Nebenwirkungsprofil der verschiedenen TKIs beim radiojodrefraktären DTC und Nebenwirkungsmanagement

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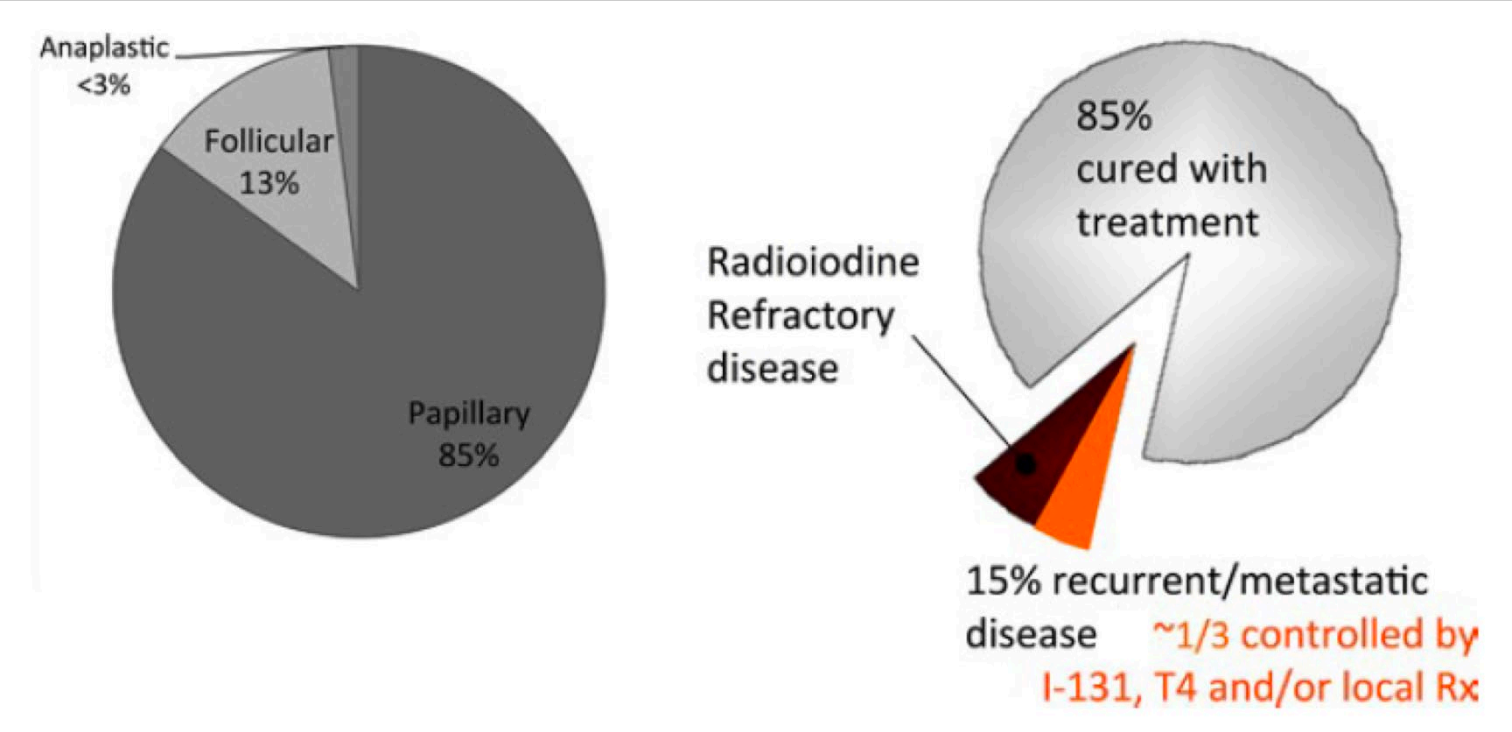
Disclosures

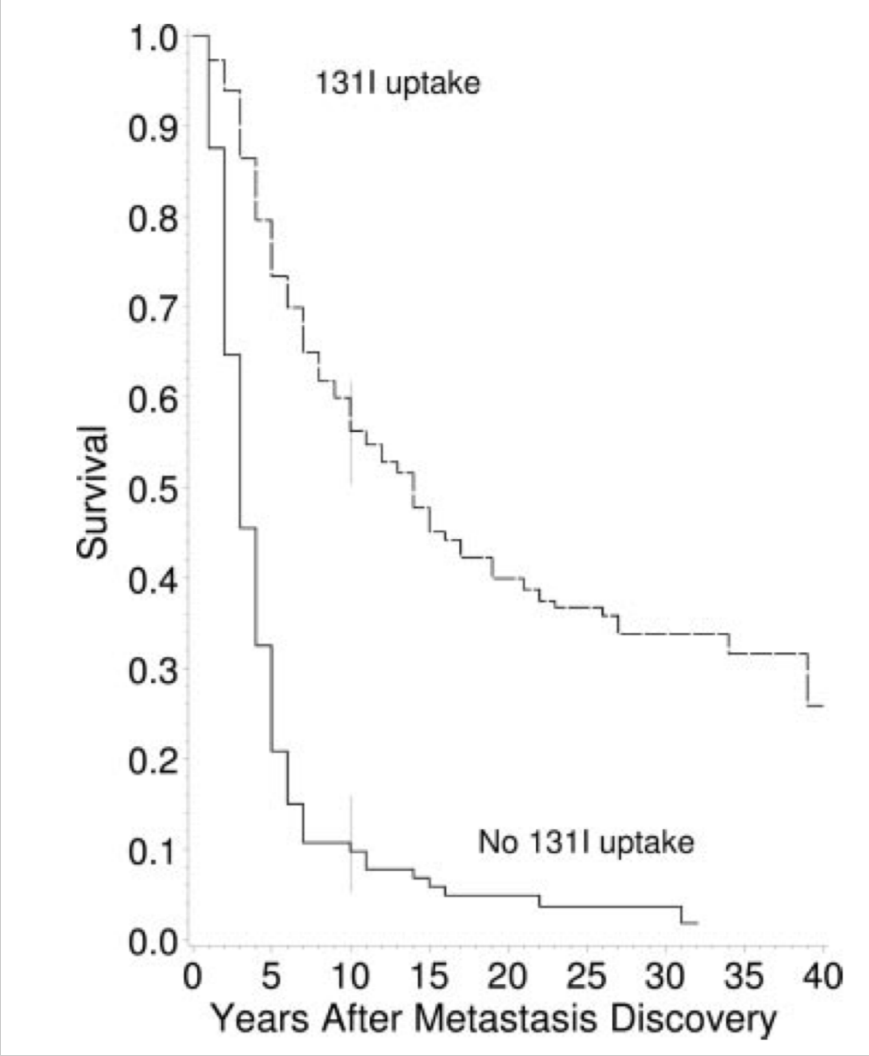
- Honoraria
  - Amgen, Bayer, Eisai, Incyte, Ipsen, Janssen, Novartis, Pfizer, Roche, Takeda
- Wissenschaftliche Unterstützung
  - Bayer, Incyte, Ipsen, Pfizer

DTC: Subtypen und Prognose



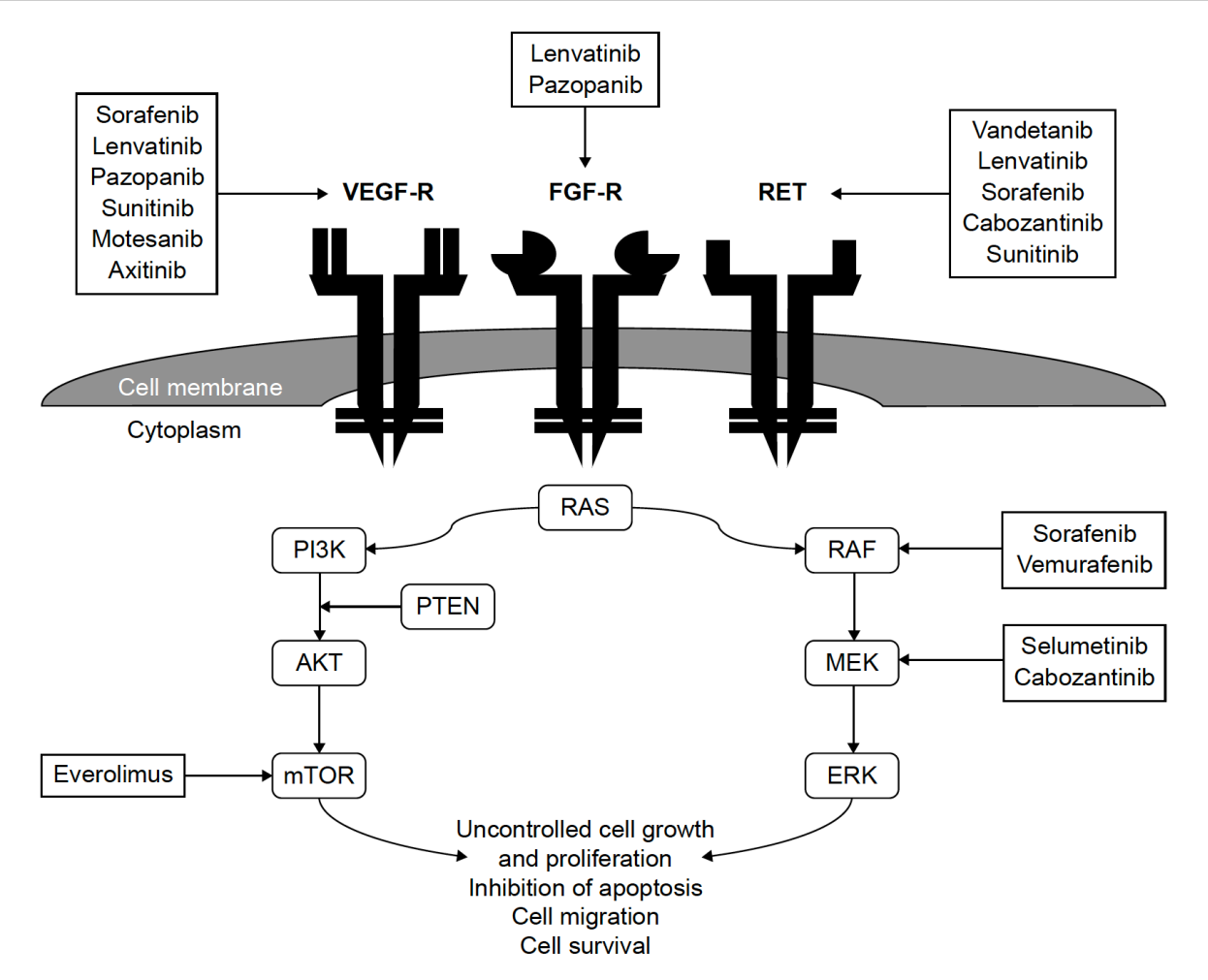
Gild et al. Clin Endocrinol 88: 529; 2018

Korrelation zwischen ^{131}I Aufnahme und OS bei nachweislicher Metastasierung



Durante et al. J Clin Endocr Metab 91: 2892; 2006

MAPK und PI3K-AKT-mTOR Signalkaskade



Larusso et al. OncoTargets Ther 9: 6467: 2016

FDA und EMA Zulassung zur Behandlung des RAI-R fortgeschrittenen DTC für Lenvatinib und Sorafenib

Drug study name	Daily dose	Enrolled subjects	Prior TKI	PFS (months)	SD (%)	CR (%)	PR (%)	Dose reduction or interruption (%)[a]	Number of deaths[c]
Lenvatinib SELECT	24 mg ×1	392	Yes	18.3 vs 3.6[b]	15.3	1.5	63.2	78.5; 14.2	6
Sorafenib DECISION	400 mg ×2	416	No	10.8 vs 5.8[b]	42	0	12.2	77.8; 18.8	1

Notes: [a]Due to AEs; [b]drug vs placebo; [c]drug related.
Abbreviations: TKI, tyrosine kinase inhibitor; PFS, progression free survival; SD, stable disease; CR, complete response; PR, partial response; AEs, adverse events.

Unterschiede:

SELECT: Vortherapie mit TKI war erlaubt – 20%-25% (keine Vortherapie bei DECISION)

SELECT: Progression von IRB beurteilt (DECISION: Beurteilung durch Investigator)

Larusso et al. OncoTargets Ther 9: 6467: 2016

Intolerabilität

Aus Sicht klinischer Studien

Aus Sicht des Behandelnden

Aus Sicht des Patienten

Intolerabilität – aus Sicht klinischer Studien

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Gastrointestinal disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by frequent and watery bowel movements.

Pinilla-Ibarz et al. Cancer 117: 688; 2011

Intolerabilität - aus Sicht des Behandelnden

- Intoleranz liegt dann vor, wenn aufgrund einer therapieassoziierten Nebenwirkungen von signifikanter medizinischer Relevanz die relative Dosisintensität über einen längeren Zeitraum um >25% unterschritten und dadurch eine suffiziente Tumorkontrolle nicht mehr gewährleistet wird.

Pinilla-Ibarz et al. Cancer 117: 688; 2011

Intolerabilität - aus Sicht des Patienten

- Intoleranz liegt dann vor, wenn der Patient eine therapieassoziierte Nebenwirkung unbestimmten Grades subjektiv nicht toleriert.
  - AEs führen zu keinem Therapieabbruch, üben jedoch neg. Einfluss auf QoL aus.

Pinilla-Ibarz et al. Cancer 117: 688; 2011

Einfluss der Nebenwirkungen auf die Behandlung

Variable	Lenvatinib[1]	Sorafenib[2]
# Patienten	261	207
Med. Behandlungsdauer (mo)	13.8	10.6
Dosis Unterbrechung (%)	82.4	66.2
Dosisreduktion (%)	67.8	64.3
Therapieabbruch wegen AEs (%)	14.2	18.8

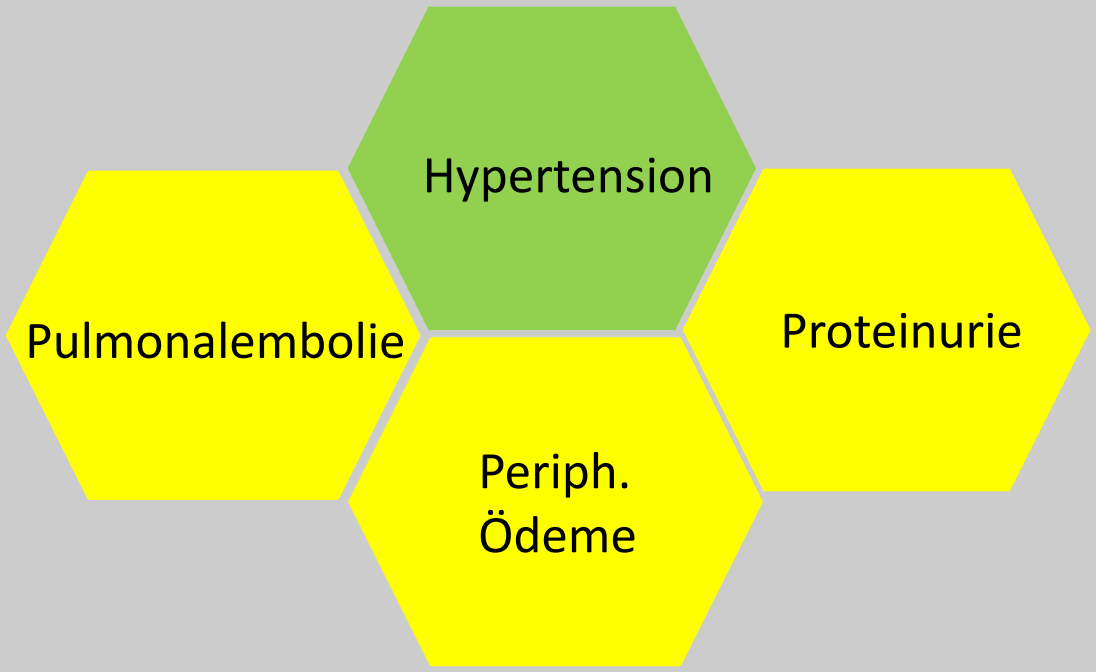
[1]Schlumberger et al. N Engl J Med 372: 621;K 2015
[2]Brose et al. Lancet 384: 319; 2014

Nicht-hämatologische Toxizitätsprofile

%	Lenvatinib[1] (N=261)	Sorafenib[2] (N=207)	Lenvatinib[1] (N=261)	Sorafenib[2] (N=207)
Hypertension	67.8	40.6	41.8	9.7
Diarrhoe	59.4	68.4	8	5.8
Fatigue	59	49.8	9.2	5.8
Inappetenz	50.2	31.9	5.4	2.4
Stomatitis	35.6	23.2	2.3	1
HFS	31.8	76.3	3.4	20.3
Proteinurie	31	-	10	-
Pruritus	-	14.5	-	1
Rash/desquam	16.1	50.2	0.4	4.8

all grades Grade: ≥ 3

[1]Schlumberger et al. N Engl J Med 372: 621;K 2015
[2]Brose et al. Lancet 384: 319; 2014



Lenvatinib

Sorafenib

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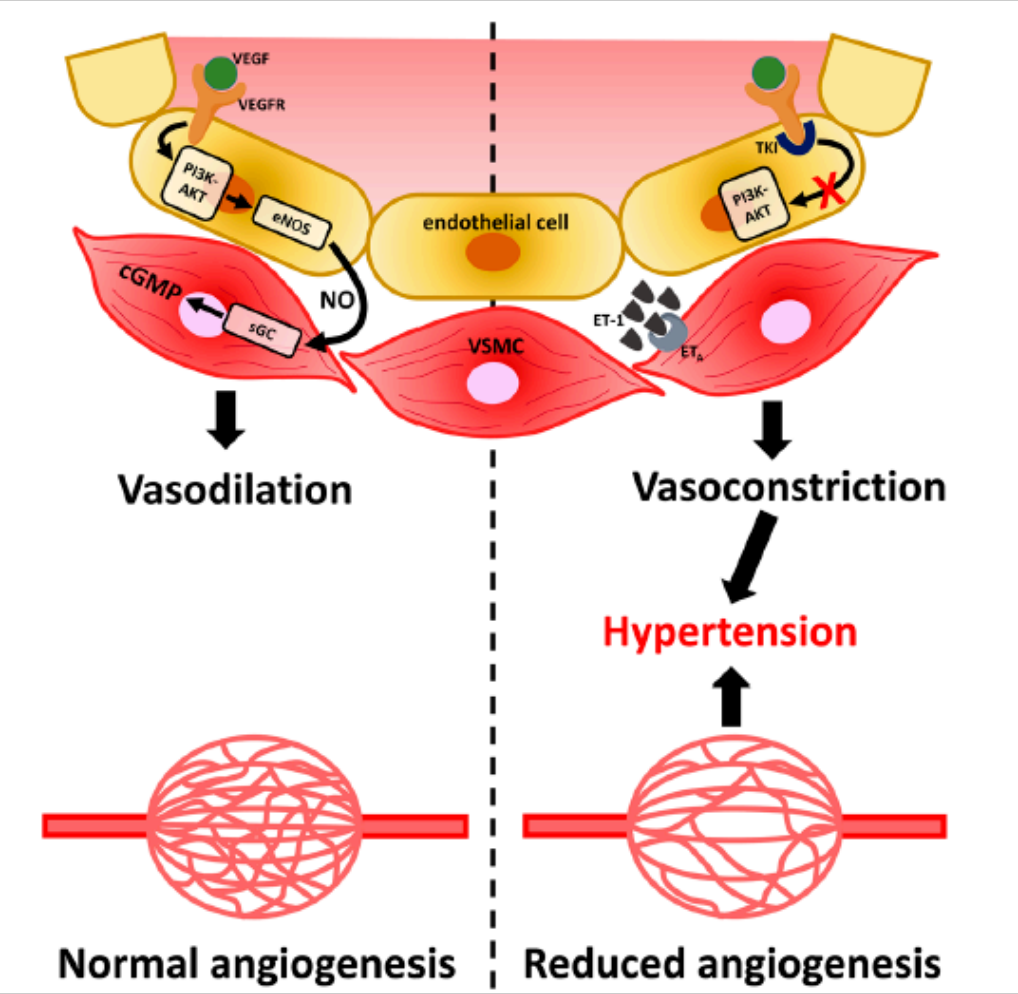
TKI Charakteristika

Drug	Targets	Half-Life	Bioavailability	Metabolism
Lenvatinib	VEGF-R1-3, FGFR1-4, PDGF-RA, c-KIT, RET	28 h	85%	Hepatic CYP3A4
Sorafenib	VEGF-R1-3, PDGF-RA-D, C-RAF, B-RAF	25–48 h	38%–49%	Hepatic CYP3A4

Ancker et al. Int J Mol Sci 18: 625; 2017

VEGF Effekt auf Blutdruck und Kapillarvaskularisation



Ancker et al. Int J Mol Sci 18: 625; 2017

Bluthochdruck – unterschiedliche Definitionen

Classification systems	CTCAE 3.0 (2006)(30)	CTCAE 4.03 (2010)(26)		JNC-7 (2003)(28)[b]		ESH/ESC (2013)(27)	
		Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Grade 1	Asymptomatic Transient (<24 h) Increase >20 (diastolic) > 150/100 if previously normal	120–139	80–89	140–159	90–99	140–159	90–99
Grade 2	Recurrent/persistent (≥24 h) symptomatic increase >20 (diastolic) > 150/100 if previously normal	140–159	90–99	≥160	≥100	160–179	100–109
Grade 3	Requiring >1 drug Requiring more intensive therapy than previously	≥160	≥100	ND	ND	≥180	≥110
Grade 4	Life-threatening consequences	Life-threatening consequences	ND	ND	ND	ND	ND
Grade 5	ND	Death	ND	ND	ND	ND	ND

Abbreviations: CTCAE common terminology criteria for adverse events, *JNC* joint national committee, *ESH* European society of hypertension, *ESC* European society of cardiology, *ND* not defined

[a] All numeric blood pressure values are in mm Hg

[b] The current JNC-8 report (2013) [115] does not classify grades of hypertension

Wasserstrum et al. Cardio-Oncol 1: 6; 2015

Beobachtungsstudie (n=74)
mcRCC: Sunitinib und Sorafenib

- Cardiovaskuläres Ereignis (33.8%)
  - Definition: Enzymauslenkung, symptomatische Arrhythmie, akutes Koronarsyndrom, neu aufgetretene linksventrikuläre Dysfunktion
  - Δ TKI Beginn bis CV-Ereignis: med. 8 Wochen
- Symptomatisches Ereignis (17.6%)
  - TKI Stopp bei allen Patienten
- Asymptomatisches Ereignis (16.2%)
  - TKI Stopp (n=2); Dosisreduktion (n=3)

- Kein Cardiovaskuläres Ereignis (66.2%)
  - EKG Veränderungen: 24.3%

Schmidinger et al. J Clin Oncol 26: 5204; 2008

Screeningparameter – cardiale Ereignisse

Variable	Baseline	3x /Tag	2x /Monat	1x /Monat
Anamnese	x		x	
CK	x		x	
CKMB	x		x	
TNT	x		x	
RR-Messung	x	x		
EKG	x			x
Echocardiographie*	x			

* Risikopersonen

Proteinurie: 1x /Monat; Blutbild + Elyte: 1x /Monat

Schmidinger et al. J Clin Oncol 26: 5204; 2008

Möglichkeiten einer medikamentösen Intervention

Class	Drug	Dose	Recommendation
CCB Dihydropyridines	Amlodipine	2.5–10 mg/day	Great potency for reducing arterial smooth muscle cell contractility [39], effective therapy [49].
ACEi	Enalapril	Start with 5–20 mg/12–24 h, then max 40 mg/12–24 h	Particularly indicated in the setting of proteinuria [39], effective [49].
	Ramipril	Start with 2.5 mg/day, then 5 mg/day after 2 weeks, after another 2 weeks max 10 mg/day	
ARB	Losartan	50–100 mg/day	Particularly indicated in the setting of proteinuria [39], effective [49].
	Valsartan	80–320 mg/day	
	Irbesartan	150–300 mg/day	
BBA	Nebivolol	2.5–5 mg/day	Indicated for DTC; begin therapy of hypertension with a BBA [53].
Diuretics/Thiazides	Hydrochlorothiazide	Start with 12.5–25 mg/day, then 12.5 mg/day	Less-effective than CCB, ACEi or ARB [39], but often used [54].
Nitrate derivates	Long-acting nitrates: Isosorbide dinitrate (ISDN) or Isosorbide mononitrate (ISMN)	40–60 mg/day	Adequate response in hypertension refractory to ACEi and CCB [51].
α-blockers	Prazosin	2–20 mg/day	Used as additional therapy if BP is not sufficiently controlled.

CCB, calcium channel blockers; ACEi, Angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BBA, β-adrenoceptor antagonists; d, day.

Ancker et al. Int J Mol Sci 18: 625; 2017

Möglichkeiten einer medikamentösen Intervention

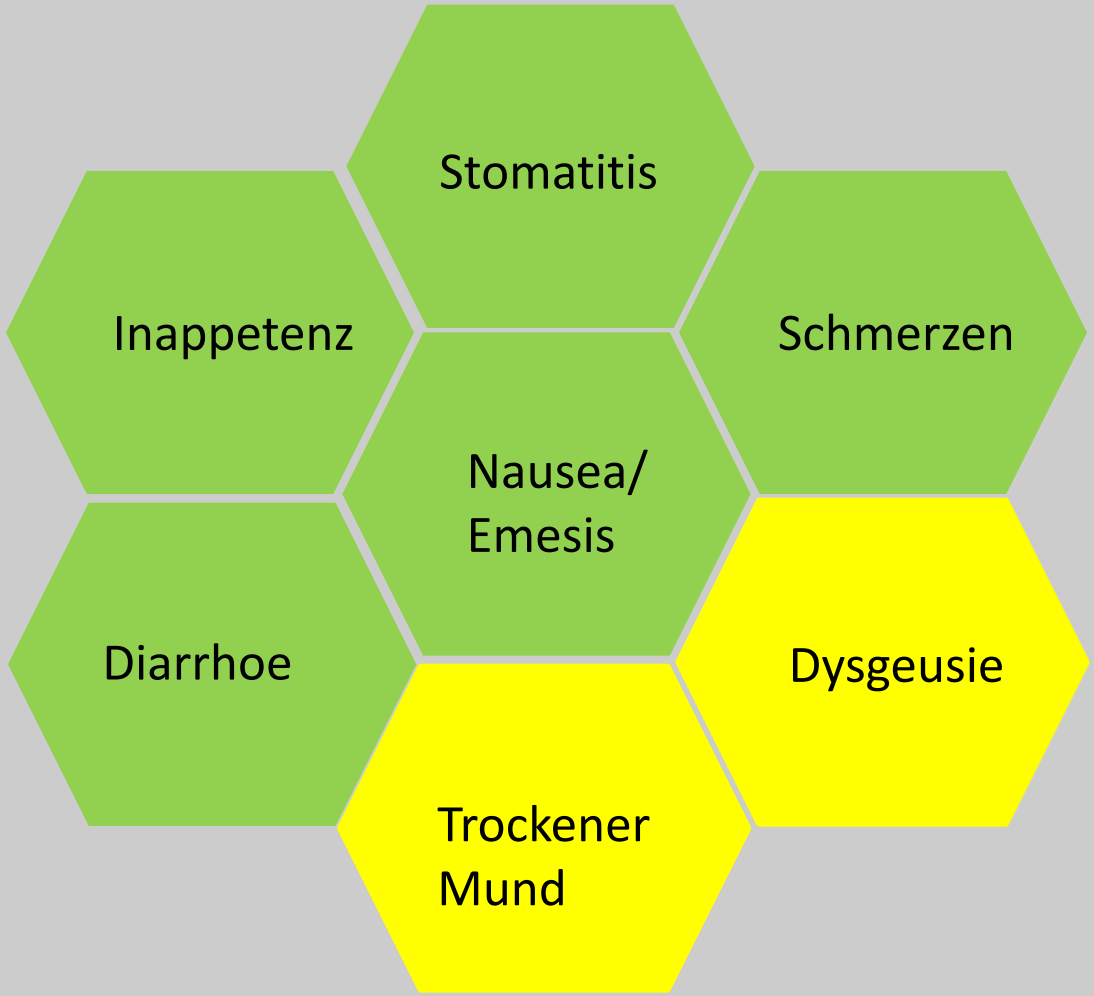
Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used.It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations (e.g. angina, post-myocardial infarction, heart failure, or heart rate control).
It is recommended to initiate antihypertensive treatment with a two-drug combination, preferably in an SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is < 150 mmHg) [342,346,351].
It is recommended that if BP is not controlled[e] with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker with a CCB and thiazide/thiazide-like diuretics, preferably as an SPC.
It is recommended that if BP is not controlled[e] with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alpha-blocker.
The combination of two RAS blockers is not recommended.

Williams et al. ESC/ESH guidelines 2018

CVD Risikomanagement bei Hypertension

Cardiovascular risk assessment with the SCORE system is recommended for hypertensive patients who are not already at high or very high risk due to established CVD, renal disease, or diabetes.
For patients at high or very high cardiovascular risk, statins are recommended.
Antiplatelet therapy, in particular low-dose aspirin, is recommended for secondary prevention in hypertensive patients.
Aspirin is not recommended for primary prevention in hypertensive patients without CVD.

Williams et al. ESC/ESH guidelines 2018



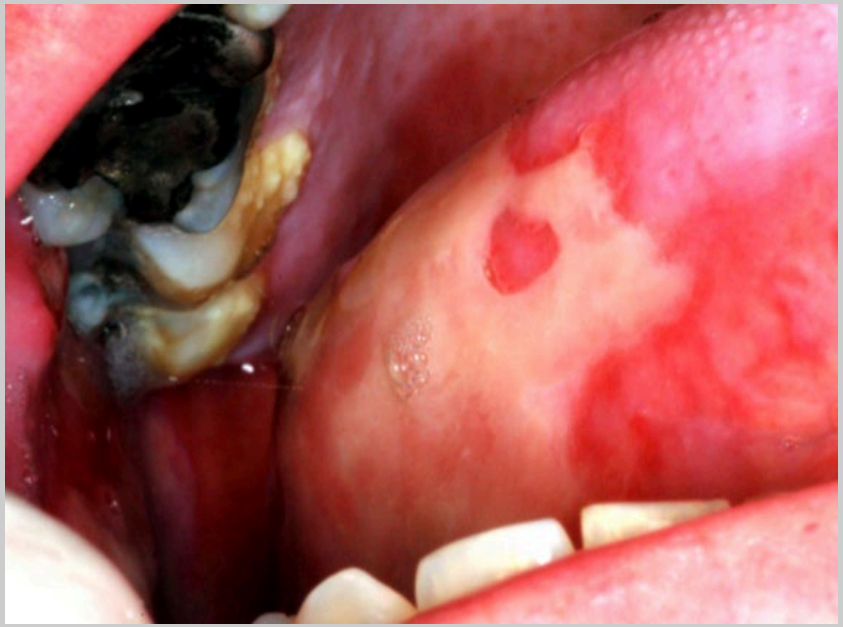
Lenvatinib

Sorafenib

Len + Sor

Stomatitis Management

- Schmerzkontrolle:
  - 2% visköses Lidocain
- Nahrungsergänzung
  - Hochkalorische, flüssige Nahrungsergänzungsmittel
- Mundhygiene
- Palliation einer trockenen Mundschleimhaut
  - Caphosol®
- Therapeutische Intervention
  - Orale Kryotherapie
  - Palifermin (rec. Humaner Keratozytenwachstumsfaktor)
  - „low-level“ Laser



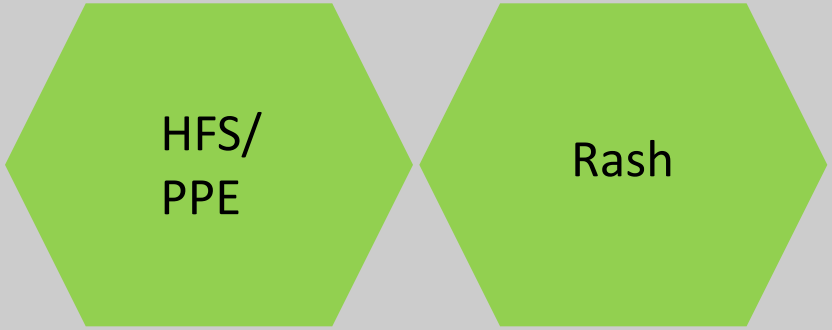
Lalla et al. MASCC/ISOO mucositis guidelines 2014

Diarrhoe Management

CTCAE Grade	Managing
1 or 2	Adjust diet Loperamide at the beginning 4 mg orally, then 2 mg every 2–4 hours after 12 hours without diarrhoea Continue TKI therapy
3 or 4	See grade 2 recommendations Hospitalisation and parenteral hydration is recommended TKI therapy should be interrupted until regression of the side effects to grade 1

CTCAE — Common Toxicity Criteria for Adverse Events

Pluzanski et al. Oncol Clin Pract 12: 113: 2016



Lenvatinib

Sorafenib

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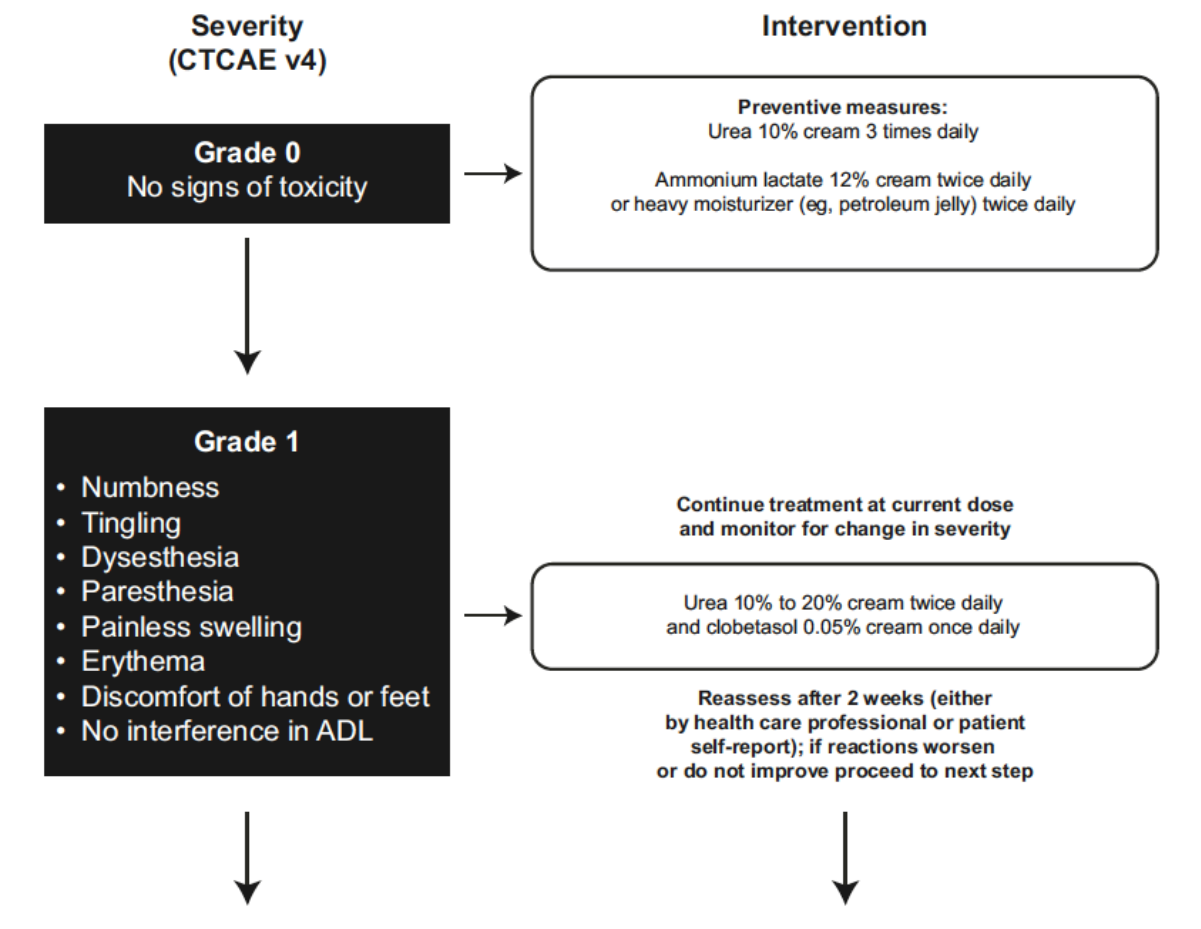
Hand-Fuss Syndrom/Palmar-plantare Erythrodysästhesie (HFS/PPE)

- Hitze vermeiden
  - Heisses Wasser, Sonne, Sauna etc
- Reibung und Krafteinwirkung vermeiden
  - Sportliche Aktivitäten (Tennis, Gewichte, Joggen etc), barfuss Gehen
- Tragen von Baumwollhandschuhen unter Gummihandschuhen
  - Für Haushaltstätigkeiten
- Lockeres Schuhwerk tragen
- Pädiküre/Maniküre
  - Entfernung einer derben Hornhautschicht, Nagelpflege

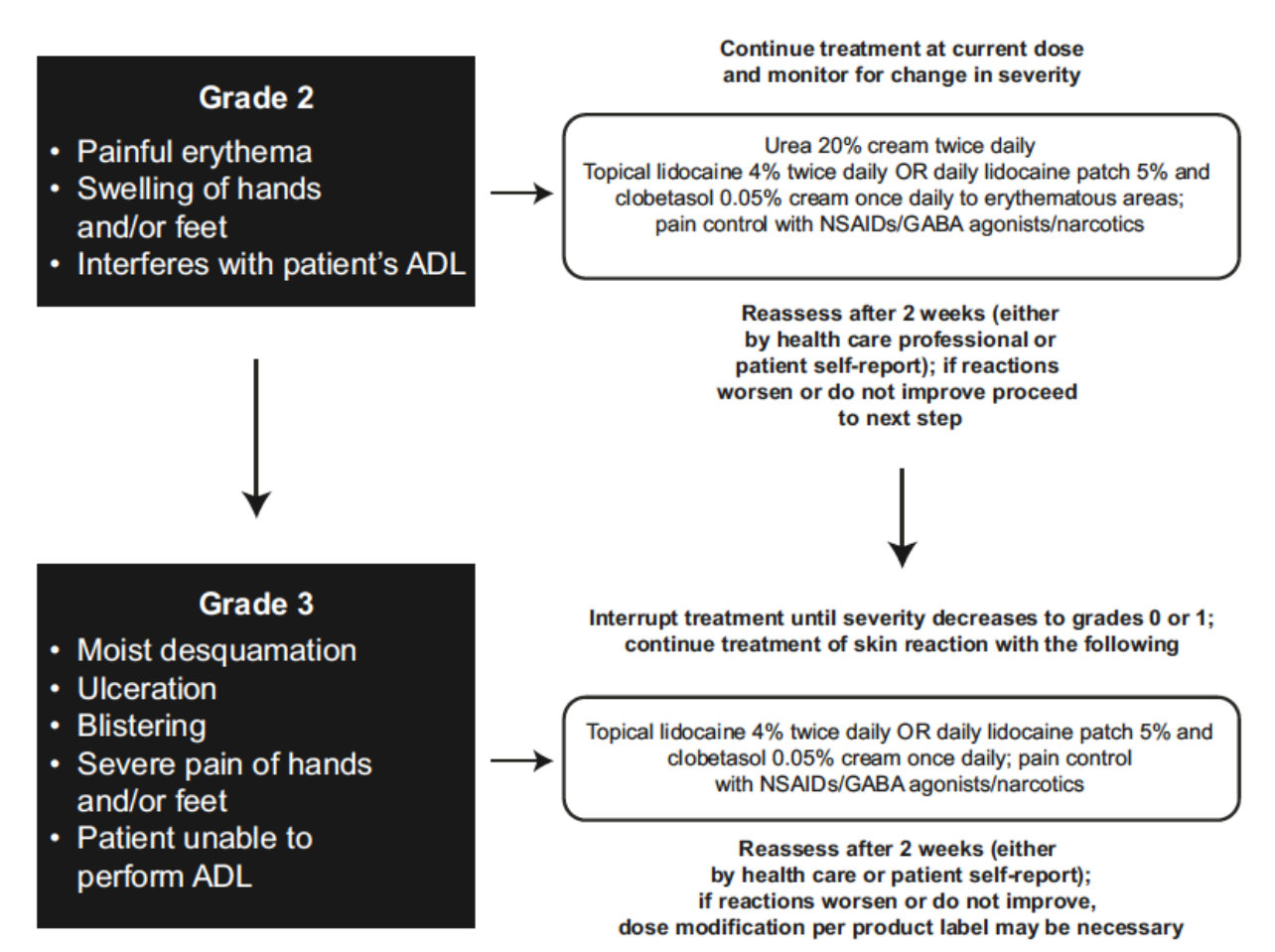
Cancer.net 2019 (ASCO.org)

Hand-Fuss Syndrom/Palmar-plantare Erythrodysästhesie (HFS/PPE)



Cabanillas et al. Sem Oncol 46: 57; 2019

Hand-Fuss Syndrom/Palmar-plantare Erythrodysästhesie (HFS/PPE)



Cabanillas et al. Sem Oncol 46: 57; 2019

Rash - Behandlungsalgorithmus

CLEANSING	+	SKIN CARE	+	ANTIBIOTICS AND PROPHYLAXIS
Sunlight protection (factor ≥ 25)		**Hydrophilic cream**		**Oral antibiotics prophylaxis**
For example: Daylong extreme® ► **LOE IB recommendation degree B**		For example: DAC basic cream, Hydroderm® face fluid ► **LOE IV recommendation degree B**		For example: Doxycycline (100–200 mg/day for ≥ 8 weeks) ► **LOE IA recommendation degree A** OR Minocycline (100 mg/day for ≥ 8 weeks) ► **LOE IA recommendation degree A**

Severity grade of skin rash?

mild

Oral antibiotics – options:
Doxycycline 100-200 mg / day
Minocycline 100 mg / day *or / and*

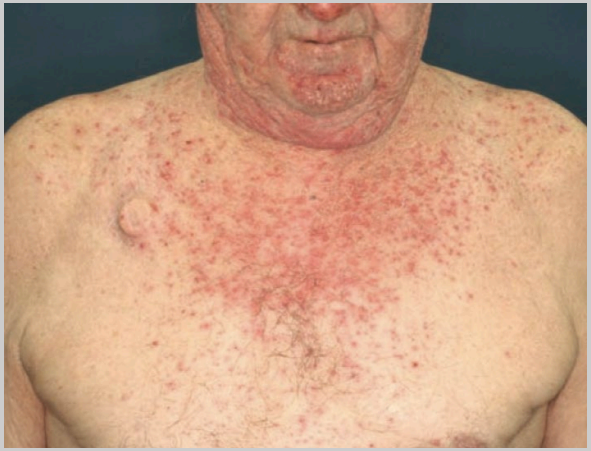
Topical antibiotics – options:
Erythromycin 2% in DAC basis cream
Nadifloxacin cream
Metronidazole cream
Alternatively, vitamin K1 cream

No effect or worsening with topical antibiotics → **Topical antibiotics (see left side) plus twice-daily topical corticosteroids:**
Prednicarbate cream (face)
Betamethasone lotion / cream (body)

No effect or worsening →
- **Dose reduction according to label**
- **Therapy as for "moderate." If no immediate improvements - consultation of dermatologist**
- **Experienced therapists - isotretinoin if oral antibiotics are not successful (discontinue oral antibiotics)**

moderate → **Topical antibiotics (see left side) plus twice-daily topical corticosteroids:**

severe →
- **Dose reduction according to label**
- **Therapy as for "moderate." If no immediate improvements - consultation of dermatologist**
- **Experienced therapists - isotretinoin if oral antibiotics are not successful (discontinue oral antibiotics)**



Hofheinz et al. Oncologist 21: 1483; 2016

Fatigue

Lenvatinib

Sorafenib

Len + Sor

Fatigue – screening Instrumente

TABLE 2. Selected Self-Report Instruments for Assessing Cancer-Related Fatigue

MEASURE (SOURCE)	OUTCOMES	ADDITIONAL COMMENTS
BFI (Mendoza 1999[55])	Total fatigue score and scores for fatigue severity and interference	
EORTC QLQ-C30 fatigue scale (Whitehead 2009[56])	Total score reflecting fatigue severity	Embedded within the 30-item EORTC QLQ-C30
EORTC QLQ-FA13 (Weis 2013[57])	Scores for physical, emotional, and cognitive fatigue; fatigue interference; and social sequelae of fatigue	Currently undergoing psychometric validation in a large international sample
FACIT-F scale (Yellen 1997[58])	Total score reflecting fatigue severity	Referred to as FACIT-F when used with the 27-item FACT-G
FQ (Chandler 1993[59])	Scores for physical and mental fatigue	Also known as the CFS and the BFS
FS-A (Mandrell 2011[60])	Total score reflecting fatigue severity	For ages 13–18 y
FS-C (Hinds 2010[61])	Total score reflecting fatigue severity	For ages 7–12 y; parent and staff versions also available
FSI (Hann 1998[62])	Scores for fatigue severity, interference, and duration and for diurnal variation in fatigue	
MFI (Smets 1995[63])	Scores for general, physical, and mental fatigue and for reduced activity and motivation	
MFSI-SF (Stein 1998[64])	Total fatigue score and scores for general, physical, emotional, and mental fatigue and for vigor	
PedsQL MFS (Varni 2002[65])	Scores for general fatigue, sleep/rest fatigue, and cognitive fatigue	Separate self-report forms for ages 5–7 y, 8–12 y, and 13–18 y; parent proxy form also available
PFS-12 (Reeve 2012[66])	Scores for behavioral, affective, sensory, and cognitive fatigue	
POMS-F (McNair 1971[67])	Total score reflecting fatigue severity	Embedded within the 65-item POMS
PROMIS-F short forms (PROMIS 2014[68])	Total score reflecting fatigue severity can be obtained based on raw scoring or response pattern scoring	
PROMIS-F pediatric short form (PROMIS 2014[68])	Total score reflecting fatigue severity can be obtained based on raw scoring or response pattern scoring	For ages 8–17 y; parent proxy form also available
SCFS-R (Schwartz & Meek 1999[69])	Yields total fatigue score and scores for physical and perceptual fatigue	

Abbreviations: BFI, Brief Fatigue Inventory; BFS, Bidimensional Fatigue Scale; CFS, Chalder Fatigue Scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30; EORTC QLQ-FA13, European Organization for Research and Treatment of Cancer-Fatigue Quality-of-Life Questionnaire-13; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-G, Functional Assessment of Cancer Therapy-General; FQ, Fatigue Questionnaire; FS-A, Fatigue Scale-Adolescent; FS-C, Fatigue Scale-Child; FSI, Fatigue Symptom Inventory; MFI, Multidimensional Fatigue Inventory; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; PedsQL MFS, Pediatric Quality-of-Life Inventory Multidimensional Fatigue Scale; PFS-12, Piper Fatigue Scale-12; PFS-R, Piper Fatigue Scale-Revised; POMS, Profile of Mood States; POMS-F, Profile of Mood States-Fatigue; PROMIS-F, Patient Reported Outcome Measurement Information System-Fatigue; SCFS-R, Schwartz Cancer Fatigue Scale-Revised.

Berger et al. CA Cancer J Clin 65: 190; 2015

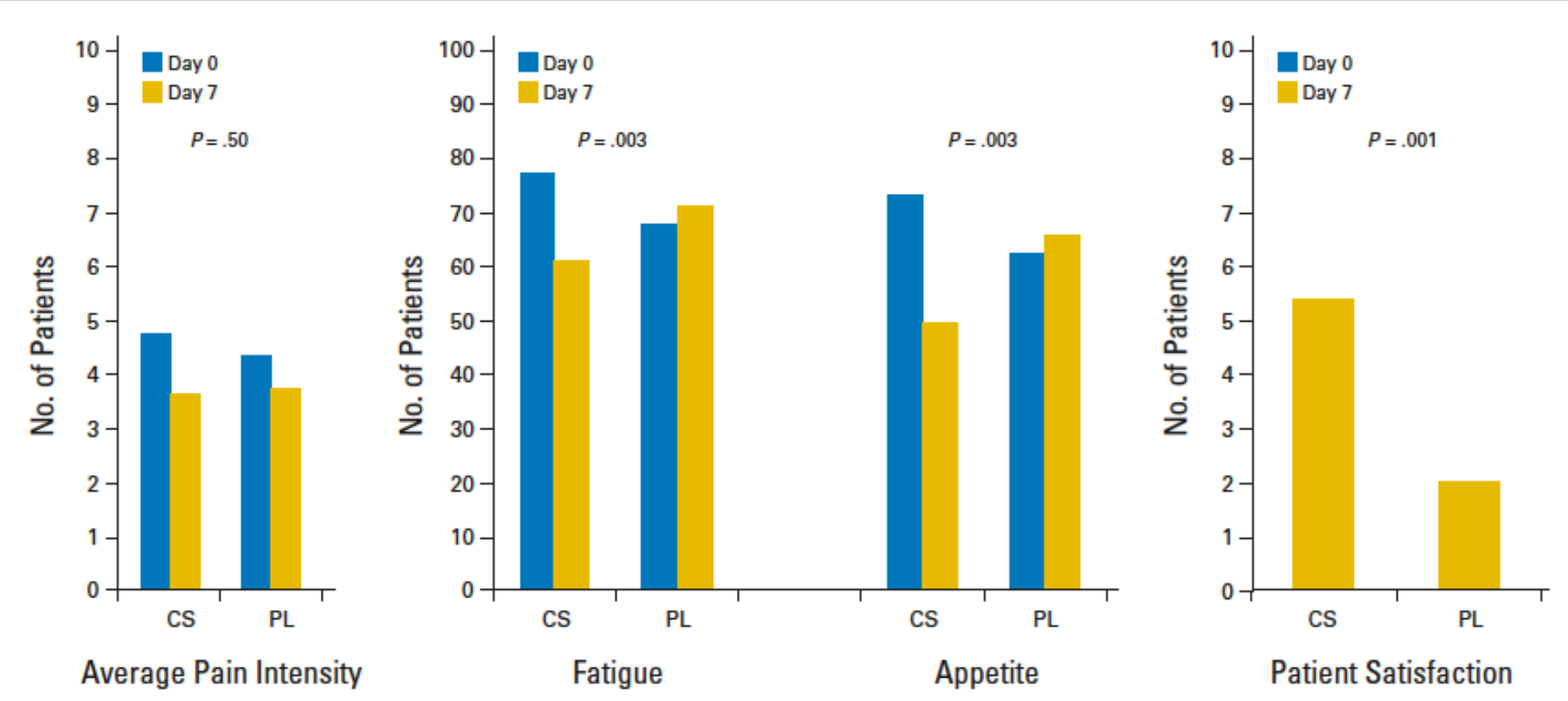
Fatigue – nicht-medikamentöse Interventionen

INTERVENTIONS IDENTIFIED AS LIKELY TO BE BENEFICIAL BY THE NCCN (NCCN 2015[4]), ONS (ONS 2014[7]), CPAC/CAPO (HOWELL 2013[9]), AND ASCO (BOWER 2014[10])
Address treatable contributors to fatigue
Manage concurrent symptoms
Physical activity/exercise
Rehabilitation
Psychoeducation
Meditation, mindfulness-based stress reduction, and cognitive-behavioral stress management
Relaxation
Cognitive-behavioral therapy for fatigue, depression, and pain
Cognitive-behavioral therapy for sleep
Yoga

Abbreviations: ASCO, American Society of Clinical Oncology; CPAC/CAPO, Canadian Partnership Against Cancer/Canadian Association of Psychosocial Oncology; NCCN, National Comprehensive Cancer Network; ONS, Oncology Nursing Society.

Berger et al. CA Cancer J Clin 65: 190; 2015

RCT: Methylprednisolon 2x16mg für 7 Tage (n=49)



Paulson et al. J Clin Oncol 32: 3221; 2014

Zusammenfassung

- Ein Großteil der TKI-assoziierten Nebenwirkungen kann durch prophylaktische und/oder Supportivmaßnahmen gut kontrolliert werden
- Therapieunterbrechungen oder Dosismodifikationen können bei bestimmten Nebenwirkungen erforderlich sein.

- Sorgfältige Indikationsstellung
  - Beginn der Therapie
  - Relative Kontraindikationen (Schlechte cardiale Pumpfunktion, Wundheilungsstörungen, geringes Körpergewicht, Tumor infiltriert große Gefäße, Trachea, Ösophagus etc)