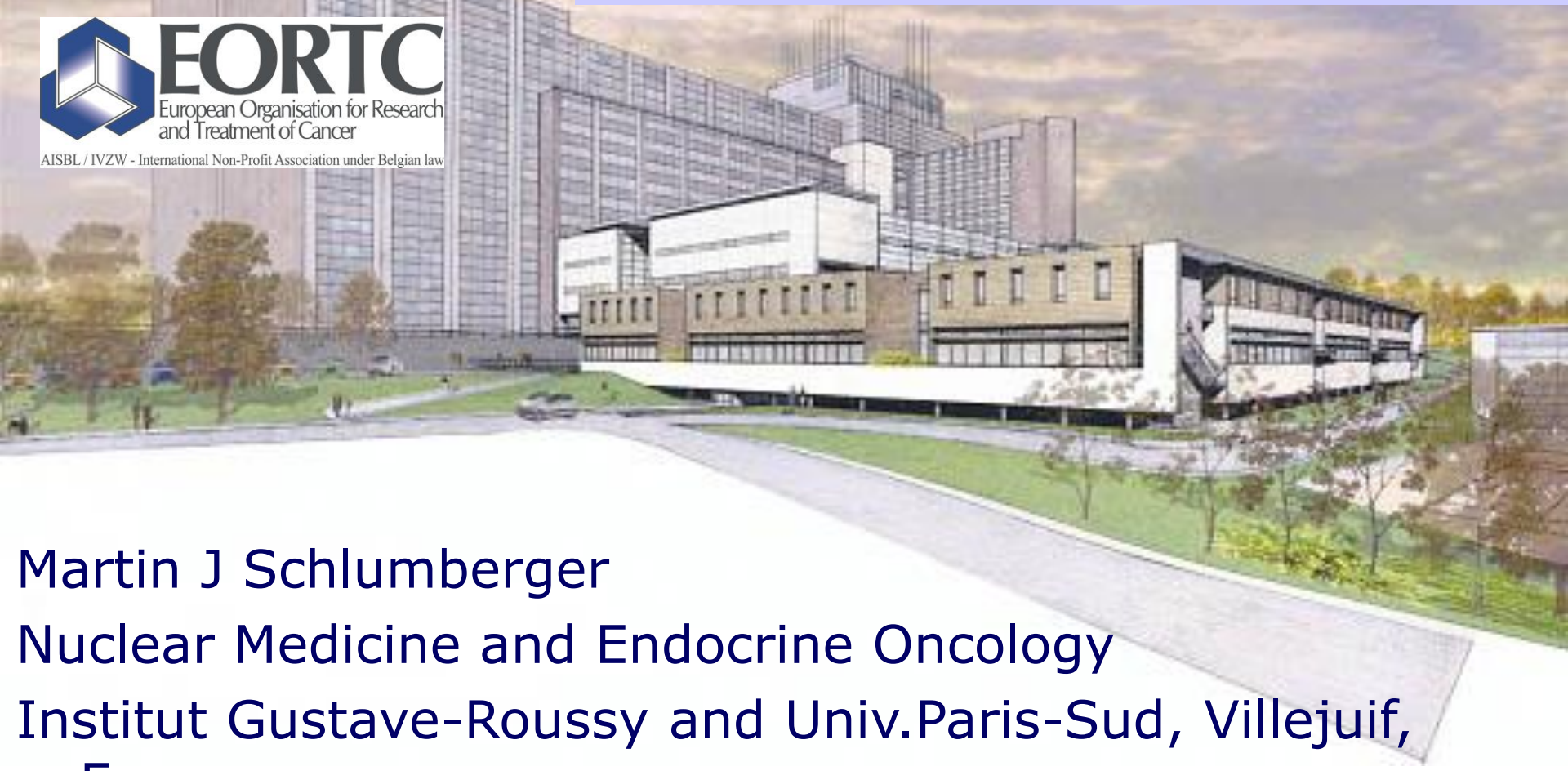
Treatment for Metastatic Medullary Thyroid Cancer



Martin J Schlumberger

Nuclear Medicine and Endocrine Oncology

Institut Gustave-Roussy and Univ.Paris-Sud, Villejuif, France

Relevant Financial Relationships

Company Name: Amgen, Astra-Zeneca, Bayer, BI, Eisai, Exelixis, Genzyme, GSK, Roche.

Nature of Relationship: research grants

Objectives

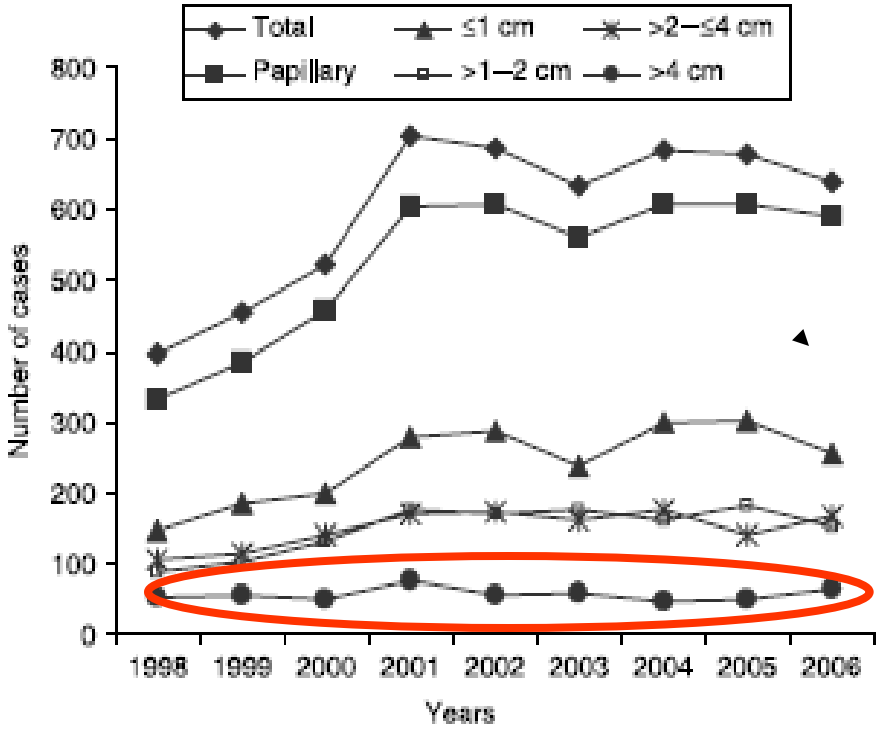
Medullary thyroid cancer: definition and role of RET

Treatment of metastatic disease

Use of TKI:

- benefits
- adverse events and resistance

Thyroid cancer: incidence and extent of disease



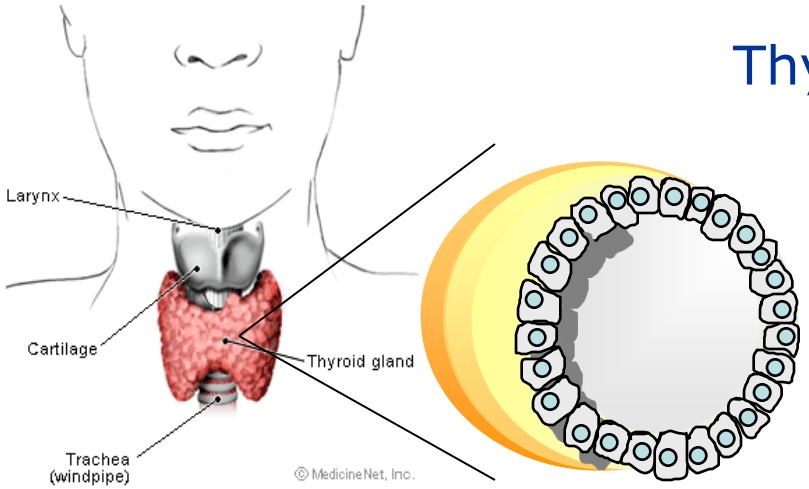
Increasing incidence of cancers (3%-6%/year for 30 years).

Attributed mainly to improved screening

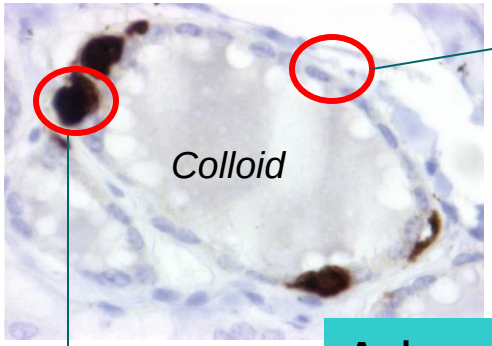
Cancer is present in only 5% of all thyroid tumors: diagnosis is first based on FNAC

Sassolas et al. Eur J Endocrinol 2009;160:71

Thyroid tumors: classification



Thyroid follicle

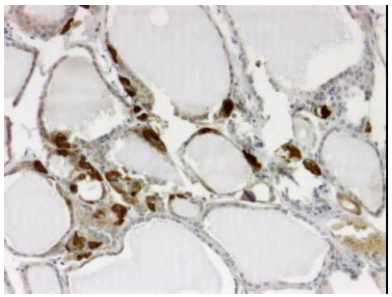


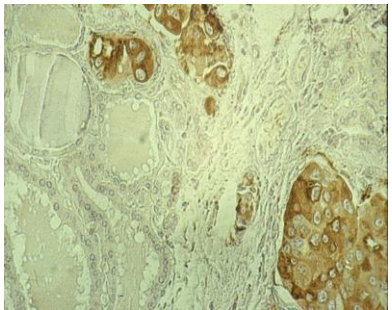
Thyrocyte

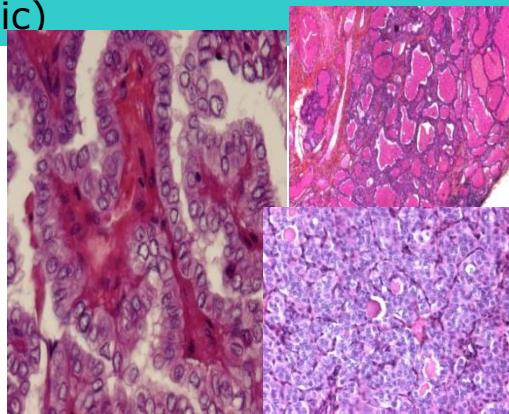
C Cell

Medullary thyroid cancer
(<5% of all cancers)

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







Epidemiology of medullary thyroid cancer

- Incidence
  - <5% of all thyroid cancers (1500-2000 cases/year in Europe)
  - Distant metastases requiring systemic treatment: 1 / 1.5 million population (~50 cases/year in France)
- Genetics
  - MTC may be hereditary:
    - Germline RET mutation. Autosomic dominant trait
    - Identification of gene carriers: prophylactic treatment
  - MTC is sporadic in >2/3 of cases:
    - Discovery at a clinical stage
    - Somatic RET mutation in >40% of tumors

Oncogenic Addiction

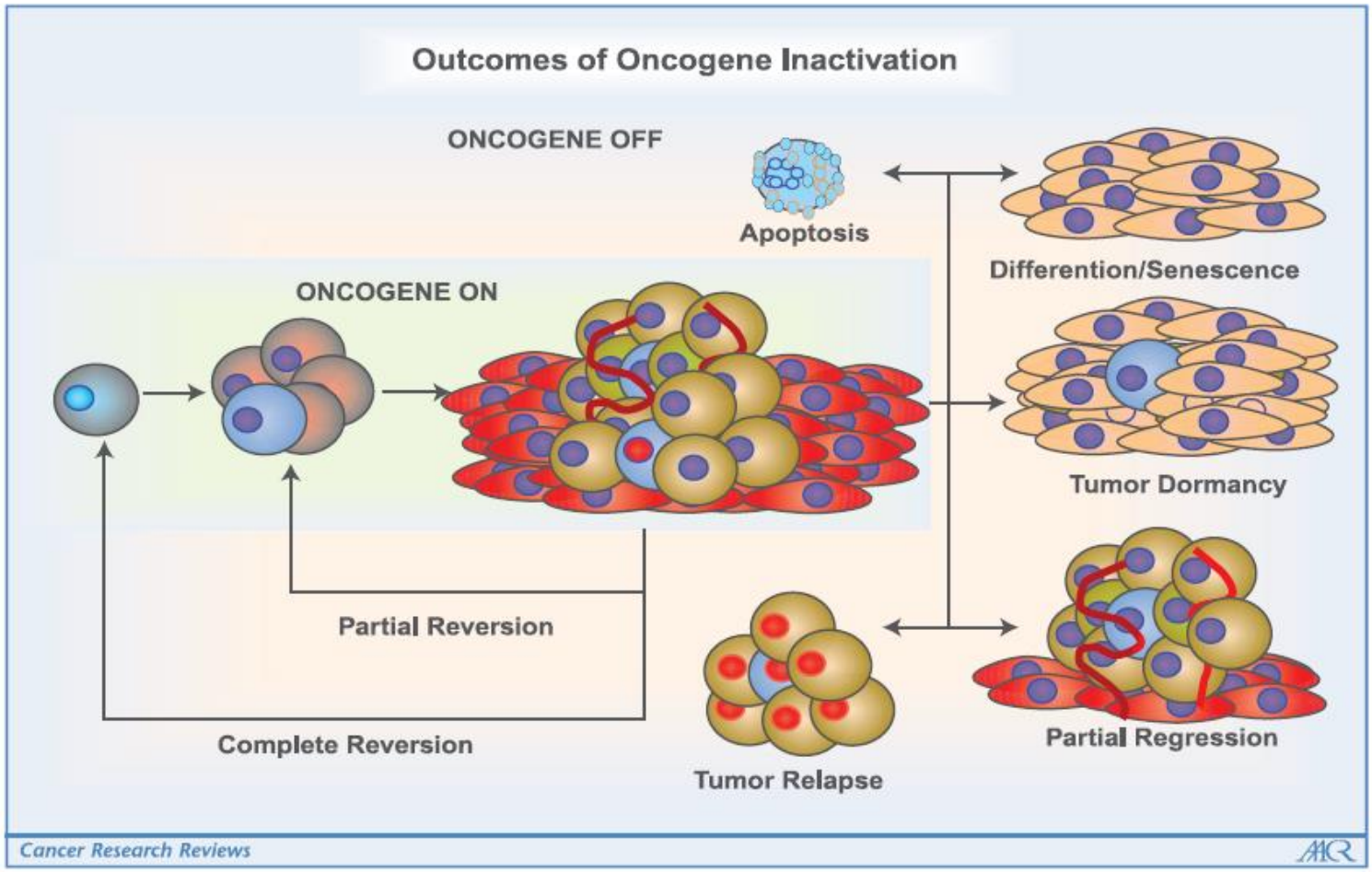
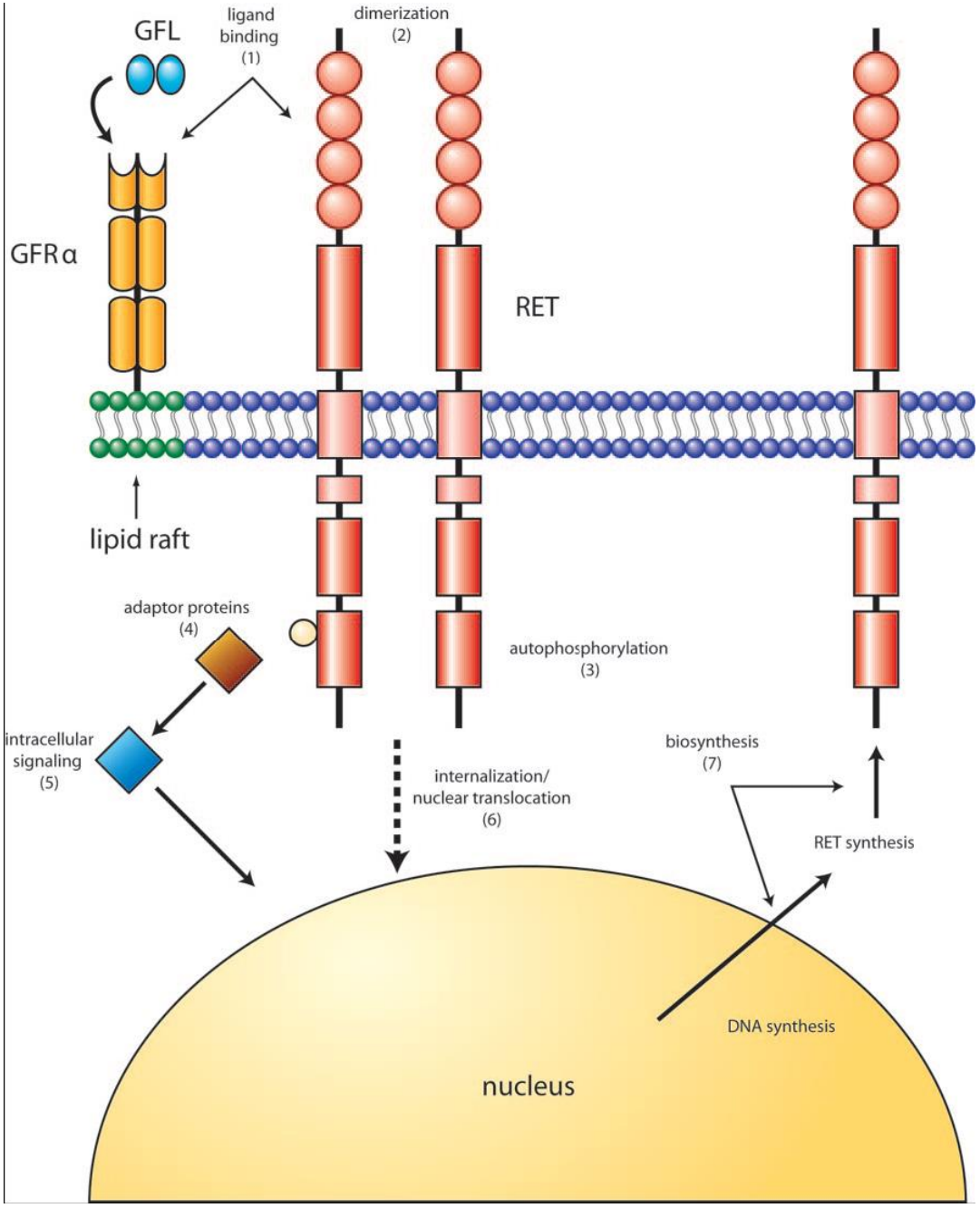
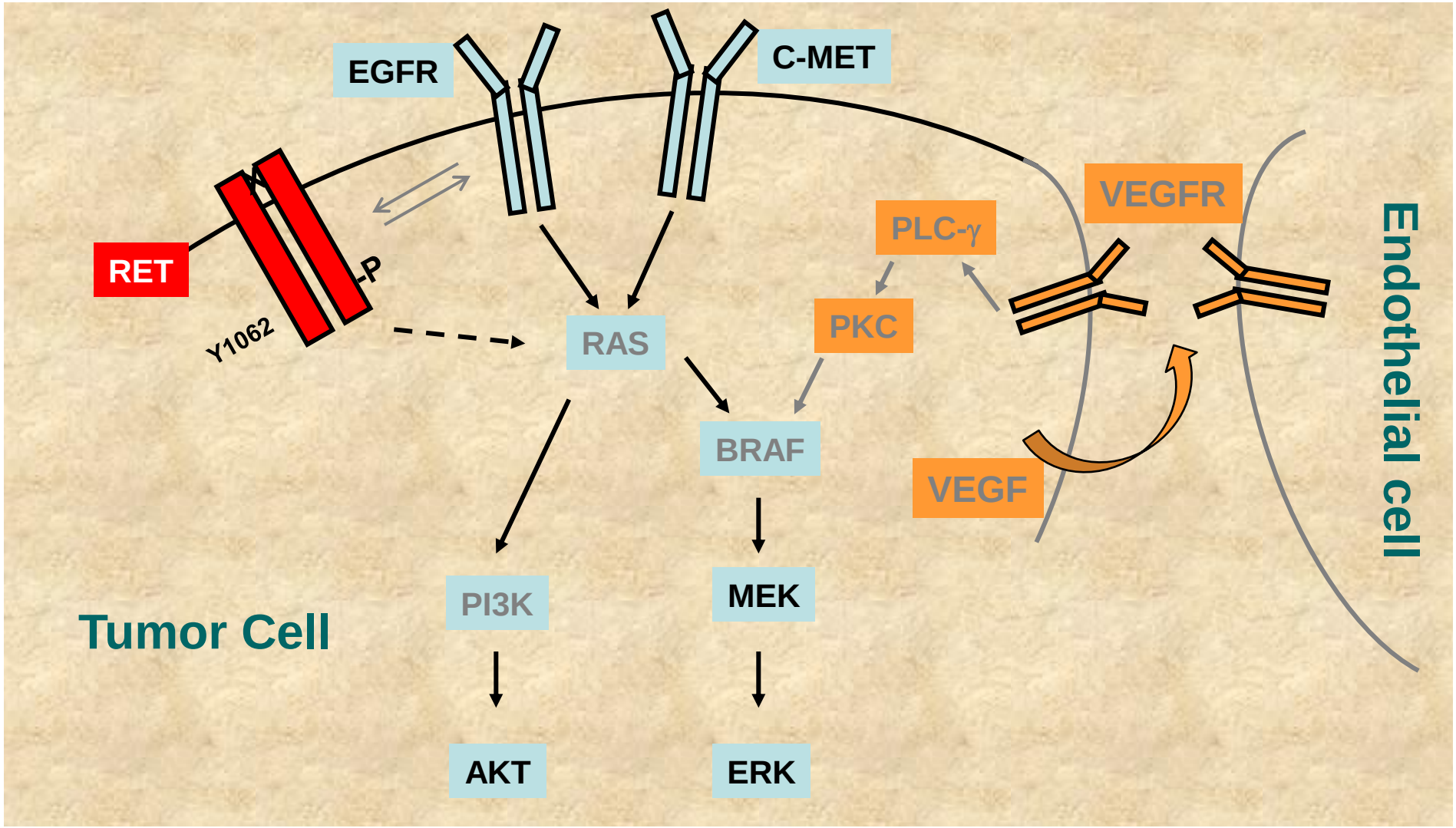


Figure 1. Many possible outcomes to oncogene inactivation: no effect, complete, or partial tumor reversion. Tumor death, dormancy, differentiation, or relapse.

Ret (1993): transmembrane receptor with tyrosine kinase activity.
Ligand: GDNF
Co-receptor: GFR alpha
Ligand binding induces its dimerisation and TK activation
This in turn activates several transduction pathways including the MAP kinase pathway

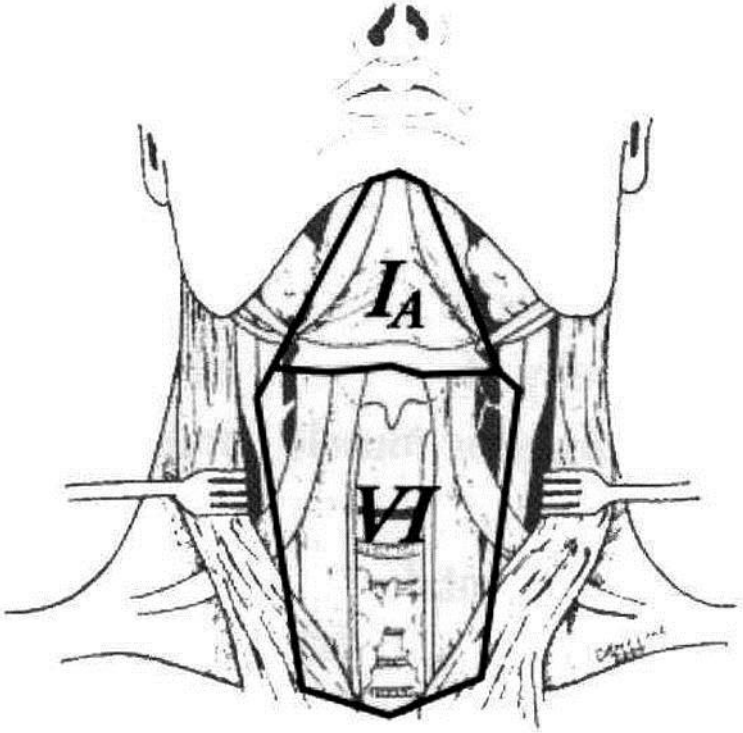


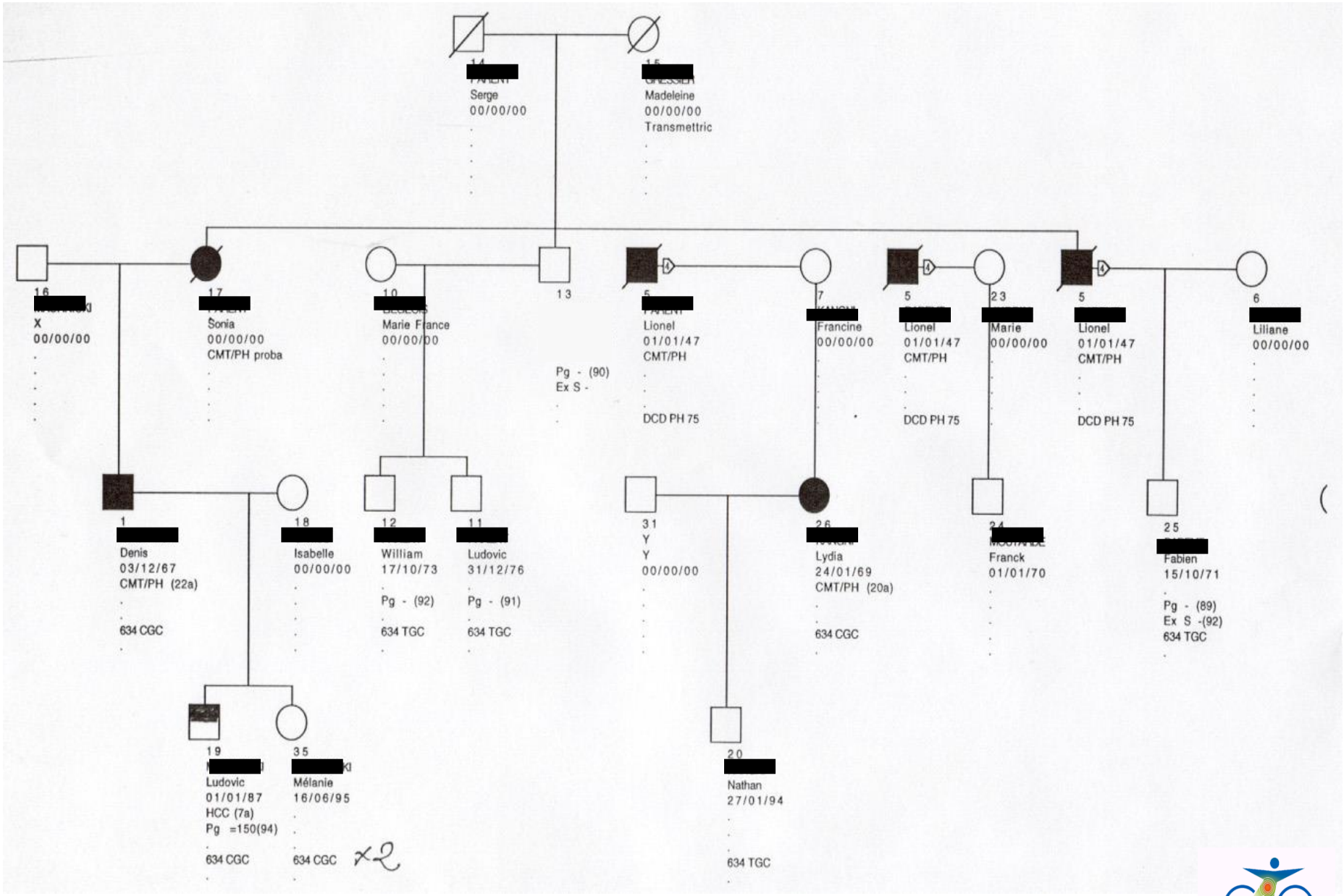
Signal transduction pathways in thyroid cancers



MTC: initial surgery

- Surgery consists for all MTCs in:
  - Total thyroidectomy
  - Bilateral dissection of lateral and central compartments.
- Success is mainly dependent upon the adequacy of the initial operation (complete protocol/skilled hands).




14
Serge
00/00/00
15
Madeleine
00/00/00
Transmettric
16
X
00/00/00
17
Sonia
00/00/00
CMT/PH proba
10
Marie France
00/00/00
13
Pg - (90)
Ex S -
5
Lionel
01/01/47
CMT/PH
DCD PH 75
7
Francine
00/00/00
5
Lionel
01/01/47
CMT/PH
DCD PH 75
23
Marie
00/00/00
5
Lionel
01/01/47
CMT/PH
DCD PH 75
6
Liliane
00/00/00
1
Denis
03/12/67
CMT/PH (22a)
634 CGC
18
Isabelle
00/00/00
12
William
17/10/73
Pg - (92)
634 TGC
11
Ludovic
31/12/76
Pg - (91)
634 TGC
31
Y
Y
00/00/00
26
Lydia
24/01/69
CMT/PH (20a)
634 CGC
24
Franck
01/01/70
25
Fabien
15/10/71
Pg - (89)
Ex S -(92)
634 TGC
19
Ludovic
01/01/87
HCC (7a)
Pg =150(94)
634 CGC
35
Mélanie
16/06/95
634 CGC
x2
20
Nathan
27/01/94
634 TGC

RET 634 CGC

MTC management based on stratified genetic testing

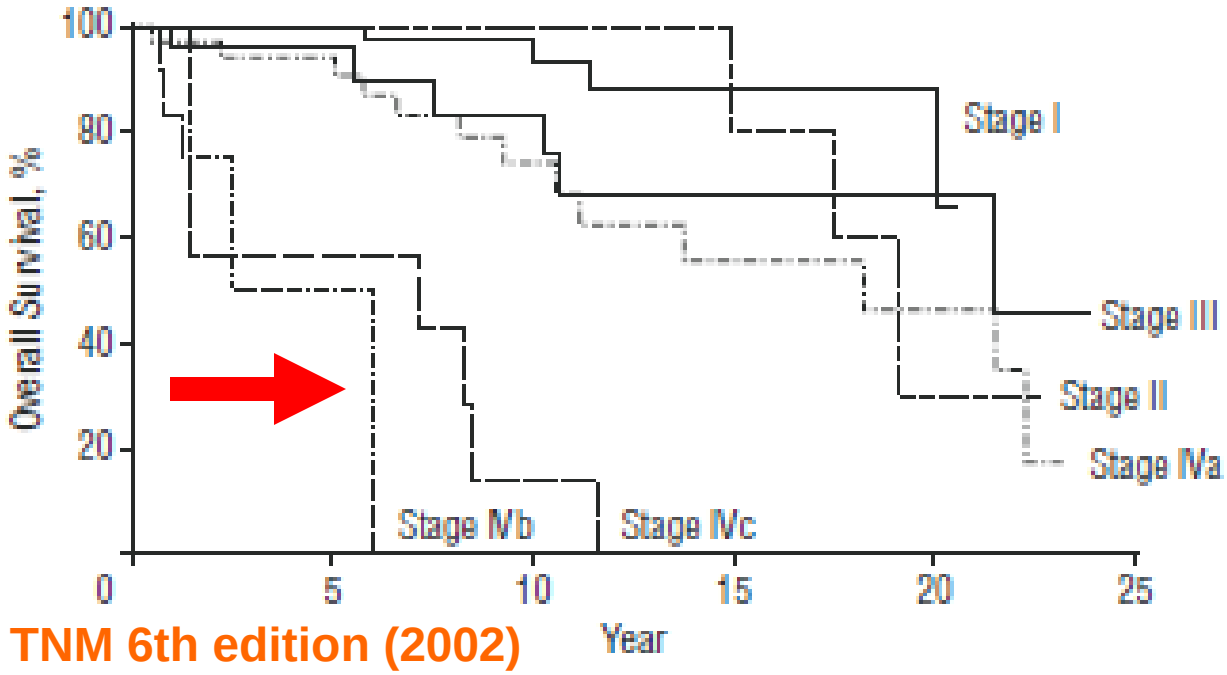
- Genetic testing permits prophylactic surgery with cure rates >95%

- MEN 2B.
  - Thyroidectomy within the first year of life, preferably within the first month.

- RET codon 634 mutation.
  - Thyroidectomy before the age of 5 years

- RET codon 611, 618, 620 mutation and RET codon 609, 768, 790, 804 or 891 mutation.
  - Thyroidectomy possibly later than 5 years if Ct is normal, neck US is normal, familial history is not aggressive and family preference

Focus on advanced MTC



TNM 6th edition (2002)

Stage IVb: T4b (tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels), Any N, M0.
Stage IVc: Any T, Any N, M1

Boostrom et al. Arch Surg 2009;144(7):663-669

MTC: distant metastases

- At MTC discovery: 2% (Mayo Clinic) - >15% (IGR) of patients
- During the 10 first years of follow-up, DM are detected in ~30-50% of patients with post-operative detectable Ct levels
- Diarrhea: ~30%; flushes: ~15%.
- Often present in several sites
- Often multiple in each site.

Guidelines ATA (2009) and ETA (2012)

MTC: natural history

GP
Endocrinologist
Nuclear Med
Surgeon

Thyroid nodule +/- N1: surgery

MDT

Post-operative calcitonin (Ct)

Detectable: 10-yr survival rate >90%

Undetectable = cure

Endocrinologist
Nuclear Med
Surgeon

Neck persistence / neck recurrence

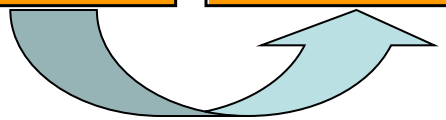
Distant metastases

MDT

Stable disease → follow-up

Progressive disease → treatment

Oncologist



Three problems

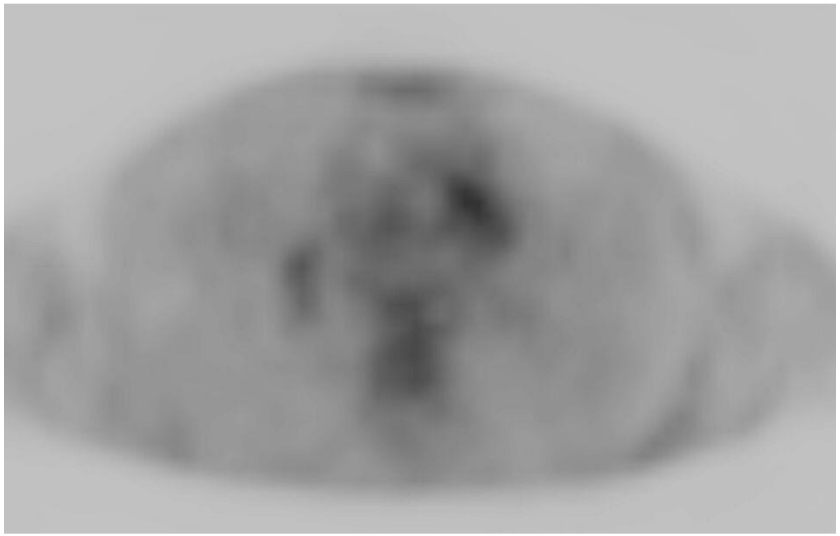
- Recognizing aggressive MTC
- Therapy inertia vs treatment
- Selecting adequate treatment

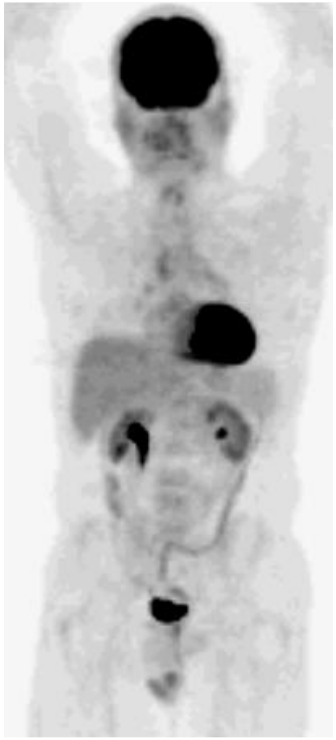
MTC: distant metastases

- Assessment of disease extent – standardized imaging
  - Neck: US-spiral CT scan
  - Mediastinum and lung: spiral 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 or FDOPA-PET scan?
- MTC patients
  - post-operative serum Ct levels ≥150 pg/mL: imaging techniques to evaluate for distant metastases.
  - If negative, should be repeated when Ct level increases by >20-100%.

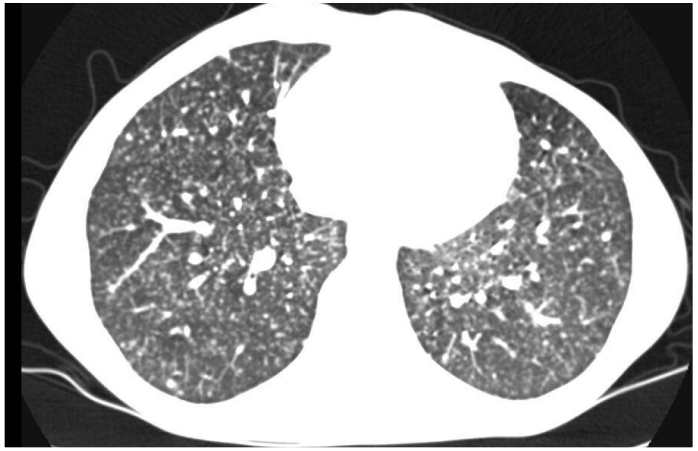
Giraudet AL *et al*. *J Clin Endocrinol Metab* 2007;92:4185–4190

MTC: FDG-PET scan





- Slowly progressive disease: **low FDG uptake in metastases (standardized uptake value <6)**
- Low diagnostic sensitivity/not appropriate for assessing progression or tumor response

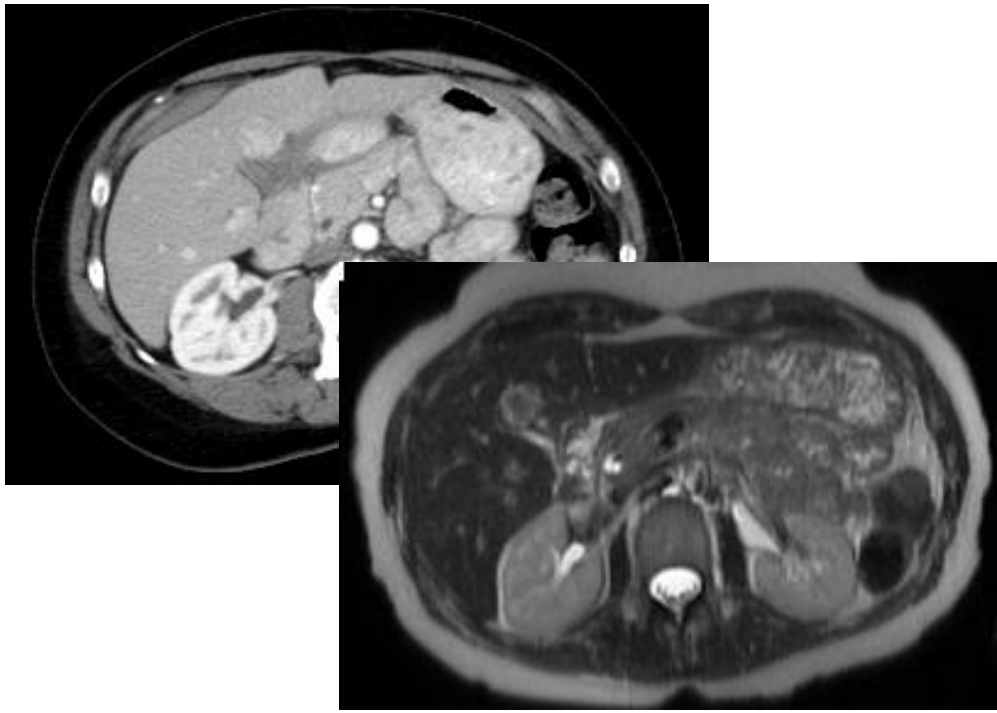


MTC: FDG-PET scan

- Slowly progressive disease: **low FDG uptake in metastases (standardized uptake value <6)**
- Low diagnostic sensitivity/not appropriate for assessing progression or tumor response
- Exceptions: MTC patients with rapidly progressive disease
- Role of F-DOPA: expensive/does it improve sensitivity of the complete imaging

MTC: liver metastases

- Liver metastases may be difficult to visualize
- US: angiomatous appearance
- MRI scan (T1, T2) with arterial phase > CT scan with arterial and venous phases
- MRI is more reliable than CT scan for assessment during treatment with antiangiogenic agents



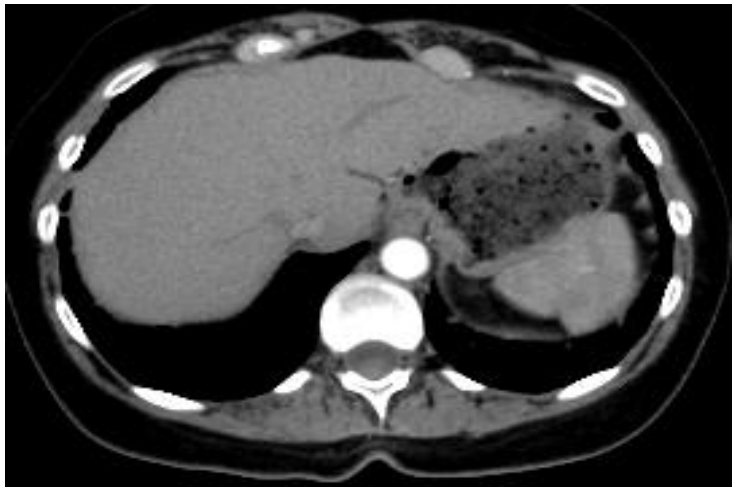
25 MTC patients with liver metastases; miliary in 18 patients

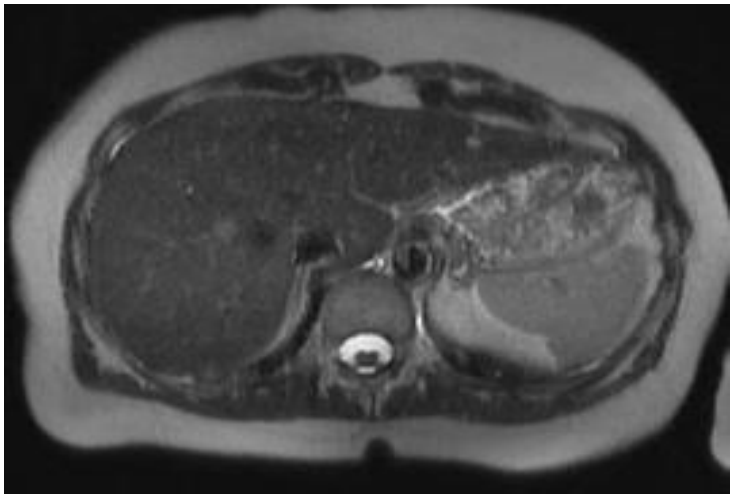
	US	CT	MRI	PET
Patients	18	21	**25**	12
Lesions	164	178	**233**	52

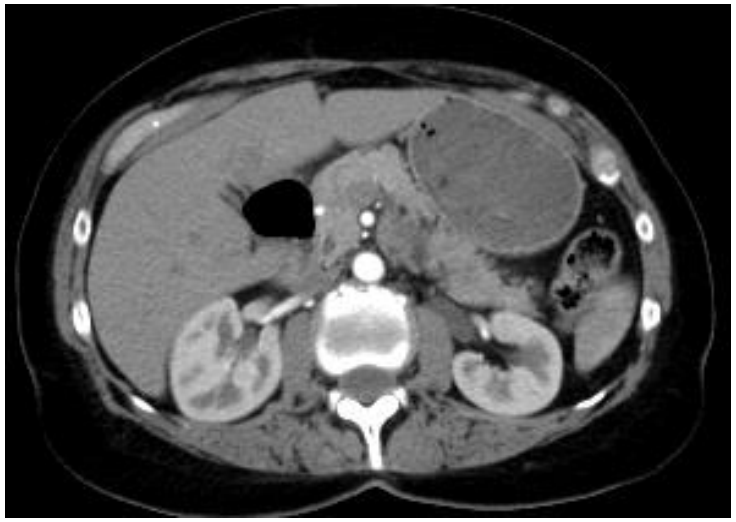
Giraudet AL *et al*. *J Clin Endocrinol Metab* 2007;92:4185–4190

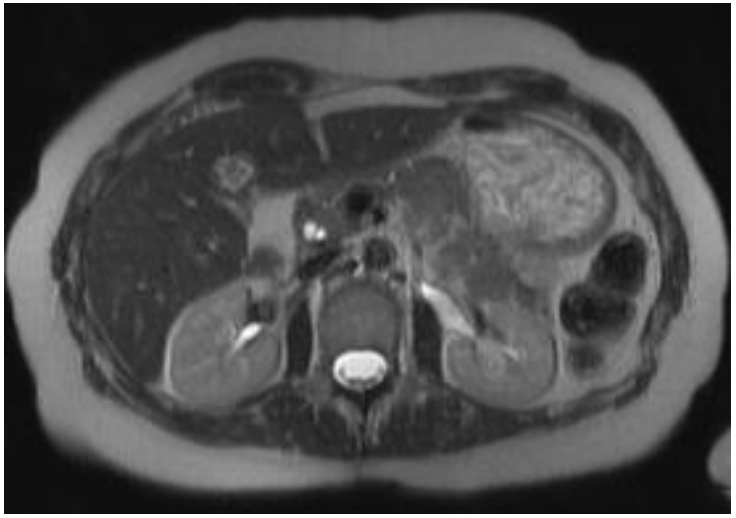
Liver metastases: vandetanib treatment

- During antiangiogenic treatment, liver metastases may not be visible on CT but still be visible on MRI









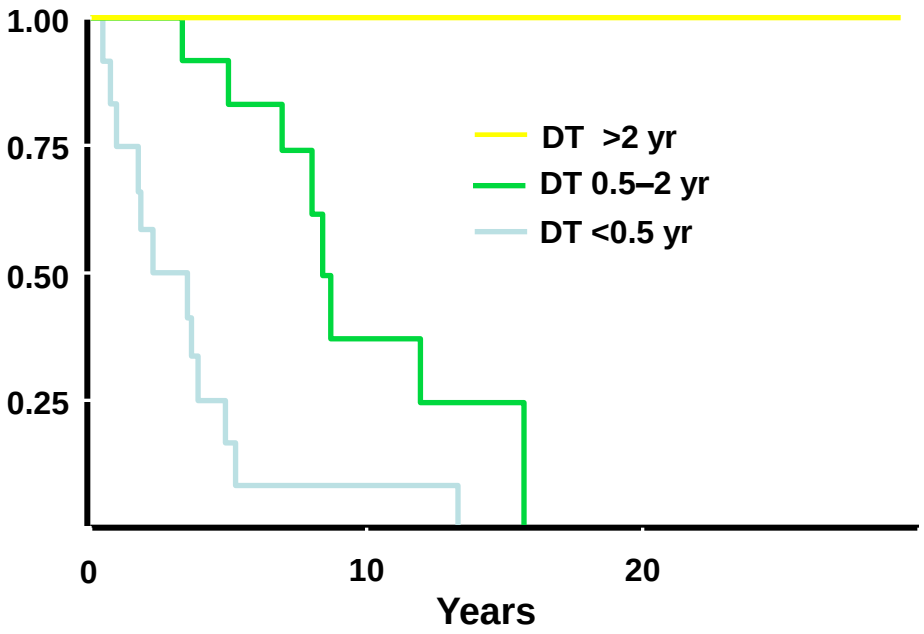
Metastatic MTC: prognosis

- Tumor burden: complete imaging
- Progression
  - There is no evidence that the efficacy of a systemic treatment at an early stage may be better than at a later stage
  - FU and local treatment modalities should be used as long as reasonably possible

Candidates for systemic treatment
- Large tumor burden: imaging
- Symptomatic or progressive disease on imaging (not only on DT-Ct and CEA)

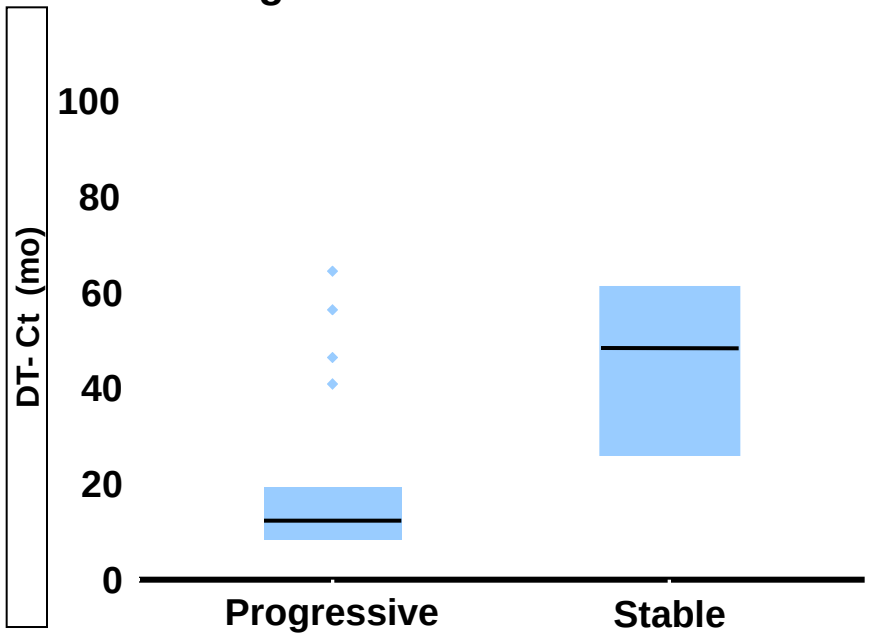
Ct: doubling time (DT)

Survival rate and DT (n=65)



DT **< 2 years in 24/65 patients**

Progression and DT-Ct



IGR: Progression at 1 year (RECIST: 24/45)

- **DT <2 years: 94% had progressive disease**
- **DT>2 years: 86% had stable disease**

Barbet J *et al*. *J Clin Endocrinol Metab* 2005;90:6077–6084
Giraudet AL *et al*. *Eur J Endocrinol* 2008; 158: 239–246

Why is imaging so important?

During treatment with vandetanib, serum Ct and CEA levels decrease in > 80% of patients. This decrease is related to the inhibition of the ret tyrosine kinase.
It may be not paralleled by a decrease in tumor masses on imaging (efficacy).

What to do in a patient with stable disease before and on treatment when toxicity appears?

Indication for treatment: progressive disease on imaging
Efficacy: tumor targets on imaging (RECIST)

Do not treat: elevated Ct levels, patients with small tumor burden; patients with no evidence of progression on imaging

Metastatic MTC: prognosis

- Candidates for local treatment modalities:
  - Before any systemic treatment
  - Local symptoms or risk of local complication:
    - Surgery
    - External radiation beam therapy,
    - Percutaneous intervention (Therapeutic imaging):
      - Radiofrequency ablaation, cryoablation
      - Cement injection
      - Hepatic embolization

- Candidates for systemic treatment
  - Large tumor burden: imaging
  - Symptomatic or progressive disease on imaging (not only on DT-Ct and Dt-CEA)

Initiation of systemic treatment in patients with metastatic MTC

	Tumor burden	
Progression	Small <1cm	Large/Multiple >1.5-2 cm
<12-14 months	No	Yes
>12-14 months	No	?? (High SUV? Symptoms?)

Metastatic MTC: systemic treatment

- Symptomatic treatment (pain, diarrhea)
- Somatostatin analogs: no benefits
- Chemotherapy (ADR or 5FU/DTIC)
  - Low efficacy (ORR< 5-20%; no demonstrated benefits on survival); high toxicity
- Metabolic radiation therapy (anti CEA mAb, ^{90}Yttrium-DOTA-TOC) (Chatal JF, J Clin Oncol 2006;24:1705)
  - Low efficacy, potential toxicity
- Targetted therapy (Kloos et al,Thyroid. 2009 ;19:565)

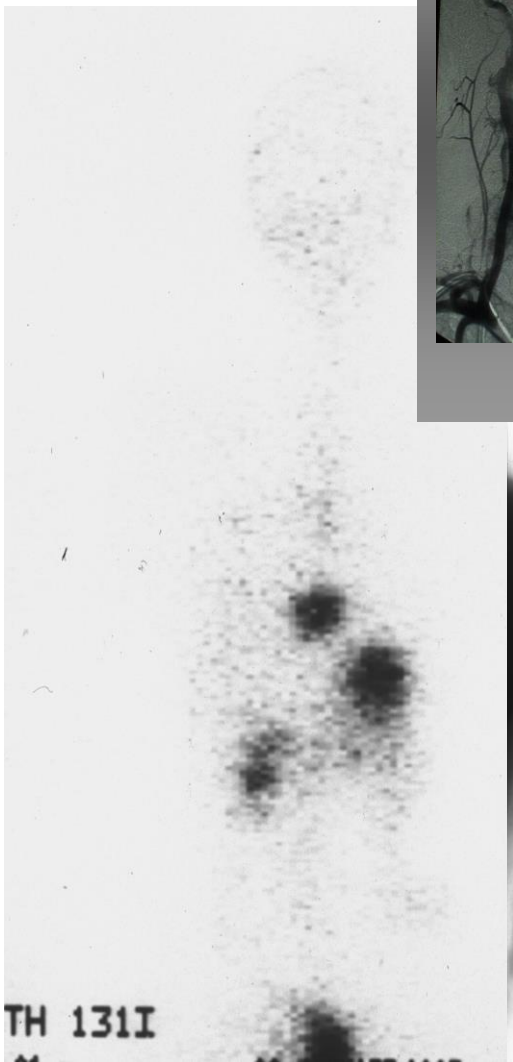
Local treatment for advanced disease

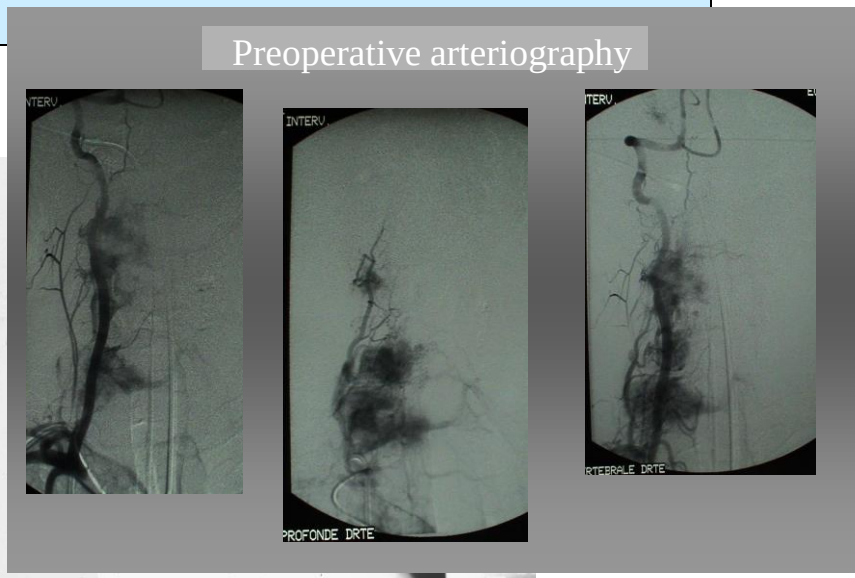
- Brain metastases:
  - Surgery and/or external radiation beam therapy
- Bone metastases with imaging abnormalities:
  - Surgery and ERBT
  - Radiofrequency-cryoablation, cement injection
- Lung metastases, in case of predominant lesions:
  - Radiofrequency ablation
  - Surgery

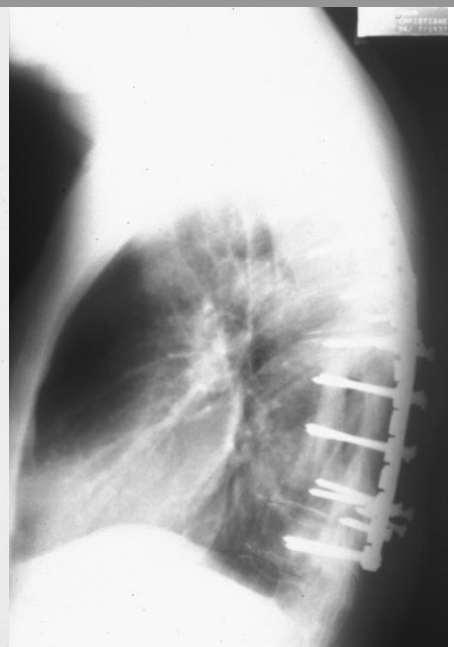
- Local treatment modalities may be used alone or in combination with systemic treatment

Surgery for bone metastases

- Single vertebral metastasis: ^{131}I (3.7GBq x 6) and EBRT: persistent ^{131}I uptake.
- Surgical resection after embolization: cure.





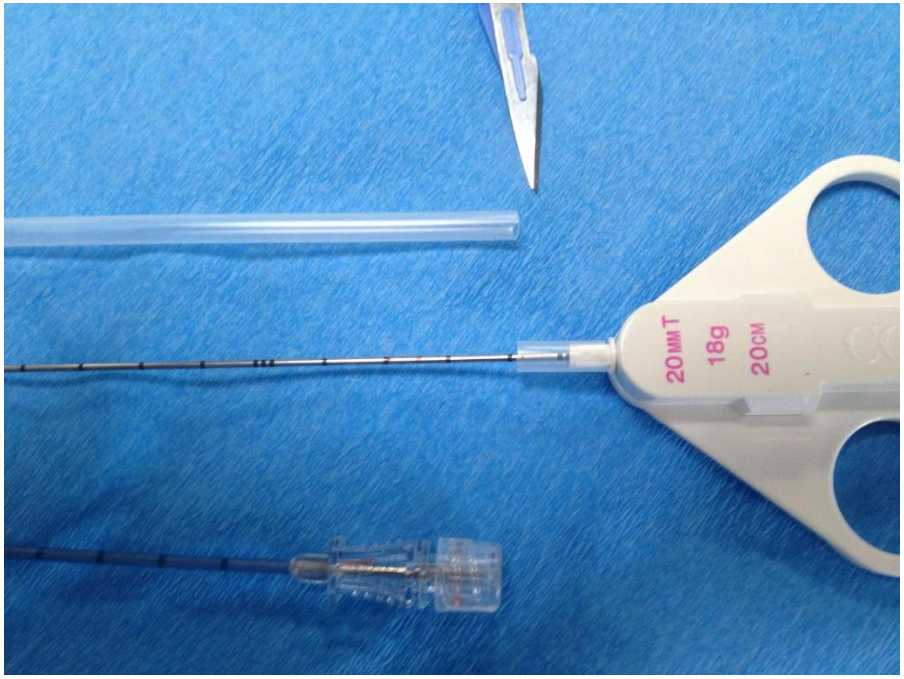


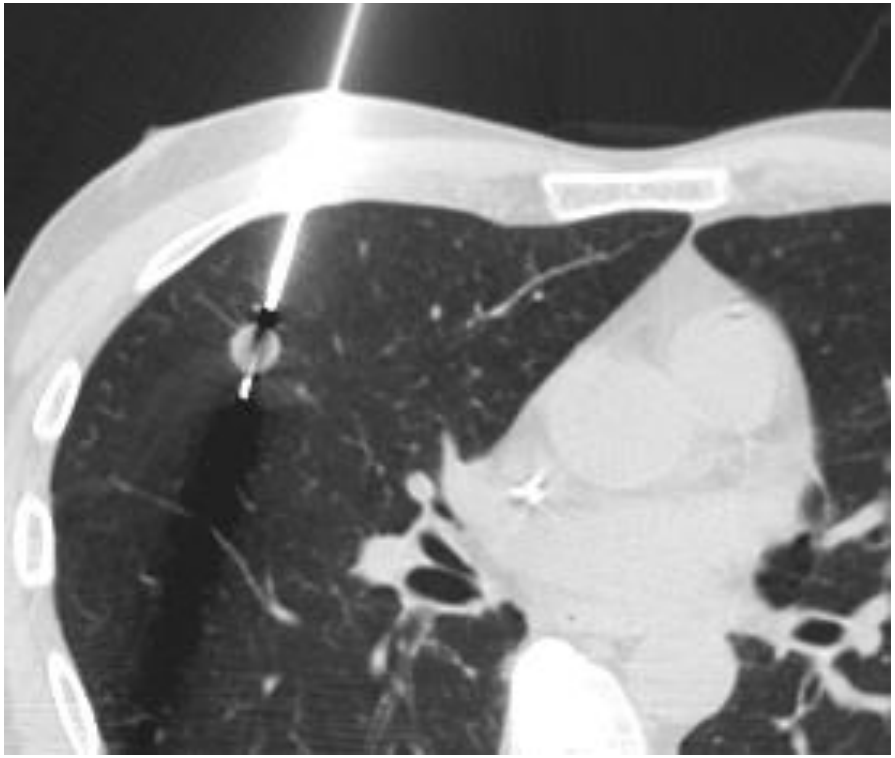
CT-guidance

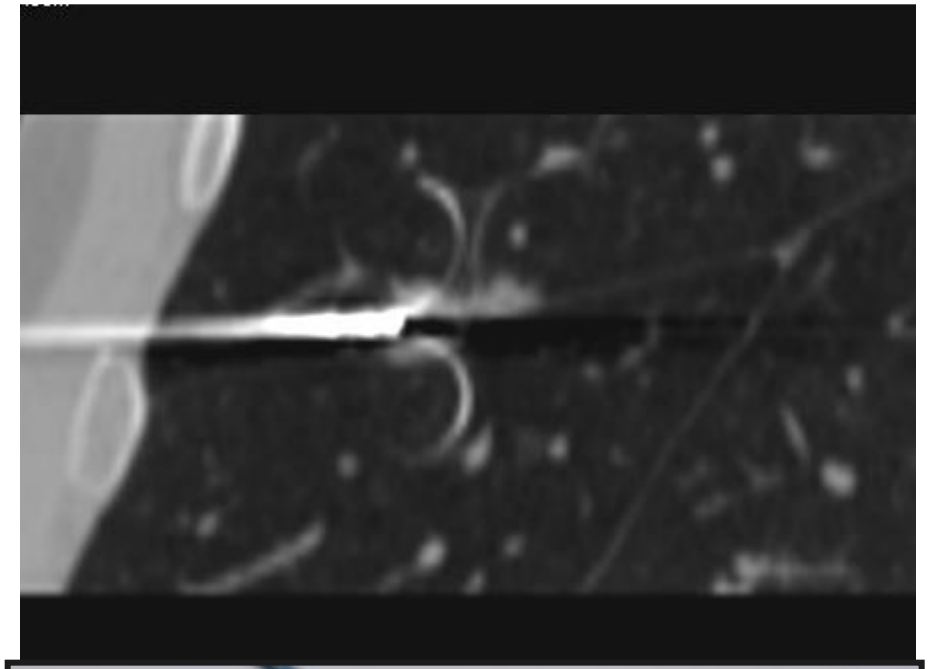
« Real time »

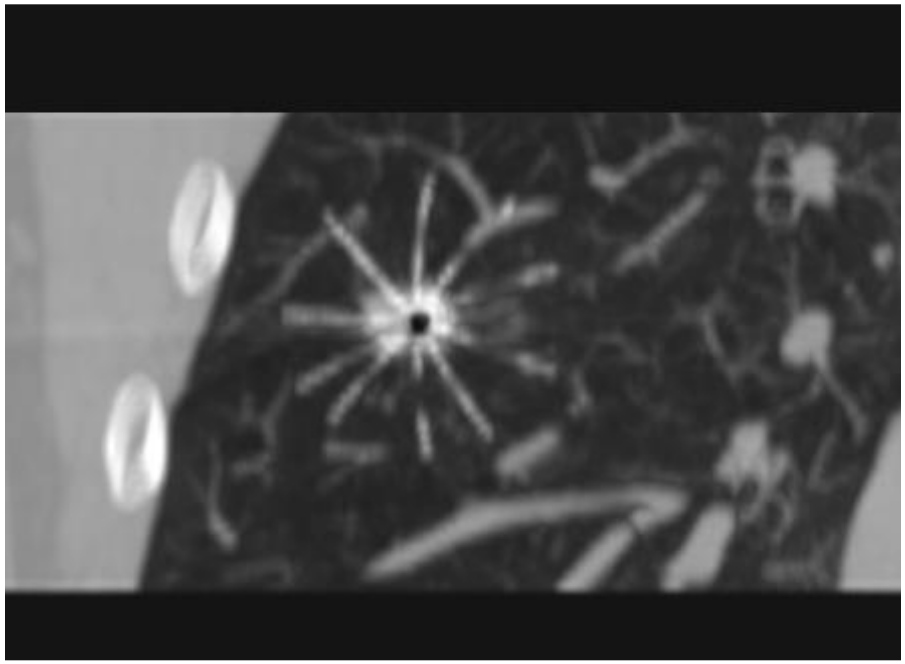
Anesthésie générale

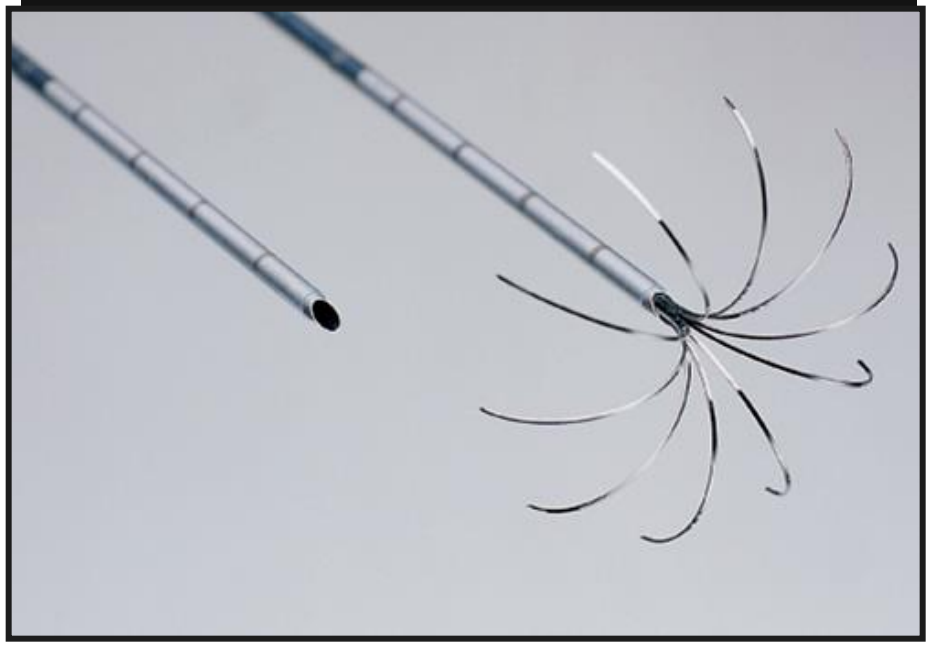
Biopsie si indiquée

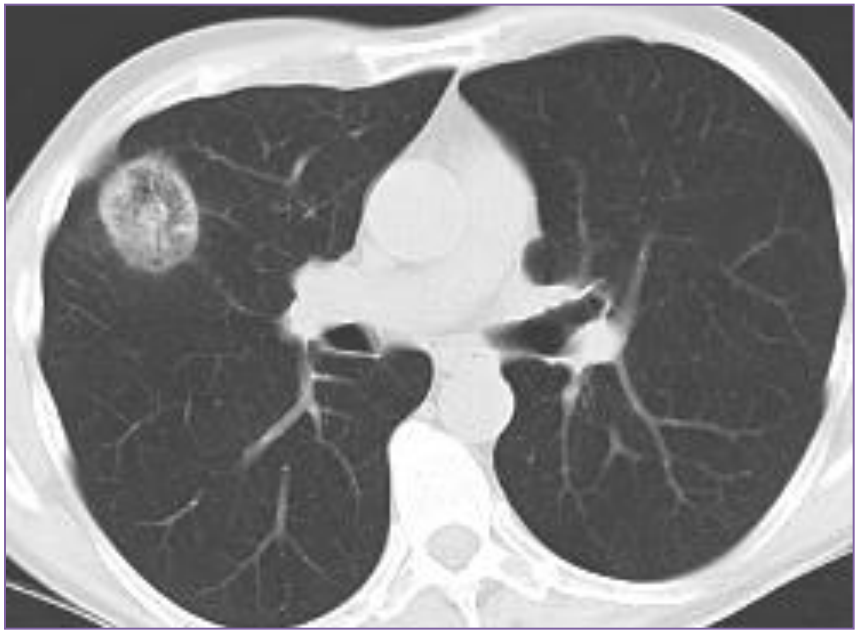




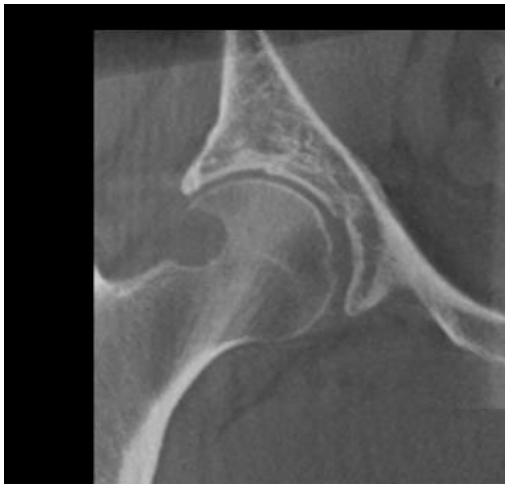


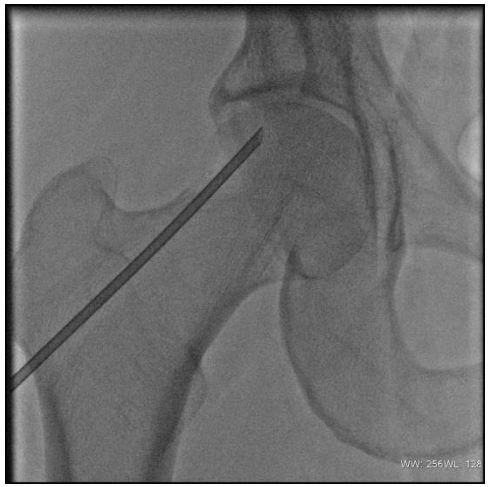


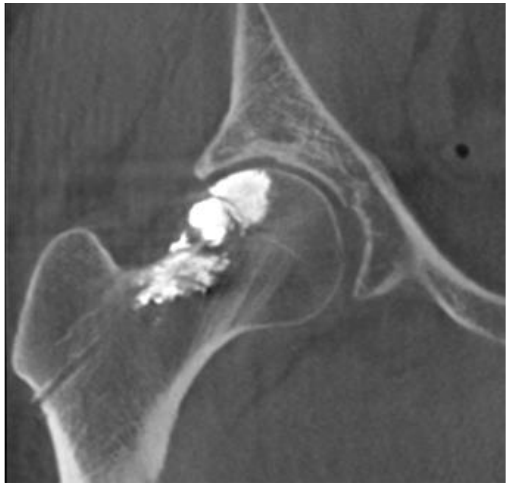




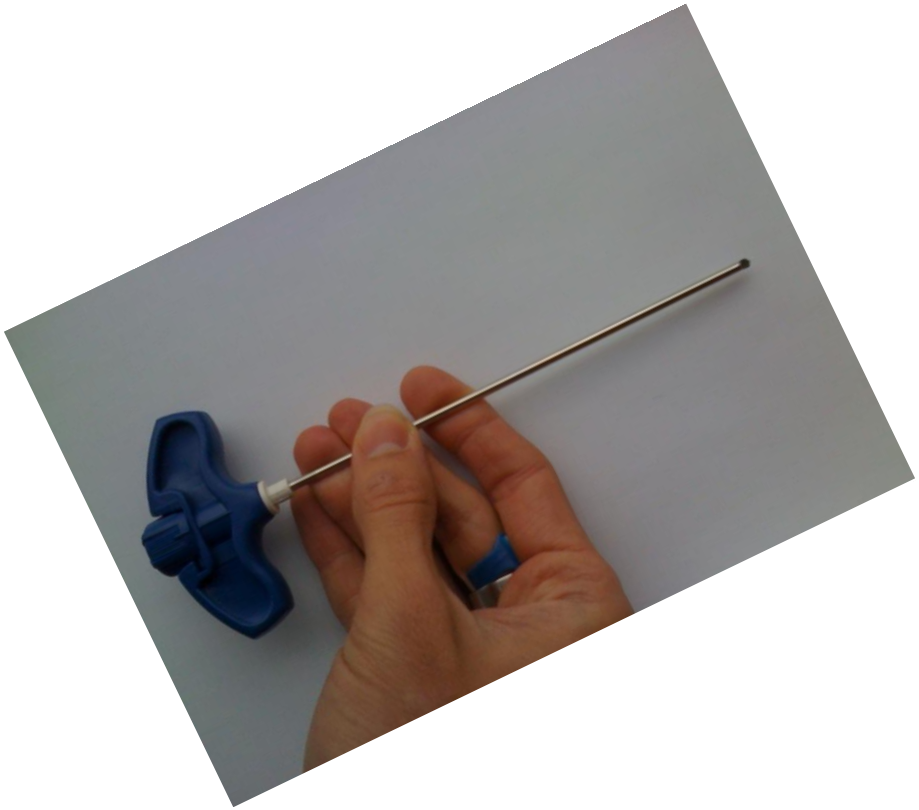
Ablation par radiofréquence d’une méta pulmonaire







Résultats à 1 an

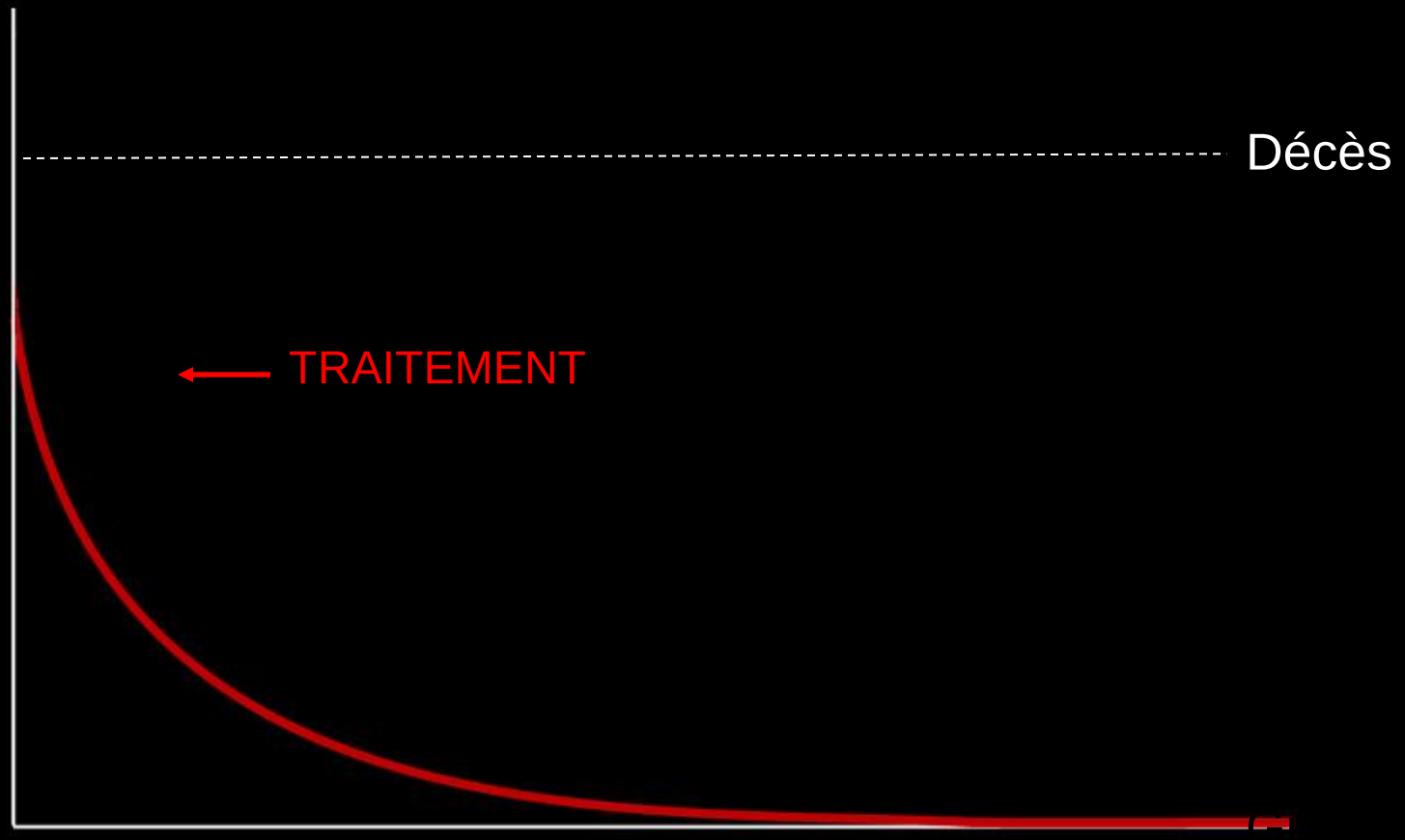


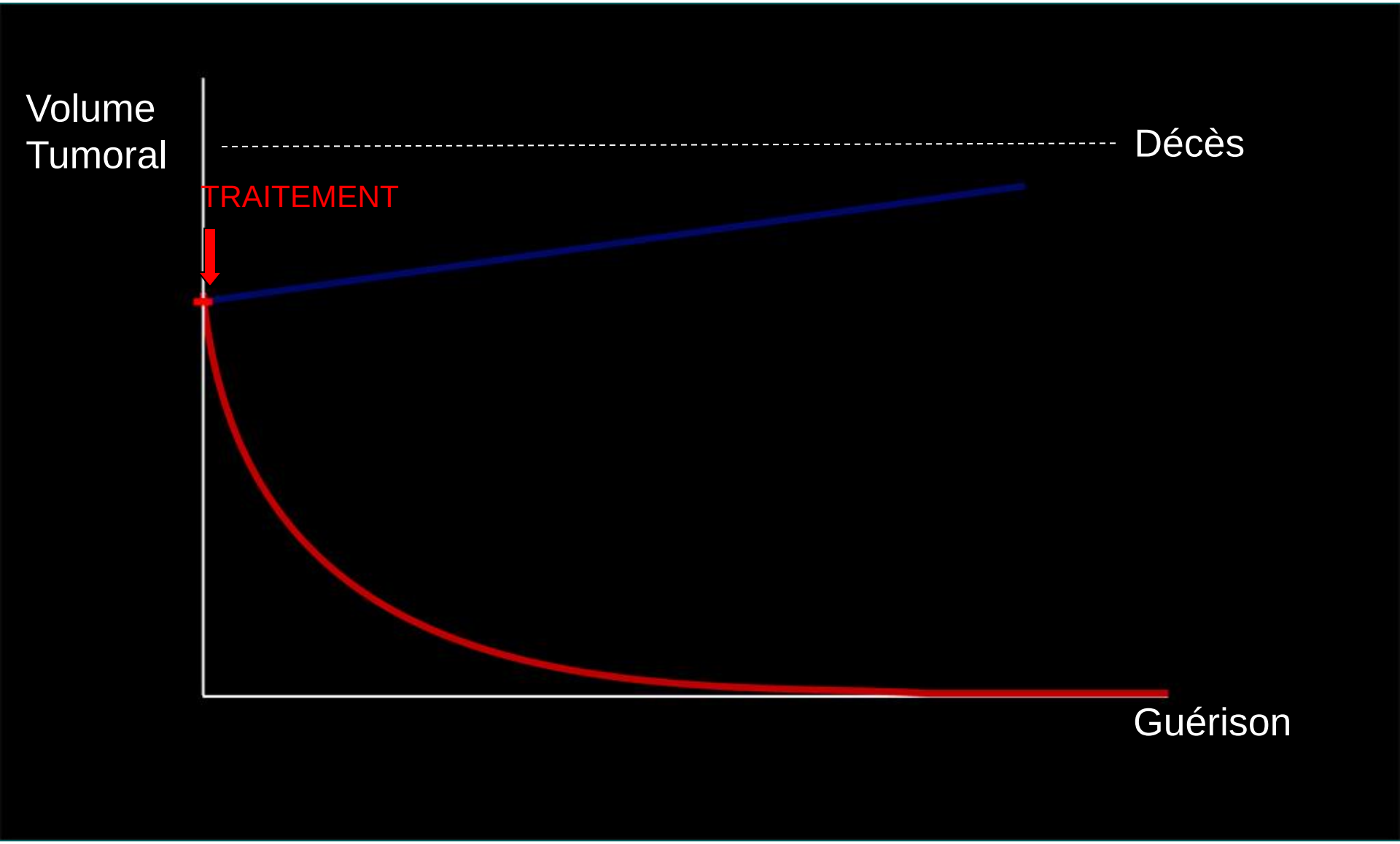
Cryothérapie suivie de cimentoplastie

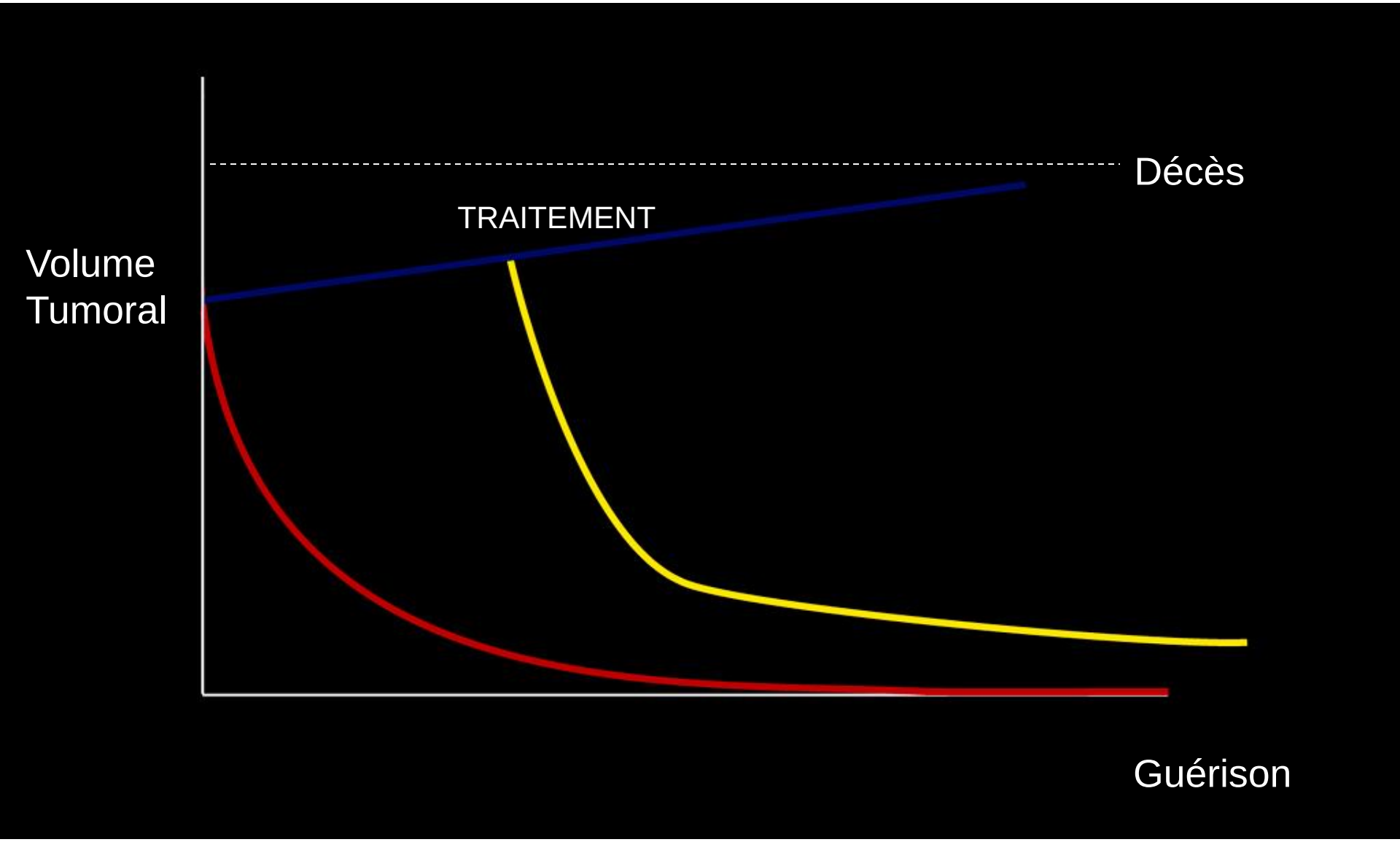
Tumor response, a surrogate marker of survival

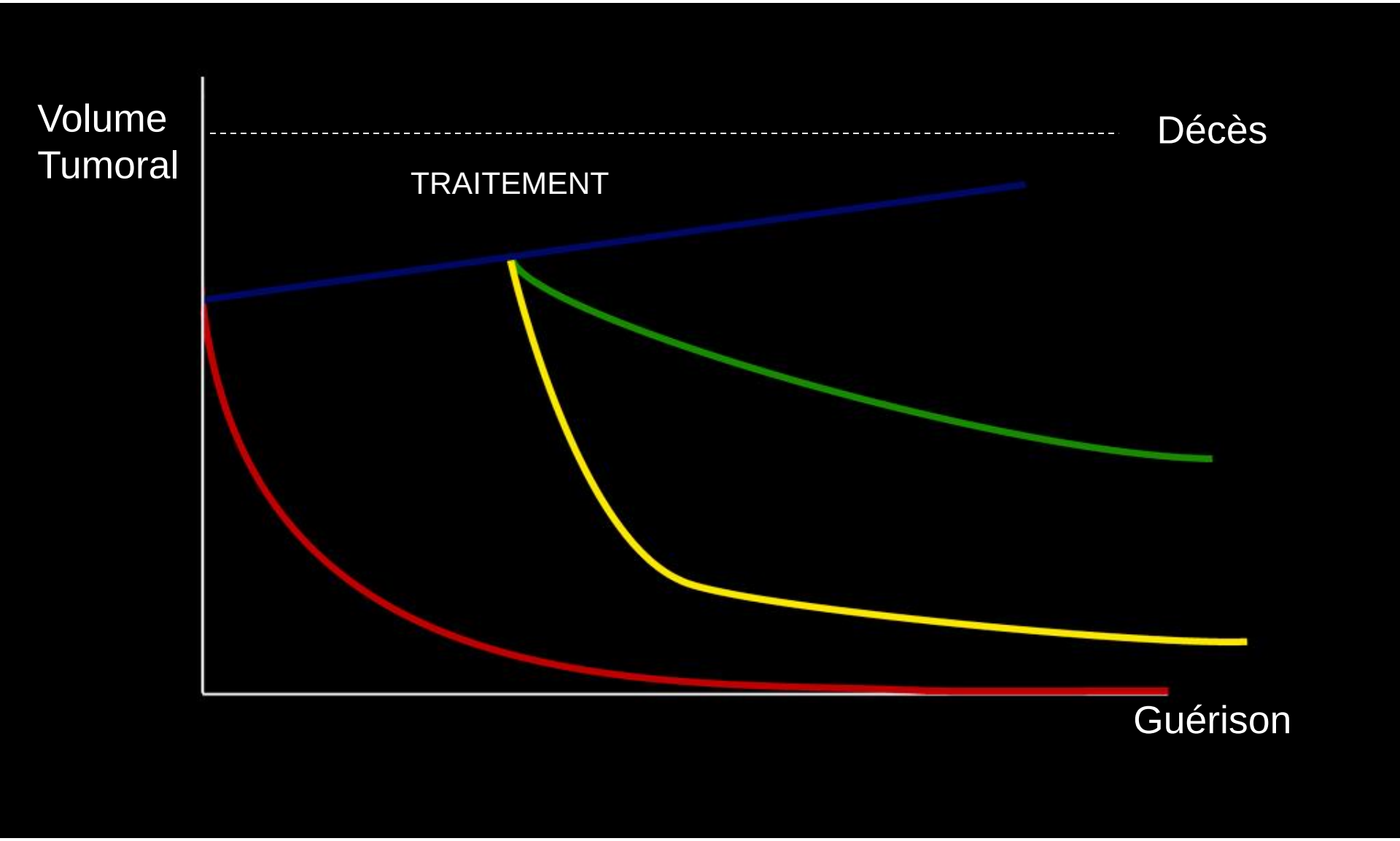
Treatment	Marker	Aim
Anti-hypertension	Blood pressure	Stroke
Anti-osteoporosis	Bone mineralisation	Fracture
Anti-neoplastic	Tumor response (ORR, PFS)	Survival

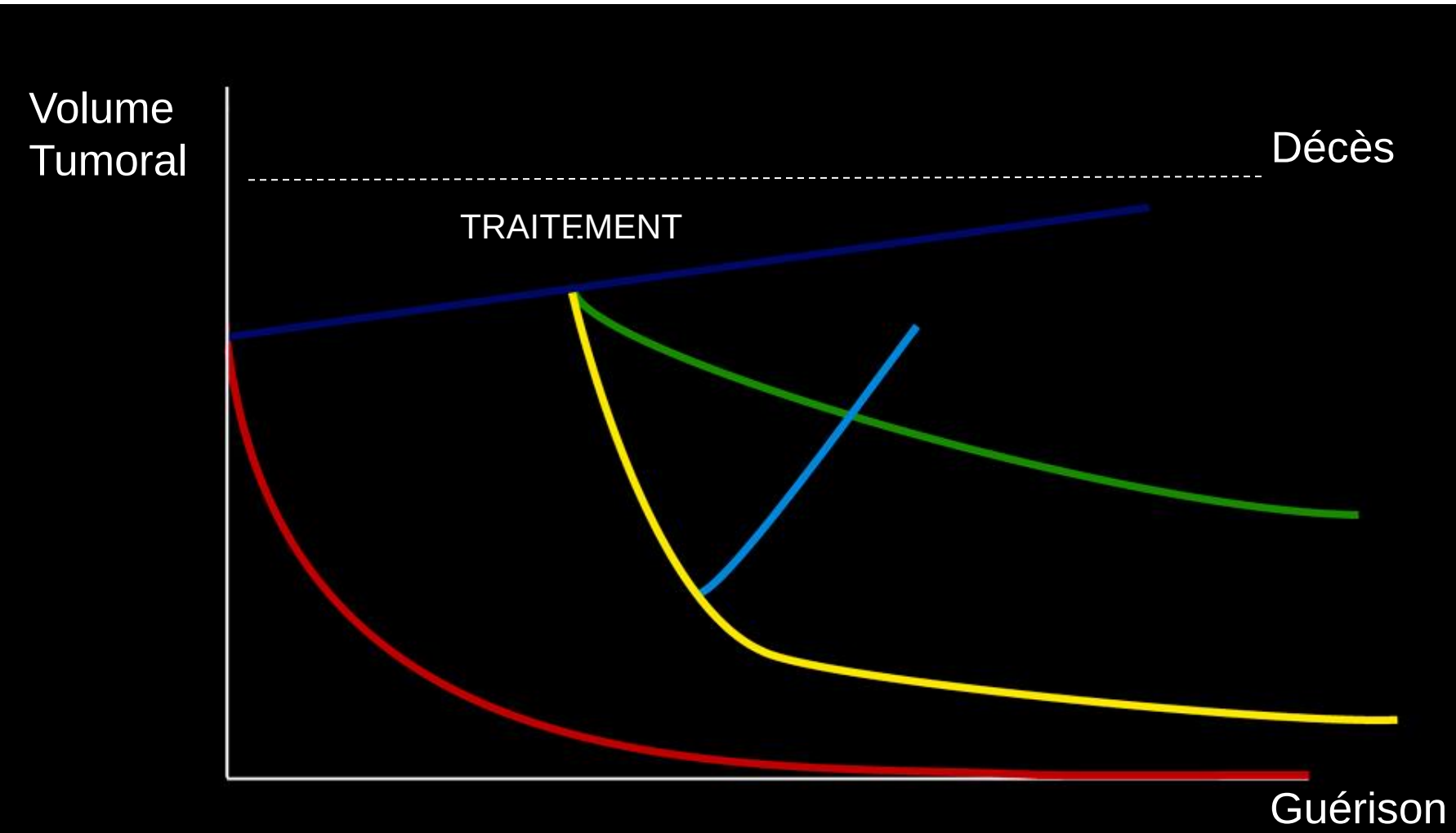
Buyse M *et al*. *Lancet* 2000;356:373–378


Décès
TRAITEMENT


Volume
Tumoral
Décès
TRAITEMENT
Guérison


Décès
TRAITEMENT
Volume
Tumoral
Guérison


Volume
Tumoral
Décès
TRAITEMENT
Guérison


Volume
Tumoral
Décès
TRAITEMENT
Guérison

Tumor response: a surrogate marker of survival

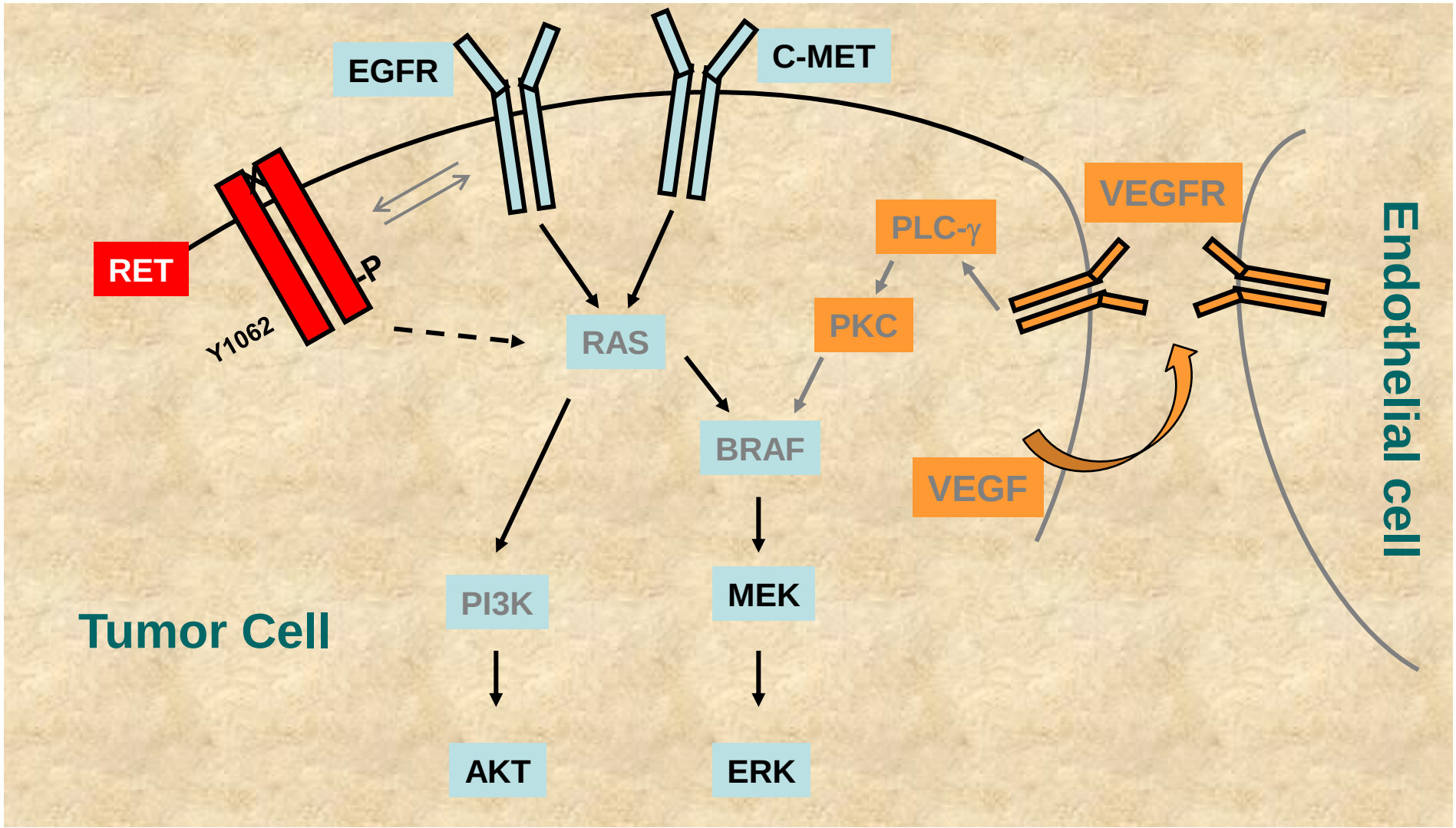
Benefits on survival may be difficult to demonstrate, and this is the case for patients with a significant life expectancy who will receive several lines of treatment

Objective response rate (ORR) that includes CR, PR and SD is measured in phase II trial but is poorly related to overall survival

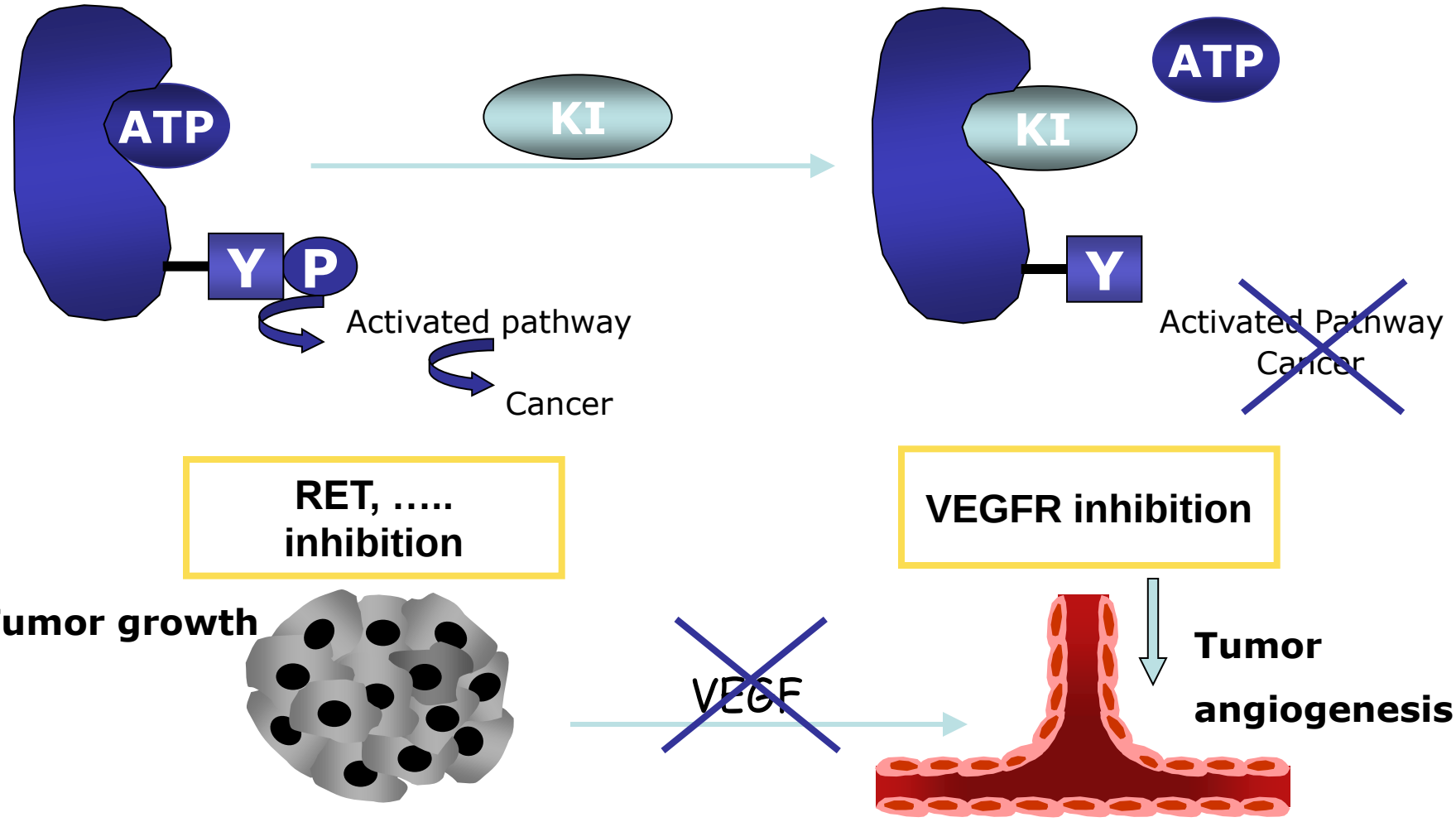
Progression free survival is better related to OS: it takes into account response duration: improvement of PFS can only be measured in randomized trials

MTC

Activating RET mutation: 100% hereditary, > 40% sporadic MTCs
Activating RAS mutation: > 2/3 of MTCs without RET mutation



Kinase Inhibitors



Kinase inhibitors and MTC

Compound	IC_{50} (nm)							
	VEGFR1	**VEGFR2**	VEGFR3	RET	RET/PTC3	RAF	Other targets	
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: phases 1-2. Inhibiteurs de kinases

	Cibles	n	RP (%)	SD > 6 mo (%)
Vandetanib (Wells)	VEGFR, RET, EGFR	30	30	53
Sorafenib (Lam)	VEGFR,BRAF	19	11	68
Motesanib (Schlumberger)	VEGFR, PDGFR, C-KIT	83	2	43
Axitinib (Cohen)	VEGFR1,2,3	12	22	50
Sunitinib (Carr)	VEGFR, RET	6	50	
Cabozantinib (XL-184) (Kurzrock)	VEGFR, RET, C-MET	35	49	
Lenvatinib (E7080) (Schlumberger)	VEGFR, RET	59	36	
Gefitinib (Pennell)	EGFR	4	0	
Imatinib (De Groot,	C-KIT, PDGFR	15	0	27
Frank-Raue)		9	0	56

Toxicities associated with inhibition of kinases

Cardiovascular
- **Hypertension**
- QT prolongation
- CHF
- Acute coronary syndrome

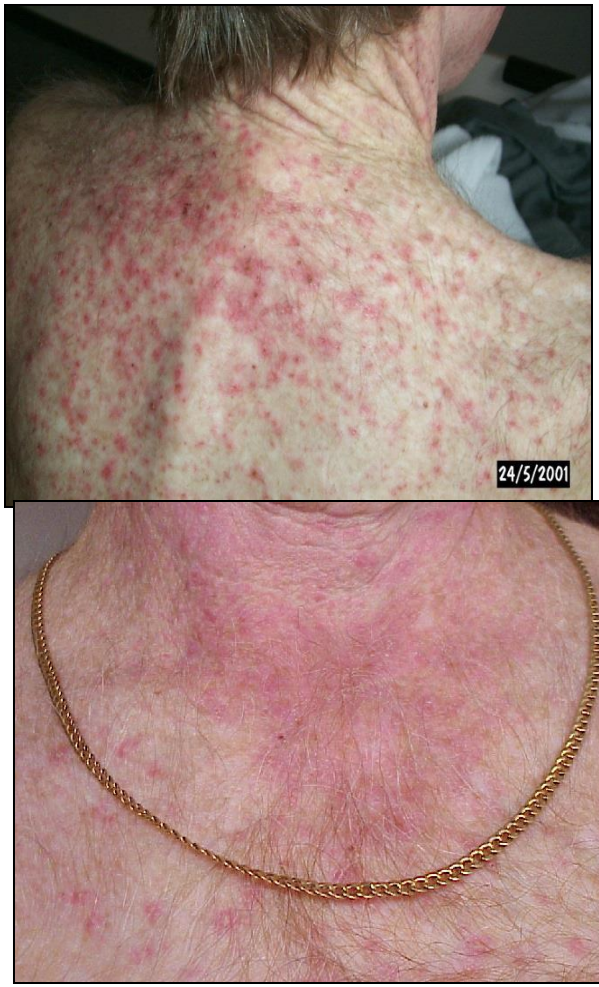
Diarrhea

Fatigue

Weight loss

Skin toxicity: rashes, folliculitis, HFS, squamous cell skin cancer

Hypothyroidism: frequent serum TSH determination/ Increased need in LT4

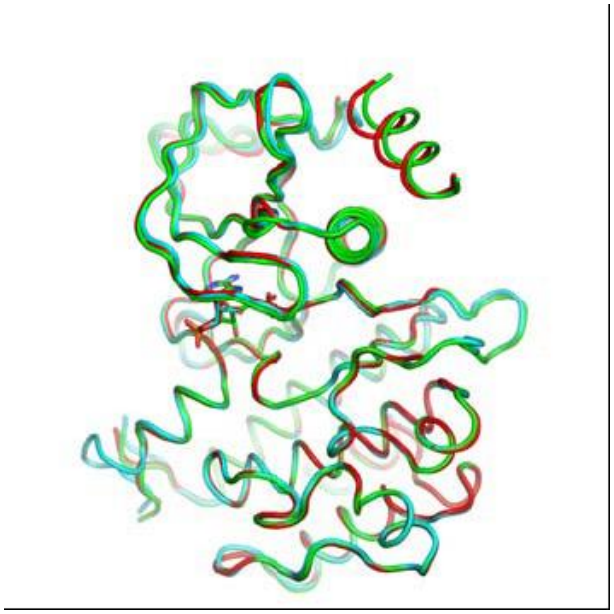


Dose reduction: 11-73%
Drug withdrawal: 7-25%

Two phase 3 trials vs placebo

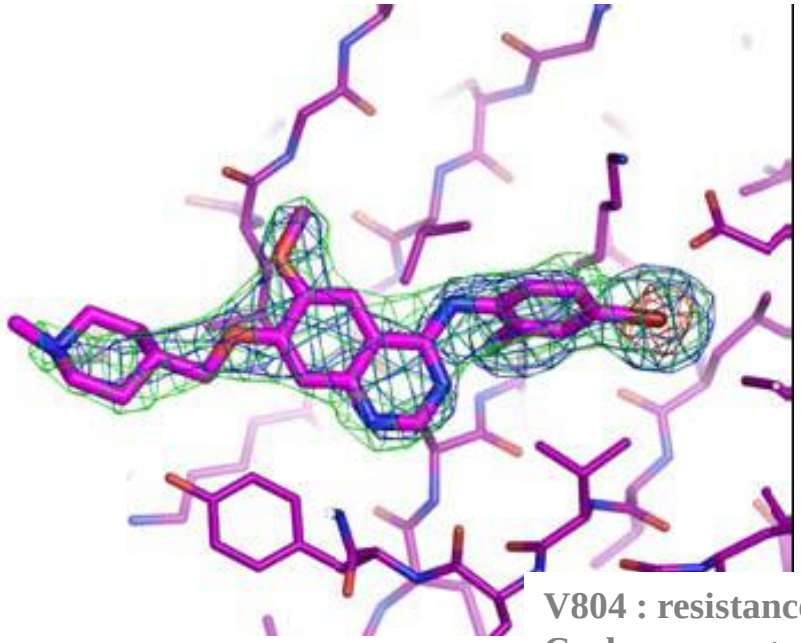
- Vandetanib (300mg/d) vs placebo with cross over in 331 advanced MTCs: PFS
- XL-184 (175mg/d) vs placebo without cross-over in progressive MTCs: OS
  - Improved PFS- 4.0 (placebo) vs 11.2 months (treatment) (HR: 0.28 (95%CI: 0.19-0.40, $p<0.0001$)

Vandetanib inhibits tyrosine kinase of VEGFR2-3, EGF et RET



RET protein

KNOWLES, JBC 2006

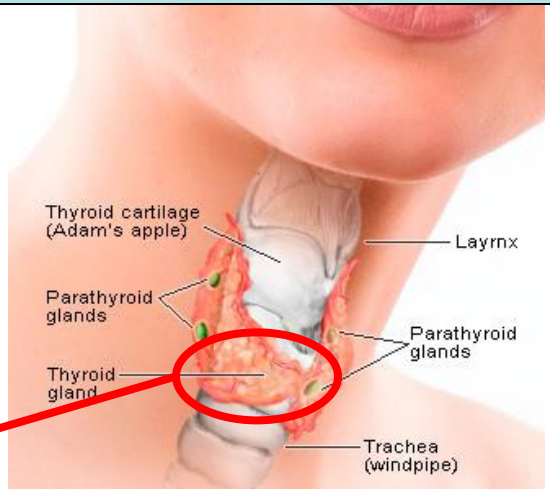


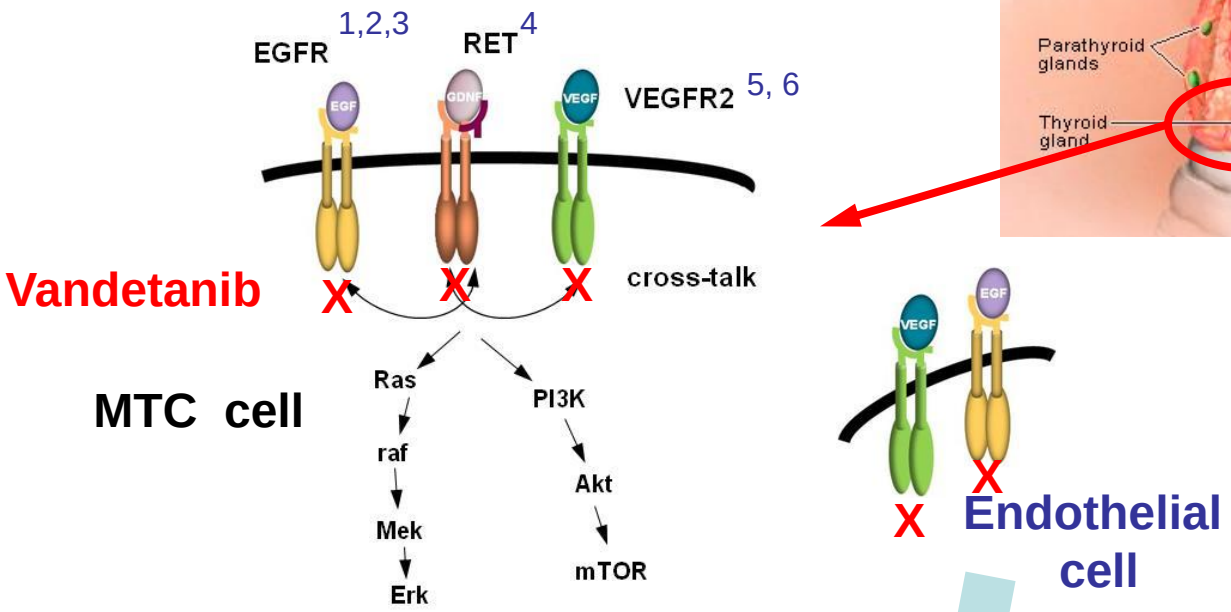
V804 : resistance ?
Carlomagno et al 2004)

ZD6474

Vandetanib Inhibits Key Molecular Targets in MTC

Vandetanib inhibits EGFR, VEGFR2, wild type and mutated RET

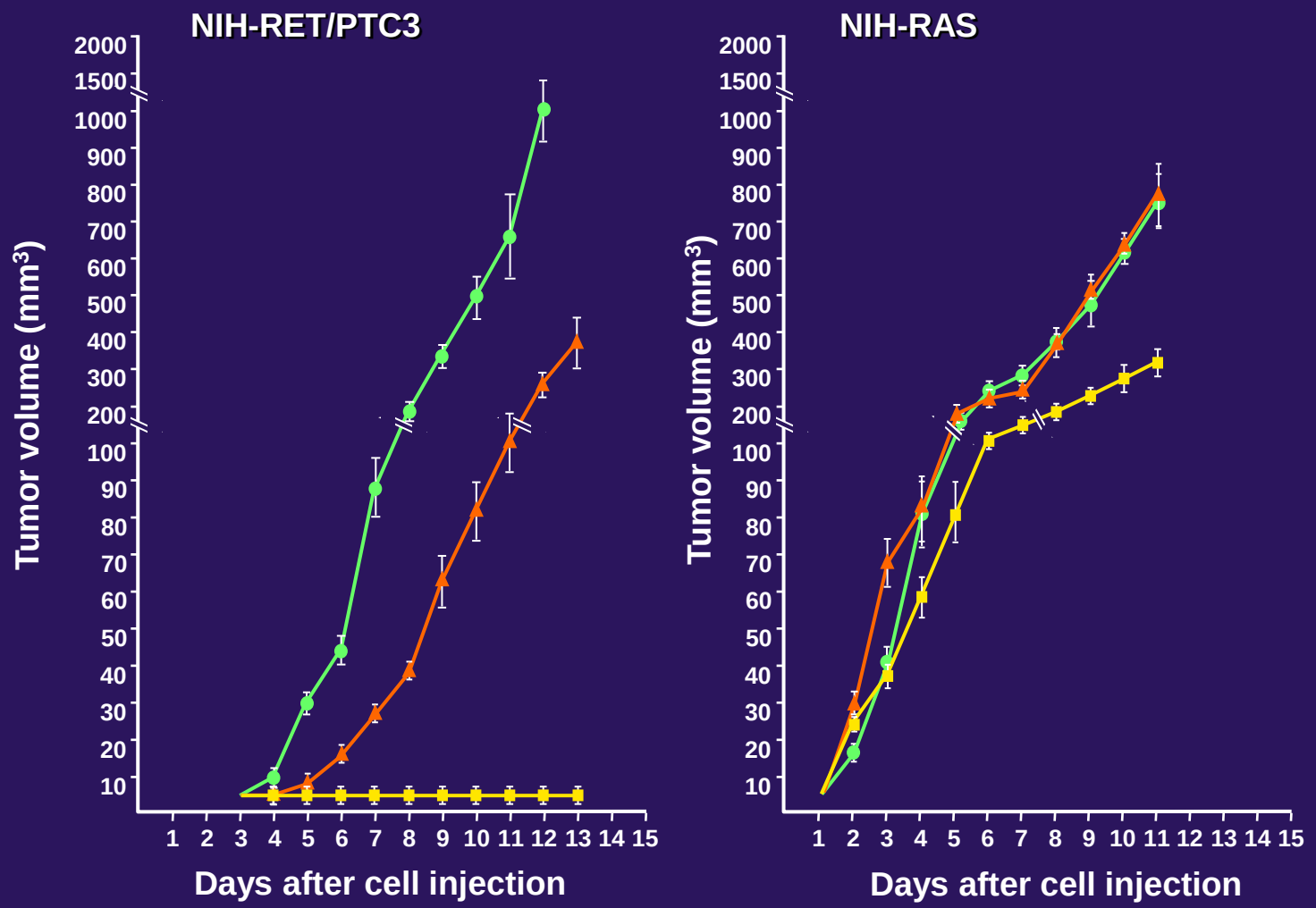




tumour growth / metastasis / angiogenesis

[1]Rodrıguez-Antona *et a*l 2010; [2]Gorla *et al*, 2008; [3]Croyle *et al*, 2008; [4] Akeno-Stuart *et al* 2007, [5] Vitagliano *et al* , 2011; [6]Capp *et al* 2010

Vandetanib treatment of nude mice



Carlomagno F *et al*.
Cancer Res 2002;62:7284–7290

Vandetanib treatment of nude mice

NIH-RET/PTC3-injected mice

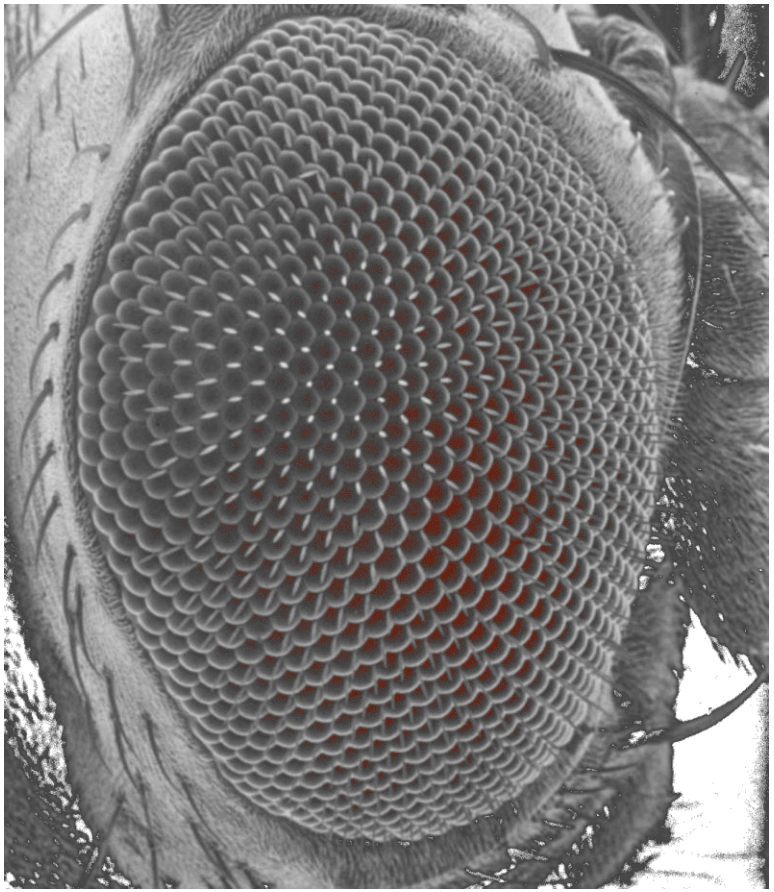
Fly eye – a model for cancer

The Drosophila retina

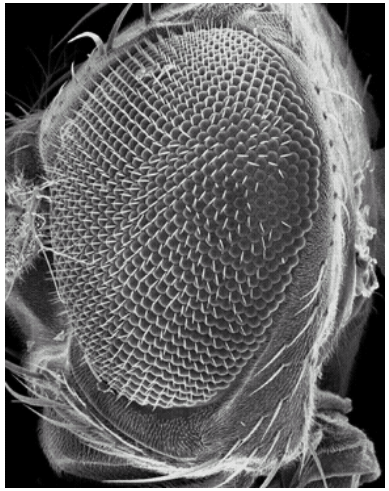
- Simple epithelium; few cell types
- Much is known about signaling pathways that guide development

Two cancer models

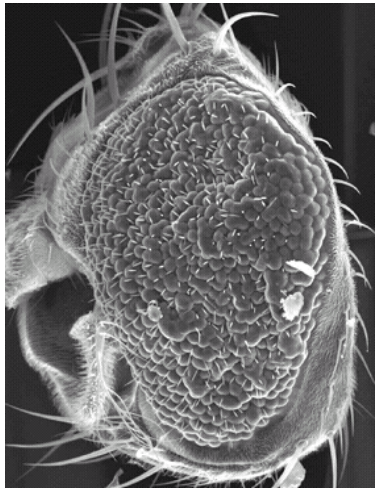
- Multiple Endocrine Neoplasia Type 2
- *Csk/Src* (breast, colon, etc)



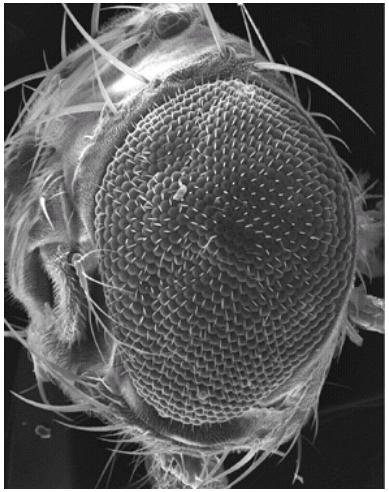
Vandetanib suppresses RET signaling *in vivo*



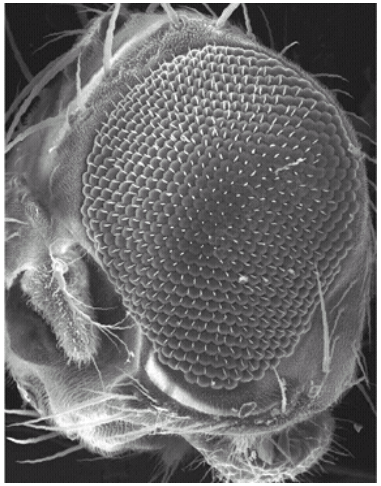
Wild type



RET^{MEN2B}



RET^{MEN2B}
+ 0.2 mM vandetanib



RET^{MEN2B}
+ 1 mM vandetanib

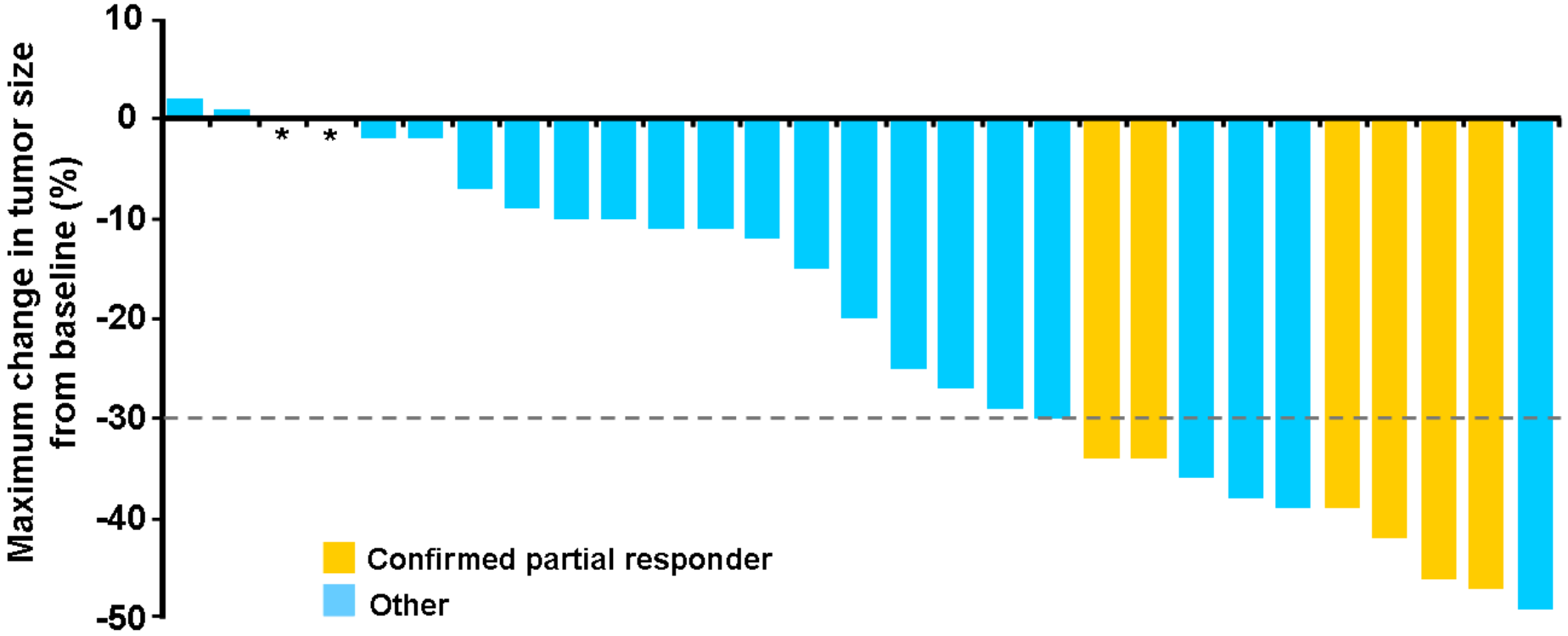
Vidal M *et al*. *Cancer Res* 2005;65:3538–3541

Vandetanib in metastatic hereditary medullary thyroid cancer: follow-up results of an open-label Phase II trial

SA Wells,[1] JE Gosnell,[2] RF Gagel,[3] J Moley,[1] D Pfister,[4] JA Sosa,[5] M Skinner,[6] A Krebs,[7] J Hou,[7] J Vasselli[7] and M Schlumberger[8]

[1]Washington University School of Medicine, St Louis, MO, USA
[2]University of California at San Francisco, San Francisco, CA, USA
[3]UTMD Anderson Cancer Center, Houston, TX, USA
[4]Memorial Sloan-Kettering Cancer Center, NY, USA
[5]Yale University School of Medicine, New Haven, CT, USA
[6]University of Texas, Southwestern Medical Center, Dallas, TX, USA
[7]AstraZeneca, Wilmington, DE, USA
[8]Institut Gustave Roussy, Villejuif, France

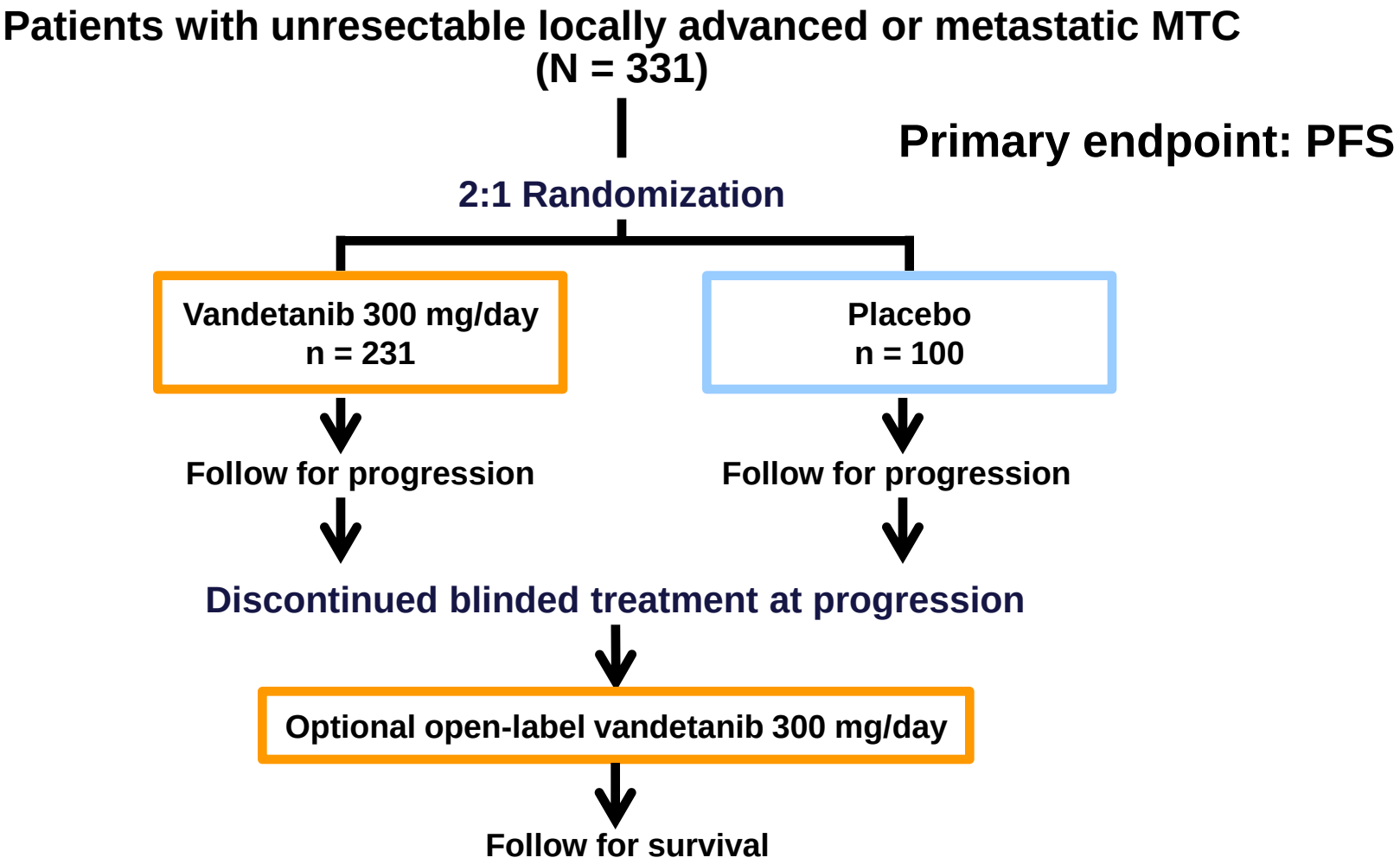
Vandetanib (300 mg): phase II, 30 patients with hereditary MTC



PR 10/30; confirmed PR: 6/30 (mean duration: 311 days+)
Stable disease>24 weeks: 16/30 (53%)

Wells S, JCO 2009

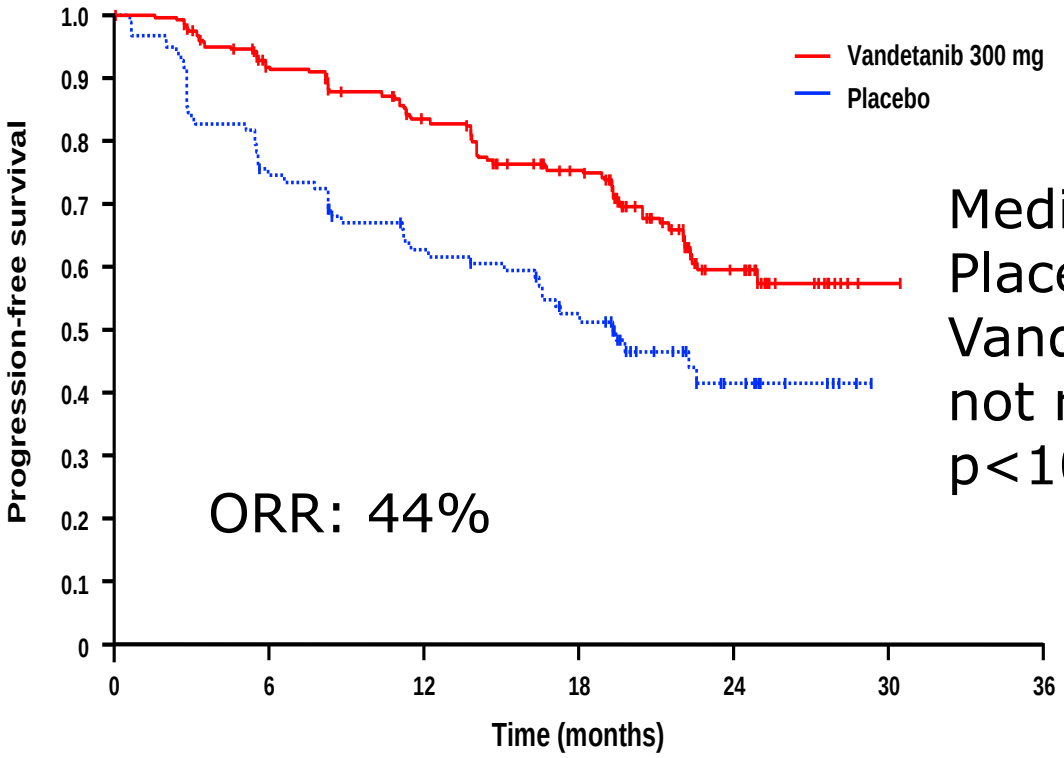
Vandetanib in Locally Advanced or Metastatic MTC: Randomized, Double-Blind Phase III Trial (ZETA)



PFS, Progression-free survival

Wells SA, et al. *J Clin Oncol*. 2010;28(15S): Abstract 5503. Wells SA Jr, et al. *J Clin Oncol*. 2012;30(2):134-141.

Phase 3 trial: vandetanib vs placebo (Zeta study)



ORR: 44%

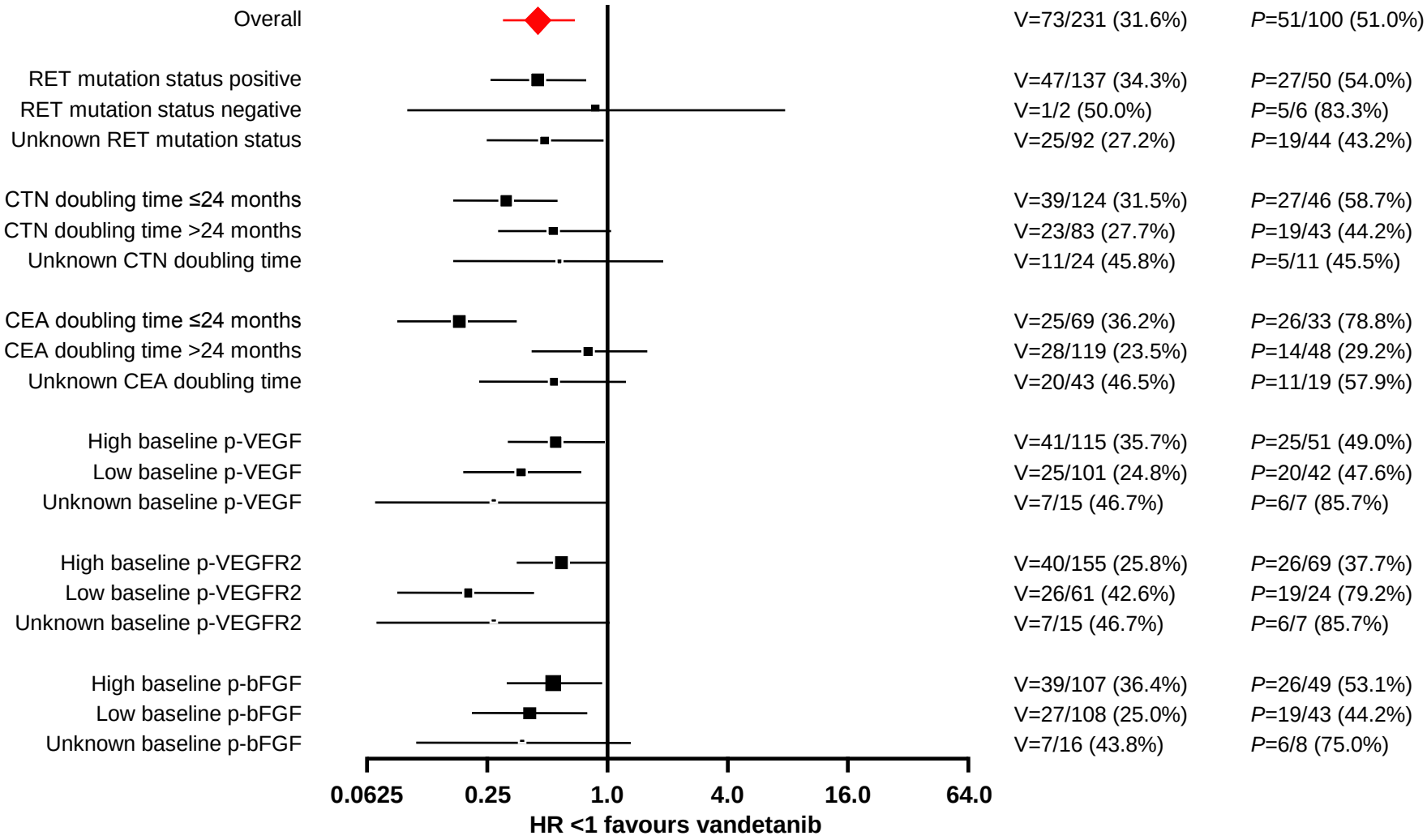
Median PFS:
Placebo: 19.3 mo
Vandetanib: >30.5 mo, not reached (HR: 0.46; $p<10^{-4}$)

Number of patients							
Vandetanib 300 mg	231	198	171	141	42	1	0
Placebo	100	72	57	45	13	0	0

Vandetanib: toxicity

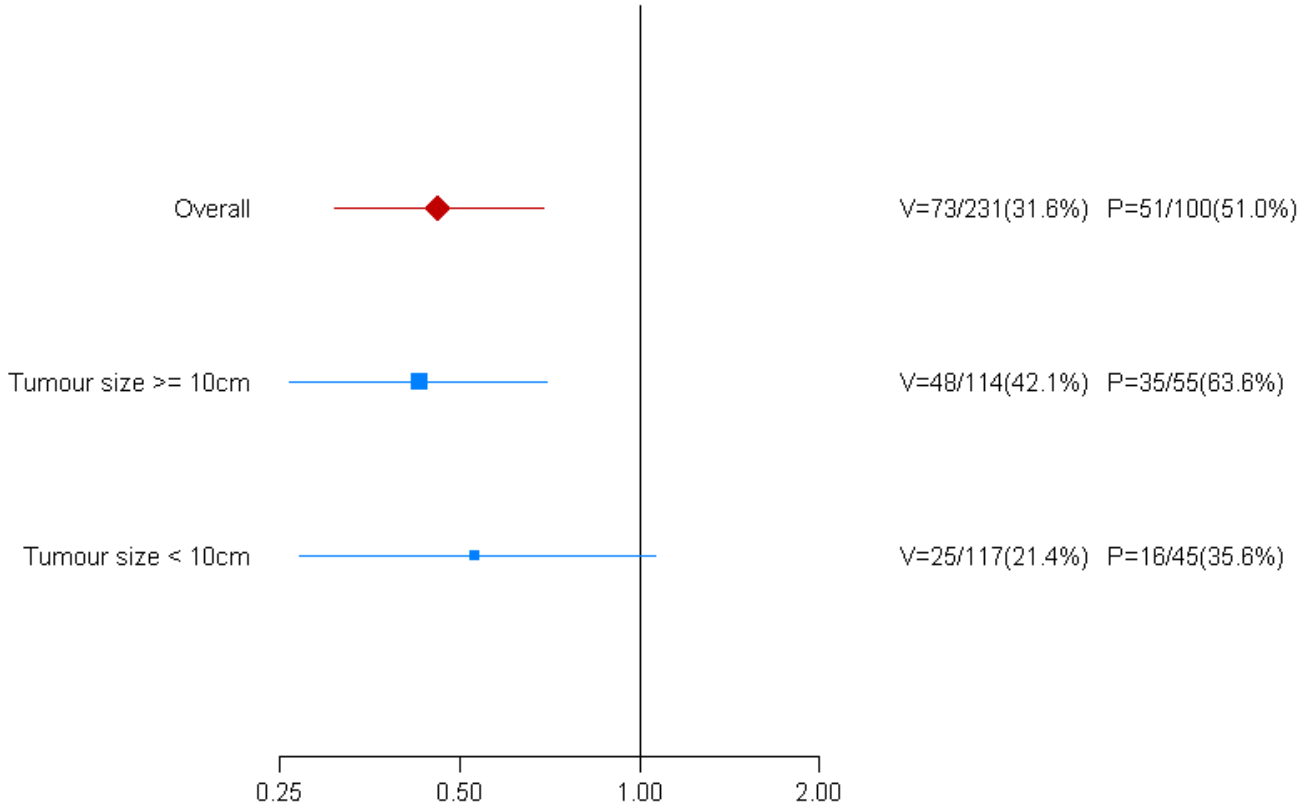
- Adverse event profile consistent with EGFR and VEGFR inhibition: diarrhea, rash and folliculitis, nausea, hypertension, fatigue
- QT prolongation common (>20ms in 90% of patients): (long QTc before treatment (450ms), other treatments, electrolyte abnormalities (diarrhea)), but "torsades de pointes" and sudden death are rare
- Long median duration of treatment (21 months): AEs managed with dose reduction / standard medical treatment. Tolerance is usually good
- Rate of discontinuation for AE – 13%

Vandetanib benefited all patient groups in a predefined subgroup analysis of PFS



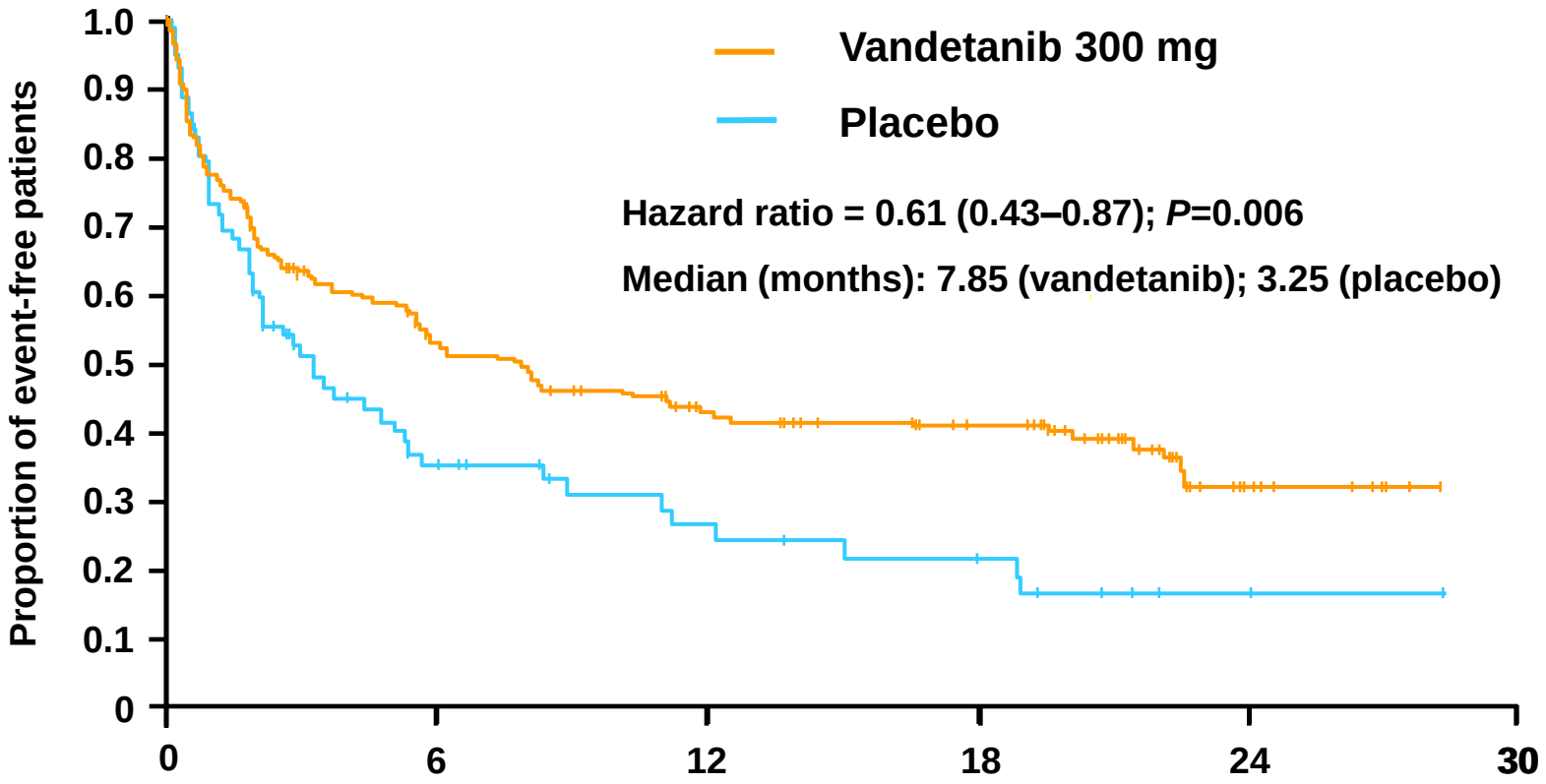
The analyses were performed using a log-rank test with treatment as the only factor

PFS by tumor size at baseline



Group	n	ORR
Tumor size ≥10cm (n=114)	57	50.0%
Tumor size <10cm (n= 17)	47	40.2%

Vandetanib treatment significantly prolonged time to worsening of pain*



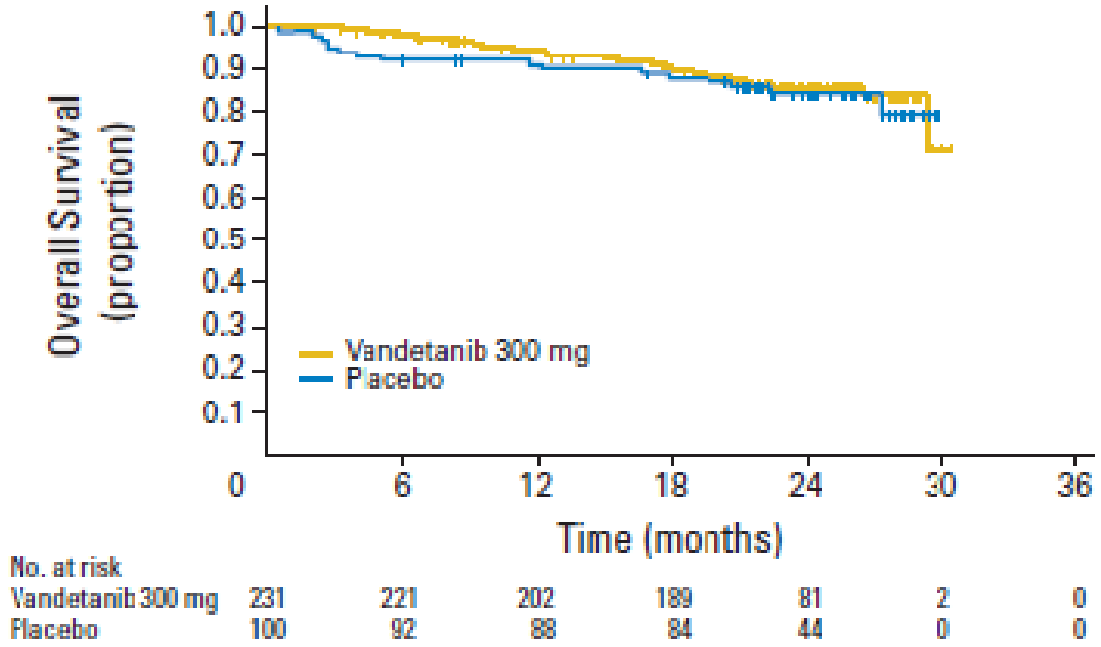
At risk (n)						
Vandetanib	231	88	62	48	10	0
Placebo	100	21	12	8	2	0

*Determined from patient-reported opioid analgesic use and responses to the Brief Pain Inventory questionnaire

Hazard ratio <1 favours vandetanib

Vandetanib : overall survival

A delay of 11 months in initiating vandetanib treatment does not alter OS in a "Vandetanib-phase III MTC patients"



OS is affected by the cross over (93% in the placebo group)

Mature OS analysis : >=2012

Data on RET mutation status (Study 58)

- 298 Sporadic MTC Patients on Study 58
  - 155 proven RET mutation positive – 92% with 918T mutation
  - **79 proven to have No mutation at M918T and No other mutation identified**:
    - 8 patients found negative by all other mutation tests
    - 71 patients had some or all of the other tests failed, but those that worked demonstrated no mutation
  - 64 No information on M918T mutation

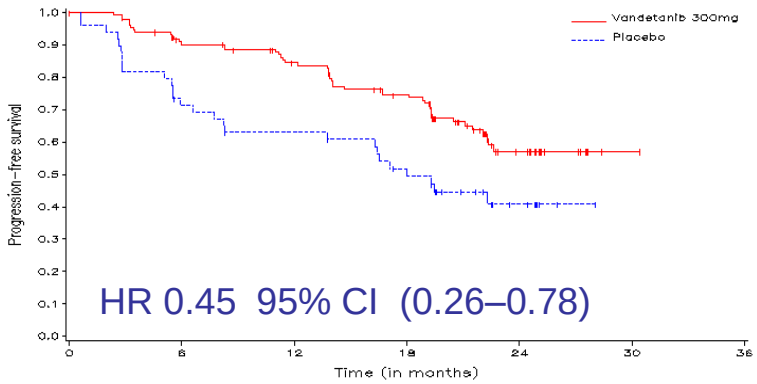
Benefit in 79 M918T mutation negative patients

	RET Mutation Positive Patients (n=187)*	Patients with No M918T Mutation and No Other Identified Mutation (n=79)
Efficacy Endpoint PFS HR (95%) confidence interval)	0.45 (0.26, 0.78)	0.57 (0.29, 1.13)
Predicted Median PFS (months) (vandetanib vs placebo)	29 vs 18	28 vs 18
Objective Response Rate (vandetanib arm)	52%	35%
Duration of Response (months)	22	18

* This includes RET mutation positive hereditary MTC patients

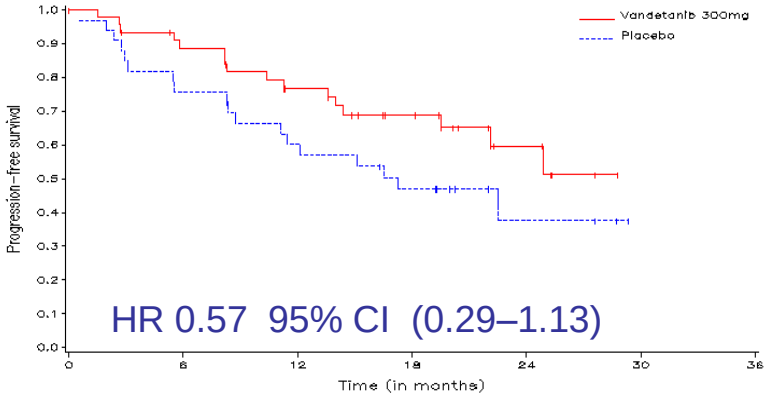
Kaplan-Meier plot of PFS and RET M918T

PFS in RET positive patients



n at months	0	6	12	18	24	30	36
Vandetanib 300mg	137	116	103	87	27	1	0
Placebo	50	34	29	22	8	0	0

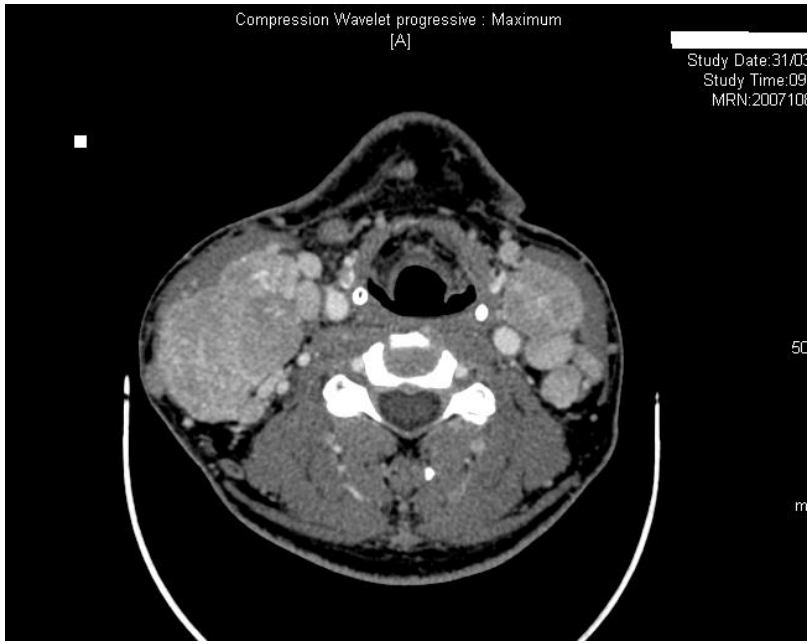
PFS in RET M918T negative patients



n at months	0	6	12	18	24	30	36
Vandetanib 300mg	46	38	30	20	8	0	0
Placebo	33	25	19	14	4	0	0

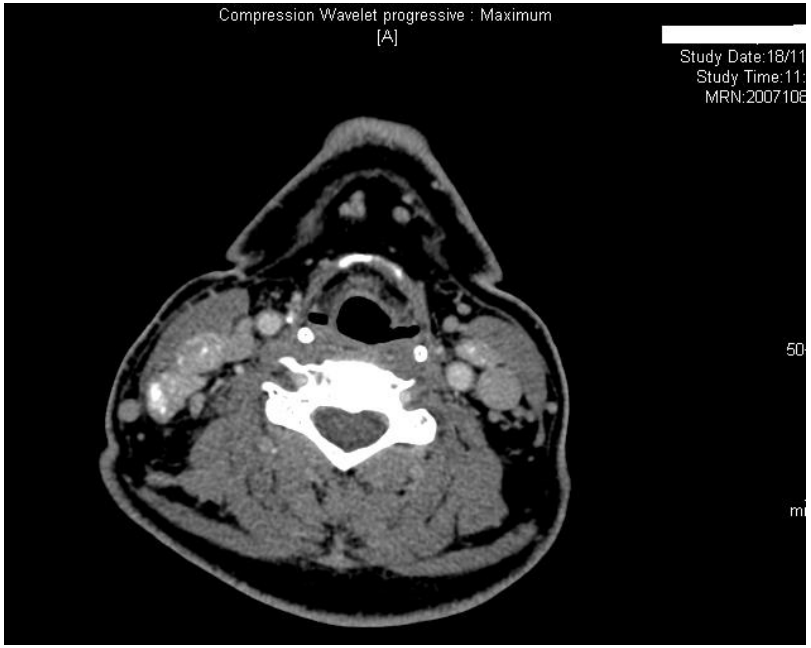
RET mutation negative MTC: patient 2801035

Baseline November 2008



Calcitonin: 35,000pg/mL

Vandetanib 300mg/d. November 2009



850 pg/ml

Molecular Biological Rationale for Vandetanib Activity in RET Mutation Negative MTC

Vandetanib- multi-kinase inhibitor: VEGFR, EGFR and RET:

RET: Vandetanib inhibits Non Mutated RET
RET mutation negative MTC – express Non-Mutated RET
Functional role of Non-Mutated RET carried over to MTC [1]
– Calcitonin secretion decreases on RET inhibition

VEGFR: Expressed by MTC cells[2]
Increased expression in both hereditary and sporadic MTC[3]
Increased expression in RET mutation negative MTC[4]

EGFR: Evidence for amplification and overexpression in MTC[4, 5]
Cross talk between EGFR and RET leading to trans-activation of the receptors has also been described[6]

RAS: Frequent in RET<0 MTCs. Paradigms of EGFR/KRAS mutations in colon carcinoma may not apply

[1] Akeno-Stuart *et al* 2007 [2] Vitagliano *et al* , 2011; [3]Capp *et al* 2010; [4]Rodrıguez-Antona *et a*l 2010; [5]Gorla *et al*, 2008; [6]Croyle *et al*, 2008

Metastatic MTC: vandetanib

- Higher efficacy than any other systemic treatment:
  - High ORR with many long lasting responses (> 3-5 years)
  - Significantly prolonged PFS
  - Symptomatic benefits in many patients

- Vandetanib was available in the frame of an Autorisation Temporaire d'Utilisation (ATU) in France since august 2010: on august 2011, 47 MTC patients have been included (1/1.5 millions/year). 30 AEs have been reported, including 18 serious AEs, but no unexpected toxicities.

- Vandetanib was approved
  - By FDA in april 2011
  - By EMA in november 2011 for the treatment of aggressive and symptomatic MTC in patients with unresectable locally advanced or metastatic disease, but further data are needed to quantify drug benefits in patients with no RET mutation in their metastatic tissue.
  - By France in april 2012.

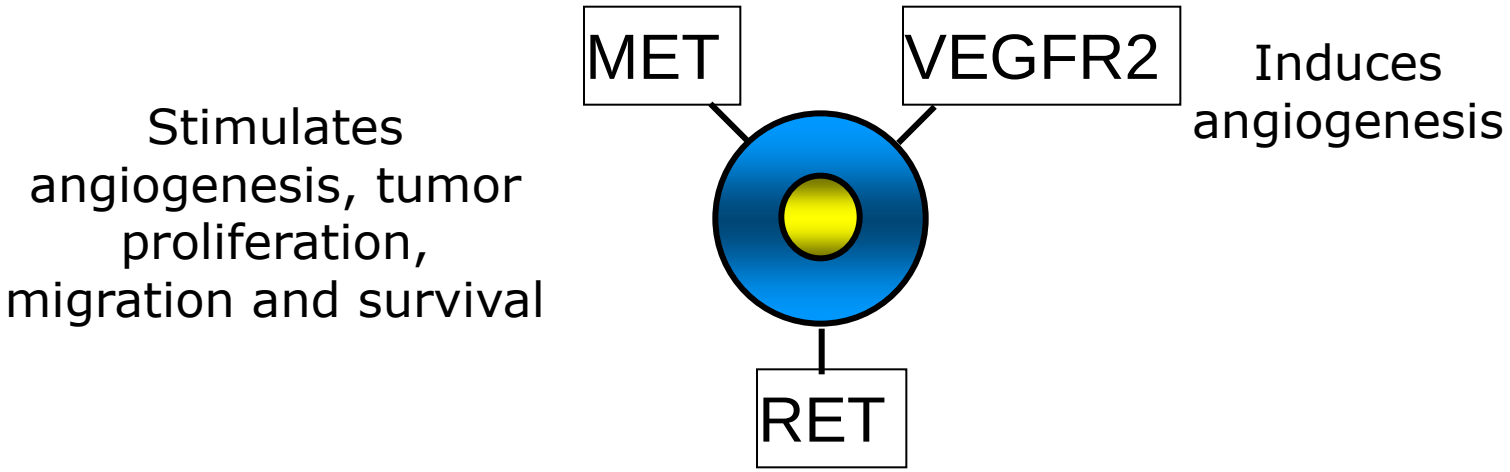
Pour mieux soigner : des médicaments à écarter

le *vandétanib* (Caprelsa°), sans efficacité démontrée sur la survie dans les cancers médullaires de la thyroïde, expose à des effets indésirables graves chez 1 patient sur 3 (diarrhées, pneumonies, hypertensions) et à des morts subites (n° 342 p. 256-259) ;

LA REVUE PRESCRIRE FÉVRIER 2013/TOME 33 N° 352

XL184: preclinical rationale

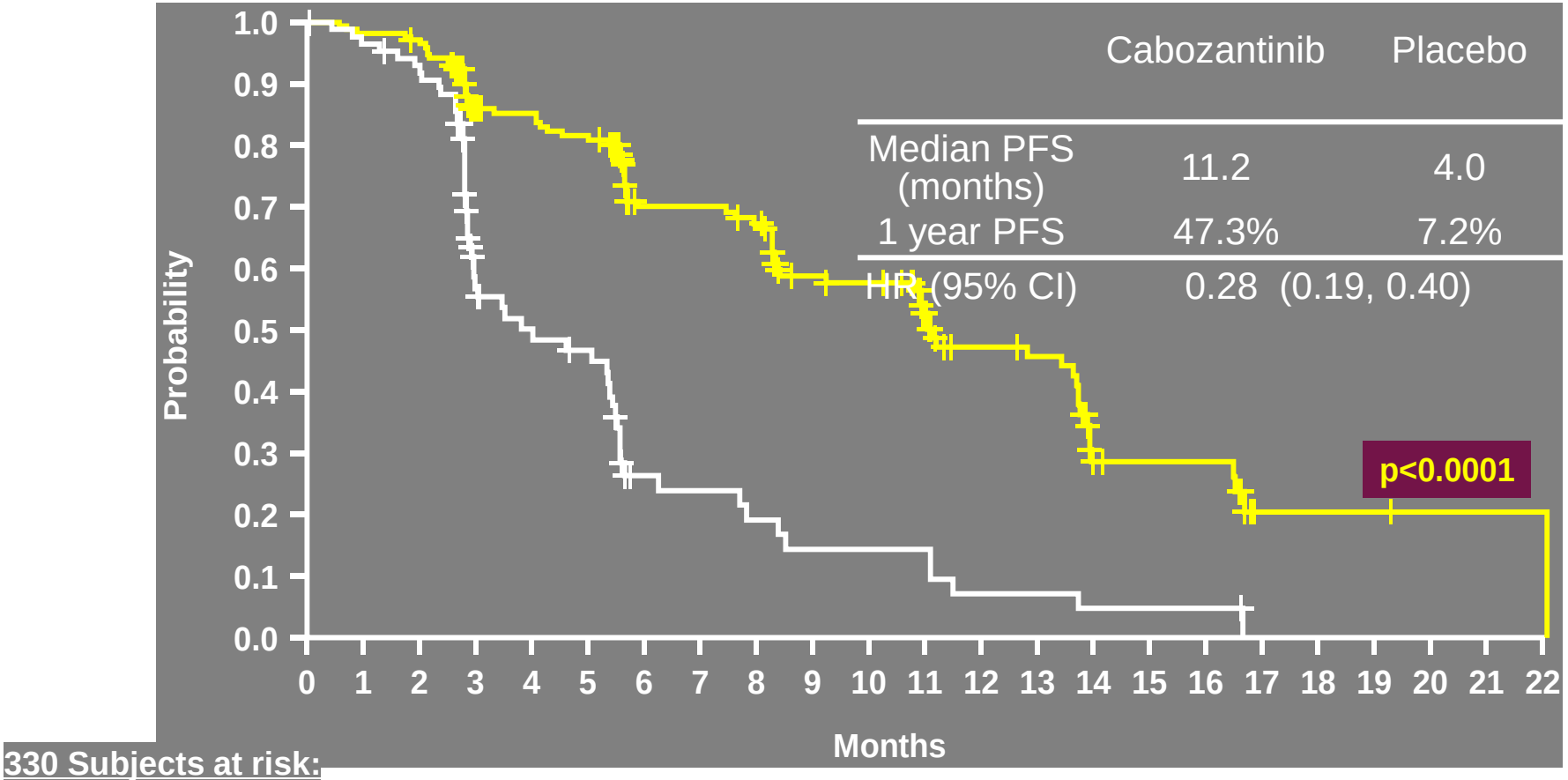
- Inhibits MET, VEGFR2, RET
- Including usual mutants of MET and RET
- Active in animal models
  - *In vivo: inhibition of MET, VEGFR2, RET*
  - *Regression of tumors*



MTC phase 3 trial : cabozantinib vs placebo

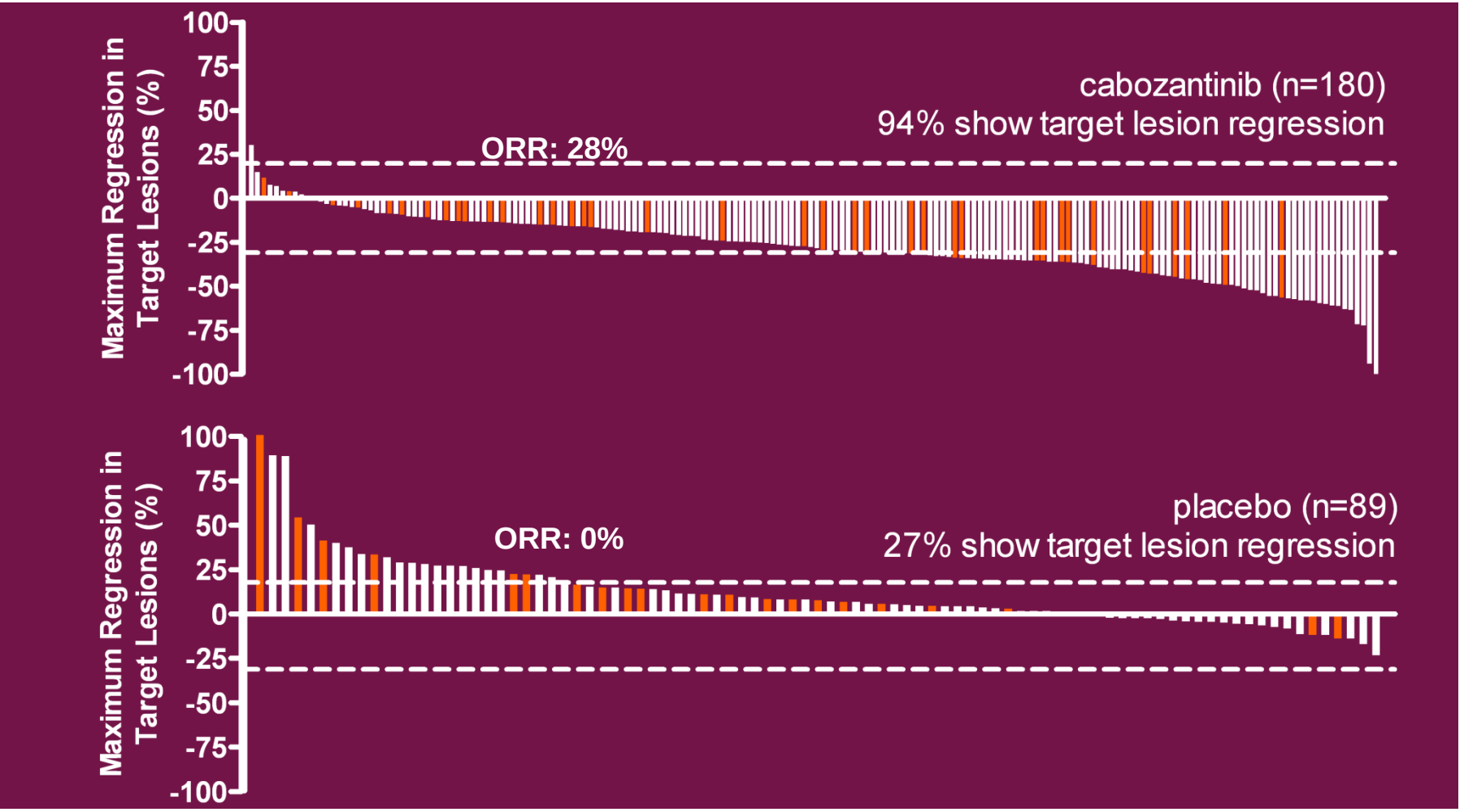
- Cabozantinib (XL-184) (175mg/d) vs placebo without cross-over:
  - 330 patients with progressive disease in <14 months
  - Randomization 2/1
  - ORR: 28%.
  - PFS: 4.0 (placebo) vs 11.2 months (cabozantinib) (HR: 0.28 (95%CI: 0.19-0.40, p<0.0001))
  - OS not mature

Phase 3. Cabozantinib: progression free survival



Schöffski P et al., ASCO Annual Meeting, Chicago, 04 June 2012

Cabozantinib: best tumor response



Prior tyrosine kinase inhibitor therapy (21% of patients)

Median response duration: 14.7 months

Schöffski et al., ASCO Annual Meeting, Chicago, 04 June 2012

Cabozantinib: adverse reactions

Adverse reactions observed in ≥ 25% and grade 3-4 in ≥ 5%: diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome (PPES), decreased weight, decreased appetite, nausea, fatigue, hypertension, abdominal pain.

Laboratory abnormalities (≥25%): increased AST- ALT, lymphopenia, increased alkaline phosphatase, hypocalcemia, neutropenia, thrombocytopenia, hypophosphatemia, and hyperbilirubinemia.

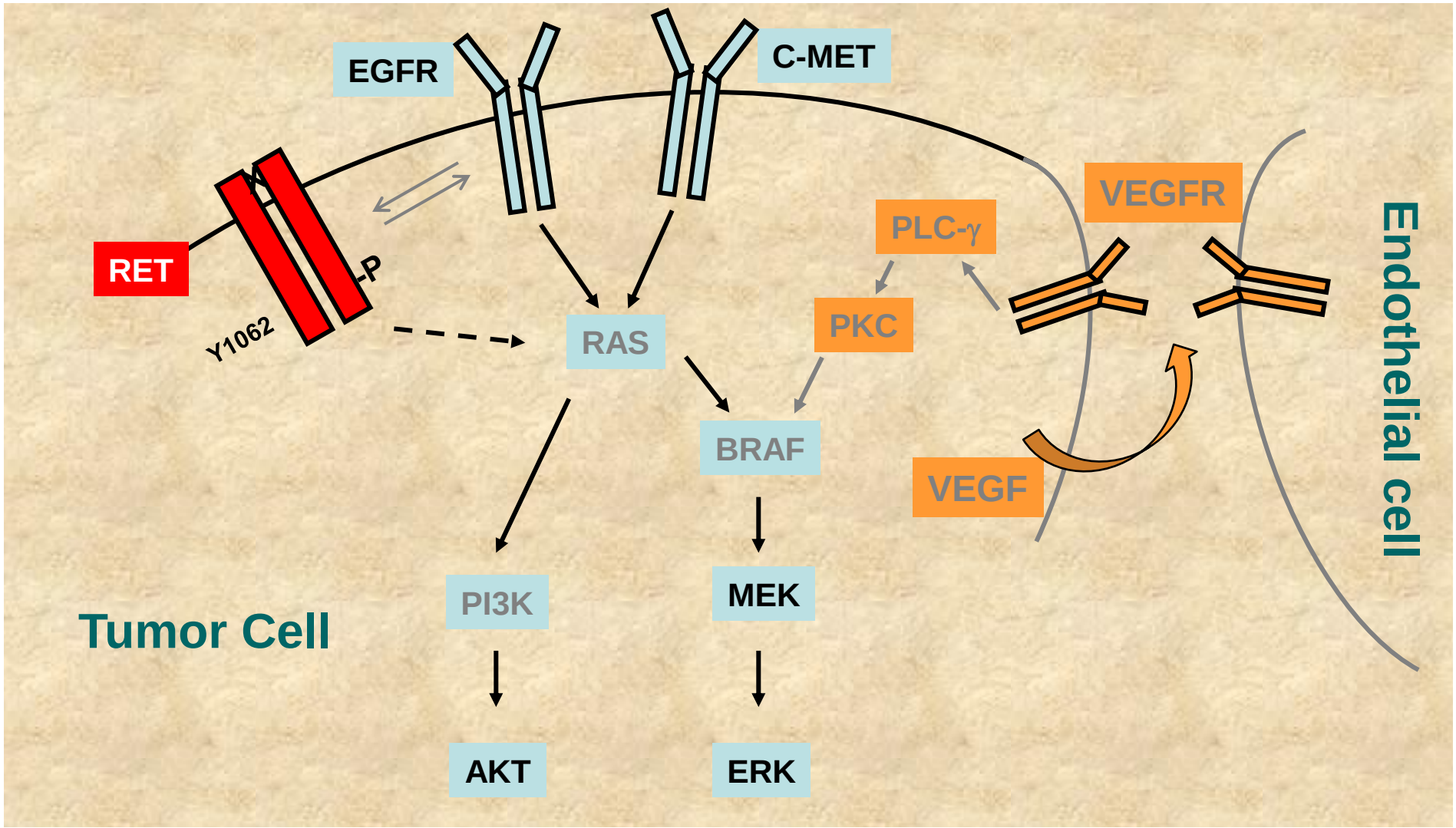
The following serious adverse reactions attributed to cabozantinib included osteonecrosis of the jaw (n=1), reversible posterior leukoencephalopathy syndrome (n=1), pancreatitis (n=3), nephrotic syndrome (n=1), fatal hemorrhage (n=2), and fatal perforation/fistula (n=2).

Dose reduction was required in 79% of patients.

	ZETA Vandetanib	EXAM Cabozantinib
Dose reduction (%)	35	79
Discontinuation for toxicity (%)	12	16
Grade 3 & 4 toxicity (%)		
Diarrhea	11	15.9
HFS	N/A	12.6
Rash	4	0.9
Hypertension	9	8.4
QTc prolongation	8	N/A
Fatigue	6	9.3
Decreased appetite	4	4.7

MTC

Activating RET mutation: 100% hereditary, > 40% sporadic MTCs
Activating RAS mutation: > 2/3 of MTCs without RET mutation



Response to cabozantinib and mutational status (ASCO, 2013)

- *RET* status was determined in 216/330 pts
- 79% harbored an activating mutation, and 21% were mutation negative.
- All *RET* mutational subgroups (positive, negative, and unknown) showed hazard ratios indicating PFS benefit from cabo treatment, and an ORR between 22% and 32%.
- Pts with *RET* M918T mutation showed a statistically significant longer median PFS on cabo treatment (61 weeks) than other *RET* mutation positive pts (36 weeks, p=0.049).
- 16/85 tested pts with negative or unknown *RET*-mutation status had a RAS gene mutation: the RAS-positive pts showed a similar ORR (31%) and PFS (47 weeks) as the *RET* positive population.

Cabozantinib: FDA approval

On November 29, 2012, the U. S. Food and Drug Administration approved cabozantinib (COMETRIQ capsules, Exelixis, Inc), for the treatment of patients with progressive metastatic medullary thyroid cancer (MTC).
On March 2014 by EMA.

Natural history of a 52-year-old sporadic MTC patient

1986	Total thyroidectomy + lymph node dissection (T4, N1, M0) Radiation therapy to the neck	
1987	Ct = 134 pg/mL Negative imaging	
1993	Ct = 698 pg/mL Liver mets: 7, 7, 7 mm	
1996	Ct = 1,500 pg/mL Liver mets: 12, 16, 17 mm	
1999	Ct = 3,400 pg/mL Liver mets: 10, 15, 16, 20 mm	Local treatment
2002 (2012)	Ct = 5,500 pg/mL Liver mets: 14, 18, 15, 24 mm Good quality of life, no diarrhea	
2004	Ct = 12,200 pg/mL Lung and bone mets Bone surgery and chemotherapy (no benefits)	TKI
2005	Brain mets Radiation therapy	
July 2006	Death	

Ct and tumor doubling times ~3 years

Metastatic MTC: molecular targeted therapies

- Duration of treatment (years?), short and long-term toxicity, quality of life, improvement of survival are still under evaluation: *local treatment modalities of distant metastases may control the disease and delay the initiation of systemic treatment*

- There is no indication:
  - For patients with elevated Ct and or CEA levels and no other evidence of disease
  - For patients with minimal disease (< 2cm), when asymptomatic and stable

- Decision to treat has to be validated by a multidisciplinary team

- Control of toxicities

Advanced MTC's new unmet need: progression following treatment with TKIs

- Patients progress, but maintain good performance status
- Many patients respond, then progress in a new lesion or a subset of lesions.
- Need for studies:
  - Get tissue! – Perform translational analysis - perform trials
    - Sequential treatment with MKIs, but all molecules are anti-angiogenic
    - Find other targets. New agents in development may also play a role in the treatment of thyroid cancer in the first- or second-line settings (PI3K) and PD-1-PDL-1

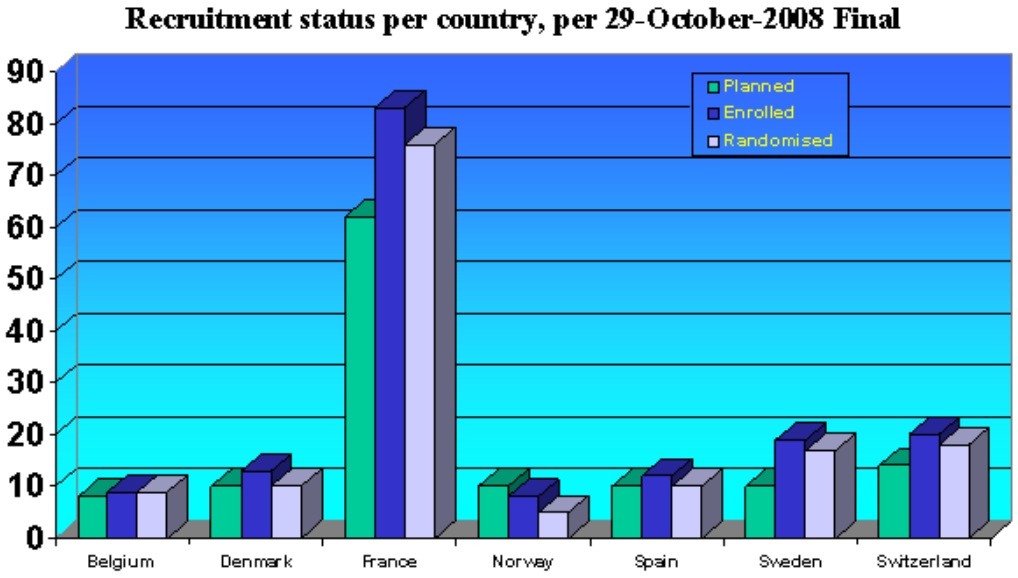
French network for rare cancers: TUTHYREF: TUmeurs de la THYroïde REfractaires supported by the French Institut National du Cancer

- Referral center: IGR
- 30 competence centres

-Web conference every 2 weeks, annual meeting, protocols

- Objectives:
  - -Recommendations: ATA/ETA
  - -Research
  - -Access to innovation for all patients

TUTHYREF



Networks for refractory thyroid cancers: a need for a new era

- Several compounds are partially effective, and there is a need for:
  - Improving drug efficacy
  - Decreasing drug toxicity
  - Predicting drug efficacy (biomarkers, ….)
- Need for large series of patients (Phase II and III trials) in National, European (Endocrine Group of the EORTC) and International (ITOG) networks

- Inclusion of patients in trials rather than off label use of drugs.
- Getting the right drug to each patient