Guidelines Breast
Version 2023.1D

Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Supportive Therapie und Nebenwirkungsmanagement

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

Supportive Therapie und Nebenwirkungsmanagement

- **Versionen 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

Leitlinien – Umfeld

Nationale und internationale spezifische Leitlinien befassen sich mit verschiedenen Aspekten der evidenzbasierten supportiven Therapie von Karzinompatientinnen und –patienten.

Ohne Anspruch auf Vollständigkeit werden derartige (bes. deutsche) Leitlinienwerke genannt.

Hier soll insbesondere auf die Aspekte Wert gelegt werden, die Brustkrebspatientinnen betreffen:

- **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.

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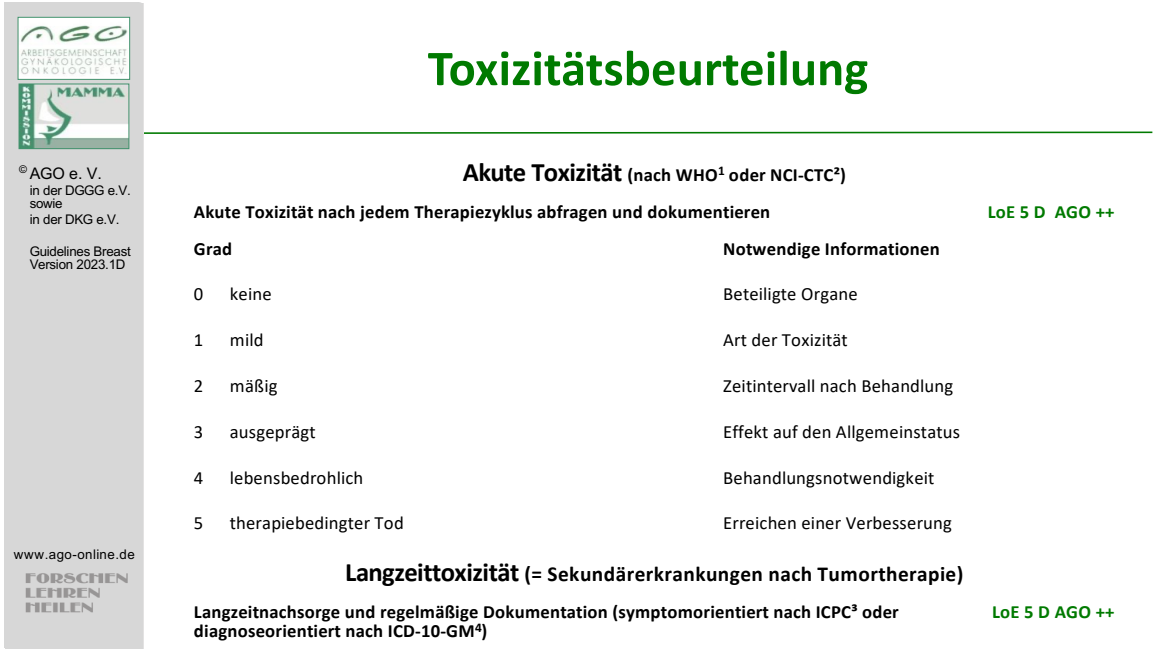
Toxizitätsbeurteilung

- **Akute Toxizität (NCI-CTCAE)**
- **Langzeittoxizität (ICPC, ICD-GM)**



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)

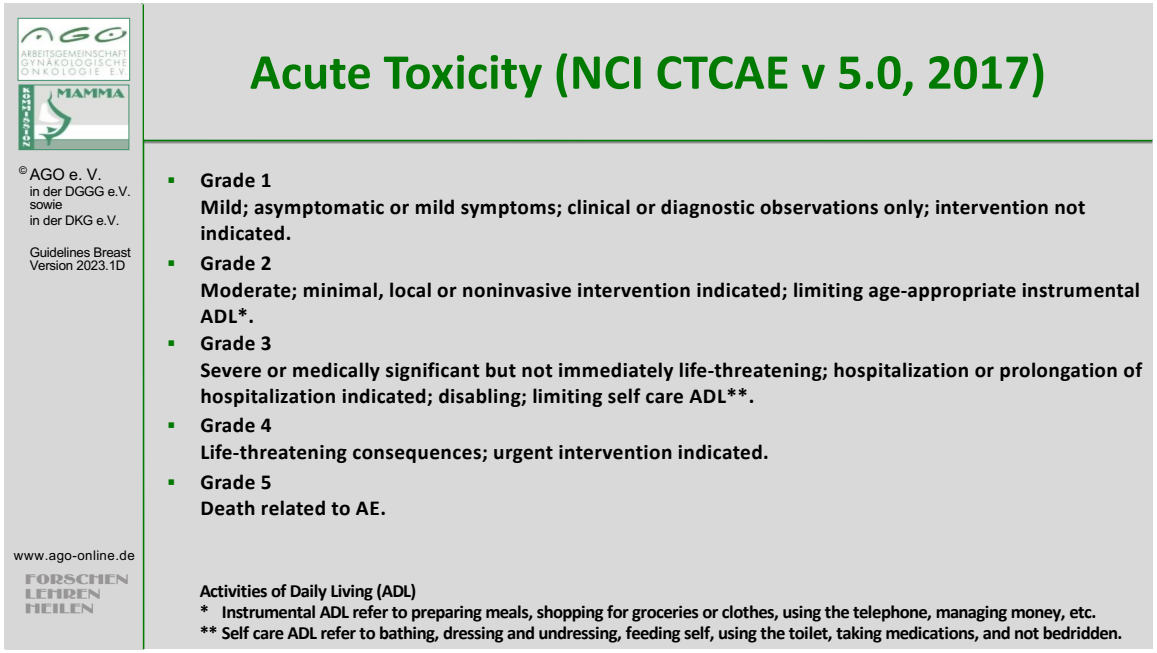
Akute Toxizität nach jedem Therapiezyklus abfragen

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

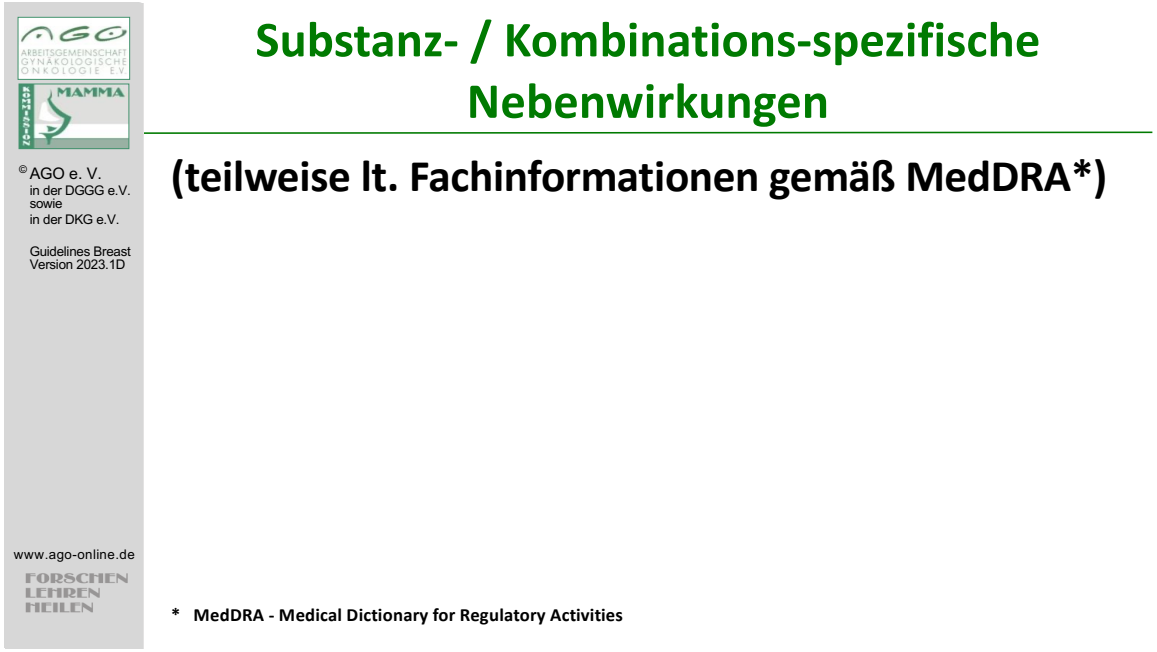
Langzeittoxizität

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)



*MedDRA - Medical Dictionary for Regulatory Activities

https://www.meddra.org/

Chemotherapie – Akute Toxizitäten I

Substanz	Systemorganklasse											
	Infektionen und parasitäre Erkrank.	Neubildungen, sek. Malignome	Blut, Lymphsystem	Immunsystem, Allergien	Endokrine Erkrankungen	Stoffwechsel- und Ernährungs.-Stör.	Psychiatrische Erkrankungen	Erkrankungen des Nervensystems	Augenerkrank.	Erkrank. des Ohrs und des Labyrinths	Herzerkrankungen	Gefäßerkrank.
Alkylantien												
Cyclophosphamid	4	2	5	5	1	-	1	3	2	3	3	3
Antimetabolite												
Methotrexat	1	-	4	3	3	-	3	4	2	-	1	2
5-Fluorouracil*	5	-	5	2	2	5	-	3	3	-	5	3
Capecitabin	4	3 (Lipom)	4	3	-	5	4	4	4	3	3	4
Gemcitabin	4	-	5	1	-	4	-:	4	-	-	2	2
Platin-Komplexe												
Cisplatin	4	2	5	3	2	5	-	4	2	5	4	4
Carboplatin	4	-	5	4	-	-	-	4	4	4	4	-
Anthrazykline / Anthrachinone												
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	-
Mitoxantron	5	3	5	3	-	4	-	4	3	3	4	3
Taxane												
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
Andere Spindelgifte												
Vinorelbin IV (PO)	5(5)	-	-(5)	2(-)	-	-	-(5)	-(5)	-(4)	-	2(3)	3(4)
Eribulin	4	-	4	-	-:	5	4	5	4	4	4	4

Die Liste und Graduierung der Nebenwirkungen ist nach Systemorganklassen, MedDRA-Terminologie und den folgenden Häufigkeitskategorien dargestellt:
1. Sehr selten (< 1/10.000); 2. Selten (≥ 1/1.000 bis < 1/10.000); 3. Gelegentlich (≥ 1/1.000 bis < 1/100); 4. Häufig (≥ 1/100 bis < 1/10); 5. Sehr häufig (≥ 1/10).
- Nicht bekannt (Häufigkeit auf Grundlage der verfügbaren Daten nicht abschätzbar)

Nebenwirkungskategorien - 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

Quellen für die Fachinformationen (Download 19.01.2018) **s. aktuelle Fachinformation www. Fachinfo.de**

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

Weitere Referenzen (Auswahl)

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.

Chemotherapie – Akute Toxizitäten II

Guidelines Breast
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	Systemorganklasse										
Substanz	Erkr. d. Atemwege, Brustraum, Mediast.	Erkr. d. GI.-Traktes (Übelk./Erbrechen)	Leber- und Gallen-erkrankungen	Erkr. d. Haut/Unter-haut (inkl. Alopezie)	Skelettmus.-, Binde-gew.-u.Knochenerkr.	Erkr. der Nieren und Harnwege	Schwang.-, Wochen-bett u. perinatale E.	Erkr. d. Geschlechts-organe u. Brustdrüse	Allg. Erkr. u. Beschw. am Applikationsort	Kongenit., famil. und genet. Erkr.	Besonderheiten
Alkylantien											
Cyclophosphamid	2	4	4	5	-	5	-	4	5	-	Hyponatriämie
Antimetabolite											
Methotrexat	4	5	5	4	3	3	-	3	1	-	Mukositits, Risiko "third space"-Toxizität
5-Fluorouracil	5	5	3	5	-	-	-	-	5	-	Risiko DPD-Mangel: leicht 5%, schwer 0,1%; Diarrhoe, Herz
Capecitabin	4	5	4	5	4	3	-	3	5	-	Hand-Fuß-.Syndrom (HFS), Risiko DPD-Mangel; Herz
Gemcitabin	5	5	5	5	4	5	-	-	5	-	Flu-like Symptome, Ödeme, Herz
Platin-Komplexe											
Cisplatin	4	5	4	4	-	5	-	3	5	-	Nierentoxizität, Ototoxizität, CIPN
Carboplatin	4	5	-	4	4	4	-	-	4	-	Kolitis, (Nierentox.)
Anthrazykline / Anthrachinone											
Epi-/Doxorubicin	2	5	-	5	1	4		1	5	-	Kardiotoxizität (CHF), sek. Malignome, Paravast
Lipo. Doxorubicin	4	5	4	5	4	3	-	(4)	5	-	
PEG-lipo. Doxo.	4	5	-	5	4	-	-	4	5	-	Palmares und plantares Erythem (PPE)
Mitoxantron	4	5	3	5	-	3	-	3	4	-	Sek. AML, Kardiomyopathie
Taxane											
Paclitaxel	2	5	1	5	5	-	-	-	5	-	Periphere Neuropathie (CIPN); Hypersensit., Myalgien
nab-Paclitaxel	4	5	3	5	5	3	-	3	5	-	Periphere Neuropathie (CIPN)
Docetaxel	5	5	-	5	5	-	-	-	5	-	Fluid retention, Paronychie, Kolitis, Myalgie
Andere Spindelgifte											
Vinorelbin 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	-	Obstipation, CIPN

Die Liste und Graduierung der Nebenwirkungen ist nach Systemorganklassen, MedDRA-Terminologie und den folgenden Häufigkeitskategorien dargestellt:
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- Nicht bekannt (Häufigkeit auf Grundlage der verfügbaren Daten nicht abschätzbar)

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)

1. 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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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
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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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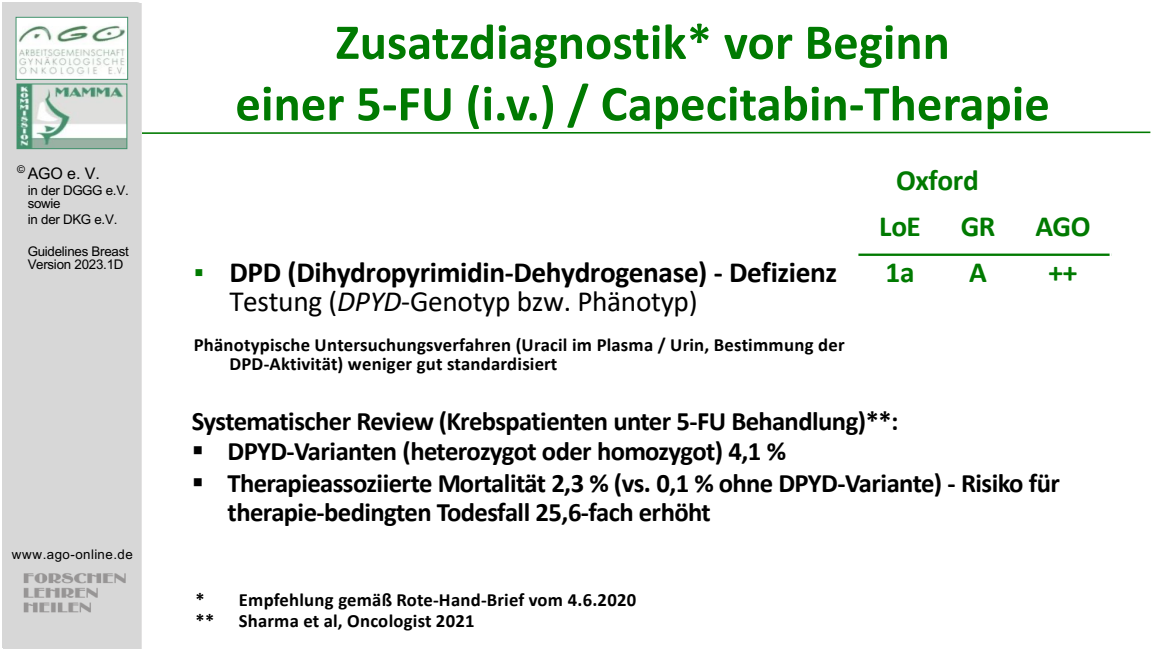
4. Cortes J, O'Shaughnessy J, Loesch D et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377:914-23
5. Link, H. and S. Schmitz (2013). "Treatment of cancer-associated anaemia: results from a two-day cross-sectional survey in Germany."

Onkologie 36(5): 266-272.
6. Fox P, Darley A, Furlong E, Miaskowski C, Patiraki E, Armes J, Ream E, Papadopoulou C, McCann L, Kearney N, Maguire R. 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.



DPD Defizienz:

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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Endokrine Therapie – Toxizitäten

Substanz	Infektionen und parasitäre Erkrank.	Neubildungen, sek. Malignome	Blut, Lymphsystem	Immunsystem, Allergien	Endokrine Erkrankungen	Stoffwechsel- und Ernährungs.-Stör.	Psychiatrische Erkrankungen	Erkrankungen des Nervensystems	Augenerkrank.	Erkrank. des Ohrs und des Labyrinths	Herzerkrankungen	Gefäßerkrank. (inkl. Hitzewall.)
SERM												
Tamoxifen	-	3	4	-	3	5	-	4	4	-	-	4
AI												
Anastrozol	-	-	-	-	-	4	5	5	4	-	4	5
Exemestan			4			4	5	4				5
Letrozol	3	-	3	-	-	5	4	4	3	-	3	5
SERD												
Fulvestrant	4	-	3	4	-	4	-	4	-	-	-	4

Substanz	Erkr. d. Atemwege, Thorax, Mediastin.	Erkrankungen des Gastrointestinaltr.	Leber- und Gallenerkrankungen	Erkr. Haut u. Unterhautgewebes	Skelettmus., Bindegew.-u.Knochenerk.	Erkr. der Nieren und Harnwege	Schwang., Wochenbett u. perinatale E.	Erkr. d. Geschlechtsorgane / Brustdrüse	Allg. Erkr. u. Besch. am Applikationsort	Kongenit., famil. und genet. Erkr.	Besonderheiten
SERM											
Tamoxifen	3	5	4	5	4	-	-	5	5	1	Hitzewallungen, selten: EndometriumCa (>55 J.); Thrombose
AI											
Anastrozol	-	5	4	5	5	-	-	5	5	-	Hitzewallungen, Arthralgie, Osteoporose; Kognition
Exemestan		5		5	5				5	-	Hitzewallungen, Arthralgie, Osteoporose; Kognition
Letrozol	3	4	3	5	5	3	-	4	5	-	Hitzewallungen, Arthralgie, Osteoporose; Kognition
SERD											
Fulvestrant	-	5	5	4	4	4	-	3	5	-	Hitzewallungen

Die Liste und Graduierung der Nebenwirkungen ist nach Systemorganklassen, MedDRA-Terminologie und den folgenden Häufigkeitskategorien dargestellt:
1. Sehr selten (< 1/10.000); 2. Selten (≥ 1/1.000 bis < 1/10.000); 3. Gelegentlich (≥ 1/1.000 bis < 1/100); 4. Häufig (≥ 1/100 bis < 1/10); 5. Sehr häufig (≥ 1/10).
- Nicht bekannt (Häufigkeit auf Grundlage der verfügbaren Daten nicht abschätzbar)

Nebenwirkungskategorien - 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

Quellen für die Fachinformationen (Download 19.01.2018) **s. aktuelle Fachinformation www. Fachinfo.de**

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

Nebenwirkungen – Antikörper

	Oxford LoE	Oxford GR
Trastuzumab		
▪ Kardiotoxizität in der adjuvanten Therapie (1,0–2,0 %)	1b	A
▪ Troponin I als Marker für Kardiotoxizität	2b	B
Pertuzumab		
▪ Ekzem, Diarrhoe, Mukositis	1b	A
Bevacizumab		
▪ Hypertonus, linksventrikuläre Dysfunktion, Blutung, Proteinurie	1a	A

Cardiotoxicity

1. Slamon D, Eiermann W, Robert N et al: Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365:1273-1283, 2011
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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
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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.
2. Drucker AM, Wu S, Dang CT, et al.: Risk of rash with the anti-HER2 dimerization antibody pertuzumab: a meta-analysis. Breast Cancer Res Treat. 2012 Sep;135(2):347-54.
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

Nebenwirkungen anti-HER2 TKI: Neratinib, Lapatinib

Lapatinib

UE, %	Alle Grade	Grad >/= 3
Diarrhöe	61 %	6 %
Nausea	18 %	4 %
Hautausschlag	60 %	6 %
Fatigue	16 %	4 %
Kardiale NW	3 %	< 1 % SAE
Hepatobiliäre NW	8 %	
Alle UE	92 %	SAE 6 %

	LoE	GR	AGO
Primäre Prophylaxe mit Loperamid	2b	B	++

Neratinib

UE, %	Alle Grade (%)	Grad >/=3 (%)
Diarrhöe	90	40,1
Nausea	43	2
Bauchschmerzen	36	2
Fatigue	27	2
Erbrechen	26	3
Hautausschlag	18	0,6
Stomatitis	14	0,6
Appetitverlust	12	0,2
Dyspepsie	10	0,4
ALAT-Erhöhungen	9	1,2
ASAT-Erhöhungen	7	0,7
Nagelstörungen	8	0,3
Trockene Haut	6	0

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, Lapatinb s. aktuelle Fachinformation www. Fachinfo.de

Nebenwirkungen anti-HER2 TKI
Tucatinib + Trastuzumab + Capecitabin

NW	Alle Grade (%)	≥ Grad 3 (%)
Alle Ereignisse	99.3	55.2
Diarrhoe	80.9	12.9
PPE Syndrom	63.4	13.1
Übelkeit	58.4	3.7
Fatigue	45.0	4.7
Erbrechen	35.9	3.0
Stomatitis	25.5	2.5
Red. Appetit	24.8	0.5
Kopfschmerz	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

Nebenwirkungen – Antikörper-Wirkstoff-Konjugate

	Oxford LoE	Oxford GR
Sacituzumab Govitecan		
▪ (Febrile) Neutropenie, Leukopenie, Anämie, Diarrhoe, Übelkeit, Alopezie	1b	A
Trastuzumab-Emtansin (T-DM1)		
▪ Thrombozytopenie, Anstieg Leberenzyme Fieber, Kopfschmerzen, Pneumonitis, Polyneuropathie	1b	A
Trastuzumab-Deruxtecan		
▪ Interstitielle Lungenerkrankung, Neutropenie, Übelkeit, Alopezie,	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.
2. Rugo HS, Tolaney SM, Loirat D, et al. Safety analyses from the phase 3 ASCENT trial of sacituzumab govitecan in metastatic triple-negative breast cancer. NPJ Breast Cancer. 2022 Aug 29;8(1):98.

T-DM1

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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

1. Cortés J, Kim SB, Chung WP et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. N Engl J Med. 2022 Mar 24;386(12):1143-1154.
2. Modi S, Jacot W, Yamashita T et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022 Jul 7;387(1):9-20.
3. Hurvitz SA, Hegg R, Chung WP et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet. 2022 Dec 6:S0140-6736(22)02420-5.
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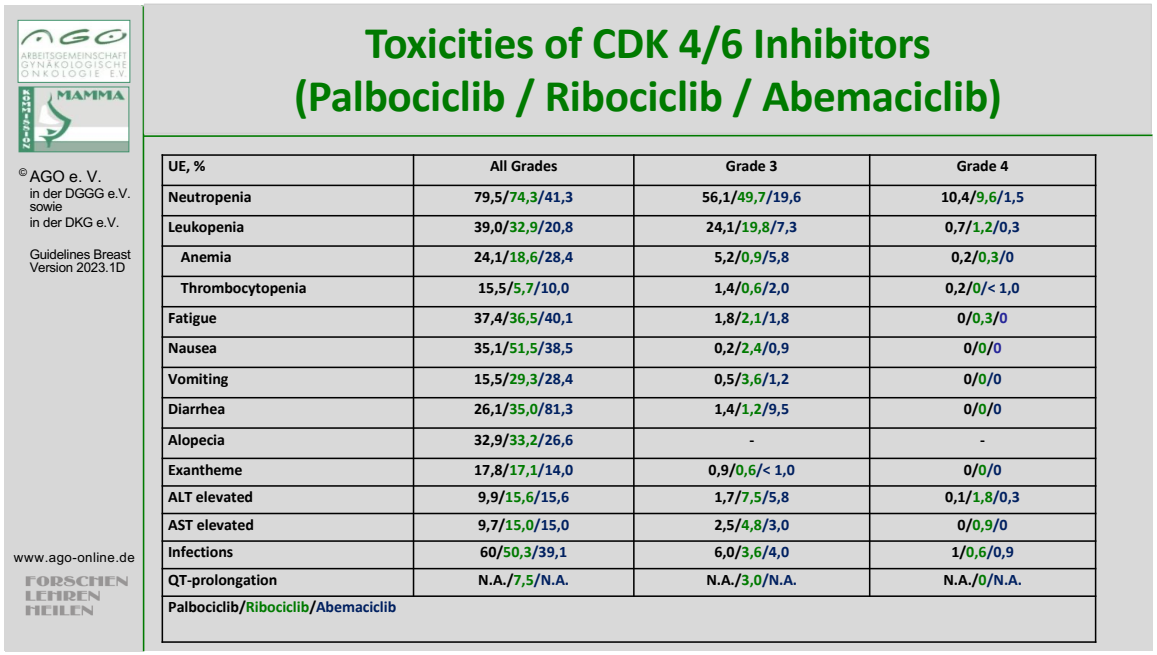

UE, %	All Grades	Grade 3	Grade 4
Neutropenia	79,5/74,3/41,3	56,1/49,7/19,6	10,4/9,6/1,5
Leukopenia	39,0/32,9/20,8	24,1/19,8/7,3	0,7/1,2/0,3
Anemia	24,1/18,6/28,4	5,2/0,9/5,8	0,2/0,3/0
Thrombocytopenia	15,5/5,7/10,0	1,4/0,6/2,0	0,2/0/< 1,0
Fatigue	37,4/36,5/40,1	1,8/2,1/1,8	0/0,3/0
Nausea	35,1/51,5/38,5	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
3. Berger F, Marce M, Delaloge S et al. Randomised, open-label, multicentric phase III trial to evaluate the safety and efficacy of palbociclib in combination with endocrine therapy, guided by ESR1 mutation monitoring in oestrogen receptor-positive, HER2-negative metastatic breast cancer patients: study design of PADA-1. BMJ Open. 2022 Mar 3;12(3):e055821.
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Ribociclib

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2. Hortobagyi GN, Stemmer SM, Burris HA. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. N Engl J Med. 2022 Mar 10;386(10):942-950.
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Abemaciclib

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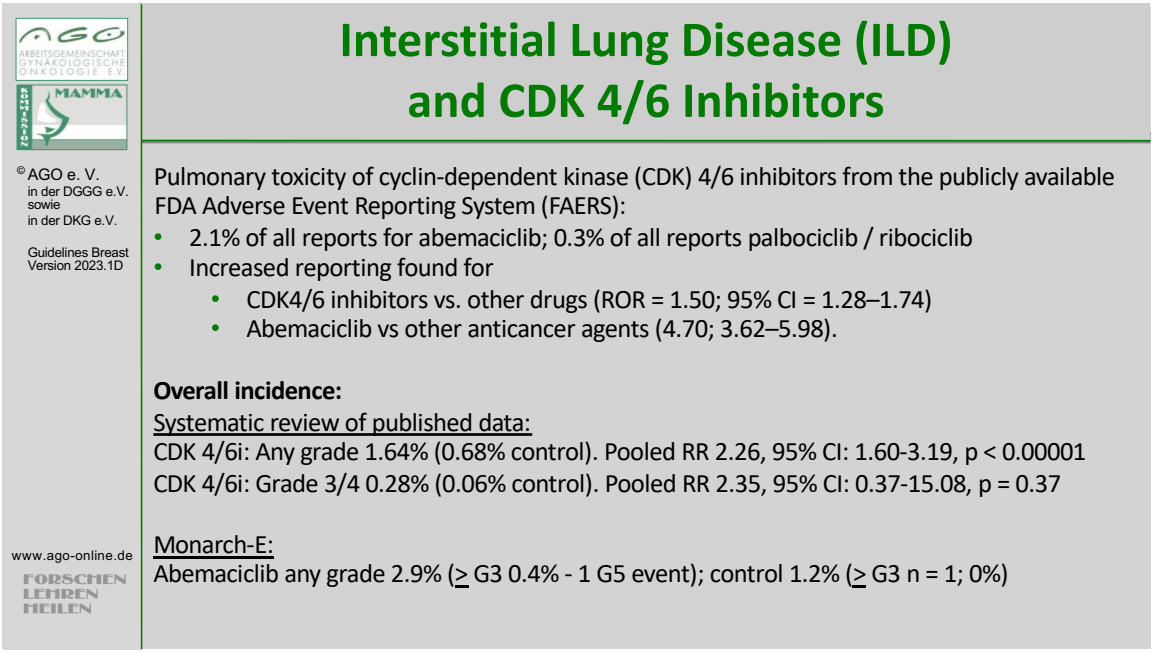
2. Goetz MP, Toi M, Campone M, et al: Monarch 3: Abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol 2017;35:3638-3646.
3. Lu YS, Im SA, Colleoni M et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. Clin Cancer Res. 2022 Mar 1;28(5):851-859.



1. Raschi E, Fusaroli M, Ardizzoni A, et al. Cyclin-dependent kinase 4/6 inhibitors and interstitial lung disease in the FDA adverse event reporting system: a pharmacovigilance assessment. Breast Cancer Res Treat 2021 Feb;186(1):219-227.
2. Toi M, Harbeck N, Puig JM et al. Characterization of venous thromboembolic events (VTE), elevated aminotransferases (EAT) and interstitial lung disease (ILD) in monarchE. ESMO Breast 2021
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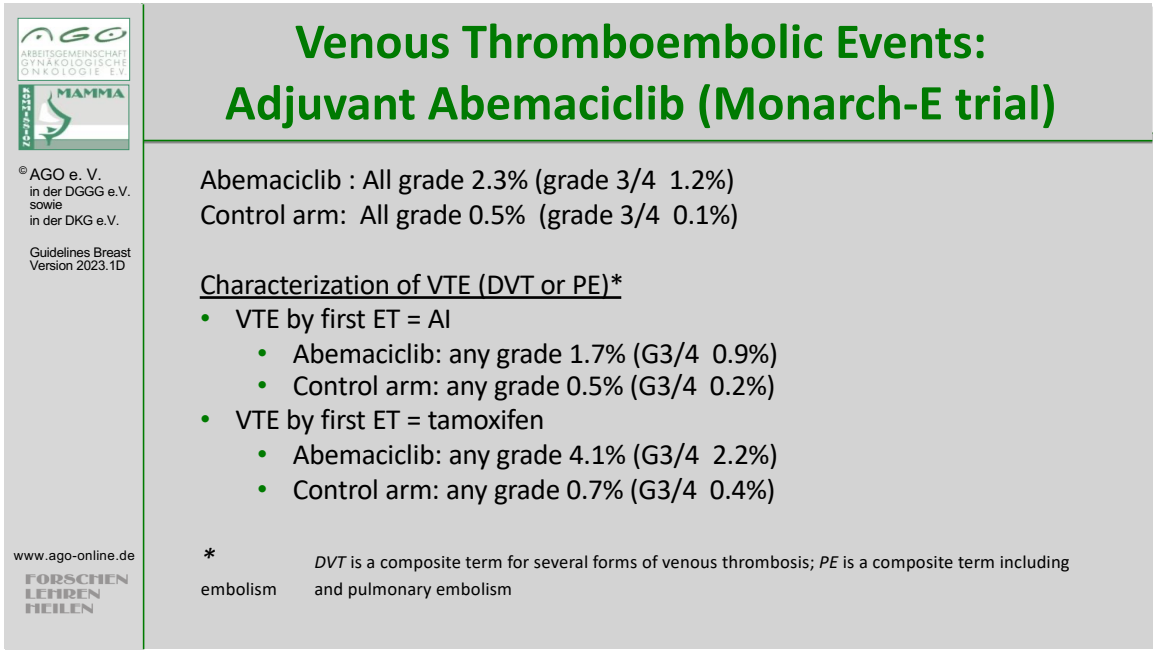
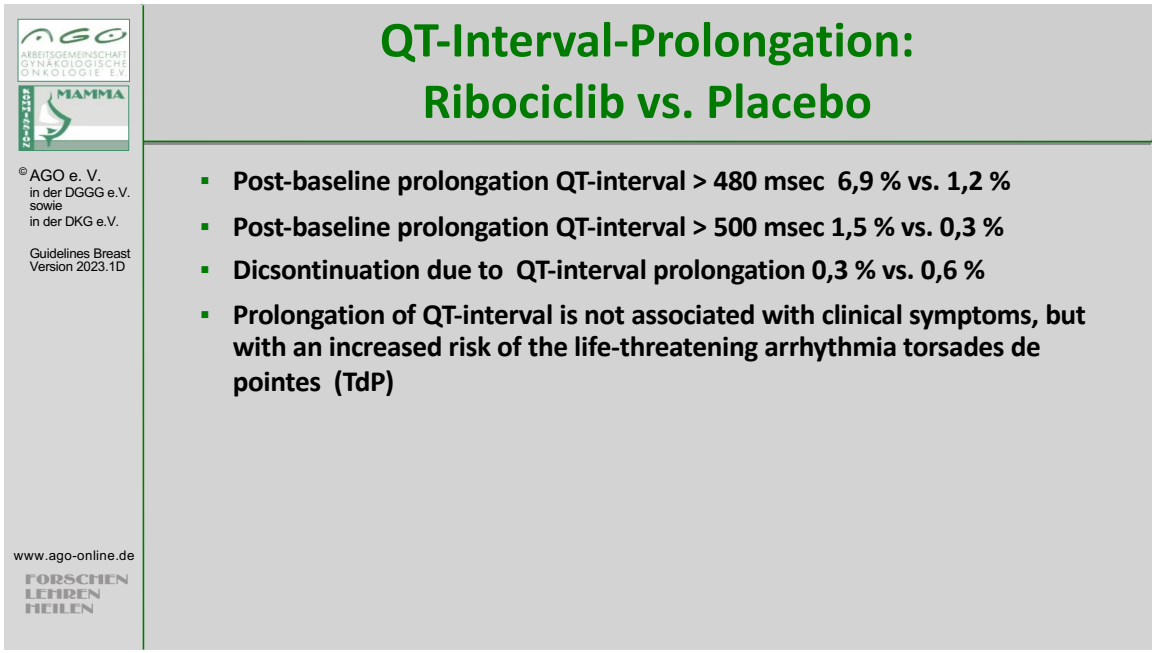


1. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol. 2020 Dec 1;38(34):3987-3998.
2. Toi M, Harbeck N, Puig JM et al. Characterization of venous thromboembolic events (VTE), elevated aminotransferases (EAT) and interstitial lung disease (ILD) in monarchE. ESMO Breast 2021



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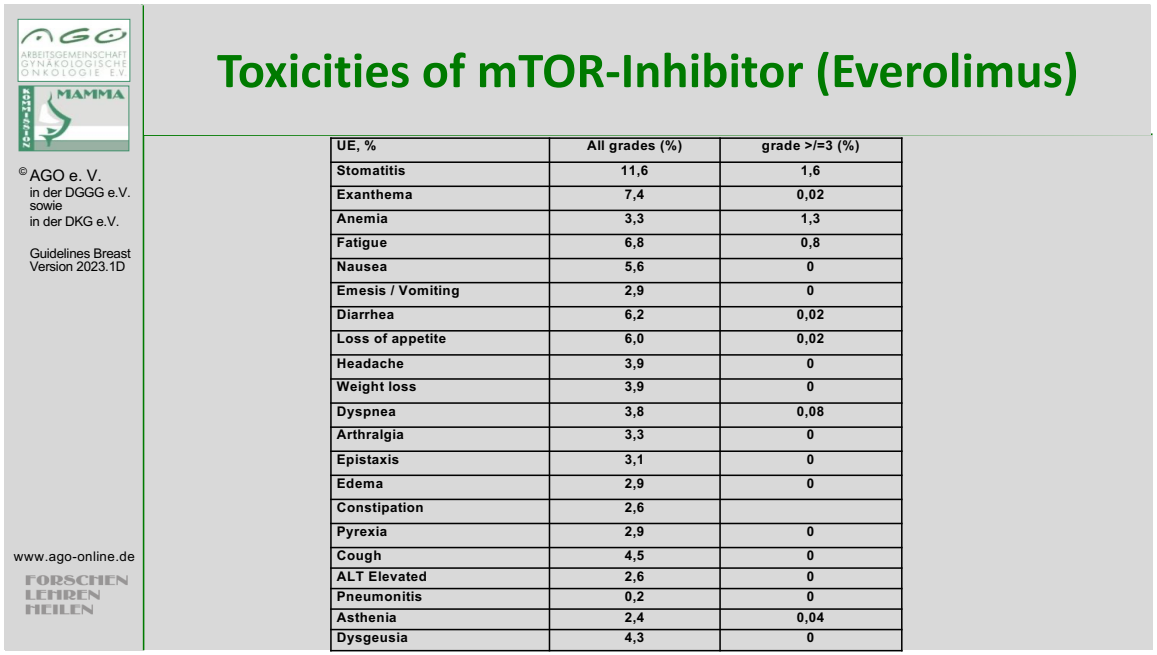

Toxicities of mTOR-Inhibitor (Everolimus)

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

Guidelines Breast
Version 2023.1D

Nebenwirkungen Alpelisib (PI3K-Inhibitor) in Kombination mit endokriner Therapie

Alpelisib + Fulvestrant

UE, %	Alle Grade	Grad ≥ 3
Hypergykämie	63,7 %	32,7 %
Diarrhö	57,7 %	6,7 %
Übelkeit	44,7 %	2,5 %
Appetitlosigkeit	35,6 %	< 1 % SAE
Hautausschlag	35,5 %	9,9 %
Erbrechen	27,1 %	< 1 % SAE
Gewichtsverlust	26,8 %	3,9 %
Stomatitis	24,6 %	2,5 %
Fatique	24,3 %	3,5
Asthenie	20,4 %	1,8
Haarverlust	19,7 %	0
Mucositis	18,3 %	2,1

Berücksichtigung der Empfehlungen zum Nebenwirkungsmanagement (Diabetes mellitus, Hyperglykämie, Insulinresistenz und metabolisches Syndrom)

LoE	GR	AGO
2b	B	++

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

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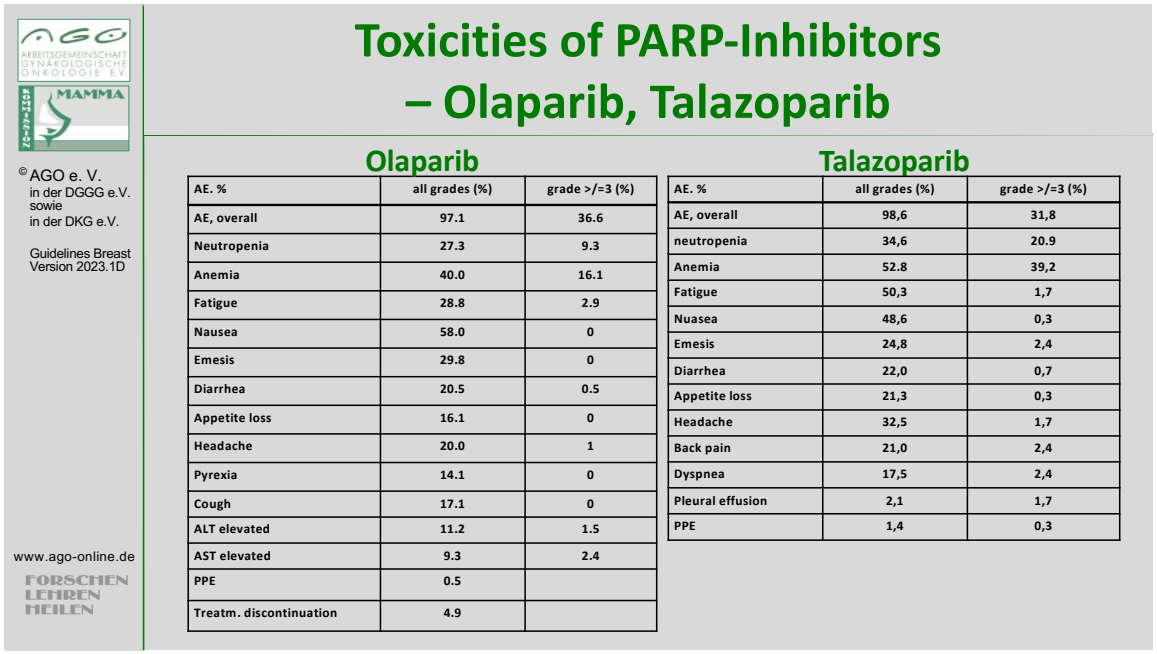


Toxicities of PARP-Inhibitors – Olaparib, Talazoparib

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.
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

Immun-Checkpoint-Inhibitoren

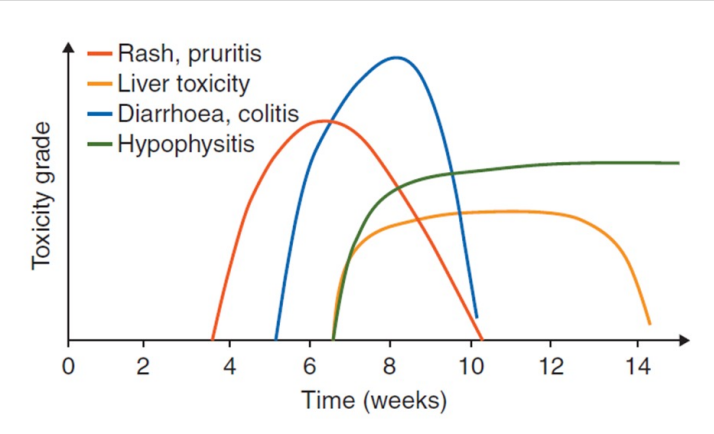
- **Therapeutische Ansätze (Antikörper)**
  - **PD-1 / PD-L1**

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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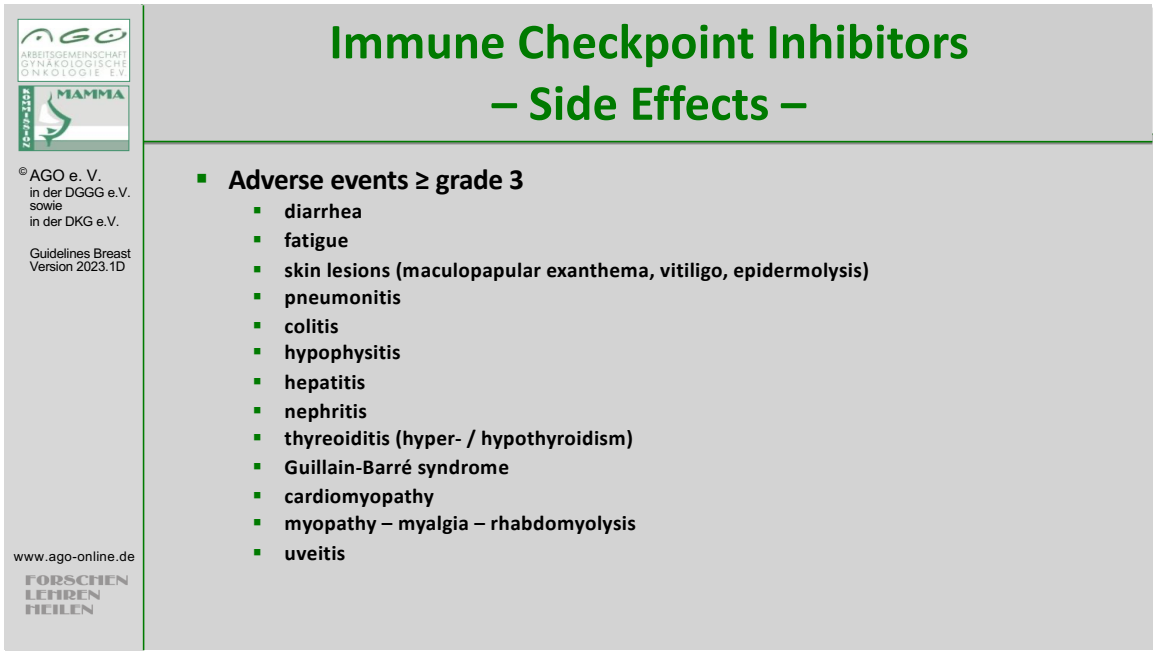

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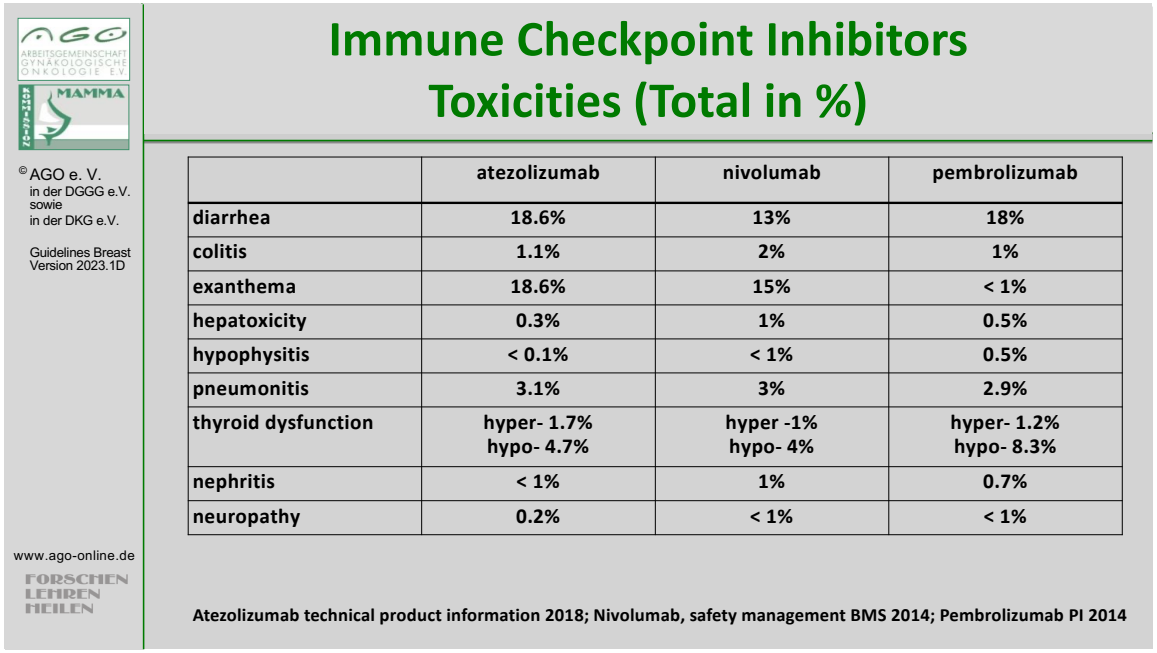
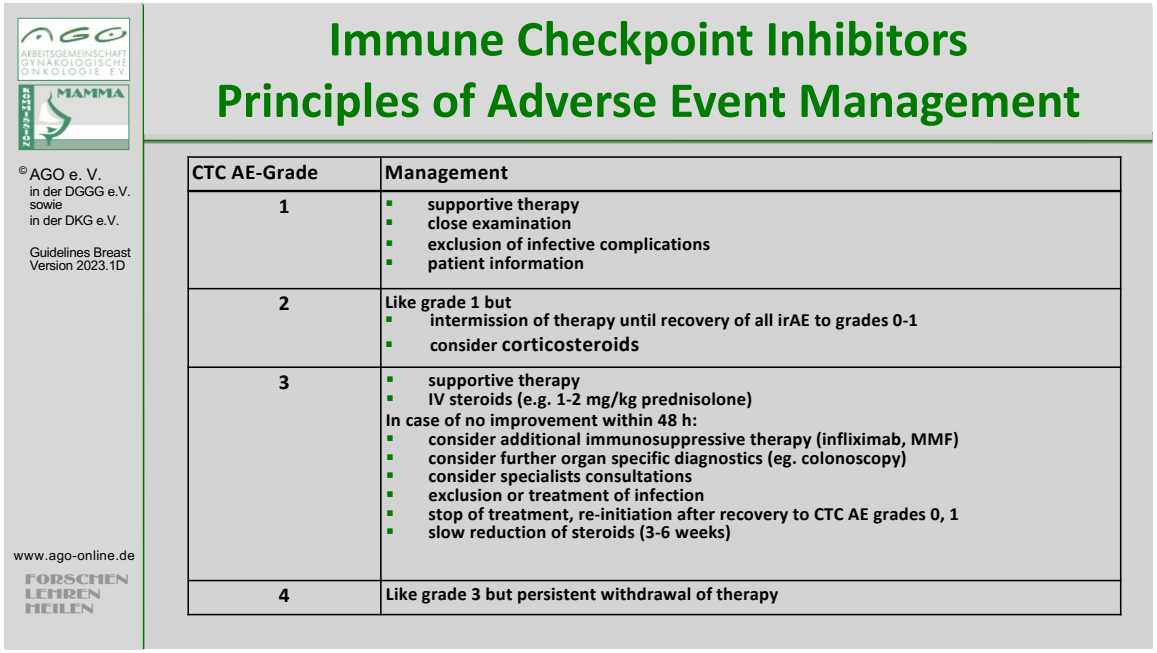


Immune Checkpoint Inhibitors Toxicities (Total in %)

	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.
2. 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.
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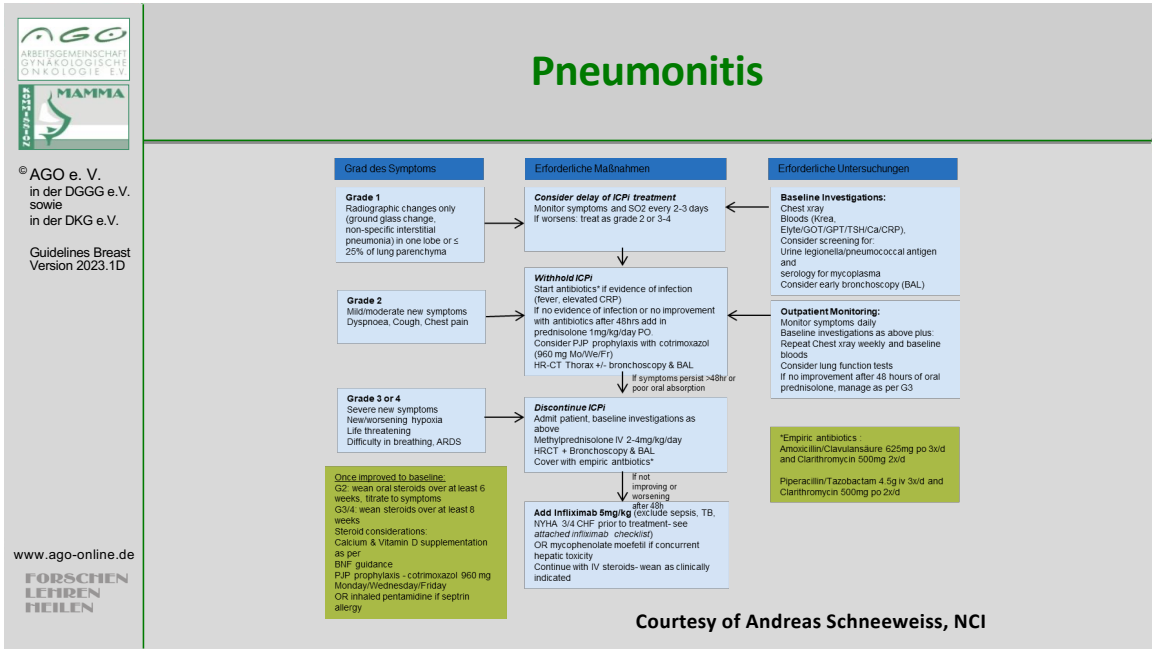

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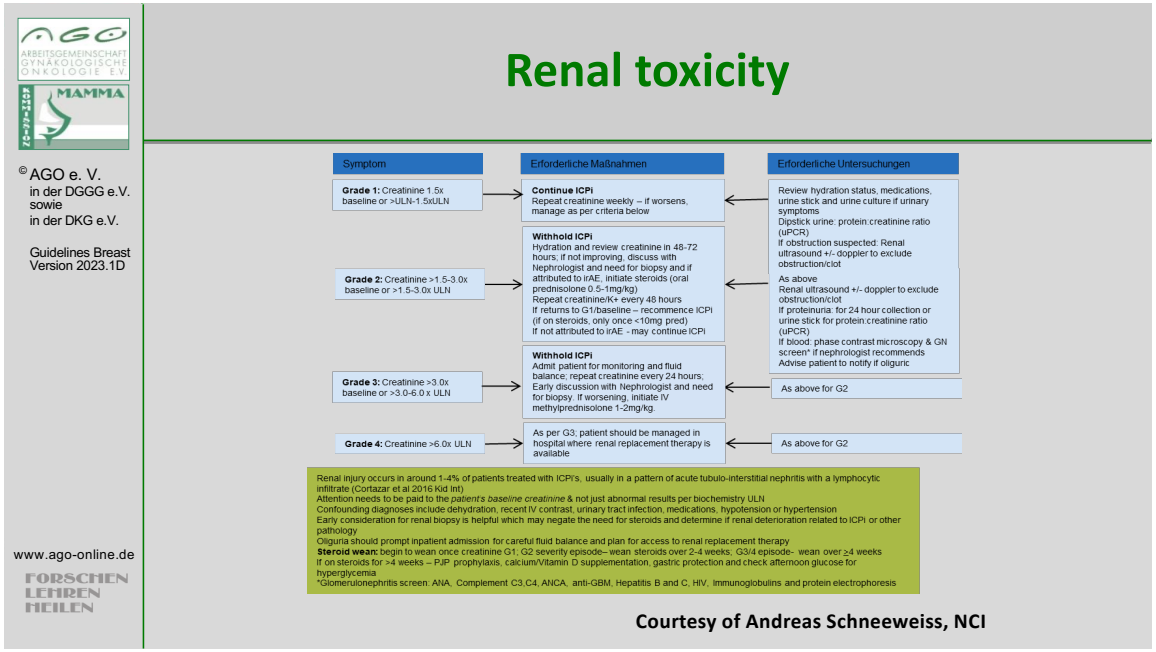

Courtesy of Andreas Schneeweiss, NCI

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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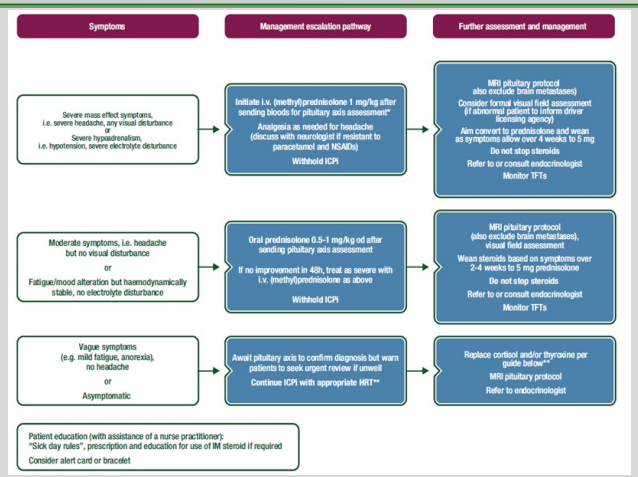
Hypophysitis



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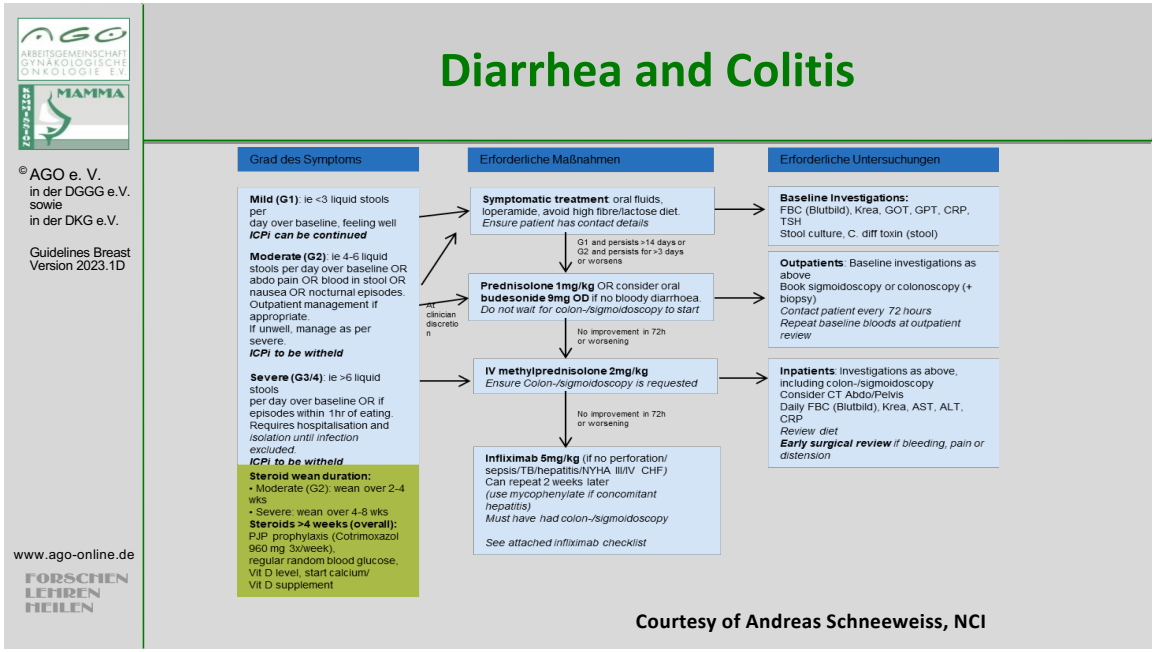

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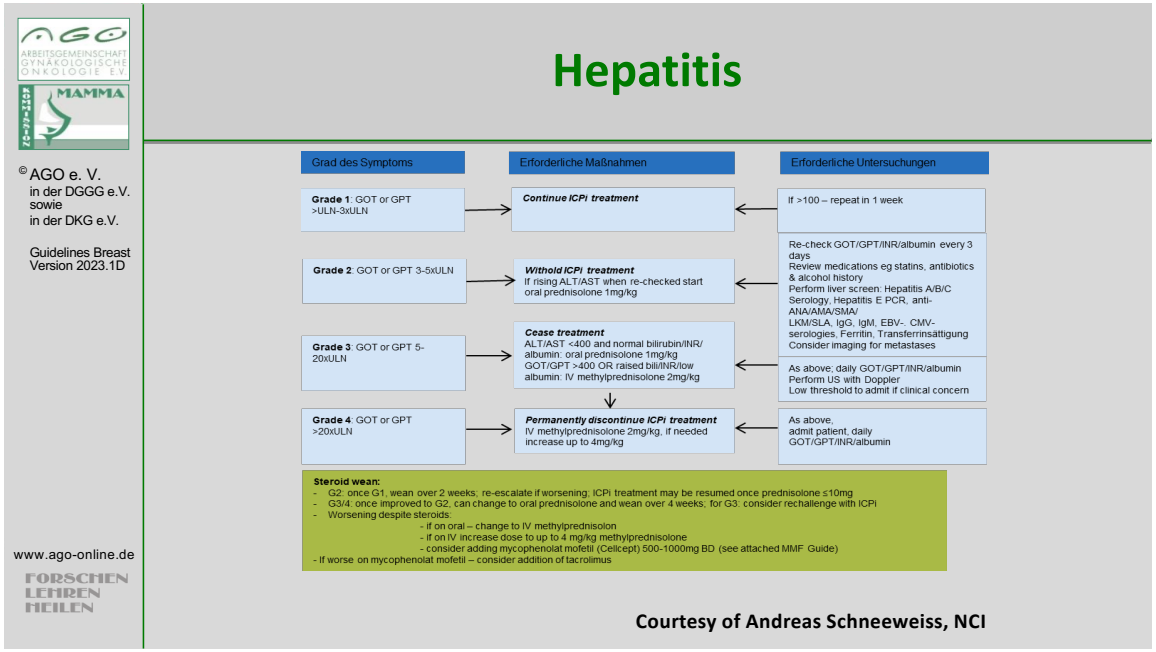

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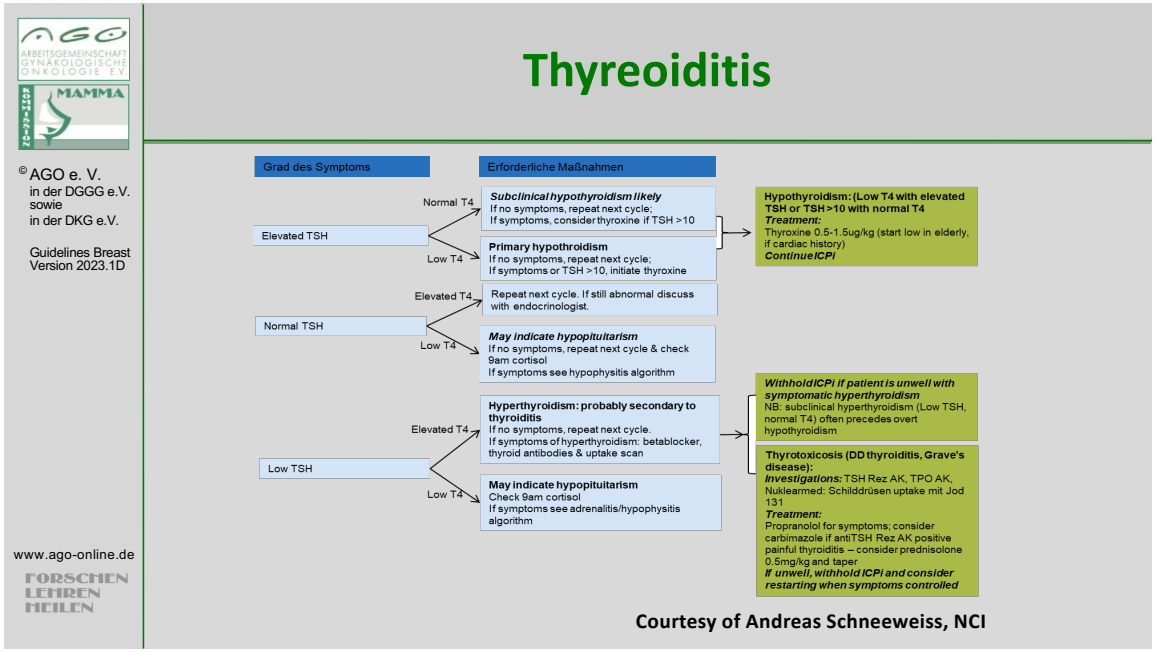

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Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

1. Infektionen

- **Allgemeine Infektionsprophylaxe**
- **Hepatitis B-Screening**
- **Covid-19 (s. gemeinsame Stellungnahme mit 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-Screening vor Chemotherapie

	Oxford		
	LoE	GR	AGO
▪ **Hepatitis B-Screening vor Beginn einer Chemotherapie (HBsAg, anti-HBc, anti-HBs)**	2c	B	+
Bei Reaktivierung bzw. bei positiver Serologie			
▪ **Prophylaktische Therapie mit Virustatika bei Nachweis von HBV-DNA (entsprechend AGIHO / DGHO – Empfehlungen)**	1b	A	++
▪ **Hepatitis C-Screening vor Beginn einer Chemotherapie**	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.
2. Robert-Koch-Institut. Epidemiologisches Bulletin**.** 20. Juli 2015 / Nr. 29
3. Di Bisceglie AM, Lok AS, Martin P, et al. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? Hepatology. 2015 Feb;61(2):703-11.
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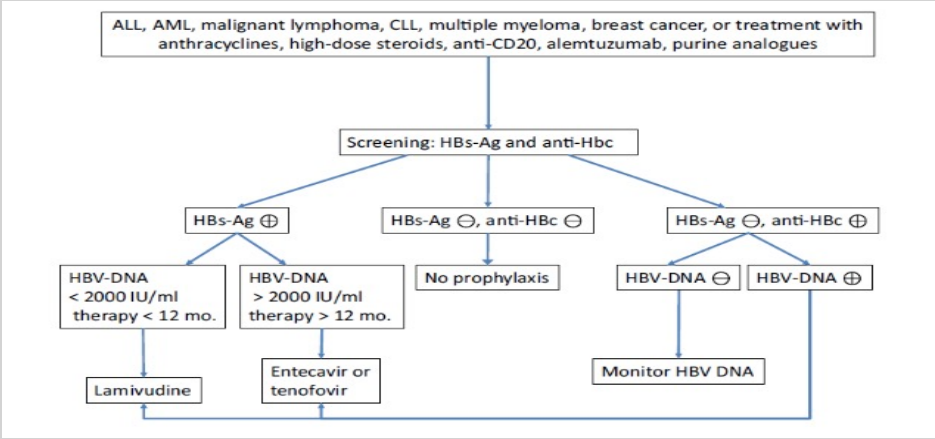
AGIHO / DGHO – Recommendations on Hepatitis B Virus Screening in Oncology

Guidelines Breast
Version 2023.1D



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

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2. Maschmeyer G, De Greef J, Mellinghoff SC et al.: European Conference on Infections in L: Infections associated with immunotherapeutic and molecular targeted agents in hematology and oncology. A position paper by the european conference on infections in leukemia (ecil). Leukemia 2019;33:844-862.

Guidelines Breast
Version 2023.1D

Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

2. Gutartige, bösartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen)

Sekundäre Malignome I

	Oxford LoE	Oxford GR
▪ Die Induktion von soliden, malignen Tumoren durch Chemotherapie ist selten	2a	
▪ Alkylantien erhöhen dosisabhängig das Risiko für Leukämien auf 0,2–0,4 % innerhalb von 10–15 Jahren	2a	
▪ Anthrazyklinhaltige Regime erhöhen das Risiko für MDS und Leukämie auf 0,2–1,7 % innerhalb von 8–10 Jahren	2a	
▪ PARP-Inihibitoren sind assoziiert mit einem erhöhten Risiko für AML und MDS von 0,5–1 %	2b	
▪ Radiotherapie erhöht das Risiko einer Leukämie bei Pat. mit einer anthrazyklinhaltigen Therapie um 0,2–0,4 %	2b	
▪ Tamoxifen verdoppelt das Risiko für die Entwicklung eines Endometriumkarzinoms (bei Therapiebeginn ab 55. Lj.)	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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5. Hershman D, Neugut A, Jacobson J et al.(2007) Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte colony-stmulating factors during breast cancer adjuvant chemotherapy. J Natl Cancer Inst 99: 196-205
6. Jabagi MJ, Goncalves A, Vey N, et al.: Risk of hematologic malignant neoplasms after postoperative treatment of breast cancer. Cancers (Basel) 2019;11.
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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.
9. Jabagi MJ, Vey N, Goncalves A, et al.: Evaluation of the incidence of hematologic malignant neoplasms among breast cancer survivors in france. JAMA network open 2019;2:e187147.
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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.
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.

Sekundäre Malignome II (nach Radiotherapie)

	Oxford LoE
▪ **Eine Radiotherapie (PMRT, BET) kann das Risiko für ein ipsilaterales Lungenkarzinom und Angiosarkom mäßiggradig anheben (10–15/10.000) (Auftreten 5–10 Jahre nach PMRT)**	1a
▪ **Erhöhtes Risiko besonders für Raucher**	2b
▪ **Kein Unterschied bezgl. sekundärer Malignome zwischen PBI (Teil-) und WBI (Ganzbrustbestrahlung)**	2c

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13. Zareie B, Rasouli MA, Poorolajal J.Risk of primary lung cancer after breast cancer radiotherapy: a systematic review and meta-analysis. Breast Cancer. 2022 Mar;29(2):361-367.

Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

3. Erkrankungen des Blutes und des Lymphsystems

- Anämie
- Neutropenie
- Febrile Neutropenie

Anämie – Indikationen für den Einsatz von Erythropoese-stimulierenden Faktoren (ESF)

	Oxford		
	LoE	GR	AGO
▪ Indiziert bei asymptomatischer Anämie	1a	B	-
▪ Therapie und sekundäre Prophylaxe bei CTx-induzierter Anämie	1a	A	+
▪ Adjuvante Situation	1b	A	+
▪ Neoadjuvante / metastasierte Situation	1a	A	+/-
▪ Bei dosisdichter / dosiseskalierter CTx (iddETC)	1b	A	+
▪ Therapie beginnt bei Hb-Werten < 10 g/dl	1a	A	+
▪ Ziel-Hb 11–12 g/dL	1a	A	+
▪ Verbesserung der Prognose (krankheitsfreies Intervall, Gesamtüberleben)	1a	B	--
▪ ESF erhöht das Risiko von thromboembolischen Komplikationen	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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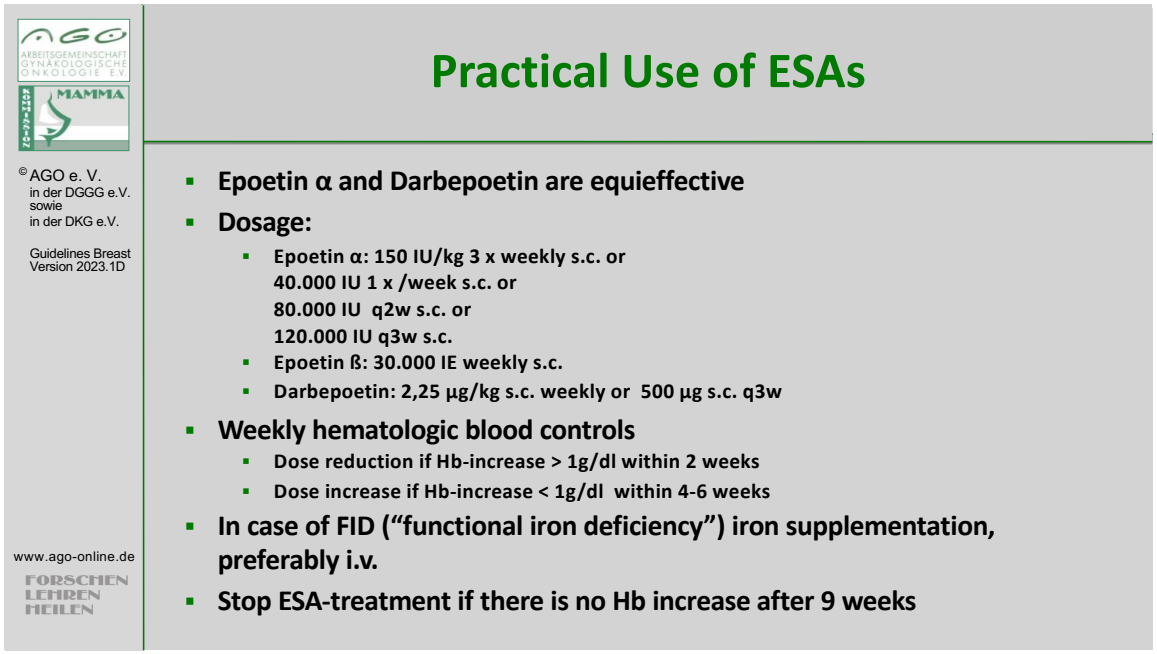

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<u>Relevant guidelines</u>

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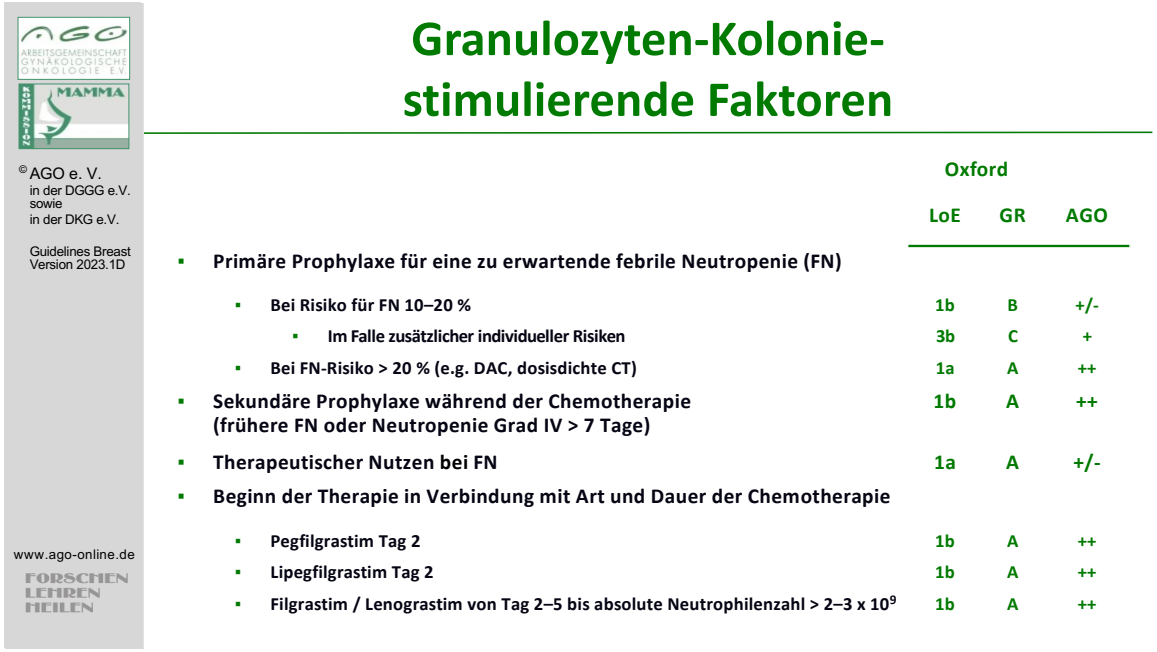

Granulozyten-Kolonie-stimulierende Faktoren

	Oxford LoE	Oxford GR	AGO
▪ **Primäre Prophylaxe für eine zu erwartende febrile Neutropenie (FN)**			
▪ Bei Risiko für FN 10–20 %	1b	B	+/-
▪ Im Falle zusätzlicher individueller Risiken	3b	C	+
▪ Bei FN-Risiko > 20 % (e.g. DAC, dosisdichte CT)	1a	A	++
▪ **Sekundäre Prophylaxe während der Chemotherapie (frühere FN oder Neutropenie Grad IV > 7 Tage)**	1b	A	++
▪ **Therapeutischer Nutzen bei FN**	1a	A	+/-
▪ **Beginn der Therapie in Verbindung mit Art und Dauer der Chemotherapie**			
▪ Pegfilgrastim Tag 2	1b	A	++
▪ Lipegfilgrastim Tag 2	1b	A	++
▪ Filgrastim / Lenograstim von Tag 2–5 bis absolute Neutrophilenzahl > 2–3 x 10^9	1b	A	++

Relevante Leitlinien

1. S3-Leitlinie: Supportive Therapie:
   Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3 – Februar 2020
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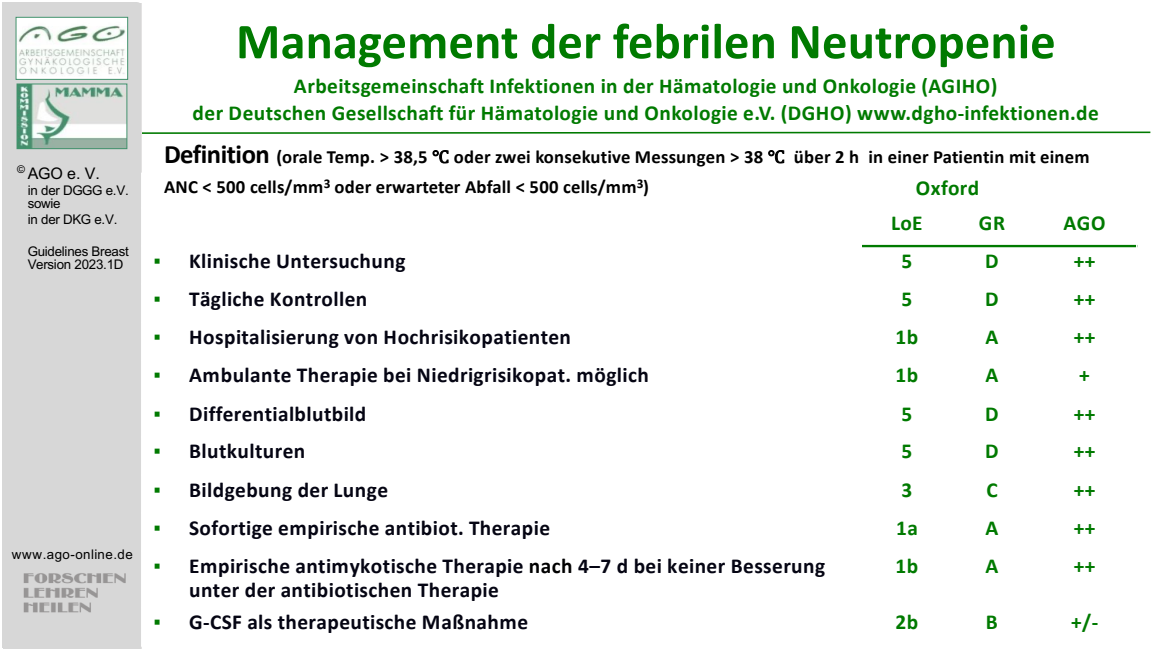

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S3-Leitlinie: Supportive Therapie:

1. S3-Leitlinie: Supportive Therapie:
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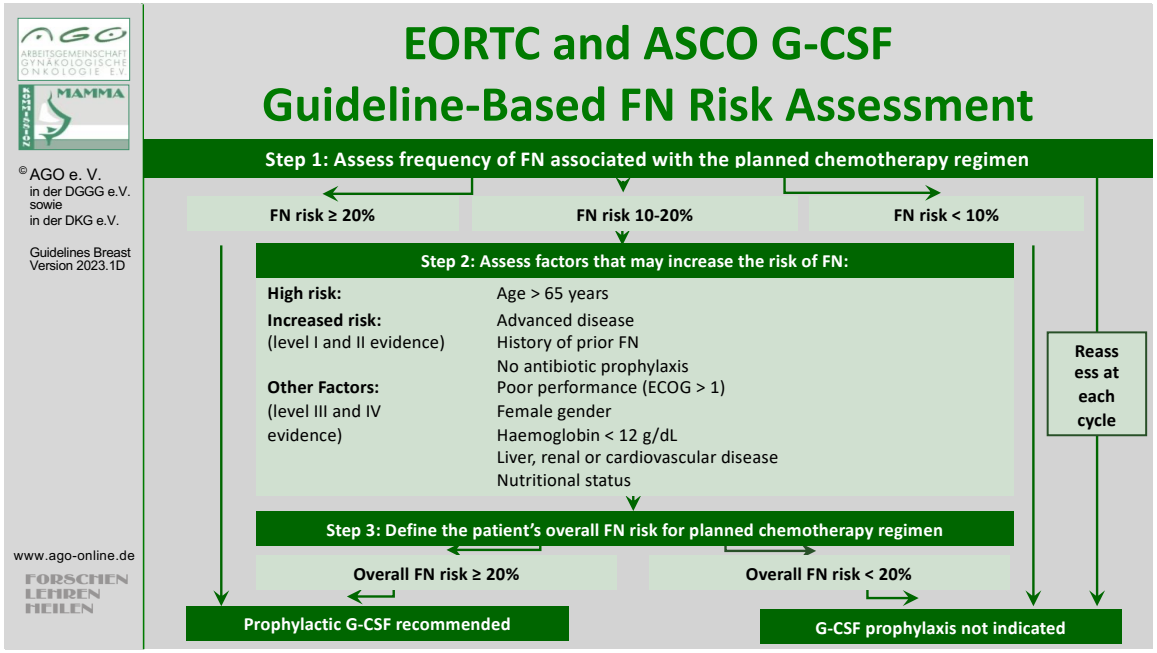

EORTC and ASCO G-CSF Guideline-Based FN Risk Assessment

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4. Nebenwirkungen am Ovar

Therapie-assoziierte Amenorrhoe (CRA, CIA, TIA)	Oxford LoE
▪ Eine CRA kann dauerhaft oder vorübergehend sein (abhängig vom Alter der Pat. und der Art der Chemotherapie)	2b
▪ Das Risiko der CRA steigt mit dem Alter / Therapiedauer	2b
▪ CRA ist ein (unsicherer) Surrogatmarker für Menopause und Fertilität	5
▪ Eine adjuvante endokrine Therapie mit einem GnRHa induziert eine reversible Amenorrhoe, und verschiebt eine Konzeption in eine weniger fertile Phase	5
▪ Die Ovarialreserve der nach Chemotherapie prämenopausal gebliebenen Frauen ist reduziert	2b
▪ CRA ist mit einer verbesserten Prognose (DFS / OS) assoziiert	1b

Synonyma: Chemotherapie / Therapie-induzierte Amenorhoe (TIA/CIA)

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Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

5. Psychiatrische Erkrankungen

- Depression
- Fatigue
- Kognitive Störungen
- Schlafstörungen

(Therapie-assoziierte) Depression

	Oxford LoE	Oxford GR	Oxford AGO
▪ **Depressive Episoden bei 20–30 % der Mammakarzinompatientinnen**	2a	B	
▪ **Psychosoziale Interventionen verbessern Depression, allerdings ohne günstige Auswirkungen auf Mortalität**	1b	A	
▪ **Antidepressiva können Depression bei Brustkrebspatientinnen verbessern**	1b	A	
▪ **Körperliches Training kann Depression bei Brustkrebspatientinnen verhindern**	2b	B	+

Statements 1-4

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meta-analysis. PLoS One. 2012;7(1):e30955. doi: 10.1371/journal.pone.0030955.
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Guidelines Breast
Version 2023.1D

(Therapie-assoziierte) Fatigue

	Oxford		
	LoE	GR	AGO
▪ Fatigue häufiges Symptom bei Brustkrebspatientinnen (30–60 %)	2a	B	
▪ Ausschluss anderer Ursachen (Anämie, Tumorausdehnung, Begleiterkrankungen, Medikamente) für Fatigue	1a	A	++
▪ Gezielte psychosoziale Interventionen können Fatigue lindern	1a	A	++
▪ Körperliches Training kann Fatigue verbessern	1b	D	+
▪ Yoga kann Fatigue verbessern	2b	B	+
▪ Methylphenidate oder Kortikosteroide (Kurzzeit-Gabe) können Fatigue verbessern	1a	D	+

Guideline:
1. Fabi A, Bhargava R, Fatigoni S, et al. Cancer-related fatigue: ESMO Clinical Practice Guidelines for diagnosis and treatment. Ann Oncol 2020;31:713-723.

2. S3-Leitlinie: Supportive Therapie:Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3 – Februar 2020
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Fatigue is frequently present…
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(Therapie-assoziierte) Kognitive Störungen

	Oxford LoE	Oxford GR
▪ **Therapiebedingte kognitive Störungen (sog. „Chemobrain“) häufig beschrieben (16–75 %)**	2a	B
▪ **Verhaltenstherapie kann kognitive Funktion verbessern**	2b	B
▪ **Methylphenidate kann kognitive Funktion bei Patientinnen mit Krebs verbessern**	3a	C
▪ **Unter Aromatasehemmertherapie wurden kognitive Störungen beobachtet (insbes. Wortgedächtnis)**	1a	B

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

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(Therapie-assoziierte) Schlafstörungen

	Oxford LoE	Oxford GR	AGO
▪ **Schlafstörungen häufig bei Mammakarzinom-patientinnen während und nach Therapie beschrieben (20–70 %)**	2a	B	
▪ **Verhaltenstherapie ist effektiv in der Behandlung von Schlafstörungen und Steigerung der Lebensqualität**	1b	A	++

Sleep disturbances are a common problem….

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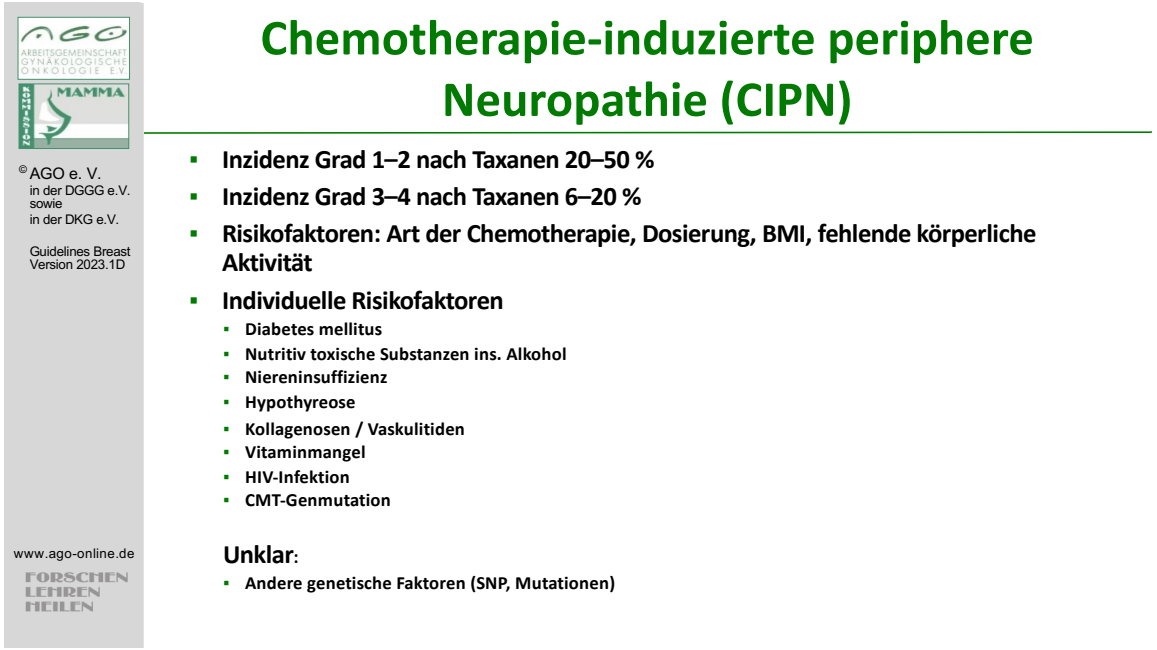
Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

6. Erkrankungen des Nervensystems

- **Chemotherapie induzierte periphere Neuropathie (CIPN)**



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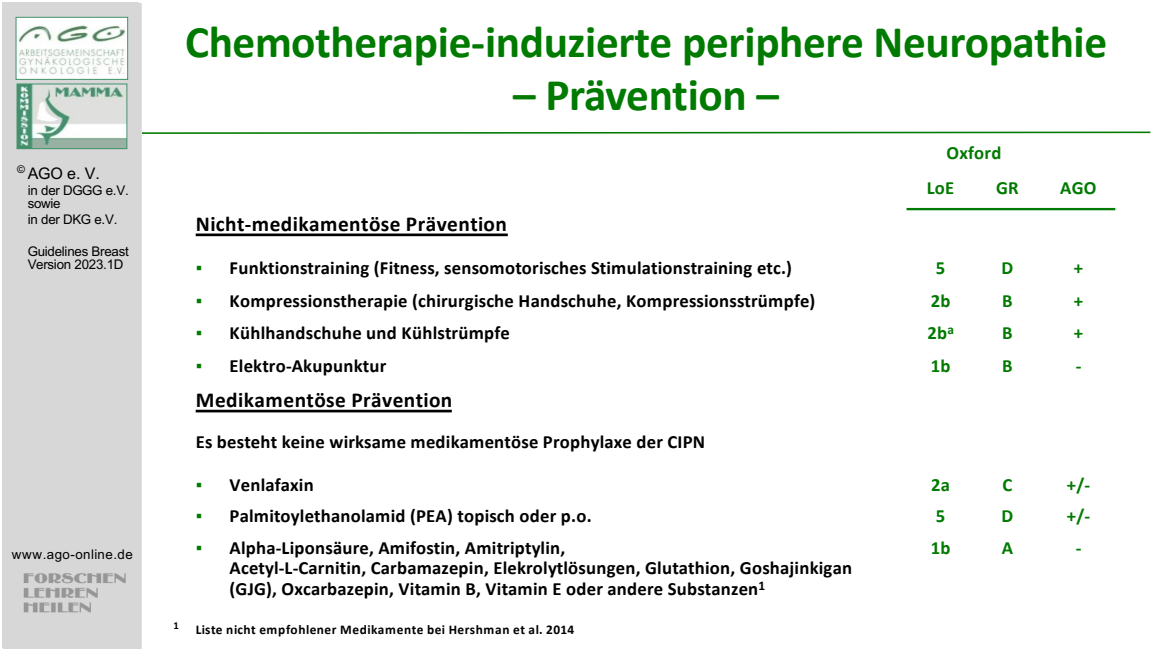

Chemotherapie-induzierte periphere Neuropathie – Prävention –

	Oxford LoE	Oxford GR	AGO
Nicht-medikamentöse Prävention			
▪ Funktionstraining (Fitness, sensomotorisches Stimulationstraining etc.)	5	D	+
▪ Kompressionstherapie (chirurgische Handschuhe, Kompressionsstrümpfe)	2b	B	+
▪ Kühlhandschuhe und Kühlstrümpfe	2b[a]	B	+
▪ Elektro-Akupunktur	1b	B	-
Medikamentöse Prävention			
Es besteht keine wirksame medikamentöse Prophylaxe der CIPN			
▪ Venlafaxin	2a	C	+/-
▪ Palmitoylethanolamid (PEA) topisch oder p.o.	5	D	+/-
▪ Alpha-Liponsäure, Amifostin, Amitriptylin, Acetyl-L-Carnitin, Carbamazepin, Elekrolytlösungen, Glutathion, Goshajinkigan (GJG), Oxcarbazepin, Vitamin B, Vitamin E oder andere Substanzen[1]	1b	A	-

[1] Liste nicht empfohlener Medikamente bei Hershman et al. 2014

Reviews/Leitlinien

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Nicht-medikamentöse Prävention

Funktionstraining

1. Kleckner I, Kamen JS, Peppone LJ et al (2016) A URCC NCORP nationwide randomized controlled trial investigating the effect of exercise on chemotherapy-induced peripheral neuropathy in 314 cancer patients. JClinOncol34(suppl): abstr 10000). http://meetinglibrary. asco.org/content/170470-176.
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<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
3. Gallagher HC, Gallagher RM, Butler M, et al.: Venlafaxine for neuropathic pain in adults. Cochrane Database Syst Rev. 2015 Aug 23;(8):CD011091.

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

2. Di Cesare Mannelli L, Pacini A, Corti F, et al.: Antineuropathic profile of N-palmitoylethanolamine in a rat model of oxaliplatin-induced neurotoxicity. PLoS One. 2015 Jun 3;10(6):e0128080.
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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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5. Schloss JM, Colosimo M, Airey C, et al.: A randomised, placebo-controlled trial assessing the efficacy of an oral B group vitamin in preventing the development of chemotherapy-induced peripheral neuropathy (CIPN). Support Care Cancer. 2017 Jan;25(1):195-204.
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Acetyl-L-Carnitin

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.
2. Hershman DL, Unger JM, Crew KD, et al.: Two-Year Trends of Taxane-Induced Neuropathy in Women Enrolled in a Randomized Trial of Acetyl-L-Carnitine (SWOG S0715). J Natl Cancer Inst. 2018 Jan 18.

Chemotherapie-induzierte periphere Neuropathie – Therapie –

	Oxford LoE	GR	AGO
Nicht-medikamentöse Therapie			
▪ Funktionstraining (Fitness, sensomotorisches Stimulationstraining etc.)	2a	C	+
▪ Physiotherapie / physikalische Therapie	5	D	+
▪ Akupunktur	2b	B	+
Medikamentöse Therapie			
▪ Menthol lokal (1 %), Capsaicin / Lidocain lokal	5	D	+
▪ Baclofen / Amitryptilin / Ketamin-Creme	2b	B	+
▪ Duloxetin zur Behandlung von Schmerzen durch CIPN	1b	B	+
▪ Opioide zur Behandlung von Schmerzen durch CIPN	5	D	+
▪ Palmitoylethanolamid (PEA) topisch oder p.o.	5	D	+/-
▪ Venlafaxin	5	D	+/-
▪ Gabapentin, Pregabalin	1b	B	+/-
▪ Amitryptilin / Nortripylin, Imipramin / Desipramin	1b	B	+/-
▪ Acetyl-L-Carnitin, Lamotrigin oder andere Substanzen[1]	1b	B	-

[1] Liste nicht empfohlener Medikamente bei Hershman et al. 2014

Reviews / Leitlinien

1. 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.
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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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Medikamentöse Therapie

Menthol / Capsaicin

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Rev. 2017 Jan 13;1:CD007393
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5. Anand P. Capsaicin and menthol in the treatment of itch and pain: recently cloned receptors provide the key. Gut. 2003 Sep;52(9):1233-5.

Baclofen/Amitryptilin/Ketamin-Creme

1. Barton DL, Wos EJ, Qin R, et al.: A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. Support Care Cancer. 2011 Jun;19(6):833-41.
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Duloxetin

1. Smith EM, Pang H, Cirrincione C, et al.: Alliance for Clinical Trials in Oncology. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA. 2013 Apr 3;309(13):1359-67

Akupunktur:

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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

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.
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Gabapentin, Pregabalin:

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Amitryptilin/Nortriptylin

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2. Hammack JE, Michalak JC, Loprinzi CL, et al.: Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum-induced peripheral neuropathy. Pain. 2002 Jul;98(1-2):195-203.

Acetyl-L-Carnitin, Lamotrigin oder andere Substanzen:

1. Rao RD, Flynn PJ, Sloan JA, et al.: Efficacy of lamotrigine in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled trial, N01C3. Cancer. 2008 Jun 15;112(12):2802-8
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Guidelines Breast
Version 2023.1D

7. Herzerkrankungen

Langzeittoxizität
Kardiotoxizität

	Oxford		
	LoE	GR	AGO
▪ Äquivalente Kardiotoxizität von Doxorubicin und Epirubicin in den empfohlenen Dosierungen (450-500 bzw. 900-1000 mg/m² kum. Dosis)	2b	B	
▪ Weniger Kardiotoxizität nach liposomalem Doxorubicin	1b	B	
▪ Risikofaktoren für Anthrazyklin- oder Trastuzumab-assoziierte Kardiotoxizität	2b	B	
▪ Alter, Übergewicht, Hypertonus, Hypercholesterinämie, vorbestehende Herzerkrankungen (inkl. grenzwertige LVEF), Diabetes mellitus			
Überwachung der Herzfunktion:			
▪ Standardisierte Echokardiographie (LVEF oder SF in %)	3b	C	+
▪ EKG (QT-Intervall)	1a	A	+
▪ Troponin I als Marker für Kardiotoxizität	2b	B	+/-
▪ Betablocker-Prophylaxe während Anthrazyklin-Therapie	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"

1. van Dalen EC Different anthracycline derivates for reducing cardiotoxicity in cancer patients. Cochrane Database Syst Rev. 2010 Mar 17;(3):CD005006. Review. Update in: Cochrane Database Syst Rev. 2010;(5):CD005006.

"Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently…"

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

1. Serrano C, Cortés J, De Mattos-Arruda L, et al.: Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors. Ann Oncol. 2011 Aug 9.
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*"*Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)"

1. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments: what the cardiologist needs to know. Nat Rev Cardiol. 2010 Oct;7(10):564-75. Review.
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Statement: Cardiac Monitoring (5 D ++)

Vote result of the AGO recommendation: 100%

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Toxizitätssteigerungen durch Behandlungskombinationen

	Oxford		
	LoE	GR	AGO
Kardiale Toxizität			
▪ Trastuzumab simultan zur Radiotherapie	2b	B	+
▪ Trastuzumab simultan zu Epirubicin	2b	B	+/-
▪ Trastuzumab simultan zu Doxorubicin	2b	B	-
▪ Anthrazykline simultan zur Radiotherapie	2c	C	-
Risiko Lungen- / Brustparenchymfibrosen			
▪ Tamoxifen simultan zu Radiotherapie	3	C	+/-
▪ Chemotherapie simultan zu Radiotherapie	1b	B	-

"Trastuzumab simultaneous to radiotherapy"

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"Trastuzumab simultaneous to epirubicin"

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"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.

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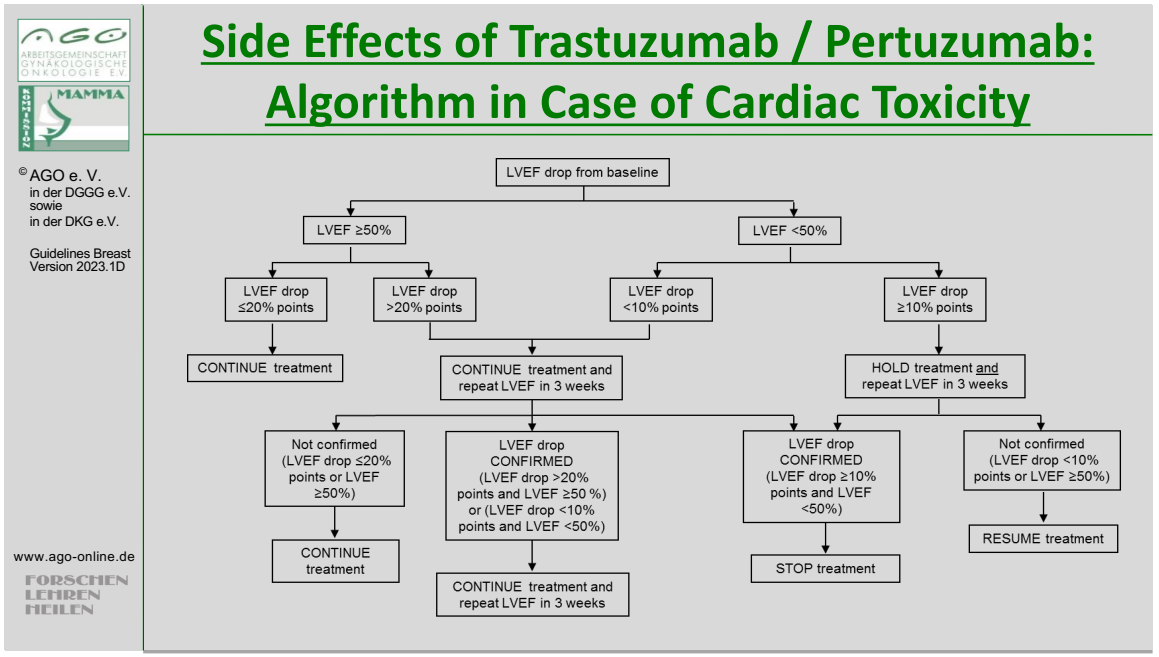
Side Effects of Trastuzumab / Pertuzumab: Algorithm in Case of Cardiac Toxicity



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Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

8. **Erkrankungen des Gastrointestinaltrakts**
   - **Nausea, Emesis (Übelkeit, Erbrechen)**
   - **Mukositis**
     - **Stomatitis (Everolimus)**
   - **Diarrhoe**
   - **Obstipation**

Antiemetische Therapie

nach MASCC und ASCO

	Oxford		
	LoE	GR	AGO
▪ **Abschätzen des emetogenen Potenzials des jeweiligen Chemotherapie-Protokolls**	5	D	++
▪ **Neurokinin-1-Rezeptor-Antagonisten**	1b	A	++
▪ **Dexamethason (auch bei Kombinationen mit ICPi)**	1a	A	++
▪ **5-HT_3-Antagonisten**	1b	A	++
▪ **Feste Kombination mehrerer Substanzen**	1b	A	++
▪ **Reserveantiemetika (Rescue Medication)**			
▪ Olanzapin	1b	A	+
▪ Levomepromazin, Benzodiazepine	3b	C	+
▪ Cannabinoide, Ingwer	3b	C	+/-

ICPi = Immun-Checkpoint Inhibitor

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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.

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

Guidelines Breast
Version 2023.1D

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

ACUTE Nausea and Vomiting: SUMMARY

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

5-HT$_3$ = serotonin$_3$ receptor antagonist	DEX = DEXAMETHASONE	NK$_1$ = neurokinin$_1$ receptor antagonist such as APREPITANT or FOSAPREPITANT or ROLAPITANT or NEPA (combination of netupitant and palonosetron)	OLZ = OLANZAPINE	DOP = dopamine receptor antagonist

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

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

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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

Antiemetic Therapy

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

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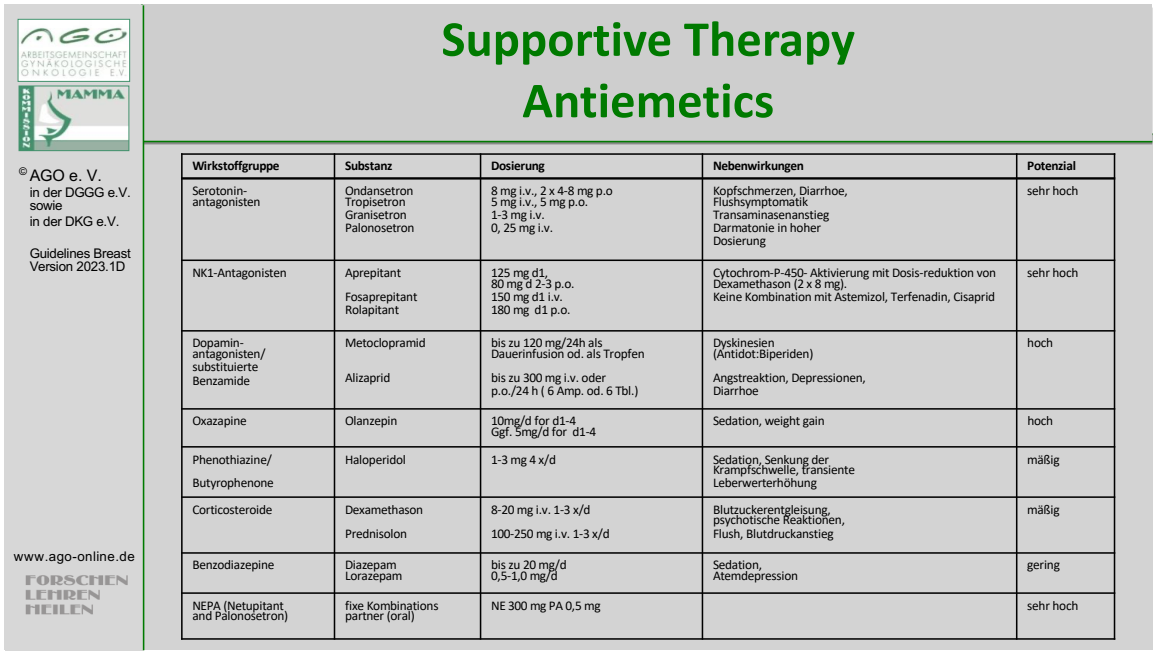

Wirkstoffgruppe	Substanz	Dosierung	Nebenwirkungen	Potenzial
Serotonin-antagonisten	Ondansetron Tropisetron Granisetron Palonosetron	8 mg i.v., 2 x 4-8 mg p.o 5 mg i.v., 5 mg p.o. 1-3 mg i.v. 0, 25 mg i.v.	Kopfschmerzen, Diarrhoe, Flushsymptomatik Transaminasenanstieg Darmatonie in hoher Dosierung	sehr 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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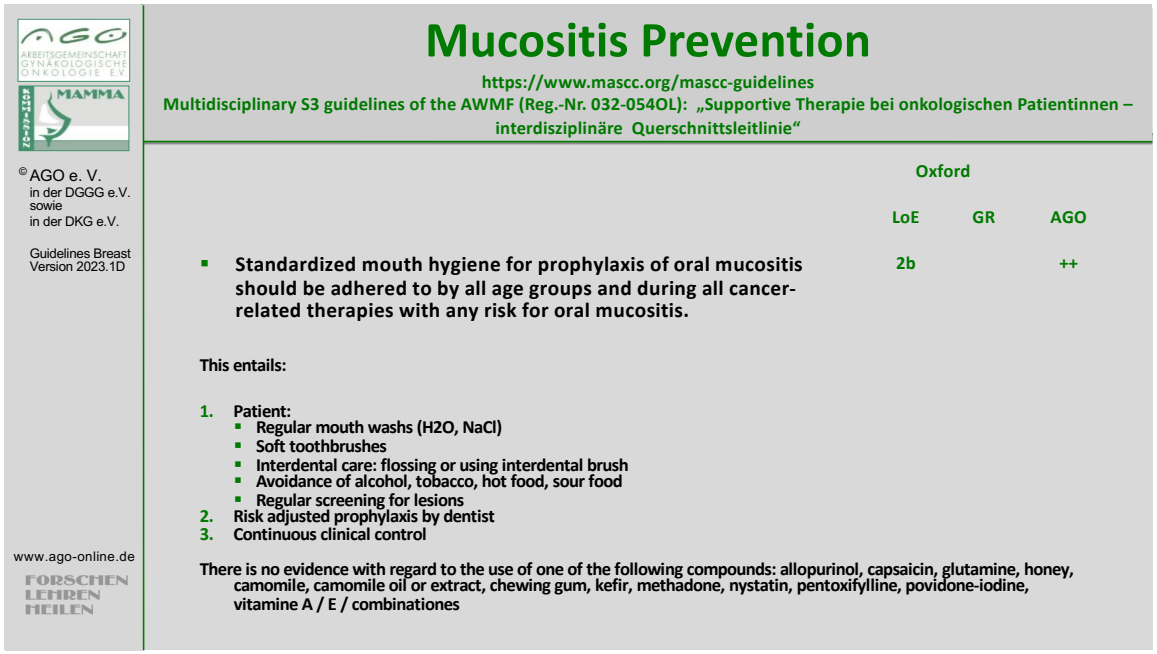

Relevant practice guideline

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)

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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

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9. Yarom, N., A. Ariyawardana, A. Hovan, et al.: Systematic review of natural agents for the management of oral mucositis in cancer patients. Support Care Cancer 2013;21(11):3209-21.
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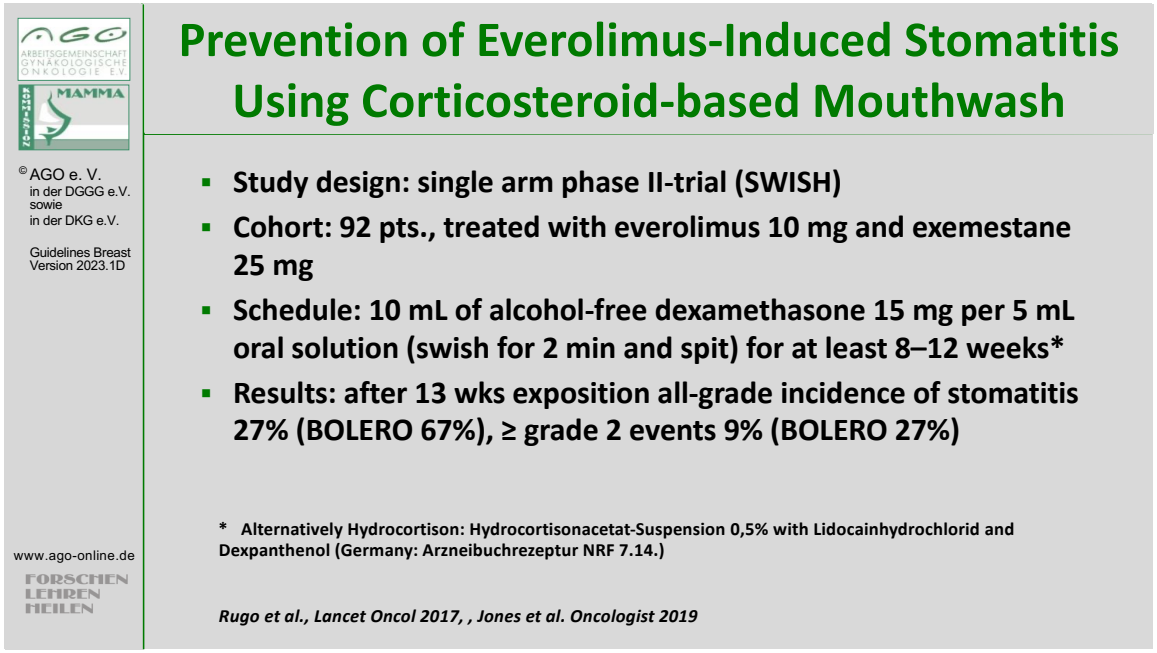

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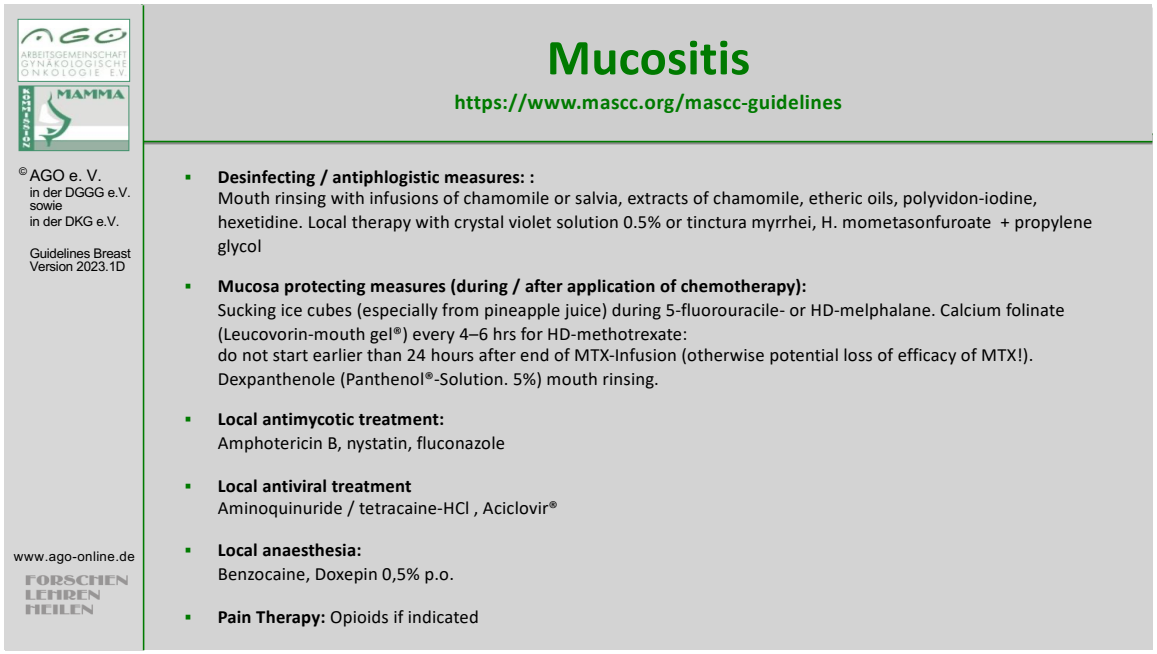

Relevant practice guideline

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

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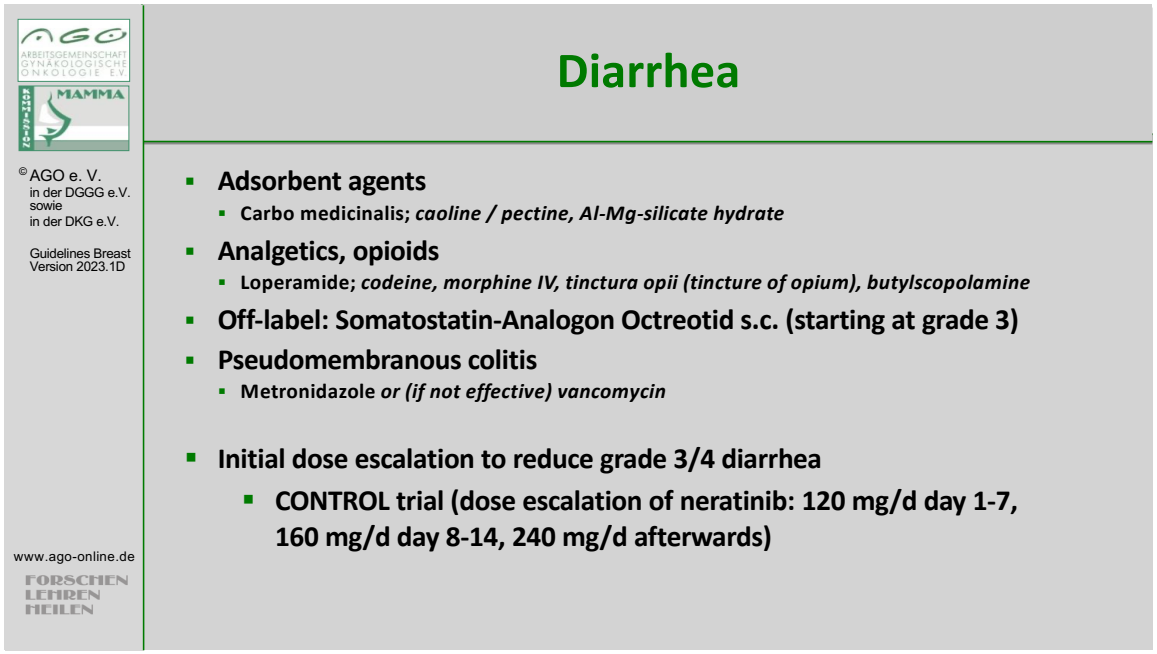

Relevant practice guideline

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.
2. Stein A, Voigt W, Jordan K. Chemotherapy-induced diarrhea: pathophysiology, frequency and guideline-based management Ther Adv Med Oncol 2010:2(1) 51-63
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.
4. Hoff, P. M., D. F. Saragiotto, C. H. Barrios, et al. (2014). "Randomized Phase III Trial Exploring the Use of Long-Acting Release Octreotide in the Prevention of Chemotherapy-Induced Diarrhea in Patients With Colorectal Cancer: The LARCID Trial." J Clin Oncol 2014:32;1006-11
5. Kee, B. K., J. S. Morris, R. S. Slack, et al. "A phase II, randomized, double blind
6. trial of calcium aluminosilicate clay versus placebo for the prevention of diarrhea in patients with metastatic colorectal cancer

treated with irinotecan." Support Care Cancer 2015:23;661-70.
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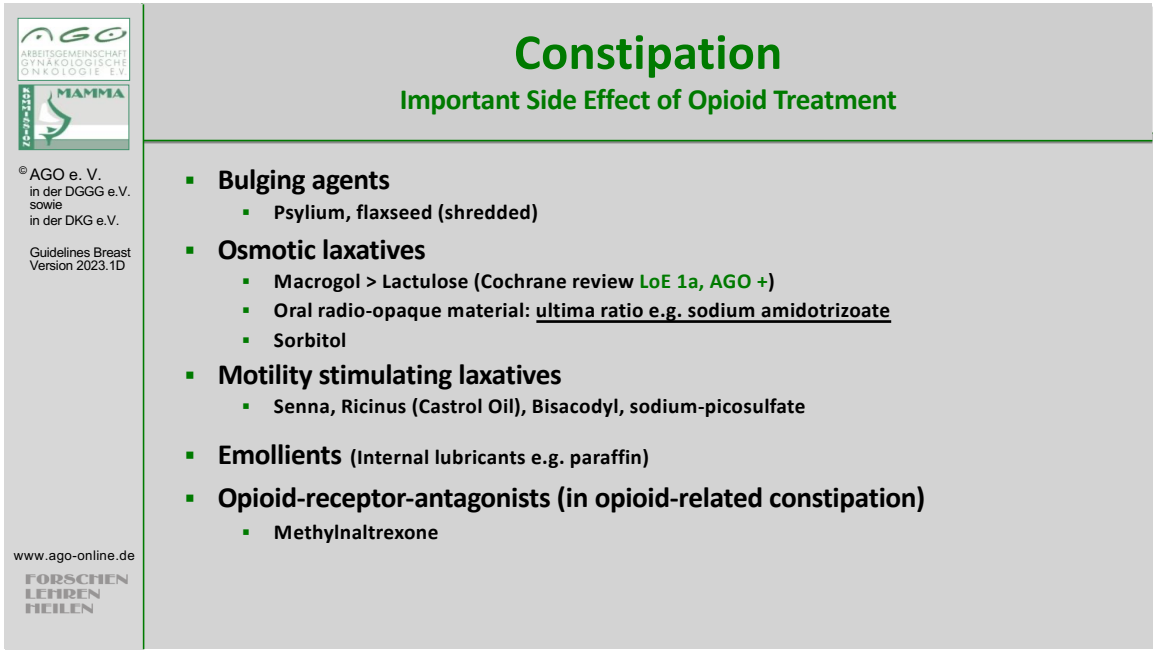
8. Barcenas CH, Hurvitz SA, Di Palma JA, et al. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: the CONTROL trial. Ann Oncol 2020;31:1223-1230.



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)

9. Erkrankungen der Haut und des Unterhautgewebes

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)

Hauttoxizität

	Oxford		
	LoE	GR	AGO
▪ Vermeidung einer ausgeprägten chemotherapie-induzierten Alopezie durch Kopfhautkühlung*	1b		+/-
▪ Eine Prophylaxe des HFS mit harnstoffhaltigen 5-10 % Cremes kann erfolgen (mehrfach tägl.)	1b		+
▪ Unter Docetaxel sollte eine Prophylaxe der Nagelveränderungen / HFS durch Kühlung erfolgen	2b		+

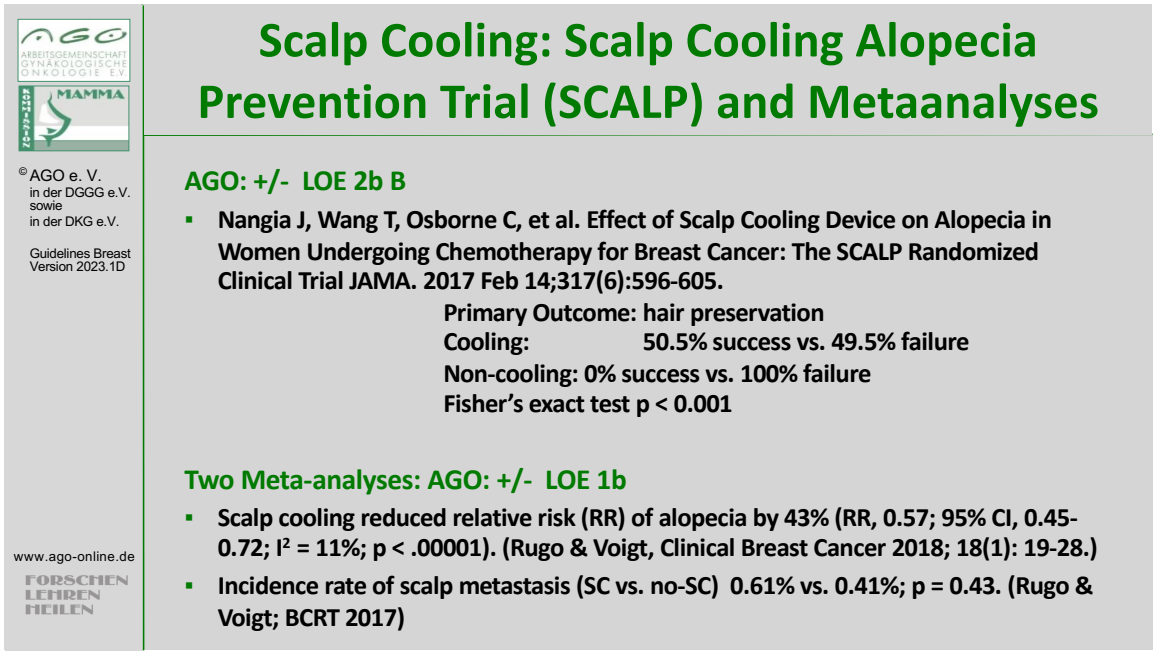
* Substanz- und regimeabhängig

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.

10. Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen

(siehe Kapitel Osteoonkologie)

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. Allgemeine Erkrankungen und Beschwerden am Verabreichungsort

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)

Paravasate mit potenziell nekrotisierenden Substanzen (Anthracycline, Taxane, Vinorelbin)

	Oxford		
	LoE	GR	AGO
▪ **Dexrazoxane zur Behandlung von Anthracyclin-Paravasaten (Ausnahme liposomales A)**	2b	B	++
▪ **Hyaluronsäure zur Behandlung von Taxan / Vinorelbin-Paravasaten (off-label use)**	3b	B	+

Relevant practice guideline:

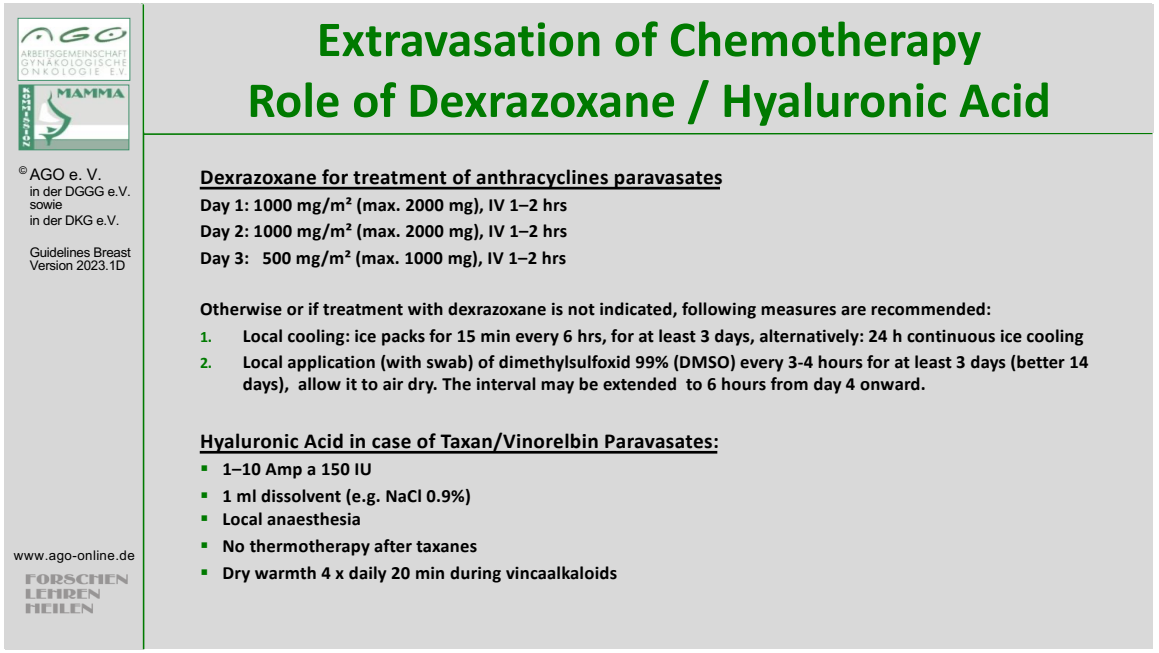
1. Hensley ML, Hagerty KL, Kewalramani T et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol. 2009 Jan 1;27(1):127-45.
2. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, 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)

12. Lunge

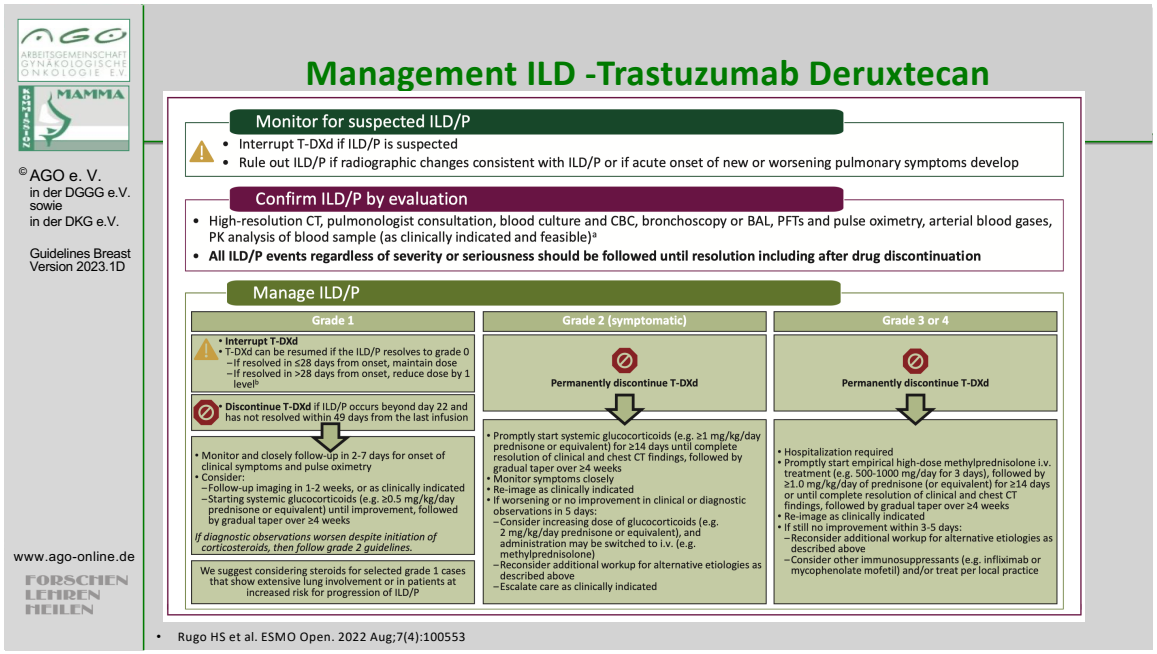
Relevant practice guideline

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)

Medikamenten-induzierte Pneumonitis, Interstitielle Lungenerkrankung (ILD)

	Oxford		
	LoE	GR	AGO
▪ **Diagnostische Abklärung mittels CT-Thorax**	1a	B	++
Therapie je nach Schweregrad und auslösender Noxe*			
▪ **Kortikosteroidtherapie (Beginn mit ≥ 0,5 mg/kg/d Prednisolon-Äquivalent)**	1a	B	++
▪ **Dosisunterbrechung bzw. Therapieabbruch***			++
▪ **(s. jeweilige Fachinformation)**			

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.

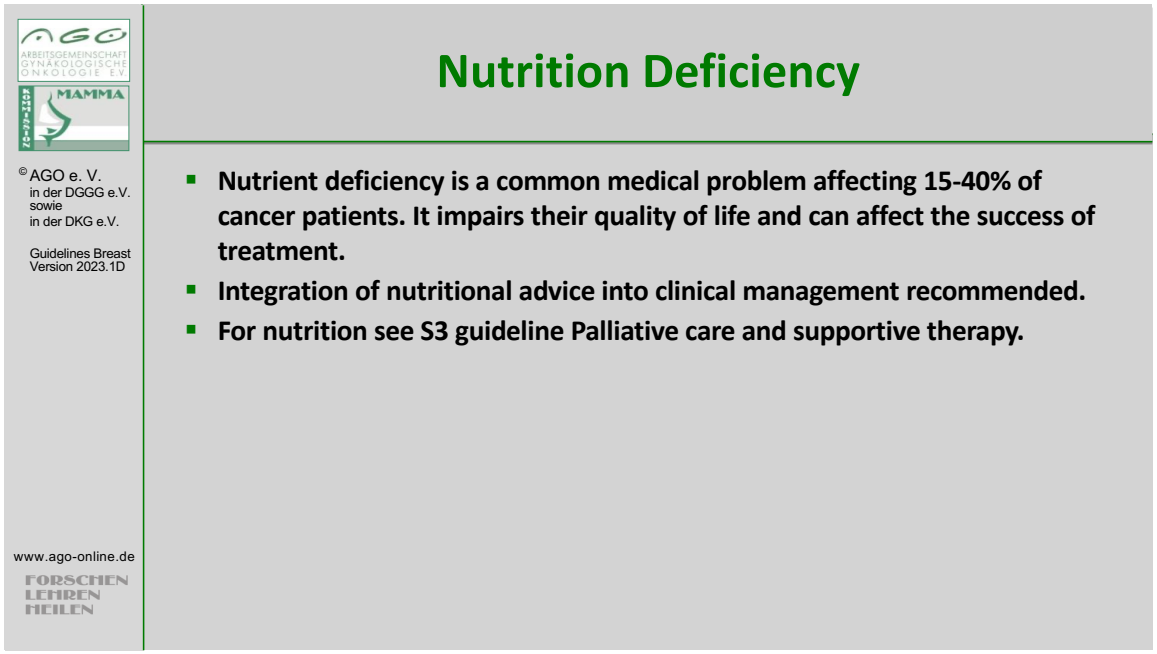
Andere supportive und palliative Fragestellungen

Guidelines Breast
Version 2023.1D

- **Seltene Symptome (aus der ESMO-Leitlinie für orphan symptoms 2020):**
  - **Muskelkrämpfe**
  - **Myoklonus**
  - **Geschmacksveränderungen**
  - **Trockener Mund (Xerostomie)**
  - **Hustenreiz, Schluckauf**
  - **Rectal tenesmus**
  - **Restless legs-Syndrom**

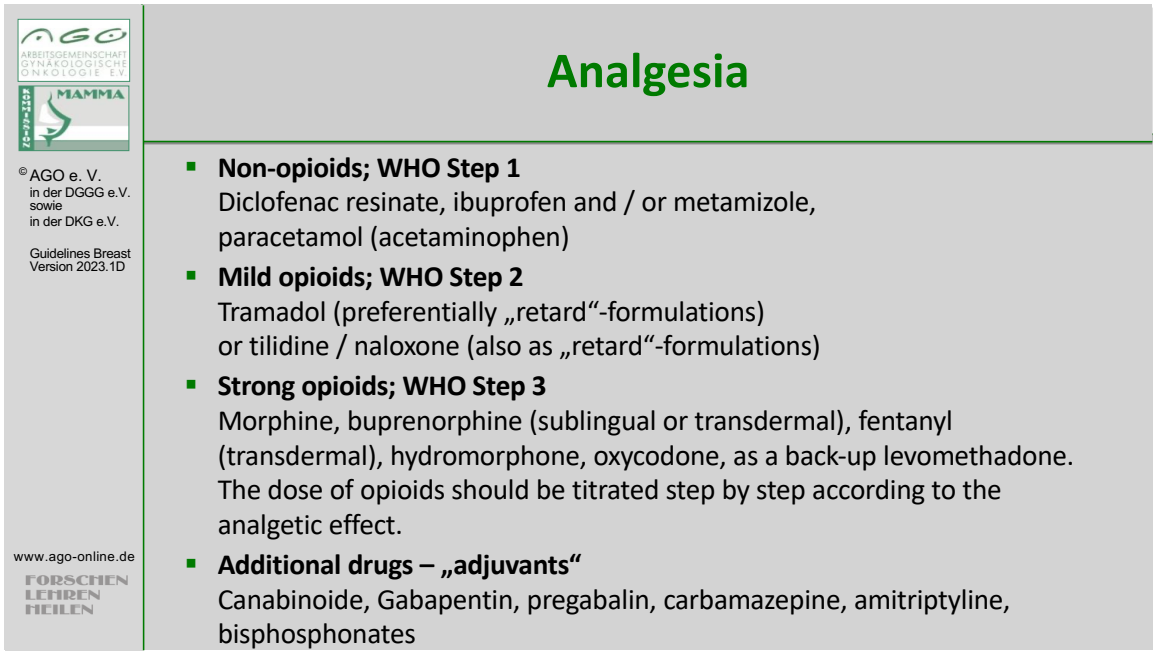
- **Weitere Fragestellungen**
  - **Ernährung**
  - **Schmerztherapie**
  - **Palliative Care**

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.



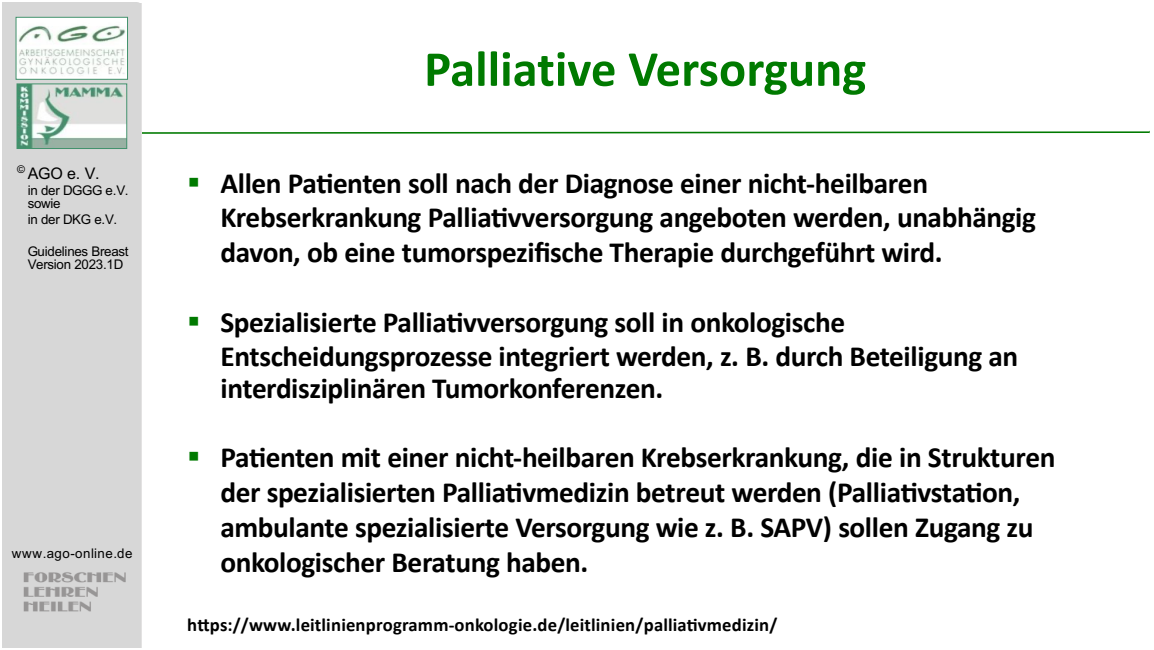
Klinische Ernährung

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)



Palliative Versorgung

- **Allen Patienten soll nach der Diagnose einer nicht-heilbaren Krebserkrankung Palliativversorgung angeboten werden, unabhängig davon, ob eine tumorspezifische Therapie durchgeführt wird.**
- **Spezialisierte Palliativversorgung soll in onkologische Entscheidungsprozesse integriert werden, z. B. durch Beteiligung an interdisziplinären Tumorkonferenzen.**
- **Patienten mit einer nicht-heilbaren Krebserkrankung, die in Strukturen der spezialisierten Palliativmedizin betreut werden (Palliativstation, ambulante spezialisierte Versorgung wie z. B. SAPV) sollen Zugang zu onkologischer Beratung haben.**

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

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)