	Oxford		
	LoE	GR	AGO
▪ **Standardized mouth hygiene for prophylaxis of oral mucositis should be adhered to by all age groups and during all cancer-related therapies with any risk for oral mucositis.**	2b		++

This entails:

1. **Patient:**
   - **Regular mouth washs (H2O, NaCl)**
   - **Soft toothbrushes**
   - **Interdental care: flossing or using interdental brush**
   - **Avoidance of alcohol, tobacco, hot food, sour food**
   - **Regular screening for lesions**
2. **Risk adjusted prophylaxis by dentist**
3. **Continuous clinical control**

There is no evidence with regard to the use of one of the following compounds: allopurinol, capsaicin, glutamine, honey, camomile, camomile oil or extract, chewing gum, kefir, methadone, nystatin, pentoxifylline, povidone-iodine, vitamine A / E / combinationes

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Prevention of Everolimus-Induced Stomatitis Using Corticosteroid-based Mouthwash

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- **Study design: single arm phase II-trial (SWISH)**
- **Cohort: 92 pts., treated with everolimus 10 mg and exemestane 25 mg**
- **Schedule: 10 mL of alcohol-free dexamethasone 15 mg per 5 mL oral solution (swish for 2 min and spit) for at least 8–12 weeks***
- **Results: after 13 wks exposition all-grade incidence of stomatitis 27% (BOLERO 67%), ≥ grade 2 events 9% (BOLERO 27%)**

* **Alternatively Hydrocortison: Hydrocortisonacetat-Suspension 0,5% with Lidocainhydrochlorid and Dexpanthenol (Germany: Arzneibuchrezeptur NRF 7.14.)**

Rugo et al., Lancet Oncol 2017, , Jones et al. Oncologist 2019

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Mucositis

https://www.mascc.org/mascc-guidelines

- **Desinfecting / antiphlogistic measures: :**
  Mouth rinsing with infusions of chamomile or salvia, extracts of chamomile, etheric oils, polyvidon-iodine, hexetidine. Local therapy with crystal violet solution 0.5% or tinctura myrrhei, H. mometasonfuroate + propylene glycol

- **Mucosa protecting measures (during / after application of chemotherapy):**
  Sucking ice cubes (especially from pineapple juice) during 5-fluorouracile- or HD-melphalane. Calcium folinate (Leucovorin-mouth gel®) every 4–6 hrs for HD-methotrexate:
  do not start earlier than 24 hours after end of MTX-Infusion (otherwise potential loss of efficacy of MTX!).
  Dexpanthenole (Panthenol®-Solution. 5%) mouth rinsing.

- **Local antimycotic treatment:**
  Amphotericin B, nystatin, fluconazole

- **Local antiviral treatment**
  Aminoquinuride / tetracaine-HCl , Aciclovir®

- **Local anaesthesia:**
  Benzocaine, Doxepin 0,5% p.o.

- **Pain Therapy:** Opioids if indicated

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Diarrhea

- **Adsorbent agents**
  - **Carbo medicinalis; *caoline / pectine, Al-Mg-silicate hydrate***
- **Analgetics, opioids**
  - **Loperamide; *codeine, morphine IV, tinctura opii (tincture of opium), butylscopolamine***
- **Off-label: Somatostatin-Analogon Octreotid s.c. (starting at grade 3)**
- **Pseudomembranous colitis**
  - **Metronidazole *or (if not effective) vancomycin***

- **Initial dose escalation to reduce grade 3/4 diarrhea**
  - **CONTROL trial (dose escalation of neratinib: 120 mg/d day 1-7, 160 mg/d day 8-14, 240 mg/d afterwards)**

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Constipation

Important Side Effect of Opioid Treatment

- **Bulging agents**
  - **Psylium, flaxseed (shredded)**
- **Osmotic laxatives**
  - **Macrogol > Lactulose (Cochrane review LoE 1a, AGO +)**
  - **Oral radio-opaque material: ultima ratio e.g. sodium amidotrizoate**
  - **Sorbitol**
- **Motility stimulating laxatives**
  - **Senna, Ricinus (Castrol Oil), Bisacodyl, sodium-picosulfate**
- **Emollients (Internal lubricants e.g. paraffin)**
- **Opioid-receptor-antagonists (in opioid-related constipation)**
  - **Methylnaltrexone**

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9. Skin & Subcutaneous Tissue Disorders (Alopecia)

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Skin Toxicities

	Oxford		
	LoE	GR	AGO
▪ Avoidance of chemotherapy-induced alopecia by cooling the patient‘s scalp*	1b		+/-
▪ Prophylaxis of hand-foot-syndrome using urea containing lotions (5-10%)	1b		+
▪ Prophylaxis of nail changes and hand-foot-syndrome by cooling hands during application of docetaxel	2b		+

* Substance- and regimen specific

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Scalp Cooling: Scalp Cooling Alopecia Prevention Trial (SCALP) and Metaanalyses

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AGO: +/- LOE 2b B

- Nangia J, Wang T, Osborne C, et al. Effect of Scalp Cooling Device on Alopecia in Women Undergoing Chemotherapy for Breast Cancer: The SCALP Randomized Clinical Trial JAMA. 2017 Feb 14;317(6):596-605.
  Primary Outcome: hair preservation
  Cooling: 50.5% success vs. 49.5% failure
  Non-cooling: 0% success vs. 100% failure
  Fisher's exact test $p < 0.001$

Two Meta-analyses: AGO: +/- LOE 1b

- Scalp cooling reduced relative risk (RR) of alopecia by 43% (RR, 0.57; 95% CI, 0.45-0.72; $I^2 = 11\%$; $p < .00001$). (Rugo & Voigt, Clinical Breast Cancer 2018; 18(1): 19-28.)
- Incidence rate of scalp metastasis (SC vs. no-SC) 0.61% vs. 0.41%; p = 0.43. (Rugo & Voigt; BCRT 2017)

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10. Musculoskeletal & connective tissue disorders

(see Chapter Osteooncology)

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11. General Disorders & Administration Site Conditions

Extravasation of Potentially Necrotizing Compounds (Anthracyclines, Taxanes, Vinorelbine)

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	Oxford		
	LoE	GR	AGO
▪ Dexrazoxane for treatment of anthracycline-extravasations (exception: liposomal Anthracyclines)	2b	B	++
▪ Hyaluronic acid for treatment of taxane / vinorelbine-extravasations (off-label use)	3b	B	+

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Extravasation of Chemotherapy
Role of Dexrazoxane / Hyaluronic Acid

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Dexrazoxane for treatment of anthracyclines paravasates

Day 1: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs

Day 2: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs

Day 3: 500 mg/m² (max. 1000 mg), IV 1–2 hrs

Otherwise or if treatment with dexrazoxane is not indicated, following measures are recommended:

1. **Local cooling: ice packs for 15 min every 6 hrs, for at least 3 days, alternatively: 24 h continuous ice cooling**
2. **Local application (with swab) of dimethylsulfoxid 99% (DMSO) every 3-4 hours for at least 3 days (better 14 days), allow it to air dry. The interval may be extended to 6 hours from day 4 onward.**

Hyaluronic Acid in case of Taxan/Vinorelbin Paravasates:

- **1–10 Amp a 150 IU**
- **1 ml dissolvent (e.g. NaCl 0.9%)**
- **Local anaesthesia**
- **No thermotherapy after taxanes**
- **Dry warmth 4 x daily 20 min during vincaalkaloids**

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11. Lung

Drug-induced Pneumonitis, Interstitial Lung Disease (ILD)

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	Oxford		
	LoE	GR	AGO
▪ Diagnostic work-up with chest CT	1a	B	++

Therapy according to grade and drug*

▪ Corticosteroids (start with ≥ 0.5 mg/kg/d prednisolone-equivalent)	1a	B	++
▪ Dose hold or therapy discontinuation* (according to respective product information)			++

Management ILD
Trastuzumab Deruxtecan

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For asymptomatic ILD / pneumonitis (grade 1)*

- Consider corticosteroid treatment (eg, ≥ 0.5 mg/kg/day prednisolone or equivalent)
- Interrupt T-DXd until resolved to Grade 0, then:

– If resolved in 28 days or less from date of onset, maintain dose

– If resolved in greater than 28 days from date of onset, reduce dose one level

For symptomatic ILD / pneumonitis (grade 2 or greater)*

- Promptly initiate systemic corticosteroid treatment (eg, ≥ 1 mg/kg/day prednisolone or equivalent)

– Continue for at least 14 days followed by gradual taper for at least 4 weeks

- Permanently discontinue T-DXd in patients who are diagnosed with any symptomatic ILD / pneumonitis

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* ENHERTU [prescribing information]. Daiichi Sankyo Inc., Basking Ridge, NJ and AstraZeneca Pharmaceuticals LP, Wilmington, DE, 2021.

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Further Supportive and Palliative Issues

- **Orphan symptome (from ESMO-guideline for orphan symptoms 2020):**
  - **Muscle cramps**
  - **Myoclonus**
  - **Taste alterations**
  - **Dry mouth (Xerostomia)**
  - **Cough, Hiccup**
  - **Rectal tenesmus**
  - **Restless legs-syndrom**

- **Further issues**
  - **Nutrition**
  - **Pain management**
  - **Palliative Care**

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Nutrition Deficiency

- **Nutrient deficiency is a common medical problem affecting 15-40% of cancer patients. It impairs their quality of life and can affect the success of treatment.**
- **Integration of nutritional advice into clinical management recommended.**
- **For nutrition see S3 guideline Palliative care and supportive therapy.**

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Analgesia

- **Non-opioids; WHO Step 1**
  Diclofenac resinate, ibuprofen and / or metamizole, paracetamol (acetaminophen)
- **Mild opioids; WHO Step 2**
  Tramadol (preferentially „retard“-formulations)
  or tilidine / naloxone (also as „retard“-formulations)
- **Strong opioids; WHO Step 3**
  Morphine, buprenorphine (sublingual or transdermal), fentanyl (transdermal), hydromorphone, oxycodone, as a back-up levomethadone.
  The dose of opioids should be titrated step by step according to the analgetic effect.
- **Additional drugs – „adjuvants“**
  Canabinoide, Gabapentin, pregabalin, carbamazepine, amitriptyline, bisphosphonates

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Palliative Care

- **All patients should be offered palliative care after the diagnosis of a non-curable cancer, regardless of whether a tumour-specific therapy is carried out.**
- **Specialized palliative care should be integrated into oncological decision-making processes, e.g. by participating in interdisciplinary tumor conferences.**
- **Patients with incurable cancer who are cared for in structures of specialized palliative care (palliative care ward, specialized outpatient care such as SAPV) should have access to oncological councelling.**

https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/

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Breast Cancer: Specific Situations

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Breast Cancer:
Specific Situations

- **Versions 2005–2021:**
  Dall / Ditsch / Fehm / Fersis / Friedrich / Gerber / Gluz / Göhring / Harbeck / Huober / Janni / Kolberg-Liedtke / Loibl / Lück / Lux / Maass / Mundhenke / Müller / Oberhoff / Rody / Scharl / Schneeweiss / Schütz / Sinn / Solomayer / Stickeler / Thomssen

- **Version 2022:**
  Fehm / Loibl

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Breast Cancer: Specific Situations

- Young patients
- Pregnancy- and breast-feeding-associated BC
- Elderly patients
- Male patients
- Inflammatory BC
- Occult Breast Cancer (Cancer of unknown primary – axillary CUP)
- Paget‘s disease
- Malignant and Borderline Phyllodes Tumor
- Angiosarcoma
- Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL)
- Metaplastic breast cancer

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Breast Cancer in Young Women ≤ 40 Years

	Oxford LoE	Oxford GR	AGO
▪ Aggressive biological behavior with worse prognosis	2a	B	
▪ Local therapy independent of young age	2b	B	+
▪ Guidelines adapted (neo-)adjuvant systemic treatment (see respective chapters)	1b	A	++
▪ GnRHa as ovarian protection (see chapter gynecological problems)	1a	B	+
▪ Genetic and fertility counseling	2b	B	++
▪ Contraception counseling	2b	B	++

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Breast Cancer During Pregnancy* or Breast Feeding – Diagnostics and Surgery

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	Oxford LoE	GR	AGO
▪ Breast imaging and biopsy like as in non-pregnant patients (no general indication for MRI)	4	C	++
▪ Staging if indicated (bone scan after delivery)	5	D	+
▪ Full body MRI (without contrast agent)	4	C	+/-
▪ Surgery like in non-pregnant patients	4	C	++
▪ Sentinel node excision (technetium only)	2b	B	+
▪ SLNE during 1st trimester	5	D	+/-
▪ Sensitivity and specificity not established (during lactation); breast feeding should be avoided for 24 hrs	4	C	++
▪ Blue dye (not tested in pregnant animals or humans)	4	C	--

* Participation in register study recommended

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Breast Cancer During Pregnancy
- (Neo-)adjuvant Therapy -

	Oxford LoE	Oxford GR	AGO
▪ Radiation therapy during pregnancy	4	C	-
▪ (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)			++
▪ Anthracyclines: AC, EC	2b	B	++
▪ Taxanes	2b	B	+
▪ Platinum salts (carboplatin, cisplatin)	4	C	+/-
▪ MTX (e.g. CMF)	4	D	--
▪ Endocrine treatment	4	D	--
▪ HER2-targeted treatment	3a	C	--
▪ Checkpoint inhibitors	4	D	--
▪ Bisphosphonates, denosumab	4	D	-

Treatment (Chemotherapy, surgical procedure and radiotherapy) of patients with breast cancer during pregnancy should be as similar as possible to standard treatment of young, not pregnant patients with breast cancer.

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Breast Cancer During Pregnancy*
– Delivery and Breast-Feeding –

	Oxford LoE	Oxford GR	AGO
▪ Delivery should be postponed until sufficient fetal maturation (avoid iatrogenic prematurity)	2b	C	++
▪ Termination of pregnancy does not improve maternal outcome	3b	C	
▪ Delivery mode like in healthy women; avoid delivery during chemotherapy-induced leucocyte nadir	4	C	++
▪ If further systemic therapy is needed after delivery, breast feeding may be contra-indicated depending on drug toxicities	5	D	++

* Participation in register study recommended

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Breast Cancer and Pregnancy
– Family Planning –

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	Oxford LoE	Oxford GR	AGO
▪ After breast cancer diagnosis, reproductive techniques can be used to induce pregnancy	3b	D	
▪ Success rates for getting pregnant and for delivering a child lower in breast cancer patients compared to non-cancer patients	3b	D	
▪ Breast cancer patients of reproductive age should be offered fertility counseling before starting any kind of treatment	5	D	++
▪ Breast cancer patients should not be advised against getting pregnant independent of their tumor‘s hormone receptor status and g*BRCA* status	3a	D	

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Breast Cancer During Pregnancy and Lactation*
- Outcome -

	Oxford LoE
▪ **BC during pregnancy**	
▪ **Prognosis is not worse if adequately treated**	3a
▪ **BC during lactation and within the first year after pregnancy**	3a
▪ **Prognosis worse than in BCP and if unrelated to pregnancy**	
▪ **Pregnancy / lactation after BC**	
▪ **Outcome not compromised**	3a

* **Participation in register study recommended**

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Geriatric Assessment

- **No specific algorithm is available**
- **Ability to tolerate treatment varies greatly („functional reserve“)**
- **Comprehensive geriatric assessment (CGA) describes a multidisciplinary evaluation of independent predictors of morbidity and mortality for older individuals**
  - **Physical, mental, and psycho-social health**
  - **Basic activities of daily living (dressing, bathing, meal preparation, medication management, etc.)**
  - **Living arrangements, social network, access to support services**
- **Assessment tools:**
  - **Charlson Comorbidity Index (widely used; good predictor over a 10-year period)**
  - **12 prognostic indicators to estimate 4-year mortality risk**
  - **Short screening tests (more qualitative evaluation)**
  - **IADL (IADL = The Lawton Instrumental Activities of Daily Living Scale with 8 domains of function, that are measured), G8**
  - **Geriatric Prognostic Index (GPI), 3 parameters in oncological patients (psychological distress or acute disease, >3 prescribed drugs, neuropsychological problems)**

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Treatment for Fit Elderly Patients

(Life Expectancy > 5 yrs. and Acceptable Comorbidities)

	Oxford LoE	Oxford GR	AGO
▪ **Clinical geriatric assessment**	2b	B	++
▪ **Treatment according to guidelines**	2a	C	++
▪ Surgery similar to „younger“ age	2b	B	++
▪ Endocrine treatment (endocrine responsive)	1a	A	++
▪ Chemotherapy (standard regimens)			
▪ < 70 years	1a	A	+
▪ > 70 years (especially N+, ER / PR-)	2a	C	+*
▪ Radiotherapy	1a	A	+
▪ Omit radiotherapy after BCS if low-risk, and if endocrine treatment is administered	1b	B	+
▪ Anti-HER2-therapy	2b	C	+

* Study participation recommended

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Treatment for Frail Patients

(Life Expectancy < 5 yrs., Substantial Comorbidities)

	Oxford LoE	Oxford GR	AGO
▪ **Reduced standard treatment**	2b	C	++
▪ **Options extrapolated from trials in elderly:**			
▪ No breast surgery (consider endocrine options)	2b	C	+
▪ No axillary clearing (≥ 60 y, cN0, HR-pos)	2b	B	+
▪ No radiotherapy (Tumor size < 3 cm, pN0, HR-pos)	1b	B	++
▪ Hypofractionated radiotherapy	2b	B	+
▪ No chemotherapy if > 70 yrs. and negative risk-benefit analysis	2b	C	+

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Male Breast Cancer*: Diagnostic Work-Up and Loco-Regional Therapy

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	Oxford LoE	Oxford GR	AGO
▪ Diagnostic work-up as in women	4	C	+
▪ Ultrasound	2b	B	++
▪ Mammography	3b	C	+
▪ Standard-surgery: Mastectomy	4	C	++**
▪ BCT is an option (tumor / breast relation)	4	C	+**
▪ Sentinel-node excision (SLNE)	2b	B	+
▪ Radiotherapy as in women (consider tumor / breast relation!)	4	C	+
▪ Genetic counseling if one additional relative affected (breast / ovarian cancer)	2b	B	++
▪ Screening for 2nd malignancies according to guidelines	GCP		++

* Treatment in certified breast cancer centers recommended

** Participation in register study recommended

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Male Breast Cancer-Prognostic Factors

	Oxford		
	LoE	GR	AGO
▪ Nodal status	2b	A	++
▪ Age	2b	B	+
▪ Tumor size	2b	A	++
▪ ER / PR Expression	2b	A	++
▪ Ki-67 Expression	2b	C	+/-
▪ Grade	2b	C	+/-
▪ Genomic signatures (e.g. OncotypeDx)	2b	B	+

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Male Breast Cancer: Systemic Therapy

	Oxford		
	LoE	GR	AGO
▪ (Neo-)adjuvant chemotherapy as in women	2a	B	++
▪ HER2-targeted therapy (if HER2-positive)	5	D	++
▪ Endocrine therapy	4	D	++
▪ Tamoxifen	2b	B	++
▪ GnRHa and AI	4	C	+
▪ Aromatase inhibitors without GnRHa	2b	B	-
▪ Fulvestrant (metastatic BC)	4	C	+/-
▪ CDK4/6i (in combination)	2b	B	+
▪ Palliative chemotherapy as in women	4	C	++

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Benefit from Trimodal Treatment in Inflammatory Breast Cancer

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Median survival probability		
Trimodal therapy	72 months	p < 0.05
Surgery alone	26 months	

Overall survival-probability (OS)	10 years-OS	5 years-OS
Trimodal therapy	55.4%	37.3%
Surgery & chemotherapy	42.9%	28.5%
Surgery & radiotherapy	40.7%	23.5%
Surgery alone		16.5%

Multivariate analysis of OS	Hazard Ratio	95% CI
Surgery & chemotherapy & RT (trimodal therapy)	1.00	-
Surgery & chemotherapy	1.64	1.46 to 1.84
Surgery & radiotherapy	1.47	0.96 to 2.24
Surgery alone	2.28	1.80 to 2.89

Rueth et al. J Clin Oncol 2014; 32:2018–2024

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Inflammatory Breast Cancer (IBC, cT4d)

	Oxford		
	LoE	GR	AGO
▪ Invasive BC and clinical signs of inflammation (e.g. ≥ 1/3 of the breast affected) determine stage cT4d			++
▪ Staging	2c	B	++
▪ Skin punch biopsy (at least 2; detection rate < 75%)	2c	B	+
▪ Treatment according to guidelines (neoadjuvant or adjuvant – as in non-IBC)	2c	B	++
▪ Mastectomy after chemotherapy	2c	B	+
▪ Breast conserving therapy in case of pCR (individual)	2b	C	+/-
▪ Delayed breast reconstruction	3b	C	+
▪ Sentinel excision only	3b	C	-
▪ Radiotherapy of the chest wall including regional lymph nodes independent of therapy response	2c	B	++

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Axillary Metastasis in Occult Breast Cancer (Cancer of Unknown Primary – Axillary CUP)

- **Incidence: < 1% of metastatic axillary disease**
- **In > 95% occult breast cancer, < 5% other primary**
- **Immunhistology**
  ER-positive: 55%
  HER2 3+: 35%
  Triple-negative: 38%
- **Nodal status:**
- **1 - 3 Ln-Met. in 48%**
  > 3 Ln-Met in 52%
- **Outcome similar or better compared to breast cancer with similar tumor biology and tumor stage**

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Axillary Metastasis in Occult Breast Cancer (Axillary CUP) Imaging Diagnostics

	Oxford		
	LoE	GR	AGO
▪ **Breast imaging incl. Breast-MRI**	3	B	++
▪ **Exclude contralateral cancer**	3	B	++
▪ **Exclude non-breast malignancy, especially in case of TNBC** (e.g. skin, female genital tract, lung, thyroid gland, stomach)	5	D	++
▪ **Staging** (CT thorax / abdomen, pelvis, in certain circumstances also thyroid sonography, HNT-exam)	3	B	++
▪ **PET / PET-CT**	3b	B	+

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Axillary Metastasis in Occult Breast Cancer (ex. CUP)

Pathology, Molecular Pathology

	Oxford LoE	Oxford GR	AGO
▪ ER, PR, HER2, GATA3 (in some cases Ck5/6, Ck7, Ck20, SOX-10, PAX-8, TTF1, and others)	5	D	++
▪ Exclusion of other primary malignancies in case of triple-negative phenotype or unusual histology, e.g. lung, female genital tract, HNT tumors, neuroendocrine ca.	5	D	++
▪ Gene expression profiling for determination or primary site (e.g. CUPprint, Pathwork, TOT, CancerType)	2c	B	+/-
▪ NGS, epigenetics for determination of primary site (Panel-Sequencing, e.g. EPICup)	2c	B	+/-
▪ Prognostic gene expression tests	5	D	--

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Axillary Metastasis in Occult Breast Cancer (Axillary CUP): Therapy

	Oxford		
	LoE	GR	AGO
▪ Axillary dissection	3a	C	++
▪ Targeted axillary dissection after NACT (in case of clinical complete remission	3b	C	+/-
▪ Mastectomy if breast MRI is negative	3a	C	--
▪ (Neo-)adjuvant systemic therapy according to breast cancer guidelines (AGO)	5	D	++
▪ Breast irradiation if breast MRI is negative	2c	B	+
▪ Irradiation of regional lymph nodes according to breast cancer guidelines (AGO)	3b	B	+

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Paget‘s Disease of the Breast

- **Definition: Paget‘s disease of the breast is characterized by an intraepidermal tumor manifestation originating in intraductal or invasive breast cancer.**
- **Clinical presentation: skin eczema of the nipple, areola and surrounding skin; thickening, pigmentation and scaly skin**

Feature	Frequency
Presentation	Paget‘s disease with invasive Ca. (37-58%) Paget‘s disease mit DCIS (30-63%) Isolated Paget‘s disease (4-7%) Isolated Paget‘s disease with invasion (rare)
IHC	HER2-positive (83-97%) ER-positive (10-14%) AR-positive (71-88%)
Prognosis and tumor biology	Better in isolated Paget‘s disease Worse if in combination with invasive breast cancer or DCIS compared to isolated Paget‘s disease

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Paget‘s Disease of the Breast Diagnosis

	Oxford		
	LoE	GR	AGO
▪ Histological verification by skin biopsy			++
▪ Mammography, sonography	4	D	++
▪ MRI of the breast if other imaging negative	4	C	+
▪ Immunohistochemistry (ER, PR, HER2, CK7) to detect benign and HER2-negative cases	5	D	++

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Paget‘s Disease of the Breast - Therapy

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	Oxford LoE	Oxford GR	AGO
Paget‘s disease with underlying disease (invasive breast cancer, DCIS)			
▪ Therapy according to standard of underlying disease	5	D	++
▪ Surgery must achieve R0	1c	B	++
Isolated Paget‘s disease of the NAC:			
▪ Surgery must achieve R0	1c	B	++
▪ Surgical resection only, no adjuvant radiotherapy	4	D	++
▪ Sentinel-node excision (SLNE)	2b	B	--

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Borderline and Malignant Phyllodes Tumor

- **Name derived from greek term of “Phyllon” (leaf) due to its lobulated histological aspect**
- **Differential diagnosis may be problematic on core biopsy**
- **Resection margin is independent prognostic parameter**
- **Comparable rates of recurrence in association with BCT or mastectomy**
- **In-Breast recurrence relatively frequently seen (10 - 30%)**
- **Distant metastasis relatively rare (< 10%) and almost exclusively seen in malignant phyllodes tumor.**
- **Adverse pathological criteria: marked stromal cellularity and overgrowth, increased nuclear atypia, presence of large necrohemorrhagic areas, and high mitotic activity associated with increased risk of distant recurrence**

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Phyllodes Tumor

- **Frequency 0.3 – 1% of all primary breast tumors**

parameter	frequencies
Grading (3-STEP histological grading system)	Benign (75%) Borderline (16%) Malignant (9%)
Median age at time of diagnosis	Benign PT: 39 y Borderline PT: 45 y Malignant PT: 47 y
Local recurrence	Benign PT: 4 – 17% Borderline PT: 14 – 25% Malignant PT: 23 – 30%
Metastasis	Benign PT: < 1% Borderline: PT: 1.6% Malignant PT: 16-22%

10 y OS: 86–90% (range: 57–100%) depending on subtype and unfavorable histological criteria

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Borderline and Malignant Phyllodes Tumor Diagnosis

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	Oxford		
	LoE	GR	AGO
▪ Mammography, sonography	3	C	++
▪ Diagnosis on core biopsy, grade determination on resection specimen	3	C	++
▪ Breast MRI	3	C	+/-
▪ Staging only malignant PT (CT thorax, skeletal system)	5	D	++

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Borderline and Malignant Phyllodes Tumor Surgery

	Oxford		
	LoE	GR	AGO
▪ Borderline / malignant phyllodes tumor: Complete resection with adequate margins, min. > 1 mm	2b	B	++
▪ SLNE / Axillary dissection	4	C	--
▪ Treatment of local recurrence			
▪ R0 resection or simple mastectomy	4	C	++

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Systematic Reviews (2016-2021)

Optimal Surgical Margins for Phyllodes and Borderline Tumors

Rosenberger LH, et al. J Clin Oncol 39: 178-189, 2021. PMID 33301374	Contemporary Multi-Institutional Cohort of 550 Cases of Phyllodes Tumors (2007-2017) Demonstrates a Need for More Individualized Margin Guidelines.	Local recurrence (all PT grades) was not reduced with wider negative margin width (≤ 2 mm v. > 2 mm); or final margin status (positive v negative).
Thind A, et al. Ann R Coll Surg Engl. 102(3):165-173, 2020. PMID 31918563	Surgical margins for borderline and malignant phyllodes tumours. (10 studies, 456 cases, 1990 – 2019).	No statistically significant difference between <1cm and ≥1cm margins in terms of local recurrence rates or distant metastasis.
Lu Y, et al. Ann Surg Oncol. 90:342–13, 2019. PMID 30617873.	Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis. (54 studies, 9234 cases, 1995 – 2018).	A positive margin and BCS both were significantly correlated with a higher LR risk for malignant PTs but not for benign and borderline PTs.
Tan BY, et al. Histo-pathology. 2016;68(1):5-21. PMID: 26768026	Phyllodes tumours of the breast: a consensus review.	Tumour on ink, or <1 mm, should be considered as a positive margin. Excision with negative margins should be achieved for recurrent and malignant phyllodes tumours.

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Borderline and Malignant Phyllodes Tumor Adjuvant Therapy

	Oxford LoE	Oxford GR	AGO
▪ Adjuvant radiotherapy (younger age, increased tumor volume > 5 cm, close resection margin)			
▪ Local control	2b	B	+
▪ Effect on disease-free survival	2b	B	-
▪ Systemic adjuvant therapy (chemo, endocrine)	4	C	-
▪ Adjuvant Treatment of local recurrence			
▪ Radiotherapy, chemotherapy after R1 resection	4	C	+/-
▪ Distant metastasis (very rare)			
▪ Treatment like soft tissue sarcomas	4	C	++

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Sarcomas of the Breast

- **Not infrequently associated with familial syndromes (Li-Fraumeni, familial adenomatous polyposis, neurofibromatosis type 1)**
- **Primary sarcomas: angiosarcoma, undifferentiated sarcoma, leiomyosarcoma, liposarcoma, osteosarcoma**
- **Secondary malignancies of the breast:**
  - **Radiotherapy-Associated Angiosarcoma**
  - **Breast Implant Associated Large-Cell Anaplastic Lymphoma (BI-ALCL)**
- **Rare: intramammary sarcoma metastases**
- **Staging: TNM (UICC) or AJCC scheme of the soft tissue sarcoma analogous to sarcoma of the breast**
- **Grading: Analogous to the FNCLCC system for sarcoma or according to Rosen (1988) for angiosarcomas**

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Primary Angiosarcoma of the Breast

- Most common primary sarcoma of the breast
- Young age (median: 24–46 years)
- Indistinct tumor borders
- Large tumor (median: 5–7 cm)
- Uncharacteristic findings on mammography and sonography
- High local recurrence risk, even after mastectomy
- More unfavorable prognosis than other primary sarcoma of the breast
- Metastasize early, often to the lung and liver

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Primary Angiosarcoma of the Breast*
Diagnosis

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	Oxford		
	LoE	GR	AGO
▪ Mammography, sonography to determine extent of disease	3a	C	--
▪ Preoperative MRI to determine the extent of disease	3a	C	++
▪ Diagnosis by core biopsy	3a	C	++
▪ Diagnosis by FNB	3a	C	--
▪ Staging (CT thorax & abd.; angiosarcoma: MRI brain)	4	D	++
▪ Prognostic factors: size, grade, margins	3a	C	++

* Therapy in specialized centers recommended

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Primary Angiosarcoma of the Breast* Therapy

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	Oxford		
	LoE	GR	AGO
▪ Surgery with wide clear margins, mostly as mastectomy	2b	C	++
▪ Breast-conserving therapy	3a	C	-
▪ SLNE or axillary dissection if cN0	3a	C	--
▪ Adjuvant chemotherapy (anthracycline / taxane-based)	4	C	+/-
▪ Adjuvant radiotherapy if high risk (size > 5 cm, R1)	4	C	+/-

* Therapy in specialized centres recommended

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Secondary Angiosarcoma of the Breast Therapy

	Oxford		
	LoE	GR	AGO
▪ Tumor resection (BCT / mastectomy) Radical surgery ist not associated with better outcome	3a	C	+
▪ (Neo-)adjuvant chemotherapy	3a	C	+/-
▪ Adjuvant radiotherapy if high risk (size > 5 cm, R1)	2b	B	+/-
▪ Regional hyperthermia (to improve local control) plus chemotherapy and / or radiotherapy	2b	B	+/-

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Secondary (Radiotherapy-associated) Angiosarcoma of the Breast

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- **Cumulative incidence of radiotherapy-associated sarcoma: 3.2 per 1,000 after 15 years**
- **Clinical presentation**
  - **> 5 years after BCT or mastectomy with irradiation**
  - **usually intracutaneously or subcutaneously in the irradiation area with livid discoloration**
  - **multiple foci**
  - **most often in advanced stages (II - III)**
  - **metastasis mostly pulmonary**
  - **lymph node metastasis possible**
- **Prognosis is more unfavorable than in non-radiotherapy-associated sarcoma**
- **Survival: after 5 yrs. up to 50.5%, after 10 yrs. up to 25.2%**

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Angiosarcoma of the Breast
Treatment of Local Recurrence and Metastases

	Oxford LoE	Oxford GR	AGO
Treatment of Local Recurrence:			
▪ R0 resection	4	C	++
▪ Adjuvant radiotherapy for high-risk patients (tumor size > 5 cm, R1)	4	C	+/-
Distant Metastases / Unresectable Tumors:			
▪ Treatment like as for soft tissue sarcomas (according to S3 guideline)	4	C	++
▪ Paclitaxel weekly / liposomal doxorubicin (as in angiosarcoma)	2b	B	+
▪ Antiangiogenic treatment (e.g. in angiosarcoma)	4	C	+/-

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Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

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- **Aproximately 10.000.000 implant carrier**
- **Rare disease, 3% of T-cell Non-Hodgkin Lymphomas, 0.04-0.5% of all malignant breast diseases**
- **1:3.000 – 30.000 in women with textured implants (caveat: underreporting!)**
- **Estimated incidence 0.6-1.2/100.000 women with implants (median age: 54 y)**
- **Mainly associated with textured implants (1:300 women)**
- **Interval to diagnosis: 8 years (median)**
- **Clinical symptoms**
  - **Erythema, swelling and seroma. (60%)**
  - **Solid tumor (17%)**
  - **Seroma and solid tumor (20%)**
  - **Axillary lymphadenopathia (20%)**
- **Histology: CD30+ / ALK-T-Cell Lymphoma**
- **Compulsory registration as SAE (§3 MPSV to BfArM) (https://www.bfarm.de/SharedDocs/Formulare/DE/Medizinprodukte/BIA-ALCL-Meldung.html)**

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BIA-ALCL - Surfaces of Breast Implants

- The cause of BIA-ALCL is not established; however, it has been proposed that lymphomagenesis may be driven by a chronic inflammatory reaction induced by capsule contents or surface. **The risk for BIA-ALCL has been shown to be significantly higher for implants with grade 3 and 4 surfaces.**

Process	Polyurethane foam	Salt Loss (Biocell/ Eurosilicone)	Gas Diffusion	Salt Loss (Nagotex)	Imprinting	Smooth/ Nano
Surface Area	high	intermediate	intermediate	low	low	minimal
Roughness	high	intermediate	low	low	low	minimal
SURFACE TYPE	4	3	3	2	2	1

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BIA-ALCL– Diagnosis

	Oxford LoE	Oxford GR	AGO
▪ Breast US (assessment of new seromas > 1 year after implant insert, solid lesion (sensitivity: 84%, specificity: 75%))	3a	D	++
▪ Mamma-MRT in confirmed cases	3a	D	++
▪ Staging (Imaging, e.g. CT, PET-CT)	3a	D	++
▪ Cytology of late seromas ▪ - > 50 ml ▪ - Complete assessment ▪ - flow-cytology (T-cell clone) ▪ - BIA-ALCL specific cytologic diagnostic (e.g. CD 30+)	3a	D	++
▪ Core needle biopsy in solid lesions ▪ Lymphoma assessment of resected tissue and histologic staging	3a	D	++
▪ Documentation of the implant and enter in registry	5	D	++

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BIA-ALCL – Therapy

	Oxford		
	LoE	GR	AGO
▪ Implant resection and complete capsulectomy including tumorectomy	3a	C	++
▪ Contralateral implant resection including capsulectomy in case of bilateral implants (2-4% BIA-ALCL bilateral)	4	D	+/-
▪ Resection of suspicious lymph nodes, no routine use of Sentinel-Node-Biopsy, no axillarx dissection	4	D	++
▪ Polychemotherapy (e.g. CHOP / CHOEP) in cases of extra capsular extension, Brentuximab-Vedotin-CHP as an alternative	4	D	+
▪ Radiotherapy in unresectable tumors	5	D	+/-
▪ Case discussion in an interdisciplinary tumor board in the presence of a specialist for lymphomas	5	D	++

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TNM Staging of BIA-ALCL (proposed)

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	TNM-Kategorie	Definition
Tumor extent (cT/pT)	T1	Confined to seroma or a layer on luminal side of capsule
	T2	Early capsule infiltration
	T3	Cell aggregates or sheets infiltrating the capsule
	T4	Lymphoma infiltrates beyond the capsule
Regional lymph nodes (cN/pN)	N0	No lymph node involvement
	N1	One regional lymph node positive
	N2	Multiple regional lymph nodes positive
Metastasis (cM/pM)	M0	No distant spread
	M1	Spread to other organs or distant sites

Stage	Definition
IA	T1 N0 M0
TB	T2 N0 M0
TC	T3 N0 M0
IIA	T4 N0 M0
IIB	T1-3 N1 M0
III	T4 N1-2 M0
IV	T any N any M1

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Diagnostic Pathways and Assessment

Adapted from the NCCN and UK guidelines

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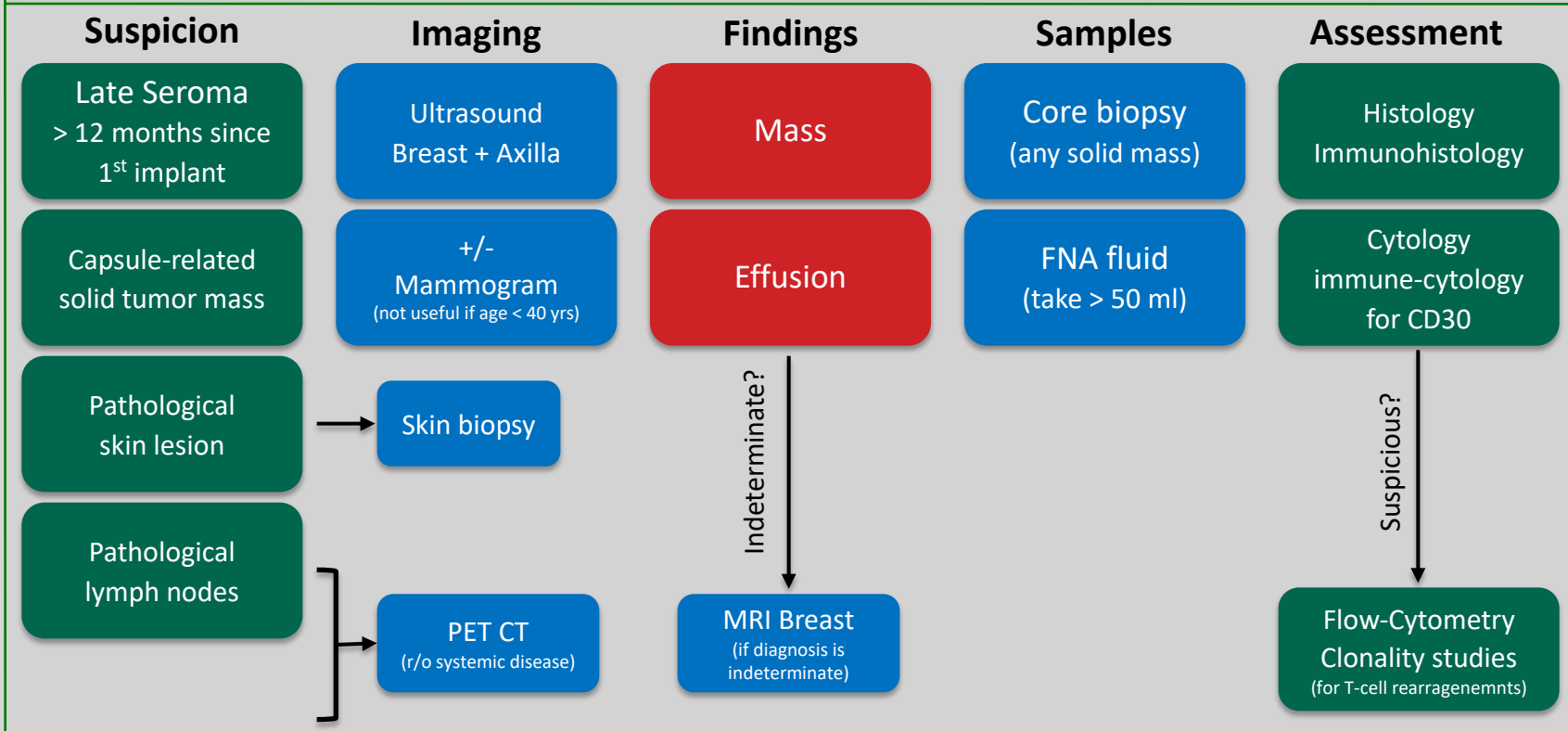

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BIA-ALCL Treatment Pathways

Adapted from the NCCN and UK guidelines

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Outcome

- BIA-ALCL confirmed
- Indeterminate
  - Options: Further imaging US/MRI/Repeat FNAC , Tertiary referral
- Negative for BIA-ALCL
  - Treatment of infection/ benign seroma (serial aspiration, implant exchange with capsulectomy)

Workup

- Referral to experienced breast cancer center
- PET-CT & breast MRI
- Routine bloods (+/- bone marrow bx)
- MTD Discussion
- Clinical suspicion remains
  - Consider diagnostic capsulectomy

Surgery

- En-bloc capsulectomy and complete excision (mass)
- +/- other breast +/- axilla biopsy (SNB not recommended)
- Histological Staging (Clemens et al. 2016)
- MTD Discussion
- Reports to BfArM, manufacturer, DGPRÄC, PROFILE database (FDA)

Adjuvant Therapy

- Stage I : No further treatment
- Stage II - IV: Consider adjuvant treatment
- Chemo-immunotherapy
- Radiotherapy for positive margins / irresectable thoracic wall infiltration but N0/M0

Follow-up

- Clinical follow-up (ultrasound /CT scan) 3–6 m for 2y, afterwards for 5y
- PET-CT if symptomatic

Treatment as per systemic ALCL regimes

24-36 Gy in 15 fractions

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BIA-ALCL – EUSOMA-Recommendation

- **Despite an increase of BIA-ALCL in association with texture implants the use of textured implants is still permitted!**

„For the moment, textured implants can safely continue to be used with patient's fully informed consent, and that women that have these type of implants already in place don't need to remove or substitute them, which would undoubtedly cause harm to many tens of thousands of women, to prevent an exceptionally rare, largely curable and currently poorly understood disease."

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Metaplastisches Mammakarzinom

Definition: Metaplastische Transformation der glandulären Tumorzellen

- Bei epithelialer Differenzierung: Plattenepithelkarzinom, Spindelzellkarzinom
- Bei heterologer (mesenchymaler) Differenzierung: chondroides, ossäres oder rhabdoides metaplastisches Mammakarzinom

Klinisch-pathologische Charakteristika:

- < 1 % der Malignome der Mamma
- Gleiche Altersgruppe wie NST-Karzinome
- Umschrieben, tastbar
- Schnell wachsend, schlechtes Ansprechen auf Chemotherapie
- > 90 % triple-negativ

Aggressivität:

- Hoch maligne bei heterologer (mesenchymaler), plattenepithelialer oder high-grade spindelzelliger Differenzierung
- Unsicheres malignes Potential (low-grade) bei adenosquamöser oder Fibromatose-ähnliche Differenzierung

Frequent mutations:

- TP53, *EGFR*, *PIK3CA*, *PTEN*

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Metaplastic breast carcinoma*
- high-grade -

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	Oxford		
	LoE	GR	AGO
▪ Operative therapy surgery and axillary staging according to standard	4	C	++
▪ Adjuvant chemotherapy (rather chemoresistant)	4	C	+/-
▪ Neoadjuvant chemotherapy (rather chemoresistant)	4	C	-
▪ Adjuvant endocrine therapy if HR-positive	4	C	+
▪ Adjuvant radiotherapy according to standard	4	C	+ +

* Reference pathology recommended

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Metaplastic Breast Carcinoma with Uncertain Malignant Potential (Fibromatous and Adenosquamous Ca.)*

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	Oxford		
	LoE	GR	AGO
▪ Operative therapy and axillary staging according to standard	4	C	++
▪ Adjuvant chemotherapy	4	C	-
▪ Neoadjuvant chemotherapy	4	C	- -
▪ Adjuvant endocrine therapy (not applicable, since triple-negative tumors)	4	C	-
▪ Adjuvant radiotherapy according to standard	4	C	+

* Reference pathology recommended

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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Breast Cancer Follow-Up

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Breast Cancer
Follow-Up

- **Versions 2002–2021:**

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- **Version 2022:**

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Breast Cancer Follow-Up Objectives

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	Oxford		
	LoE	GR	AGO
Early detection of curable events			
▪ In-breast recurrence	1a	B	++
▪ Loco-regional recurrence*	1a	B	++
Early detection of contralateral cancers	1a	B	++
Early detection of metastasis			
▪ Early detection of symptomatic metastases	3b	C	+
▪ Early detection of asymptomatic metastases	1a	A	-

* loco-regional recurrence is associated with a higher risk of mortality in node-positive, PR-negative, younger patients and in patients with a short time between primary diagnosis and recurrence

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Breast Cancer Follow-Up Objectives

	Oxford		
	LoE	GR	AGO
▪ Improve quality of life	2b	B	+
▪ Improve physical performance	2a	B	+
▪ Reduction and / or early detection of therapy-related side effects (such as osteoporosis, cardiac failure, fatigue, neurotoxicity, lymphedema, web axillary pain syndrome (abacterial lymphangitis), sexual disorders, cognitive impairment, sterility, and secondary tumors) and start of necessary therapies	2b	B	+
▪ Participation in interventional programs during follow-up for breast cancer survivors in order to maximize therapy adherence, assess life-style interventions, and improve quality of life	3b	B	+

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Monitoring after Cardiotoxic Therapy (Anthracycliens, anti-HER2)

After anthracyclines / Trastuzumab:

- **ECG and echocardiography:**
  - **6, 12, 24 months and yearly up to 5 years after therapy.**
  - **After 5th year, every 5 years and if patient is symptomatic.**
- **If cardiovascular risk factors:**
  - **blood pressure at least yearly**
  - **lipids and HbA1c in serum yearly**
- **Modify risk factors if possible:**
  - **nicotine, body weight, bmi.**
- **Education about individual risk profile and lifestyle**

Risk factors:

radiotherapy of left breast, nicotine, hypertonus, diabetes mell., dyslipidaemia, adiposity, age > 60, cardiac diseases: reduced ejection fraction, post-myocardial infarction status , ≥ moderate heart defects

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Breast Cancer Follow-Up Objectives

	Oxford LoE	Oxford GR	AGO
▪ **Evaluation of current adjuvant therapy**	2b	B	++
▪ **incl. monitoring of adherence to endocrine therapies**			
▪ **Control of menopausal status, e.g. in case of CT-induced amenorrhea (FSH/2 or bleeding history) and addition of GnRH analogs (up to 2 years after CT) if premenopausal status in women < 45 years old, or switch to aromatase inhibitors (if postmenopausal)**			
▪ **Pro-active improvement of therapy adherence**	5	D	++
▪ **Patient information about efficacy data for 5-10 years endocrine therapy**			
▪ **Early therapy of side effects (sports, NSAIDs, vitamin D / calcium)**			

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Breast Cancer Follow-Up Objectives

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	Oxford		
	LoE	GR	AGO
▪ **Psycho-social aspects of support and counseling** ▪ Pregnancy, contraception, sexuality, quality of life, menopausal symptoms, fear of recurrence ▪ Inclusion of related persons (partner, family, friends, caregivers)	4	C	+
▪ **Second opinion regarding primary therapy**	2c	B	++
▪ **General counseling (e.g. changes in family history of breast, ovarian, prostate, pancreas carcinoma with new indication for genetic counseling, HRT, prophylactic surgery, breast reconstruction)**	2c	C	+

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Breast Cancer Follow-Up
Recommended Interventions

Interventions regarding lifestyle risks and comorbidity in order to reduce an unfavorable impact on disease outcome

	Oxford		
	LoE	GR	AGO
▪ **Treatment of type II-diabetes** (> 25% undetected DM in postmenopausal BC patients, endocrine therapy improves risk for DM)	2a	B	++
▪ **Weight/lifestyle intervention** (if BMI < 18.5 and > 30)	2a	B	+
▪ **Nightly fastening > 13 h**	2b	B	+
▪ **Reduction of dietary intake (at least 15 % calories from fat) in HR-negative BC is associated with improved overall survival**	2b	B	+
▪ **Stop smoking** (smoking causes 2-fold increase in BC-specific and 4-fold increase in not directly BC-associated mortality)	2b	B	++
▪ **Alcohol consumption reduction (below 6g/d)**	2b	B	+
▪ **Moderate sport (in patients with reduced physical activity prior to diagnosis) (at least 150 minutes/w, 2x/w)**	1b	A	++
▪ **Distress reduction**	3b	B	+

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Nightly Fasting

Prolonged nightly fasting improves prognosis in breast cancer patients

retrospective cohort study:

2413 BC-pat. (no diabetes), nightly fasting more or less than 13 hrs

Fasting < 13 hrs: **HR 1.36, 36% increase of risk for recurrence**
HR 1.21, n.s. increase of risk for mortality

every 2-hrs-prolonged fasting was correlated with a 20% increase of sleeping duration

Marinac CR, Nelson SH, Breen CI et al. JAMA Oncol 2016: 2:1049-1055

Routine Follow-Up Examinations in Asymptomatic Patients

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Tests:	Oxford LoE	GR	AGO
▪ History (specific symptoms)	1a	A	++
▪ Physical examination	1a	B	++
▪ Breast self-examination	5	D	+
▪ Mammography	1a	A	++
▪ Sonography of the breast	2a	B	++
▪ Routine MRI of the breast*	3a	B	+/-
▪ Breast MRI if conventional imaging is inconclusive	3b	B	+
▪ Pelvic examination	5	D	++
▪ DXA-scan at baseline and repeat scan according to individual risk in women with premature menopause or women taking an AI	5	D	+

* Consider in case of increased risk (age < 50 y, HR-neg., diagnostic assessability C/D in mammography + ultrasound)

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	Oxford		
	LoE	GR	AGO
▪ Routine biochemistry (incl. tumor markers)	1a	A	-
▪ Blood tests for monitoring of acute and late toxicities	5	D	+
▪ Ultrasound of the liver	1a	A	-
▪ Bone scan	1a	A	-
▪ Chest X-ray	1a	A	-
▪ CT of chest, abdomen, and pelvis	2a	D	-
▪ Detection of isolated / circulating tumor cells	2a	D	-
▪ PET	2b	B	-
▪ Whole body MRI	2b	B	-

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Background for Toxicity Management

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Tamoxifen:	Cholesterol, Triglycerides, Bilirubin, ALAT, ASAT, gamma-GT, Glucose
Aromatase inhibitors:	Cholesterol, Triglycerides, Bilirubin, ALAT, ASAT, gamma-GT
Anthracyclines:	pro-BNP, possibly Troponin
Trastuzumab:	pro-BNP, possibly Troponin
Checkpoint inhibitors:	Bilirubin, ALAT, ASAT, gamma-GT, Creatinine, TSH, fT3/T4, Myoglobin

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Early Detection of Potentially Curable Events

	Oxford		
	LoE	GR	AGO
Locoregional recurrence (chest wall, in-breast):			
▪ Incidence 7–20% (depending on time of F/U)			
▪ Breast self-examination	5	D	+
▪ Physical examination, mammography & US	1a	A	++
▪ Magnetic resonance imaging (MRI)*	3a	B	+/-

* Consider in case of increased risk (age < 50 y, HR-neg., diagnostic assessability C/D in mammography + ultrasound)

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Early Detection of Potentially Curable Events

	Oxford LoE	Oxford GR	Oxford AGO
Contralateral breast cancer:			
▪ Relative risk: 2.5–5			
▪ Incidence: 0.5–1.0 %/year			
▪ Breast self-examination	5	D	+
▪ Physical examination, mammography & US	1a	A	++
▪ Routine breast MRI*	3b	B	+/-
Male breast cancer: analogous to BC in women**	5	D	+

* Consider in case of increased risk: age < 50 y, HR-neg., diagnostic assessability C/D in mammography + ultrasound.

** See chapter “Breast Cancer Specific Situations”

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Early Detection of Potentially Curable Events

	Oxford		
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Unrelated site carcinoma:			
▪ MDS (RR 10.9), AML (RR 2.6–5.3), Colon RR 3.0; endometrium RR 1.6; ovary RR 1.5; lymphoma RR			
▪ Screening for secondary malignancies according to current guidelines	5	D	++
▪ Pelvic examination and PAP smear	5	D	++
▪ Routine endometrial ultrasound / biopsy	1b	B	-

Follow-Up Care
for invasive / non-invasive Breast Cancer

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Recommendations for asymptomatic pts.

(mod. according to ASCO-ACS recommendations 2016, NCCN 2021, ESMO 2019 and S3-guidelines 2017)

Clinical follow-up		Follow-up*		Screening/ Follow-up
Years after primary therapy		1 2 3	4 5	> 5
History, physical examination, counseling		every 3 months DCIS every 6 months	every 6 months	inv.: every 12 months
Self-examination		monthly		
Imaging modalities and biochemistry		indicated only if complaints, clinical findings, or suspicion of recurrence Monitoring of side effects of therapy		
Mammo-graphy and additional sonography	BCT**	both sides: every 12 months		
	Mastectomy	contralateral every 12 months		
Echocardiography		6,12,24 months and yearly up to 5 years after completion of cardiotoxic therapy, after 5th year, every 5 years and if patient is symptomatic.		

* Continued follow-up visits if still on adjuvant treatment

** In pts after breast-conserving therapy (BCT): First mammography 1 year after initial mammography or at least 6 months after completion of radiotherapy

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Breast Cancer Follow-up
Duration and Breast Nurses

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	Oxford		
	LoE	GR	AGO
▪ **Duration of follow-up**			
▪ up to 5 years	1c	A	++
▪ up to 10 years	1c	A	+
▪ **Surveillance by specialized breast nurses**	2b	B	+/-*

* **Studies recommended**

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Luminal-like, HER2-positive and Triple-negative Breast Cancer Patients

- **Intrinsic typing of breast cancer leads to subgroups with different course of disease. Thus, postoperative surveillance should be adapted to specific time-dependent hazards of recurrence.**
- **ER-positive patients have stable risk over many years requiring long term surveillance.**
- **However, patients with HER2-positive disease and TNBC have more risk in the early phase of follow-up and should therefore receive more intense surveillance in the first years of follow-up.**

Ribelles et al. BCR 2013

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Loco-Regional Recurrence

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Loco-regional Recurrence

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Loco-regional Recurrence
Incidence and Prognosis

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Localization	10-y. incidence (%)	5-y. Overall Survival (%)
Ipsilateral recurrence[1] (post BEO + irradiation)	**10 (2–20)**	**65 (45–79)**
Chest wall[1] (post mastectomy)	**4 (2–20)**	**50 (24–78)**
As above plus supraclavicular fossa[2] Axilla:	**34**	**49 (3-y. OS)**
After **ALND[1]**	**1 (0.1–8)**	**55 (31–77)**
After **SLNE[4]**	1	**93**
Multiple localizations[2]	**16 (8–19)**	**21 (18–23)**

1 Haffty et al. Int J Radiat Oncol Biol Phys 21(2):293-298, 1991;
2 Reddy JP. Int J Radiat Oncol Biol Phys 80(5):1453-7, 201;
3 Karabali-Dalamaga S et al. Br Med J 2(6139):730-733,1978;
4 Andersson Y, et al. Br J Surg 99(2):226-31,2012

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Loco-regional Recurrence Staging

	Oxford		
	LoE	GR	AGO
Examinations before treatment			
▪ Tissue biopsy	3b	B	++
▪ Re-assessment of ER, PR, HER2	3b	B	++
▪ Complete re-staging (slice imaging*)	2b	B	++
▪ „Liquid biopsy“	5	D	-

*** Standard: CT thorax / abdomen and bone scan, in certain cases whole body MRI or ^{18}F FDG PET-CT may be used**

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Risk Factors for another Relapse*

	Oxford		
	LoE	GR	AGO
▪ Tumor size	2a	B	
▪ Multifocality	2a	B	
▪ Localisation	2b	B	
▪ Negative progesterone receptor	3b	B	
▪ High grade	3b	C	
▪ Omitted radiotherapy at first recurrence	3b	C	
▪ Omitted chemotherapy at first recurrence	3b	C	
Parameters of the locally recurrent tumor to define the risk for distant metastasis / survival			
▪ Early (< 2-3 yrs.) vs. late recurrence	2b	B	
▪ LVSI / Grade / ER-neg / positive margins (if ≥ 2 factors positive)	3b	B	
Predictive factors for treatment considerations			
▪ HER2	2b	B	++
▪ ER and PR	2b	B	++

* Risk factors for local relapse see chapter "prognostic factors"

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Ipsilateral Locoregional Recurrence
Surgical Treatment

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	Oxford		
	LoE	GR	AGO
▪ After mastectomy: wide exzision (aim R0)	3b	B	++
▪ After BCS:			
▪ Mastectomy (aim: R0)	3b	B	++
▪ Re-BCS with tumor-free margins (R0) +partial breast irradiation*	2b	B	+
▪ Re-BCS with tumor-free margins (R0)	2b	B	+/-
▪ rcN0:			
▪ Axillary intervention after prior AxDiss	4	C	-
▪ Re-SLNE after prior SLNE	2a	B	-
▪ rfnN+: (Re-)Axillary dissection (R0)	5	C	+
▪ Palliative surgery in M1-situation or R0 not achievable (e.g. pain, ulceration, psychosocial indication)	5	D	+

* After consideration of risk factors for repeated relapse (time from primary diagnosis, tumor size)

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Mastectomy vs. BCS + Partial Breast Irradiation

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- **1327 pts. from 7 European countries with first local recurrence 01/1995 - 06/2017**
- **ME vs. BCS + Brachytherapy**
- **Propensity Score matched control (1:1): clinical and histopathological factors**
- **Primary endpoint: 5-y OS; secondary endpoints: e.g. 5-y-DFS, complications**
- **Median follow-up 75.4 months**
- **No differences in 5-y OS and sec. Endpoints: 5-y -OS: 88 vs. 87%**
- **cumulative incidence 2. recurrence: 2.3 vs. 2.8%**
- **5-y incidence of mastectomy after 1. recurrence 3.1%**

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Hannoun-Levi et al. Int J Radiat Oncol Biol Phys. 2020

Loco-regional Recurrence after R0-Resection Systemic Treatment

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	Oxford LoE	GR	AGO
According to pathohistological re-evaluation of the recurrent tumor (ER, PR, HER2) and in consideration of time from primary diagnosis, pre-treatment, co-morbidities and patient's preference			
▪ Endocrine therapy in endocrine responsive tumors	2b	B	++
▪ Chemotherapy (consider preoperative) in particular in case of first HR-negative relapse	2b	B	+
▪ In case of HER2-positive disease, chemotherapy + HER2-targeted therapy	5	D	+

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Locoregional Recurrence Chemotherapy

- **CALOR Trial update**
  - **n = 163 (2003–2010), median follow-up of 4.9 years, all R0 resection**
  - **5-y DFS: 69% (95% CI 56–79) with chemotherapy vs. 57% (44–67) without chemotherapy (hazard ratio 0.59 [95% CI 0.35–0.99]; p = 0.046): 24 (28%) patients vs. 34 (44%).**
  - **Adjuvant chemotherapy was significantly more effective in ER negative disease ($p_{interaction}$= 0.046).**
  - **Multivariate analysis: predictors of survival**
  - **chemotherapy for primary cancer (HR 3.55, p = 0.03)**
  - **interval from primary surgery (HR 0.87, p = 0.05)**

Wapnir IL et al. Annals of Surgical Oncology, February 2017, Volume 24, Issue 2, pp 398–406

Loco-regional Recurrence Chemotherapy

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- **CALOR Trial update**

	ER-positive			ER-negative		
Endpoint	**CT**	**No-CT**	**HR (95% CI)**	**CT**	**No-CT**	**HR (95% CI)**
10-yr DFS	**50%**	**59%**	**1.07 (0.57 – 2.00)**	**70%**	**34%**	**0.29 (0.13 – 0.67)**
	Interaction P-Value =0.013					
10-yr OS	**76%**	**66%**	**0.70 (0.32 – 1.55)**	**73%**	**53%**	**0.48 (0.19 – 1.20)**
	Interaction P-value =0.53					
10-yr BCFI	**58%**	**62%**	**0.94 (0.47 – 0.85)**	**70%**	**34%**	**0.29 (0.13 – 0.67)**
	Interaction P-value = 0.034					

Wapnir IL et al. Annals of Surgical Oncology, February 2017, Volume 24, Issue 2, pp 398–406

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Locoregional Recurrence in Case of R1-Resection / Inoperability – Systemic Treatment

	Oxford		
	LoE	GR	AGO
According to pathohistological re-evaluation of the recurrent tumor (ER, PR, HER2)			
▪ **Endocrine based therapy in endocrine responsive tumors corresponding to metastatic disease**	2b	B	++
▪ **Chemotherapy and targeted therapy (pre- or postoperative) corresponding to metastatic disease**	2b	B	++

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Ipsilateral Recurrence after BCT Radiotherapy

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	Oxford		
	LoE	GR	AGO
After Re-BCS			
▪ Whole breast irradiation (in case of no prior adjuvant radiotherapy)	3b	C	++
▪ Repeated (2.)-breast irradiation (Partial breast irradiation, brachytherapy/ external beam RT, in case of prior adjuvant radiotherapy)	2b	B	+
After mastectomy			
▪ Radiation of chest wall +/- regional lymph nodes (in case of no prior adjuvant radiotherapy)	2b	B	+
▪ Radiation dose escalation (+ 10 %)	3b	C	-
▪ Repeated (2.) irradiation			
▪ in case of R0 resection (according to risk factors, preferentially with hyperthermia	1b	B	+/-
▪ in case of R1/R2 reception (e.g. as brachytherapy) with hyperthermia	1b	B	+

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Loco-Regional Recurrence
Treatment Options in Non-Curative Cases

	Oxford		
	LoE	GR	AGO
▪ Concomitant radio-chemotherapy	3b	C	+
▪ Hyperthermia (in centers listed on DKG website)			
▪ In combination with radiotherapy	1b	B	+
▪ In combination with chemotherapy	4	C	+/-
▪ Intra-arterial chemotherapy	4	C	+/-
▪ Photodynamic therapy	4	C	+/-
▪ Electrochemotherapy	3b	C	+/-

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Endocrine based and targeted Therapy of Metastatic Breast Cancer

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Endocrine Therapy of Metastatic Breast Cancer

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Endocrine Therapy of Metastatic Breast Cancer

Indication

Oxford LoE: 1a **GR: A** **AGO: ++**

Endocrine-based therapy is first line treatment in patients with metastatic breast cancer and positive (or unknown) hormone receptor (HR) status.

Exception: imminent organ failure

Caveat: HR may change during the course of disease.
Histology of recurrent site should be obtained whenever possible

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Comparison ER / PR and HER2 Metastasis vs. Primary Tumor (n = 5.521)

Meta-analysis based on 39 (mostly retrospective) analyses, exclusively comparing primary tumor and metastasis (no lymph nodes):

Pooled discordance proportions were:

- 19,3% (95 % CI 1⁄4 15.8% to 23.4%) for ER
- 30,9% (95% CI1⁄4 26.6% to 35.6%) for PR
- 10,3% (95% CI 1⁄4 7.8% to 13.6%) for HER2

Pooled proportions of tumors shifting from positive to negative

- 22.5% (95% CI = 16.4% to 30.0%) for ER
- 49.4% (95% CI = 40.5% to 58.2%) for PR
- 21.3% (95% CI = 14.3% to 30.5%)) for HER2

Pooled proportions of tumors shifting from negative to positive

- 21.5% (95% CI = 18.1% to 25.5%) for ER
- 15.9% (95% CI = 11.3% to 22.0%) for PR
- 9.5% (95% CI = 7.4% to 12.1%) for HER2

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Endocrine Therapy
General Considerations

- **Within all lines of treatment, treatment options should consider prior endocrine therapies, age and comorbidities as well as the respective approval status.**

- **Premenopausal patients treated with GnRH analogues or after ovarectomy can be treated like postmenopausal patients.**

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Metastatic Breast Cancer
Endocrine Resistance

Primary endocrine resistance:

- **Relapse within 2 years of adjuvant endocrine treatment (ETx)**
- **Progressive disease within first 6 months of first-line ETx for MBC**

Secondary (required) endocrine resistance:

- **Relapse while on adjuvant ETx but after the first 2 years or a relapse within 12 months after completing adjuvant ETx**
- **PD ≥ 6 months after initiation of ET for MBC**

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Endocrine Therapy in Premenopausal Patients with HER2-Negative Metastatic Breast Cancer

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	Oxford		
	LoE	GR	AGO
▪ GnRHa + Fulvestrant + CDK4/6i	2b	B	++
▪ GnRHa + AI + Ribociclib	1b	B	++
▪ GnRHa + AI + Palbociclib / Abemaciclib	3b/5	C	+
▪ GnRHa + Tamoxifen + Palbociclib / Abemaciclib	2b	B	+/-
▪ GnRHa + Tamoxifen	1a	A	+
▪ Tamoxifen	2b	B	+/-
▪ GnRHa + AI (first + second line)	2b	B	+
▪ GnRHa + Fulvestrant	1b	B	+
▪ Aromataseinhibitors without OFS	3	D	- -

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Endocrine Mono-Therapy in Postmenopausal Patients with HER2-Negative Metastatic Breast Cancer

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	Oxford		
	LoE	GR	AGO
▪ Fulvestrant 500 mg	1b	B	+
▪ Aromatase inhibitor*	1a	A	+
▪ Tamoxifen	1a	A	+
▪ Fulvestrant 250 mg + Anastrozole	1b	B	+/-
▪ Repeat prior treatments	5	D	+/-

* There is no evidence for superiority of a single aromatase inhibitor. As everolimus plus exemestane is indicated after AI treatment, a non-steroidal AI should be used in first line.

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Endocrine-Based Treatment Options for Postmenopausal Patients with HER2-Negative Metastatic Breast Cancer

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	Oxford		
	LoE	GR	AGO
▪ CDK4/6-Inhibitor (Abemaciclib, Palbociclib, Ribociclib)			
▪ + non-steroidal AI	1a	A	++
▪ + Fulvestrant	1a	A	++
▪ Abemaciclib monotherapy	3	C	+/-
▪ Alpelisib + Fulvestrant (PIK3CA mutated)	1b	B	+
▪ Everolimus			
▪ + Exemestane	1b	A	+
▪ + Tamoxifen	2b	B	+
▪ + Letrozole	2b	B	+/-
▪ + Fulvestrant	2b	B	+
▪ CDK4/6-Inhibitor beyond progression	3b	C	+/-
▪ CDK4/6-Inhibitor switch based on toxicity	5	D	+/-

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CDK4/6 Inhibitors in First-line Studies

Study name	Paloma-2	Monarch-3	Monaleesa-2	Monaleesa-7
Treatment arms	Palbociclib / placebo with letrozole	Abemaciclib / placebo with nonsteroidal AI	Ribociclib / placebo with letrozole	Ribociclib / placebo with tamoxifen or non-steroidal aromatase inhibitor, all with goserelin
Patients	666	493	668	672
Menopausal status	postmenopausal	postmenopausal	postmenopausal	premenopausal
Progression-free survival (months, m)	27.6 vs. 14.5 m (+ 13.1 m) (HR 0.563)	28.2 vs. 14.8 m (+ 13.4 m) (HR 0.540)	25.3 vs. 16.0 m (+ 9.3 m) (HR 0.568)	23.8 vs. 13.0 m (+ 10.8 m) (HR 0.55)
Overall survival (months, m)	not reported	not reported	63.9 vs. 51.4 m (+ 12.5 m) (HR 0.76)	58.7 vs. 48.0 m (+ 10.7 m) (HR, 0.76)

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Endocrine Therapy in Postmenopausal HER2-Negative Metastatic Breast Cancer in Combination with Bevacizumab

	Oxford		
	LoE	GR	AGO
▪ Maintenance bevacizumab plus endocrine therapy after remission with chemotherapy and bevacizumab	1b	B	+/-
▪ Bevacizumab plus endocrine treatment as first line therapy for advanced disease	1b	B	+/-

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PARP Inhibitors in Patients with HER2-negative, gBRCA-Mutant, Metastatic Breast Cancer

- **Olaparib**

Oxford		
LoE	GR	AGO
1b	A	++

- **Talazoparib**

Oxford		
LoE	GR	AGO
1b	A	++

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HER2-Positive and HR-Positive Metastatic Breast Cancer

Endocrine Therapy in Postmenopausal HER2-Positive Metastatic Breast Cancer Patients

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	Oxford		
	LoE	GR	AGO
▪ Anastrozole + trastuzumab	1b	B	+/-
▪ Letrozole + trastuzumab	2b	B	+/-
▪ Letrozole + lapatinib	1b	B	+/-
▪ Fulvestrant + lapatinib	1b	B	+/-
▪ Abemaciclib + fulvestrant + trastuzumab (after T-DM1)	2b	B	+/-
▪ Aromatase inhibitors + trastuzumab / pertuzumab*	2b	B	+/-

Poor efficacy of endocrine therapy alone.
Consider induction chemotherapy + anti-HER2-therapy (followed by endocrine + anti-HER2-therapy as maintenance therapy)!

* **Study participation recommended**

Concomitant or Sequential Endocrine-Cytostatic Treatment

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	Oxford		
	LoE	GR	AGO
■ **Concomitant endocrine-cytotoxic treatment**	1b	A	-
▪ May increase response rate and progression free interval but not overall survival			
▪ May increase toxicity			
■ **Endocrine maintenance therapy after chemotherapy +/- anti-HER2 therapy-induced response +/- anti HER2 therapy**	2b	B	+
▪ Increases progression free interval			

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Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer

*** Substances without published evidence based on at least one phase III/II b trial were omitted**

Chemotherapy ± Targeted Drugs in Metastatic Breast Cancer

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Metastatic Breast Cancer (mBC)
Disease-Free and Overall Survival

	Oxford LoE
▪ In MBC, an increase in survival over time has been shown in clinical trials	1b
▪ Multiple lines of sequential therapy are beneficial (at least same efficacy, less toxicity)	1b
▪ Targeted drugs in combination with chemotherapy can induce substantial survival benefits	1b

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Metastatic Breast Cancer
Endocrine Resistance

Primary endocrine resistance:

- **Relapse within 2 years of adjuvant endocrine treatment (ET)**
- **Progressive disease within first 6 months of first-line ET for MBC**

Secondary (required) endocrine resistance:

- **Relapse while on adjuvant ET but after the first 2 years or a relapse within 12 months after completing adjuvant ET**
- **PD ≥ 6 months after initiation of ET for MBC**

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Treatment of Metastatic Breast Cancer
Predictive Factors for Response

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Therapy	Factor	Oxford LoE	Oxford GR	AGO
▪ Endocrine therapy	ER / PR (prim. tumor, better: metastasis)	1a	A	++
	Response to prior therapy	2b	B	++
	Autocrine receptor mutation (ESR1)	1b#	B	+
▪ Alpelisib	PIK3CA mutation (prim. tumor, metastases, plasma)	1b	A	+
▪ Chemotherapy	Response to prior therapy	1b	A	++
▪ Anti-HER2-therapy	HER2 (prim. tumor, better: metastasis)	1a	A	++
▪ Checkpoint-Inhibitors	PD-L1 positivity# (PD-L1ic, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
▪ PARP-Inhibitors	gBRCA1/2-mutation	1a	A	++
▪ Any therapy	CTC monitoring	1b	A	+*

* In clinical trials

\# see chapter „pathology“

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Metastatic Breast Cancer
Treatment Rationale

Oxford LoE: 1b **GR: A** **AGO: ++**

- **Mono-Chemotherapy:**
  - **Favorable therapeutic index***
  - **Indicated in case of**
    - **Slow, not life-threatening progression**
    - **Insensitivity to or progression during endocrine therapy**

- **Poly-Chemotherapy:**
  - **Unfavorable therapeutic index**
  - **Indicated to achieve rapid remission in the case of**
    - **Extensive symptoms**
    - **Visceral crisis (ABC-5 definition)**
  - **Survival benefit in comparison to sequential single-agent therapies with the same compounds not proven**

* **Therapeutic index evaluates overall efficacy, toxicity, and impact on quality of life**

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Definition of Visceral Crisis (ABC 5)

- **Visceral crisis** is defined as severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy.

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Metastatic Breast Cancer
Systemic Therapy

GR: A **AGO: ++**

- **Evaluate compliance before and during therapy (especially in patients of older age, with reduced performance status, or significant co-morbidities and secondary primaries)**
- **Assess subjective and objective toxicities, symptoms, and performance as well as quality of life (QoL) status repeatedly**
- **Use dosages according to published protocols**
- **Assess tumor burden at baseline and approx. every 2 months, i.e. every 2-4 cycles. In slowly growing disease, longer intervals are acceptable.**

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Metastatic Breast Cancer
Duration of Cytotoxic Therapy

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	LoE	GR	AGO
▪ As long as therapeutic index* remains positive	1a	A	++
▪ Treatment until progression	2b	B	+
▪ Treatment until best response	2b	B	+/-
▪ Change to alternative regimen before progression	2b	B	+/-
▪ Stop therapy in case of	1c	A	++
▪ Progression			
▪ Non tolerable toxicity			

* Therapeutic index evaluates overall efficacy, toxicity, and impact on quality of life

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Chemotherapy in mBC
General Considerations - Drug Selection

AGO: ++

- **Participation in clinical trials is recommended**
- **The choice of systemic therapy depends on:**
  - **ER / PR, HER2, PD-L1 status, gBRCA status (p.r.n. sBRCA status, p.r.n. PALB2), PIK3CA, p.r.n. MSI, NTRK, p.r.n. mESR1 (clinical actionability of molecular targets)**
  - **Prior therapies (and their toxicities)**
  - **Disease-free interval after end of adjuvant treatment**
  - **Progression-free interval achieved by the previous line of therapy**
  - **Disease aggressiveness and localization of metastases**
  - **Estimated life expectancy**
  - **Co-morbidities (including organ dysfunction)**
  - **Patient preferences and expectations**

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mBC HER2-negative / HR-positive 1st-Line Chemotherapy*

	Oxford LoE	Oxford GR	AGO
Monotherapy:			
Paclitaxel (q1w), Docetaxel (q3w)	1a	A	++
Doxorubicin, epirubicin, Peg-liposomal doxorubicin (A_{lip})	1b	A	++
Vinorelbine	3b	B	+
Capecitabine	2b	B	+
Nab-paclitaxel	2b	B	+
Polychemotherapy:			
A + T	1b	A	++
Paclitaxel + capecitabine	2b	B	+
Docetaxel + capecitabine after adj. A	1b	A	+
T + gemcitabine after adj. A	2b	B	++
A + C or A_{lip} + C	1b	B	++

* In ER pos. patients only if endocrine therapy is not indicated or should be discontinued

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mBC HER2-negative / HR-positive: Chemotherapy after Anthracycline Treatment*

	Oxford		
	LoE	GR	AGO
▪ Paclitaxel q1w	1a	A	++
▪ Docetaxel q3w	1a	A	++
▪ Capecitabine	2b	B	++
▪ Nab-paclitaxel	2b	B	++
▪ Peg-liposomal doxorubicin	2b	B	+
▪ Eribulin	1b	B	+
▪ Vinorelbine	2b	B	+
▪ Docetaxel + Peg-liposomal doxorubicin	1b	B	+/-

* Independent whether anthracyclines were used in adjuvant or 1st line metastatic situation

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mBC HER2-negative / HR-positive: Chemotherapy after Taxane and Anthracycline Treatment

	Oxford		
	LoE	GR	AGO
▪ Capecitabine	2b	B	++
▪ Eribulin	1b	B	++
▪ Vinorelbine	2b	B	++
▪ (Peg)-liposomal Doxorubicin	2b	B	+
▪ Taxane re-challenge*	2b	B	+
▪ Anthracycline re-challenge*	3b	C	+
▪ Metronomic therapy (e.g. cyclophos. + MTX)	2b	B	+
▪ Gemcitabine + Cisplatin / Carboplatin	2b	B	+/-

* At least one year disease-free after adjuvant treatment

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Triple negative mBC PD-L1+
Independent of germline mutation in *BRCA 1/2*

	Oxford LoE	Oxford GR	Oxford AGO
▪ Pembrolizumab + Chemotherapy* first-line PD-L1 CPS ≥ 10# (if TFI ≥ 6 months)	1b	B	++
▪ Atezolizumab + Nab-Paclitaxel first-line PD-L1 IC ≥ 1# (if TFI ≥ 12 months)	1b	B	+
▪ Atezolizumab + Paclitaxel first-line PD-L1 IC ≥ 1#	1b[a]	B	-
▪ Pembrolizumab monotherapy (after chemotherapy w/o previous immune oncology based therapy) in case of CPS ≥ 20#	1b[a]	B	+/-

(see chapter „Pathology“)
***** nab-Paclitaxel or Paclitaxel or Carboplatin / Gemcitabine
TFI = therapy-free interval

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Triple negative mBC independent of PD-L1 Status and Germline Mutations in *BRCA 1/2*

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	Oxford		
	LoE	GR	AGO
▪ Sacituzumab Govitecan (≥ 2nd line)	1b	B	++
▪ Bevacizumab 1st line in combination with			
▪ Paclitaxel (weekly)	1b	B	+
▪ Capecitabine	1b	B	+
▪ nab-Paclitaxel	2b	B	+/-
▪ Carboplatin (vs. Docetaxel)	1b	B	+/-
▪ Gemcitabin / Cisplatin (vs. Gem / Pac)	1b	A	+
▪ Nab-Paclitaxel / Carboplatin (vs. Carbo / Gem)	2b	B	+

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Treatment Options in mBC with BRCA 1/2 or gPALB2 Mutation

	Oxford LoE	Oxford GR	AGO
▪ Standard of care i.e. gBRCA 1/2-negative disease			++
▪ Carboplatin (vs. docetaxel) (if Platinum-naive)	1b	B	+
▪ PARP-Inhibitors (HER2-negative mBC)			
▪ HER2-negative, g*BRCA 1/2* mutation			
▪ Olaparib	1b	A	++
▪ Talazoparib	1b	A	++
▪ s*BRCA* 1/2 mutation			
▪ Olaparib	2b	B	+/-
▪ *gPALB2* mutation			
▪ Olaparib	2b	B	+/-

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HER2-pos. mBC

1st line without Pretreatment or after Trastuzumab

	Oxford		
	LoE	GR	AGO
Primary metastatic			
▪ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
▪ Paclitaxel (weekly) + Trastuzumab + Pertuzumab	2b	B	++
▪ nab-Paclitaxel + Trastuzumab + Pertuzumab	2b	C	+
After Trastuzumab in the adjuvant setting (TFI > 6 months)			
▪ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
▪ Paclitaxel (weekly) + Trastuzumab + Pertuzumab	2b	B	++
▪ nab-Paclitaxel + Trastuzumab + Pertuzumab	2b	C	+
▪ Vinorelbin + Trastuzumab + Pertuzumab	3b	B	+
After pretreatment with only Trastuzumab in the adjuvant setting (TFI < 6 months)			
▪ Trastuzumab Deruxtecan (T-DXd)	5	D	+
▪ T-DM1	2b	B	+/-
▪ Chemotherapy + Trastuzumab + Pertuzumab	5	D	+/-

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HER2-pos. mBC

1st line after Trastuzumab / Pertuzumab +/- TDM-1

	Oxford		
	LoE	GR	AGO
After Trastuzumab / Pertuzumab in the (neo-)adjuvant setting			
▪ Re-induction CTx + Trastuzumab + Pertuzumab (TFI > 6-12 months)	5	D	++
▪ Trastuzumab Deruxtecan (T-DXd) (TFI < 6-12 months)	5	D	+
▪ T-DM1 (TFI < 6-12 months)	5	D	+/-
▪ Capecitabine + Lapatinib	1b	B	+/-
After Trastuzumab / Pertuzumab in the (neo-)adjuvant setting and T-DM1 in the post-neoadjuvant setting			
▪ Re-induction CTx + Trastuzumab + Pertuzumab (TFI > 6-12 months)	5	D	+
▪ T-DXd	5	D	+
▪ Tucatinib + Capecitabine + Trastuzumab	5	D	+
▪ Capecitabine + Lapatinib	5	D	+/-

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HER2-pos. mBC

2nd line

	Oxford		
	LoE	GR	AGO
▪ Trastuzumab Deruxtecan (T-DXd)	1b	B	++
▪ Tucatinib + Trastuzumab + Capecitabine (after pretreatment with T-DM1)	1b	B	++
▪ T-DM 1	1b	A	+
▪ Capecitabine + Lapatinib / Trastuzumab	1b	B	+/-
▪ TBP: 2nd line Chemotherapy* + Trastuzumab / Pertuzumab	2b	B	+/-
▪ Trastuzumab + Pertuzumab	2b	B	+/-
▪ Trastuzumab + Lapatinib (HR neg.)	2b	B	+/-

* e.g. Taxane; Vinorelbin; Taxane / Carboplatin; Capecitabine; Capecitabin / Docetaxel (Toxizität!)

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HER2-pos. mBC

≥ third-line

Depending on the previous therapy (substance)	Oxford LoE	Oxford GR	Oxford AGO
▪ Tucatinib + Trastuzumab + Capecitabine	1b	B	++
▪ Trastuzumab Deruxtecan	1b	B	+
▪ T-DM 1	1b	A	+
▪ Capecitabine + Trastuzumab / Lapatinib	1b	B	+
▪ Capecitabine + Neratinib	1b	B	+
▪ Margetuximab + Chemotherapy	1b	B	+/-
▪ Experimental anti-HER2 regimens	5	D	+

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HER2-pos. mBC

No Chemotherapy Possible or Desired

	Oxford		
	LoE	GR	AGO
▪ Trastuzumab + Aromatase inhibitor (HR+)	2b	B	+/-
▪ Lapatinib + Aromatase inhibitor (HR+)	2b	B	+/-
▪ Aromatase inhibitor + Trastuzumab + Pertuzumab (HR+)	2b	B	+
▪ Abemaciclib + Trastuzumab + Fulvestrant	2b[a]	B	+/-
▪ Trastuzumab + Pertuzumab	2b	B	+/-
▪ Trastuzumab + Lapatinib (HR neg.)	2b	B	+
▪ Trastuzumab mono	2b	B	+/-

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Osteooncology and Bone Health

Osteooncology and Bone Health

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Bisphosphonates in Metastatic Breast Cancer

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	Oxford		
	LoE	GR	AGO
▪ Therapy of hypercalcemia	1a	A	++
▪ Reduction of skeletal events / complications	1a	A	++
▪ Reduction of bone pain	1a	A	++
▪ Increasing bone pain-free survival	1a	A	++
▪ Treatment beyond osseous progression	5	D	++
▪ Use of bone resorption marker for therapy monitoring	5	D	-
▪ Bisphosphonates alone for pain control	5	D	-

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Denosumab in Metastatic Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ Therapy of hypercalcemia	1a	A	++
▪ Reduction of skeletal events / complications	1a	A	++
▪ Reduction of bone pain	1a	A	++
▪ Increasing bone pain-free survival	1b	A	++
▪ Treatment beyond progression	5	D	+
▪ Progression while on bisphosphonates	4	C	+/-
▪ Use of bone resorption markers for therapy monitoring	5	D	-
▪ Denosumab alone for pain control	5	D	-

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Longer-Interval vs. Standard Dosing of Bone-Targeted Agents

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- **CALGB 70604 trial: n = 1822 patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma, 795 completed the study**

  SRE after 2 years: 29.5% zoledronic acid every 4 weeks
  28.6% zoledronic acid every 12 weeks

- **OPTIMIZE-2 trial: n = 416 women with metastatic breast cancer, prior exposure to zoledronate or pamidronate for approx. 1 year or more**

  SRE after 1 year: 22.0% zoledronic acid every 4 weeks
  23.2% zoledronic acid every 12 weeks

- **REaCT-BTA trial: n = 263 metastatic cancer (160 breast, 103 prostate)**

  Denosumab (n = 148), zoledronate (n = 63) or pamidronate (n = 52) q4w vs. q12w

  Primary endpoint (non-inferiority of q12w vs. q4w in HRQoL) reached

  Cumulative SSE after 1 year: 7.6% bone-targeted agent every 4 weeks
  16.6% bone-targeted agent every 12 weeks (p = 0.27)

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Bone Modifying Agents for the Therapy of Bone Metastases

	Oxford LoE	Oxford GR	AGO
▪ Clodronate PO 1600 mg daily	1a	A	++
▪ Clodronate IV 1500 mg q3w / q4w	1a	A	++
▪ Pamidronate IV 90 mg			
▪ q3w / q4w	1a	A	++
▪ q12w	2b	B	+/-
▪ Ibandronate IV 6 mg q3w / q4w	1a	A	++
▪ Ibandronate PO 50 mg daily	1a	A	++
▪ Zoledronate IV 4 mg			
▪ q4w	1a	A	+
▪ q12w	1a	A	++
▪ Denosumab 120 mg SC			
▪ q4w	1a	A	++
▪ q12w	2b	B	+/-
▪ Other dosing or schedules, e.g. derived from adjuvant studies or therapy of osteoporosis	5	D	--
▪ Planned sequential therapy with multiple agents	2b	B	+/-

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Skeletal Metastases
Treatment with Radionuclids

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	Oxford		
	LoE	GR	AGO
▪ **Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain**	1b	B	+
▪ ^{186}Rhenium-hydroxyethyliden-diphosphonat	2b	B	+
▪ ^{153}Samarium	1b	B	+
▪ ^{89}Strontium	1b	B	+
▪ ^{223}Radium	2b	C	+
▪ ^{177}Lu-EDTMP	2b	C	+
▪ ^{188} Rhenium-HEDP	1b	B	+

Cave: the potential benefits should be weighed against the risk of myelosuppression with pancytopenia

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Metastatic Bone Disease of the Spine

Indications for surgery

Oxford LoE: 2b **GR: C** **AGO: ++**

- **Spinal cord compression**
  - **With progressive neurological symptoms**
  - **With pathological fractures**
- **Instability of the spine**
- **Lesions in pre-irradiated parts of the spine**

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Bone Metastases Acute Spinal Cord Compression / Paraplegia

	Oxford		
	LoE	GR	AGO
▪ **Decompression surgery, reduction of tumor volume, stabilization surgery (< 24 h) and irradiation of the spine**	2b	C	++
▪ **Irradiation of the spine (< 24 h)** ▪ Radiatiotherapy regimen (1 x 8-10 Gy vs. multiple fractions) depending on prognosis, performance status and patient‘s preference	3b	C	++
▪ **Immediate start of treatment**	1c	D	++
▪ **Steroids (start at first symptoms)**	2a	C	+

Clinical trials have included patients with different tumor entities!

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Surgery for Bone Metastases
Technical Aspects

Spine and limbs

Oxford LoE: 3b **GR: C** **AGO: +**

- Marrow splints
- Plate osteosynthesis
- Compound osteosynthesis (replacement by PMMA and osteosynthesis)
- Vertebral replacement by titanspacer
- Tumor-Endoprothesis
- Vertebroplasty / Kyphoplasty +/- thermoablation of the tumor
- Kypho-IORT (in studies only)*
- Resection of involved bone in oligometastatic disease (sternum, ribs, vertebrae)

* **Study participation recommended**

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Metastatic Bone Disease: Radiotherapy (RT)

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	Oxford		
	LoE	GR	AGO
Bone metastases			
▪ With fracture risk	1a	B	++
▪ With functional impairment	1a	B	++
▪ With bone pain	1a	B	++
Single dose RT = fractionated RT	2a	B	++
▪ With neuropathic bone pain	1b	B	++
▪ Asymptomatic isolated bone metastasis	5	D	+/-
▪ Reduction of radiation induced pain flare-up by dexamethasone	1b	B	+
▪ Radiotherapy in combination with hyperthermia	2b	B	+/-

Limited studies included breast cancer patients!

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Metastatic Bone Disease
Recurrent Bone Pain after RT

	Oxford		
	LoE	GR	AGO
Recurrent bone pain in pre-irradiated parts of skeleton			
▪ Single dose RT *	3b	C	++
▪ Fractionated RT *	3b	C	++
▪ Radionuclide therapy	2b	B	+
▪ Magnetic resonance-guided focused ultrasound	1b	B	+
▪ Radiofrequency ablation	4	C	+
▪ Cryoablation	4	C	+

* **Dose and fractionation depending on location, interval from first RT, and dose and fractionation of first radiotherapy.**

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Side-Effects and Toxicity: Bisphosphonates (BP) and Denosumab (Dmab)

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	LoE
▪ **Renal function deterioration due to IV-aminobisphosphonates**	**1b**
▪ **Osteonecrosis of the jaw (ONJ) mostly under IV-BP and Dmab therapy (1.4 – 2.8% / 1.3 – 3.2%)**	**1b**
▪ **Association with (simultaneous) anti-angiogenetic therapies**	**3b**
▪ **Severe hypocalcemia (Dmab > BPs)**	**1b**
▪ **Acute Phase Reaction (IV Amino-BPs, Dmab) 10–30%**	**1b**
▪ **Gastrointestinal side effects (oral BPs) 2–10%**	**1b**
▪ **Atypical femur fractures** (absolute risk of 11 per 10,000 person years of BP use)	**2b**
▪ **Extremely rare: Uveitis / Scleritis under BP treatment**	**4**

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Frequent side effects under treatment with BPs / Denosumab

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Drug	Acute phase-reaction	Kidney Tox.	Upper GI	Diarrhea	ONJ	
Clodronate 1500 IV	0	+	0	0	0	Non-Amino.
Clodronate 1600 PO	0	0	+	+	0	Non-Amino.
Ibandronate 50 mg PO	0	0	+	0	0	Aminobisph.
Ibandronate 6 mg IV	+	0	0	0	+	Aminobisph.
Zoledronate 4 mg IV (q4w or q12w)	+	+	0	0	+	Aminobisph.
Pamidronate 90 mg IV	+	+	0	0	+	Aminobisph.
Zoledronate 4 mg IV q6m	+	0	0	0	0	Aminobisph.
Denosumab 120 mg SC q4w	+	0	0	+	+	

Cave: Hypocalcemia under antiresorptive therapy in pts with bone metastases!

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Recommendations for Prevention of Osteonecrosis of the Jaw (ONJ)

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Oxford LoE: 2a **GR: A** **AGO: ++**

- **During bisphosphonate or denosumab treatment, avoid any elective dental procedures involving jaw bone manipulations during treatment with bisphosphonates or denosumab (LoE 2a, recommendation grade A)**
- **Optimize dental status before start of bisphosphonate or denosumab treatment (LoE 2a, recommendation grade A)**
- **Inform patients about ONJ risk and educate about early symptom reporting**
- **In case of high risk for ONJ, use oral bisphosphonate**
- **Good oral hygiene, limiting of alcohol intake and stopping smoking should be recommended**
- **In adjuvant bisphosphonate therapy, ONJ was rare (< 1%)**

ASORS Evaluation
https://www.onkosupport.de/asors/content/e4126/e1743/e1861/e1862/e4628/LaufzettelAGSMOFarbefinal.pdf

Adjuvant Bone Targeted Therapy for Improvement of Prognosis

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	Oxford		
	LoE	GR	AGO
▪ **Clodronate (oral)**			
▪ Postmenopausal patients	1a	A	+
▪ Premenopausal patients	1a	B	+/-
▪ **Aminobisphosphonate (IV or oral)**			
▪ Postmenopausal patients	1a	A	+
▪ Premenopausal patients	1a	B	+/-
▪ **Denosumab (6 x 120 mg/3–4w + 14 x 120 mg/3m)**			
▪ Postmenopausal patients Stage II and III	1b	B	-
▪ **Denosumab (60 mg SC q6m)**			
▪ Postmenopausal patients undergoing AI therapy	1b	B	+/-

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Dosage of Adjuvant Bisphosphonates for Improvement of Survival

- **Non-Aminobisphosphonates:**
  - **Clodronate PO 1600 mg/d (Bonefos / Clodronic acid)**
  - **Clodronate PO 1040 mg/d (Ostac / Clodronic acid)**

- **Aminobisphosphonates:**
  - **Zoledronate IV 4 mg/6 m (Zometa / Zoledronic acid)**
  - **Ibandronate PO 50 mg/d (Bondronat / Ibandronic acid)**
  - **Pamidronate PO (orally not available in most countries)**
  - **Risedronate PO 35 mg/w*(Actonel / Risedronic acid)**
  - **Alendronate PO 70 mg/w (Fosamax / Alendronic acid)**
  - **Optimal duration yet to be defined; in adjuvant studies duration of BP treatment varied from 2–5 years**

Aminobisphosphonates include:
Zoledronic acid (65%), oral ibandronate (24%), oral pamidronate (8%),
oral risedronate (2%), oral alendronate (1%) (data from EBCTCG meta-analysis)

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Reduction in Bone Density of Individual Agents

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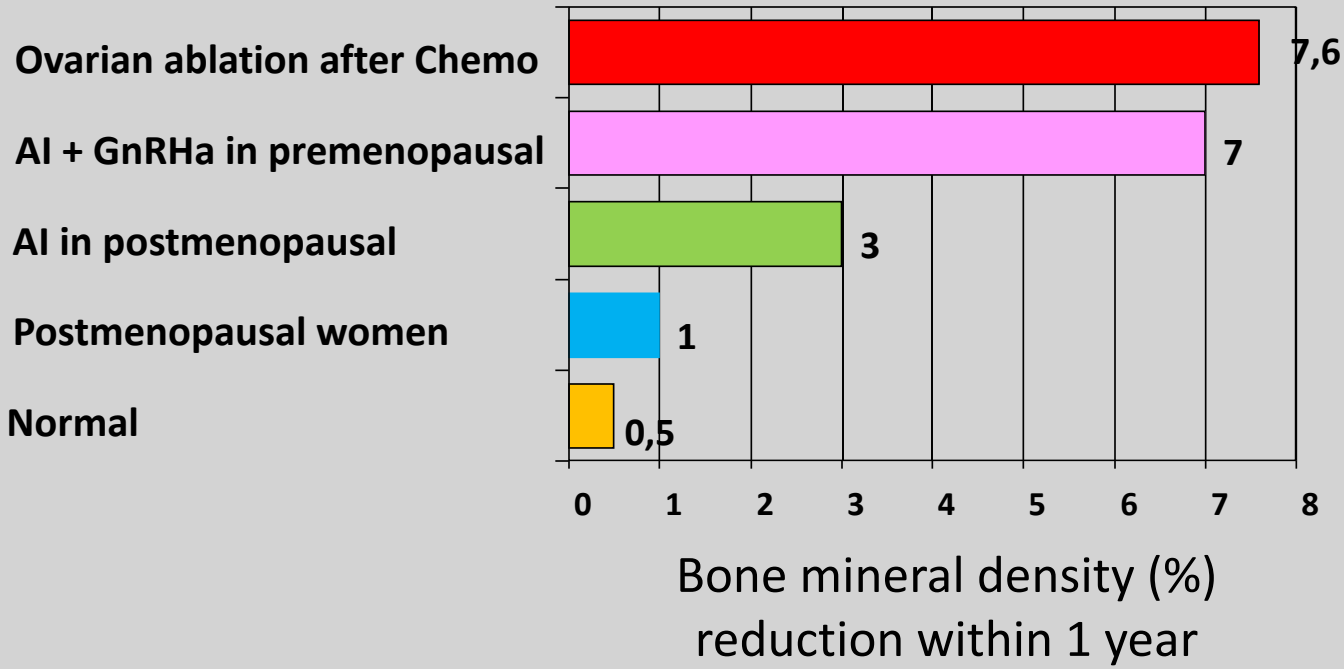

(1) Kanis JA Osteoporosis 22, 1997, (2) Gnant M SABCS 2004, (3) Shapiro CL, JCO 19:3305, 2001

Risk of Osteoporosis and Tamoxifen
(Fracture Risk)

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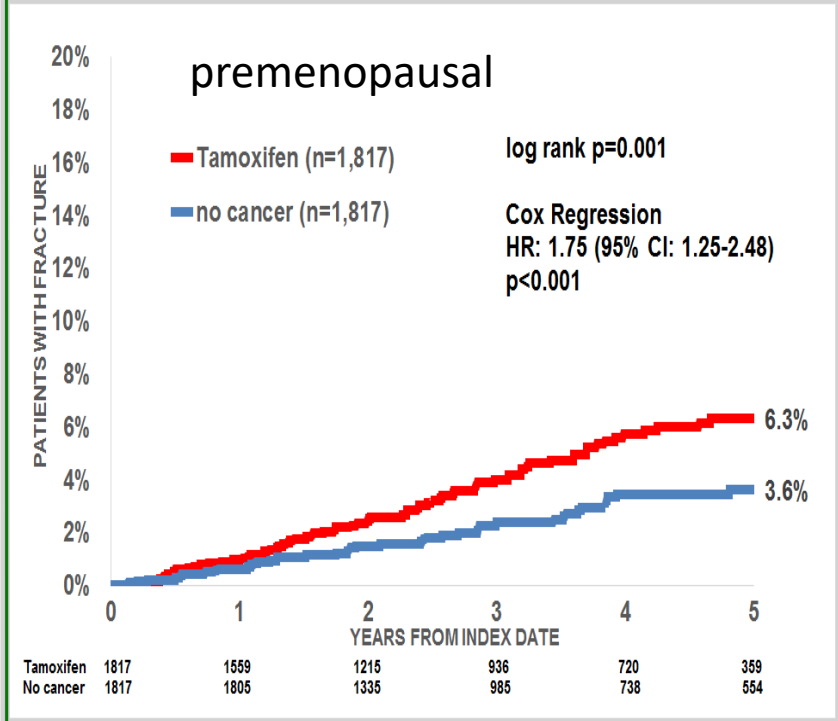

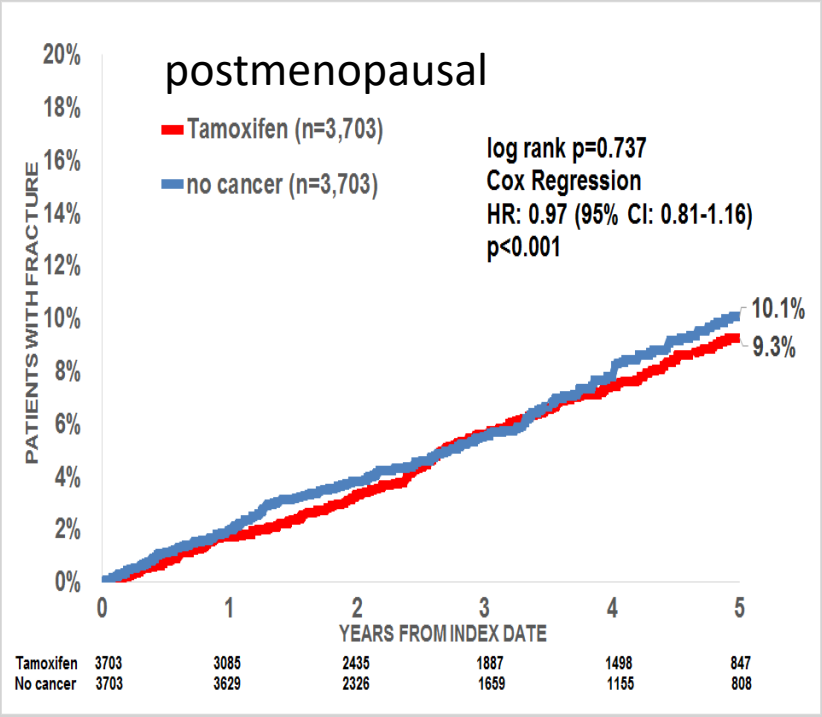

Kyvernitakis et al Osteoporosis Int 2018

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Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

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	Oxford LoE	Oxford GR	AGO
Bisphosphonates			
Therapy	1b	B	++
Prevention (2–5 yrs)	1b	A	+
after discontinuation of Denosumab (1-2 years)	3c	C	+
Denosumab			
Therapy	1b	B	++
Prevention (up to max. 3 yrs)	1b	A	+/-
Hormone replacement therapy	5	D	-
Clinical risk assessment for osteoporosis at baseline according to DVO S3 - guidelines			++
DXA-Scan at baseline in pts with endocrine therapy and / or premature menopause	5	D	+
Antiresorptive therapy according to DVO S3 - guidelines			++
Repeat DXA-scan based on risk	5	D	+

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Further recommendations (based on DVO-guidelines for treatment, diagnosis and prevention of osteoporosis)*	Oxford LoE	Oxford GR	AGO
▪ Physical activity	4	C	++
▪ Avoiding immobilisation	4	C	++
▪ Calcium (1000–1500 mg/d)**	4	C	++
▪ Vitamine D3 suppl. (800–2000 U/d or 20,000 U/w)	4	C	++
▪ Stop smoking, reduction of alcohol	2b	B	++
▪ Avoiding BMI < 20 kg/m^2	3b	C	++
▪ Bisphosphonates after discontinuation of Denosumab (1-2 years)	3c	C	+
▪ Drugs approved for osteoporosis treatment in adults (see next slide)			

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* http://www.dv-osteologie.org/osteoporose-leitlinien

** if nutritional supply is insufficient (in combination with Vit D3 only)

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Effect of Denosumab Discontinuation

FREEDOM / FREEDOM Extension Trial

n = 1001, ≥ 2 dose of Denosumab or placebo, follow up ≤ 7 months after discontinuation treatment

Vertebral fracture rate per 100 participant year:

- 1.2 during denosumab therapy
- 7.1 after denosumab therapy
- 8.5 placebo

Non vertebral fracture rate per 100 participant year:

- 2.8 after denosumab vs. 3.8 placebo (n.s.)

Multiple vertebral fracture (% of all vertebral fractures):

- **60.7% after denosumab therapy vs. 38.7% placebo; p = 0.049**

Cummings SR et al. J Bone Miner Res 2017

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Medical Treatment of Osteoporosis

	Oxford LoE	Oxford GR	AGO
▪ Alendronate 70 mg PO/w*	1b	B	++
▪ Denosumab 60 mg SC/6m*	1b	B	++
▪ Ibandronate 150 mg PO/m*	1b	B	++
▪ Ibandronate 3 mg IV/3 m	1b	B	++
▪ Parathyroid hormone (1-84) 100 µg SC/d	1b	B	+
▪ Raloxifene 60 mg PO/d (improves spine only)	1b	B	+/-
▪ Risedronate 35 mg PO/w*	1b	B	++
▪ Strontium ranelate 2 g PO/d**	1b	B	+
▪ Teriparatide (1-34) 20 µg SC/d	1b	B	+
▪ Zoledronate 5 mg IV/12m*	1b	B	++

* Drugs tested in clinical studies with breast cancer patients and tumor therapy-induced osteoporosis

** Elevated risk of myocardial infarction. Substance restricted to postmenopausal pts. with severe osteoporosis and high fracture risk.

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https://www.dv-osteologie.org/uploads/Leitlinie%202017/DVO%20Leitlinie_Kitteltaschenversion_16012020.pdf

TABELLE 4.2.: INDIKATION FÜR EINE MEDIKAMENTÖSE OSTEOPOROSETHERAPIE NACH RISIKOPROFIL in Abhängigkeit von Geschlecht, Lebensalter, DXA-Knochendichte und weiteren Risikofaktoren.[1]

Lebensalter in Jahren		T-Score (Nur anwendbar auf DXA-Werte. Die Wirksamkeit einer medikamentösen Therapie ist für periphere Frakturen bei einem T-Score > -2,0 nicht sicher belegt.)				
Frau	**Mann[2]**	**-2,0 bis -2,5**	**-2,5 bis -3,0**	**-3,0 bis -3,5**	**-3,5 bis -4,0**	**< -4,0**
50-60	60-70	Nein	Nein	Nein	Nein	Ja
60-65	70-75	Nein	Nein	Nein	Ja	Ja
65-70	75-80	Nein	Nein	Ja	Ja	Ja
70-75	80-85	Nein	Ja	Ja	Ja	Ja
>75	>85	Ja	Ja	Ja	Ja	Ja

[1] Alternative Risikomodellierungen können bei Bedarf vergleichend zu Rate gezogen werden (siehe Langfassung).
[2] bei Verwendung eines männlichen Referenzkollektivs für die T-Scores

Therapieindikation auch schon bei um 1,0 höherem T-Score [3,4], wenn:
- Glukokortikoide oral ≥ 2,5 mg und < 7,5 mg Prednisolonäquivalent tgl. (außer bei rheumatoider Arthritis +0,5)
- Diabetes mellitus Typ 1
- ≥ 3 niedrigtraumatische Frakturen in den letzten 10 Jahren im Einzelfall (mit Ausnahme von Finger-, Zehen-, Schädel- und Knöchelfrakturen)

Diagram courtesy of the DVO

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Sites of Metastases

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Sites Of Metastases
Specific Approaches to Metastatic Disease

- **Versionen 2002–2021:**
  Albert / Bauerfeind / Bischoff / Böhme / Brunnert / Dall / Diel / Fehm / Fersis / Friedrich / Friedrichs / Gerber / Hanf / Janni / Kolberg-Liedtke / Kreipe / Loibl / Lück / Lux / Maass / Mundhenke / Oberhoff / Park-Simon / Rezai / Rody / Schaller / Schütz / Seegenschmiedt / Solomayer / Souchon / Thomssen

- **Version 2022:**
  Kolberg-Liedtke / Solbach

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Sites of Metastases

- Liver and lung metastases
- Malignant pleural and pericardial effusions
- Ascites
- Bone marrow involvement
- Soft tissue metastases
- Contralateral axillary metastasis

See also chapters „CNS Metastases “ and „Locoregional Recurrence (Loco-Regional Recurrence Treatment Options in Non Curative Cases)“

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Distribution of Breast Cancer Metastases

Risk of breast cancer metastases

- is approx. 20%
- is dependent on molecular breast cancer subtype (i.e., lower in luminal A and higher in HER2-enriched and basal-like breast cancer)
- is decreasing due to more efficacious therapeutic regimens
- about 6% of new breast cancer diagnosis are stage IV and have an estimated 5-y OS rate of 27%

Pattern of breast cancer metastases

- Bone metastases are most common metastases (30-40%), followed by lung (20%) pleura (8%) and liver metastases (isolated liver metastases approx. 5%). Other locations are rare
- Breast cancer is the most common origin of cutaneous metastases and is considered to be the most prevalent primary tumor of all metastases to the orbit
- Metastatic pattern strongly depends on breast cancer molecular biology and efficacy of (targeted) therapy (i.e., compared with luminal A tumors, luminal/HER2 and HER2-enriched tumors are associated with a significantly higher rate of brain, liver, and lung metastases, while Basal-like tumors show a higher rate of brain, lung, and distant nodal metastases but a significantly lower rate of liver and bone metastases)
- Pattern of breast cancer metastases is one of several factors determining disease prognosis

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General Treatment Aspects of Metastases

	Oxford		
	LoE	GR	AGO
▪ Histological / cytological verification	3	B	+
▪ Systemic therapy preferred	2a	B	++*
▪ Consider surgery of metastases only in case of good response to palliative treatment, oligometastases	2b	C	+
▪ Stereotatic Radiotherapy for patients with oligometastases	2a	B	+
▪ Local treatment in the case of pain, exulceration, persistence after systemic treatment, bowel obstruction, hydrocephalus occlusus, spinal cord compression	5	D	+/-
▪ Systemic treatment after surgery	2c	B	++

* See chapters with systemic treatment recommendations

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Local Therapy in Primary Metastatic Disease

	Oxford		
	LoE	GR	AGO
▪ **Surgery (R0) of the primary tumor (individualized procedure in case of oligometastatic disease)**			
▪ In case of bone metastases only	1b	B	+/-
▪ In case of visceral metastases	1b	B	-
▪ **Axillary surgery for cN1**	3b	B	+/-
▪ **Sentinel biopsy if cN0**	5	D	-
▪ **Radiotherapy of the primary tumor**			
▪ Alone (without surgery)	3a	C	+/-
▪ After local surgical treatment with BCS or mastectomy (according to adjuvant indication)	2c	B	+

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Randomized Phase III Trials
ST +/- Surgery of the Primary Tumor

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Trial	n	Therapy prior to randomization	Local Control	Improved OS Primary Endpoint	QoL
ECOG 2108 *[1,2] (USA/Kanada) 2001-2016	256	4-8 months systemic therapy	yes	no	ns
Tata Memorial Hospital *[3] (India) 2005-2012	350	chemotherapy	yes	no	-
MF07-01 *[4,5,6,7] (Turkey) 2008-2012	278	no systemic therapy	no 10 y LRP: LRT 1% vs 14% ST, s	10 y fu OS: LRT 19% vs. ST 5%, s (HR+, Her2-, < 55 y, solitary bone only metastasis)	ns
ABCSG-28#*[8.9] (Austria) 2010-2019	90	no systemic therapy	yes	no	ns
JCOG 1017 (Japan) 2011-2018	410	primary ST	Completed, results not reported so far		

ns not significant, s: significant #trial terminated due to poor recruitment
ST = systemic therapy, LRT= locoregional therapy, LRP = locoregional progression

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Prospective Registry Study (Bone only)

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Trial	n	Randomization	Local Control	Improved OS Primary Endpoint	QoL
BOMET MF 14-01# 2014-	505	ST vs LRT (LRT+ST vs. ST+LRT)	yes	3 y fu: improved OS in the LRT group (HR 0.40) HR+, Her2-; Her2+ subgroups, no benefit in triple neg. patients	-

ST = systemic therapy, LRT = locoregional therapy,

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Liver Metastases
Local Therapy

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	Oxford		
	LoE	GR	AGO
▪ Resection of liver metastases (R0)	3a	B	+/-
• HR-positive: chemotherapy-sensitive, long disease-free interval, absence of extrahepatic disease, ≤ 3 metastases			
• HER2-positive: age < 50 y, metastases < 5 cm, no further metastases			
▪ Interventional regional chemotherapy (TACE)*	3b	C	+/-
▪ Interventional regional radiotherapy (SIRT/TARE)*	3b	C	+/-
▪ Stereotactic Radiotherapy with VMAT (SRS-VMAT), other modalities*	2a	B	+/-
▪ Regional ablative procedures (RFA, MWA)	3b	C	+/-
▪ IRE, LITT, HIFU	5	D	-
▪ Cryoablation	3b	C	-

* interdisciplinary decision

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Pulmonary Metastases
Local Therapy

	Oxford LoE	Oxford GR	AGO
▪ Before any local therapy: staging and biopsy (CT-guided FNA / CNB or transbronchial FNA, EBUS, VATS)	3a	B	+
▪ Resection of pulmonary metastases by VATS or conventional resection			
▪ In case of multi-locular metastatic disease	3a	B	-
▪ In case of single / few unilateral metastasis with curative intent	3a	B	+/-
▪ Thermoablation (CT-guided RFA, LITT)	3b	C	+/-
▪ Regional radiotherapy (stereotactic radiotherapy with volumetric intensity modulated arc therapy (SRS-VMAT))	2a	B	+/-

* VATS = video-assisted thoracic surgery

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Malignant Pleural Effusion (MPE)
Local Therapy

	Oxford		
	LoE	GR	AGO
▪ If short life expectancy, less invasive procedures should be considered	4	C	++
▪ VATS and Talcum-pleurodesis*	1b	B	++
▪ Continuous pleural drainage	2a	B	++
▪ Chemical pleurodesis*			
▪ Talcum powder	1a	B	+
▪ Bleomycin, Doxycycline, Mitoxantrone	2b	C	+/-
▪ Povidone-iodine (20 ml of 10% solution)	1b	B	+
▪ Systemic treatment after pleurodesis	3b	C	+/-
▪ Serial thoracocentesis	4	C	+/-

* Adequate pain-relief
VATS: video-assisted thoracoscopic surgery

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Malignant Ascites
Local Therapy

	Oxford		
	LoE	GR	AGO
Ascites:			
▪ Puncture, drainage in symptomatic patiens	4	D	++
▪ Continous drainage of ascites	3b	D	+
▪ Systemic therapy	3b	D	++
▪ Local chemotherapy	3b	D	+/-

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Malignant Pericardial Effusion
Local Therapy

Symptomatic pericardial effusion:	Oxford LoE	Oxford GR	AGO
▪ Drainage, fenestration	3b	B	++
▪ Combination with optimized systemic therapy	4	C	++
▪ VATS (video-assisted thoracic surgery)	4	C	+
▪ Ultrasound-guided puncture and instillation of cytotoxic / targeted compounds			
▪ Bleomycin, cisplatinum, mitomycin C, mitoxantrone etc., Bevacizumab	4	C	+/-

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Bone Marrow Infiltration Associated with Pancytopenia

	Oxford		
	LoE	GR	AGO
▪ **Weekly chemotherapy with*:**			
▪ **Epirubicin, Doxorubicin, Paclitaxel**	4	D	++
▪ **Capecitabine**	4	D	++
▪ **HER2-positive:**			
▪ **Add anti-HER2-treatment**	5	D	++
▪ **Hormone receptor-positive:**			
▪ **Endocrine-based therapy**	4	C	+

* **Consider pre-treatment**

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Soft Tissue Metastasis
Local Therapy

	Oxford		
	LoE	GR	AGO
▪ Surgery of limited locoregional metastasis (skin, muscular, nodal) with complete resection (R0) after exclusion of further metastases	4	C	+
▪ Radiotherapy (after surgery or, if immediate surgery is not indicated):			
▪ Soft tissue metastases	3b	C	+
▪ Paresis, spinal cord compression	2b	C	++
▪ Plexus infiltration	3b	C	++

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Oligo-Metastases
Contralateral Axillary Metastasis

"OLIGO-METASTATIC DISEASE in CONTRALATERAL AXILLA Contralateral axillary nodal metastasis (in the absence of contralateral primary) as initial diagnosis of recurrent disease is considered stage 4 metastatic breast cancer.
However, after prior local therapy to ipsilateral axilla for early breast cancer, subsequent metachronous contralateral axillary nodal metastasis, either alone or concurrent with an in-breast ipsilateral recurrence, could be considered and treated as a regional metastasis (due to altered lymphatic drainage), and has the potential for long survival or cure with a multidisciplinary approach"

ABC6 2021: LoE: Expert opinion/NA (85%)

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CNS Metastases in Breast Cancer

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CNS Metastases in Breast Cancer

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CNS Metastases in Breast Cancer

- **Breast cancer is the 2nd most common cause of CNS metastases.**
- **At autopsy:**
  - **Parenchymal CNS metastases: ~ 30–40%**
  - **Leptomeningeal CNS metastases: ~ 5–16%**
- **Increasing incidence (10% ⇨ 40%)**
- **Increasing incidence due to**
  - **More effective treatment of extra-cerebral sites with improved prognosis**
  - **Increasing use of MRI for diagnostic evaluation**
- **Lack of specific knowledge about treatment of brain metastases in breast cancer since most studies are not breast cancer specific. Therefore, participation in the German registry study is recommended (www.gbg.de).**

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Incidence of Brain Metastases among Patients with Metastatic Breast Cancer – Meta-Analysis of 25 Trials between 2010-2020

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Subtype	No patients	Incidence per patient-year	Pooled cumulative incidence	Median follow-up (months)
HER2 positive (all)	5971	13% 95% CI: 0.22–0.38	31%	31
HR- / HER2 positive	2092	13% 95% CI: 0.08–0.20	-	-
HR+ / HER2 positive	3480	8% 95% CI: 0.05–0.13	-	-
HR- / HER2 negative	4102	13% 95% CI: 0.09–0.20	32% 95% CI: 0.19–0.49	33
HR+ / HER2 negative	14656	5% 95% CI: 0.03–0.08	15% 95% CI: 0.078–0.27	33

Kuksis M, Gao Y, Tran W et al. Neuro Oncol. 2021 Jun 1;23(6):894-904

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CNS Metastases in Breast Cancer
Tumour biology

- **Primary Tumor:**
  - **Negative hormone receptor status (basal-like cell type / triple-negative)**
  - **High grade, high Ki-67 index**
  - **HER2 and / or EGFR (HER1) overexpression**
  - **Molecular subtype (Luminal B, HER2 positive, triple-negative)**
- **Brain metastases are more likely estrogen receptor negative and overexpress HER2 and / or EGFR.**
- **Discordance of molecular subtype between primary tumor and brain metastases: for ER = 16,7%, for PR = 25,2% and Her2/neu = 10,4%**
- **There is no evidence for BM-screening in asymptomatic BC-patients.**

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Updated Breast-GPA (Graded Prognostic Assessment) Worksheet to Estimate Survival from Brain Metastases (BM)

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Prognostic Factor	0	0.5	1	1.5	Score
KPS	≤ 60	70-80	90–100	n/a	
Subtype	Basal	LumA	n/a	HER2 or LumB	
Age, years	≥ 60	< 60	n/a	n/a	
ECM	present	absent	n/a	n/a	
No of BM	≥ 2	1	n/a	n/a	
					Sum total

Median survival by Breast-GPA:

Breast-GPA 0–1.0 = 6 months
Breast-GPA 1.5–2.0 = 10 months
Breast-GPA 2.5–3.0 = 13 months

Subtype: Basal: triple negative; LumA: ER / PR positive, HER2 negative; LumB: triple positive; HER2: ER / PR negative, HER2 positive. ECM: extracranial metastases BM: brain metastases

Sperduto PW et al, JCO 2020

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Single / Solitary Brain Metastasis and Oligo-Brain Metastases*

	Oxford		
	LoE	GR	AGO
Local therapy alone: SRS (≤ 4 cm) o. FSRT	1b	B	++
Single / Solitary Metastasis:	1b	B	++
Resection (if indicated) + irradiation of the tumor bed (without WBRT)			
Oligo-Brain Metastases:	1b	B	++
Resection (if indicated) + irradiation of the tumor bed and SRS or FSRT of unresected metastases (without WBRT)			
WBRT + Boost (SRS, FSRT) or resection + WBRT	2a	B	+
WBRT alone	2b	B	+
Patients with reduced general condition and limited life expectancy			
Hippocampal-sparing (if prognosis is favourable)**	1b	B	+

*** Oligometastases or limited tumour volume refers to ≤ 4 brain metastases or cumulative tumour volume < 15 ml in 5-10 brain metastases**

**** Metastases in hippocampus excluded**

SRS = stereotactic radiosurgery (single session), FSRT = fractionated stereotactic RT; WBRT = whole brain radiotherapy

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Single / Solitary Brain Metastasis and Oligo-Brain Metastases*

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- **Local therapy (surgery, SRS, FSRT) depends on localization, size, number of metastases, previous therapy, Karnofsky-Performance-Scale, prognosis.**
- **WBRT in addition to SRS/FSRT improves intracranial control, but does not improve duration of functional independence and overall survival.**
- **WBRT impairs neurocognitive function.**
- **In case of limited* number of brain metastases, SRS / FSRT are preferred.**
- **Postoperative radiotherapy:**

  Single/solitary brain metastasis (resection cavity < 5 cm): SRS v. WBRT no difference in overall survival.

  Oligo-brain metastases: SRS of surgical cavity and SRS of unresected metastases v. WBRT

  no difference in overall survival.

*** Oligometastases or limited tumour volume refers to ≤ 4 brain metastases or cumulative tumour volume < 15 ml in 5-10 brain metastases**

****Metastases in Hippocampus excluded**

SRS = stereotactic radiosurgery (single session), FSRT = fractionated stereotactic RT; WBRT = whole brain radiotherapy

NCCTG N0574 (Alliance): A Phase III Randomized Trial of Whole Brain Radiation Therapy (WBRT) in Addition to Radiosurgery (SRS) in Patients with 1 to 3 Brain Metastases

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Study design:

Patients with 1-3 brain metastases, each < 3 cm by contrast MRI, were randomized to SRS alone or SRS + WBRT and underwent cognitive testing before and after treatment. The primary endpoint was cognitive progression (CP) defined as decline > 1 SD from baseline in any of the 6 cognitive tests at 3 months. Time to CP was estimated using cumulative incidence adjusting for survival as a competing risk.*

Conclusion:

Decline in cognitive function, specifically immediate recall, memory and verbal fluency, was more frequent with the addition of WBRT to SRS. Adjuvant WBRT did not improve OS despite better brain control. Initial treatment with SRS and close monitoring is recommended to better preserve cognitive function in patients with newly diagnosed brain metastases that are amenable to SRS.

* **Remark: No hippocampus-sparing was applied**

Brown PD, Jaeckle K, Ballman KV et al.: Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases JAMA 2016 Jul 26;316(4): 401-409.

Adjuvant Whole-brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952- 26001 Study

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2-year relapse rate after whole-brain radiotherapy (WBRT) versus observation after surgical resection or radiosurgery				
	after surgical resection (n = 160)		after radiosurgery (n = 199)	
	WBRT	observation	WBRT	observation
Local recurrence	27%	59% (p < 0.001)	19%	31% (p = 0.040)
New lesions	23%	42% (p = 0.008)	33%	48% (p = 0.023)

- **Only 12% of the patients had brain metastases from breast cancer.**
- **Overall survival was similar in the WBRT and observation arms (median, 10.9 vs. 10.7 months, respectively; P = .89).**
- **Intracranial progression caused death in 44% patients in the OBS arm and in 28% patients in the WBRT arm.**

Kocher M. J Clin Oncol 2011, 29:134-141

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Possible Factors for Decision Making Neurosurgery versus Stereotactic Radiosurgery

Factors in favor of neurosurgery:

- **Histological verification e.g. after a long recurrence-free interval**
- **Need for immediate decompression, life-threatening symptoms**
- **Tumor size not allowing stereotactic radiotherapy**

Factors in favor of primary radiotherapy*:

- **Tumor location poorly amenable to surgery**
- **More than four lesions**

*** stereotactic radiotherapy should be preferred if possible**

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Multiple Brain Metastases
if Stereotactic Radiotherapy is not indicated

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	Oxford		
	LoE	GR	AGO
▪ WBRT (supportive steroids*)	1a	A	++
▪ Hippocampal-sparing radiotherapy** (if prognosis is favourable)	1b	B	+
▪ Corticosteroids alone*	3a	B	+/-
▪ Chemotherapy +/- targeted therapy alone	3a	D	+/-
▪ Radiochemotherapy for intracerebral control	3b	C	-
▪ WBRT in case of recurrence***	4	C	+/-

* adapted to symptoms

** metastases in hippocampus excluded

*** can be discussed depending on time-interval from first radiation, prior dose, and localization if local therapy (surgery, SRS, FSRT) is not indicated and / or possible

SRS = stereotactic radiosurgery; FSRT = fractionated stereotactic radiotherapy; WBRT = whole brain radiotherapy

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Symptomatic Therapy of Brain Metastases

	Oxford		
	LoE	GR	AGO
▪ Anticonvulsants only if symptoms of seizures	3a	C	+
▪ Glucocorticoids only if symptoms and / or mass effect (Dexamethasone with best evidence)	3a	C	++
▪ For patients with bad prognosis and reduced physical common conditions best supportive care is an option	5	D	+

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Clinical Classification of Brain Metastases

Stable brain metastases (definition: RECIST / RANO):
stabilization after treatment of brain metastases.

Stable brain metastases (definition: DESTINY-BREAST03):
stable brain metastases ≥ 2 weeks after whole brain radiotherapy, asymptomatic, no requirement of corticosteroid or anticonvulsant therapy

Active brain metastases (definition: HER2Climb):
locally pretreated brain metastases with progressive disease or newly diagnosed brain metastases not needing immediate local therapy
or
untreated brain metastases not needing immediate local therapy

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Systemic Therapy of Brain Metastases

	Oxford		
	LoE	GR	AGO
▪ Interdisciplinary treatment planning	5	D	++
▪ Chemotherapy +/- targeted therapy alone as primary treatment	3a	D	+/-
▪ Continuation of the current systemic therapy if first diagnosis of brain metastasis and stable extracranial disease	2c	C	+

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Systemic Therapy of Brain Metastases: HER2 positive

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	Oxford		
	LoE	GR	AGO
▪ Tucatinib + Trastuzumab + Capecitabine*	2b	B	+
▪ Trastuzumab-Deruxtecan**	2b	B	+
▪ T-DM1	2b	B	+/-
▪ Lapatinib + Capecitabine	2b	B	+/-
▪ Neratinib + Capecitabine	2b	B	+/-
▪ Neratinib + Paclitaxel	2b	B	+/-

* efficacy demonstrated in active and stable brain metastases

** efficacy demonstrated in stable asymptomatic brain metastases requiring neither corticoids nor anticonvulsant therapy

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Leptomeningeal Carcinomatosis: Local Therapy

	Oxford		
	LoE	GR	AGO
Intrathecal or ventricular therapy			
▪ MTX 10–15 mg 2–3 x/ week (+/- folinic acid rescue)	2b	B	+/-
▪ Steroids	4	D	+/-
▪ Trastuzumab (HER2 pos. disease)	4	C	+/-
Systemic therapy	3b	B	+
Radiotherapy			
▪ Focal (bulky disease)	4	D	+
▪ WBRT	4	D	+
▪ Neuroaxis (disseminated spinal lesions)	4	D	+/-

Due to poor prognosis, consider best supportive care, especially in patients with poor performance status

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Complementary Therapy Survivorship

Complementary Therapy – Hormonal Treatment and Alternatives in Breast Cancer Survivors – Survivorship

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CAM

„Integrative Oncology“

„Unconventional methods“

CAM
Complementary + alternative medicine

Complementary

In addition to scientifically based medicine

Alternative

Instead of scientifically based medicine

UCT
Unconventional Tx

Unconventional

Unproven outsider methods

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Good Clinical Practice

All patients should be consulted as early as possible and in the course of the process repeatedly on the interest in information complementary medical measures and, if interested, reliable sources of information should be referred.

S3 LL “Komplementärmedizin in der Behandlung von onkologischen PatientInnen“

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General Considerations

	Oxford		
	LoE	GR	AGO
▪ CAM instead of loco-regional interventions	2b	B	--
▪ CAM instead of systemic treatment	2b	B	--

- Patients should be asked and advised about their use of CAM modalities
- Diagnostic procedures in connection with complementary and alternative therapy concepts without evidence (e.g. iris diagnostics, bioresonance) should not be recommended.
- *During anti-cancer treatment:* Beware of drug interactions

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Complementary Therapy
Pre- and Postoperative

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	Oxford		
	LoE	GR	AGO
Preoperative:			
▪ Hypnosis (reduces anxiety, pain, nausea)	1b	B	+
Postoperative:			
▪ Acupuncture (pain relief, anxiety)	1b	B	+/-
▪ Acupuncture (nausea, vomiting)	2b	B	+
▪ Massage therapy (pain relief)	2b	C	+/-
▪ Early postoperative exercise reduces upper-limb dysfunction (beware: increased wound drainage)	1a	A	+
▪ Physical exercise			
▪ to reduce breast cancer related secondary lymphedema	1a	A	+
▪ as a prophylaxis of lymphedema	1b	B	+/-
▪ Prophylactic lymphatic drainage	1b	B	--
▪ Yoga (arm and shoulder pain)	2b	C	+
▪ Music therapy (reduces pain after mastectomy)	2b	C	+/-

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Complementary Treatment
While on Cancer Treatment – Impact on Toxicity I

During anti-cancer treatment: Beware of drug interactions

	Oxford LoE	GR	AGO
▪ **Mistletoe (Viscum album)** in order to reduce side effects	1a	B	+/-
▪ **Thymic peptides** lower risk of severe infections	2a	B	+/-
▪ **Ginseng** reduces fatigue; note: interacts with cytochrome P enzymes e.g. CYP 3A4	2b	C	-
▪ **Ganoderma Lucidum** reduces fatigue, note: inhibits cytochrome P enzymes (e.g. CYP 3A4)	2b	C	-
▪ **L-Carnitine**			
▪ peripheral neuropathy	1b	B	--
▪ treatment of fatigue	1b	B	-
▪ **Melatonin** (reduces fatigue, improve sleep, depressive symptoms, cognition)	2b	B	+/-
▪ **Curcumin** adjunct to reduce radiation-induced dermatitis	1b	B	+/-
▪ **Ginger** adjunct to guideline-oriented medication to treat chemotherapy induced nausea & vomiting – beware of drug interactions	1b	C	+/-

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Complementary Treatment
While on Cancer Treatment – Impact on Toxicity II

	Oxford LoE	Oxford GR	Oxford AGO
▪ **Antioxidant supplements**	1b	B	-
• **various antioxidative extracts** (to reduce anthracyclin-induced cardiotoxicity)	2b	B	+/-
▪ **High dose vitamin C**	1b	C	-
▪ **Vitamine E**	2b	D	-
▪ **Selenium** (for alleviating therapy side effects)	1b	B	-
▪ **Co-Enzyme Q 10** (fatique, QoL)	1b	B	-
▪ **Proteolytic enzymes** (for reduction of chemotherapy-induced toxicity)	3b	B	-
▪ **Chinese herbal medicine improves wound healing**	1b	B	-*inf
▪ **Oxygen and ozone therapy**	5	D	--
▪ **Short-term fasting** (Qol, Fatigue)	2b	B	+/-*

* **inf: i.v.-infusion (in Germany not approved)**
treatment in clinical trials recommended

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Additional Complementary Therapy of Side Effects Related to Cancer Treatments

	Oxford		
	LoE	GR	AGO
▪ **Chinese medicinal herbs** (to treat the side effects of chemotherapy)	1b	B	-
▪ **Homoeopathic medicine** (against therapy side effects / Placeboeffect)	1b	B	+/-
▪ **Topical Silymarin (**to prevent acute dermatitis during radiotherapy)	3a	B	+/-
▪ **Massage** (to improve on fatigue, pain, anxiety, nausea)	1b	C	+/-
▪ **Transcutaneous Electrical Nerve stimulation (TENS)** (against cancer pain)	2b	D	+/-
▪ **Hydrotherapy** (for supportive skin care)	3b	C	+/-

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Additional Complementary Therapy of Side Effects Related to Cancer Treatments

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Acupuncture in order to improve on	Oxford LoE	Oxford GR	AGO
Chemotherapy-induced nausea and vomiting			
(Electro)-Acupuncture as adjunct to entiemetic treatment	1b	B	+
Acupressure as adjunct to entiemetic treatment	1b	B	+
Pain			
Cancer pain	1b	B	+
Aromatase-inhibitor – induced athralgia	1a	B	+
TENS – Transcutaneous Electrical Nerve Stimulations to relieve cancer pain	2b	D	+/-
Fatigue	1a	B	+
Acupressure	1b	B	+
Anxiety and depression	2b	B	+
Cognitive dysfunction	5	D	+/-
Menopause syndrome in Breast Cancer Patients	1b	B	+
to improve on frequency and severity of hot flashes	1b	B	+/-
Electro-Acupuncture to improve on sleep and hot flashes	2a	B	+
Leucopenia (Moxibustion)	2b	B	+/-
Treatment of chemotherapy induced polyneuropathy			
prophylactically	1b	B	-
therapeutically	2b	B	+/-
Chronic lymph edema after Breast Cancer Treatment	2b	B	+/-

Complementary Treatment
Mind-Body Medicine I

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	Oxford		
	LoE	GR	AGO
MBSR (Mindfulness-Based Stress Reduction)	1a	A	+
Program improves quality of life, coping strategies, attentiveness, and lowers stress, anxiety, depression, fatigue, and sleep disturbances			
Physical exercise / sport	1a	A	++
min. 3x/week moderate endurance training in combination with workout exercises (2x per week) improve quality of life, cardio-respiratory fitness, physical performance, sleep, pain, depression, lymphedema, and fatigue			

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Complementary Treatment
Mind-Body Medicine II

	Oxford LoE	Oxford GR	AGO
Relaxation techniques Reduction of anxiety and nausea, improvement of quality of life, reduction of psychological stress	2b	C	+/-
Yoga Improves sleep, quality of life, stress, anxiety, depression, fatigue, and sleep	1b	A	+
Qi Gong May improve quality of life, fatigue, and mood	2a	B	+/-
Tai Chi Improves quality of life, muscular strength, sleep	2a	B	+/-
Hypnosis (in combination with cognitive training) Improves fatigue and muscle weakness under radiotherapy; also reduces distress	1b	A	+

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CAM
Prevention of Recurrence / Improvement of Overall Survival I
Modifiable Lifestyle Factors

	Oxford		
	LoE	GR	AGO
▪ **Physical exercise** (equivalent to 3–5 hrs moderate walking per week) improves DFS and OS, cardio-respiratory fitness, physical functioning	2a	A	++
▪ **Reduce smoking**	2b	A	+
▪ **Reduce alcohol consumption (< 6 g/day)**	2b	A	+

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Modifiable Lifestyle Factors

Nutrition after Breast Cancer Diagnosis

Prevention of Recurrence / Improvement of Overall Survival II

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	Oxford		
	LoE	GR	AGO
▪ **Adherence to normal BMI / weight loss if overweight, irrespective of HR-status**	1a	A	++
▪ **Low fat diet** dietary counseling recommended	1a	B	+
▪ **Increased fiber intake (e.g. Flaxseed)**	2a	B	+
▪ **Adherence to general nutrition guidelines** (e.g. DGE, WCRF) similar to a Mediterranean Diet	2a	B	++
▪ **Dietary extremes**	2a	B	--

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Complementary Treatment

Prevention of Recurrence / Improvement of Overall Survival III.1

Dietary Supplements – Herbal Therapies

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During anti-cancer treatment: Beware of drug interactions

	Oxford		
	LoE	GR	AGO
Post treatment vitamine / antioxidant supplements does not appear to be associated with increased risk of recurrence (beware of drug / treatment interactions)	2b	B	
Smokers on antioxidant supplements are at higher risk for lung cancer	1b	A	
For Prevention of BC Recurrence:			
▪ **Antioxidants**	2a	B	+/-
▪ **Vitamine supplementation in patients on a balanced diet** (esp. Vitamine C, E)	2a	B	+/-
▪ **Vitamine D**	2b	B	+/-
▪ **Soy-food** (natural source of phytoestrogenes)	2a	B	+/-
– **food or concentrates containing ≥ 100 mg) isoflavones per day**	2a	B	-
▪ **Black Cohosh** (Cimicifuga racemosa)	3b	C	+/-
▪ **Antioxidant supplements** (after completion of radiotherapy)	2b	B	+/-
▪ **Green tea**	3a	C	+/-
▪ **Selenium**	2b	B	+/-

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Complementary Treatment

Prevention of Recurrence / Improvement of Overall Survival III.2

Dietary Supplements – Herbal Therapies

During anti-cancer treatment: Beware of drug interactions

	Oxford		
	LoE	GR	AGO
▪ **Other orthomolecular substances** (Zinc...)	5	D	-
▪ **Artificial carotenoids appear to be associated with worse outcome**	2b	B	-
▪ **Proteolytic enzymes** (Papain, Trypsin, Chymotrypsin)	3b	B	-
▪ **Mistletoe** (Viscum album)	1b	C	-
▪ **Thymic peptides** (impact on OS)	2a	B	-
▪ **Oxygen- and ozone therapy**	5	D	- -
▪ **Laetrile (**Amygdalin, „Vitamine B17“)	1c	D	- -
▪ **Methadone**	5	D	- -
▪ **Cancer bush** (Sutherlandia frutescens), **Devil's claw** (Harpagophytum procumbens), **Rooibos tea** (Aspalathus linearis), **Bambara groundnut** (Vignea subterranean)	4	C	-
▪ **Incense**	5	D	-
▪ **Curcuma, curcumine**	5	D	-

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Gynecological Issues in Breast Cancer Patients

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  Albert / Bauerfeind / Blohmer/ Fersis / Gerber / Hanf / Huober/ Loibl / Maas / Reimer / Rody / Scharl / Thill / Thomssen / Witzel
- **Version 2022:**
  Loibl / Mundhenke

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Hormone (Replacement) Therapy (HT) of Estrogen Deficiency after Diagnosis of Breast Cancer

	Oxford LoE	Oxford GR	AGO
Systemic hormone (replacement-) therapy			
▪ **Endocrine responsive disease (ER pos.)**	1b	B	-
▪ **Combined treatment TAM plus low dose HT**	2b	B	+/-
▪ **Endocrine non-responsive disease (ER neg.)**	2b	D	+/-
▪ **Tibolone**	1b	A	- -
Topical vaginal application of			
▪ **Estriol** (E3 0.03 mg as treatment course*)	2b	B	+/-
▪ **DHEA locally**	2b	B	-
▪ **Testosterone locally**	2b	B	-
▪ **Estradiol (E2)** during AI therapy	4	C	-

* **4 weeks daily 1 x 1, followed by 8 weeks 3 x 1 per week –** Note:. Elevated E3-blood levels only with start of therapy; oncological endpoints were not studied. Non-hormonal alternatives should be preferred, see slide „Sexual Health“

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Further Medical Approaches to Reduce Menopausal Symptoms I

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	Oxford		
Medical approaches* (reduction of hot flushes)	**LoE**	**GR**	**AGO**
▪ **Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI): reduce hot flashes in BC patients**			
▪ **Venlafaxine**	1a	A	+
▪ **Desvenlafaxine**	1b	A	+/-
▪ **Sertraline, escitalopram**	1b	A	+/-
▪ **Gabapentin** (patients using TAM)	1a	A	+
▪ **Oxybutynine** (2.5 mg / 5 mg)	1b	A	+/-
▪ **Pregabalin**	1b	A	+/-
▪ **Clonidine** 0.05-0.15 mg/die (patients uasing TAM)	2a	B	+/-
▪ **MPA** (i.m. 500 mg single shot) (most potent, but endocrine agent!)	1b	A	+/-
▪ **Vitamin E**	1b	A	-
▪ **Omega-3 fatty acids**	1b	A	+/-
Medical approaches (other treatment goals)			
▪ **Melatonin (improvement in sleep quality)**	2b	C	+
▪ **Duloxetine (treating arthralgias while on AI)**	1b	B	+

* **Note: Substantial placebo-effect has been proven (23-57%) LoE 1b A +**

CAM* - Approaches to Reduce Menopausal Symptoms II

* Complementary and Alternative Medicine

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During anti-cancer treatment: Beware of drug interactions!

	Oxford LoE	Oxford GR	AGO
▪ **Soy-derived phytoestrogens – isoflavonoids***			
Hot flushes	1b	B	-
Sleep disturbance	1b	B	+/-
Topical vaginal application	1b	B	+/-
▪ **Red Clover isoflavonoids***			
Hot flushes, sleep disturbance	1b	B	+/-
▪ **Flaxseed-supplementation** (40 g/d) (in HR+ ≤ 10 g/d) (reduces relapses, no effect on hot flashes)	2b	B	+/-
▪ **Black Cohosh for hot flushes**	1b	B	+/-
▪ **Black cohosh + St. John's Wort** (fixed combination)	1b	B	+/-
▪ **St. John's Wort** (pharmacokinetic interference with endocrine therapy, cyctotoxic drugs, and tyrosin kinase inhibitors)	1b	B	+/-
▪ **Ginseng root** (Panax ginseng or P. quinquefolius)	1b	B	-
▪ **Bromelain + Papain + Selenium + Lectin (for AI induced joint symptoms)**	3b	B	+
▪ **Homeopathic medicine to reduce hot flushes** (consider placebo-effect)	1b	B	+/-

* might stimulate BC, especially in endocrine responsive disease

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General Approaches to Reduce Menopausal Symptoms III - Integrative Oncology Aspects

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General approaches:	Oxford LoE	GR	AGO
▪ Physical exercise	1a	A	++
▪ Cognitive behavioral therapy (CBT), hypnosis	1a	A	++
▪ Mind body-medicine (yoga, education, counselling, mindfulness training)	1b	B	+
▪ Short interruption of endocrine therapy in case of unacceptable side effects	5	D	+
(Electro) Acupuncture			
▪ Aromatase-inhibitor treatment induced arthralgia	1a	B	+
▪ Hot flushes	2a	B	+
▪ Anxiety, Depression	2b	B	+
▪ Sleep	2a	C	+

* as in SOLE Trial

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Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)

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	Oxford LoE	Oxford GR	AGO
▪ Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists (further information *https://fertiprotekt.com/english*)			++
▪ CTx + GnRHa (preservation of ovarian function) (GnRHa application > 2 weeks prior to chemo-therapy, independent of hormone receptor status)	1a	A	+
▪ CTx + GnRHa (preservation of fertility)	2a	B	+/-

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Ovarian Protection – Synopsis of Randomized Trials

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	ZORO	PROMISE	Munster et al. - US	POEMS	Option
Patient number	60 (60 HR-)	281 (50 HR-)	49 (13 HR-) of 124	218 (218 HR-)	227 (126 HR-)
Age median	38 years	39 years	39 years	Premenop. < 50 years	premenopausal
Treatment	goserelin	triptorelin	triptorelin	goserelin	goserelin
Start of treatment	> 2 weeks prior to cht	> 1 week prior to cht	> 1 week prior to cht	> 1 week prior to cht	> 1 week prior to cht
Primary Endpoint	menstruation at month 6 after chemotherapy	rate of early menopause at month 12 after cht	menstruation rate within 2 years after cht	Ovarian failure at 2 yrs after cht	Amenorrhea with elevated FSH levels between 12 and 24 months
Primary objective	to detect 30% absolute increase of menstruation rate	to detect at least 20% absolute reduction in early menopause	to detect 20% difference in amenorrhea rate – from 10% to 30%		To detect 20%-25% absolute reduction in early menopause
Multivar. analysis	age as only independent predictive factor	treatment as only independent predictive factor	n.d.	Treatment as only Independent predictive factor	Age, total cyclophosphamide dose and baseline AMH
Resumption of menses at month 12	83% with LHRH vs. 80% w/o	93% with LHRHa vs. 74% w/o	74% with LHRH vs. 68% w/o	78% with LHRH vs. 75% w/o; at 2 years; 22% with LHRH vs. 8%	78% with LHRHa vs. 62% amnorrhea rate between month 12 and 24
Median time to restoration of menses (months)	6.1 with LHRHa vs. 6.8 w/o; p = 0.30	not reached with LHRH vs. 6.7 w/o; p = 0.07	5.8 with LHRH vs. 5.0 w/o; p = 0.58	n.d.	n.d.
Cyclophosph. dose	4600 vs. 4700 mg	4080 vs. 4008 mg	n.r.	n.a.	5940 vs. 5940 mg

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Assessment of Ovarian Reserve

Tests for fertility assessment	Oxford LoE	Oxford GR	AGO
▪ Anti-Mullerian Hormone	1b	B	+
▪ Antral follicle count	3b	B	+
▪ FSH	2b[a]	B	+
▪ Combined test procedures for assessment of ovarian reserve*	5	C	+

* Tests are suggested for women > 35 y and infertility for 6-12 months; the tests do not predict failure to conceive. They should be used in counselling patients and to provide a rough estimate of the fertility window. Results may decrease patient referral time to infertility centers.

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Contraceptive Options for Women after Diagnosis of Breast Cancer

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	Oxford		
	LoE	GR	AGO
▪ Barrier methods	5	D	+
▪ Sterilization (tubal ligation / salpingectomy / vasectomy)	5	D	+
▪ Non-hormonal intrauterine devices (IUDs)	3b	D	+
▪ Levonorgestrel-releasing IUDs	2b	C	-
▪ Removal in newly diagnosed patients	4	D	+/-
▪ Timing methods	5	D	-
▪ Injectable progestin-only contraceptives	5	D	-
▪ Progestin-only oral contraceptives	5	D	-
▪ Combined oral contraceptives	5	D	-
▪ Options of emergency contraception			
▪ Copper intrauterine device (Copper-IUD)	5	D	+
▪ Levonorgestrel, Ulipristal orally	5	D	+

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Sexual Health / Vaginal Dryness

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	Oxford		
Evaluation	**LoE**	**GR**	**AGO**
▪ **Assessment of sexual dysfunction**	**5**	**D**	**+**
▪ **Use of patient-reported questionnaires**	**4**	**C**	**+**
Therapy of dyspareunia and vaginal dryness			
▪ **Psychoeducational support, group therapy, sexual counselling, marital counselling, psychotherapy**	**1b**	**B**	**+**
▪ **Topical vaginal treatment**			
▪ **Non-hormonal lubricants / moisturizers** (also with physiotherapy)	**1b**	**B**	**+**
▪ **Estriol** (E3 0.03 mg as treatment course*)	**2b**	**B**	**+/-**
▪ **DHEA local application**	**2b**	**B**	**-**
▪ **Testosterone local application**	**2b**	**B**	**-**
▪ **Estradiol** (E2) during AI therapy	**4**	**C**	**-**
▪ **Fractionated microablative CO2-Laser / Vaginal Erbium:YAG-Laser**	**2a**	**B**	**+/-**

* **4 weeks daily 1 x 1, followed by 8 weeks 3 x 1 per week –** Note:. Elevated E3-blood levels only with start of therapy; oncological endpoints were not studied. Non-hormonal alternatives should be preferred.

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Assessment of Sexual Health

- **Brief Sexual Symptom Checklist (BSSC-W)[ref2]**
  - **Screening-Questionnaire: Overall Sexual Function**

1. Are you satisfied with your sexual life? *Yes - No*

If NO, please continue to question 2

2. How long have you been dissatisfied with your sexual life? ……
3. The problem(s) with your sexual life is: *(mark one or more)*
   1. Problem with little or no interest in sex *0*
   2. Problem with decreased genital sensation of clitoris or vagina (feeling) *0*
   3. Problem with decreased vaginal lubrication (dryness) *0*
   4. Problem reaching orgasm *0*
   5. Problem with pain and/or cramping during sex *0*
   6. Other …….
4. Which problem is most bothersome? *1 – 2 – 3 – 4 – 5 – 6 (circle)*
5. Would you like to talk about it with your doctor? *Yes – No*

- **Sexual Complaints Screener For Women (SCS-W)[ref3]**
- **FSFI-19, FSFI-6[ref5]**

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Health Literacy and Communication

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Health Literacy

- **Versions 2020-2021:**
  Bauerfeind / Rhiem / Schmidt / Schütz

- **Version 2022:**
  Maass / Schütz

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Health Literacy Definition

“Health literacy is linked to literacy and entails people’s knowledge, motivation and competences to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve quality of life during the life course.”

Sørensen et al., (2012)

Health Literacy Model

(according to Sörensen)

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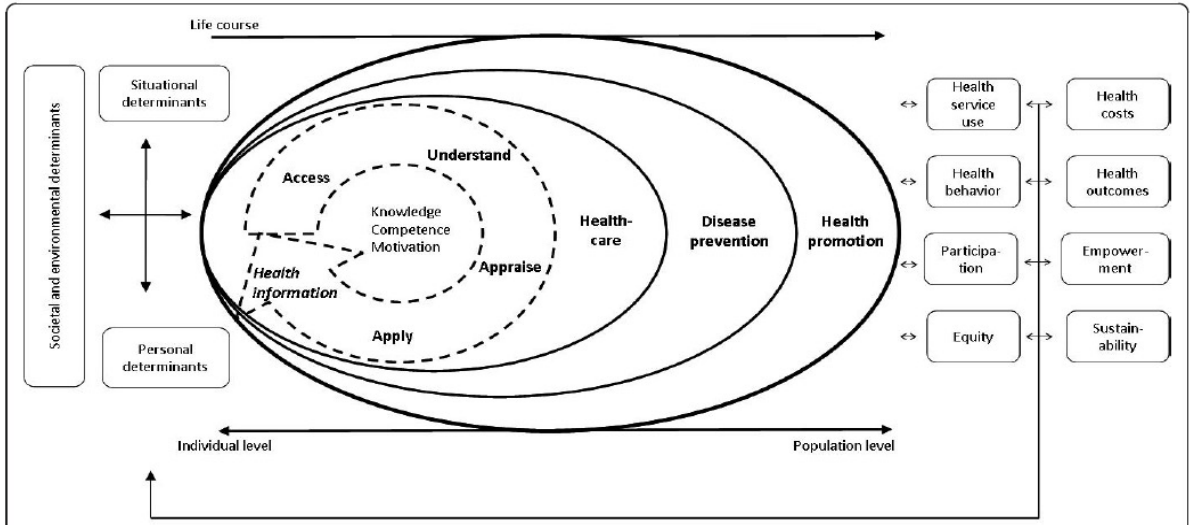

Figure 1 Integrated model of health literacy–see separate file.

Competencies

Access: seek, find, obtain health information.

Understand: Understanding the health information received

Appraise: Interpret, select, assess, review health information

Apply: Use health information to make decisions that support and improve health

Sørensen K, Van den Broucke S, Fullam J, Doyle G, Pelikan J, Slonska Z, Brand H. Health literacy and public health: A systematic review and integration of definitions and models. BMC Public Health. 2012, 12:80

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Health Literacy

- The more developed health literacy is, the better a person can **inform** himself or herself about health (e.g. prevention, therapy) in everyday life, **form** an **opinion** and **make self-determined decisions** that maintain or improve the quality of life and health throughout the self-determined course of life.

- However, the extent of health literacy of a person depends not only on his or her individual prerequisites and acquired competencies, but especially on the **professional quality, appropriateness, comprehensibility, form of communication and availability of the information provided.**

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Health Literacy

User Participation

Reasons cited for overuse, underuse and misuse in the health care system include the weak position of patients (SVR 2001).

In the context of health literacy, the patient is

- More autonomous **actor and co-designer**
- The one who takes **responsibility** and an **active role** in medical decisions
- the person who extracts the **individually relevant meaning** from professionally offered information and **behaves in accordance with individual ideas about** certain health situations

SVR - Council of Experts for the Assessment of Developments in the Health Care System
Health Literacy and Communication

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Health Literacy

Communication

Aim of a physician-patient communication: enable a self-determined decision based on sufficient health competence (Shared Decision Making)

Oxford	
LoE	AGO
3a	+

Doctor-patient communication is key for acquiring health competence. It is the basis for successful oncological treatment and support. Core elements are, for example:

- **Non-directive communication** - i.e. those seeking advice have the right to choose their own goals in life, even if they contradict generally accepted, even evidence-based, recommendations after well-founded consideration.
- **Comprehensible communication** - i.e. geared to the level of knowledge, reception habits, competence requirements and preferences of the different patients

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Health Literacy

Basic Principles of Communication

- Communicate information truthfully and empathetically
- Impart medical evidence-based knowledge
- Critical debate of pseude-scientific recommendations
- Active listening
- Showing empathy
- actively listening and expressing empathy
- Find out if and how the patient wants to be informed about his / her situation
- use understandable language avoiding or explaining technical terms
- Continuously improve understanding through e.g. repetitions, breaks, summary, comprehensible information material
- Encourage asking questions and expressing feelings
- Identifying individual stresses, problems and needs
- Motivating self-determination and personal activities ("empowerment")
- Giving hope for healing and relief
- Offer further assistance (e.g. psycho-oncology, self-help)

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Health Literacy

Evidence-based Information

Evidence-based information in health care should be used to answer patients' questions in an understandable way. They are based on the current state of knowledge and are free from influence:

<u>requirement for evidence-based health information as a discremination against pseude-scientific recommendations:</u>

- **The information on services or products may not be used directly or indirectly for marketing purposes.**
- **The systematic search corresponds to the questions relevant to the target group.**
- **The selection of evidence suitable for the research question is justified.**
- **An undistorted presentation of the results relevant to the patients (e.g. mortality, complaints, complications, health-related QoL) is available.**
- **The presentation of uncertainties is appropriate in terms of content and language.**
- **The presentation of results is clearly separated from the derivation of recommendations.**
- **Consideration of current evidence to communicate figures, risk information and probabilities.**
- **there must be sufficient time for the decision.**
- **The possibility that the measure may be refused must not be a reason for withholding information.**

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Health Literacy

Communication

Non-directive and evidence-based doctor-patient communication geared to the current needs, values, problems, resources and preferences of patients has beneficial effects.

	Oxford
	LoE
▪ Reduction of fear	2b
▪ Trust in treating oncologists is increased	2b
▪ Treatment satisfaction is increased	2a
▪ Therapy adherence is increased	2a
▪ Decision making is improved	2a
▪ Mental complaints are improved	2a

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Health Literacy

Communication

	Oxford LoE	AGO
Qualified training measures can help to promote communicative skills.		+
communication training for doctors can e.g.		
▪ **Enhance empathy**	2a	
▪ **Extend and enrich communication skills**	2a	
▪ **Increase patient satisfaction (information, support, consideration of concerns)**	2b	
▪ **Improve transmission of information**	2b	

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Health Literacy

Shared Decision Making - Participatory Decision

	Oxford		
	LoE	GR	AGO
▪ Patients want to be integrated actively into decision making and open discussions about prognosis, treatment options, and quality of life	1b	A	
▪ Doctors should motivate patients to ask questions, demand clarification, express emotions, opinions, and preferences	3b	C	+

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Health Competence
Decision Support for Patients

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	Oxford LoE	AGO
The use of decision support in the physician-patient communication		+
▪ improves knowledge about treatment options	1a	
▪ reduces the decision conflict	1a	
▪ improves the level of information	1a	
▪ increases the feeling about the clarity of personal values	1a	
▪ encourages a more active role in decision-making	2b	
▪ improves risk perception	2b	
▪ improves the match between the chosen option and the patient's values	3a	

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Therapy Algorithms

Preamble:

Therapy options shown in the algorithms are based on the current AGO recommendations, but cannot represent all evidence-based treatment options, since prior therapies, performance status, comorbidities, patient preference, special tumor biology etc. must be taken into account for the actual treatment choice.

In individual cases, other evidence-based treatment options (not listed here) may also be appropriate and justified.

Regardless of approval status, the algorithms only take into account drugs that were available in Germany at the time the algorithm was last updated.

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Therapy Algorithms

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- **Version 2021:**
  Schneeweiss / Bauerfeind / Fehm / Müller / Thomssen / Witzel / Wöckel / Janni

- **Version 2022:**
  Schneeweiss/ Müller with the Breast Committee of the AGO

- **Format legend:**
  - Text — **Definitions, features, parameters**
  - Text — **Therapy with grade of recommendation AGO+ or AGO++**
  - Text — **Therapy with grade of recommendation AGO+/- (case by case decision)**
  - **Recommended path with grade of recommendation AGO+ oder AGO++**
  - **Crossing without transition**
  - **Path of case by case decision (grade of recommendation AGO+/-)**
  - **Arrow points to the next therapy option**
  - *AGO++* — **AGO grade of recommendation of this path**

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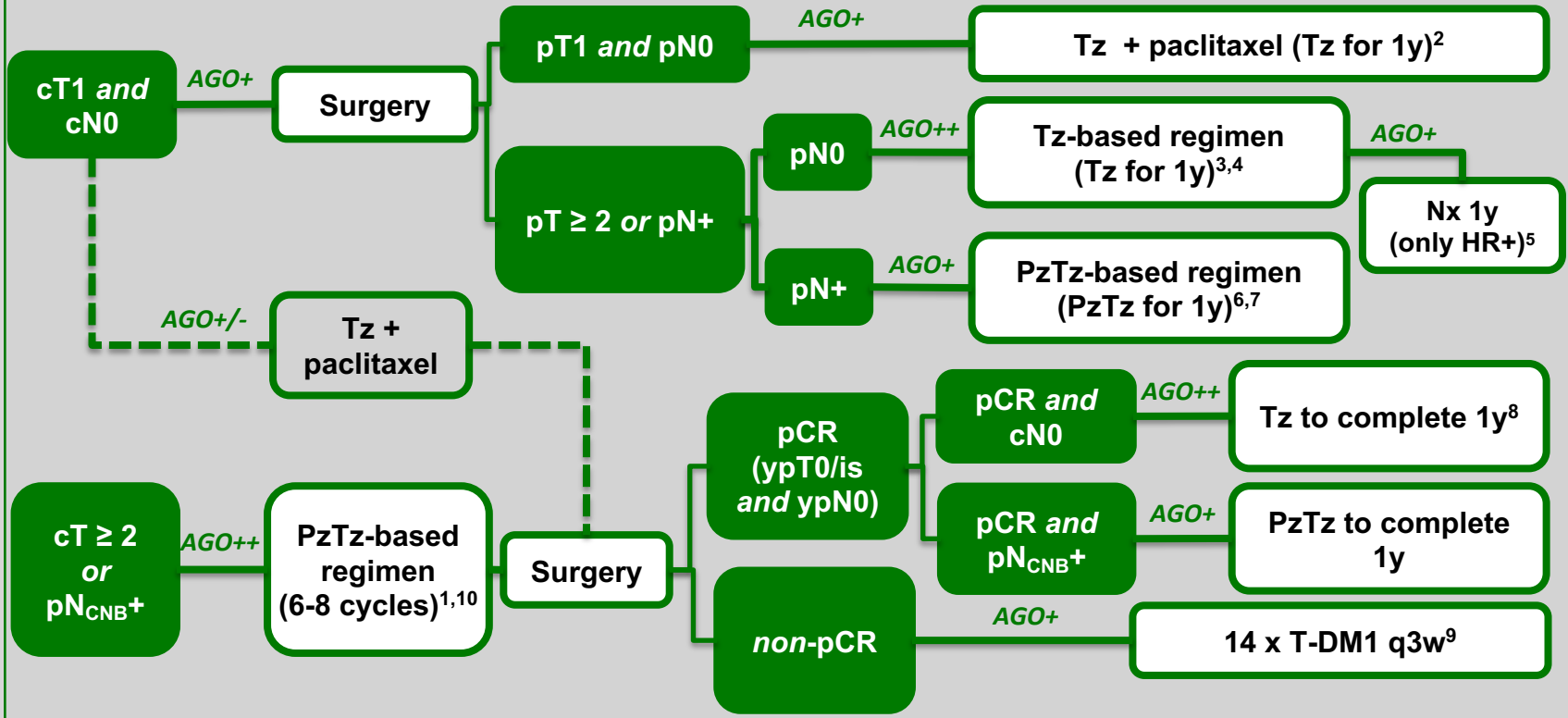
Content

- **eBC**
  - **(Neo)adjuvant therapy of HER2-positive breast cancer**
  - **(Neo)adjuvant therapy of triple-negativem breast cancer**
  - **Axillary surgery and neoadjuvant chemotherapy (NACT)**
  - **Adjuvant endocrine therapy in premenopausal patients**
  - **Adjuvant endocrine therapy in postmenopausal patients**

- **mBC**
  - **HR-positive / HER2-negative metastatic breast cancer: strategies**
  - **HR-positive / HER2-negative metastatic breast cancer: endocrine-based first line treatment**
  - **HER2-positive metastatic breast cancer: 1st-3rd-line**
  - **Triple-negative metastatic breast cancer**

(Neo)adjuvant Therapy of HER2-positive Breast Cancer



CNB, core needle biopsy; HR, hormone receptor; Nx, Neratinib; pCR, pathological complete response; Pz, Pertuzumab; q3w, every 3 weeks; T-DM1, Trastuzumab emtansine; Tz, Trastuzumab; y, year; if HR+ adjuvant endocrine therapy

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(Neo)adjuvant Therapy of Triple-negative Breast Cancer

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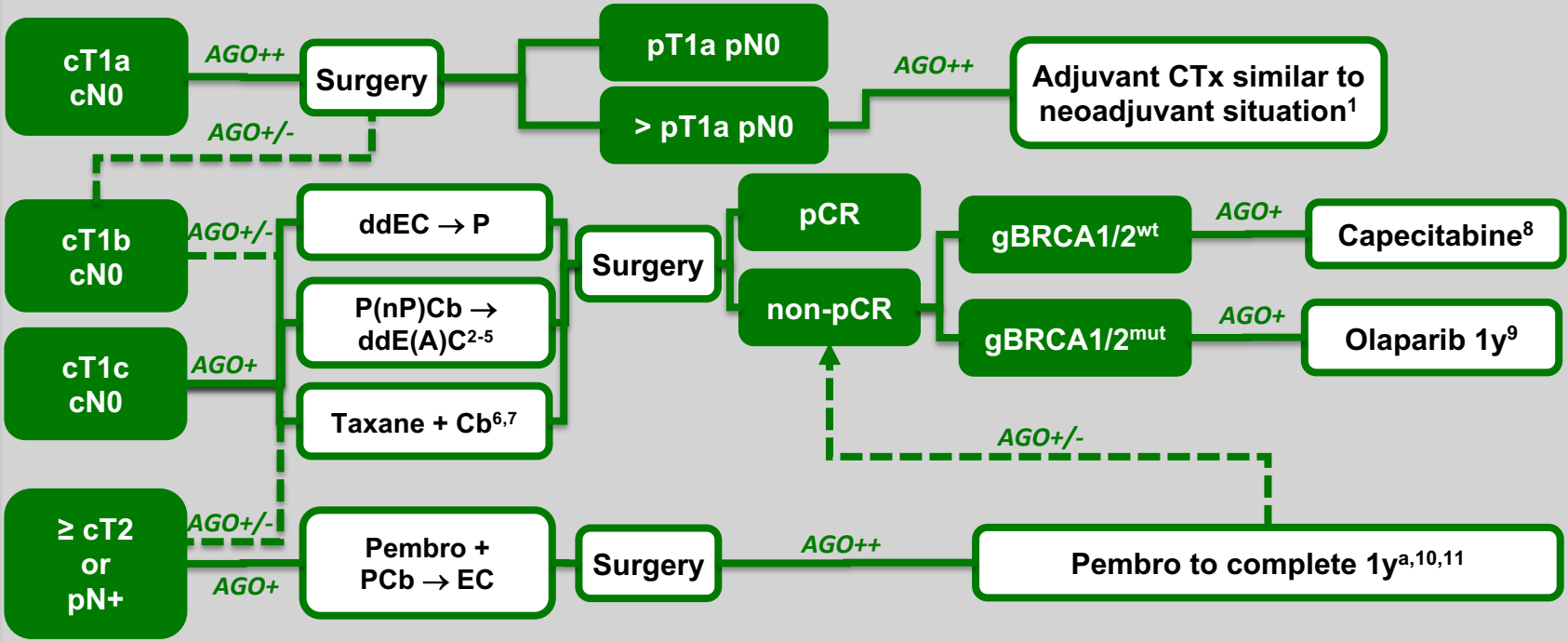

A, doxorubicin; C, cyclophosphamide; Cb, carboplatin; CTx, chemotherapy; dd, dose dense (every 2 weeks); E, epirubicin; mut, mutated; nP, nab-paclitaxel; Pembro, pembrolizumab; P, paclitaxel; wt, wild type; y, year; [a] if Pembro was started before surgery

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Axillary Surgery and Neoadjuvant Chemotherapy (NACT)

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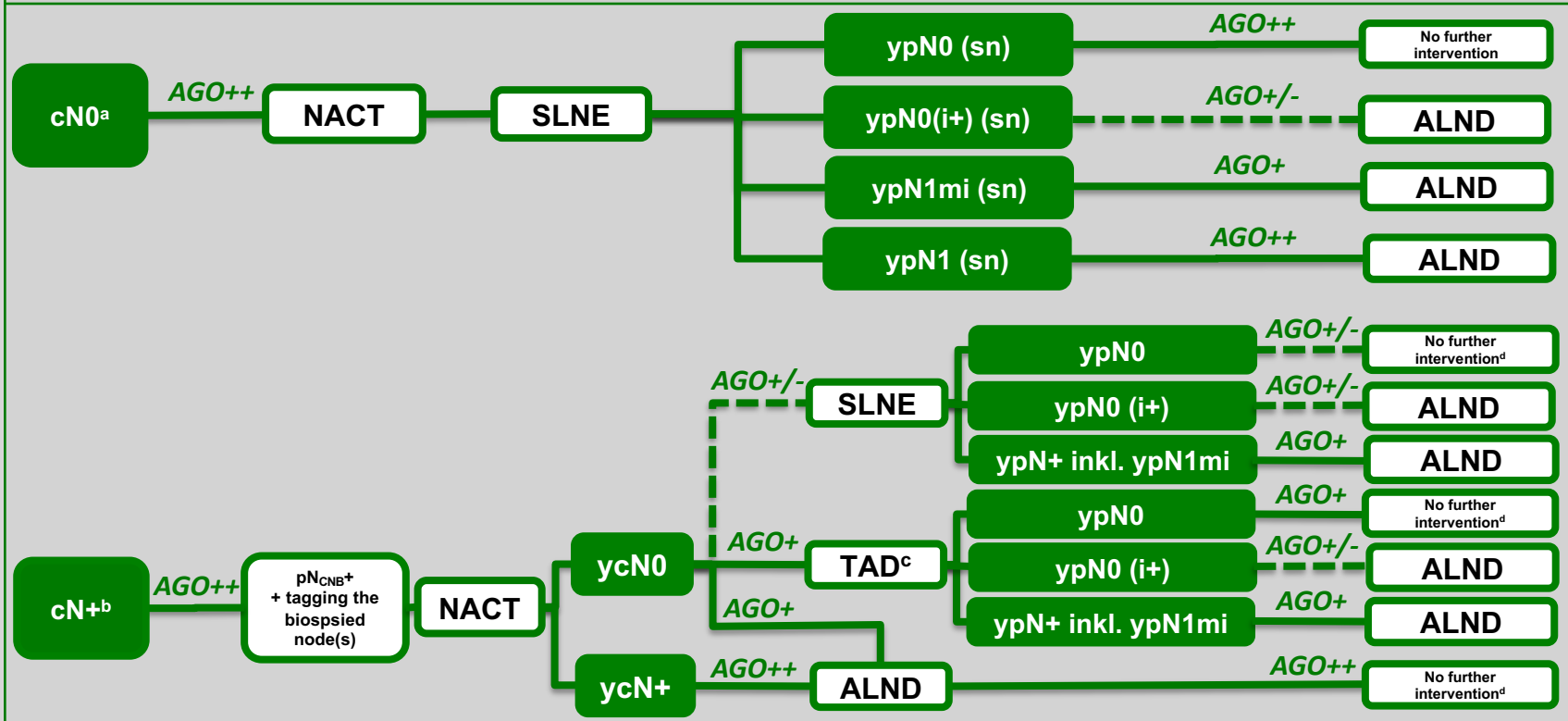

ALND, axillary lymph node dissection; CNB, core needle biopsy; NACT, neoadjuvant chemotherapy; SN, sentinel node; SLNE, sentinel lymph node excision; TAD , targeted axillary dissection (SLNE + TLNE); TLNE, targeted lymph node excision; [a] participation in EUBREAST-01 study recommended; [b] participation in AXSANA study recommended; [c] TAD in case of 1-3 suspicious lymph nodes before NACT: +, in case of ≥ 4 suspicious lymph nodes before NACT: +/-; [d] for radiotherapy procedures see recommendations for radiotherapy

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Adjuvant Endocrine-based Therapy in Premenopausal Patients

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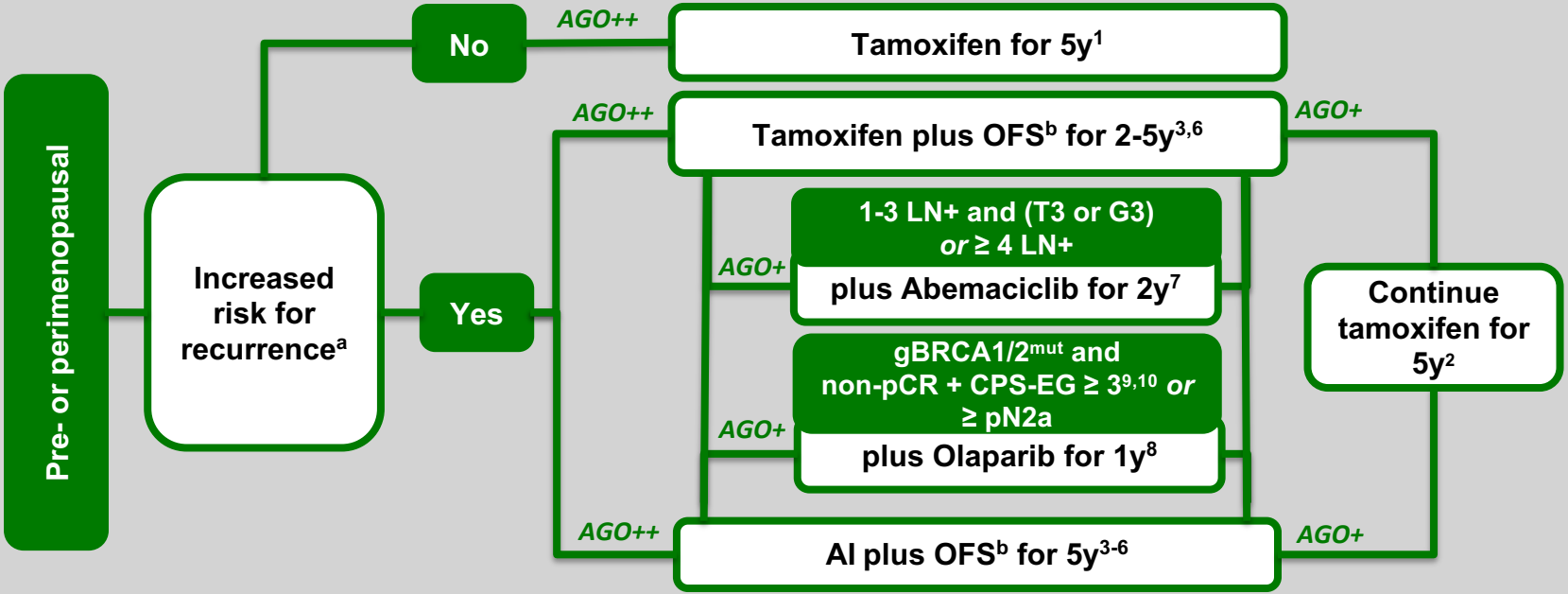

AI, aromatase inhibitor; CPS-EG, clinical pathological stage + estrogen receptor status and grade score; gBRCA1/2[mut], germ line BRCA1/2 mutation; LN, lymph node; OFS, ovarian function suppression; pCR, pathologic complete response; y, years; [a] Administration of chemotherapy was a surrogate marker for higher risk of recurrence in clinical trials; [b] OFS also in case of remaining or recurring ovarian function within 24 months after chemotherapy induced amenorrhea

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Adjuvant Endocrine-based Therapy in Postmenopausal Patients

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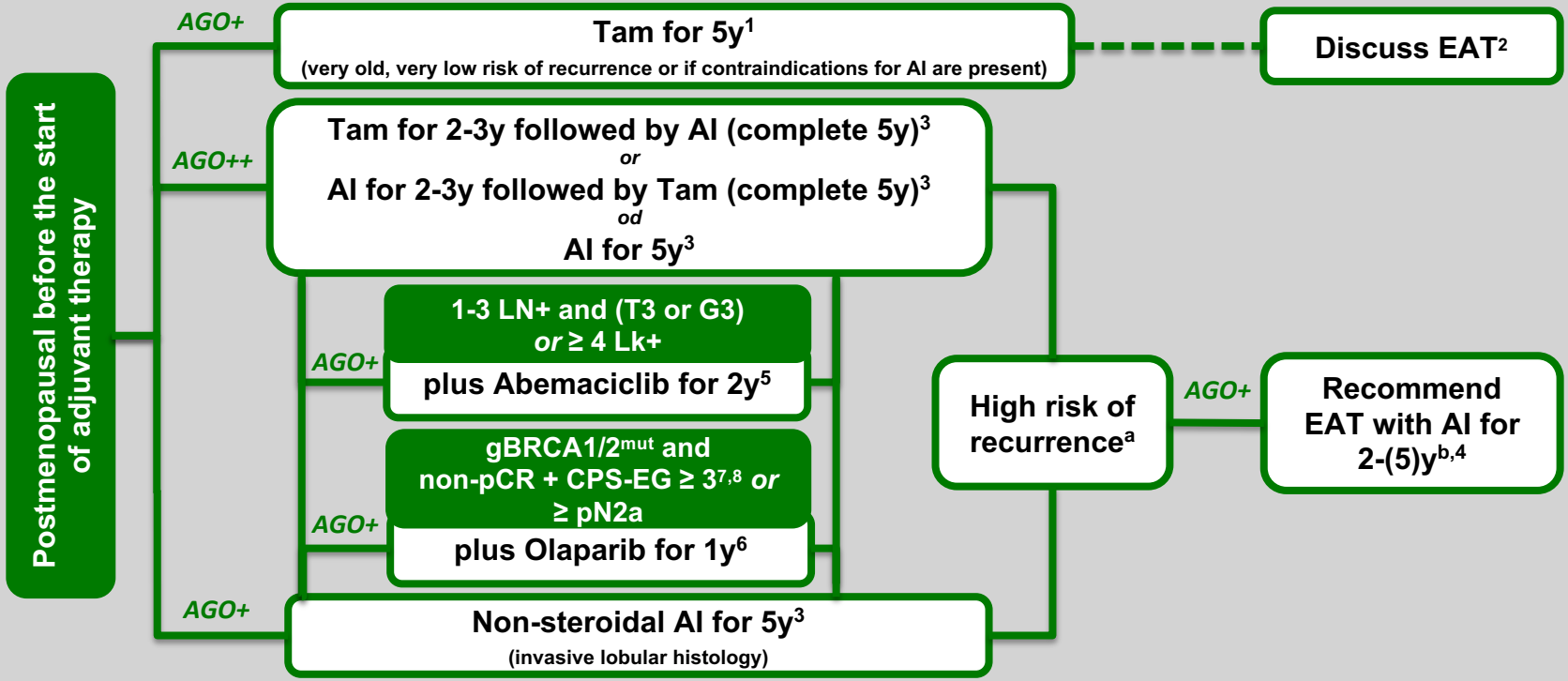

AI, aromatase inhibitor; CPS-EG, clinical pathological stage + estrogen receptor status and grade score; EAT, extended adjuvant therapy; gBRCA1/2^{mut}, germ line BRCA1/2 mutation; LN, lymph node; Tam, tamoxifen; y, years; [a] decision criteria may include: condition after neo(adjuvant) chemotherapy (indicating high risk), positive lymph node status, T2/T3 tumors, elevated risk of recurrence based on immuno-histochemical criteria or based on multi-gene expression assays, high CTS5-Score; [b] up to date no impact on overall survival

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HR-positive/HER2-negative Metastatic Breast Cancer: Strategies

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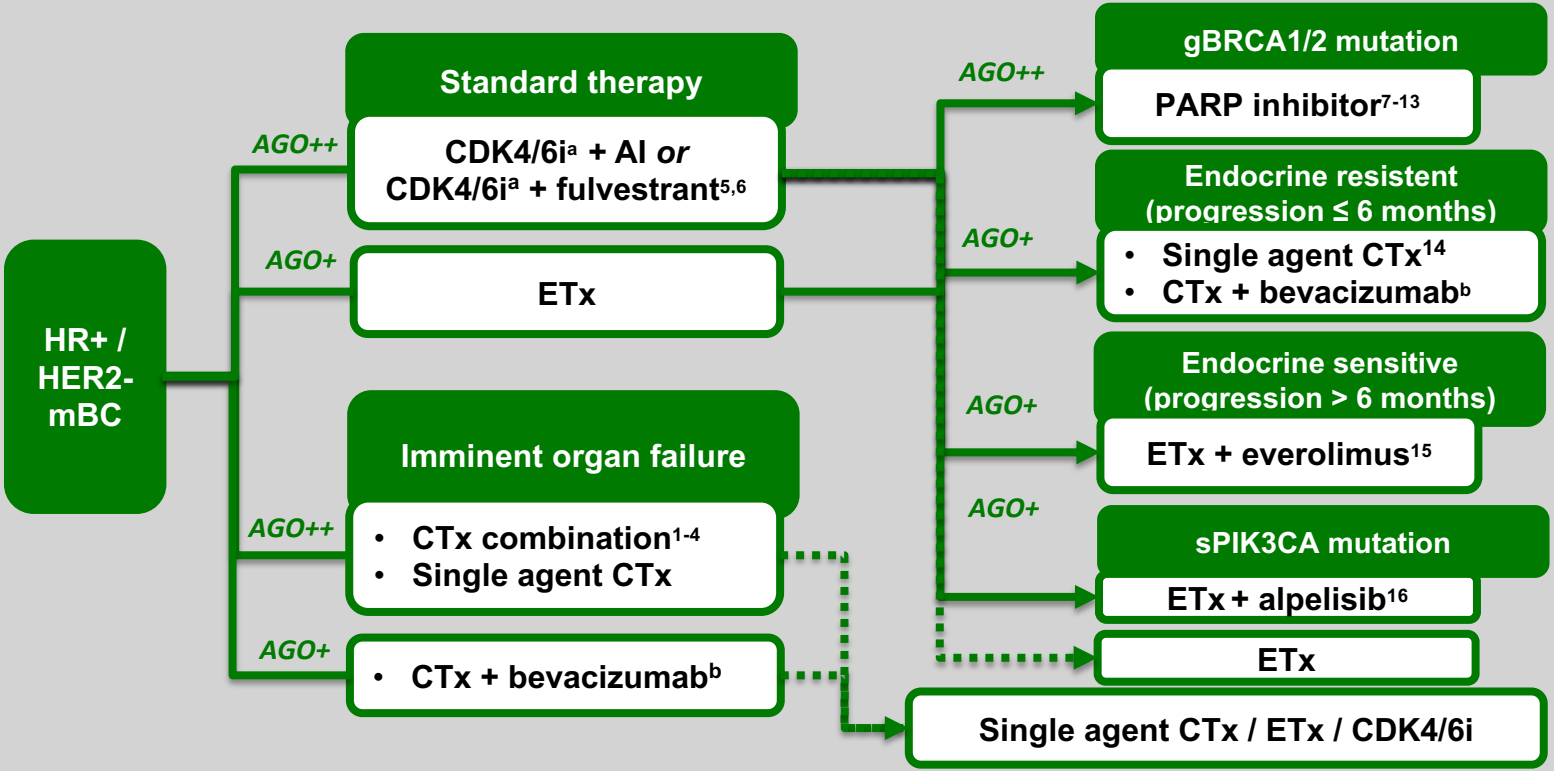

AI, aromatase inhibitor; CDK4/6i, CDK4/6 inhibitor; CTx, chemotherapy; ETx, endocrine therapy; gBRCA1/2, germ line BRCA1/2; HR, hormone receptor; mBC, metastatic breast cancer; sPIK3CA, somatic PIK3CA mutation; [a] premenopausal add ovarian function suppression; [b] bevacizumab + paclitaxel or + capecitabine

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HR-positive / HER2-negative Metastatic Breast Cancer: Endocrine-based First Line Treatment

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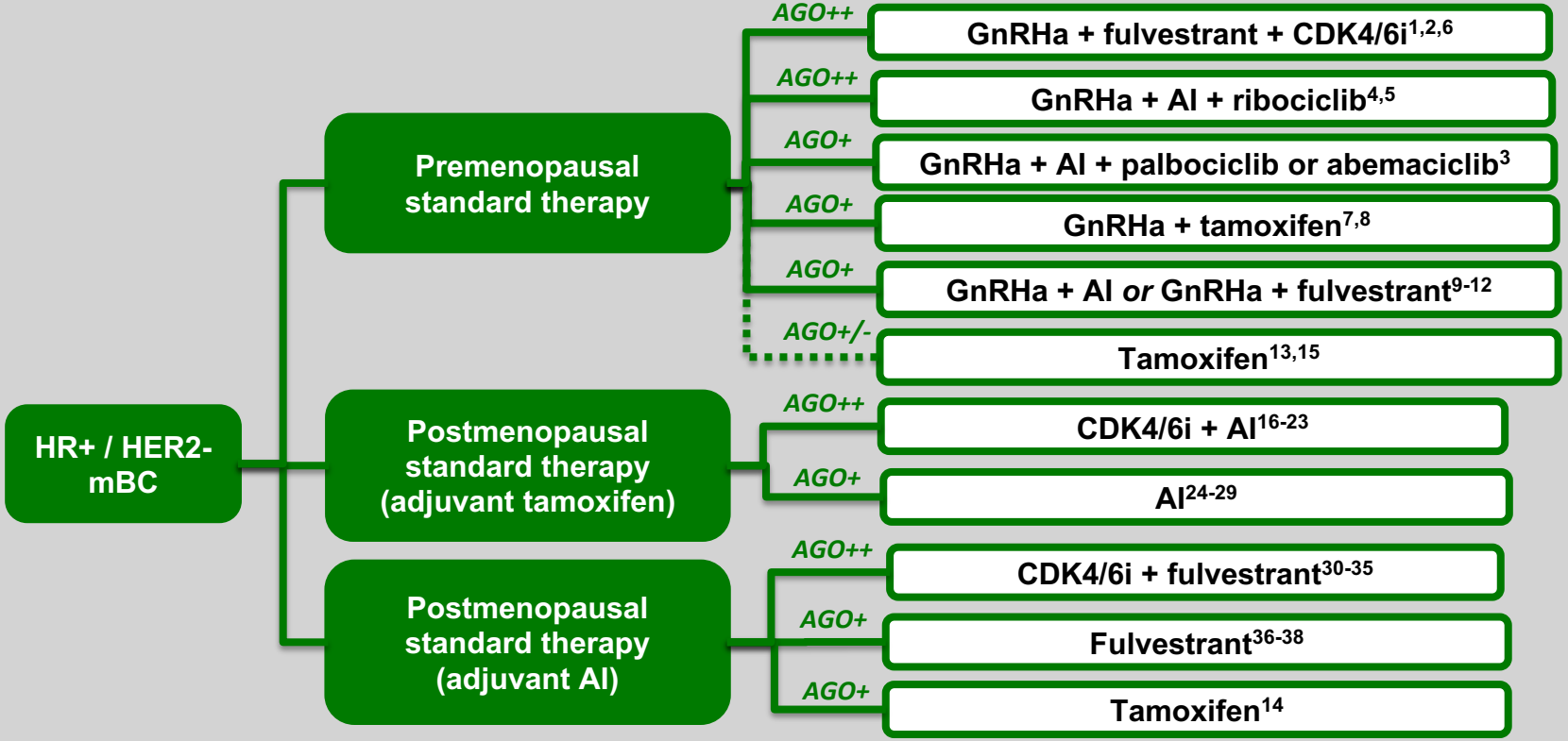

AI, aromatase inhibitor; CDK4/6i, CDK4/6 inhibitor; GnRHa, GnRH agonist; HR, hormone receptor; mBC, metastatic breast cancer

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HER2-positive Metastatic Breast Cancer: 1st-3rd-line

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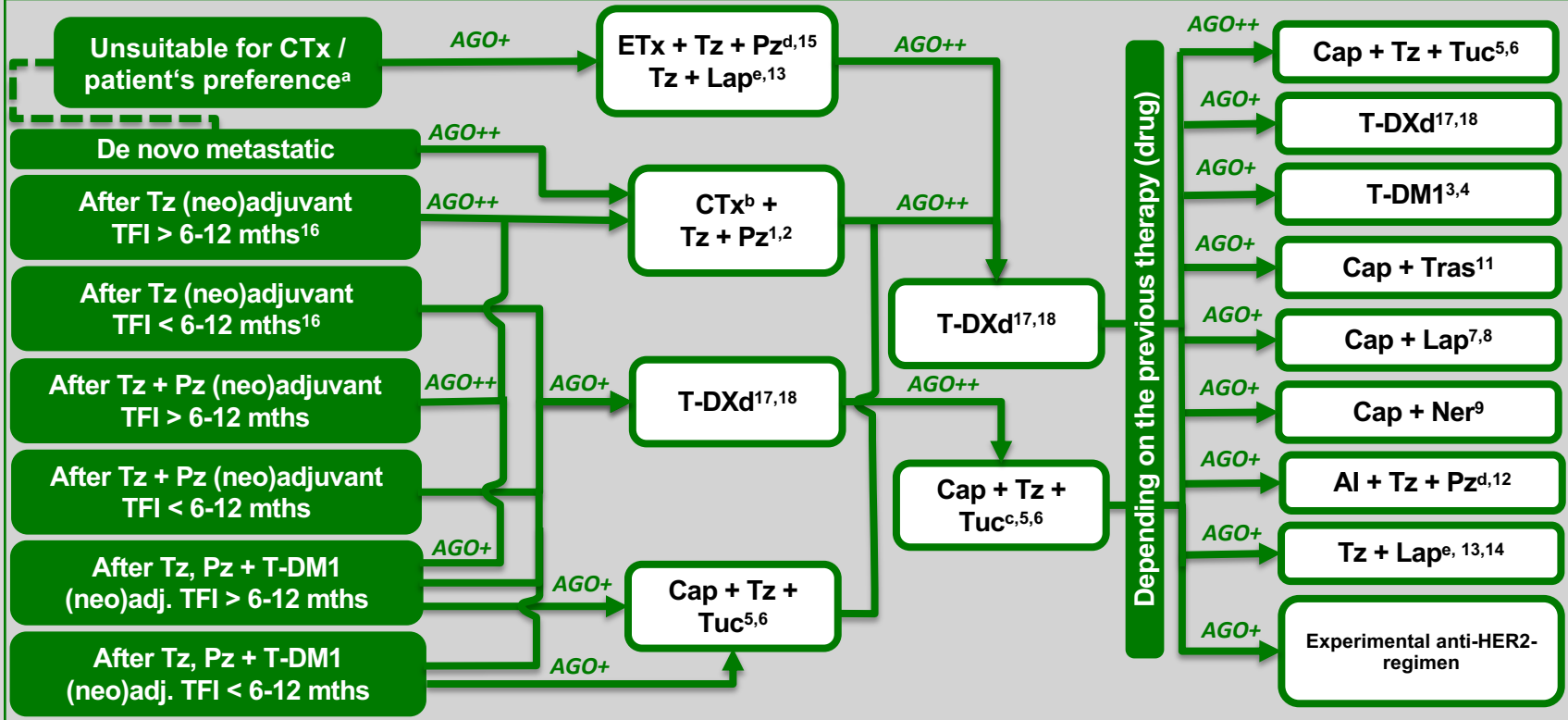

AI, aromatase inhibitor; Cap, capecitabine; CTx, chemotherapy; ETx, endocrine therapy; HR, hormone receptor; Lap, lapatinib; mths, months; Ner, neratinib; Pz, pertuzumab; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TFI, treatment-free interval; Tuc, tucatinib; Tz, trastuzumab; [a] no overall survival benefit, consider induction chemotherapy; [b] docetaxel (++), paclitaxel (++) or nab-paclitaxel (+); [c] only after T-DM1; [d] only if HR pos; [e] only if HR neg

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Triple-negative Metastatic Breast Cancer

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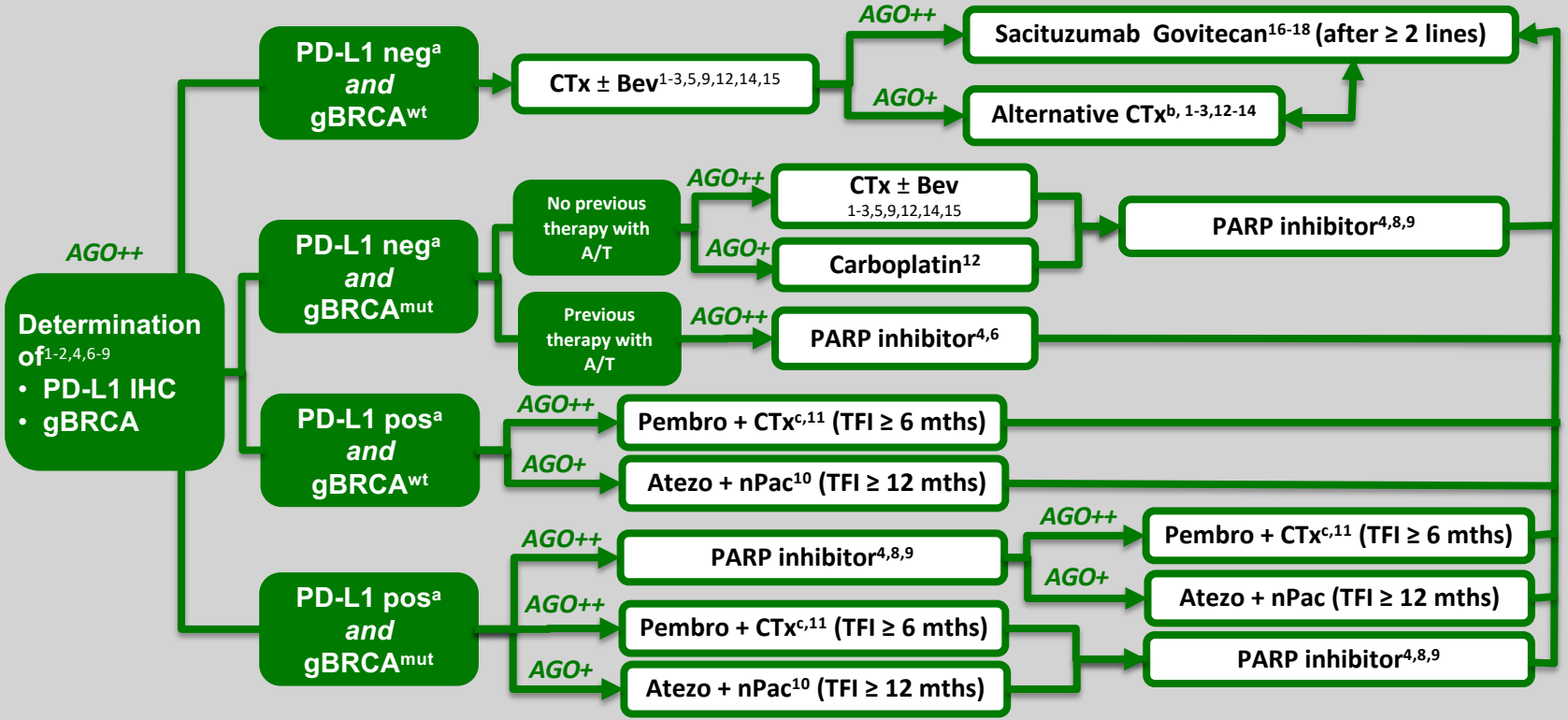

A, anthracycline; Atezo, atezolizumab; Bev, bevacizumab; CTx, chemotherapy; gBRCA, germ line BRCA status; IHC, immunohistochemistry; mths, months; mut, mutated; neg, negative; ; nPac, nab-paclitaxel; Pembro, pembrolizumab; PD-L1, programmed cell death ligand 1; pos, positive; T, taxane; TFI, treatment-free interval; wt, wild type; [a] Pembro: CPS < 10 (neg) oder CPS ≥ 10 (pos), Atezo: IC < 1% (neg), IC ≥ 1% (pos); [b] use of not previously used compounds or regimen; [c] nPac, Pac or Carboplatin+Gemcitabin

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