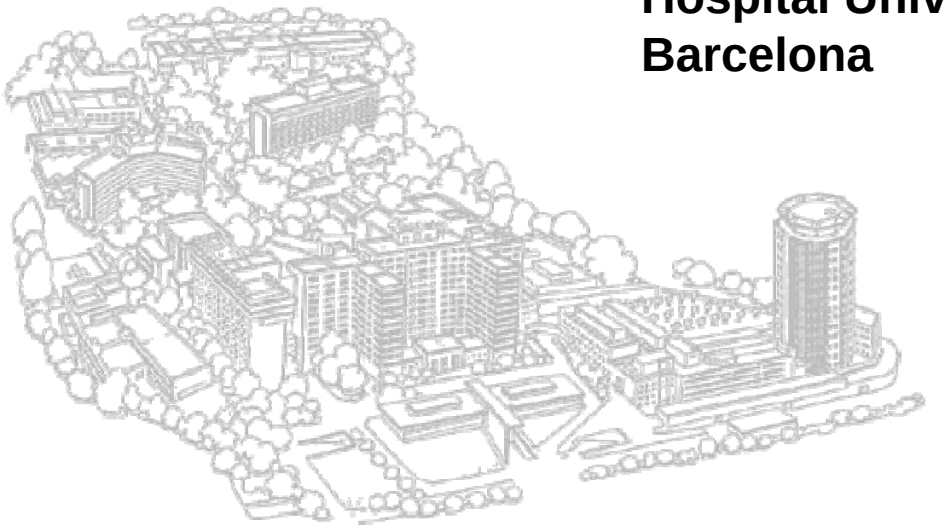
Cáncer de Tiroides Avanzado:
Nuevas Opciones Terapéuticas

Jaume Capdevila

Hospital Universitario Vall d'Hebron
Barcelona



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Epidemiology of Thyroid C.

- Rare tumor but most common endocrine malignancy
- > 44.000 new cases in 2010 (US)
- Female > Male
- 25-65 y
- 3 main tumor types:
  - Differentiated (papillary, follicular, Hürthle cell carcinoma)
  - Medullary
  - Anaplastic
- Increasing incidence: 1950-2010 → >300%

- Prognostic factors:
  - > 45 y
  - Follicular histology
  - Primary tumor > 4 cm or T4
  - Distant metastases
  - Molecular markers: VEGF and p53

Mazzaferri EL, J Clin Endocrinol Metab 2001

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Management and Outcome of Thyroid C.

- Main treatment: total or near-total thyroidectomy.
- Radioactive Iodine treatment: Tumors > 1.5 cm → benefit in recurrence rate, disease-progression and overall survival.
- Thyroid hormone suppression therapy: high-risk patients (stage III and IV).

- 10-y OS:
  - Papillary → 93%
  - Follicular → 85%
  - Medullary → 50-75%
- Recurrence rate: 30%
  - Locoregional → 80% (cervical lymph nodes, thyroid remnant)
  - Distant → 20% (lung, bone, SNC)
- 3-y OS refractory setting: 50%

Mazzaferri EL, J Clin Endocrinol Metab 2001

Management and Outcome of Thyroid C.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Chemotherapy of Thyroid Cancer with Adriamycin — Experience with 30 Patients

Jeffrey A. Gottlieb, M.D., and C. Stratton Hill, Jr., M.D.

N Engl J Med 1974; 290:193-197

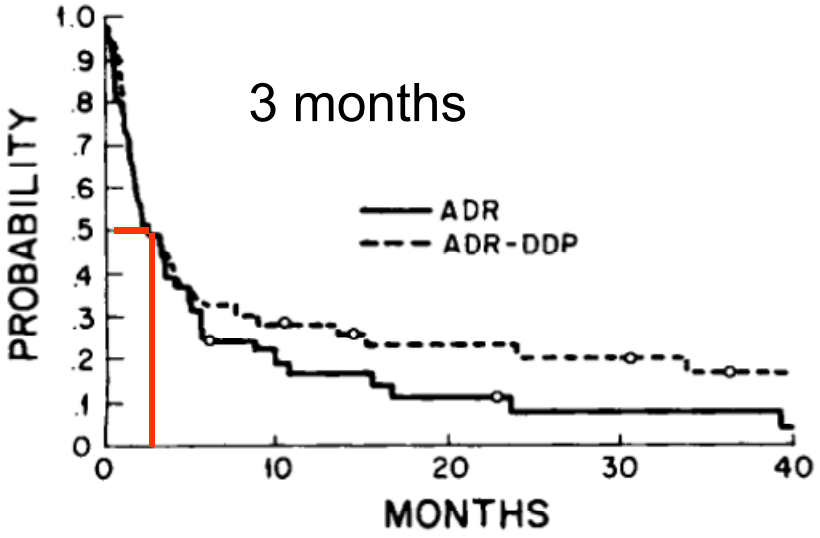


FIG. 1. Time to treatment failure.

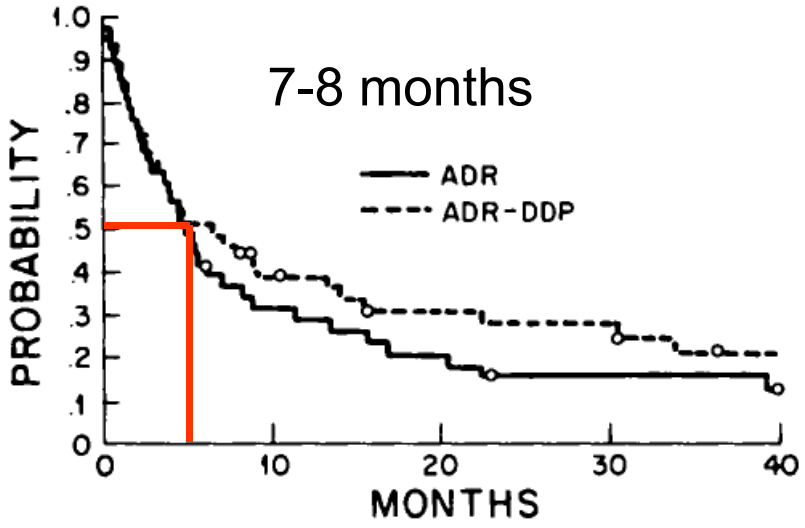
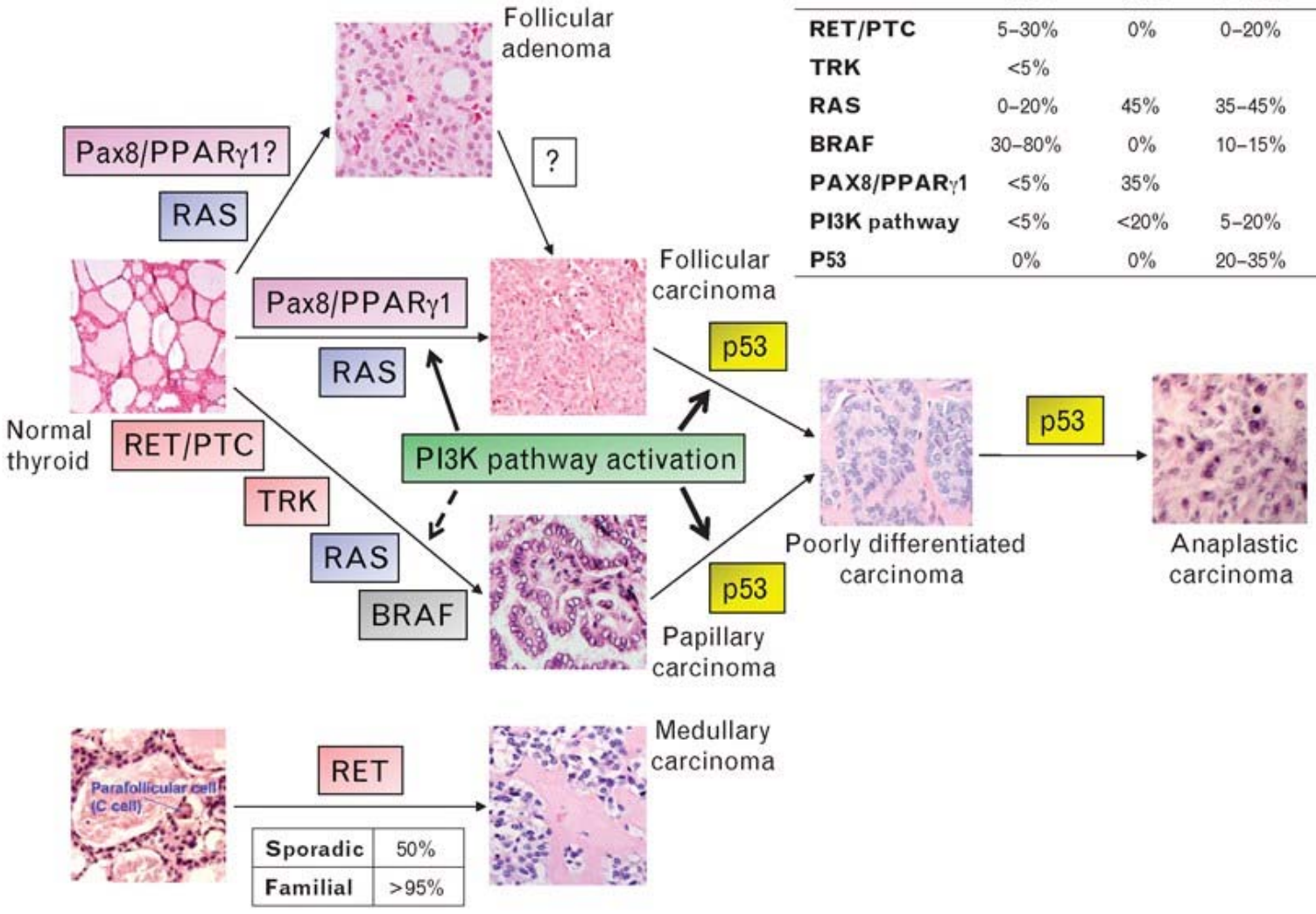


FIG. 2. Survival by treatment.

Gottlieb JA, et al. NEJM, 1974; Shimaoka K, et al. Cancer, 1985

Multistep model of thyroid carcinogenesis

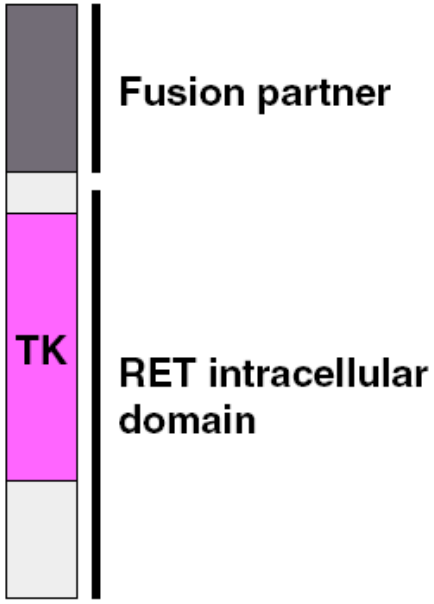


	PTC	FTC	PDTC	ATC
RET/PTC	5–30%	0%	0–20%	0%
TRK	<5%			
RAS	0–20%	45%	35–45%	20–55%
BRAF	30–80%	0%	10–15%	20–45%
PAX8/PPARγ1	<5%	35%		
PI3K pathway	<5%	<20%	5–20%	30%
P53	0%	0%	20–35%	70%

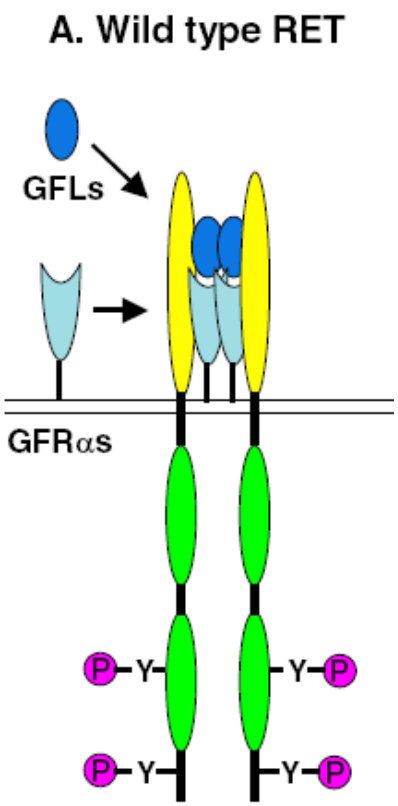
Puxeddu E, Curr Opin Oncol 2011

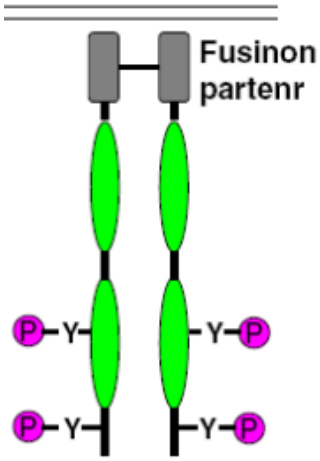
RET Pathway in DTC

Oncoprotein	Fusion partner
RET/PTC1:	H4/D10S170
RET/PTC2:	RIα of PKA
RET/PTC3:	ΕΛΕ1/APA70/Νχοα4
RET/PTC4:	ΕΛΕ1/APA70/Νχοα4
RET/PTC5:	RFG5/golgin-84
RET/PTC6:	hTIF1
RET/PTC7:	GFG7/hTIFγ
RET/PTC8:	KTN1/kinectin
RET/PTC9:	RFG9
ELKS/RET:	ELKS
PCM1/RET:	PCM1
RFP/RET:	RFP



RET/PTC oncoprotein





Murakumo Y, Pituitary 2006

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Prevalence of mutations in thyroid cancer

Tumor type	Prevalence (%)	
Papillary carcinoma		
BRAF	45	
RET/PTC	20	66%
RAS	10	
Follicular carcinoma		
RAS	45	80%
PAX8-PPAR	35	
PI3K	<10	
PTEN	<10	
Poorly differentiated carcinoma		
RAS	35	
β-catenin	20	
P53	20	
BRAF	15	

Anaplastic carcinoma	
p53	70
β-catenin	65
RAS	55
BRAF	20
PI3K	20
PTEN	10
Medullary carcinoma	
Familial forms RET	>95
Sporadic RET	40-50

Nikiforova MN, Expert Rev Mol Diagn 2008

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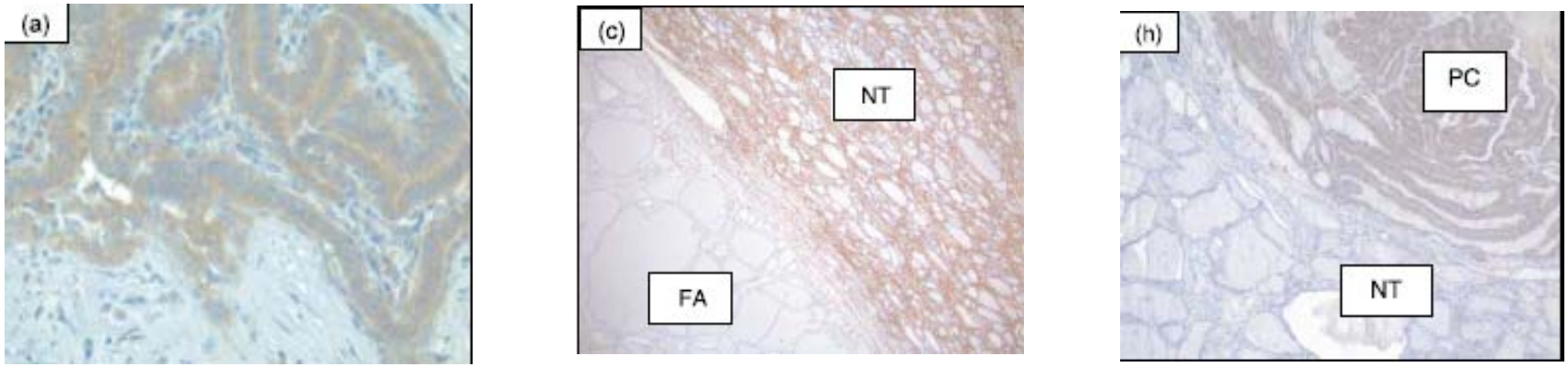
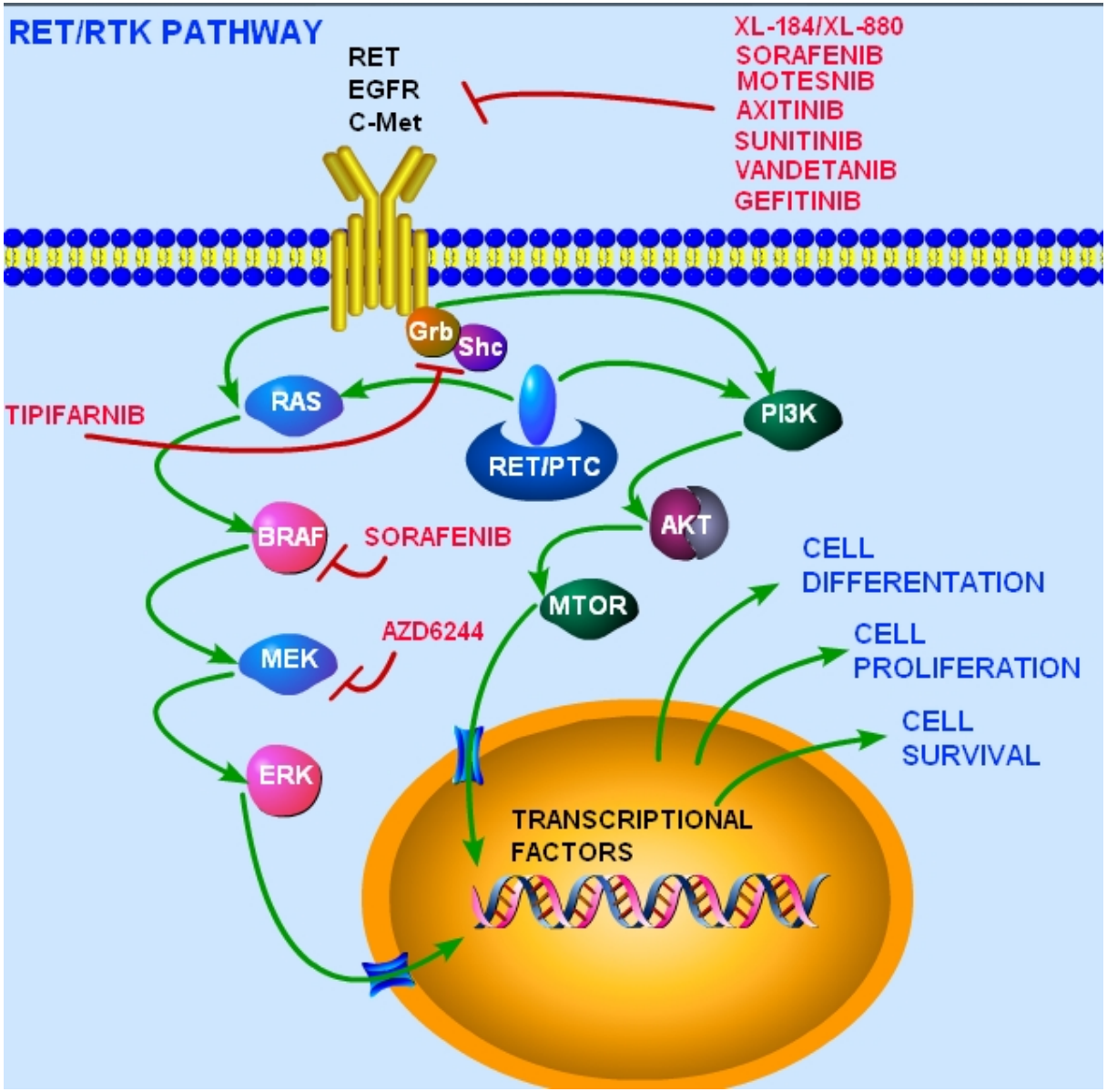
Angiogenesis



- Higher VEGF levels and microvessel density in thyroid cancers compared with normal thyroid tissue.
- VEGF levels correlated with stage, large tumor size, nodal involvement, extrathyroidal invasion and metastases.
- VEGF levels correlated with risk of recurrence and inferior recurrence-free survival.
- LOH of VHL tumor suppressor gene has been described in thyroid cancer. VHL loss leads HIF1α, HIF2α accumulation → angiogenic events (↑ VEGF, PDGF, TGFα...).

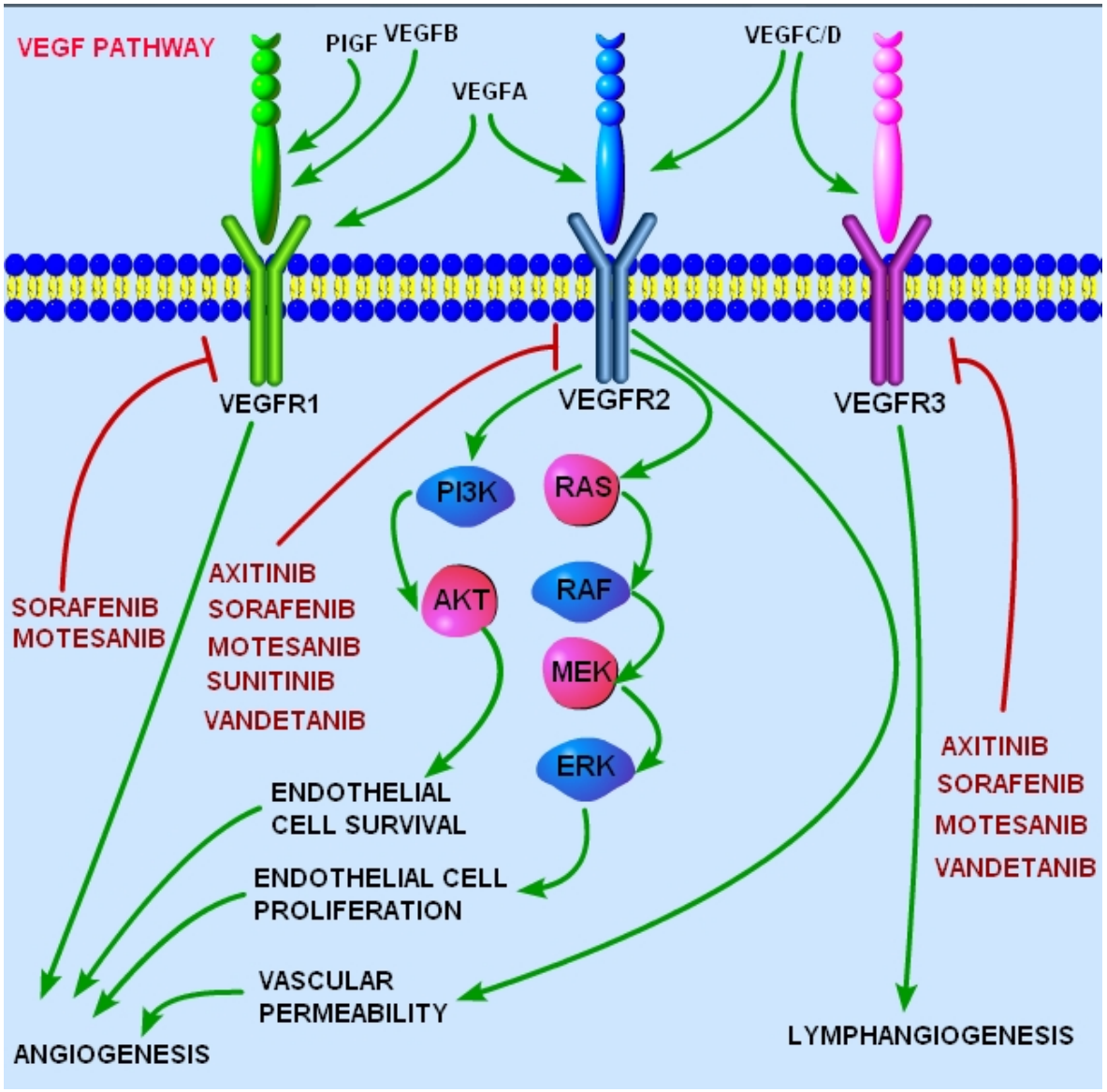
Bauer AJ, Ann Clin Lab Sci 2003
Viglietto G, Oncogene 1995
Klein M, J Endocrinol 1999
Yu XM, Clin Cancer Res 2005

Targeted therapies in thyroid cancer



Capdevila J, et al. Target Oncol, 2009

Targeted therapies in thyroid cancer



Capdevila J, et al. Target Oncol, 2009

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Targeted therapies in thyroid cancer

Small molecules inhibitors of multiple proteins with kinase activity in clinical trials for 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)	130	-	40	110	-	-	-	-	-	EGFR 500
Pazopanib (GW786034)	-	10	30	47	-	84	-	74	-	
Lenvatinib E7080	35	22	4	5.2	-	39	-	-	-	FGFR1 46
Cabozantinib XL-184	4	-	0.035	-	-	-	-	-	-	C-MET 1.8

Capdevila J, et al. Target Oncol, 2009

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Phase II trials in thyroid cancer

Study	Drug	N	Population	Response Rate	Stable disease	Progression-free Survival
Gupta	Sorafenib	30	DTC	23%	53%	20 months
Kloss	Sorafenib	41	PTC	15%	56%	15 months
Capdevila	Sorafenib	34	DTC MTC	20% (DTC) 50% (MTC)	48%	12 months
Sherman	Motesanib	93	DTC	24%*	67%	10 months
Cohen	Axitinib	60	All types	30%	38%	18 months
Ravaud	Sunitinib	17	DTC & MTC	8.3% (DTC) 12.5% (MTC)	66.7% (DTC) 87.5% (MTC)	NR
Carr	Sunitinib	33	DTC & MTC	13% (DTC) 0% (MTC)	68% (DTC) 83% (MTC)	NR
De Souza	Sunitinib	25	MTC	33%	54%	12 months
Leboulleux	Vandetanib	145	DTC	8.3% vs 5.5%	48% vs 37%	11 vs 5.8 months
Wells	Vandetanib	331	MTC	20%	30%	NR
Bible	Pazopanib	37	DTC	49%	46%	11.7 months
Sherman	Lenvatinib	58	DTC	59%	36%	13.3 months
Pennell	Gefitinib	27	All types	0	48%	3.7 months
Ain	Thalidomide	36	DTC & MTC	18%	32%	NR
Ain	Lenalidomide	18	DTC	39%	50%	NR

DTC: differentiated thyroid cancer; PTC: papillary thyroid cancer; MTC: medullar thyroid cancer; NR: not reported;
*10% of unconfirmed responses.

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Sorafenib in thyroid cancer