Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2023.1E

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Supportive Care and Management of Side Effects

Screened data bases
Pubmed 2007 - 2022, ASCO 2010 – 2022, SABCS 2010 – 2022, Cochrane Data Base (2022)

Screened guidelines

1. Cardoso F, Paluch-Shimon S, Senkus E, et. al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020 Dec;31(12):1623-1649.
2. Thomssen C., Lüftner D, Untch M, et al. International Consensus Conference for Advanced Breast Cancer, Lisbon 2019: ABC5 Consensus - Assessment by a German Group of Experts. Breast Care (Basel). 2020
3. ASCO (American Association of Clinical Oncology, Practice Guidelines, 2021) 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 , 2021): http://www.nccn.org
8. S3-Leitlinie: Supportive Therapie: Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3 – Februar 2020 AWMF-Registernummer: 032/054OL

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Supportive Care and Management of Side Effects

- **Versions 2002–2022:**
  Albert / Bauerfeind / Brunnert / Bischoff / Costa / Dall / Diel / Fersis / Friedrich / Friedrichs / Gerber / Göhring / Hanf / Harbeck / Heinrich / Huober / Jackisch / Lisboa / Lück / Lüftner / von Minckwitz / Möbus / Müller / Mundhenke / Nitz / Oberhoff / Reimer/ Rody / Schaller / Scharl / Schmidt / Schneeweiss / Schütz / Solomayer / Souchon / Stickeler / Thomssen / Untch

- **Version 2023:**
  Maass / Park-Simon

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Guidelines – Evidence

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

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

Aspects concerning breast cancer patients will especially be highlighted.

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

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

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

1. S3-Leitlinie Supportive Therapie:
Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3 – Februar 2020 AWMF-Registernummer: 032/054OL Zugriff 25.12.2021 https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.pdf

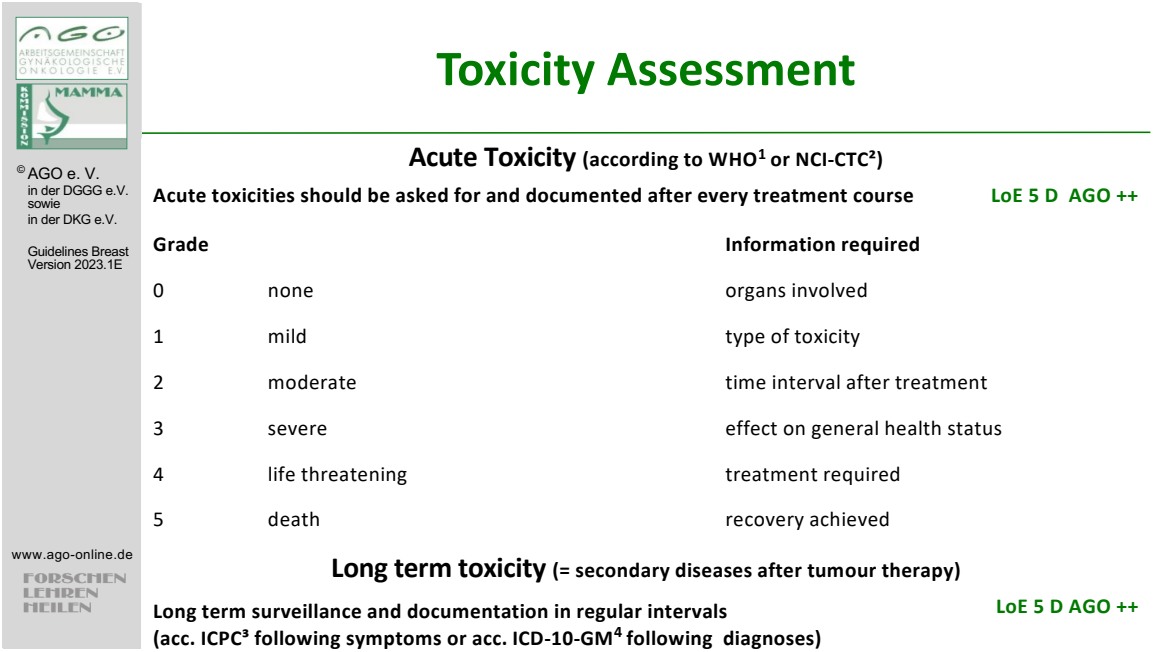
2. ESMO Clinical Practice Guidelines: Supportive and Palliative Care. www.esmo.org

3. Jordan K, Aapro M, Kaasa S, et al. European Society for Medical Oncology (ESMO) position paper on supportive and palliative care. Ann Oncol. 2018 Jan 1;29(1):36-43.

4. Schneider BJ, Naidoo J, Santomasso BD, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update. J Clin Oncol. 2021 Dec 20;39(36):4073-4126.

Toxicity Assessment

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



Toxicity Assessment

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

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

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

Long term toxicity (= secondary diseases after tumour therapy)

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

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)

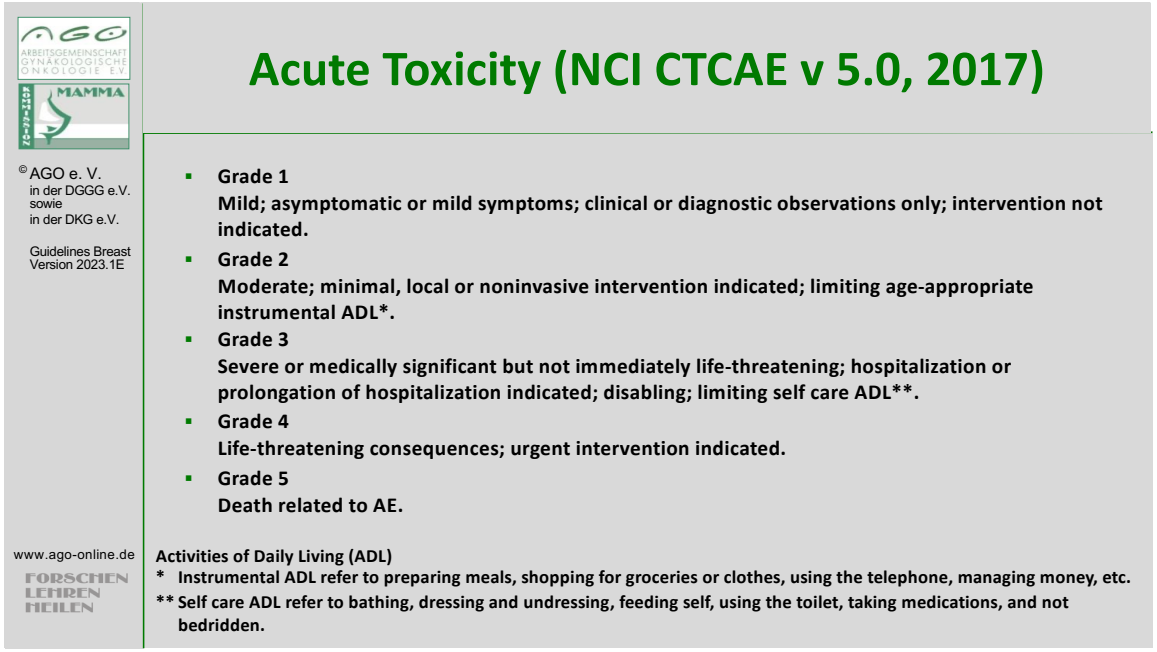
Akute Toxizität nach jedem Therapiezyklus abfragen

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.



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)

Incidence of Side Effects

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

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

*MedDRA - Medical Dictionary for Regulatory Activities

https://www.meddra.org/

Chemotherapy – Acute Toxicities I

Guidelines Breast
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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)

Side effect categories - MedDRA (Medical Dictionary for Regulatory Activities)

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

Sources for product information (Download 19.01.2018)

1. Cyclophosphamid: http://www.baxter.de/de_DE/assets/downloads/fachinformation/endoxan.pdf
2. Methotrexat: https://www.gelbe-liste.de/produkte/MTX-HEXAL-10-mg-Tabletten_117469/fachinformation
3. 5-Fluorouracil: https://www.gelbe-liste.de/produkte/Fluorouracil-HEXAL-50-mg-ml-Injektionsloesung-100-ml_546519/fachinformation
4. Capecitabin: https://www.zentiva.de/Produkte/Capecitabin-Zentiva/Downloads?id=a63946ee-51ce-46ac-8184-a468b705ed9b
5. Gemcitabin: http://www.success-studie.de/b/downloads/Fachinfo/GemzarFI07Jan.pdf
6. Cisplatin: https://www.gelbe-liste.de/produkte/Cisplatin-Teva-1-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-100-ml_543960/fachinformation
7. Carboplatin: http://www.teva.de/index.php?eID=dumpFile&t=f&f=37532&g=-1&r=11068%2C11068&token=eebfb22e78f1cc8d9935d59c087e80630146f49e

8. Epirubicin:
9. Doxorubicin:
10. Liposomales Doxorubicin: https://www.gelbe-liste.de/produkte/Myocet-50-mg-Pulver-Dispersion-u-Loesungsmittel-fuer-ein-Konzentrat-zur-Herstellung-einer-Infusionsdispersion_359323/fachinformation
11. PEG-lipo. Doxorubicin: https://www.gelbe-liste.de/produkte/Caelyx-2-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-10-ml_121890/fachinformation
12. Mitoxantron: https://www.gelbe-liste.de/produkte/Mitoxantron-Teva-2-mg-ml-Injektionsloesung-15ml_543783/fachinformation
13. Paclitaxel: https://medikamio.com/de-de/medikamente/paclitaxel-ratiopharm/pil
14. Nab-Paclitaxel: https://www.gelbe-liste.de/produkte/Abraxane-5-mg-ml-Pulver-zur-Herstellung-einer-Infusionssuspension_514889/fachinformation
15. Docetaxel: https://mein.sanofi.de/produkte/Taxotere/Downloads?id=89447754-dfb2-450b-b35a-36950de8a74d
16. Vinorelbin: http://www.detect-studien.de/dokumente/d3/fachinfo/Navelbine.pdf
17. Eribulin: http://www.detect-studien.de/dokumente/d4/fachinfo/Fachinfo_Eribulin_Halaven.pdf

Further references (selection)

1. Azim HA Jr, de Azambuja E, Colozza M, et al.: Long-term toxic effects of adjuvant chemotherapy in breast cancer. Ann Oncol. 2011 Sep;22(9):1939-47.
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 Antiblastic Drugs and Cardioprotection:e12-e18. Review.

Chemotherapy – Acute Toxicities II

Guidelines Breast
Version 2023.1E

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

- unknown (based on available data incidence not assessable)

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

Abbreviations

AML = Acute myeloid Leucemia; DPD = Dihydropyrimidin-Dehydrogenase); CHF = congestive heart failure; CIPN = Chemotherapy-induced peripheral neuropathy; HFS = Hand-Foot-Syndrom; PPE = Palmar and plantar Erythema

Side effect categories - MedDRA (Medical Dictionary for Regulatory Activities)

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

Sources for product information (Download 19.01.2018)

1. Cyclophosphamid: http://www.baxter.de/de_DE/assets/downloads/fachinformation/endoxan.pdf
2. Methotrexat: https://www.gelbe-liste.de/produkte/MTX-HEXAL-10-mg-Tabletten_117469/fachinformation
3. 5-Fluorouracil: https://www.gelbe-liste.de/produkte/Fluorouracil-HEXAL-50-mg-ml-Injektionsloesung-100-ml_546519/fachinformation
4. Capecitabin: https://www.zentiva.de/Produkte/Capecitabin-Zentiva/Downloads?id=a63946ee-51ce-46ac-8184-a468b705ed9b
5. Gemcitabin: http://www.success-studie.de/b/downloads/Fachinfo/GemzarFI07Jan.pdf

6. Cisplatin: https://www.gelbe-liste.de/produkte/Cisplatin-Teva-1-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-100-ml_543960/fachinformation
7. Carboplatin: http://www.teva.de/index.php?eID=dumpFile&t=f&f=37532&g=-1&r=11068%2C11068&token=eebfb22e78f1cc8d9935d59c087e80630146f49e
8. Epirubicin:
9. Doxorubicin:
10. Liposomales Doxorubicin: https://www.gelbe-liste.de/produkte/Myocet-50-mg-Pulver-Dispersion-u-Loesungsmittel-fuer-ein-Konzentrat-zur-Herstellung-einer-Infusionsdispersion_359323/fachinformation
11. PEG-lipo. Doxorubicin: https://www.gelbe-liste.de/produkte/Caelyx-2-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-10-ml_121890/fachinformation
12. Mitoxantron: https://www.gelbe-liste.de/produkte/Mitoxantron-Teva-2-mg-ml-Injektionsloesung-15ml_543783/fachinformation
13. Paclitaxel: https://medikamio.com/de-de/medikamente/paclitaxel-ratiopharm/pil
14. Nab-Paclitaxel: https://www.gelbe-liste.de/produkte/Abraxane-5-mg-ml-Pulver-zur-Herstellung-einer-Infusionssuspension_514889/fachinformation
15. Docetaxel: https://mein.sanofi.de/produkte/Taxotere/Downloads?id=89447754-dfb2-450b-b35a-36950de8a74d
16. Vinorelbin: http://www.detect-studien.de/dokumente/d3/fachinfo/Navelbine.pdf
17. Eribulin: http://www.detect-studien.de/dokumente/d4/fachinfo/Fachinfo_Eribulin_Halaven.pdf

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1. Azim HA Jr, de Azambuja E, Colozza M, et al.: Long-term toxic effects of adjuvant chemotherapy in breast cancer. Ann Oncol. 2011 Sep;22(9):1939-47.
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Onkologie 36(5): 266-272.
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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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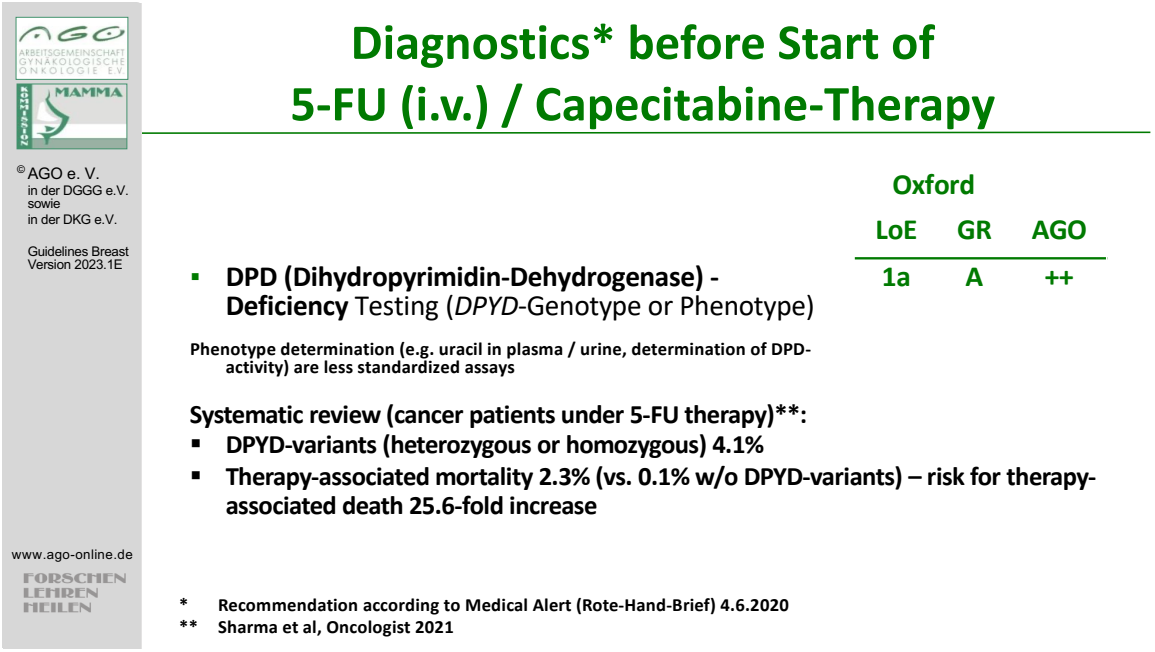
12. Madeddu C, Deidda M, Piras A, et al. Pathophysiology of cardiotoxicity induced by nonanthracycline chemotherapy. J Cardiovasc Med (Hagerstown). 2016 May;17 Suppl 1 Special issue on Cardiotoxicity from Antiblastic Drugs and Cardioprotection:e12-e18. Review.



DPD Deficiency:

1. Rote-Hand-Brief vom 04.06.2020: https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RHB/2020/rhb-fluorouracil.html (Zugriff am 17.01.2022)
2. García-Alfonso P, Saiz-Rodríguez M, Mondéjar R, et al. Consensus of experts from the Spanish Pharmacogenetics and Pharmacogenomics Society and the Spanish Society of Medical Oncology for the genotyping of DPYD in cancer patients who are candidates for treatment with fluoropyrimidines. Clin Transl Oncol. 2021 Nov 13.
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Endocrine Therapy – Toxicities

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

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

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

Side effect categories- MedDRA (Medical Dictionary for Regulatory Activities)

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

Sources for product information (Download 19.01.2018)

1. Tamoxifen: https://www.gelbe-liste.de/produkte/Tamoxifen-20-mg-HEXAL-Filmtbl_8660/fachinformation
2. Anastrozol: https://imedikament.de/anastrozol-ratiopharm-1-mg-filmtabletten/fachinformation
3. Exemestan: http://www.success-studie.de/c/downloads/Fachinfo/FI_ExemestanAromasin.pdf
4. Letrozol: http://www.success-studie.de/b/downloads/Fachinfo/Femara_Juli_2014.pdf
5. Fulvestrant: https://www.gelbe-liste.de/produkte/Fulvestrant-HEXAL-250-mg-Injektionsloesung-in-einer-Fertigspritze_912622/fachinformation

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

Cardiotoxicity

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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.

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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

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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3. Baselga J, Cortes J, Kim S-B et al. Pertuzumab plus Trastuzumab plus Docetaxel for metastatic breast cancer. N Engl J Med 2012; 366:109-119

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

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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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, Lapatinb s. aktuelle Fachinformation www. Fachinfo.de

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

1. Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med. 2020 Feb 13;382(7):597-609. doi: 10.1056/NEJMoa1914609. Epub 2019 Dec 11.
2. Tucatinib, Trastuzumab, Capecitabin s. aktuelle Fachinformation www. Fachinfo.de

Key-Toxicities – Antibody-Drug-Conjugates

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

Sacituzumab Govitecan…

1. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2021 Apr 22;384(16):1529-1541.
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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
3. Barroso-Sousa R, Tarantino P, Tayob N et al. Cardiac outcomes of subjects on adjuvant trastuzumab emtansine vs paclitaxel in combination with trastuzumab for stage I HER2-positive breast cancer (ATEMPT) study (TBCRC033): a randomized controlled trial. NPJ Breast Cancer. 2022 Feb 16;8(1):18.
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Trastuzumab-Deruxtecan

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4. Modi S, Saura C, Yamashita T, et al.: Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020 Feb 13;382(7):610-621.
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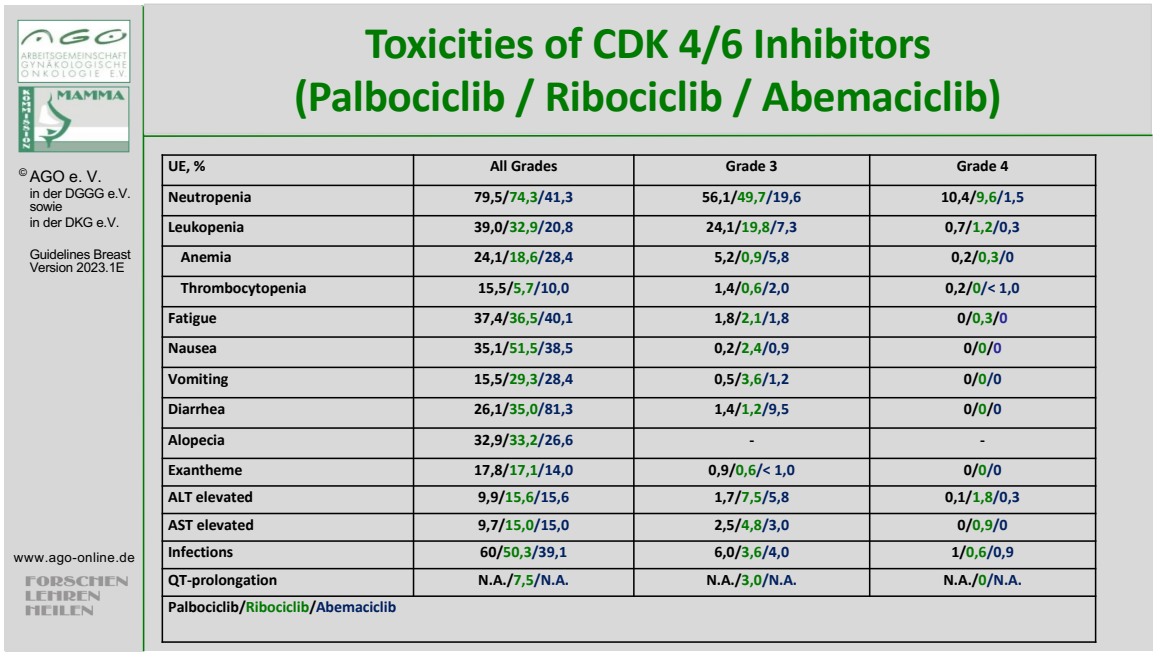

UE, %	All Grades	Grade 3	Grade 4
Neutropenia	79,5/74,3/41,3	56,1/49,7/19,6	10,4/9,6/1,5
Leukopenia	39,0/32,9/20,8	24,1/19,8/7,3	0,7/1,2/0,3
Anemia	24,1/18,6/28,4	5,2/0,9/5,8	0,2/0,3/0
Thrombocytopenia	15,5/5,7/10,0	1,4/0,6/2,0	0,2/0/< 1,0
Fatigue	37,4/36,5/40,1	1,8/2,1/1,8	0/0,3/0
Nausea	35,1/51,5/38,5	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.
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Ribociclib

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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.
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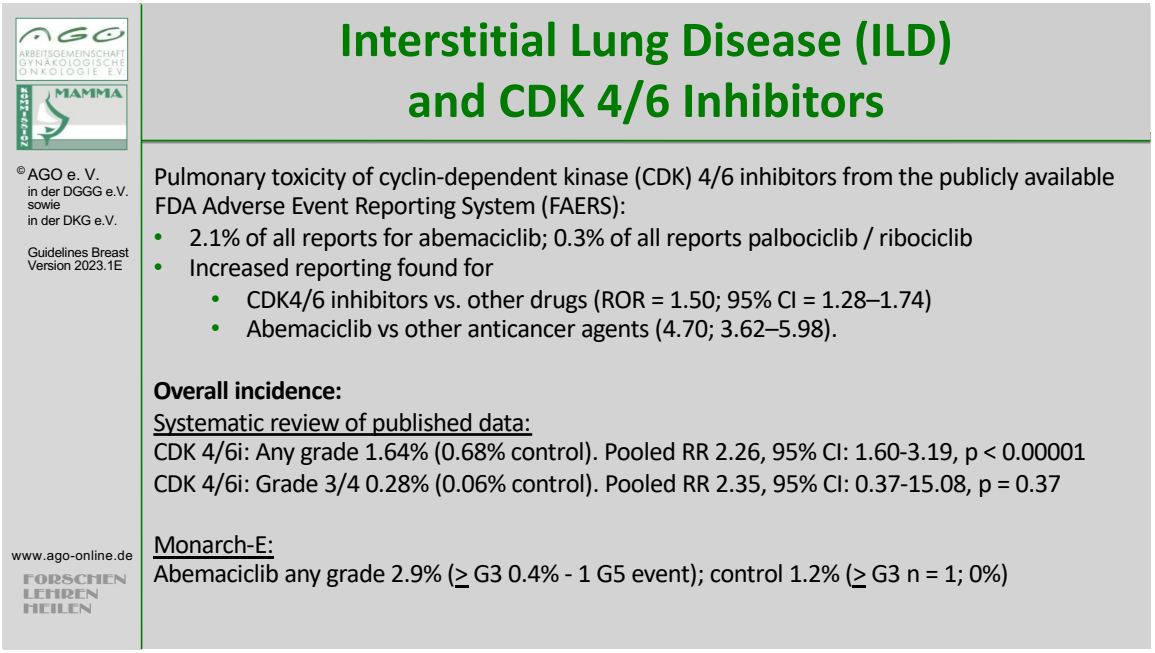

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3. Jahan N, Wongsaengsak S, Rehman A, et al. Relative risk of pneumonitis or interstitial lung disease (ILD) associated with the use of cyclin-dependent kinase inhibitors (CDK4/6i): A systematic review and meta-analysis of phase 3 randomized controlled trials. ASCO 2021, #1072
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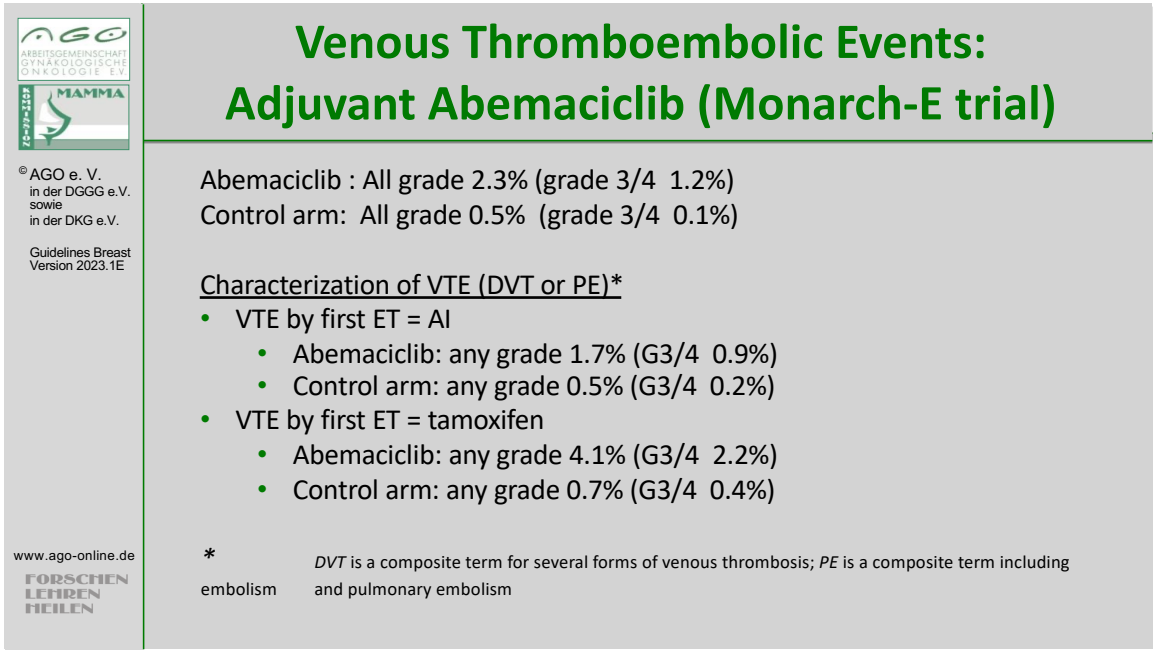

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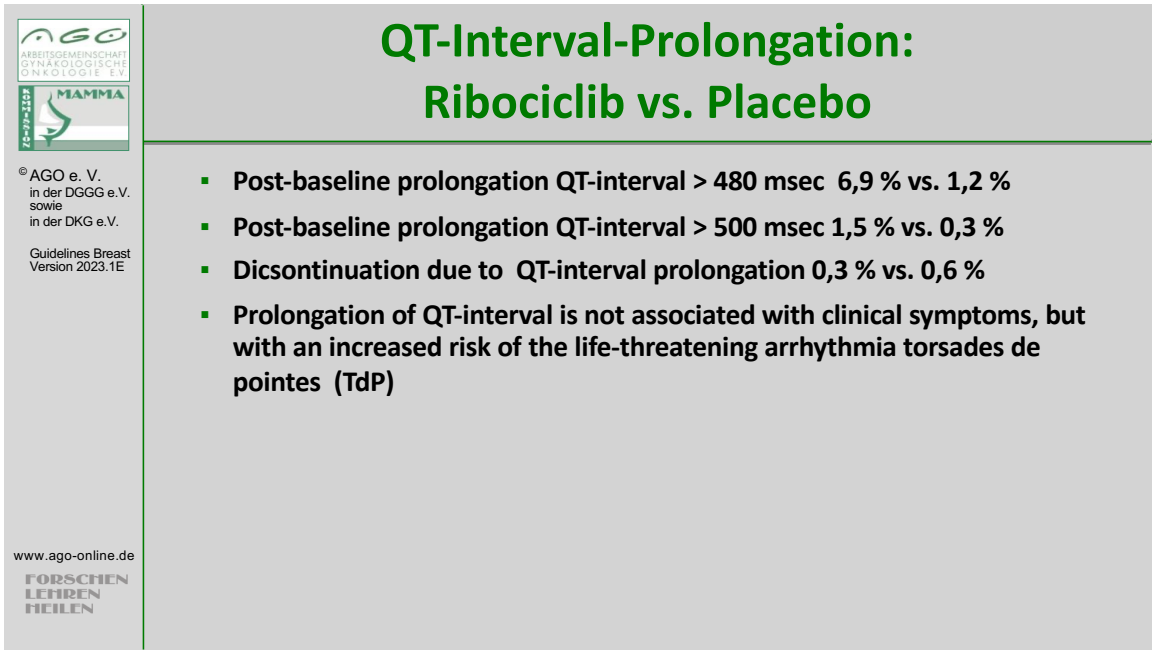

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Toxicities of mTOR-Inhibitor (Everolimus)

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

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

Toxicities of PI3K Inhibitor Alpelisib in Combination with Endocrine Therapy

Alpelisib + Fulvestrant

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

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

LoE	GR	AGO
2b	B	++

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

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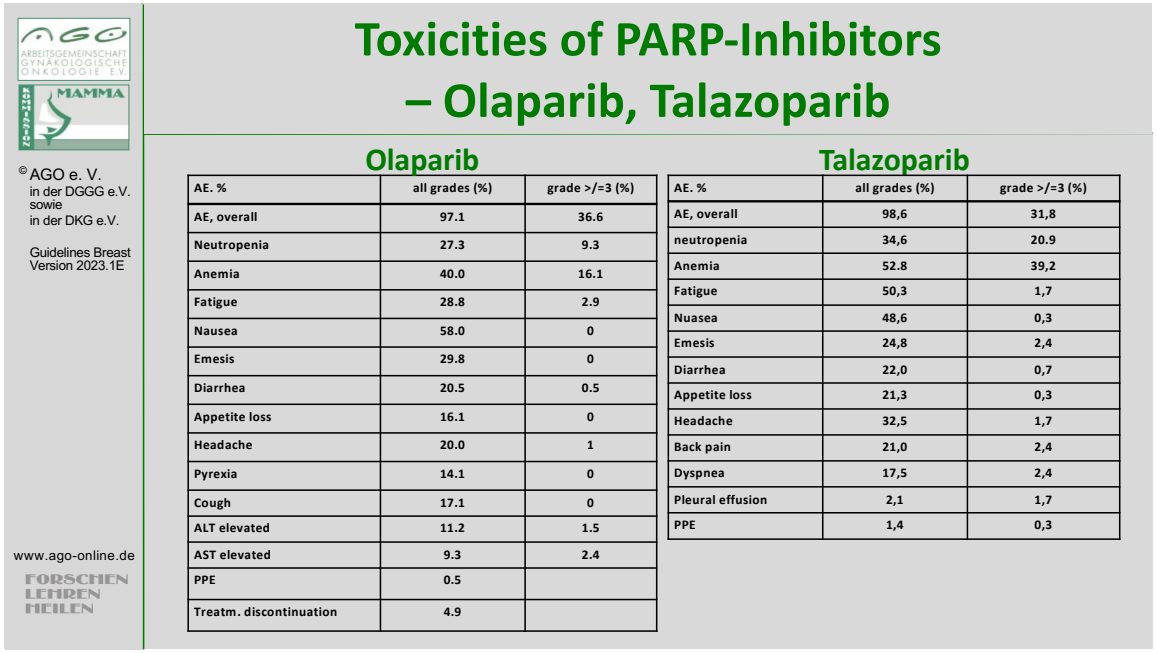

Toxicities of PARP-Inhibitors – Olaparib, Talazoparib

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

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.
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Immune Checkpoint Inhibitors

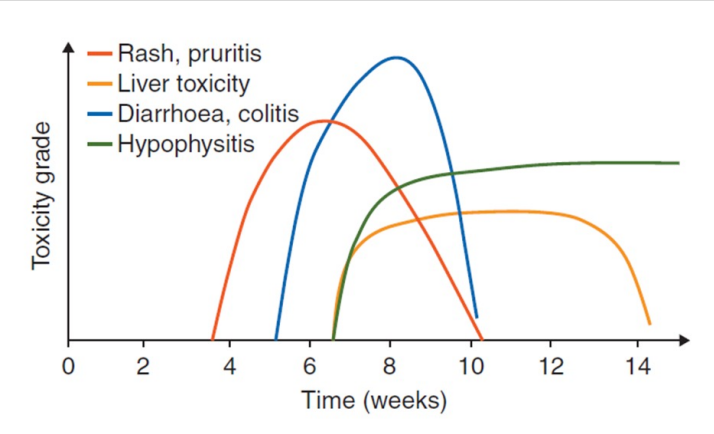
- **Therapeutic approaches (antibodies)**
  - **PD-1 / PD-L1**

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

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

1. Haanen J, Carbonnel 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: ^0.1093/annonc/mdx225
2. Mayer IA, Prat A, Egle D, 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.

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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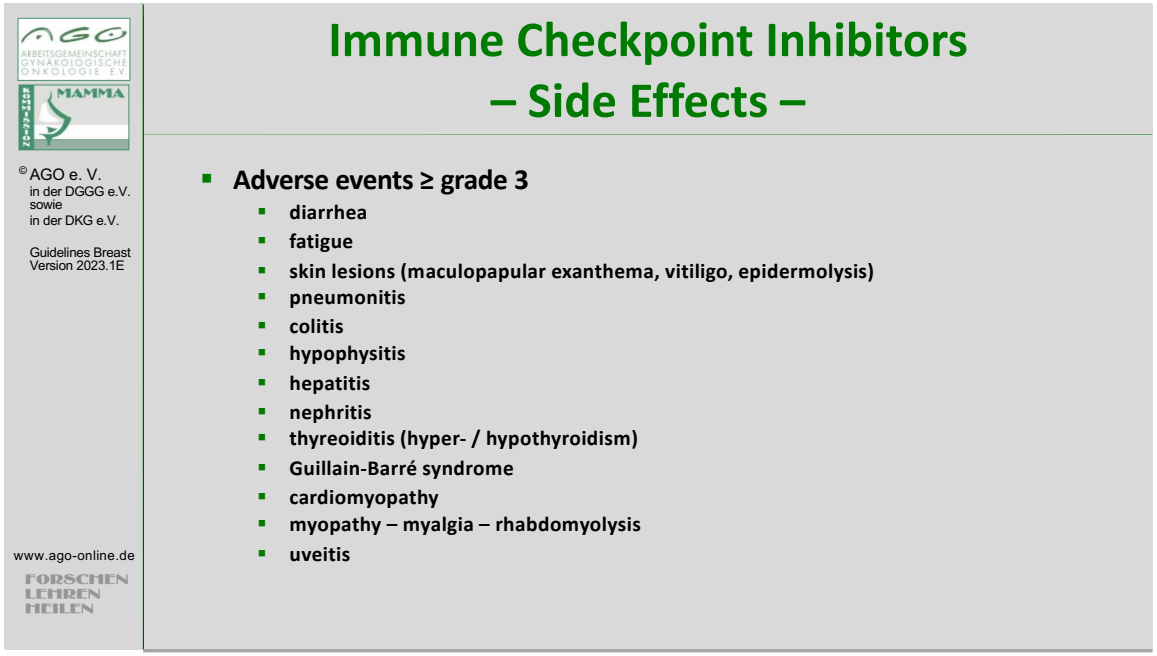

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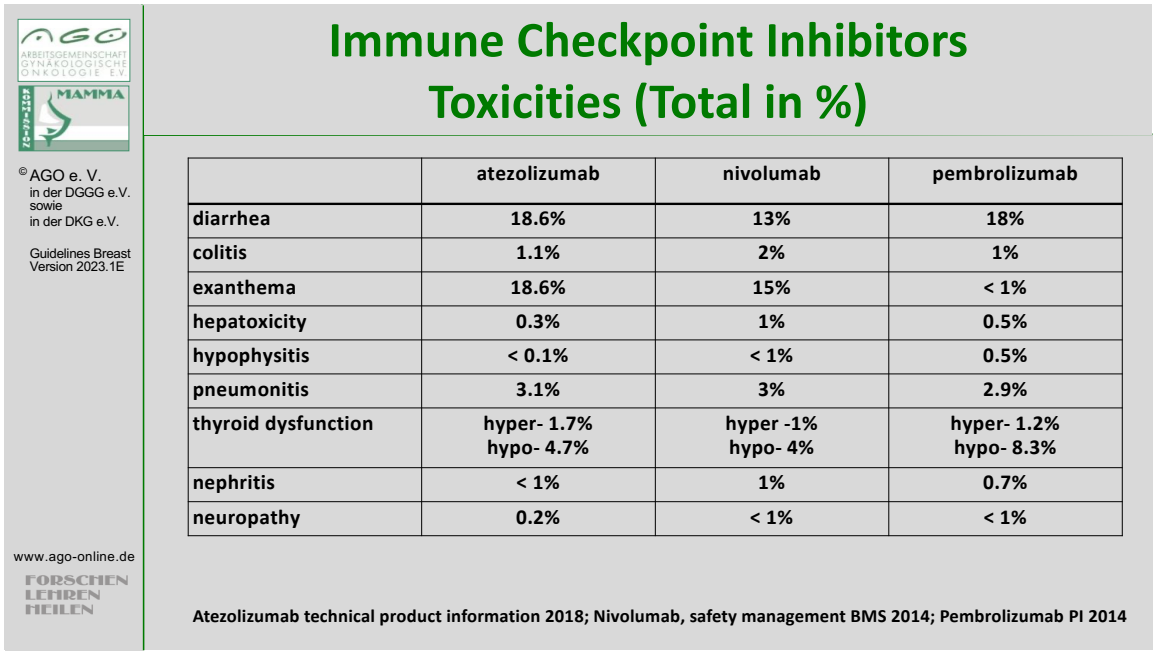
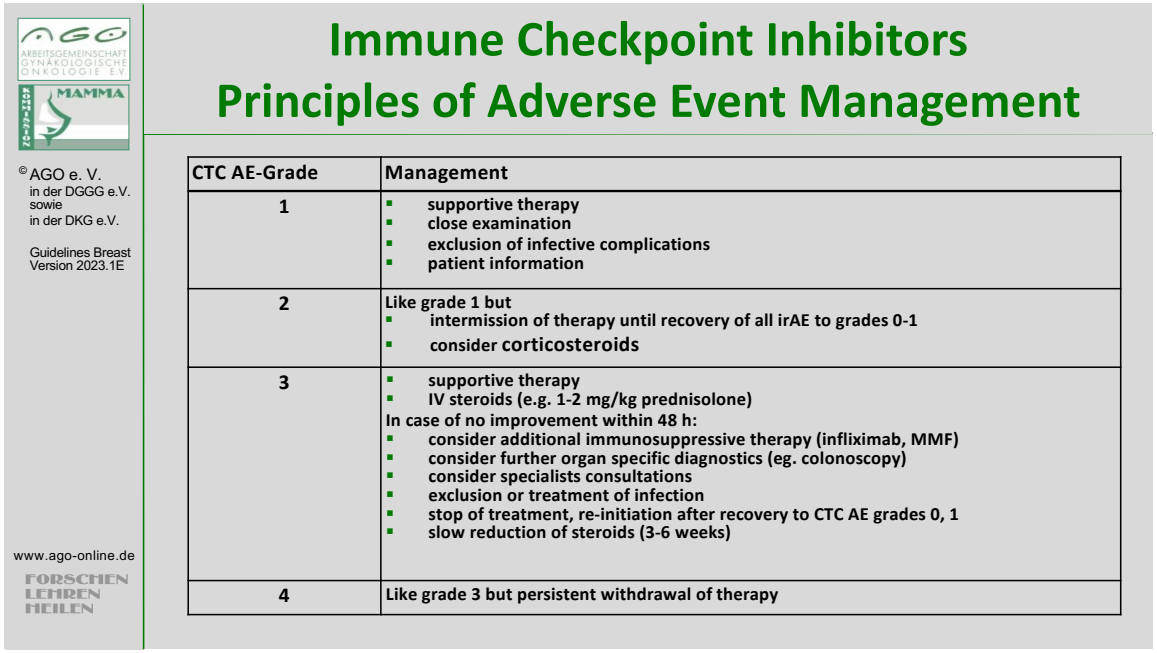


Immune Checkpoint Inhibitors Toxicities (Total in %)

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

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

1. Atezolizumab: https://www.fachinfo.de/suche/fi/021700
2. Nivolumab: https://www.fachinfo.de/suche/fi/020675
3. Pembrolizumab: https://www.fachinfo.de/suche/fi/020716



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

1. Haanen J, Carbonnel 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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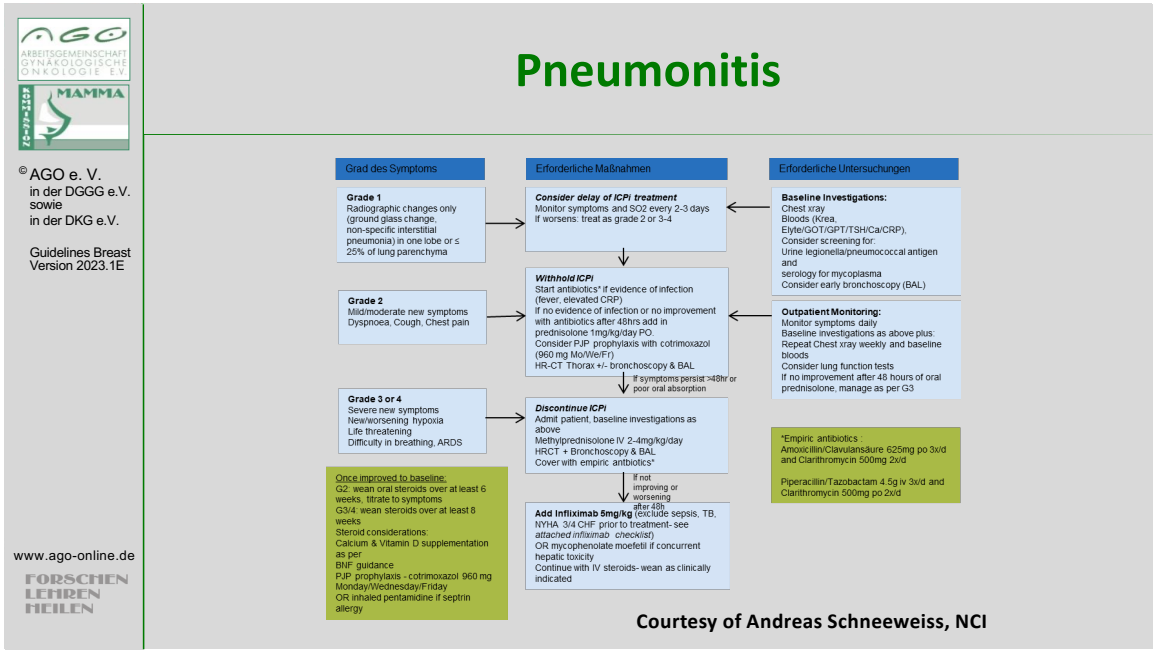

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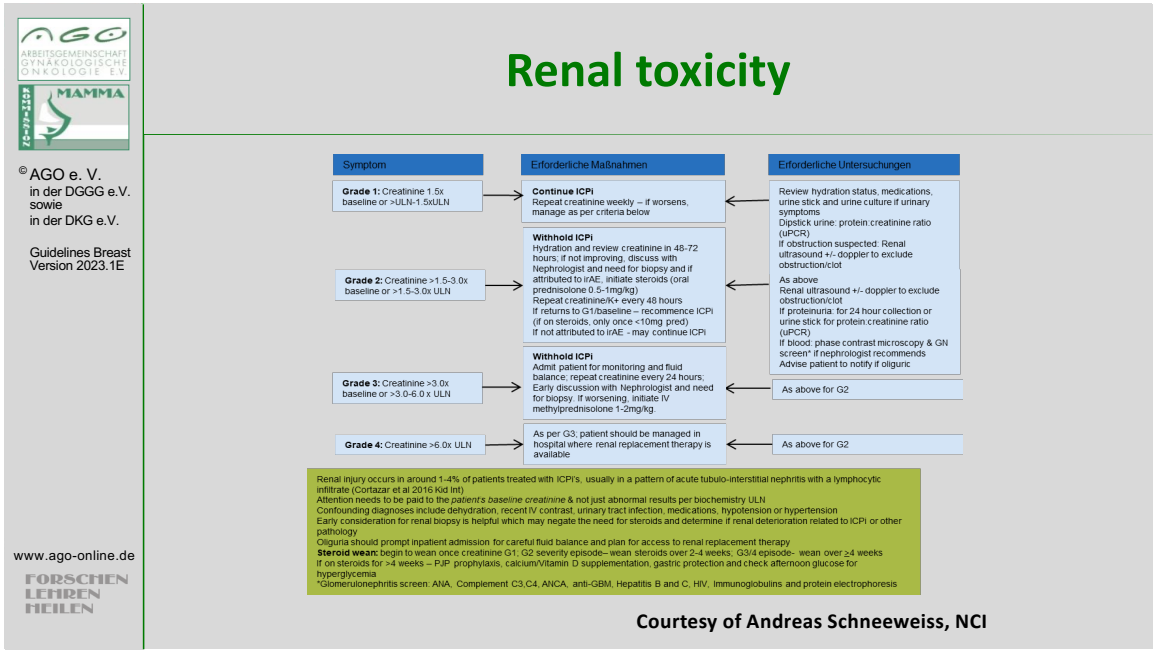

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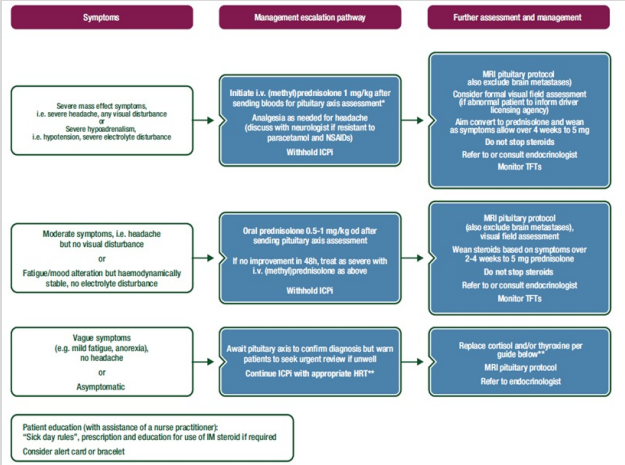
Hypophysitis



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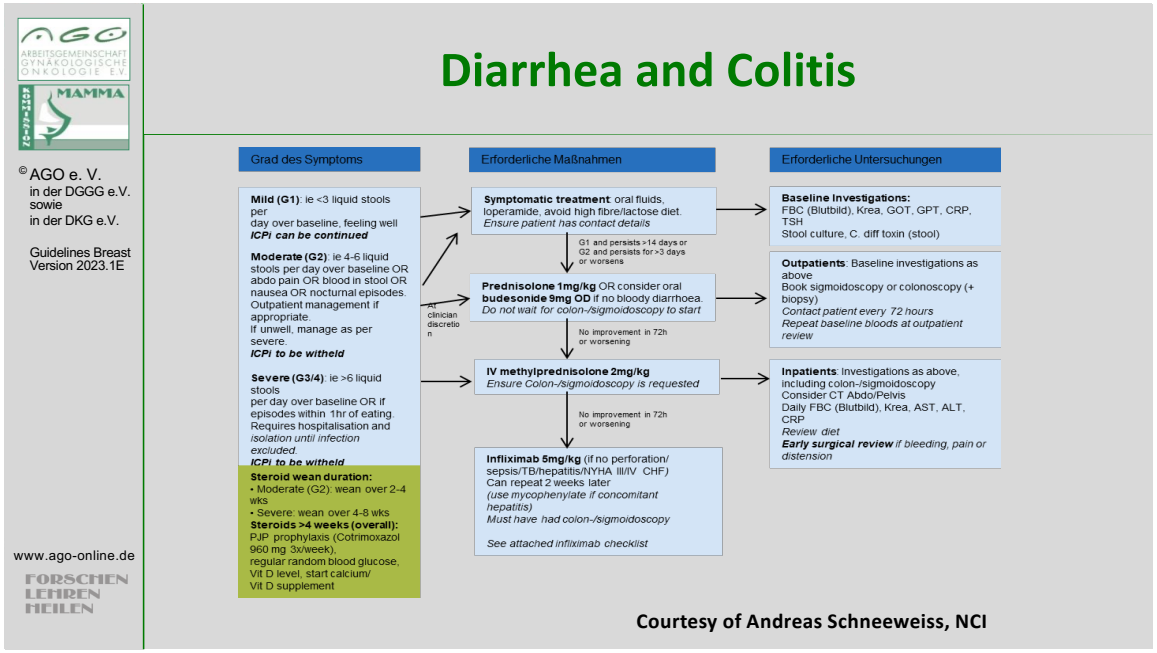

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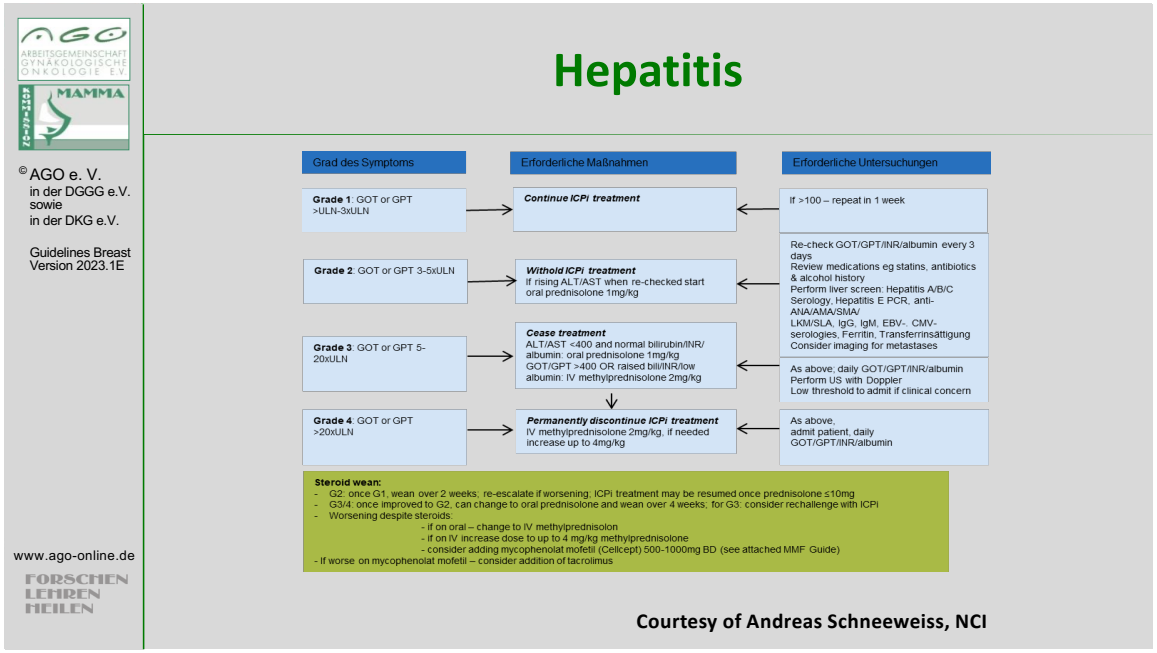

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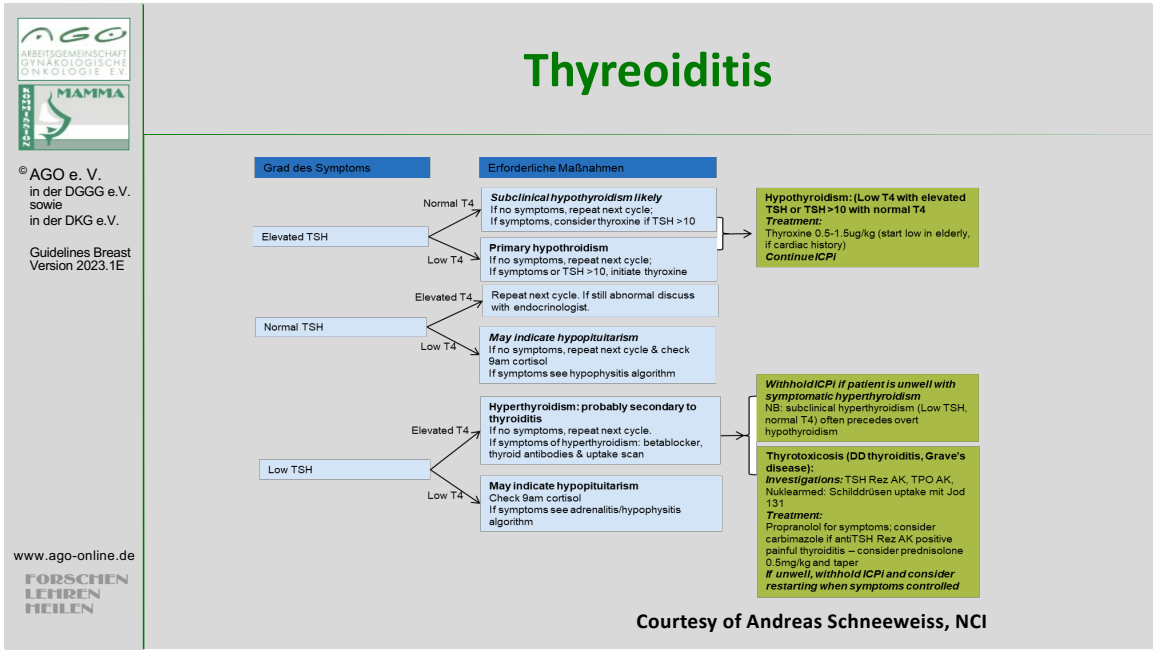

Courtesy of Andreas Schneeweiss, NCI

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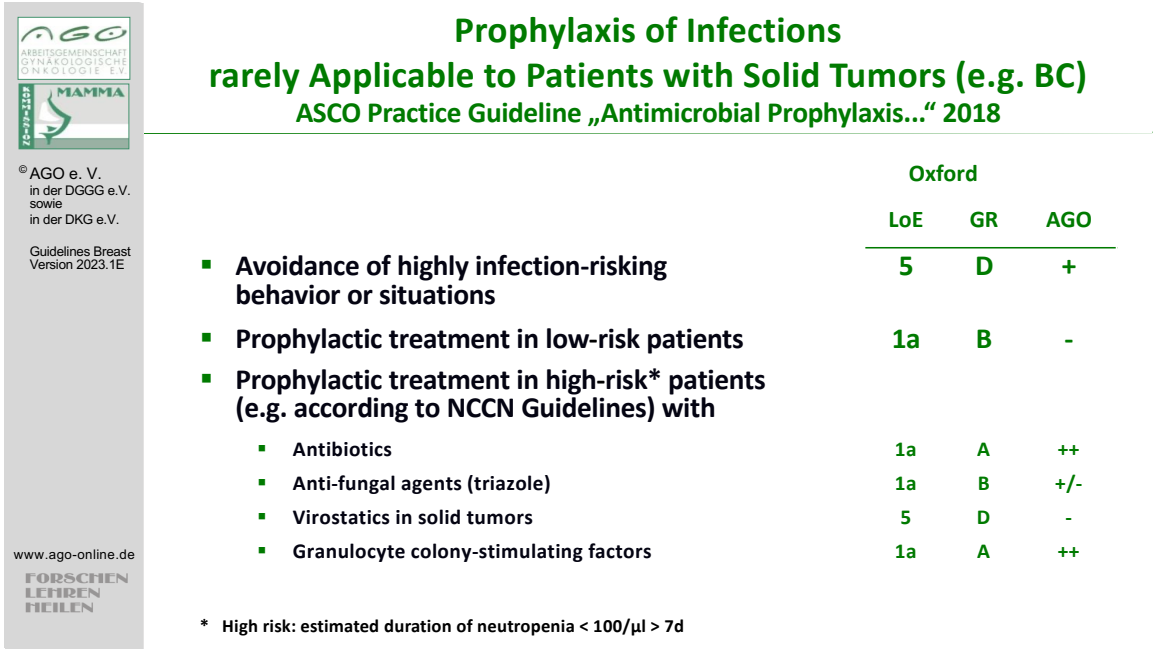
Side Effects According Organ Systems
Incidence, Prevention, Therapy

1. Infections

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

1. Hwang JP, Feld JJ, Hammond SP, et al. Hepatitis B Virus Screening and Management for Patients With Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update. J Clin Oncol 2020;38:3698-3715.
2. Giesen N, Sprute R, Rüthrich M et al. 2021 update of the AGIHO guideline on evidence-based management of COVID-19 in patients with cancer regarding diagnostics, viral shedding, vaccination and therapy. COVID-19 guideline panel of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). Eur J Cancer. 2021 Apr;147:154-160.



ASCO:

1. Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update. J Clin Oncol 2018;36:3043-3054.
2. Taplitz RA, Kennedy EB, Bow EJ, et al. 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:

1. NCCN Guidelines Version 1.2021 Prevention and Treatment of Cancer-Related Infections. https://www.nccn.org/professionals/physician_gls/PDF/infections.pdf

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	+/-

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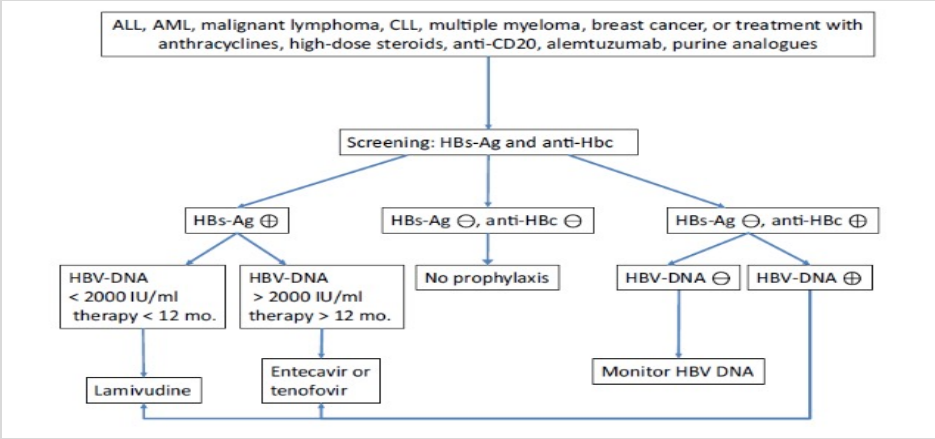
AGIHO / DGHO – Recommendations on Hepatitis B Virus Screening in Oncology

Guidelines Breast
Version 2023.1E



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

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Guidelines Breast
Version 2023.1E

Side Effects According Organ Systems
Incidence, Prevention, Therapy

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

Guidelines Breast
Version 2023.1E

Secondary Malignancies I

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

Statements 1-5

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

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2. Rosell J, Nordenskjöld B, Bengtsson NO, et al. Long-term effects on the incidence of second primary cancers in a randomized trial of two and five years of adjuvant tamoxifen. Acta Oncol. 2017 Jan 12:1-4. doi: 10.1080/0284186X.2016.1273547.
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.

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**

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. Berrington de Gonzalez A, Curtis R, Gilbert E et al.(2010) Second solid cancers after radiotherapy for breast cancer in SEER cancer registries. B J Cancer 102: 220-6.
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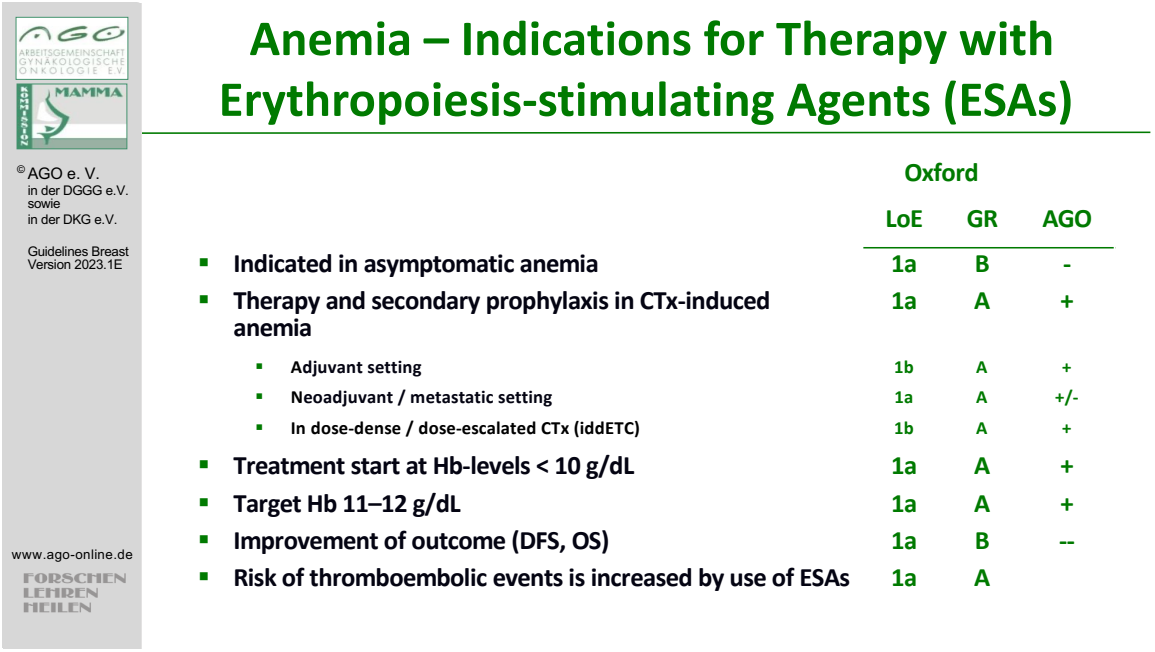
Side Effects According Organ Systems
Incidence, Prevention, Therapy

3. Blood and Lymphatic System Disorders

- Anemia
- Neutropenia
- Febrile Neutropenia (FN)



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

	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	

Leitlinie:

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020,
AWMF Registernummer: 032/054OL

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a meta-analysis. Annals of Oncology 26: 688-695, 2015.
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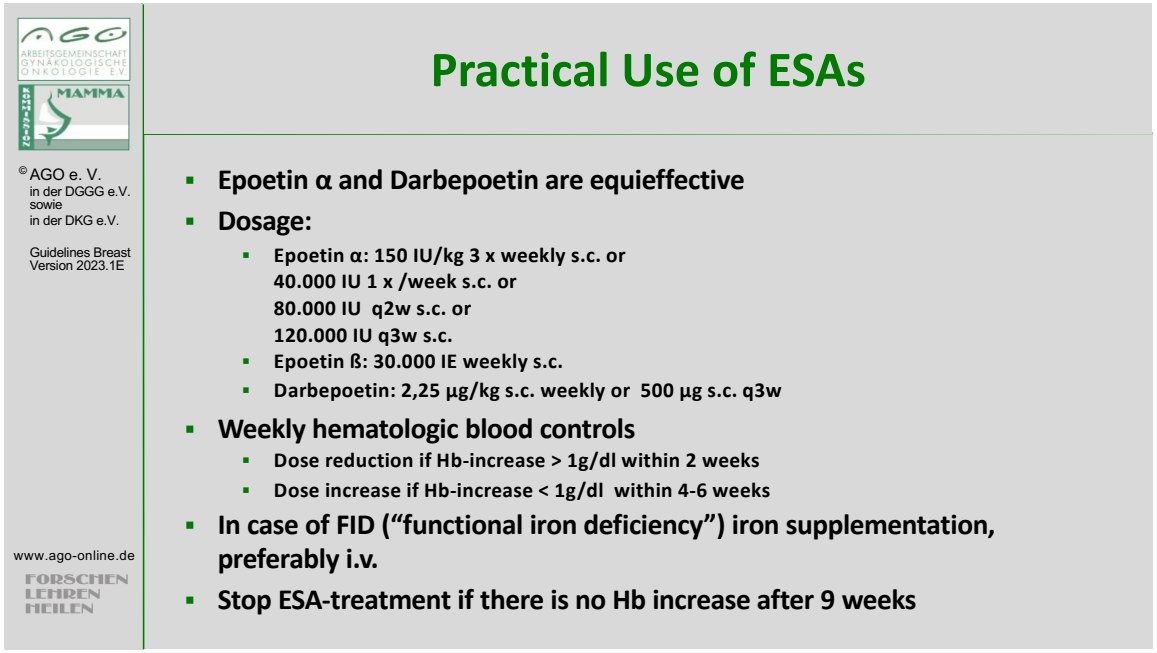

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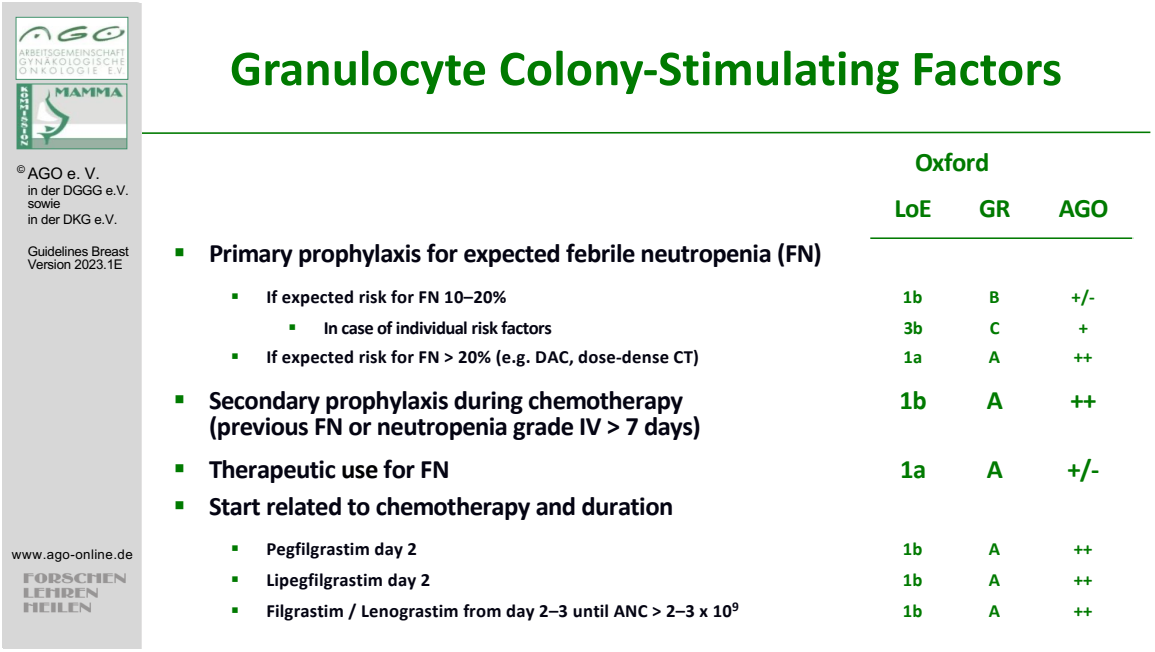

Granulocyte Colony-Stimulating Factors

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

Relevante Leitlinien

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   Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3 – Februar 2020
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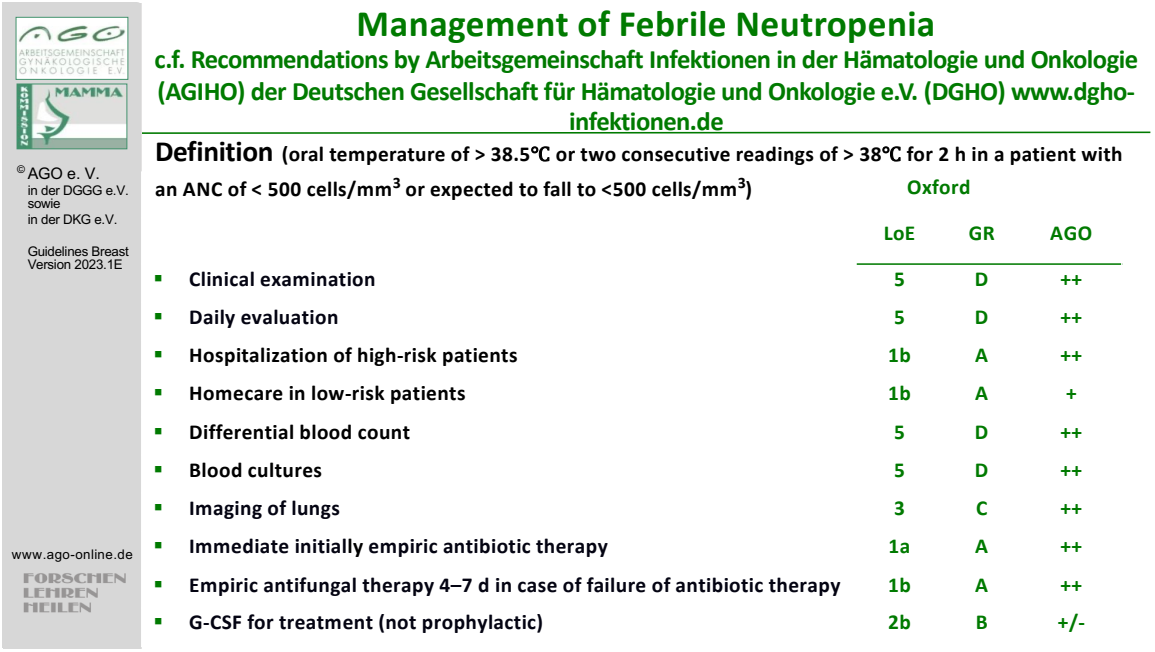

Management of Febrile Neutropenia

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

Definition (oral temperature of > 38.5°C or two consecutive readings of > 38°C for 2 h in a patient with an ANC of < 500 cells/mm^3 or expected to fall to <500 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 4–7 d in case of failure of antibiotic therapy	1b	A	++
▪ G-CSF for treatment (not prophylactic)	2b	B	+/-

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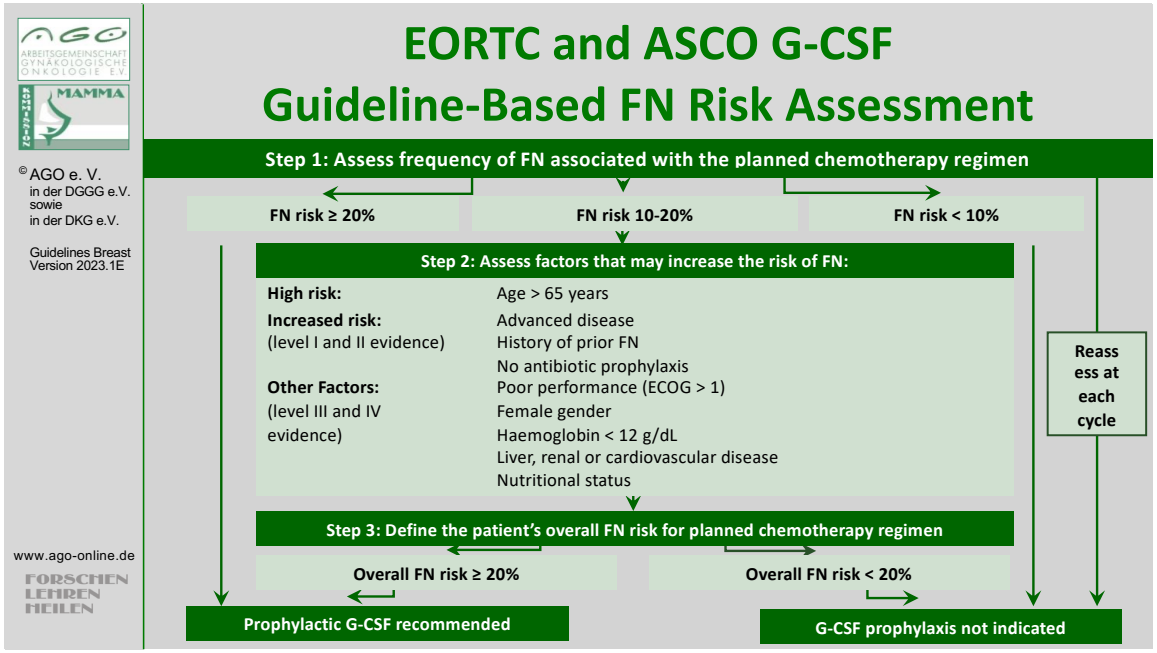

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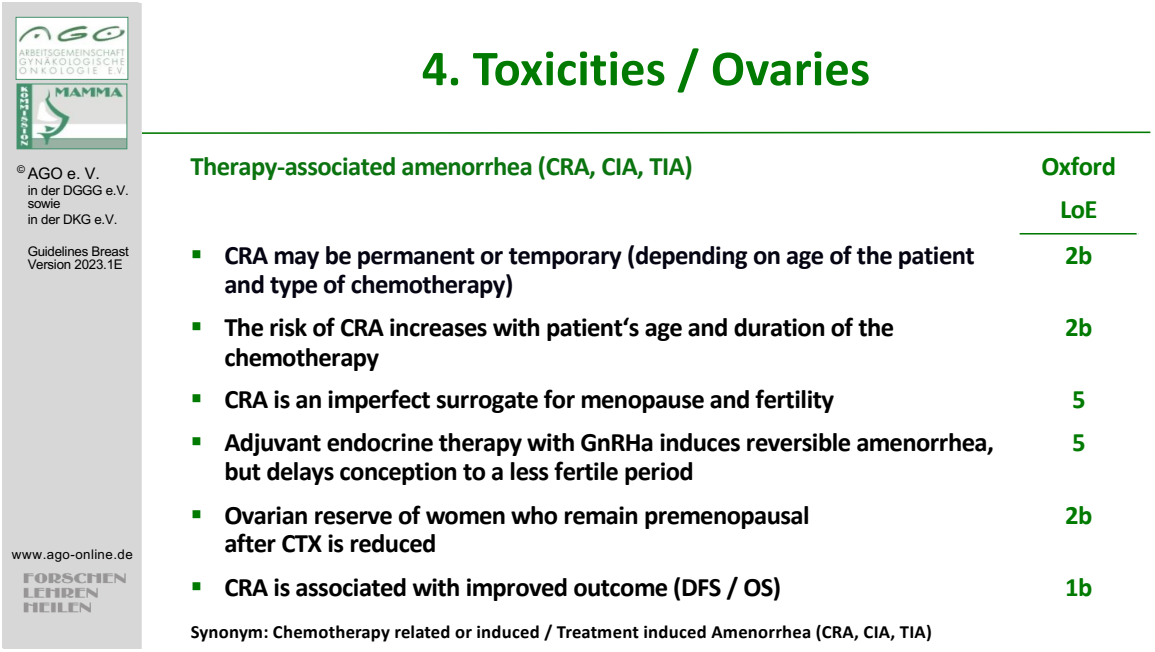

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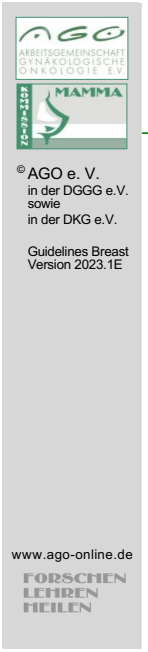
Side Effects According Organ Systems
Incidence, Prevention, Therapy

5. Psychiatric Disorders

- Depression
- Fatigue
- Cognitive impairment
- Sleep disturbances



(Therapy-associated) Depression

	Oxford LoE	Oxford 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	+

Guideline:

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Fatigue is frequently present…

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Methylphenidate…

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(Therapy-associated) Cognitive Impairment

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

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

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<u>Verhaltenstherapie kann kognitive Funktion verbessern</u>

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Methylphenidate kann kognitive Funktion bei Patientinnen mit Krebs verbessern

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Unter Aromatasehemmertherapie wurden kogmitive Störungen beobachtet

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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	++

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)**

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
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

Reviews/Leitlinien

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Nicht-medikamentöse Prävention

Funktionstraining

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Kühlung

1. Hanai A, Ishiguro H, Sozu T et al. (2016) The effects of frozen gloves and socks on paclitaxel-induced peripheral neuropathy among patientswith breast cancer: A selfcontrolled clinical trial. J ClinOncol 34(suppl): (abstr 10022). http://meetinglibrary.asco.org/content/166655-176.
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Akupunktur

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3. Zhi WI, Baser RE, Talukder D et al. Mechanistic and thermal characterization of acupuncture for chemotherapy-induced peripheral neuropathy as measured by quantitative sensory testing. Breast Cancer Res Treat. 2023 Feb;197(3):535-545.

<u>Medikamentöse Prävention</u>

Venlafaxin

1. Aziz MT, Good BL, Lowe DK. Serotonin-norepinephrine reuptake inhibitors for the management of chemotherapy-induced peripheral neuropathy. Ann Pharmacother. 2014 May;48(5):626-32.
2. Durand JP, Deplanque G, Montheil V, et al.: Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: results of EFFOX, a randomized, double-blind, placebo-controlled phase III trial. Ann Oncol. 2012 Jan;23(1):200-5
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Palmitoylethanolamid (PEA)

1. Lombardi G, Miglio G, Varsaldi F, et al.: Oxyhomologation of the amide bond potentiates neuroprotective effects of the endolipid N-palmitoylethanolamine.
   J Pharmacol Exp Ther. 2007 Feb;320(2):599-606

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Verschiedene Substanzen

1. Schloss J, Colosimo M, Vitetta L. Herbal medicines and chemotherapy induced peripheral neuropathy (CIPN): A critical literature review. Crit Rev Food Sci Nutr. 2017 Apr 13;57(6):1107-1118.
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7. Memeo A, Loiero M. Thioctic acid and acetyl-L-carnitine in the treatment of sciatic pain caused by a herniated disc: a randomized, double-blind, comparative study. Clin Drug Investig. 2008;28(8):495-500.

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1. Hershman DL, Unger JM, Crew KD, et al.: Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy. J Clin Oncol. 2013 Jul 10;31(20):2627-33.
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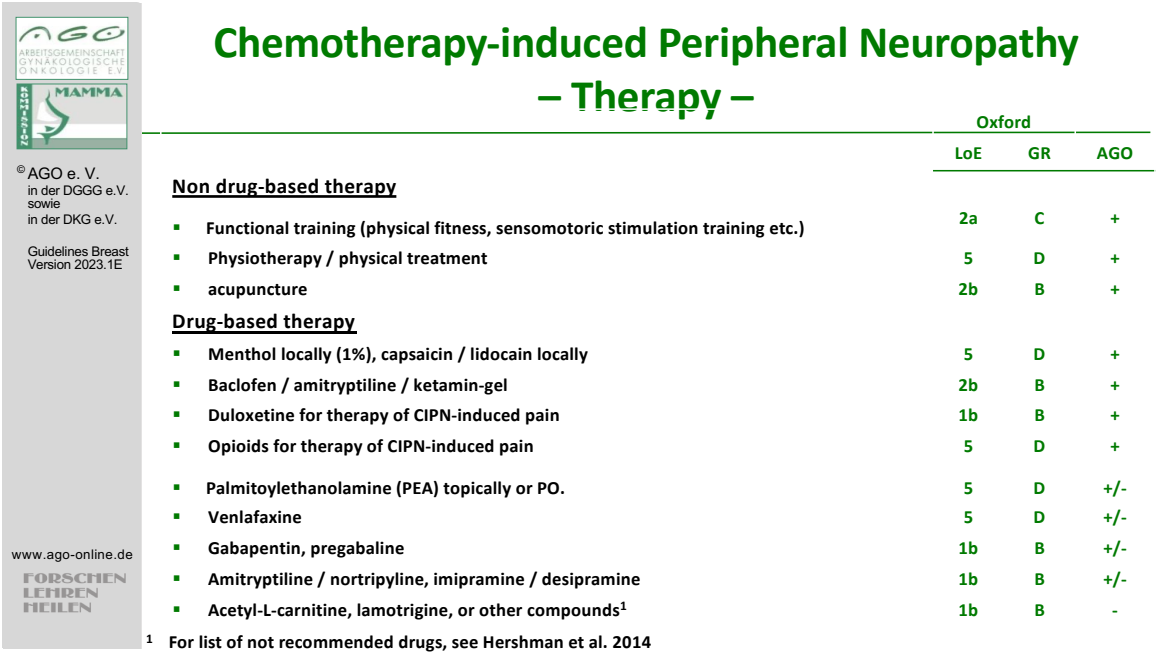

Chemotherapy-induced Peripheral Neuropathy – Therapy –

	Oxford LoE	Oxford 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

Reviews / Leitlinien

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4. Greenlee H, Hershman DL, Shi Z, et al.:BMI, Lifestyle Factors and Taxane-Induced Neuropathy in Breast Cancer Patients: The Pathways Study. J Natl Cancer Inst. 2016 Oct 28;109(2). pii: djw206. Print 2017 Feb.
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chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial." JAMA 309(13): 1359-1367.
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Nicht-medikamentöse Therapie

Funktionstraining

1. Duregon F, Vendramin B, Bullo V, et al.: Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: A systematic review. Crit Rev Oncol Hematol. 2018 Jan;121:90-100.
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Palmitoylethanolamid (PEA)

1. Lombardi G, Miglio G, Varsaldi F, et al.: Oxyhomologation of the amide bond potentiates neuroprotective effects of the endolipid N-palmitoylethanolamine.
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Venlafaxin

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Gabapentin, Pregabalin:

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Guidelines Breast
Version 2023.1E

7. Cardiac Disorders

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	+/-

Consensus recommendations:

1. Curigliano G, Lenihan D, Fradley M, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol 2020 Feb;31(2):171-190.

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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*"*Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors."

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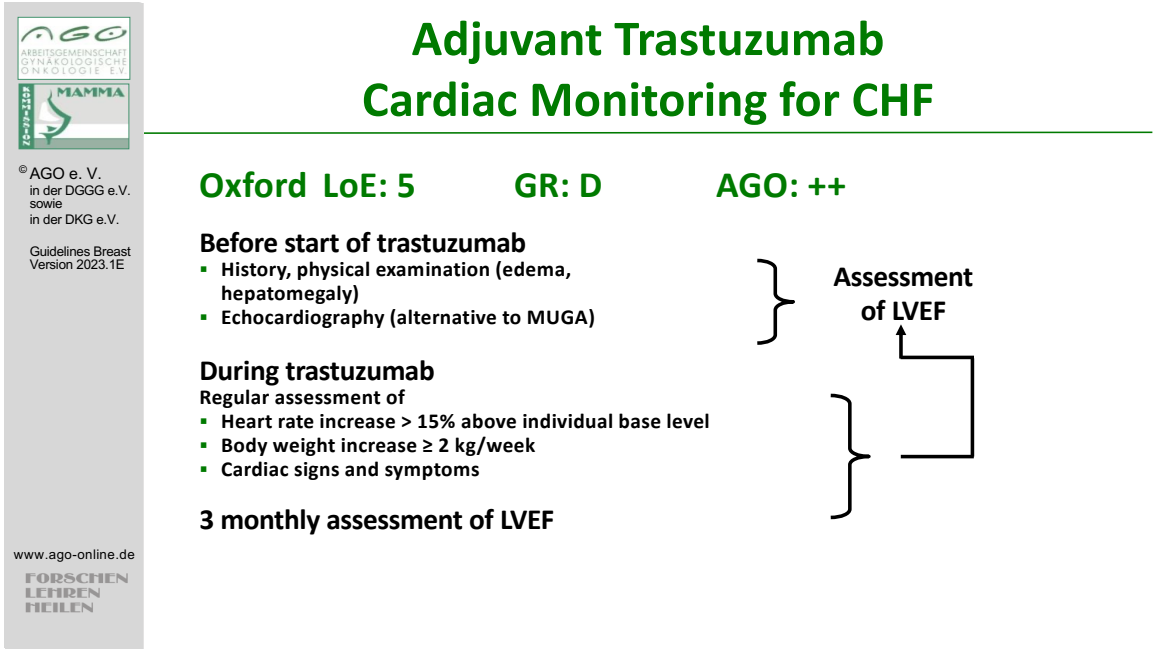

Statement: Cardiac Monitoring (5 D ++)

Vote result of the AGO recommendation: 100%

1. Perez EA, Suman VJ, Davidson NE, et al.: Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol. 2008 Mar 10;26(8):1231-8. Epub 2008 Feb 4.
2. Mackey JR, Clemons M, Côté MA, et al.: Cardiac management during adjuvant trastuzumab therapy: recommendations of the Canadian Trastuzumab Working Group. Curr Oncol. 2008 Feb;15(1):24-35.

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	-

Trastuzumab simultaneous to radiotherapy"

1. Halyard MY, Pisansky TM, Dueck AC: Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the NCCTG Phase III Trial N9831.J Clin Oncol 27: 2638-2644, 2009
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"Trastuzumab simultaneous to epirubicin"

1. Untch M, Muscholl M, Tjulandin S, et al.: First-line trastuzumab plus epirubicin and cyclophosphamide therapy in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: cardiac safety and efficacy data from the Herceptin, Cyclophosphamide, and Epirubicin (HERCULES) trial. J Clin Oncol. 2010 Mar 20;28(9):1473-80.
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3. van Ramshorst MS, van Werkhoven E, Honkoop AH, et al.: Toxicity of dual HER2-blockade with pertuzumab added to anthracycline versus non-anthracycline containing chemotherapy as neoadjuvant treatment in HER2-positive breast cancer: The TRAIN-2 study.

Breast. 2016 Oct;29:153-9. doi: 10.1016/j.breast.2016.07.017. Epub 2016 Aug 5.

"Trastuzumab simultaneous to doxorubicin"

1. Slamon D, Eiermann W, Robert N, et al.: Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011 Oct 6;365(14):1273-83

"Anthracycline simultaneous to radiotherapy"

1. Toledano A, Garaud P, Serin D, et al.: Concurrent administration of adjuvant chemotherapy and radiotherapy after breast-conserving surgery enhances late toxicities: long-term results of the ARCOSEIN multicenter randomized study. Int J Radiation Oncology Biol. Phys. 2006; 65: 324-332.

"Tamoxifen simultaneous to radiotherapy"

1. Kraus-Tiefenbacher U, Sfintizky A, Welzel G, et al.: Factors of influence on acute skin toxicity of breast cancer patients treated with standard external beam radiotherapy (EBRT) after breast conserving surgery (BCS). Radiat Oncol. 2012 Dec 18;7(1):217. [Epub ahead of print]
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1. Valakh V, Trombetta MG, Werts ED, et al.: Influence of concurrent anastrozole on acute and late side effects of whole breast radiotherapy. Am J Clin Oncol. 2011 Jun;34(3):245-8.
2. Telli ML, Hunt SA, Carlson RW, et al.: Trastuzumab-Related Cardiotoxicity: Calling Into Question the Concept of Reversibility. Journal of Clin Oncol, 2007; 25: 3525-3533
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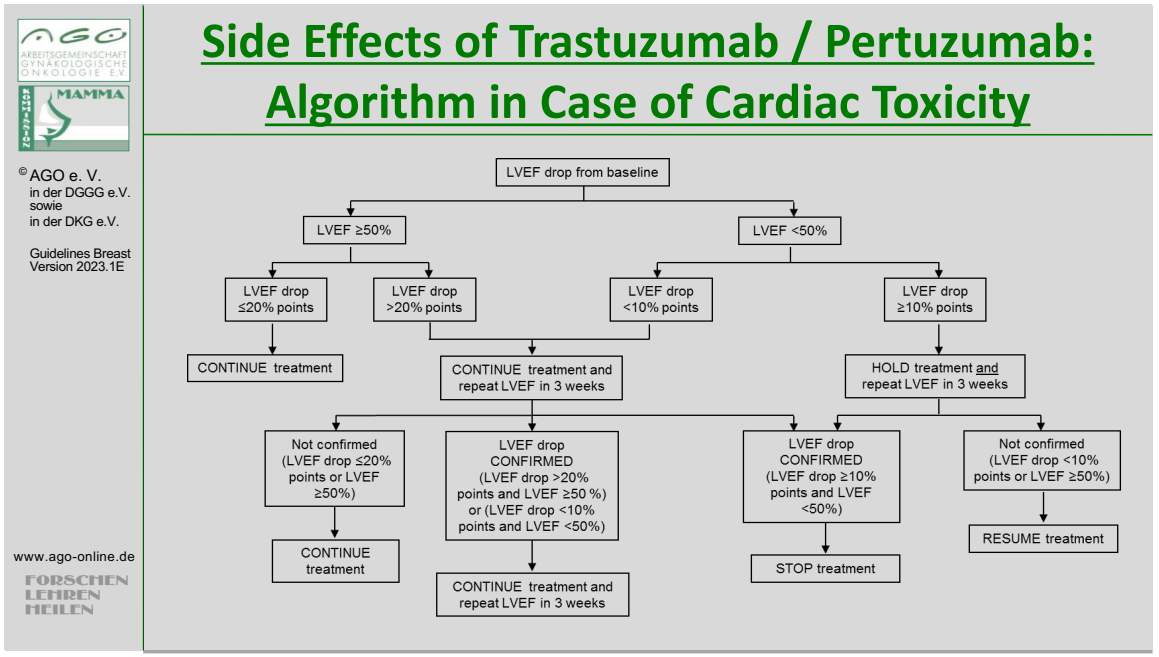
Side Effects of Trastuzumab / Pertuzumab: Algorithm in Case of Cardiac Toxicity



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5. Perez EA, Barrios C, Eiermann W, et al.: Trastuzumab Emtansine With or Without Pertuzumab Versus Trastuzumab Plus Taxane for Human Epidermal Growth Factor Receptor 2-Positive, Advanced Breast Cancer: Primary Results From the Phase III MARIANNE Study. J Clin Oncol. 2017 Jan 10;35(2):141-148. Epub 2016 Nov
6. Loibl S, Jackisch C, Schneeweiss A, et al.: investigators of the German Breast Group (GBG) and the Arbeitsgemeinschaft Gynäkologische Onkologie—Breast (AGO-B) study groups..Dual HER2-blockade with pertuzumab and trastuzumab in HER2-positive early breast cancer: a subanalysis of data from the randomized phase III GeparSepto trial. Ann Oncol. 2016 Nov 9.
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Side Effects According Organ Systems
Incidence, Prevention, Therapy

8. Gastrointestinal Disorders

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

Antiemetic Therapy

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

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

ICPi=Immune Checkpoint inhibitor

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2. Walsh D, Davis M, Ripamonti C, et al. 2016 updated MASCC/ESMO consensus recommendations: Management of nausea and vomiting in advanced cancer. Support Care Cancer 2017;25:333-340.
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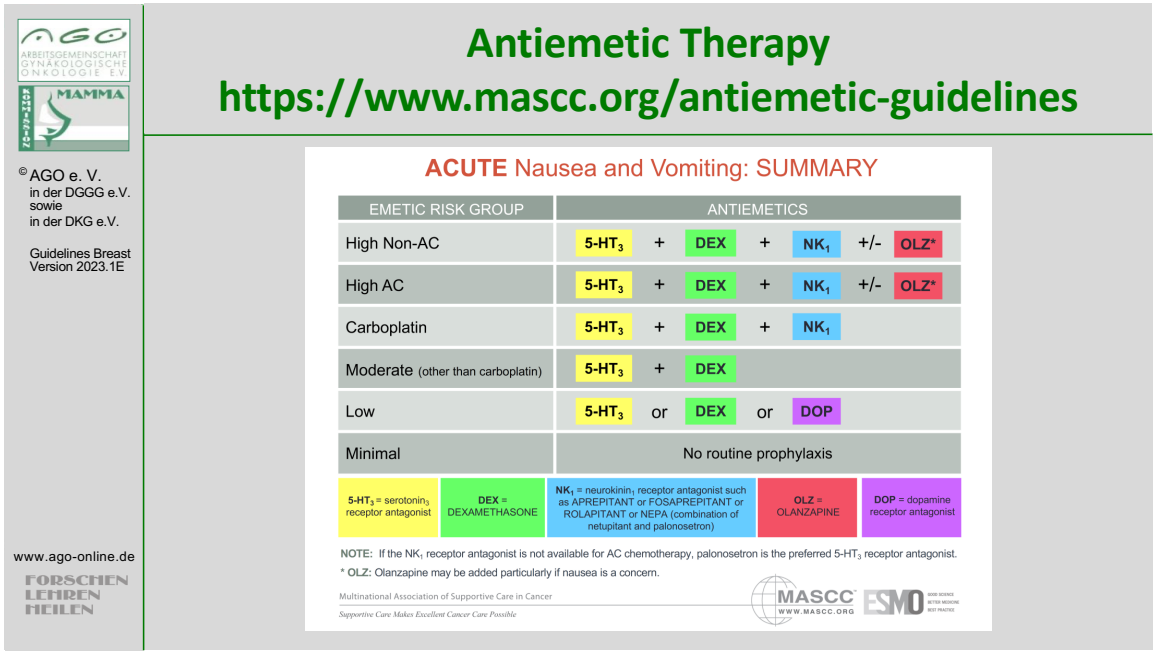
Olanzapine

1 Slimano F, Netzer F, Borget I et al.: Olanzapine as antiemetic drug in oncology: a retrospective study in non-responders to standard antiemetic therapy. Int J Clin Pharm. 2018 Oct;40(5):1265-1271. doi: 10.1007/s11096-018-0649-1. Epub 2018 May 9.

2 Hashimoto H, Abe M, Tokuyama O, 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 Oncol 2020;21:242-249.

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



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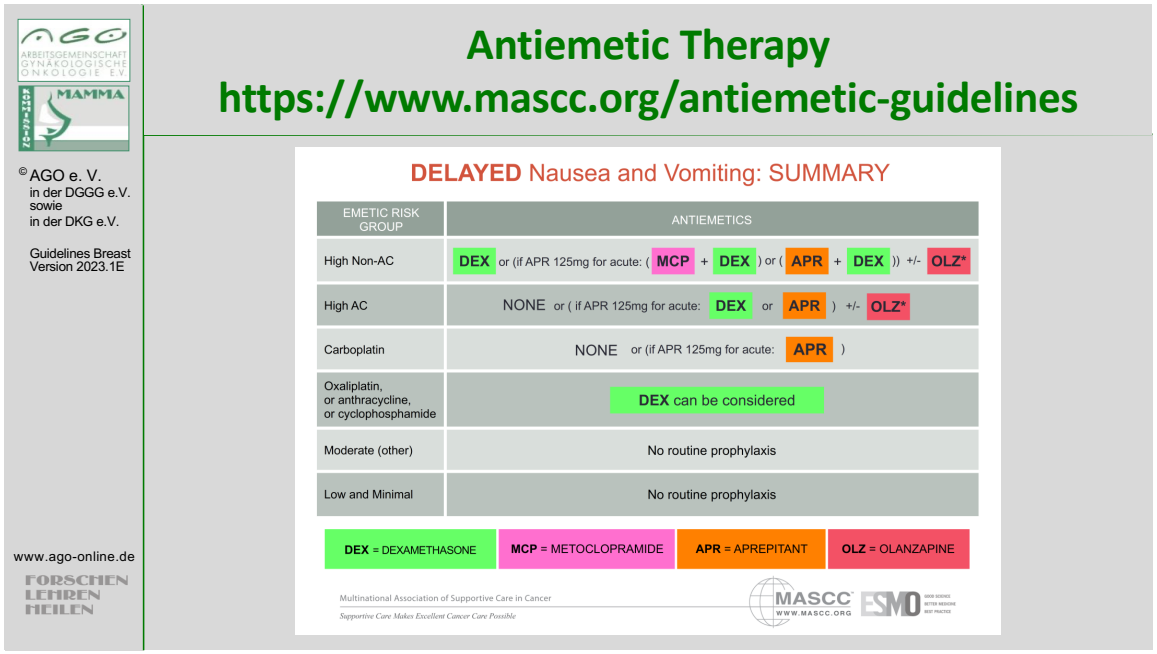

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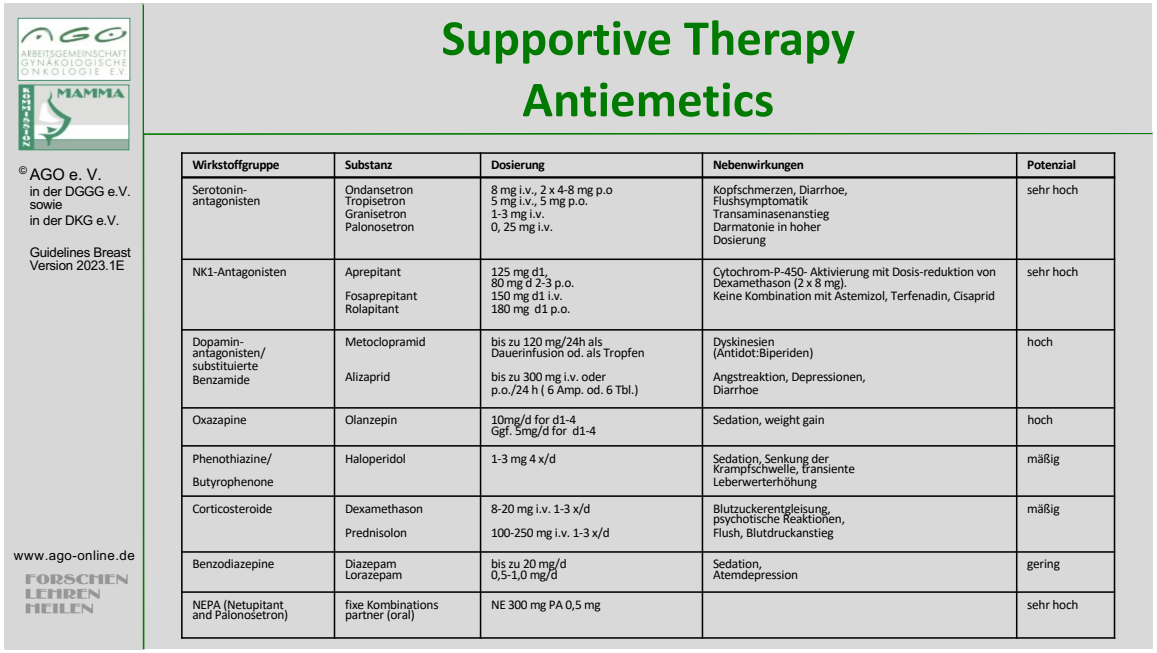

Supportive Therapy
Antiemetics

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

Olanzapine

1. Slimano F, Netzer F, Borget I et al.Olanzapine as antiemetic drug in oncology: a retrospective study in non-responders to standard antiemetic therapy. Int J Clin Pharm 2018 Oct;40(5):1265-1271. doi: 10.1007/s11096-018-0649-1. Epub 2018 May 9.
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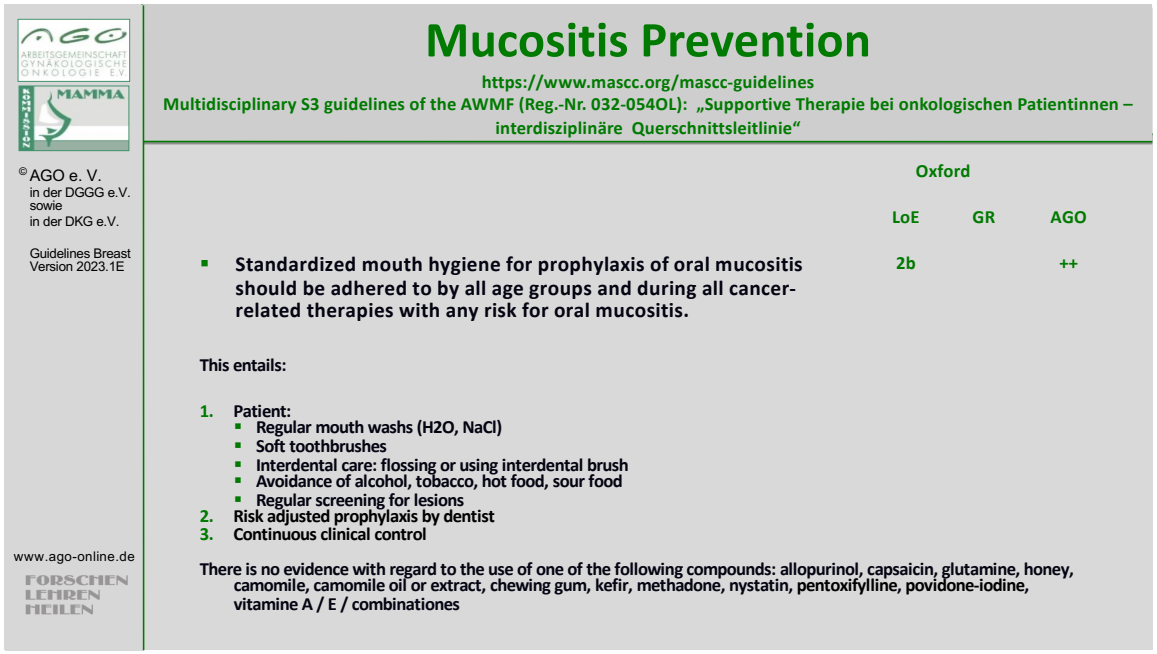

Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,

AWMF Registernummer: 032/054OL, http://leitlinienprogramm- onkologie.de/Supportive-Therapie.95.0.html (Zugriff am 27.12.2021)

1. Elad S, Fong Cheng KK, Lalla RV, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2020;126:4423-4431.
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3. Jensen, S. B., V. Jarvis, Y. Zadik, et al.: "Systematic review of miscellaneous agents for the management of oral mucositis in cancer patients."
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6. Nicolatou-Galitis, O., T. Sarri, J. Bowen, et al.: Systematic review of amifostine for the management of oral mucositis in cancer

patients. Support Care Cancer 2013; 21(1): 357-364.
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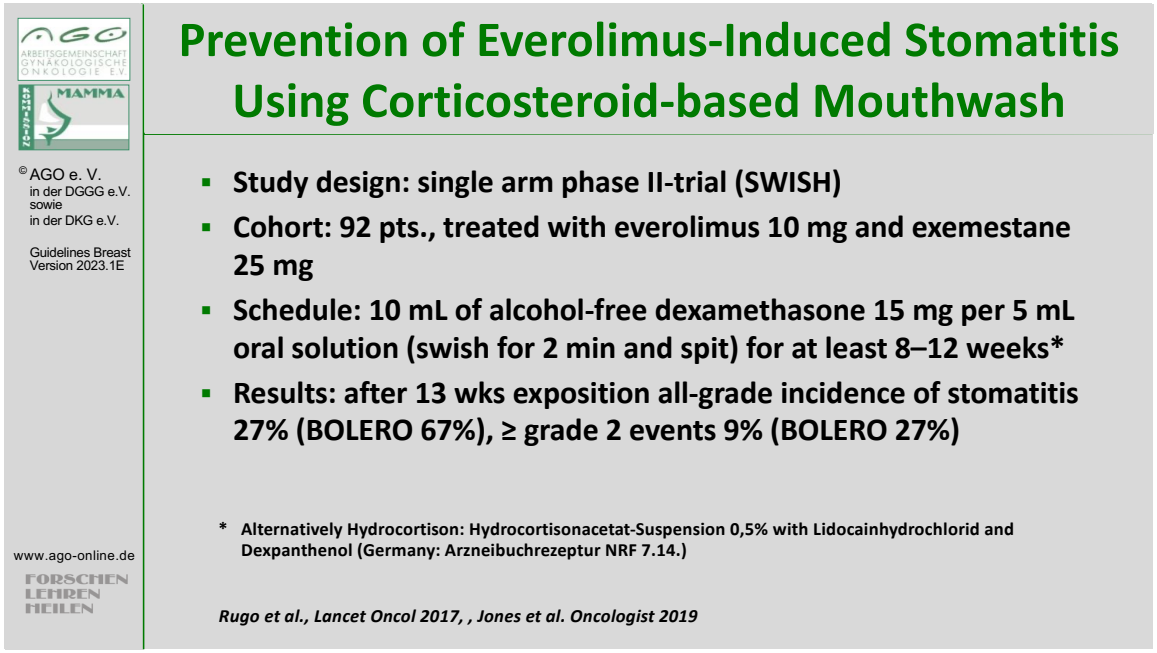

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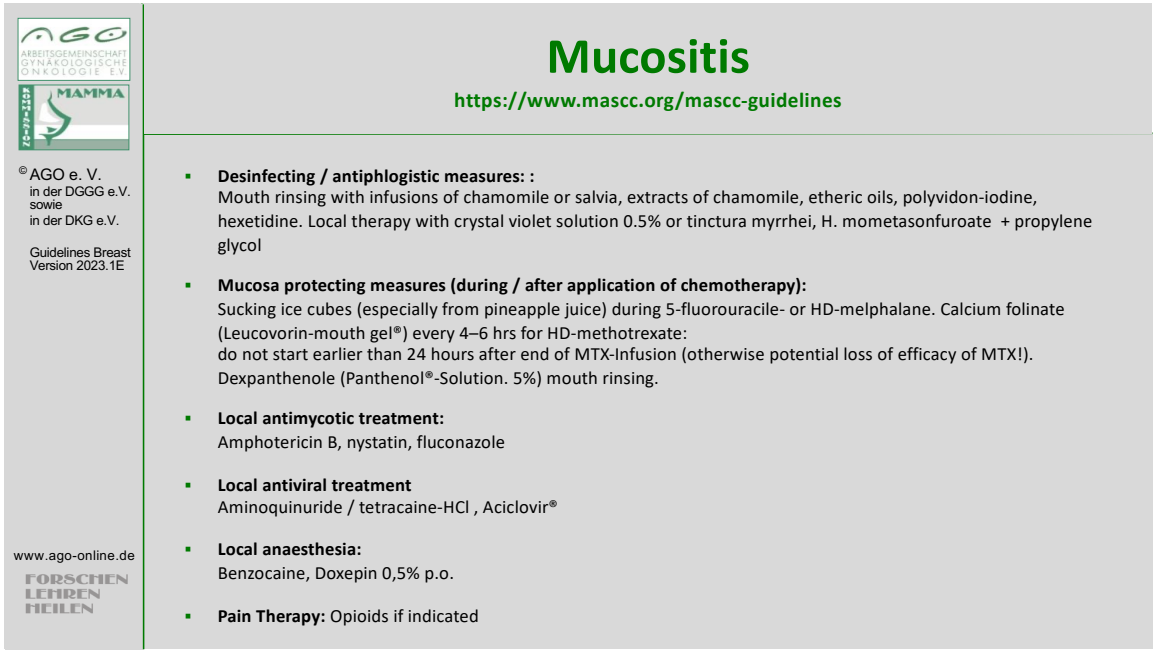

Relevant practice guideline

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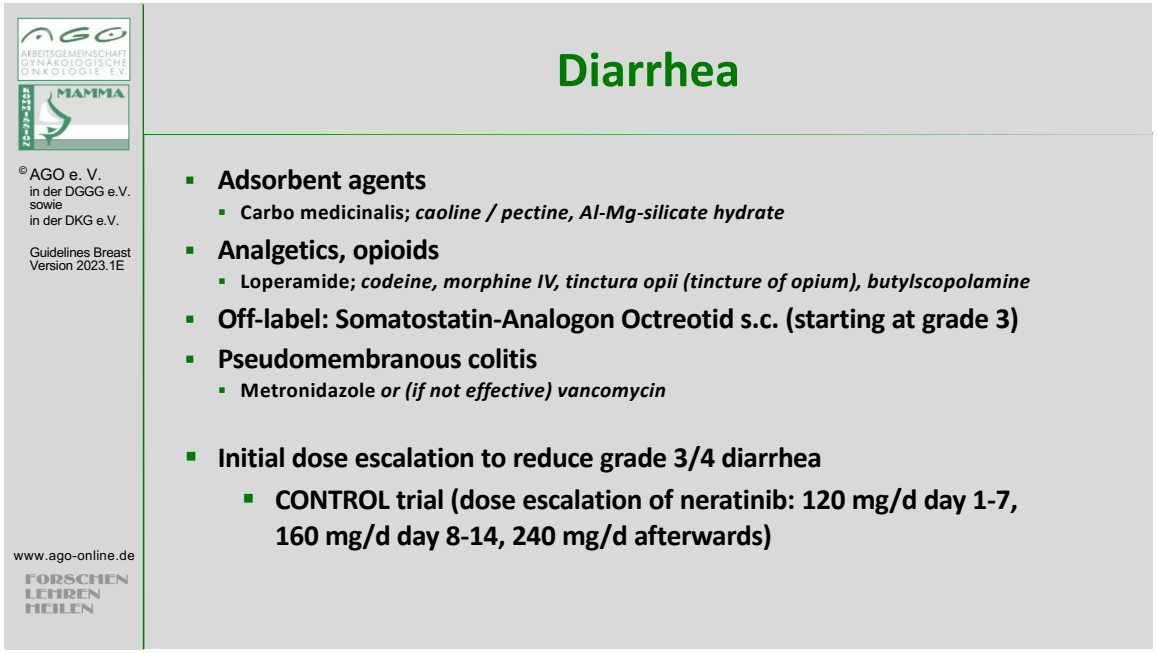

Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,

AWMF Registernummer: 032/054OL, http://leitlinienprogramm- onkologie.de/Supportive-Therapie.95.0.html (Zugriff am 27.12.2021)

1. D. E. Peterson, C. B. Boers-Doets, R. J. Bensadoun, et al. on behalf of the ESMO Guidelines Committee: Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol 2015:26 (Supplement 5): v139–v151.
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3. Coyle, V. M., D. Lungulescu, C. Toganel, et al. (2013). "A randomised double-blind placebo-controlled phase II study of AGI004 for control of chemotherapy-induced diarrhoea." Br J Cancer 2013:108(5);1027-1033.
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treated with irinotecan." Support Care Cancer 2015:23;661-70.
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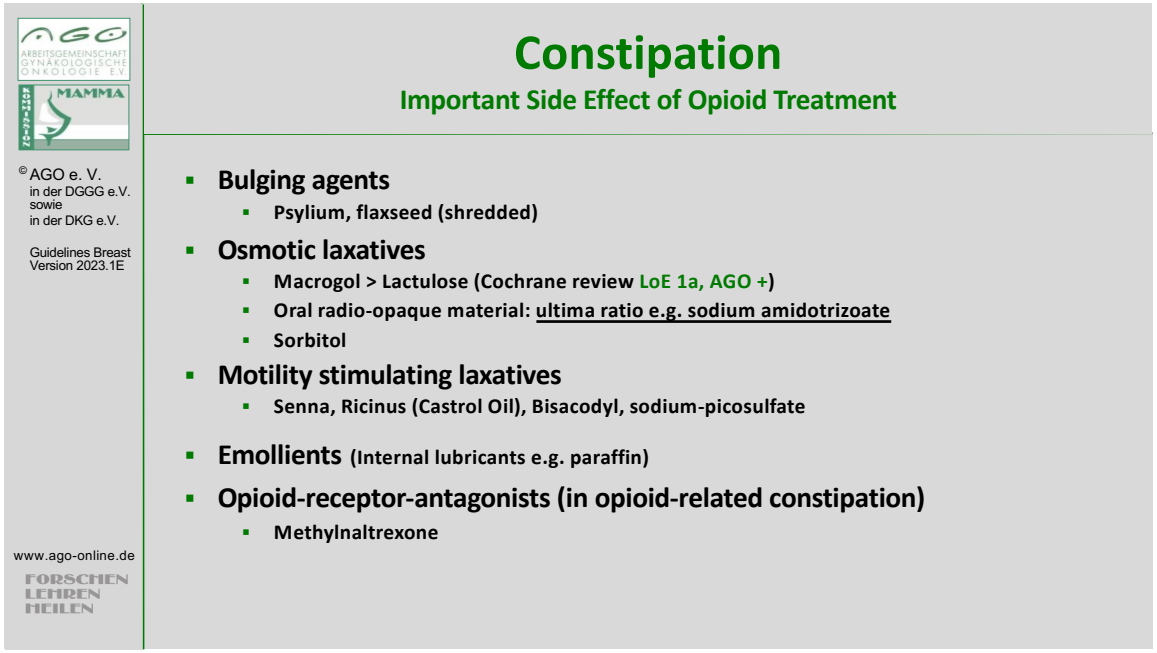


Relevant practice guideline

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,
2. AWMF Registernummer: 032/054OL, http://leitlinienprogramm- onkologie.de/Supportive-Therapie.95.0.html (Zugriff am 27.12.2021)

Guidelines Breast
Version 2023.1E

9. Skin & Subcutaneous Tissue Disorders (Alopecia)

Relevant practice guideline

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,
2. AWMF Registernummer: 032/054OL, http://leitlinienprogramm- onkologie.de/Supportive-Therapie.95.0.html (Zugriff am 08.01.2020)

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		+

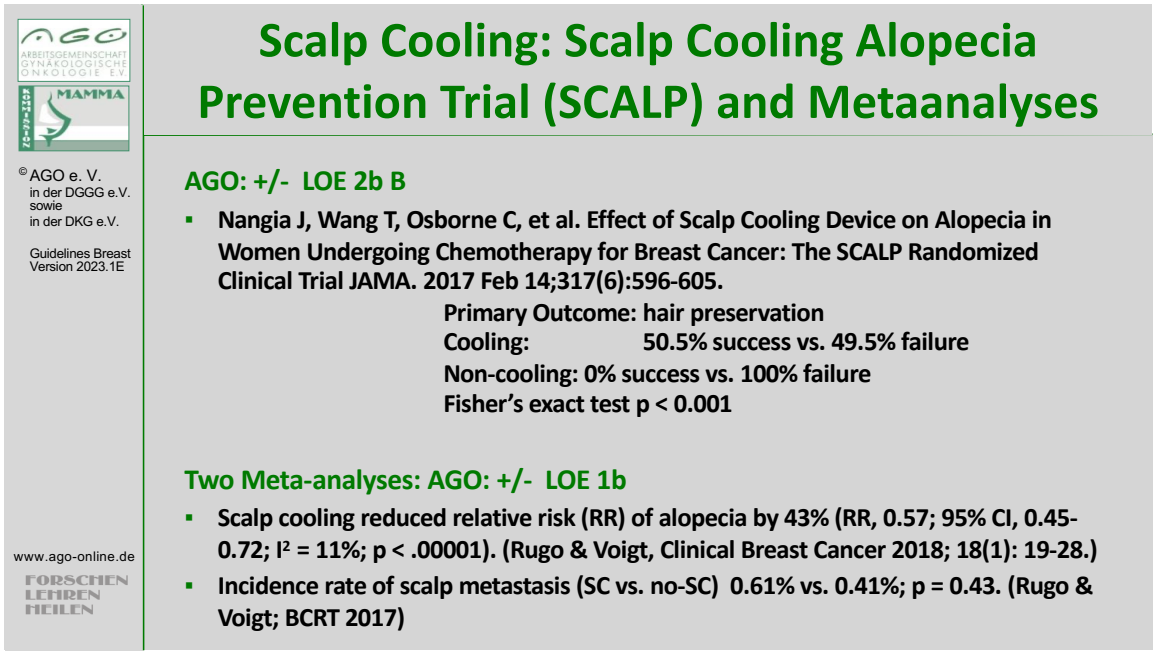
* Substance- and regimen specific

Relevant practice guidelines

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,
2. AWMF Registernummer: 032/054OL, http://leitlinienprogramm- onkologie.de/Supportive-Therapie.95.0.html (Zugriff am 27.12.2021)
3. Lacouture ME, Sibaud V, Gerber PA, et al. Prevention and management of dermatological toxicities related to anticancer agents: ESMO Clinical Practice Guidelines. Ann Oncol 2021;32:157-170.

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.



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.

Guidelines Breast
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10. Musculoskeletal & connective tissue disorders

(see Chapter Osteooncology)

Relevant practice guideline

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,
2. AWMF Registernummer: 032/054OL, http://leitlinienprogramm- onkologie.de/Supportive-Therapie.95.0.html (Zugriff am 27.12.2021)

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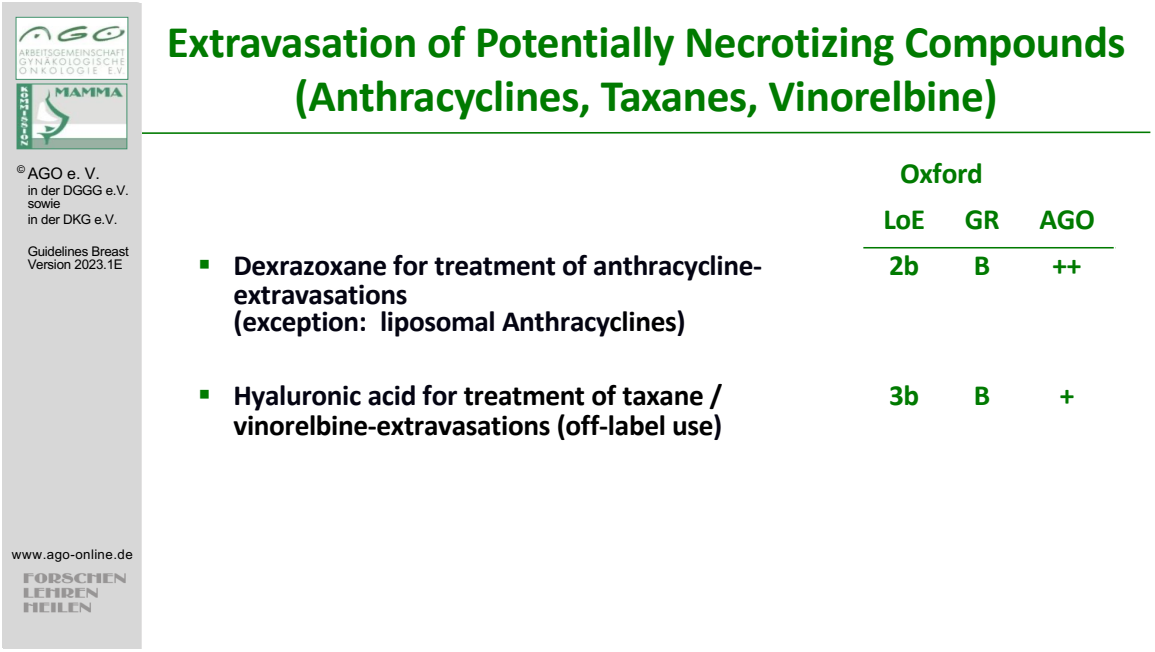
11. General Disorders & Administration Site Conditions

Relevant practice guideline

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,
2. AWMF Registernummer: 032/054OL, http://leitlinienprogramm- onkologie.de/Supportive-Therapie.95.0.html (Zugriff am 08.01.2020)



Relevant practice guideline:

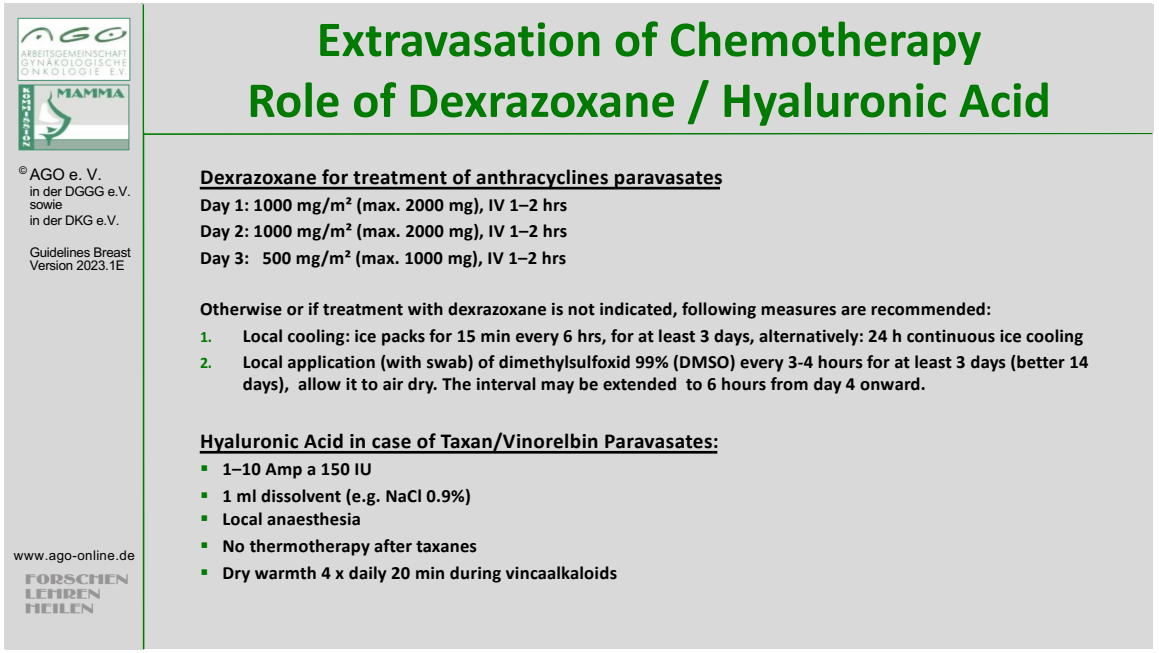
1. Hensley ML, Hagerty KL, Kewalramani T et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol. 2009 Jan 1;27(1):127-45.
2. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020, AWMF Registernummer: 032/054OL

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.
2. Testore F, Milanese S, Ceste M, et al.: Dexrazoxane (Totect): FDA review and approval for the treatment of accidental extravasation following intravenous anthracycline chemotherapy. Oncologist. 2008 Apr;13(4):445-50.
3. Mouridsen HT, Langer SW, Buter J, et al.: Treatment of anthracycline extravasation with Savene (dexrazoxane): results from two prospective clinical multicentre studies. Ann Oncol. 2007 Mar;18(3):546-50.

Hyaluronsäure

siehe S3-Leitlinie, Kapitel 11: Paravasate.



Relevant practice guideline

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,
2. AWMF Registernummer: 032/054OL, http://leitlinienprogramm- onkologie.de/Supportive-Therapie.95.0.html (Zugriff am 27.12.2021)

11. Lung

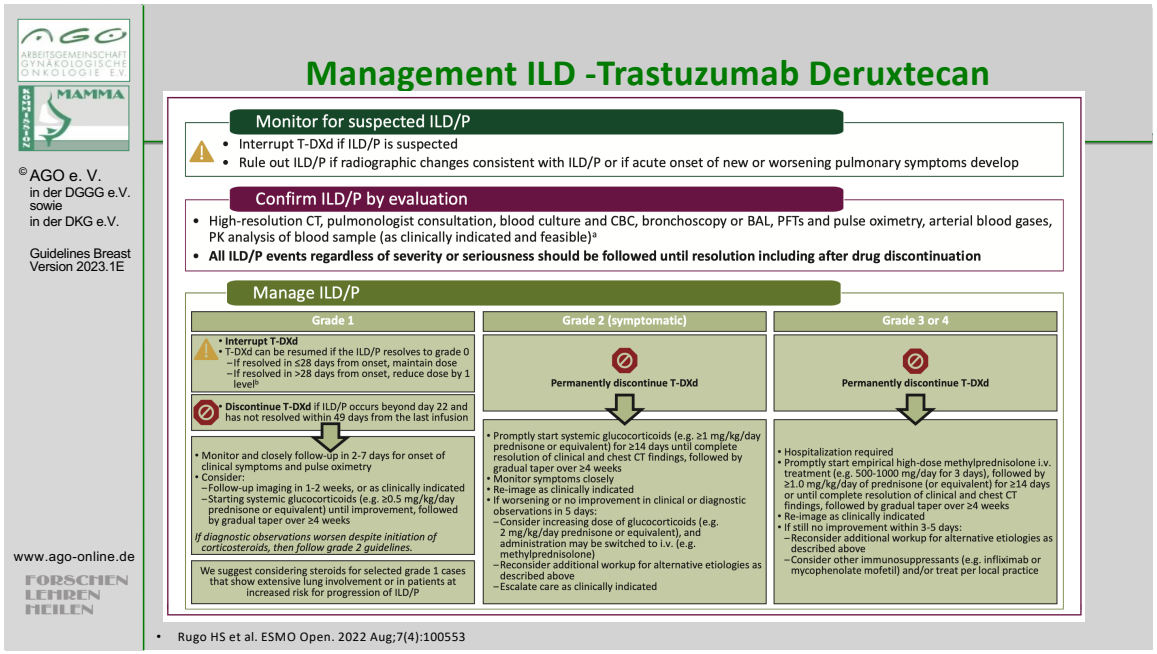
Relevant practice guideline

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020,
2. AWMF Registernummer: 032/054OL, http://leitlinienprogramm- onkologie.de/Supportive-Therapie.95.0.html (Zugriff am 17.01.2022)

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)**			++

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020, AWMF Registernummer: 032/054OL
2. Skeoch S, Weatherley N, Swift AJ, et al. Drug-Induced Interstitial Lung Disease: A Systematic Review. J Clin Med. 2018 Oct 15;7(10):356.
3. Hackshaw MD, Danysh HE, Singh J, et al. Incidence of pneumonitis/interstitial lung disease induced by HER2-targeting therapy for HER2-positive metastatic breast cancer. Breast Cancer Res Treat. 2020 Aug;183(1):23-39.
4. Law JW, Campbell A, Weller C et al. Epidemiology of interstitial lung disease in patients with metastatic breast cancer at baseline and after treatment with HER2-directed therapy: a real-world data analysis. Breast Cancer Res Treat. 2022 Dec;196(3):603-611



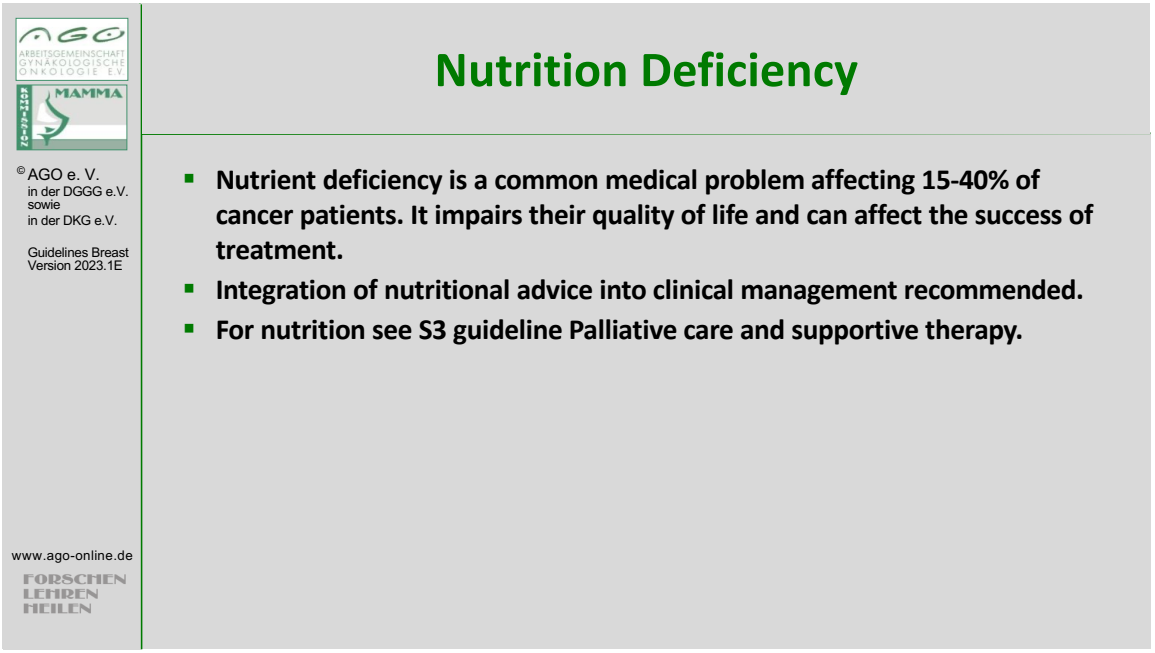
1. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382(7):610-621.
2. Modi S, Park H, Murthy RK, et al. Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients With HER2-Low-Expressing Advanced Breast Cancer: Results From a Phase Ib Study. .J Clin Oncol. 2020 Jun 10;38(17):1887-1896.
3. Tarantino P, Modi S, Tolaney SM, et. al. Interstitial Lung Disease Induced by Anti-ERBB2 Antibody-Drug Conjugates: A Review. JAMA Oncol. 2021 Dec 1;7(12):1873-1881.
4. Rugo HS, Bianchini G, Cortes J et al. Optimizing treatment management of trastuzumab deruxtecan in clinical practice of breast cancer. ESMO Open. 2022 Aug;7(4):100553.
5. Powell CA, Modi S, Iwata H. et al. Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies. ESMO Open. 2022 Aug;7(4):100554.

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**

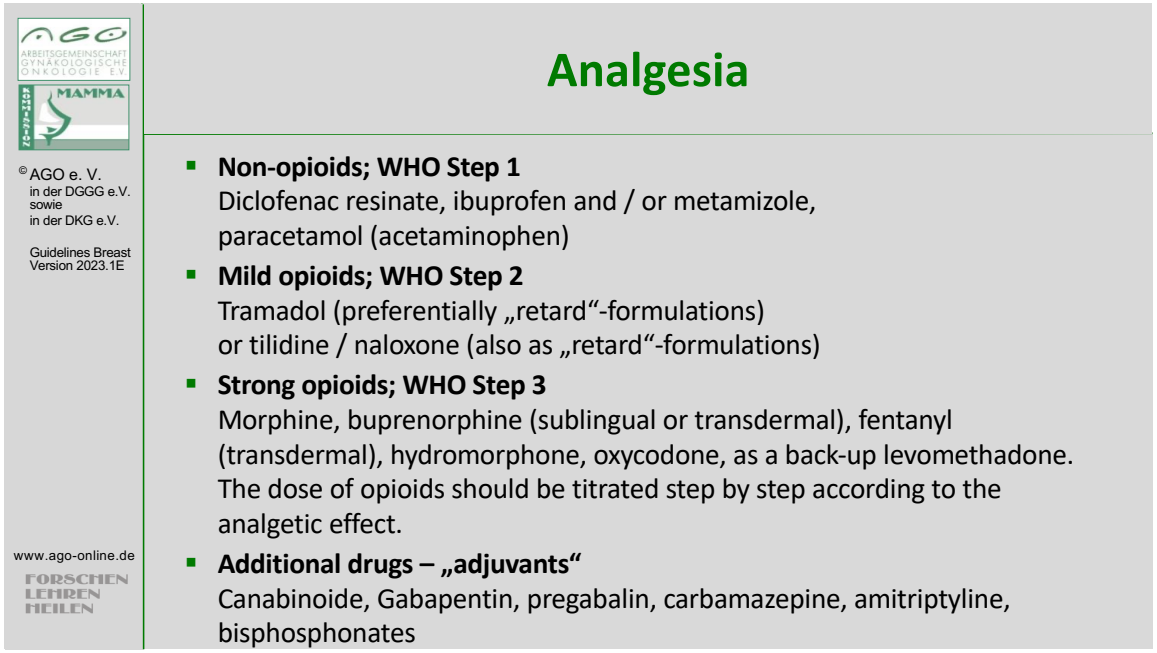
- **Further issues**
  - **Nutrition**
  - **Pain management**
  - **Palliative Care**

1. Santini D, Armento G, Giusti R, et al. Management of orphan symptoms: ESMO Clinical Practice Guidelines for diagnosis and treatment. ESMO Open 2020 Nov;5(6):e000933.



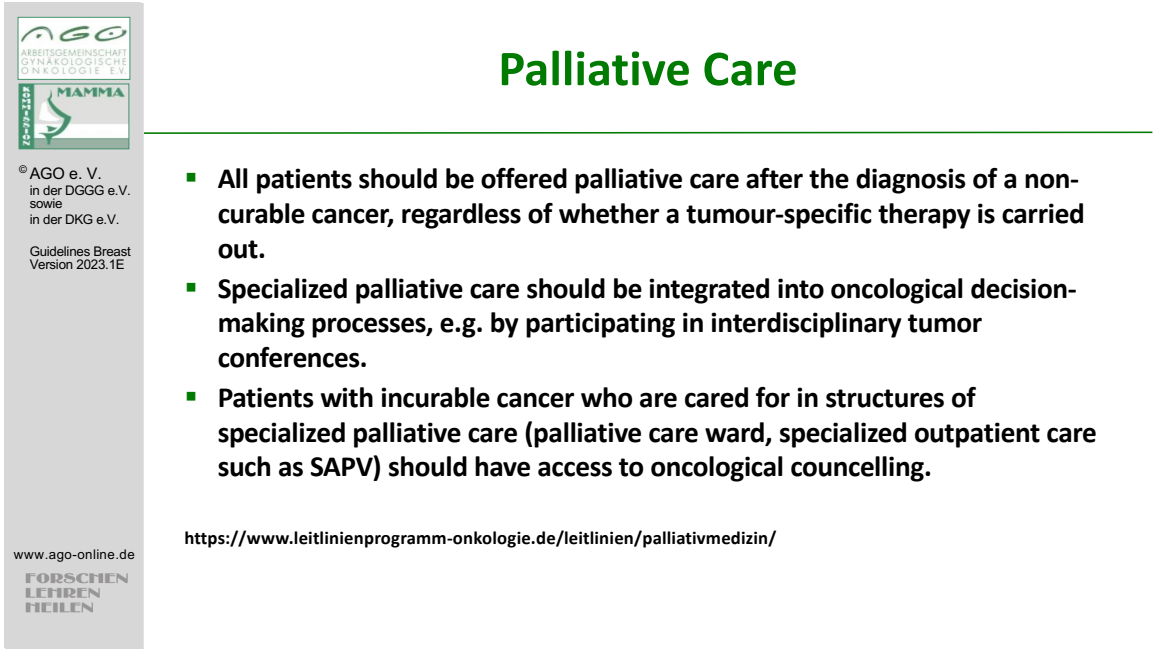
Klinische Ernährung

1. Arends J, Bertz H, Bischoff SC, et al. Klinische Ernährung in der Onkologie. S3-Leitlinie (AWMF Reg.: 073-006) Aktuel Ernahrungsmed. 2015; 40: e1–e74. https://www.dgem.de/sites/default/files/PDFs/Leitlinien/S3-Leitlinien/073-006l_S3_Klin_Ern%C3%A4hrung_in_der_Onkologie_2015-10.pdf (abgerufen 28.12.2021)
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.
3. van den Berg MMGA, Kok DE, Posthuma L, et al. Body composition is associated with risk of toxicity-induced modifications of treatment in women with stage I-IIIB breast cancer receiving chemotherapy. Breast Cancer Res Treat. 2019 Jan;173(2):475-481.



Relevant practice guideline:

1. World Health Organization (2018). WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. World Health Organization. https://apps.who.int/iris/handle/10665/279700. Lizenz: CC BY-NC-SA 3.0 IGO (Zugriff 27.12.2021)
2. NCCN guideline: Adult cancer pain. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf (Zugriff 27.12.2021)
3. Horlemann J, Schürmann N. DGS Praxisleitlinien in der Schmerztherapie. Cannabis in der Schmerzmedizin v1.0. https://dgs-praxisleitlinien.de/cannabis/ (Zugriff 27.12.2021)



1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Palliativmedizin für Patienten mit einer nicht-heilbaren Krebserkrankung, Langversion 2.2, September 2020, AWMF-Registernummer: 128/001OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/ (abgerufen am: 27.12.2021)