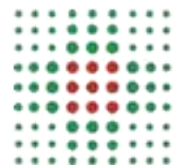


# Medullary Thyroid Cancer (MTC): How I treat the advanced disease?

**Toni Ibrahim, BSc, MSc, MD, PhD**  
Osteoncology and Rare Tumors Center  
National Cancer Institute of Romagna  
Meldola (FC)- Italy

ISTITUT  
SCIENTIFIC  
ROMAGNOL  
PER LO STUDI  
DEI TUMORI



SERVIZIO SANITARIO REGIONALE  
EMILIA-ROMAGNA



# Outline

**1- Natural history of MTC**

2- Local treatments of advanced MTC

3- Systemic treatments of advanced MTC

4- How i treat patients with advanced MTC ?

## Medullary Thyroid Carcinoma (MTC)

MTC is a rare tumor (3-5 % of all thyroid cancers) arising the calcitonine-producing parafollicular C cells of the thyroid gland. These tumors secrete calcitonin and carcinoembryonic antigen (CEA), which are sensitive biomarkers for the disease.

MTC occurs in

- 75% of pts sporadically;
- 25% in a hereditary form as a component of the type 2 Multiple Endocrine Neoplasia syndromes MEN2A and 2B and the related syndrome familial MTC (FMTC) associated with germline RET (rearranged during transfection) mutations.

Wells SA, Thyroid 2015

Hadoux J, Lancet Diab and Endo 2016

### **Sporadic:**

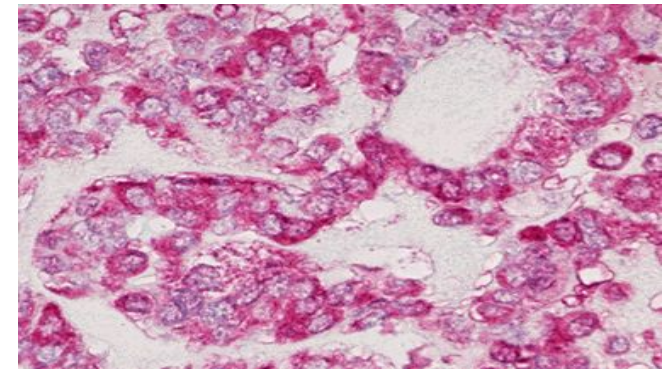
- Patients present between the 4<sup>th</sup> and the 6th decade of life with disease
- Unifocal disease usually
- Usually without parafollicular cell hyperplasia
- No associated endocrinopathy
- 50-60 % somatic RET mutations

### **Inherited:**

- FMTC present in 4th decade,
- MEN 2a in 3rd decade
- MEN 2b during childhood
  
- Autosomal dominant inheritance
- Multifocal disease
- Parafollicular cell hyperplasia present
- 100 % germline RET mutations

## Clinical presentation

- Present with a mass, and/or symptoms of local invasion and/or of hormone secretion  
70% of patient with MTC with present a palpable thyroid nodule have cervical metastasis and 10% have distant metastasis
- Symptoms associated with local/systemic invasion:
  - dysphagia, stridor, or hoarseness
  - lung, liver, bone, CNS
- Symptoms associated with hormone secretion:
  - flushing, diarrhea, and Cushing's disease



Immunohistochemical anti-calcitonin antibody stain of a medullary carcinoma showing strong red positivity

## Diagnosis/Staging

- FNA with calcitonin immunohistochemical screening
- Calcitonin testing: baseline level, as well as Pentagastrin stimulation test
- CEA level
- Calcium, PTH, urinary catecholamines, vanilylmandelic acid, and metanephrines
- Genetic testing for RET mutations
- Radiographic testing including US, CT scan, MRI, bone scintigraphy, 18F-FDG/DOPA-PET

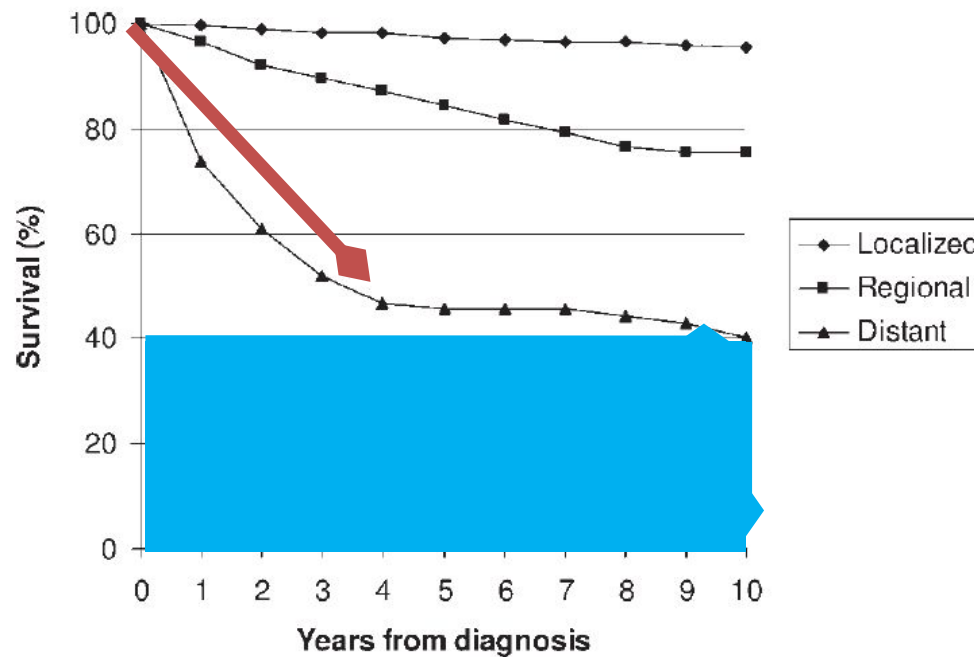
Most patients with MTC have a relatively good prognosis. Stage at diagnosis is highly predictive of overall survival.

## The 10-year survival rate

96% among patients with localized disease (tumor confined to the thyroid gland)  
Stage I-II

20-40 % with distant metastasis (liver, lung, bone, brain)  
Stage IV

76% in patients with regional disease (extension beyond the thyroid directly into surrounding tissues or regional lymph nodes)  
Stage III



**FIGURE 2.** Ten-year, disease-specific survival by Surveillance, Epidemiology, and End Results (SEER) stage for patients with histologically confirmed medullary thyroid cancer. SEER, 1973–2002.

Roman S, Cancer 2006;  
Bostrom SY, Arch Surg 2009

Distant metastases are the main cause of MTC-related death, often affect multiple organs including the lungs, bones and liver, and more rarely the brain, skin and breast.

Distant metastases are observed at presentation in 7–23% of unselected patients with MTC, and in patients with persistently elevated calcitonin levels clinical recurrence will occur at different time intervals after surgery, depending on the amount of persistent disease and the progression rate.

With comprehensive follow-up, clinical recurrence can be detected by imaging techniques within 10 years in 35–65% of patients with detectable calcitonin levels.

**Some patients with advanced MTC still have an indolent course with stable disease or slow progression over years associated with good quality of life...**

## In the management of advanced MTC, with heterogenous clinical course, from indolent to aggressive forms

### Prognostic assessment of patient:

- TNM (extension of disease), progressive vs stable
- Symptomatic or asymptomatic life threatening or become LT
- Age ( > 40 yrs)
- Gender (Male vs female)
- Calcitonin and CEA doubling times (1 year)
- MTC subtype: MEN 2b > MEN 2a = Sporadic > FMTC
- RET mutations: 3 ATA categories of risk:
  - > Highest risk: MEN2b and RET codon M918T mutation
  - > High risk: RET codons C634 and A883F mutations
  - > Moderate risk: other mutations

**RET protooncogene** is located in chromosome band 10q11.2, encodes a single-pass transmembrane tyrosine kinase receptor, and its known to play a central role in the tumorigenesis of sporadic and hereditary MTC. The TK activation triggering parallel downstream signaling pathway activation including RAS/RAF/MAPK, PI3K/AKT and JAK-STAT pathways .

**Hereditary MTC:**

**More than 80 germline mutation**

**Sporadic MTC:**

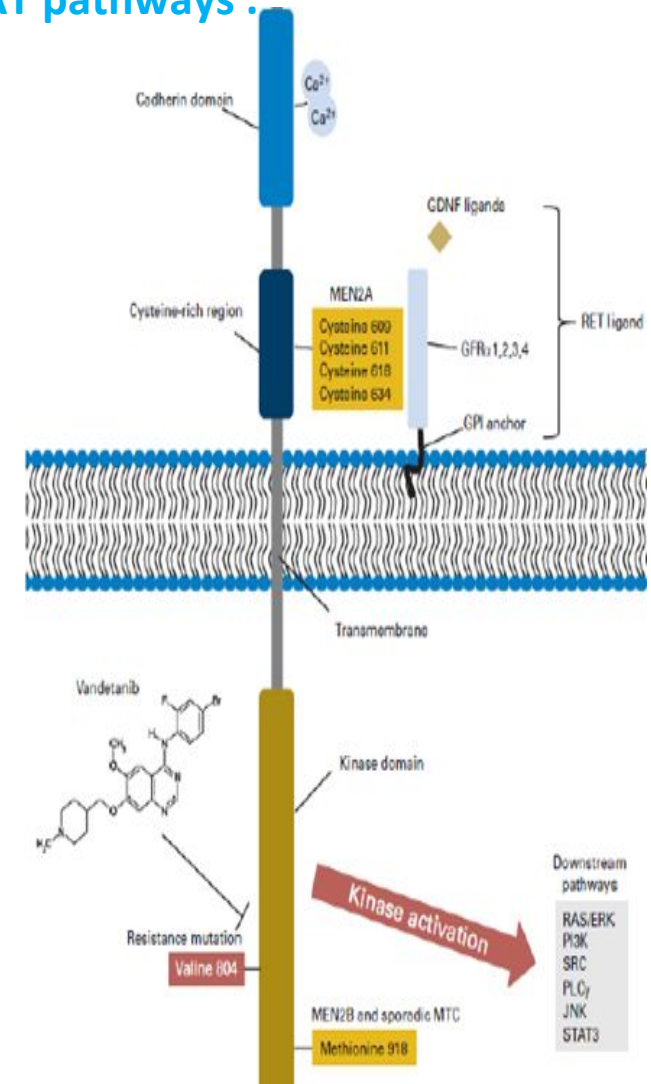
**somatic RET mutation are identified in 50%-60% of cases**

**The most common somatic mutation is RET (M918T)**

RET mutation status can differ between primary tumor and metastases.

**ATA guidelines identify different risk of aggressiveness associated with specific RET mutations:**

- > Highest risk: MEN2b and RET codon M918T mutation
- > High risk: RET codons C634 and A883F mutations
- > Moderate risk: other mutations



## Non-RET molecular alteration

NO-RET MOLECULAR ALTERATION DETECTED IN MTC	Prevalence %
NRAS	0 – 1.8
HRAS	0 – 41.2
KRAS	0 - 40.9
BRAF	0-7
KIT, MLH1, STK11, MET	1
ALK	2

- Activation of the proto-oncogenes *RAS* and *MET* represents alternative genetic events in sporadic MTC tumorigenesis
- Several studies suggest that MTCs harboring a *RAS* mutation show less aggressive behaviour

## Management of advanced Medullary Thyroid Cancer



**Prognostic assessment of patient**



**Watchful Waiting**

**Local treatments**

**Surgery  
EBRT**

**Thermo/Cryoablation  
Chemo or radioembolization**

**Systemic treatments**

**Chemotherapy  
Targeted Therapy  
Clinical trials**

# Outline

1- Natural history of MTC

**2- Local treatments of advanced MTC**

3- Systemic treatments of advanced MTC

4- How i treat patients with advanced MTC ?

## Local treatment of advanced MTC

**Surgery:** remain the only curative treatment for localized MTC.

The use of surgery is more limited and controversial in advanced disease.

In some data patients with distant disease, surgery of the primitive tumor was associated with improved survival. However, surgery is indicated to debulk the tumor burden, relieve symptoms and prevent complications.

Usually, surgery is not recommended for systemic visceral metastases, given that military hepatic or disseminated lung disease is common.

Surgery may be indicated in selected patients of bone metastases.

**EBRT:** localized bulky disease (neck, mediastinum), bone metastases, CNS

**Thermo/Cryoablation:** liver, lung (may be indicated in patients with few lesions: <5, ideally <3 of < 30-40 mm in size) and bone metastases

**Chemo/radio/embolization:** liver (disseminated lesions) and bone metastases.

# Outline

1- Natural history of MTC

2- Local treatments of advanced MTC

**3- Systemic treatments of advanced MTC**

4- How i treat patients with advanced MTC ?

## Systemic treatment of advanced MTC: Chemotherapy

Among cytotoxic drugs, the most frequently agent tested in MTC patients is **Doxorubicin**, used either alone or in combination with **Cisplatinum**

Response rates ranged from 0 to 22%, with all responses being partial and only lasting a few months.

As MTC is a well-differentiated endocrine tumor, various combinations of **5'-Fluorouracil**, **Dacarbazine**, **Streptozocin**, **Cyclophosphamide** and **Vincristine** have been used, leading to response rates of approximately 20%, with symptomatic improvement in a limited number of patients.

Given the limited effectiveness, with the arrival of target drugs, today the use of chemotherapy is very limited in MTC

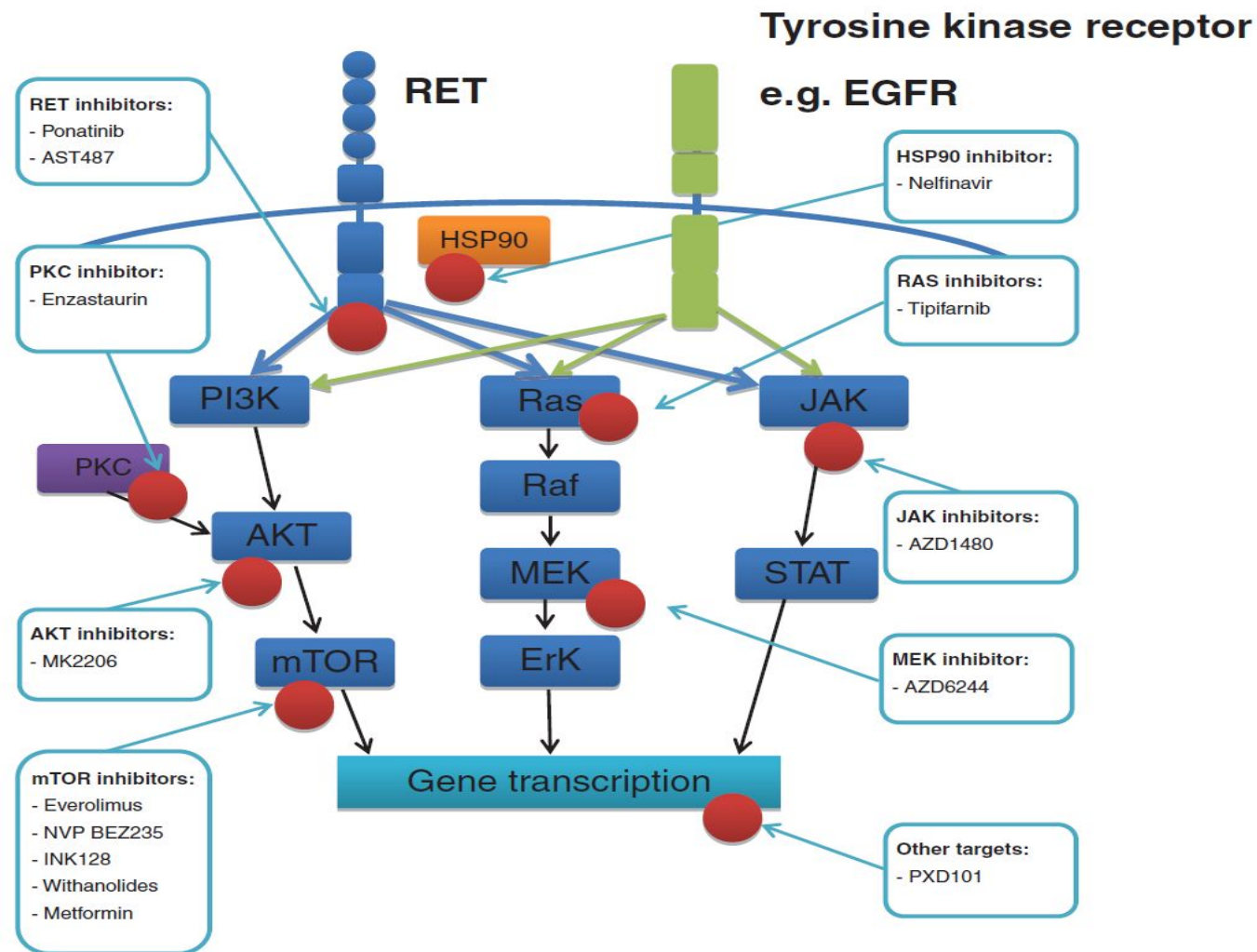
## Systemic treatment of advanced MTC: Bone targeted therapy

Bisphosphonate or Denosumab are indicated in the treatment of bone metastases from MTC

## Systemic treatment of advanced MTC: Targeted therapy

### 2011 A NEW ERA IN MTC

thanks to the new knowledge in the molecular pathogenesis of MTC through identification of genetic alterations and dysregulated signaling pathways, therapeutic molecular targets as multitargeted kinase inhibitors have been investigated in MTC.

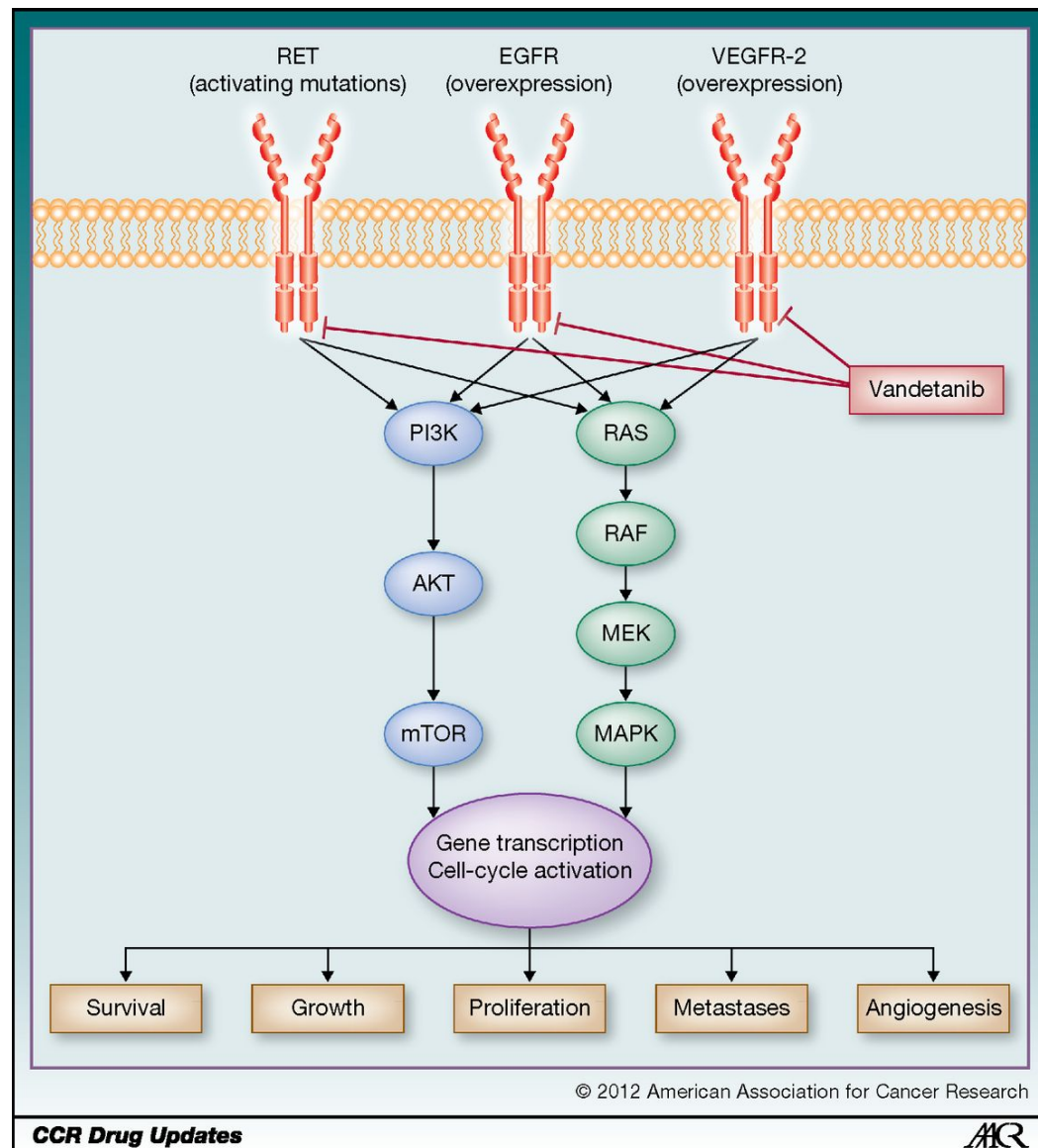


Agent	Targets	Study	No.	ORR (%)	Median PFS	Adverse events
<b>Phase II</b>						
Vandetanib	VEGFR2, VEGFR3, RET, EGFR	[91]	30	20	27.9 months	Diarrhea, rash, fatigue, nausea
		[92]	19	16		Diarrhea, fatigue, rash, QT prolongation
Cabozantinib	VEGFR1, VEGFR2, VEGFR3, KIT, FLT3, RET, c-MET	[93]	35	29		Diarrhea, fatigue, PPE, mucositis
Sorafenib	VEGFR1, VEGFR2, VEGFR3, RET, PDGFR, BRAF, KIT	[94]	16	6	17.9 months	Diarrhea, PPE, rash, hypertension
		[75]	15	25		PPE, diarrhea alopecia
Sorafenib + tipifarnib	Tipifarnib: farnesyl transferase	[74]	13	38	15 months	Diarrhea, fatigue, PPE, neuropathy
Axitinib	VEGFR1, VEGFR2, VEGFR3, PDGFR, KIT	[95]	11	18		Diarrhea, anorexia, fatigue, nausea
		[96]	6	0		Diarrhea, anorexia, fatigue, hypertension
Motesanib	VEGFR1, VEGFR2, VEGFR3, RET, PDGFR, KIT	[96]	91	2	48 weeks	Diarrhea, fatigue, hypothyroidism, hypertension
Sunitinib	VEGFR1, VEGFR2, VEGFR3, RET, PDGFR, KIT, FLT3, CSF1R	[97]	6	0		Fatigue, diarrhea, PPE, neutropenia
		[98]	24	35		Fatigue, lymphopenia, neutropenia, nausea
		[99]	6	50		Fatigue, neutropenia, PPE, diarrhea
Everolimus	mTOR complex 1 via binding to FKBP12	[100]	7	0	33 weeks	Mucositis, fatigue, hypertriglyceridemia
Lenvatinib	VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR2, FGFR3, FGFR4, PDGFR, KIT, RET	[101]	59	36	9 months	Diarrhea, anorexia, fatigue, hypertension
Pazopanib	KIT, FGFR1, FGFR3, PDGFR, VEGFR1, VEGFR2, VEGFR3,	[102]	35	14	9.4 months	Diarrhea, fatigue, hypertension, abnormal liver tests
Imatinib	BCR-ABL tyrosine kinase, PDGFR, KIT	[103]	15	0		Hypothyroidism, laryngeal mucosal swelling, fatigue
<b>Phase III</b>						
Vandetanib		[104]	231	45	Not reached <sup>a</sup>	Diarrhea, rash, hypertension, nausea
Placebo			100	13	19.3 months	
Cabozantinib		[105]	219	28	11.2 months	Diarrhea, PEE, anorexia, weight loss
Placebo			111	0	4 months	

## VANDETANIB

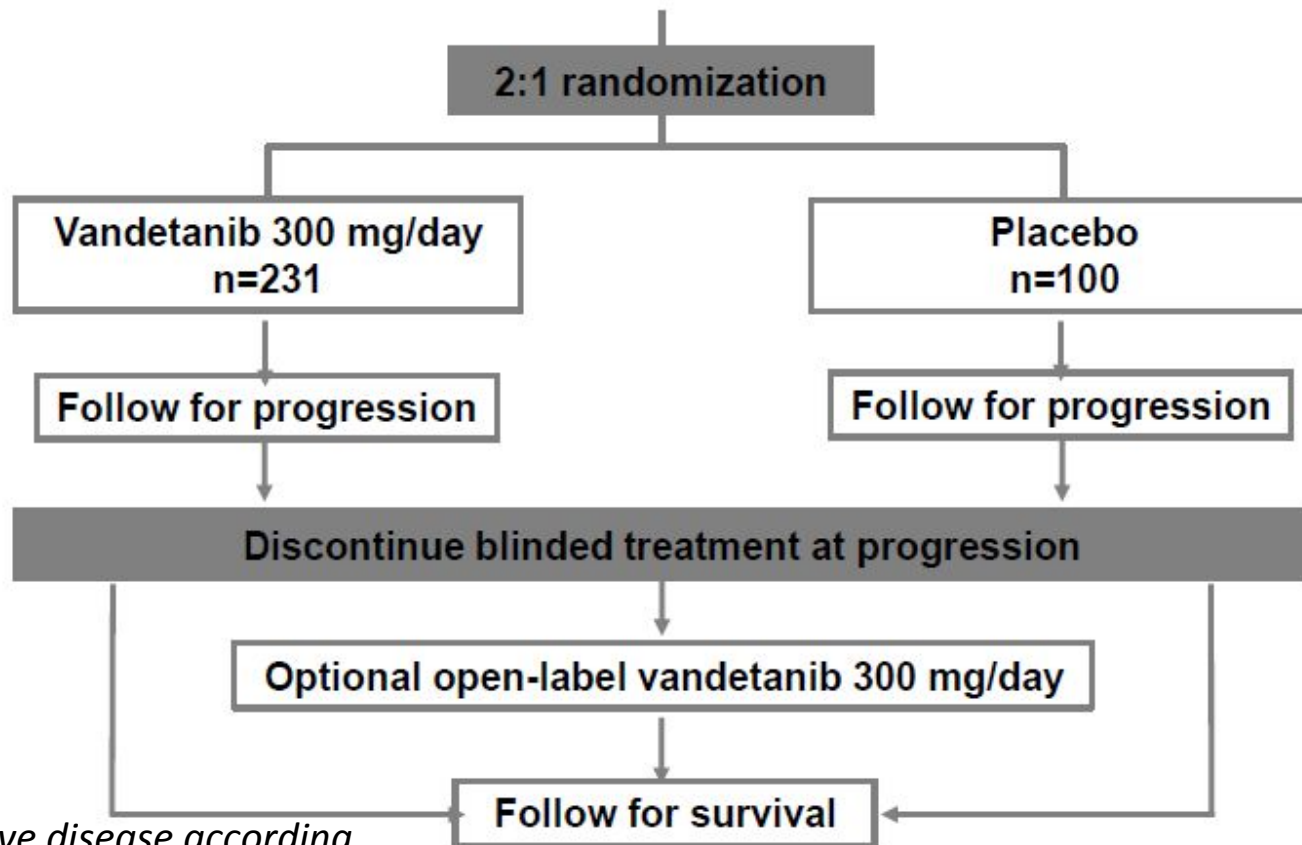
Vadetanib is the first oral multikinase inhibitors investigated in advanced MTC patients

Phase 3 ZETA drug registration trial: efficacy and safety of Vandetanib were compared with placebo in patients with locally advanced/metastatic hereditary/sporadic MTC

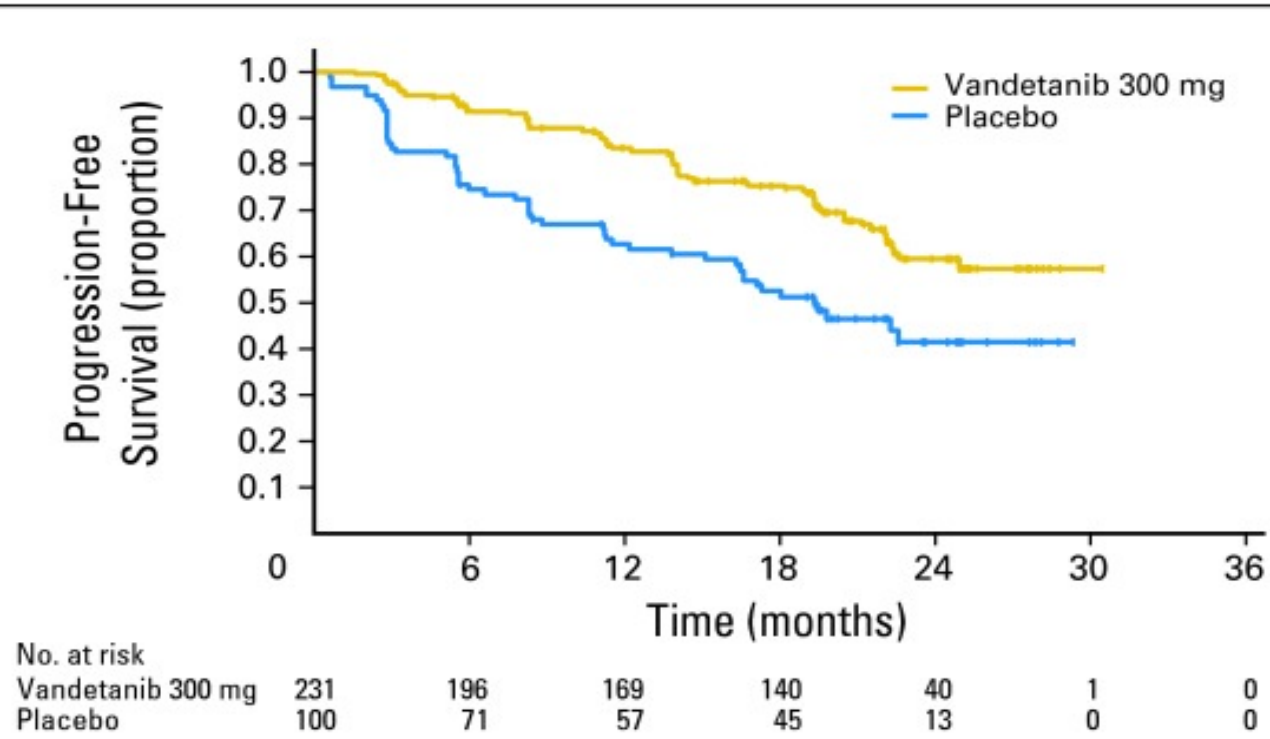


# ZETA Phase III Study design

Patients with unresectable locally advanced or metastatic MTC (N=331)

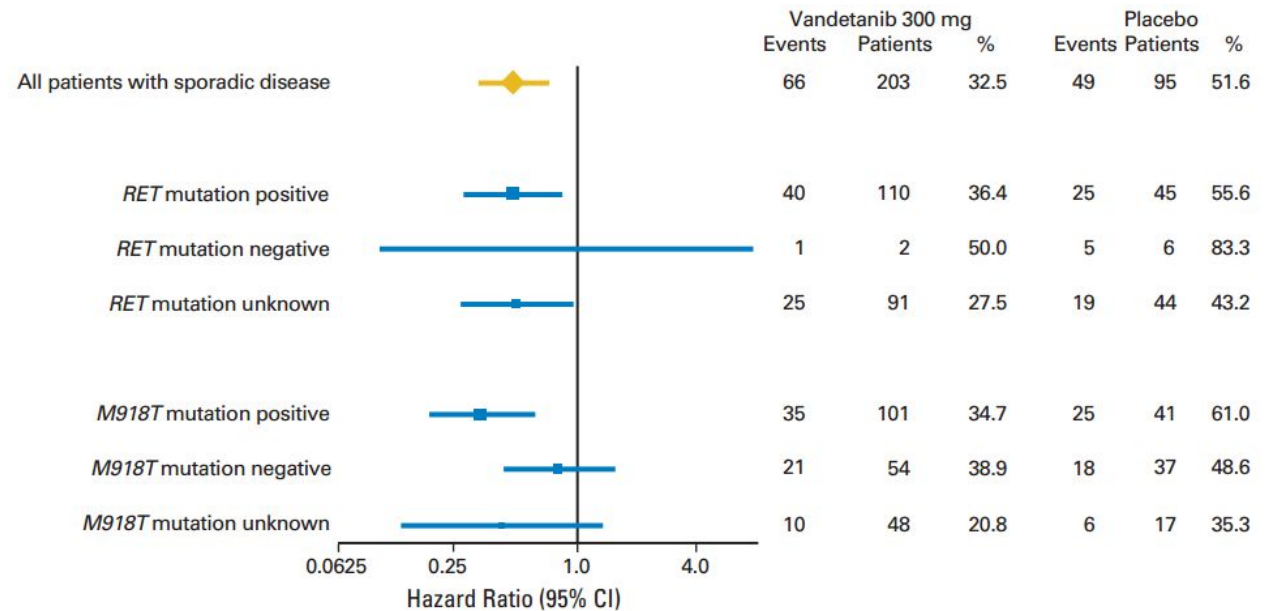
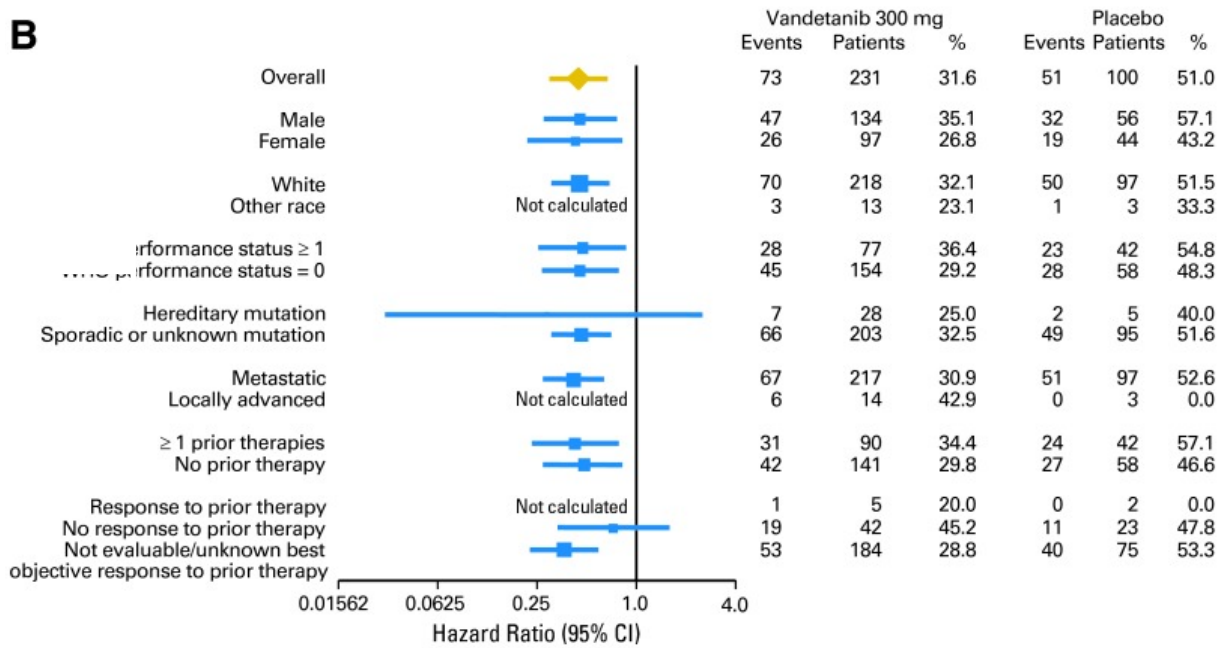


*Significantly progressive disease according  
RECIST was not required for inclusion in the trial*



- PFS is not reached and estimated at 30.5 month in the Vandetanib group vs 19.3 month in the placebo group (HR 0.46; 95% CI: 0.31 – 0.69;  $p < 0.001$ )
- PRs observed in 45% of vandetanib patients

**B**

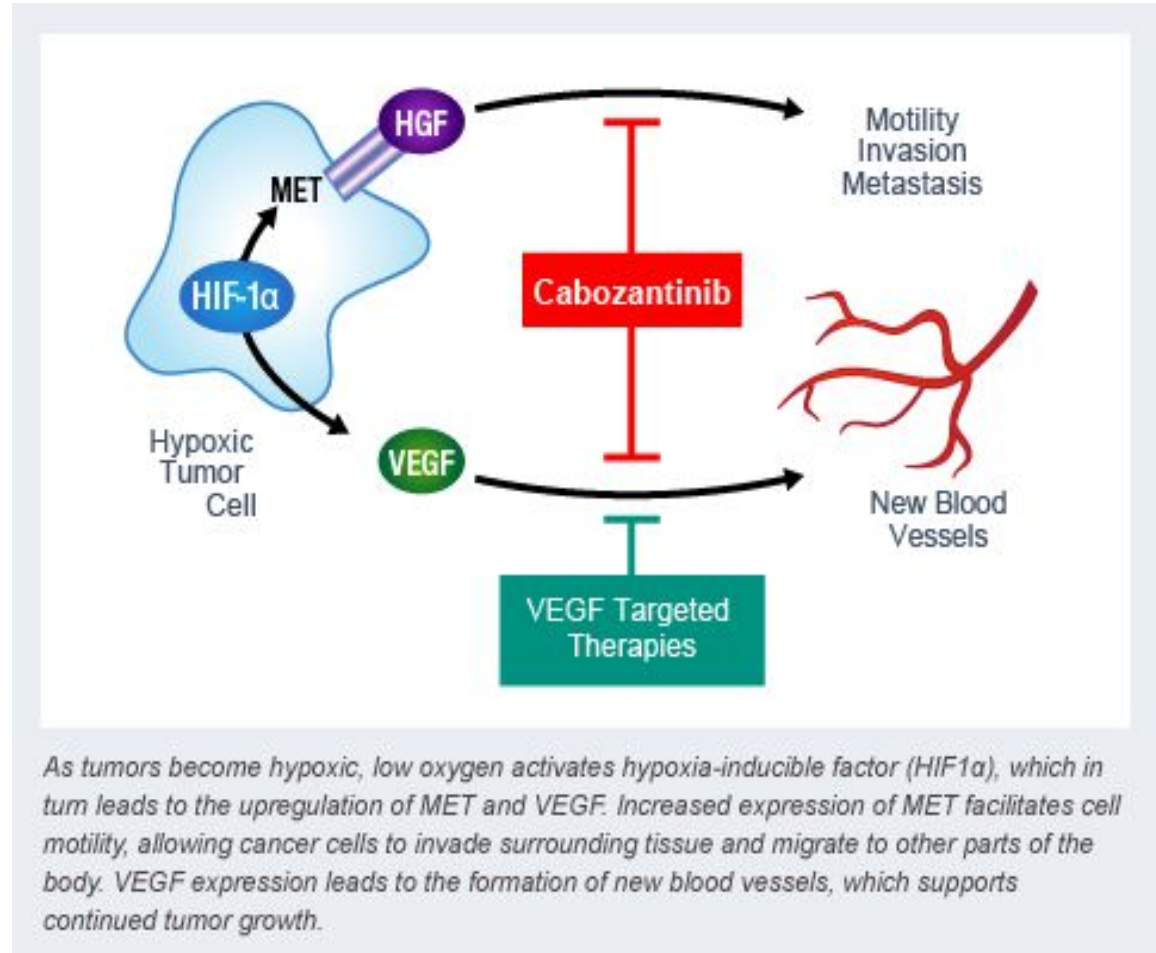


## CABOZANTINIB

Cabozantinib (XL184) is a multitargeted kinase inhibitor most potently targeting VEGFR2, c-MET, and RET.

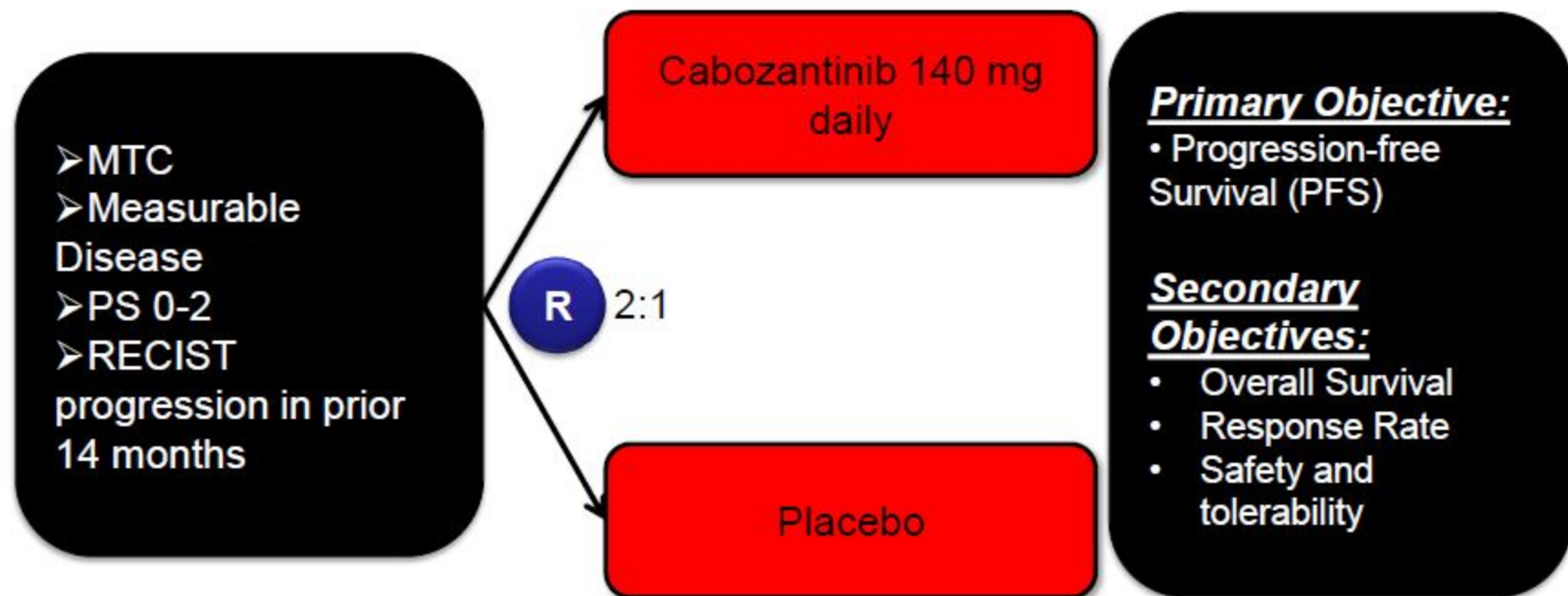
The simultaneous inhibition of both VEGFR and c-MET is thought to reduce c-MET-driven resistance observed in the course of VEGFR-targeted TKI therapy.

Phase 3 drug registration trial (EXAM) was conducted to evaluate safety and efficacy of cabozantinib vs placebo in patients with metastatic MTC



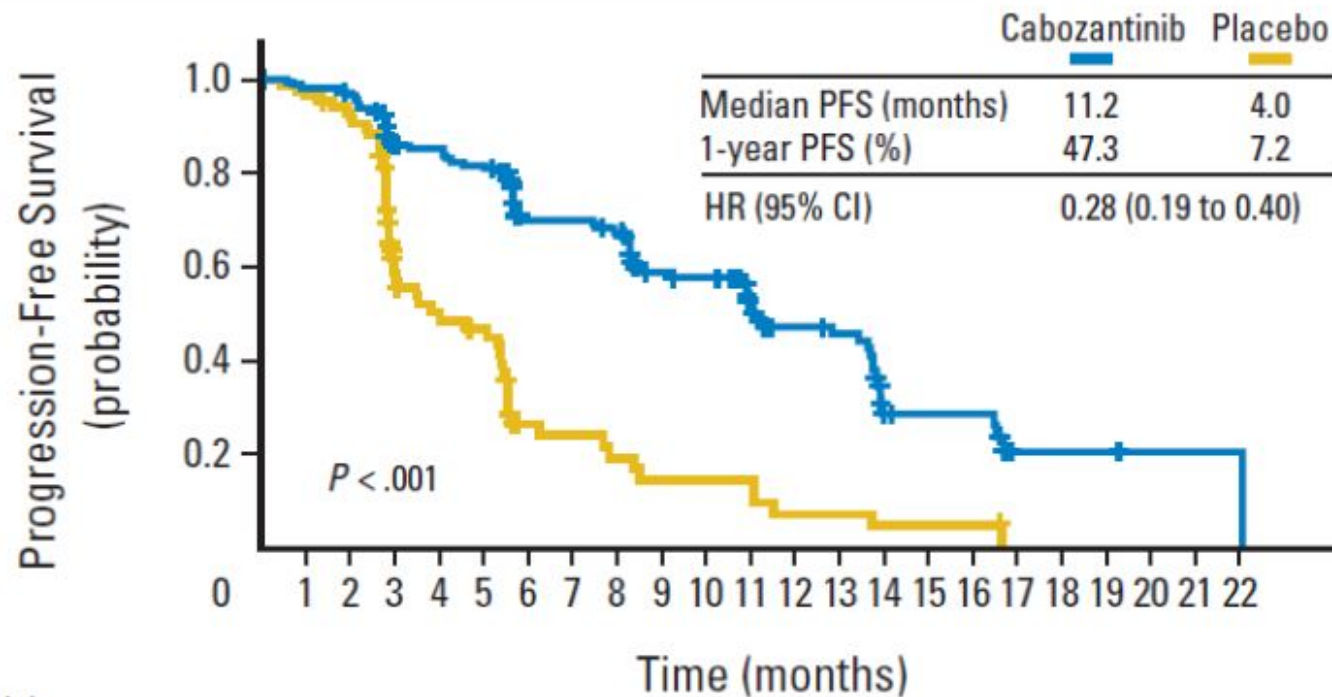
In contrast to the vandetanib ZETA trial, documented radiographic disease progression according to RECIST within 14 months before study entry was required.

# EXAM Phase II Design



International n = 330

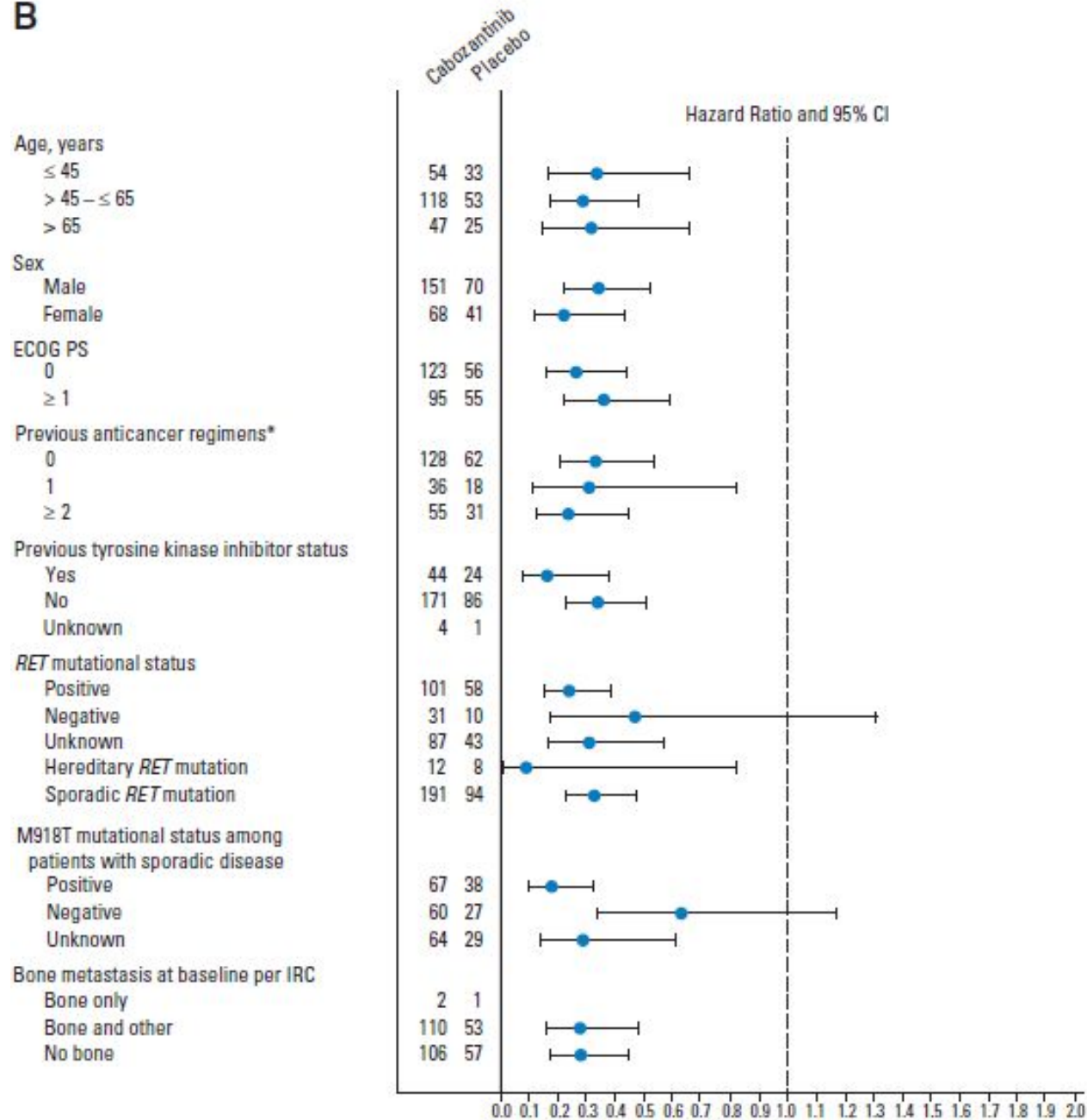
# PFS by Independent Review



No. at risk	Time (months)		Time (months)		Time (months)		Time (months)	
Cabozantinib	219	121	78	55	31	12	2	1
Placebo	111	35	11	6	3	2	0	0

ORR 28% in cabozantinib arm, 0% in placebo arm,  $p < 0.001$   
Median Duration of Response 14.6 months

**B**



## Patients on the 2 studies belong to different moments in the history of patients with advanced MTC...

	Vandetanib	Cabozantenib
Previous progression	No	Yes
Previous therapy	39	40
PS (0-2)	96 % (0-1) 4 % (2)	56.2 (0) 43.4 (1-2)
Median duration of treatment	22.5 m	6.8 m
mPFS	Not reached (estimated 30.5 m) Vs 19.3 m (placebo)	11.2 m Vs 4 (placebo)
Median duration of response	Not reached	14.6 m
Survival	?	?

**Message:** treat patients early or later in their medical history, benefit in terms of tumor growth control in a different way, but we don't have definitive data on survival.

**Table 1** EXAM and ZETA studies in medullary thyroid carcinoma: indirect comparison

Variable	EXAM study Cabozantinib	EXAM study Placebo	ZETA study Vandetanib	ZETA study Placebo
Dosage	140 mg daily		300 mg daily	
Common signaling	VEGFR-2, RET		VEGFR-2, RET	
Specific signaling	MET, KIT, AXL, FLT3		EGFR, VEGFR-3	
Phase III clinical trial	NCT00704730		NCT00410761	
Number of patients	219	111	231	100
Progression-free survival	11.2 months	4	30 months (estimated) <sup>a</sup>	19.3
Statistical significance: <i>p</i>	<0.001		<0.001	
Response rate	28 %	0 %	45 %	13 %
Statistical significance: <i>p</i>	<0.001		<0.001	
Disease control rate	94 %	27 %	87 %	71 %
Dose reduction	79 %	9 %	35 %	3 %
Discontinuation due to toxicity	16 %	8 %	8 %	0 %
Grade ≥3 adverse events	69 %		47 %	
Grade ≥3 diarrhea	34 (15.9 %)	2 (1.8 %)	25 (11 %)	2 (2 %)
Grade ≥3 palmar-plantar syndrome	27 (12.6 %)	0	NA	NA
Grade ≥3 fatigue	20 (9.3 %)	3 (2.8 %)	13 (6 %)	1 (1 %)
Grade ≥3 hypertension	18 (7.9 %)	1 (1 %)	20 (9 %)	0
Grade ≥3 QTc prolongation	NA	NA	18 (8 %) <sup>a</sup>	1 (1 %)
Grade ≥3 loss of appetite	10 (5 %)	1 (1 %)	9 (4 %)	0
Grade ≥3 rash	2 (1 %)	0	8 (4 %)	1 (1 %)
Grade 5 adverse events (death)	5 %		2 %	

EXAM Efficacy of XL184 in Advanced Medullary Thyroid Cancer, ZETA Zactima Efficacy in Thyroid Cancer Assessment, VEGFR-3 vascular endothelial growth factor receptor 3, RET rearranged during transfection, MET mesenchymal-epithelial transition, KIT tyrosine protein kinase kit or CD117, FLT3 FMS-like tyrosine kinase 3, EGFR epidermal growth factor receptor, NA not applicable

<sup>a</sup> Median progression-free survival: vandetanib estimated at 30 months (not reached)

## A Study of Two Different Doses of Cabozantinib (XL184) in Progressive, Metastatic Medullary Thyroid Cancer (EXAMINER)

**This study is currently recruiting participants.** (see [Contacts and Locations](#))

*Verified May 2016 by Exelixis*

**Sponsor:**  
Exelixis

**Information provided by (Responsible Party):**  
Exelixis

ClinicalTrials.gov Identifier:  
NCT01896479

First received: July 8, 2013

Last updated: May 4, 2016

Last verified: May 2016

[History of Changes](#)

The objective of this study is to evaluate the efficacy and safety of oral cabozantinib at a 60 mg dose compared with a 140 mg dose in subjects with progressive, metastatic MTC.

It will test if the lower dose results in similar progression free survival (PFS) and overall response rate (ORR) with fewer adverse events compared to the PFS, ORR and adverse events found in previous clinical trials of 140 mg.

## FUTURE TARGETED THERAPY

Clinical studies	Molecular target	Thyroid cancer types
<b>Nintedanib</b> (phase 2 ongoing)	VEGFR1-3, FGFR1-3 PDGFR $\alpha$ / $\beta$ RET	MTC, DC
<b>Anlotinib</b> (phase 2 ongoing)	VEGFR2, 3, PDGFR $\beta$ , c-Kit	MTC
<b>Ponatinib</b> (phase 2 terminated)	RET kinase, BCRABL, VEGFR, PDGFR, KIT, FGFR, FLT3	MTC
<b>Combination Vandetanib + Bortezomib</b> (phase 2 ongoing but not recruiting)	VEGFR2, c-MET, and RET+ proteasome inhibitor	MTC
<b>Regorafenib</b> (phase 2 ongoing)	VEGFR, TIE2, KIT, RET, RAF-1, BRAF, PDGFR, and FGFR,	MTC
<b>Sulfatinib</b> (phase 2 ongoing)	VEGFR, TIE2, KIT, RET, RAF-1, BRAF, PDGFR, and FGFR,	MTC, DTC

## **Systemic treatment of advanced MTC: Somatostatine Analoghs SSA and Peptide Receptor Radionuclide Therapy PRRT**

*In vitro data has demonstrated that MTC cells not only produce somatostatin, but also express corresponding receptors on their membranes.*

In a immunohistochemistry study of the distribution of the five somatostatin receptors subtypes (sst1–5) in medullary thyroid cancer specimens, a heterogeneous expression of somatostatin receptor subtypes was detected, with an expression of octreotide sensitive types (sst2, sst3, and sst5) in 75% of cases.

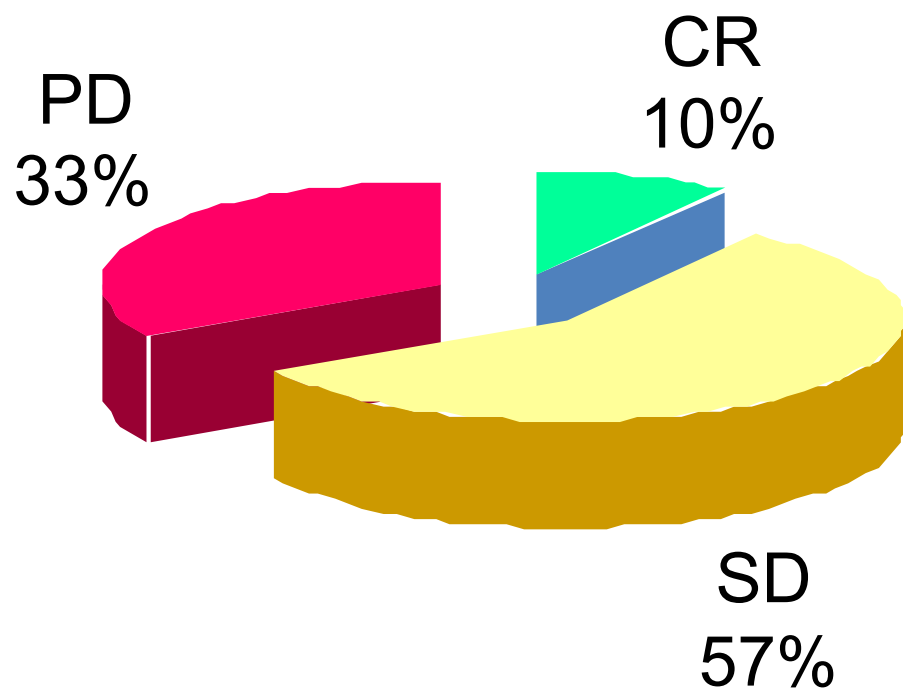
However, probably because of the low density of expression of sst2, only about 50–70% of medullary thyroid cancer can be visualized by scintigraphy with radiolabeled octreotide.

Patients with SSTR positive may be considered to use somatostatin analogues for symptomatic treatment of diarrhoea if other drugs are ineffective.

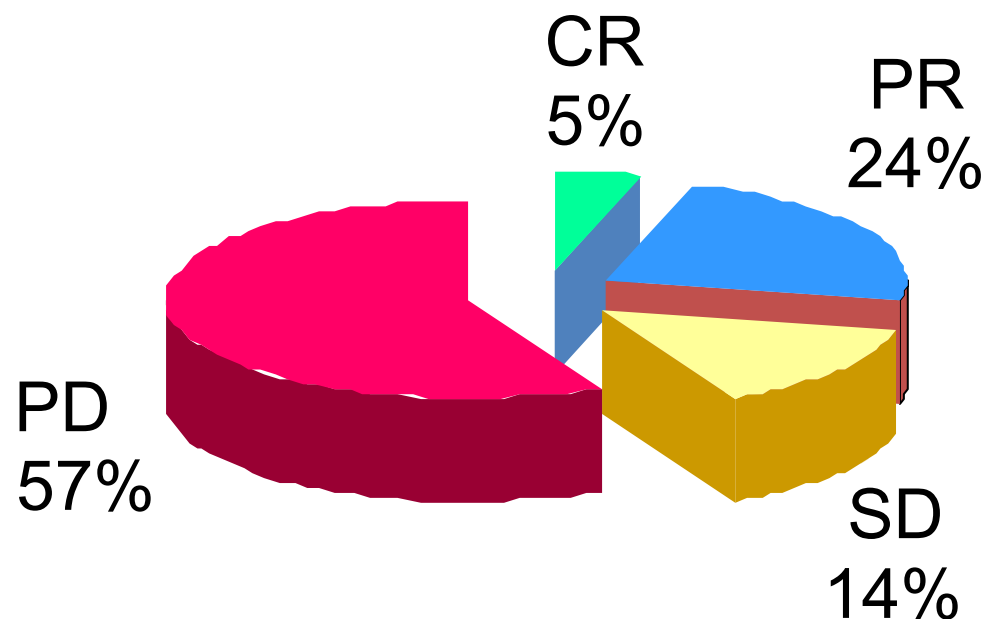
Newly developed somatostatin analog [DOTA0, Tyr3]octreotide (DOTATOC), labeled with Yttrium- 90 or Luthetium, is presently used in therapy trials in patients affected by endocrine tumors expressing sst2 receptors.

## Receptor Radionuclide Therapy with <sup>90</sup>Y-DOTATOC in Patients with MTC

### Objective response (21 pts)



### Biochemical response



Bodei L, Paganelli G, Cancer Bioth & Radioph 2004

# Outline

- 1- Natural history of MTC
- 2- Local treatments of advanced MTC
- 3- Systemic treatments of advanced MTC
- 4- How i treat patients with advanced MTC ?**

**1- To Treat or Not to Treat ?**

**2- and With Which Drug ?**

**Those are the questions !**

# Controversies in Thyroid Carcinoma

“In the new era of approved multi-targeted TKIs, Active Surveillance of patients diagnosed with RAI-Refractory DTC, should become the new standard of care”

Chicago, June 5<sup>th</sup> 2016



Lenvatinib-EU0049g Date of Preparation June 2016;  
This meeting is initiated, funded and organised by Eisai  
Europe Ltd



# *Active surveillance vs Watchful waiting*



**Toni Ibrahim**

**vs**

**Jaume Capdevila**



# Shared Closing Remarks: Controversies in DTC, June 5<sup>th</sup> 2016

## M Taylor- J Capdevila- T Ibrahim

- IN THIS NEW ERA of TKIs, it is required a personalized management of patients with RAI refractory DTC, with a careful documentation of:

- . disease progression,
- . the presence or absence of symptoms and
- . disease in areas that are life-threatening or have the potential to become life-threatening, in order to help intervene at the right time without much delay.

- **Watchful Waiting : Asymptomatic, stable or slow growing, low tumor burden and biology vs**

- **PERSONALIZED MANAGEMENT IN AN ACTIVE SURVEILLANCE: Symptomatic, asymptomatic LT or become LT (high tumor burden (local or systemic) and tumor biology, bulky, invasion of air-digestive way/vascular structures/CNS/Bone at high risk).**

This classification indicate different prognostic groups and consequently require a PERSONALIZED active surveillance at various intensity (clinical, biochemical and imaging exams) and therapeutic implications.

- Patients should be followed by a multidisciplinary dedicated team offering a total care from diagnosis to treatment including the management of any complications from the disease or the treatments.

- Guidelines to prevent and manage possible side effects from TKIs (hypertension, mucous, dermatologic and gastrointestinal) as well as the reduction of the doses according to toxicity, must be available to the clinician who is in charge of the patient. Clinicians should be trained for the application of these guidelines.

- We hope that the next few years will allow us to better understand the biology of the disease and especially to identify not only prognostic factors but also predictive factors of response to treatments. We need also clinical studies which explore combined therapy (local and systemic ) and the risk/benefit of treatments

IN THIS NEW ERA, it is required a PERSONALIZED management of patients with MTC, with a <sup>?</sup> careful documentation of:

## To Treat or Not To Treat advanced MTC

- . disease progression,
- . the presence or absence of symptoms and
- . disease in areas that are life-threatening or have the potential to become life-threatening, in order to help intervene at the right time and avoid delay

**Not To Treat**

**To Treat**

- **Watchful Waiting** : asymptomatic, stable or slow growing, low tumor burden

and biology

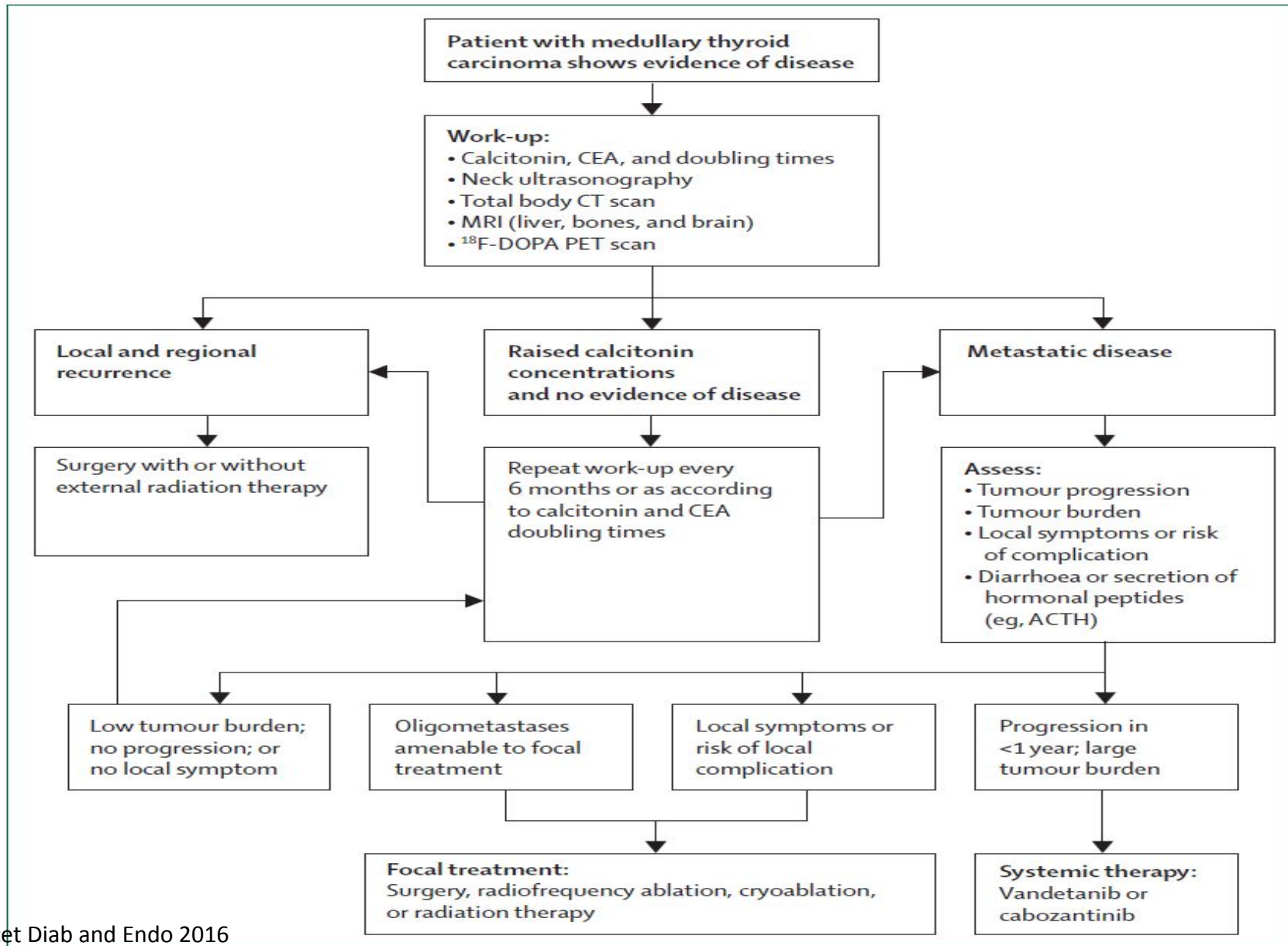
VS

- **Local or systemic treatment**: symptomatic, asymptomatic LT or become

LT: rapid progression, high tumor burden (local or systemic) and tumor

biology, bulky, invasion of air-digestive way/vascular structures/CNS/Bone

# Management of advanced medullary thyroid cancer



1- To Treat or Not to Treat ?

**2- and With Which Drug ?**

## ...and With Which Drug ?

The choice of drug may be dictated by



The results of clinical trials and the experience of each institution



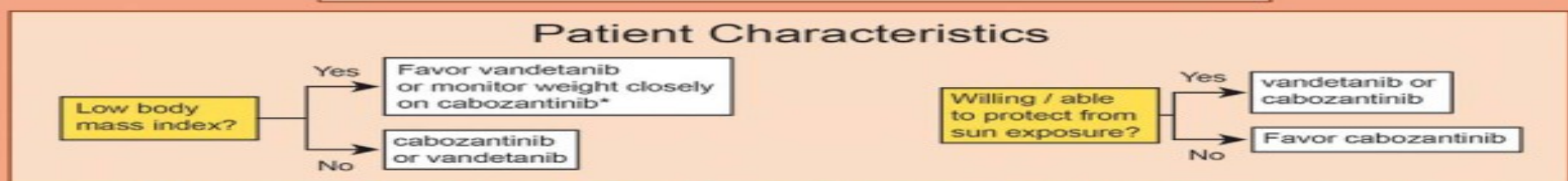
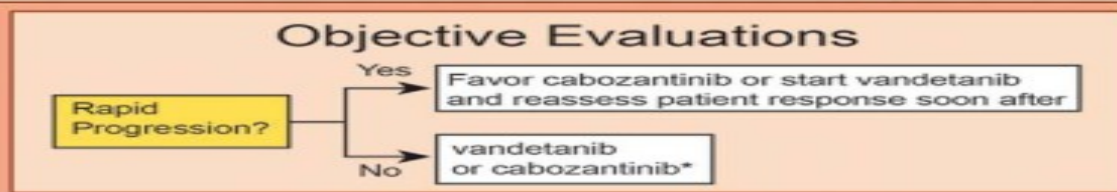
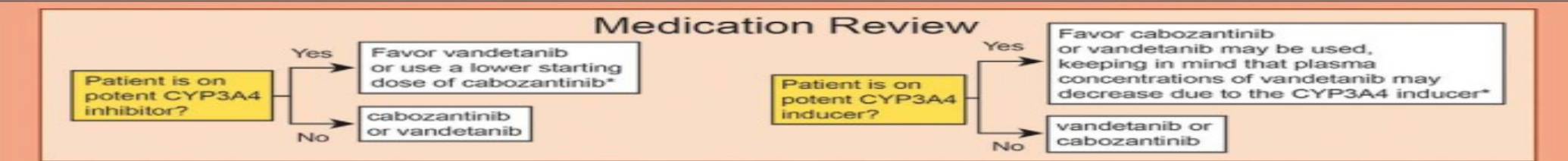
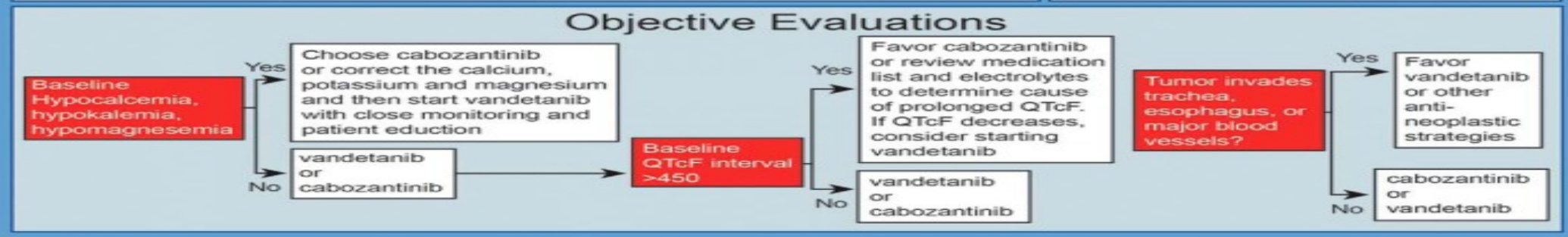
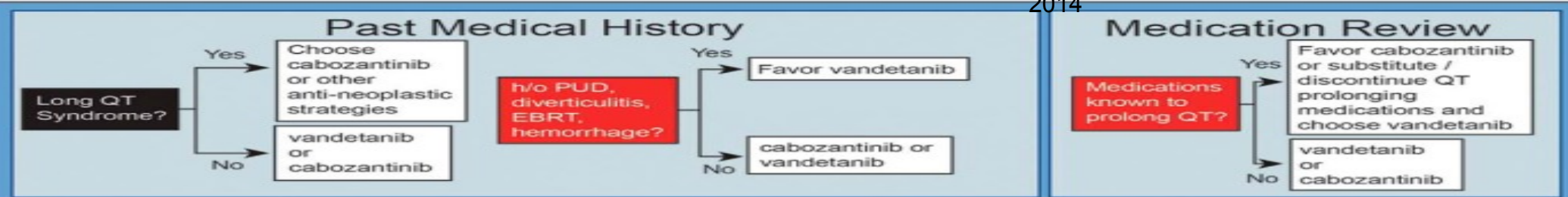
**PERSONALIZED TREATMENT**



with careful consideration of patient's medical history, physical examination, laboratory tests, EKG findings and the behavior of the tumor.

## Medullary Thyroid Cancer in the Era of Tyrosine Kinase Inhibitors...

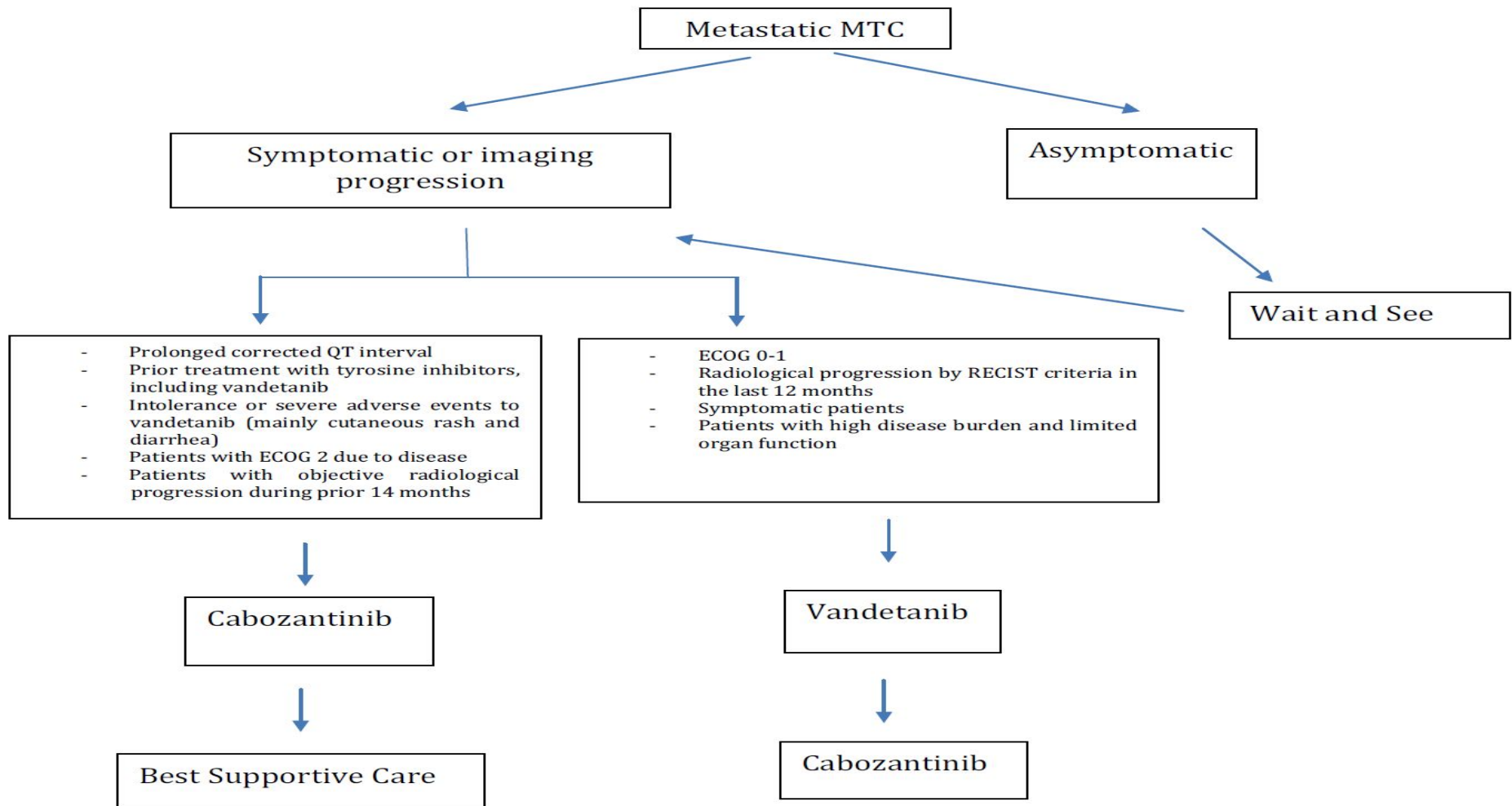
Cabanillas ME, Clin Endocrinol Metab.  
2014



\*Concomitant use of CYP3A4 inhibitors may increase the plasma concentration, resulting in toxicity, while inducers may decrease the plasma concentration of the TKI, resulting in decreased efficacy.

# Consensus on management of advanced medullary thyroid carcinoma on behalf of the Working Group of Thyroid Cancer of the Spanish Society of Endocrinology (SEEN) and the Spanish Task Force Group for Orphan and Infrequent Tumors (GETHI)

E. Grande<sup>1</sup> · J. Santamaría Sandi<sup>2</sup> · J. Capdevila<sup>3</sup> · E. Navarro González<sup>4</sup> ·  
C. Zafón Llopis<sup>5</sup> · T. Ramón y Cajal Asensio<sup>6</sup> · J. M. Gómez Sáez<sup>7</sup> ·  
P. Jiménez-Fonseca<sup>8</sup> · G. Riesco-Eizaguirre<sup>9</sup> · J. C. Galofré<sup>10</sup>



**Fig. 1** Multidisciplinary approach algorithm for the management of advanced medullary thyroid carcinoma. *MTC* medullary thyroid carcinoma, *RECIST* Response Evaluation Criteria in Solid Tumors, *ECOG* Eastern Cooperative Oncology Group

## Conclusions

- In the new era of the management of MTC, the presence of advanced disease does not justify automatic treatment. A personalized treatment should always direct our decisions both when we decide for watchful waiting or interventional treatment.
- Patients should be followed by a multidisciplinary dedicated team offering a total care from diagnosis to treatment including the management of any complications from the disease or the treatments.
- Guidelines to prevent and manage possible side effects from TKIs (hypertension, QTc prolongation, mucous, dermatologic, gastrointestinal, hemorrhage, etc) as well as the reduction of the doses according to toxicity, must be available to the clinician who is in charge of the patient. Clinicians should be trained for the application of these guidelines.
- We hope that the next few years will allow us to better understand the natural history and the biology of the disease and especially to identify not only prognostic factors but also predictive factors of response to treatments. We need also clinical studies which explore combined therapy (local and systemic) and the risk/benefit of treatments.



ISTITUT  
SCIENTIFICO  
ROMAGNOLI  
PER LO STUDIO  
DEI TUMORI

E LA CURA



## Osteoncology and Rare Tumors Center CDO-TR

### **Oncologists:**

Alberto Bongiovanni  
Davide Bruschi  
Sebastiano Calpona  
Marina Faedi  
Federica Recine  
Nada Riva

### **Lab Researchers:**

Laura Mercatali  
Chiara Liverani  
Alessandro De Vita  
Chiara Spadazzi  
Giacomo Miserocchi

### **Data Manager:**

Manuela Monti  
Monia Dall'Agata

### **Nurse:**

Venetia Zavoiu  
Rossana Ricci

### **Statistic:**

Flavia Foca

### **Pharmacist:**

Valentina Di Iorio

# Thanks For your attention