MEDÜLLER TİROİD KANSERİNDE GÜNCELLEME

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37 yaş, erkek, bekar, Rize

- 2011→ Öksürük, balgam şikayetleri ile acil
- Toraks BT→multipl metastazla uyumlu görünüm

- Özgeçmiş
  - Menenjit hikayesi
  - Mental retardasyon

- **PET-BT:** Tiroid bezi üst polden başlayarak retrosternal uzanım gösteren lezyonlar, boyunda sol juguler zincir boyunca ve akciğerde multiple metastazlar ile uyumlu lezyonlar

- Tiroid sol lob bx→ Medüller tiroid karsinomu ile uyumlu

- Kalsitonin: 2000 pg/mL...

- CEA: 100 U/mL

- **Nisan 2011**→ Bilateral total tiroidektomi ve fonksiyonel boyun diseksiyonu

- Patoloji:
  - Medüller karsinom,
  - Sol lob lokalizasyonlu
  - En geniş çap 4 cm
  - 4/9 metastatik LAP

- **Mayıs 2011- Ağustos 2013**→ Kemoterapi ve Sorafenib
- Stabil Hastalık

Ağustos 2013

- Stabil hastalık nedeniyle sorafenibe devam edilmiş

- Aralık 2014→ PET-BT'de progresyon… Sorafenib kesilip kapesitabin ve temozolomid (CapTem) başlanmış.

RTEÜ- Medikal Onkoloji

Haziran 2016

- Stabil hastalık
- Kalsitonin >2000 pg/mL
- CEA: 509 U/mL

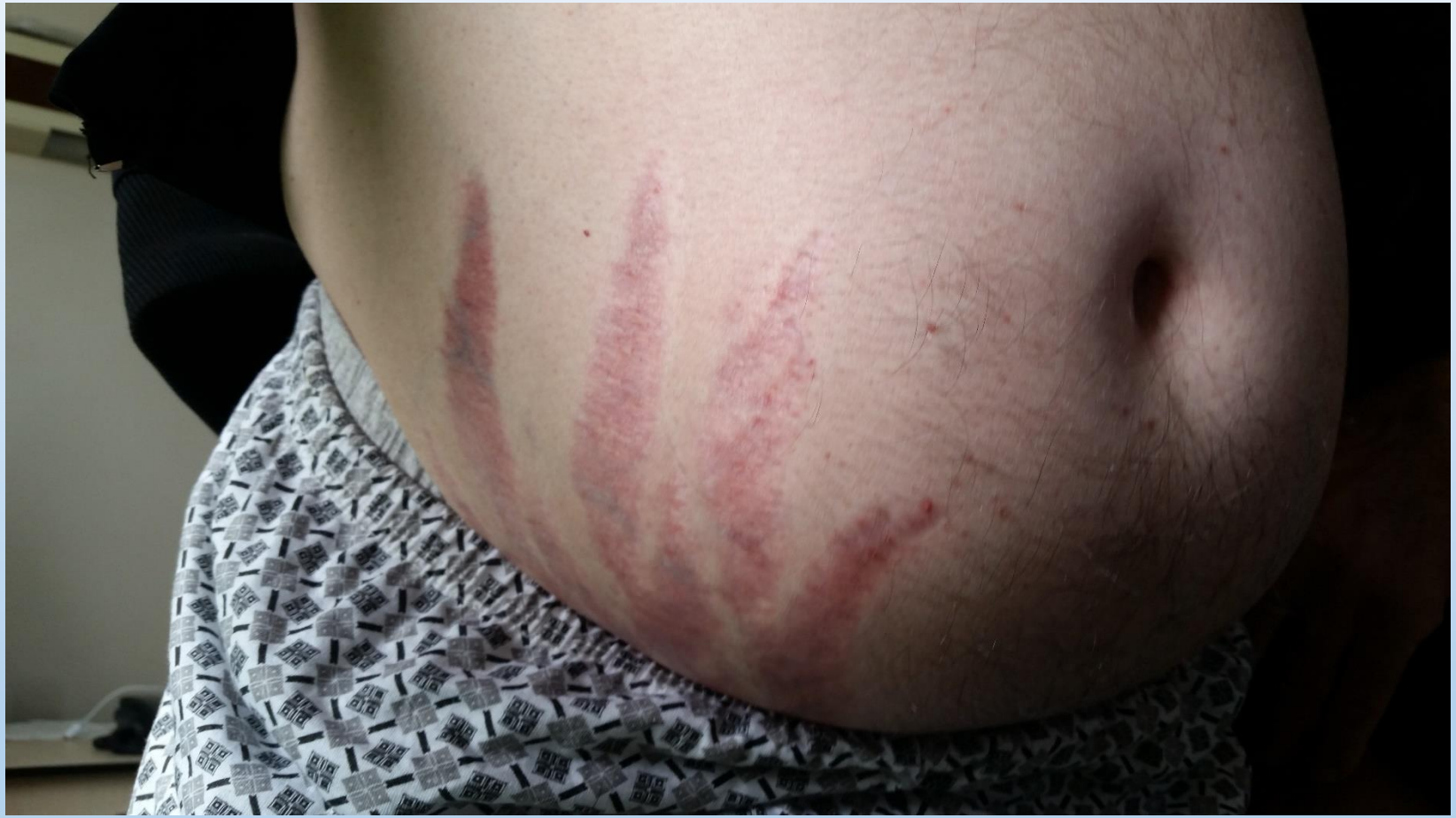
Hastanın kemoterapi tolerasyonu zorlaştığı ve 2 yıldır KT ile stabil hastalık olduğu için KT'ye ara verilmiş.

Vandetanib

RTEÜ- Medikal Onkoloji

- **Ekim 2016**
  - Kalsitonin: 8242 pg/mL
  - CEA: 606 U/mL

  - Cushingoid görünüm? → Endokrinoloji



RTEÜ- Endokrinoloji

- 2011→ Medüller tiroid karsinomu
- Haziran 2016→ düşük travma sonrası sol ayak bileği fraktürü

Ekim-Kasım 2016

24 saatlik idrar kortizol: >1196 µg/gün
2 gün 2mg DST kortizol: 22 µg/dL
2 gün 8mg DST kortizol: 31.3 µg/dL
CEA: 606.5 U/mL Kalsitonin: 8242 pg/mL

Endokrinoloji-Cerrahi Konseyi-Kasım 2016

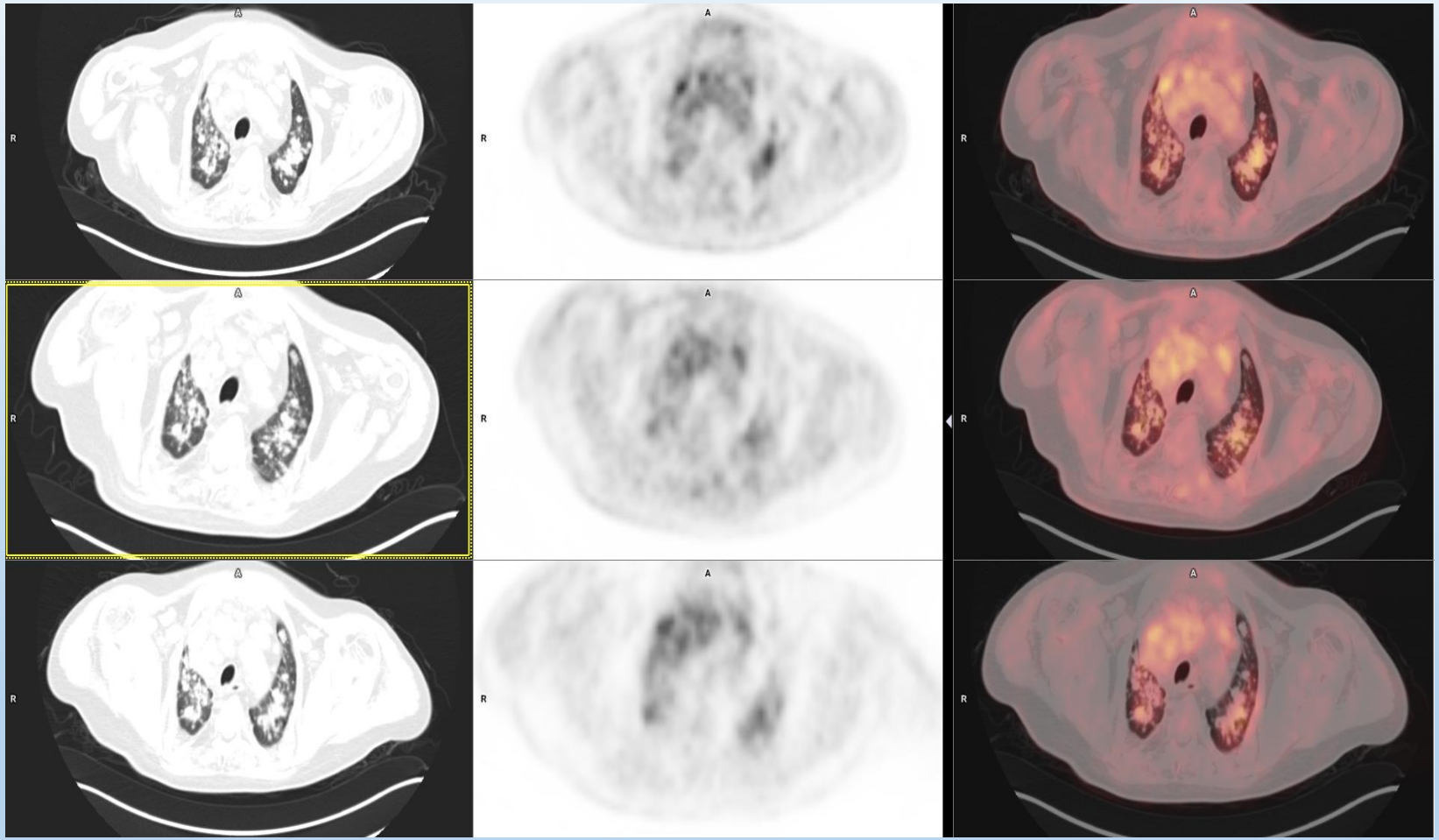
- Metastatik medüller tiroid karsinomu ve ektopik ACTH sendromu
  - Multipl kosta kırıkları!

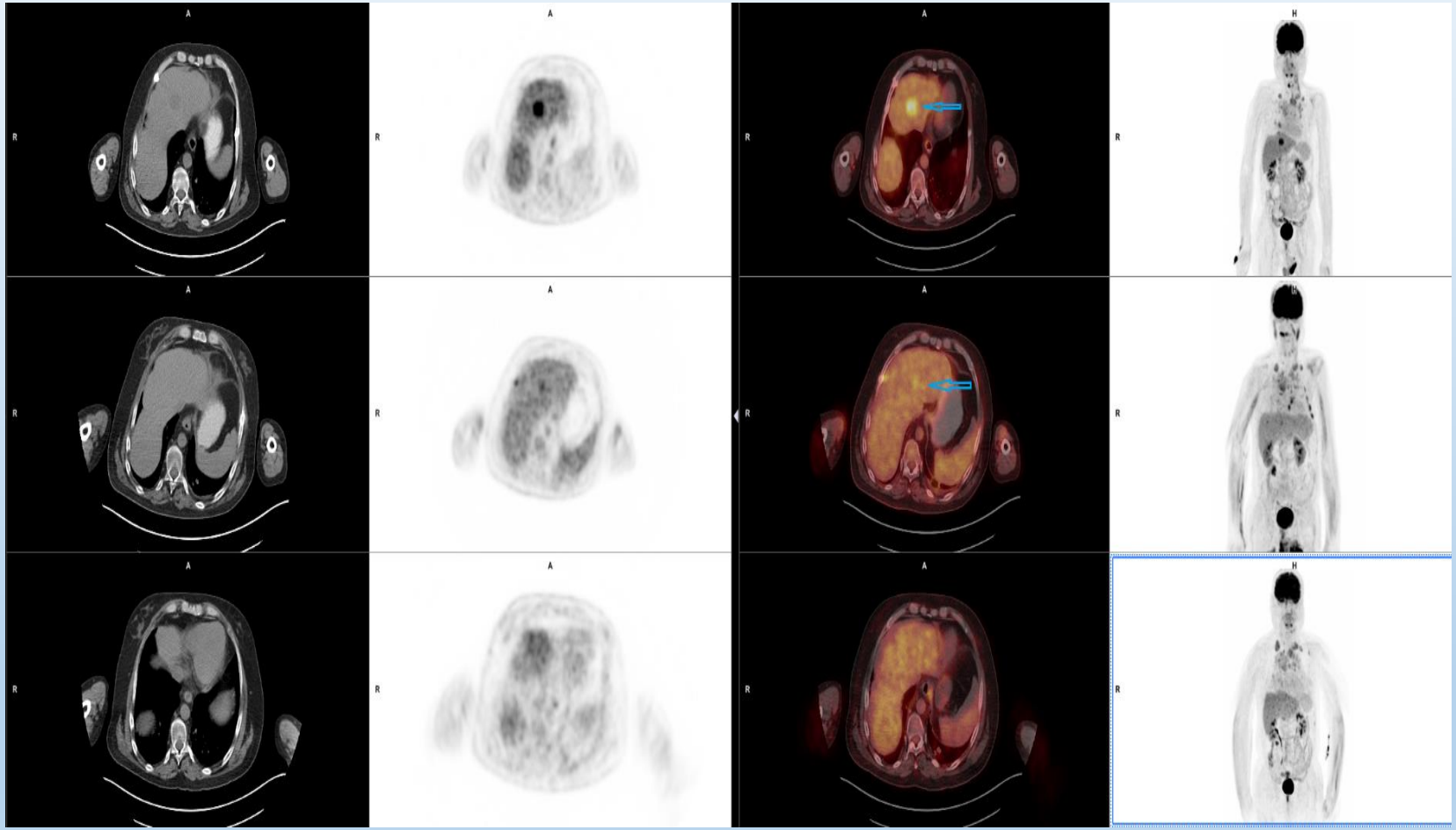
	Kortizol (µg/dL)	ACTH (pg/mL)	Kalsitonin (pg/mL)	CEA (U/mL)	24 saatlik idrarda kortizol (µg/gün)
Ekim 2016	23.7	118	8242	606	>1196
Kasım 2016	25.6	121			
Ketokanazol başlanıyor					
Aralık 2016					>807
Ocak 2017	26.4	121			
Vandetanib başlanıyor					
Ocak 2017			859	443	
01.02.2017	Acil→ ketokanazol ve vandetanib kesiliyor				
09.02.2017	15.2	86.6			

	Kortizol (µg/dL)	ACTH (pg/mL)	Kalsitonin (pg/mL)	CEA (U/mL)	24 saatlik idrarda kortizol (µg/gün)
16.02.2017	6.1	120			
20.02.2017	5.7	104			
02.03.2017	13.6	88	840	374	
Vandetanib geri başlanıyor					
10.03.2017	13.0	94			
24.03.2017	9.2	69		6979	442
14					

- **Mayıs 2017**
- Sağ ayak baş parmakta fraktür
- **Ekim 2017**
- Sol tibia şaft ve fibula fraktürü!
- Ortopedi servisinde hospitalize

PET-BT

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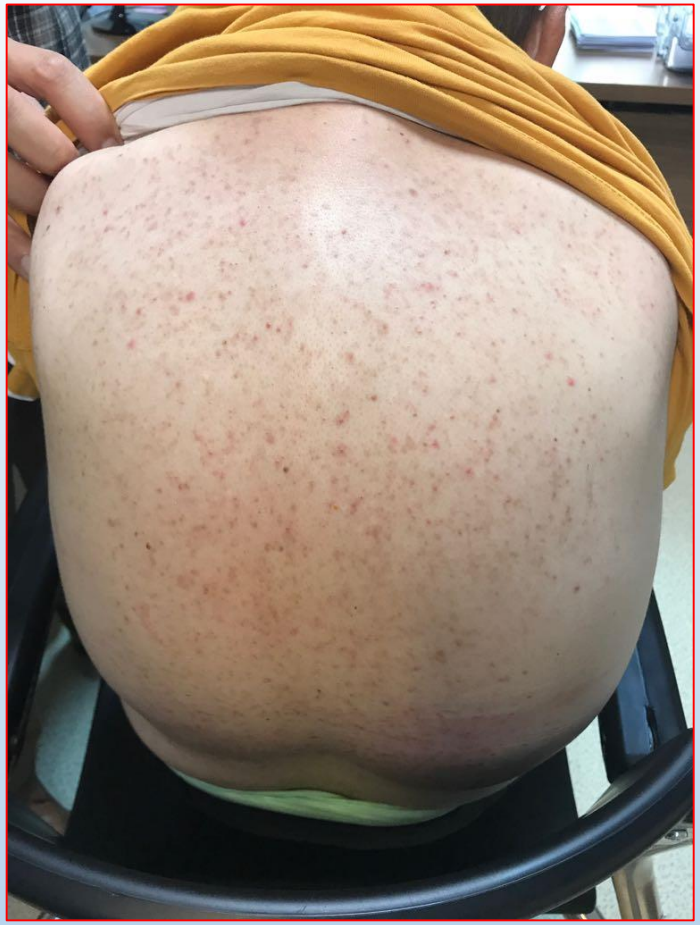
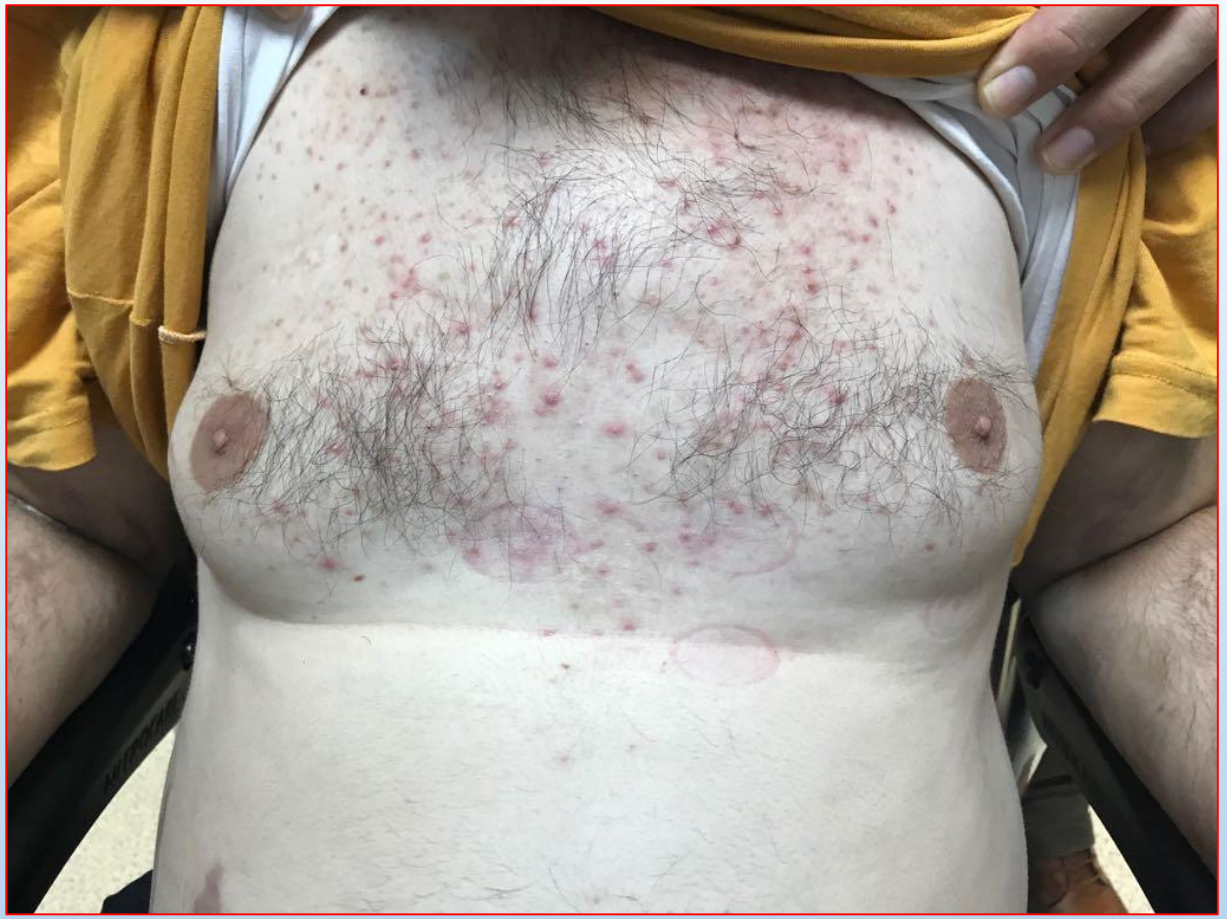




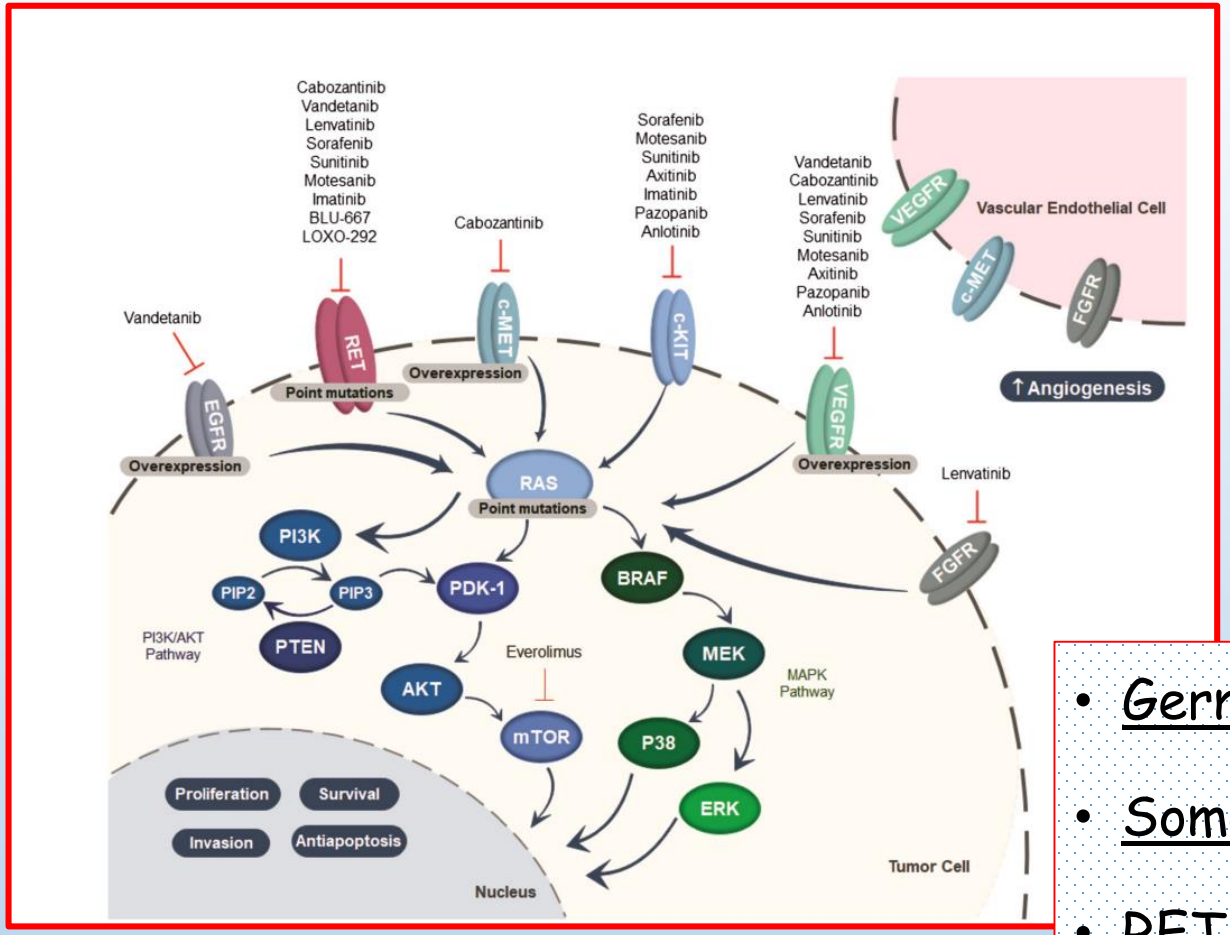
2019 da septik şok nedeniyle kaybediliyor...

Medüller Tiroid Kanseri (MTK)

- Tiroidin kalsitonin üreten parafoliküler C-hücrelerinden köken alır
  - Kalsitonin üretimi
  - CEA
- Tüm tiroid nodüllerinin %0.4-1.4'ü
- Tüm tiroid kanserlerinin %3'ünden azı
- Otopsi serilerinde %0.14
- En sık 4-6. dekadlar
- Vakaların→
  - %75'i sporadik
  - %25'i herediter (MEN2)

Wells SA Jr, et al., Thyroid, 2015; 25: 567-610
Valle&Kloos 2011
Tuttle et al., 2014
Lim et al., 2017

Alt tip	İnsidans	Tanı yaşı	Bileşenleri
Sporadik	%75	40-60	-
MEN2A	Herediter formların %34	20-40	Feokromositoma (%40-60) Paratiroid hastalığı (%10-30)
MEN2B	Herediter formların %6.8	3-8	Feokromositoma (%40-60) Paratiroid hastalığı nadir Marfanoid, dilde nöroma, barsaklarda ganglinöromatozis
FMTK	Herediter formların %57.6	45-65	-



RET
REaranged during Transfection

- Germ-line mutasyonları herediter kanserlere
- Somatik mutasyonlar sporadik vakalara sebep olur
- RET-->
  - Transmembran kodlanması
  - Değişik tiroizin rezidülerinin sürekli fosforilasyonu-> hücre survisi-diferensiyasyonu ve proliferasyonu için gerekli intraselüler yolakların aktivasyonu

609-611-618-620-634-->MEN 2A;

611-->Yavaş progresyon

M918T-->MEN 2B

Endocrine-Related Cancer, (2019) 26

- Hastaların %75-95'inde soliter nodül
- Hastaların%35'inde tanı anında servikal metastazı+
- Hastaların %0-15'inde bası semptomları+
- Hastaların %5-15'inde uzak metastaz+
  - Karaciğer, kemikler, akciğer, beyin, cilt
- Bazen de sistemik bulgularla gelir
  - Diyare, flushing, ağrılı kemik metastazları

Wells SA Jr, et al., Thyroid, 2015; 25: 567-610
Kebebew et al. 2000, Elisei et al. 2008, Hannah-Shmouni et al. 2016

- Başarılı cerrahiden sonra kalsitonin yüksek seyreden hastalarda aslında -muhtemelen klinik bulgu vermeyen- uzak metastazların olduğu düşünülür

- İlerleyen zamanda da hastaların %18-38'inde tespit edilirler

- 10 yıllık hastalığa spesifik mortalite %13.5-38

Roman S, et al., Cancer, 2006
Leboulleux S, et al., Clin Endocrinol, 2004
Girelli et al., 1998
Kuo et al., 2018

- SEER→10 yıllık survi %95.6
- Jung ve arkadaşları→
  - 5 yıllık survi %92
  - 10 yıllık survi %87
  - Uzak metastaz tanısı konduktan sonra→
  - 5 yıllık survi %26
  - 10 yıllık survi %10

Jung KY, et al., Clin Endocrinol, 2016
Bergholm U, et al., Cncer, 1997
Modigliani E, et al., Clin Endocrinol, 1998

TANI

- TİİAB %50-80 duyarlı
  - İmmüno-histokimyasal boyama
  - TİİAB *wash-out*
- Kalsitonin
  - Genelde tm boyutuyla/hastalık yaygınlığıyla korele
  - Hiperkalsemi, hipergastrinemi, nöroendokrin tümörler, ranl yetmezlik, papiller-foliküler tiroid Ca, guvatr, otoimmün tiroidit, uzun süreli PPI tedavisi, kalsitonine karşı heterofil antikor varlığı
- CEA
  - Heterofil antikorlar, akciğer hastalıkları, tiroid dışı malignensiler, sigara

Wells SA Jr, et al., Thyroid, 2015; 25: 567-610

Cerrahi

- Tek küratif tedavi...
- Sporadik vakaların %10'unda ve genetik hastaların tamamında multifokal hastalık var
  - Total tiroidektomi+Santral kompartman diseksiyonu
- Lenf nodu diseksiyonu
  - Preoperatif kalsitonin
  - Preoperatif USG bulguları
  - Intraoperatif bulgular

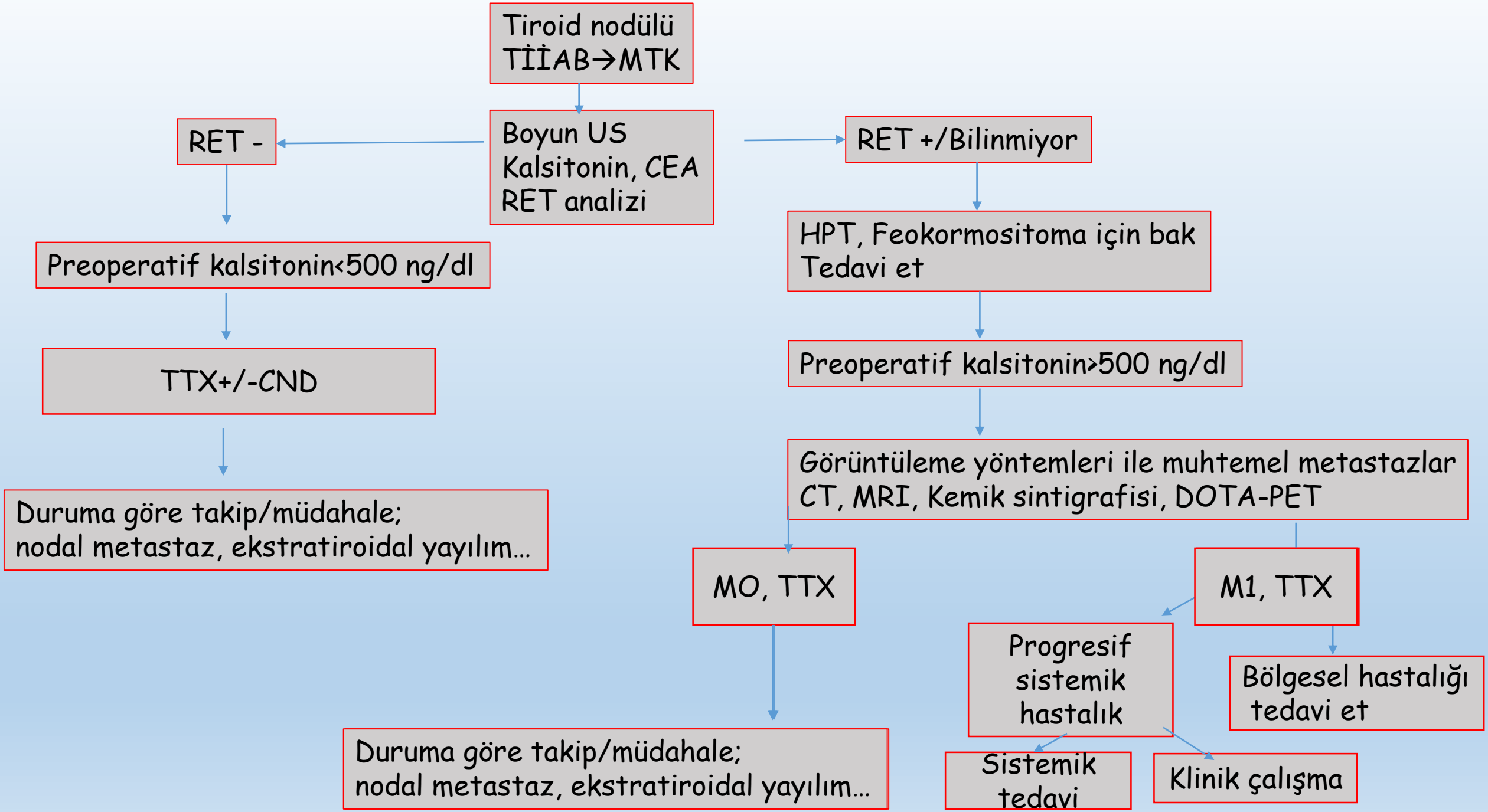
Machens A, Dralle H, J Clin Endocrinol Metab. 2010 Jun;95(6):2655-63
Scollo C, Baudin E, Travagli JP, Caillou B, Bellon N, Leboulleux S, Schlumberger M, J Clin Endocrinol Metab. 2003;88(5):2070.

- TM çapı≥1 cm/Bilateral hastalık var→total tiroidektomi+bilateral santral lenf nodu diseksiyonu
- Kontralateral lenf nodu diseksiyonu→
  - Bazal kalsitonin>200pg/ml
  - İpsi lateral lenf nodu+
- Bilateral santral lenf nodu diseksiyonu+ipsilateral lenf nodu diseksiyonu→
  - Bazal kalsitonin 50-200 pg/ml
  - Boyun USG (-)
- Santral diseksiyona gerek yok
  - Bazal kalsitonin<20 pg/ml

Kalsitonin> ...pg/ml

- 20→İpsilateral santral, ipsilateral lateral
- 50→Kontralateral santral

- Tanı **postoperatif** konmuşsa →
  - Sporadik vakada tamamlayıcı cerahi gereksiz
    - USG bulgusu veya post-operatif ölçülebilir kalsitonin varsa gerekli



Wells SA Jr, et al., Thyroid, 2015; 25: 567-610

- **Prognostik faktörler**
  - Yaş
  - Tümör çapı
    - Tümörün intratiroidal olması
  - Lokal ve uzak metastaz varlığı
    - Lenf nodu sayısı...
  - Somatik M918 mutasyonu
  - Kalsitonin-CEA yarılanma ömrü
  - CA 19.9? Prokalsitonin? Micro-RNA?

Roman et al. 2006; Scollo et al. 2003; Sosa et al. 2017
Elisei R, et al, 2015; Lorusso L,et al, 2021; Machens A, et al, 2014; Karagiannis AKA, et al, 2016

Elevated level of serum carbohydrate antigen 19.9 as predictor of mortality in patients with advanced medullary thyroid cancer

Rossella Elisei[1], Loredana Lorusso[1], Paolo Piaggi[1], Liborio Torregrossa[2], Giovanni Pellegrini[3], Eleonora Molinaro[1], Laura Agate[1], Valeria Bottici[1], Fabiana Pani[1], Andrea Cacciato Insilla[2], Francesca Casella[1], Raffaele Ciampi[1], Ilaria Tognetti[3], Gabriele Materazzi[2], Fulvio Basolo[2] and **Cristina Romei[1]**

[1]Endocrine Unit, Department of Clinical and Experimental Medicine and [2]Department of Surgical, Medical, Molecular Pathology, University of Pisa, Pisa, Italy and [3]Clinical Chemistry Laboratory, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy

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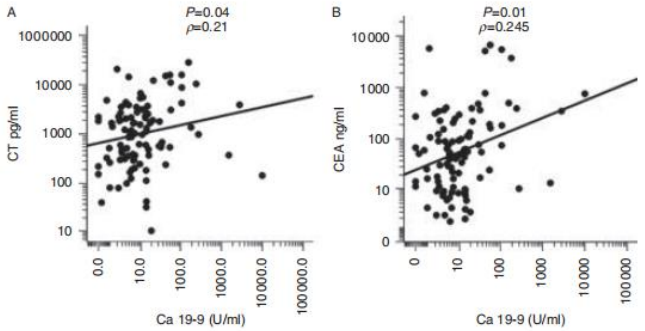


Figure 1
Positive linear correlation between the serum levels of Ct (ρ=0.21; P=0.04) (A) and CEA (ρ=0.245; P=0.01) (B) with Ca 19.9 serum values.

Table 2 Comparison of lymph node and distant metastases at the time of our observation in the two groups of structurally persistent/recurrent MTC patients with normal and abnormal levels of serum Ca 19.9.

Type of metastases	Ca 19.9-positive patients (%)	Ca 19.9-negative patients (%)	*P* value
Lymph node metastases	13/16 (81)	71/84 (84)	0.7
Distant metastases (all)	16/16 (100)	66/84 (78)	0.04
Bone metastases	5/16 (31)	10/84 (11)	0.03
Lung metastases	10/16 (62)	37/84 (44)	0.17
Liver metastases	12/16 (75)	39/84 (46)	0.03

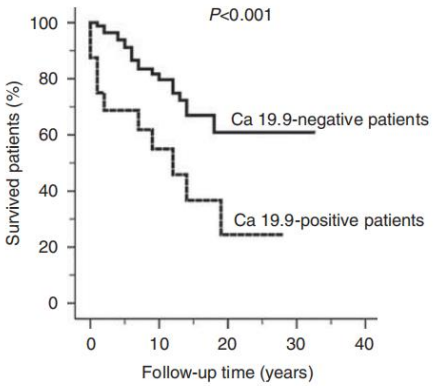


Figure 3
The Kaplan–Meier curve of survival in patients with normal and abnormal levels of Ca 19.9.

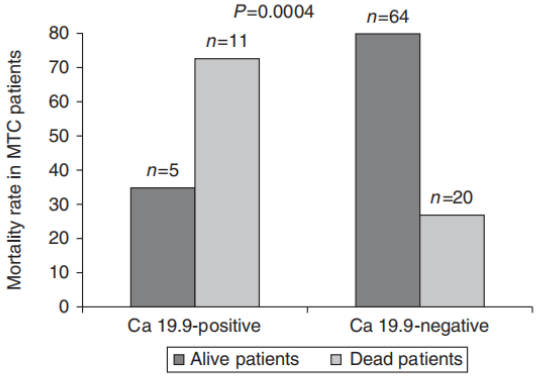


Figure 2
Mortality rate of patients with abnormal and normal levels of Ca 19.9: a statistically significant higher percentage of death was observed in the group with abnormal levels of serum Ca 19.9.

European Journal of Endocrinology (2015) 173, 297–304

ANTICANCER RESEARCH *36*: 3803-3810 (2016)

Review

Procalcitonin: A New Biomarker for Medullary Thyroid Cancer? A Systematic Review

APOSTOLOS K.A. KARAGIANNIS[1], CONSTANTINE GIRIO-FRAGKOULAKIS[2] and THEODORA NAKOUTI[3]

Review | P Trimboli et al. | Procalcitonin in the diagnosis of MTC | 22:3 | R157–R164

Procalcitonin for detecting medullary thyroid carcinoma: a systematic review

Pierpaolo Trimboli[1,2], Ettore Seregni[3], Giorgio Treglia[1], Maria Alevizaki[4] and Luca Giovanella[1]

- Stabil bir molekül
- Kalsitonin-hastalık yaygınlığı-tümör çapı-lenf nodu metastazı-ile korelasyon
- Prokalsitonin>0.1 ng/ml→%98-100 özgünlük, %91-100 duyarlılık

Endocrine-Related Cancer (2015) 22, R157-R164
Anticancer Research 36: 3803-3810 (2016)

Endocrine-Related Cancer | P Romeo *et al.* | Plasma miR-375 prognostic marker in advanced MTC | 25:3 | 217–231

RESEARCH

Circulating miR-375 as a novel prognostic marker for metastatic medullary thyroid cancer patients

Paola Romeo[1], Carla Colombo[2,3], Roberta Granata[4], Giuseppina Calareso[5], Ambra Vittoria Gualeni[6], Matteo Dugo[7], Loris De Cecco[7], Maria Grazia Rizzetti[1], Angela Zanframundo[6], Antonella Aiello[6], Maria Luisa Carcangiu[6], Annunziata Gloghini[6], Stefano Ferrero[8,9], Lisa Licitra[4,10], Angela Greco[1], Laura Fugazzola[2,3]*, Laura Deborah Locati[4]* and Maria Grazia Borrello[1]*

cells

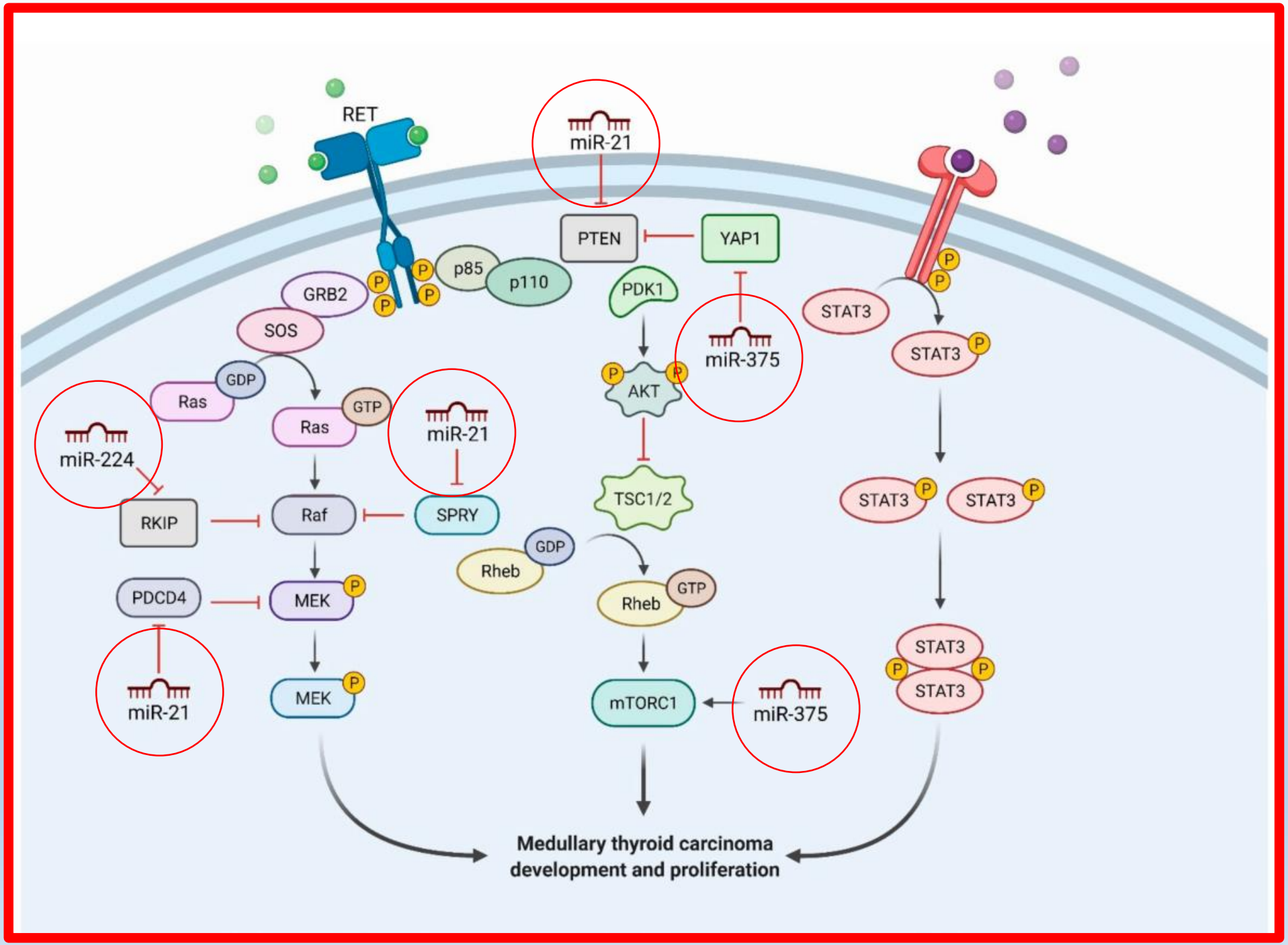
MDPI

Review

MicroRNAs in Medullary Thyroid Carcinoma: A State of the Art Review of the Regulatory Mechanisms and Future Perspectives

Francesca Galuppini [1], Simona Censi [2], Margherita Moro [1], Stefano Carraro [1], Marta Sbaraglia [1], Maurizio Iacobone [3], Matteo Fassan [1,4], Caterina Mian [2] and Gianmaria Pennelli [1,*]

Endocrine-Related Cancer (2018) 25, 217-231
Cells 2021, 10, 955



Cells 2021, 10, 955

Table 1. The main miRNAs involved in medullary thyroid carcinoma, including gene mechanisms and actions.

miRNA	Gene Mechanism	Actions
miR-21	Upregulates RAS/ERK pathway (targets RASA1 and SPRED1), inhibits PDCD4 and apoptosis	High levels associated with lymph node metastases, advanced stage and postoperative chronic disease; potential therapeutic target [19]
miR-375	Downregulates the PI3K/Akt pathway (targets YAP1, SLC16a2, SEC23A, PARP, JAK2 and NGFR)	Potential biomarker, plasma levels correlate with tumor burden, distant metastasis and response to vandetinib treatment [25]
miR-224	Dysregulates the PI3K/Akt pathway	Low levels in advanced MTC, high levels and positive prognostic factor in sporadic MTC with RAS mutations [31]
miR-183	Inhibits PDCD4 and apoptosis	High levels associated with lateral cervical lymph node metastases, distant metastases and mortality [14,34]
miR-127	Downregulates BAG5 and SEPT7, upregulates Wnt7a	Low levels in sporadic MTC harboring RET mutation [40]
miR-153-3p	Downregulates mTOR pathway (targets RPS6KB1)	Potential therapeutic effects in combination with tyrosine kinase inhibitors [41]
Long-non-coding-RNA—MALAT1	Downregulates B-MYB, p53, upregulates EMT (targets E-cadherin)	High levels in MTC, in vitro inhibition reduces tumor cell proliferation and invasion [46]
miR-31-3p	Downregulates RAS pathway (targets RASA2)	Low levels in MTC, reduces in vitro MTC cell proliferation [52]
miR-34a; miR-144	Dysregulates PI3K/Akt/mTOR pathway (targets AXL)	High levels in MTC, proposed as biomarkers but lack sufficient specificity and sensitivity [63,64]
miR-10a	Downregulates HOXD4	High levels in primary MTC but downregulated in metastases [15]
miR-200 family	Upregulates TGF-β2 (targets ZEB1 and ZEB2) and EMT (targets E-cadherin)	May correlate with metastatic potential [21]

Total tiroidektomi

Kalsitonin (-)/normal gösterilebilen nüks veya persistan hastalık yok

Fizik muayene ve US normal→ İlk yıl 6 ayda bir, sonrasında yıllık takip

Fizik muayene, Boyun US Kalsitonin, CEA

Kalsitonin ölçülebilir ama <150 ng/dl ve gösterilebilen nüks veya persistan hastalık yok

*6 ayda bir FM/US
*Her 3-6 ayda bir kalsitonin ve CEA (dt)
*Kalsitonin>150 ng/dl→odak ara

Kalsitonin>150 ng/dl

Metastazların tespiti için görüntüleme

Görüntüleme (+)

Görüntüleme (-)

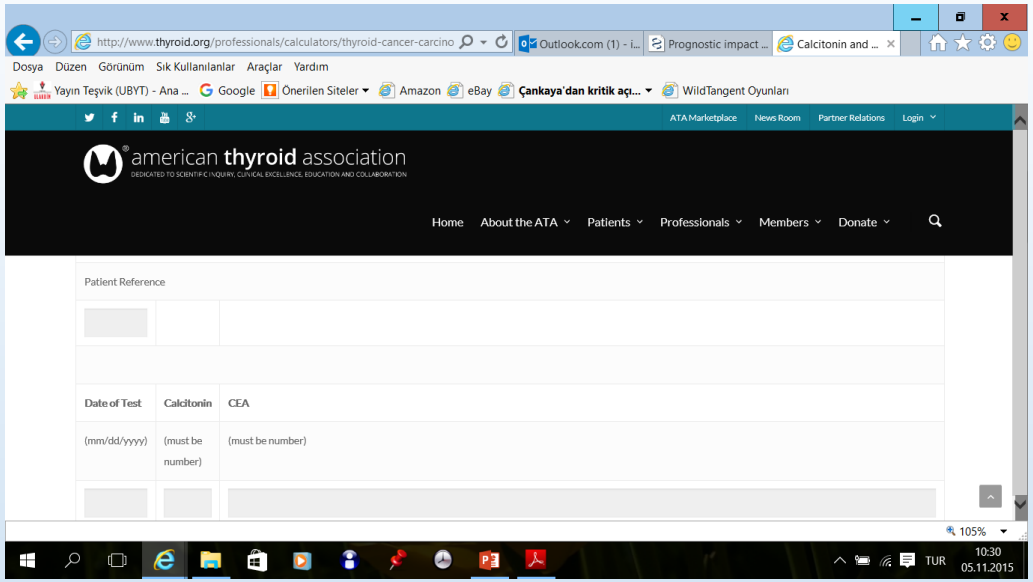
*Bölgesel hastalık→ Cerrahi, EBRT, …
*Progresif hastalığı olanlar→ Sistemik tedavi (TKI) Klinik Çalışma

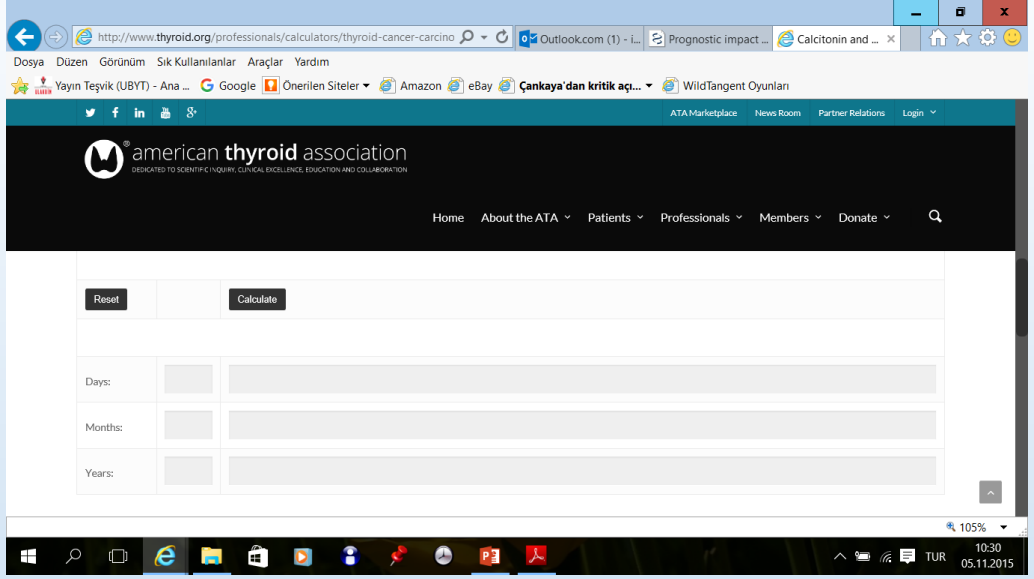
*Fizik muayene ve görüntüleme her 6 ayda bir
*Her 3-6 ayda bir kalsitonin ve CEA (dt)

MTK/Tedavi cevabı

- Mükemmel cevap:
  - Ölçülemeyen kalsitonin, normal aralıklarda CEA, tespit edilebilir hastalık yok
- Biyokimyasal inkomplet cevap
  - Ölçülebilir CEA ya da kalsitonin
  - Tespit edilebilir/gösterilebilir hastalık
- Yapısal inkomplet hastalık
  - Rekürren ya da persistan hastalık varlığı

- Serum kalsitonin ve CEA operasyondan 2-3 ay sonra ölçülmeli
- Bazı hastalarda kalsitonin düşmesi ayları bulabilir
- Cerrahi olarak kür olan hastalarda saatler içinde de düşebilir
  - Ameliyat sonrası erken dönem bakmak?
- Bazı hastalarda tm dediferansiyasyonu nedeniyle CEA yükselirken kalsitonin yükselmeyebilir
  - İkisine birden bakılmalı





http://www.thyroid.org/professionals/calculators/thyroid-cancer-carcinoma/

***Doubling time* hesaplaması için en az 4 ölçüm**

***Doubling time* 6 aydan kısa olanlar ilk 12 ayda anlaşılabilir**

DT<6 ay-->5-10 yıllık survi→%25-8
DT 6-12 ay-->5-10 yıllık survi→%92-37

■ **RECOMMENDATION 49**

In patients with detectable serum levels of Ctn and CEA following thyroidectomy, the levels of the markers should be measured at least every 6 months to determine their doubling times. Grade B recommendation

Meijer et al. 2010

Küçük-izole metastazlar kalsitonin stabilse izlenebilir

Sistemik, progresif hastalık için sistemik tedavi düşünülmeli

Priya SR, et al., Frontiers in Oncology, 2017

Tedavi

- Cerrahiye uygun olmayan lokal ilerlemiş hastalık
- Uzak metastazı olan hastalar

Görüntüleme

- Tüm ilgili alanlara bakılmalı
  - Kontrastlı CT→baş-boyun, toraks, abdomen
  - MRI→KC metastazları için daha uygun olabilir
  - Kemik sintigrafisi
  - ^{18}F-DOPA PET *gösterilemeyen metastazlarda*
  - Gallium-68 DOTATATE
    - Sensitivite %50-80

MEDİKAL/SİSTEMİK TEDAVİ

Semptomatik tedavi

- Diyare
  - Diyet, loperamid, difenoksilat/atropin, kodein…
  - Interferon alfa, somatostatin analogları
- Cushing sendromu
  - KC metastaz *debulking*
    - Cerrahi, kemoembolizasyon
  - Ketokanozol, mifepriston, aminoglutetemid, metirapon, mitotan
  - Bilateral adrenalektomi
  - Vandetanib
- Kemik metastazları
  - Denosumab, bisfosfonatlar

Julien Hadoux &Martin Schlumberger, Best Practice & Research Clinical Endocrinology & Metabolism, 2017
Baudry C, et al., NEJM, 2013

Sitotoksik kemoterapi

- Çok çeşitli tedaviler/kombinasyonlar denenmiş
  - Doksorubisin, Sisplatin…
  - Doksorubisin+Sisplatin

KT BAŞARI ŞANSI %20 CİVARINDA

  - Doksorubisin+Sisplatin+Vindesin…
  - Bleomisin+Doksorubisin+Sisplatin
  - Parsiyel cevaplar
  - Toksisite artmış kombinasyon arttıkça
    - Miyelosupresyon, mukozal toksisite

Julien Hadoux &Martin Schlumberger, Best Practice & Research Clinical Endocrinology & Metabolism, 2017

Sitotoksik kemoterapi

- Dakarbazinin stabilize edici etkisi
- Dakarbazin+5-FU ile başarılı subkütan ve akciğer hastalığı tedavisi
- Dakarbazin+Siklofosfamid+Vinkristin
  - Stabil hastalık, parsiyel cevap
- Çalışmalar eski, hasta sayıları görece az
- RECIST Kriterleri tam olarak kullanılmamış
- Dakarbazin+5-FU en başarılı tedavi gibi görünüyor

Julien Hadoux &Martin Schlumberger, Best Practice & Research Clinical Endocrinology & Metabolism, 2017

Sitotoksik kemoterapi

- Oral tedaviler hakkında bilgiler çok az
  - Kapesitabin
  - Kapesitabin+Temozolomid
- Biyomarkerlar ve RET üzerine etkileri bilinmiyor
- TKI ile başarısız olan vakalarda?

Julien Hadoux &Martin Schlumberger, Best Practice & Research Clinical Endocrinology & Metabolism, 2017

EBRT

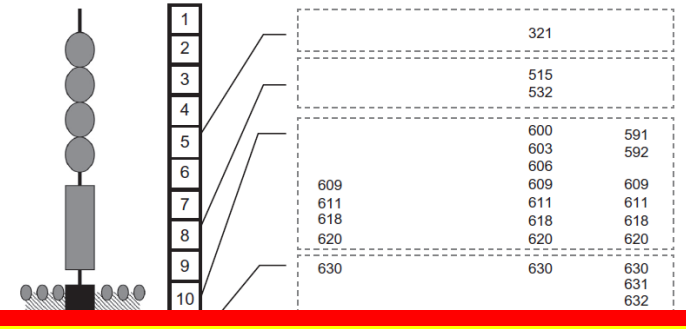
- Servikal nüks ihtimali yüksek olan hastalarda lokorejyonel kontrolü sağlamak için?
  - Lokorejyonel metastazlarda %38 azalma
- Surviye etkisi yok

Schwartz et al. 2008
Martinez et al. 2010
Brierley & Sherman 2012
Call et al. 2013

- RET proto-onkogeninde→
  - Herediter vakaların hemen hepsinde aktive edici germline mutasyonu
  - Sporadik vakaların yaklaşık %50-60'ında somatik RET mutasyonları
    - %85'i kodon 918'de→kötü prognoz
- RET mutasyonu olmayan vakaların %68'inde RAS mutasyonu

Moura MM, et al., Br J Cancer, 2009
Moura MM, et al, JCEM, 2011
Elisei R, et al, JCEM, 2008

- 10. kromozom üzerinde
- Nöral krest ve ürogenital sistem gibi gelişmekte olan dokularda büyüme ve diferansiyasyonu düzenleyen tirozin kinaz reseptörünü kodlayan RET-protoonkogende genetik defekt



→hücre proliferasyonu, diferansiyasyonu, motilitesi, apopitoz ve survisi

- RET aktivasyonu-->
  - MAPK, PI3K/Akt/mTOR/JNK yolaklarını da stimüle eder

Curr Genomics 2011; 12: 618-25

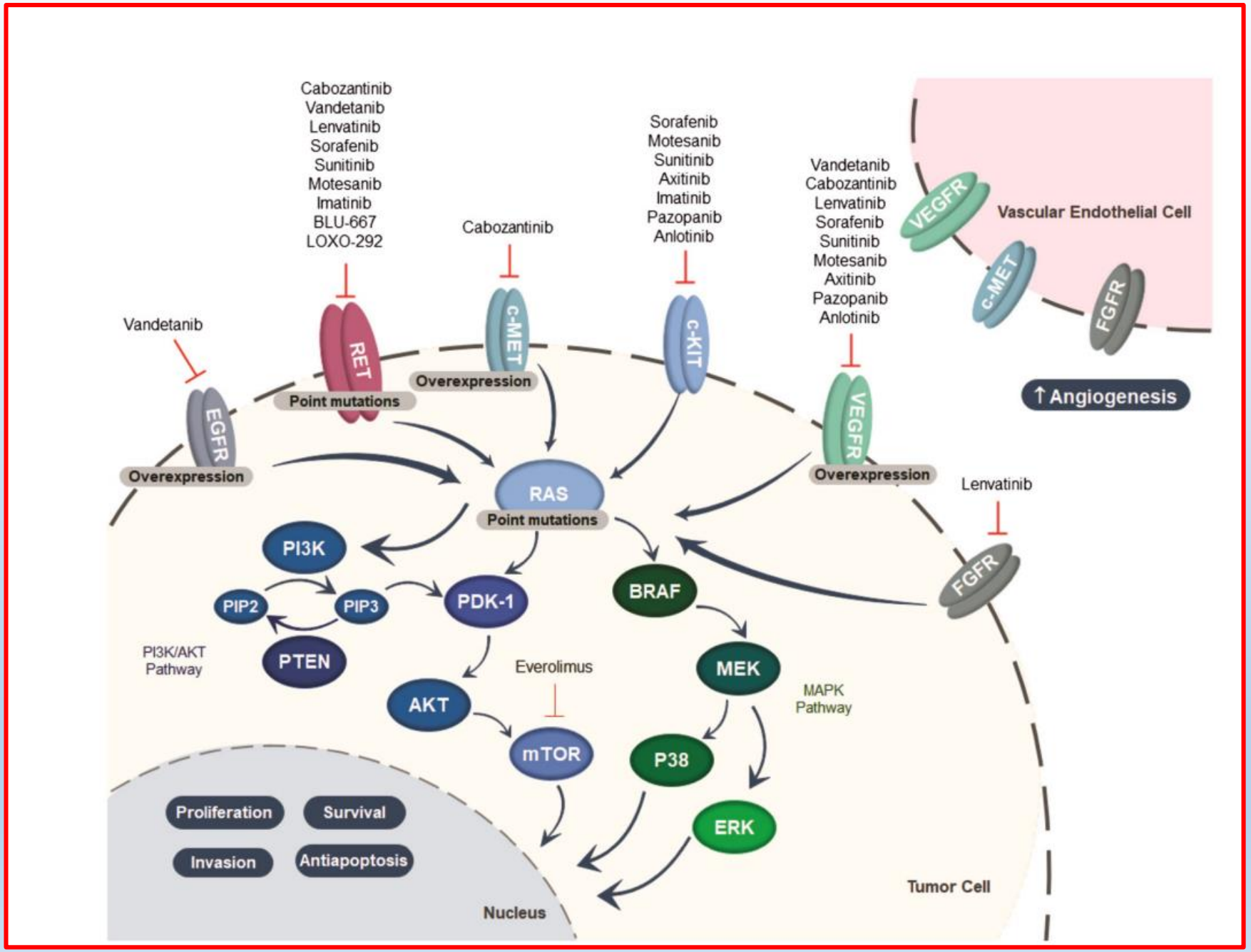
- Vasküler endotelyal büyüme faktörü (VEGF) ve VEGF reseptörleri [**VEGFR-1 (Flt-1) /VEGFR-2 (Flk-1, KDR)**]→
  - MTK dokularında tümör hücrelerinde ve vasküler endotelyumda eksprese ediliyorlar

- Fibroblast büyüme faktörü reseptörleri (FGF)
- Trombosit kaynaklı büyüme faktörü (PDGF)

- Hepatosit büyüme faktörü (HGF) ve reseptörü c-met
- Epitelyal büyüme faktörü reseptörü (EGFR)

Tirozin Kinaz İnhibitörleri (TKİ)

- Hedefe yönelik tedavi/*Molecular targeted therapy*



Endocrine-Related Cancer, (2019) 26

Table 2
Common AEs and their frequency (%) in clinical trials investigating TKIs in MTC.

	Lenvatinib [9][a]	Vandetanib [10]	Pazopanib [11]	Sorafenib [12]	Cabozantinib [13]
Hypertension	51	32	51	43	33
Diarrhea	75	56	77	71	63
Stomatitis				48 + 62 oral pain	29
Weight loss	42			48	48
HF syn				76	50
Fatigue	53	24 + 14 asthenia	63		41
Skin rash		45		67	
Alopecia				76	
TSH increase					
Proteinuria	59		37		
Nausea	48	33	34		43
Vomiting	37	14	26		
Dry skin				48	
Nail changes				48	
Blood creatinine increase					
Decreased appetite	49	21			46
Skin papilloma					
Arthralgia					
Skin hypopigmentation			63		
AST increase			40		
Anorexia			46		
Leucocyte count decrease			40		
Dysgeusia					34
Headache	41	26			
Acne		20			
Cough	22				
Flushing				43	
Hair color changes					
Constipation					27
Discontinuation due to AE			9		

[a] At baseline, 53% of patients had diarrhea and 44% musculoskeletal pain.

C. Resteghini et al.,Best Practice & Research Clinical Endocrinology & Metabolism, 2017

Table 2. Summary of Phase 3 Clinical Trials of Vandetanib or Cabozantinib versus Placebo in Patients with Advanced Medullary Thyroid Cancer

Variable	Vandetanib (300 mg/day)	Cabozantinib (140 mg/day)
Targets	VEGFR, RET, EGFR, c-KIT	VEGFR, RET, c-MET, c-KIT
Phase 3 clinical trial	ZETA study	EXAM study
No. of patients (mean age, years)	Vandetanib 231 (50.7) vs. Placebo 100 (53.4)	Cabozantinib 219 (55.0) vs. Placebo 111 (55.0)
Postprogression, open-label treatment	Yes	No
Radiologic progression before enrolment	Not requested	Yes (within 14 mo)
Previous treatment	40%	38%
Previous TKIs	Unknown	20%
Hereditary disease	10%	5.5%
RET mutation positive	59% Vandetanib arm	46.1% Cabozantinib arm
RET 918 mutation positive	Not available	34.2% Cabozantinib arm
Median time of follow-up, mo	24	13.9
Results		
Median progression-free survival, mo	30.5 vs. 19.3 (HR, 0.46; 95% CI, 0.31–0.69; $P<0.001$)	11.2 vs. 4.0 (HR, 0.28; 95% CI, 0.19–0.40; $P<0.001$)
Objective response rate	45% vs. 13% ($P<0.001$)	28% vs. 0% ($P<0.001$)
Overall survival, mo	Not available	26.6 vs. 21.1 (HR, 0.85; 95% CI, 0.64–1.12; $P=0.24$)
Overall survival in RET positive, mo	Not available	44.3 vs. 18.9 (HR, 0.60; 95% CI, 0.38–0.94; $P=0.03$)
Safety		
Most common adverse events at least grade 3	Diarrhea, hypertension, QTc prolongation, fatigue	Diarrhea, palmar-plantar erythrodysesthesia, fatigue

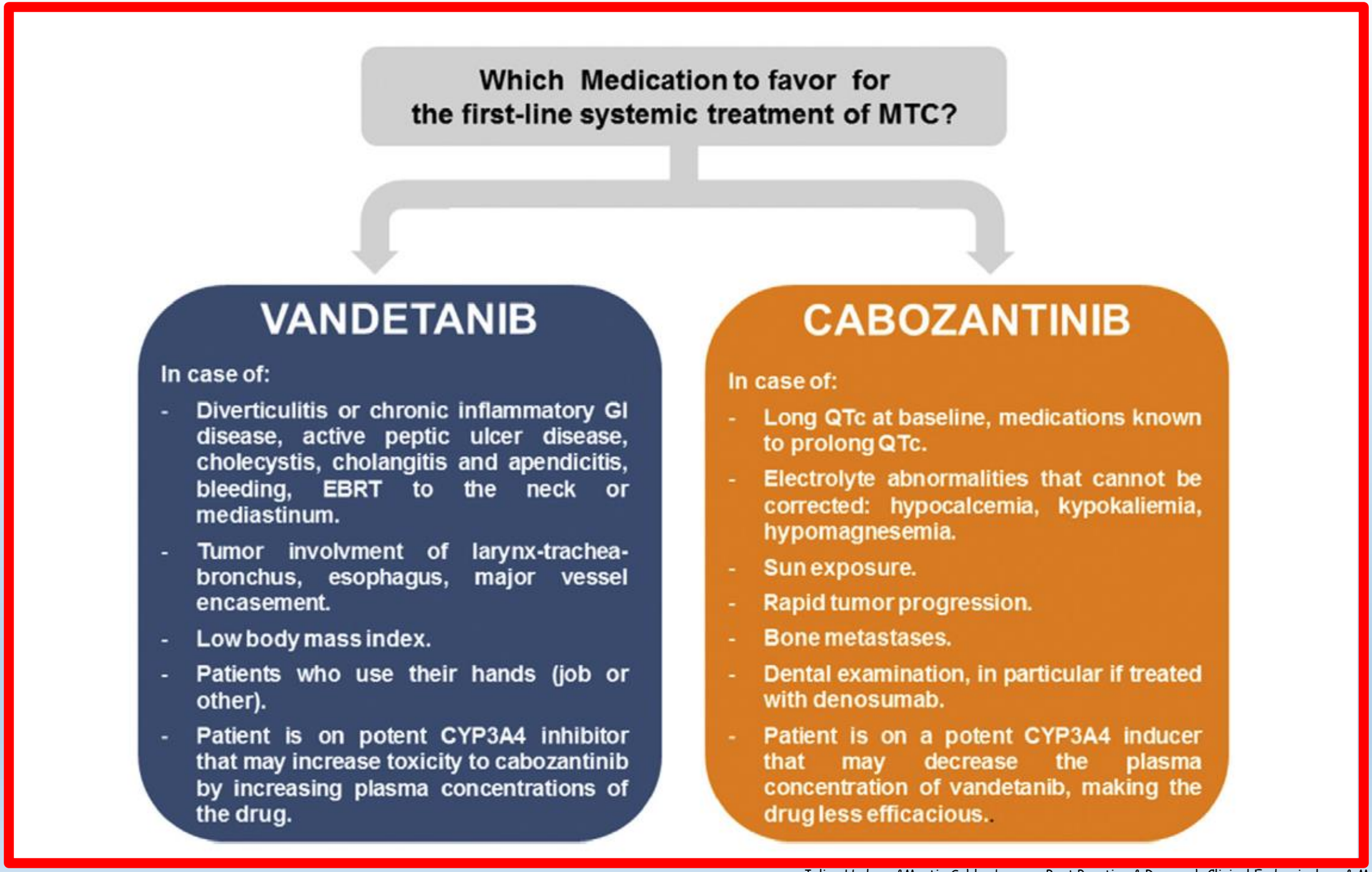
Wells et al.2012
Elisei et al. 2013

Endocrinol Metab 2021;36:514-524

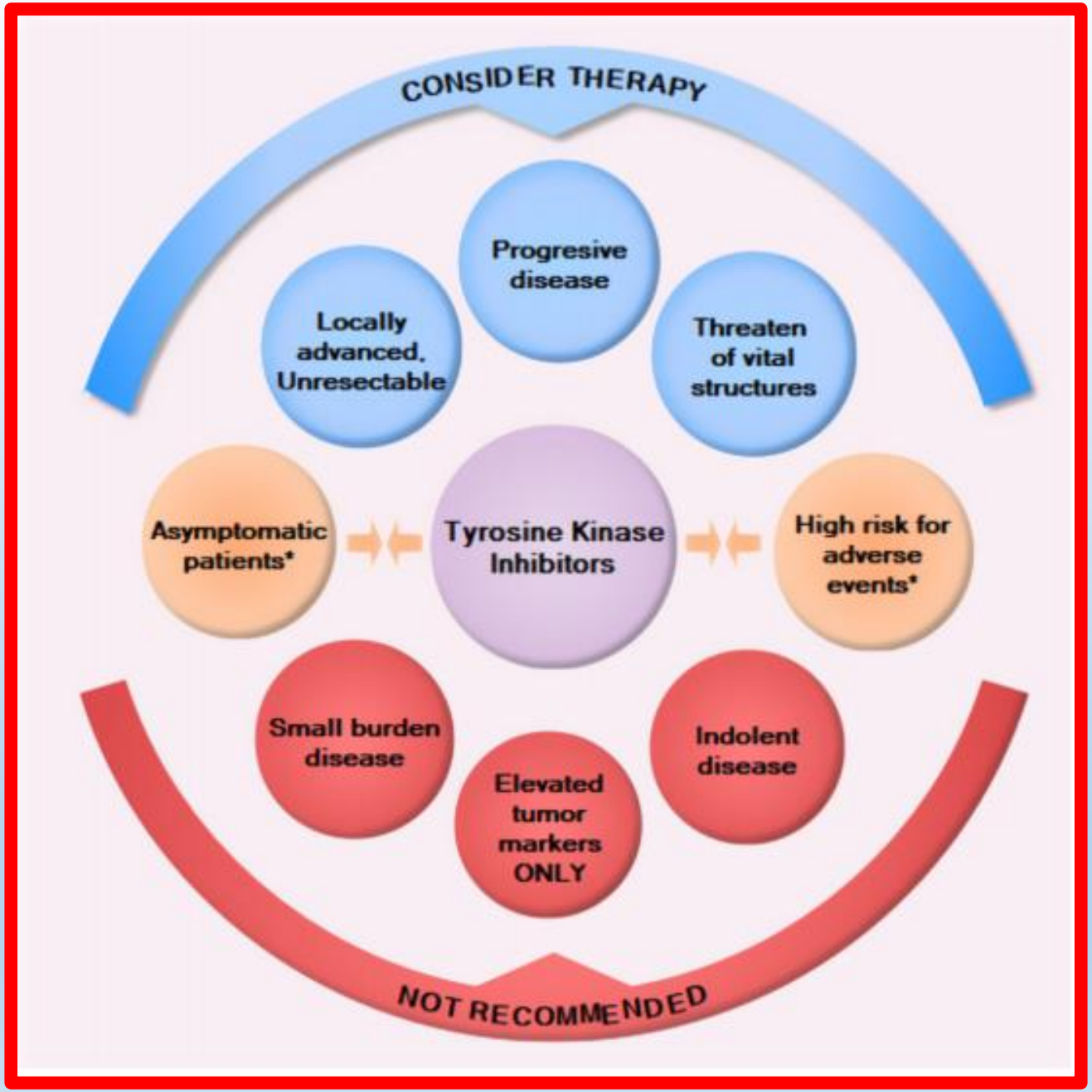
- Kardiyovasküler
  - Hipertansiyon, kanama, pulmoner/venöz tromboemboli, QT uzaması
- GIS
  - Bulantı-kusma, diyare, mukozit, kilo kaybı, tat alma bozukluğu, akalküloz kolesistit, GI perforasyon, nonGI-fistül, hepatik yetmezlik

- Cilt bozuklukları
- Tiroid fonksiyon bozukluklar
- Böbrek yetmezliği
- Proteinüri
- Hipokalsemi
- Miyelotoksisite
- Yorgunluk
- Oküler toksisite
- Osteonekroz

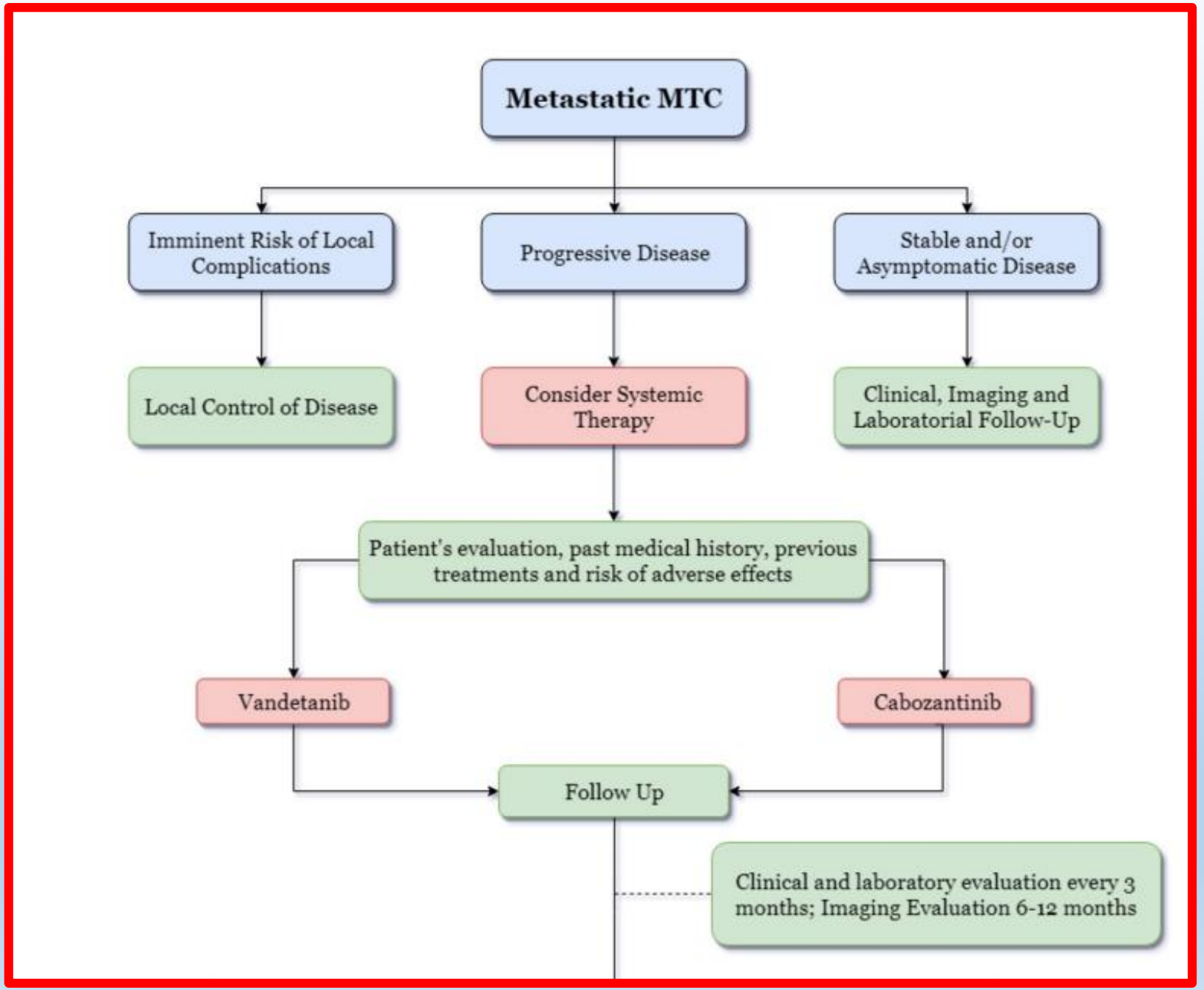
C. Resteghini et al.,Best Practice &Research Clinical Endocrinology & Metabolism, 2017



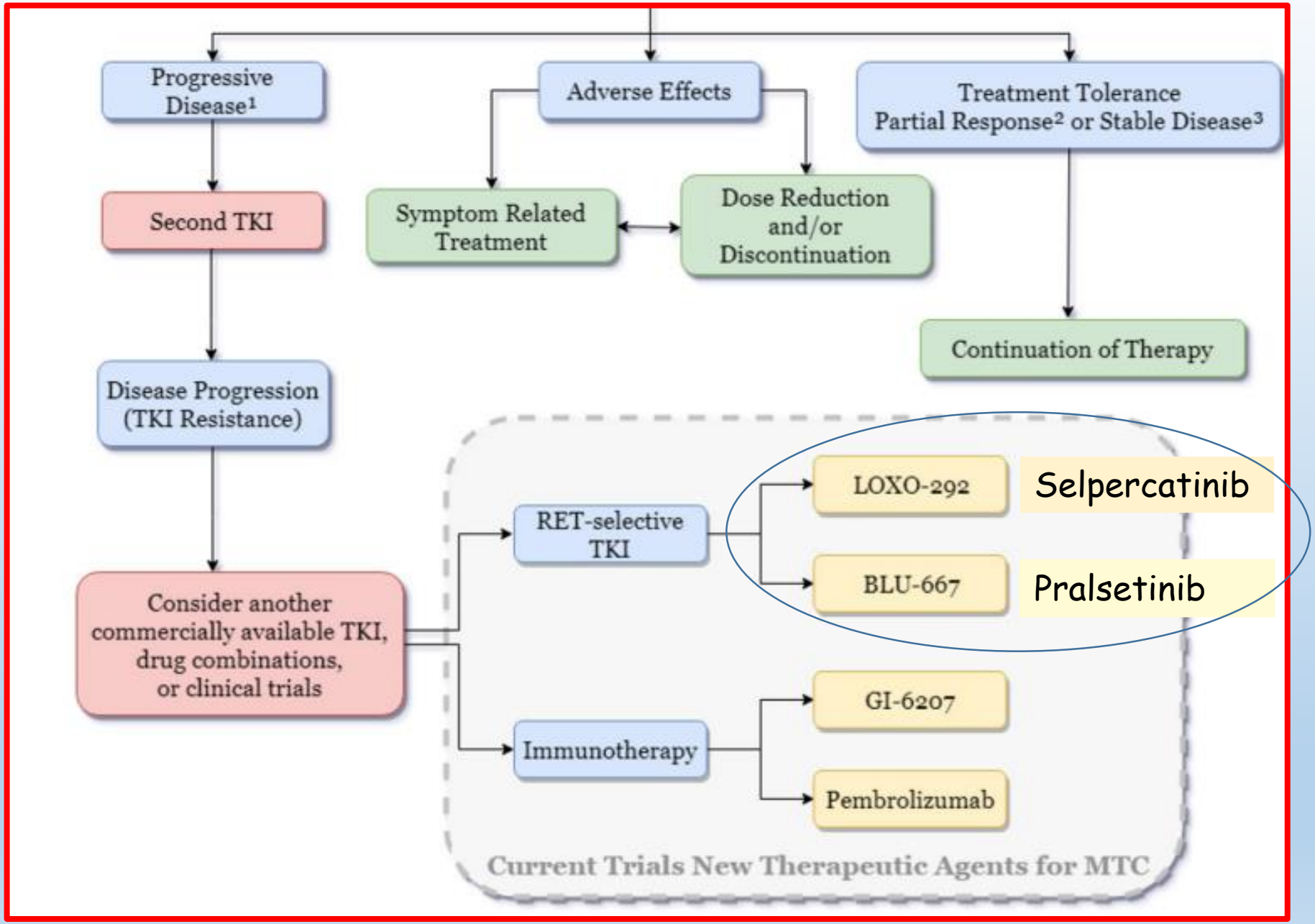
Julien Hadoux &Martin Schlumberger, Best Practice & Research Clinical Endocrinology & Metabolism, 2017



Endocrine-Related Cancer, (2019) 26



Endocrine-Related Cancer, (2019) 26

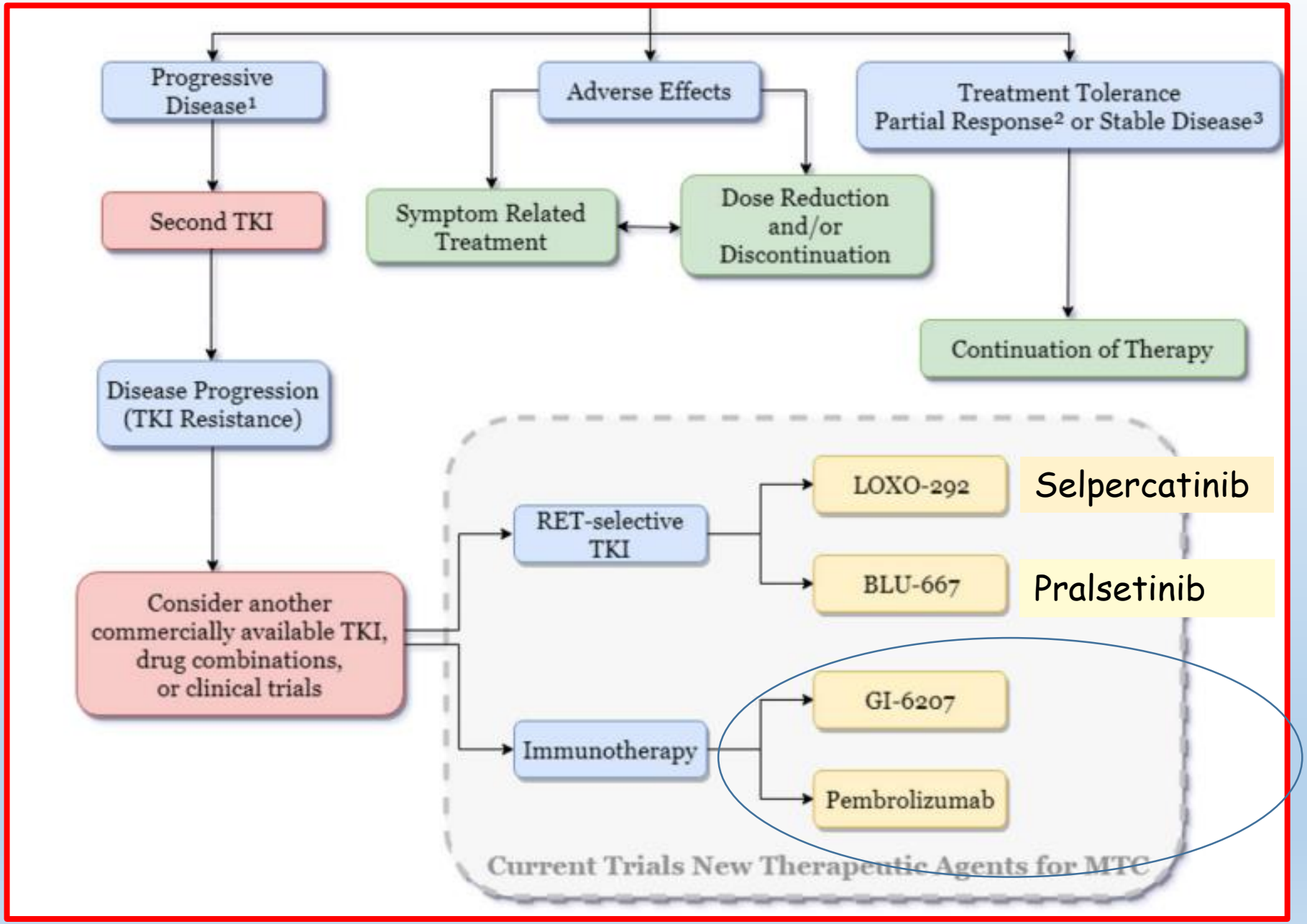


Endocrine-Related Cancer, (2019) 26

Table 3. Summary of Clinical Trials of Selpercatinib and Pralsetinib versus Placebo in Patients with Advanced MTC with *RET* Alteration

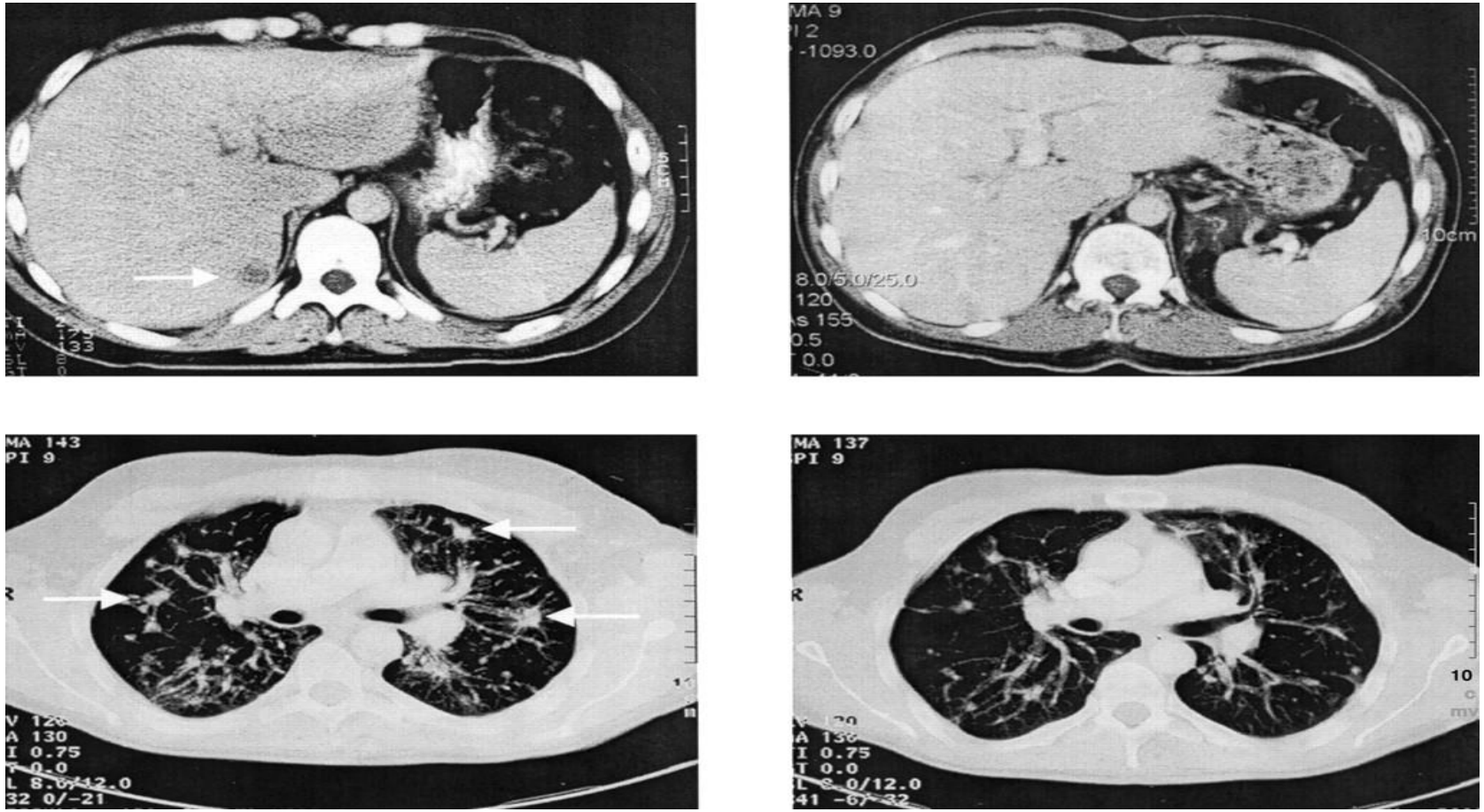
Variable	Selpercatinib		Pralsetinib[a]	
	RET-mutant MTC with prior TKI (n=55)	*RET*-mutant MTC without prior TKI (n=88)	*RET*-mutant MTC with prior TKI (n=61)	*RET*-mutant MTC without prior TKI (n=22)
Clinical trial name	LIBRETTO-001 (phase 1/2)		ARROW (phase 1/2)	
Dosage (Phase 2)	160 mg twice daily		400 mg once daily	
Median age, yr (range)	57 (17–84)	58 (15–82)	58 (25–83)	60 (19–81)
Male sex	36 (65)	58 (66)	41 (67)	16 (73)
Previous regimen				
Vandetanib	18 (33)	0		
Cabozantinib	13 (24)	0		
Vandetanib and cabozantinib	24 (44)	0		
Vandetanib and/or cabozantinib			61 (100)	0
RET alteration				
RET M918T mutation	33 (60)	49 (56)	41 (67)	8 (36)
RET V804M/L mutation	5 (9)	6 (7)	2 (3)	1 (5)
RET extracellular cysteine mutation[b]	7 (13)	20 (23)	14 (23)	11 (50)
Other mutations[c]	10 (18)	13 (15)	4 (7)	2 (9)
Objective response, % (95% CI)	69 (55–81)	73 (62–82)	60 (46–74)	74 (49–91)
Complete response	5 (9)	10 (11)	1 (2)	1 (5)
Partial response	33 (60)	54 (61)	31 (58)	13 (68)
Stable disease	14 (25)	20 (23)	19 (36)	5 (26)
Progressive disease	1 (2)	2 (2)	2 (4)	0
Duration of response				
Median, mo (95% CI)	NE (19.1–NE)	22.0 (NE–NE)[d]	NR	NR
Median follow-up, mo	14.1	7.8		
Progression-free survival				
Median, mo (95% CI)	NE (24.4–NE)	23.6 (NE–NE)[d]	NR	NR
Median follow-up, mo	16.7	11.1		
Disease control rate, % (95% CI)	94	95	96 (87–100)	100 (82–100)

Endocrinol Metab 2021;36:514-524



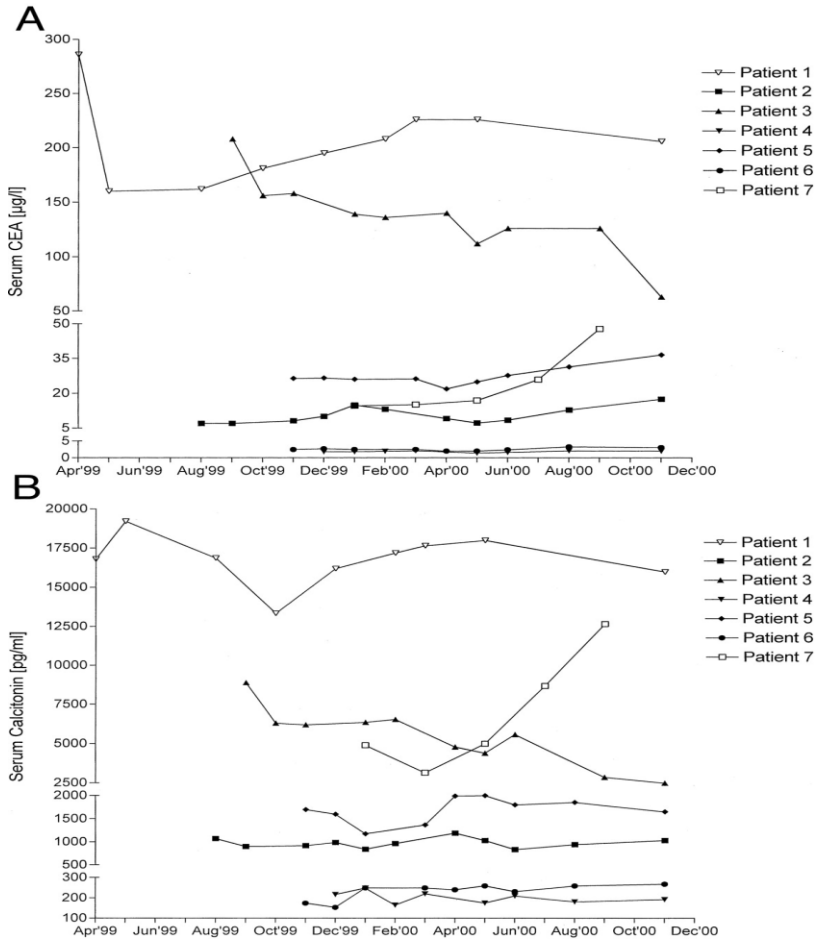
Endocrine-Related Cancer, (2019) 26

Figure 1. Clinical response to DC vaccination. CT scan of patient 3 before (September 1999, left) and 13 months after ...



J Clin Endocrinol Metab, Volume 86, Issue 10, 1 October 2001, Pages 4965–4969, https://doi.org/10.1210/jcem.86.10.7949

Figure 2. Tumor marker levels during therapy. Plasma calcitonin (lower panel) and CEA (upper panel) levels obtained at ...



J Clin Endocrinol Metab, Volume 86, Issue 10, 1 October 2001, Pages 4965–4969, https://doi.org/10.1210/jcem.86.10.7949

frontiers in Endocrinology

MINI REVIEW
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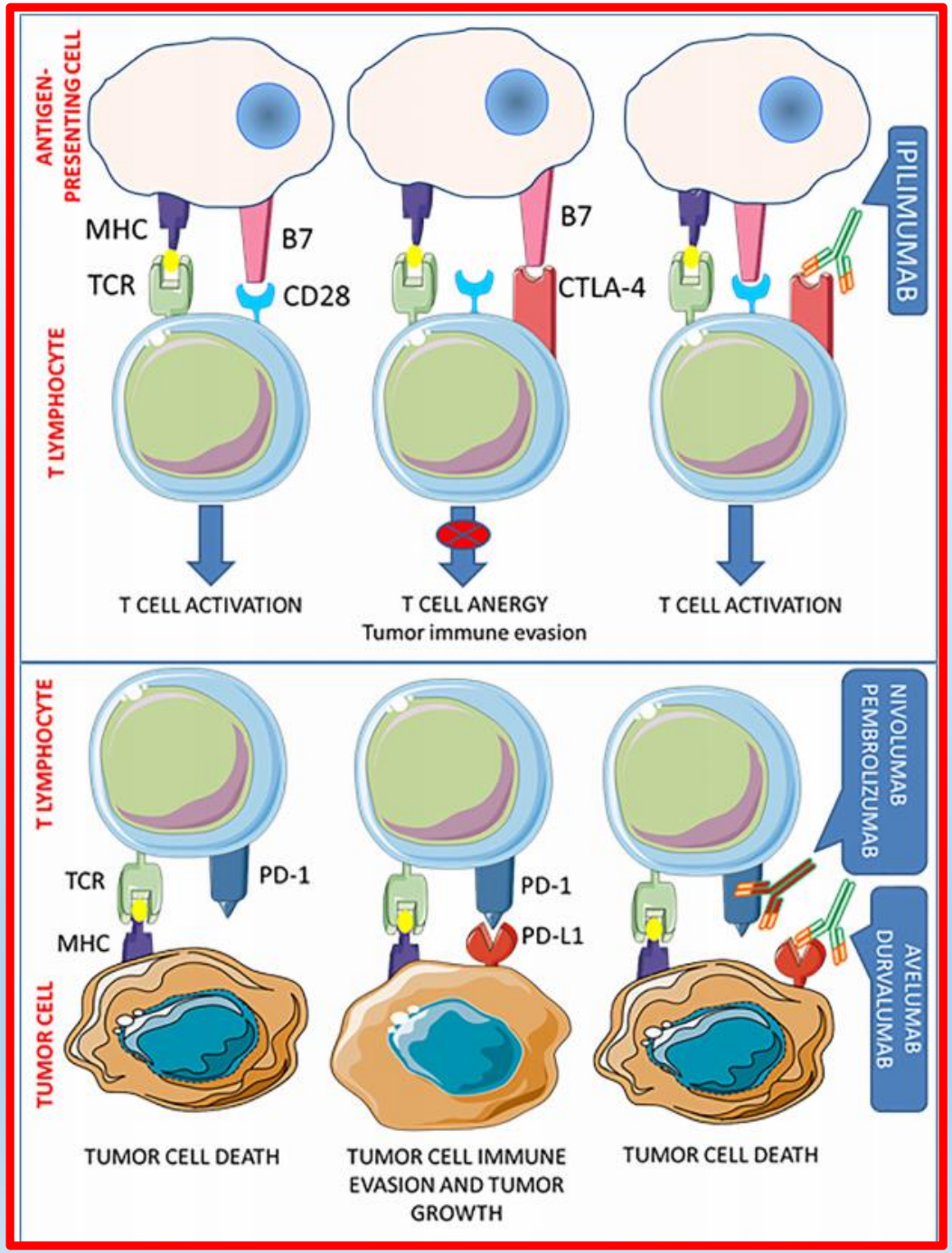
Immune Checkpoint Inhibitors: New Weapons Against Medullary Thyroid Cancer?

OPEN ACCESS

Edited by:
Michele Caraglia

Sergio Di Molfetta[1*†‡], *Andrea Dotto*[2,3†‡], *Giuseppe Fanciulli*[4†], *Tullio Florio*[3,5†], *Tiziana Feola*[6,7†], *Annamaria Colao*[8†] *and Antongiulio Faggiano*[9†] *on behalf of NIKE Group*



Research Letter
Open Access
M Bongiovanni et al. | Very low expression of PD-L1 in MTC | 24:6 | L35–L38

Very low expression of PD-L1 in medullary thyroid carcinoma

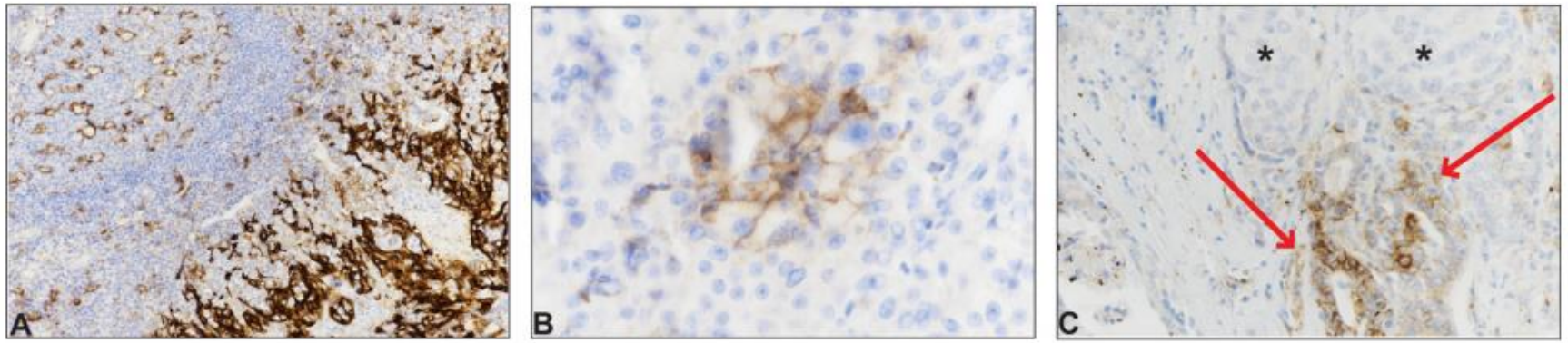


Figure 1
PD-L1 expression in medullary thyroid carcinoma. A. Benign tonsil tissue was used as positive control: on the right side of the picture, the reticulated crypt epithelial cells show strong membranous positivity for PD-L1; on the left side, some lymphocytes and macrophages in germinal centers show weak membranous positivity (PD-L1 immunostain, ×200). B. Focal and membranous expression for PD-L1 in malignant cells in case n° 10. The overall expression in malignant cells was scored at 5% (PD-L1 immunostain, ×400). C. One of the two cases showing PD-L1 positivity in the lymphocytic infiltrate (case n° 12); PD-L1 was expressed by reactive follicular cells (arrows) and was not expressed by malignant C-cells (asterisks) (PD-L1 immunostain, ×200).

http://erc.endocrinology-journals.org
DOI: 10.1530/ERC-17-0104

TABLE 2 | Registered clinical trials evaluating FDA-approved immune checkpoint inhibitors in medullary thyroid carcinoma.

ClinicalTrials.gov Identifier	Molecule	Trial name	Study phase	Medical condition under investigation	Assigned intervention	Primary outcome(s)	Estimated enrollment, n	Estimated study completion date	Trial status
NCT03753919	Durvalumab	A Phase II Study of Durvalumab (MEDI4736) Plus Tremelimumab for the Treatment of Patients With Progressive,	Phase II	Metastatic thyroid cancer, including differentiated thyroid carcinoma, medullary thyroid carcinoma, and anaplastic thyroid cancer	Durvalumab 1500 mg plus tremelimumab 75 mg every 4 weeks up to 4 cycles followed by durvalumab 1500 mg every 4 weeks until disease progression, unacceptable toxicity or patients' decision. Cohort 2 is	Progression-free survival rate at 6 months [time frame: 6 months] according to RECIST 1.1 criteria Overall survival rate at	46	July 2021	Recruiting
NCT03246958									e, not uiting
NCT04514484									uiting
NCT03072160	P								pleted sults nitted)
NCT03012620	Pembrolizumab	Secured Access to Pembrolizumab for Patients With Selected Rare Cancer Types	Phase II	Sarcoma, ovarian neoplasm, central nervous system neoplasm, thyroid neoplasm (including medullary thyroid carcinoma), neuroendocrine carcinoma, germ cell and embryonal neoplasms, NK/T-cell lymphoma	Pembrolizumab 200 mg on day 1 of every 21 day cycle	[time frame: one year] Objective response rate [time frame: measured at the first scheduled disease assessment following study treatment initiation (day 84 ± 7 days)] according to RECIST v1.1	350	December 2023	Recruiting

- 13 hasta aşı kolu→
  - 2/3 tedaviyi tamamlamış
  - 1 hastada progresyon
- 4 hasta→hiçbirisi tedaviyi tamamlayamış
  - 1 hastada progresyon

www.clinicaltrials.gov

Peptid Receptor Radionuclide Therapy (PRRT)

- Yttrium-90, Luteium-177
- Radyografik iyileşme %62.4
  - %1.3 ilaç kesilmiş
- Hastalık kontrolü %60
  - %2.79 ilaç kesilmiş

Lee et al., 2020
Rosen et al., 2018

0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(4):2029–2034

doi: 10.1210/jc.2004-1836

Prospects of Remission in Medullary Thyroid Carcinoma According to Basal Calcitonin Level

Andreas Machens, Ulrich Schneyer, Hans-Jürgen Holzhausen, and Henning Dralle

- Hem sporadik hem herediter vakalarda kalsitonin>150 pg/ml→
  - Uzak metastaz ve ekstratiroidal yayılım ile ilişkili
- Preoperatif kalsitonin >500 pg/ml
- Nodal metastaz
- Reoperatif durum

} En iyi biyokimyasal remisyon belirteçleri

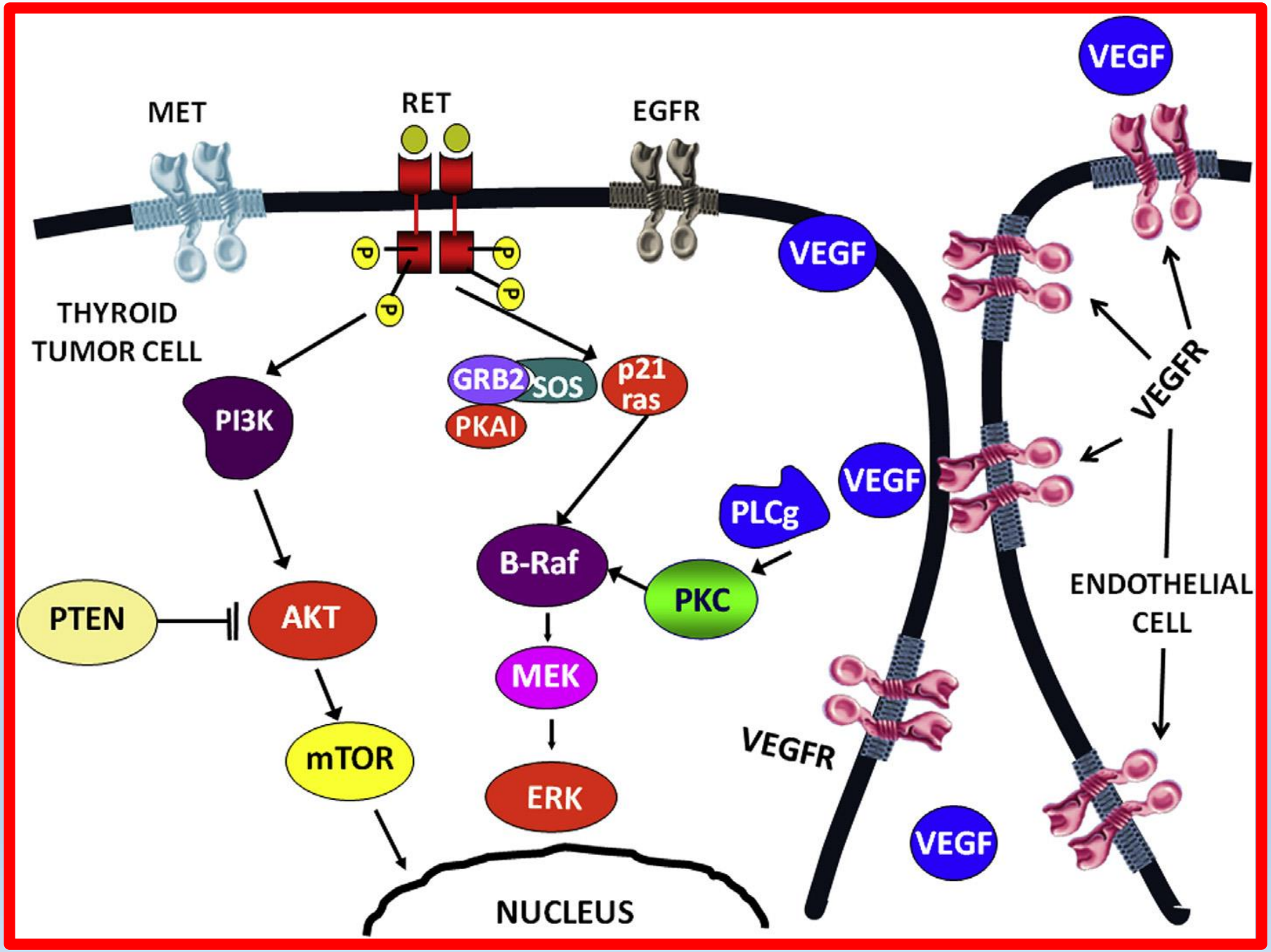
European Journal of Endocrinology (2008) 158 239–246 ISSN 0804-4643

CLINICAL STUDY

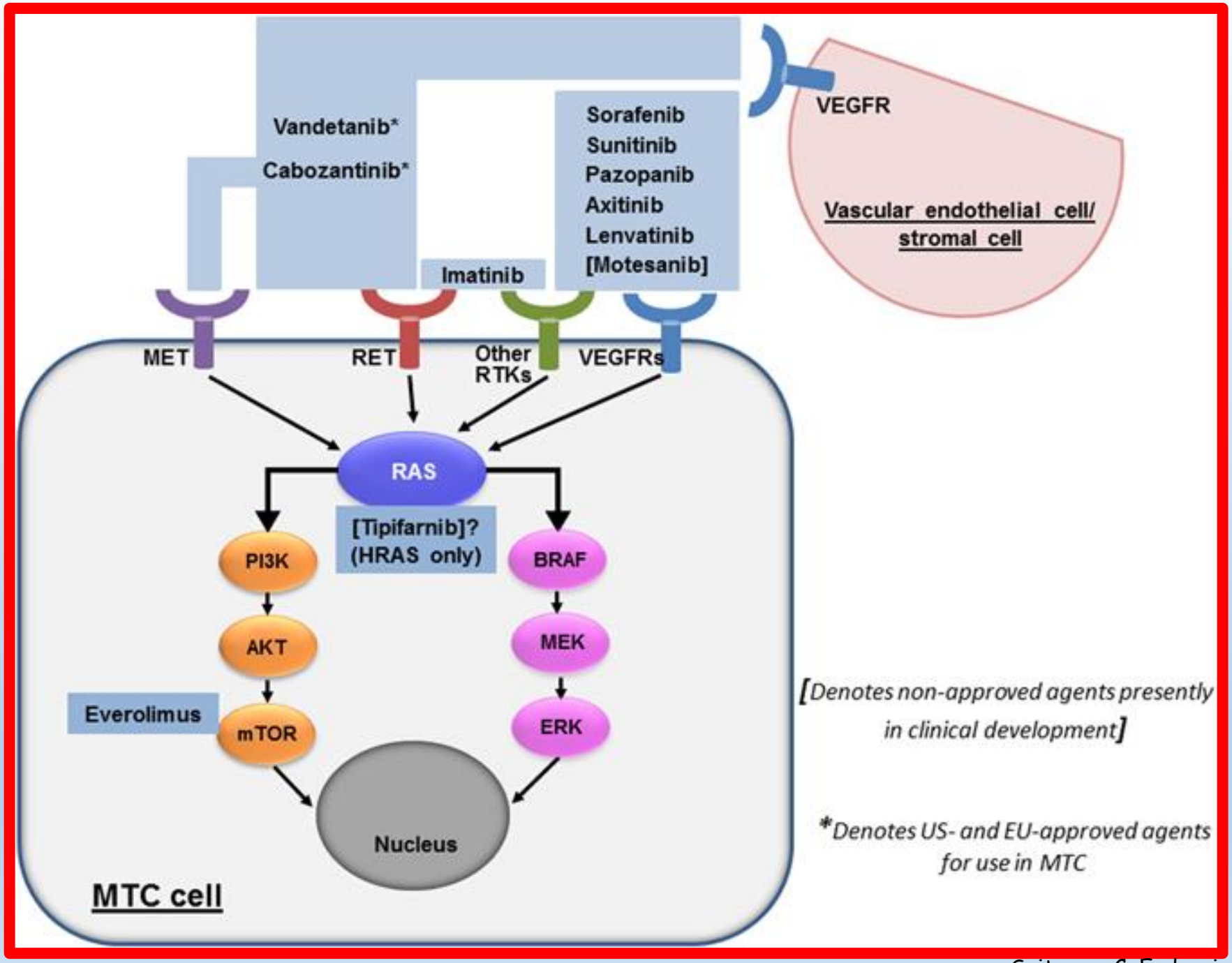
Progression of medullary thyroid carcinoma: assessment with calcitonin and carcinoembryonic antigen doubling times

Anne Laure Giraudet[1], Abir Al Ghulzan[2], Anne Aupérin[4], Sophie Leboulleux[1], Ahmed Chehboun[1], Frédéric Troalen[2], Clarisse Dromain[3], Jean Lumbroso[1], Eric Baudin[1] and Martin Schlumberger[1]

- Nodal metastaz
  - Kalsitonin 40 pg/mL seviyesinde belirmeye başlıyor
  - Opere olanlarda 10 pg/mL seviyesinde
- Uzak metastazlar 150 pg/mL seviyesinden itibaren
- Kalsitonin>500 pg/mL olanların yarısında uzak metastaz



A. Matrone et al., Best Practice & Research Clinical Endocrinology & Metabolism, 2017



Spitzweg C, Endocrine-Related Cancer, 2016

Table 2. Multikinase inhibitors targeting signaling pathways in medullary thyroid cancer.

Agent	Targeted pathway	Stage of study	Main adverse events	Ref.
Vandetanib	RET, VEGFR-2 and -3 and EGFR	Approved in 2011	Skin toxicity, diarrhea and asthenia	[91]
Cabozantinib	VEGFR2, c-MET and RET	Approved in 2012	Diarrhea, fatigue, decreased appetite, nausea, palmar-plantar erythrodysesthesia, rash, increased aspartate transaminase, vomiting and mucositis	[92]
Sorafenib	VEGFR, PDGFR, FGFR, c-KIT, BRAF and RET,	Phase II	Skin toxicity, weight loss and fatigue	[93]
Sunitinib	VEGFR, c-KIT, PDGFR and RET	Phase II	Fatigue, neutropenia, hand–foot syndrome, diarrhea and leukopenia	[94]
Pazopanib	VEGFR1–3, PDGFR, c-KIT, FGFR1/3/4 and RET	Phase II	Fatigue and diarrhea	[95,96]
Axitinib	VEGFR1–3	Phase II	Fatigue, dyspnea, diarrhea, decreased weight, pain in extremity, hypertension, decreased appetite, palmar-plantar erythrodysesthesia, hypocalcemia and myalgia	[97]
Lenvatinib	VEGFR1–3, FGFR1–4, RET, KIT and PDGFR	Phase II	Diarrhea, hypertension, decreased appetite, fatigue, dysphagia and increased alanine aminotransferase levels	[98]
Motesanib	VEGFR1–3, PDGFR and c-KIT	Phase II	Diarrhea, fatigue, hypothyroidism, hypertension and anorexia	[99,100]
Imatinib	Bcr-Abl, PDGFR, c-KIT and RET	Phase II	Gastrointestinal problems such as diarrhea, vomiting and abdominal pain, and facial edema, especially periorbital edema	[101,102]
Everolimus	mTOR	Phase II	Mucositis, fatigue, hypertriglyceridemia	[103]

Bcr-Abl: Breakpoint cluster region-abelson; RET: Rearranged during transfection.

Nozhat Z, et al., Int J Endocrinol, 2017

	Vandetanib (ZETA study)[60]	Cabozantinib (EXAM study)[61,62]
Number of patients	331	330
Randomisation ratio (active treatment: placebo)	2:1	2:1
Hereditary disease	10%	6%
RET		
Positive	38%	45%
Unknown	41%	39%
RET 918	Not available	35%
Distant metastasis	94%	95%
Previous treatment	40%	38%
Previous tyrosine kinase inhibitors	Unknown	20%
Progressive disease before enrolment	Not requested	Yes (within 14 months)
Safety		
Toxic effects (≥grade 3)	55% (24%)	69% (33%)
Deaths	2% vs 2% (placebo)	5·6 vs 2·8% (placebo)
Results		
Follow-up	24 months	14 months
Median PFS	30·5 (estimated) vs 19·3 months (reported)	11·2 vs 4·0 months
PFS at 6 months	83% vs 63%	Not available
PFS at 12 months	Not available	47% vs 7%
Objective response rate	45% vs 13%	28% vs 0%
Complete response	0%	0%
Survival	Not available	27 vs 21 months

RET=rearranged during transfection. PFS=progression-free survival.

Table 2: **Summary of phase 3 clinical trials of vandetanib and cabozantinib versus placebo in patients with medullary thyroid cancer**

VANDETANIB: RET, VEGRF, EPGF inhibitörü

CABOZANTINIB: RET, VEGFR2, HGF, c-met inhibibtörü

FAZ III ÇALIŞMALAR

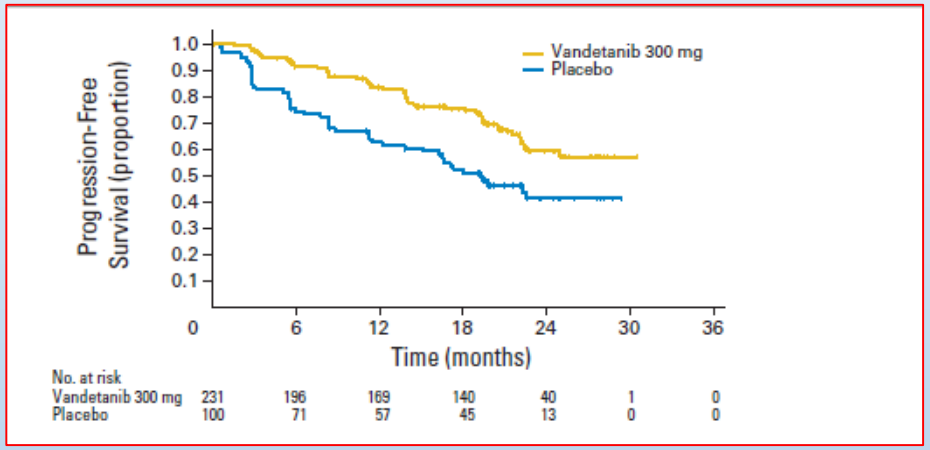
Hadoux et al., Lancet Diabetes Endocrinol, 2015

VOLUME 30 · NUMBER 2 · JANUARY 10 2012

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Vandetanib in Patients With Locally Advanced or Metastatic Medullary Thyroid Cancer: A Randomized, Double-Blind Phase III Trial

Samuel A. Wells Jr, Bruce G. Robinson, Robert F. Gagel, Henning Dralle, James A. Fagin, Massimo Santoro, Eric Baudin, Rossella Elisei, Barbara Jarzab, James R. Vasselli, Jessica Read, Peter Langmuir, Anderson J. Ryan, and Martin J. Schlumberger



%45 hastada parsiyel cevap

	Vandetanib (ZETA study)[50]
Number of patients	331
Randomisation ratio (active treatment: placebo)	2:1
Hereditary disease	10%
RET	
Positive	38%
Unknown	41%
RET 918	Not available
Distant metastasis	94%
Previous treatment	40%
Previous tyrosine kinase inhibitors	Unknown
Progressive disease before enrolment	Not requested
Safety	
Toxic effects (≥grade 3)	55% (24%)
Deaths	2% vs 2% (placebo)
Results	
Follow-up	24 months
Median PFS	30·5 (estimated) vs 19·3 months (reported)
PFS at 6 months	83% vs 63%
PFS at 12 months	Not available
Objective response rate	45% vs 13%
	0%
	Not available

ransfection. PFS=progression-free survival.

hase 3 clinical trials of vandetanib and cabozantinib versus placebo in patients with cer

- Hastaların %12'si yan etki nedeniyle ilacı bırakmış
- %35'inde yan etkiler nedeniyle doz azaltılması gerekmiş

Hadoux et al., Lancet Diabetes Endocrinol, 2015

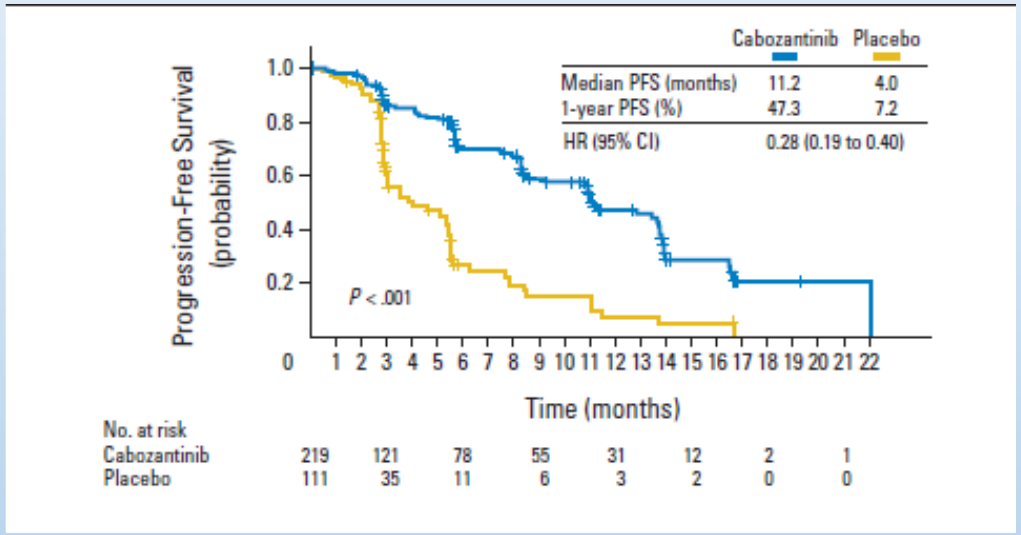
VOLUME 31 · NUMBER 29 · OCTOBER 10 2013

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



	Cabozantinib (EXAM study)[61,62]
Number of patients	330
Randomisation ratio (active treatment: placeb	2:1
Hereditary disease	6%
RET	
Positive	45%
Unknown	39%
RET 918	35%
Distant metastasis	95%
Previous treatment	38%
Previous tyrosine kinase inhibitors	20%
Progressive disease before enrolment	Yes (within 14 months)
Safety	
Toxic effects (≥grade 3)	69% (33%)
Deaths	5·6 *vs* 2·8% (placebo)
Results	
Follow-up	14 months
Median PFS	11·2 *vs* 4·0 months
PFS at 6 months	Not available
PFS at 12 months	47% *vs* 7%
Objective response rate	28% *vs* 0%
Complete response	0%
Survival	27 *vs* 21 months

RET=rearranged during transfection. PFS=progression-free survival.

Table 2: **Summary of phase 3 clinical trials of vandetanib and cabozantinib versus placebo in patients with medullary thyroid cancer**

Hastaların %16'sı yan etki nedeniyle ilacı bırakmış

%79'unda yan etkiler nedeniyle doz azaltılması gerekmiş

Hadoux et al., Lancet Diabetes Endocrinol, 2015

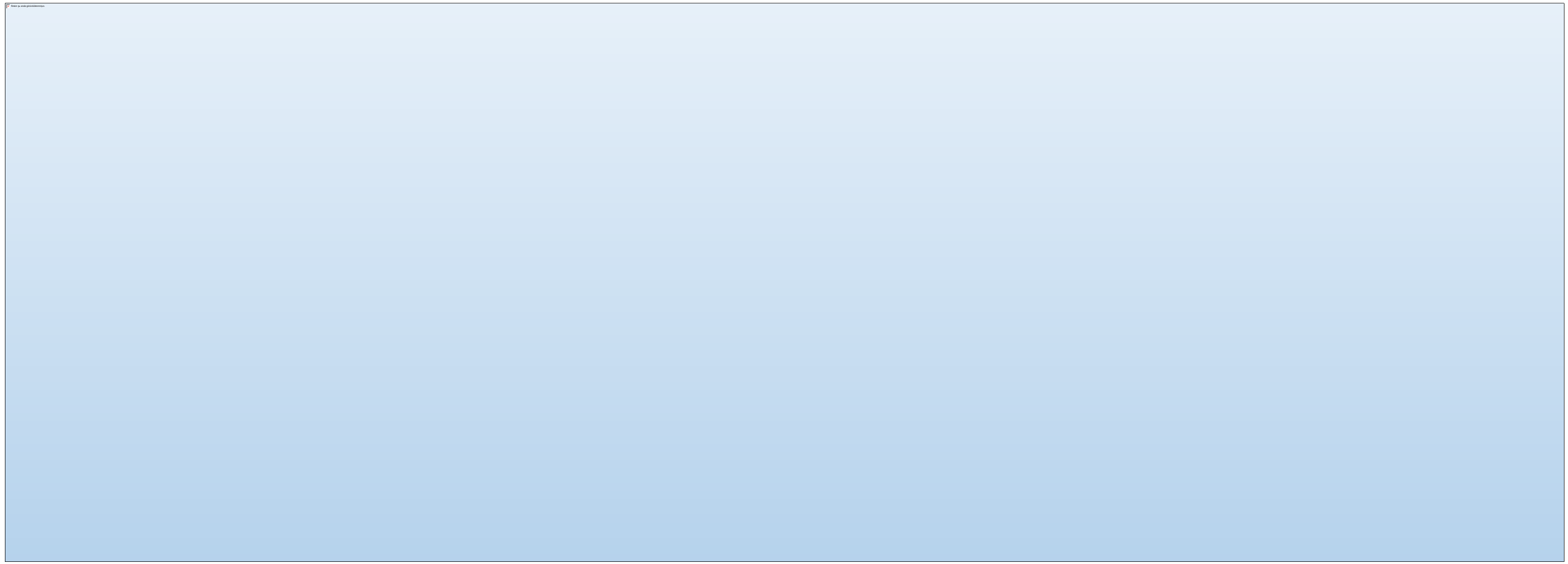
Vandetanib (Caprelsa®)

- 100 mg (30): $ 7722.72
- 300 mg (30): $ 15445.43
- 100 mg (30): € 1400
- 300 mg (30): € 4070

Cabozantinib (Cabometyx®/Cometriq®)

- 20 mg (30): $19100.82
- 40 mg (30): $19100.82
- 60 mg (30): $19100.82

- COMETRIQ→4 ADET 140 MG (7X80 MG, 21X20 MG KAPSÜL) € 6000



- **Sorular**
- FDA'in önerdiği dozlar toksik mi?
- İlaç seçimi?
- Yan etkiler?
- Direnç mekanizmaları neler?
- Stabil hastalığı olanlarda ilaca ne kadar devam edelim?
- TKI ile tedavi sağ kalımı etkiliyor mu?
- Maliyet?/Yaşam kalitesi?

Ethical Perspective

Protein kinase inhibitor therapy in advanced thyroid cancer: ethical challenges and potential solutions

International Journal of Endocrine Oncology

Protein kinase inhibitors (PKIs) have emerged as highly promising therapies in progressive metastatic radioiodine-refractory differentiated thyroid cancer and in medullary thyroid cancer; two were recently approved in the USA for use in medullary thyroid cancer (vandetanib, cabozantinib), and another for use in progressive metastatic radioiodine-refractory differentiated thyroid cancer (sorafenib). Although more than 90% of thyroid cancer patients fare well in response to conventional treatment, PKI therapy has the potential to provide benefit. Nonetheless, PKIs produce numerous side effects, may worsen quality of life, may hasten mortality (by 1–2%), require discerning clinical acumen, are not yet proven to improve thyroid cancer survival and are very costly. This raises questions about who should prescribe PKIs, and about whether their use in thyroid cancer is truly beneficent and ethically justified. Restraint should be exercised in their use in thyroid cancer, with potential risks and benefits carefully weighed and solutions devised to help ameliorate many of the problems associated with their use.

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CASE STUDY and PATIENTS WITH REMARKABLE FEATURES OR RARE DISORDERS

Recurrent Metastatic Medullary Thyroid Carcinoma: A Case of Sustained Response to Prolonged Treatment with Somatostatin Analogues

Juana Maria Cano, Rocío Galán, and Rafael López

period. The findings in the present case raise the possibility that in asymptomatic cases with a low tumor burden and a positive Octreoscan following recurrence, prolonged treatment with somatostatin analogues may be beneficial.

Deneysel tedaviler

- Immunoterapi
- Aşı tedavisi

Kumarasamy *et al. BMC Cancer* (2015) 15:599
DOI 10.1186/s12885-015-1610-5

BMC Cancer

RESEARCH ARTICLE Open Access

Selective repression of *RET* proto-oncogene in medullary thyroid carcinoma by a natural alkaloid berberine

Vishnu Muthuraj Kumarasamy[1], Yoon-Joo Shin[1], John White[1] and Daek

Endocrine-Related Cancer (2012) **19** 447–456

Metformin inhibits growth and decreases resistance to anoikis in medullary thyroid cancer cells

Joanna Klubo-Gwiezdzinska[1], Kirk Jensen, John Costello, Aneeta Patel, Victoria Hoperia[2], Andrew Bauer, Kenneth D Burman[1], Leonard Wartofsky[1] and Vasyl Vasko

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