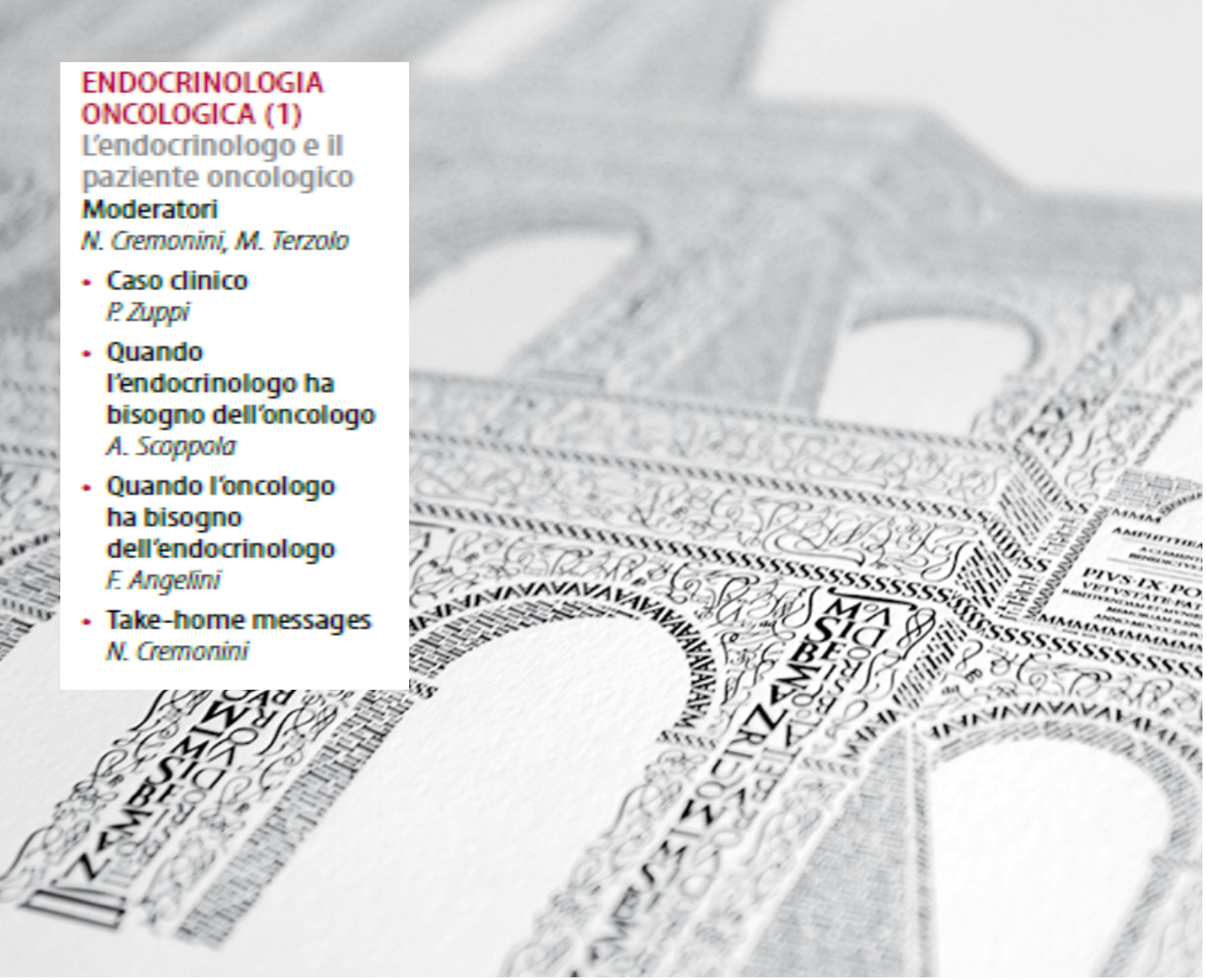


Francesco Angelini
Ospedale Regina Apostolorum
Albano LAziale

ROMA
9__11
NOVEMBRE
2012

1° CORSO NAZIONALE DI AGGIORNAMENTO

Associazione Medici Endocrinologi

I PER[CORSI]AME

Quando l'oncologo ha bisogno dell'endocrinologo
Topics

- ***Tumori della tiroide***

- ***Tumori del surrene***

Quando l'oncologo ha bisogno dell'endocrinologo
Topics

- ***Tumori della tiroide***

Background :
Come sono andate le cose per gli oncologi negli anni ’90
per i tumori avanzati della tiroide ?

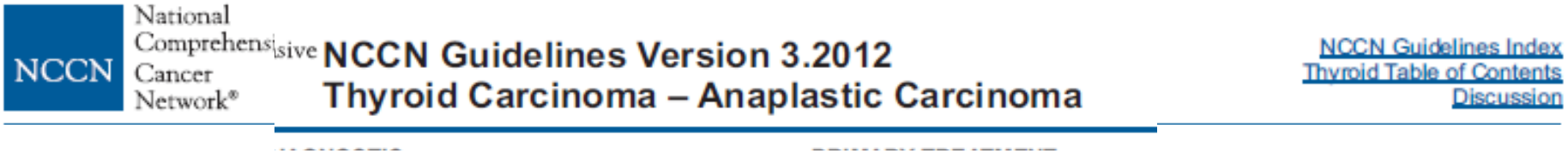
***DTC** : soppressione TSH , radioiodio , terapie palliative locoregionali (RT , chirurgia , tentativi di chemioterapia sostanzialmente inefficaci*

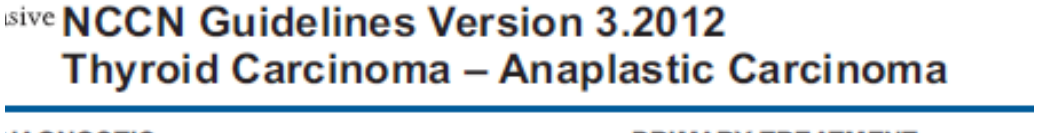
***MTC** : forse anche peggio , radioiodio e soppressione TSH non servono*

***ATC** : chirurgia , radioterapia esterna , approcci loco-regionali . chemioterapia sostanzialmente inefficace*

Chemioterapia nei DTC
La Storia

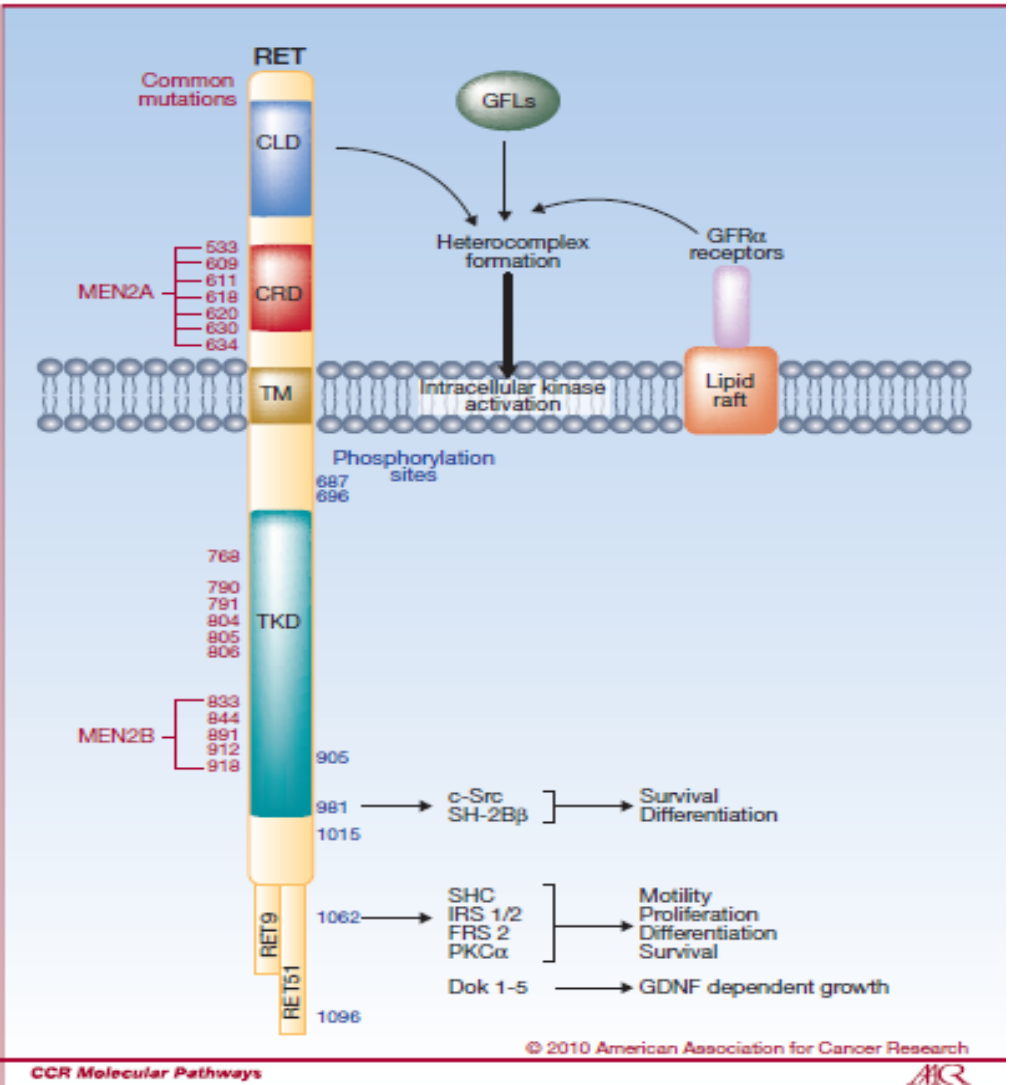
Farmaco/combinazione	dose	risposte obiettive
Doxorubicina	60 mg/mq q 21d	4-25%
Doxorubicina + Cisplatino	60 mg/mq q 21d 60 mg/mq q 21d	5-27%





Cytotoxic chemotherapy has shown to have minimal efficacy ….consider clinical trial or best supportive care ….

Cosa ha cambiato questo sconfortante panorama nei tumori della tiroide ?



Mutations in the cysteine-rich domain of RET (codons 609, 611, 618, 620, 630, and 634) give rise to MEN2A and FMTC.

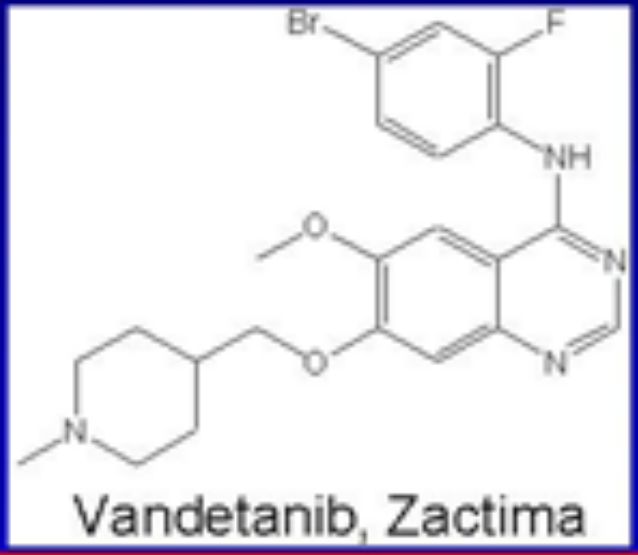
Mutations in the cysteine-rich domain (codons 609, 611, 618, and 620) are not only found in families with MEN2A/FMTC but also in patients with Hirschsprung's disease, characterized by an absence of colon ganglia cells.

Distinct mutations in the tyrosine kinase domain of RET give rise to FMTC (codons 768, 790, 791, 804, and 891) or to MEN2B (codons 883 and 918).

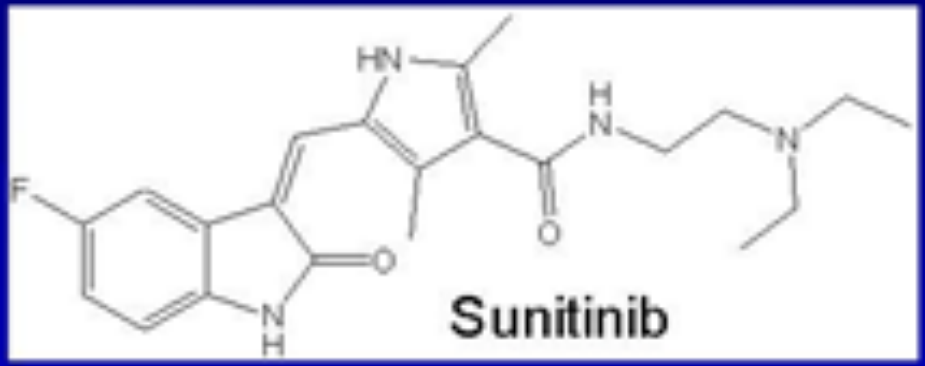
...availability of drugs directed against the molecular target

Small Molecule ATP Mimetics Can Inhibit the Activities of RET and Other Kinases

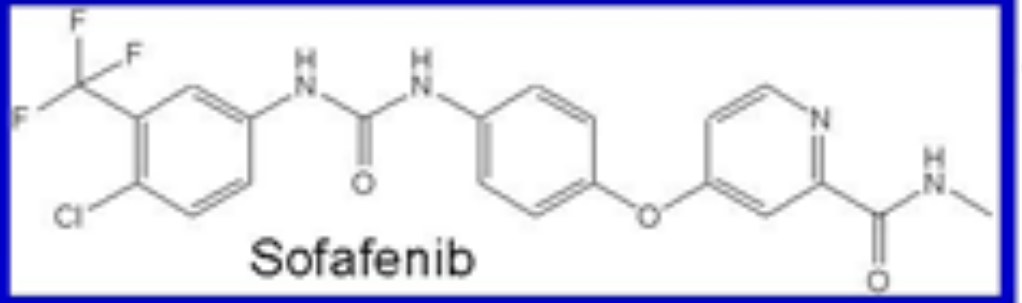
Structures of Selected RET Inhibitors in MTC Clinical Trials:



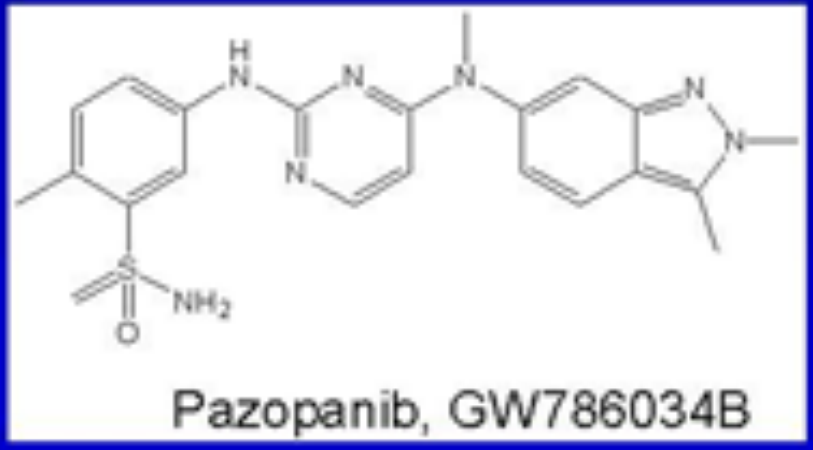
Vandetanib, Zactima



Sunitinib

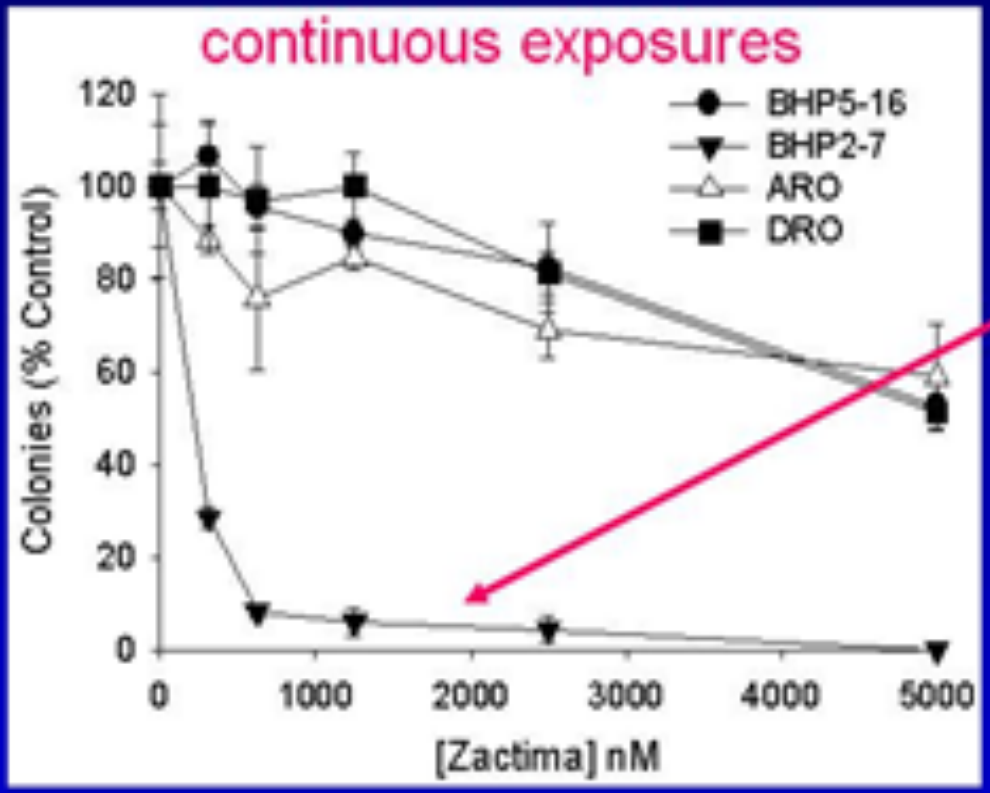


Sofafenib



Pazopanib, GW786034B

Preclinical Data Indicated Promising anti-Tumor Effects of TKIs in RET-mutant Tumors



- BHP5-16 (Papillary, RET wt)
- BHP2-7 (Papillary, RET mut)
- ARO (RET wt)
- DRO (RET wt)

So, continuous vandetanib has RET-dependant effects in thyroid cancer cells – DTC included...

Table 1. Summary of clinical trials using multikinase inhibitors in medullary thyroid carcinoma

Trial Characteristics	Drug Tested					
	Imatinib	Vandetanib	Motesanib[a]	Sorafenib[b]	Sunitinib[a,c]	XL-184[c]
RET IC_{50} (nM)	25,000	130	59	50	224	4
Key targets besides RET	PDGFR, KIT	VEGFRs, EGFR	VEGFRs, PDGFR, KIT	VEGFRs, PDGFR, BRAF, KIT	VEGFRs, PDGFR, KIT	VEGFRs, c-MET, KIT
Phase of the trial	Phase II	Phase II	Phase II	Phase II	Phase II	Phase I-II
Period of accrual	January 2003 to January 2005	November 2004 to August 2006	July 2005 to March 2006	November 2006 to January 2008	November 2006 to August 2009	Unknown to August 2008
Oral drug dose	600 mg PO qd ongoing	300 mg PO qd ongoing	125 mg PO qd × 48 weeks	400 mg PO BID ongoing	50 mg qd × 4 weeks on-2 weeks off cycle; ongoing	75 mg to 175 mg qd ongoing
No. of patients (sporadic/hereditary/unknown)	15 (11/4/0)	30 (0/30/0)	91 (76/13/2)	21 (16/5/0)	25 (14/2/9)	37 (3/28/6)
No. of patients with RET+ genotype/no. of patients tested[d] (Codon of RET mutation × no. patients)[d]	3/3 sporadic (918 × 2, 883 × 1)	N/A sporadic	28/39 sporadic (918 × 25, other × 3)	10/12 sporadic (918 × 9, 634 × 1)	9/14 sporadic (918 × 8, 634 × 1)	22/28 sporadic (918 × 15, 634 × 2, 620 × 1, other × 4)
	4/4 hereditary (634 × 3, 618 × 1)	30/30 hereditary (634 × 10, 618 × 8, 620 and 918 × 4 each; others × 4)	3/4 hereditary (918 × 2, other × 1)	5/5 hereditary (634 × 3, 618 × 1, 918 × 1)	2/2 hereditary (618 × 1, 804 × 1)	3/3 hereditary (611, 620, 634 × 1 each)
No. partial response (%)[e]	0	6 (20)	2 (2)	1 (6)	8 (33)	10 (29)
No. stable disease > 6 months (%)	4 (27)	16 (53)	44 (48)	10 (62)	11 (46)	15 (41)
Median progression-free survival (months)	Not reported	28	12	18	12	Not reported
≥50% decline in serum calcitonin compared with baseline percent of patients	Not reported	80%	37%	42%	50%	72% (16 of 19 assessable patients)
Reference	de Groot et al. (26)	Wells et al. (25)	Schlumberger et al. (20)	Lam et al. (21)	De Souza et al. (22)	Kurzrock et al. (23)

John E Phay ,2010

Clinical Cancer Research

VOLUME 30 · NUMBER 2 · JANUARY 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

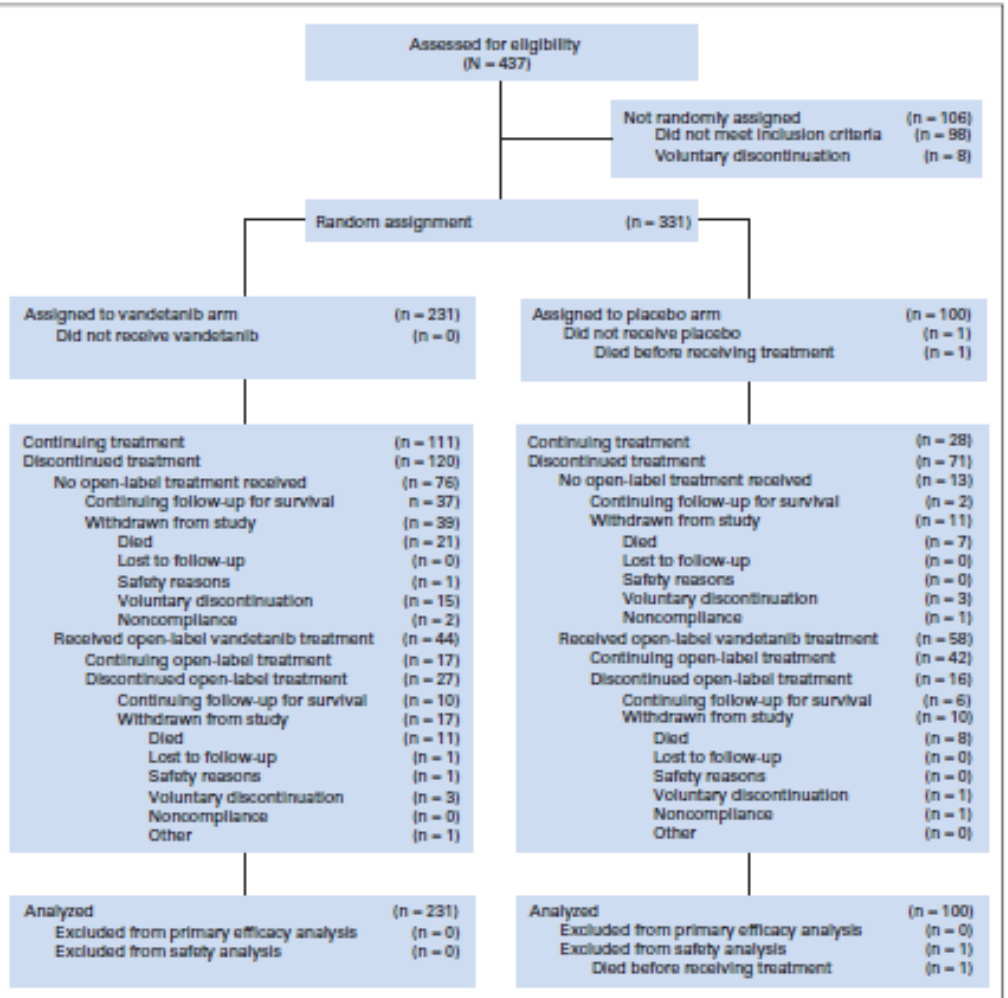
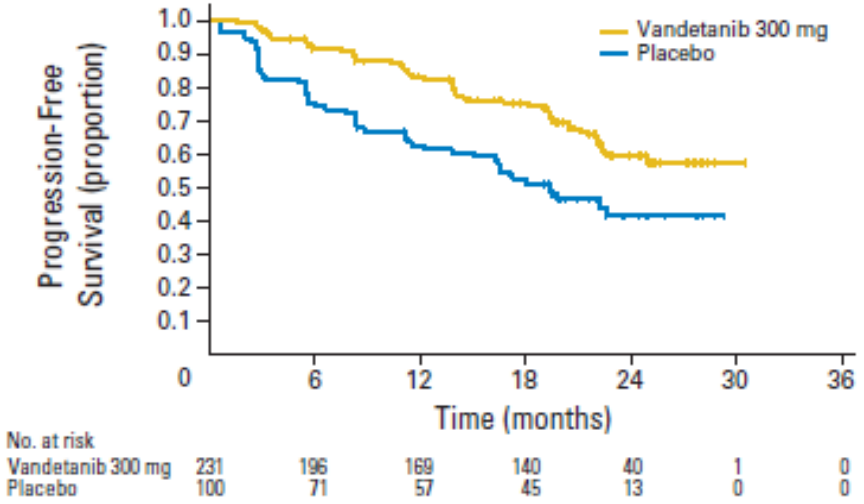
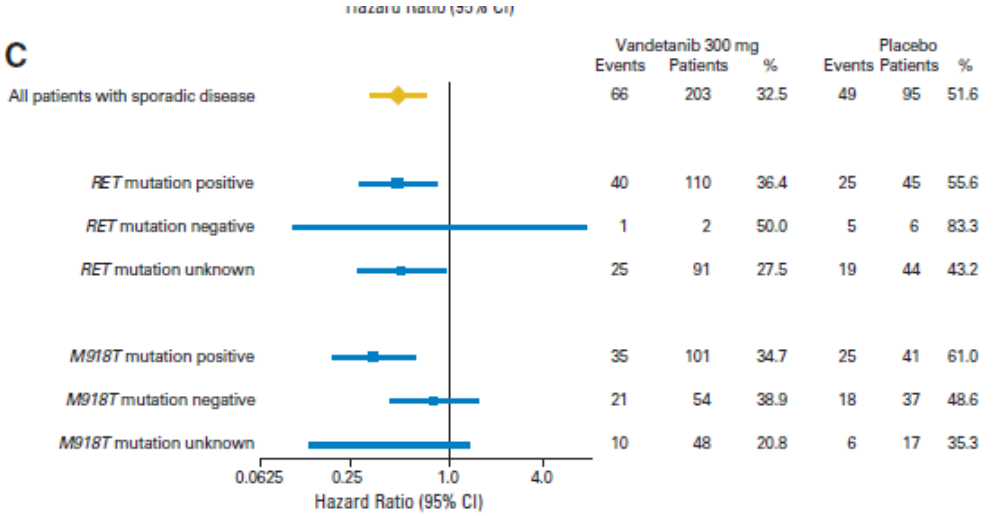


Table 1. Baseline Demographics and Patient Characteristics (intention-to-treat population; all randomly assigned patients)

Characteristic	Vandetanib (300 mg) (n = 231) No.	%	Placebo (n = 100) No.	%
Sex				
Male	134	58	56	56
Female	97	42	44	44
Mean age, years	50.7		53.4	
WHO performance status				
0	154	67	58	58
1	67	29	38	38
2	10	4	4	4
Disease type				
Hereditary	28	12	5	5
Sporadic or unknown	203	88	95	95
Locally advanced	14	6	3	3
Metastatic	217	94	97	97
Hepatic	154	67	64	64
Lymph nodes	135	58	68	68
Respiratory	126	54	60	60
Bone/locomotor	78	34	40	40
Neck	33	14	17	17
No. of organs involved (excluding thyroid)				
0 or 1	29	13	8	8
≥ 2	202	87	92	92
Prior systemic therapy for MTC				
0	141	61	58	58
≥ 1	90	39	42	42
RET mutation				
Positive	137	59	50	50
Negative	2	1	6	6
Unknown	92	40	44	44

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


Vandetanib 300 mg
Placebo
Progression-Free Survival (proportion)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
6
12
18
24
30
36
Time (months)
No. at risk
Vandetanib 300 mg 231 196 169 140 40 1 0
Placebo 100 71 57 45 13 0 0


C
Vandetanib 300 mg
Placebo
Events Patients % Events Patients %
All patients with sporadic disease 66 203 32.5 49 95 51.6
RET mutation positive 40 110 36.4 25 45 55.6
RET mutation negative 1 2 50.0 5 6 83.3
RET mutation unknown 25 91 27.5 19 44 43.2
M918T mutation positive 35 101 34.7 25 41 61.0
M918T mutation negative 21 54 38.9 18 37 48.6
M918T mutation unknown 10 48 20.8 6 17 35.3
0.0625
0.25
1.0
4.0
Hazard Ratio (95% CI)

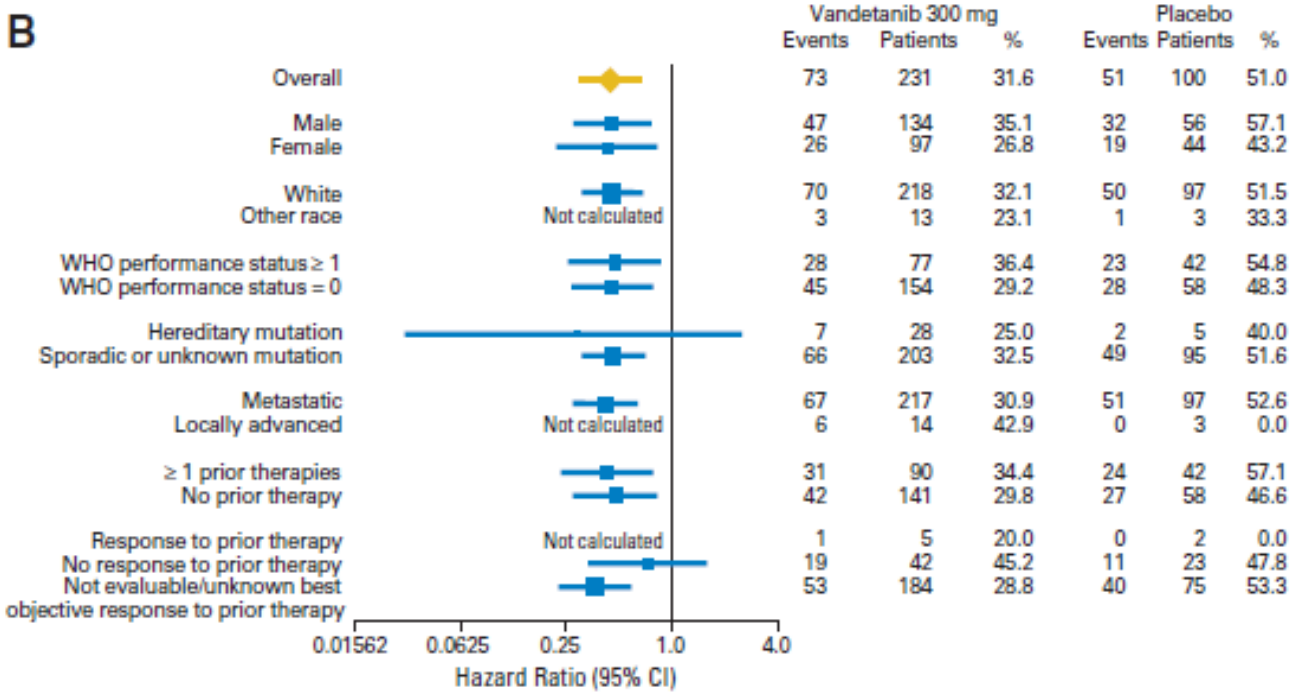

B
Vandetanib 300 mg
Placebo
Events Patients % Events Patients %
Overall 73 231 31.6 51 100 51.0
Male 47 134 35.1 32 56 57.1
Female 26 97 26.8 19 44 43.2
White 70 218 32.1 50 97 51.5
Other race Not calculated 3 13 23.1 1 3 33.3
WHO performance status ≥ 1 28 77 36.4 23 42 54.8
WHO performance status = 0 45 154 29.2 28 58 48.3
Hereditary mutation 7 28 25.0 2 5 40.0
Sporadic or unknown mutation 66 203 32.5 49 95 51.6
Metastatic 67 217 30.9 51 97 52.6
Locally advanced Not calculated 6 14 42.9 0 3 0.0
≥ 1 prior therapies 31 90 34.4 24 42 57.1
No prior therapy 42 141 29.8 27 58 46.6
Response to prior therapy Not calculated 1 5 20.0 0 2 0.0
No response to prior therapy 19 42 45.2 11 23 47.8
Not evaluable/unknown best objective response to prior therapy 53 184 28.8 40 75 53.3
0.01562
0.0625
0.25
1.0
4.0
Hazard Ratio (95% CI)

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	

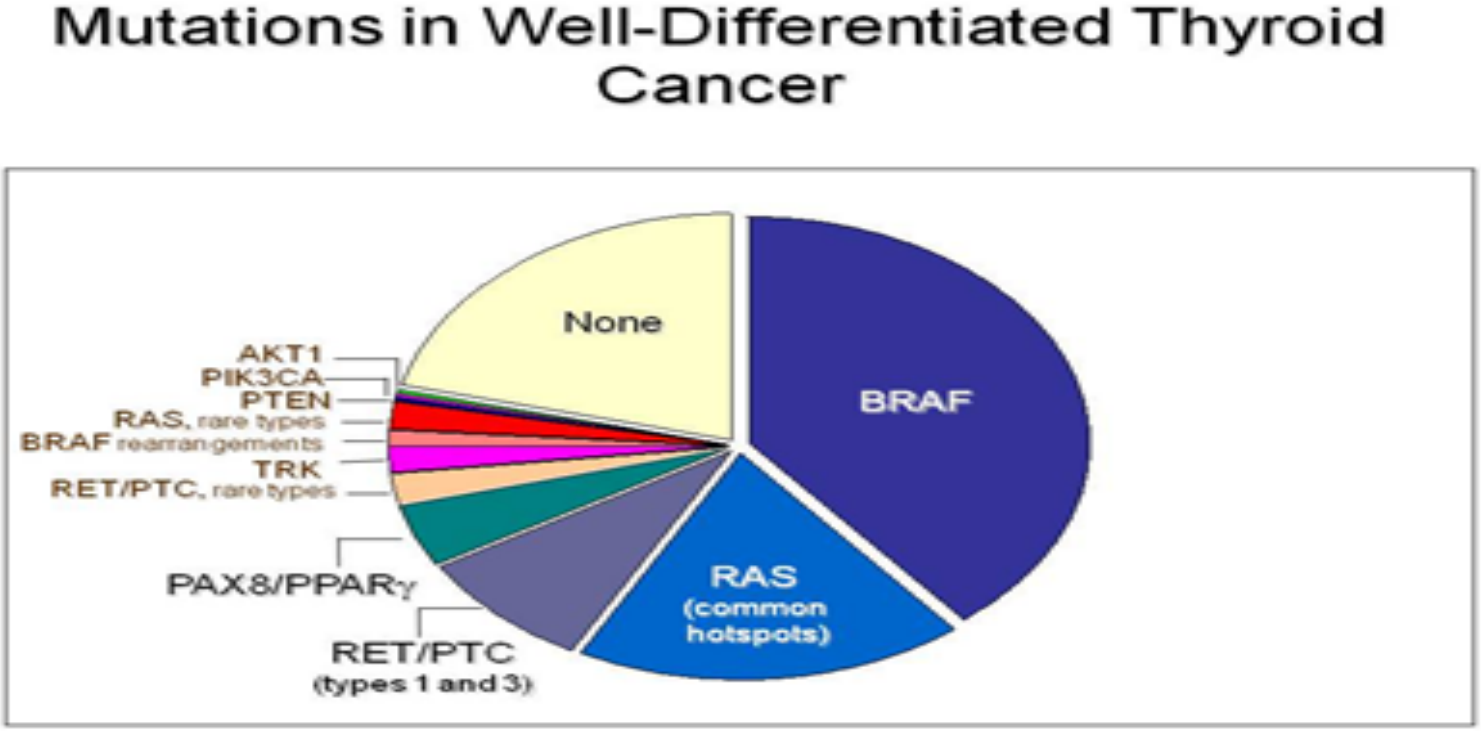
Abbreviations: MTC, medullary thyroid cancer; *RET*, rearranged during transfection.

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

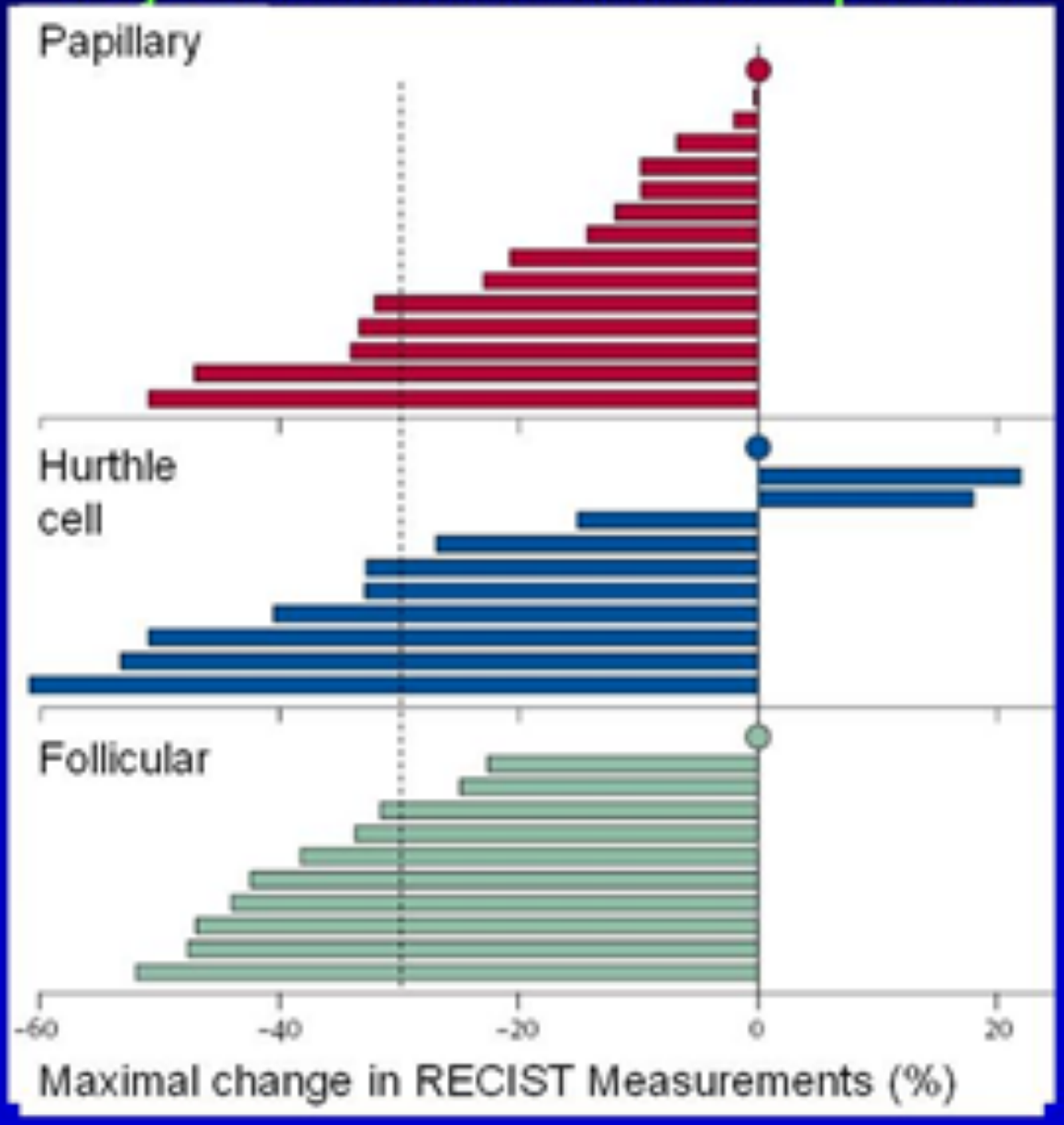
Vandetanib approvato FDA per MTC avanzato

E i tumori tiroidei differenziati ?



VEGF-R sta emergendo come un target molecolare importante
sunitinib , sorafenib , pazopanib e axitinib
sono tutti anche inibitori VEGFR

Pazopanib DTC Phase 2 Trial: Objective RECIST Responses



Bible, et al, Lancet Oncology 2010

Selected therapeutics for advanced differentiated thyroid cancers.

Agent	*Molecular target(s)*	*RECIST RESPONSE (%)*
Axitinib[6]	Kinases, inc. VEGF-R	30% (n=60) all PRs
Gemcitabine/Oxaliplatin (GEMOX)[9]	DNA	57% (n=14) 50% PRs, 7% CR (1)
Lenalidomide[8]	(Incompletely defined)	22% (n=18) all PRs
*Motesanib**	*Kinases, inc. VEGF-R*	*14% (n=93) all PRs*
Pazopanib[3]	Kinases, inc. VEGF-R	49% (n=37) all PRs
Thalidomide[7]	(Incompletely defined)	18% (n=28) all PRs
Sorafenib[4,5]	Kinases, inc. VEGF-R	15% (n=41) all PRs (all PTC) 23% (n=30) all PRS
Sunitinib[23]	Kinases, inc. VEGF-R	28% (n=29) all PRs

*Sherman SI, Wirth LJ, Droz JP, Hofmann M, Bastholt L, Martins RG, Licitra L, Eschenberg MJ, Sun YN, Juan T, Stepan DE, Schlumberger MJ; Motesanib Thyroid Cancer Study Group. Motesanib diphosphate in Progressive differentiated thyroid cancer. N Engl J Med. 2008;359:31-42.

Denotes agent not clinical available-- saving for through clinical trial or on a compassionate use basis.

Cosa non conosciamo degli inibitori TKI nei DTC?

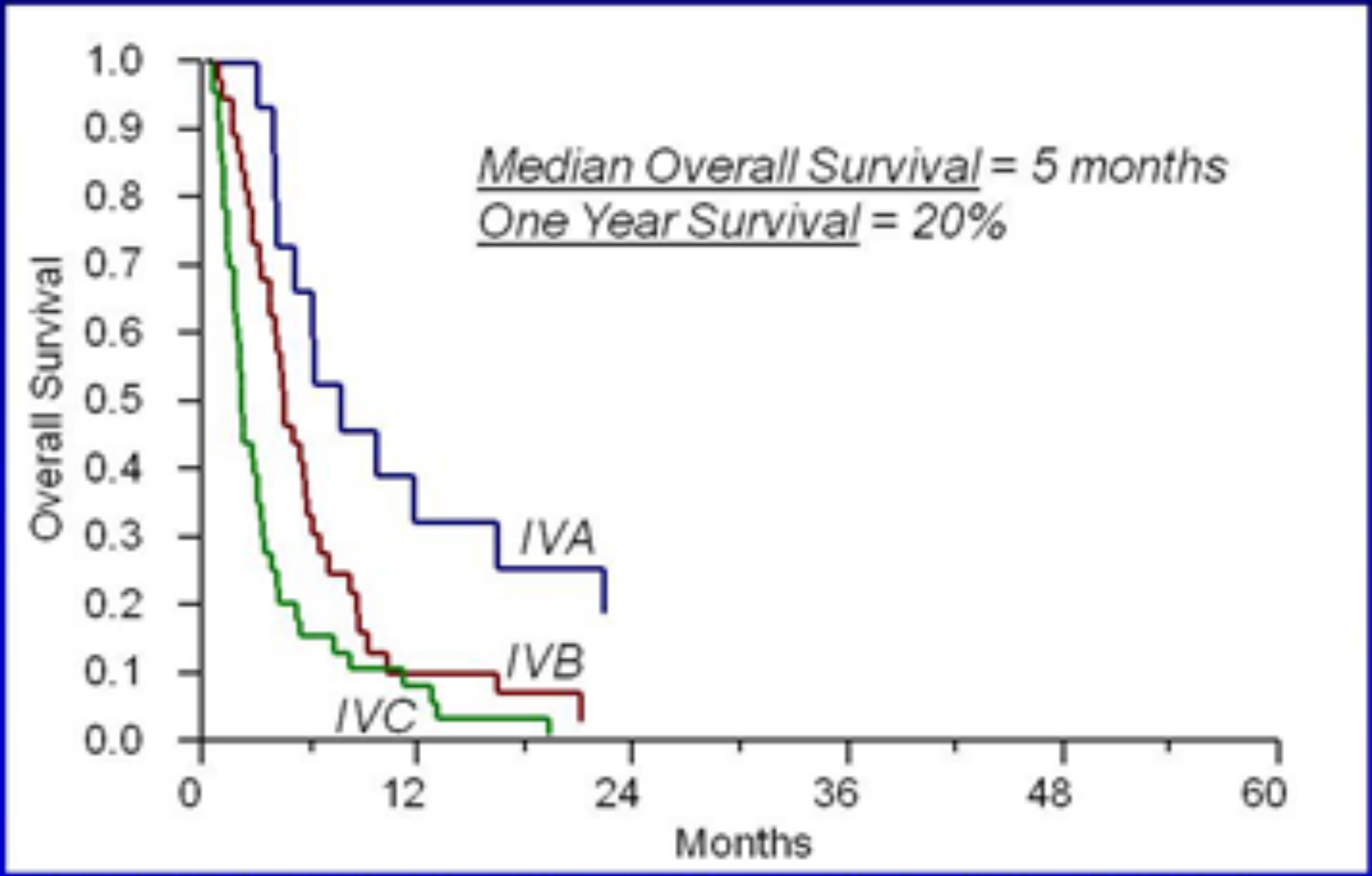
- *Quando i benefici eccedono i rischi ?*
- *Quali eventuali benefici sulla sopravvivenza ?*
- *Qual è il migliore inibitore?*
- *Cosa fare dopo la progressione ?*
- *Ruolo degli inibitori di altre pathways ?*
- *Potenziale ruolo dei nuovi regimi chemioterapici ?*

E gli anaplastici ?

- *Prognosi invariabilmente severa*
- *Sopravvivenza mediana intorno ai 5 mesi!*
- *Rapidità di crescita e sensibilità alla chemioterapia tra le piu' sconfortanti in oncologia*

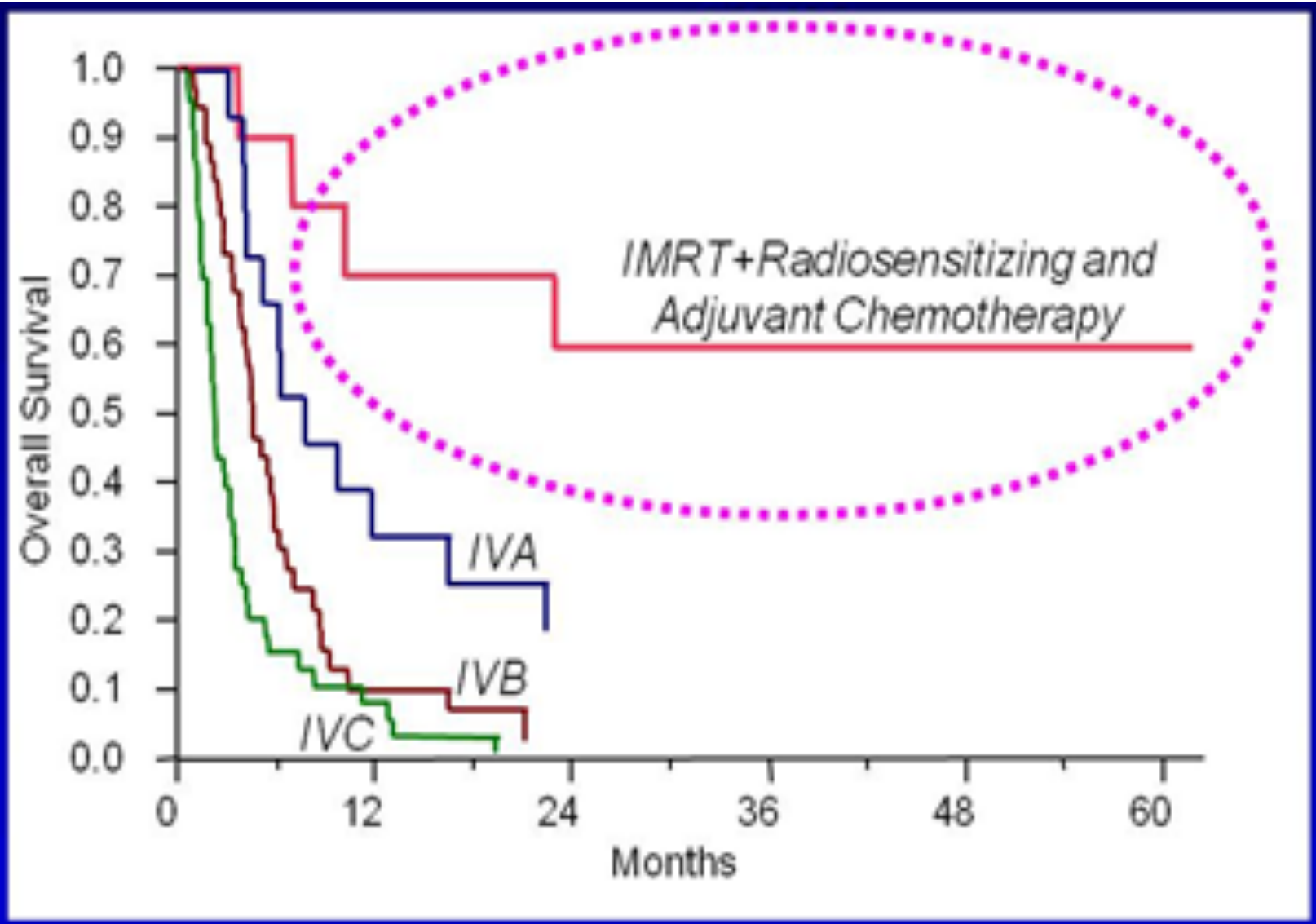
ATC

Historical Mortality By Stage



McIver B, Hay ID, Giuffrida DF, Dvorak CE, Grant CS, Thompson GB, van Heerden JA, Goellner JR. Anaplastic thyroid carcinoma: A 50-year experience at a single institution. Surgery 2001; 130:1028-34.

Terapia adiuvante "aggressiva" per gli stadi IV A e B



Foote, et al, Thyroid 2011

Gli inibitori TKI hanno un ruolo nei ATC ?

- *In monoterapia risutati deludenti : risposte rare e transitorie*
- *Possibile ruolo in combinazione con chemioterapia e IMRT (trial RTOG randomizzato IMRT+paclitaxel+/- pazopanib NCTO1236547)*

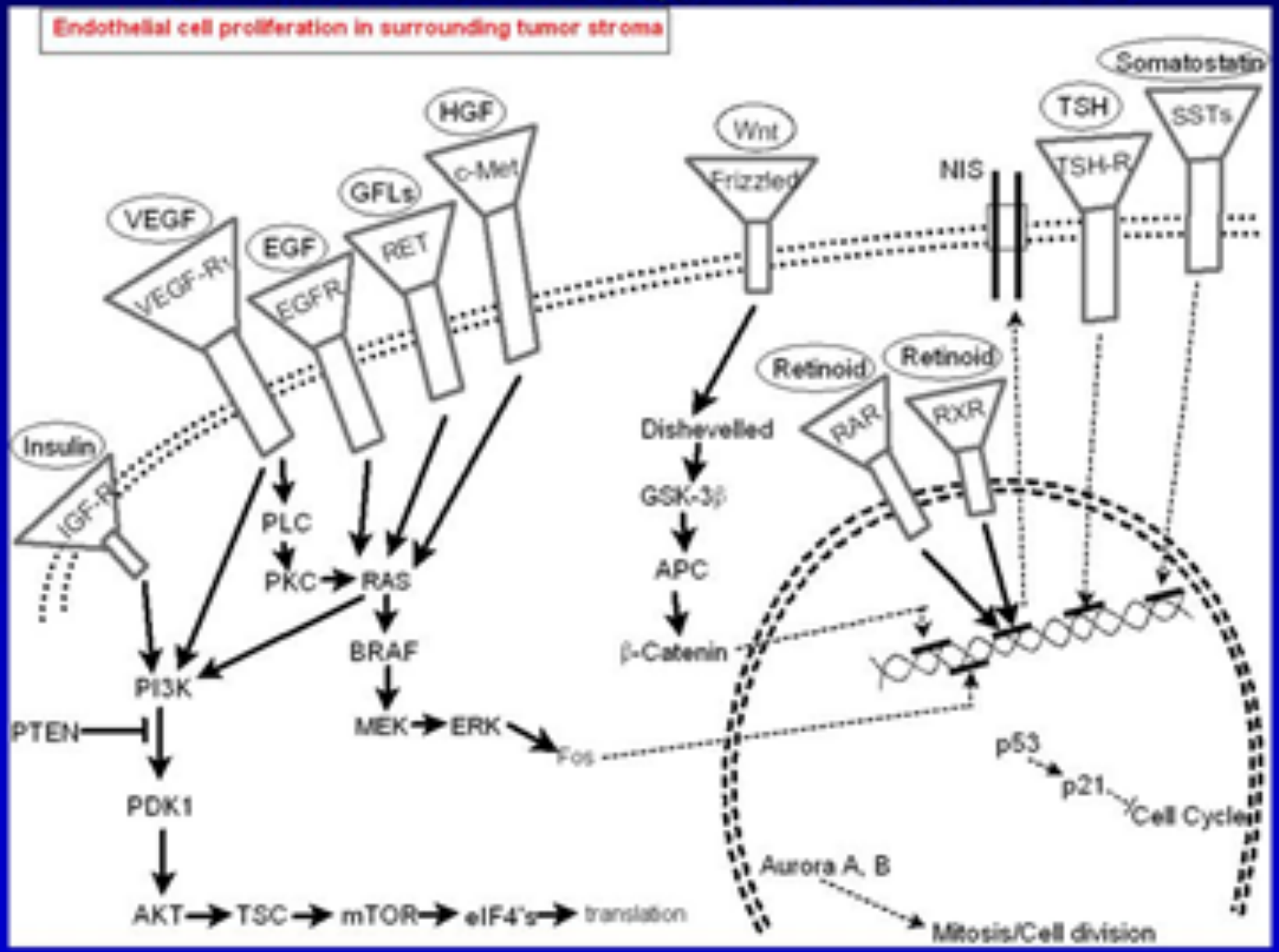
Selected therapeutics for advanced anaplastic thyroid cancer.

Agent	*Molecular target(s)*
Combretastatin/Fosbretabulin[17,18]	*Microtubules*
Docetaxel[16]	Microtubules
Doxorubicin#+Cisplatin[19]	Topoisomerase II/DNA
Paclitaxel[15]	Microtubules

Denotes agent not clinical available-- saving for through clinical trial or on a compassionate use basis.

#FDA approved for use in thyroid cancer (1973)

What About the Future of Molecular Markers in Advanced Thyroid Cancers?



Most Dysregulated Pathways in Thyroid Cancers Can Now Be Targeted !