MADRID 2014 ESMO congress

Clinical cases
Sub-classification and treatment of MTC

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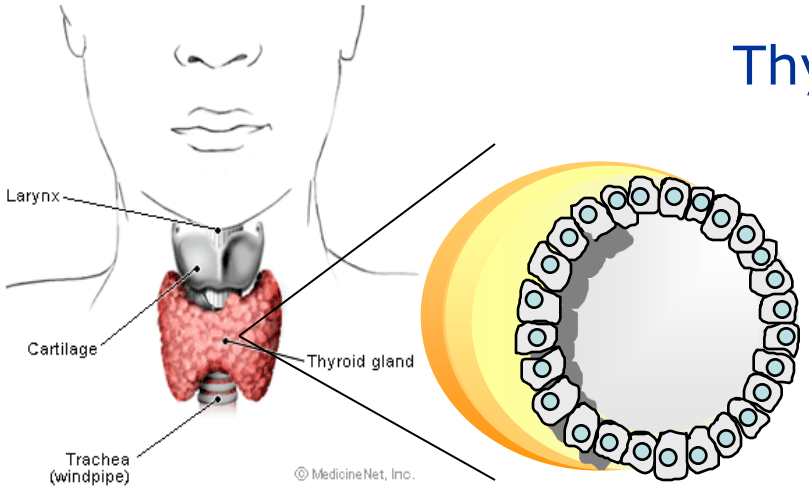
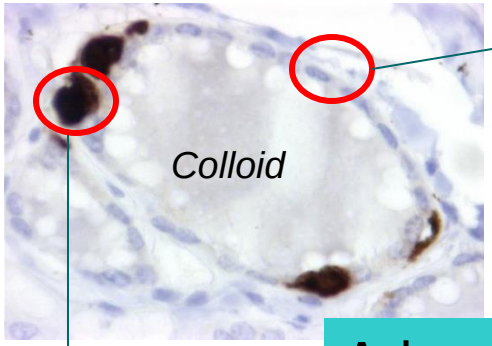
GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Thyroid tumors: classification



Thyroid follicle

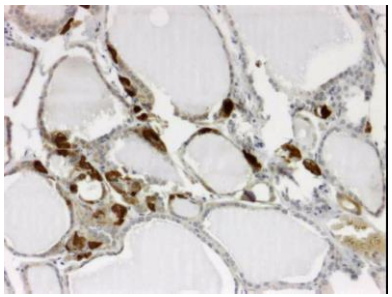


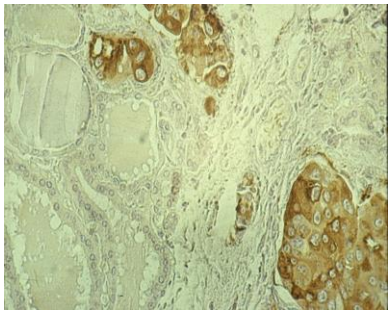
Thyrocyte

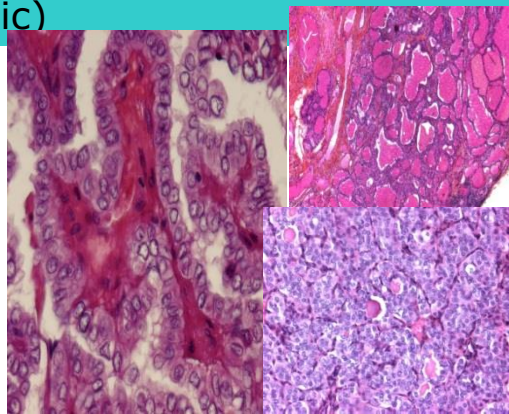
C Cell

Medullary thyroid cancer
(<5% of all cancers)

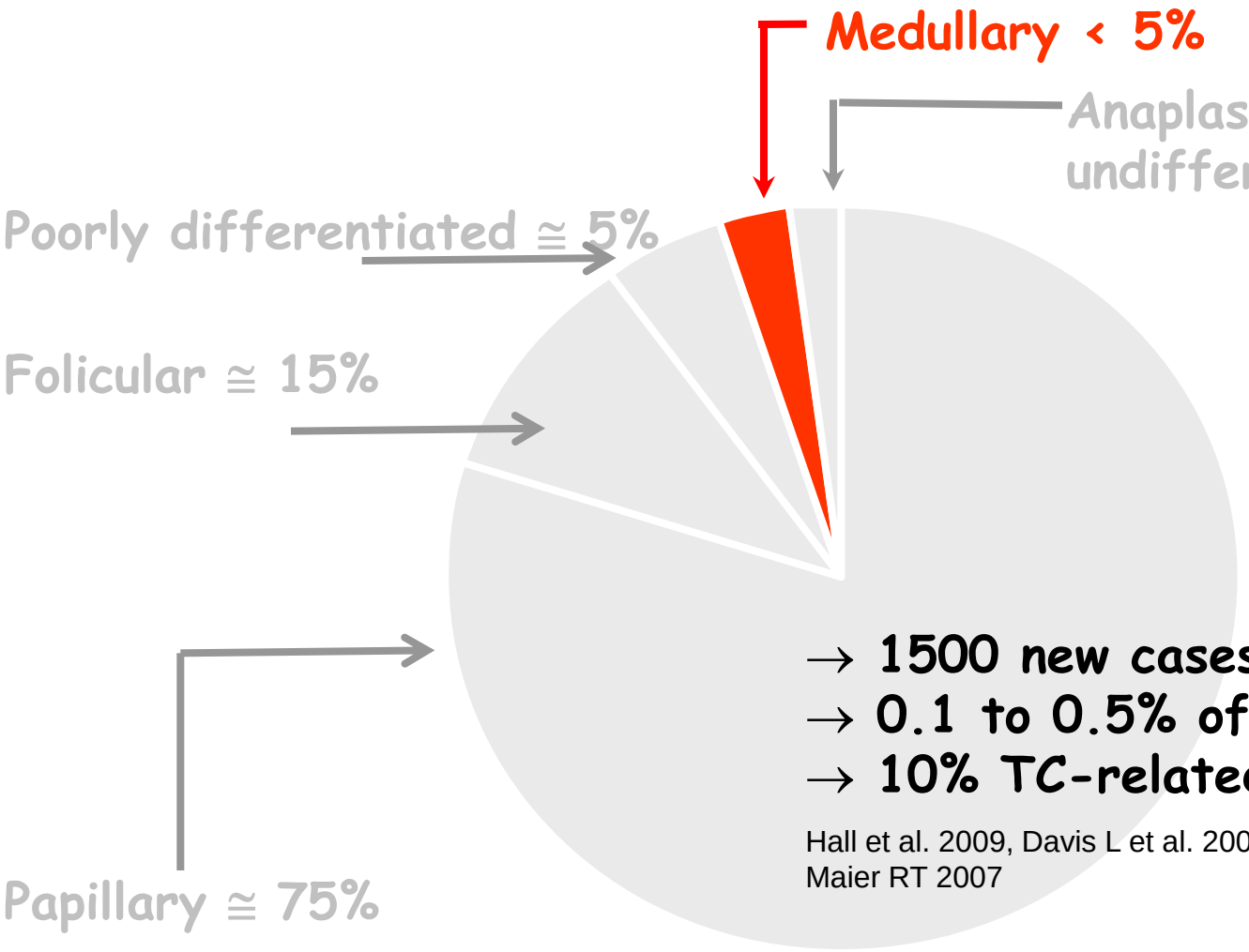
<u>Adenomas</u>
<u>Cancer</u>
- Differentiated (>90% of all cancers): Papillary, follicular, poorly differentiated
- Undifferentiated (anaplastic)







Thyroid Cancers



→ 1500 new cases/year in Europe
→ 0.1 to 0.5% of thyroid nodules
→ 10% TC-related deaths

Hall et al. 2009, Davis L et al. 2006, Colonna m et al. 2007, Netea-Maier RT 2007

Medullary Thyroid Cancer subclassification

- ✓ Hereditary ?
- ✓ Symptoms ?
- ✓ Distant Metastases or unresectable locoregional disease ?
- ✓ Progressive disease,

  → decide whether a treatment is needed

  → Focal or systemic ?

Proto oncogene RET

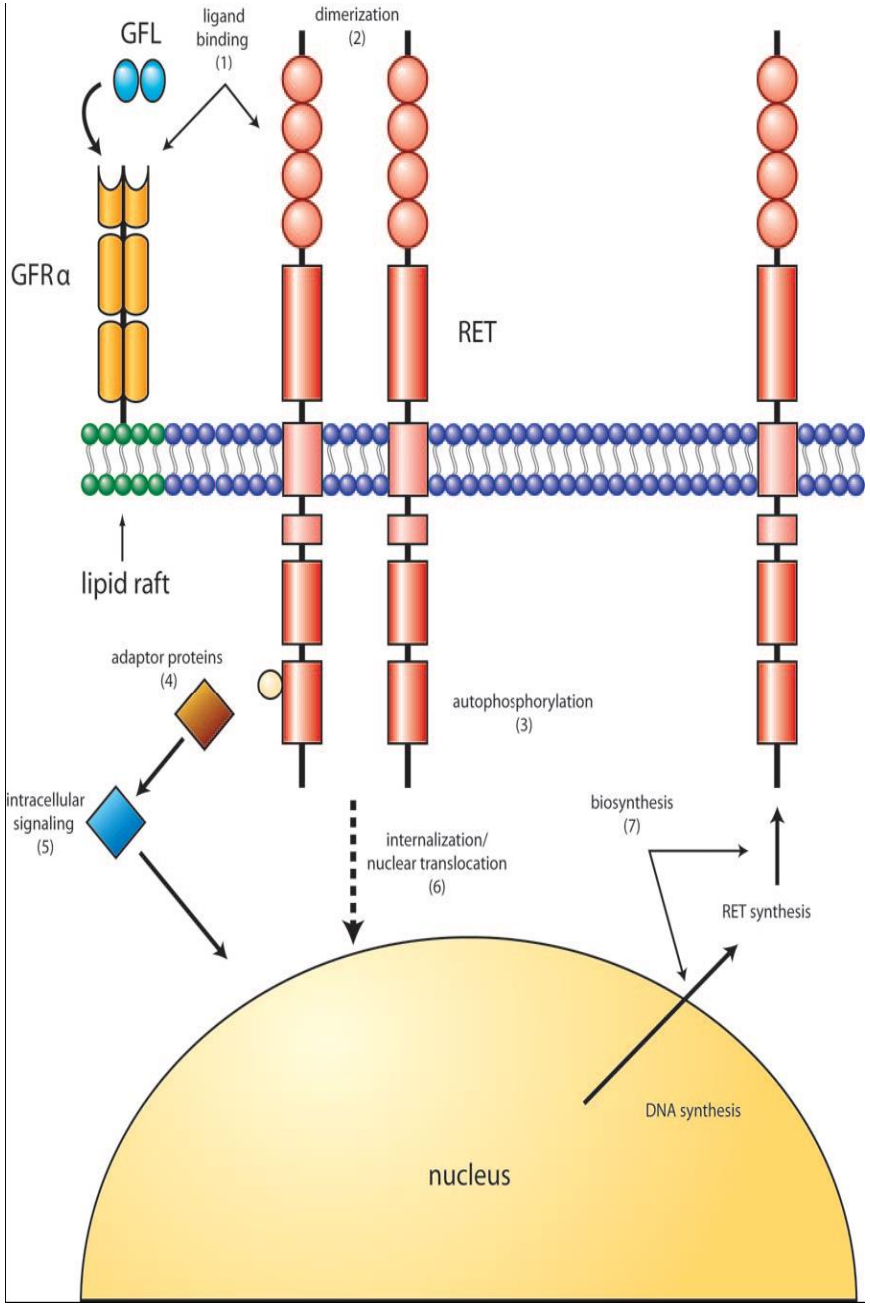
✓Tyrosine kinase membrane receptor

✓ Ligand: GDNF
Co-receptor: GFR alpha

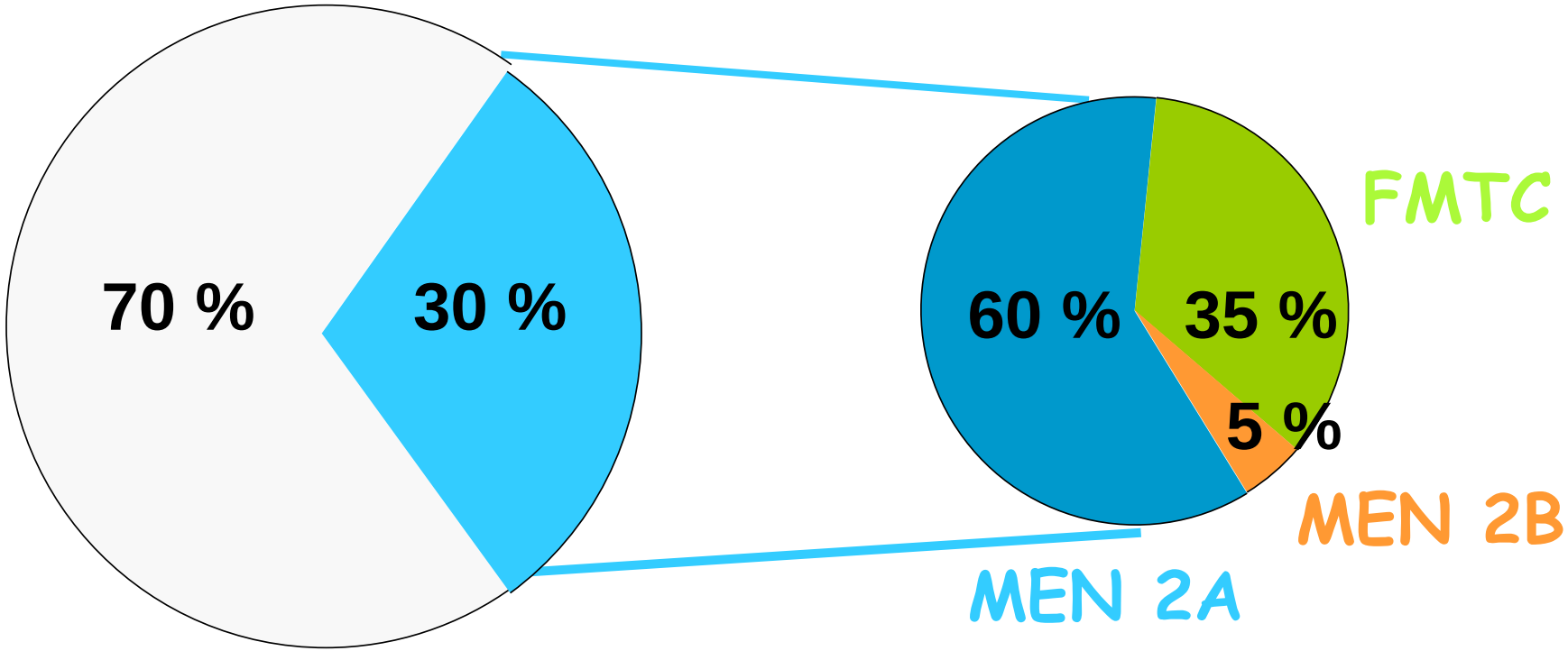
✓ Ligand binding induces dimerization and kinase activation

✓Germinal mutation is found in almost all hereditary cases
Present in 25%-30% of cases: hereditary disease.

✓ Somatic mutation in > 40% of cases
If not, RAS mutation in > 60% cases



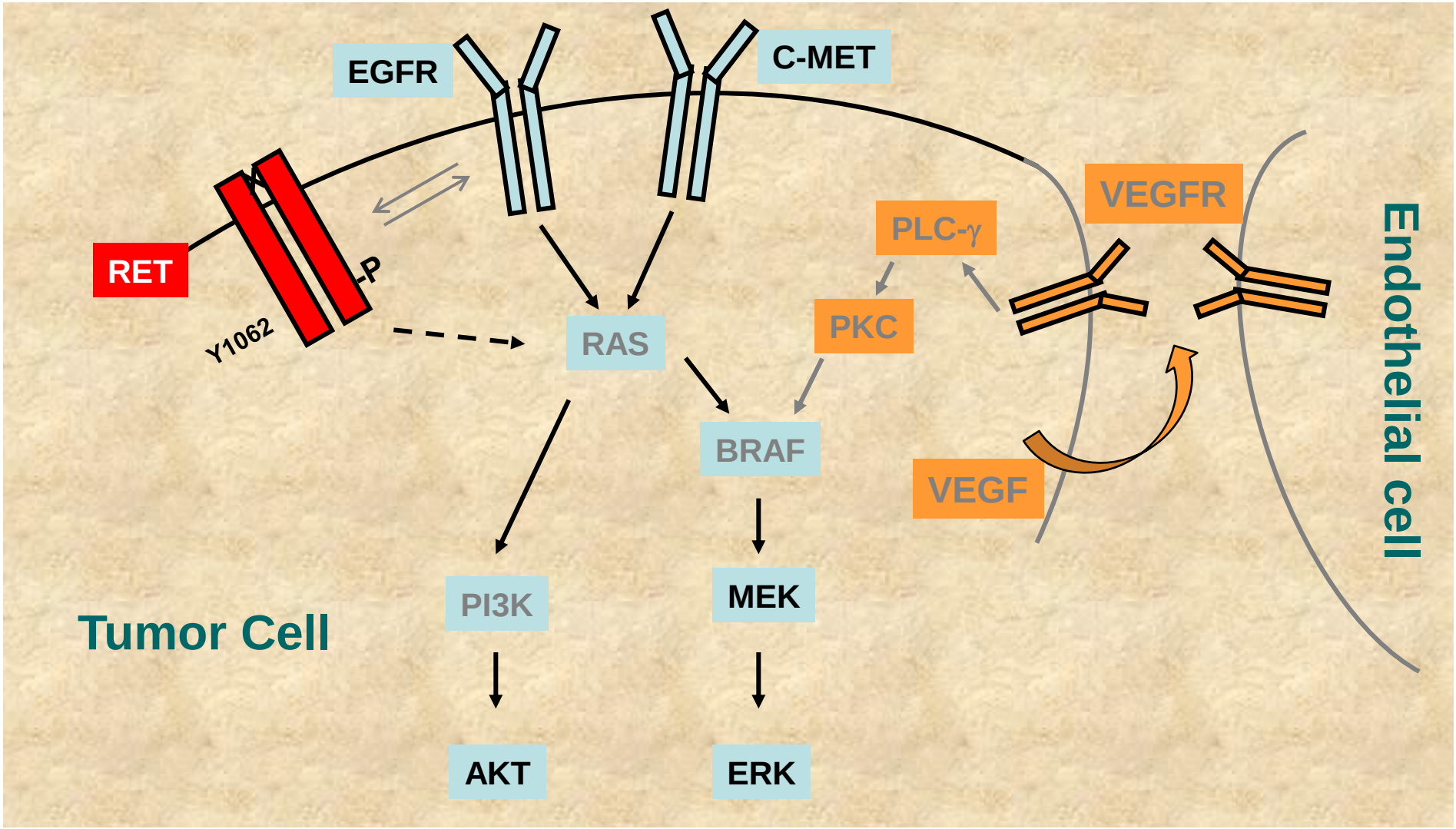
Hereditary MTC : RET mutation



Germline RET screening in all MTC patients:
RET mutation: hereditary:
Familial screening
Search for associated lesions
No RET mutation: sporadic

- ✓ MTC
- ✓ Pheochromocytoma
- ✓ Hyperparathyroidism
- ✓ Other

Signal transduction pathways in thyroid cancers



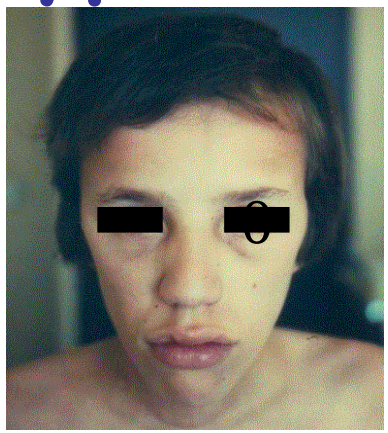
Phenotype-Genotype Correlation

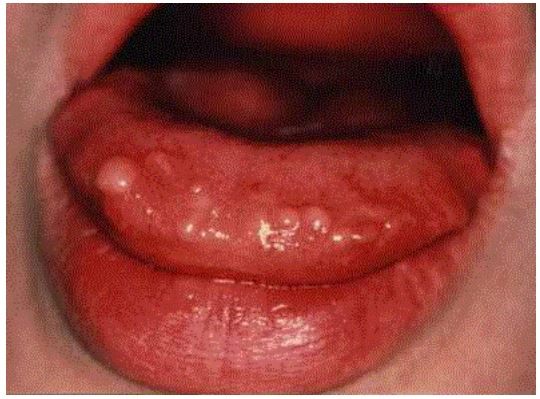
Multiple Endocrine Neoplasia (MEN)	MTC %	Pheochromocytoma %	Hyperparathyroidism %	Other
Familial MTC	100	-	-	
MEN 2A	100	10-50	10-20	Lichen amyloidosis, Hirshprung
MEN 2B	100	50	-	Ganglioneuromatosis, Marfanoid syndrome

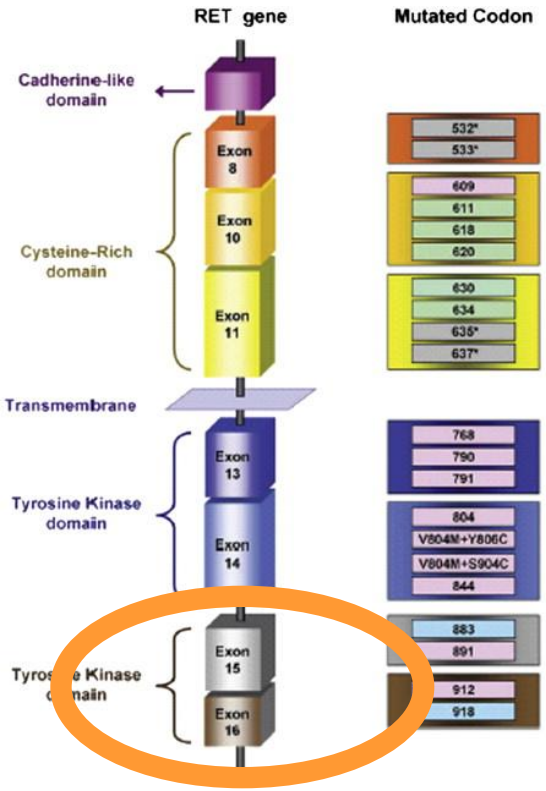
- ✓ Penetrance of MTC is ≅ 100%
- ✓ Age at MTC occurrence and age for prophylactic surgery depend on the mutation
- ✓ Occurrence of Pheo-Hyperparathyroidism and other features is dependent on the mutation

MEN 2B Phenotype

- ✓ Marfanoid habitus
- ✓ Mucosal neuromas (intestinal, urinary, prominent corneal nerve)
- ✓ Skeletal deformation







From Kouvaraki M et al.

Phenotype-Genotype Correlation

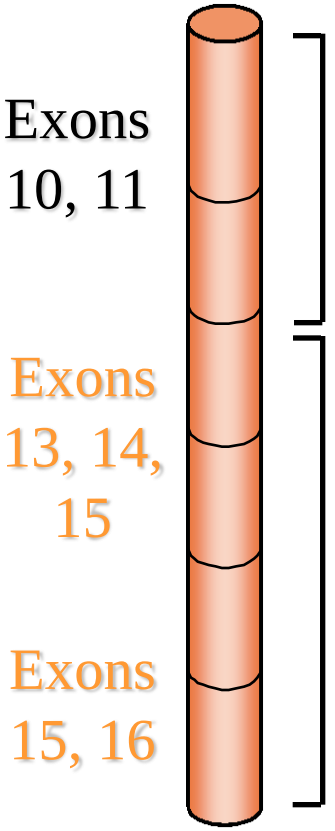
In patients with a germline RET mutation, there is a progression of the disease:

C cell- diffuse C cell hyperplasia-microMTC-clinical MTC

N1 occurs early

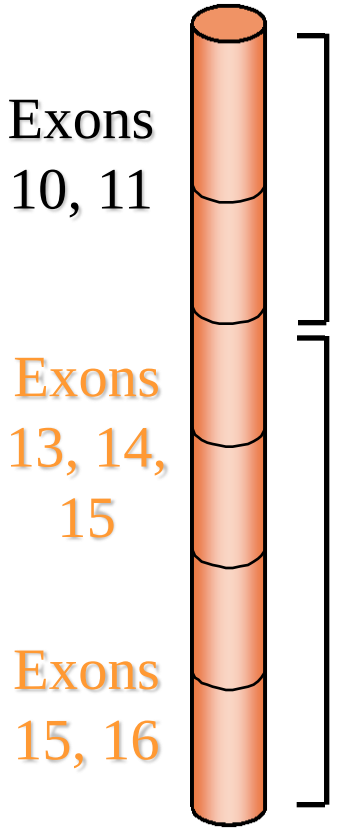
C cell growth starts at an age that is related to the mutation
Serum Ct level is related to the mass of C cells

Total thyroidectomy should be performed before the occurrence of a MTC: it will prevent the occurrence of the disease



Phenotype-Genotype Correlation

Multiple Endocrine Neoplasia (MEN)	Mutated Exon
Familial MTC	10 / 13 / 14 / 15 > 11
MEN 2A	**11 (80%)** > 10 / 13 / 14 / 15
MEN 2B	**16 (95%)** > 15



- Three groups for age at prophylactic thyroidectomy:
  - MEN2B: during the first year of life
  - MEN2A-634: before the age of 6 years
  - Other mutations: may be performed later if Ct is undetectable

Medullary Thyroid Cancer subclassification

- ✓ **Hereditary ?**

Pheochromocytoma is to be treated FIRST → metanephrines

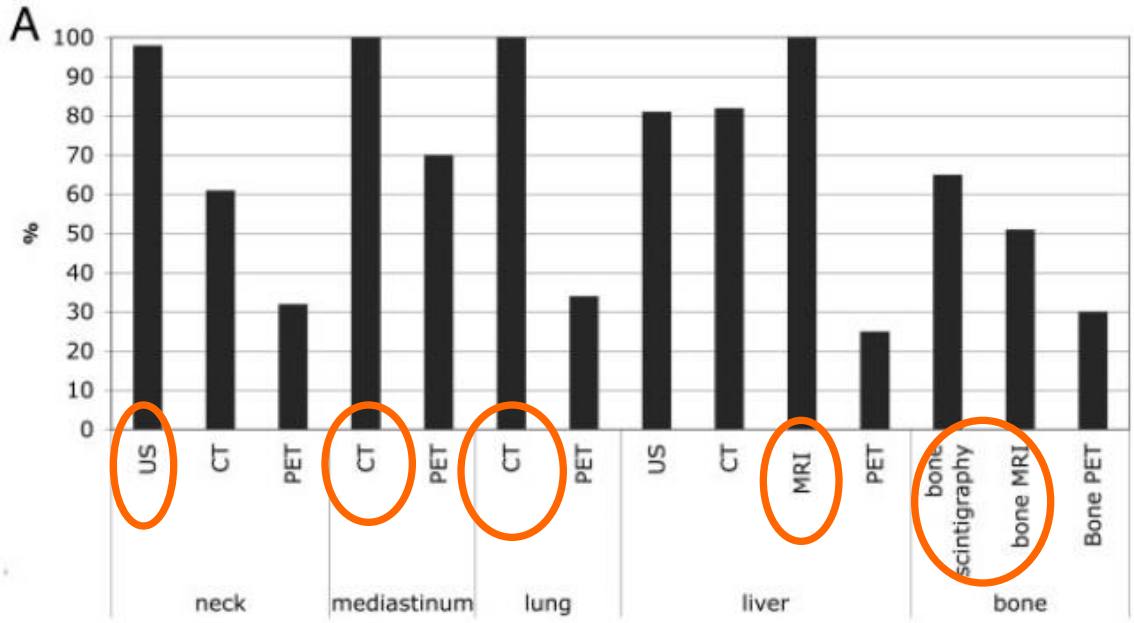
- ✓ Symptoms?
- ✓Distant metastases or unresectable locoregional disease?
- ✓ Progressive disease,

→ decide whether a treatment is needed

→ Focal or systemic?

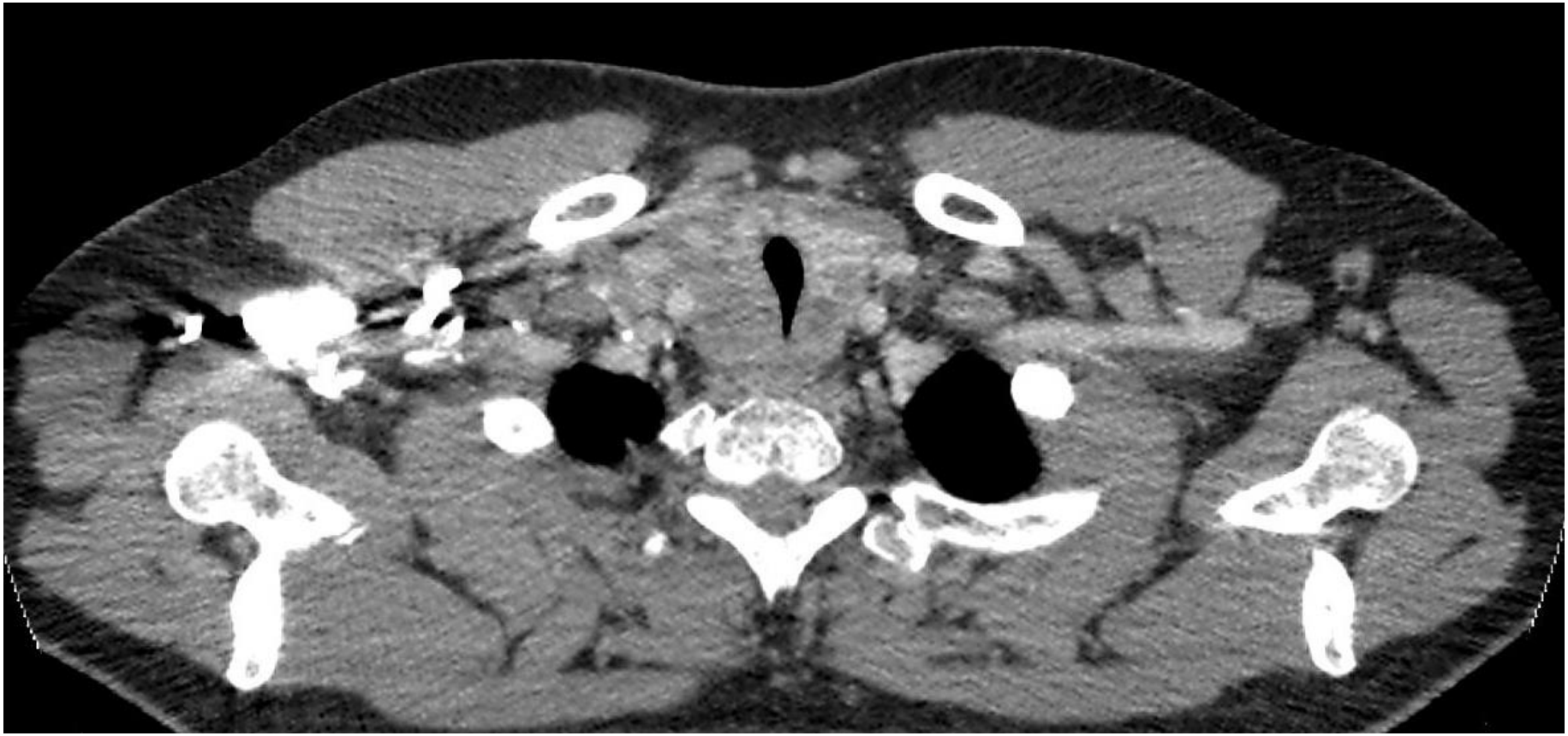
MTC: complete work up

- Assessment of disease extent – standardized imaging
  - Neck US - CT scan with contrast medium
  - Chest CT scan with contrast medium
  - Liver MRI, and if not feasible, dual-phase CT scan
  - Bone: bone scintigraphy + axial MRI
  - Brain: MRI or spiral CT scan
  - FDG-PET:poorly sensitive. FDOPA-PET ?

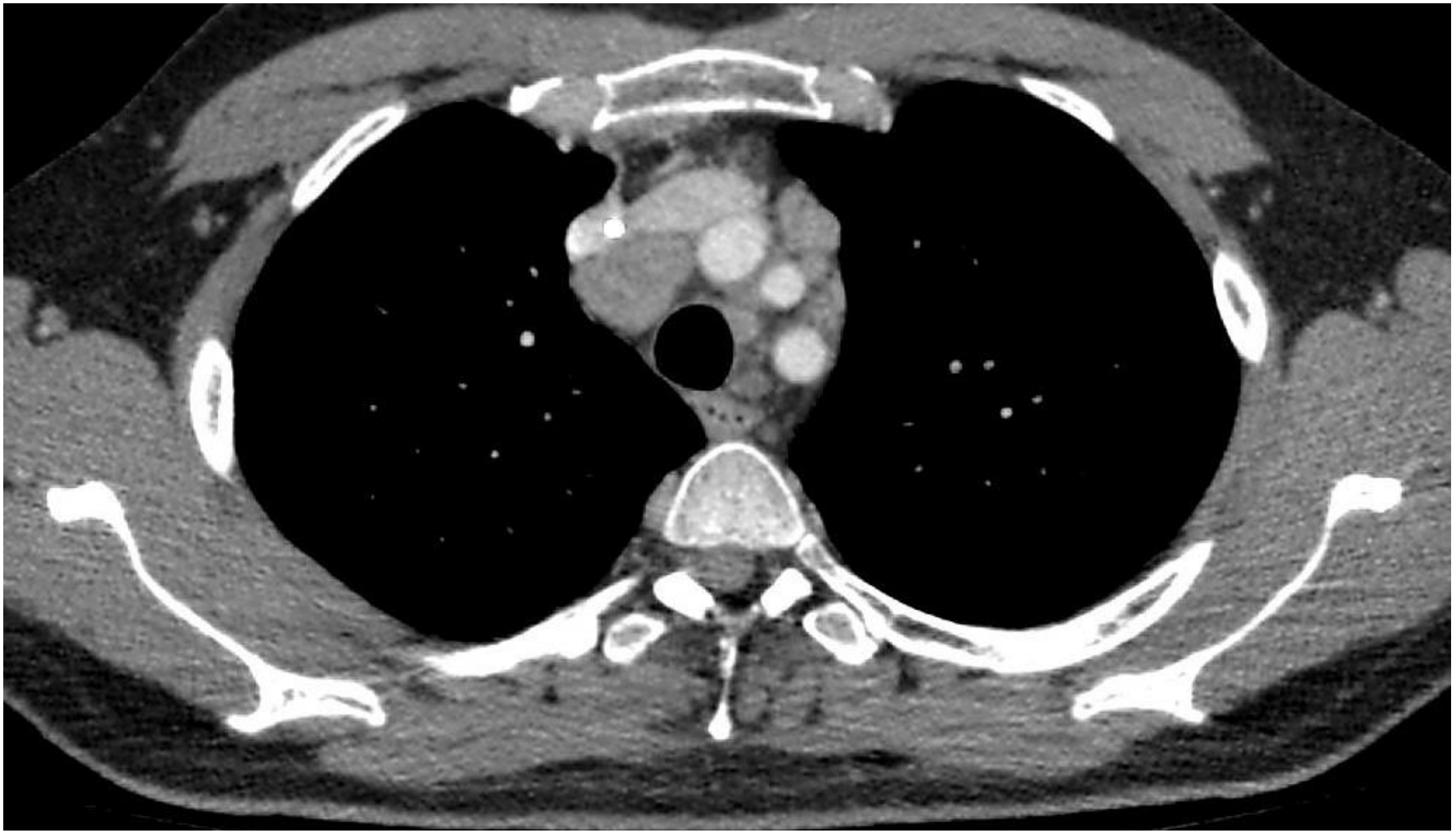


Giraudet AL *et al*. *J Clin Endocrinol Metab* 2007;92:4185–4190

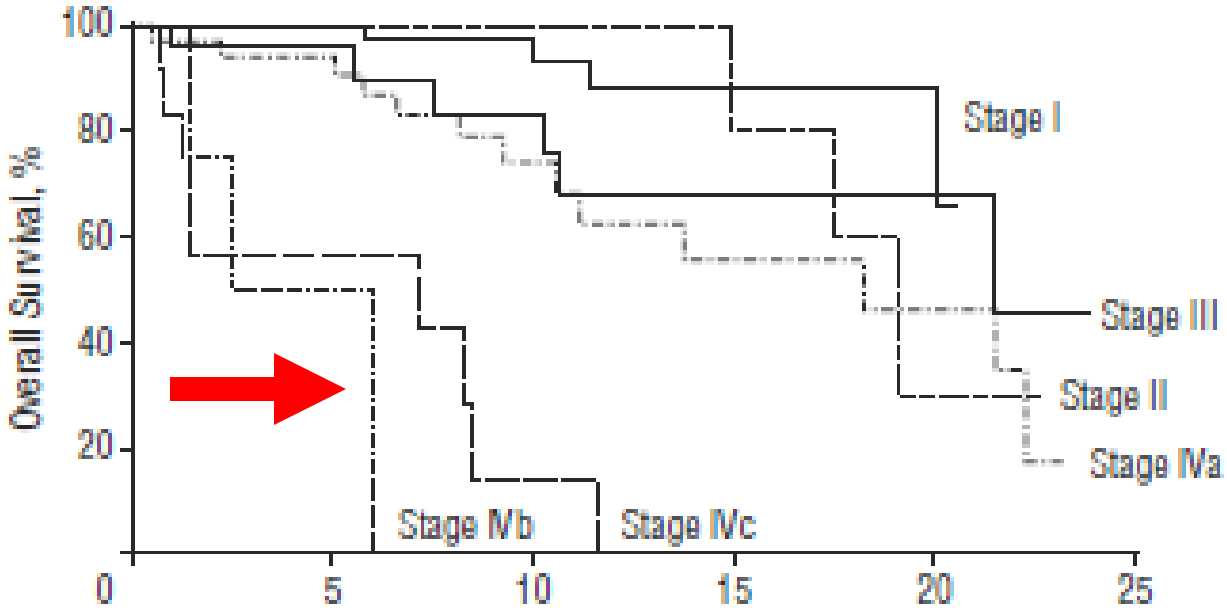
Non resectable locoregional disease



Non resectable locoregional disease



MTC : Overall survival



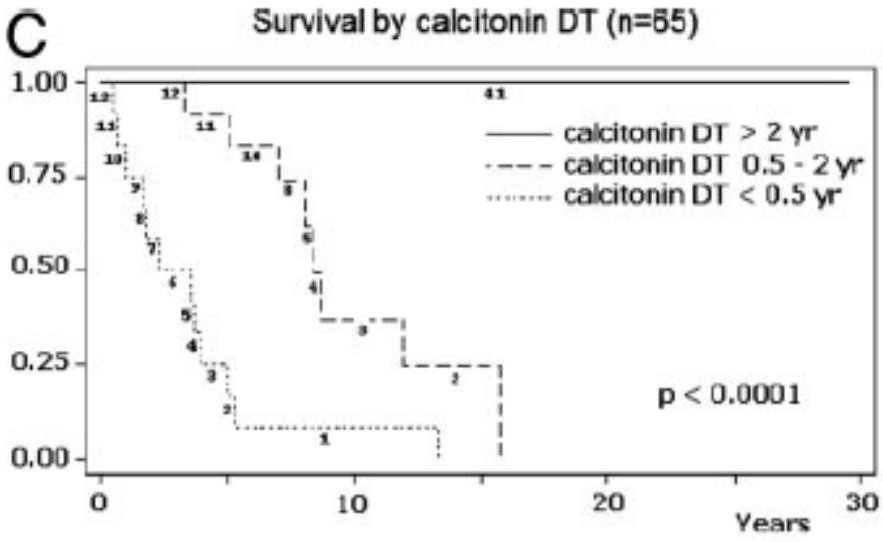
TNM 6th edition (2002)

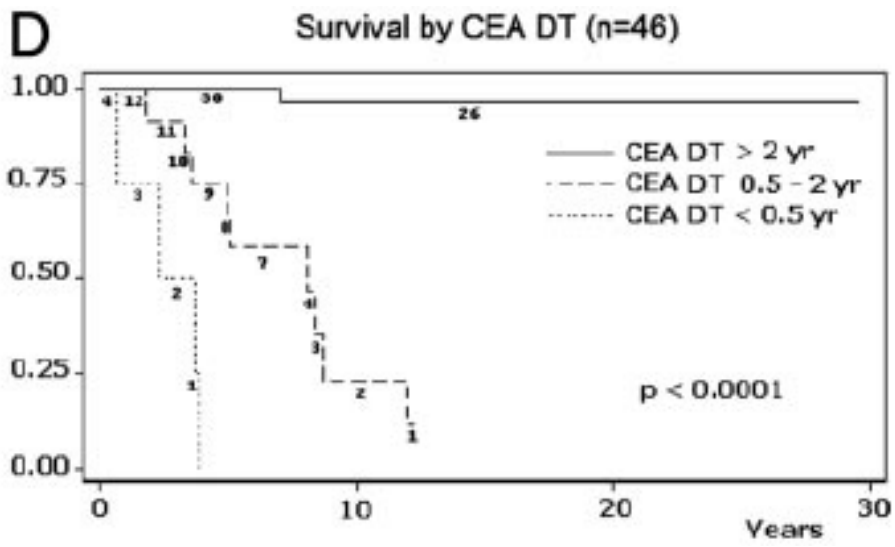
Boostrom. Arch Surg 2009;144:663

Stage IVb: T4b (tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels), Any N, M0.

Stage IVc: Any T, Any N, M1: some patients with long survival: 10 years survival ranges from 21 to 40% (Modigliani 98, Raue 93, Roman 06)

Ct & CEA doubling time < 6 months: prognostic factor





Barbet et al. JCEM 2005

Correlation between CEA & Ct doubling time and RECIST progression

55 consecutive MTC patients
Correlation of Ct & CEA doubling time to RECIST progression

RECIST	Stable	Progression	p
Basal Calcitonin (Ct) (pg/mL)	1510	1564	NS
Basal CEA (ng/mL)	37	109	
Ct Doubling time (months)	**48**	**12**	**<0.0001**
CEA Doubling time (months)	**58**	**12**	

AL Giraudet et al. EJE 2007

Medullary Thyroid Cancer subclassification

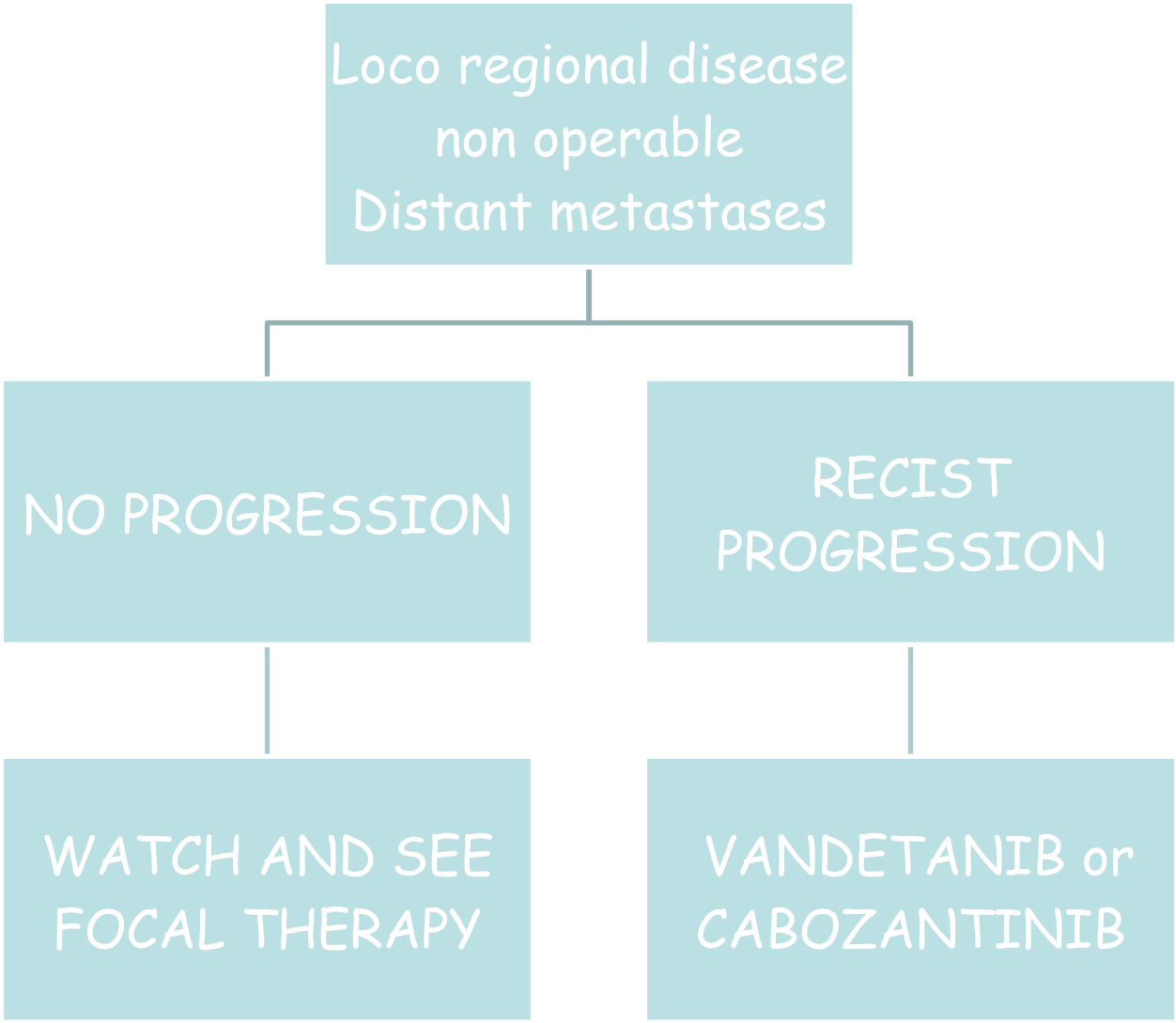
- ✓ Hereditary ?
- ✓ Symptomatic?
- ✓ Distant Metastases or unresectable locoregional disease ?
- ✓ Progressive disease,

→ decide whether treatment is needed

Systemic treatment in patients with metastatic or unresectable locoregional disease, with documented progression, and if not accessible to focal treatment.

Symptoms (diarrhea, pain) are frequently present.

MTC systemic therapy



Clinical case

✓Male, 51 years at diagnosis

Thyroid nodule < 5 mm. Ct level of 1119 pg/mL
RET testing < 0
Metanephrines to exclude a pheochromocytoma

January 26th, 2006: Total Thyroidectomy + neck lymph node dissection: central bilateral + lateral (II-III-IV) bilateral

→ **pT1N1b (2N1, 0R+/29)** (3cm level VI, 3mm level II)

✓**Post-operative assessment :**

Ct level: April 2006 : <10 pg/mL
March 2007: 22 pg/mL
April 2008: 74 pg/mL

CEA levels : <10 ng/mL

Doubling time of Ct : ≅ 6 months

Imaging in 12/2008 (Ct: 235pg/mL) included :
- Neck US
- Neck, Chest, abdominopelvic CT scan
- Liver MRI
- Spine MRI

} **NORMAL**

- **September 2009:**
  - Ct level : 379 pg/mL
  - CEA level : 1 ng/mL

  Imaging work up : Normal

- **Mai 2010**
  - Ct: 745pg/mL
  - Neck recurrence (US): 7 mm lymph node
  - Liver metastases (US): 7 mm & 11 mm

- **What to do:**
  - Follow-up?
  - Systemic treatment ?
  - Local treatments ?

September 2009:

Ct level : 379 pg/mL
CEA level : 1 ng/mL
Imaging work up : Normal

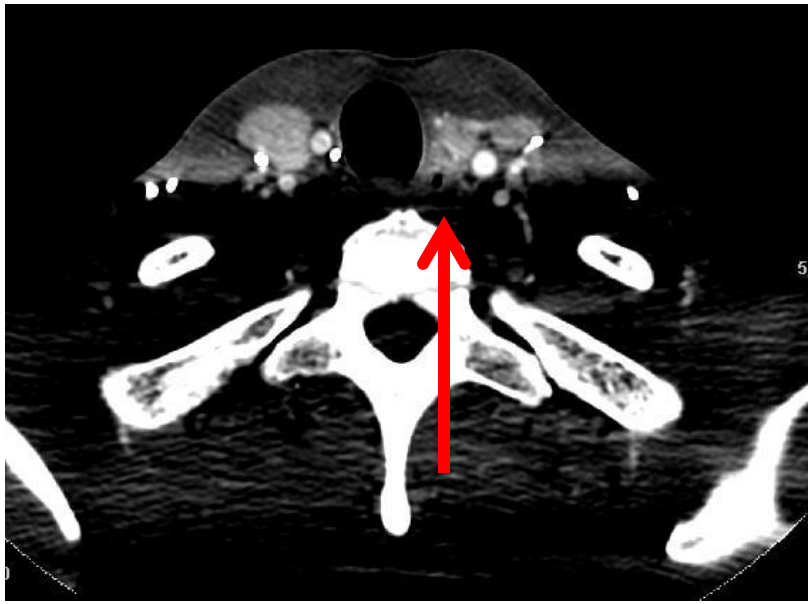
Mai 2010

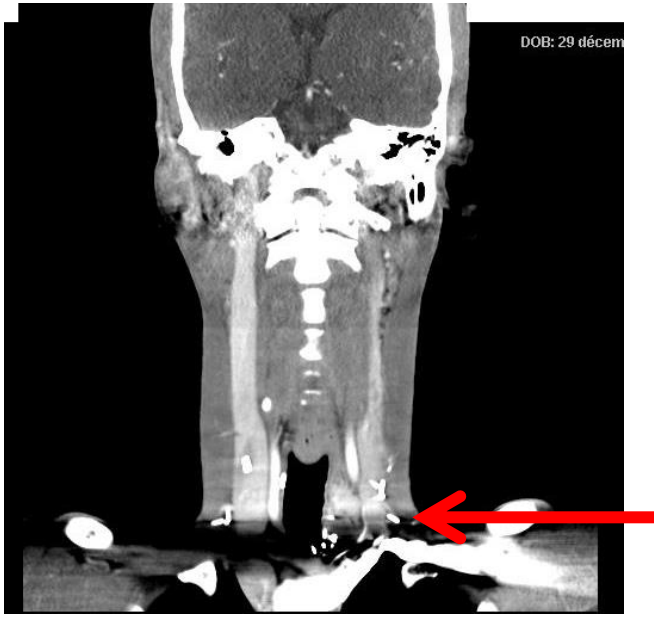
Ct: 745 pg/mL
Neck recurrence (US) : 7 mm lymph node
Liver metastases (US): 7 mm & 11 mm

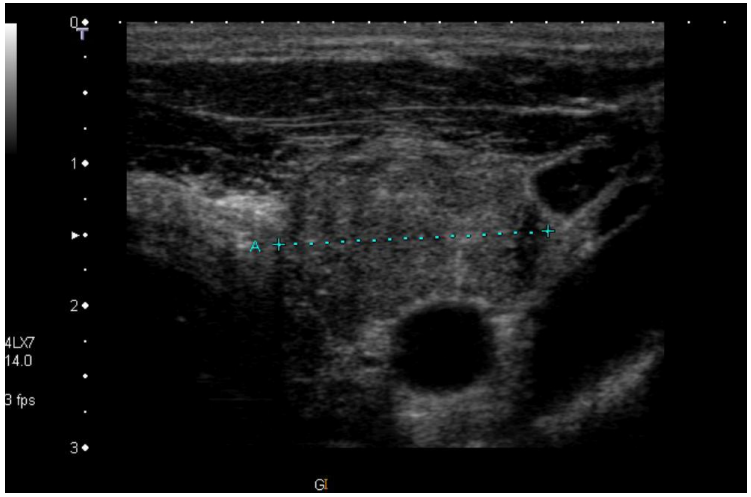
December 2010:

Ct level : 1931 pg/mL
CEA level : 1 ng/mL

Left Neck recurrence: May to December 2010

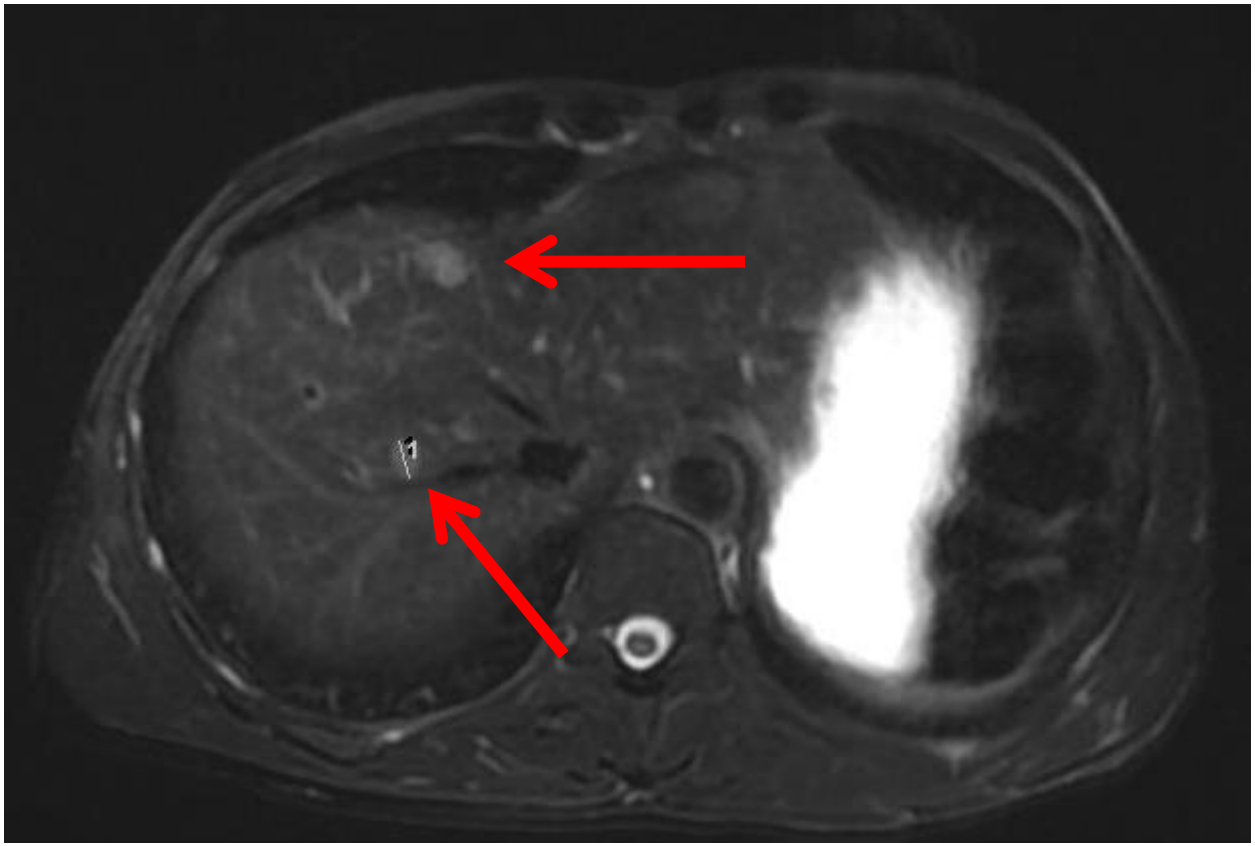






20 mm vs 7 mm

Liver metastases



Bone is normal

15 mm vs 11 mm

- ✓**Distant metastases**
- ✓**Targets lesions**
- ✓**Progressive within 6 months**
- ✓**Low volume target**
- ✓**No symptoms**

- ✓**What to do:**
  - Follow-up?
  - Systemic treatment ?
  - Focal treatments ?

✓**Patient refused any systemic treatment**

Neck surgery : January 17th, 2011

Central
Left recurrent nerve voluntary sacrificed
R1 surgery

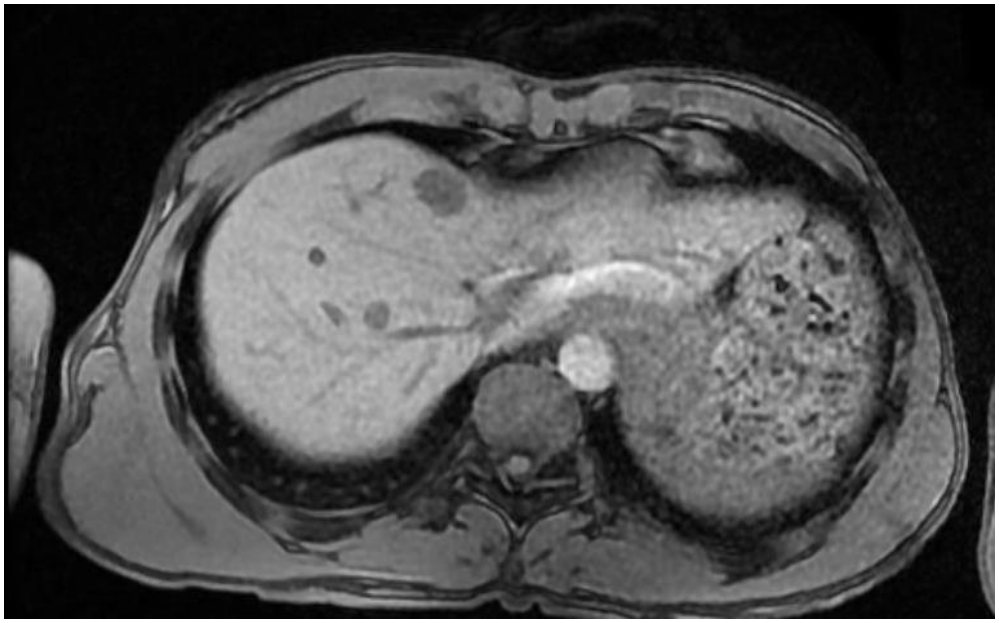
Pathology : 5cm N1

+ **Neck external radiation therapy**

Rapid progression
R1 surgery

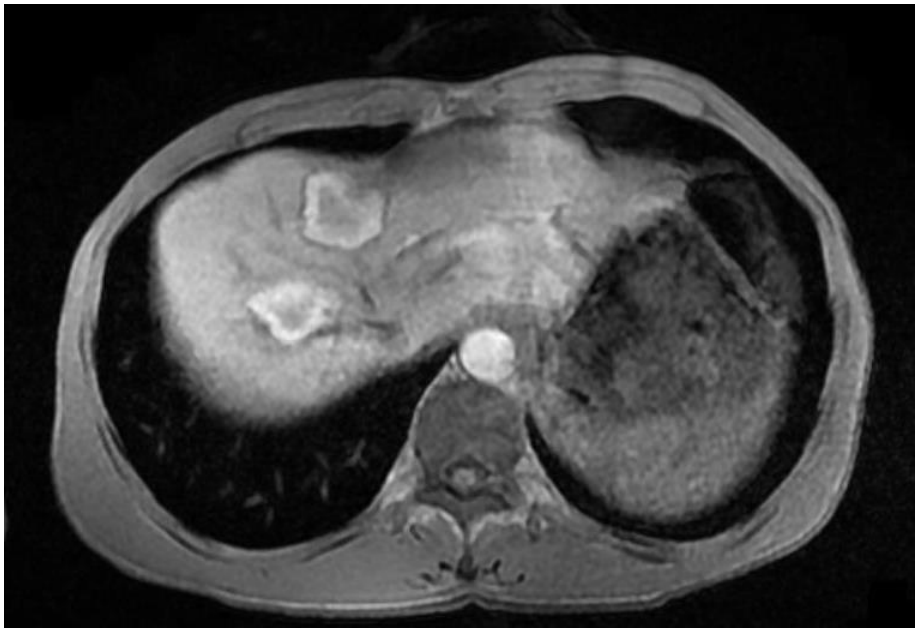
+ **Liver Radiofrequency ablation: June 9th, 2011**

RFA in June 2011



Before RFA

Ct : 2580 pg/mL



After RFA

Ct : 1788 pg/mL

November 2011

Ct level : 2025 pg/mL vs 1788 (August 2011)
No target lesion on CT scan, neck US or liver MRI

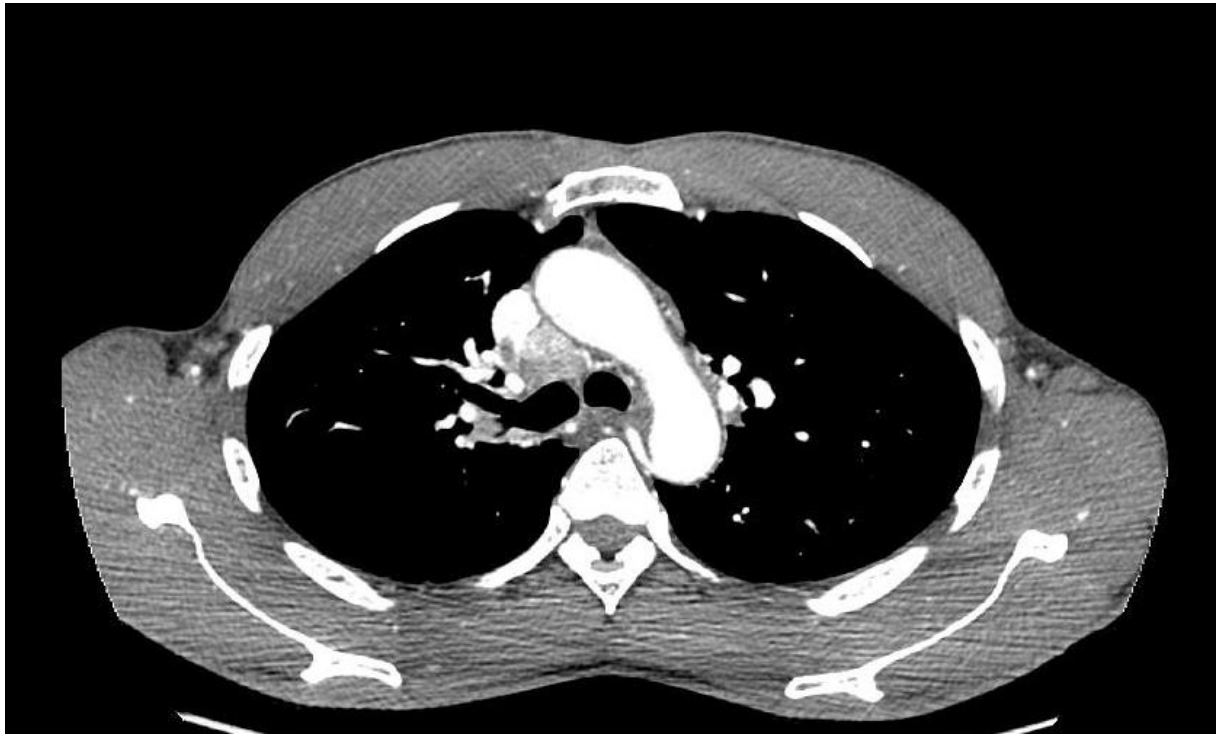
November 2012

Ct level : 1968 pg/mL
No target lesion on CT scan, neck US
liver recurrence in one of the lesions treated with RFA

→ Second session of liver RFA

April 2013

Ct level : 4783 pg/mL
→ mediastinal lymph nodes + 5 mm liver recurrence

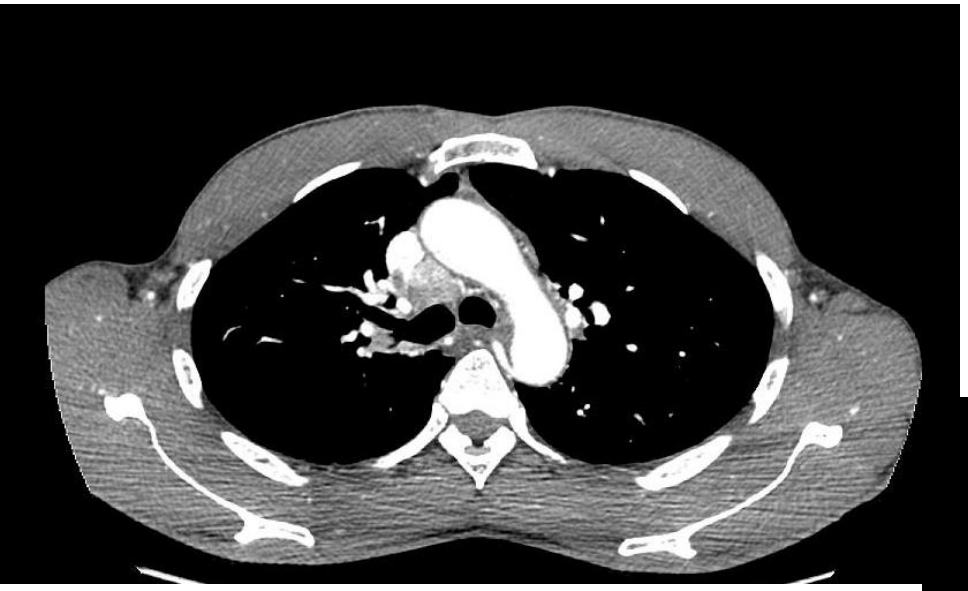


Distant metastases
Targets lesions
Progressive but low volume lesions
No symptoms

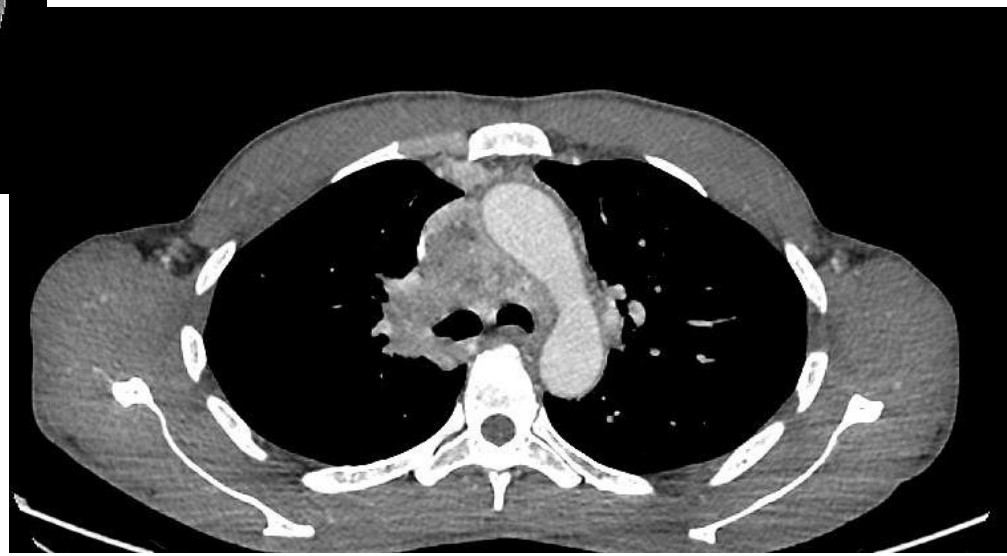
What to do:

Follow-up?
Systemic treatment ?
Local treatments ?

April 2013



February 2014



Systemic treatment to start !

Which treatment ?

TKI, Chemo?

Which TKI ?

	FDA	EMA
Vandetanib	07 april 2011 treatment of **symptomatic or progressive** MTC in patients with **unresectable locally advanced or metastatic disease**	21 February 2012 treatment of **aggressive and symptomatic** MTC in patients with **unresectable locally advanced or metastatic disease.**
Cabozantinib	29 November 2012 treatment of **progressive, unresectable, locally advanced, or metastatic** MTC.	25 mars 2014 treatment of adult patients with **progressive, unresectable locally advanced or metastatic** MTC

Thanks to …

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Department of Surgery

Dr Ellen Benhamou
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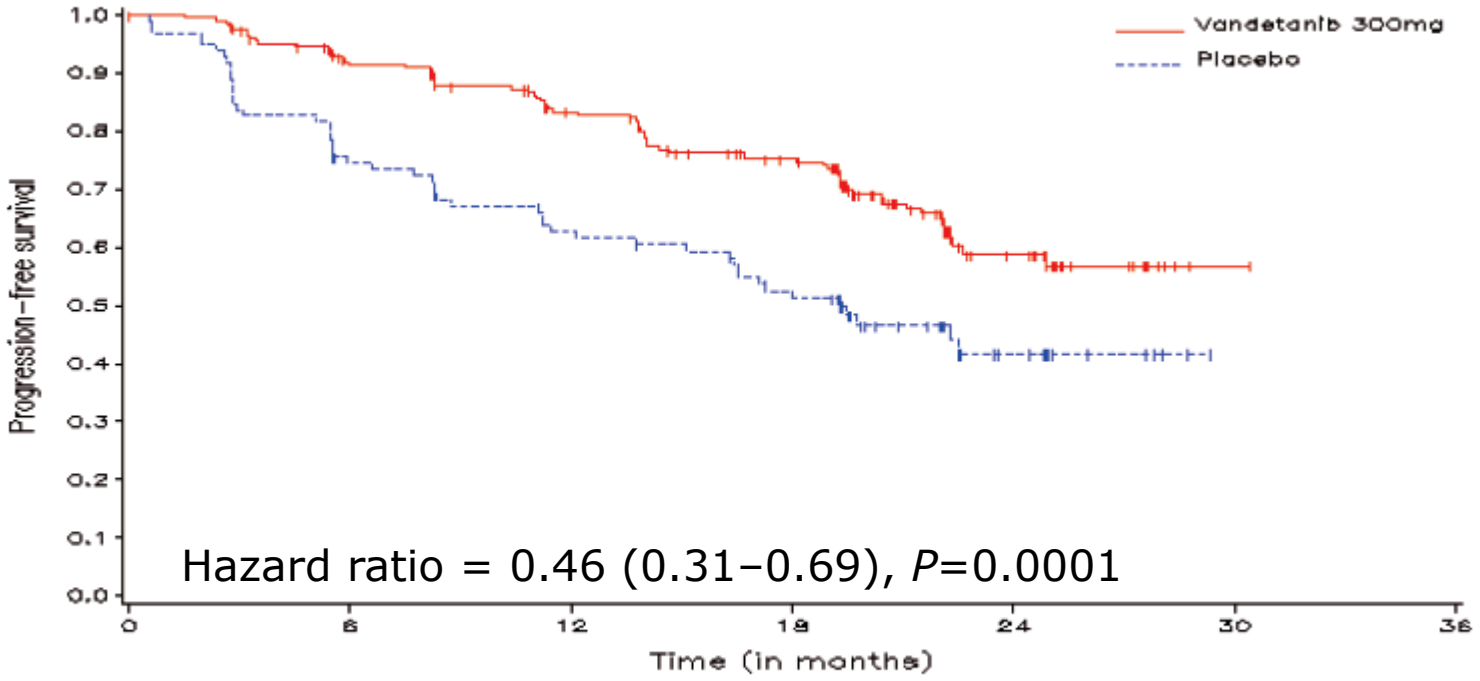
ITK : Vandetanib et Cabozantinib

Compound	IC_{50} (nm)						
	VEGFR1	**VEGFR2**	VEGFR3	**RET**	RET/PTC3	RAF	**Autres cibles**
Axitinib	1.2	**0.25**	0.29	-	-	-	-
Vandetanib	1600	**40**	110	100	50-100	-	EGFR
Motesanib diphosphate	2	**3**	6	59	-	-	PDGF-R, C-KIT
Sunitinib	2	**9**	17	41	224	-	-
Sorafenib	-	**90**	20	49	50	6	-
Lenvatinib (E7080)	22	**4**	5	35			PDGF-R, FGFR-1
Cabozantinib (XL184)	-	**0.035**	14	4	-	-	C-MET, C-KIT
Pazopanib	10	**30**	47				PDGF-R, C-KIT

CMT: Phase III

	Vandetanib ZETA	Cabozantinib EXAM
nomber	331	330
OMS 0	64%	54%
Hereditary	10%	6%
RET positive RET unkown RET 918	38% 41% -	45% 39% 35%
Distant Metastases	94%	95%
Bone Metastases	35%	35%
Previous treatment Previous TKI treatment	40% Inconnue	38% 20%
Progression	no	Yes (14 months)
Placebo vs ITK	≅	≅

Vandetanib improves PFS

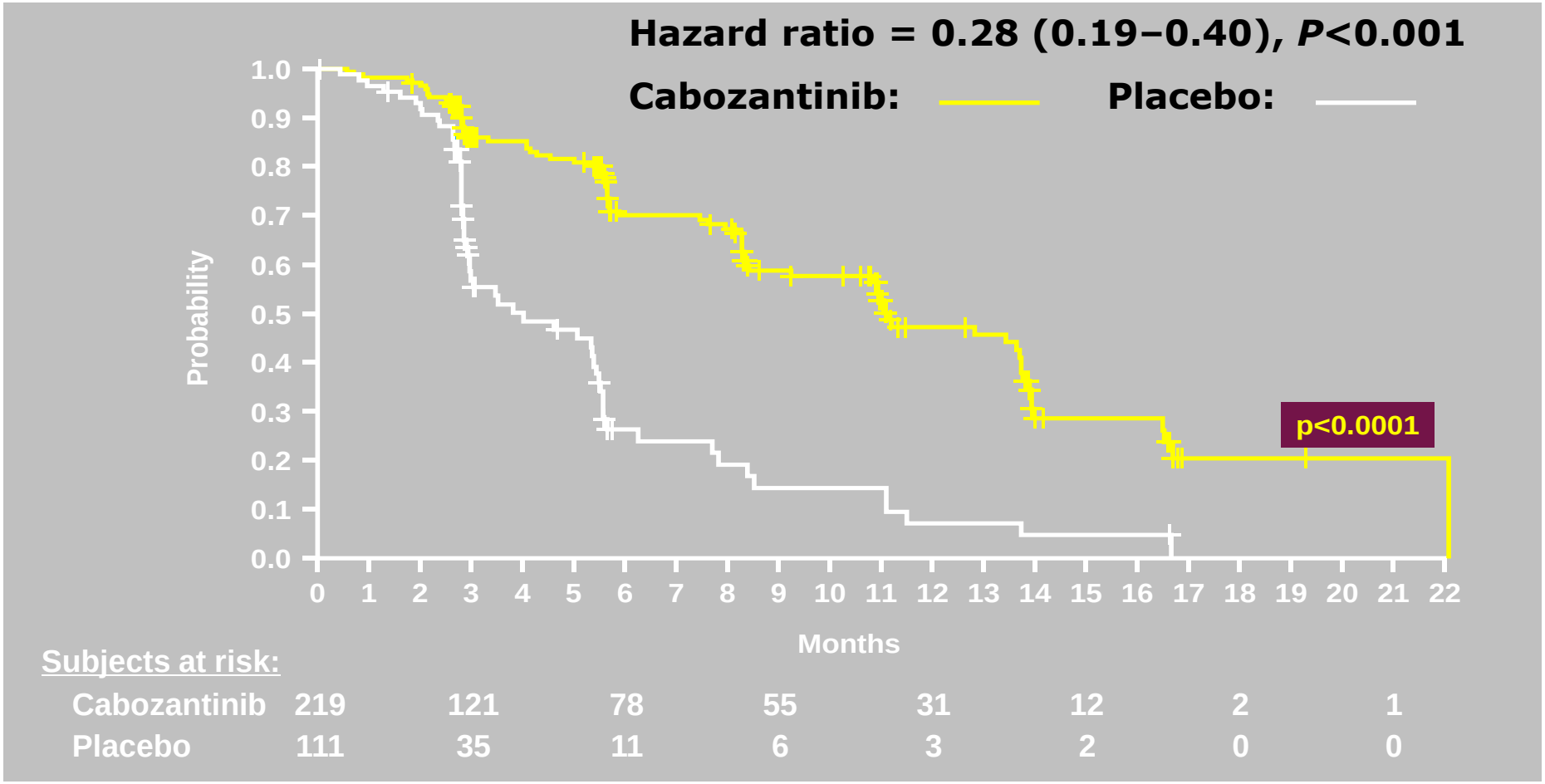


n at months	0	6	12	18	24	30	36
Vandetanib 300mg	231	196	169	140	40	1	0
Placebo	100	71	57	45	13	0	0

Placebo: PFS median: 19.3 mo
Vandetanib: PFS median >30.5 mo, (not reached)

Wells S et al JCO 2011

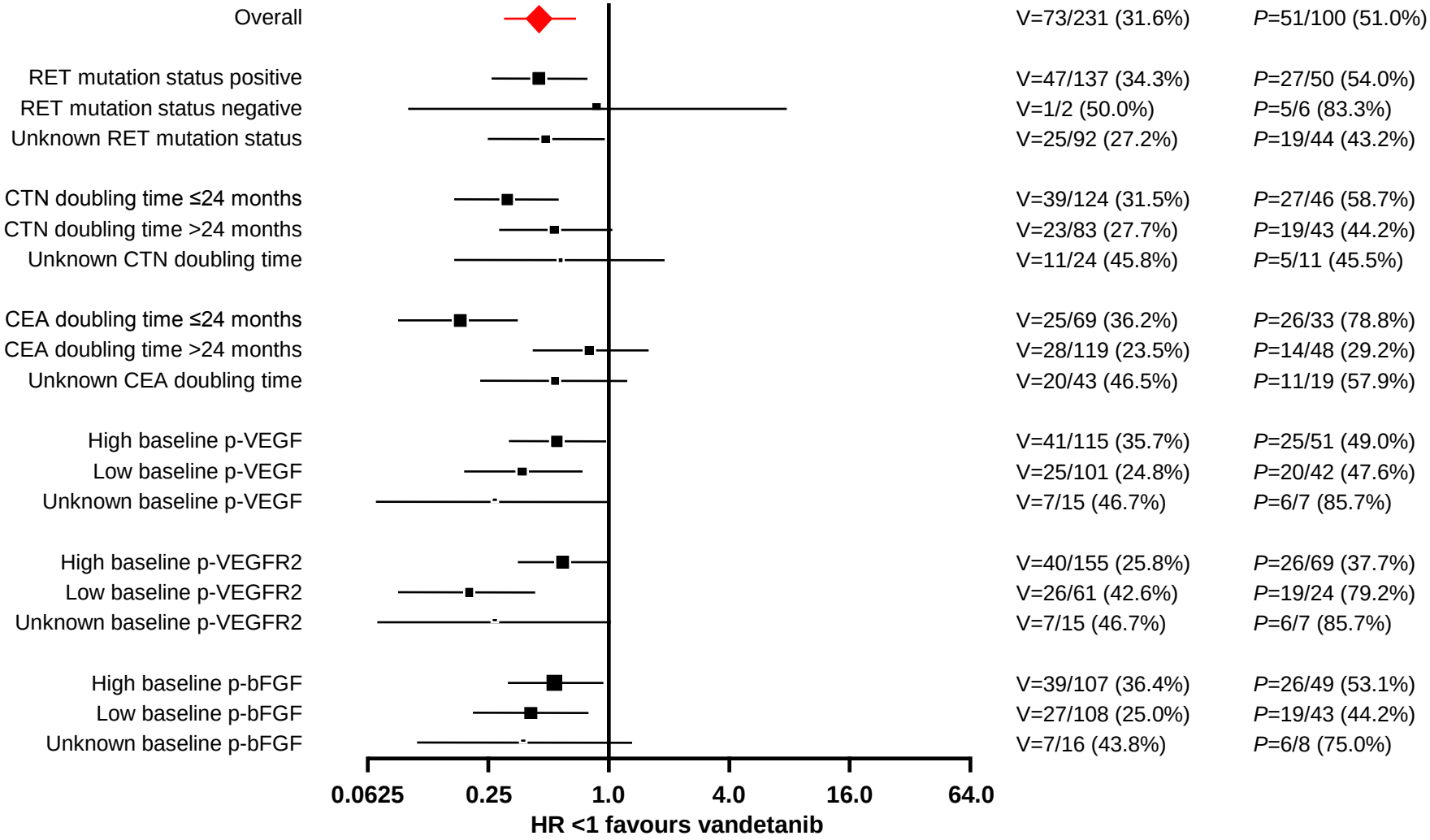
Cabozantinib improves PFS



Elisei et al. 2013

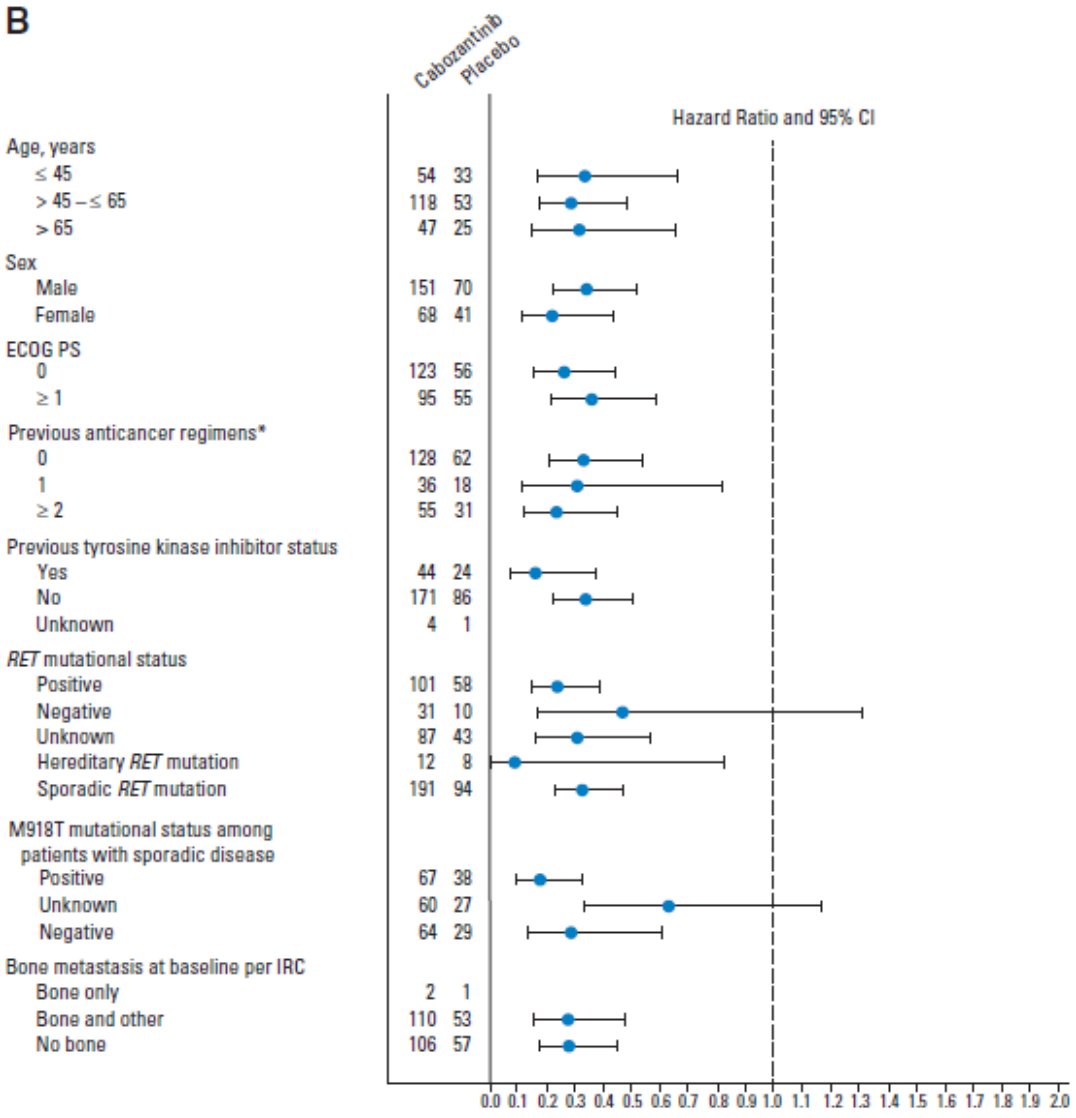
Placebo: PFS median: 4 months
Cabozantinib: PFS median : 11.2 months

Vandetanib benefited all predefined subgroups of patients



The analyses were performed using a log-rank test with treatment as the only factor

Cabozantinib benefits in all predefined subgroups of patients



Elisei et al. 2013

Vandetanib according to RET M918T Mutation

	RET Mutation RET Present (n=187)*	No M918T muttaion and no other RET mutation identified (n=79)
Efficacy Endpoint SSP HR (95%) confidence interval)	0.45 (0.26, 0.78)	0.57 (0.29, 1.13)
PFS median estimation (months) (vandetanib vs placebo)	29 vs 18	28 vs 18
Objective response rate (vandetanib arm)	52%	35%
Reponse length (months)	22	18

* Germinal RET mutation + sporadic RET mutation, 92% being M918T

Cabozantinib efficacy according to RET mutation

	PFS benefit	ORR	Length of PFS (vs placebo)
RET + (169)	yes	0.23	60 weeks (vs. 20) (61 if RET M918T pl17)
RET- (46)	no		25 weeks (vs.23)
Unknown (115)	yes	0.3	45 weeks (vs.13)
Ras and no RET mutation	yes	0.15	45 weeks (vs.l8)

Sherman et al ASCO 2013