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MANEJO DE LA TOXICIDAD DE LOS NUEVOS TRATAMIENTOS EN TUMORES UROLÓGICOS

Valencia, 23 de abril de 2024

Organizado por: GUARD CONSORTIUM

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¿Por qué producen toxicidad las nuevas terapias dirigidas (TKIs, inh.FGFR) Mecanismos principales

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Organizado por: GUARD CONSORTIUM

DISCLOSURES

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- He proporcionado asesoramiento científico a IPSEN, Roche, Bayer, Sanofi, Janssen, Astellas, Eisai, Adacap, Lilly, Pfizer, MSD, Novartis.

- He participado en reuniones médicas organizadas por IPSEN, Lilly, Bayer, Janssen, Astellas, Eisai, Adacap, MSD.

- He recibido fondos para investigación de Roche, IPSEN, Pfizer, Janssen.

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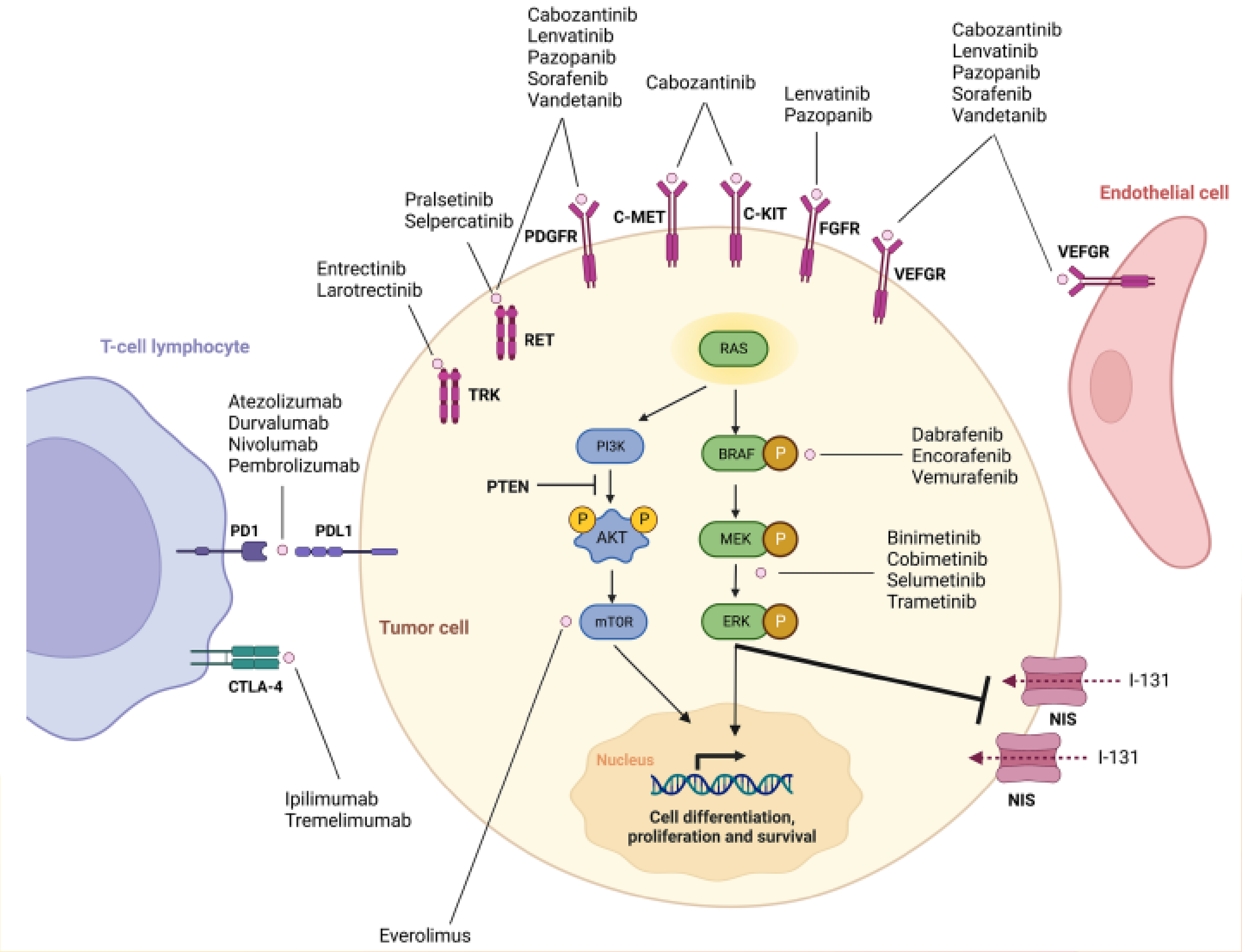
TIROSIN KINASE INHIBITORS



Nature, Nat Rev Clin Oncol, Evolving Molecularly Targeted Therapies for Advanced-Stage Thyroid Cancers, Bible KC, Ryder M.

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TKI -> targets & affinity

	VEGFR 1	VEGFR 2	VEGFR 3	PDGFRa	PDGFR b	c-KIT	RET	Flt-3	MET	CSF-1R	FGFR1	FGFR2	FGFR3	FGFR4	Axl
Sunitinib	2	9	17	7	8	7	10	250	-	890	830	-	-	-	9
Pazopanib	10	30	47	71	81	74	-	-	-		140	-	130	80	-
Tivozanib	30	6	15	40	49	78	-	2550	550	-	525	-	1250	1400	-
Axitinib	0,1	0,2	0,1-0,3	5	1,6	1,7	>1000	>1000	-	73	100	-	-	-	-
Cabozantinib	-	0,035	-	-	234	4,6	5,2	11,3	1,3	-	5294	-	-	-	7
Lenvatinib	22	4	5,2	25	39	0,7	12	-	1900	-	46	-	-	43	-
Sorafenib	26	90	20	-	57	68	-	33	-	-	580	-	-	-	-
Regorafenib	13	4,2	46		22	7	1,5				202				
Nintedanib	34	21	13	59	65	-	-	26	-	-	69	37	100	610	-
Vandetanib	-	40	110	-	-	-	100	-	-	-	-	-	-	-	-

Esteban-Villarrubia J, et al. IJMS 2020

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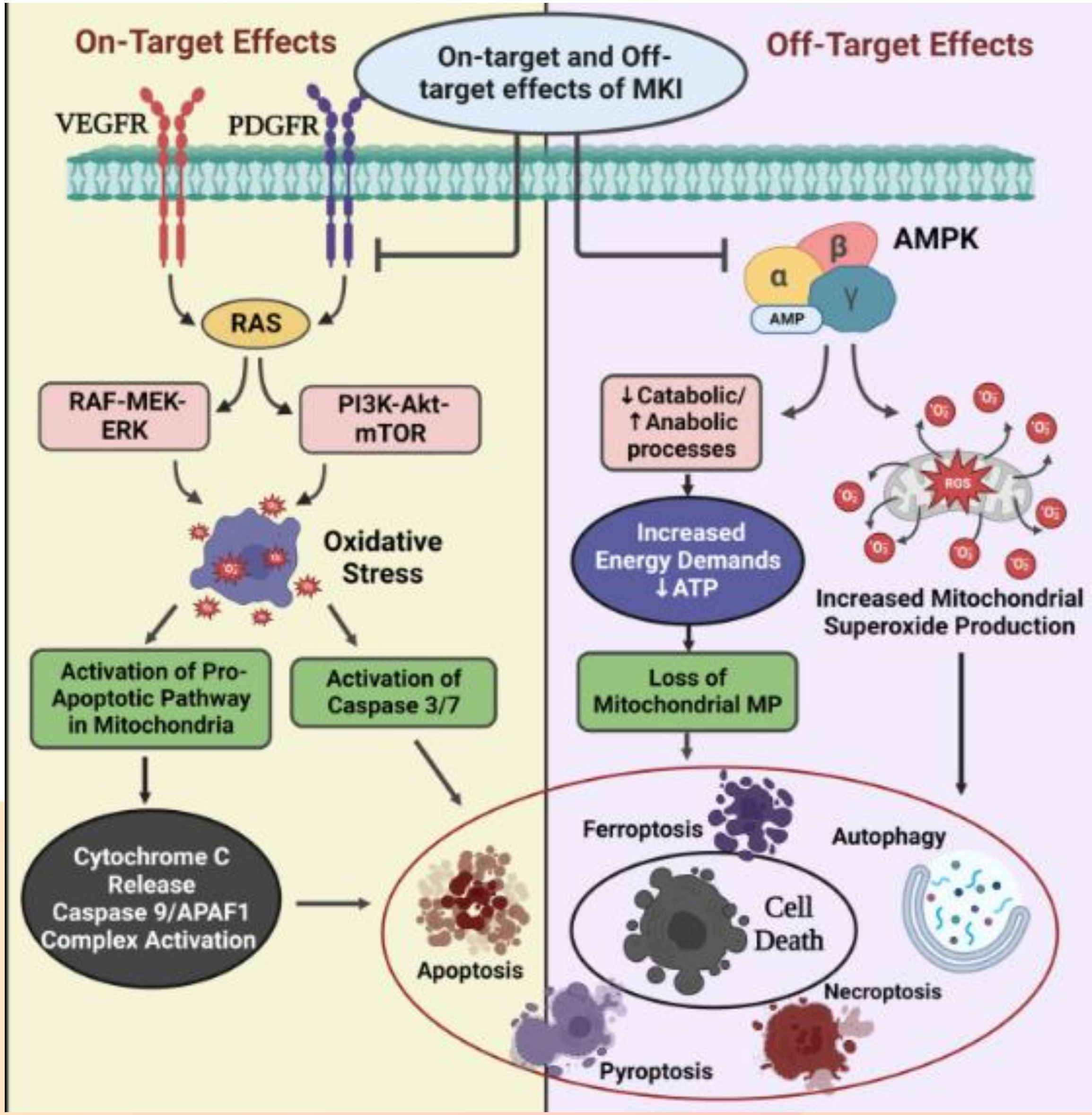
TKI-VEGFR inhibitors

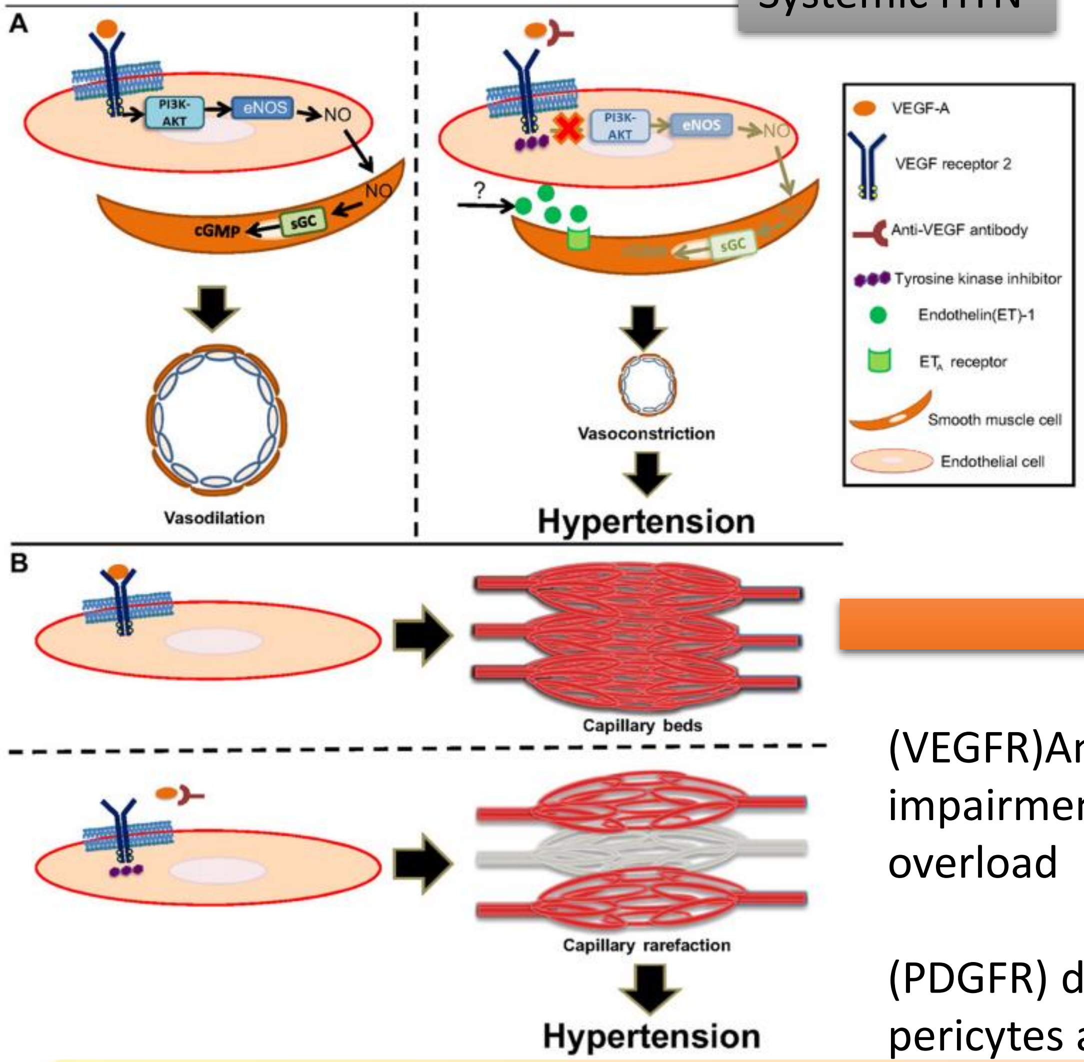
On-target effects have been implicated in the causation of adverse reactions such as hypertension (HTN), hypothyroidism, skin reactions, and proteinuria.



Sunder SS, et al. Signal Transduct Target Ther. 2023 Jul 7;8(1):262.

HYPERTENSION & CV EFFECTS

Systemic HTN



VEGF inhibition is known to increase mitochondrial superoxide generation and decrease nitric oxide (NO) production

(VEGFR)Angiogenic response impairment to HTN-induce pressure overload

(PDGFR) decreased myocardial pericytes and microvascular density

Loss glomerular capillarity
Loss podocytes
Impaired endothelial cell prolif
Nefrin inhibition

Proteinuria

Myocardial ischemia/infarction

Endotelial dysfunction

Thromboembolic disease

LVD and Heart Failure

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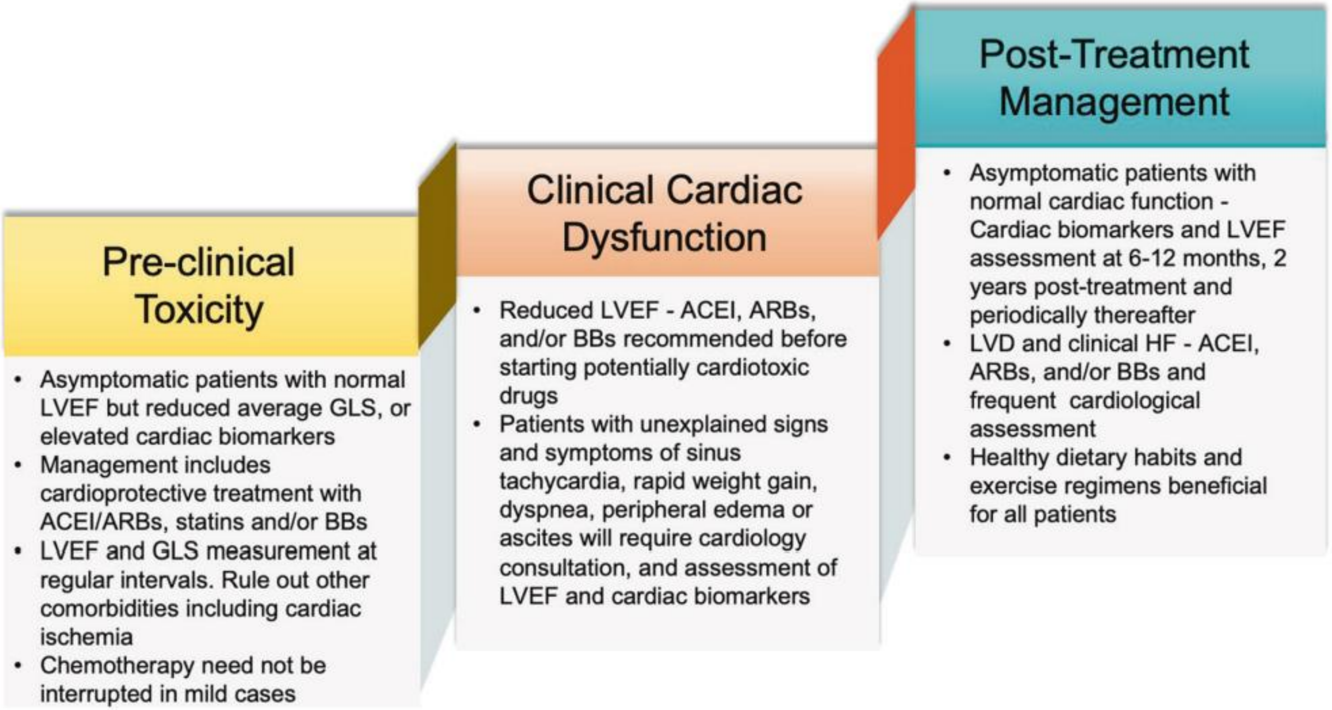
Agarwal M, et al. Curr Oncol Rep. 2018 Jun 21;20(8):65.

Tips



Supportive care

- Avoid Salt
- Avoid CYP3A4 inhibitors
- Antihypertensive treatment should be initiated (IECAs, ARAII, Ca+2 antagonist, diuretics or combinations)
- In some cases, refer to cardiologist/nephrologist

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Gastrointestinal adverse events

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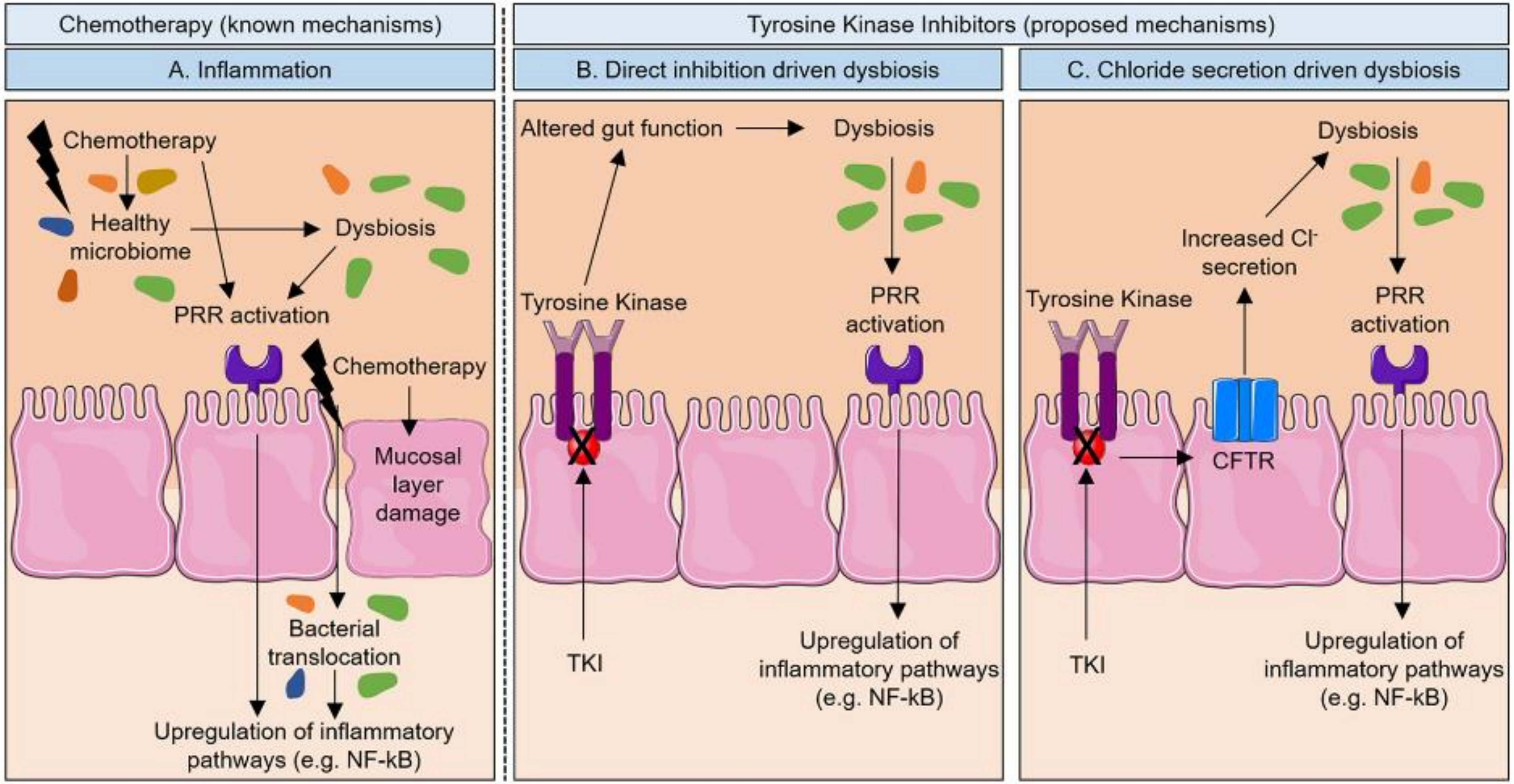

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Secombe KR, et al. Integr Cancer Ther. 2020 Jan-Dec:19:1534735420928493.

Dermatological adverse events

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Tyrosine Kinase Inhibitors	Associated dermatological lesions
Imatinib	**Maculopapular eruptions** along with pigmentary changes, Photosensitization, Superficial edema affecting the periorbital area (epiphora, chemosis, and conjunctivochalasis), Urticarial, Lichenoid, and Psoriasiform eruptions, Exacerbations of the existing Psoriasis, Hypo-/Hyperpigmentation, Neutrophilic eccrine hidradenitis, and neutrophilic panniculitis, Mycosis fungoides like reaction, Follicular mucinosis, Malpighian epithelium, Porphyria Cutanea trade, and Pseudoporphyria, Exanthematous pustulosis, Sweet Syndrome, Panniculitis, SJS Rare cases - Small vessel vasculitis, Erythema nodosum, and GVHD of skin
Nilotinib	**Perifollicular, Hyperkeratotic, and Erythematous Maculopapular Eruptions**, Mild to moderate pruritus, Skin xerosis, Alopecia, Body hair loss, and Bullous Sweet syndrome
Bosutinib	Erythema, Maculopapular Eruption, Pruritic Rash, Allergic Dermatitis, Acne, Folliculitis, and Skin Exfoliation
Ponatinib	Erythematous and papular rashes **Skin xerosis**
Dasatinib	Macular, Papular or Exfoliative rash, Pruritus, Localized and generalized erythema, Papular Eruptions, Exfoliative rash, Pruritus, Hyperhidrosis, Alopecia, Xerosis, Acne, Urticaria, Dermatitis, Photosensitivity, Nail Disorders, and Pigmentary Changes, Skin Ulcers, Palmoplantar Erythrodysesthesia Syndrome. Rare Cases - Panniculitis, Acute Febrile Neutrophilic Dermatosis, And Bullous Disorders
Sorafenib	Stomatitis, Seborrheic dermatitis-like facial and scalp erythema, Subungual splinter hemorrhages, Periungual erythema, EM and EM-like eruptions, SJS, Eruptive melanocytic nevi and Drug-induced lentigines, Pyoderma gangrenosum, Generalized keratosis pilaris like eruption, Epidermal cysts, Nipple hyperkeratosis and/ or dysesthesia or dyskeratotic plaque with milia, New squamous cell carcinomas, Keratoacanthomas, and Inflammation of Preexisting Actinic Keratosis
Sunitinib	All grade hand-foot skin reactions, Seborrheic dermatitis-like facial and scalp erythema, Skin discoloration, Hair depigmentation, Facial edema, Transient scalp dysesthesia, Yellow skin pigmentation of the face Dry skin, Dermatitis, Stomatitis, Alopecia, Subungual splinter hemorrhages Phototoxicity, Pyoderma gangrenosum, Generalized keratosis pilaris-like eruption, Epidermal cysts, Nipple hyperkeratosis and/ or dysesthesia or Dyskeratotic plaque with milia
Erlotinib	Acneiform rash, Xeroderma, Pruritus, Paronychia
Cabozantinib	Hand-foot skin reaction, Generalized pigment dilution and/or Hair depigmentation, Xerosis, Scrotal erythema/ulceration, Subungual splinter hemorrhages
Vemurafenib	Dose-dependent papulopustular rash, Photosensitivity, Xerosis, Pruritus, Paronychia, Alopecia and hair follicle alterations, Hyperkeratosis, Pyogenic granulomas, Verrucous keratosis, Acantholytic dermatosis, Seborrheic keratosis, Verruca vulgaris, Hypertrophic actinic keratosis, Cutaneous squamous cell carcinoma and/ or Keratoacanthoma
Dabrafenib	Dose-dependent papulopustular rash, Xerosis, Pruritus, Paronychia, Alopecia and Hair follicle alterations, Hyperkeratosis, Pyogenic granulomas Verruca vulgaris, Hypertrophic actinic keratosis, Cutaneous squamous cell carcinoma and/ or Keratoacanthoma
Trametinib	Acneiform rash, Pruritus, Xerosis. Squamous cell carcinoma

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Sunder S, et al. Signal Transduction and Targeted Therapy (2023) 8:262

Tips

- Inform patient for possible AE
- Avoid hot water
- Use emollient creams
- Avoid pressure in hands and feet, use cotton gloves and socks
- Avoid use of alcoholic solutions
- Use sunscreen if available > 50SPF

Supportive care

- Use cream containing urea or salicylic acid to soften hyperkeratotic areas areas
- Clobetasol o betamethasone can help in symptom relief and treatment for lesions
- Topical lidocaine can help in pain control
- Cooling hand and foot baths containing magnesium sulphate can reduce pain
- Oral analgesic in some cases
- Refer patient to dermatologist in special cases

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Endocrine-related adverse events

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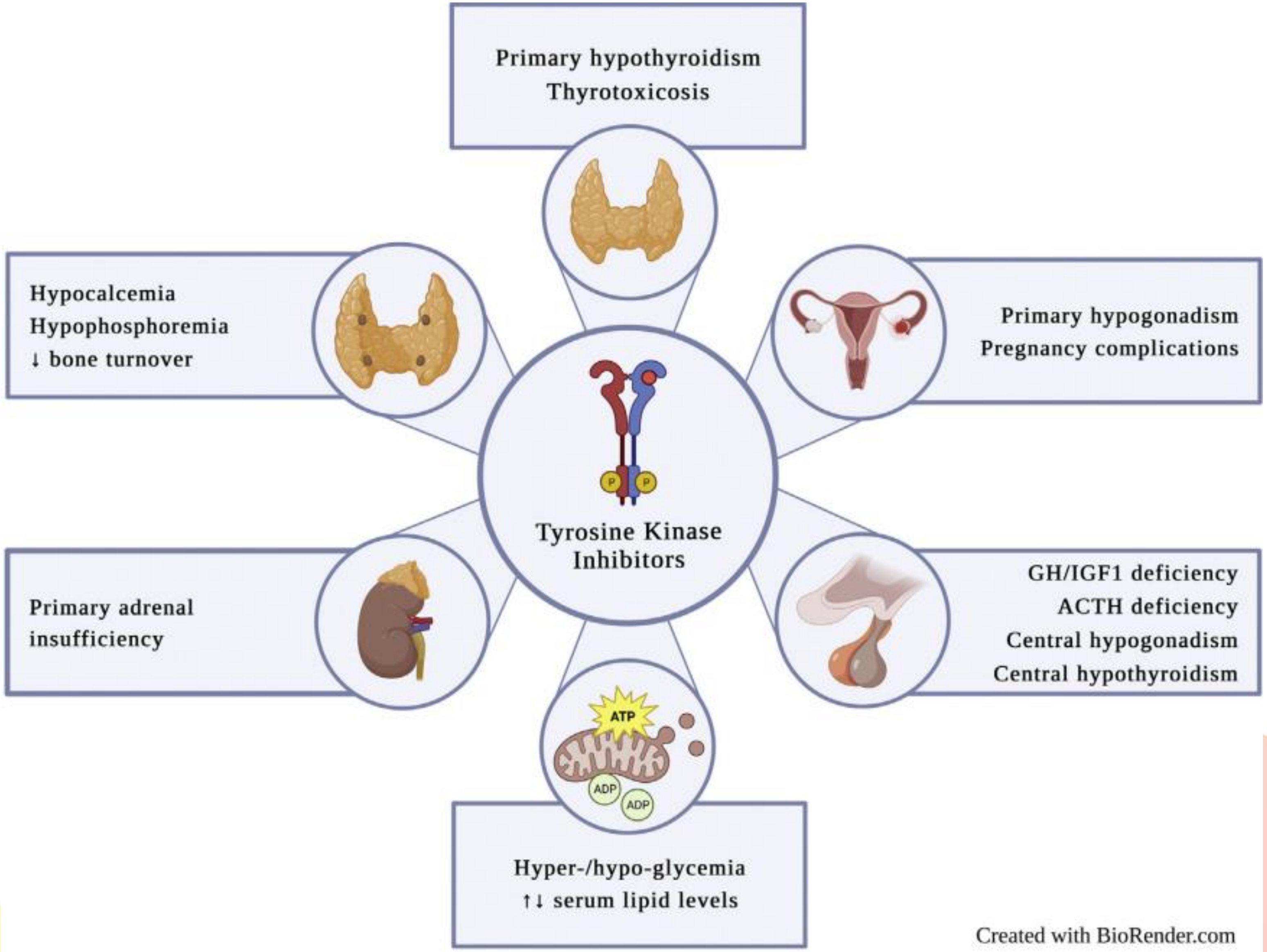

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Endocrine-related adverse events

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THYROID DISORDERS

➔ The most common TKI-related endocrine toxicity.

➔ Thyroid microcirculation subverted by VEGFR and PDGFR inhibition -> damage to thyroid follicules -> Transient thyrotoxicosis before developing hypothyroidism (loss of functional parenchima).

➔ Induction of iatrogenic thyroiditis (triggering thyroid autoimmunity)

➔ Thyroperoxidase inactivation and iodine uptake inhibition by thyrocytes, as a consequence of hypoxic damage.

➔ Impairment of thyroid hormone metabolism (inactive metabolites)

➔ Gastrointestinal toxicity may reduce levothyroxine absorption.

➔ Hypothyroidism; usually asymptomatic. Overt hypothyroidism (symptomatic or high TSH levels >10 mU/L) levothyroxine, but TKI therapy can still be continued

➔ Initially intermittent, but may become permanent.

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Endocrine-related adverse events

ADRENAL INSUFFICIENCY

- ➔ The real mechanisms are still not known, but it may involve adrenal damage through severe alteration of physiologic angiogenesis.
- ➔ Described as subclinical glucocorticoid deficiency, confirmed by inadequate cortisol response on ACTH stimulation test.
- ➔ Of interest in patients with fatigue (dif. Diagnosis). Glucocorticoid supplementation.

GONADAL DYSFUNCTION

- ➔ Hypogonadism (central and gonadal dysregulation); seems a chronic effect.
- ➔ Adverse TKI effects on ovarian stimulation and spermatogenesis, probably due to blocking effects on c-KIT and PDGFR.
- ➔ Few data regarding long-term consequences

Valerio L, et al. J Endocrinol Invest. 2023 Aug;46(8):1663-1671.

Endocrine-related adverse events

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PARATHYROID AND BONE METABOLISM DYSFUNCTION

➔ A reduction of both, bone formation (osteocalcin) and/or resorption (urine N-telopeptide) (RET-TKI). As a consequence, this may alter calcium and phosphate metabolism.

Hypophosphatemia:

➔ Decreased gut absorption

➔ Elevated PTH levels, renal tubular damage/dysfunction, fibroblast growth factor 23 (FGF23)

➔ Acute shift of extracellular phosphate into the cells (i.e. hungry bone syndrome or refeeding)

➔ Correct nutritional vitamin D deficiency and consider calcitriol rather than oral phosphate supplements, which have the potential to bind dietary calcium.

METABOLIC DISEASE (hypoglycemia 11-24%; hyperlipidemia well controlled with statins)

Body composition (tumor & treatment)

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Anorexia and limited food intake

Anorexia is associated with poor food intake by:

- Altered CNS appetite signals with symptoms resulting from cancer or its treatments (nausea, diarrhea, pain)
- Physical limitations to food intake and use (mouth ulcers, GI obstruction)

Precachexia and cachexia

With cachexia, anorexia and weight loss are worsened by:

- Catabolic drivers (inflammatory cytokines) that further reduce nutrient intake and increase metabolic needs

Sarcopenia

Sarcopenia ensues as:

- Body reserves are depleted
- Lean body mass, mostly muscle, is lost

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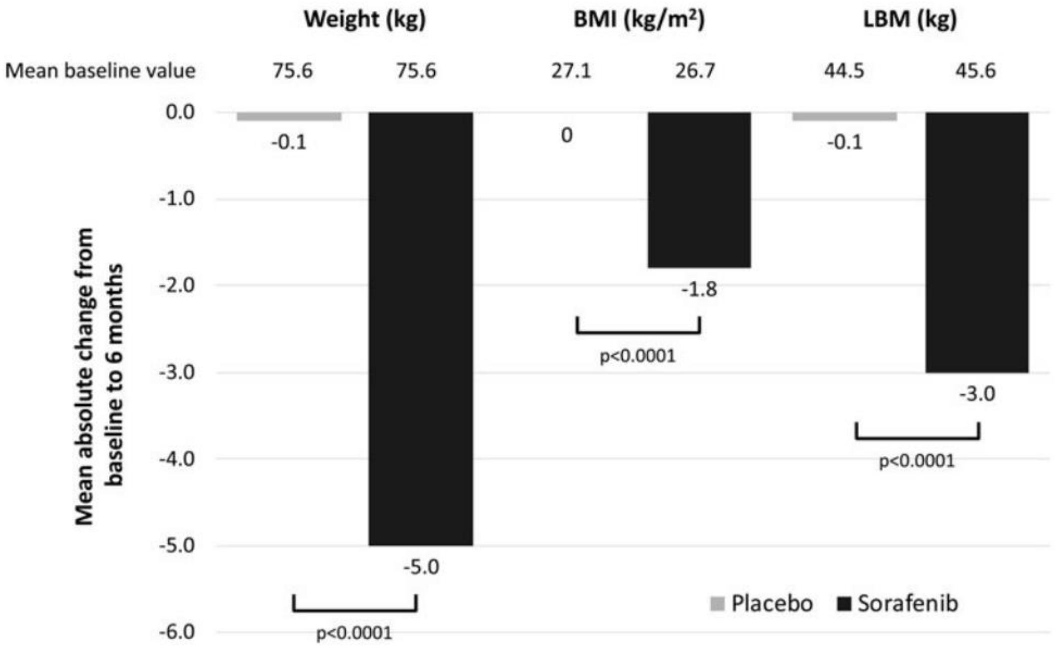
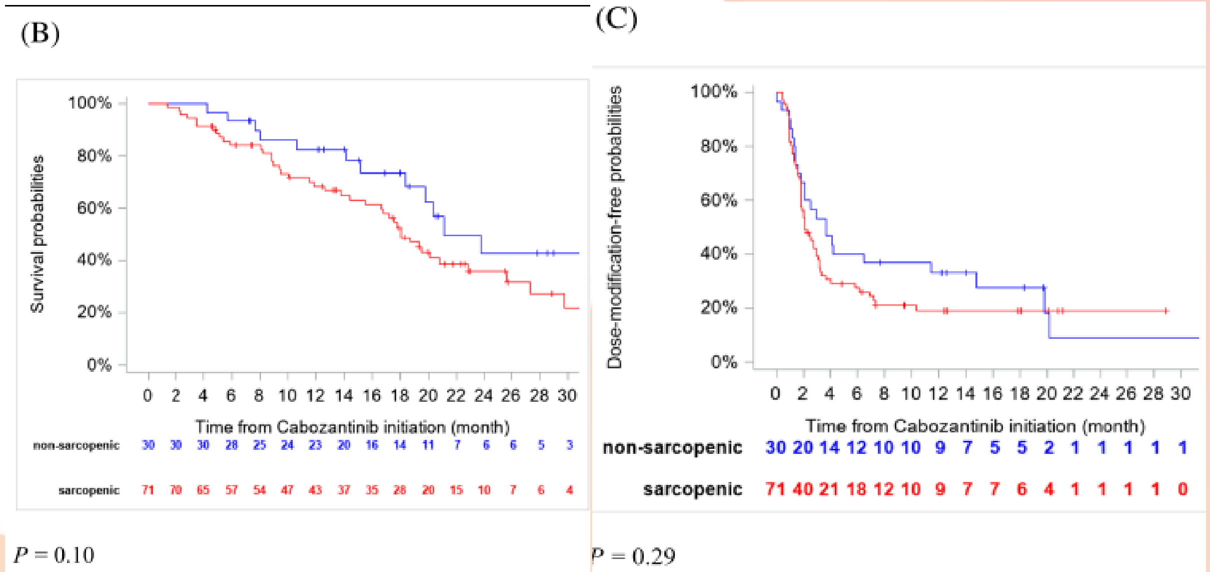
Arends J, Baracos V, Bertz H, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. *Clin Nutr*. 2017;36(5):1187-1196. doi:10.1016/j.clnu.2017.06.017

Body composition (tumor & treatment)

Changes in body composition from baseline to 6 months post sorafenib



Overall survival, dose-modification-free survival according to sarcopenia at baseline in mRCC patients treated with cabozantinib.



At 6 months, the mean weight, body mass index, and lean body mass of patients receiving sorafenib were lower than at baseline and significantly lower than for patients receiving placebo (all p < 0.0001).

Huillard O, Jouinot A, Tlemsani C, et al. Thyroid. 2019;29(12):1820-1827. doi:10.1089/thy.2018.0784

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Prehabilitation

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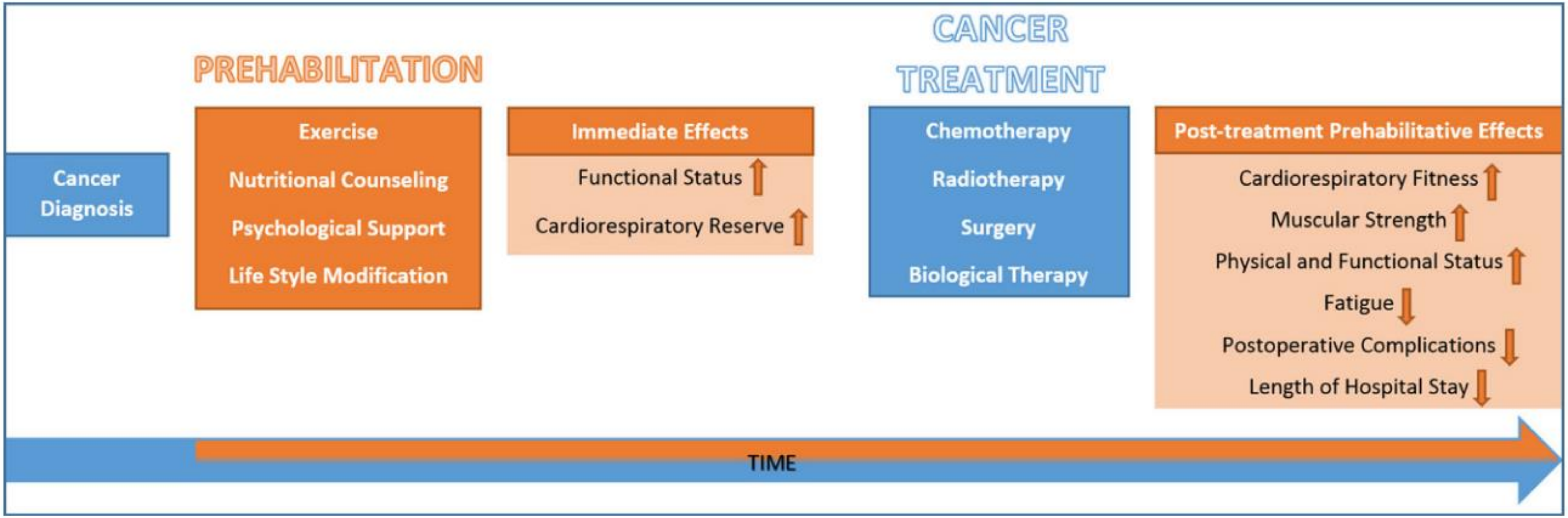
Fatigue



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Crevenna, R., Palma, S. & Licht, T. Cancer prehabilitation—a short review. memo **14,** 39–43 (2021). https://doi.org/10.1007/s12254-021-00686-5

AE frequency according to TKI

AE G≥ 3	Lenvatinib	Cabozantinib	Axitinib
Hypertension	27.6%	11%	22.1%
Diarrhea	9.7%	6%	9.1%
Hypothyroidism	1.4%	<1%	0.2%
Decreased appetite	4.0%	1%	2.8%
Fatigue	4.3%	3%	2.8%
Nausea	2.6%	<1%	0.9%
Stomatitis	1.7%	2%	0.7%
Dysphonia	0%	-	0.2%
Weight decrease	8.0%	-	3.0%
Proteinuria	7.7%	-	2.8%
PPE	4.0%	8%	5.1%
Rash	3.7%	-	0.2%
Vomiting	3.4%	-	0.2%
Arthralgias	1.4%	-	0.9%
Asthenia	5.4%	-	2.6%
Abdominal pain	2.0%	-	1.2%

AE frequency according to TKI

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AE G≥ 3	Lenvatinib	Cabozantinib	Axitinib
Anemia	2.0%	-	0.7%
Lipase increased	12.8%	-	-
Amylase increased	9.1%	-	-
ALT increased	4.3%	3%	13.3%
AST increased	3.1%	3%	7.0%
Hypertriglyceridemia	4.8%	-	-
Hypercholesterolemia	1.4%	-	-
Platelet count decreased	1.1%	-	0.2%
Thrombocytopenia	0.6%	-	0%
Neutropenia	0.6%	-	0.2%
Neutrophil count decreased	1.7%	-	0.2%

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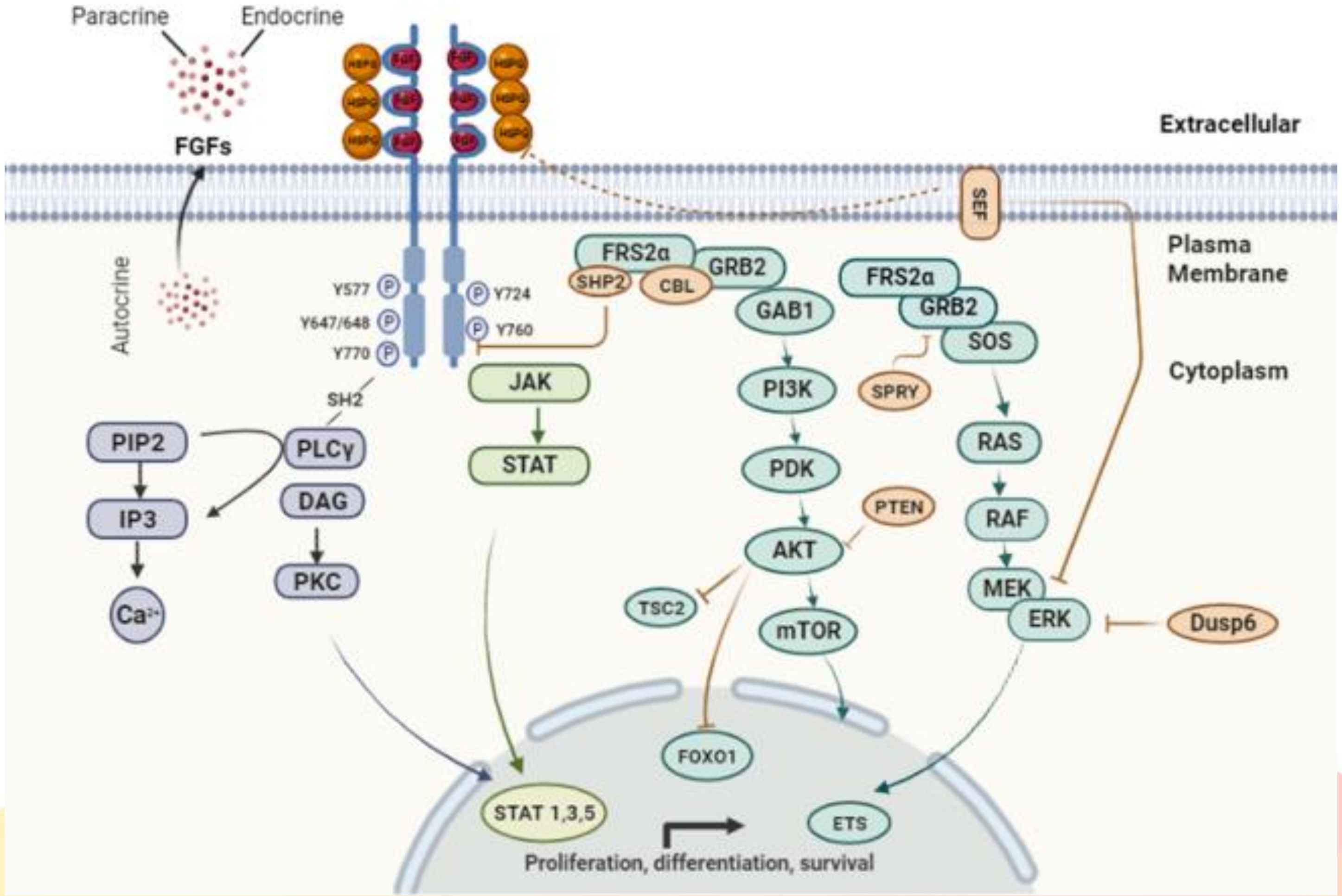
Motzer RJ, et al. N Engl J Med, 2021
Choueiri TK, et al. Annals of Oncology (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325
Rini BI, et al. N Engl J Med 2019; 380:1116-1127

FGFR-TKI inhibitor



Ascione MC, et al. Cancer Treatment Reviews, 2023 Apr:115:102530.

FGFR inhibitor

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C. Urotelial vesical pT2G3

Recaída metastásica ósea/adenopática

30 meses | 10 meses | 12 meses

Cisplatino + Gemcitabina

CTX RADICAL

Cisplatino + Gemcitabina

1FR

Nivolumab + PI3Ki/Pbo

1FR

Enfermedad Localizada

30 meses

Enfermedad Metastásica

22 meses ….

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Alonso Gordoa T, Unpublished

HYPERPHOSPHOREMIA

El paciente inicia tratamiento con erdafitinib 8mg/24h en septiembre de 2020

DOSIS

8mg/24h continuo — 2 SEM — 9mg/24h continuo — 2 SEM — 9mg/24h continuo — 2 SEM + 2 SEM — C3D1 9mg/24h continuo

EVENTOS ADVERSOS

- Fósforo 4.9 mg/dL (2.7 - 4.5)
  Calcio 9.3 mg/dL (8.7 - 10.3)
- Fósforo 6.2 mg/dL (2.7 - 4.5)
  Náuseas G1
- Fósforo 6.6 mg/dL (2.7 - 4.5)

TTO SOPORTE

- Oxicodona 40mg/12h
  Fentanilo sl 200 mcg
  Losartan/HTZ 100/12.5mg/24h
- Reducción ingesta de P 600-800mg/24h
  Inicio sevelamer 800mg/8h
- Reducción ingesta de P 600-800mg/24h
  Inicio sevelamer 800mg/8h + acetazolamida 250 mg/24h
  Oxicodona 20mg/12h

Alonso Gordoa T, Unpublished

Toxicidad-Manejo EA

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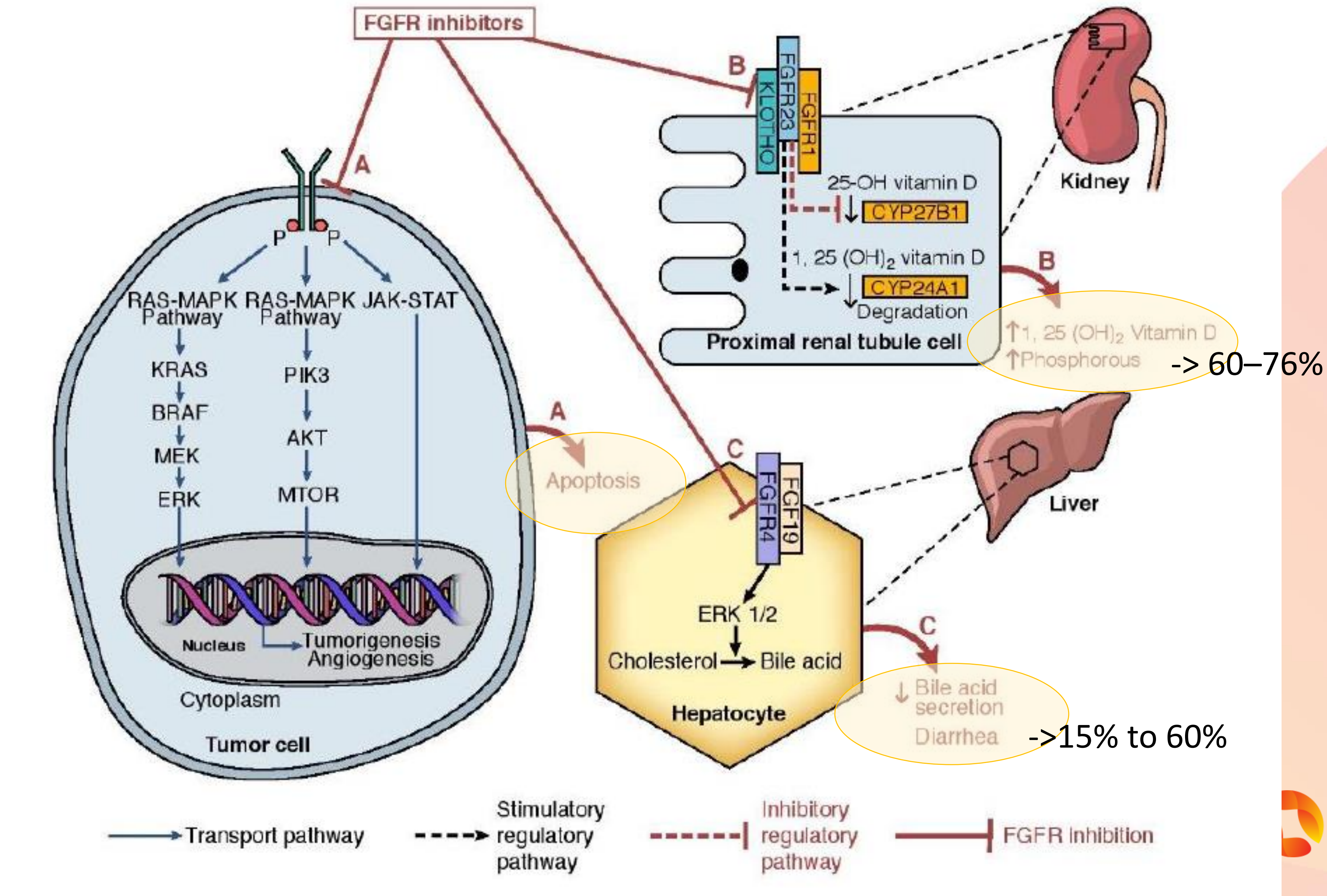
Level	Grade	Intervention
Sharp rise P 25% at first check; 3.5 – 5.5 mg/dL	Grade 1	Low phosphate diet
5.5 – 6.9 mg/dL	Grade 2	No dose adjustments Start phosphate binder at a low dose. If remain G2 in 1w: increase phosphate binder or add phosphaturic agent, acetazolamide.
7 – 9.9 mg/dL	Grade 3	MRD of phosphate binder + phosphaturic agent, acetazolamide. If remain G3 in 1w: stop FGFRi. If P<7 mg/dl: restart FGFRi If P≥ 7mg/dl: restart -1 or -2 dose level when P<7mg/dl
≥ 10 mg/dL	Grade 4	Stop FGFRi MRD of phospate binder + phosphaturic agent, acetazolamide If P<7 mg/dl: restart -1 or -2 dose level. If P<10 mg/dl after -2 dose level: Permanent discontinuation

Prevention:
Medications known to increase serum levels of phosphate, such as potassium phosphate supplements (oral or IV), vitamin D supplements, antacids, and phosphate-containing enemas and laxatives (oral/rectal).

	Initial Dose	Max. Recommended dose
Calcium Carbonate	500 mg (comp masticables) o 600 mg (comp) 3 veces al día	500 mg (comp masticables) o 600 mg (comp) 3 veces al día
Sevelamer hydrochloride; Sevelamer carbonate	800 mg 3 veces al día	1000 mg 3 veces al día con comidas
Sucroferric oxyhidroxide	500 mg 3 veces al día en comidas	2 gr al día
Acetazolamide	250 mg una vez al día	250 mg 2 o 3 veces al día

Kommalapati A, et al. cancers (Basel) 2021; 13 (12): 2968



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Kommalapati A, et al. cancers (Basel) 2021; 13 (12): 2968

El paciente inicia tratamiento con erdafitinib 8mg/24h en septiembre de 2020

Toxicidad-Manejo EA

DOSIS	8mg/24h continuo	2 SEM	9mg/24h continuo	2 SEM	9mg/24h continuo	2 SEM + 2 SEM	C3D1 9mg/24h continuo
EVENTOS ADVERSOS			Fósforo 4.9 mg/dL (2.7 - 4.5) Calcio 9.3 mg/dL (8.7 - 10.3)		Fósforo 6.2 mg/dL (2.7 - 4.5) Náuseas G1 Mucositis G1		Fósforo 6.6 mg/dL (2.7 - 4.5) Mucositis G2 Onicolisis G1
TTO SOPORTE	Oxicodona 40mg/12h Fentanilo sl 200 mcg Losartan/HTZ 100/12.5mg/24h				Reducción ingesta de P 600-800mg/24h Inicio sevelamer 800mg/8h Fórmula magistral mucositis/6h		Reducción ingesta de P 600-800mg/24h Sevelamer 800mg/8h + acetazolamida 250 mg/24h Fórmula magistral mucositis/6h Oxicodona 20mg/12h

Alonso Gordoa T, Unpublished

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Toxicidad-Manejo EA

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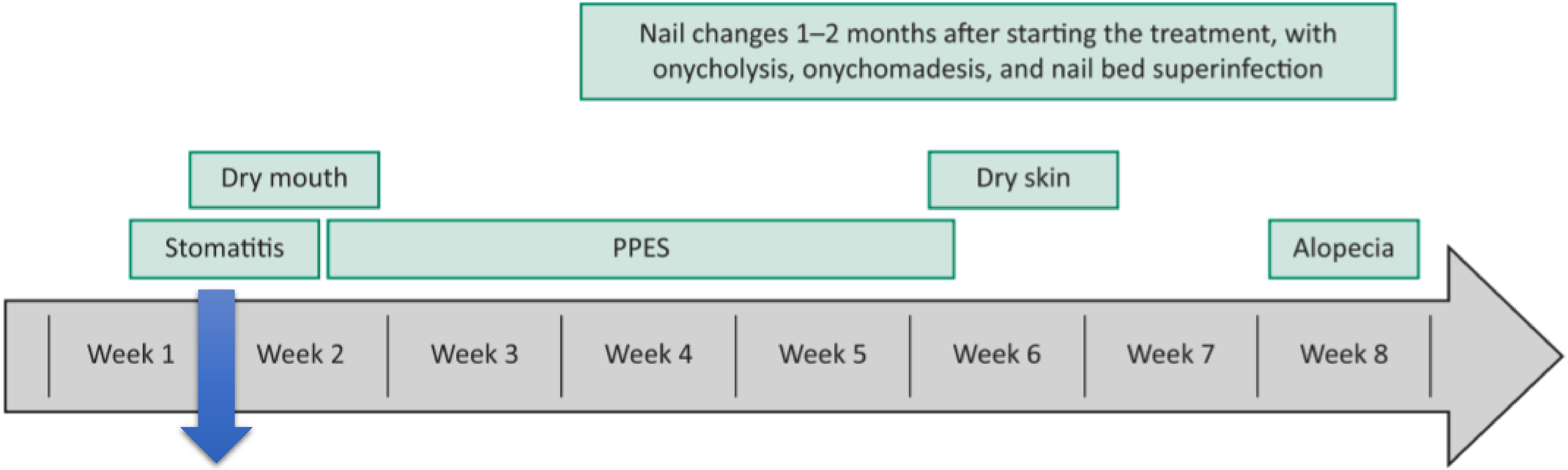

General Prophylaxis
- Good oral hygiene
- Use a soft toothbrush
- Avoidance of spicy, acidic, hard, and hot food and beverages
- Use of mild-flavored toothpastes
- Use of saline-peroxide or salt and baking soda mouthwashes 3 or 4 times per day
- Water soluble lubrication agents like artificial saliva (for xerostomia or dry mouth)

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Lacouture ME, et al. The Oncologist 2021; 26 (2): e316-e326

El paciente inicia tratamiento con erdafitinib 8mg/24h en septiembre de 2020

Toxicidad-Manejo EA

DOSIS

C3D15: Interrupción

2 SEM

C4D1: 8mg/24h continuo

2 SEM/2SEM

C6D1: 6mg/24h continuo

	C3D15	C4D1	C6D1
EVENTOS ADVERSOS	Fósforo 5.6 mg/dL (2.7 - 4.5) Mucositis G3 Onicolisis G1	Fósforo 4.6 mg/dL (2.7 - 4.5) Resolución mucositis	Reducción ingesta de P 600-800mg/24h Sevelamer 800mg/12h
TTO SOPORTE	Fórmula magistral mucositis/6h Clotrimazol Oxicodona 20mg/12h Fentanilo sl 200 mcg	Fórmula magistral mucositis/6h Oxicodona 15mg/12h	Fórmula magistral mucositis/6h Oxicodona 10 mg/12h

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Alonso Gordoa T, Unpublished

OCULAR TOXICITIES

GRADE (Clinical visit)

GRADE (Clinical visit)		
Grade 1 : Asymptomatic or mild symptoms; clinical or diagnostic observations only Or abnormal Amsler grid test	Continue (if ophtalmologic exam ok)	
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Interrupt	If: Keratitis central serous retinopathy/ retinal pigment epithelial detachments → -1 level
Grade 3: Grade 3: Severe or medically significant but not immediate sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Interrupt	If: Keratitis central serous retinopathy/ retinal pigment epithelial detachments → -2 level
Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye		Permanently discontinue

If reversible within 4 weeks, reintroduce

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Kommalapati A, et al. cancers (Basel) 2021; 13 (12): 2968

C. Urotelial vesical pT2G3

Recaída metastásica ósea/adenopática (10/2018)

08/2019

09/2020

02/2024

30 meses	10 meses	12 meses	42 meses
Cisplatino + Gemcitabina neady.	Cisplatino + Gemcitabina	Nivolumab + PI3Ki/Pbo	Erdafitinib
CTX RADICAL	1FR	1FR	

Enfermedad Localizada

30 meses

Enfermedad Metastásica

64 meses ….

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Alonso Gordoa T, Unpublished

CONCLUSIONS

- TKI are a are a unique class of emerging targeted therapies that have shown promising results in different tumors.
- On-target and off-target adverse events should be considered when managing those drugs.
- It is important that patients be educated about these TK-inhibitor-related unique side effects and possible preventive mechanisms.
- Overall, allowing an optimal drug effectiveness.

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¡Gracias!

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