EVENTI AVVERSI DELLA TERAPIA SISTEMICA:

QUALI CAUSE? QUALI TERAPIE?

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UNIVERSITÀ DEGLI STUDI DI MILANO
LA STATALE

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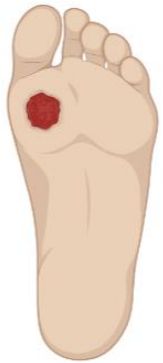
Endo-ERN
European Reference Network on Rare Endocrine Conditions

European Reference Network

The initiation of TKI treatment for advanced MTC
needs to balance the improvement in PFS with tolerability of adverse effects.

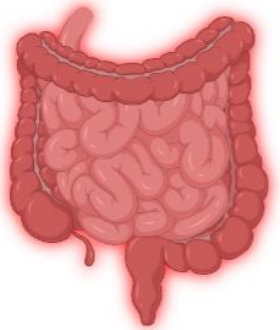


fatigue

skin reactions

Main severe toxicities

Gastro intestinal system



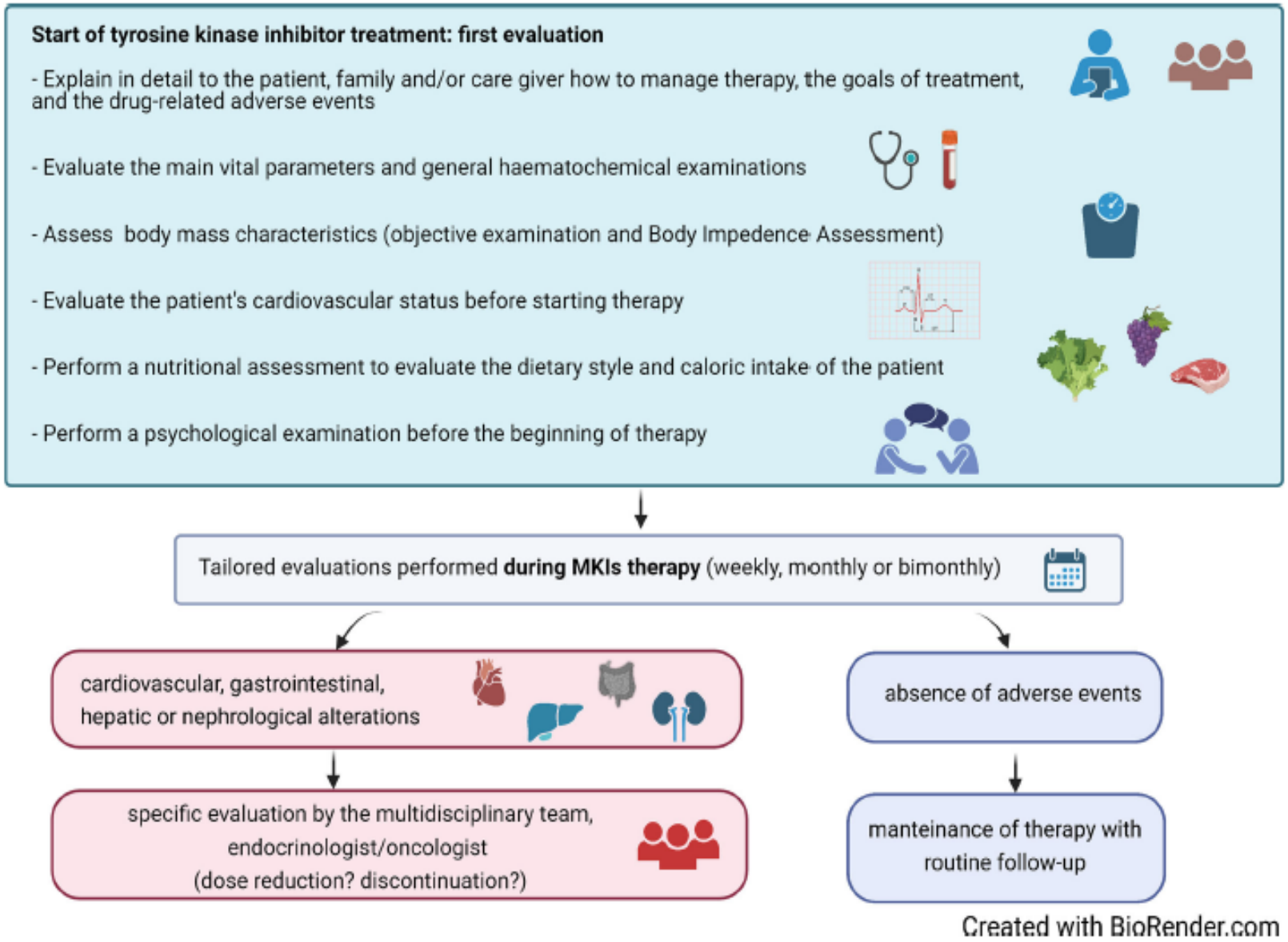
VEGF block of cardiovascular system (hypertension, long QT interval, renal dysfunction, proteinuria, haemorrhage, arterial/ venous thromboembolism)

AEs Treatment

symptomatic treatment of adverse events

dose reduction

Drug interruption, restarting at a lower dose



Colombo et al., Front Oncol. 2022

Clinical Trials

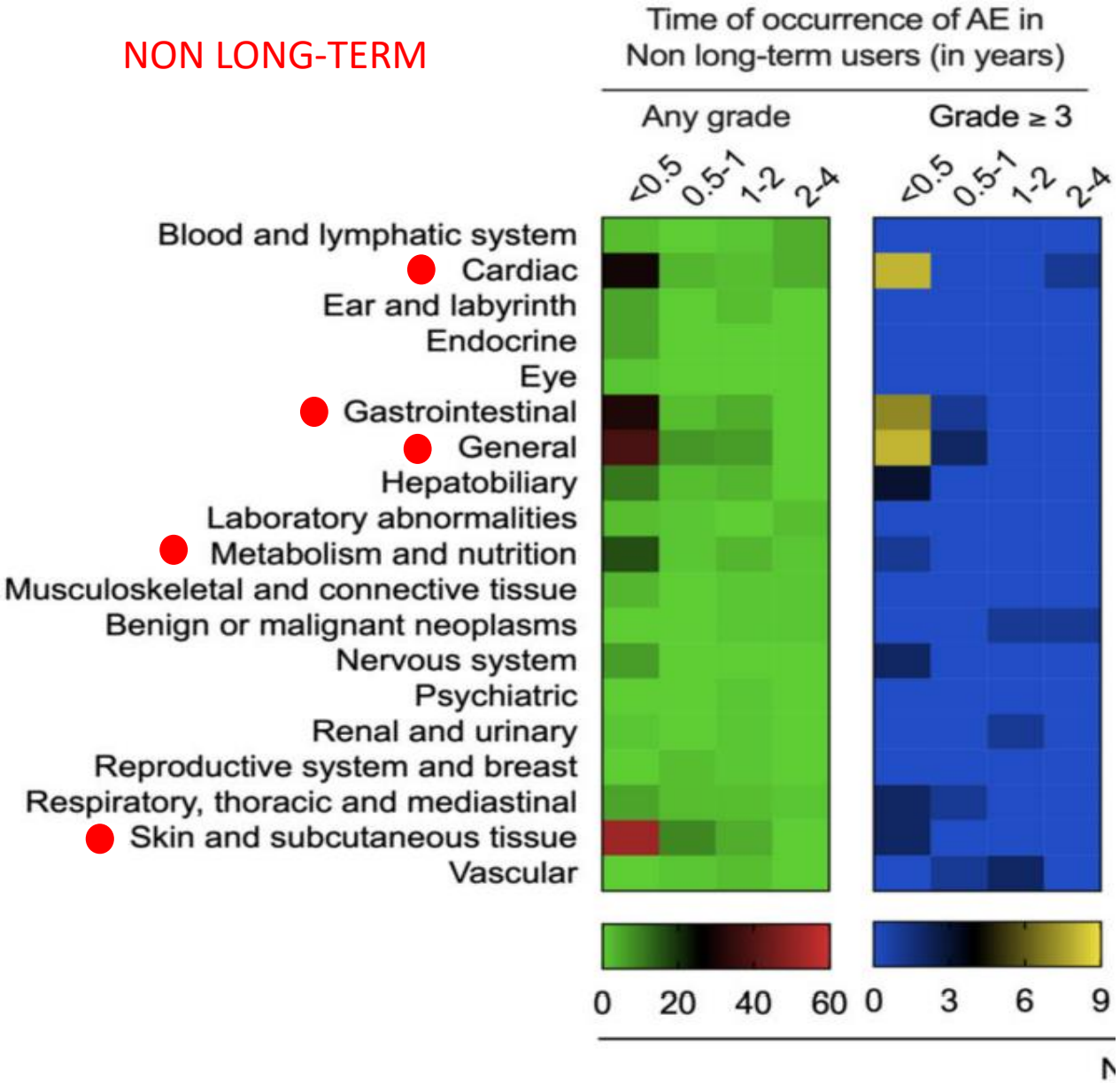
TABLE 1 | The main characteristics of the ZETA, EXAM, and SELECT trials, including eligibility criteria and adverse events (AEs).

Drug	Trial	Trialdesign	Patients (n)	Eligibility criteria	All grades AEs (%)		Grade > 3 AEs (%)	
Lenvatinib	SELECT Schlumberger et al., 2015 (2)	Phase III, randomized, double-blind, vs. placebo	261	18 years or older + measurable, pathologically confirmed DTC + 131I-refractory disease	Hypertension	67.8	Fatigue/asthenia	27.5
					Diarrhea	59.4	Nausea	13.7
					Fatigue/asthenia	59	Decreased appetite	11.5
					Decreased weight	50.2	Decreased weight	9.2
					Nausea	41	Hypertension	9.2
					Stomatitis	35.6	Diarrhea	8.4
Vandetanib	ZETA Wells et al., 2011 (17)	Phase III, randomized, double-blind, vs placebo	231	Adults + measurable, unresectable, advanced/ metastatic MTC + performance status ¾ 2 + serum CT ≥ 500 pg/ml	Diarrhea	56	Diarrhea	11
					Rash	45	Hypertension	9
					Nausea	33	QT prolonged	8
					Hypertension	32	Fatigue	6
					Headache	26	Decreased appetite	4
					Fatigue	24	Rash	4
Cabozantinib	EXAM Elisei et al., 2013 (25)	Phase III, randomized, double-blind, vs. placebo	219	Adults + unresectable, advanced/metastatic MTC + disease progression within the prior 14 months	Hypertension	32.7	Hypertension	8.4
					Hemorrhage	25.2	Venous thrombosis	5.6
					Venous thrombosis	5.6	Non-GI fistula	3.7
					GI perforation	3.7	Hemorrhage	3.3
					Non-GI fistula	3.7	GI perforation	3.3
					Arterial thrombosis	2.3	Arterial thrombosis	0.9

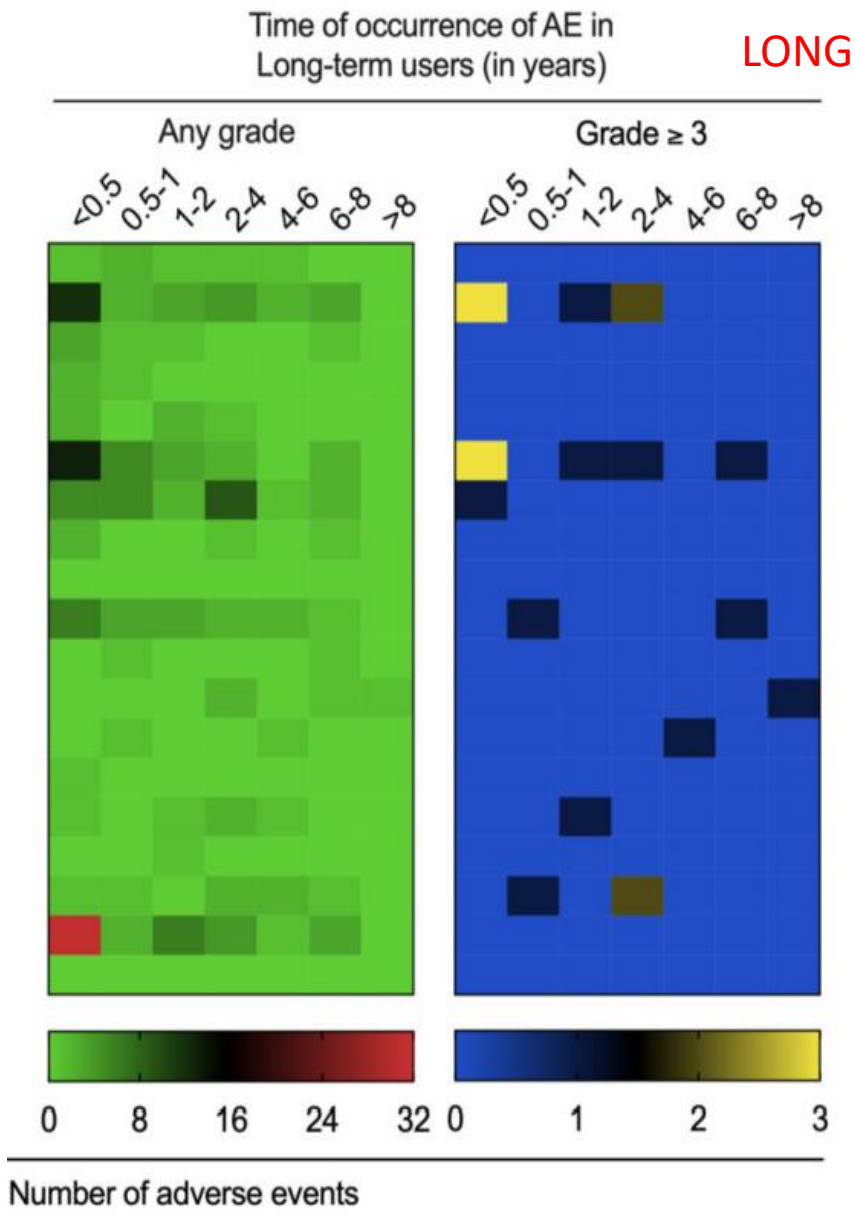
Colombo et al., Front Oncol. 2022

Long-term follow-up and safety of Vandetanib for advanced medullary thyroid cancer

NON LONG-TERM



LONG-TERM



Helton Estrela Ramos et al., Endocrine 2021

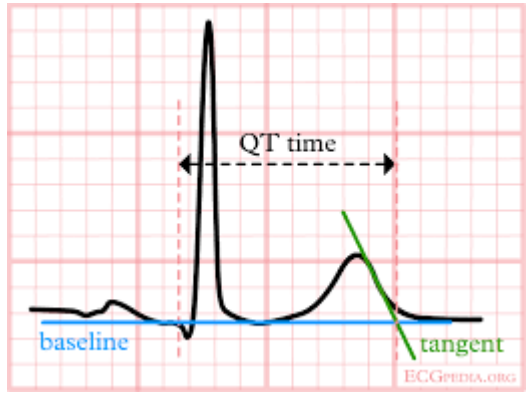
In Long-term Vandetanib Users

More frequently observed:

- Folliculitis
- Diarrhea
- Hypertension (in some patients uncontrolled)
- Weight loss
- Blue spot
- Corneal deposits

Adverse events (grade ≥ 3):

- QTC prolongation



Helton Estrela Ramos et al., Endocrine 2021

VOLUME 31 · NUMBER 29 · OCTOBER 10 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cabozantinib in Progressive Medullary Thyroid Cancer

Rossella Elisei, Martin J. Schlumberger, Stefan P. Müller, Patrick Schöffski, Marcia S. Brose, Manisha H. Shah, Lisa Licitra, Barbara Jarzab, Viktor Medvedev, Michael C. Kreissl, Bruno Niederle, Ezra E.W. Cohen, Lori J. Wirth, Haythem Ali, Colin Hessel, Yifah Yaron, Douglas Ball, Barry Nelkin, and Steven I. Sherman

Table 2. AEs Occurring in ≥ 10% of Cabozantinib-Treated Patients, by Maximum Severity Reported

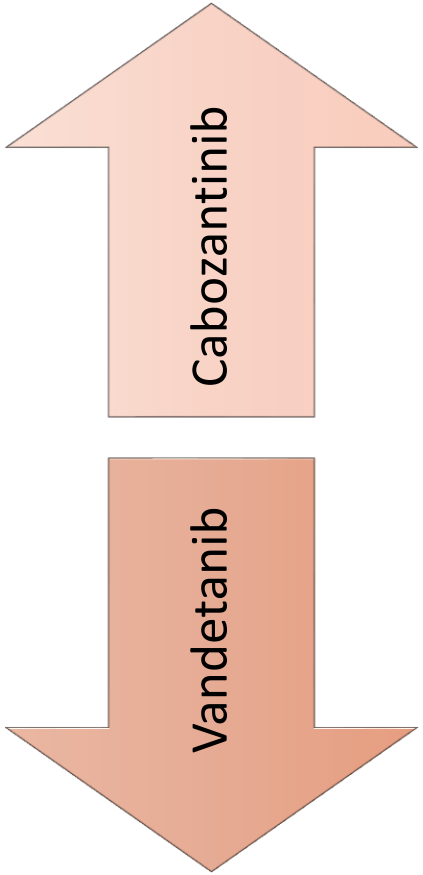
	Cabozantinib (n = 214)				Placebo (n = 109)			
	All Grades		Grade ≥ 3		All Grades		Grade ≥ 3	
AE	No.	%	No.	%	No.	%	No.	%
Diarrhea	135	63.1	34	15.9	36	33.0	2	1.8
Palmar-plantar erythrodysesthesia*	107	50.0	27	12.6	2	1.8	0	
Decreased weight	102	47.7	10	4.7	11	10.1	0	
Decreased appetite	98	45.8	10	4.7	17	15.6	1	0.9
Nausea	92	43.0	3	1.4	23	21.1	0	
Fatigue	87	40.7	20	9.3	31	28.4	3	2.8
Dysgeusia	73	34.1	1	0.5	6	5.5	0	
Hair color changes	72	33.6	1	0.5	1	0.9	0	
Hypertension	70	32.7	18	8.4	5	4.6	1	0.9
Stomatitis	62	29.0	4	1.9	3	2.8	0	
Constipation	57	26.6	0		6	5.5	0	
Hemorrhage	54	25.2	7	3.3	17	15.6	1	0.9
Vomiting	52	24.3	5	2.3	2	1.8	1	0.9
Mucosal inflammation	50	23.4	7	3.3	4	3.7	0	
Asthenia	45	21.0	12	5.6	16	14.7	2	1.8
Dysphonia	43	20.1	0		10	9.2	0	
Rash	41	19.2	2	0.9	11	10.1	0	
Dry skin	41	19.2	0		3	2.8	0	
Headache	39	18.2	1	0.5	9	8.3	0	
Oropharyngeal pain	38	17.8	1	0.5	5	4.6	0	
Abdominal pain	36	16.8	6	2.8	7	6.4	1	0.9
Alopecia	35	16.4	0		2	1.8	0	
Pain in extremity	33	15.4	3	1.4	12	11.0	1	0.9
Back pain	32	15.0	5	2.3	12	11.0	1	0.9
Dyspnea	29	13.6	5	2.3	19	17.4	11	10.1
Arthralgia	29	13.6	2	0.9	8	7.3	0	
Dizziness	29	13.6	1	0.5	8	7.3	0	
Oral pain	29	13.6	1	0.5	1	0.9	0	
Dry mouth	28	13.1	0		9	8.3	0	
Dysphagia	27	12.6	9	4.2	7	6.4	1	0.9
Cough	26	12.1	1	0.5	14	12.8	0	
Muscle spasms	26	12.1	1	0.5	5	4.6	0	
Dyspepsia	24	11.2	0		0		0	
Insomnia	23	10.7	0		7	6.4	0	
Erythema	23	10.7	2	0.9	2	1.8	0	
Glossodynia	22	10.3	3	1.4	0		0	

Table 3. AEs Associated With VEGF Pathway Inhibition

	Cabozantinib (n = 214)				Placebo (n = 109)			
	All Grades		Grade ≥ 3		All Grades		Grade ≥ 3	
AE	No.	%	No.	%	No.	%	No.	%
Hypertension	70	32.7	18	8.4	5	4.6	1	0.9
Hemorrhage	54	25.2	7	3.3	17	15.6	1	0.9
Venous thrombosis	12	5.6	8	3.7	3	2.8	2	1.8
GI perforation	7	3.3	7	3.3	0		0	
GI fistula	2	0.9	1	0.5	0		0	
Abdominal/pelvic abscess	5	2.3	2	0.9	0		0	
Non-GI fistula	8	3.7	4	1.9	0		0	
Arterial thrombosis	5	2.3	2	0.9	0		0	
Proteinuria	4	1.9	2	0.9	0		0	
Wound complication	4	1.9	2	0.9	1	0.9	0	
Osteonecrosis	3	1.4	1	0.5	0		0	
RPLS	1	0.5	1	0.5	0		0	

Abbreviations: AE, adverse event; RPLS, reversible posterior leukoencephalopathy syndrome; VEGF, vascular endothelial growth factor.

- Hypertension
- Hemorrhage
- Venous thrombosis
- GI perforation
- Non-GI fistula
- Arterial thrombosis
- **NO** QT prolonged



CABO:

- a higher incidence of **blood count changes**

- change in **electrolytes**

- **TSH elevation**

- **Handfoot** syndrome was more frequent

- CABO: no patient had QT prolongation

- VAND: **21%** patients showed prolongation of QT interval.

Koehler et al., Thyroid 2021

Cardiovascular AE

Hypertension and cardiovascular toxicities can be life-threatening AEs

(especially in patients receiving Vandetanib)

Hypertension

Before starting treatment,

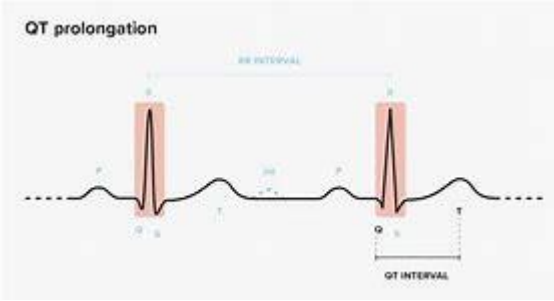
control patients blood pressure.

Blood pressure < 140/90 mm/Hg and checked

daily in the first 2 months of treatment.

If necessary antihypertensive agents

QT prolongation



13 clinical trials (4.204 patients) with multitumor types who received vandetanib 100 or 300 mg daily

- The incidence of QT prolongation ranged from **0.3 to 23.9%**

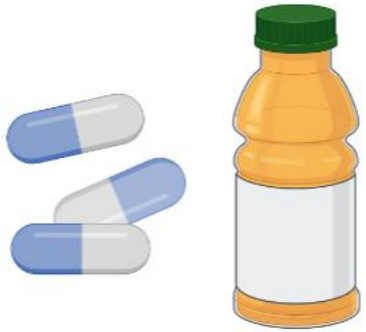
- AF incidence ranged from **0.43 to 1.79%**

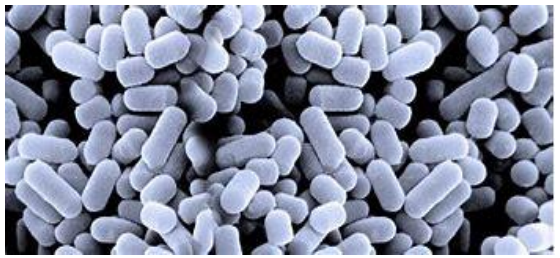
EKG cardiac should be done **every 1–2 weeks in the first month** of treatment, then **once a month** for the first three months, and then according to the patient's overall health status

In addition, **other drugs which may induce QT prolongation** need to be considered in the drug combination

Ghatalia et al., Br J Cancer . 2015

Gastrointestinal AE





Dietary supplements

anti-emetic drugs and appetite stimulants

Diarrhoea,

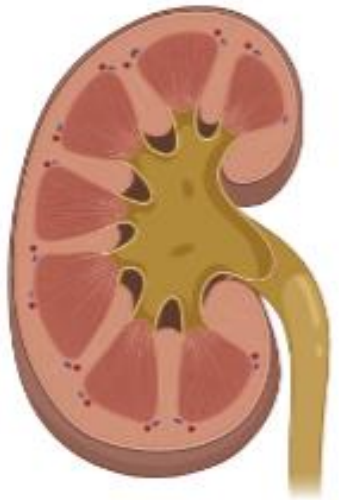
Weight loss

nutritional supports

Probiotics

lactic ferments

Proteinuria



in MTC trials, the prevalence was

- **1.9%** for cabozantinib
- **59%** for lenvatinib
- **0%** for vandetanib

- Proteinuria significantly **related to TKI duration**

- a **late-onset** toxicity occurring after a mean treatment period of 38 months

- proteinuria is a sign of renal damage during TKI, but **usually asymptomatic and well manageable**

- not a valid reason for discontinuing the therapy because of <u>its presumed role as marker of anti-tumoral efficacy.</u>

-a **mild decline of renal function**, independently from proteinuria

-related to the aging and/or to the several contrast medium of CT scan

Nervo et al., Crit Rev Oncol Hematol 2021;
Cappagli et al., JENI 2021

Skin AEs

rash and folliculitis

photosensitivity

dry skin, acne

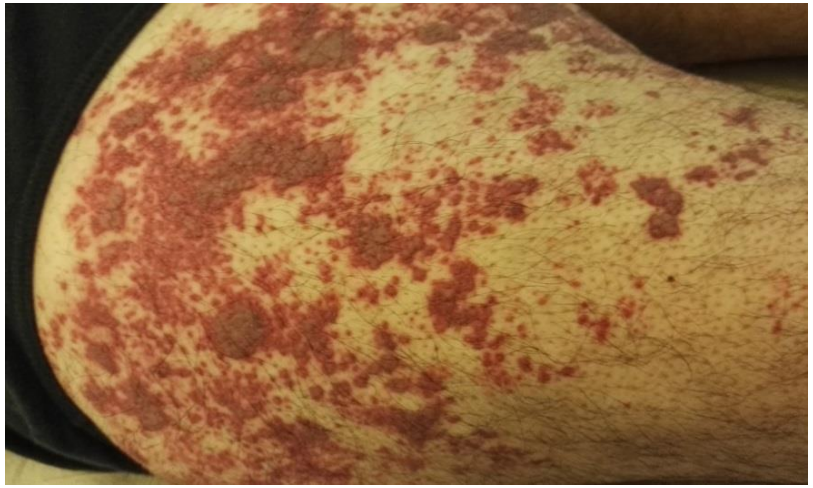
palmar plantar erythrodysesthesia

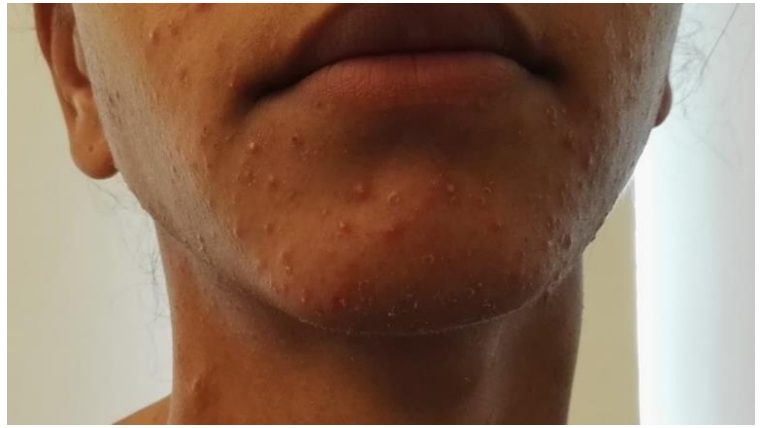
Practical measures:

- urea or aluminium lactate-based topical creams

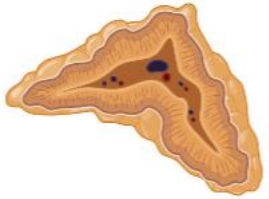
- comfortable gloves and shoes

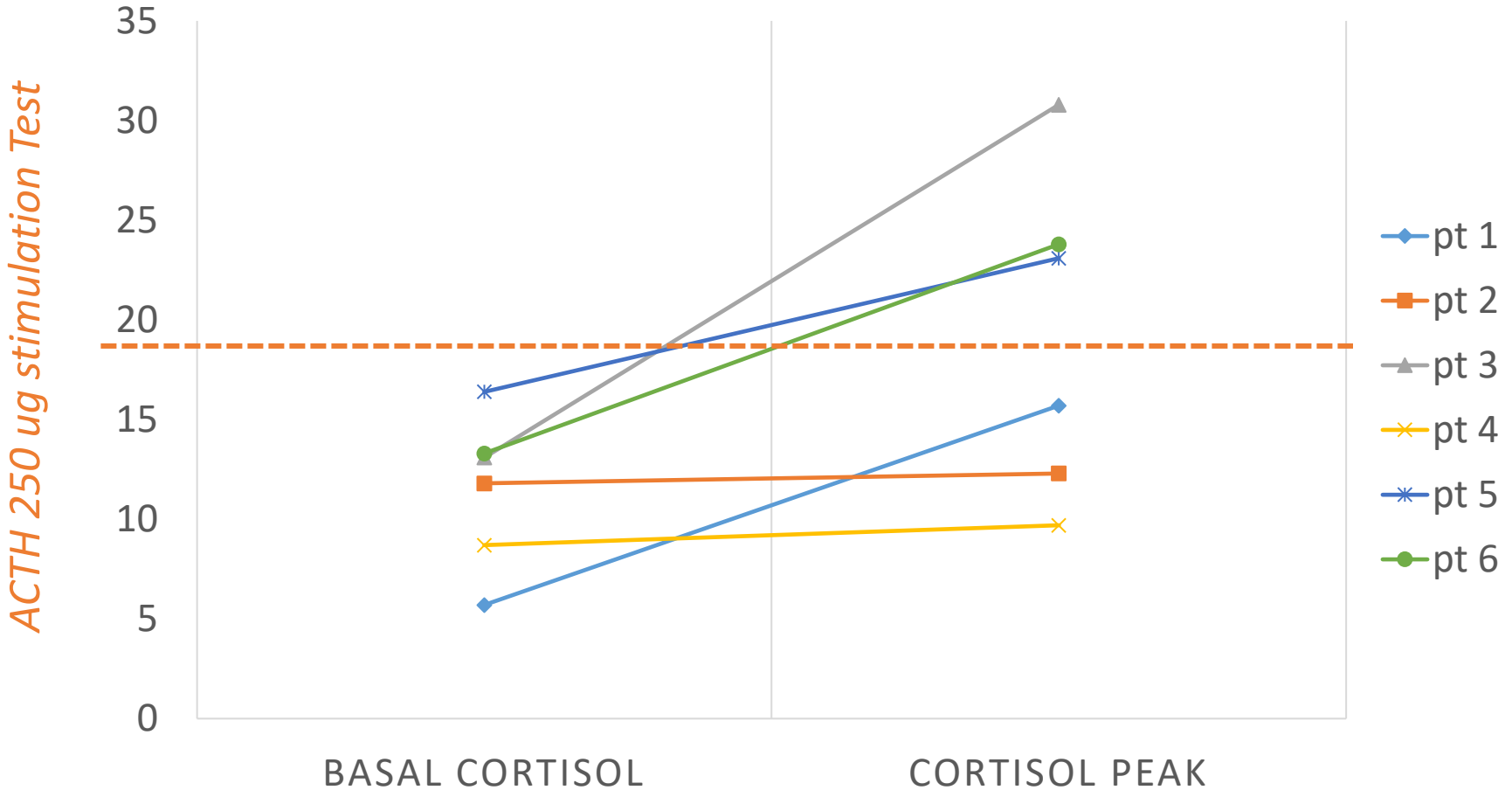
- Avoid aggressive soaps, hot water, trauma and friction





Fatigue → ADRENAL INSUFFICIENCY → suggested replacement treatment





Colombo et al., JCEM 2018; Monti et al., Thyroid 2022

Selpercatinib

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Selpercatinib in *RET*-Altered Thyroid Cancers

L.J. Wirth, E. Sherman, B. Robinson, B. Solomon, H. Kang, J. Lorch, F. Worden, M. Brose, J. Patel, S. Leboulleux, Y. Godbert, F. Barlesi, J.C. Morris, T.K. Owonikoko, D.S.W. Tan, O. Gautschi, J. Weiss, C. de la Fouchardière, M.E. Burkard, J. Laskin, M.H. Taylor, M. Kroiss, J. Medioni, J.W. Goldman, T.M. Bauer, B. Levy, V.W. Zhu, N. Lakhani, V. Moreno, K. Ebata, M. Nguyen, D. Heirich, E.Y. Zhu, X. Huang, L. Yang, J. Kherani, S.M. Rothenberg, A. Drilon, V. Subbiah, M.H. Shah, and M.E. Cabanillas

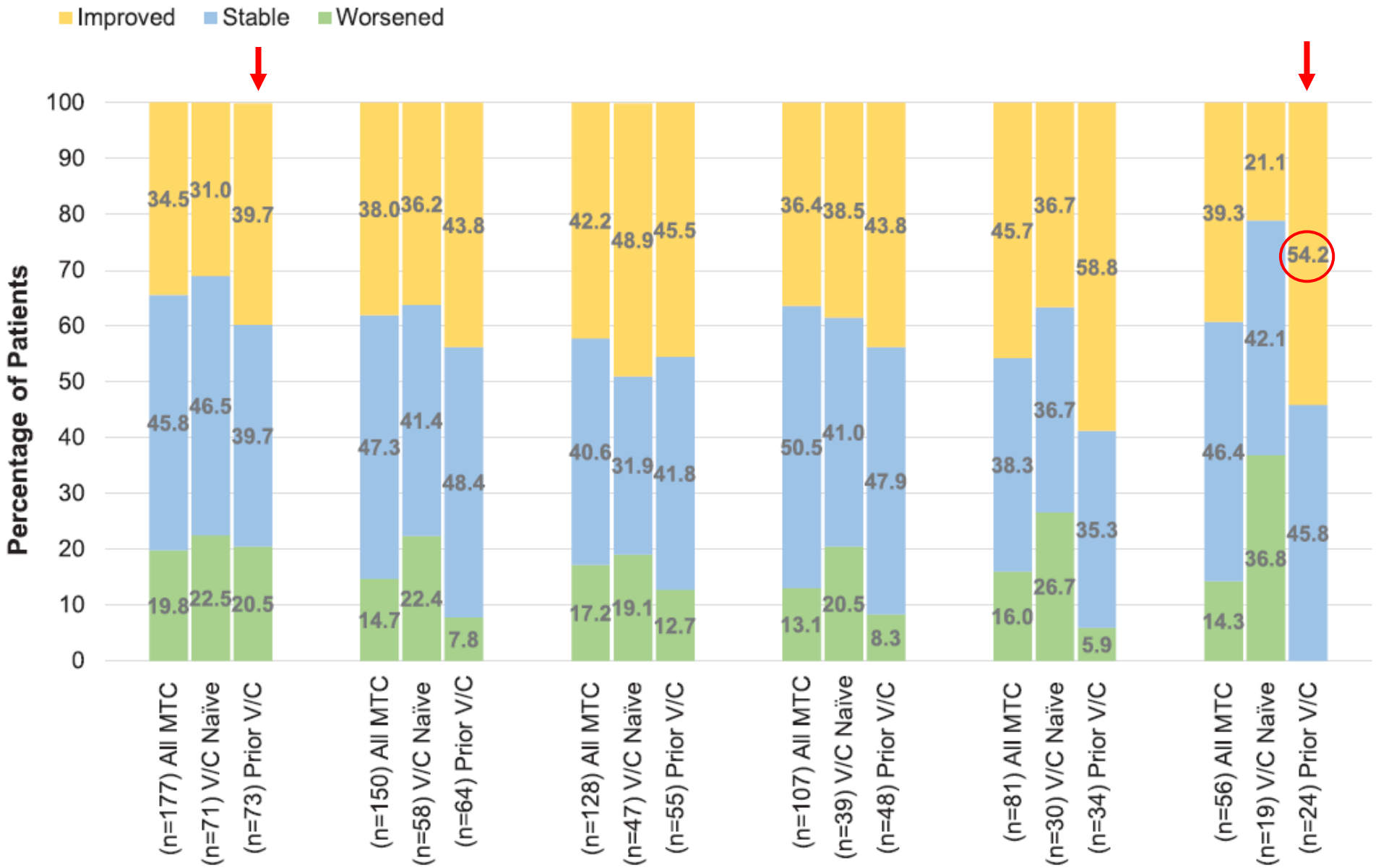
Table 3. Adverse Events in 162 Patients with *RET*-Mutant MTC or *RET* Fusion–Positive Thyroid Cancer Who Received Selpercatinib.*

Adverse Event	Treatment-Related Adverse Events		
	Grade 3	Grade 4	Any Grade
	t)		
Any adverse event	45 (28)	3 (2)	153 (94)
Dry mouth	0	0	63 (39)
Hypertension	19 (12)	0	49 (30)
Diarrhea	4 (3)	0	27 (17)
Fatigue	1 (1)	0	41 (25)
Increased aspartate aminotransferase level	12 (7)	1 (1)	45 (28)
Nausea	0	0	25 (15)
Constipation	0	0	26 (16)
Increased alanine aminotransferase level	16 (10)	1 (1)	42 (26)
Headache	1 (1)	0	21 (13)
Peripheral edema	0	0	29 (18)
Increased blood creatinine level	0	0	22 (14)
Abdominal pain	0	0	6 (4)
Arthralgia	0	0	8 (5)
Vomiting	0	0	12 (7)
Hypocalcemia	0	0	5 (3)
Back pain	0	0	1 (1)
QT interval prolonged on electrocardiography	3 (2)	0	21 (13)
Cough	0	0	2 (1)
Rash	0	0	13 (8)
Dizziness	0	0	9 (6)
Abdominal distension	0	0	12 (7)
Hypothyroidism	0	0	12 (7)
Weight increased	1 (1)	0	8 (5)

Grade 3:

- Hypertension
- Increased AST/ALT

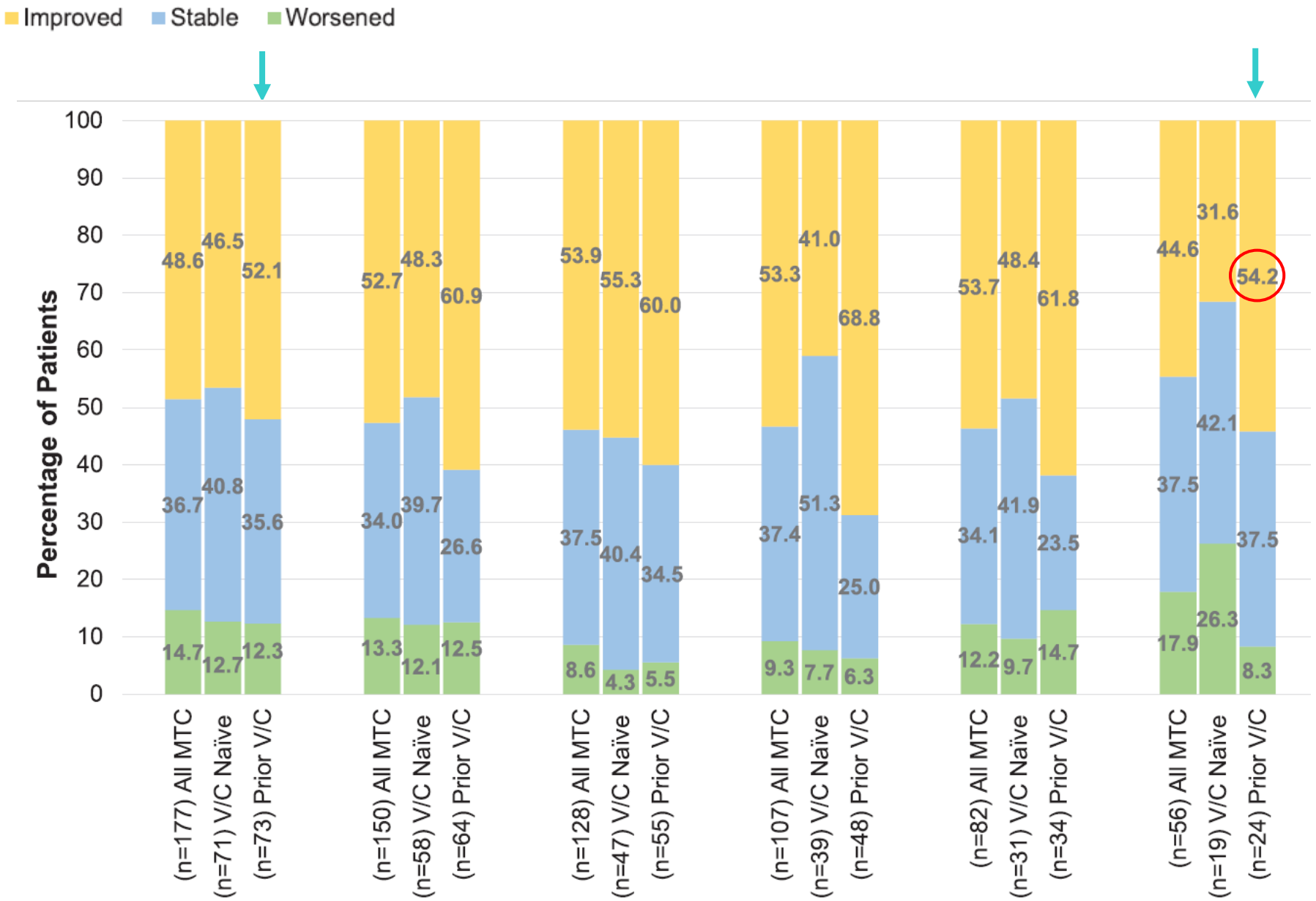
Change in global health status/quality of life



Patients with *RET*-mutant MTC improved/remained stable on all domains of HRQoL during treatment with selpercatinib.

Wirth et al, The Oncologist, 2022

Change in global health status/quality of life



Change in **diarrhea** from baseline in patients treated with Selpercatinib

Wirth et al, The Oncologist, 2022

Pz 58 anni

28.05.2021: inizia terapia con

Selpercatinib 160 mg x 2/die

23.06.2021: AE grade 3 (CTCAE v 5)

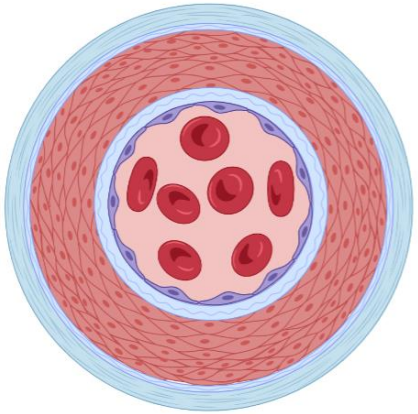
Hb 19.4 g/dl
Ht 58%

Sospensione Selpercatinib

e idratazione ev

27.06.2021: progressivo miglioramento degli esami ematici

Hb 17.6 g/dl
Ht 51.4%



Hb 17.3 g/dl
Ht 52.3 %

Hb 16.7 g/dl
Ht 49.7 %

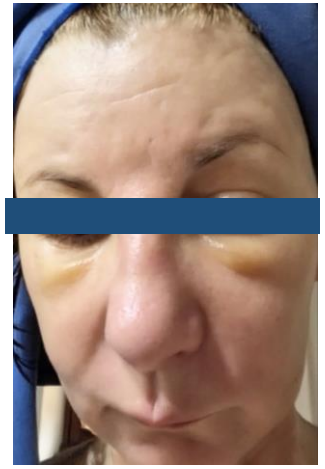
28.06.2021:

stabilità e successiva normalizzazione degli esami ematici

Selpercatinib 160 mg x 2/die

O2.2023: prosegue terapia con PR

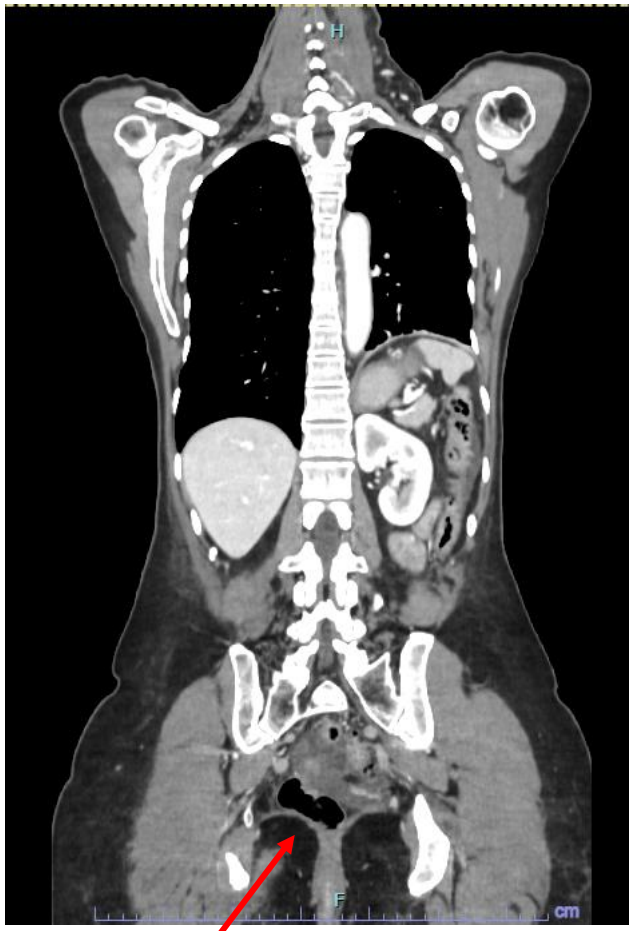
Personal records



11.2022: sviluppo di edema periferico diffuso

01.06.2022: Paziente di 51 anni inizia Selpercatinib 160 mg x 2 volte/die

02.2023: Nello scavo pelvico falda liquida in sede periuterina e inguinale destra



Personal records

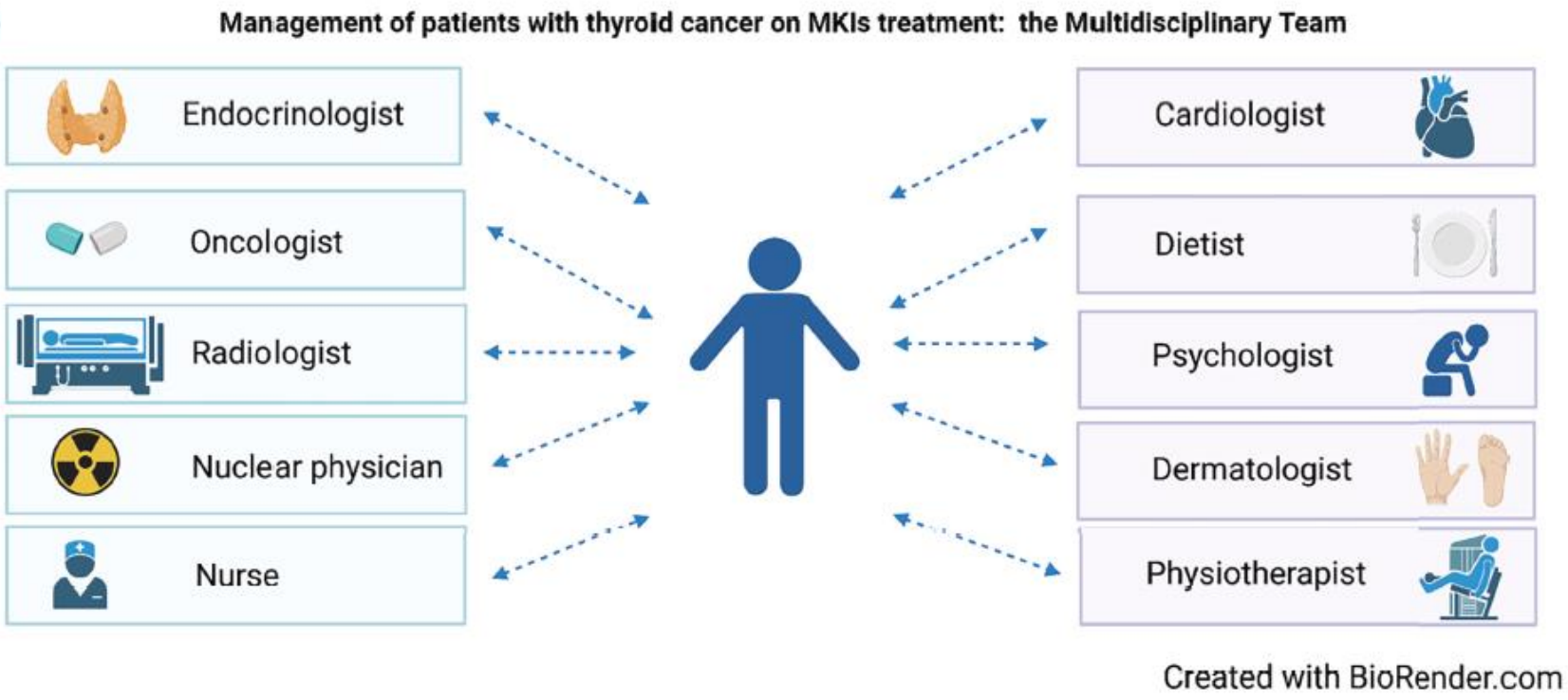
Multidisciplinary healthcare team

A

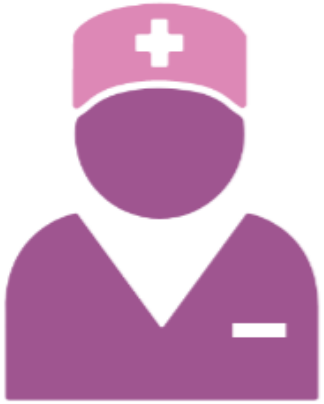
Telephone contact always available for communications between patients and the clinician team (WhatsApp or Telegram) for:

- questions about drug intake, need to reduce the dosage
- reports on the outcome of adverse events
- suggestions related to the management of adverse events
- motivation and psychological support of the patient
- individualization of follow-up visits

B



Colombo et al., Front Oncol. 2022



cancers

MDPI

Review

Nursing Management and Adverse Events in Thyroid Cancer Treatments with Tyrosine Kinase Inhibitors. A Narrative Review

Aurora De Leo [1,2], Emanuele Di Simone [1], Alessandro Spano [1,*], Giulia Puliani [3,4] and Fabrizio Petrone [1]

proactive educational **nursing** approach, together with a contribution of a multidisciplinary healthcare team, is essential

- optimizing therapeutic adherence
- satisfying a patients' need for information
- maximizing benefits
- reducing risks and medication errors
- positively impacting the QoL of both patient and their family

Grazie per l'attenzione

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