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Therapy Side Effects

Therapy Side Effects

- **Versions 2004–2016:**
  Albert / Bischoff / Brunnert / Costa / Dall / Friedrich / Friedrichs / Gerber / Göhring / Huober / Jackisch / Lisboa / Lück / Müller / Nitz / Schmidt / Souchon / Stickeler / Untch

- **Version 2017:**
  Untch / Solomayer

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References

Toxicity Assessment

Acute Toxicity

According to WHO[1] or NCI-CTC[2]

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

Long-Term Toxicity

No general assessment scale

[1] WHO Handbook for reporting results of cancer treatment, N0 48 (1979) (WHO offset Publications, Geneva)

[2] NCI, NHI,Bethesda, USA, Common Toxicity Criteria, CTCAE v4.03, (2010) http://evs.nci.nih.gov/ftp1/CTCAE/About.html
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Acute Toxicity (NCI CTCAE vs 4.03, 2010)

- **Grade 1**
  Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2**
  Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- **Grade 3**
  Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.**
- **Grade 4**
  Life-threatening consequences; urgent intervention indicated.
- **Grade 5**
  Death related to AE.

Activities of Daily Living (ADL)

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

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

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Cytotoxic Anti-Cancer Drugs
Acute Toxicity I

	Haematol. Toxicity	Nausea/ Vomit.	Alopecia	Mucositis/ Stomatits	Cardiac Toxicity	Renal Toxicity	Hepatic Toxicity
Cyclophosphamide	++	++	+	+	+	++	
Methotrexate	++	+	+	++	+	++	+
5-Fluorouracil	++	++		++	+		
Carboplatin	++	++	+			++	
Cisplatin	+	+++				+++	
Capecitabine	+	+		+			
Gemcitabine	++	+		+			+
Epi-/Doxorubicin	++	++	+++	++	+		
Pegliposomal Doxorubicin	+	+	+	++	(+)		
Liposomal Doxorubicin	+	+	+	++	(+)		
Mitoxantrone	++	++	+	+	+		
Paclitaxel	++	+	+++	+			+
nab-Paclitaxel	+	+	+++				+
Docetaxel	++	+	+++	++			
Vinorelbine	++		(+)	+			
Eribulin	++	+	+				

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Cytotoxic Anti-Cancer Drugs
Acute Toxicity II

	Allergy	Bladder	Neuro-toxicity	Cutane Tox	Diarrhea	
Cyclophosphamide	+	+	+	+		
Methotrexate	+		+	++		
5-Fluorouracil				+	+	
Carboplatin						
Cisplatin			+++			
Capecitabine				++	++	
Gemcitabine						**Flue-like Synd., Edema**
Epi-/Doxorubicin	+					**Paravasate, Dexraxozane**
Liposomal Doxo.	+			+		
Pegliposomal Doxo.	+			+++		
Mitoxantrone						
Paclitaxel	+++		++		+	**Myalgia**
nab-Paclitaxel	+		++		+	**Myalgia**
Docetaxel	++		+	++	+	**Myalgia, Fluid retention, nails!**
Vinorelbine			++			**Thrombophlebitis, Obstipation**
Eribulin				++		

Peripheral Neuropathy

- **Incidence grade 1-2 after taxane therapy 20-50 %**
- **Incidence grade 3-4 after taxane therapy 6-20 %**
- **Risk factors: Type of chemotherapy, dose, BMI, no physical activity**

- **Individual risk factors:**
  - **Diabetes mellitus**
  - **Nutritionally toxic substances (e.g. alcohol)**
  - **Renal insufficiency**
  - **Hypothyroidism**
  - **Collagenosis / Vasculitis**
  - **Vitamine deficiency**
  - **HIV-Infection**
  - **CMT-Gene Mutation**

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S3 Guideline November 2016

Chemotherapy Induced Peripheral Neuropathy

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	Oxford / AGO LOE / GR		
Prophylaxis			
➢ **Non drug**			
➢ **Functional training**	**2c**	**C**	**+**
➢ **Peripheral compressions therapy**	**2b**	**B**	**+**
➢ **By drugs**	**1b**	**B**	**-**

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Long-Term Toxicity
Cardiotoxicity

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	Oxford / AGO LoE	GR	
➢ Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)	2b	B	
➢ Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity	1b	B	
➢ Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently:	2b	B	
➢ Elderly patients			
➢ Obesity			
➢ Hypertension			
➢ Hypercholesterolemia			
➢ Pre-existing cardiac diseases (incl. borderline LVEF)			
➢ Diabetes mellitus			
➢ Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)	3b	C	+

Feasibility of Treatment Combinations Considering Toxicities

	Oxford / AGO LoE	GR	
Regarding cardiac toxicity			
➢ Trastuzumab simultaneous to radiotherapy	2b	B	+
➢ Trastuzumab simultaneous to epirubicin	2b	B	+/-
➢ Trastuzumab simultaneous to doxorubicin	2b	B	-
➢ Anthracycline simultaneous to radiotherapy	2c	C	-
Regarding lung and breast fibrosis			
➢ Tamoxifen simultaneous to radiotherapy	3	C	+/-
➢ Chemotherapy simultaneous to radiotherapy	1b	B	-

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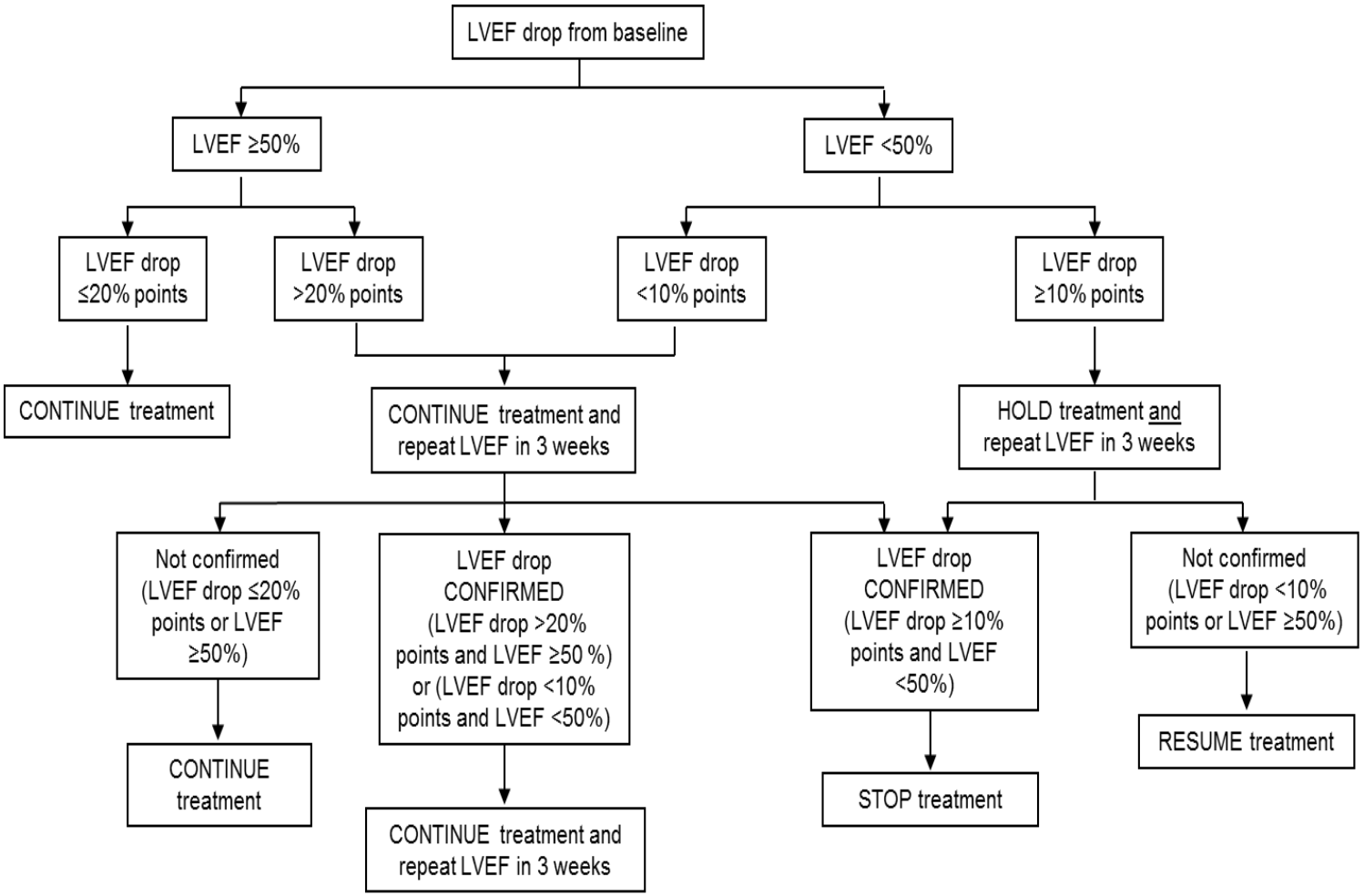
References

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



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Secondary Malignancies I

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	Oxford / LoE
➢ With regard to solid tumors, chemotherapy induced secondary malignancies are rare events	2a
➢ Alkylating agents increase the risk of leukaemia dose-dependently to a total of 0,2–0,4 % within 10 - 15 years	2a
➢ Anthracycline-containing regimens increase the risk of MDS and leukaemia to 0,2–1,7 % within 8 to 10 years	2a
➢ PARP-inihibitors are associated with an increased risk of AML and MDS to 0.5-1%	2b
➢ Radiotherapy increases the risk of leukaemia by 0,2–0,4% in patients treated with anthracycline-containing chemotherapy	2b
➢ Tamoxifen approximately doubles the risk for developing endometrial cancer	2b

Secondary Malignancies II (after Radiotherapy)

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	Oxford LoE
➢ **The risk of developing secondary cancers is low if modern radiation techniques are applied and should not deter the use of radiotherapy when indicated**	**2b**
➢ **Radiotherapy may moderately enhance the risk of ipsilateral lung cancer and angiosarcoma (10-15 / 10.000) 5–10 years after treatment**	**1a**
➢ **Enhanced risk especially among ever smokers**	**2b**
No difference of secondary malignancy between PBI und WBI	**2c**

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Chemotherapy Related Amenorrhea (CRA)

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	Oxford /LoE
➢ CRA may be permanent or temporary	
➢ Depends on CTX regimen used	
➢ CRA is an (imperfect) surrogate for menopause and fertility	
➢ Adjuvant endocrine therapy induces reversible amenorrhea, but delays conception to a less fertile period	
➢ Risk of CRA increases with age / treatment duration	2b
➢ Ovarian reserve of women who remain premenopausal after CTX is reduced	2b
➢ CRA is associated with improved outcome (DFS/OS)	1b

Synonyma: Chemotherapy / Treatment induced Amenorrhea (TIA, CIA)

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(Therapy Related) Fatigue

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	Oxford / AGO LoE / GR		
➢ Fatigue frequently present in breast cancer patients (30–60%)	2a	B	
➢ Exclusion of somatic reasons (anemia, tumor burden, co-morbidity, medication) for fatigue	1a	A	++
➢ Psycho-social interventions specifically addressing fatigue are efficient in reducing fatigue	1a	A	++
➢ Physical exercise can improve fatigue	1b	D	+
➢ Diet, Yoga can improve fatigue	2b	B	+
➢ Methylphenidate can improve fatigue	1a	D	+

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(Therapy Associated) Sleeping disturbance

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	Oxford / AGO LoE / GR
➢ **Sleep disturbances are a common problem of breast cancer patients during and after therapy (20–70%)**	**2a B**
➢ **Behavioral therapies demonstrated efficacy in the treatment of insomnia and improved the quality of life**	**1b A ++**

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(Therapy Associated) Depression

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	Oxford /LoE		
➢ Depression is an often reported adverse event in breast cancer patients (20–30%)	2a	B	
➢ Psychological interventions are effective to improve mood, but not survival in distressed and depressed patients	1b	A	
➢ Antidepressents have shown to improve depression in breast cancer patients	1b	A	
➢ Regular exercise participation can prevent depression among breast cancer survivors	2b	B	+

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(Therapy Associated) Cognitive Impairment

	Oxford / AGO LoE / GR	
➢ Therapy-related cognitive deficits (chemobrain frequently described (16–75%))	2a	B
➢ Cognitive-behavioral therapy is beneficial for cognitive function	2b	B
➢ Methylphenidate might improve cognitive function in patients with cancer	3a	C

Side-effects and Toxicity of Endocrine Agents

	Visual Disturbances	Osteoporosis	Cerebro-Vascular Events *	Fracture	Cardiac risk	Cognitive functions
SERMs	(+)		+			+
AI 3rd Gen*		+		+	+	(+)
SERD (Fulvestrant)		+		+		
GnRHa		+		+		

	Arthralgia Myalgia	Flush	Dysfunctional Bleeding*	Endometrial Changes	Deep Venous Thrombosis	Lipid Profile Impaired
SERMs	(+)	+	+	+	(+)	
	(+)	+	+	+		
AIs	+	(+)				(+)
SERD (Fulvestrant)						
Goserelin	(+)	+				

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Side-Effects and Toxicity of Bone Modifying Agents (BMA) Bisphosphonates (BP) and Denosumab (DB)

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	Oxford LoE
➢ Renal function deterioration due to IV-amino-BP	1b
➢ Osteonecrosis of the jaw (ONJ) mostly under IV-BP and DB therapy (appr. 2%)	1b
➢ Acute phase reaction (IV Amino-BPs, DB) 10–30%	1b
➢ Gastrointestinal side effects (oral BPs) 2–10%	2b

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Recommendations for Precautions to Prevent Osteonecrosis of the Jaw (ONJ)

Oxford LoE: 4 **GR: C** **AGO: +**

- **During bisphosphonate treatment, avoid any elective dental procedures, which involve jaw bone manipulations – if interventions are inevitable, prophylactic antibiotics are recommended (LoE 2b)**
- **Optimize dental status before start of bisphosphonate treatment, if feasible (LoE 2b)**
- **Inform patients about ONJ risk and educate about early symptom reporting**
- **In case of high risk for ONJ, use oral bisphosphonate**

**In adjuvant bisphosphonate therapy,
ONJ was rare**

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Frequent Side Effects of Bone Modifying Agents (BMA)

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Drug	Acute Phase React.	Renal Tox.	Upper GI-SE	Diar-rhea	ONJ	
Clodronate 1500 i.v.	0	+	0	0	0	
Clodronate 1600 p.o.	0	0	+	+	0	Non-A
Ibandronate 50 mg p.o.	0	0	+	0	0	Amino
Ibandronate 6 mg i.v.	+	0	0	0	+	
Zoledronate 4 mg i.v.						
q4w or q12w	+	+	0	0	+	
Pamidronate 90 mg i.v.	+	+	0	0	+	
Zoledronate 4 mg i.v. q6m	+	0	0	0	0	
Denosumab 120 mg sc q4w	0	0	0	+	+	Hypo-calcemia

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Key-Toxicities – Antibodies/Antibody-drug-conjugates

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	Oxford / AGO LoE / GR
Trastuzumab	
➢ Cardiotoxicity in the adjuvant setting (0,8–4,0%)	1b A
➢ Troponin I might identify patients who are at risk for cardiotoxicity	2b B
Bevacizumab	
➢ Hypertonus, proteinuria, bleeding, left ventricular dysfunction,	1a A
Pertuzumab	
➢ Skin rash, diarrhea, mucositis	2b B
T-DM1	
➢ Thrombocytopenia, hepatotoxicity pyrexia, headache, pneumonitis	2b B

Small Molecules

	Oxford / AGO LoE	GR
Lapatinib		
➢ Diarrhea, skin rash, fatigue	1b	A
Everolimus		
➢ Pneumonitis, stomatitis, hyperglycemia, infections, skin rash, thrombocytopenia	2b	B
PARP-inhibitors (olaparib)		
➢ Fatigue, myelosuppression	3	C
CDK4/6 inhibitors (palbociclip, LEE011)		
➢ Myelosuppression, neutropenia	3	C

Immun-Checkpoint Inhibitors

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- **Therapeutic options (Antibodies)**
  - **PD1 /PD-L1**
    - **Nivolumab**
    - **Pembrolizumab**
    - **Atezolizumab**
  - **CTLA-4**
    - **Ipilimumab**

Immune-Checkpoint Inhibitors

- **Side effects ≥ Grade 3**
  - **Diarrhea**
  - **Fatigue**
  - **Colitis**
  - **Hypophysitis**
  - **Hepatitis**
  - **Skin changes**
  - **Thyreoiditis**

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Pneumonitis-Management PD1/ PDL1-Inhibitors

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I° (asymptomatic, CT-morphological changes)	Continue	If necessary follow up by imaging
II° (oligosymptomatic, coughing/ dyspnea on exertion)	Discontinue	oral 0,5-1 mg/kg BW methylprednisolone* †
III° (dyspnea at rest , ADL-limitation, oxygen need)	Discontinue	i.v. 1-2 mg/kg BW methylprednisolone † ‡
IV° (life threatening, Indication for tracheo-tomy / intubation)	Discontinue	i.v. 1-2 mg/kg BW methylprednisolone, evtl. after 48-72h + Infliximab/ MMF/ Endoxane ‡

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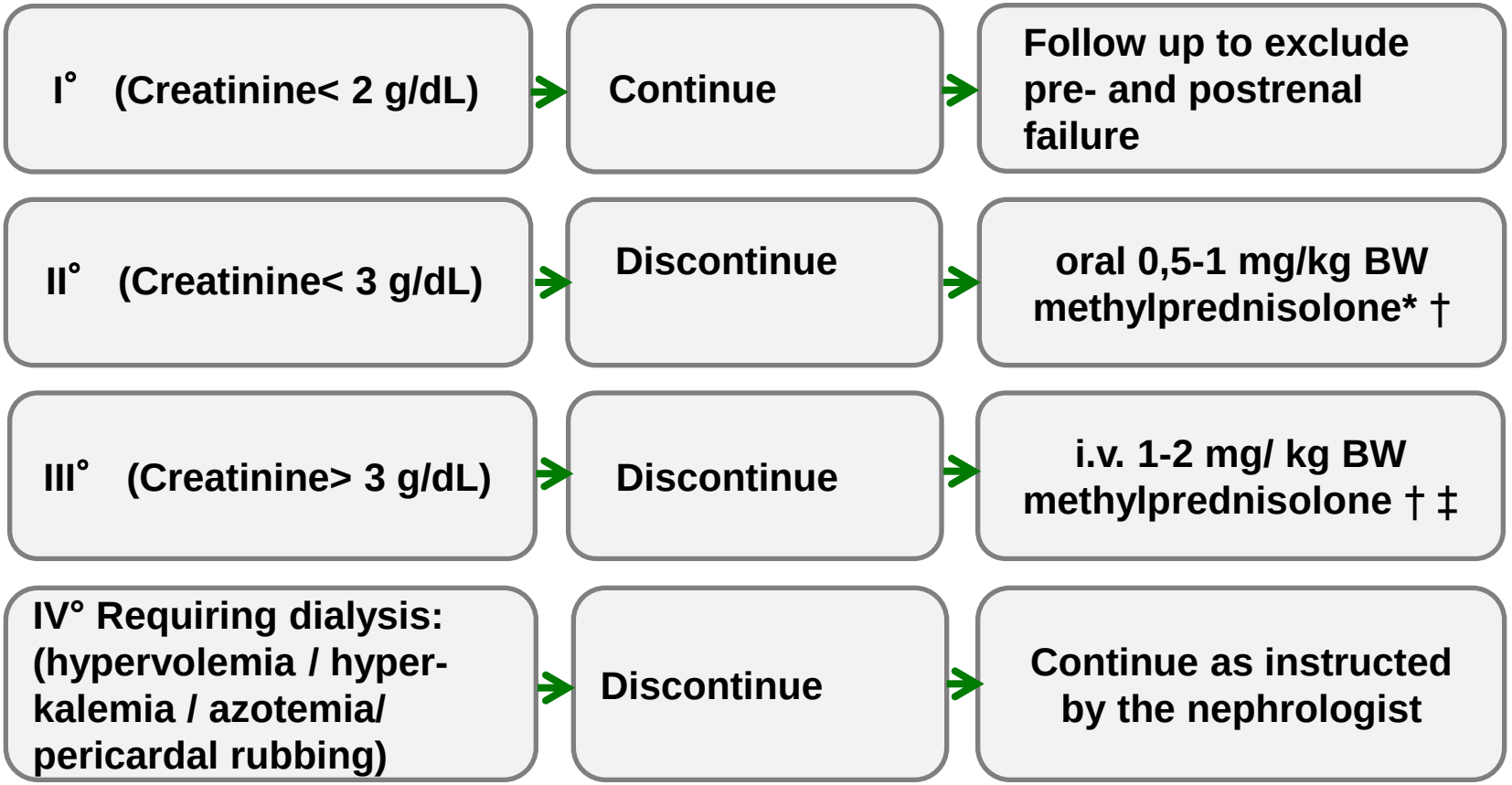
*** Prophylactic antibiotics using ciprofloxacine 500 mg bid p.o., Prophylaxis against gastric ulcer using PPI, oral potassium substitution. If no improvement treatment like pneumonitis grade III**
† If improvement, steroids can be deescalated over 1 month
‡ Any Pneumonitis ≥ grade III bronchoscopy using BAL/ with sampling

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

Nephritis-Management PD1/PDL1-Inhibitors



* * Prophylactic antibiotics using ciprofloxacine 500 mg bid p.o., Prophylaxis against gastric ulcer using PPI, oral potassium substitution. If no improvement treatment like pneumonitis grade III
† If improvement, steroids can be deescalated over 1 month
‡ Starting from nephritis grade III counselling nephrology to obtain tissue samples

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

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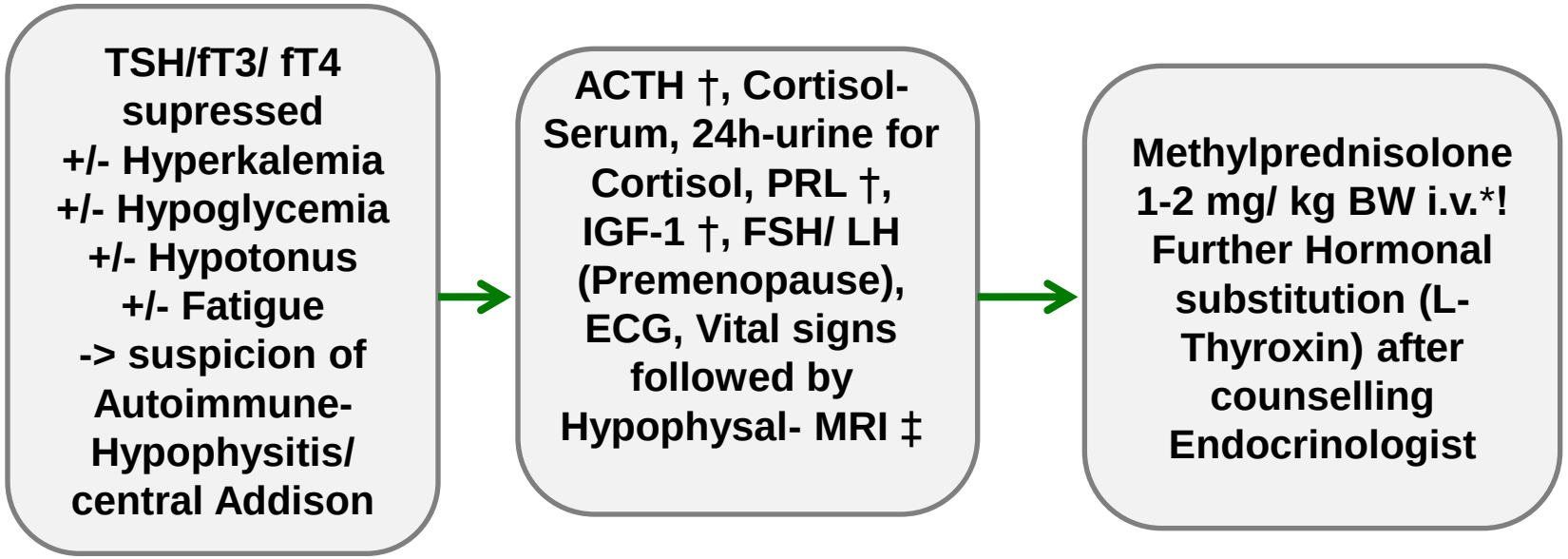
Hypophysitis-Management PD1/ PDL1-Inhibitors



† ACTH: adrenocorticotropal hormone, PRL: Prolactin, IGF-1: insulin growth factor-1
‡ Hypophysal-MRI after counselling neuroradiologist
* Stop treatment with Checkpoint-Inhibitors, prophylactic antibiotics with Ciprofloxacin 500 mg bid p.o., gastric ulcus prophylaxis with PPI, oral Potassium substitution.
Deescalate Methylprednisolone (reduced bioavailabilty of oral steroids), if Methylprednisolone 8 mg/d p.o. -> change to Hydrocortisone maintenance therapy (15-10-5 mg daily); no ACTH- controls
Addison-emergency pass; -> if stress (fever, deterioration of condition) increase dose to 45-30-15 mg tgl.
Continue treatment with Checkpoint-Inhibitors after clinical judgement

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

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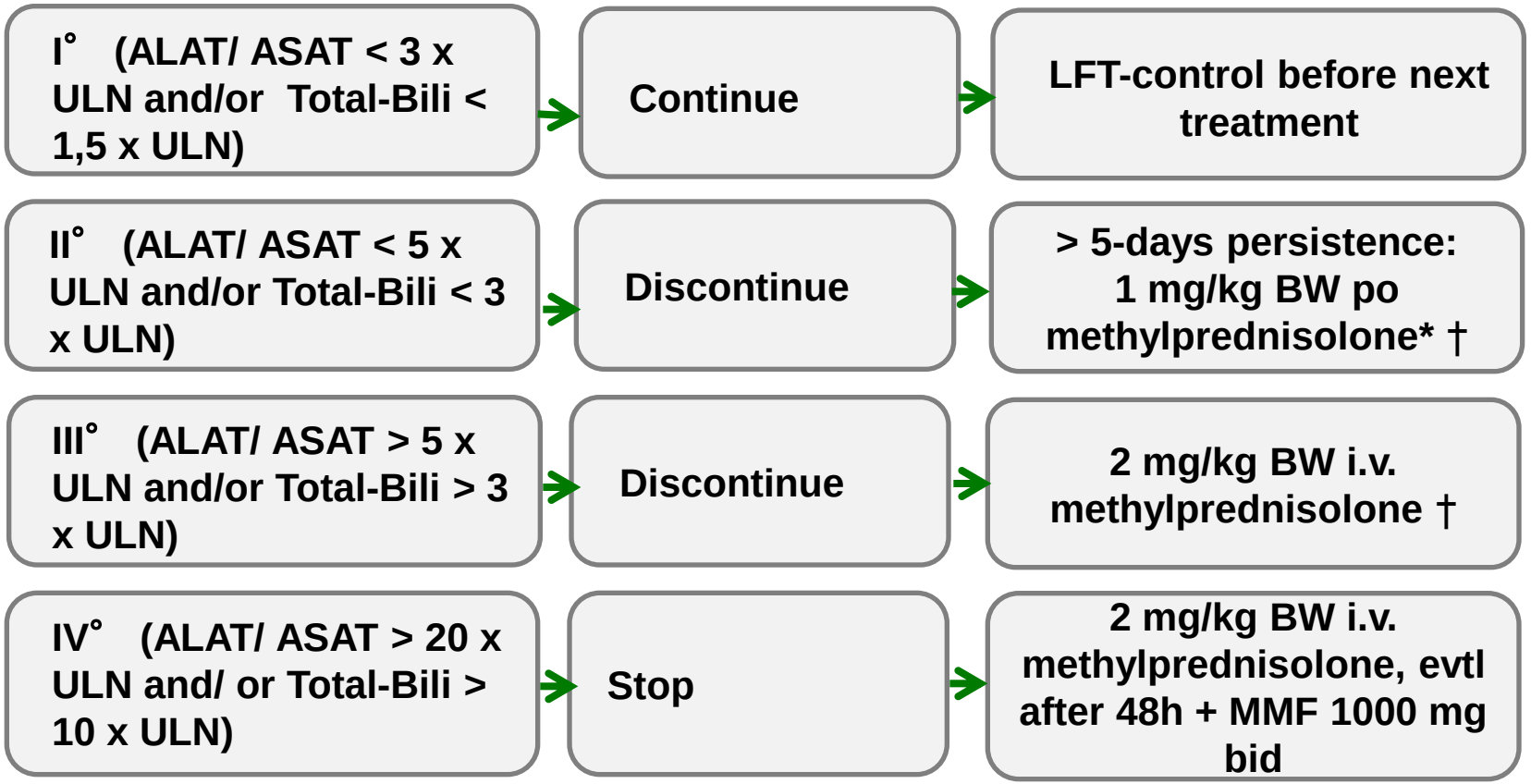
Hepatitis-Management PD1/ PDL1-Inhibitors



*** Prophylactic antibiotics with ciprofloxacine 500 mg bid p.o., gastric ulcer prophylaxis with PPI, oral potassium substitution. Reduced bioavailability of oral steroids, if no amelioration treat like Hepatitis III°**
† Sonography / CT Abd., HBV-/ HCV-/ CMV-/ EBV Serolog, IG-Elektrophoresis, ANA, ANCA, ASMA, AMA, anti-LKM1, anti-SLA, evtl liver biopsy. If amelioration, reduce to 1 mg/kg BW methylprednisolone i.v. (2 weeks followed by Steroid-Tapering (1 month), Start with PD1/ PDL1 Inhibitors when 10 mg/d prednisolone (8 mg/d methylprednisolone)

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

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Colitis-Management PD1/ PDL1-Inhibitors

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Diarrhea I° (< 3 x day)	Continue	Symptomatic treatment (Loperamide)
Diarrhea II° (4-6 x day)	Discontinue	> 5-days persistence: 1 mg/kg BW po methylprednisolone*
Diarrhea III° (7-10 x day)	Discontinue	2 mg/kg BW i.v. methylprednisolone †
Diarrhea IV° (>10 x day)	Stop	2 mg/kg BW i.v. methylprednisolone + evtl infliximab 5 mg/kg BW ‡

* Microbio dg (C-diff. exclusion). Prophylactic antibiotics with ciprofloxacin 500 mg bid p.o., gastric ulcer prophylaxis with PPI, oral potassium substitution. Reduced bioavailability of oral steroids: if no amelioration, treat like Diarrhea III°

† Coloscopy with sampling, CT-Abdomen if left Colitis (Diverticulitis-exclusion). If amelioration reduce to 1 mg/kg BW methylprednisolone i.v. (2 weeks) followed by Steroid-Tapering (1 month), Start with PD1/ PDL1 Inhibitors when 10 mg/d prednisolone (8 mg/d methylprednisolone)

‡ pretherapeutic HBV/ HCV/ CMV/ Tb-(Quantiferon) Serology, infliximab contraindicated if perforation/ sepsis; Apply 2h i.v. with 1,2 µm Filter (up to15% infusion reactions), evtl repeat day 15

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Thyroiditis-management PD1/PDL1-inhibitors

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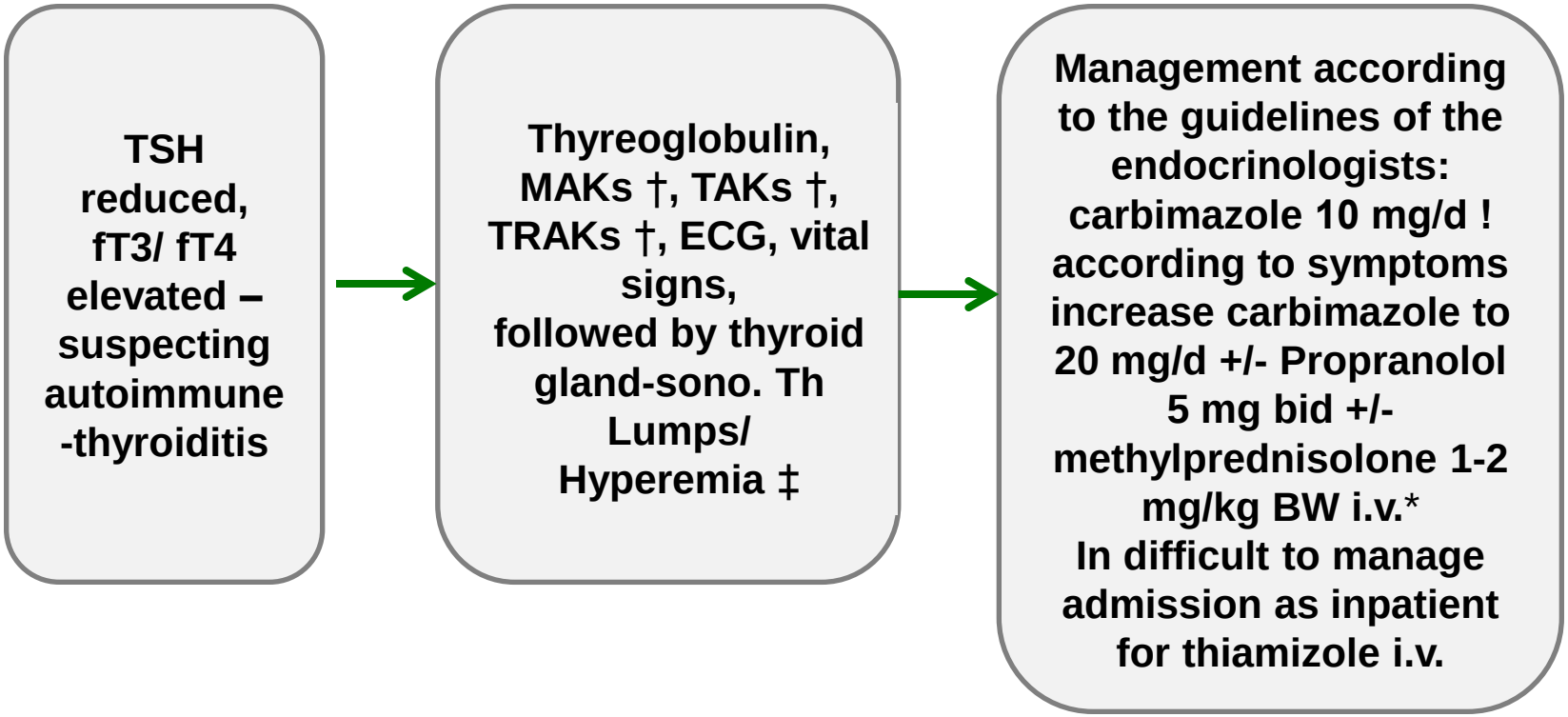

† MAKs: anti-TPO antibdoes, TAKs: anti-thyroglobulin-antibodies, TRAKs: anti-TSH-receptor-antibodies
‡ Thyroid gland sonography in endocrinology-outpatient clinic, refer
! With carbimazol discontinue therapy using checkpoint-inhibitors and weekly follow-ups of TSH/ fT3/ fT4/CBC, ALAT/ ASAT/ AP, continue treatment only if fT3/ fT4 are falling
* Prophylactic antibiotic using ciprofloxacine 500 mg bid p.o., gastric ulcer prophylaxis using PPI, oral potassium substitution, continue the management using checkpoint-inhibitors and oral methylprednisolone. N.B.: reduced bioavailabitiy of oral steroids

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

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Toxicities of New Drugs

Häufigste Nebenwirkungen im Verlauf einer Langzeit-Therapie mit Palbociclib in PALOMA-1

	Therapiedauer				
UE, %	**0 ≤ 6 Monate (n = 95)**	**6 ≤ 12 Monate (n = 77)**	**12 ≤ 18 Monate (n = 59)**	**18 ≤ 24 Monate (n = 40)**	**≥ 25 Monate (n = 29)**
Jegliche UE	97,9	88,3	81,4	72,5	79,3
Neutropenie	69,5	54,5	44,1	40,0	51,7
Leukopenie	33,7	27,3	16,9	20,0	13,8
Fatigue	33,7	14,3	13,6	10,0	10,3
Übelkeit	23,2	6,5	5,1	2,5	6,9
Anämie	22,1	19,5	15,3	15,0	13,8
Diarrhoe	18,9	0	5,1	2,5	10,3
Alopezie	16,8	2,6	1,7	0	3,4
Hitzewallung	16,8	7,8	0	0	0
Gelenkschmerzen	12,6	10,4	15,3	7,5	13,8
Dyspnoe	12,6	2,6	6,8	0	3,4
Appetitminderung	10,5	7,8	0	2,5	0
UE: unerwünschtes Ereignis					

N. Harbeck, J.Ettl, Drug Report, 2017

Monitoring Palbociclib

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Mögliche Neutropenie unter Palbociclib: Monitoring und Dosisanpassung	
Vor Beginn der Behandlung und zu Beginn jedes Zyklus sowie am 14. Tag der ersten 2 Behandlungszyklen und sofern klinisch indiziert, sollte eine Kontrolle des großen Blutbildes erfolgen.	
Hämatologische Toxizitäten	
CTCAE-Grad (Neutrophilenzahl)	**Dosisanpassungen**
Grad 1 (< unterer Grenzwert bis 1500/ml) **Grad 2** (1000 bis ≤ 1500/µl)	keine Dosisanpassung erforderlich
Grad 3[a] (500 bis < 1000/µl)	1. Tag des Zyklus: **Therapiepause** bis ≥ 1000/µl Neutrophilie wieder erreicht sind, nach 1 Woche erneute Blutbildkontrolle. Bei ≥ 1000/µl Neutrophilie den nächsten Zyklus in gleicher Dosierung beginnen. 14. Tag der ersten 2 Zyklen: Palbociclib mit aktueller Dosierung bis Zyklusende fortsetzen. Am 21. Tag erneute Blutbildkontrolle. Bei Grad-3-Neutropenie > 1 Woche oder rezidivierender Grad-3-Neutropenie Dosisreduktion in nachfolgenden Behandlungszyklen erwägen.
Grad 3 (500 bis < 1000/µl) + Fieber ≥ 38,5 °C und/oder Infektion	**Therapiepause** bis ≥ 1000/µl Neutrophilie. Wiederaufnahme mit 1 Dosisstufe niedriger.
Grad 4[a] (< 500/µl)	**Therapiepause** bis ≥ 1000/µl Neutrophilie. Wiederaufnahme in der nächst niedrigeren Dosisstufe.

N. Harbeck, J.Ettl, Drug Report, 2017

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Adverse Effects of Olaparib

Adverse effects (AE):	Grade and occurence	Management
Gastrointestinal AE (Nausea, vomiting, diarrhea):	- mostly gr. 1-2, - no prophylactic antiemetics necessary	- interruption / - dose reduction - antiemetics
Hematological AE (anemia, leucopenia, thrombocytopenia):	- mostly gr. 1-2, - CBC at the start and monthly (in the first 12 montlhs	- interruption / - dose reduction - if nec. GCSF, transfusion
Neurological system (headache, dizziness):	- mostly gr. 1-2,	- interruption / - dose reduction
Metabolism / Diet (reduced appetite):	- mostly gr. 1-2,	- interruption / - dose reduction