Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Supportive Care and Management of Side Effects

Guidelines Breast
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Supportive Care and Management of Side Effects

- **Versions 2002–2023:**
  Albert / Bauerfeind / Brunnert / Bischoff / Costa / Dall / Diel / Fersis / Friedrich / Friedrichs / Gerber / Göhring / Hanf / Harbeck / Heinrich / Huober / Jackisch / Lisboa / Lück / Lüftner / Maass / von Minckwitz / Möbus / Müller / Mundhenke / Nitz / Oberhoff / Park-Simon / Reimer/ Rody / Schaller / Scharl / Schmidt / Schneeweiss / Schütz / Solomayer / Souchon / Stickeler / Thomssen / Untch

- **Version 2024:**
  Kolberg-Liedtke / Würstlein

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 (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
(acc. ICPC[3] following symptoms or acc. ICD-10-GM[4] following diagnoses) **LoE 5 D AGO ++**

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.

ADL = Activities of Daily Living

*** 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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Use of eHealth (DiGA)

	Oxford		
	LoE	GR	AGO
Use of DiGA to improve quality of life during and after breast cancer therapy	2b	B	+/-
Use of PROs for improved collection of therapy-associated side effects and quality of life	2b	B	+/-

* See current DiGA status / reimbursement

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)

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)

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

	Oxford		
	LoE	GR	AGO
DPD (Dihydropyrimidin-Dehydrogenase) - Deficiency Testing (*DPYD*-Genotype or Phenotype)	1a	A	++

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**

Endocrine Therapy – Toxicities

	Tamoxifen	Anastrazole	Exemestane	Letrozole	Fulvestrant	Elacstrant
Infections / Infestations	-	-	-	3	4	-
Neoplasms (benin, malignant, unspecified)	3	-	-	-	-	-
Blood and lymphatic system disorders	4	-	4	3	3	-
Immune system disorders (allergies)	-	-	-	-	4	-
Endocrine disorders	3	-	-	-	-	5
Metabolism and nutrition disorders	5	4	4	5	4	5
Psychiatric disorders	-	5	5	4	-	5
Nervous system disorders	4	5	4	4	4	-
Eye disorders	4	4	-	3	-	-
Ear and lapyrinth disorders	-	-	-	-	-	-
Cardiac disorders	-	4	-	3	-	-
Vascular disorders (including hot flashes)	4	5	5	5	4	5

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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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Endocrine Therapy – Toxicities

	Tamoxifen	Anastrazole	Exemestane	Letrozole	Fulvestrant	Elacstrant
Respiratory, thoracic and mediastinal disorders	3	-	-	3	-	-
Gastrointestinal disorders (nausea, emesis)	5	5	5	4	5	5
Hepatobiliary disorders	4	4	-	3	5	4
Skin and subcutis disorders (incl alopecia)	5	5	5	5	4	-
Musculosceletal and connective tissue	4	5	5	5	4	5
Renal and urinary disorders	-	-	-	3	4	-
Pregnancy, peurperal and perinatal disorders	-	-	-	-	-	-
Reproductive tract and breast disorders	5	5	-	4	3	-
General disorders / administration site conditions	5	5	5	5	5	-
Congenital, familiary and genetic disorders	1	-	-	-	-	-
Special features	*	**	**	**	***	
* Hot flushes; rarely endometrial cancer, thrombosis ** hot flashes, arthralgia, osteoporosis, cognition ***hot flushes						

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

	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
Bevacizumab		
▪ Hypertension, proteinuria, bleeding, left ventricular dysfunction	1a	A

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

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 – Antibody-Drug-Conjugates

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	Oxford LoE	Oxford GR
Sacituzumab Govitecan		
▪ (Febrile) neutropenia, leukopenia, anemia, diarrhea, nausea, alopecia, fatigue	1b	A
Trastuzumab-Emtansin (T-DM1)		
Thrombozytopenia, elevation liver enzymes, pyrrexia, headache pneumonitis, neuropathy, fatigue	1b	A
Trastuzumab-Deruxtecan		
Interstitial lung disease, neuropenia, nausea, alopecia, fatigue	1b	A

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

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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			

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%)

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

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

Characterization of VTE (DVT or PE)*

- 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

QT-Interval-Prolongation: Ribociclib vs. Placebo

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Post-baseline prolongation QT-interval > 480 msec 6,9% vs. 1,2%

Post-baseline prolongation QT-interval > 500 msec 1,5% vs. 0,3%

Dicsontinuation due to QT-interval prolongation 0,3% vs. 0,6%

Prolongation of QT-interval is not associated with clinical symptoms, but with an increased risk of the life-threatening arrhythmia torsades de pointes (TdP)

Use of QT check tools might be helpful (www.arzneimitteltherapie.de)

Toxicities of mTOR-Inhibitor (Everolimus)

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	++

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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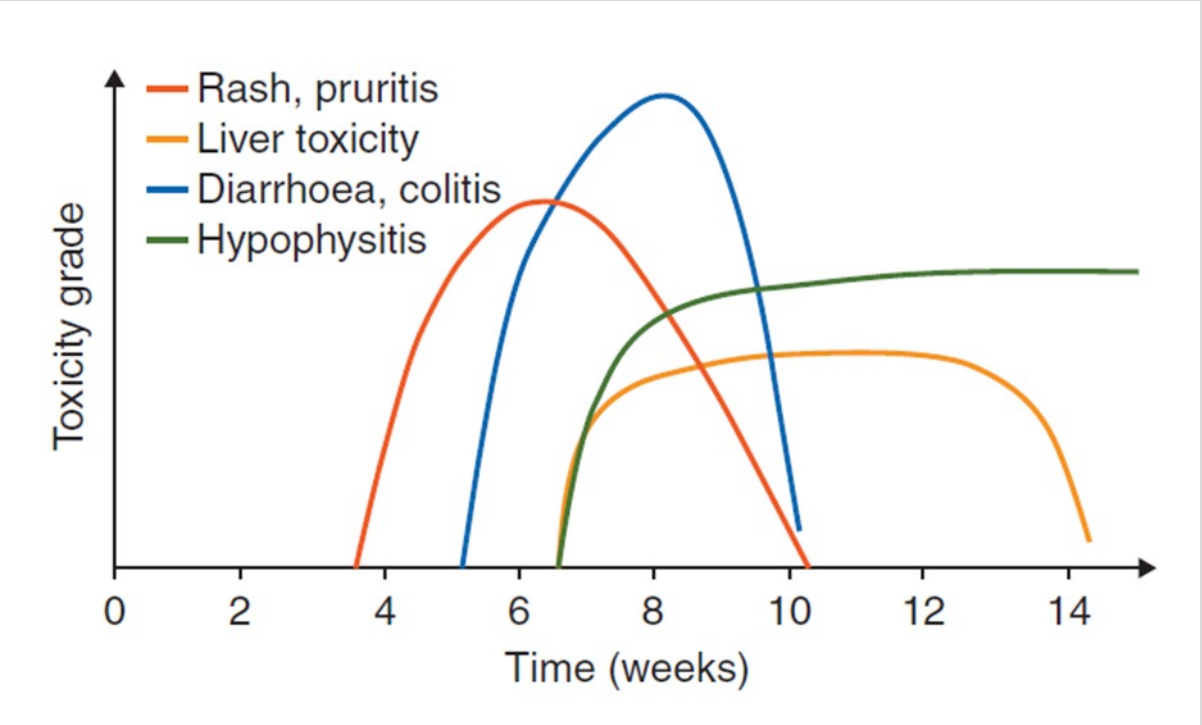
Immune Checkpoint Inhibitors

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

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

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

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



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**

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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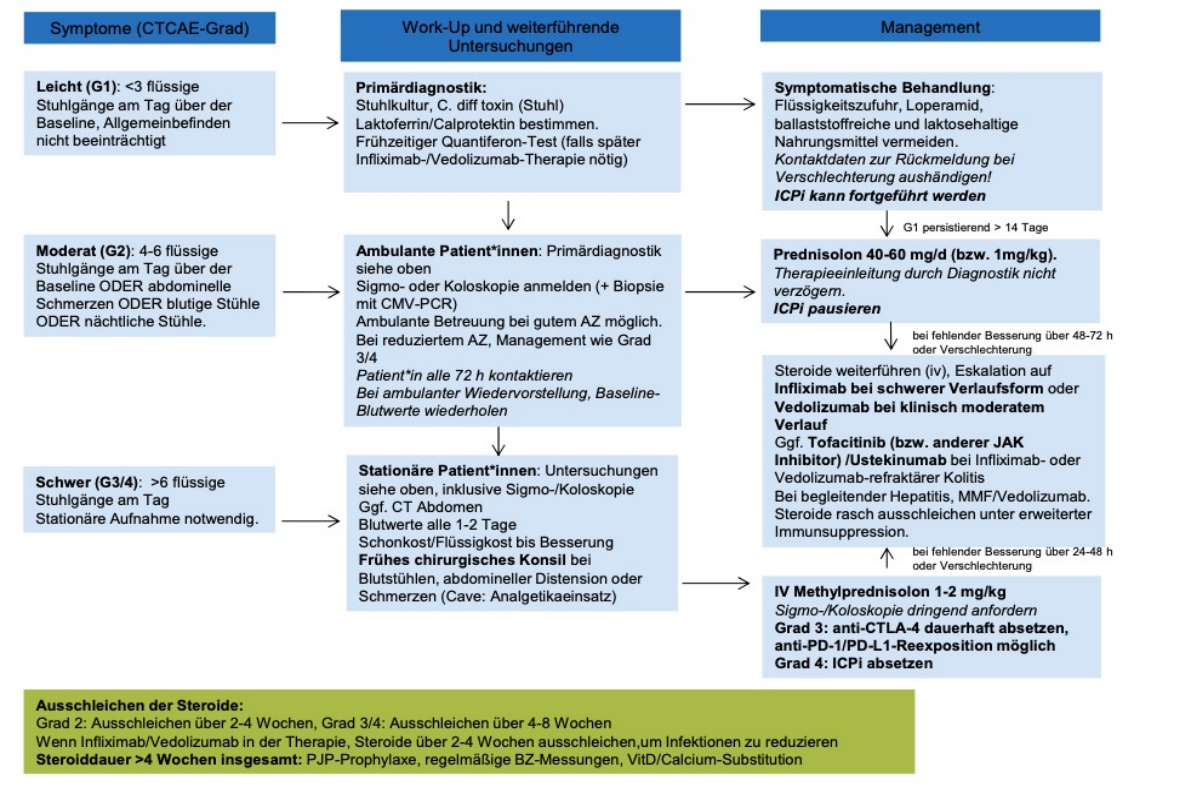
Diarrhoea and Colitis



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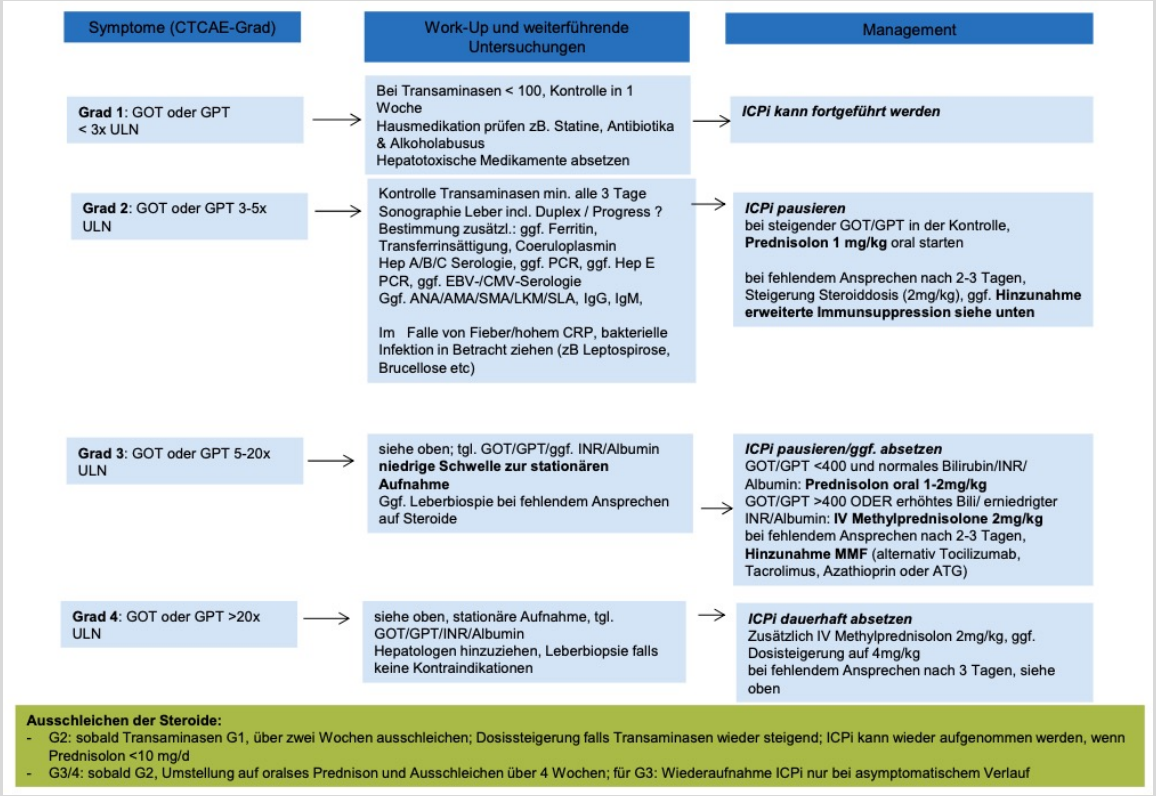
HEILEN

Hepatitis



Symptome (CTCAE-Grad)	Work-Up und weiterführende Untersuchungen	Management
Grad 1: GOT oder GPT < 3x ULN	Bei Transaminasen < 100, Kontrolle in 1 Woche Hausmedikation prüfen zB. Statine, Antibiotika & Alkoholabusus Hepatotoxische Medikamente absetzen	***ICPi kann fortgeführt werden***
Grad 2: GOT oder GPT 3-5x ULN	Kontrolle Transaminasen min. alle 3 Tage Sonographie Leber incl. Duplex / Progress ? Bestimmung zusätzl.: ggf. Ferritin, Transferrinsättigung, Coeruloplasmin Hep A/B/C Serologie, ggf. PCR, ggf. Hep E PCR, ggf. EBV-/CMV-Serologie Ggf. ANA/AMA/SMA/LKM/SLA, IgG, IgM, Im Falle von Fieber/hohem CRP, bakterielle Infektion in Betracht ziehen (zB Leptospirose, Brucellose etc)	***ICPi pausieren*** bei steigender GOT/GPT in der Kontrolle, **Prednisolon 1 mg/kg** oral starten bei fehlendem Ansprechen nach 2-3 Tagen, Steigerung Steroiddosis (2mg/kg), ggf. **Hinzunahme erweiterte Immunsuppression siehe unten**
Grad 3: GOT oder GPT 5-20x ULN	siehe oben; tgl. GOT/GPT/ggf. INR/Albumin **niedrige Schwelle zur stationären Aufnahme** Ggf. Leberbiospie bei fehlendem Ansprechen auf Steroide	***ICPi pausieren/ggf. absetzen*** GOT/GPT <400 und normales Bilirubin/INR/ Albumin: **Prednisolon oral 1-2mg/kg** GOT/GPT >400 ODER erhöhtes Bili/ erniedrigter INR/Albumin: **IV Methylprednisolone 2mg/kg** bei fehlendem Ansprechen nach 2-3 Tagen, **Hinzunahme MMF** (alternativ Tocilizumab, Tacrolimus, Azathioprin oder ATG)
Grad 4: GOT oder GPT >20x ULN	siehe oben, stationäre Aufnahme, tgl. GOT/GPT/INR/Albumin Hepatologen hinzuziehen, Leberbiopsie falls keine Kontraindikationen	***ICPi dauerhaft absetzen*** Zusätzlich IV Methylprednisolon 2mg/kg, ggf. Dosisteigerung auf 4mg/kg bei fehlendem Ansprechen nach 3 Tagen, siehe oben

Ausschleichen der Steroide:
- G2: sobald Transaminasen G1, über zwei Wochen ausschleichen; Dosissteigerung falls Transaminasen wieder steigend; ICPi kann wieder aufgenommen werden, wenn Prednisolon <10 mg/d
- G3/4: sobald G2, Umstellung auf oralses Prednison und Ausschleichen über 4 Wochen; für G3: Wiederaufnahme ICPi nur bei asymptomatischem Verlauf

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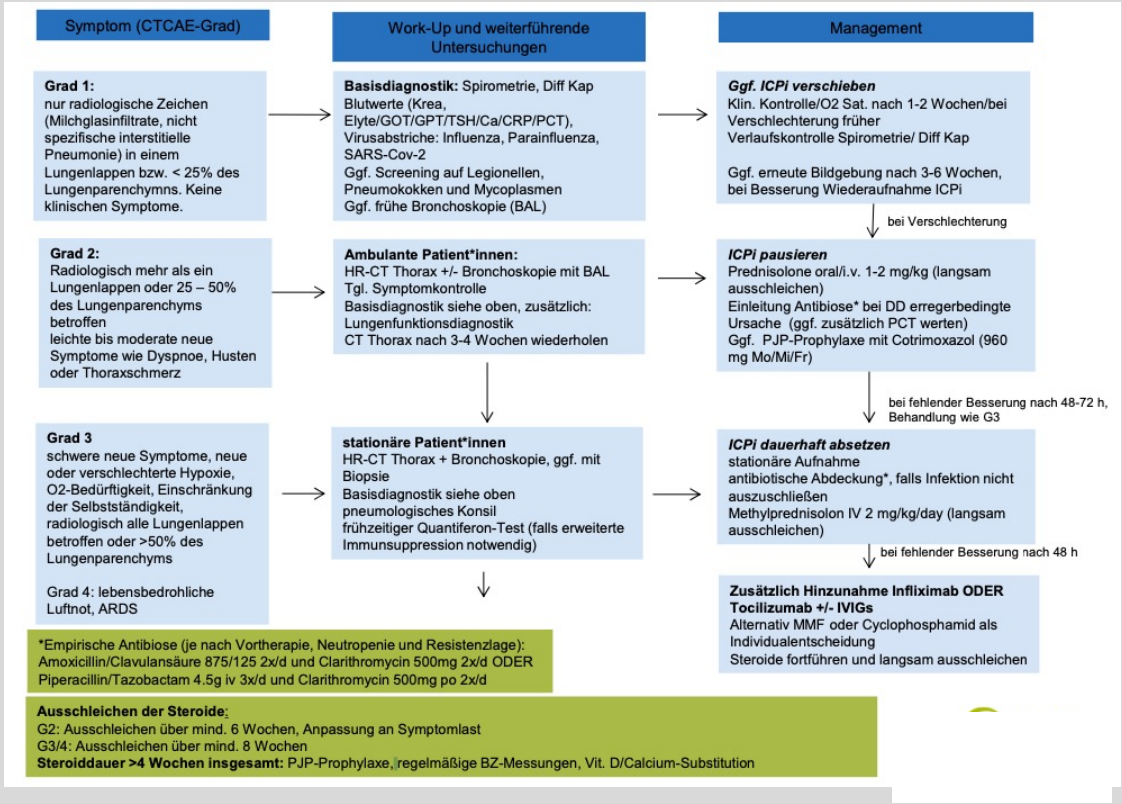
Pneumonitis



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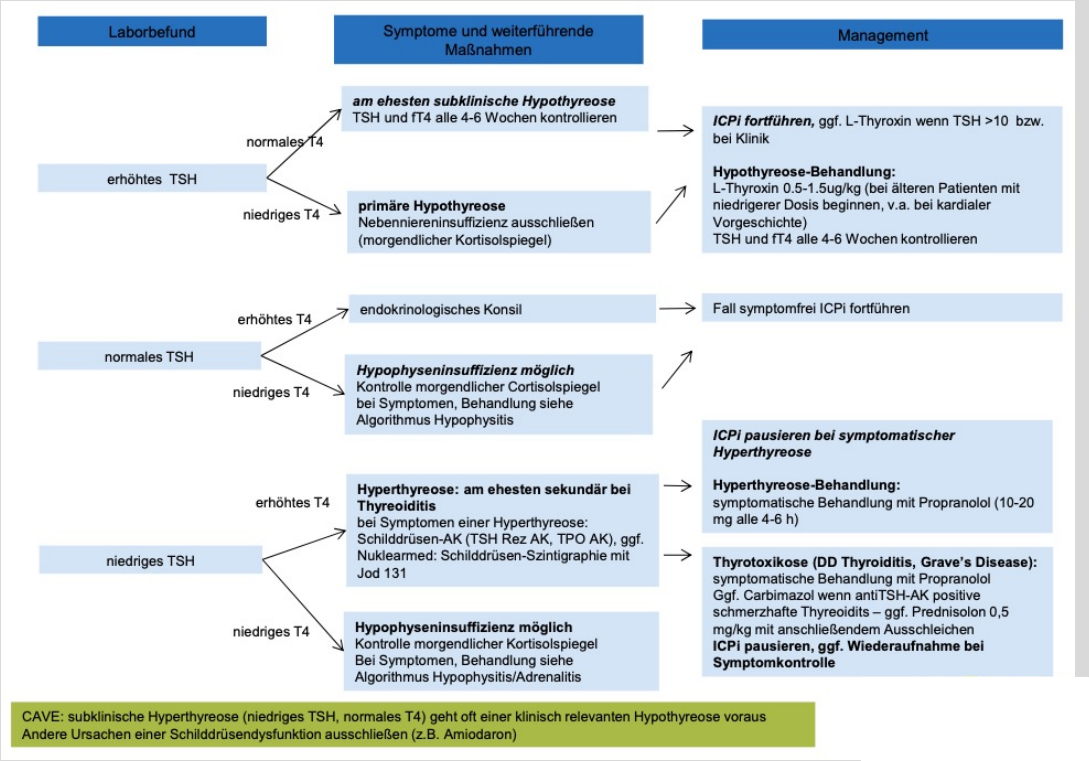
Thyreoiditis



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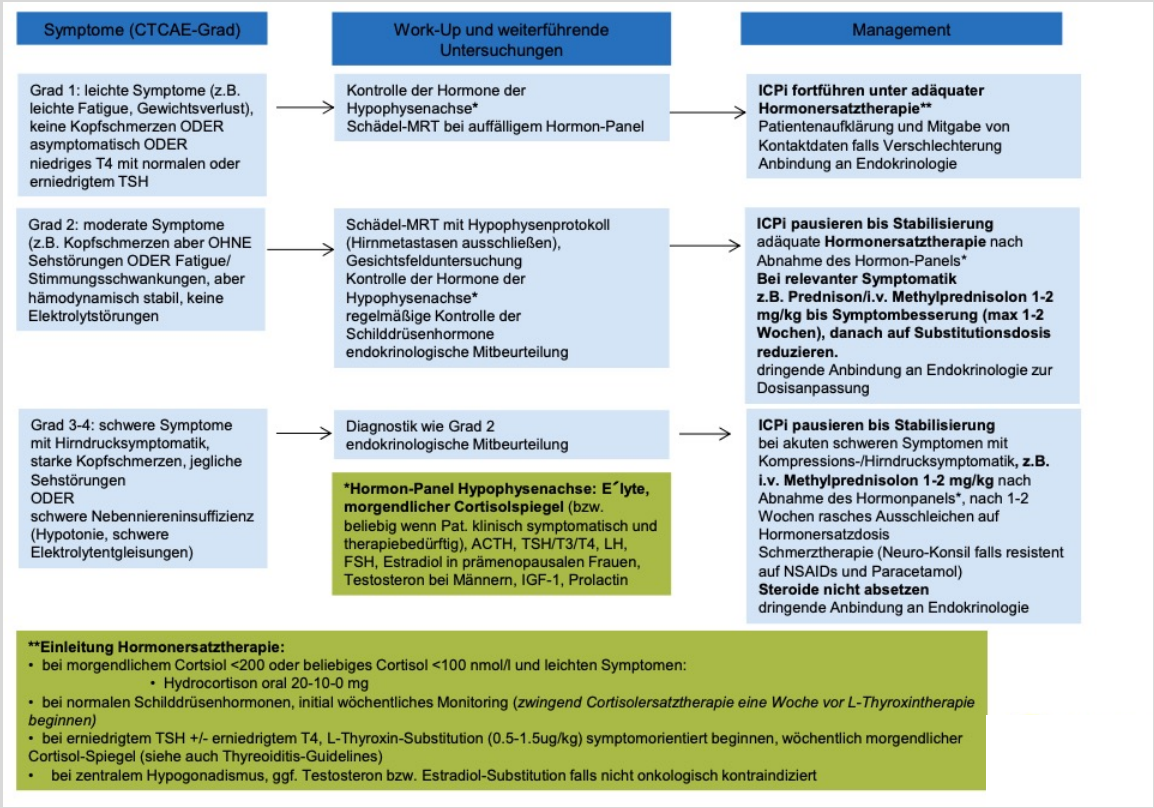
Hypophysitis



Symptome (CTCAE-Grad)	Work-Up und weiterführende Untersuchungen	Management
Grad 1: leichte Symptome (z.B. leichte Fatigue, Gewichtsverlust), keine Kopfschmerzen ODER asymptomatisch ODER niedriges T4 mit normalen oder erniedrigtem TSH	Kontrolle der Hormone der Hypophysenachse* Schädel-MRT bei auffälligem Hormon-Panel	**ICPi fortführen unter adäquater Hormonersatztherapie**** Patientenaufklärung und Mitgabe von Kontaktdaten falls Verschlechterung Anbindung an Endokrinologie
Grad 2: moderate Symptome (z.B. Kopfschmerzen aber OHNE Sehstörungen ODER Fatigue/ Stimmungsschwankungen, aber hämodynamisch stabil, keine Elektrolytstörungen	Schädel-MRT mit Hypophysenprotokoll (Hirnmetastasen ausschließen), Gesichtsfelduntersuchung Kontrolle der Hormone der Hypophysenachse* regelmäßige Kontrolle der Schilddrüsenhormone endokrinologische Mitbeurteilung	**ICPi pausieren bis Stabilisierung** adäquate **Hormonersatztherapie** nach Abnahme des Hormon-Panels* **Bei relevanter Symptomatik z.B. Prednison/i.v. Methylprednisolon 1-2 mg/kg bis Symptombesserung (max 1-2 Wochen), danach auf Substitutionsdosis reduzieren.** dringende Anbindung an Endokrinologie zur Dosisanpassung
Grad 3-4: schwere Symptome mit Hirndrucksymptomatik, starke Kopfschmerzen, jegliche Sehstörungen ODER schwere Nebenniereninsuffizienz (Hypotonie, schwere Elektrolytentgleisungen)	Diagnostik wie Grad 2 endokrinologische Mitbeurteilung ***Hormon-Panel Hypophysenachse: E´lyte, morgendlicher Cortisolspiegel** (bzw. beliebig wenn Pat. klinisch symptomatisch und therapiebedürftig), ACTH, TSH/T3/T4, LH, FSH, Estradiol in prämenopausalen Frauen, Testosteron bei Männern, IGF-1, Prolactin	**ICPi pausieren bis Stabilisierung** bei akuten schweren Symptomen mit Kompressions-/Hirndrucksymptomatik, **z.B. i.v. Methylprednisolon 1-2 mg/kg** nach Abnahme des Hormonpanels*, nach 1-2 Wochen rasches Ausschleichen auf Hormonersatzdosis Schmerztherapie (Neuro-Konsil falls resistent auf NSAIDs und Paracetamol) **Steroide nicht absetzen** dringende Anbindung an Endokrinologie

****Einleitung Hormonersatztherapie:**

- bei morgendlichem Cortsiol <200 oder beliebiges Cortisol <100 nmol/l und leichten Symptomen:
  - Hydrocortison oral 20-10-0 mg
- bei normalen Schilddrüsenhormonen, initial wöchentliches Monitoring (*zwingend Cortisolersatztherapie eine Woche vor L-Thyroxintherapie beginnen)*
- bei erniedrigtem TSH +/- erniedrigtem T4, L-Thyroxin-Substitution (0.5-1.5ug/kg) symptomorientiert beginnen, wöchentlich morgendlicher Cortisol-Spiegel (siehe auch Thyreoiditis-Guidelines)
- bei zentralem Hypogonadismus, ggf. Testosteron bzw. Estradiol-Substitution falls nicht onkologisch kontraindiziert

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Adrenalitis

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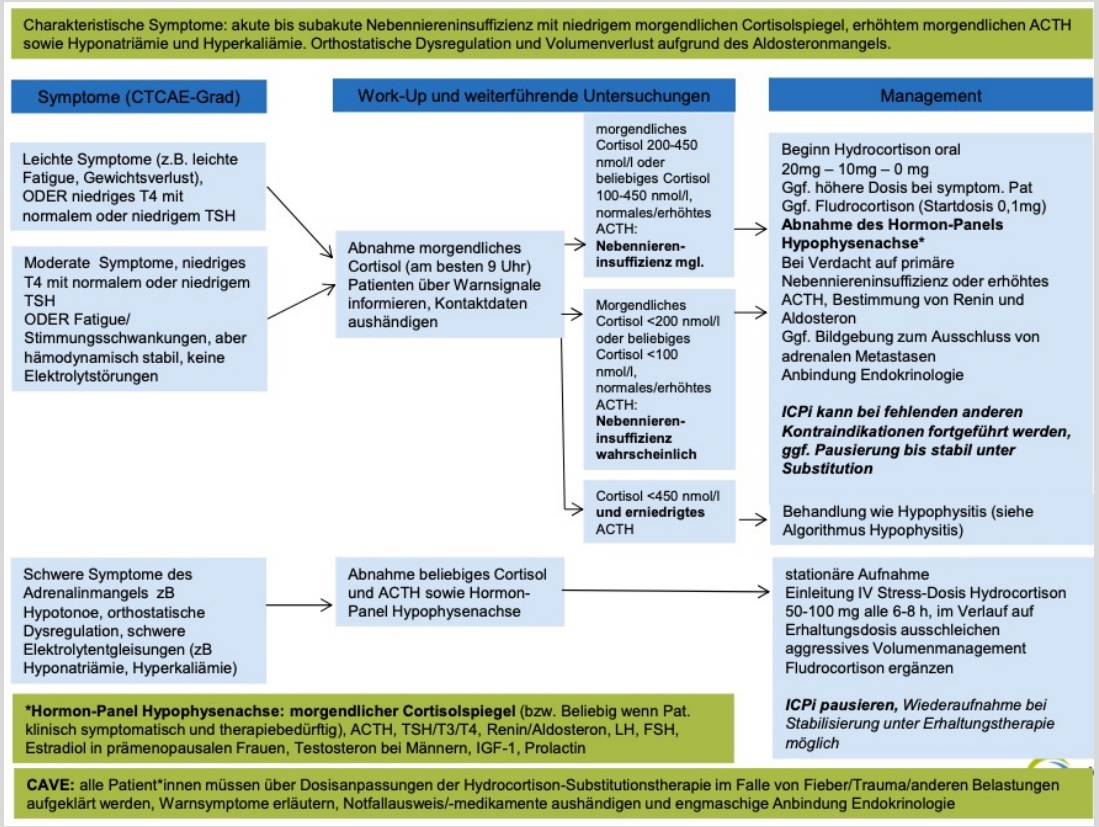
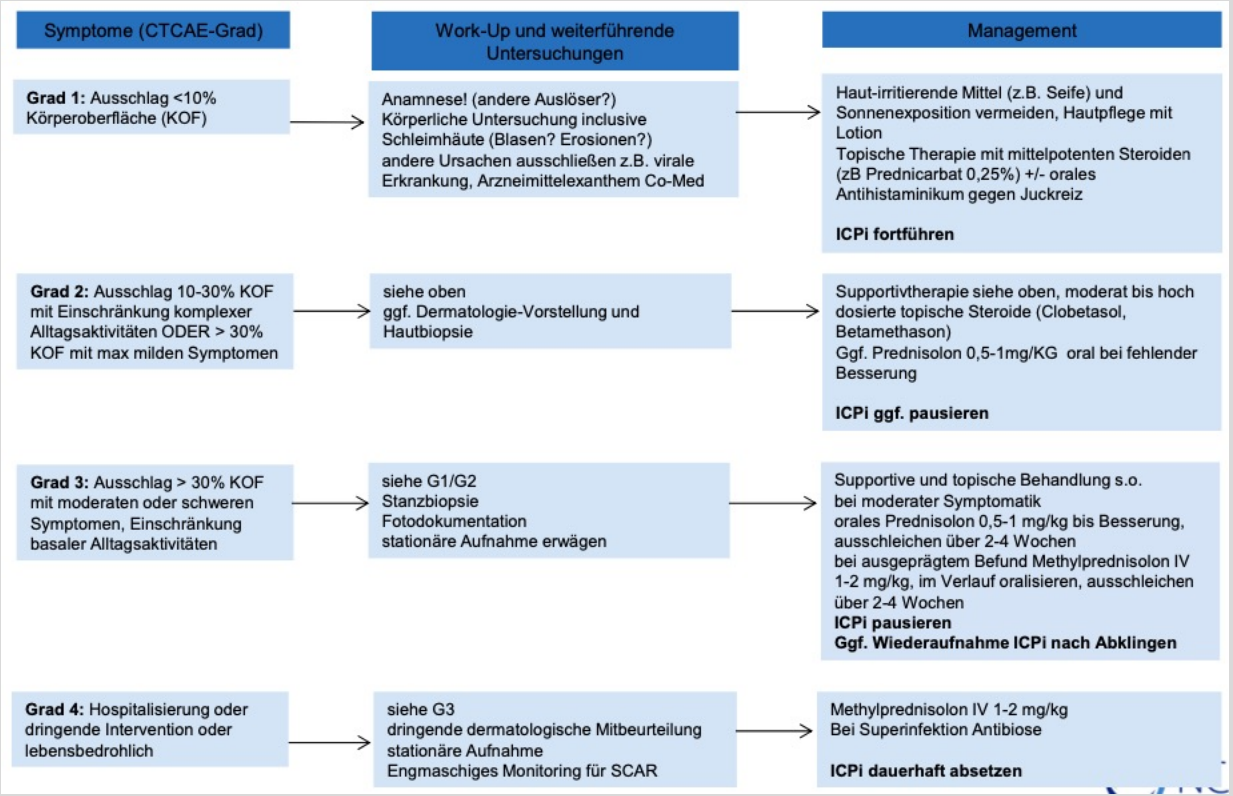


Cutaneous Toxicity



Symptome (CTCAE-Grad)	Work-Up und weiterführende Untersuchungen	Management
Grad 1: Ausschlag <10% Körperoberfläche (KOF)	Anamnese! (andere Auslöser?) Körperliche Untersuchung inclusive Schleimhäute (Blasen? Erosionen?) andere Ursachen ausschließen z.B. virale Erkrankung, Arzneimittelexanthem Co-Med	Haut-irritierende Mittel (z.B. Seife) und Sonnenexposition vermeiden, Hautpflege mit Lotion Topische Therapie mit mittelpotenten Steroiden (zB Prednicarbat 0,25%) +/- orales Antihistaminikum gegen Juckreiz **ICPi fortführen**
Grad 2: Ausschlag 10-30% KOF mit Einschränkung komplexer Alltagsaktivitäten ODER > 30% KOF mit max milden Symptomen	siehe oben ggf. Dermatologie-Vorstellung und Hautbiopsie	Supportivtherapie siehe oben, moderat bis hoch dosierte topische Steroide (Clobetasol, Betamethason) Ggf. Prednisolon 0,5-1mg/KG oral bei fehlender Besserung **ICPi ggf. pausieren**
Grad 3: Ausschlag > 30% KOF mit moderaten oder schweren Symptomen, Einschränkung basaler Alltagsaktivitäten	siehe G1/G2 Stanzbiopsie Fotodokumentation stationäre Aufnahme erwägen	Supportive und topische Behandlung s.o. bei moderater Symptomatik orales Prednisolon 0,5-1 mg/kg bis Besserung, ausschleichen über 2-4 Wochen bei ausgeprägtem Befund Methylprednisolon IV 1-2 mg/kg, im Verlauf oralisieren, ausschleichen über 2-4 Wochen **ICPi pausieren** **Ggf. Wiederaufnahme ICPi nach Abklingen**
Grad 4: Hospitalisierung oder dringende Intervention oder lebensbedrohlich	siehe G3 dringende dermatologische Mitbeurteilung stationäre Aufnahme Engmaschiges Monitoring für SCAR	Methylprednisolon IV 1-2 mg/kg Bei Superinfektion Antibiose **ICPi dauerhaft absetzen**

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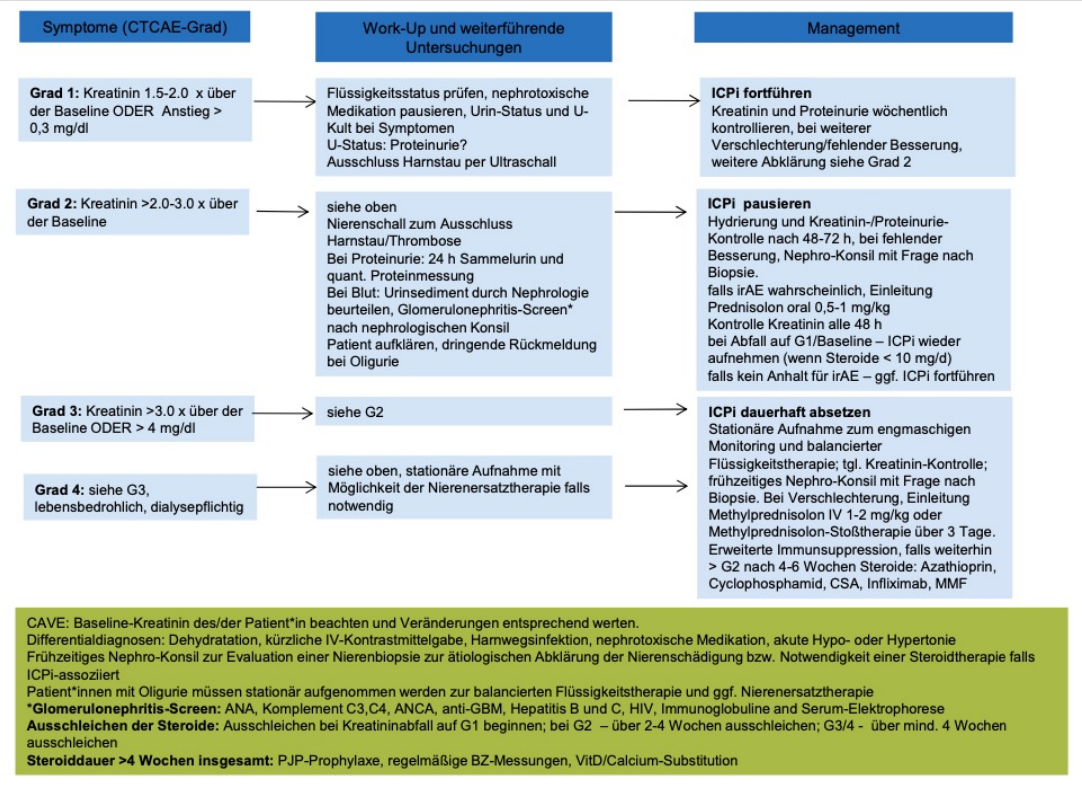
Nephrotoxicity



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Arthritis, Arthralgia, Myalgia

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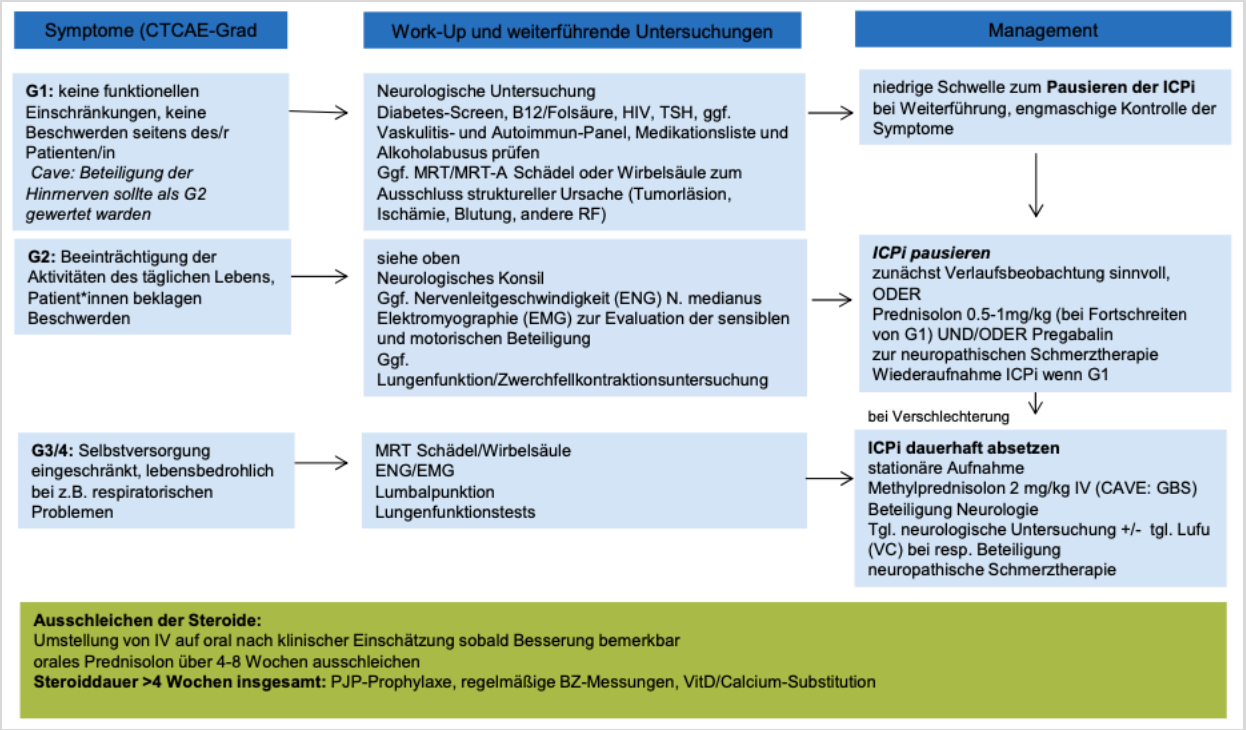
Symptome (CTCAE-Grad)	Work-Up und weiterführende Untersuchungen	Management
Grad 1: leichte Gelenk- oder Muskelschmerzen mit Enzündungszeichen, Schwellung oder leichter funktionaler Einschränkung	Komplette rheumatologische Anamnese mit DD wie unten aufgelistet Klinische Untersuchung aller Gelenke und Hautstatus Ggf. Röntgen bzw. Bildgebung zum Metastasenausschluss falls notwendig. Autoimmun-Panel (siehe unten) und CK	Schmerztherapie mit Metamizol +/- NSAID (z.B. Ibuprofen, Diclofenac, Celecoxib) (CAVE: Nierenfunktion prüfen, Comedikation mit ASS vermeiden) Bei unzureichender Einstellung, Einleitung Prednisolon 5-10 mg oral UND/ODER ggf. intraartikuläre Steroidinjektion in große Gelenke ***ICPi fortführen, Verlaufsmonitoring Rheuma-Untersuchung, CRP/BSG alle 4-6 Wochen***
Grad 2: moderate Schmerzen mit oben genannten Begleitsymptomen, Einschränkung der Tätigkeiten des täglichen Lebens	Anamnese, klinische Untersuchung und Autoimmunes-Panel/CK siehe oben Ultraschall +/- MRT der betroffenen Gelenke Rheumatologisches Konsil	Schmerztherapie steigern (CAVE: Nierenfunktion prüfen) Einleitung Prednisolon bei Leichter Klinik 10-20mg/Tag, ansonsten 0,5-1 mg/kg über 2-3 Wochen, bei fehlender Besserung, Behandlung wie G3/4 **Ggf. ICPi pausieren** und Wiederaufnahme bei Symptomkontrolle und Steroide < 10 mg Prednisolon, Verlaufsmonitoring siehe oben
Grad 3: starke Schmerzen; potentiell irreversible Gelenkschädigung, Einschränkung der häuslichen Selbstversorgung, deutliche Einschränkungen	siehe Grad 2 dringliche rheumatologische Mitbeurteilung	Einleitung Prednisolon 1(-2) mg/kg bei fehlender Besserung innerhalb von 1 Woche/frustranem Ausschleichen nach 2 Wochen oder Verschlechterung, erweiterte Immunsuppression mit Rheumatologie besprechen (zB Infliximab, MTX, Tocilizumab, Adalimumab, Sulfasalazin, Azathioprin, Etanercept, Hydroxychloroquin) ***ICPi pausieren, ggf. dauerhaft absetzen***
Grad 4: Myositis und schwere Organbeteiligung		

Zu bedenkende Differentialdiagnosen in der Evaluation der inflammatorischen Arhropathie:
- Rheumatoide Arthritis (seropositiv oder seronegativ) – normalerweise symmetrische Beteiligung der kleinen Gelenke
- periphere Spondyloarthritis (seronegativ) – häufig asymmetrisch, Beteiligung der großen Gelenke
- Reaktive Arthritis – postinfektiös (Diarrhoe oder Harnwegsinfektion) mit asymmettischer Beteiligung der großen Gelenke und/oder der Augen
- Bindegewebserkrankungen zB systemischer Lupus erythematosis (SLE), Myositis oder Dermatomyositis
- Psoriatsisarthritis- normalerweise kleine Gelenke, Beteiligung der distalen Interphalangealgelenke, assoziiert mit Hautläsionen der Kopfhaut oder an den Streckseiten
- virale Arthritis (zB Parvovirus B19) oder postinfektiös (zB post-Streptokokken)

Nicht-inflammatorische Differentialdiagnosen:
- Gicht, Pseudogicht, Trauma, Osteoarthritis – alle gehen normalerweise mit einer Monoartrhitis mit Rötung einher (Ausnahme Gicht mehrere Gelenke möglich)

Autoimmun-Panel:
ANA, dsDNA, ENA, C3/4, Rheumafaktor, Anti-Citrullinisches-Peptid Ab, BSG, CRP, ANCA, Hep B/C, Harnsäure, CK, sCD25, bei Verdacht auf Sarkoidose ACE, Calcium und 25-OH-D3

Peripheral Neurotoxicity (I)



Peripheral Neurotoxicity (II)

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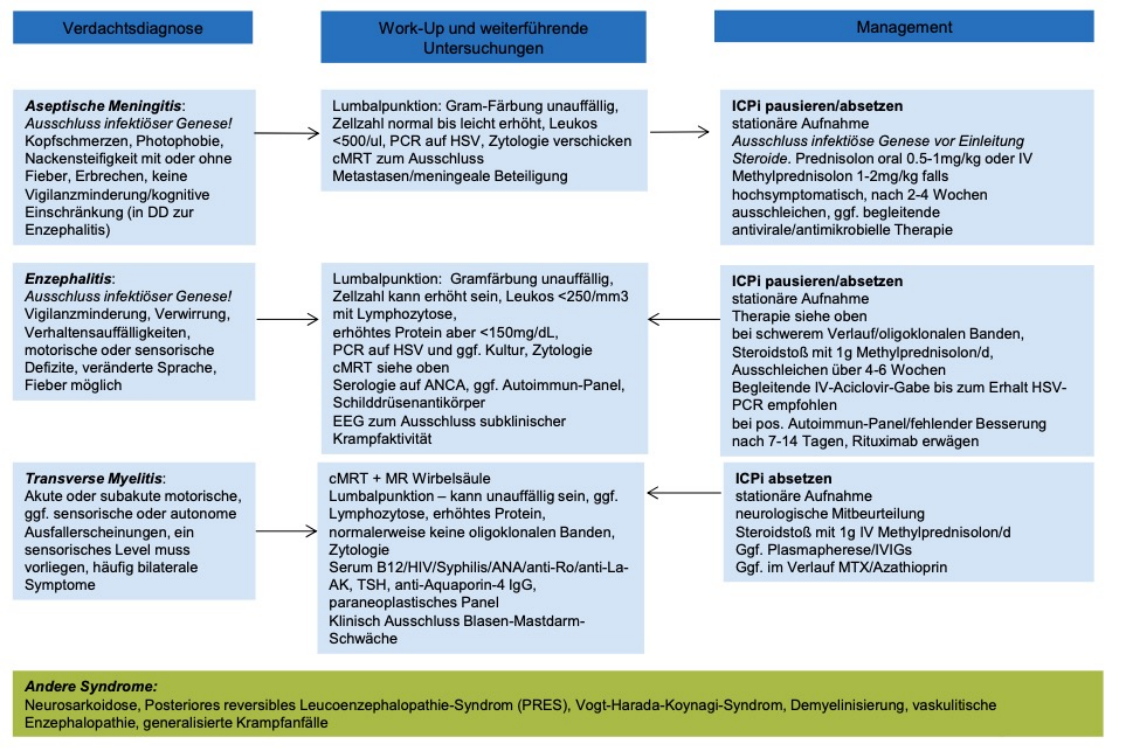
Verdachtsdiagnose	Work-Up und weiterführende Untersuchungen	Management
Guillain-Barre-Syndrom(GBS): Progrediente symmetrische Muskelschwäche mit fehlenden oder abgeschwächten Sehnenreflexen, Beteiligung von Extremitäten-, Gesichts-, Atem- und Schluck- sowie Augenmuskeln, Dysregulation der autonomen Nerven	Untersuchung der Nervenleitgeschwindigkeit (akute Polyneuropathie) Lumbalpunktion (typischerweise erhöhtes Protein bei normaler Zellzahl) Lungenfunktionsdiagnostik mit VC und max. In- und Exspirationsfluss Serologie auf GBS-Antikörper (zB GQ1b bei Miller-Fisher-Variante)	**ICPi dauerhaft absetzen** stationäre Aufnahme, neurologische Mitbeurteilung Steroide bei idiopathischem GBS nicht empfohlen, bei V.a. ICPi-ass. GBS Versuch mit Methylprednisolon 1 g/d über 5 Tage, Ausschleichen über 4 Wochen Gabapentin, Pregabalin oder Duloxetin bei Schmerzen Bei fehlender Besserung/Verschlechterung, Plasmapherese oder IVIGs indiziert CAVE: ggf. invasive Beatmung notwendig (ca. 15-30% der idiopathischen GBS)
Myasthenia gravis: Fluktuierende Muskelschwäche (Arme, Stamm, Augen- und Schluckmuskeln inklusive Doppelbilder und Schluckstörungen) mit Erschöpfbarkeit, Atemhilfsmuskeln/Zwerchfell können auch betroffen sein ***Myositis:*** Proximale Muskelschwäche begleitet von Muschkelschmerzen und CK-Erhöhung, Schluckbeschwerden, häufig Myokardbeteiligung, kann begleitend zu myasthenen Symptomen auftreten	Myasthenia gravis: Untersuchung auf Erschöpfbarkeit der Augenmuskeln bzw. proximalen Extremitätenmuskeln Serologische Bestimmung der Acetylcholin-Rezeptor-AK (AChR) Bedside-Test per Tensilon-Test or Eis-Test, repetitive Nervenstimulation Myositis: Bestimmung CK, EMG, Kontrolle der Nierenfunktion im Fall von Rhabdomyolyse	**ICPi dauerhaft absetzen** stationäre Aufnahme, neurologische Mitbeurteilung Steroidtherapie indiziert (oral oder IV je nach Symptomlast) Myasthena gravis: Pyridostigmine 30mg 3x/d beginnen, Dosisanpassung je nach Symptomen bis zu 120 mg 4x/d Bei fehlender Besserung/Verschlechterung, Plasmapherese oder IVIGs prüfen Zusätzliche Immunsuppression: Azathioprin, Ciclosporin, MMF CAVE: Ciprofloxacin und Beta-blocker vermeiden, können cholinerge Krise provozieren

Andere Syndrome:
Motorische und sensorische periphere Neuropathie, mulitfokale radikuläre Neuropathie/Plexopathie, autonome Neuropathie, Lähmungen des N. phrenicus oder der Hirnnerven (zB faziale Parese, N. opticus, N. hypoglossus). Steroidue empfohlen sowie Anbindung Neurologie und engmaschiges Monitoring auf respiratorische bzw. visuelle Einschränkungen.

Central Neurotoxicity



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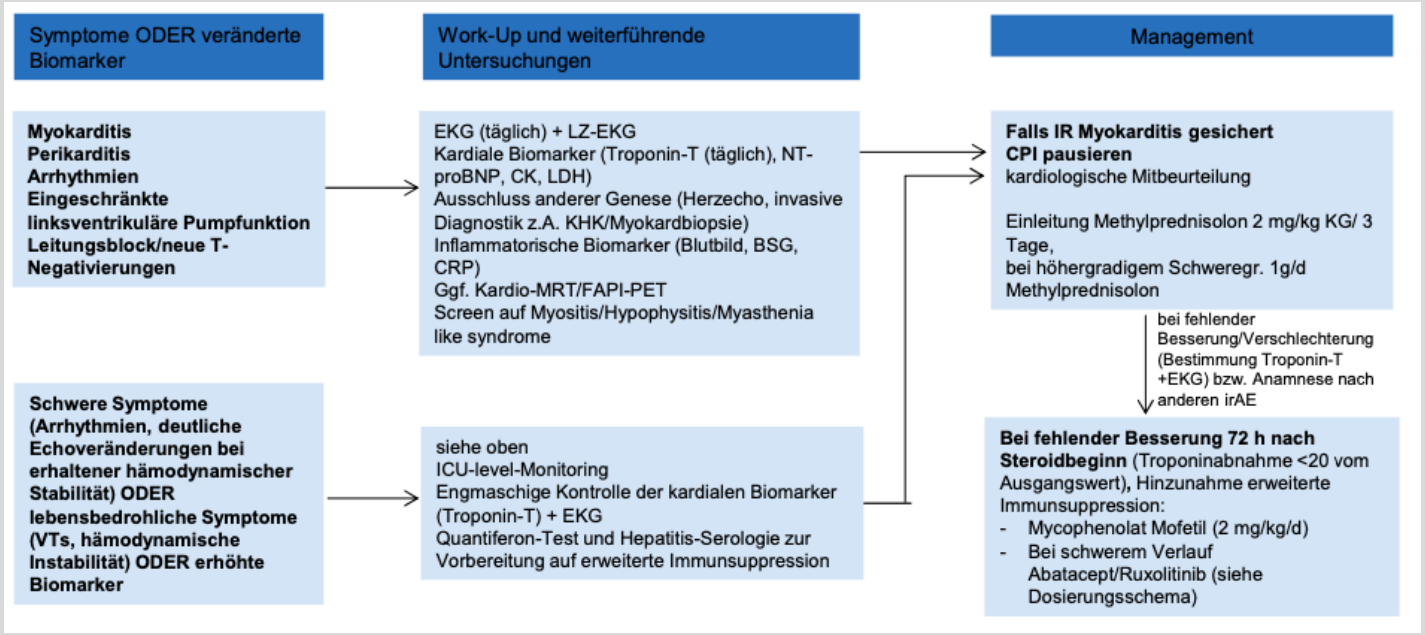
Cardiovascular Toxicity



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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

	Oxford		
	LoE	GR	AGO
▪ Avoidance of highly infection-risking behavior or situations	5	D	+
Review and potential update of vaccination status prior to initiation of therapy (according to recommendations by RKI, STIKO, DGHO	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

	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	+/-

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

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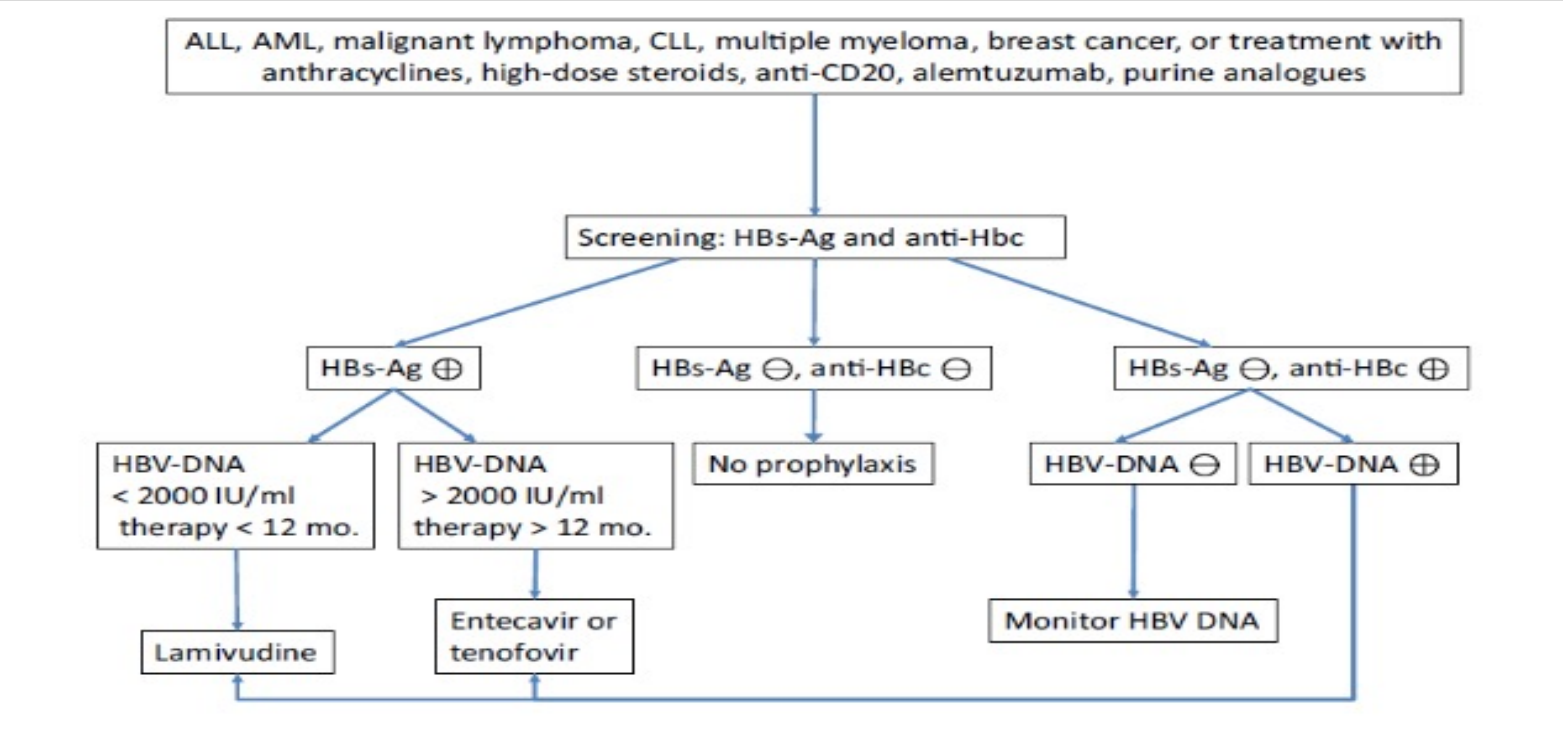

Sandherr M et al. Ann Hematol. 2015 Sep;94(9):1441-50

Side Effects According Organ Systems
Incidence, Prevention, Therapy

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

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Secondary Malignancies I

	Oxford	
	LoE	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)

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	GR	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	++

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

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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	+/-

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

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Step 1: Assess frequency of FN associated with the planned chemotherapy regimen

FN risk ≥ 20% | **FN risk 10-20%** | **FN risk < 10%**

Step 2: Assess factors that may increase the risk of FN:

High risk:	Age > 65 years
Increased risk: (level I and II evidence)	Advanced disease History of prior FN No antibiotic prophylaxis
Other Factors: (level III and IV evidence)	Poor performance (ECOG > 1) Female gender Haemoglobin < 12 g/dL Liver, renal or cardiovascular disease Nutritional status

Step 3: Define the patient's overall FN risk for planned chemotherapy regimen

Overall FN risk ≥ 20% | **Overall FN risk < 20%**

Prophylactic G-CSF recommended

G-CSF prophylaxis not indicated

Reass ess at each cycle

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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)

Side Effects According Organ Systems
Incidence, Prevention, Therapy

Guidelines Breast
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5. Psychiatric Disorders

- Depression
- Fatigue
- Cognitive impairment
- Sleep disturbances

Guidelines Breast
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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	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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Side Effects According Organ Systems
Incidence, Prevention, Therapy

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)**

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

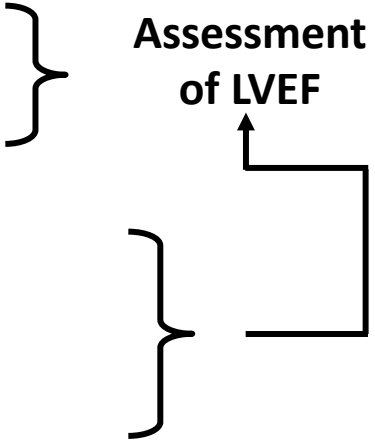
- History, physical examination (edema, hepatomegaly)
- Echocardiography (alternative to MUGA)

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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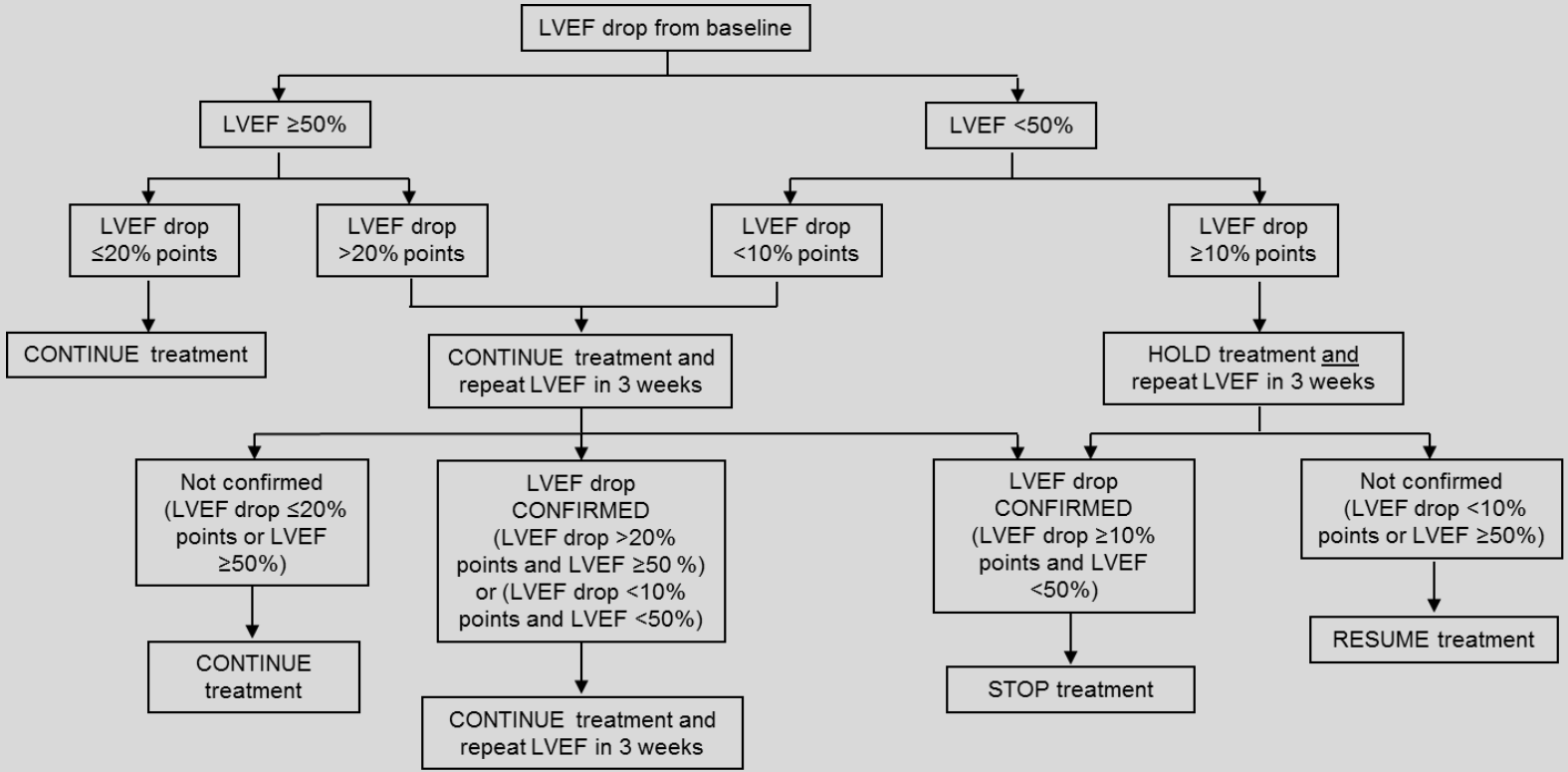
Feasibility of Treatment Combinations Considering Toxicities

	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	-

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



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www.ago-online.de

FORSCHEN
LEHREN
HEILEN

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Side Effects According Organ Systems
Incidence, Prevention, Therapy

8. Gastrointestinal Disorders

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

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Antiemetic Therapy

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

	Oxford		
	LoE	GR	AGO
▪ After assessment of emetic potential of therapy protocol (p.o., i.v., s.c., i.m.)	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	+/-

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.

Multinational Association of Supportive Care in Cancer

Supportive Care Makes Excellent Cancer Care Possible

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

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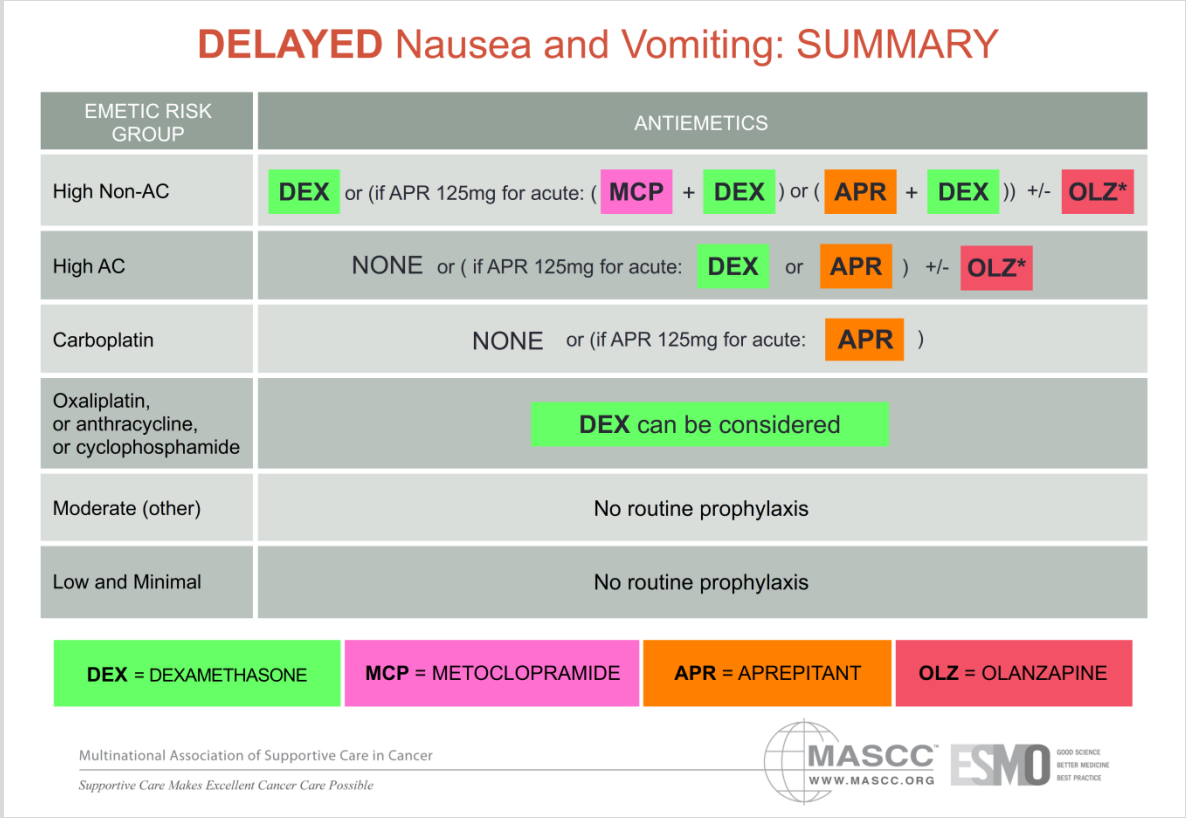

Supportive Therapy
Antiemetics

Wirkstoffgruppe	Substanz	Dosierung	Nebenwirkungen	Antiemetic potential
Serotonin-antagonists	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.	Headache, diarrheea, flush, elevated transaminases, intestinal atony (higher doses)	Very high
NK1-Antagonists	Aprepitant Fosaprepitant Rolapitant	125 mg d1, 80 mg d 2-3 p.o. 150 mg d1 i.v. 180 mg d1 p.o.	Activation of cytochrome-P-450-, dose reduction of dexamethasone (2 x 8 mg). No combination with Astemizole, Terfenadine, Cisaprid	Very high
Dopamin-antagonists/ substituted Benzamides	Metoclopramid Alizaprid	Up to 120 mg/24h als continuous infusion or drop bis zu 300 mg i.v. oder p.o./24 h (6 Amp. od. 6 Tbl.)	Dyskinesia (Antidote: Biperiden) Anxiety, depression, diarrhoea	high
Oxazapine	Olanzepin	10mg/d for d1-4 Ggf. 5mg/d for d1-4	Sedation, weight gain	high
Phenothiazine/ Butyrophenone	Haloperidol	1-3 mg 4 x/d	Sedation, reduction of seizure threshold, transient elevation of liver enzymes	intermediate
Corticosteroids	Dexamethasone Prednisolone	8-20 mg i.v. 1-3 x/d 100-250 mg i.v. 1-3 x/d	Hyperglycaemia, psychosis, flush, hypertension	intermediate
Benzodiazepine	Diazepam Lorazepam	Up to 20 mg/d 0,5-1,0 mg/d	Sedation, respiratory depression	Low
NEPA (Netupitant and Palonosetron)	Fixed combination	NE 300 mg PA 0,5 mg		Very high

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“

Guidelines Breast
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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

Prevention of Everolimus-Induced Stomatitis Using Corticosteroid-based Mouthwash

- **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 3 Metaanalyses

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	+

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**

Side Effects According Organ Systems
Incidence, Prevention, Therapy

Guidelines Breast
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11. Lung

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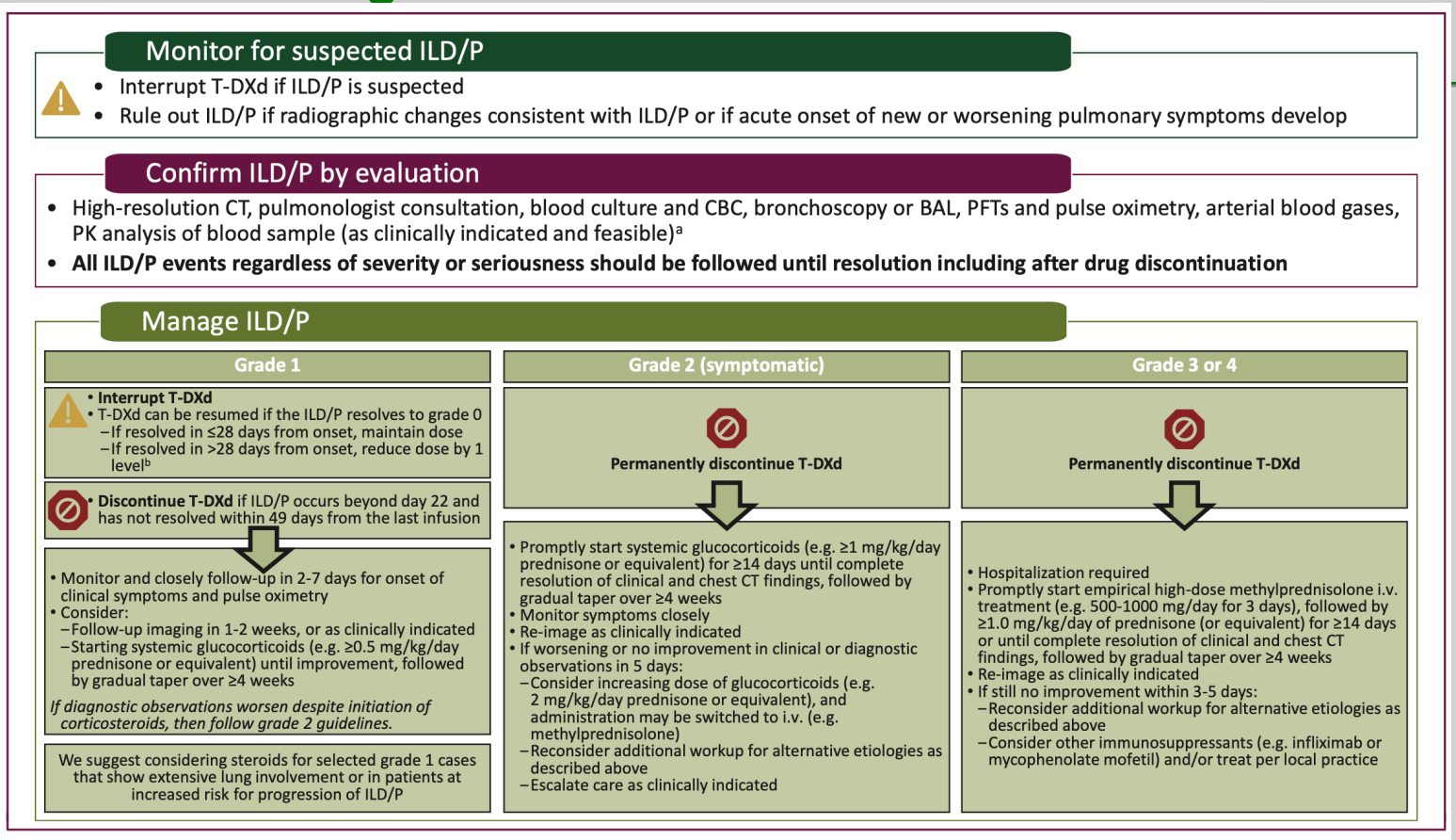
Drug-induced Pneumonitis, Interstitial Lung Disease (ILD)

	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)	1b	B	++

Management ILD -Trastuzumab Deruxtecan



- Rugo HS et al. ESMO Open. 2022 Aug;7(4):100553

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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**
  - **CNS metastases (see chapter)**

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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.**
- **In patients with incurable disease advance care planning (incl. advance directive) should be recommended.**
- **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/