MADRID 2014 ESMO congress

Practical Management of Tyrosine-Kinase Inhibitors

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Disclosures

- Research funding
  - Bayer, Astrazeneca, Exelixis, Eisai
- Advisory role
  - Bayer, Astrazeneca, Exelixis, Eisai

Patient Case

- 52-y old male. No medical/family past history of interest
- First Treatment
  - November 2006: Total Thyroidectomy and bilateral lymphadenectomy
- Pathological Report
  - 4 cm invasive medullary bilateral thyroid carcinoma with invasion of subcutaneous soft tissue and metastases in 16 out of 20 lymph nodes of the right neck and 3 out of 15 lymph nodes of the left side.
  - Ki 67: 9%; Mitotic count: 5 x 10 HPF (Grade 2)
  - T4aN1bM0, Stage IVA
- Adjuvant therapy: External Beam Radiotherapy (EBRT)

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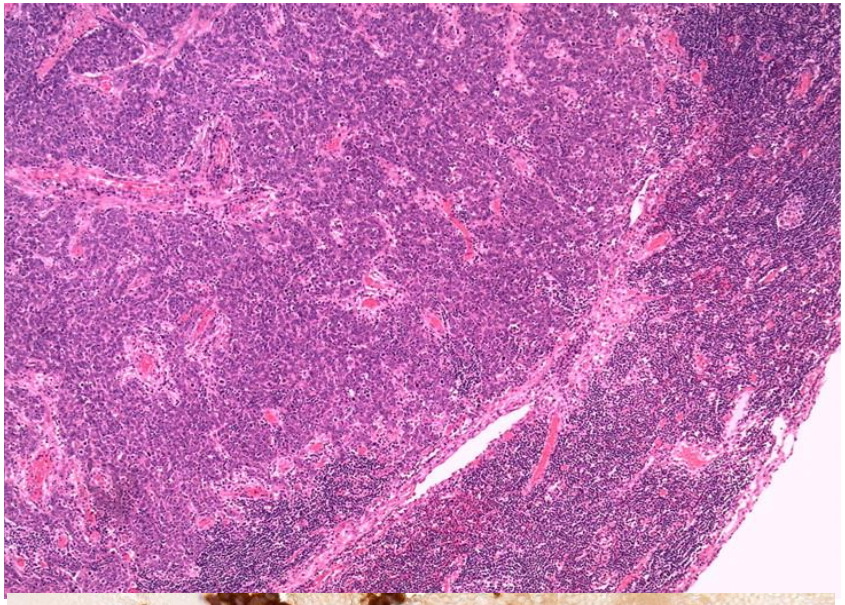
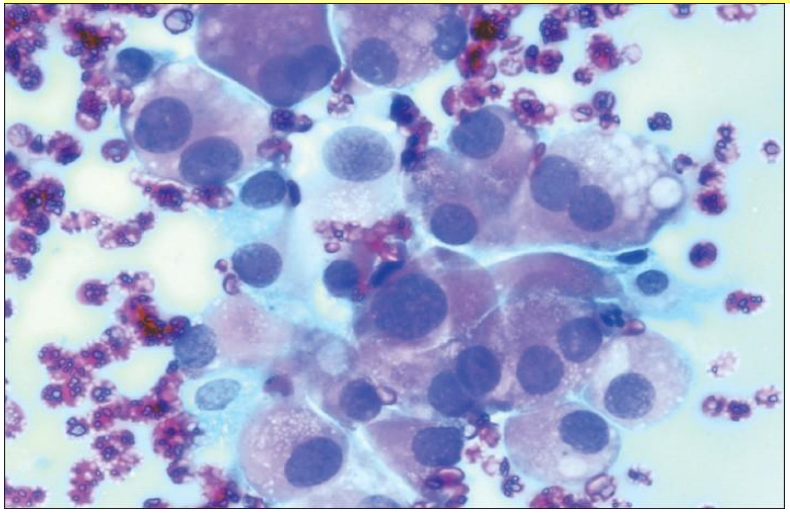
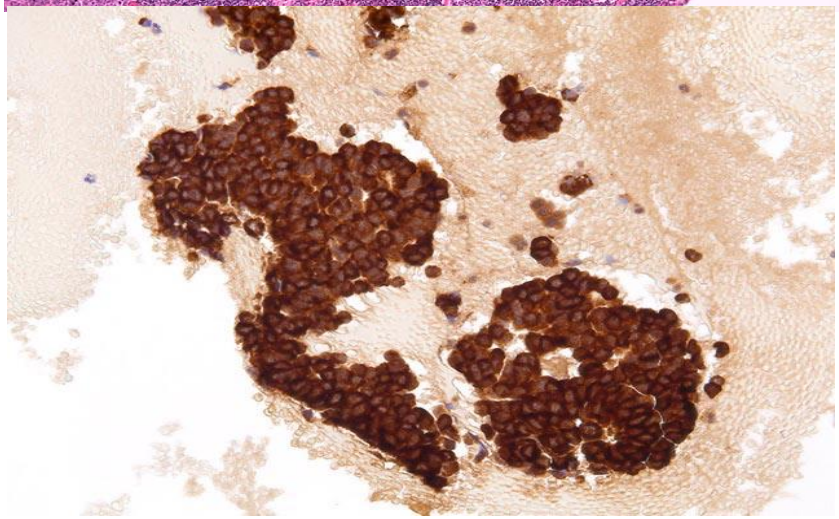


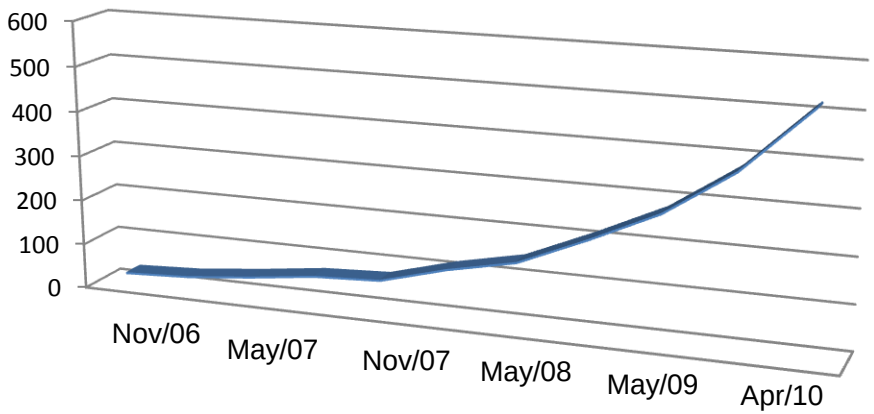




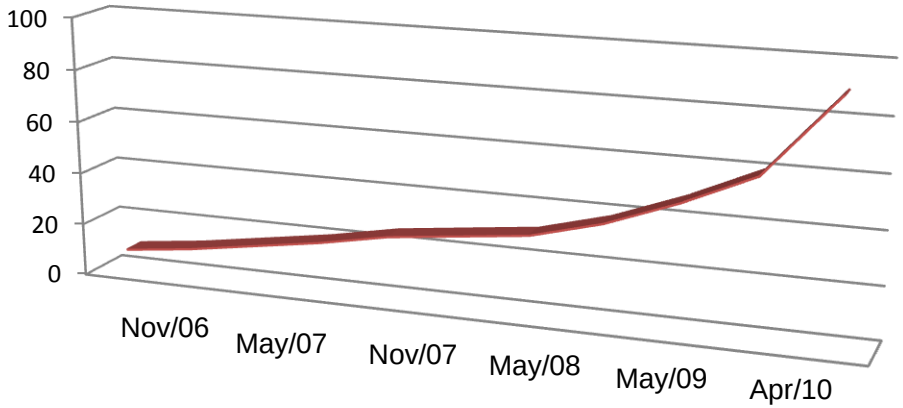
Disease Evolution

- November 2006 until April 2010 the patient was asymptomatic, with progressive increase in Calcitonin and CEA levels with no suggestive images of relapse (CT, Neck US & PET-CT scan). Diarrhea started in July 2009.

Calcitonin

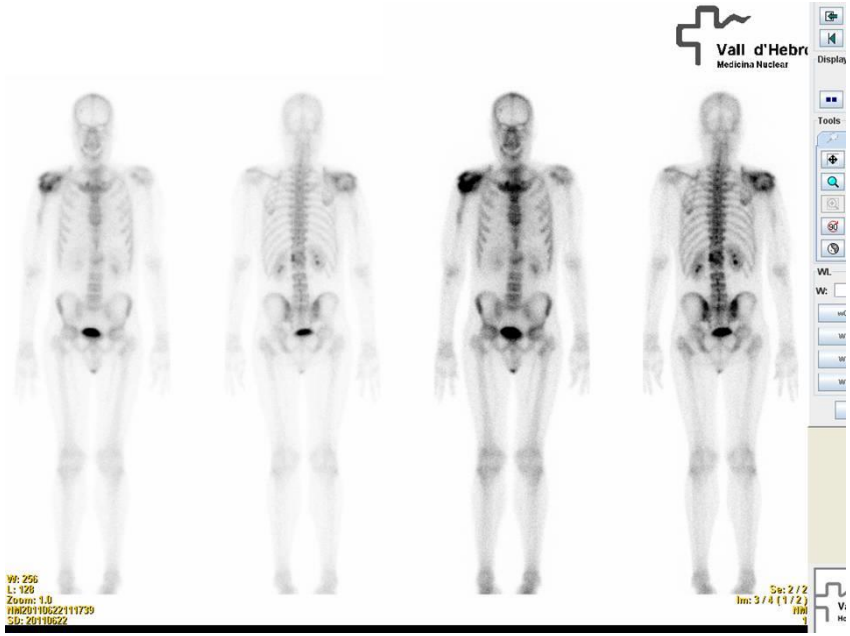


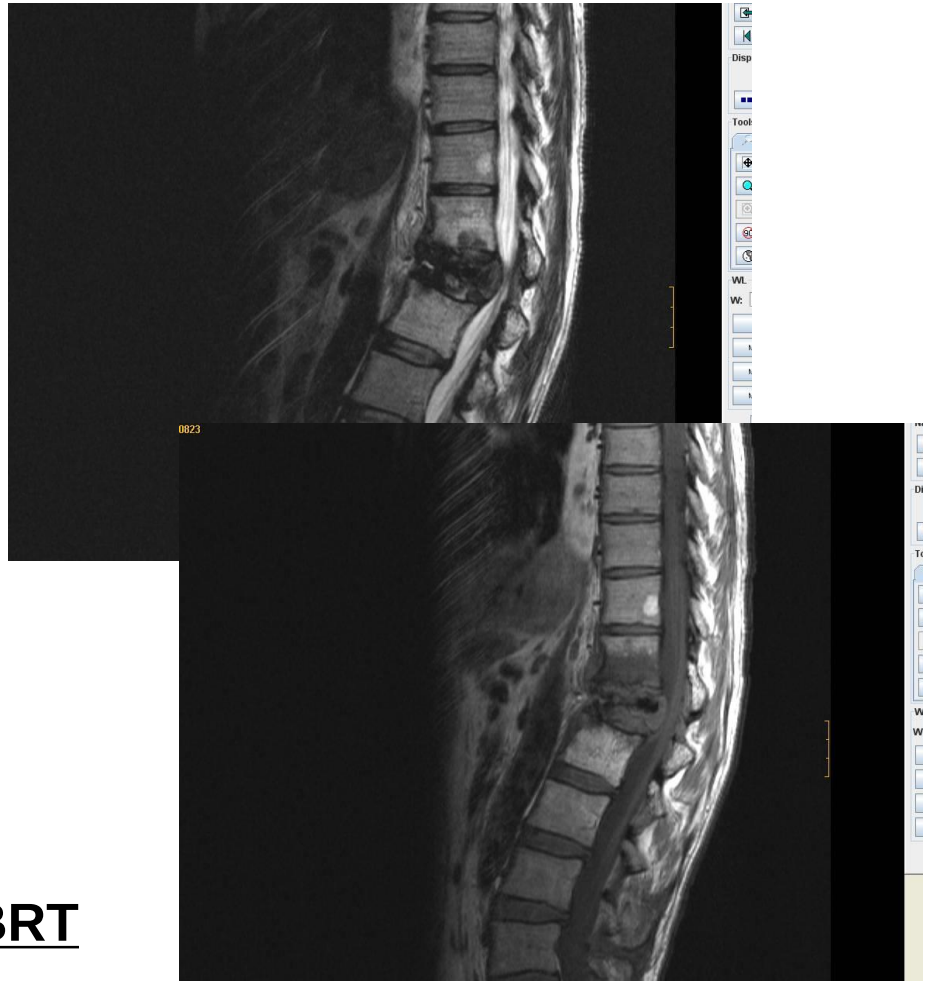
CEA



Disease Evolution

- December 2010: back pain

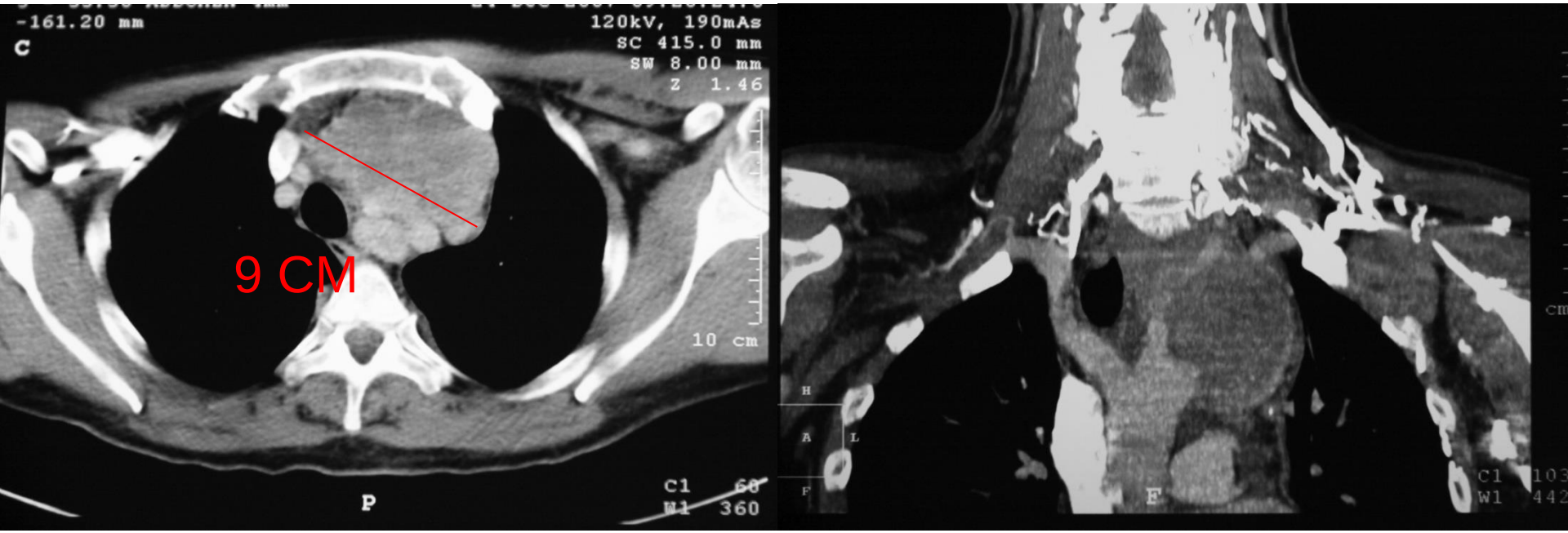




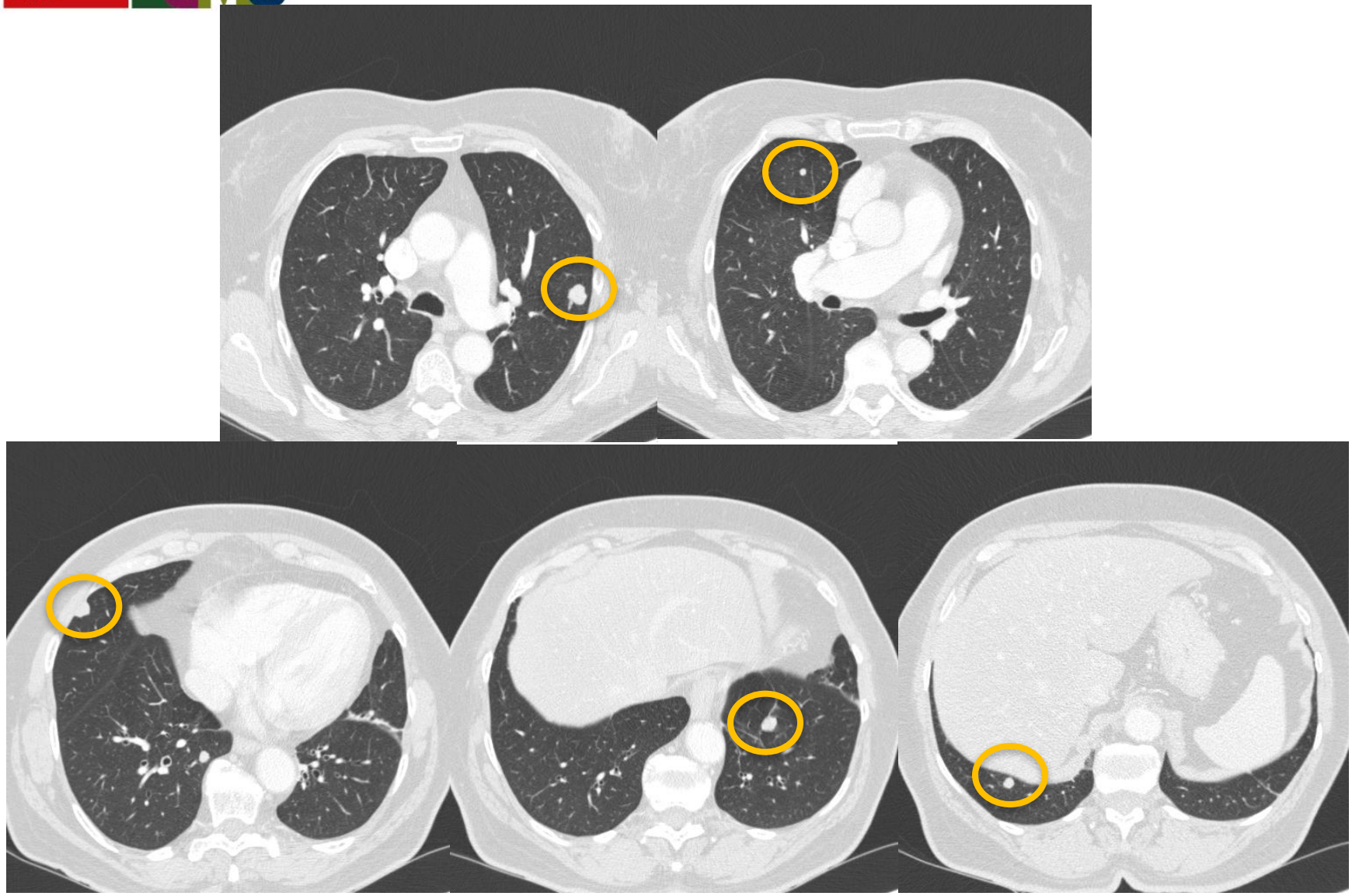
- **Arthrodesis D12-L3 followed by EBRT**

Disease Evolution

- July 2011…



Calcitonin doubling time < 1 year

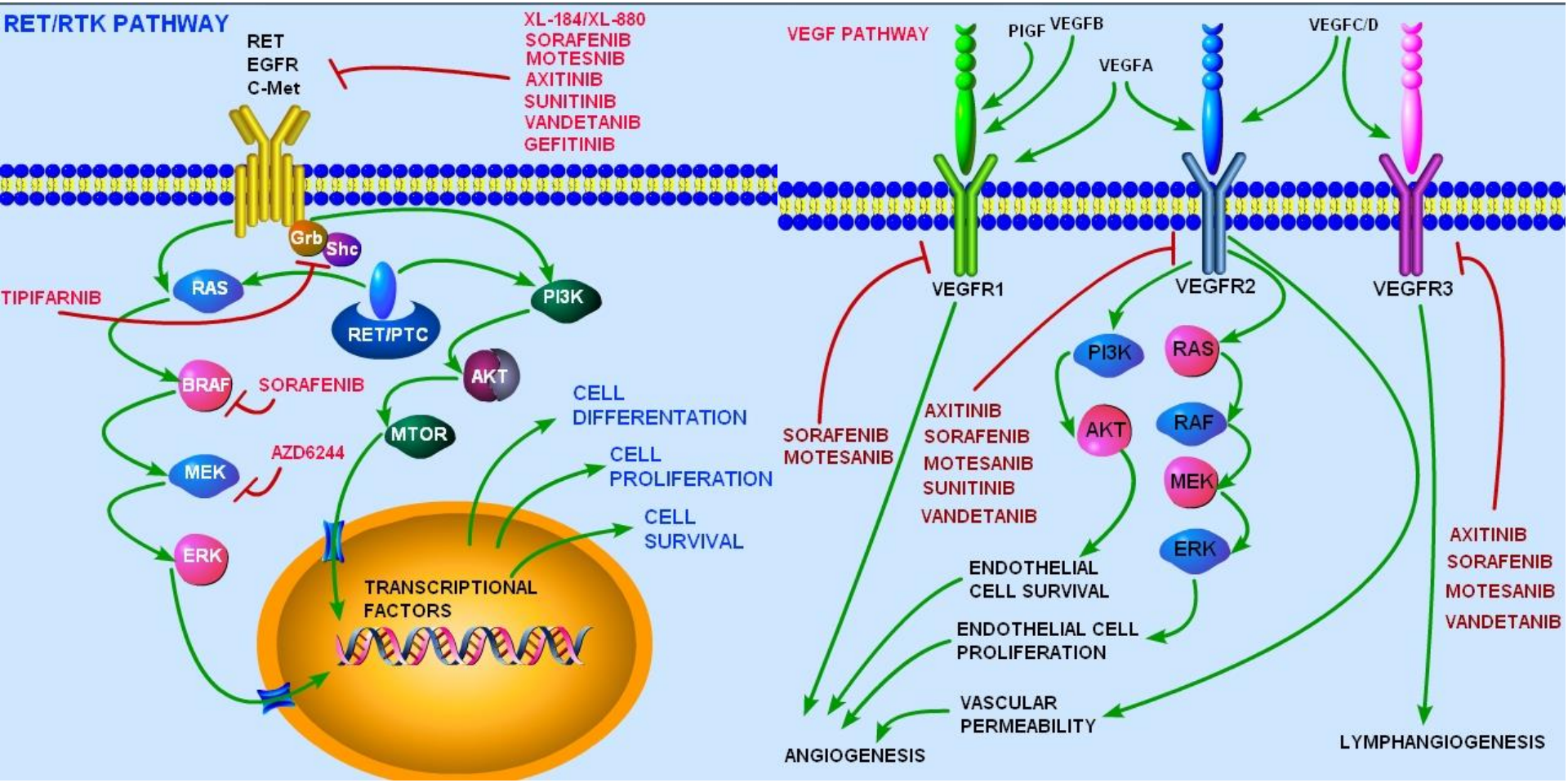


Orphan Tumor: Low Clinical Evidence

CHT SCHEDULE	RESPONSE RATE*	AUTHOR/YEAR
DOXORUBICIN	1/4 (25%)	Shimoaka/1985
DOXORUBICIN + CISPLATIN	2/6 (33%)	Shimoaka/1985
STREPTOZOCIN/5FU or DTIC/5FU	3/20 (15%)	Schlumberger/1995
LANREOTIDE + INTERFERON α2b	0/7**	Vitale/2000

* Tumor Evaluation: physical exam, chest radiography, neck or liver ultrasound, tumor markers decrease
** Tumor Evaluation: CT scan. Symptomatic improvement and tumor marker decrease in 6/7 pts

Molecular Rational for MKIs



Capdevila J, et al. *Target Oncol*, 2009

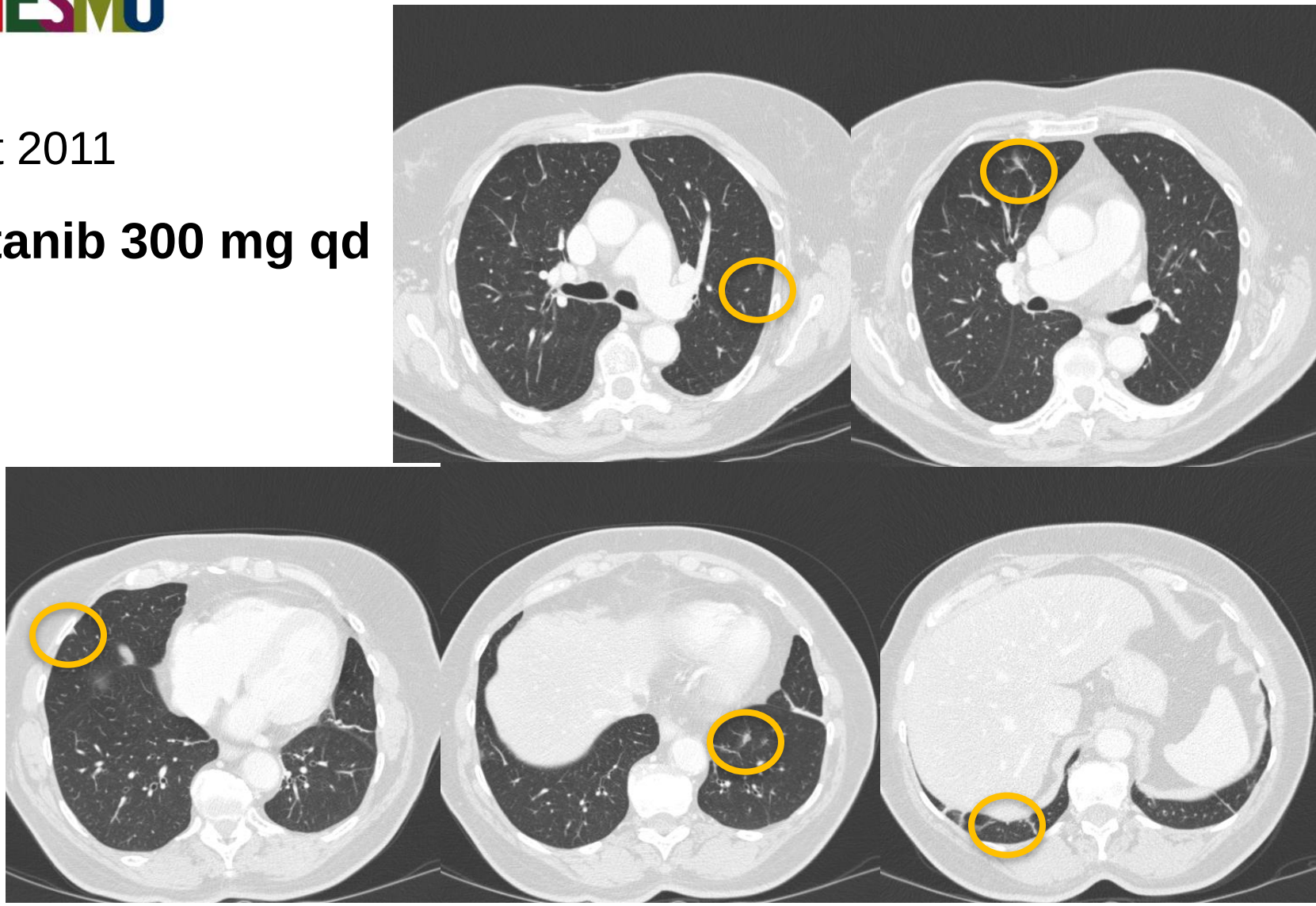
Multikinase Inhibitors in MTC

Small molecules inhibitors of multiple proteins with kinase activity in clinical trials for medullary thyroid carcinomas										
Drug	Targets with IC_{50} values (nmol/l)									
	RET	VEGFR1	VEGFR2	VEGFR3	PDGFRα	PDGFRβ	BRAF	KIT	FLT_3	Other
Sorafenib (BAY-439006)	47	26	90	20	-	57	25	68	33	
Motesanib (AMG 706)	59	2	3	6	-	84		8	33	
Axitinib (AG-013736)	1.2	1.2	0.16	0.29	5.2	1.6	-	1.7	-	
Sunitinib (SU011248)	100	-	4	-	-	39	-	1-10	8-14	
Vandetanib (ZD6474)	60	-	40	110	-	-	-	-	-	EGFR 500
Cabozantinib (XL-184)	4	-	0.035	-	-	-	-	-	-	C-MET 1.8
Lenvatinib (E7080)	35	22	4	5.2	-	39	-	-	-	FGFR1 46

Capdevila J et al. *Target Oncol*, 2009

- August 2011

Vandetanib 300 mg qd



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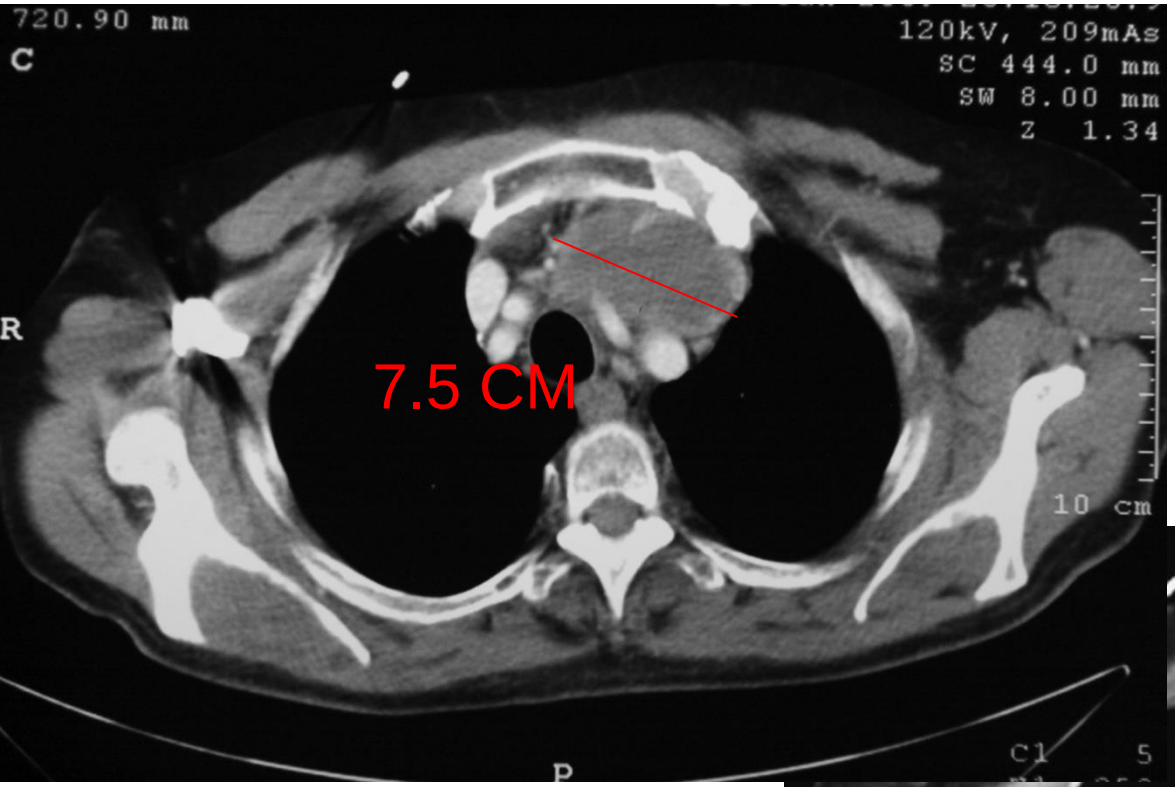
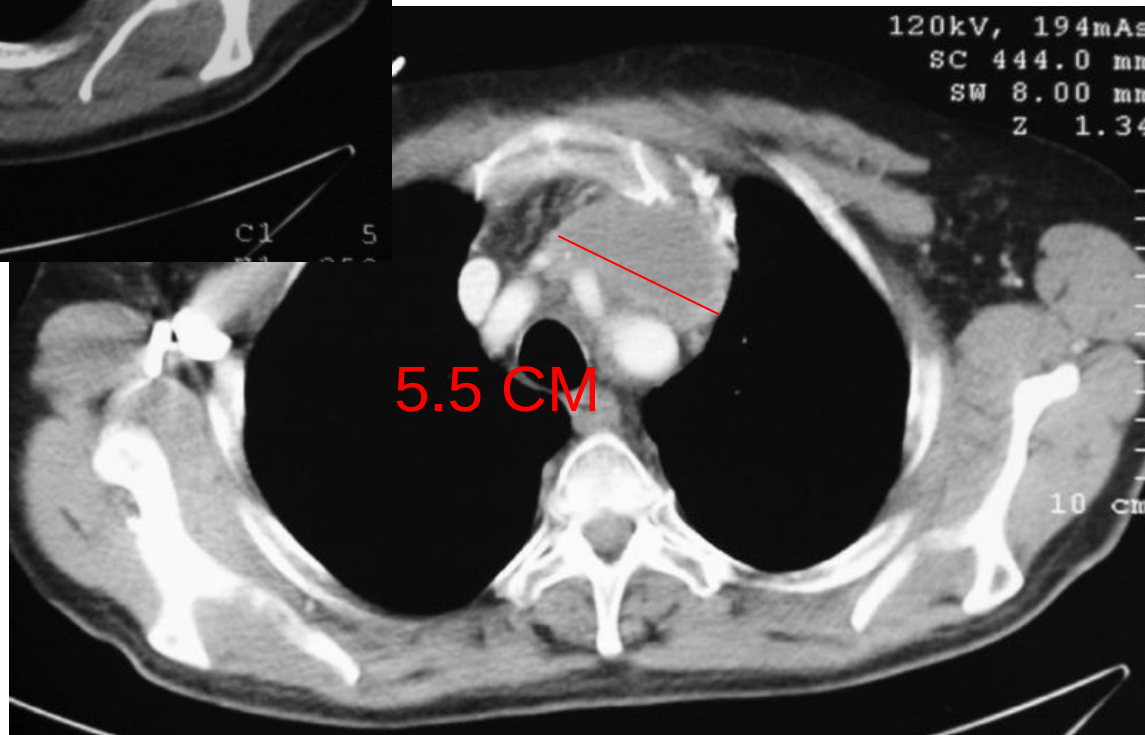


AFTER 2 MONTHS



AFTER 4 MONTHS

26-30 September 2014, Madrid, Spain

Drug-Related Toxicity

- Grade II skin rash
  - Mainly on face, thorax and arms
- Grade II nausea and vomiting
- Grade II QTc prolongation
  - asymptomatic
- Grade III photosensitivity skin reaction
  - Interfering with ADL

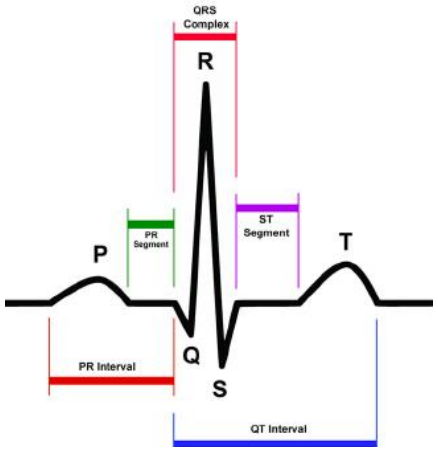
Toxicity Profile of Vandetanib

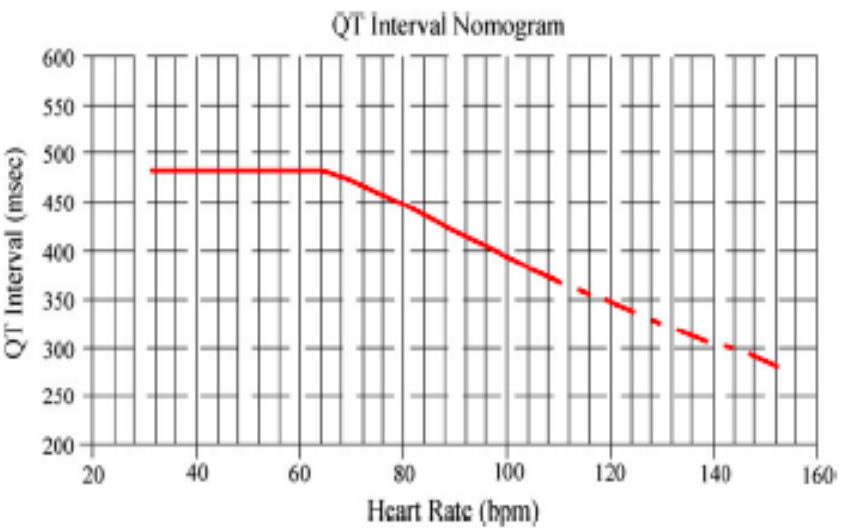
Any grade AE	Vandetanib 300 mg (n=231)	Placebo (n=99)
Diarrhea	130 (56%)	26 (26%)
Rash	104 (45%)	11 (11%)
Nausea	77 (33%)	16 (16%)
Hypertension	73 (32%)	5 (5%)
Fatigue	55 (24%)	23 (23%)
Headache	59 (26%)	9 (9%)
Decreased appetite	49 (21%)	12 (12%)
Acne	46 (20%)	5 (5%)
Asthenia	34 (14%)	11 (11%)
Vomiting	34 (14%)	7 (7%)

Any grade AE	Vandetanib 300 mg (n=231)	Placebo (n=99)
Back pain	21 (9%)	20 (20%)
Dry skin	35 (15%)	5 (5%)
Insomnia	30 (13%)	10 (10%)
Abdominal pain	33 (14%)	5 (5%)
Dermatitis acneiform	35 (15%)	2 (2%)
Cough	25 (10%)	10 (10%)
Nasopharyngitis	26 (11%)	9 (9%)
ECG QT prolonged*	33 (14%)	1 (1%)
Weight decreased	24 (10%)	9 (9%)

Wells SA Jr, et al. *J Clin Oncol.* 2012

Drug-Related QTc Prolongation





- **Factors related with QTc prolongation**
  - **Electrolyte levels**
  - **Thyroid function**
  - **Concomitant medication**

Grande E,…,Capdevila J. *Adv Ther.* 2013

QTc Prolongation Management

Table 5 Selection of agents that are contraindicated or not recommended for coadministration with vandetanib

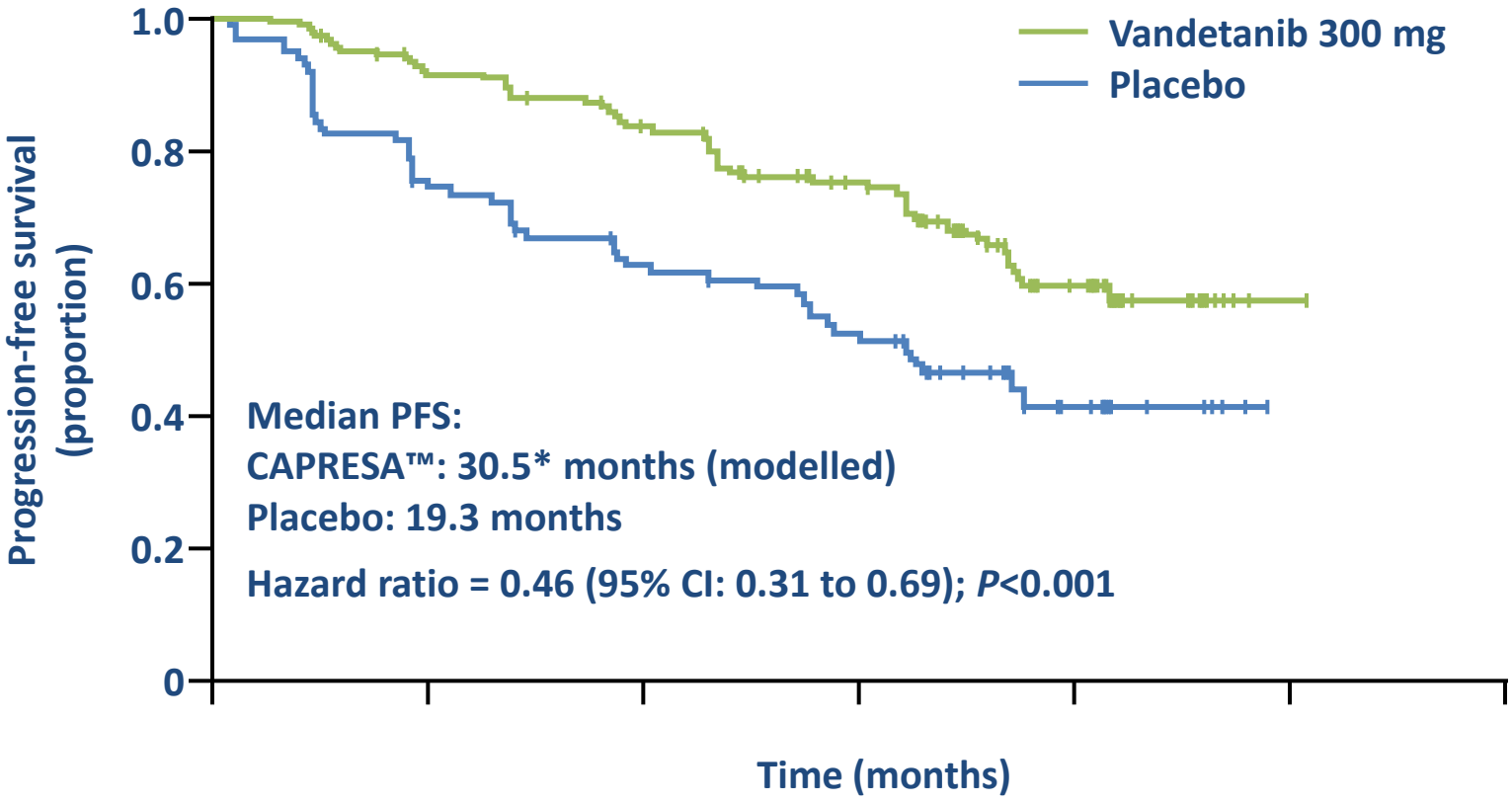
Contraindicated	Not recommended
Arsenic	Amisulpride
Cisapride	Chlorpromazine
Class IA and III antiarrhythmics	Halofantrine
Intravenous erythromycin	Haloperidol
Mizolastine	Lumefantrine
Moxifloxacin	Methadone
Toremifene	Metoclopramide
	Ondansetron
	Pentamidine
	Sulpiride
	Zuclopenthixol

- K^+: 3.1 (NL > 3.6)
- Ca^+: 7.9 (NL > 8.8)

- Electrolyte reposition
- Avoiding drugs that prolong QTc

Grande E,…,Capdevila J. *Adv Ther.* 2013

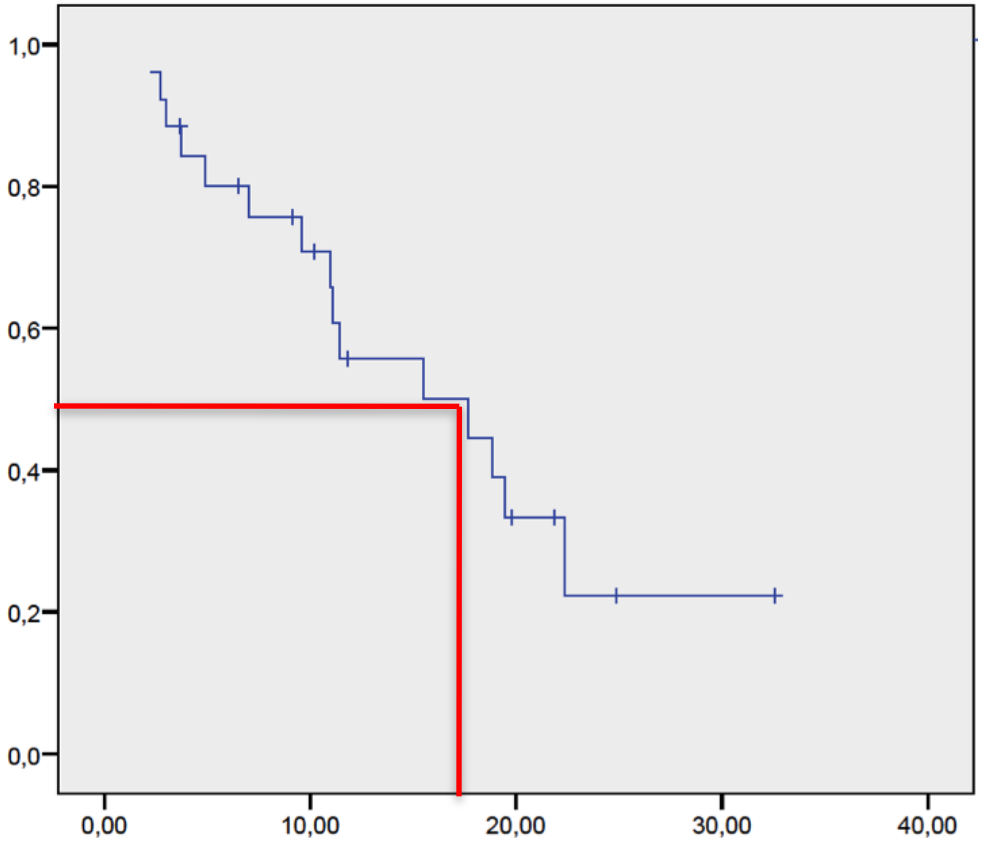
Progression-Free Survival



Wells SA Jr, et al. *J Clin Oncol.* 2012

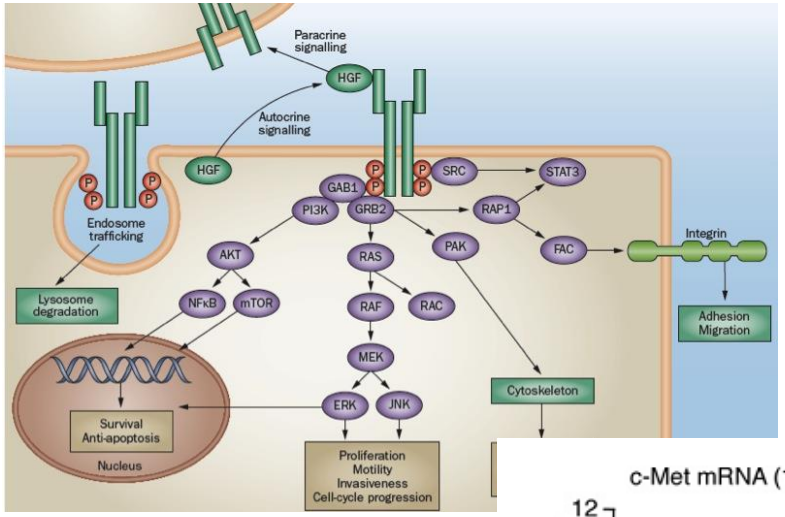
Real World Data with Vandetanib

- mPFS: 17.6 months
- August 2011-May 2013 (21 months)

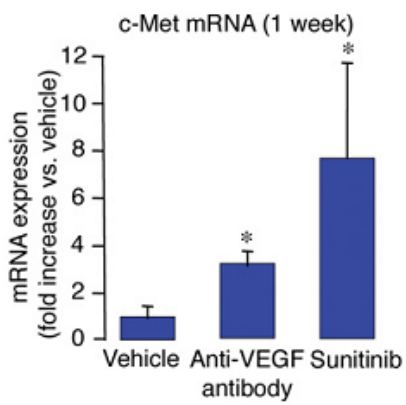


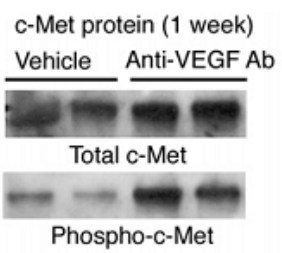
Grande E,…,Capdevila J. *ESMO* 2014. 1161P

Mechanism of Resistance to VEGFR Inhibition: Role of C-MET



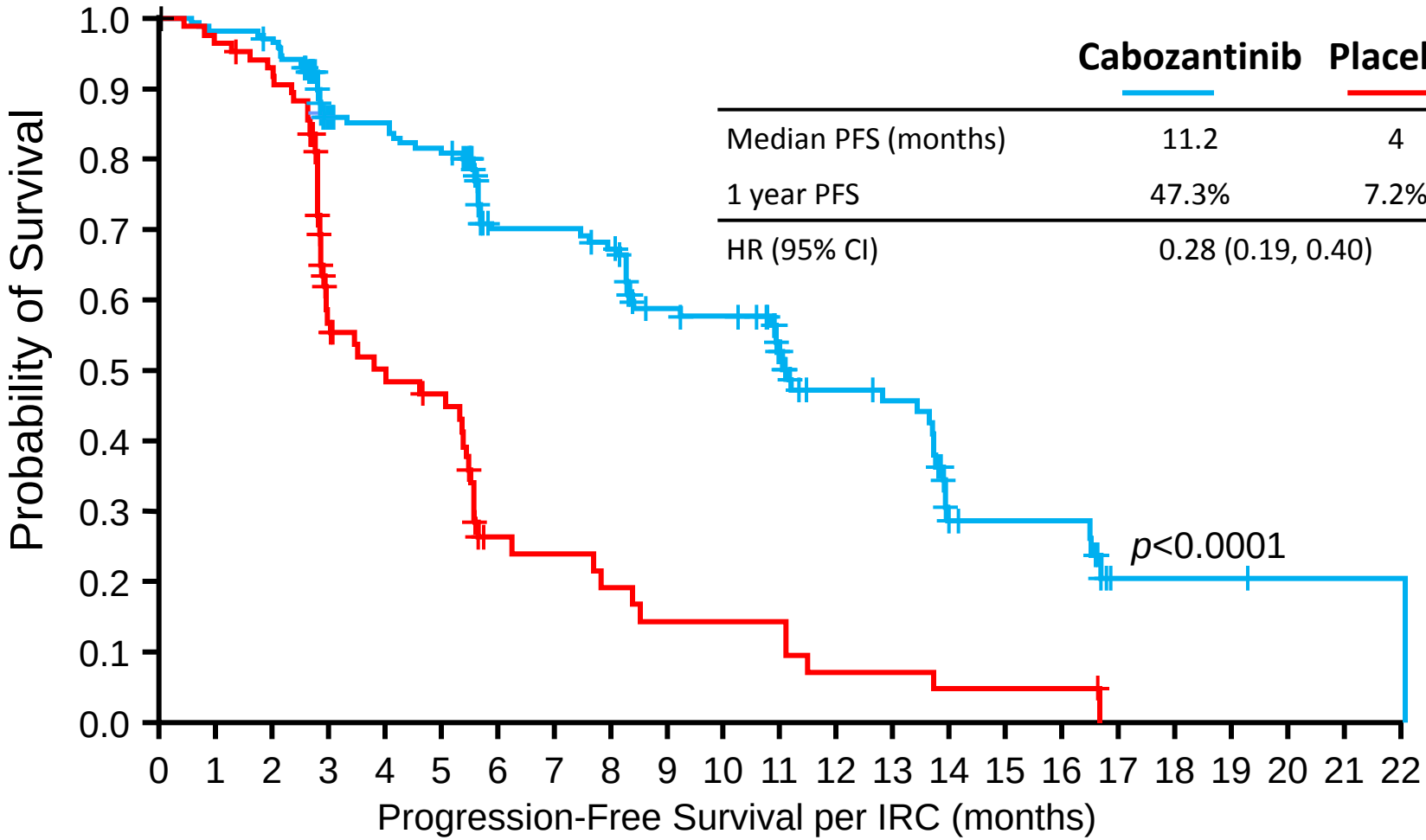
	Expression[a]			Mutation[a]		Association
	MET (+)	HGF (+)	Elevated MET RNA	*MET* Gene amplified	*MET* mutation[b]	Poor prognosis
Carcinomas						
Bladder	+	+				+
Breast cancer	25–60%	+	+			+
Cervical cancer	30–72%	+				+
Cholangiocarcinoma	+	+				
Colorectal (incl. liver mets)	55–78%[c]	+	+	4–89%		+
Endometrial	+	+				
Oesophageal carcinoma	+	+		+		+
Gastric carcinoma	75–90%	+		5–10%	g	+
Head and neck (incl. lymph node mets)	52–68%	+			s (11–27%)	+
Renal cell/papillary renal	54–87%	+	+	Trisomy 7	g/s (13–100%)	+
Hepatocellular	68–69%	+	+		s (0–30%)	+
Lung (non-small cell)	41–72%	+		5–10%	8–13%	+
Lung (small cell)	+	+				+
Nasopharyngeal	+	+				+
Oral squamous cell carcinoma		+	+			+
Ovarian	64%	+	+		0–4%	+
Pancreatic/gallbladder	+	+	+			+
Prostate	+	+	+			+
Thyroid	40–91%	+	+		6–10%	+
Sarcomas	20–87%				0–3%	
Other tumor types						
				9–20%	0–9%	+
				+		
						+





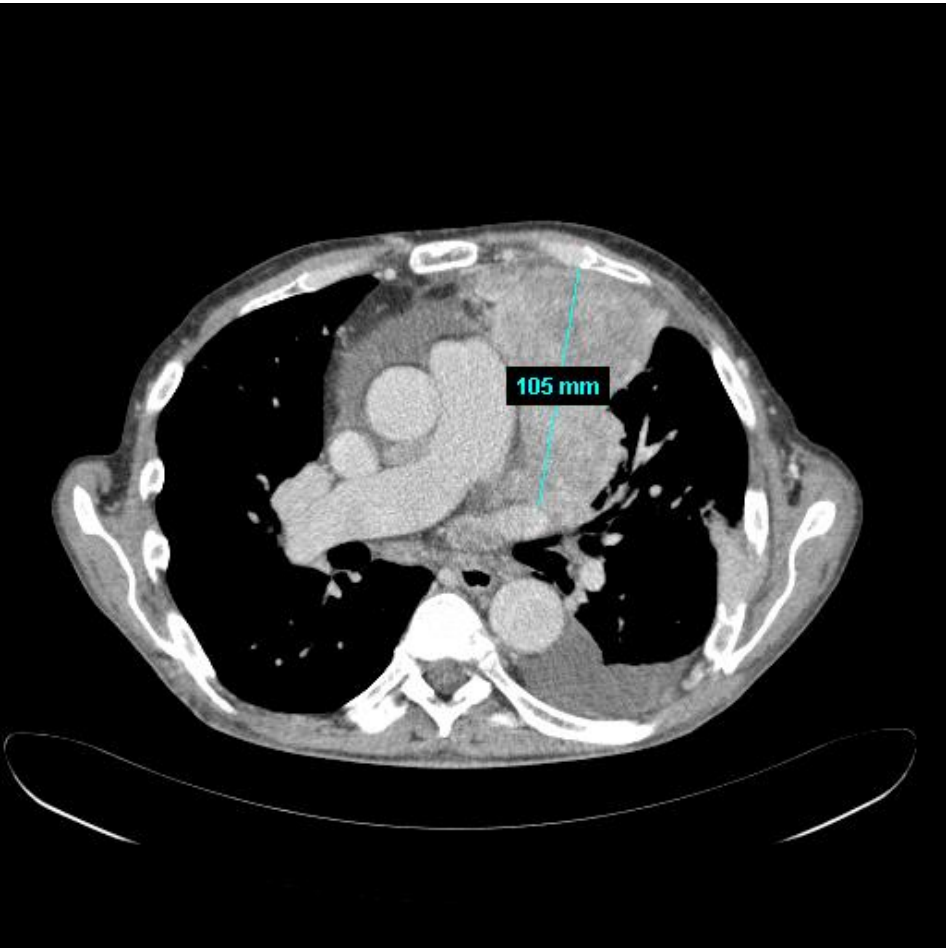
Peters & Adjei. *Nat Rev Clin Oncol* 2012
Scagliotti GV, et al. *Cancer Treatment Reviews* 2013
Sennino B, et al. *Cancer Discovery* 2012

Cabozantinib: VEGFR + c-MET Inh



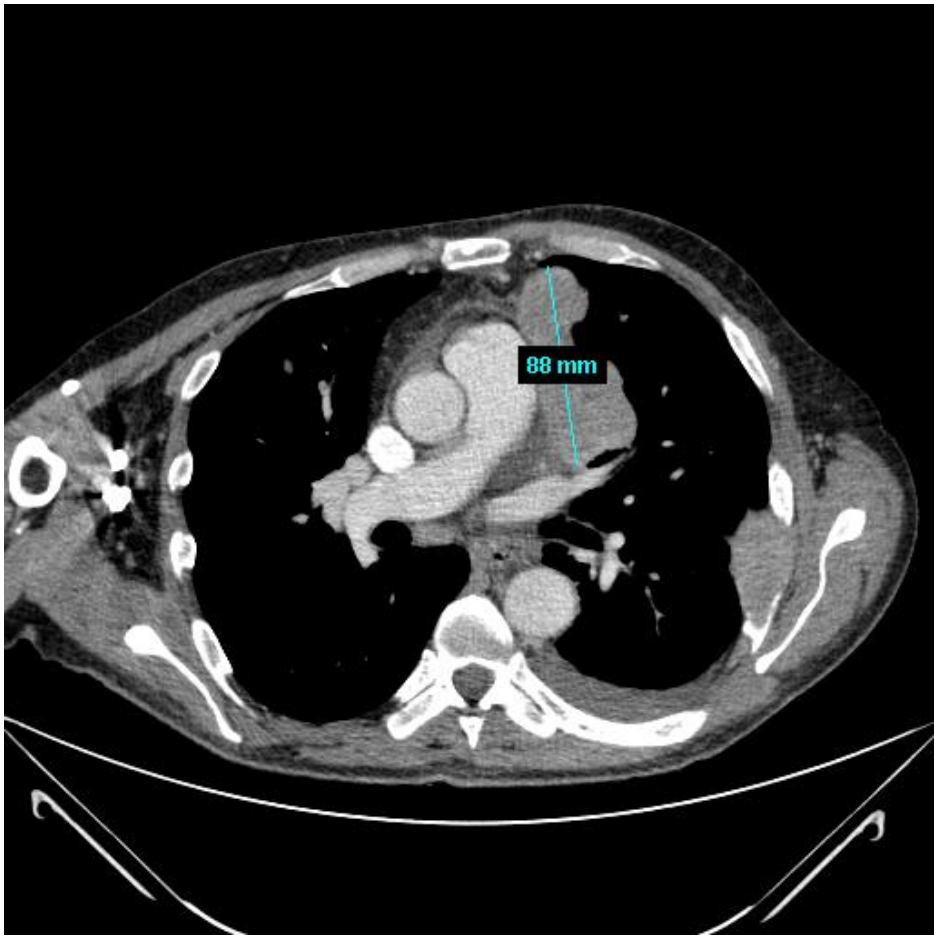
	Cabozantinib	Placebo
Median PFS (months)	11.2	4
1 year PFS	47.3%	7.2%
HR (95% CI)	0.28 (0.19, 0.40)	

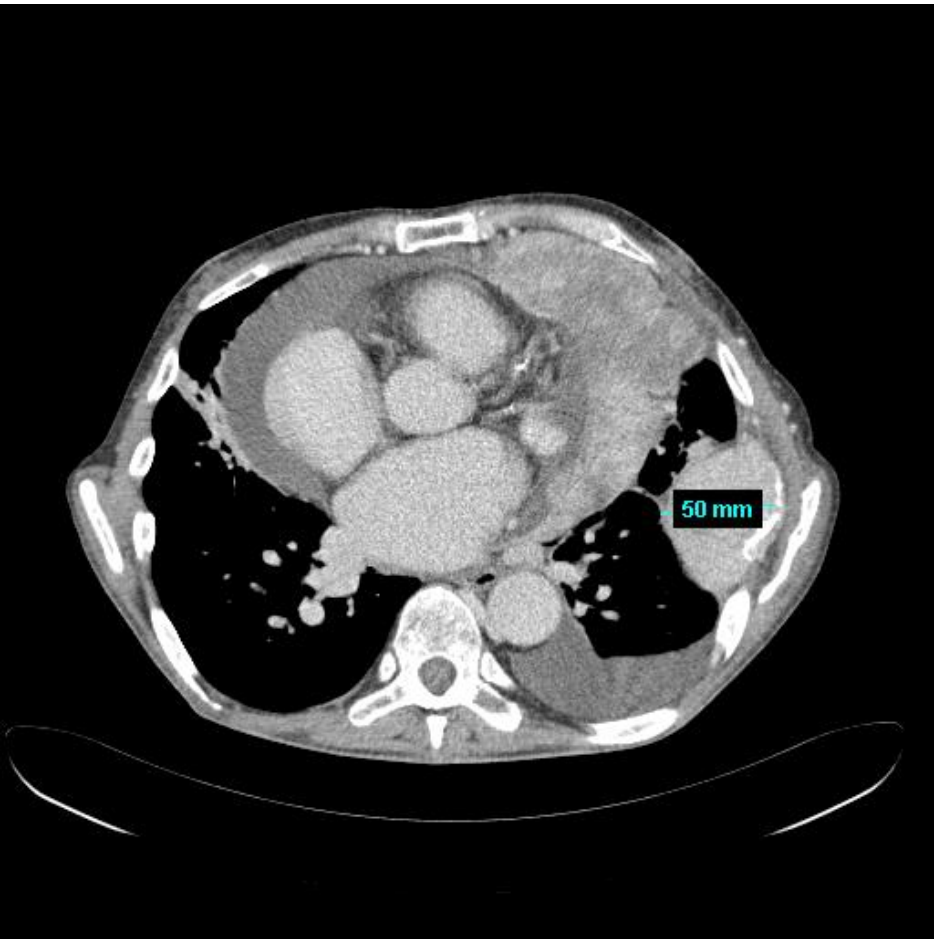
Elisei R, et al. *J Clin Oncol* 2012



- July 2013…

Cabozantinib 140 mg qd





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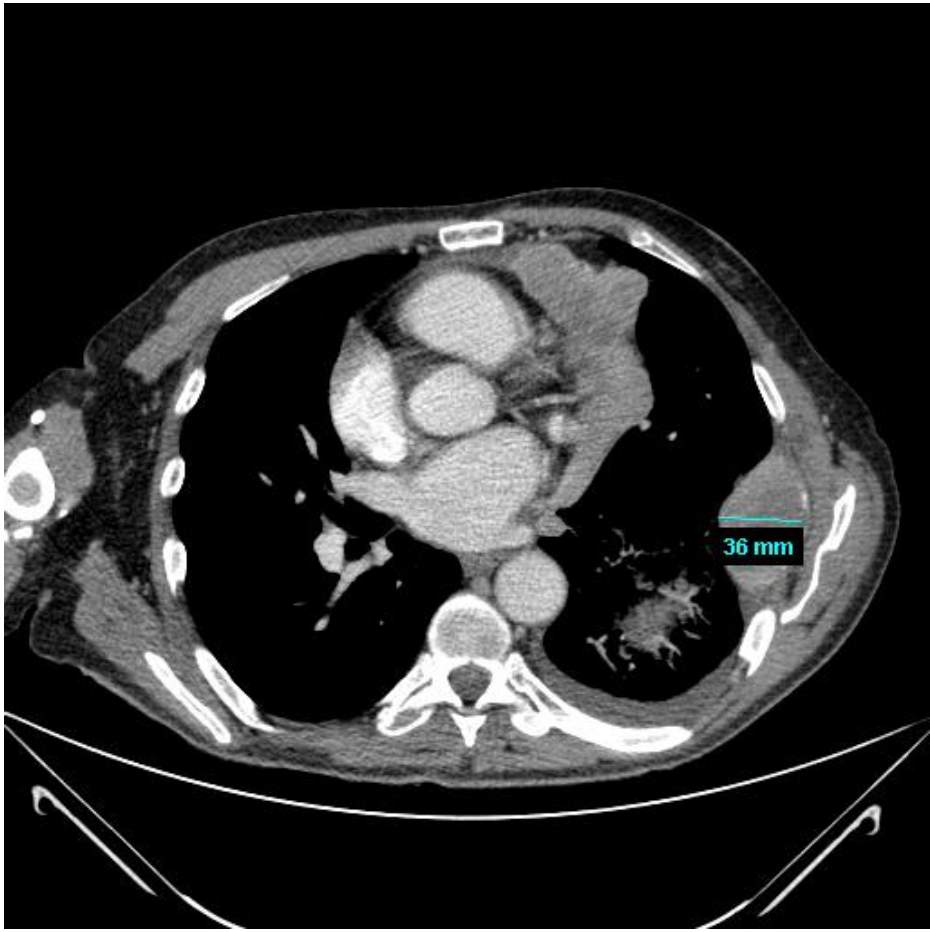
Cabozantinib 140 mg qd



Take Home Messages

- Patient selection is crucial for treatment optimization
  - Avoid unnecessary therapy (only tumor markers)
  - Early initiation when necessary (tumor burden, progression, organ in failure risk...)
- Vandetanib and Cabozantinib are new effective drugs in a paradigm for targeted therapies
- Optimal management of side effect will guarantee maximum efficacy and sequential treatment

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Thank you for your Attention

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