An Update on Novel Therapies for Advanced Differentiated Thyroid Cancer: When to Start and What to Use

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DISCLAMER:

- My goal is to present information on a several agents currently under investigation for the treatment of advanced differentiated thyroid cancer. As none of the agents are FDA approved for this use at this time, all of the data presented will be data collected from clinical trials that have been reported over the past 5 years.

DISCLOSURE:

I have financial interest/arrangement or affiliation with:

Name of Organization	Relationship
Bayer Healthcare	research funding, honorarium
Onyx	research funding, honorarium
Novartis	research funding,
Exelixis	research funding honorarium
Astrazeneca	research funding, consulting
Genentech/Roche	research funding

Objectives:

- By the end of this talk it is hoped that you will have a better understanding of:

1. when we consider a patient is a candidate for kinase inhibitor therapy

2. What kinase inhibitors are in the pipeline for treatment of patients with progressive RAI refractory differentiated thyroid cancer

Radioactive-iodine (RAI)-refractory differentiated thyroid cancer (DTC)

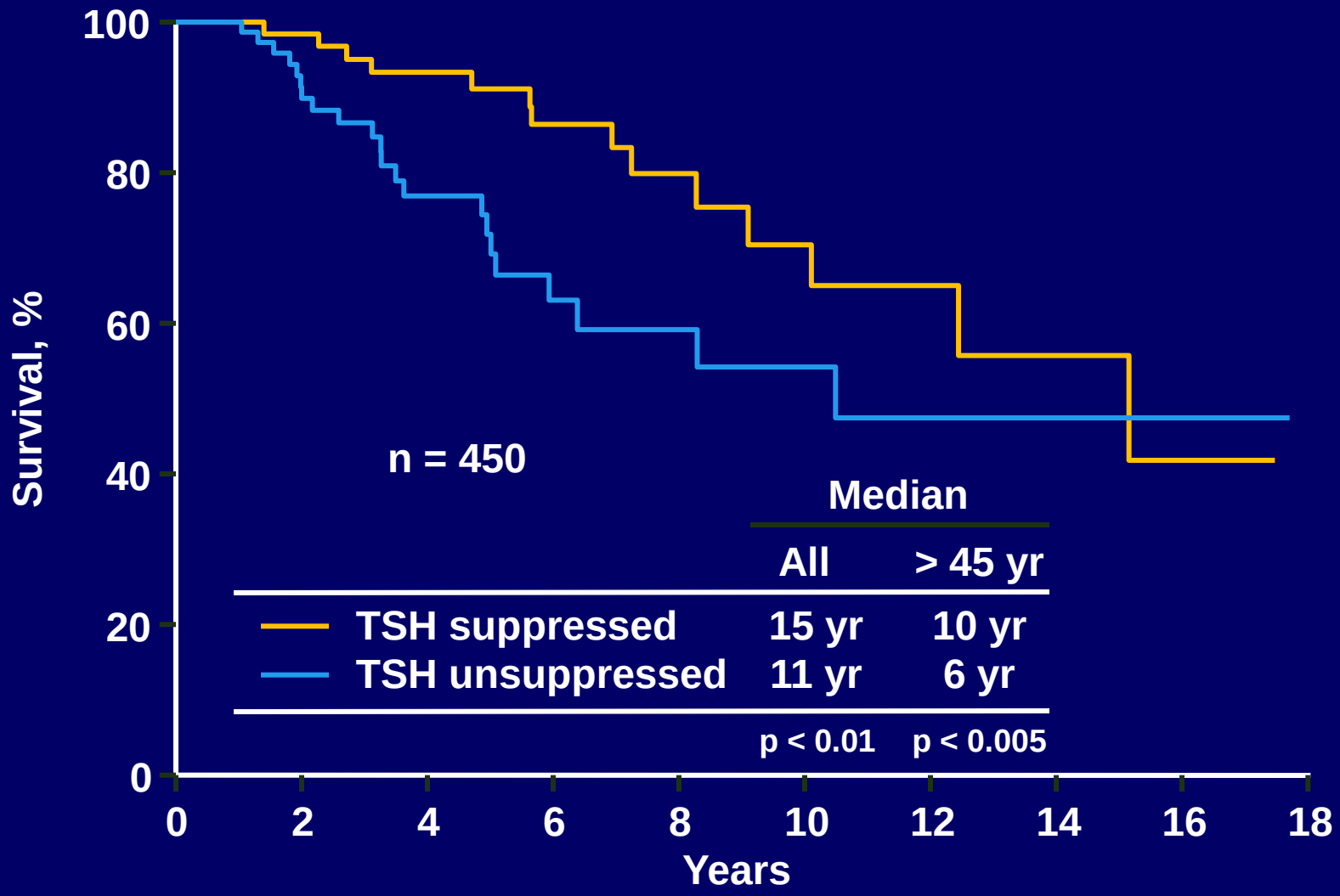
- It is estimated[1] that in the USA in 2013 there will be:
  - >60 000 new cases of thyroid cancer, and
  - 1850 deaths due to thyroid cancer
- In approximately 5–15% of patients with thyroid cancer, the disease becomes refractory to RAI[2,3]
- Median survival for patients with RAI-refractory DTC and distant metastases is estimated to be 2.5–3.5 years[4,5]
- Patients often suffer multiple complications associated with disease progression
- There is no standard therapy for patients with RAI-refractory DTC

1. Howlader N et al. SEER Cancer Statistics Review; http://seer.cancer.gov/statfacts/html/thyro.html;
2. Xing M et al. Lancet 2013; 381:1058–69; 3. Pacini F et al. Expert Rev Endocrinol Metab 2012;7:541–54;
4. Durante C et al. J Clin Endocrinol Metab 2006;91:2892–99. 5. Robbins RJ et al. J Clin Endocrinol Metab 2006;91:498–505.

Differentiated Thyroid Cancer: Treatment Strategy

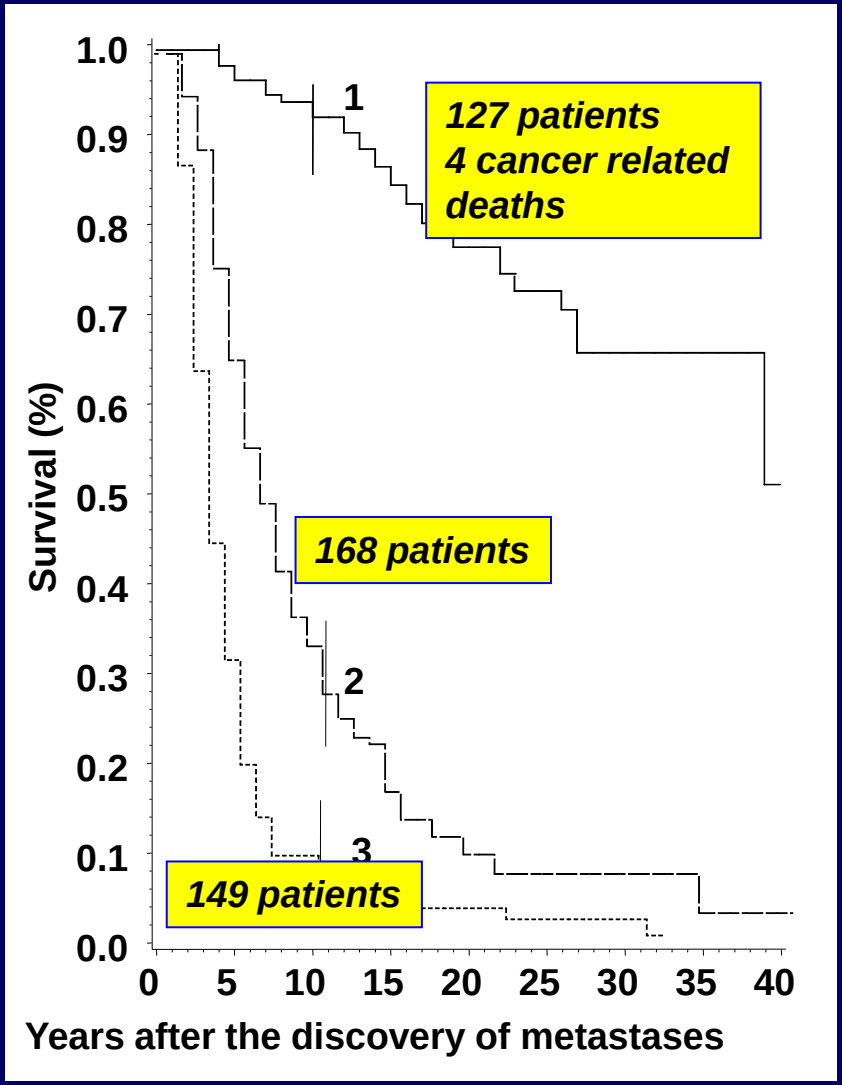
- High Risk: (Age >45, male, metastasis, extrathyroidal extension, >4cm)
  - Total Thyroidectomy
  - **RAI (^{131}I) Ablation**
  - **TSH Suppression Therapy with Thyroid Hormone**
  - Follow Serial Thyroglobulin Levels (Tg)
  - XRT for recurrent local disease/positive margins
  - Surveillance: NeckUS, Tg, Neck MRI, Chest CT, RAI Whole body scan, FDG-PET

TSH Suppression Improves Survival for DTC Patients With Metastases



Jonklaas et al. *Thyroid.* 2006;16:1299-1242.

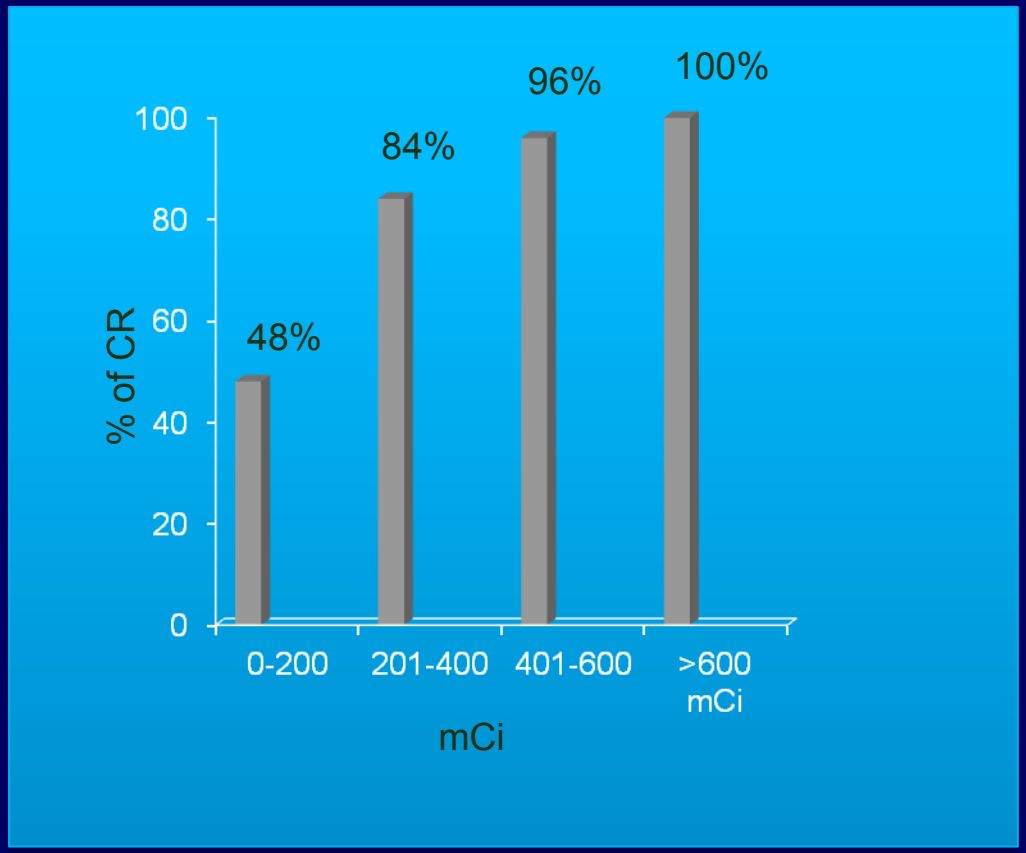
Survival is determined by Response to RAI Treatment



- Group 1: initial ^{131}I uptake and CR
  - Age < 40 years
  - Well-differentiated cancer
  - Small size of metastases
- Group 2: initial ^{131}I uptake and persistent disease
- Group 3: no initial ^{131}I uptake

Durante et al. *J Clin Endocrinol Metab.* 2006;91:2892-2899.

Absence of Detectable Disease As a Function of RAI Cumulative Activity



From a retrospective study of a total of 444 patients were treated from 1953–1994 for distant metastases from papillary and follicular thyroid carcinoma in order to estimate the cumulative activity of I^{131} .

- Most CRs (96%) are obtained with a cumulative activity of 22 GBq (600 mCi) or less.
- Administration of activities >22 GBq on an individual basis

RAI, radioactive iodine
Durante, JCEM 2006

RAI-refractory disease: consensus criteria used for most Phase II and III trials

- Patients had progressive disease in the 6-14 months prior to enrollment as defined by RECIST criteria (20%).
- RAI refractory means that there are **progressing lesions** that **do not take up RAI** (Note: there may still be some that do)
  - RAI uptake scan is negative and CT scan shows nodules
  - RAI uptake scan has uptake but not in some nodules that are progressing
  - Patient has exceeded total lifetime dose of 600 mCi

Cooper DS, et al. Thyroid. 2009;9:1176-214.
Hodak SP, Carty SE. Oncology. 2009;23:775-6.
Mehra R, Cohen RB. Hematol Oncol Clin North Am. 2008;22:1279-95,xi.

Thyroid Cancer is associated with aberrant cell signaling

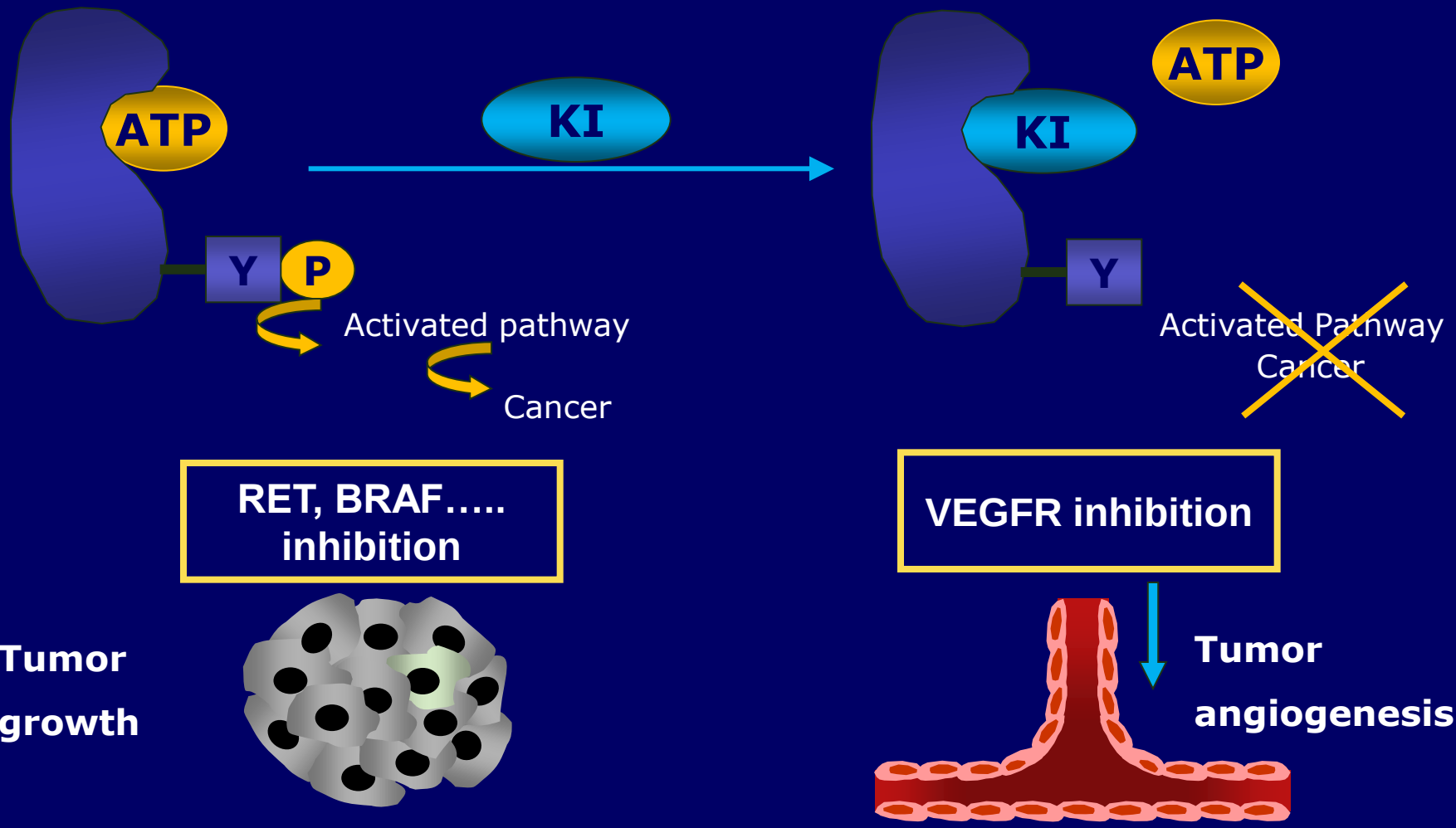
MAP Kinase

PI3K/AKT

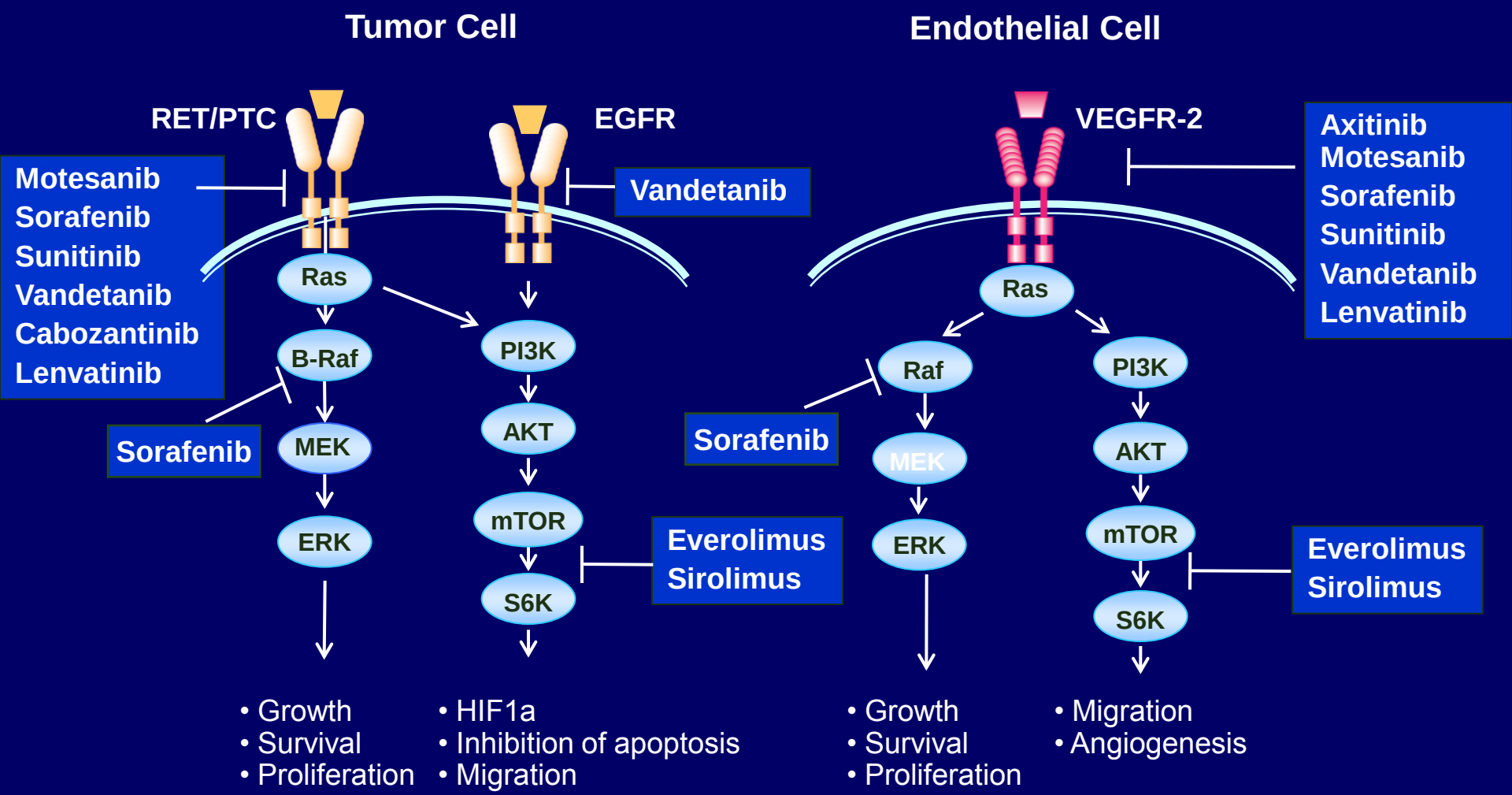
Genetic Alteration	PTC	FTC
BRAF V600E	44%	0%
BRAF copy gain	3%	35%
RET/PTC (1 and 3)	20%	0%
RAS	8-10%	17-45%
PI3KCA mutations	3%	6%
PI3KCA copy gain	12%	28%
PTEN	2%	7%
Pax8/PPARγ	0%	35%
Total	>70%	>65%

Nikiforov, Mod Path, 2008, Xing Endocrine Rel Ca(2005), Wang et al, 2007

Kinase Inhibitors



Targeting cell signaling in thyroid cancer



Graphic adapted from
Keefe SM, et al. Clin Cancer Res. 2010;16:778-83.

Targets of Kinase Inhibitors

Compound Name	VEGFR	BRAF	PDGFR	KIT	RET	Other
Sorafenib (Nexavar)	+	+	+	+	+	FLT-3
Sunitinib (Sutent)	+		+	+		FLT-3
Axitinib (AG-013736)	+		+	+		
Motesanib (AMG-706)	+		+	+	+	
Pazopanib (GW786034)	+		+	+		
Vandetanib (Zactima)	+				+	EGFR
Cabozotanib (XL184)	+				+	C-MET
Lenvatinib (E7080)	+		+	+	+	FGFR

Targeted Agents: Phase II Clinical Data

Drug	Key Baseline Characteristics	n	PFS	PR	SD	PD
Sorafenib (Brose)	•DTC+ PDTC(90%),	47	**20**	**38%**	**47%**	2%
Sunitinib (Cohen)	• DTC (74%); MTC (26%)	51	**-**	**17% DTC**	**74% DTC**	9% DTC
Axitinib (Cohen)	•Papillary (50%); Medullary (18%); Follicular/Hurthle (25%/18%); Anaplastic (3%)	60	**18.1**	**30%**	**48%**	7%
Motesanib (Sherman)	•Papillary (61%); Follicular/Hurthle (34%)	93	**10**	**14%**	**67%**	8%
Pazopanib (Bible)	PD and DTC (Progression <6months)	37	**12**	**49%**	**-**	-
Lenvatinib (Sherman)	•DTC 100%	58	**13.3**	**45%**	**46%**	5%
Vemurafenib (Brose)	•BRAF V600E DTC first line	26	**15.6**	**35%**	**23%**	0%

Background and rationale for sorafenib in DTC

- Sorafenib is a multikinase inhibitor targeting VEGFRs1-3 and PDGFRs, BRAF, RET and c-Kit[1]
- Sorafenib is approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma
- Sorafenib has been shown to have activity as monotherapy in Phase 2 trials in patients with advanced refractory thyroid cancer[2-6]
- DECISION is a randomized, double-blinded, placebo-controlled Phase 3 trial designed to explore the efficacy and safety of sorafenib in patients with RAI-refractory DTC
  - stuDy of sorafEnib in loCally advanced or metastatIc patientS with radioactive Iodine refractory thyrOid caNcer

1. Wilhelm SM, et al. Nature Rev Drug Discovery 2006;5:835-844; 2. Gupta-Abramson V, et al. J Clin Oncol 2008;26:4714–4719; 3. Kloos RT, et al. JCO 2009; 27:1675–1684; 4. Lam ET, et al. J Clin Oncol 2010; 28:2323–2330; 5. Ahmed M, et al. Eur J Endocrinol 2011; 165:315–322; 6. Schneider TC, et al. Eur J Endocrinol 2012; 167:643–650

PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

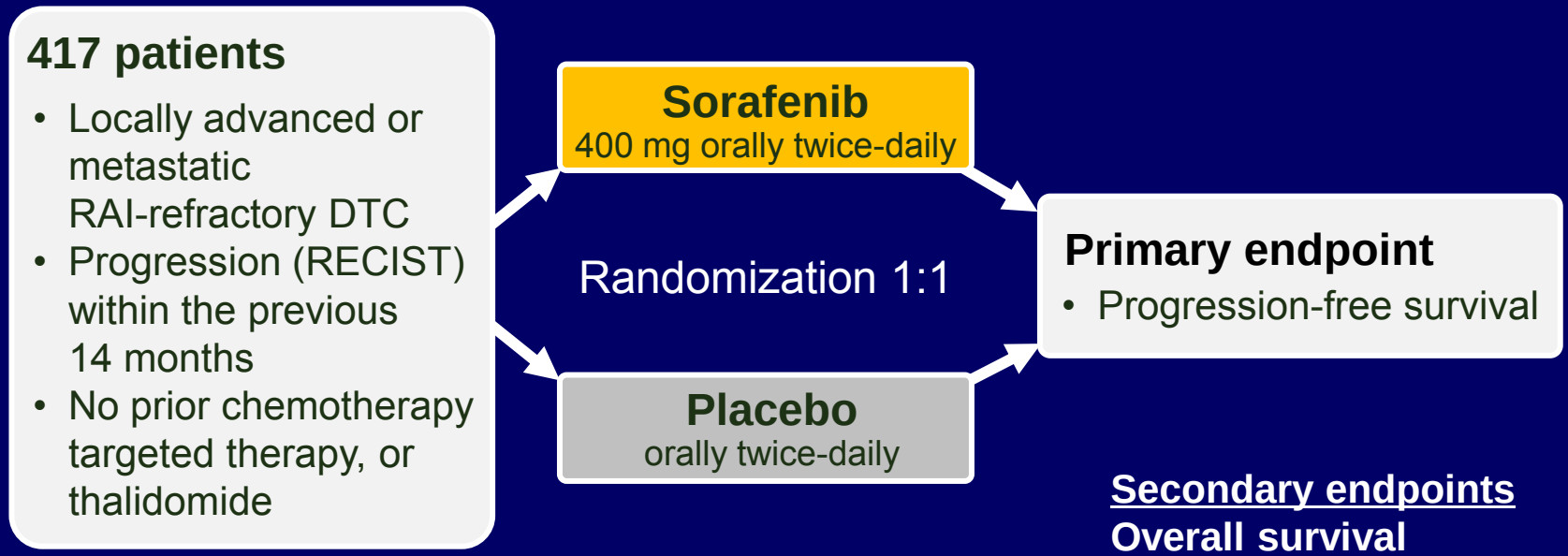
Investigator-Sponsored Studies (Phase 2)

Study Phase	Study Population	Subjects	Main Outcomes
Phase 2	Subjects with progressive metastatic or locally advanced RAI-refractory DTC	Total: 32 Treated: 31	No reinduction of RAI uptake at metastatic sites PR: 25% (n = 8); SD: 34% (n = 11); PD: 22% (n = 7) DCR: 59% (n = 19)
Single center, pilot study	Subjects with metastatic advanced DTC and MTC considered unsuitable for treatment with RAI	34 19 with DTC (15 with MTC)	RR (6 months): 15% RR (12 months): 21% mPFS and mOS not reached at 19 months OS (1 year): 88% PFS (1 year): 79%
Phase 2	Subjects with metastatic, iodine-refractory thyroid carcinoma	55 47 with DTC	mPFS: 84 weeks Median time on study: 39 weeks
Phase 2	Subjects with iodine-refractory metastatic PTC	56 41 with DTC	ORR: 15% mPFS: 16 months mOS: 23 months SD: 57%

AE, adverse event; DCR, disease control rate; DTC, differentiated thyroid cancer; mOS, median OS; mPFS, median PFS; MTC, medullary thyroid carcinoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; RR, response rate; SD, stable disease.

.1. Hoftijzer H, et al. *Eur J Endocrinol*. 2009;161(6):923-931. 2. Schneider T, et al. *Eur J Endocrinol*. 2012;167(5):643-650. 3. Ahmed M, et al. *Eur J Endocrinol*. 2011;165(2):315-322. 4. Brose M, et al. *Eur J Cancer* . 2009;3(7 suppl):21.Abstract 51LBA. 5. Hoefe S, et al. *J Clin Oncol*. 2011;29(15 suppl). Abstract 5562. 6. Kloos R, et al. *J Clin Oncol*. 2009;27(10):1675-1684.

DECISION study design

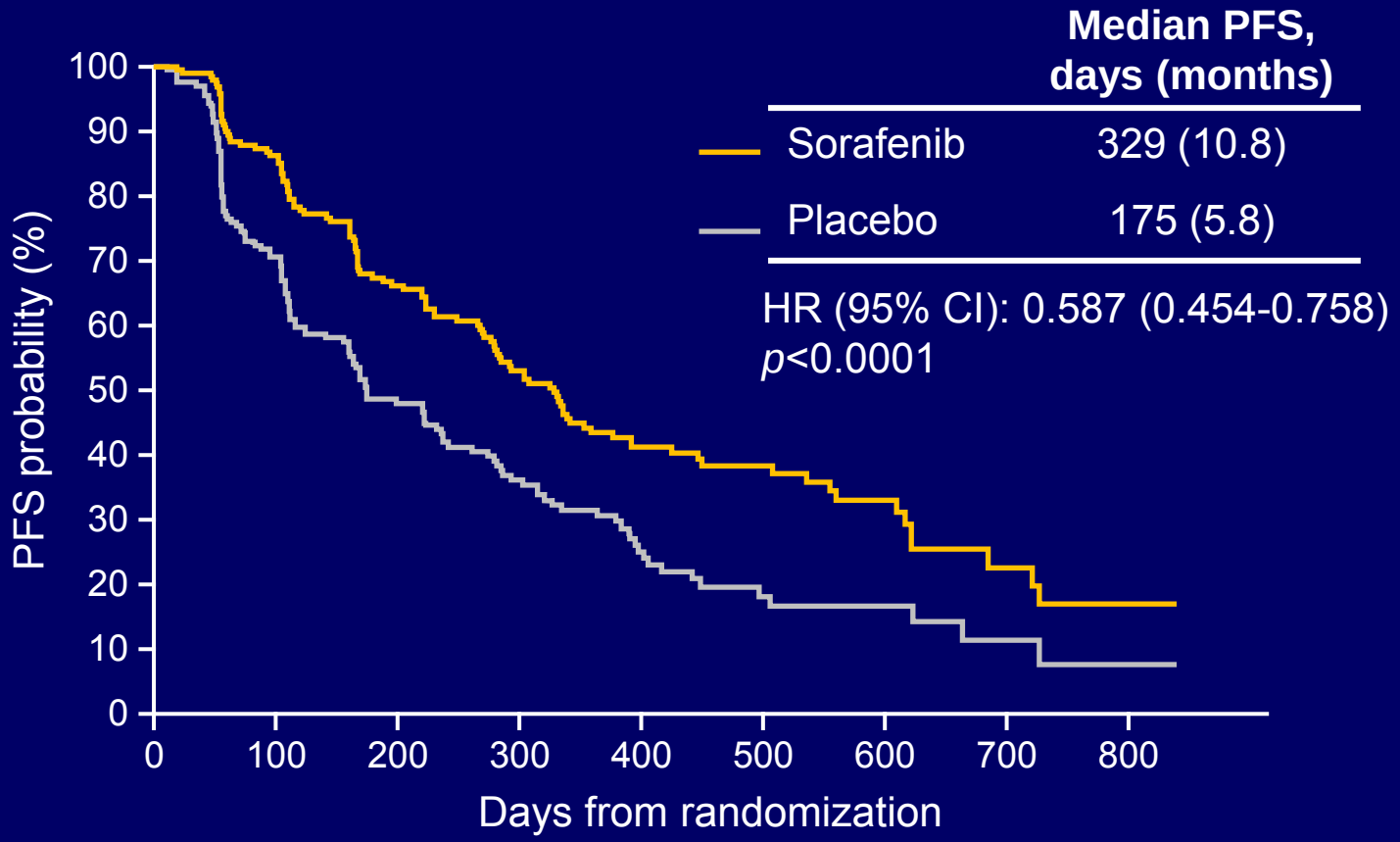


- **Stratified by:**
  - **geographical region (North America or Europe or Asia)**
  - **age (<60 or ≥60 years)**
- Progression assessed every 8 weeks (independent central review)
- Patients were allowed to receive open-label sorafenib after progression

Secondary endpoints
Overall survival
Response rate
Safety
Time to progression
Disease control rate
Duration of response
Sorafenib exposure (AUC_{0-12})

Brose MS et al. BMC Cancer 2011;11:349;
www.clinicaltrials.gov. NCT00984282

Progression-free survival
(by independent central review)



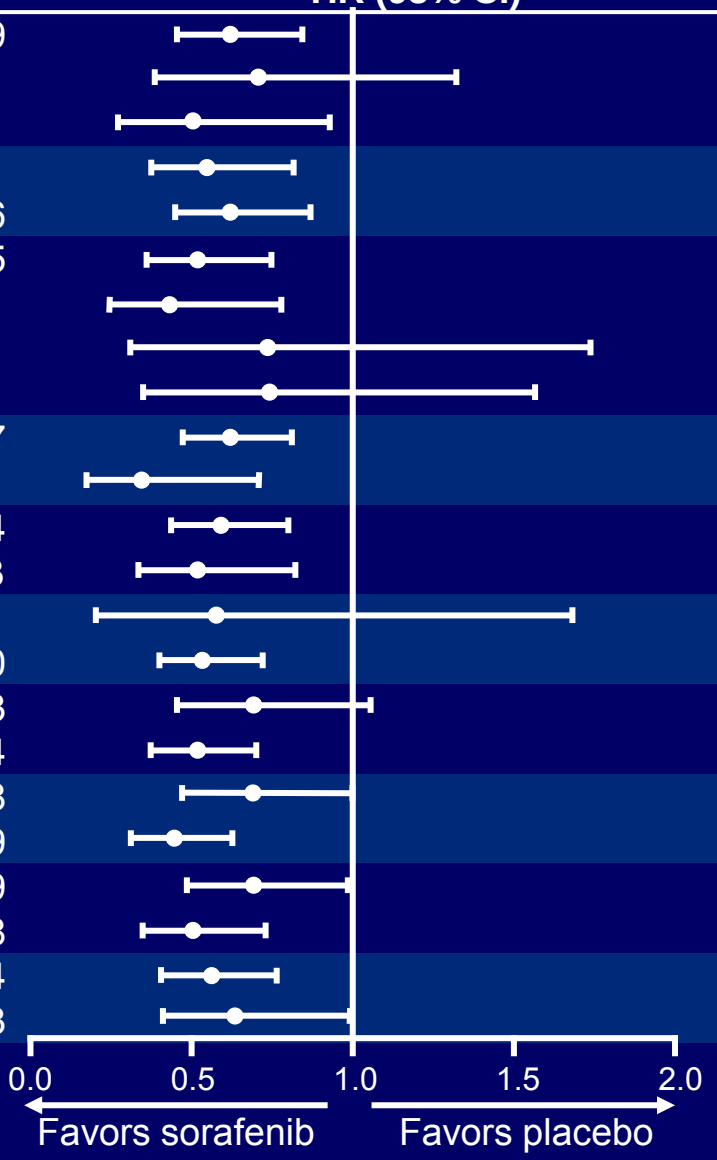
	Median PFS, days (months)
Sorafenib	329 (10.8)
Placebo	175 (5.8)

HR (95% CI): 0.587 (0.454-0.758)
p<0.0001

Full analysis set; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

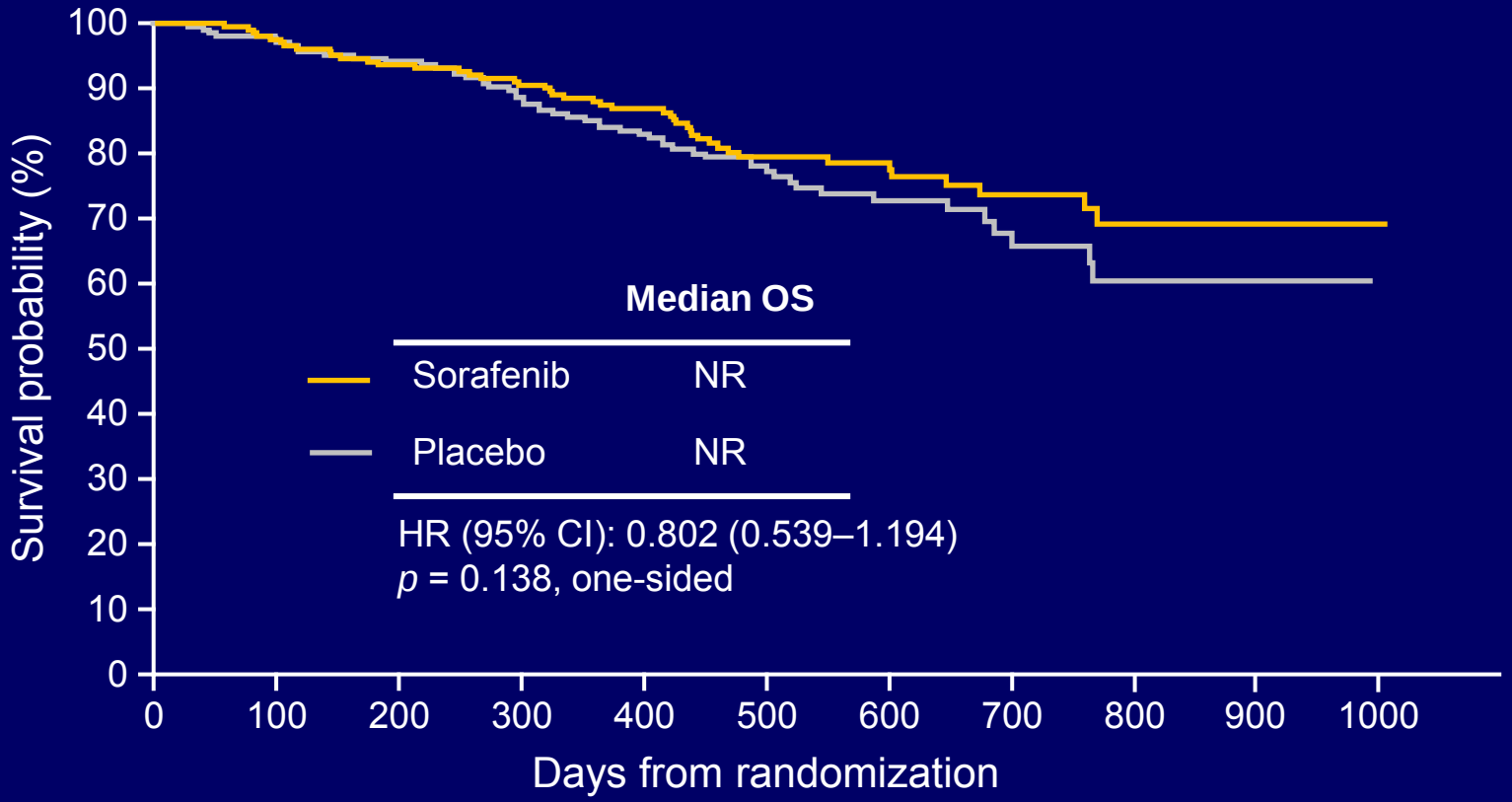
PFS in predefined subgroups

Variable		n
Region	Europe	249
	North America	72
	Asia	96
Age group	<60 years	161
	≥60 years	256
Histology (central review)	Papillary	235
	Hürthle cell	74
	Follicular	31
	Poorly differentiated	38
Lung metastases only	No	347
	Yes	70
Bone metastases only	No	304
	Yes	113
FDG uptake	Negative	29
	Positive	320
No. target or non-target lesions	< median	163
	≥ median	254
Target lesion size	< median	208
	≥ median	209
Gender	Male	199
	Female	218
Cumulative RAI ≥600 mCi	No	264
	Yes	133



FDG, fluorodeoxyglucose

Overall survival



- A total of 150 placebo patients (71%) and 55 sorafenib patients (27%) received open-label sorafenib after progression

Full analysis set. NR, not reached.

Other secondary efficacy endpoints

	Sorafenib n (%)	Placebo n (%)	p value
Total evaluable patients	196	201	
Response rate	24 (12.2)	1 (0.5)	<0.0001
Complete response	0	0	–
Partial response	24 (12.2)	1 (0.5)	–
Stable disease for ≥6 months	82 (41.8)	67 (33.2)	–
Disease control rate (CR + PR +SD ≥6 months)	106 (54.1)	68 (33.8)	<0.0001
Median duration of response, months (range)	10.2 (7.4-16.6)	NA	–

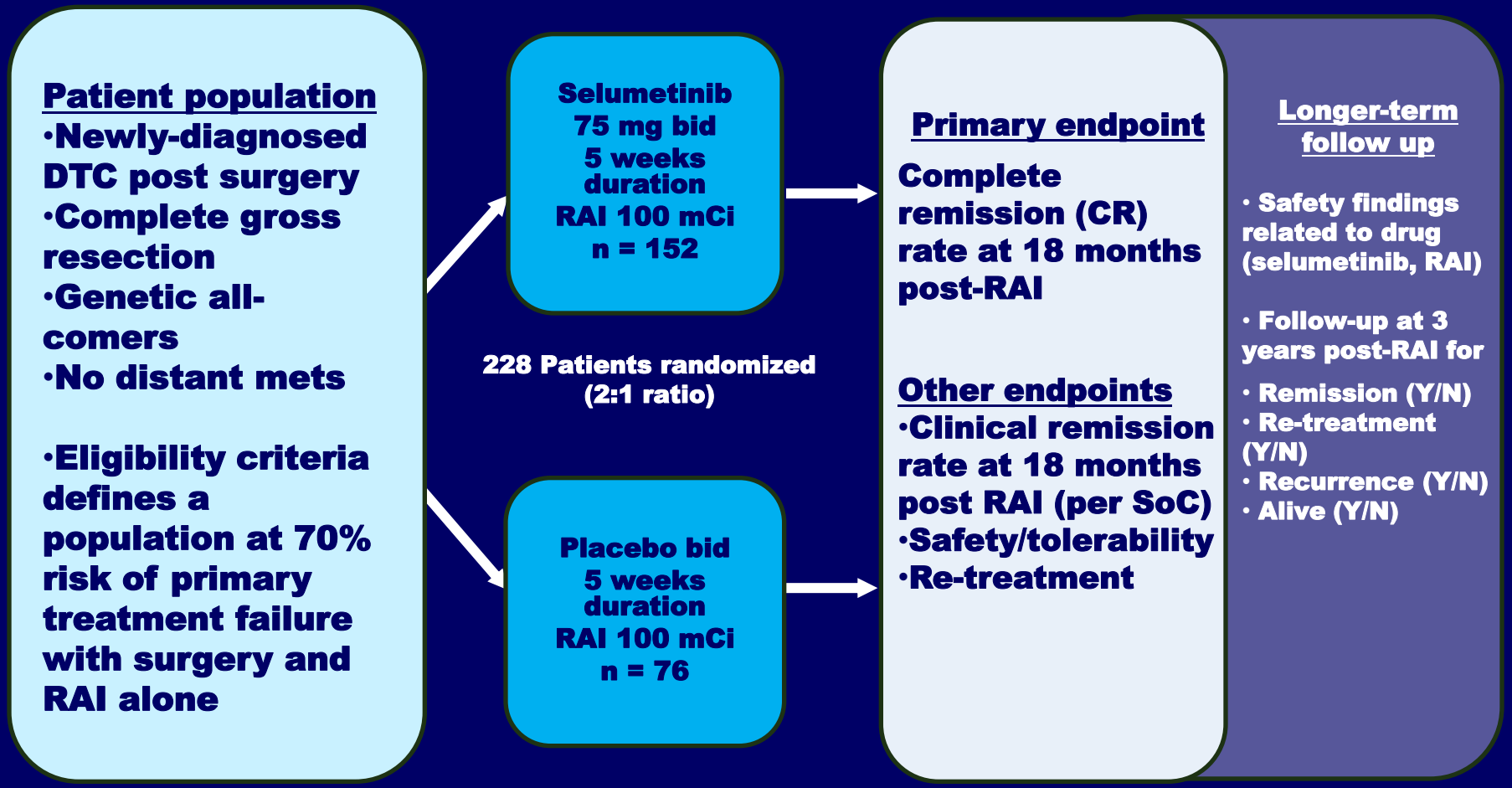
Complete response (CR); partial response (PR); stable disease (SD)
–, *p* value not determined; NA, not assessed

Summary: Phase III trials for RAI refractory DTC

- DECISION is the first phase 3 study completed of a targeted agent in Progressing RAI-refractory DTC, a rare condition with a poor prognosis and no effective standard treatment
- Sorafenib significantly improved PFS and extended median PFS by 5 months vs placebo
  - 10.8 vs 5.8 months (HR, 0.587; 95% CI, 0.454-0.758; $P < 0.0001$)
  - FDA submission in progress
- Two additional Phase III trials in this population are ongoing
  - Lenvatinib : Enrollment complete, results expected soon
  - Vandetanib: Enrollment open

AE, adverse event; DTC, differentiated thyroid cancer; HR, hazard ratio; PFS, progression-free survival; RAI, radioactive iodine.
Brose MS, et al. Presented at ASCO 2013. *J Clin Oncol*. 2013;31(suppl). Abstract 4.

Multi-Institutional Study Selumetinib in High-Risk DTC Patients: Phase III ASTRA Study Design



DTC, differentiated thyroid cancer; RAI, radioactive iodine; SoC, standard of care.
http://www.clinicaltrials.gov.ClinicalTrials.gov identifier # NCT01843062.

Questions

1. For which of the following kinase inhibitors currently have Phase III evidence of activity in DTC?
   a) Cabozantinib
   b) Pazopanib
   c) Solumetanib
   d) Sorafenib
   e) Sunitinib
   f) All of the above

Questions

2. Which of the following agents are actively under evaluation in Phase III studies for DTC?
   a) Lenvatinib
   b) Solumetanib
   c) Sorafenib
   d) Vandetanib
   e) All of the above

University of Pennsylvania Thyroid Cancer Therapeutics Program

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  - Andrea Troxel PhD
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  - Douglas Fraker MD
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