

Screened data bases

Pubmed 2007 - 2019, ASCO 2010 – 2019, SABCS 2010 – 2019, Cochrane Data Base (2019)

Screened guidelines

1. ABC Consensus Guidelines for Advanced Breast Cancer (ABC 1-4): Cardoso F, Costa A, Senkus E et al. 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). Ann Oncol. 2017 Jan 1;28(1):16-33.
2. Thomssen C. et al. ABC5 Consensus: assessment by a German Group of Experts. Breast Care (Basel). 2020
3. ASCO (American Association of Clinical Oncology, Practice Guidelines, 2019) <http://www.asco.org>
4. American Society of Clinical Oncology Clinical Practice Survivorship Guidelines, Endorsements and Adaptations: <https://www.asco.org/practice-policy/cancer-care-initiatives/prevention-survivorship/survivorship-compendium-0>
5. 2016 Updated American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards, Including Standards for Pediatric Oncology: <http://ascopubs.org/doi/pdfdirect/10.1200/JOP.2016.017905>
6. Hershman DL, Lacchetti C, Dworkin RH et al. American Society of Clinical Oncology. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014 Jun 20;32(18):1941-67.

7. NCCN (National Comprehensive Cancer Network , 2019): <http://www.nccn.org>
8. S3-Leitlinie: Supportive Therapie:
Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2 – November 2019 AWMF-Registernummer: 032/054OL Zugriff 26.12.2019

Supportive Care and Management of Side Effects

- **Versionen 2002–2019:**

Albert / Bauerfeind / Brunnert / Bischoff / Costa / Dall / Diel / Fersis /
Friedrich / Friedrichs / Gerber / Göhring / Hanf / Harbeck / Heinrich /
Huober / Jackisch / Lisboa / Lück / Lüftner / von Minckwitz / Möbus
/Müller / Nitz / Oberhoff / Rody / Schaller / Scharl / Schmidt /
Schneeweiss / Schütz / Solomayer / Souchon / Stickeler / Thomssen /
Untch

- **Version 2020:**

Müller / Albert



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Content

- **Guidelines**
- **Assessment of toxicity**
- **Incidence of side effects (according technical product information; MedDRA-standard)**
- **Side effects according organ systems**
 - Incidence, prevention, therapy
- **Substance specific side effects**
 - Targeted drugs
- **Further issues**
 - Pain management, palliative care




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■ Guideline - environment



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Guideline Environment

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>).

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


- **S3-Leitlinie: Supportive Therapie bei onkologischen Patientinnen Langversion 1.1 –April 2017 AWMF-Registernummer: 032/054OL**

1. S3-Leitlinie: Supportive Therapie:

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2 – November 2019 AWMF-Registernummer: 032/054OL Zugriff 26.12.2019

https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.2.pdf

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



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Assessment of toxicity

Acute Toxicity (according to WHO¹ or NCI-CTC²)

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. ICPC³ following symptoms or acc. ICD-10-GM⁴ following diagnoses) LoE 5 D AGO ++

Akute Toxizität

1. WHO Handbook for reporting results of cancer treatment, N0 48 (1979) (WHO offset Publications, Geneva)
2. NCI, Bethesda, USA, Common Terminology Criteria for Adverse Events v5.0 (CTCAE; published 2017);
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50 (Download 18.01.2018)


Akute Toxizität nach jedem Therapiezyklus abfragen

1. Cirillo M, Lunardi G, Coati F, et al: Management of oral anticancer drugs: Feasibility and patient approval of a specific monitoring program. Tumori 100: 243-248, 2014

Langzeittoxizität

1. International Classification of Primary Care (ICPC) revised December 2016,
<http://www.who.int/classifications/icd/adaptations/icpc2/en/> (Download 18.01.2018) or
<http://www.globalfamilydoctor.com/groups/WorkingParties/wicc.aspx> (Download 18.01.2018)
2. Deutschen Institut für Medizinische Dokumentation und Information (DIMDI), ICD-10-GM Version 2017;
<https://www.dimdi.de/static/de/klassi/icd-10-gm/kodesuche/onlinefassungen/htmlgm2017/> (Download 18.01.2018)

3. Kenyon M, Mayer DK, Owens AK. Late and long-term effects of breast cancer treatment and surveillance management for the general practitioner. *J Obstet Gynecol Neonatal Nurs*. 2014 May-Jun;43(3):382-98.
4. Hematopoietic Cell Transplantation Guidelines Taskforce, Auditory and Vision Guidelines Taskforce, Cardiopulmonary Guidelines Taskforce, Endocrine Guidelines Taskforce, Genitourinary and Renal Guidelines Taskforce, Oral, Dental, Gastrointestinal and Hepatic Guidelines Taskforce, et al. Late Effects Surveillance Recommendations among Survivors of Childhood Hematopoietic Cell Transplantation: A Children's Oncology Group Report. Author manuscript; available in PMC 2017 May 1. Published in final edited form as: *Biol Blood Marrow Transplant*. 2016 May; 22(5): 782–795.
5. Inge Spronk, Joke C Korevaar, Francois G Schellevis, et al. Evidence-based recommendations on care for breast cancer survivors for primary care providers: a review of evidence-based breast cancer guidelines. *BMJ Open*. 2017; 7(12): e015118.
6. M.J. Heins, J.C. Korevaar, P.M. Rijken, et al. For which health problems do cancer survivors visit their General Practitioner? *European Journal of Cancer* (2013) 49, 211– 218.



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Acute Toxicity (NCI CTCAE vs 5.0, 2017)


- **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.

1. NCI, Bethesda, USA, Common Terminology Criteria for Adverse Events v5.0 (CTCAE; published 2017); https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50 (Download 18.01.2018)



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- **Incidence of side effects
(according to technical product information by
MedDRA* classification)**

* MedDRA - Medical Dictionary for Regulatory Activities

*MedDRA - Medical Dictionary for Regulatory Activities

<https://www.meddra.org/>



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Chemotherapy – Acute Toxicities I

DRUGS	SYSTEM ORGAN CLASS											
	INFECTIONS AND INFESTATIONS	NEOPLASMS BEN., ALIGNED AND NSPECIFIED (INCL CYSTS & POLYPS)	BLOOD & LYMPH. SYST. DISORDERS	IMMUNE /STEM 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												
Cisplatin	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
PEG-lipos. Doxorubicin	4	-	4	-	-	5	-	4	-	-	4	-
Mitoxantrone	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 (PD)	5(5)	-	(5)	2(1)	-	-	-(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)

Nebenwirkungskategorien - MedDRA (Medical Dictionary for Regulatory Activities)

MedDRA: <https://www.meddra.org/ bzw.>

https://www.meddra.org/sites/default/files/guidance/file/intguide_20_1_english_0.pdf

Quellen für die Fachinformationen (Download 19.01.2018)

Cyclophosphamid: http://www.baxter.de/de_DE/assets/downloads/fachinformation/endoxan.pdf

Methotrexat: https://www.gelbe-liste.de/produkte/MTX-HEXAL-10-mg-Tabletten_117469/fachinformation

5-Fluorouracil: https://www.gelbe-liste.de/produkte/Fluorouracil-HEXAL-50-mg-ml-Injektionsloesung-100-ml_546519/fachinformation

Capecitabin: <https://www.zentiva.de/Produkte/Capecitabin-Zentiva/Downloads?id=a63946ee-51ce-46ac-8184-a468b705ed9b>

Gemcitabin: <http://www.success-studie.de/b/downloads/Fachinfo/GemzarFI07Jan.pdf>

Cisplatin: https://www.gelbe-liste.de/produkte/Cisplatin-Teva-1-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-100-ml_543960/fachinformation

Carboplatin: <http://www.teva.de/index.php?eID=dumpFile&t=f&f=37532&g=-1&r=11068%2C11068&token=eebf22e78f1cc8d9935d59c087e80630146f49e>

Epirubicin:

Doxorubicin:

Liposomales Doxorubicin: https://www.gelbe-liste.de/produkte/Myocet-50-mg-Pulver-Dispersion-u-Loesungsmittel-fuer-ein-Konzentrat-zur-Herstellung-einer-Infusionsdispersion_359323/fachinformation

PEG-lipo. Doxorubicin: https://www.gelbe-liste.de/produkte/Caelyx-2-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-10-ml_121890/fachinformation

Mitoxantron: https://www.gelbe-liste.de/produkte/Mitoxantron-Teva-2-mg-ml-Injektionsloesung-15ml_543783/fachinformation

Paclitaxel: <https://medikamio.com/de-de/medikamente/paclitaxel-ratiopharm/pil>

Nab-Paclitaxel: https://www.gelbe-liste.de/produkte/Abbraxane-5-mg-ml-Pulver-zur-Herstellung-einer-Infusionssuspension_514889/fachinformation

Docetaxel: <https://mein.sanofi.de/produkte/Taxotere/Downloads?id=89447754-dfb2-450b-b35a-36950de8a74d>


Vinorelbin: <http://www.detect-studien.de/dokumente/d3/fachinfo/Navelbine.pdf>

Eribulin: http://www.detect-studien.de/dokumente/d4/fachinfo/Fachinfo_Eribulin_Halaven.pdf

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2. Petrelli F et al: Mortality, leukemic risk, and cardiovascular toxicity of adjuvant anthracycline and taxane chemotherapy in breast cancer: a meta-analysis. *Breast Cancer Res Treat*. 2012 Sep;135(2):335-46
3. Jim HS et al: Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *J Clin Oncol*. 2012 Oct 10;30(29):3578-87
4. Cortes J, O'Shaughnessy J, Loesch D et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet*. 2011;377:914-23
5. Link, H. and S. Schmitz (2013). "Treatment of cancer-associated anaemia: results from a two-day cross-sectional survey in Germany." *Onkologie* 36(5): 266-272.
6. Fox P, Darley A, Furlong E, et al: The assessment and management of chemotherapy-related toxicities in patients with breast cancer, colorectal cancer, and Hodgkin's and non-Hodgkin's lymphomas: A scoping review. *Eur J Oncol Nurs*. 2017 Feb;26:63-82. doi:

- 10.1016/j.ejon.2016.12.008. Epub 2016 Dec 22.
7. Maeda S, Saimura M, Minami S, et al. Efficacy and safety of eribulin as first- to third-line treatment in patients with advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. See comment in PubMed Commons below Breast. 2017 Jan 2;32:66-72. doi: 10.1016/j.breast.2016.12.017.
 8. Zhang XH, Hao S, Gao B, et al. A network meta-analysis for toxicity of eight chemotherapy regimens in the treatment of metastatic/advanced breast cancer. Oncotarget. 2016 Dec 20;7(51):84533-84543. doi: 10.18632/oncotarget.13023.
 9. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of Clinical Oncology 2011;29:4189- 4198
 10. Crawford J.
 11. NCCN, editor. NCCNR Practice Guidelines in Oncology - v.1.2011; Myeloid Growth Factors. National Comprehensive Cancer Network 2011. 18-7-2011.
 12. Madeddu C, Deidda M, Piras A, et al. Pathophysiology of cardiotoxicity induced by nonanthracycline chemotherapy. J Cardiovasc Med (Hagerstown). 2016 May;17 Suppl 1 Special issue on Cardiotoxicity from Antitubercular Drugs and Cardioprotection:e12-e18. Review.



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Chemotherapy – Acute Toxicities II

– unknown (based on available data incidence not assessable)

DRUG	SYSTEM ORGAN CLASS											SPECIAL FEATURES
	RESPIRAT., THORAC. & MEDIA- STINAL DIS.	GASTROINT.DISOR D. (NAUSEA, EMESIS)	HEPATO BILIARY DISORDERS	SKIN & SUBCUT. TIS. DISORD. (ALOPECIA)	MUSCULOSKELETA L & CONNECTIVE TISSE DISORDERS	RENAL & URINARY DISORDERS	PREGN. PUERPER. & PERINATAL CONDIT.	REPRODUCT. SYS. & BREAST DISORDERS	GENERAL DISORD. & ADMIN- STRATION SITE CONDITIONS	CONGEN. FAMILIAL GENET. DISORDERS		
Alkylating antineoplastic agent												
Cyclophosphamide	2	4	4	5	-	5	-	4	5	-		Hyponatraemia
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												
Cisplatin	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, myalgia
Further tubulin-targeting drugs												
Vinorelbine IV (PO)	3(4)	2 (5)	4(4)	2(5)	-(4)	2(4)	-	-	-	-		Phlebitis, GI-Tox (PO), CIPN
Eribulin	5	5	4	5	5	4	-	-	5	-		Constipation, CIPN

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).

Abkürzungen

AML = Akute myeloische Leukämie; DPD = Dihydropyrimidin-Dehydrogenase); CHF = Kardiomyopathie; CIPN = Chemotherapie induzierte periphere Neuropathie; HFS = Hand-Fuß-Syndrom; PPE = Palmares und plantares Erythem.

Nebenwirkungskategorien - MedDRA (Medical Dictionary for Regulatory Activities)

MedDRA: <https://www.meddra.org/> bzw.

https://www.meddra.org/sites/default/files/guidance/file/intguide_20_1_english_0.pdf

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Methotrexat: https://www.gelbe-liste.de/produkte/MTX-HEXAL-10-mg-Tabletten_117469/fachinformation

5-Fluorouracil: https://www.gelbe-liste.de/produkte/Fluorouracil-HEXAL-50-mg-ml-Injektionsloesung-100-ml_546519/fachinformation


Capecitabin: <https://www.zentiva.de/Produkte/Capecitabin-Zentiva/Downloads?id=a63946ee-51ce-46ac-8184-a468b705ed9b>

Gemcitabin: <http://www.success-studie.de/b/downloads/Fachinfo/GemzarFI07Jan.pdf>
 Cisplatin: https://www.gelbe-liste.de/produkte/Cisplatin-Teva-1-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-100-ml_543960/fachinformation
 Carboplatin: <http://www.teva.de/index.php?elD=dumpFile&t=f&f=37532&g=-1&r=11068%2C11068&token=eebf22e78f1cc8d9935d59c087e80630146f49e>
 Epirubicin:
 Doxorubicin:
 Liposomales Doxorubicin: https://www.gelbe-liste.de/produkte/Myocet-50-mg-Pulver-Dispersion-u-Loesungsmittel-fuer-ein-Konzentrat-zur-Herstellung-einer-Infusionsdispersion_359323/fachinformation
 PEG-lipo. Doxorubicin: https://www.gelbe-liste.de/produkte/Caelyx-2-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-10-ml_121890/fachinformation
 Mitoxantron: https://www.gelbe-liste.de/produkte/Mitoxantron-Teva-2-mg-ml-Injektionsloesung-15ml_543783/fachinformation
 Paclitaxel: <https://medikamio.com/de-de/medikamente/paclitaxel-ratiopharm/pil>
 Nab-Paclitaxel: https://www.gelbe-liste.de/produkte/Abbraxane-5-mg-ml-Pulver-zur-Herstellung-einer-Infusionssuspension_514889/fachinformation
 Docetaxel: <https://mein.sanofi.de/produkte/Taxotere/Downloads?id=89447754-dfb2-450b-b35a-36950de8a74d>
 Vinorelbin: <http://www.detect-studien.de/dokumente/d3/fachinfo/Navelbine.pdf>
 Eribulin: http://www.detect-studien.de/dokumente/d4/fachinfo/Fachinfo_Eribulin_Halaven.pdf

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4. Cortes J, O'Shaughnessy J, Loesch D et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic

- breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet*. 2011;377:914-23
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 8. Zhang XH, Hao S, Gao B, et al. A network meta-analysis for toxicity of eight chemotherapy regimens in the treatment of metastatic/advanced breast cancer. *Oncotarget*. 2016 Dec 20;7(51):84533-84543. doi: 10.18632/oncotarget.13023.
 9. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of Clinical Oncology* 2011;29:4189- 4198
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 12. Madeddu C, Deidda M, Piras A, et al. Pathophysiology of cardiotoxicity induced by nonanthracycline chemotherapy. *J Cardiovasc Med (Hagerstown)*. 2016 May;17 Suppl 1 Special issue on Cardiotoxicity from Antitubercular Drugs and Cardioprotection:e12-e18. Review.



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Endocrine Therapy – Toxicities

Guidelines Breast
Version 2020.1

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. & MEDIAST. DIS.	GASTROINT. DIS. (NAUSEA, EMESIS)	HEPATO BILIARY DISORDERS	SKIN & SUBCUTIS. DIS. (ALOPECIA)	MUSCULOSKELETA L & CONNECTIVE TISSUE DISORDERS	RENAL & URINARY DISORDERS	PREGN. PUERPER. & PERINAT. COND.	REPRODUCT. SYS. & INFERT.	GENERAL DIS. & ADMINISTRATION 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	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 to 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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Nebenwirkungskategorien - MedDRA (Medical Dictionary for Regulatory Activities)

MedDRA: <https://www.meddra.org/ bzw.>

https://www.meddra.org/sites/default/files/guidance/file/intguide_20_1_english_0.pdf

Quellen für die Fachinformationen (Download 19.01.2018)

Tamoxifen: https://www.gelbe-liste.de/produkte/Tamoxifen-20-mg-HEXAL-Filmtbl_8660/fachinformation

Anastrozol: <https://imedikament.de/anastrozol-ratiopharm-1-mg-filmtabletten/fachinformation>

Exemestan: http://www.success-studie.de/c/downloads/Fachinfo/FI_ExemestanAromasin.pdf

Letrozol: http://www.success-studie.de/b/downloads/Fachinfo/Femara_Juli_2014.pdf


Fulvestrant: https://www.gelbe-liste.de/produkte/Fulvestrant-HEXAL-250-mg-Injektionsloesung-in-einer-Fertigspritze_912622/fachinformation

Side effects according Organ Systems

Incidence, Prevention, Therapy

1. Infections and infestations

- General prophylaxis for infections
- Hepatitis B virus screening



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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	+
▪ 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

ASCO:

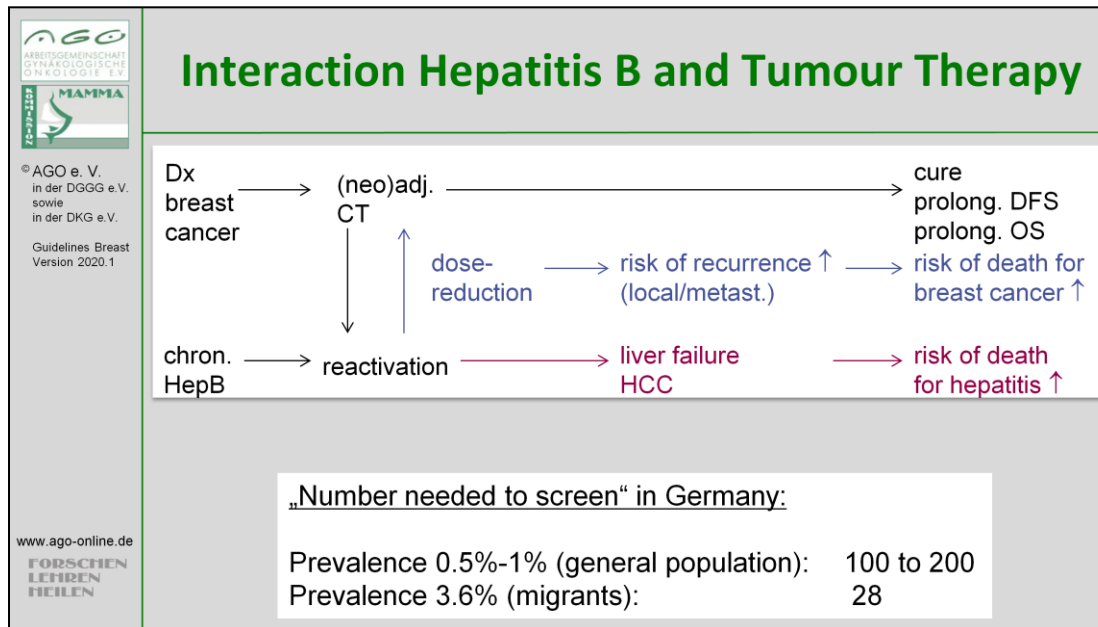
Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, Langston AA, Nastoupil LJ, Rajotte M, Rolston K, Strasfeld L, Flowers CR: Outpatient management of fever and neutropenia in adults treated for malignancy: American society of clinical oncology and infectious diseases society of america clinical practice guideline update. J Clin Oncol 2018;36:1443-1453.

NCCN:

NCCN Guidelines Version 1.2020 Prevention and Treatment of Cancer-Related Infections.
https://www.nccn.org/professionals/physician_gls/PDF/infections.pdf

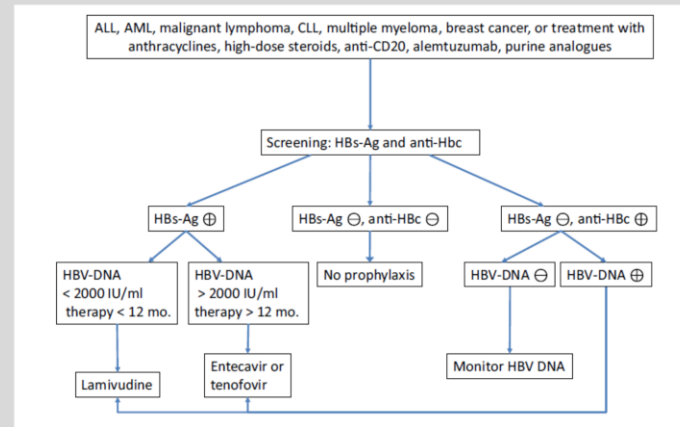
 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	Hepatitis B virus screening before chemotherapy		
	Oxford		
	LoE	GR	AGO
	<ul style="list-style-type: none"> Hepatitis B virus screening before adjuvant chemotherapy (HBsAG, anti-HBC) 		
	2c	B	+
<u>In case of positive serology or reactivation:</u>			
<ul style="list-style-type: none"> Interruption of chemotherapy 			
	5	D	++
<ul style="list-style-type: none"> Prophylactic therapy with virustatic drugs if HBV-DNA detected (according AGIHO/DGHO – recommendations) 			
	1b	A	++
<ul style="list-style-type: none"> Hepatitis C virus screening before chemotherapy 			
	5	D	+/-

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6. NCCN Guidelines Version 1.2018: Prevention and Treatment of Cancer-Related Infections.
https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf




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AGIHO / DGHO – recommendations on Hepatitis B virus screening in oncology



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

1. Sandherr M, Hentrich M, von Lilienfeld-Toal M, et al. Antiviral prophylaxis in patients with solid tumours and haematological malignancies--update of the Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). Ann Hematol. 2015 Sep;94(9):1441-50.
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International recommendations on Hepatitis B virus screening

Recommendations of Various Authoritative Bodies Regarding Screening for Hepatitis B to Mitigate the Risk of HBV Reactivation

Organization	Recommendation	Tests to Be Done
Centers for Disease Control and Prevention	Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterologic disorders	HBsAg, anti-HBc, anti-HBs
American Academy of Dermatology	Hepatitis B reactivation after treatment with tumor necrosis factor inhibitors has been reported; in the appropriate clinical setting, patients should be screened for hepatitis B infection.	Not stated
American Association for the Study of Liver Diseases	All patients before beginning immunosuppressive therapy	HBsAg, anti-HBc
Asian Pacific Association for the Study of the Liver	Before receiving immunosuppression or chemotherapy, patients should be screened for HBsAg. Patients who are going to receive biologic agents such as anti-CD20 or anti-tumor necrosis factor- α should be screened for anti-HBc.	HBsAg, anti-HBc
European Association for the Study of the Liver	All candidates for chemotherapy and immunosuppressive therapy should be screened.	HBsAg, anti-HBc
American Society of Clinical Oncology	Physicians may consider screening patients belonging to groups at heightened risk for chronic HBV infection or if highly immunosuppressive therapy is recommended.	Consider HBsAg, consider anti-HBc
US Preventive Services Task Force	Screen persons who are immunosuppressed.	HBsAg

Di Bisceglie AM et al. *Hepatology*. 2015 Feb;61(2):703-11.

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Side Effects According Organ Systems

Incidence, Prevention, Therapy

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

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	Oxford LoE GR	
<ul style="list-style-type: none"> With regard to solid tumors, chemotherapy induced secondary malignancies are rare events Alkylating agents increase the risk of leukemia dose-dependently to a total of 0.2–0.4 % within 10–15 years Anthracycline-containing regimens increase the risk of MDS and leukemia to 0.2–1.7 % within 8 to 10 years PARP-inhibitors are associated with an increased risk of AML and MDS to 0.5–1% Radiotherapy increases the risk of leukemia by 0.2–0.4% in patients treated with anthracycline-containing chemotherapy Tamoxifen approximately doubles the risk for developing endometrial cancer (in pts. older than 55y at start of therapy) 	2a	
	2a	
	2a	
	2b	
	2b	
	2b	


Statements 1-4

1. Schaapveld M, Visser O, Louweman M et al.(2008) Risk of primary non breast cancers after breast cancer treatment: a dutch population-based study. J Clin Oncol 26: 1239-46.
2. Kirova Y, De Rycke Y, Gambotti L et al.(2008) Second malignancies after breast cancer: the impact of different treatment modalities. B J Cancer 98: 870-4.
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Tamoxifen and endometrial cancer

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet.* 2011 Aug 27;378(9793):771-84.
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3. Dominick S, Hickey M, Chin J, et al. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. *Cochrane Database Syst Rev.* 2015 Dec 9;(12):CD007245. doi: 10.1002/14651858.CD007245.pub3.

	<h2>Secondary Malignancies II (After Radiotherapy)</h2>	
<p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<ul style="list-style-type: none"> ▪ Radiotherapy (PMRT, BET) may moderately enhance the risk of ipsilateral lung cancer and angiosarcoma (10-15 / 10.000) 5–10 years after treatment ▪ Enhanced risk especially among ever smokers ▪ No difference of secondary malignancy between PBI und WBI 	<p>Oxford LoE</p>
		1a
		2b
		2c

Statements 1-4

1. Schaapveld M, Visser O, Louweman M et al.(2008) Risk of primary non breast cancers after breast cancer treatment: a dutch population-based study. J Clin Oncol 26: 1239-46.
2. Kirova Y, De Rycke Y, Gambotti L et al.(2008) Second malignancies after breast cancer: the impact of different treatment modalities. B J Cancer 98: 870-4.
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8. Grantzau T, Overgaard J. Risk of second non-breast cancer among patients treated with and without postoperative radiotherapy for primary breast cancer: A systematic review and meta-analysis of population-based studies including 522,739 patients. *Radiother Oncol.* 2016 Dec;121(3):402-413. doi: 10.1016/j.radonc.2016.08.017. Epub 2016 Sep 14.
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Tamoxifen and endometrial cancer


1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet.* 2011 Aug 27;378(9793):771-84.
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3. Dominick S, Hickey M, Chin J, et al. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. *Cochrane Database Syst Rev.* 2015 Dec 9;(12):CD007245. doi: 10.1002/14651858.CD007245.pub3.

Side Effects According Organ Systems

Incidence, Prevention, Therapy

3. *Blood and Lymphatic System Disorders*

- Anemia
- Neutropenia
- Febrile Neutropenia (FN)

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	Oxford		
	LoE	GR	AGO
▪ Indicated in asymptomatic anemia	1a	B	-
▪ Therapy and secondary prophylaxis in CT-induced anemia	1a	A	+
▪ Adjuvant setting	1b	A	+
▪ Neoadjuvant/metastatic setting	1a	A	+/-
▪ In dose-dense / dose-escalated CT (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	

Leitlinie:

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)

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- best standard of care in anemic patients with metastatic breast cancer receiving standard chemotherapy. *J Clin Oncol* 34: 1197-1207, 2016.
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 11. Glaspy J, Crawford J, Vansteenkiste J, et al. Erythropoiesis-stimulating agents in oncology: a study-level meta-analysis of survival and other safety outcomes. *Br J Cancer*. 2010;102:301–315.
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Relevante Leitlinien

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Phase III Study of Epoetin Alfa Versus Best Standard of Care in Anemia Patients with Metastatic Breast Cancer


N=2.098 Pat., Hb <11g/dl; non inferiority study.
Prespecified upper non inferiority margin = 1.15

	PFS (median)		OS (median)	ORR	RBC transfusions	TVE
Epo	Invest.* 7,4 Mon	IRC** 7,6 Mon	17,2 Mon	50%	5,8%	2,8%
BSC	7,4 Mon.	7,6 Mon.	17,4 Mon	51%	11,4%	1,4%
	HR: 1,09	HR: 1,02	HR: 1,06	OR: 0,95	p<.001	p=.04
	Upper CI: 1,20	Upper CI: 1,146				

* Investigator determined
 ** Independent review committee

J Clin Oncol 2016 (34): 1197-1209

1. Leyland-Jones B, Bondarenko I et al. J Clin Oncol 2016 (34): 1197-1209



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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 β: 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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Relevante Leitlinien

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(https://www.nccn.org/professionals/physician_gls/pdf/anemia.pdf)

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Granulocyte Colony-stimulating Factors

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Primary prophylaxis for expected febrile neutropenia (FNP) <ul style="list-style-type: none"> If expected risk for FNP 10–20% <ul style="list-style-type: none"> In case of individual risk factors If expected risk for FNP >20% (e.g. DAC, dose-dense CT) Secondary prophylaxis during chemotherapy (previous FNP or neutropenia grade IV > 7 days) Therapeutic use for FNP Start related to chemotherapy and duration <ul style="list-style-type: none"> Pegfilgrastim day 2 Lipegfilgrastim day 2 Filgrastim/Lenograstim from day 2–3 until ANC > 2–3 x 10⁹ 	1b 3b 1a 1b 1a 1b 1b 1b	B C A A A A A A	+/- + ++ ++ +/- ++ ++ ++

Relevante Leitlinien

1. S3-Leitlinie: Supportive Therapie:

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2 – November 2019 AWMF-Registernummer: 032/054OL Zugriff 26.12.2019

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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 $>38.5^{\circ}\text{C}$ or two consecutive readings of $>38^{\circ}\text{C}$ for 2 h in a patient with an ANC of $<500\text{ cells/mm}^3$ or expected to fall to $<500\text{ cells/mm}^3$)

	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 4–7d in case of failure of antibiotic therapy	1b	A	++
▪ G-CSF for treatment (not prophylactic)	2b	B	+/-

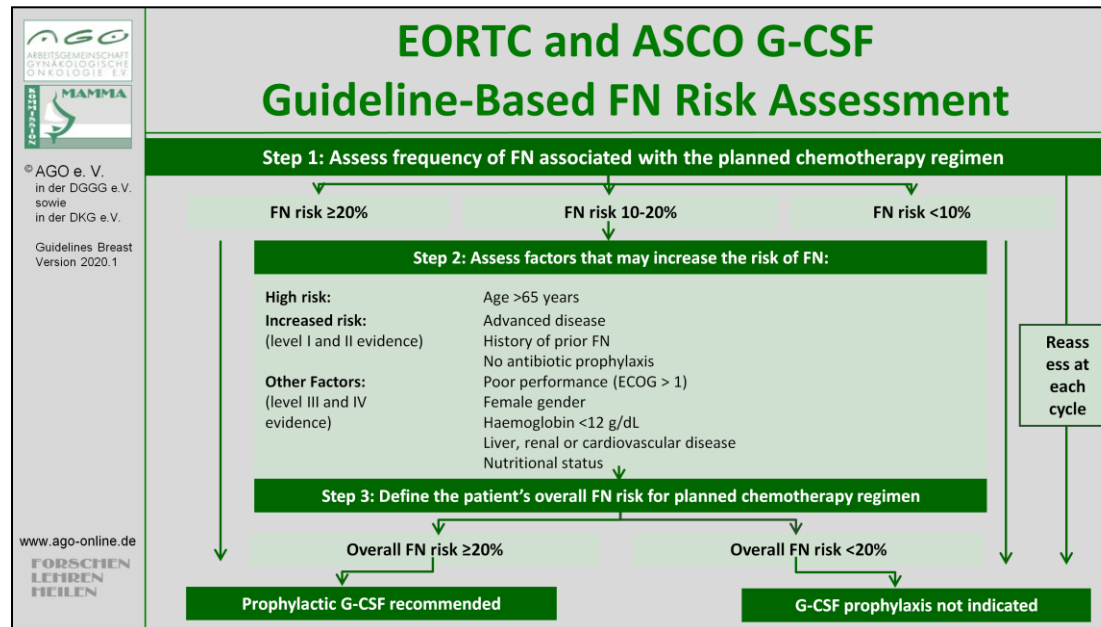
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 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<h2 style="text-align: center;">Empirical Antibiotic Therapy</h2> <p>The recommendations for empirical antibiotic therapy are currently changing because of infection biological findings.</p> <p>Current recommendations should be referred to regularly and adjusted to within personal professional judgement.</p> <p>The “Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de“ is a source for regular consultation.</p>
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Side Effects According Organ Systems

Incidence, Prevention, Therapy

4. Endocrine disorders

	<h2>Therapy-associated Amenorrhea (CRA, CIA, TIA)</h2>	
<p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<ul style="list-style-type: none"> ▪ CRA may be permanent or temporary (depending on age of the patient and type of chemotherapy) 	<p>Oxford</p> <hr/> <p>LoE</p> <p>2b</p>
	<ul style="list-style-type: none"> ▪ The risk of CRA increases with patient's age and duration of the chemotherapy 	<p>2b</p>
	<ul style="list-style-type: none"> ▪ CRA is an imperfect surrogate for menopause and fertility 	<p>5</p>
	<ul style="list-style-type: none"> ▪ Adjuvant endocrine therapy with GnRHa induces reversible amenorrhea, but delays conception to a less fertile period 	<p>5</p>
	<ul style="list-style-type: none"> ▪ Ovarian reserve of women who remain premenopausal after CTX is reduced 	<p>2b</p>
	<ul style="list-style-type: none"> ▪ CRA is associated with improved outcome (DFS/OS) 	<p>1b</p>
<p>Synonym: Chemotherapy related or induced / Treatment induced Amenorrhea (CRA, CIA, TIA)</p>		

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Side Effects According Organ Systems

Incidence, Prevention, Therapy

5. Psychiatric Disorders

- Depression
- Fatigue
- Cognitive impairment
- Sleep disturbances

	(Therapy-Associated) Depression		
	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
<div>  <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p> </div>	<ul style="list-style-type: none"> Fatigue frequent in breast cancer patients (30–60%) Exclusion of somatic reasons (anemia, tumor burden, co-morbidity, medication) for fatigue Psycho-social interventions specifically addressing fatigue efficient in reducing fatigue Physical exercise can improve fatigue Diet, Yoga can improve fatigue Methylphenidate can improve fatigue 		
	2a	B	
	1a	A	++
	1a	A	++
	1b	D	+
	2b	B	+
	1a	D	+

Fatigue is frequently present...

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	(Therapy-Associated) Cognitive Impairment	
	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, deterioration of cognitive performance was observed (espec. verbal memory)	1a	B



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Therapiebedingte kognitive Störungen (sog. „Chemobrain“) häufig beschrieben

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Methylphenidate kann kognitive Funktion bei Patientinnen mit Krebs verbessern

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(Therapy-Associated) Sleep Disturbances

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

- Sleep disturbances are a common problem in breast cancer patients during and after therapy (20–70%)
- Behavioral therapies demonstrated efficacy in treatment of insomnia and improved quality of life

Sleep disturbances are a common problem....

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Behavioral therapies have demonstrated efficacy.....


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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)

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Chemotherapy-induced Peripheral Neuropathy – Prevention –

	Oxford		
	LoE	GR	AGO
<u>Non drug-based prevention</u>			
▪ 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	-
<u>Drug-based prevention</u>			
▪ 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

Reviews/Leitlinien

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Nicht-medikamentöse Prävention

Funktionstraining

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Kompression

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Kühlung

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Elektro-Akupunktur

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Medikamentöse Prävention

Venlafaxin

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Palmitoylethanolamid (PEA)

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Acetyl-L-Carnitin

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	Oxford		
	LoE	GR	AGO
Chemotherapy-induced Peripheral Neuropathy – Therapy –			
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, pregabalin	1b	B	+/-
▪ Amitryptiline/ nortriptyline, 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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Reviews / Leitlinien

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Nicht-medikamentöse Therapie

Funktionstraining

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Side Effects According Organ Systems

Incidence, Prevention, Therapy

7. Cardiac Disorders



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GYNAKOLOGISCHE
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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/m ² cum. dose, resp.)	2b	B	
▪ Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity	1b	B	
▪ Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently: <ul style="list-style-type: none"> ▪ Elderly patients ▪ Obesity ▪ Hypertension ▪ Hypercholesterolemia ▪ Pre-existing cardiac diseases (incl. borderline LVEF) ▪ Diabetes mellitus 	2b	B	
▪ Monitoring of cardiac function: <ul style="list-style-type: none"> ▪ Standardized echocardiography (LVEF or SF in %) ▪ Troponin I as marker of cardiac toxicity 	3b	C	+
	2b	B	+/-
▪ Betablocker-prophylaxis during anthracycline therapy	2a	B	+/-

Statements

“Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)”

“Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity”

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“Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently...”

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“Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors.”

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“Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)”

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Troponin as Early Predictor for Cardiotoxicity

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Betablocker-Prophylaxe

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Adjuvant Trastuzumab Cardiac Monitoring for CHF

Oxford LoE: 5

Before start of trastuzumab

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

GR: D

AGO: ++

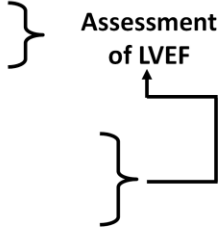
During trastuzumab

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


Assessment
of LVEF



Statement: Cardiac Monitoring (5 D ++)

Vote result of the AGO recommendation: 100%

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 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	Feasibility of Treatment Combinations Considering Toxicities		
	Oxford LoE GR AGO		
<u>Regarding cardiac toxicity</u>			
■ Trastuzumab simultaneous to radiotherapy	2b	B	+
■ Trastuzumab simultaneous to epirubicin	2b	B	+/-
■ Trastuzumab simultaneous to doxorubicin	2b	B	-
■ Anthracycline simultaneous to radiotherapy	2c	C	-
<u>Regarding lung and breast fibrosis</u>			
■ Tamoxifen simultaneous to radiotherapy	3	C	+/-
■ Chemotherapy simultaneous to radiotherapy	1b	B	-

Trastuzumab simultaneous to radiotherapy”

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“Trastuzumab simultaneous to epirubicin”

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“Trastuzumab simultaneous to doxorubicin”

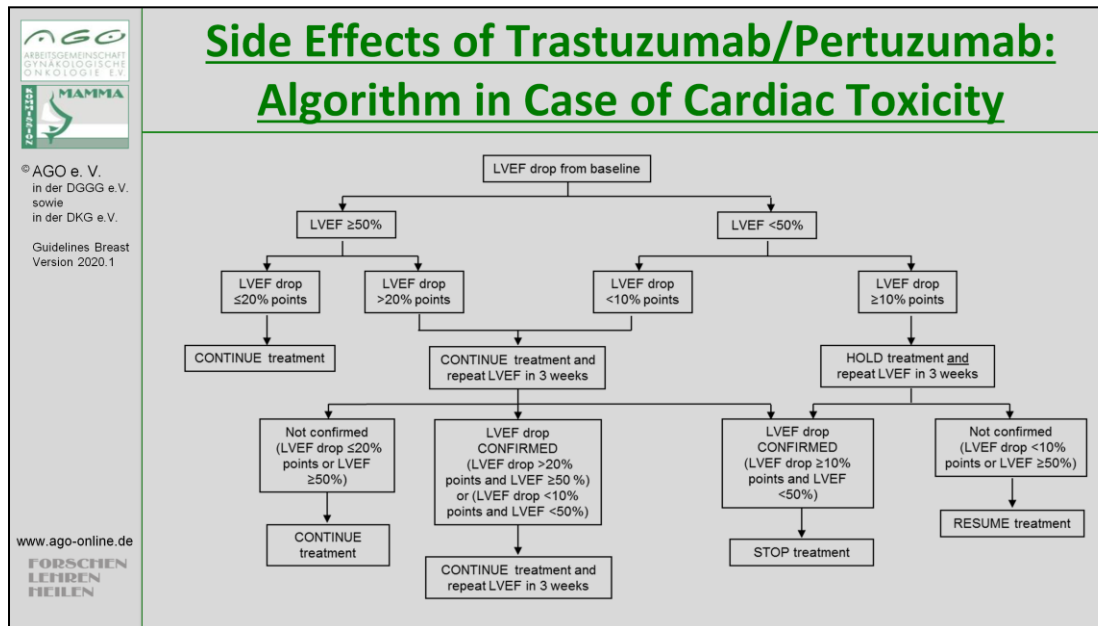
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Side Effects According Organ Systems

Incidence, Prevention, Therapy

8. Gastrointestinal Disorders

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



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Antiemetic Therapy

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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	1a	A	++
▪ 5-HT₃-antagonists	1b	A	++
▪ Fixed antiemetic combination therapy	1b	A	++
▪ Rescue Medication			
• Olanzapine	1b	A	+
▪ Levomepromazine, benzodiazepines	3b	C	+
▪ Cannabinoids, ginger			

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Olanzapine:

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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-HT₃ = serotonin receptor antagonist

DEX = DEXAMETHASONE


NK₁ = neurokinin 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 NK₁ receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT₃ receptor antagonist.
* OLZ: Olanzapine may be added particularly if nausea is a concern.

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DELAYED Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	DEX or (if APR 125mg for acute: (MCP + DEX) or (APR + DEX)) +/- OLZ*
High AC	NONE or (if APR 125mg for acute: DEX or APR) +/- OLZ*
Carboplatin	NONE or (if APR 125mg for acute: APR)
Oxaliplatin, or anthracycline, or cyclophosphamide	DEX can be considered
Moderate (other)	No routine prophylaxis
Low and Minimal	No routine prophylaxis

DEX = DEXAMETHASONE
MCP = METOCLOPRAMIDE
APR = APREPITANT
OLZ = OLANZAPINE

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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	Olanzapin	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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Olanzapine:

1. Hironobu H, Masakazu A, Osamu Tokuyama, et al. Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial Lancet Oncology December 11, 2019DOI:[https://doi.org/10.1016/S1470-2045\(19\)30678-3](https://doi.org/10.1016/S1470-2045(19)30678-3)
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Mucositis Prevention

[http://www.mascc.org/assets/documents/MucositisGuidelinesMASCC2006\(dtV\).pdf](http://www.mascc.org/assets/documents/MucositisGuidelinesMASCC2006(dtV).pdf)
 Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL):
 „Supportive Therapie bei onkologischen Patientinnen – interdisziplinäre Querschnittsleitlinie“, released 11.11.2016

		Oxford		
		LoE	GR	AGO
<ul style="list-style-type: none"> 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		++
<p>This entails:</p> <ol style="list-style-type: none"> Patient: <ul style="list-style-type: none"> Regular mouth washes (H₂O, NaCl) Soft tooth brushes Interdental care: flossing or using interdental brush Avoidance of alcohol, tobacco, hot food, sour food Regular screening for lesions Risk adjusted prophylaxis by dentist Continuous clinical control 				
<p>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/combinations</p>				

Relevant practice guideline


Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)

- RV Lalla, J Bowen, RV Lalla, et al.: MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014; 120:1453-61
- McGuire DB, Fulton JS, Park J, et al.: Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of basic oral care for the management of oral mucositis in cancer patients. Support Care Cancer 2013 Nov;21(11):3165-77.
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- Leenstra, J. L., R. C. Miller, R. Qin et al.: "Doxepin rinse versus placebo in the treatment of acute oral mucositis pain in patients receiving head and neck radiotherapy with or without chemotherapy: a phase III, randomized, double-blind trial (NCCTG-N09C6

[Alliance]). J Clin Oncol 2014;32(15): 1571-1577.

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Prevention of Everolimus-Induced Stomatitis Using Dexamethasone 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

[http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006\(dtV\).pdf](http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006(dtV).pdf)

- **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-fluorouracil- or HD-melphalan. 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!). Dexpantenole (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

Relevant practice guideline


Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)

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[Alliance])."J Clin Oncol 2014;32(15): 1571-1577.

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Diarrhea

- **Adsorbent agents**
 - Carbo medicinalis; caoline / pectine, Al-Mg-silicate hydrate
- **Analgetics, opioids**
 - Loperamide; codeine, morphine IV, tintura opii (tinture of opium), butylscopolamine
- **Pseudomembranous colitis**
 - Metronidazole or (if not effective) vancomycin


Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)

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7. Middleton, G., S. Brown, C. Lowe, T. et al. (2013). "A randomised phase III trial of the pharmacokinetic biomodulation of irinotecan using oral ciclosporin in advanced colorectal cancer: results of the Panitumumab, Irinotecan & Ciclosporin in COLOrectal cancer therapy trial (PICCOLO)." *Eur J Cancer* 2013, 49(16): 3507-3516.



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Constipation

Important Side Effect of Opioid Treatment

- **Bulging agents**
 - Psyllium, 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

Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)



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Side Effects According Organ Systems

Incidence, Prevention, Therapy

9. Skin & Subcutaneous Tissue Disorders (Alopecia)

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	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


Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)

Scalp Cooling:

1. 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.
2. Rugo HS, Voigt J. Scalp Hypothermia for Preventing Alopecia During Chemotherapy. A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Breast Cancer. 2018 Feb;18(1):19-28.
3. Rugo HS, Melin SA, Voigt J. Scalp cooling with adjuvant/neoadjuvant chemotherapy for breast cancer and the risk of scalp metastases: systematic review and meta-analysis. Breast Cancer Res Treat. 2017 Jun;163(2):199-205.



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

1. 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.
2. Rugo HS, Voigt J. Scalp Hypothermia for Preventing Alopecia During Chemotherapy. A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Breast Cancer. 2018 Feb;18(1):19-28.
3. Rugo HS, Melin SA, Voigt J. Scalp cooling with adjuvant/neoadjuvant chemotherapy for breast cancer and the risk of scalp metastases: systematic review and meta-analysis. Breast Cancer Res Treat. 2017 Jun;163(2):199-205.



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Side Effects According Organ Systems Incidence, Prevention, Therapy


10. MUSCULOSKELETAL & CONNECTIVE TISSUE DISORDERS

(see Chapter Osteooncology)


Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)



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Side Effects According Organ Systems Incidence, Prevention, Therapy

11. General Disorders & Administration Site Conditions

Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)

	Oxford		
	LoE	GR	AGO
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<ul style="list-style-type: none"> ■ Dexrazoxane for treatment of anthracycline-extravasations (exception: liposomal Anthracyclines) ■ Hyaluronic acid for treatment of taxane/vinorelbine-extravasations 	2b	B	++
	3b	D	++

Relevant practice guideline:


1. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants.
2. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019, AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)

Dexrazoxane

1. Hensley ML, Hagerty KL, Kewalramani T, et al.: Cardioprotective effect of dexrazoxane in patients with breast cancer treated with anthracyclines in adjuvant setting: a 10-year single institution experience. J Clin Oncol. 2009 Jan 1;27(1):127-45.
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Hyaluronsäure

...



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Extravasation of Chemotherapy

Role of Dexrazoxane/Hyaluronic Acid

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 (z.B. NaCl 0.9%)
- Local anaesthesia
- No thermotherapy after taxanes
- Dry warmth 4 x daily 20 min during vincaalkaloids


Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,

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Substance-Specific Side Effects

- **Antibodies and Antibody-Drug-Conjugates (ADC)**
- **CDK 4/6-Inhibitors**
- **PARP-Inhibitors**
- **Small molecules (TKI, mTOR-Inihibitor)**
- **Immun-Checkpoint-Antibodies**
- **PI3-Kinase-Inhibitoren (Alpelisib)**

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	Oxford		
	LoE	GR	AGO
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	
Bevacizumab			
▪ Hypertonus, proteinuria, bleeding, left ventricular dysfunction,	2b	B	
Trastuzumab-Deruxtecan			
▪ Interstitielle Lungenerkrankung, Neutropenie, Übelkeit	2b	B	

Cardiotoxicity....

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4. Higa GM, Abraham J: Biological mechanisms of bevacizumab-associated adverse events. Expert. Rev Anticancer Ther 2009;9:999–1007
5. Martin M, Esteva FJ, Alba E, et al: Minimizing cardiotoxicity while optimizing treatment efficacy with trastuzumab: review and expert recommendations. Oncologist 2009;14:1–11
6. Untch M, Eidtmann H, du Bois A, et al: Cardiac safety of trastuzumab in combination with epirubicin and cyclophosphamide in women with metastatic breast cancer: results of a phase I trial. Eur J Cancer 2004; 40:988–97
7. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al.: Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet.

2017 Mar 25;389(10075):1195-1205.

8. Pondé NF, Lambertini M, de Azambuja E. Twenty years of anti-HER2 therapy-associated cardiotoxicity. ESMO Open. 2016 Jul 21;1(4):e000073.

Troponin I....

1. Cardinale D, Colombo A, Torrisi R, et al: Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. J Clin Oncol 28: 3910-3916, 2010

Bevacizumab

1. Cortes J, Calvo V, Ramirez-Merino N et al: Adverse events risk associated with bevacizumab addition to breast cancer chemotherapy: a metanalysis. Ann Oncol. 2019 Jan 9. doi: 10.1093/annonc/mdy535
2. Hamilton EP, Blackwell KL: Safety of Bevacizumab in patients with metastatic breast cancer. Oncology 80:314-325, 2011
3. Syrigos KN, Karapanagiotu E, Boura P et al: Bevacizumab-induced hypertension. Biodrugs; 25:159-169, 2011
4. Blowers E, Hall K: Managing adverse events in the use of bevacizumab and chemotherapy. Br J Nurs 2009;18:351–6, 58
5. Miller K, Wang M, Gralow J, et al: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 357: 2666-2676, 2007

Lapatinib...

1. Wu PA, Balagula Y, Lacouture ME, et al.: Prophylaxis and treatment of dermatologic adverse events from epidermal growth factor receptor inhibitors. Curr Opin Oncol 23:343-351, 2011
2. Von Minckwitz G, Eidtmann H, Loibl S et al: Integrating bevacizumab, everolimus, and lapatinib into current neoadjuvant chemotherapy regimen for primary breast cancer. Safety results of the GeparQuinto trial. Ann Oncol 22:301-306, 2011
3. Sherill B, Amonkar MM, Sherif B et al: Quality of life in hormone receptor-positive Her2-positive metastatic breast cancer patients during treatment with letrozole alone or in combination with lapatinib. Oncologist 15:944-953, 2010
4. Cameron D, Casey M, Olica C et al: Lapatinib plus capecitabine in women with Her2-positive advanced breast cancer: Final survival analysis of a phase III randomized trial. Oncologist 15:924-934, 2010
5. Geyer CE, Forster J, Lindquist D; et al: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 355:2733-2743, 2006

Pertuzumab


1. von Minckwitz G, Procter M, de Azambuja E, et al. APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER-2 Positive Breast Cancer. N Engl J Med. 2017 Jul 13;377(2):122-131.
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T-DM1

1. Verma S, Miles D, Gianni L, et al: EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012 Nov 8;367(19):1783-91.
2. von Minckwitz G, Huang CS, Mano MS, et al.; KATHERINE Investigators. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2018 Dec 5. doi: 10.1056/NEJMoa1814017

Trastuzumab-Deruxtecan

1. Modi S, Saura C, Yamashita T, et al.: Trastuzumab deruxtecan in previously treated her2-positive breast cancer. N Engl J Med 2019.
2. Tamura K, Tsurutani J, Takahashi S, et al.: Trastuzumab deruxtecan (ds-8201a) in patients with advanced her2-positive breast cancer previously treated with trastuzumab emtansine: A dose-expansion, phase 1 study. Lancet Oncol 2019;20:816-826.

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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			

Palbociclib


1. Verma S, Bartlett CH, Schnell P, et al. Palbociclib in Combination With Fulvestrant in Women With Hormone Receptor-Positive/HER2-Negative Advanced Metastatic Breast Cancer: Detailed Safety Analysis From a Multicenter, Randomized, Placebo-Controlled, Phase III Study (PALOMA-3). *Oncologist*. 2016 Oct;21(10):1165-1175. Epub 2016 Jul 1.
2. N.Harbeck, J. Ettl, Palbociclib, CDK 4/ 6 Inhibition als neue Therapieoption bei Patientinnen mit fortgeschrittenem HR+/ Her – Mammakarzinom. *Drug Report*, 2017

Ribociclib

1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *N Engl J Med*. 2016 Nov 3;375(18):1738-1748. Epub 2016 Oct 7.

Abemaciclib

1. Sledge GW, Jr., Toi M, Neven P, et al: Monarch 2: Abemaciclib in combination with fulvestrant in women with hr+/her2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol* 2017;35:2875-2884.
2. Goetz MP, Toi M, Campone M, et al: Monarch 3: Abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol* 2017;35:3638-3646.



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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)**


1. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomized phase 3 trial. *Lancet Oncol.* 2018 Jul;19(7):904-915.
2. Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone-Receptor-Positive, Human Epidermal Growth Factor Receptor-2 Negative Advanced Breasts Cancer: MONALEESA-3. *J Clin Oncol.* 2018 Aug 20;36(24):2465-2472.
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4. Trinkley KE, Page RL 2nd, Lien H, et al. QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. *Curr Med Res Opin.* 2013 Dec;29(12):1719-26.

Toxicities of new compounds: mTOR-Inhibitor – Everolimus –		
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	grade >=3 (%)	
	Stomatitis	11,6
	Exanthema	7,4
	Anemia	3,3
	Fatigue	6,8
	Nausea	5,6
	Emesis / Vomiting	2,9
	Diarrhea	6,2
	Loss of appetite	6,0
	Headache	3,9
	Weight loss	3,9
	Dyspnea	3,8
	Arthralgia	3,3
	Epistaxis	3,1
	Edema	2,9
	Constipation	2,6
	Pyrexia	2,9
	Cough	4,5
	ALT Elevated	2,6
	Pneumonitis	0,2
	Asthenia	2,4
	Dysgeusia	4,3

1. Baselga J, Campone M, Piccart M et al Everolimus in postmenopausal hormone receptor positive advanced breast cancer N Engl J Med:366,: 520 -529, 2012



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Toxicities of new compounds: PARP-Inhibitors – Olaparib, Talazoparib –

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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1. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018 Aug 23;379(8):753-763.
2. Robson M, Im SA, Senkus E et al. Olaparib for metastatic breast cancer in patients with germline BRCA mutation N Engl J Med 377: 523-533, 2017

Toxicities of new compounds: antiHER2-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

Primary Prophylaxis with loperamide

LoE	AGO
2b	B ++

1. Chan A, Delagoge S, Holmes FA et al Neratinib after trastuzumab –based adjuvant therapy in patients with HER2 positive breast cancer (ExteNET): a multicentr, randomized, double.-blind, placebo controlled , phase III trial. Lancet Oncol 17(39: 367-377, 2016
2. Piccart-Gebhart M , Holmes E., Baselga J et al Adjuvant Lapatinib and Trastuzumab for Early Human Epidermal Growth Factor Receptor 2-positive Breast Cancer:Results From the Randomized Phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial. JCO 34:1034-1042, 2015
3. Neratinib: FDA Produktinformation 2017



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Toxicities of new compounds: PIK3CA - alpelisib

Alpelisib+Fulvestrant

UE, %	All Grade	Grad >=3
Hyperglycemia	63,7%	32,7%
Diarrhea	57,7%	6,7%
Nausea	44,7%	2,5%
Decreased appetite	35,6%	< 1% SAE
Rash	35,5%	9,9%
Vomiting	27,1%	< 1% SAE
Weight loss	26,8%	3,9%
Stomatitis	24,6%	2,5%
Fatigue	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 AGO

2b B ++

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

1. H. S. Rugo, F. André, et al. Time Course and Management of Key Adverse Events During the Randomized Phase 3 SOLAR-1 Study of PI3K inhibitor Alpelisib Plus Fulvestrant in Patients With HR-Positive Advanced Breast Cancer in press, 2020
2. Andre F, Ciruelos E, Rubovszky G et al.:Alpelisib for pik3ca-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 2019;380:1929-1940.
3. Mayer IA, Abramson V, Formisano L, et al.: A phase Ib study of alpelisib (byl719), a pi3kalpha-specific inhibitor, with letrozole in er+/her2-negative metastatic breast cancer. Clin Cancer Res 2016.



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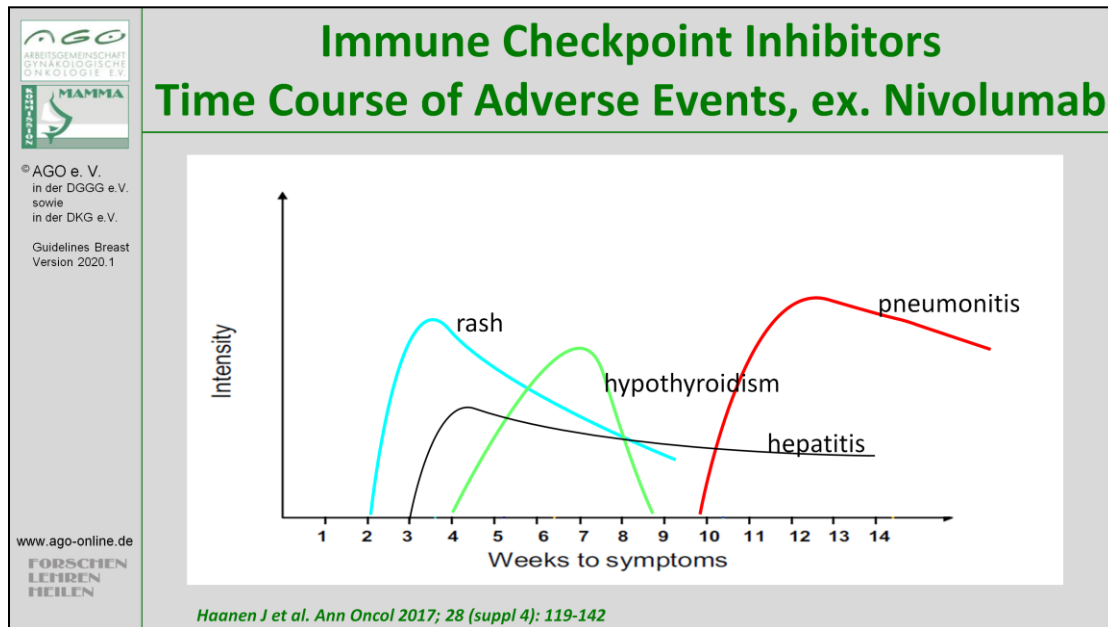
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Immune Checkpoint Inhibitors

- **Therapeutic approaches (antibodies)**
 - **PD1 /PD-L1**
 - PD1**
 - nivolumab
 - pembrolizumab
 - PDL1**
 - atezolizumab
 - durvalumab
 - avelumab

1. Haanen J, Carbone F, Robert C, et al, on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142. doi: 10.1093/annonc/mdx225
2. Ingrid A. Mayer¹, Aleix Prat², Daniel Egle³, et al.: A Phase II Randomized Study of Neoadjuvant Letrozole Plus Alpelisib for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer (NEO-ORB) Clin Cancer Res. 2019 May 15; 25(10): 2975–2987.



1. Haanen J, Carbone F, Robert C, et al. on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 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
 - thyroiditis (hyper-/hypothyroidism)
 - Guillain-Barré syndrome
 - cardiomyopathy
 - myopathy – myalgia – rhabdomyolysis
 - uveitis

1. Haanen J, Carbone F, Robert C, et al. on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142.



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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%
hepatotoxicity	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

Atezolizumab: <https://www.fachinfo.de/suche/fi/021700>

Nivolumab: <https://www.fachinfo.de/suche/fi/020675>

Pembrolizumab: <https://www.fachinfo.de/suche/fi/020716>



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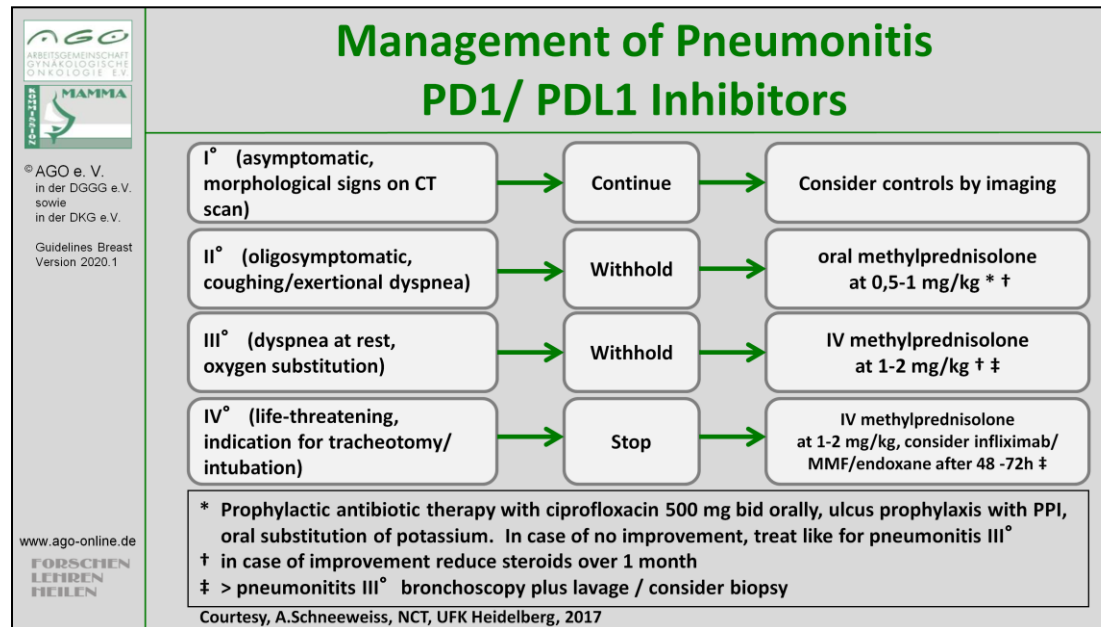
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Immune Checkpoint Inhibitors

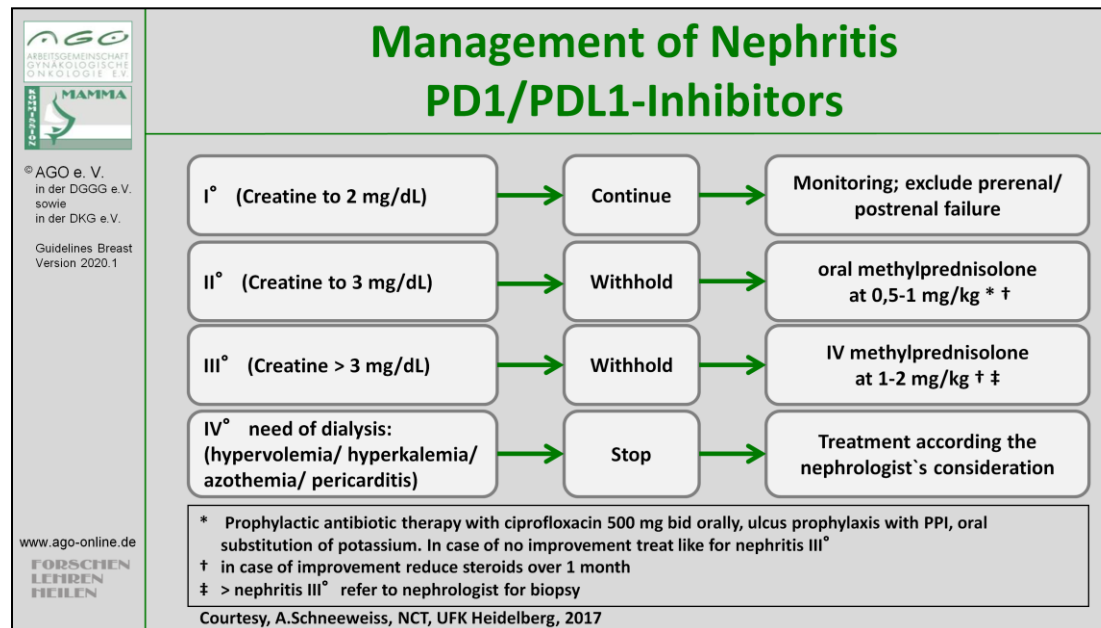
Principles of Adverse Event Management

CTC AE-Grade	Management
1	<ul style="list-style-type: none"> ▪ supportive therapy ▪ close examination ▪ exclusion of infective complications ▪ patient information
2	Like grade 1 but <ul style="list-style-type: none"> ▪ intermission of therapy until recovery of all irAE to grades 0-1 ▪ consider corticosteroids
3	<ul style="list-style-type: none"> ▪ supportive therapy ▪ IV steroids (e.g. 1-2 mg/kg prednisolone) In case of no improvement within 48 h: <ul style="list-style-type: none"> ▪ 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

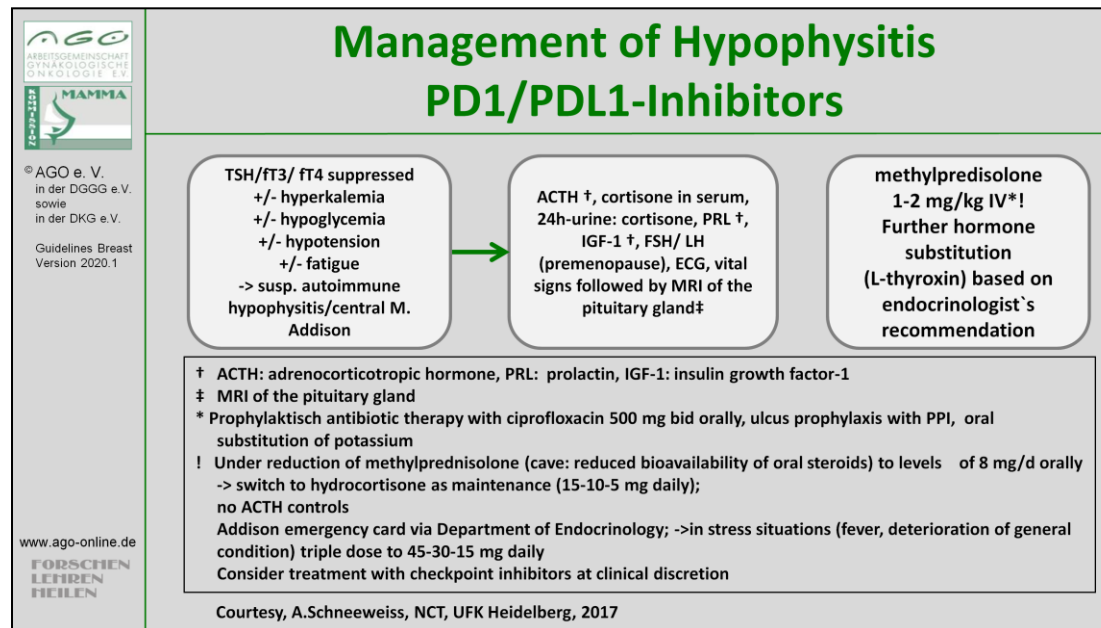
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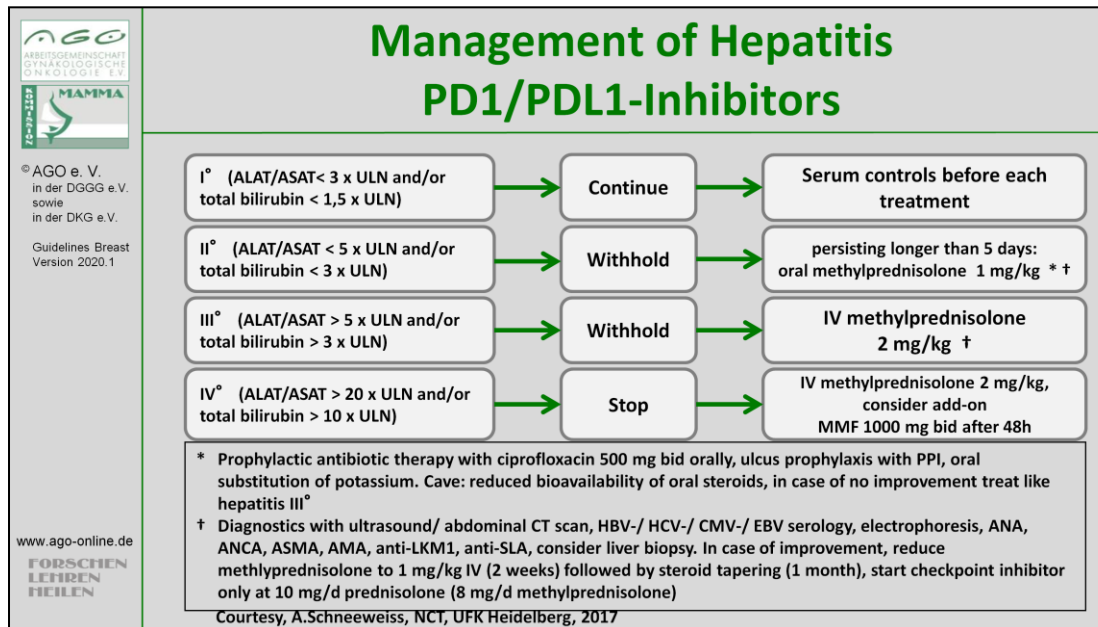
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2. Postow M, Sidlow R, Hellmann M: Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018; 378(2): 158-168. doi: 10.1056/NEJMra1703481



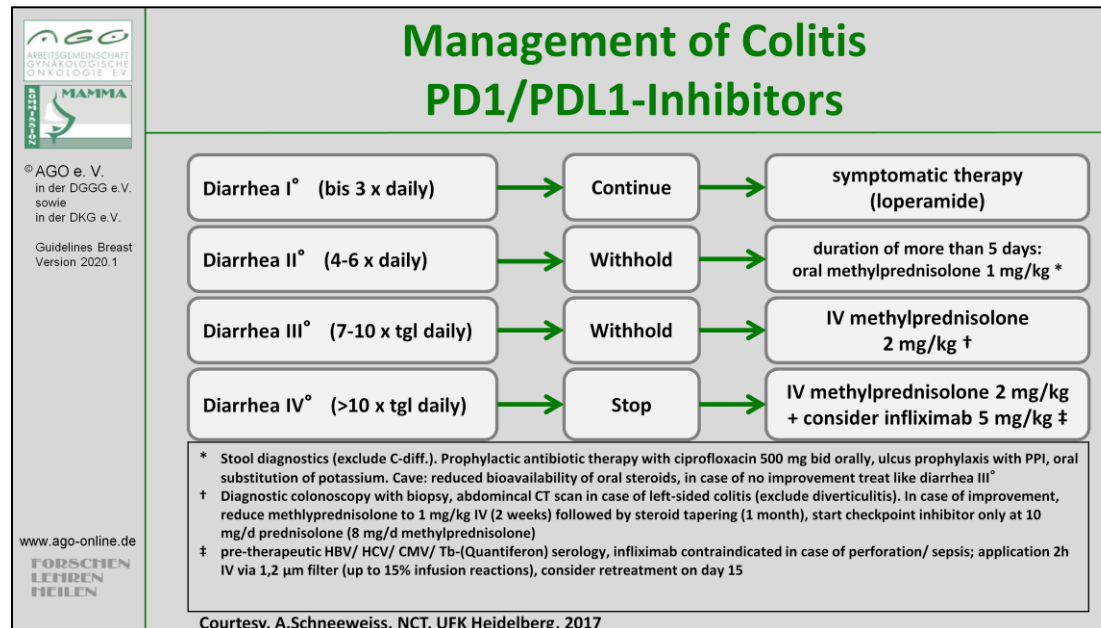
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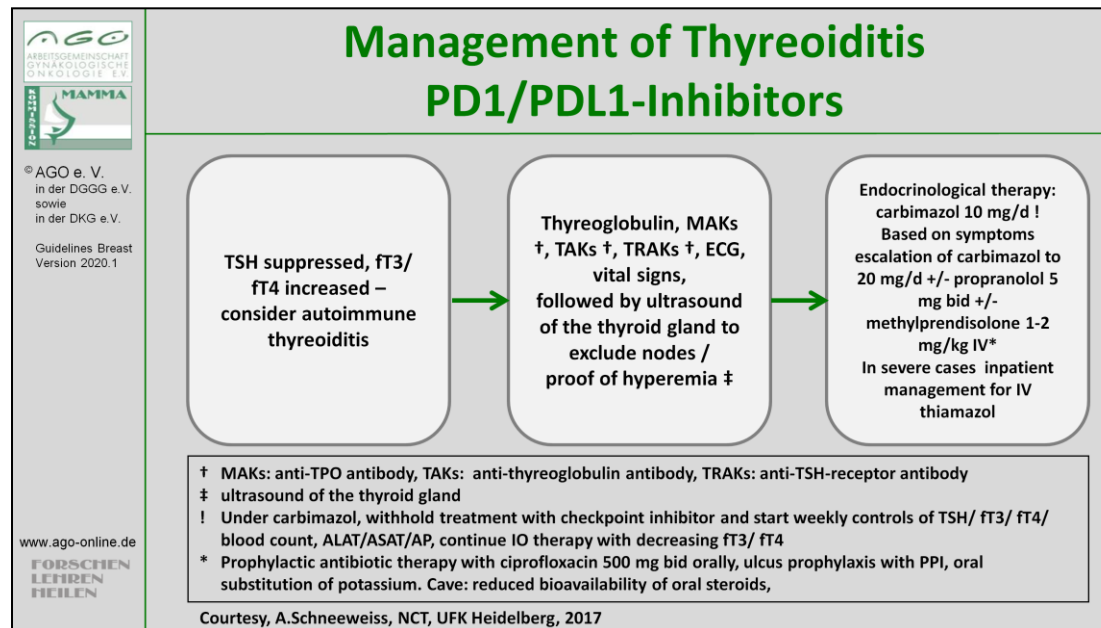
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2. Postow M, Sidlow R, Hellmann M: Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018; 378(2): 158-168. doi: 10.1056/NEJMra1703481

■ Further supportive and palliative 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**

Klinische Ernährung:

1. Arends J, Bertz H, Bischoff SC, et al. und das DGEM Steering Committee. Klinische Ernährung in der Onkologie. S3-Leitlinie AWMF Reg.: 073-0061Aktuel Ernährungsmed 2015; 40: e1–e74 www.awmf.org/uploads/tx_szleitlinien/073-0061_S3_Klin_Ernährung_in_der_Onkologie_2015-10.pdf abgerufen 2101202
2. [de Las Peñas R](#), [Majem M](#), [Perez-Altozano J](#), et al SEOM clinical guidelines on nutrition in cancer patients (2018). [Clin Transl Oncol](#). 2019 Jan;21(1):87-93. doi: 10.1007/s12094-018-02009-3. Epub 2019 Jan 8.
3. [van den Berg MMGA](#)¹, [Kok DE](#)², [Posthuma L](#)¹, et al [Breast Cancer Res Treat](#). 2019 Jan;173(2):475-481. doi: 10.1007/s10549-018-5014-5. Epub 2018 Oct 23.



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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

Relevant practice guideline:

1. WHO Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. Januar 2019 , Geneva ISBN: 978-92-4-155039-0 www.who.int/ncds/management/palliative-care/cancer-pain-guidelines/en/ Zugriff 21.01.2020

Relevant practice guideline:

2. Horlemann J, Schürmann N. DGS Praxisleitlinien in der Schmerztherapie. Cannabis in der Schmerzmedizin v 1.0 www.dgs-praxisleitlinien.de/index.php/leitlinien/cannabis



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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 counselling.**

<https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/>

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Palliativmedizin für Patienten mit einer nicht-heilbaren Krebserkrankung, Lang- version 2.0, 2019, AWMF-Registernummer: 128/001OL, <https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/> (abgerufen am: 21.01.2020)