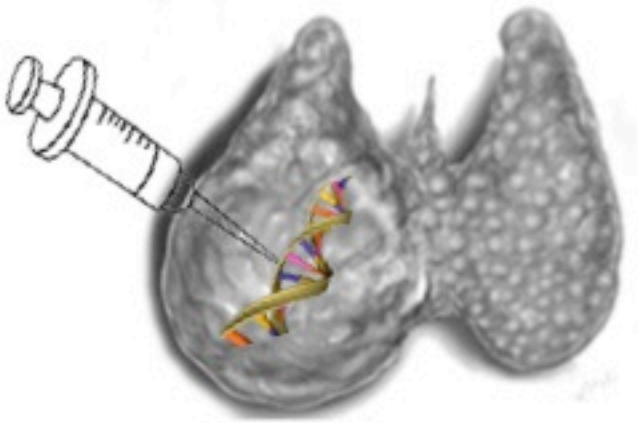
Minicorso 8
Il carcinoma tiroideo in progressione

Terapia medica



Laura Fugazzola

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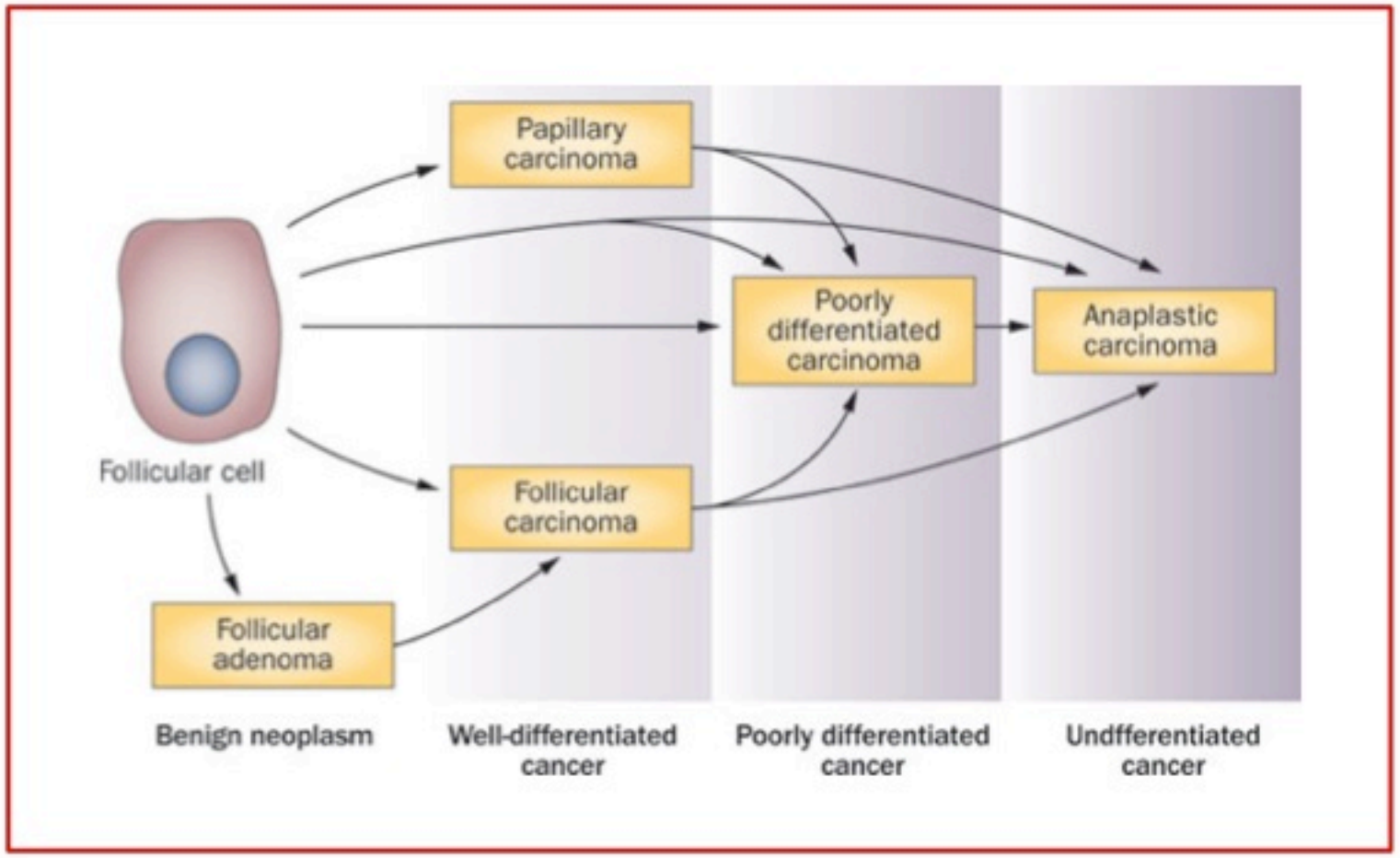
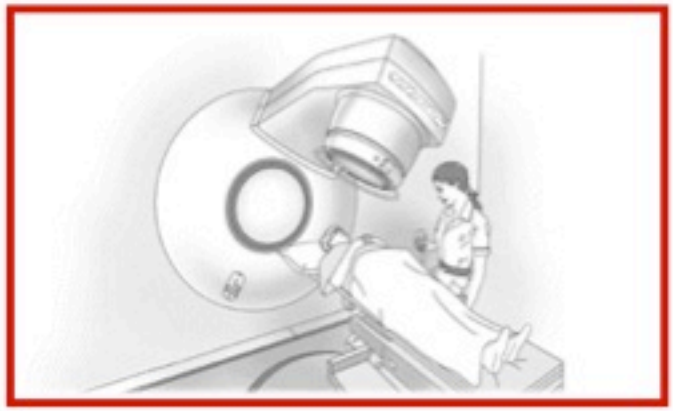
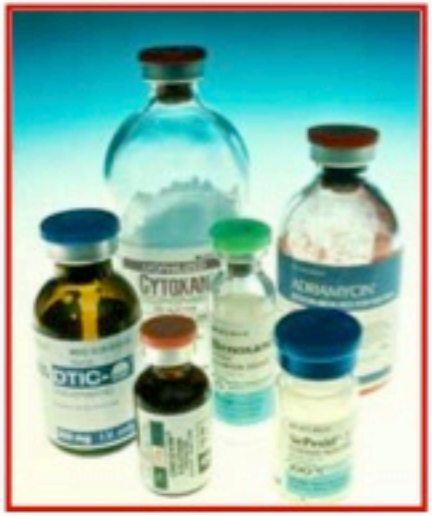
UNIVERSITÀ DEGLI STUDI DI MILANO

step-wise dedifferentiation of follicular cell-derived thyroid cancer



Nikiforov & Nikiforova, 2011





Carcinomi dedifferenziati
Carcinomi midollari in progressione

la radioterapia esterna
e la chemioterapia offrono solo minimi benefici

Terapia target

Chemioterapia "standard"

Table 1 Treatment of anaplastic thyroid cancer

Series	Year	No	Therapies	Outcomes	Notes
Voutilainen et al[22]	1999	33	S → CRT	1-y DSS = 9.7% (CI: 2.0–25.9)	Resectability ($P = 0.0002$), metastases ($P = 0.0014$), RT ($P = 0.014$), and radioiodine ablation ($P = 0.039$) = PrF
Tan et al[24]	199[illegible]				
Pierie et al[26]	200				
Schlumberger et al[28]	199				
Mitchell et al[27]	199				
Besic et al[29]	2005				RR to RT but toxicity was unacceptable
De Crevoisier et al[30]	2004				
Brignardello et al[31]	2007				
Haigh et al[32]	2000				
Kobayashi et al[33]	1996				
Swaak-Kragten et al[34]	2009				
Virbic et al[35]	2009				
Yau et al[36]	2008	50	S S + T S + CRT	OS = 97 d	Age ≤65 ($P \leq 0.01$), no metastatic disease at presentation ($P < 0.01$), surgery ($P < 0.01$), and postop RT = prF CT was not associated with longer OS
Lim et al[38]	2007	37	aRT	2-y LRC = 25% PFS = 8% OS = 18%	Better RR and LRC
Yau et al[37]	2006	15	S → RT	OS = 237 d	6, 12, 18, and 24-m OS = 33%, 26%, 13%, and 0%, respectively
Wang et al[39]	2006	47	SRT vs HRT	OS = 11 m	6-m LRC = 95% ($P = 0.0001$) with RT at 40 Gy vs 64% RT at <40 Gy. mOS with HRT: 13 m vs 10 m SRT ($P = 0.3$)
Veness et al[40]	2004	18	S + RT	OS = 6.2 m	Single modality correlates with worst prognosis
Haigh et al[41]	2001	33	S + RT	OS = 43 m (R0)	mOS = 3.3 m with only CT and RT and palliative resection ($P = 0.63$)
Mclver et al[26]	2001	134	S → RT vs S	mOS = 3–5 m	Extent of resection did not affect survival ($P > 0.4$)

(Continued)

Table 1 (Continued)

Series	Year	No	Therapies	Outcomes	Notes
Besic et al[29]	2001	142	S → CRT CRT → S		1-y OS preop versus postop CRT ($P = 0.07$)
Haroon et al[25]	2003	33	SRT	[illegible]	[illegible] associated with better OS but

pts treated with

ed postop RT 46 Gy +
Gy

e outcomes
RT is an important goal

lower in pts undergoing

ile and achieves good

OS = 1 y

<65 y → doxorubicin (60 mg/m²) + cisplatin (90 mg/m²) + RT

>65 y → mitoxantrone (14 mg/m²) + RT

OS > 20 m in 3/20 patients

S → 2 × CT → RT → 4 × CT

CT = doxorubicin (60 mg/m²) and cisplatin (120 mg/m²)

3-y OS = 7% (95% CI: 10%–44%)

mOS = 10 m

Death due to local PD in 5% and distant PD in 68%, and to both in 27%

Denaro et al., 2013

Chemioterapia "standard"

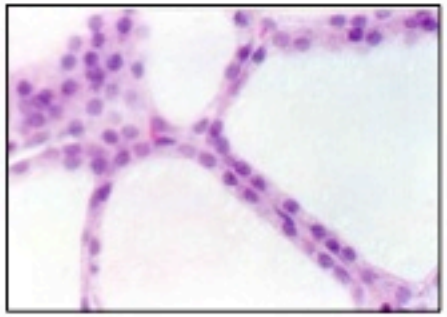
Table 3 Antiproliferative agents in medullary thyroid carcinoma.

Drugs	References	Number of patients	Type of response			
			Complete	Partial	No change	Progression
DOXO	Burgess & Hill (1978)	6	—	3	3	—
DOXO	Shimaoka *et al.* (1985)	4	—	1	—	3
DOXO	Husain *et al.* (1978)	3	—	1	—	2
DOXO	Leight *et al.* (1980)	7	—	1	—	6
DOXO	Harada *et al.* (1981)	4	—	2	—	2
DOXO	Droz *et al.* (1984)	13	1	2	4	6
DOXO	Simpson *et al.* (1982)	4	—	2	—	2
DOXO + CDDP	Shimaoka *et al.* (1985)	6	—	2	—	4
DOXO + CDDP	Williams *et al.* (1986)	6	—	—	Not specified	Not specified
DOXO + CDDP	Droz *et al.* (1984)	14	1	2	4	7
DOXO + CDDP	Sridhar *et al.* (1985)	1	—	1	—	—
DOXO + VCR + BLM	Hoskin & Harmer (1987)	2	—	2	—	—
DOXO + CDDP + BLM	De Besi *et al.* (1991)	8	—	4	4	—
CDDP	Hoskin & Harmer(1987)	4	—	1	Not specified	Not specified
CDDP	Leight *et al.* (1980)	3	—	—	—	3
CBDCA	Hoskin & Harmer (1987)	2	—	1	Not specified	Not specified
VP16	Fiore *et al.* (1984)	2	—	1	—	1
VP16	Hoskin & Harmer (1987)	4	—	3	Not specified	Not specified
MTX	Hoskin & Harmer (1987)	1	—	1	—	—
DOXO + CDDP + VDS	Scherubl *et al.* (1990)	10	—	1	6	3
VDS	Rossoff *et al.* (1979)	1	—	—	—	1
DTIC	Kessinger *et al.* (1983)	1	—	—	1	—
DTIC + 5FU	Petursson (1988)	1	1	—	—	—
DTIC + 5FU	Personal data	7	—	3	2	2
DTIC + 5FU + EPX	Bajetta *et al.* (1998)	1	—	1	—	—
DTIC + CTX + VCR	Wu *et al.* (1994)	7	—	2	2	3
5FU-DTIC or 5FU-STZ	Schlumberger *et al.* (1995)	20	—	3	11	6
DOXO + CTX + STZ	Weiss (1978)	1	—	—	—	1
Rubidazone	Stepanas *et al.* (1979)	1	—	—	—	1
Total		144	3 (2%)	39 (27%)		

DOXO, Duxorubicin; CDDP, Cisplatinum; VCR, Vincristine; BLM, Bleomycin; CBDCA, Carboplatin; VP16, Etoposide; MTX, Methotrexate; VDS, Vindesine; DTIC, Decarbazine; 5FU, 5-Fluorouacil; EPX, Epirubicin; STZ, Streptozocin.

Orlandi et al., 2001

Targeted therapy



Follicular cell

Papillary carcinoma

P53
PI3K

BRAF
ret/PTC
Ras, TRK

Poorly differentiated carcinoma

P53
PI3K

Anaplastic carcinoma

PAX8-PPARγ

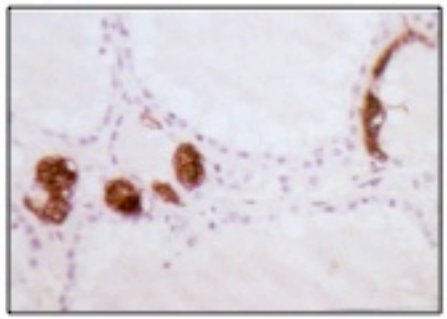
ras

P53
PI3K

Follicular adenoma

ras

Follicular carcinoma

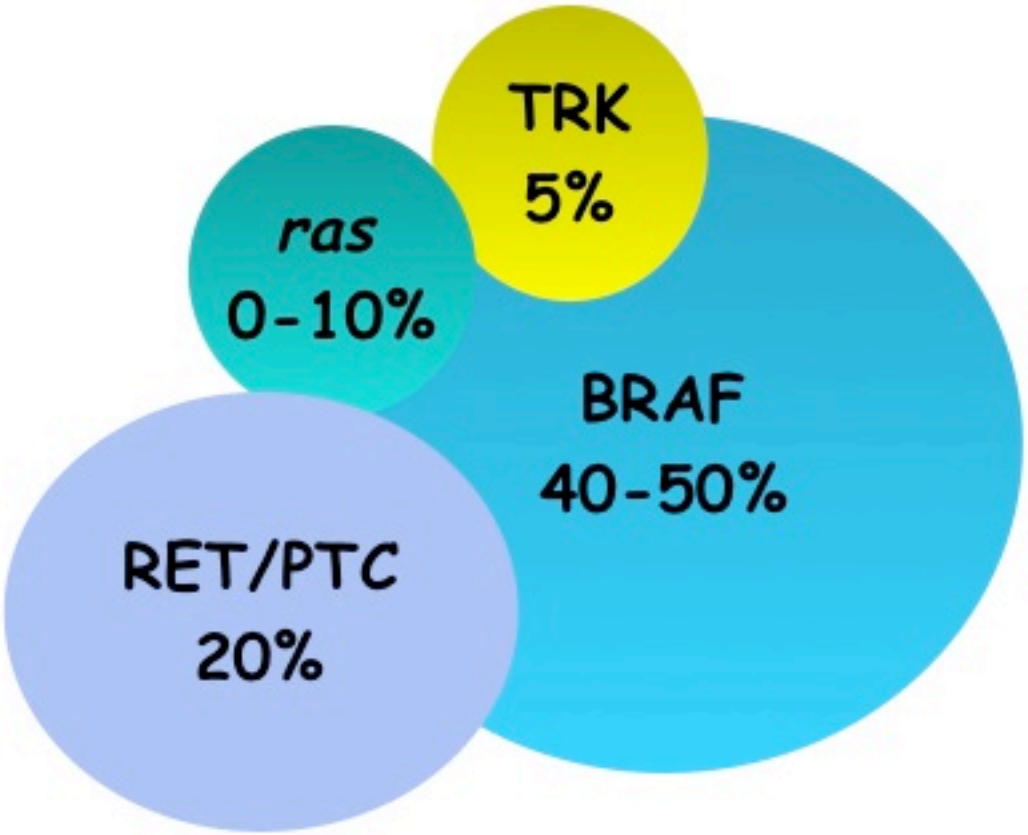


C cell

RET

Medullary carcinoma

cellule follicolari

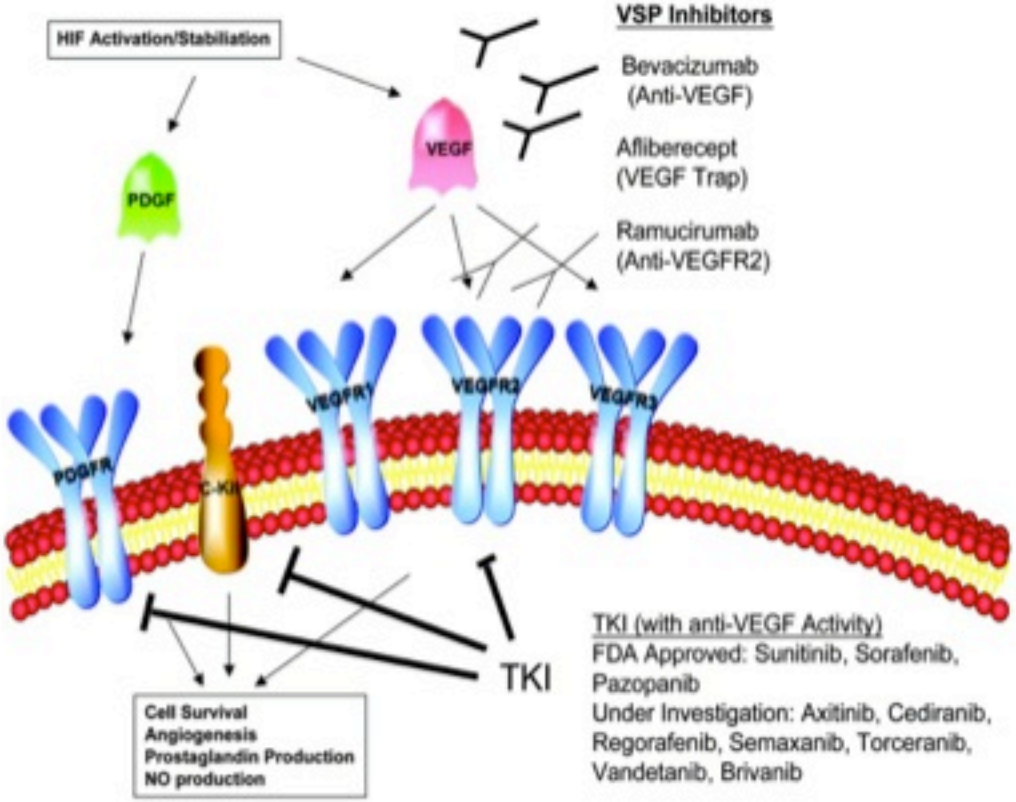


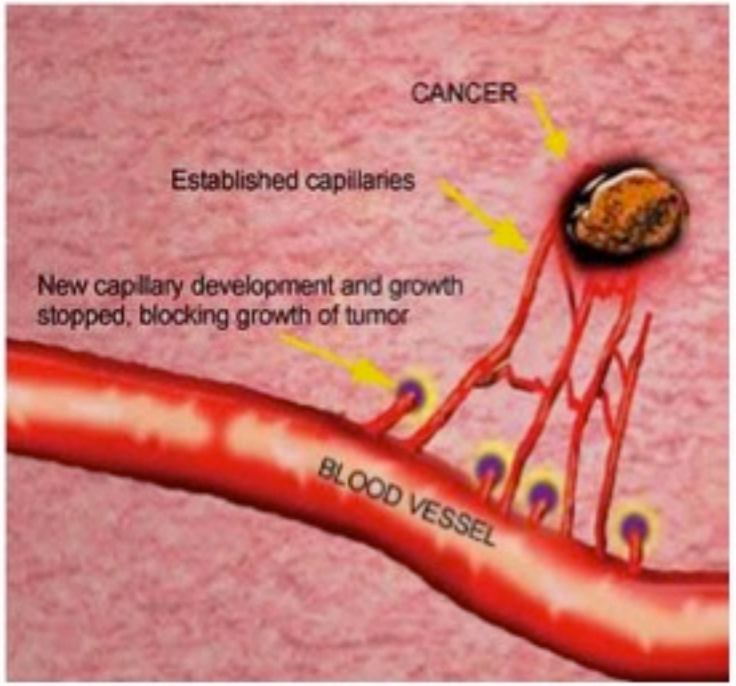
cellule C

Tutti questi geni possono essere "targettati"
a scopo terapeutico

Trattamento dei carcinomi tiroidei resistenti alle terapie standard

Molecole dirette verso meccanismi COMUNI di crescita, invasione e metastatizzazione tumorale: angiogenesi VEGF-mediata



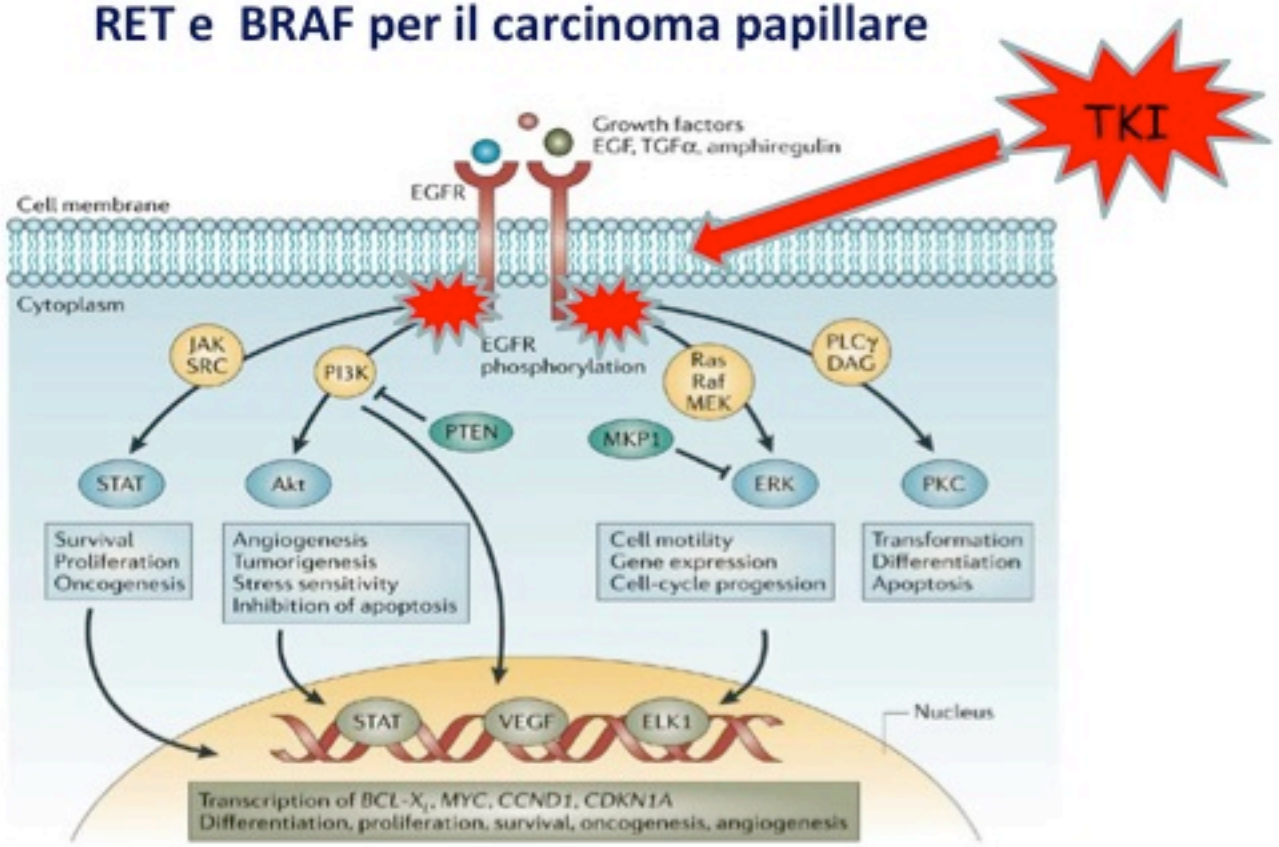


Trattamento dei carcinomi tiroidei resistenti alle terapie standard

Diretto SOLO verso i geni mutati:

RET per il carcinoma midollare

RET e BRAF per il carcinoma papillare



Proliferazione dell'apoptosi,

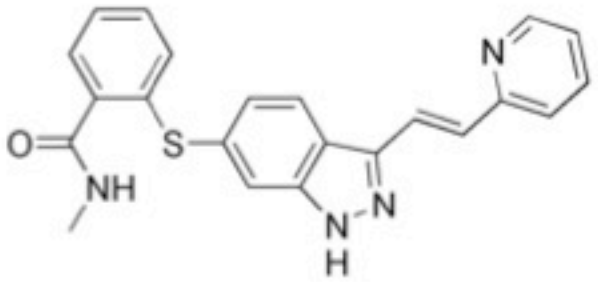
neoan sione

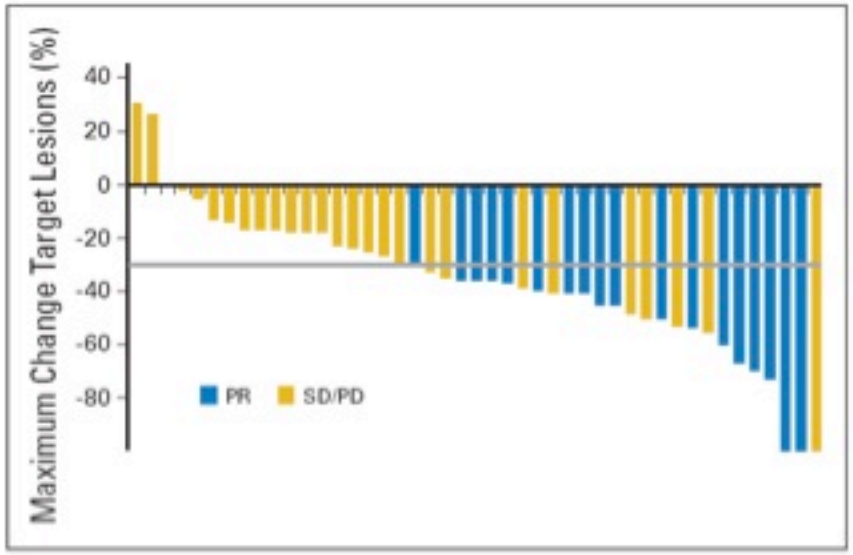
STOP

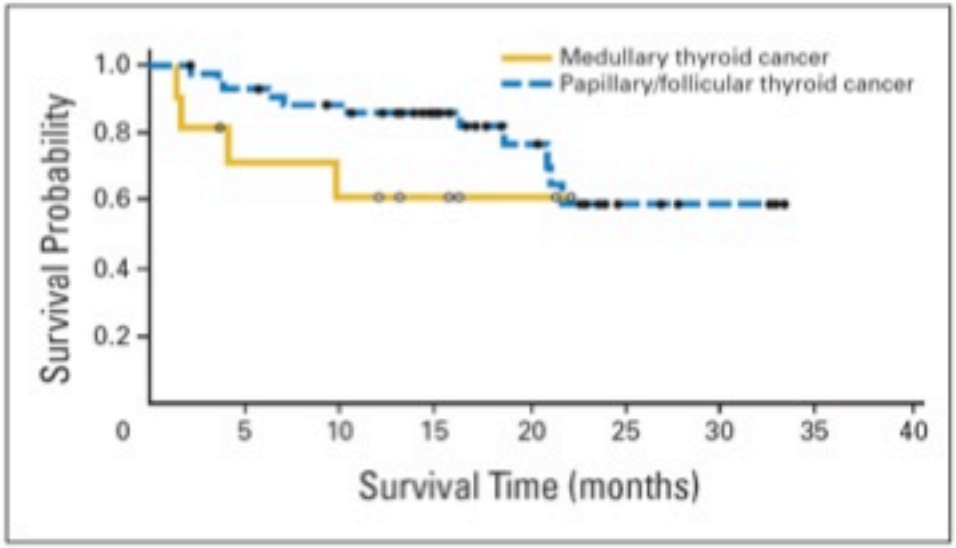
Studi clinici fase 2 per DTC in stadio avanzato (escl. Sorafenib)

DRUG	Molecular targets	N	PR n (%)	SD n (%)	Median PFS	Median OS
Axitinib	VEGFR1-3; PDGFRβ; c-KIT	60	18 (30)	23 (38)	18.1 mo	not reached
Cabozantinib	VEGFR2; cMET	25	no findings reported; currently recruiting			
Dabrafenib	BRAF (mutated forms)	10	no findings reported; currently recruiting			
Gefinitinib	EGFR	27	0 (0)	3(12)	3.7 mo	17.5 mo
Lenvatinib	VEGFR1-3; PDGFRβ; c-KIT; FGFR1-4; RET	58	29 (50)	NR	12.6 mo	NR
Motesanib	VEGFR1-3; PDGFRβ; c-KIT	93	13 (14)	62 (67)	10 mo	NR
Pazopanib	VEGFR1-3; PDGFRa/β; c-KIT	37	18 (49)	NR	11.7 mo	NR
Selumetinib	MEK1, 2	39	1 (3)	21 (54)	8 mo	NR
Sunitinib	VEGFR1, 2; PDGFR; RET; c-KIT; FLT3	31	4 (13)	21 (68)	NR	NR
		26	8 (31)	17 (65)	12.8 mo	NR
Vandetanib	RET; VEGFR2, 3; EGFR	72	6 (8)	4 (5)	11.1 mo	NR
Vemurafenib	BRAF V600E	51	no findings reported			

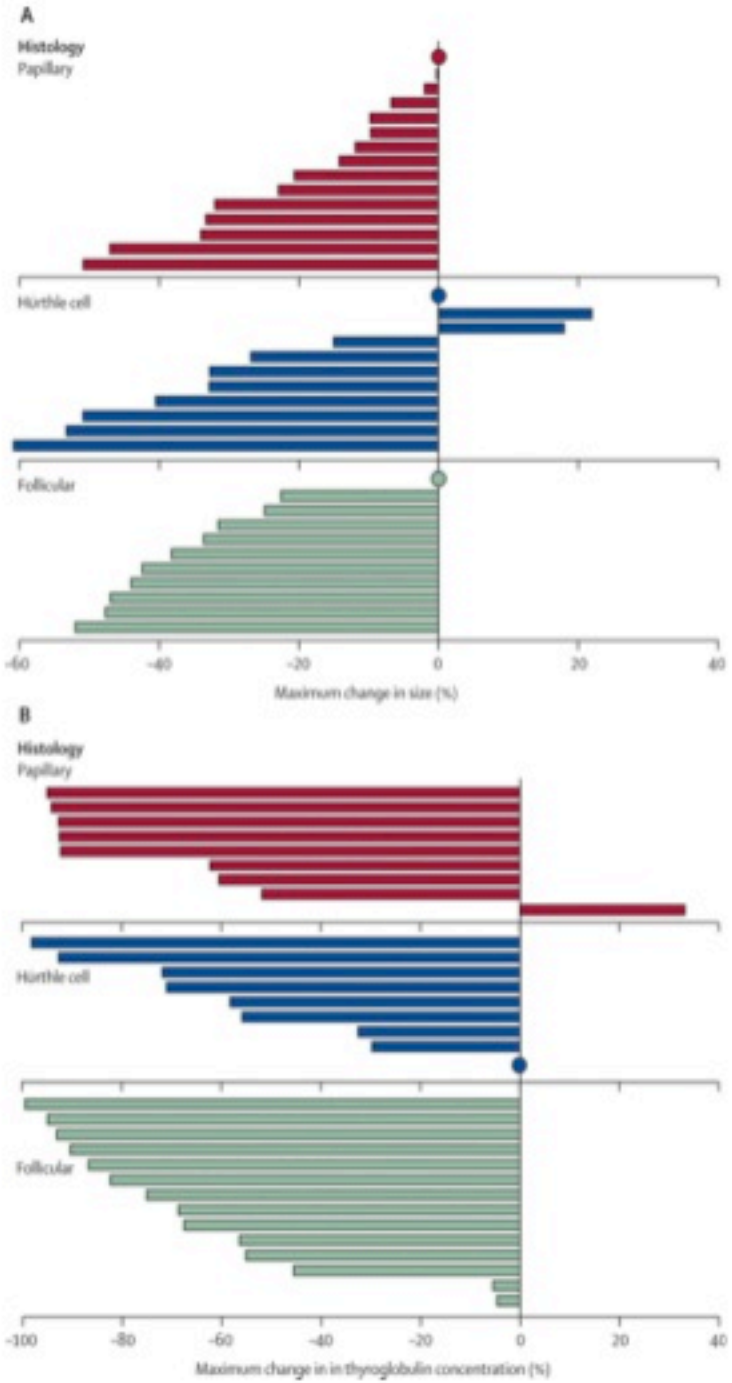
Axitinib







Cohen, 2008

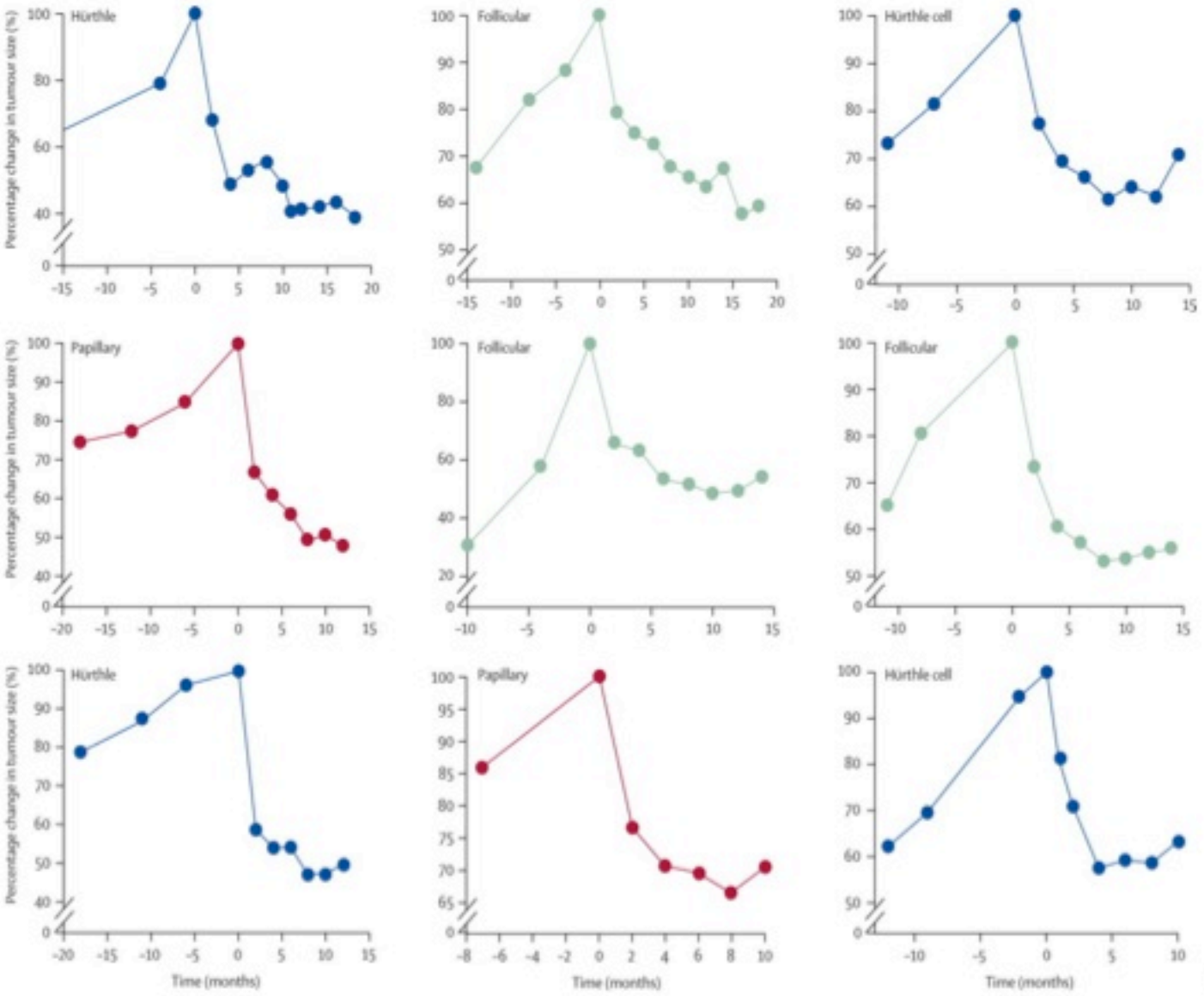


PAZOPANIB: fase II

Tyrosine-kinase inhibitor targeting VEGF receptors, platelet-derived growth factor and c-KIT

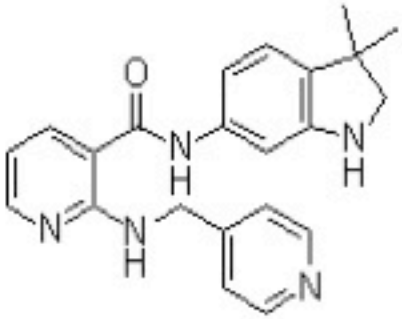
Bible et al., 2010

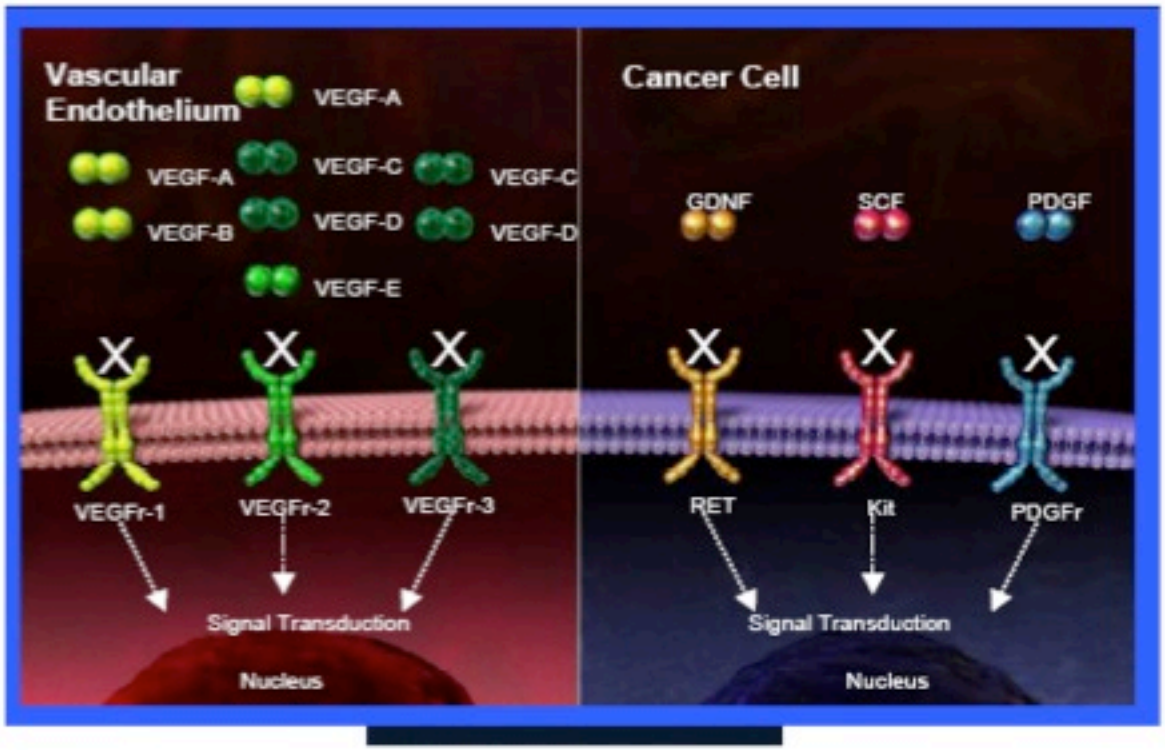
PAZOPANIB: fase 2



Bible et al., 2010

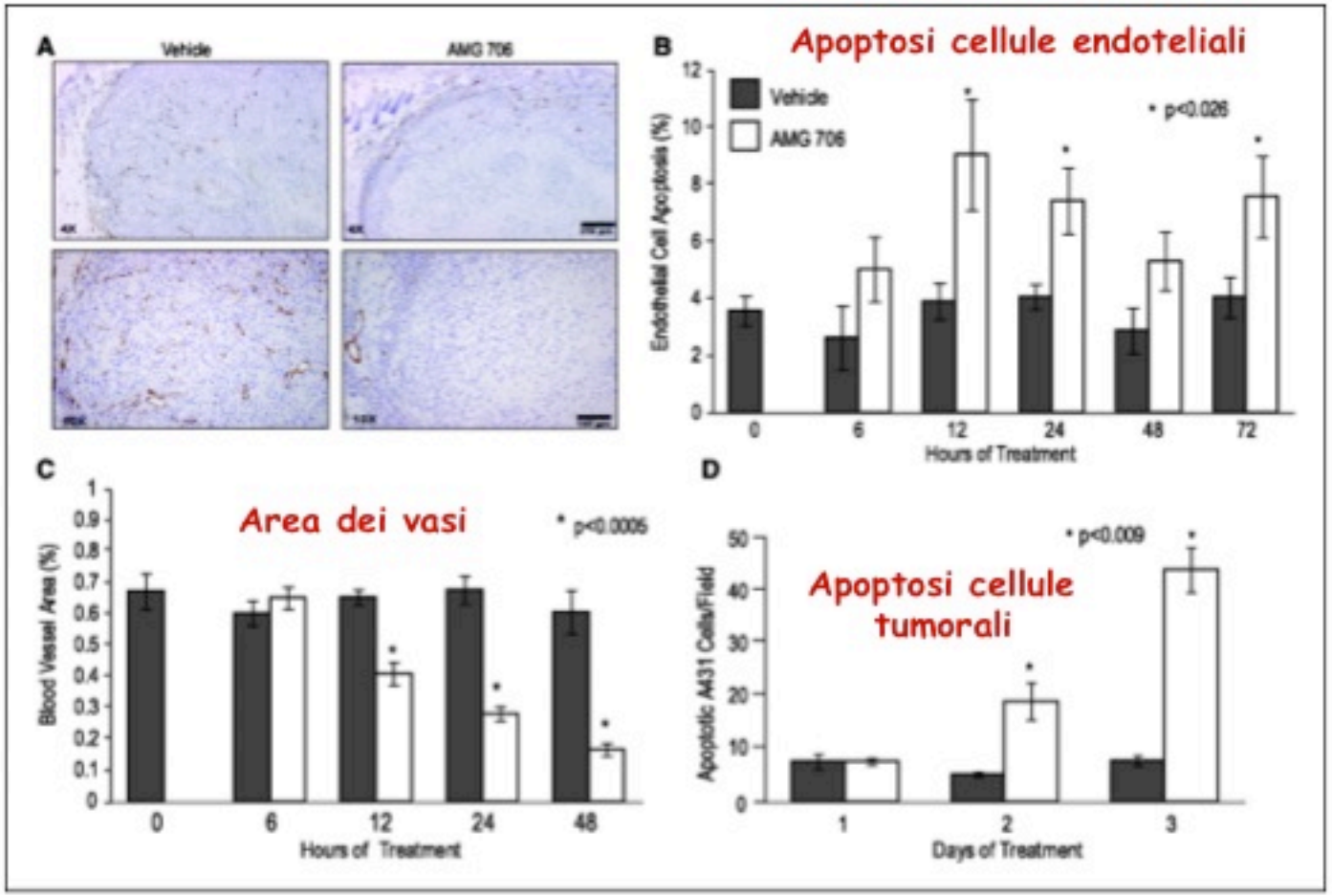
AMG 706





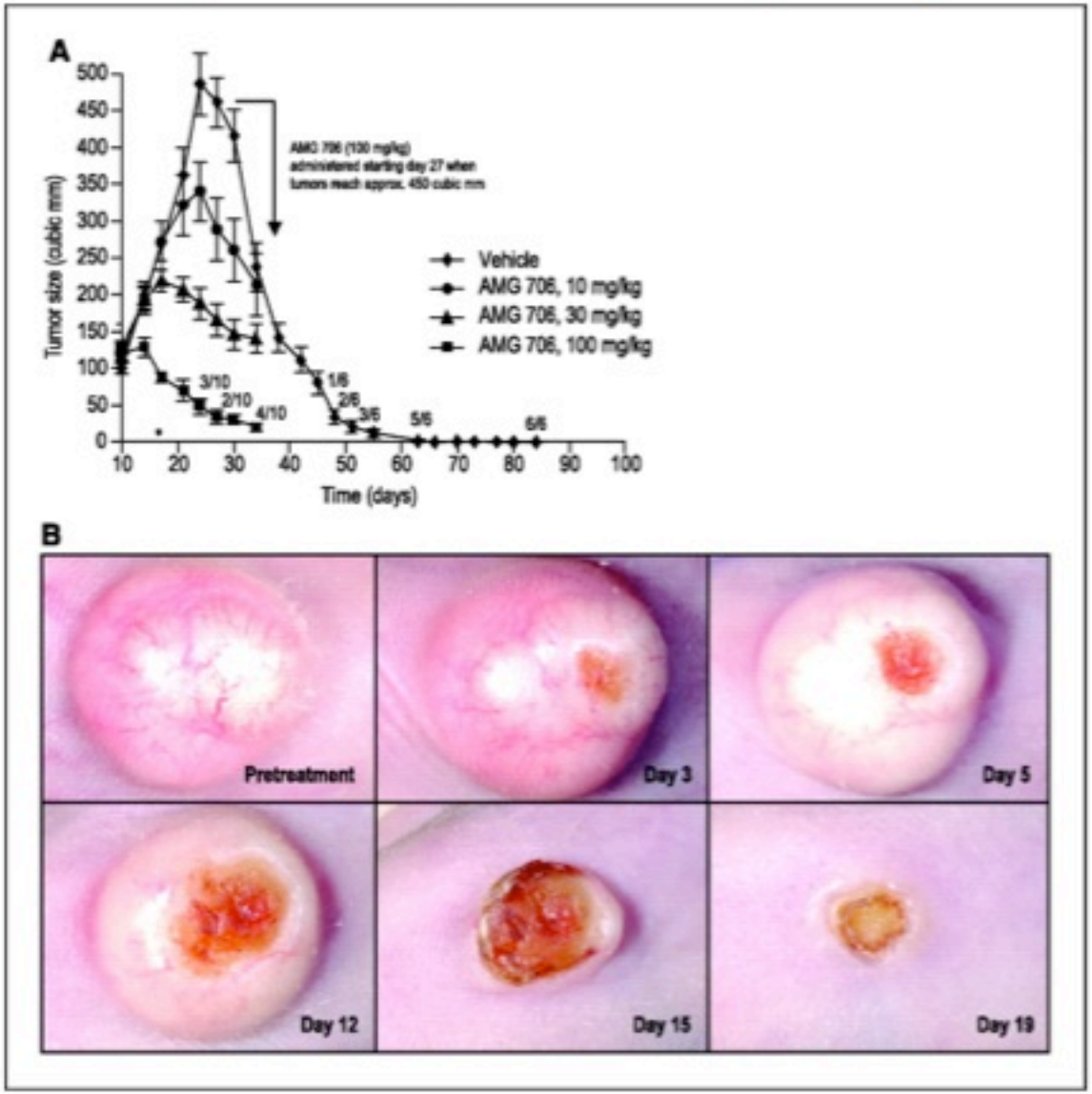
®Motesanib, Amgen

AMG706
meccanismi di inibizione e regressione tumorale



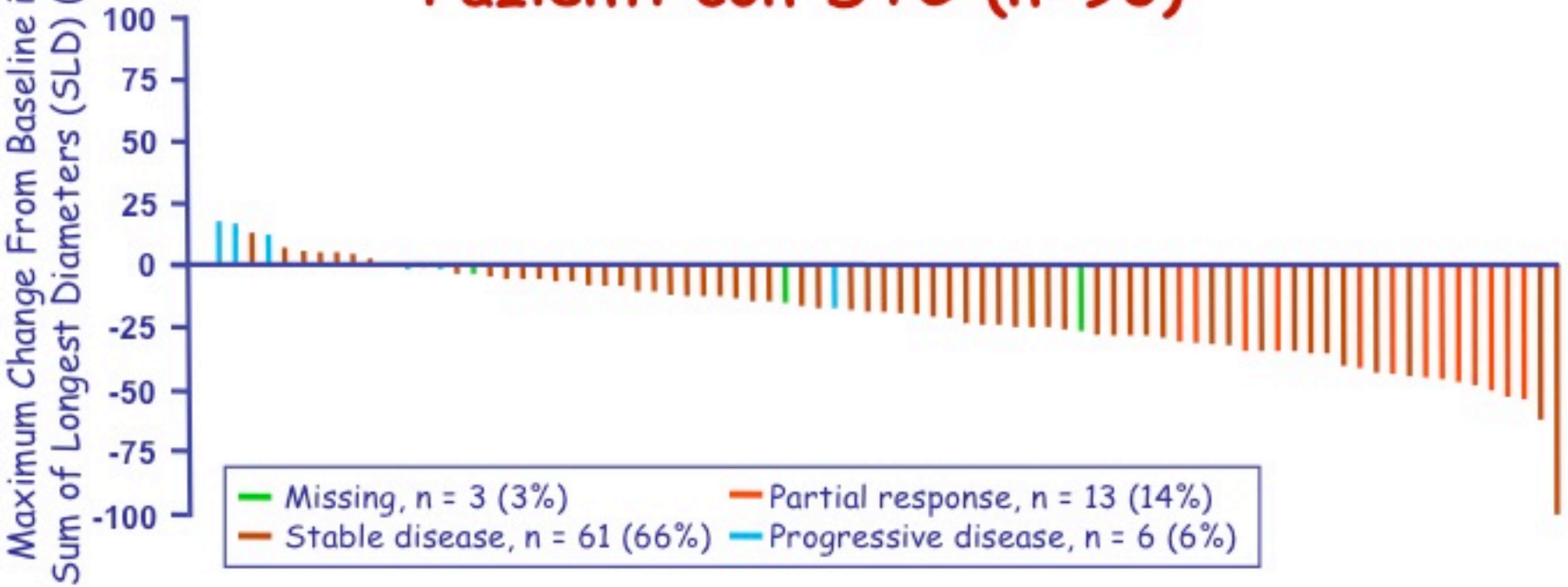
Polverino et al., 2006

Inhibition and regression of tumor xenograft growth by Motesanib



Polverino et al., 2006

Motesanib: fase 2
Pazienti con DTC (n=93)

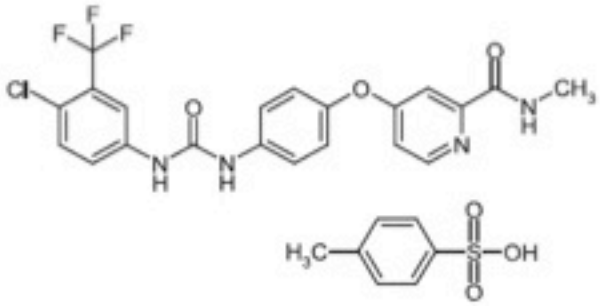


Objective tumor response rate (CR or PR)	13 (14%)
Durable SD ≥ 24 weeks	33 (35%)
Clinical benefit rate (CR + PR + durable SD)	46 (49%)

Sherman et al, NEJM 2009

Sorafenib

BAY-43-9006



BAY 43-9006 ha come target le serin-treonin chinasi RAF-1 e BRAF e altri recettori tirosino chinasici coinvolti nella neovascolarizzazione e progressione tumorale (VEGFR-2, VEGFR-3, Flt-3, PDGFR-B e KIT).

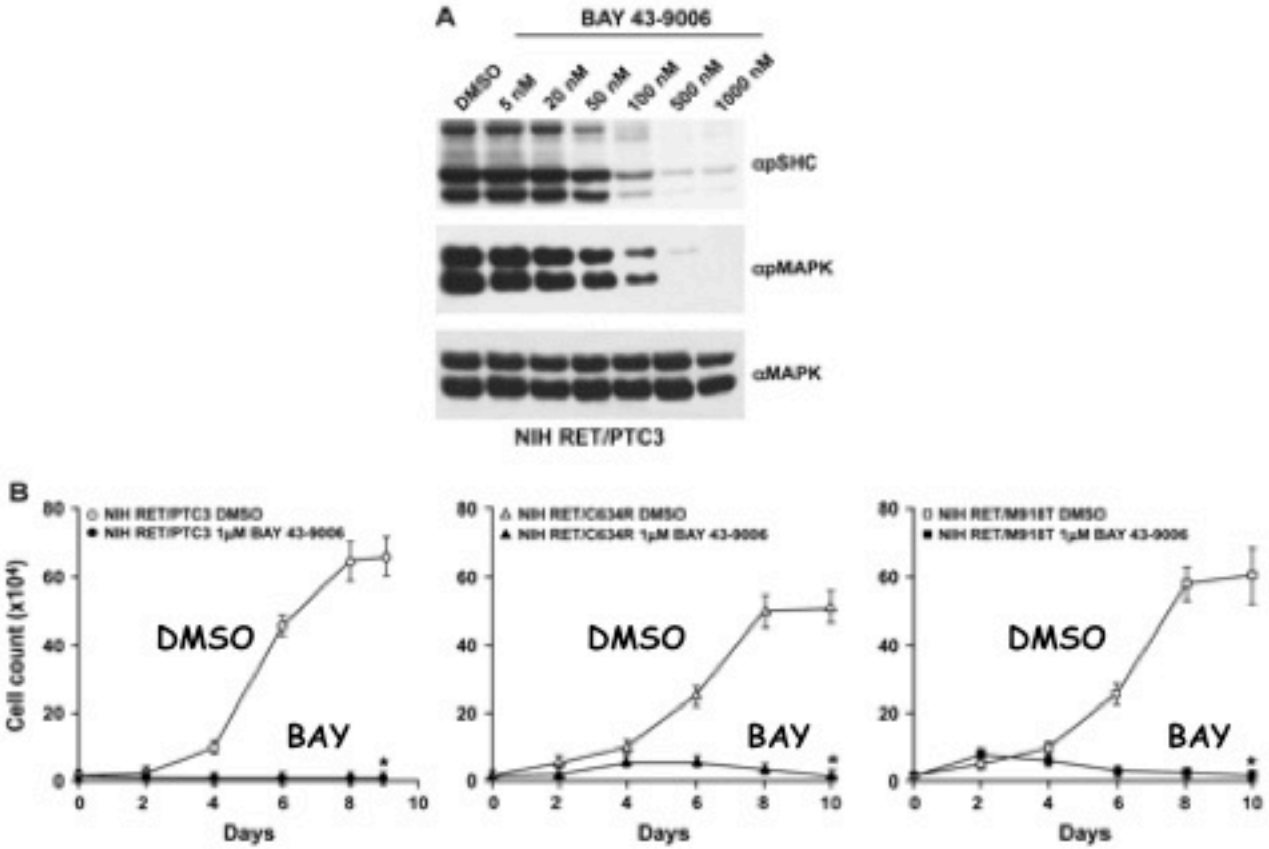
Ha un ampio spettro di attività in modelli animali di cancro del colon, della mammella e del carcinoma polmonare a piccole cellule

Sorafenib è già stato approvato per il trattamento di **carcinomi renali avanzati e epatocarcinomi.**

Il Sorafenib per il momento può essere somministrato come farmaco *OFF-LABEL.*

®Bayer

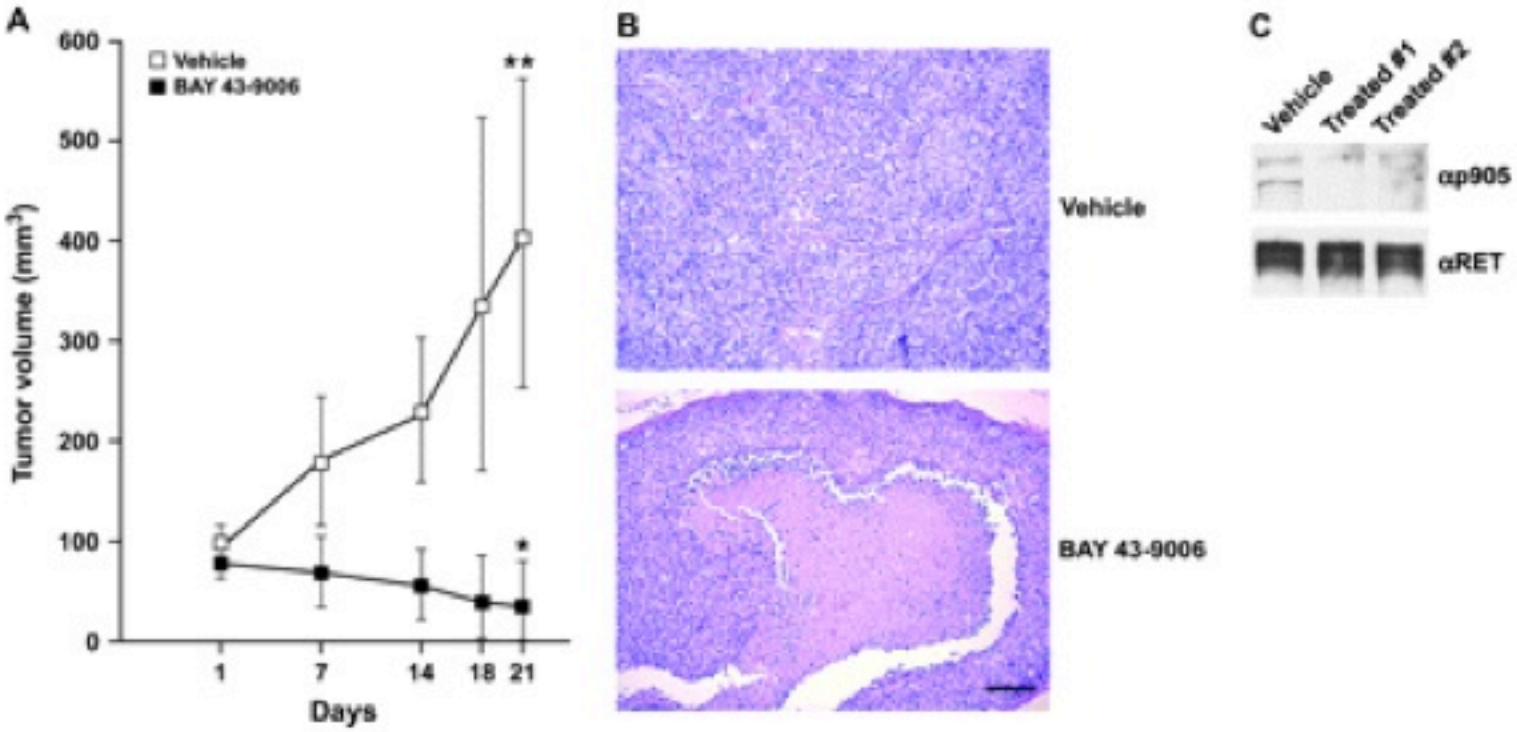
Inhibition of RET-mediated growth and signaling by BAY 43-9006 in NIH3T3



NIH RET/PTC3 NIH RET/C634R NIH RET/M918T

Carlomagno et al., 2006

Cellule TT iniettate in topo
Sviluppo tumore: randomizzazione



Carlomagno et al., 2006

Studi clinici fase 2 per DTC in stadio avanzato
Sorafenib

DRUG	Molecular targets	N	PR n (%)	SD n (%)	Median PFS	Median OS
Sorafenib	RAF; VEGFR1-3; PDGFR; RET	30	7 (23)	16 (53)	21 mo	NR
		52	6 (12)	34(65)	4.5-37.5 mo	23-37.5 mo
		31	8 (31)	11 (42)	18 mo	34.5 mo
		19	3 (16)	10 (53)	12 mo	12 mo
			20.5	**53.3**		

DECISION study fase III (ASCO 2013, ETA 2013)
Sorafenib

417 patients with metastatic, RAI-resistant DTC, progression last 14 months

Randomization: Sorafenib 400 mg x 2 or placebo (cross-over)

Cross-over in 70%

Median PFS: 10.8 mo Sorafenib *vs* 5.8 mo placebo (P<0.0001)
Median OS: not reported

Tumor shrinkage ≥ 30%: 12.2% Sorafenib *vs* 0.5% placebo (P<0.0001)

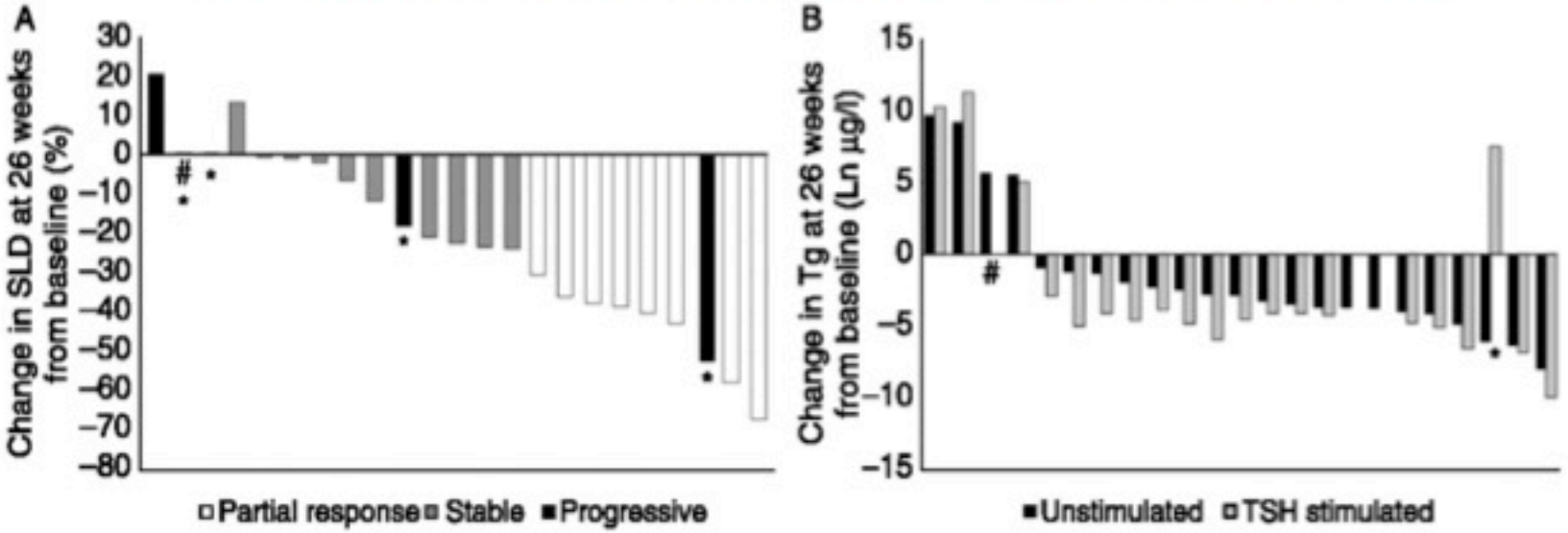
PR+SD: 54.1% Sorafenib *vs* 33.8% placebo (P<0.0001)

FDA has given priority review designation to Sorafenib (Nexavar) for the treatment of locally advanced or metastatic RAI-refractory DTC

Studi clinici di inibitori chinasici come adiuvanti per trattamento con RAI

DRUG	Molecular targets		
Dabrafenib	BRAF (mutated forms)	Pilot	3/5 developed RAI uptake
Selumetinib	MEK1, 2	-	8/12 developed RAI uptake; PR in 5, SD in 3
Pazopanib	VEGFR1-3; PDGFRa/β; c-KIT	Ph1	no findings reported; study recruiting
Sorafenib	BRAF V600E	Ph2	no findings reported; study completed
Sunitinib	VEGFR1, 2; PDGFR; RET; c-KIT; FLT3	Ph2	no findings reported; study recruiting

Sorafenib has beneficial effects on tumor progression, but not on radioiodine uptake, in patients with differentiated thyroid carcinoma



Tumor Response (RECIST)

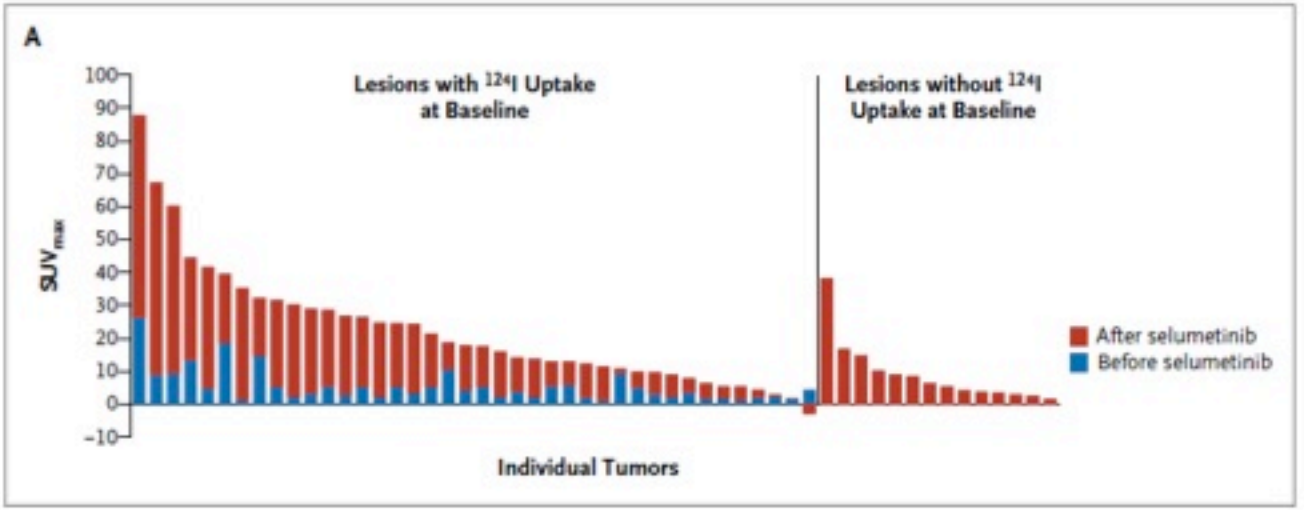
Complete	0	(0)
Partial	8	(26)
Stable	11	(35)
Progressive	7	(23)
Clinical benefit	19	(62)

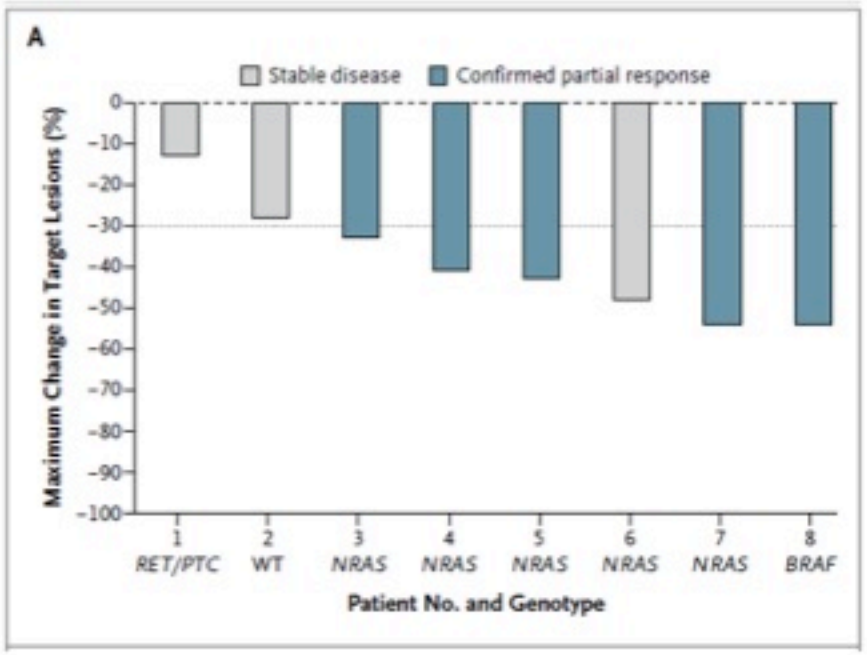
Reinduction of Iodine Uptake

N=0

Hoftijzer, EJE 2009

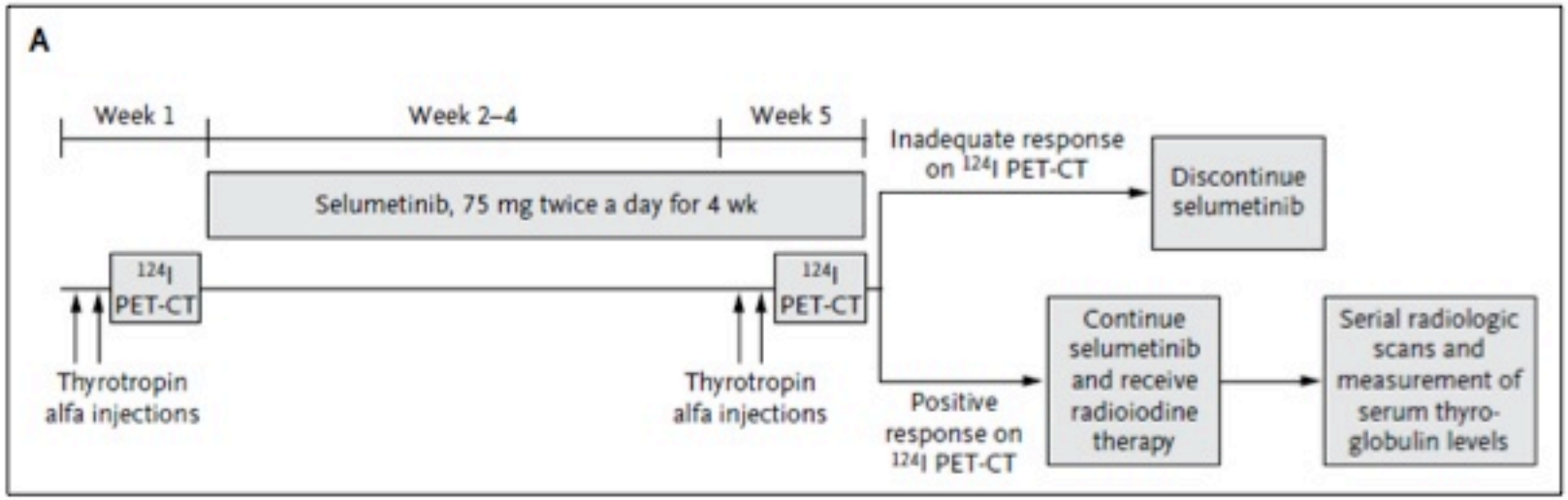
Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer (selective, allosteric MEK 1 and MEK 2 inhibitor)

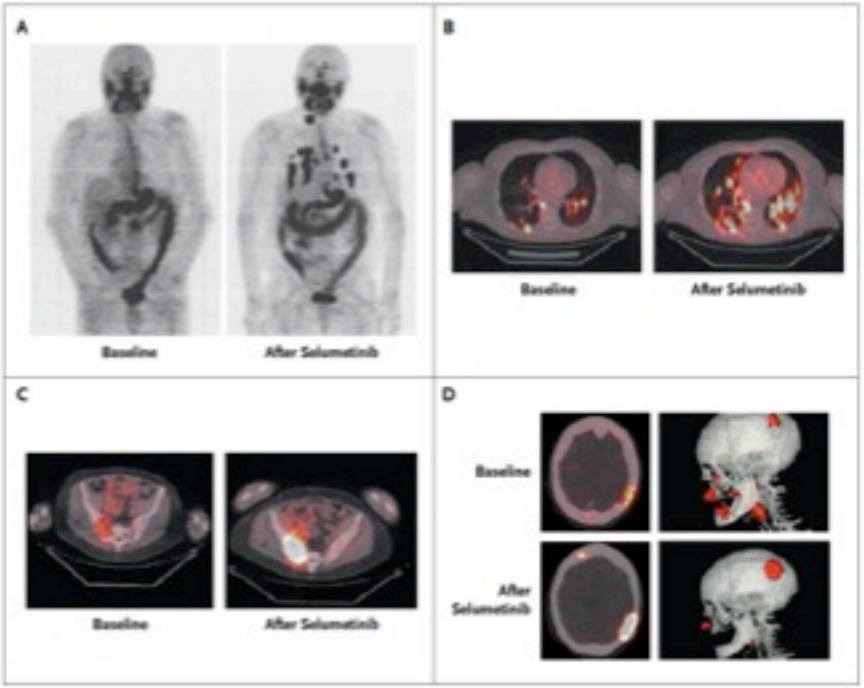




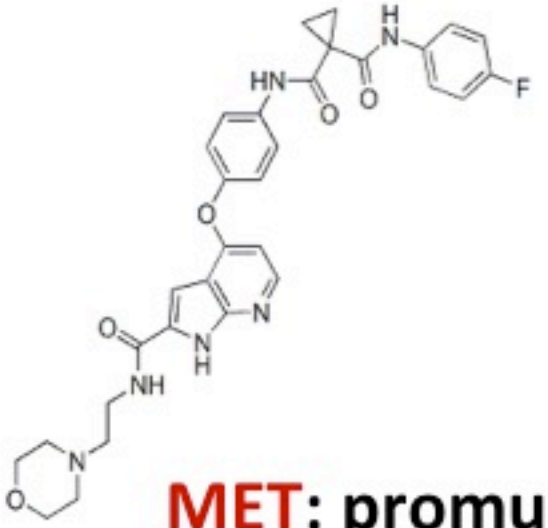
Ho et al., NEJM 2013

Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer





Ho et al., NEJM 2013



Cabozantinib (XL184)

Potente inibitore di

MET: promuove angiogenesi, proliferazione tumorale, migrazione e sopravvivenza

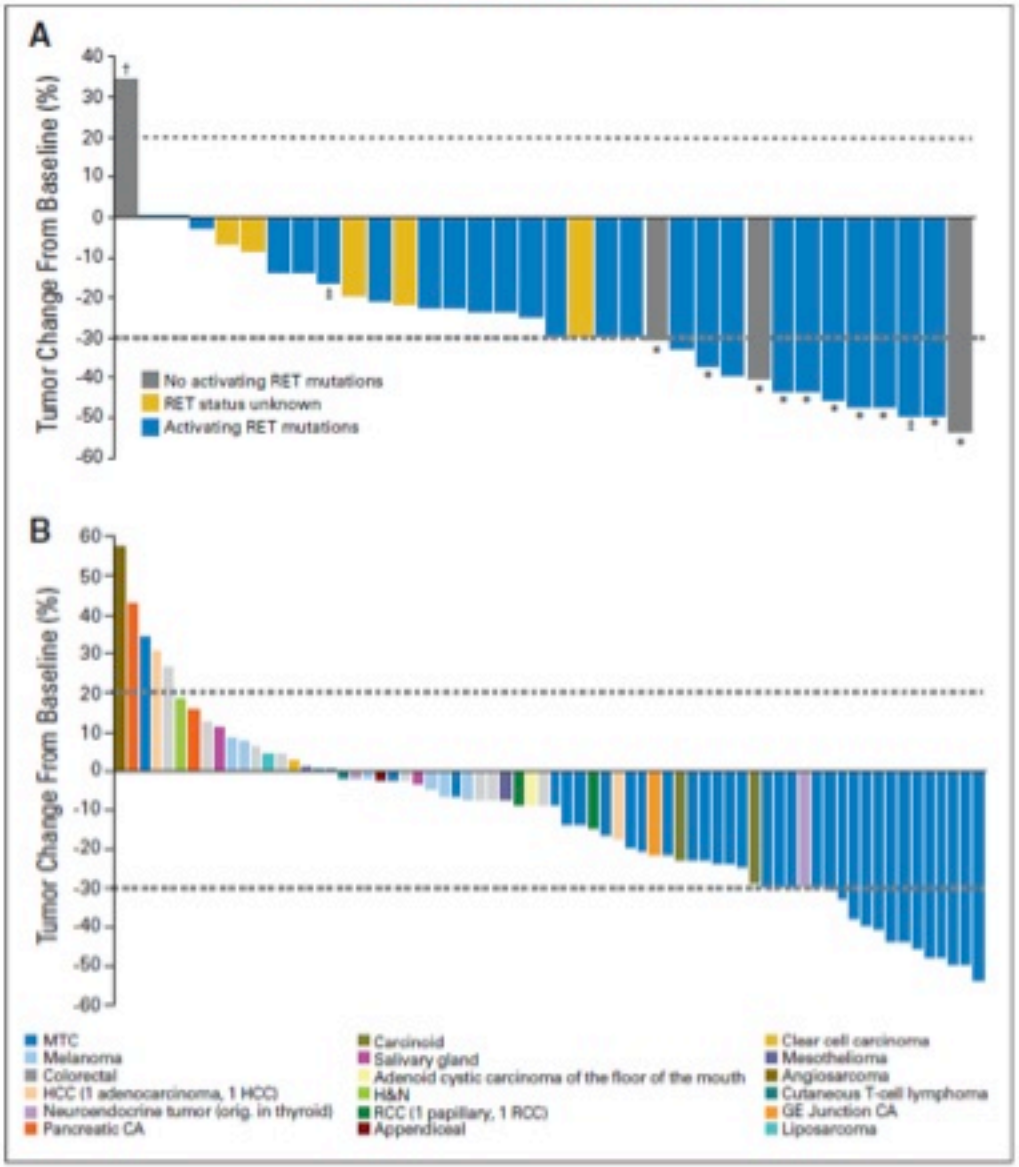
VEGFR2: induce angiogenesi

RET: coinvolto nella patogenesi del CMT

attivo contro mutanti di MET e RET in sistemi cellulari e animali

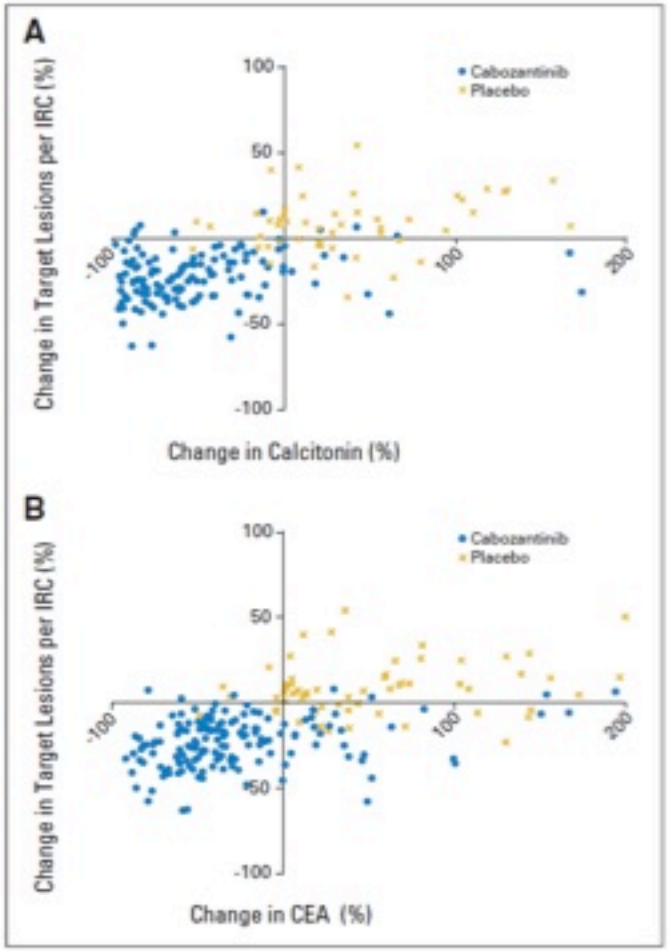
E' ben tollerato

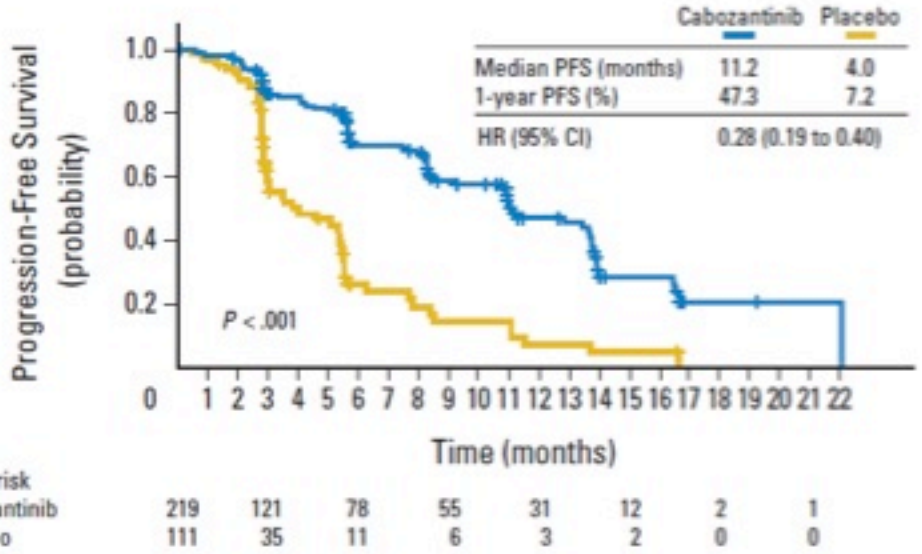
Cabozantinib: fase I



Kurzrock, JCO 2011

double-blind, phase III trial comparing cabozantinib with placebo



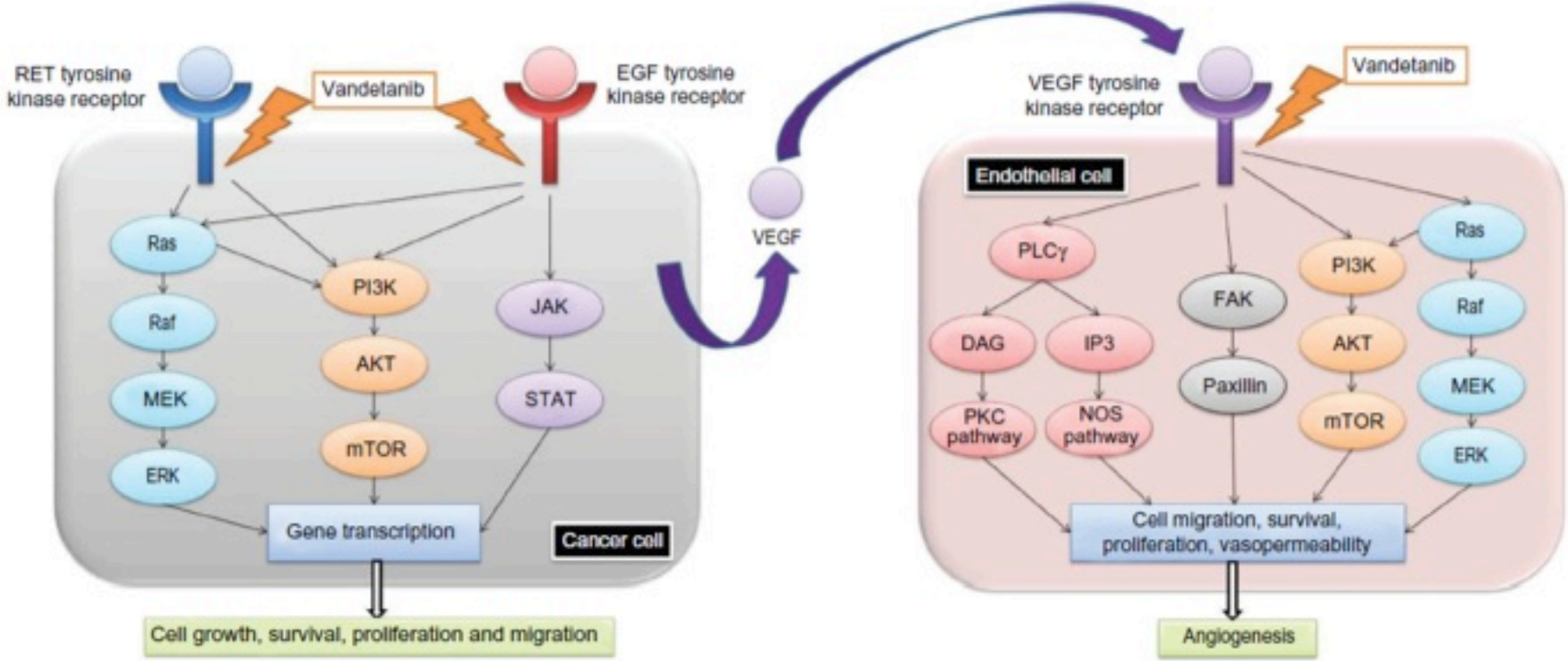


330 metastatic MTC patients randomly assigned (2:1) to cabozantinib (140 mg/day) or placebo

Elisei et al., JCO 2013

Vandetanib

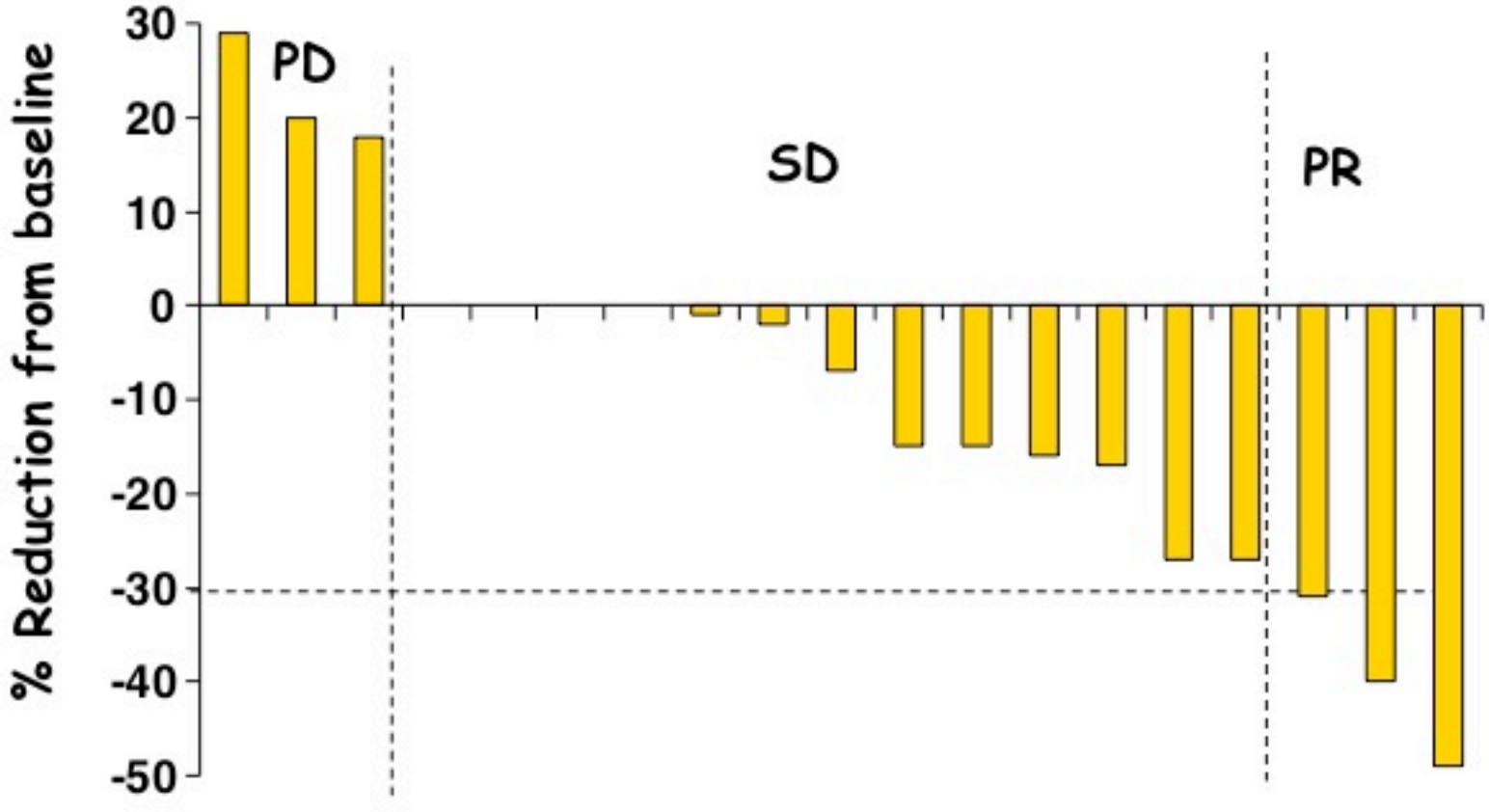
Vandetanib (anilinochinazoline ZD6474) is a potent inhibitor of vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR) and RET



Astra Zeneca

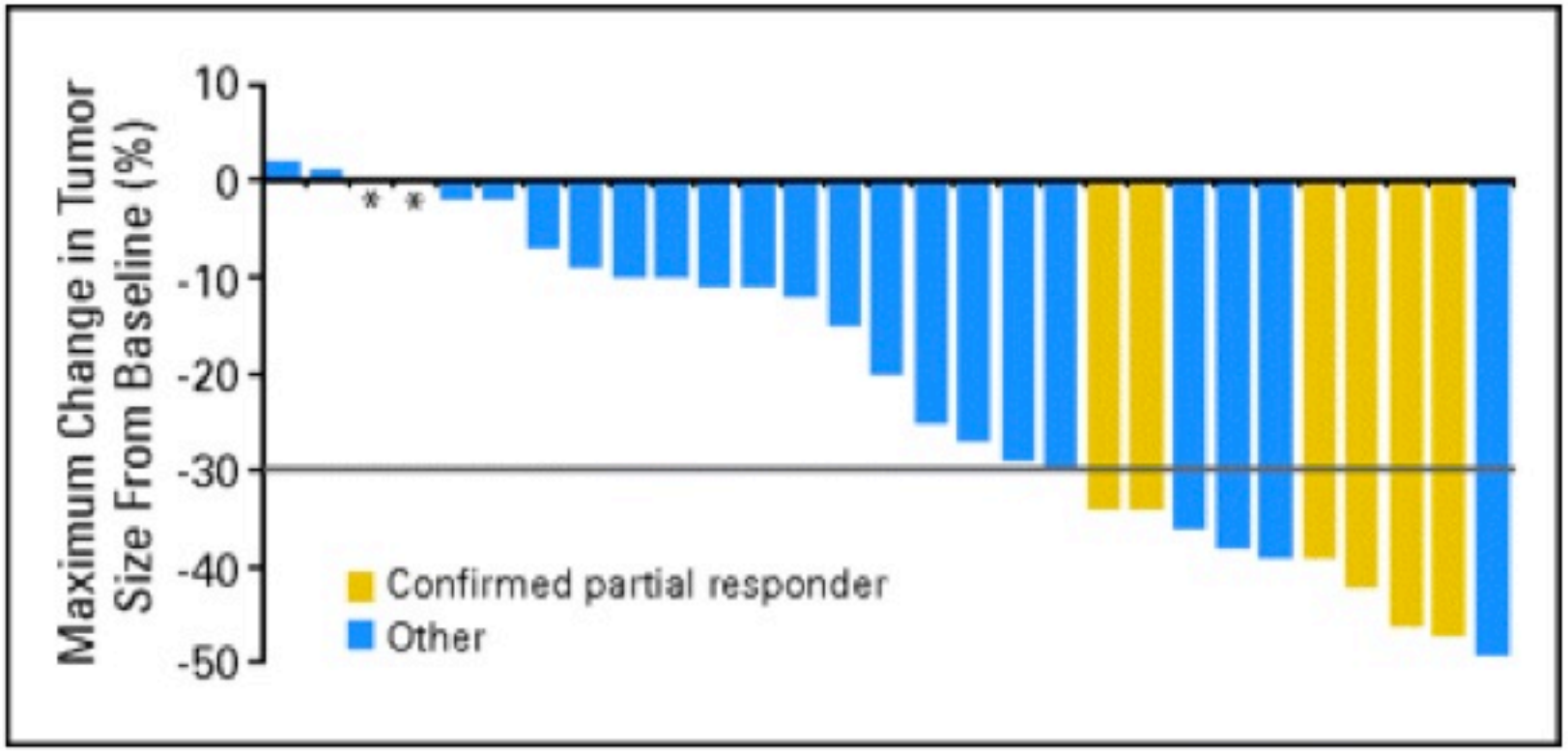
Degrauwe et al, 2012

Phase II: Vandetanib 100 mg in advanced hMTC: maximum reduction from baseline in target lesions (RECIST)



Robinson et al., JCE&M 2010

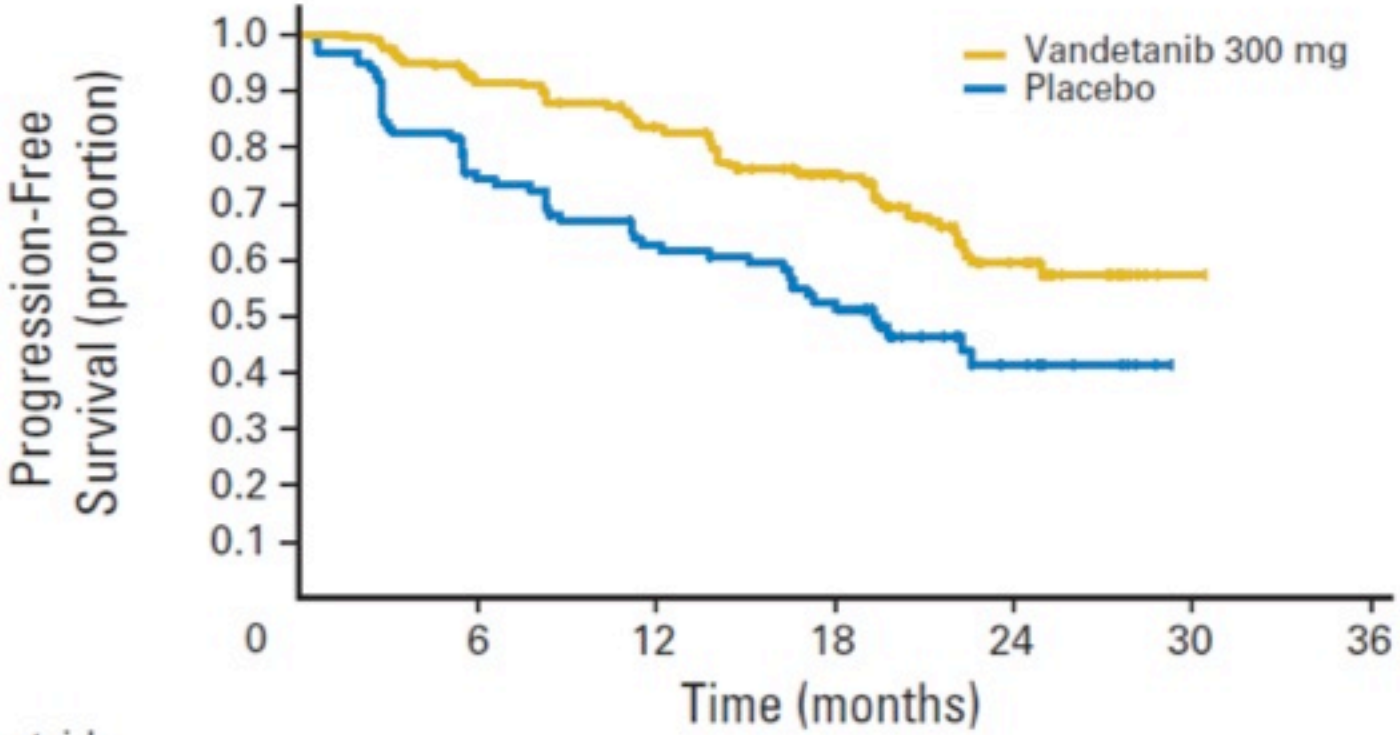
Phase II: Vandetanib 300 mg in advanced hMTC: maximum reduction from baseline in target lesions (RECIST)



Wells et al., JCO 2010

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

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



No. at risk							
Vandetanib 300 mg	231	196	169	140	40	1	0
Placebo	100	71	57	45	13	0	0

Wells, 2012

Table 3. Objective Response Rate: Summary of Subgroup Analyses (randomized phase)

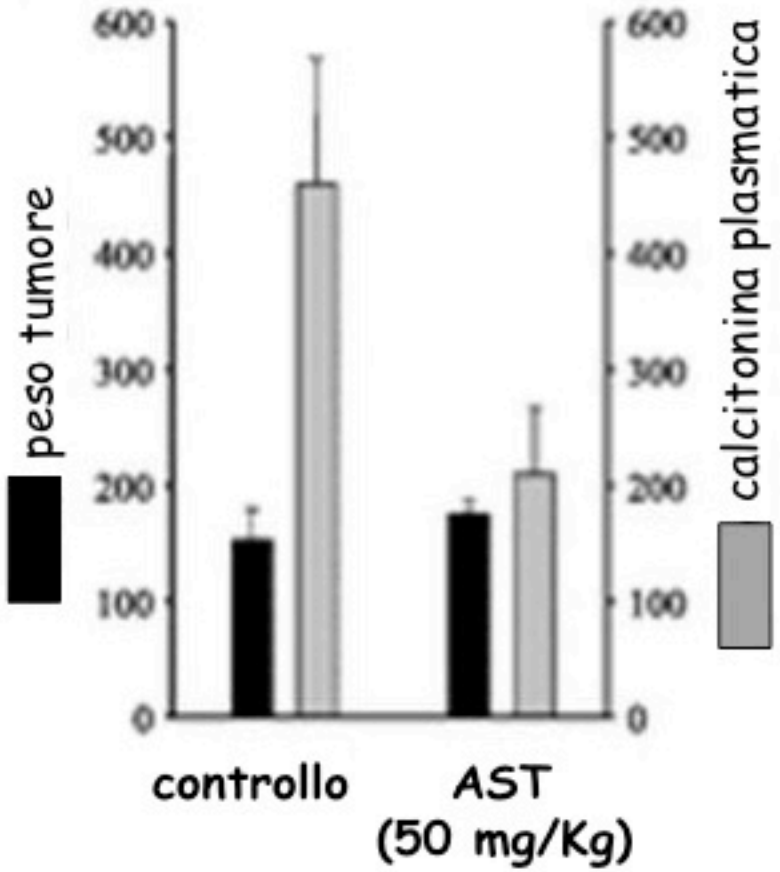
Patient Subgroup and Randomized Treatment	No. of Patients	Responses	
		No.	%
Hereditary MTC			
Vandetanib, 300 mg	28	13	46.4
Placebo	5	0	
Sporadic *RET* mutation positive			
Vandetanib, 300 mg	110	57	51.8
Placebo	45	0	
Sporadic *RET* mutation negative			
Vandetanib, 300 mg	2	0	
Placebo	6	0	
Sporadic *RET* mutation unknown			
Vandetanib, 300 mg	91	31	34.1
Placebo	44	1	2.3
Sporadic *M918T* mutation positive			
Vandetanib, 300 mg	101	55	54.5
Placebo	41	0	
Sporadic *M918T* mutation negative			
Vandetanib, 300 mg	55	17	30.9
Placebo	39	1	2.6
Sporadic *M918T* mutation unknown			
Vandetanib, 300 mg	48	16	33.3
Placebo	17	0	

Abbreviations: MTC, medullary thyroid cancer; *RET*, rearranged during transfection.

Wells, 2012

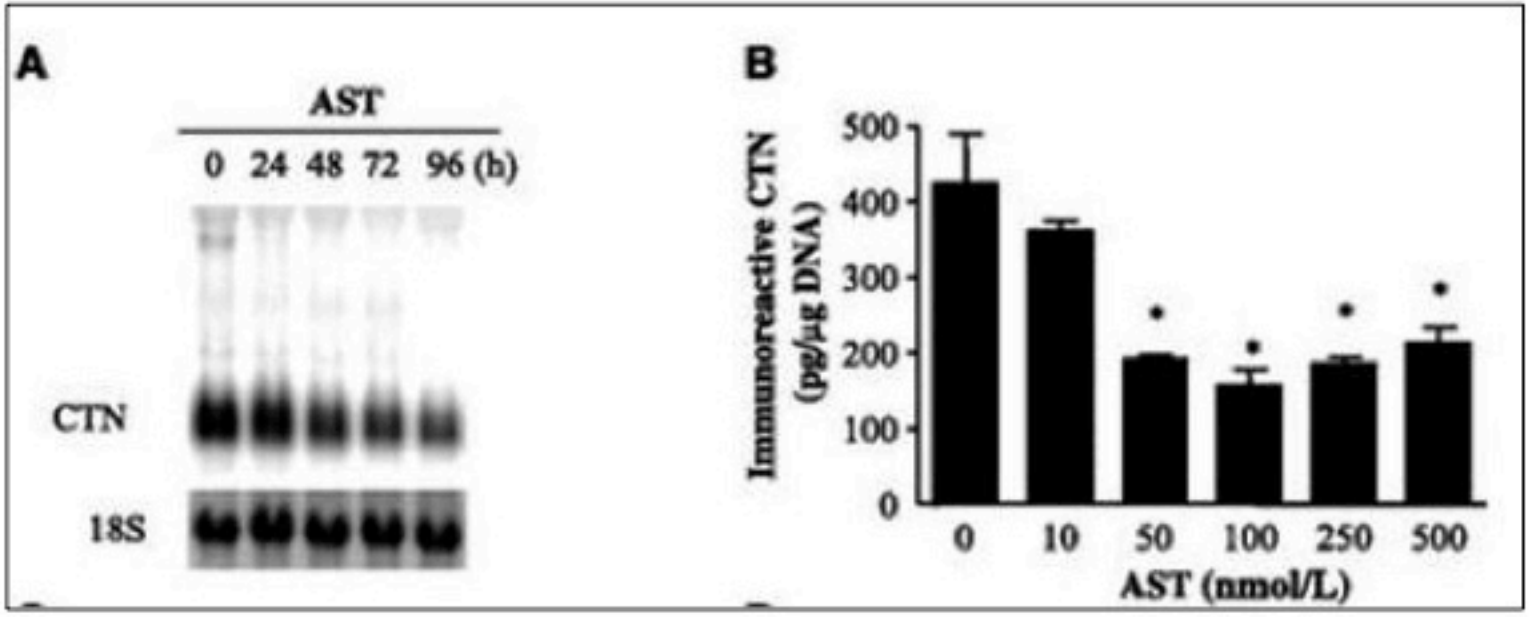
Inibitore tirosino kinasi in trapianti cellule T su topo

Rapida inibizione dei livelli di calcitonina plasmatica independente dagli effetti sul volume tumorale



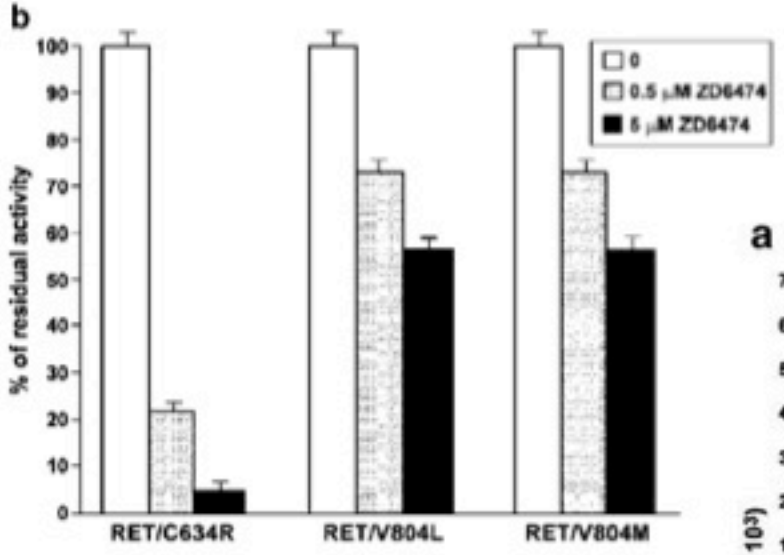
Akeno-Stuart et al., JCE&M 2007

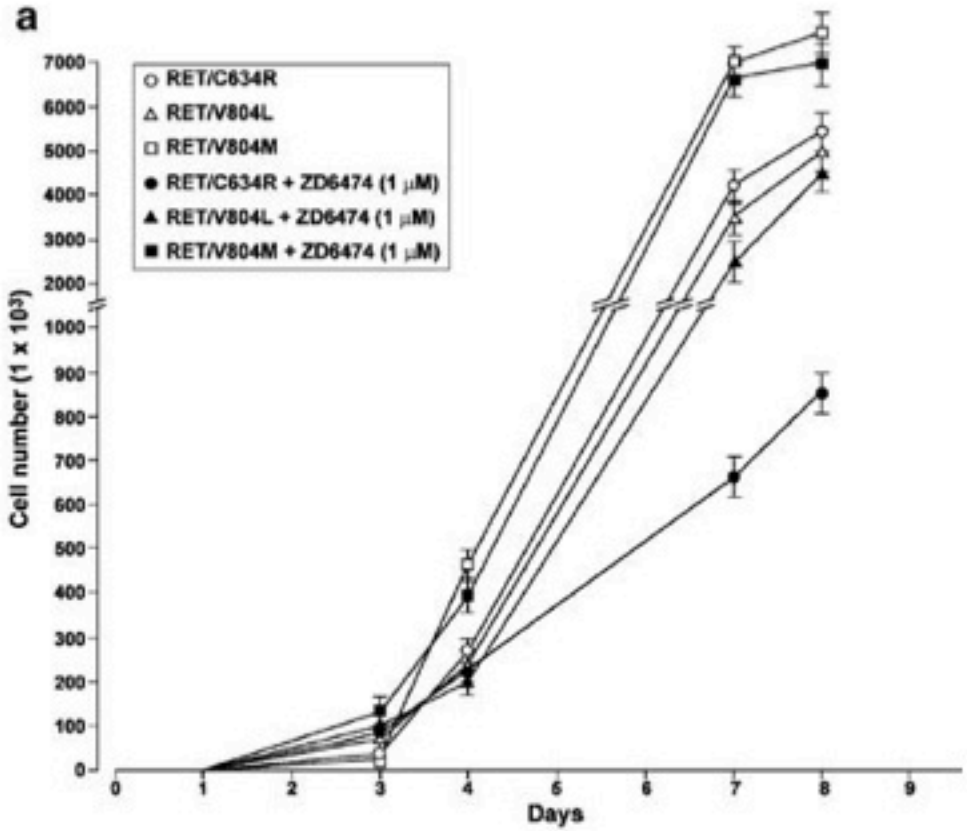
L'inibitore diminuisce la trascrizione e la secrezione di calcitonina in vitro (cellule TT)



Akeno-Stuart et al., JCE&M 2007

VANDETANIB: FARMACOGENOMICA





Carlomagno, 2004

effetti collaterali

DIARREA

IPERTENSIONE

ASTENIA

CALO PONDERALE

DOLORI ADDOMINALI

SINDROME MANO-PIEDE

ALLUNGAMENTO QT

ARTRALGIE

ANORESSIA

CEFALEA

ALTERAZIONI MUCOSA ORALE

VOMITO

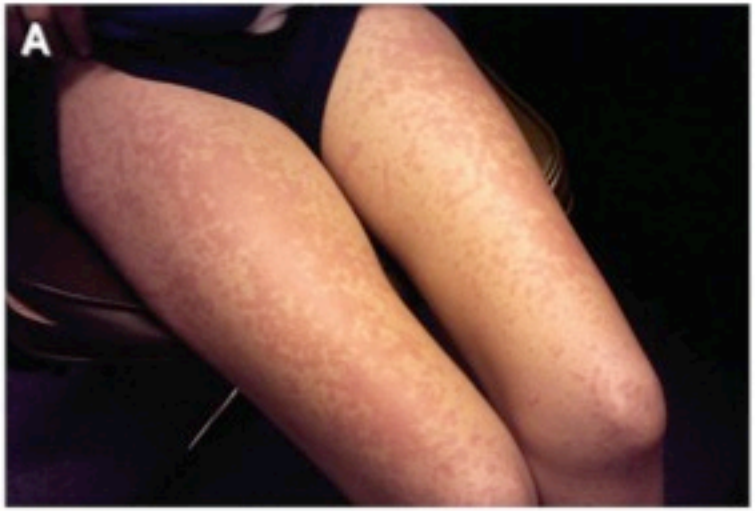
NAUSEA

RUSH CUTANEI

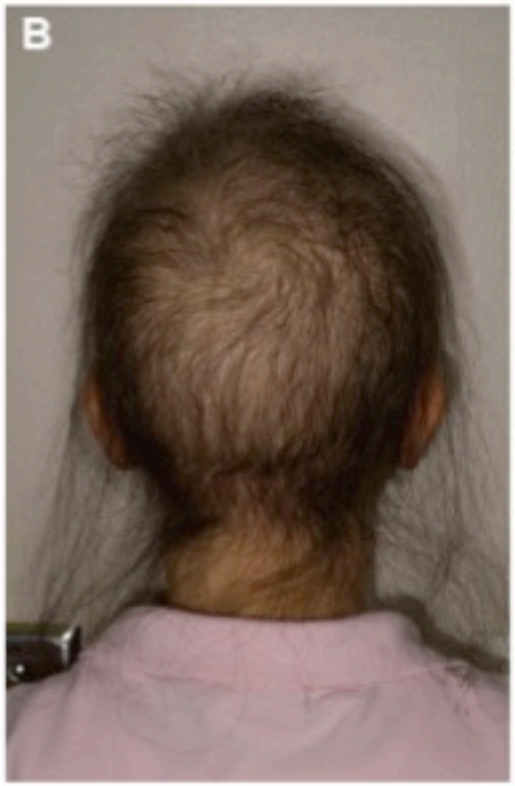
IPERTIREOTROPINEMIA

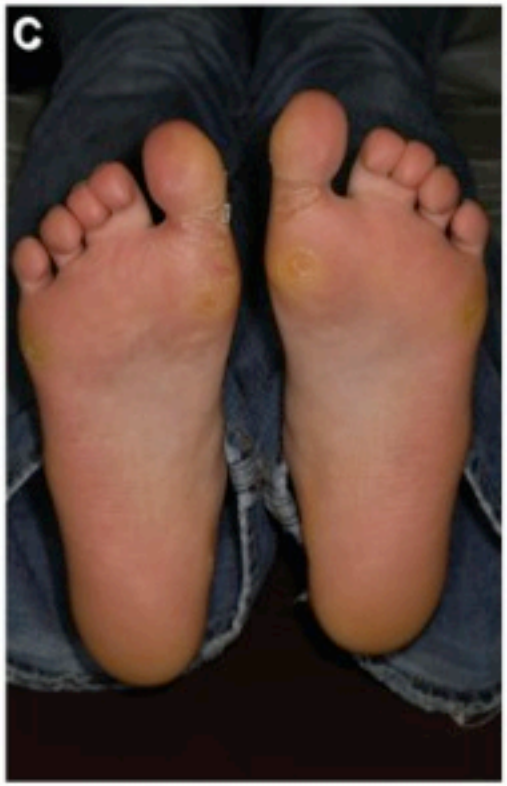
IPOTIROIDISMO

Sorafenib: effetti collaterali



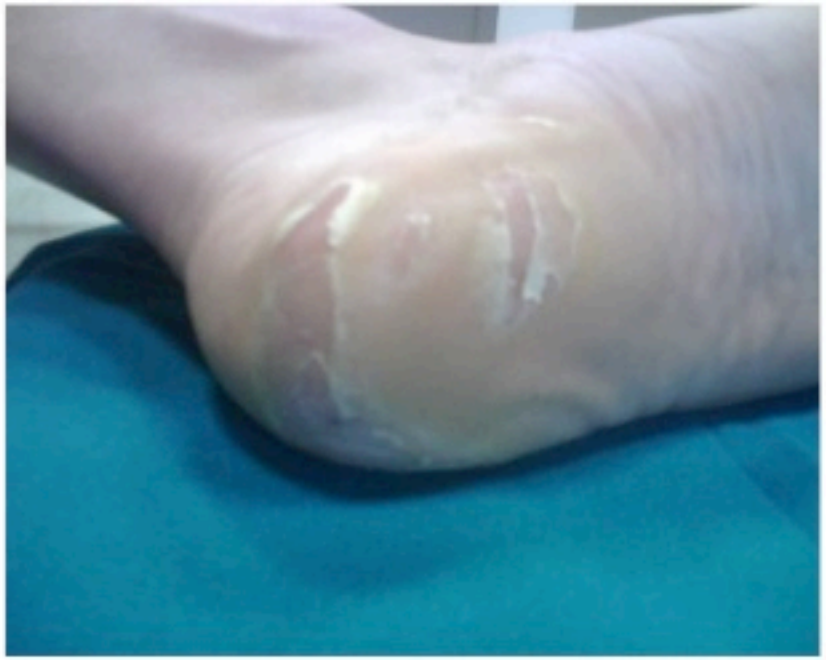
Eritema diffuso

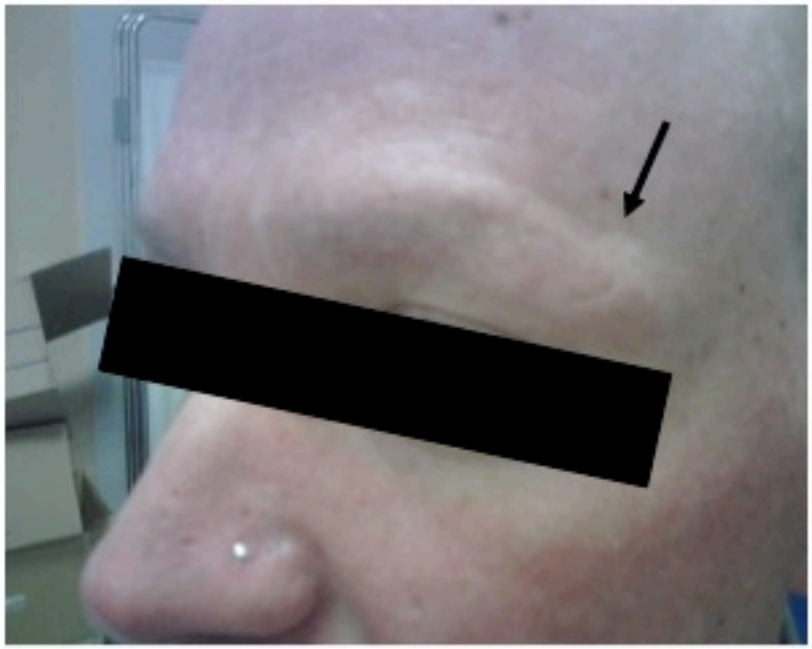


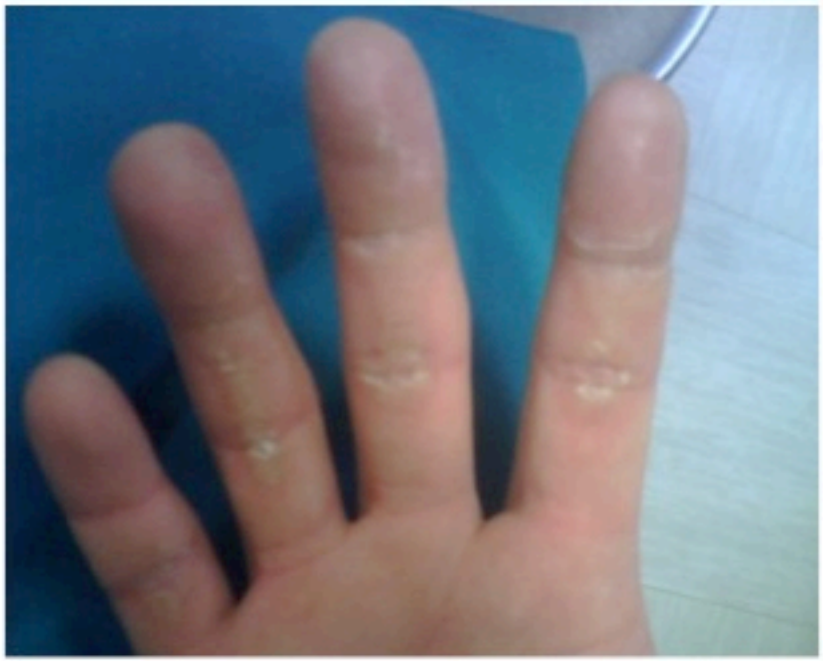


Alopecia
Sindrome mano-piede

Waguespack et al., 2009







Sorafenib: effetti collaterali

Alopecia
Sindrome mano-piede

Paziente MR

VANDETANIB: ADVERSE EFFECTS

Table 4. Common Adverse Events (safety population)

Adverse Event	Vandetanib (300 mg) (n = 231)		Placebo (n = 99)	
	No.	%	No.	%
Any grade occurring with an incidence ≥ 10% overall				
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
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
Grade 3+ occurring with an incidence of ≥ 2% on either arm				
Diarrhea	25	11	2	2
Hypertension	20	9	0	
ECG QT prolonged*	18	8	1	1
Fatigue	13	6	1	1
Decreased appetite	9	4	0	
Rash	8	4	1	1
Asthenia	6	3	1	1
Dyspnea	3	1	3	3
Back pain	1	0.4	3	3
Syncope	0		2	2

*As defined according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, v3 (see Results for the incidence of protocol-defined QTc prolongation as described in Methods, Safety and Tolerability).

Wells, 2012

Questioni aperte

CITOSTATICI vs CITOTOSSICI

Le terapie target sono citostatiche e non citotossiche. Il trattamento va pertanto proseguito per tutta la vita. Questo rappresenta un problema nel caso di farmaci ad alta tossicità e mal tollerati.

VIE METABOLICHE COMPENSATORIE

RESISTENZA

Le cellule neoplastiche sopravvissute sono verosimilmente in grado di sviluppare vie metaboliche compensatorie, tramite l'acquisizione di nuove mutazioni.

STEM CELLS

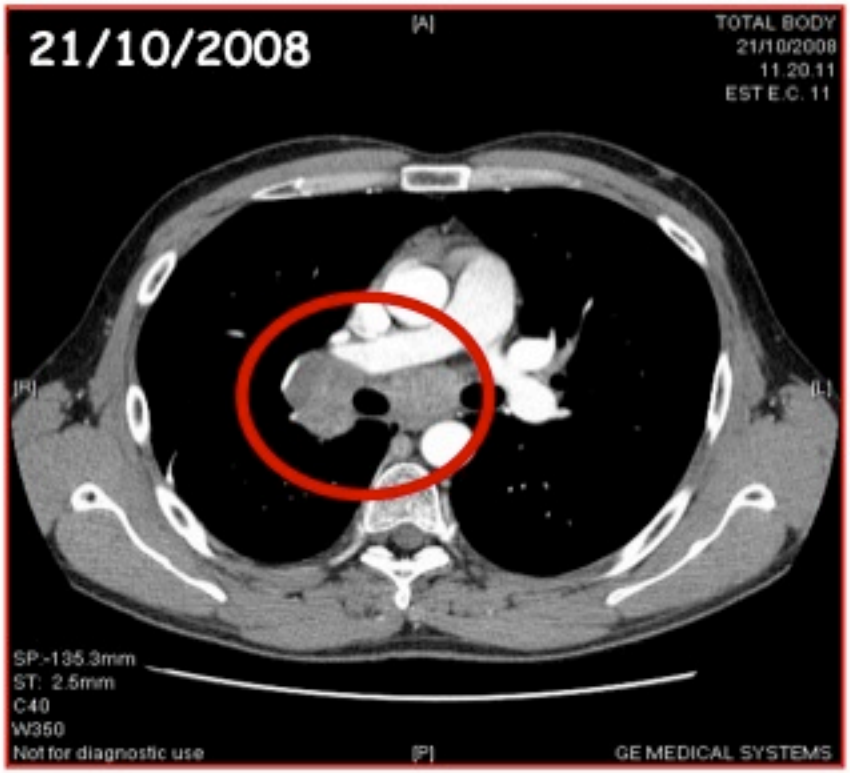
E' probabile che i farmaci attualmente disponibili non siano efficaci sulle cellule neoplastiche staminali, che sono un continuo serbatoio di nuova crescita tumorale

Pacini, *Editorial*, 2008

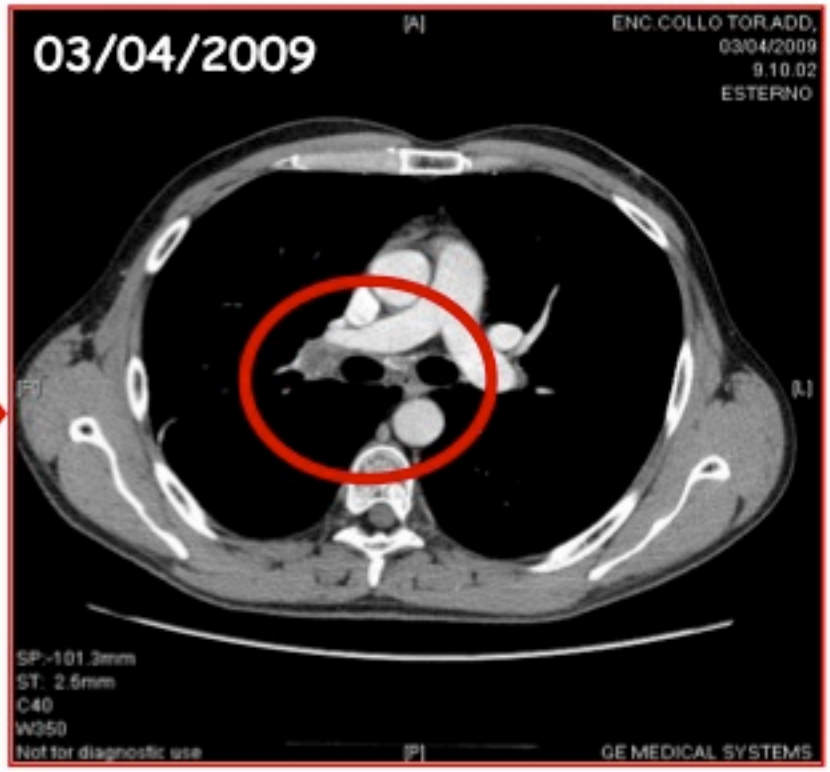
Paziente maschio di 35 anni con carcinoma follicolare refrattario alla terapia radiometabolica

Novembre 2008: inizio trattamento OFF-LABEL con Sorafenib

TAC pre-SORAFENIB

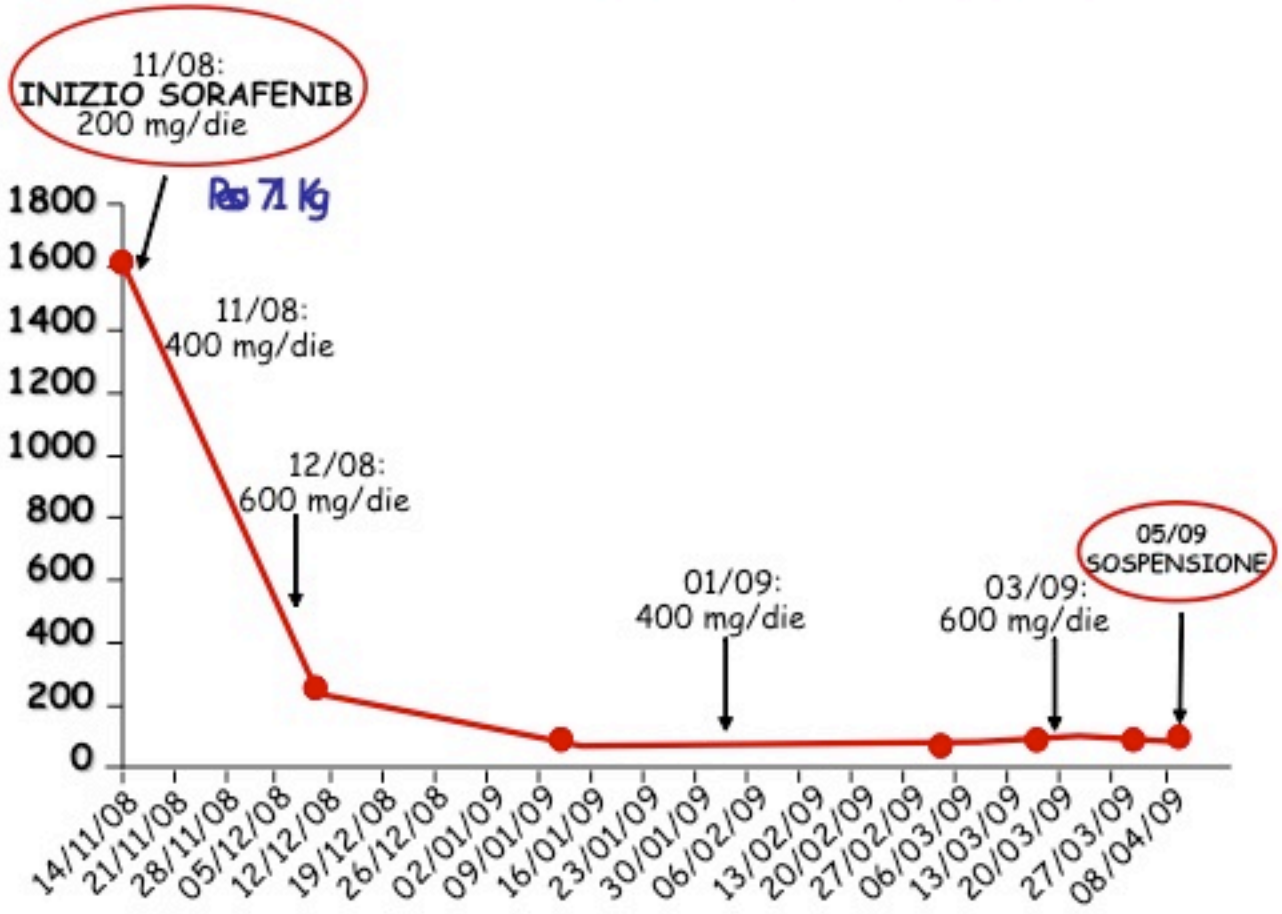


TAC post-SORAFENIB



Paziente MR

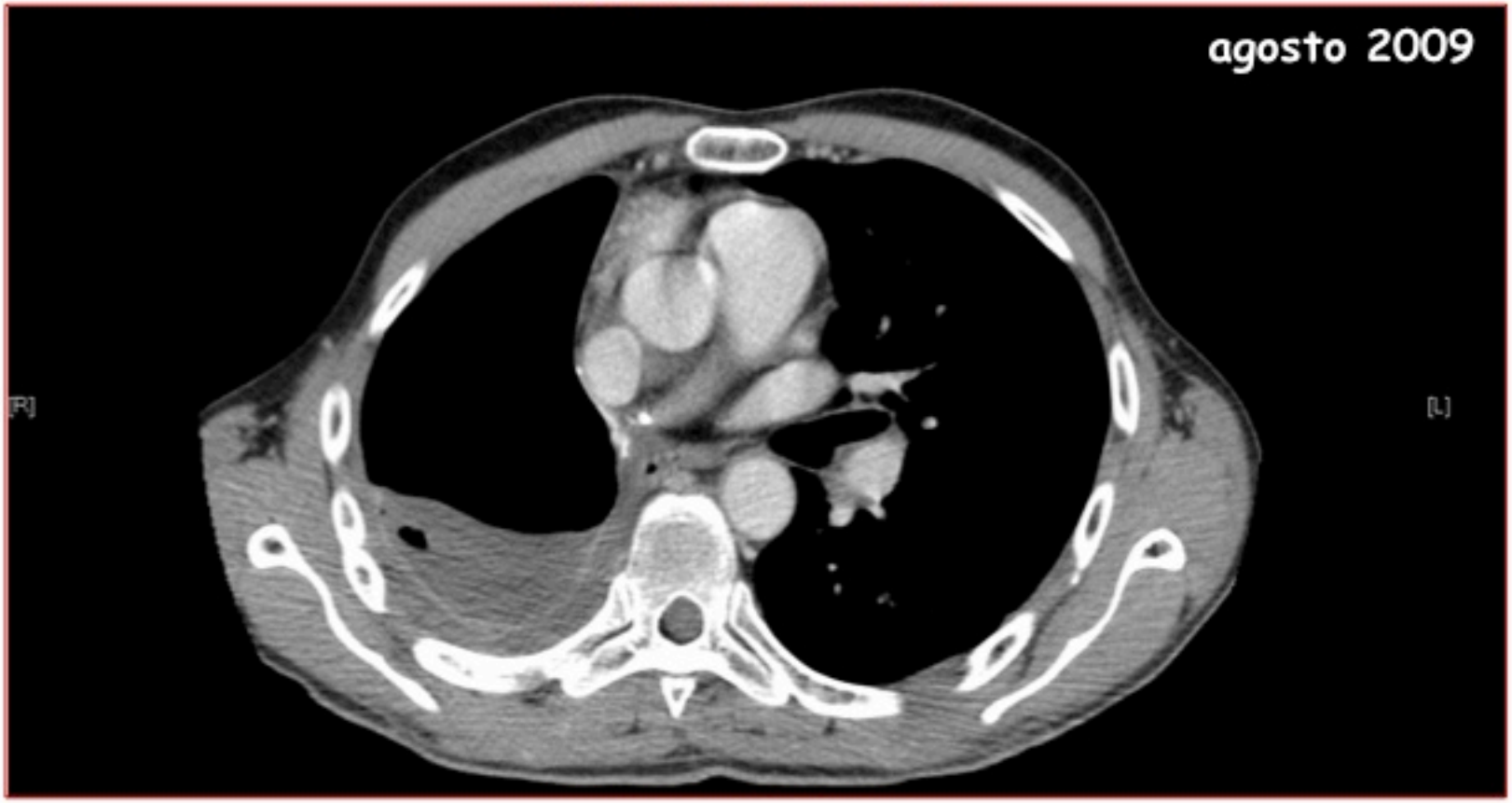
ANDAMENTO DEI VALORI DI TIREOGLOBULINA



Paziente MR

Giugno 2009: LINFOADENECTOMIA MEDIASTINICA
E PNEUMECTOMIA DESTRA

TAC TORACE a 2 mesi dall'intervento



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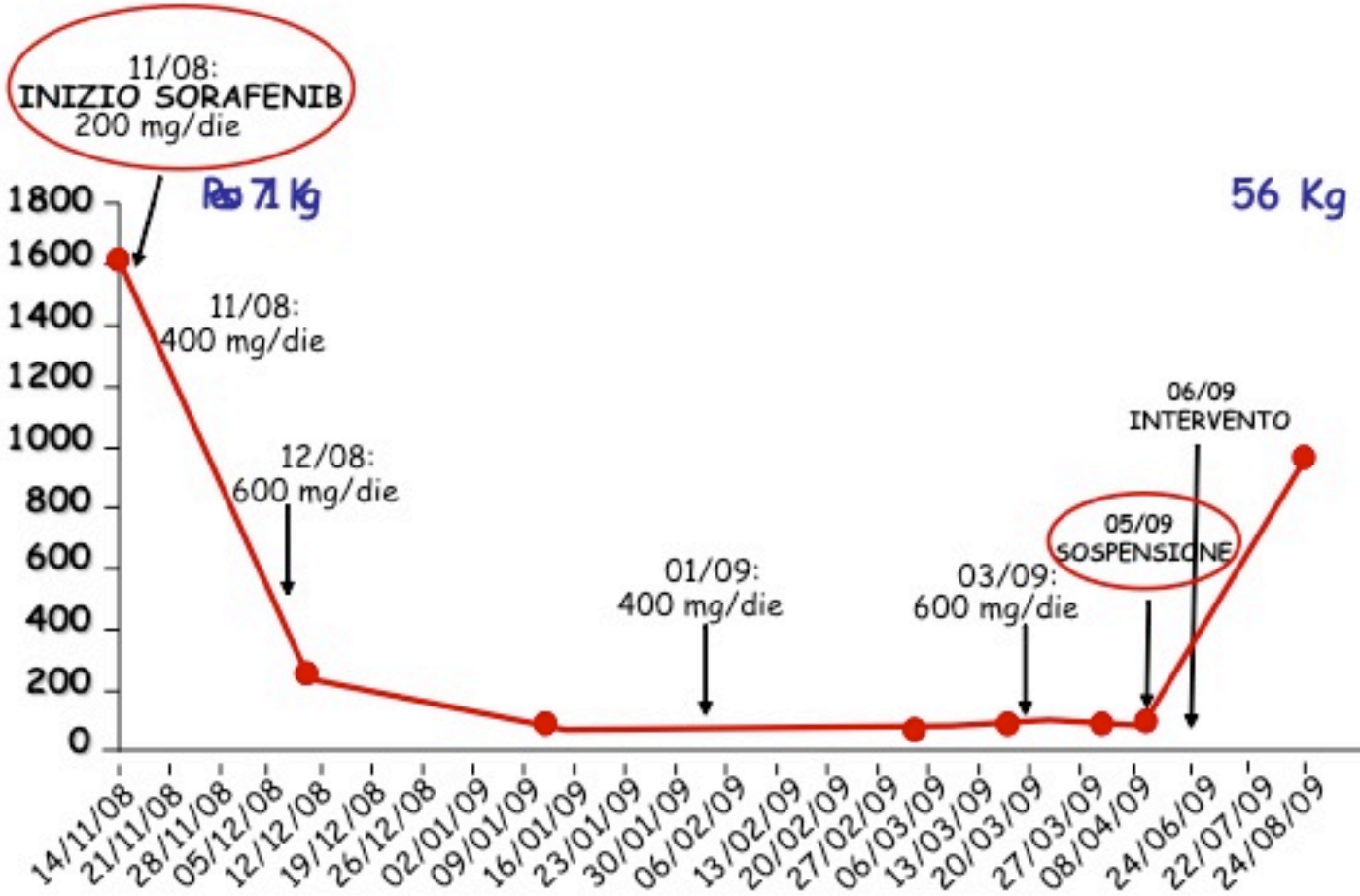
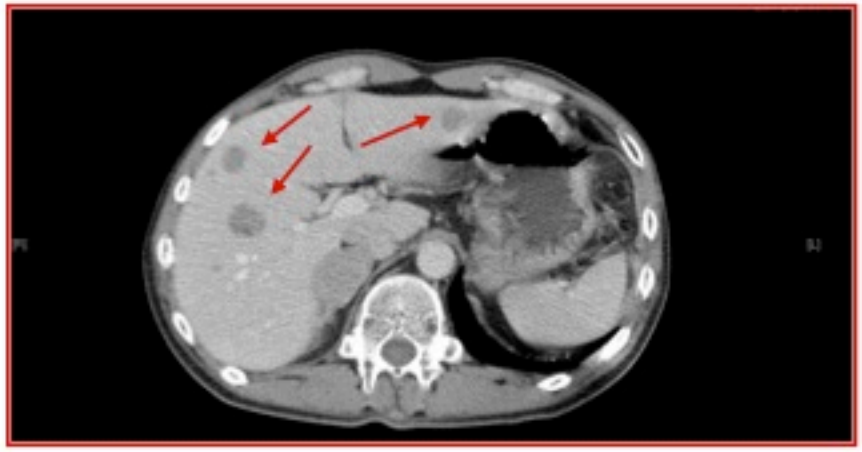
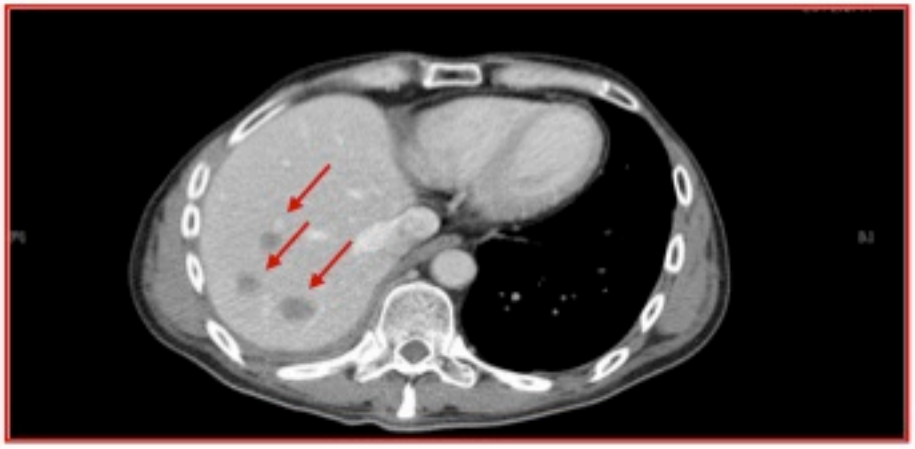


Paziente MR

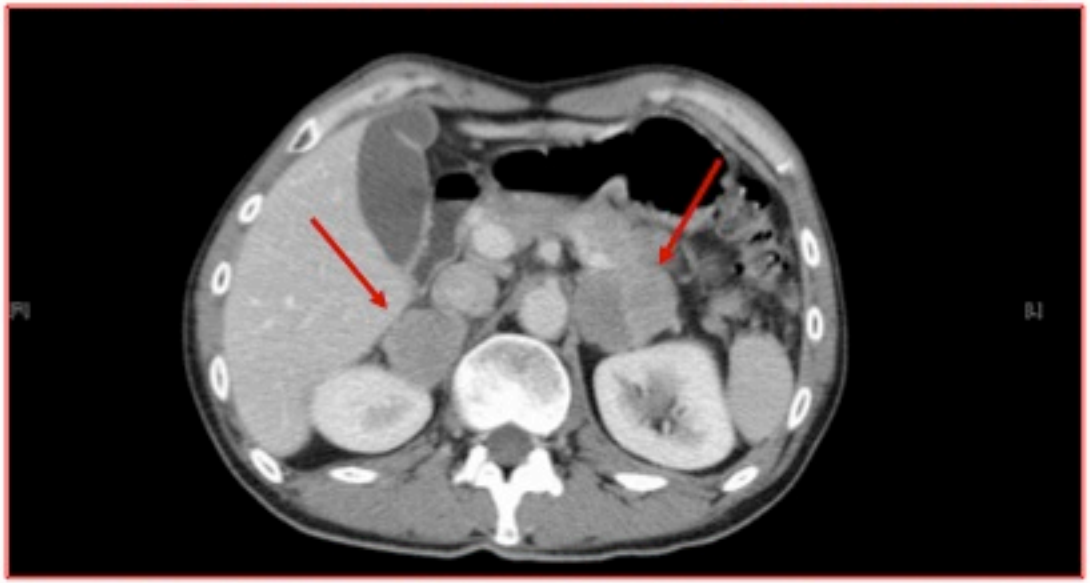
Agosto 2009

METASTASI EPATICHE



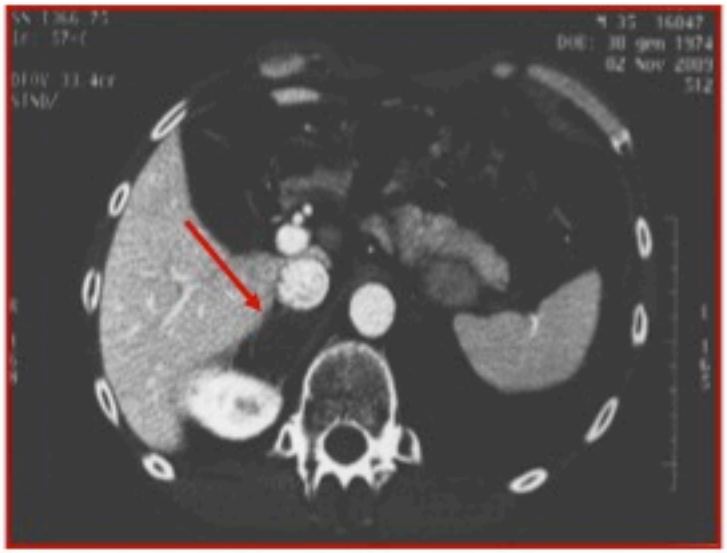


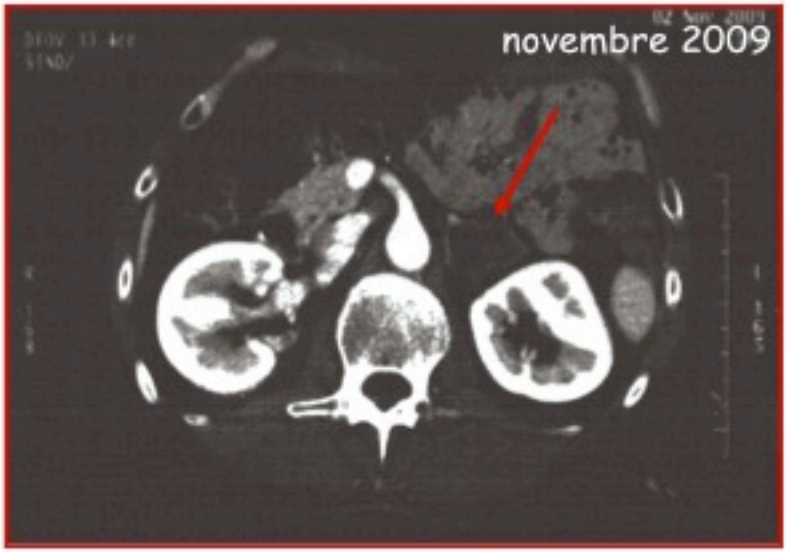
METASTASI SURRENALICHE

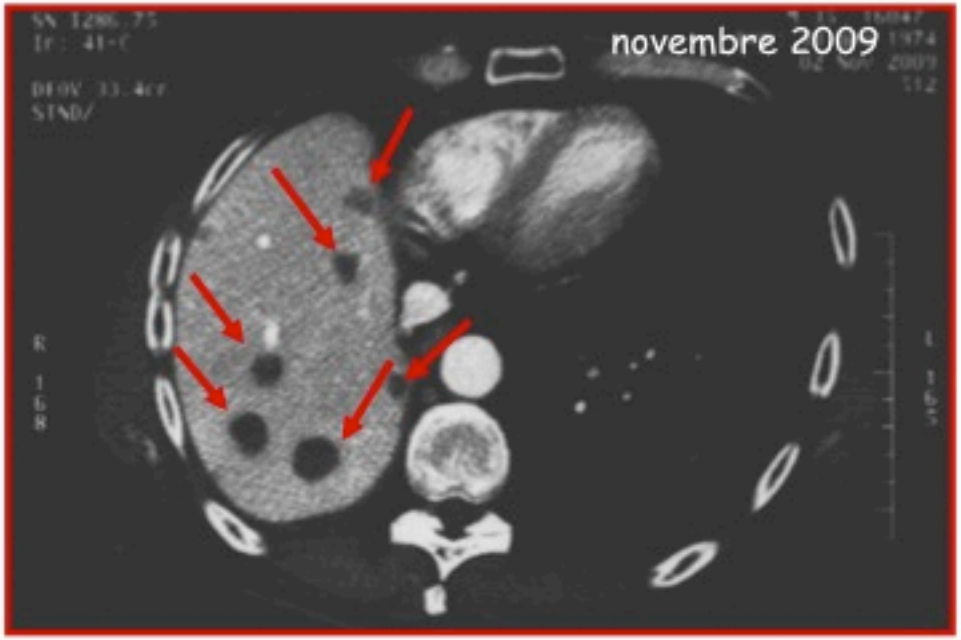


Inizio 2° ciclo di trattamento con Sorafenib

Paziente MR

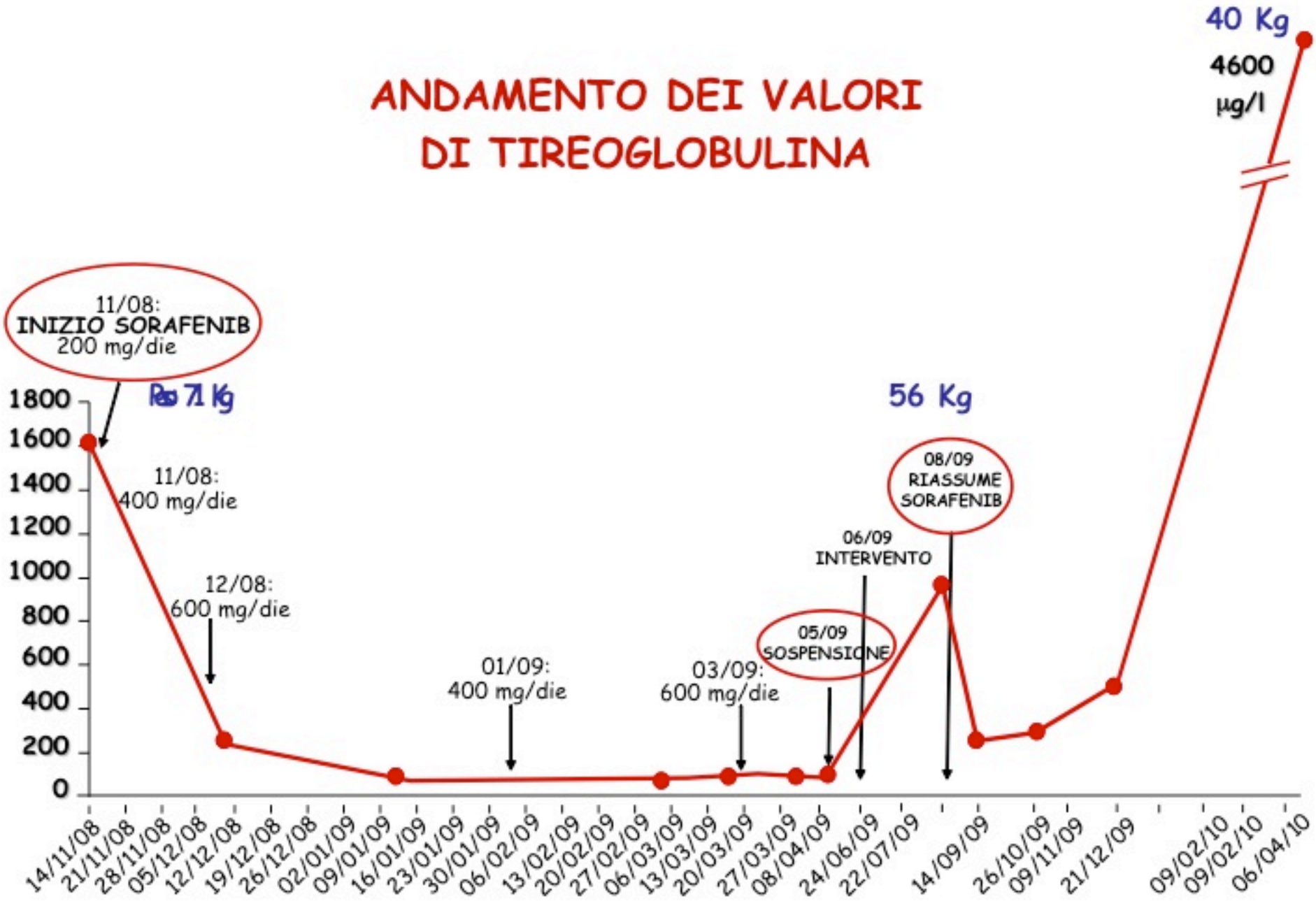






Paziente MR

ANDAMENTO DEI VALORI DI TIREOGLOBULINA



Paziente MR

CONCLUSIONI

La maggior parte dei carcinomi tiroidei differenziati e midollari risultano guariti dopo la chirurgia iniziale, quando vengono diagnosticati in stadio precoce

La malattia può essere persistente o recidivare e possono comparire metastasi

I tumori tiroidei differenziati possono perdere la capacità di captare lo iodio radioattivo e dedifferenziarsi con potenziali effetti importanti sulla qualità di vita e morte

Nuovi farmaci sono disponibili per questi pazienti

CONCLUSIONI

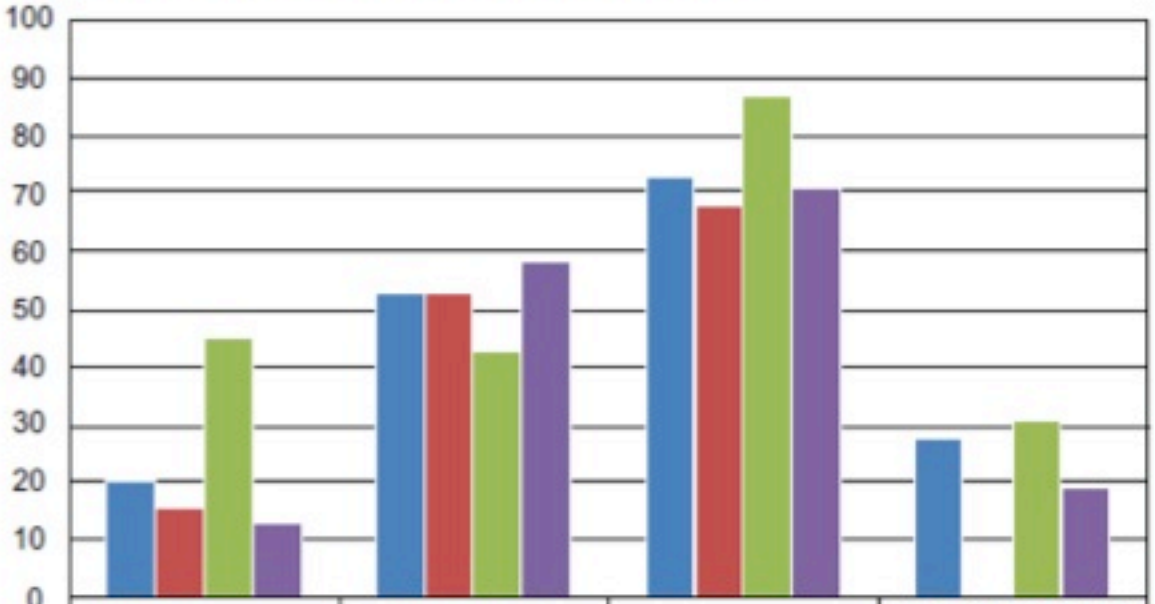
I dati preliminari confermano l'efficacia clinica degli inibitori TK in pazienti con carcinoma della tiroide avanzato, metastatico, inoperabile e non captante il radioiodio.

Tuttavia si evidenzia una possibile riduzione dell'efficacia a lungo termine.

Sarà probabilmente necessario somministrare cocktail di farmaci per inibire tutte le vie metaboliche attive

Analysis of clinical trials leading to the approval of Vandetanib

Overview of the phase II and III studies



= Not reported
* = Estimation

	Partial responders or better (%)	Durable stable disease (%)	Disease control (%)	Median progression free survival (months)
Phase II Vandetanib 300 mg/d (Wells et al)	20	53	73	27.9
Phase II Vandetanib initially 100 mg/d (Robinson et al)	16	53	68	#
Phase III Vandetanib 300 mg/d (Wells et al)	45	43	87	30.5*
Phase III placebo (Wells et al)	13	58	71	19.3

Degrauwe et al, 2012

Table 1
Comparison of study outcomes and adverse event frequencies from the phase III placebo-controlled trials of vandetanib (ZETA) and cabozantinib (EXAM) in MTC.[16,19,25,26]

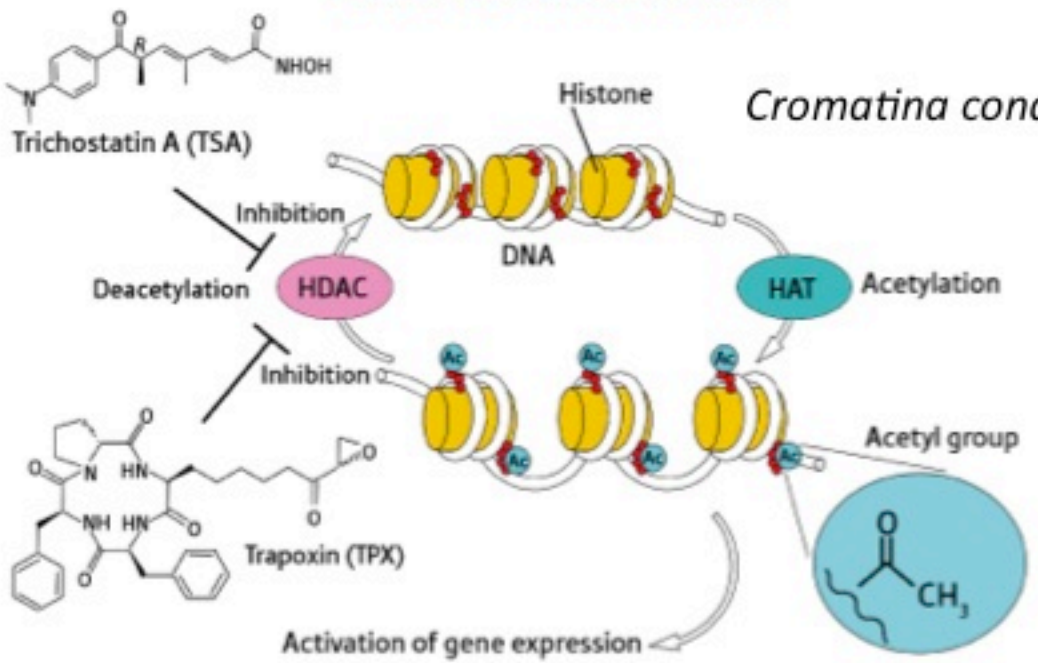
Trial	ZETA		EXAM	
Treatment arm	Vandetanib	Placebo	Cabozantinib	Placebo
Entry criteria	Locally advanced or metastatic disease		Documented progression of locally advanced or metastatic disease	
N	231	100	219	111
Median PFS, months	30.5	19.3	11.2	4
Ratio of median PFS, treatment:placebo	1.58		2.80	
Partial response rate (%)	44	1	27	0
Grade 3/4 adverse event rates				
Diarrhea (%)	11	2	16	2
Hypertension (%)	9	1	8	0
QTc prolongation (%)	8	1	0	0
Fatigue (%)	6	1	9	3
Asthenia (%)	3	1	6	1
Death due to adverse event (%)	2	2	6	5

……."cure" remains elusive, adverse events frequent, and exactly how such "targeted" agents actually function within MTC remains unclear

New approaches to clinical trial design and the **preclinical** development of targeted agents may be required to optimize the combination of maximum efficacy with minimal toxicity for patients with metastatic MTC

Sherman, 2013

To carry out gene expression, a cell must control the coiling and uncoiling of DNA around histones



HDACI induce cell cycle arrest, differentiation and/or apoptosis

inhibition of tumor cells proliferation
in culture and in vivo

Gli inibitori delle "*histone deacetylases*": HDACI

Table 2 Annexin V/propidium iodine assay

		Control (apoptosis) (%)	Panobinostat (100 nM) (apoptosis) (%)	Belinostat (50 μM) (apoptosis) (%)
KRAS	Cal62	3	37	68
BRAF	SW1736	3	11	56
RET/PTC	BHP2-7	5	16	43
PI3K/BRAF	T238	2	3	24

Effetto sinergico tra TKI e HDACI

Table 3 Combination index of (a) belinostat/panobinostat and dasatinib on SW1736 cells, (b) belinostat/panobinostat and dasatinib on Cal 62 cells, (c) belinostat/panobinostat and pazopanib on BHP 2-7 cells

Dasatinib (nM)	Belinostat (nM)				Panobinostat (nM)			
(a)								
	250	500	750	1,000	1	20	40	50
100	0.47	0.41	0.39	0.29	0.14	0.48	0.54	0.56
Dasatinib (nM)	Belinostat (nM)				Panobinostat (nM)			
(b)								
	250	500	750	1,000	8	16	24	45
100	0.13	0.14	0.15	0.14	0.17	0.16	0.18	0.29

Pazopanib (μM)	Belinostat 1 μM	Panobinostat 30 nM
1	0.66	0.50
2	0.63	0.51
3	0.52	0.47
4	0.54	–

Combination index described more fully in Fig. S1. Values ≤0.90 are consistent with synergism, and the lower the value, the greater the synergism

Cancro della tiroide: future possibilità terapeutiche

E' necessario implementare la terapia target per:

·CTD resistenti alla terapia radiometabolica

·CMT metastatico

·Anaplastico

E' inoltre auspicabile che tale terapia venga adattata alla diversa etiopatogenesi di queste categorie

GRAZIE PER L'ATTENZIONE

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