

Screened data bases

Pubmed 2007 - 2022, ASCO 2010 – 2022, SABCS 2010 – 2021, Cochrane Data Base (2019)

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 Therapie und Nebenwirkungsmanagement

■ Versionen 2002–2021:

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 / Rody / Schaller / Scharl / Schmidt
/ Schneeweiss / Schütz / Solomayer / Souchon / Stickeler / Thomssen /
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■ Version 2022:

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Leitlinien – Umfeld



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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, Santomaso 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)**

Toxizitätsbeurteilung															
<p>Akute Toxizität (nach WHO¹ oder NCI-CTC²)</p> <p>Akute Toxizität nach jedem Therapiezyklus abfragen und dokumentieren LoE 5 D AGO ++</p> <table border="1"> <thead> <tr> <th>Grad</th> <th>Notwendige Informationen</th> </tr> </thead> <tbody> <tr> <td>0 keine</td> <td>Beteiligte Organe</td> </tr> <tr> <td>1 mild</td> <td>Art der Toxizität</td> </tr> <tr> <td>2 mäßig</td> <td>Zeitintervall nach Behandlung</td> </tr> <tr> <td>3 ausgeprägt</td> <td>Effekt auf den Allgemeinzustand</td> </tr> <tr> <td>4 lebensbedrohlich</td> <td>Behandlungsnotwendigkeit</td> </tr> <tr> <td>5 therapiebedingter Tod</td> <td>Erreichen einer Verbesserung</td> </tr> </tbody> </table>		Grad	Notwendige Informationen	0 keine	Beteiligte Organe	1 mild	Art der Toxizität	2 mäßig	Zeitintervall nach Behandlung	3 ausgeprägt	Effekt auf den Allgemeinzustand	4 lebensbedrohlich	Behandlungsnotwendigkeit	5 therapiebedingter Tod	Erreichen einer Verbesserung
Grad	Notwendige Informationen														
0 keine	Beteiligte Organe														
1 mild	Art der Toxizität														
2 mäßig	Zeitintervall nach Behandlung														
3 ausgeprägt	Effekt auf den Allgemeinzustand														
4 lebensbedrohlich	Behandlungsnotwendigkeit														
5 therapiebedingter Tod	Erreichen einer Verbesserung														
<p>Langzeittoxizität (= Sekundärerkrankungen nach Tumorthherapie)</p> <p>Langzeitnachsorge und regelmäßige Dokumentation (symptomorientiert nach ICPC³ oder diagnoseorientiert nach ICD-10-GM⁴) LoE 5 D AGO ++</p>															

Akute Toxizität

1. WHO Handbook for reporting results of cancer treatment, NO 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/klasi/icd-10-gm/kodesuche/onlinefassungen/htmlgm2017/> (Download 18.01.2018)
3. Kenyon M, Mayer DK, Owens AK. Late and long-term effects of breast cancer treatment and surveillance management for the

general practitioner. J Obstet Gynecol Neonatal Nurs. 2014 May-Jun;43(3):382-98.

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



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Akute Toxizität (NCI CTCAE vs 5.0, 2017)

(Allgemeine Terminologiekriterien unerwünschter Ereignisse)

- **Grad 1**
Mild; asymptomatisch oder wenig symptomatisch; lediglich klinische oder diagnostische Beobachtung; eine Intervention ist nicht indiziert.
- **Grad 2**
Mäßig; minimale, lokale oder nicht-invasive Intervention notwendig; Beeinträchtigung des täglichen Lebens (wie Einkauf, Essenszubereitung etc. (*limiting age-appropriate instrumental ADL**)).
- **Grad 3**
Schwerwiegend oder medizinisch signifikant, aber nicht akut lebensbedrohlich; Klinikaufenthalt oder Verlängerung des Klinik-Aufenthaltes; physisch „außer Gefecht gesetzt“ (*limiting self care ADL***).
- **Grade 4**
Lebensbedrohliche Folgen; eine Intervention ist dringend notwendig
- **Grad 5**
Nebenwirkungsbedingter Tod

Activities of Daily Living (ADL)

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

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

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

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Substanz- / Kombinations-spezifische Nebenwirkungen

(teilweise lt. Fachinformationen gemäß MedDRA*)

* MedDRA - Medical Dictionary for Regulatory Activities

*MedDRA - Medical Dictionary for Regulatory Activities

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



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Chemotherapie – Akute Toxizitäten I

Substanz	Systemorganklasse											
	Infektionen und parasitäre Erkrank.	Neurologien, sek. Malignome	Blut, Lymphsystem	Immunsystem, Allergien	Endokrine Erkrank. lungen	Stoffwechsel- und Ernährungs-Stör.	Psychische Erkrankungen	Erkrankungen des Nervensystems	Augenerkrank.	Erkrank. des Ohrs und des Labyrinth	Herzkrankungen	Gefäßkrank.
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 (Epom)	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(1)	-	-	-(5)	-(5)	-(4)	-	2(5)	3(4)
Eribulin	4	-	4	-	-	5	4	5	4	4	4	4

Die Liste und Gradulierung der Nebenwirkungen ist nach Systemorganklassen, MedDRA-Terminologie und den folgenden Häufigkeitskategorien dargestellt:
 1. Sehr selten (< 1/10.000); 2. Selten (≥ 1/10.000 bis < 1/1.000); 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)


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=eebf22e78f1cc8d9935d59c087e80630146f49e>

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.
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.

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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.



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Chemotherapie – Akute Toxizitäten II

Substanz	Systemorganklasse										Besonderheiten
	Ern. d. Atmungs- trakt, Mediast.	Ern. d. G.-Traktes (Uterus/Fibrosen)	Leber- und Gallen- erkrankungen	Ern. d. Haut/Unter- haut (inkl. Alopie)	Stomatitis, Stö- runge u. Mundschleim- haut	Ern. der Nieren und Harnwege	Schwang.-, Wochen- bett u. perinatale E.	Ern. d. Geschlechts- organe u. Brustdrüse	Allg. Ern. u. Beschw. am Applikationsort	Kongenit., famili. und genet. Ern.	
Alkylantien											
Cyclophosphamid	2	4	4	5	-	5	-	4	5	-	Hyponatriämie
Antimetabolite											
Methotrexat	4	5	5	4	3	3	-	3	1	-	Mukositis, 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.)
Anthracycline / 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(6)	2(5)	- (4)	2(4)	-	-	-	-	Phlebitis, GI-Tox (PO), CIPN
Eribulin	5	5	4	5	5	4	-	-	5	-	Obstipation, CIPN

Die Liste und Gradulierung 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)

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

Quellen für die Fachinformationen (Download 19.01.2018)

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


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?elD=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/Abiraxane-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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11. NCCN, editor. NCCNR Practice Guidelines in Oncology - v.1.2011; Myeloid Growth Factors. National Comprehensive Cancer Network 2011. 18-7-2011.
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Zusatzdiagnostik* vor Beginn einer 5-FU (i.v.) / Capecitabin-Therapie

	Oxford		
	LoE	GR	AGO
1a	A	++	

- **DPD (Dihydropyrimidin-Dehydrogenase) - Defizienz**
Testung (DPYD-Genotyp bzw. Phänotyp)

Phänotypische Untersuchungsverfahren (Uracil im Plasma / Urin, Bestimmung der DPD-Aktivität) weniger gut standardisiert

Systematischer Review (Krebspatienten unter 5-FU Behandlung):**

- DPYD-Varianten (heterozygot oder homozygot) 4,1 %
- Therapieassoziierte Mortalität 2,3 % (vs. 0,1 % ohne DPYD-Variante) - Risiko für therapie-bedingten Todesfall 25,6-fach erhöht

* Empfehlung gemäß Rote-Hand-Brief vom 4.6.2020

** Sharma et al, Oncologist 2021

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)
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3. Sharma BB, Rai K, Blunt H et al. Pathogenic DPYD Variants and Treatment-Related Mortality in Patients Receiving Fluoropyrimidine Chemotherapy: A Systematic Review and Meta-Analysis. Oncologist 2021 Dec;26(12):1008-1016.

Endokrine Therapie – Toxizitäten

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Substanz	Infektionen und parasitäre Erkr.	Neubildungen, sek. Malignome	Blut, Lymphsystem	Immunsystem, Allergien	Endokrine Erkran- kungen	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	-	-	4	5	5	4	-	4	5
Exemestan	-	-	4	-	-	4	5	4	4	-	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 Gastrointest.-trakts	Leber- und Gallen- erkrankungen	Erkr. Haut u. Unterhautgewebe	Stimmritmus-, Blasen- u. Nieren- u. Harnwege	Erkr. der Nieren und Harnwege	Schwang.-, Wochen- bett u. perinatale E.	Erkr. d. Geschlechts- organe / 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	-	-	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 Gradulierung 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)

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 / Antikörper-Wirkstoff-Konjugate (HER2+)		
	Oxford	
	LoE	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
Trastuzumab-Emtansin (T-DM1)		
▪ Thrombozytopenie, Anstieg Leberenzyme Fieber, Kopfschmerzen, Pneumonitis, Polyneuropathie	1b	A
Trastuzumab-Deruxtecan		
▪ Interstitielle Lungenerkrankung, Neutropenie, Übelkeit, Alopezie	1b	A

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Cardiotoxicity

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2. Procter M, Suter TM, de Azambuja, et al: Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin Adjuvant (HERA) trial. J Clin Oncol 28: 3422-3428, 2010
3. Russell SD, Blackwell KL, Lawrence J, et al: Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: a combined review of cardiac data from the National Surgical Adjuvant breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. J Clin Oncol 28: 3416-3421, 2010
4. Higa GM, Abraham J: Biological mechanisms of bevacizumab-associated adverse events. Expert. Rev Anticancer Ther 2009;9:999–1007
5. Martin M, Esteva FJ, Alba E, et al: Minimizing cardiotoxicity while optimizing treatment efficacy with trastuzumab: review and expert recommendations. Oncologist 2009;14:1–11
6. Untch M, Eidtmann H, du Bois A, et al: Cardiac safety of trastuzumab in combination with epirubicin and cyclophosphamide in women with metastatic breast cancer: results of a phase I trial. Eur J Cancer 2004; 40:988–97
7. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al.: Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017

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

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

Troponin I

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

Lapatinib

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

Pertuzumab


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

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.
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Trastuzumab-Deruxtecan

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2. 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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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 %

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

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

1. Chan A, Delagoge S, Holmes FA et al Neratinib after trastuzumab –based adjuvant therapy in patients with HER2 positive breast cancer (ExteNET): a multicentr, randomized, double.-blind, placebo controlled , phase III trial. Lancet Oncol 17(39: 367-377, 2016
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3. Neratinib: FDA Produktinformation 2017

	Nebenwirkungen anti-HER2 TKI Tucatinib + Trastuzumab + Capecitabin		
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	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.

<div>  <h2>Nebenwirkungen CDK4/6-Inhibitoren (Palbociclib / Ribociclib / Abemaciclib)</h2> </div>			
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UE, %	Alle Grade	Grad 3	Grad 4
Neutropenie	79,5/74,3/41,3	56,1/49,7/19,6	10,4/9,6/1,5
Leukopenie	39,0/32,9/20,8	24,1/19,8/7,3	0,7/1,2/0,3
Anämie	24,1/18,6/28,4	5,2/0,9/5,8	0,2/0,3/0
Thrombopenie	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
Übelkeit	35,1/51,5/38,5	0,2/2,4/0,9	0/0/0
Erbrechen	15,5/29,3/28,4	0,5/3,6/1,2	0/0/0
Diarrhoe	26,1/35,0/81,3	1,4/1,2/9,5	0/0/0
Alopezie	32,9/33,2/26,6	-	-
Exanthem	17,8/17,1/14,0	0,9/0,6/1,0	0/0/0
ALT Erhöhung	9,9/15,6/15,6	1,7/7,5/5,8	0,1/1,8/0,3
AST Erhöhung	9,7/15,0/15,0	2,5/4,8/3,0	0/0,9/0
Infektionen	60/50,3/39,1	6,0/3,6/4,0	1/0,6/0,9
QT Prolongation	N.A./7,5/N.A.	N.A./3,0/N.A.	N.A./0/N.A.
Palbociclib/Ribociclib/Abemaciclib			

Palbociclib


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

Ribociclib

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

Abemaciclib

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



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

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

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

Overall incidence:

Systematic review of published data:


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

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

Monarch-E:

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

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
3. Jahan N, Wongsasengsak 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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Venous Thromboembolic Events: Adjuvant Abemaciclib (Monarch-E trial)


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

Characterization of VTE (DVT or PE)*

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

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

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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QT-Zeit-Verlängerung: Ribociclib vs. Placebo

- **Post-baseline Verlängerung der QT-Zeit > 480 msec 6,9 % vs. 1,2 %**
- **Post-baseline Verlängerung der QT-Zeit > 500 msec 1,5 % vs. 0,3 %**
- **Therapieabbruch wegen QT Zeit Verlängerung 0,3 % vs. 0,6 %**
- **QT-Verlängerung ist nicht mit klinischer Symptomatik assoziiert, aber mit einem erhöhten Risiko für lebensbedrohliche Arrhythmien („torsades de pointes“, TdP)**

1. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomized phase 3 trial. *Lancet Oncol.* 2018 Jul;19(7):904-915.
2. Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone-Receptor-Positive, Human Epidermal Growth Factor Receptor-2 Negative Advanced Breasts Cancer: MONALEESA-3. *J Clin Oncol.* 2018 Aug 20;36(24):2465-2472.
3. Durairaj C, Ruiz-Garcia A, Gauthier ER, et al. Palbociclib has no clinically relevant effect on the QTc interval in patients with advanced breast cancer. *Anticancer Drugs.* 2018 Mar;29(3):271-280.
4. Trinkley KE, Page RL 2nd, Lien H, et al. QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. *Curr Med Res Opin.* 2013 Dec;29(12):1719-26.


Nebenwirkungen mTOR-Inhibitor (Everolimus)			
	UE, %		
	Alle Grade (%)	Grad ≥ 3 (%)	
Stomatitis	11,6	1,6	
Ausschlag	7,4	0,02	
Anämie	3,3	1,3	
Fatigue	6,8	0,8	
Übelkeit	5,6	0	
Erbrechen	2,9	0	
Diarrhoe	6,2	0,02	
Appetitminderung	6,0	0,02	
Kopfschmerz	3,9	0	
Gewichtsverlust	3,9	0	
Dyspnoe	3,8	0,08	
Arthralgie	3,3	0	
Epistaxis	3,1	0	
Ödem	2,9	0	
Obstipation	2,6		
Pyrexie	2,9	0	
Husten	4,5	0	
ALT Erhöhung	2,6	0	
Pneumonitis	0,2	0	
Asthenie	2,4	0,04	
Dysgeusie	4,3	0	



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

Alpelisib + Fulvestrant

UE, %	Alle Grade	Grad ≥ 3
Hyperglykämie	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 %
Fatigue	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

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

			<h2 style="text-align: center;">Nebenwirkungen PARP-Inhibitoren – Olaparib, Talazoparib</h2>		
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			<h3 style="text-align: center;">Olaparib</h3>		
UE, %	Alle Grade (%)	Grad ≥ 3 (%)			
Jegliche UE	97,1	36,6			
Neutropenie	27,3	9,3			
Anämie	40,0	16,1			
Fatigue	28,8	2,9			
Übelkeit	58,0	0			
Erbrechen	29,8	0			
Diarrhoe	20,5	0,5			
Appetitminderung	16,1	0			
Kopfschmerz	20,0	1,0			
Pyrexie	14,1	0			
Husten	17,1	0			
ALT Erhöhung	11,2	1,5			
AST Erhöhung	9,3	2,4			
PPE	0,5				
Therapieabbruch	4,9				
			<h3 style="text-align: center;">Talazoparib</h3>		
UE, %	Alle Grade (%)	Grad ≥ 3 (%)			
Jegliche UE	98,6	25,5			
Neutropenie	34,6	20,9			
Febrile Neutropenie	0,3	0,3			
Anämie	52,8	39,2			
Fatigue	50,3	1,7			
Übelkeit	48,6	0,3			
Erbrechen	24,8	2,4			
Diarrhoe	22,0	0,7			
Appetitminderung	21,3	0,3			
Kopfschmerz	32,5	1,7			
Rückenschmerzen	21,0	2,4			
Dyspnoe	17,5	2,4			
Pleuraerguß	2,1	1,7			
PPE	1,4	0,3			
Therapieabbruch	5,9				

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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



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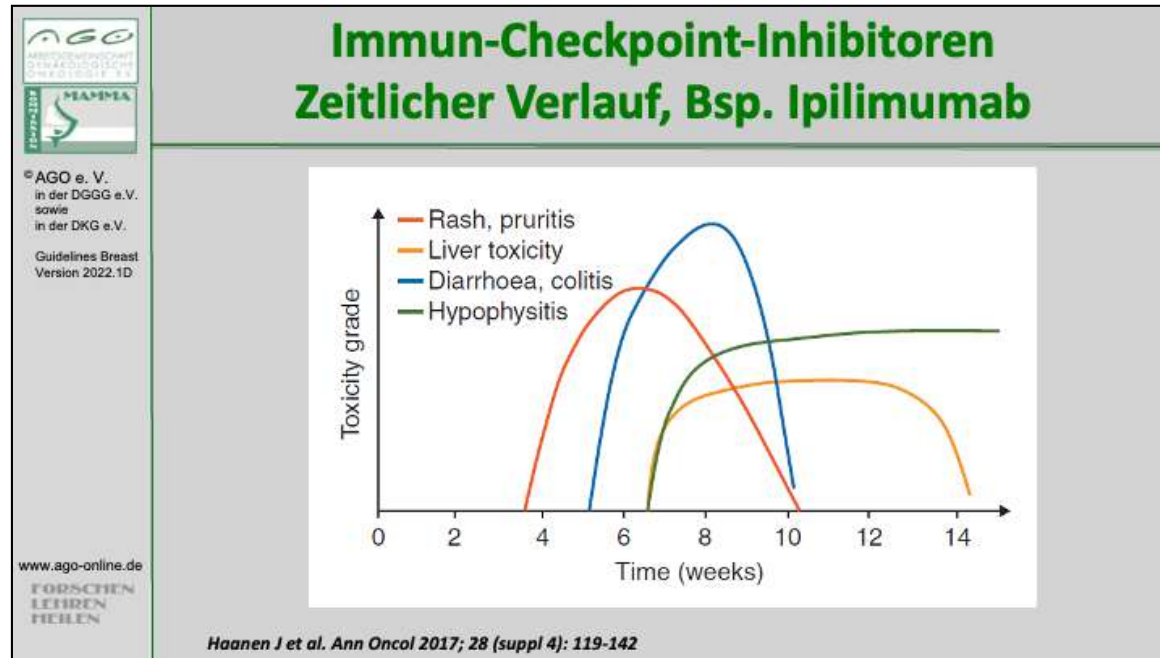
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Immun-Checkpoint-Inhibitoren

- **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
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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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Immun-Checkpoint-Inhibitoren

- **Nebenwirkungen ≥ Grad 3**
 - Diarrhoe
 - Fatigue
 - Hautveränderungen (v. a. makulopapulöses Exanthem, Vitiligo, Epidermolysen)
 - Pneumonitis
 - Colitis
 - Hypophysitis
 - Hepatitis
 - Nephritis
 - Thyreoiditis (Hyper- / Hypothyreose)
 - Guillain-Barré-Syndrom
 - Kardiomyopathie
 - Myopathie – Myalgie – Rhabdomyolyse
 - Uveitis

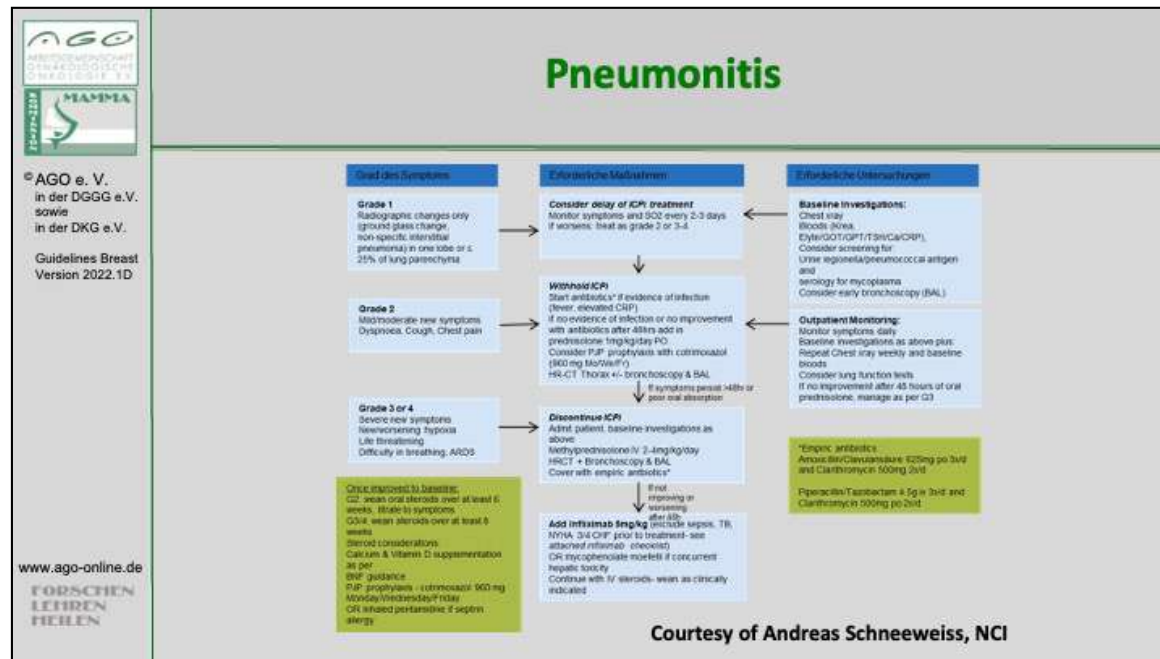
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	Immun-Checkpoint-Inhibitoren Toxizitäten (Gesamt in %)		
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	Diarrhö	18,6 %	13 %
	Kolitis	1,1 %	2 %
	Hautausschlag	18,6 %	15 %
	Hepatotoxizität	0,3 %	1 %
	Hypophysitis	<0,1 %	< 1 %
	Pneumonitis	3,1 %	3 %
	Schilddrüsen- fehlfunktion	Hyper- 1,7 %	Hyper- 1 %
		Hypo- 4,7 %	Hypo- 4 %
	Nephritis	< 1 %	1 %
	Neuropathien	0,2 %	< 1 %
www.ago-online.de	Atezolizumab Fachinformationen 2018, Nivolumab, safety management BMS 2014, Pembrolizumab PI 2014		
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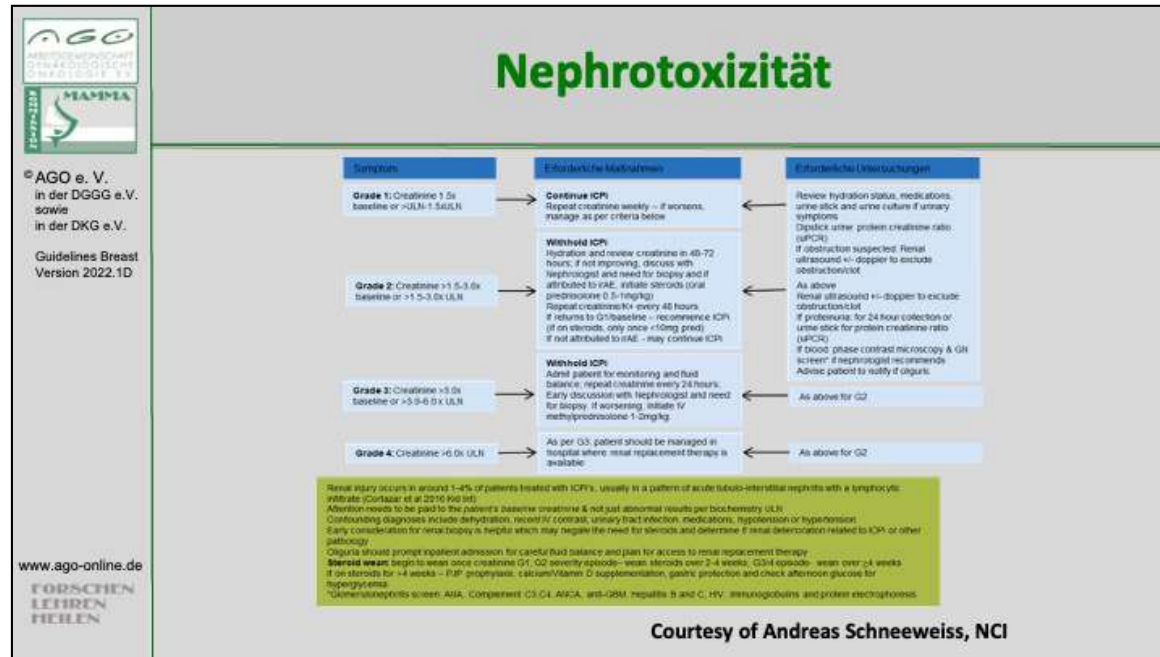
1. Atezolizumab: <https://www.fachinfo.de/suche/fi/021700>
2. Nivolumab: <https://www.fachinfo.de/suche/fi/020675>
3. Pembrolizumab: <https://www.fachinfo.de/suche/fi/020716>

 <h2>Immun-Checkpoint-Inhibitoren NW-Management - Grundsätze</h2>	
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CTC AE-Grad	Management
1	<ul style="list-style-type: none"> Supportive Therapie Engmaschige Kontrollen Ausschluss Infektion Patientenaufklärung
2	<p>Wie Grad 1 aber</p> <ul style="list-style-type: none"> Pausierung der Therapie bis alle irAE Grad 0-1 Ggf Kortikosteroide
3	<ul style="list-style-type: none"> Supportive Therapie i. v.-Steroide (z. B. 1-2 mg/kg Prednisolon) <p>Wenn keine Besserung innerhalb 48 h:</p> <ul style="list-style-type: none"> Ggf zusätzliche andere Immunsuppression (Infliximab, MMF) Ggf organspezifische weitere Diagnostik (z. B. Koloskopie) Ggf Konsil Fachspezialist Ausschluss oder Behandlung von Infektion Absetzen der Therapie, ggf Fortsetzung, wenn CTC AE Grad 0,1 Langsames Ausschleichen der Steroide (3-6 Wochen)
4	Wie Grad 3 aber dauerhaftes Absetzen der Therapie

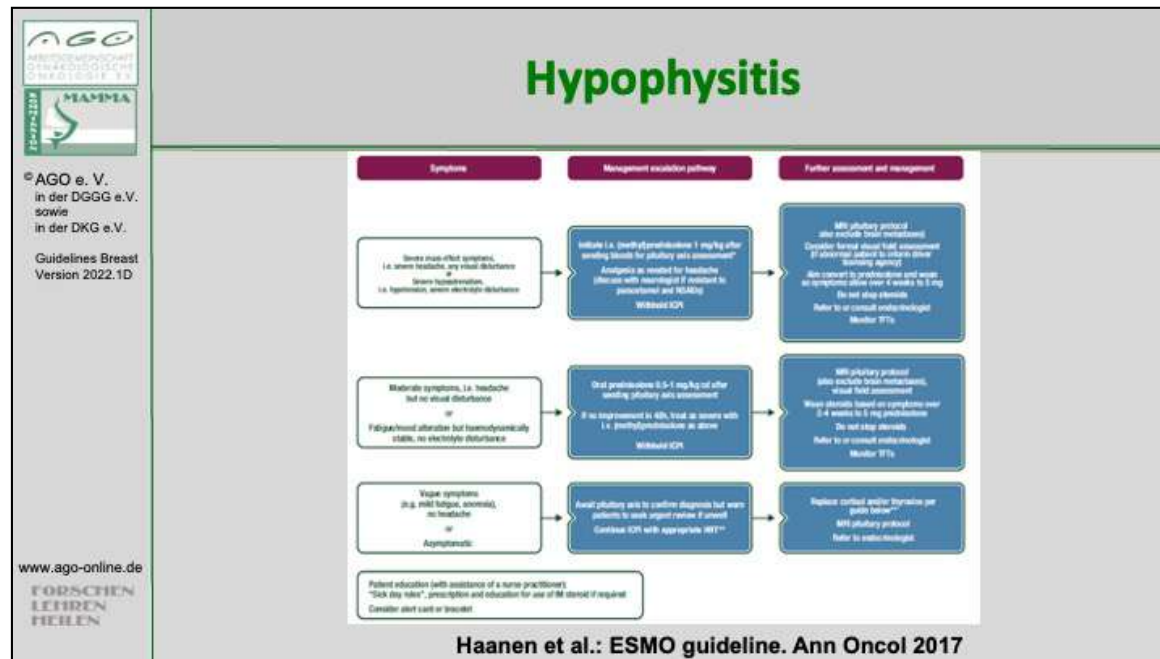
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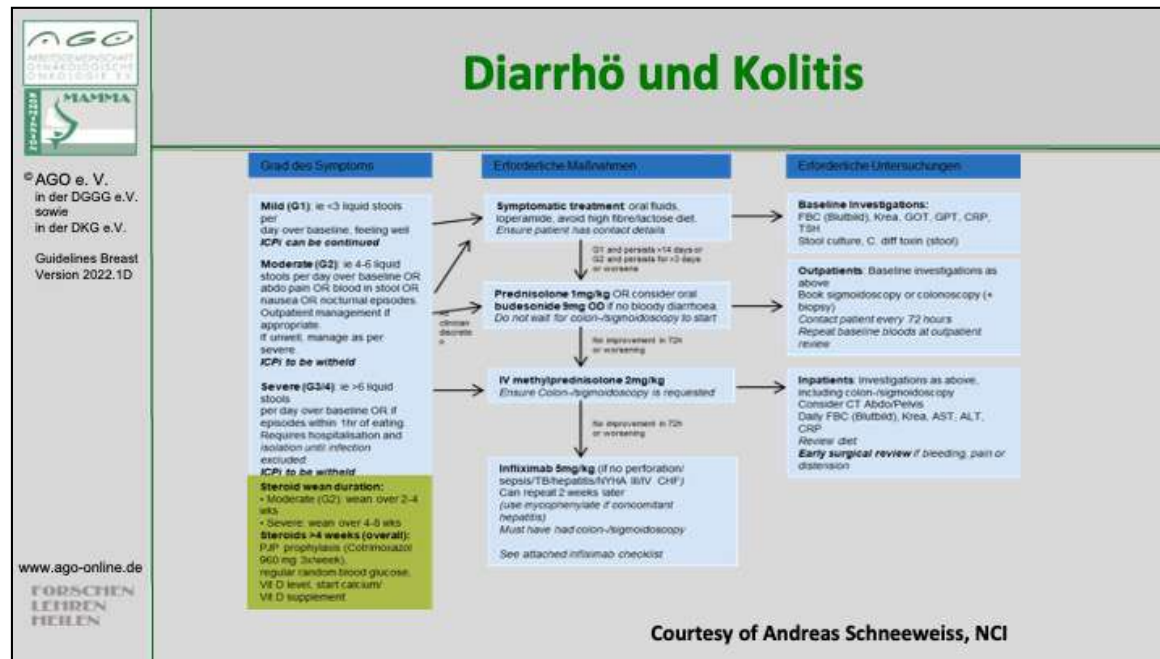
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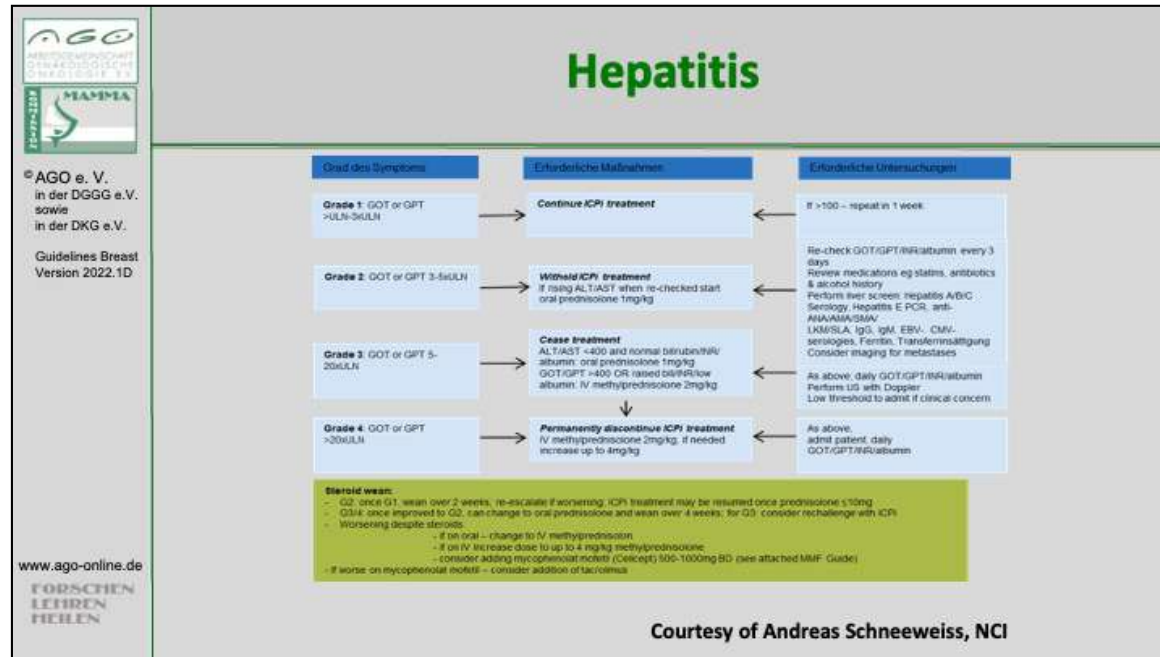
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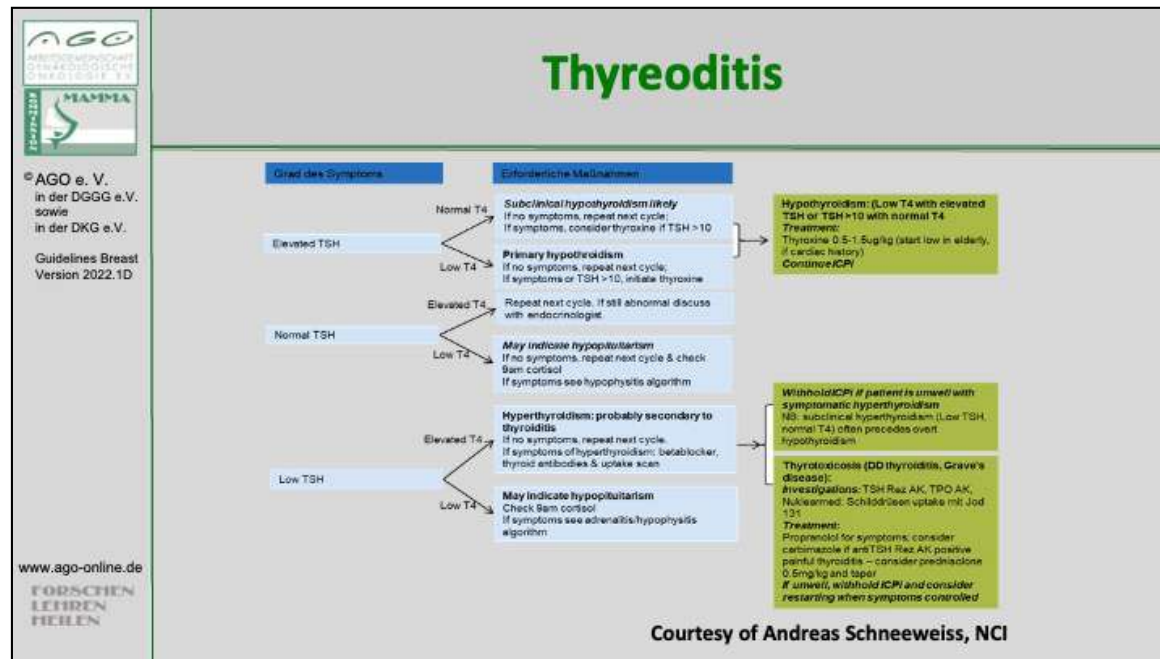
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Nebenwirkungen nach Organsystemen

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.

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Allgemeine Infektionsprophylaxe

NB nur selten für solide Tumoren wie MaCa anwendbar

ASCO Practice Guideline „Antimicrobial Prophylaxis...“ 2018

	Oxford		
	LoE	GR	AGO
▪ Vermeidung von besonders infektionsbegünstigenden Faktoren / Umgebungen	5	D	+
▪ Prophylaktische Therapie in Low-Risk-Patienten	1a	B	-
▪ Prophylaktische Therapie bei Hochrisikopatienten* (z. B. gemäß NCCN-Leitlinien) mit:			
▪ Antibiotika	1a	A	++
▪ Antimykotika (Triazol-Antimykotika)	1a	B	+/-
▪ Virostatika bei soliden Tumoren	5	D	-
▪ Granulopoese-stimulierende Faktoren	1a	A	++

* Definition Hochrisiko: vermutete Neutropeniedauer < 100/ μ l \geq 7d

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

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- Hepatitis B-Screening vor Beginn einer Chemotherapie (HBsAg, anti-HBc, anti-HBs)

Bei Reaktivierung bzw. bei positiver Serologie

- Prophylaktische Therapie mit Virustatika bei Nachweis von HBV-DNA (entsprechend AGIHO / DGHO – Empfehlungen)
- Hepatitis C-Screening vor Beginn einer Chemotherapie

Oxford

LoE	GR	AGO
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2c	B	+
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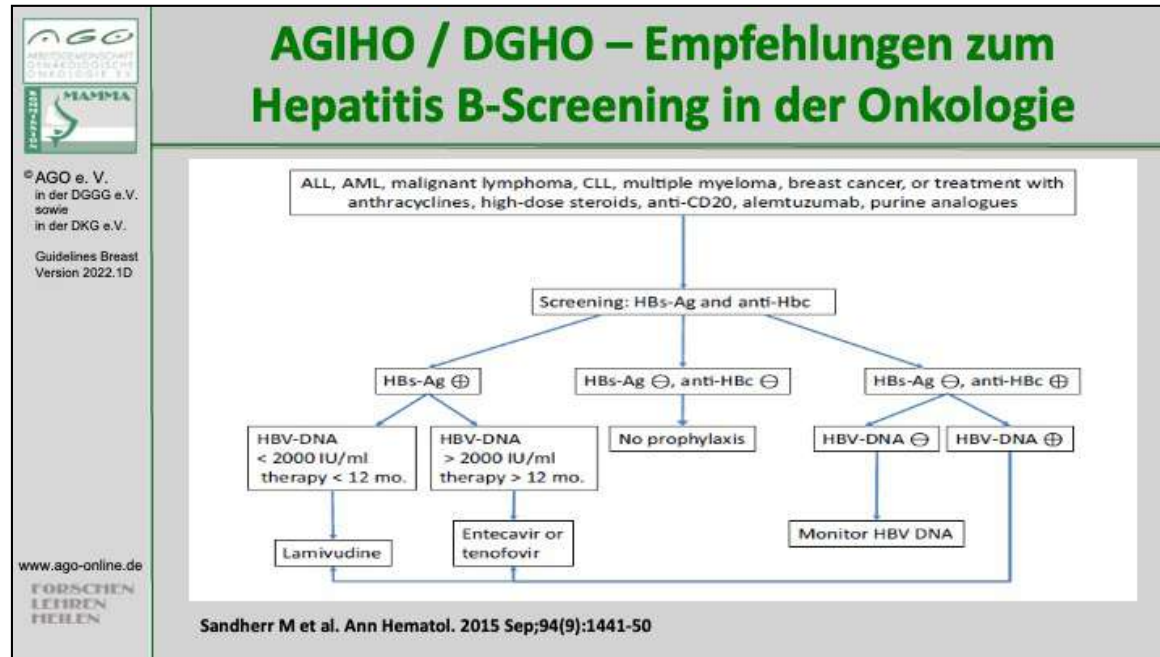
1b	A	++
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5	D	+/-
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Nebenwirkungen nach Organsystemen Inzidenz, Prävention, Therapie

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

Sekundäre Malignome I	
	Oxford
	LoE 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-Inhibitoren 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


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Statements 1-4

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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.
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Sekundäre Malignome II (nach Radiotherapie)

Oxford
LoE

1a

- **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)**
- Erhöhtes Risiko besonders für Raucher
- Kein Unterschied bezgl. sekundärer Malignome zwischen PBI (Teil-) und WBI (Ganzbrustbestrahlung)

2b

2c

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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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Praktischer Umgang mit ESF

- **Epoetin α und Darbepoetin sind äquieffektiv**
- **Dosierungen:**
 - Epoetin α: 150 IU/kg 3 x wöchentlich s.c. oder 40.000 IU 1 x / Woche s.c. oder 80.000 IU alle 2 Wochen s.c. oder 120.000 IU alle 3 Wochen s.c.
 - Epoetin β: 30.000 IE 1x /Woche s.c.
 - Darbepoetin: 2,25 µg/kg s.c. wöchentlich oder 500 µg s.c. alle 3 Wochen
- **Hb-Messungen wöchentlich**
 - Dosisreduktion bei Hb-Anstieg > 1 g/dl innerhalb von 2 Wo.
 - Dosissteigerung bei Hb-Anstieg < 1 g/dl innerhalb von 4–6 Wo.
- **Bei FED ("funktioneller Eisenmangel") Eisensubstitution präferentiell i.v.**
- **Abbruch der ESF-Gabe bei ausbleibenden Hb-Anstieg nach 9 Wo.**

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Granulozyten-Kolonie-stimulierende Faktoren			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Primäre Prophylaxe für eine zu erwartende febrile Neutropenie (FN) <ul style="list-style-type: none"> Bei Risiko für FN 10–20 % <ul style="list-style-type: none"> Im Falle zusätzlicher individueller Risiken Bei FN-Risiko > 20 % (e.g. DAC, dosisdichte CT) Sekundäre Prophylaxe während der Chemotherapie (frühere FN oder Neutropenie Grad IV > 7 Tage) Therapeutischer Nutzen bei FN Beginn der Therapie in Verbindung mit Art und Dauer der Chemotherapie <ul style="list-style-type: none"> Pegfilgrastim Tag 2 Lipegfilgrastim Tag 2 Filgrastim / Lenograstim von Tag 2–5 bis absolute Neutrophilenzahl > 2–3 x 10⁹ 	1b	B	+/-
	3b	C	+
	1a	A	++
	1b	A	++
	1a	A	+/-
	1b	A	++
	1b	A	++
	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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Statements 1-4

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Management der febrilen Neutropenie

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

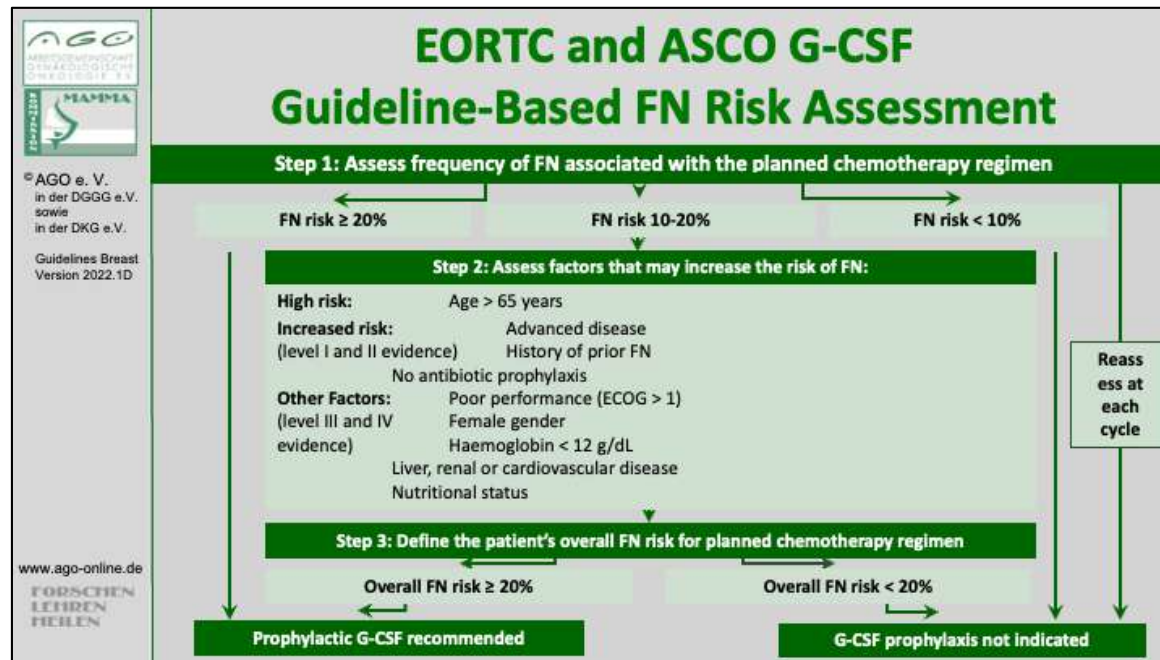
Definition (orale Temp. > 38,5 °C oder zwei konsekutive Messungen > 38 °C über 2 h in einer Patientin mit einem ANC < 500 cells/mm³ oder erwarteter Abfall < 500 cells/mm³)

- Klinische Untersuchung
- Tägliche Kontrollen
- Hospitalisierung von Hochrisikopatienten
- Ambulante Therapie bei Niedrigrisikopat. möglich
- Differentialblutbild
- Blutkulturen
- Bildgebung der Lunge
- Sofortige empirische antibiot. Therapie
- Empirische antimykotische Therapie nach 4–7 d bei keiner Besserung unter der antibiotischen Therapie
- G-CSF als therapeutische Maßnahme

Oxford		
LoE	GR	AGO
5	D	++
5	D	++
1b	A	++
1b	A	+
5	D	++
5	D	++
3	C	++
1a	A	++
1b	A	++
2b	B	+/-


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

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	4. Nebenwirkungen am Ovar	
© AGO e. V. in der DGGG e.V. sowie in der DKG e.V. Guidelines Breast Version 2022.1D www.ago-online.de FORSCHEN LEHREN HEILEN	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 Amenorrhoe (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	GR	AGO
<p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2022.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	▪ 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	+

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(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:

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Nurs. 2017 Jan/Feb;40(1):E11-E27.

(Therapie-assoziierte) Kognitive Störungen	
	Oxford
	LoE 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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Methylphenidate kann kognitive Funktion bei Patientinnen mit Krebs verbessern

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Unter Aromatasehemmertherapie wurden kognitive Störungen beobachtet

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(Therapie-assoziierte) Schlafstörungen

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Guidelines Breast
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- **Schlafstörungen häufig bei Mammakarzinom-patientinnen während und nach Therapie beschrieben (20–70 %)**
- **Verhaltenstherapie ist effektiv in der Behandlung von Schlafstörungen und Steigerung der Lebensqualität**

Oxford

LoE GR AGO

2a B

1b A ++

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Sleep disturbances are a common problem....

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Behavioral therapies have demonstrated efficacy.....

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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 (CIPN)

- **Inzidenz Grad 1–2 nach Taxanen 20–50 %**
- **Inzidenz Grad 3–4 nach Taxanen 6–20 %**
- **Risikofaktoren: Art der Chemotherapie, Dosierung, BMI, fehlende körperliche Aktivität**
- **Individuelle Risikofaktoren**
 - Diabetes mellitus
 - Nutritiv toxische Substanzen ins. Alkohol
 - Niereninsuffizienz
 - Hypothyreose
 - Kollagenosen / Vaskulitiden
 - Vitaminmangel
 - HIV-Infektion
 - CMT-Genmutation
- **Unklar:**
 - Andere genetische Faktoren (SNP, Mutationen)

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Chemotherapie-induzierte periphere Neuropathie – Prävention –			
	Oxford		
	LoE	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, Elektrolytlösungen, 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

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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6. Pachman DR, Barton DL, Watson JC, et al.: Chemotherapy-induced peripheral neuropathy: prevention and treatment. Clin Pharmacol Ther. 2011 Sep;90(3):377-87.
7. Schuler U, Heller S. Chemotherapy-induced peripheral neuropathy and neuropathic pain. Schmerz. 2017 Aug;31(4):413-425.
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chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial." JAMA 309(13): 1359-1367.

9. Cliff J, Jorgensen AL, Lord R, et al. The molecular genetics of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2017 Dec;120:127-140.
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Nicht-medikamentöse Prävention

Funktionstraining

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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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4. Kautio AL, Haanpää M, Leminen A, et al.: Amitriptyline in the prevention of chemotherapy-induced neuropathic symptoms. *Anticancer Res.* 2009 Jul;29(7):2601-6.

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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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Chemotherapie-induzierte periphere Neuropathie – Therapie –			
	Oxford		
	LoE	GR	AGO
<u>Nicht-medikamentöse Therapie</u>			
• Funktionstraining (Fitness, sensomotorisches Stimulationstraining etc.)	2a	C	+
• Physiotherapie / physikalische Therapie	5	D	+
• Akupunktur	2b	B	+
<u>Medikamentöse Therapie</u>			
• Menthol lokal (1 %), Capsaicin / Lidocain lokal	5	D	+
• Baclofen / Amitryptilin / Ketamin-Creme	2b	B	+
• Duloxetine zur Behandlung von Schmerzen durch CIPN	1b	B	+
• Opiode zur Behandlung von Schmerzen durch CIPN	5	D	+
• Palmitoylethanolamid (PEA) topisch oder p.o.	5	D	+/-
• Venlafaxin	5	D	+/-
• Gabapentin, Pregabalin	1b	B	+/-
• Amitryptilin / Nortriptylin, 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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chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial." JAMA 309(13): 1359-1367.

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Nicht-medikamentöse Therapie

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Medikamentöse Therapie

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2. Pachman DR, Barton DL, Watson JC, et al.: Chemotherapy-induced peripheral neuropathy: prevention and treatment. *Clin Pharmacol Ther*. 2011 Sep;90(3):377-87.

Duloxetine

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:

1. Han X, Wang L, Shi H, *et al.* Acupuncture combined with methylcobalamin for the treatment of chemotherapy- induced peripheral neuropathy in patients with multiple myeloma. *BMC Cancer* 2017;17:40.
2. Lu W, Giobbie-Hurder A, Freedman R, *et al.* Acupuncture for Chemotherapy-Induced Peripheral Neuropathy in Breast Cancer Survivors: A Randomized Controlled Pilot Trial. *Oncologist*. 2019 Oct 14:1-9 .

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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15. Meng H, Hanlon JG, Katznelson R, et al. *Can J Anaesth*. 2016 Mar;63(3):307-10.
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Guidelines Breast
Version 2022.1D

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FORSCHEN
LEHREN
HEILEN

Nebenwirkungen nach Organsystemen Inzidenz, Prävention, Therapie

7. Herzerkrankungen

Langzeittoxizität Kardiotoxizität			
	Oxford		
	LoE	GR	AGO
▪ Äquivalente Kardiotoxizität von Doxorubicin und Epirubicin in den empfohlenen Dosierungen (450-500 bzw. 900-1000 mg/m ² kum. Dosis)	2b	B	
▪ Weniger Kardiotoxizität nach liposomalem Doxorubicin	1b	B	
▪ Risikofaktoren für Anthrazyklin- oder Trastuzumab-assoziierte Kardiotoxizität <ul style="list-style-type: none"> Alter, Übergewicht, Hypertonus, Hypercholesterinämie, vorbestehende Herzerkrankungen (inkl. grenzwertige LVEF), Diabetes mellitus 	2b	B	
Überwachung der Herzfunktion:			
▪ Standardisierte Echokardiographie (LVEF oder SF in %)	3b	C	+
▪ EKG (QT-Intervall) <ul style="list-style-type: none"> Troponin I als Marker für Kardiotoxizität 	1a	A	+
	2b	B	+/-
▪ Betablocker-Prophylaxe während Anthrazyklin-Therapie	2a	B	+/-

Consensus recommendations:

- 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.)”

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- van Dalen EC Different anthracycline derivatives 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...”

- 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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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.
2. Slamon D: Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011 Oct 6;365(14):1273-83
3. Verma S: Is cardiotoxicity being adequately assessed in current trials of cytotoxic and targeted agents in breast cancer? *Ann Oncol*. 2011 May;22(5):1011-8. Epub 2010 Nov 22..
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Trastuzumab Adjuvant Überwachung hinsichtlich CHF

Oxford LoE: 5
GR: D
AGO: ++

Vor Beginn der Trastuzumab-Therapie

- Anamnese, klinische Untersuchung (Ödeme, Hepatomegalie)
- Echokardiographie (Alternative zu MUGA)


Während und nach der Trastuzumab-Therapie

Regelmäßige Dokumentation von

- Herzfrequenz; bei Anstieg > 15 % über das individuelle Ausgangsniveau
- Körpergewicht; bei Anstieg ≥ 2 kg/Woche
- Kardiale Zeichen und Symptome

LVEF alle 3 Monate

**Bestimmung
der LVEF**



Statement: Cardiac Monitoring (5 D ++)

Vote result of the AGO recommendation: 100%

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GYNEKOLOGISCHE
ONKOLOGIE e.V. (AGO)

DEUTSCHE
GESELLSCHAFT
FÜR
GYNEKOLOGISCHE
ONKOLOGIE (DGGG)

Toxizitätssteigerungen durch Behandlungskombinationen

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Kardiale Toxizität

- Trastuzumab simultan zur Radiotherapie
- Trastuzumab simultan zu Epirubicin
- Trastuzumab simultan zu Doxorubicin
- Anthrazykline simultan zur Radiotherapie

Risiko Lungen- / Brustparenchymfibrosen

- Tamoxifen simultan zu Radiotherapie
- Chemotherapie simultan zu Radiotherapie

Oxford

LoE	GR	AGO
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2b	B	+
2b	B	+/-
2b	B	-
2c	C	-

3	C	+/-
1b	B	-

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“Trastuzumab simultaneous to radiotherapy”

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“Trastuzumab simultaneous to epirubicin”

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

“Trastuzumab simultaneous to doxorubicin”

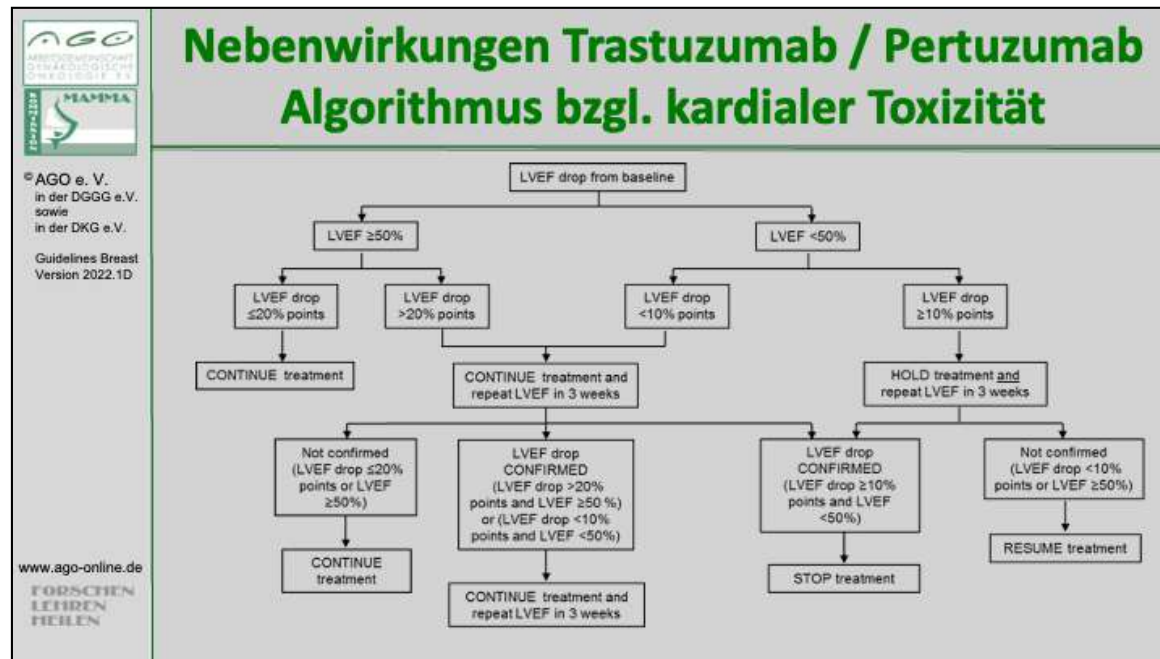
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“Anthracycline simultaneous to radiotherapy”

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“Tamoxifen simultaneous to radiotherapy”

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Nebenwirkungen nach Organsystemen Inzidenz, Prävention, Therapie

8. Erkrankungen des Gastrointestinaltrakts

- Nausea, Emesis (Übelkeit, Erbrechen)
- Mukositis
 - Stomatitis (Everolimus)
- Diarrhoe
- Obstipation

<div> </div> <h2>Antiemetische Therapie</h2> <p>nach MASCC und ASCO</p>			
	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.
- 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.

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Antiemetische Therapie

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

ACUTE Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS				
High Non-AC	5-HT ₃	+	DEX	+	NK ₁ +/- OLZ*
High AC	5-HT ₃	+	DEX	+	NK ₁ +/- OLZ*
Carboplatin	5-HT ₃	+	DEX	+	NK ₁
Moderate (other than carboplatin)	5-HT ₃	+	DEX		
Low	5-HT ₃	or		DEX	or DOP
Minimal	No routine prophylaxis				

5-HT₃ = serotonin₃ receptor antagonist

DEX = DEXAMETHASONE

NK₁ = neurokinin₁ receptor antagonist such as APREPITANT or FOSAPREPITANT or ROLAPITANT or NEPA (combination of nabilone and palonosetron)

OLZ = CLANZAPINE

DOP = dopamine receptor antagonist

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


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Supportive Care in Cancer

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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)
Oxiplatin, or anthracycline, or cyclophosphamide	DEX can be considered
Moderate (other)	No routine prophylaxis
Low and Minimal	No routine prophylaxis

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

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Aggressive Care Meets Oncology Care Can Prevail





<https://www.mascc.org/antiemetic-guidelines>

<div>  <h2>Supportive Therapie Antiemetika</h2> </div>				
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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, Flusssymptomatik Transaminasenanstieg Dermatologie 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, Diarrhö	hoch
Oxazapine	Olanzapin	10mg/d for d1-4 Ggf. 5mg/d for d1-4	Sedation, Gewichtszunahme	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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Mukositis Prävention

<https://www.mascc.org/mascc-guidelines>
 Multidisciplinary S3 guidelines of the AWMF (Reg.-Nr. 032-054OL): „Supportive Therapie bei onkologischen Patientinnen – interdisziplinäre Querschnittsleitlinie“

	Oxford		
	LoE	GR	AGO
<p>▪ Standardisierte Mundpflege zur Prophylaxe oraler Mukositis soll in allen Altersgruppen und bei allen Krebsbehandlungen mit einem Risiko für OM erfolgen</p> <p>Diese besteht aus</p> <ol style="list-style-type: none"> 1. Patientinnenseitig <ul style="list-style-type: none"> ▪ regelmässige Mundspülung (H₂O, NaCl) ▪ Weiche Zahnbürste ▪ Reinigung der Zahnzwischenräume mit Zahnseide und/oder Interdentalbürsten ▪ Vermeidung von Noxen (Alkohol, Tabak, scharfe Speisen, säurehaltige Lebensmittel) ▪ Fortlaufende Kontrolle auf Läsionen 2. Risikoadaptierte vorbeugende Maßnahmen durch den Zahnarzt 3. Engmaschige klinische Kontrolle <p>Keine Evidenz besteht für folgende Substanzen: Allopurinol, Capsaicin, Glutamin, Honig, Kamille, Kamillosan, Kaugummi, Kefir, Methadon, Nystatin, Pentoxifyllin, Polividon Jod, Vitamine A / E / Kombinationen</p>	2b		++

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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Prophylaxe der Everolimus-bedingten Stomatitis durch Kortikosteroid-basierte Mundspülung

- **Studiendesign: einarmige Phase II-Studie**
- **Kohorte: 92 Pat. behandelt mit Everolimus und Exemestane**
- **Schedule: 10 ml Dexamethason (15 mg/5 ml Lösung)
4 x täglich über 8-12 Wochen***
- **Ergebnisse: all-grade Inzidenz der Stomatitis 27 %
(13 Wochen Exposition) mit 9 % ≥ Grad 2 Events**

* alternativ Hydrocortison: Hydrocortisonacetat-Suspension 0,5 % mit Lidocainhydrochlorid und Dexpanthenol (Arzneibuchrezeptur NRF 7.14.)

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

1. Rugo HS, Seneviratne L, Beck JT, et al: Prevention of everolimus-related stomatitis in women with hormone receptor-positive, her2-negative metastatic breast cancer using dexamethasone mouthwash (swish): A single-arm, phase 2 trial. Lancet Oncol 2017;18:654-662.
2. Jones VE, McIntyre KJ, Paul D, Wilks ST, et al.:Evaluation of miracle mouthwash plus hydrocortisone versus prednisolone mouth rinses as prophylaxis for everolimus-associated stomatitis: A randomized phase ii study. Oncologist 2019;24:1153-1158.



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Mukositis

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

- **Desinfizierende / entzündungshemmende Maßnahmen:**
Mundspülung mit Kamille- oder Salbeitee bzw. Kamillenextrakt, äther. Öle, Iod-Polyvidon, Hexetidin.
Pinselfungen mit Kristallviolettlösung 0,5 % (Rezeptur) oder Myrrhentinktur, H. Mometasonfuroat + Propylenglykol
- **Schleimhautschützende Maßnahmen (während / nach Zytostatikaapplikation):**
Lutschen von Eiswürfeln (bes. geeignet: Ananassaft, über die Apotheke beziehbar) während 5-Fluorouracil- oder HD-Melphalan-Infusion. Calciumfolinat (Leucovorin-Mundgel®, H) bei HD-Methotrexat: frühestens 24 Stunden nach Ende MTX-Infusion beginnen (sonst Wirkungsverlust des Zytostatikums!), 4- bis 6-stündlich.
Dexpantenol (Panthenol®-Lsg. 5 %, H) mehrmals täglich zur Mundspülung.
- **Lokale antimykotische Therapie:**
Amphotericin B, Nystatin, Fluconazol
- **Lokale antivirale Therapie**
Aminoquinurid / Tetracain-HCl, Aciclovir
- **Lokalanästhetika:**
Orale Anwendung von Benzocain, Doxepin 0,5 %
- **Schmerztherapie:** Opiode bei Bedarf

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. <https://www.mascc.org/mascc-guidelines>
2. McGuire DB, Fulton JS, Park J, et al; Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of basic oral care for the management of oral mucositis in cancer patients. Support Care Cancer 2013 Nov;21(11):3165-77.
3. Jensen, S. B., V. Jarvis, Y. Zadik, et al. Systematic review of miscellaneous agents for the management of oral mucositis in cancer patients. Support Care Cancer 2013;21(11): 3223-3232.
4. Leenstra, J. L., R. C. Miller, R. Qin, et al.: Doxepin rinse versus placebo in the treatment of acute oral mucositis pain in patients receiving head and neck radiotherapy with or without chemotherapy: a phase III, randomized, double-blind trial (NCCTG-N09C6 [Alliance]). J Clin Oncol 2014;32(15): 1571-1577.
5. 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.
6. Peterson, D. E., K. Ohn, J. Bowen, et al.: Systematic review of oral cryotherapy for management of oral mucositis caused by cancer

therapy. Support Care Cancer 2013; 21(1): 327-332.

7. Saunders, D. P., J. B. Epstein, S. Elad, et al.: Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients. Support Care Cancer 2013; 21(11): 3191-3207.
8. 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.
9. 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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Diarrhö

- **Adsorbantien**
 - Carbo medicinalis, Kaolin / Pektin, Al-Mg-Silikathydrat
- **Analgetica, Opioide**
 - Loperamid, Codein, Morphin i.v., Tinctura opii, Butylscopolamin
- **Off-label: Somatostatin-Analogon Octreotid s.c. (ab Grad 3)**
- **Pseudomembranöse Kolitis**
 - Metronidazol oder bei Versagen Vancomycin
- **Initiale Dosisescalation zur Verringerung der Grad 3/4 - Diarrhoen**
 - **CONTROL trial (Dosisescalation von Neratinib: 120 mg/d Tag 1-7, 160 mg/d Tag 8-14, 240 mg/d danach)**

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.

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



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Obstipation

Wichtige Nebenwirkung einer Opiattherapie

- **Quellmittel**
 - Flohsamen, Leinsamen (geschrotet)
- **Osmotisch wirksame Laxanzien**
 - Macrogol > Lactulose (Cochrane Review LoE 1a AGO +)
 - Orale Kontrastmittel: Ultima ratio z. B. Natriumamidotrizoat
 - Sorbit
- **Stimulierende Laxanzien**
 - Sennesfrüchte, Rizinusöl, Bisacodyl, Natriumpicosulfat
- **Stuhlweichmacher**
 - Gleitmittel z. B. Paraffin
- **Opiod-Rezeptorantagonist bei Opiatobstipation**
 - Methylnaltrexone

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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Nebenwirkungen nach Organsystemen Inzidenz, Prävention, Therapie

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 Alopecie 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.



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Scalp Cooling: Scalp Cooling Alopecia Prevention Trial (SCALP) und Metaanalysen

AGO: +/- LOE 2b B

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

Zwei Metaanalysen: AGO: +/- LOE 1b

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

1. Nangia J, Wang T, Osborne C, et al. Effect of Scalp Cooling Device on Alopecia in Women Undergoing Chemotherapy for Breast Cancer: The SCALP Randomized Clinical Trial JAMA. 2017 Feb 14;317(6):596-605.
2. Rugo HS, Voigt J. Scalp Hypothermia for Preventing Alopecia During Chemotherapy. A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Breast Cancer. 2018 Feb;18(1):19-28.
3. Rugo HS, Melin SA, Voigt J. Scalp cooling with adjuvant/neoadjuvant chemotherapy for breast cancer and the risk of scalp metastases: systematic review and meta-analysis. Breast Cancer Res Treat. 2017 Jun;163(2):199-205.

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Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

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)

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Nebenwirkungen nach Organsystemen Inzidenz, Prävention, Therapie

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)

<div>  Paravasate mit potenziell nekrotisierenden Substanzen (Anthracycline, Taxane, Vinorelbin) </div>			
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	LoE	GR	AGO
	2b	B	++
<ul style="list-style-type: none"> Dexrazoxane zur Behandlung von Anthracyclin-Paravasaten (Ausnahme liposomales A) 			
<ul style="list-style-type: none"> 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.



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Paravasate

Dexrazoxane / Hyaluronsäure

Dexrazoxane zur Behandlung von Anthracyclin-Paravasaten

Tag 1: 1000 mg/m² (max. 2000 mg), IV 1–2 Stunden
 Tag 2: 1000 mg/m² (max. 2000 mg), IV 1–2 Stunden
 Tag 3: 500 mg/m² (max. 1000 mg), IV 1–2 Stunden

In anderen Fällen bzw. in denen eine Therapie mit Dexrazoxan nicht indiziert ist, gelten für die Anthrazyklin-Paravasate die folgenden Maßnahmen.

Lokale Kälte: Eispackung 6-stündlich jeweils für 15 Min. für 3 Tage oder: 24 h Abdeckung mit Eisbeuteln

Lokale Applikation von Dimethylsulfoxid (DMSO) 99 % mit Watteträger 3- bis 4-stündlich für mind. 3 Tage (besser 14 Tage) auftragen und an der Luft trocknen lassen. Das Intervall kann ab Tag 4 auf 6 Stunden verlängert werden.

Hyaluronsäure bei Taxan/Vinorelbin-Paravasaten:

- 1-10 Amp a 150 IU
- 1 ml Lösungsmittel (z. B. NaCl 0.9 %)
- Lokalanästhesie
- Keine Thermo-therapie bei Taxanen, trockene Wärme 4 x täglich 20 min bei Vincaalkaloiden

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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Nebenwirkungen nach Organsystemen Inzidenz, Prävention, Therapie

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
<div> <div>  <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V. Guidelines Breast Version 2022.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p> </div> <div> <ul style="list-style-type: none"> ▪ Diagnostische Abklärung mittels CT-Thorax <p>Therapie je nach Schweregrad und auslösender Noxe*</p> <ul style="list-style-type: none"> ▪ Kortikosteroidtherapie (Beginn mit $\geq 0,5$ mg/kg/d Prednisolon-Äquivalent) ▪ Dosisunterbrechung bzw. Therapieabbruch* (s. jeweilige Fachinformation) </div> </div>	1a	B	++
	1a	B	++
			++

Relevant practice guidelines:

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.



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Management ILD Trastuzumab Deruxtecan

For asymptomatic ILD / pneumonitis (Grade 1)*

- Consider corticosteroid treatment (eg, ≥ 0.5 mg/kg/day prednisolone or equivalent)
- Interrupt T-DXd until resolved to Grade 0, then:
 - If resolved in 28 days or less from date of onset, maintain dose
 - If resolved in greater than 28 days from date of onset, reduce dose one level

For symptomatic ILD / pneumonitis (Grade 2 or greater)*

- Promptly initiate systemic corticosteroid treatment (eg, ≥ 1 mg/kg/day prednisolone or equivalent)
- Continue for at least 14 days followed by gradual taper for at least 4 weeks
- Permanently discontinue T-DXd in patients who are diagnosed with any symptomatic ILD/pneumonitis

* ENHERTU [prescribing information]. Daiichi Sankyo Inc., Basking Ridge, NJ and AstraZeneca Pharmaceuticals LP, Wilmington, DE, 2021.

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.



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Andere supportive und palliative Fragestellungen

- **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.

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Ernährungsmangel

Nährstoffmangel ist ein häufiges medizinisches Problem, das 15–40 % der Krebspatienten betrifft. Es beeinträchtigt ihre Lebensqualität und kann den Erfolg der Behandlung beeinträchtigen.

- **Integration der Ernährungsberatung in das klinische Management empfohlen.**
- **Zur Ernährung siehe S3-Leitlinie Palliativmedizin und supportive Therapie.**

Klinische Ernährung

1. Arends J, Bertz H, Bischoff SC, et al. Klinische Ernährung in der Onkologie. S3-Leitlinie (AWMF Reg.: 073-006) Aktual Ernährungsmed. 2015; 40: e1–e74. https://www.dgem.de/sites/default/files/PDFs/Leitlinien/S3-Leitlinien/073-006I_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.

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Schmerztherapie

- **Nicht-Opioide; WHO Stufe 1**
Diclofenac resinat, Ibuprofen und / oder Metamizol, Paracetamol
- **Niedrig-potente Opioide; WHO Stufe 2**
Tramadol (vorzugsweise als Retard-Tabletten) bzw. Tilidin / Naloxon (ebenfalls als Retard-Tabletten)
- **Hoch-potente Opioide; WHO Stufe 3**
Morphin, Buprenorphin (sublingual oder als transdermales System), Fentanyl (transdermales System), Hydromorphon, Oxycodon, als Reserve Levomethadon. Die notwendige Opioiddosis wird schrittweise gegen den Schmerz titriert.
- **Koanalgetika**
Canabinoide, Gabapentin, Pregabalin, Carbamazepin, Amitriptylin, Bisphosphonate

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)



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FORSCHEN
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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)