Expert Review in Relapsed/Refractory Differentiated Thyroid Cancer

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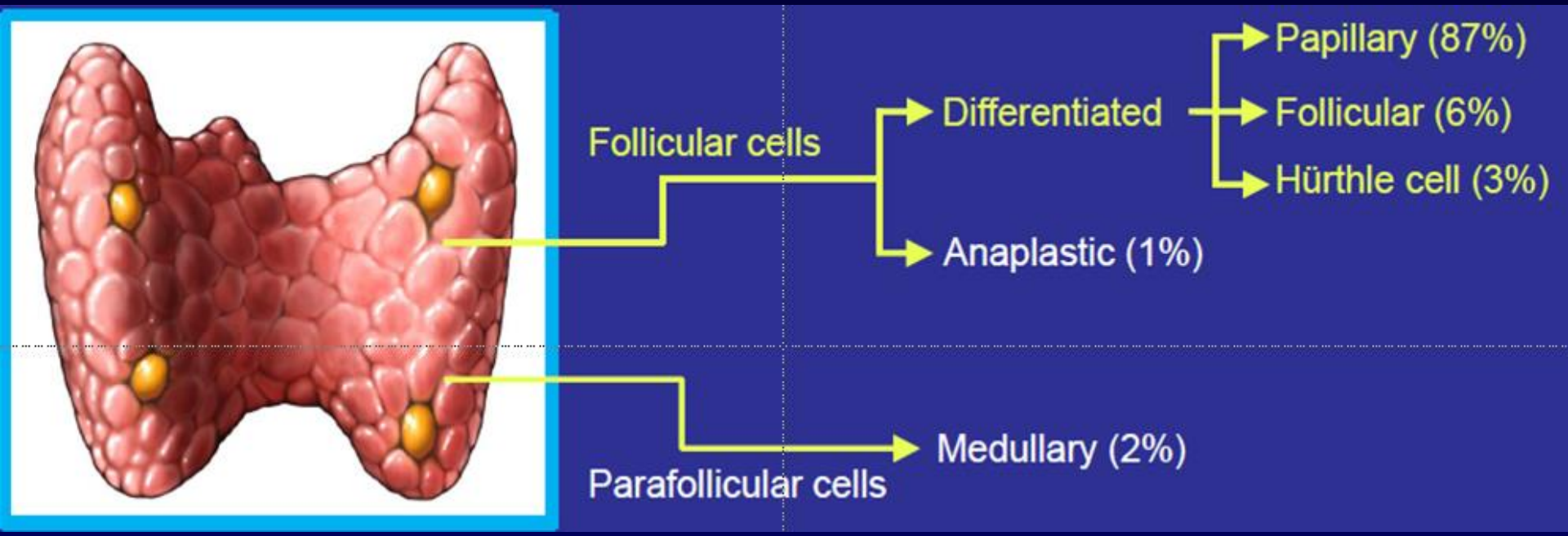
Thyroid Cancer Incidence

- It is estimated[1] that in the USA in 2014 there will be:
  - >62,000 new cases of thyroid cancer, and
  - 1890 deaths due to thyroid cancer
- 9th most common cancer
  - 5th in women
  - 2-3 times more common in women
- Continuously increasing incidence over last thirty years
  - Improved diagnostics
  - Increased environmental and medical radiation exposure, iodine intake, carcinogens
  - Ethnic and genetic factors
  - Combinations of factors

Hegedüs L. *N Engl J Med*. 2004;351(17):1764-1771; American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, et al. *Thyroid.* 2009;19(11):1167-1214; Siegel R, et al. *CA Cancer J Clin.* 2013. 63(1):11-30

Thyroid Cancer: Clinical Pathology



Treatment of differentiated thyroid cancer (DTC) includes:

- **Surgery – thyroidectomy**
- **Radioactive iodine**
- **Thyroid-stimulating hormone (TSH) suppression**

Carling T, Uldesman R. *Cancer of the endocrine system: section 2: Thyroid cancer.* Principles of Clinical Oncology. 7th edition. Lippincott Williams and Wilkins 2005; Howlader N, et al. Seer Cancer Statistics Review. Available at: http://seer.cancer.gov/statfacts/html/thyro.html. Accessed 9 October 2014.

Patient's Clinical Presentation

- Asymptomatic for a long period
- Commonly presents as a solitary thyroid nodule
- Indolent nature of this disease may lead to delay in diagnosis and worse clinical outcomes

Diagnosis based on:

- TSH level
- Ultrasound
- FNA biopsy
- Others

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology™: Thyroid Carcinoma V2.2014. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed 9 October 2014.

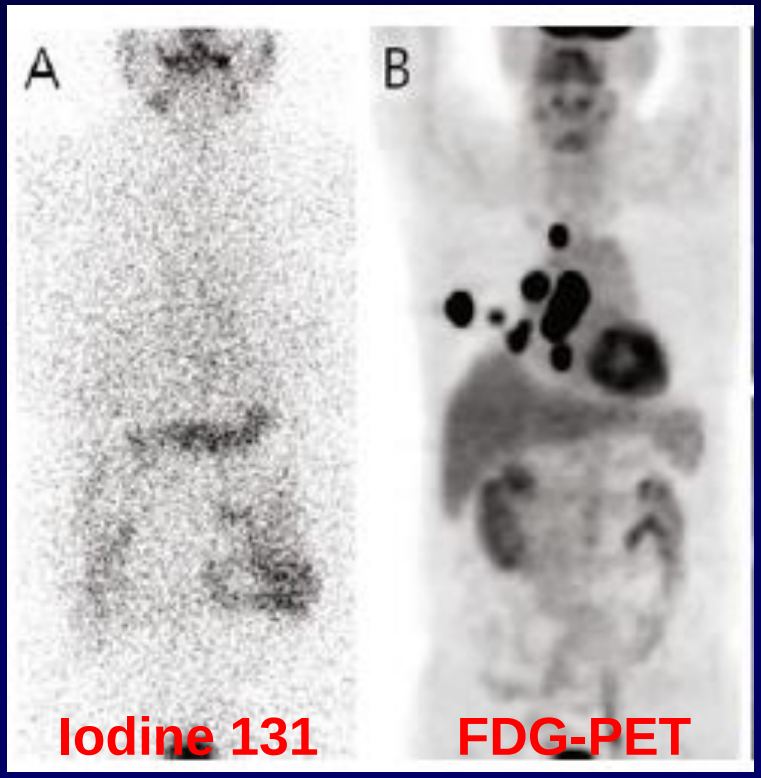
Radioactive-Iodine (RAI)-Refractory Differentiated Thyroid Cancer (DTC)

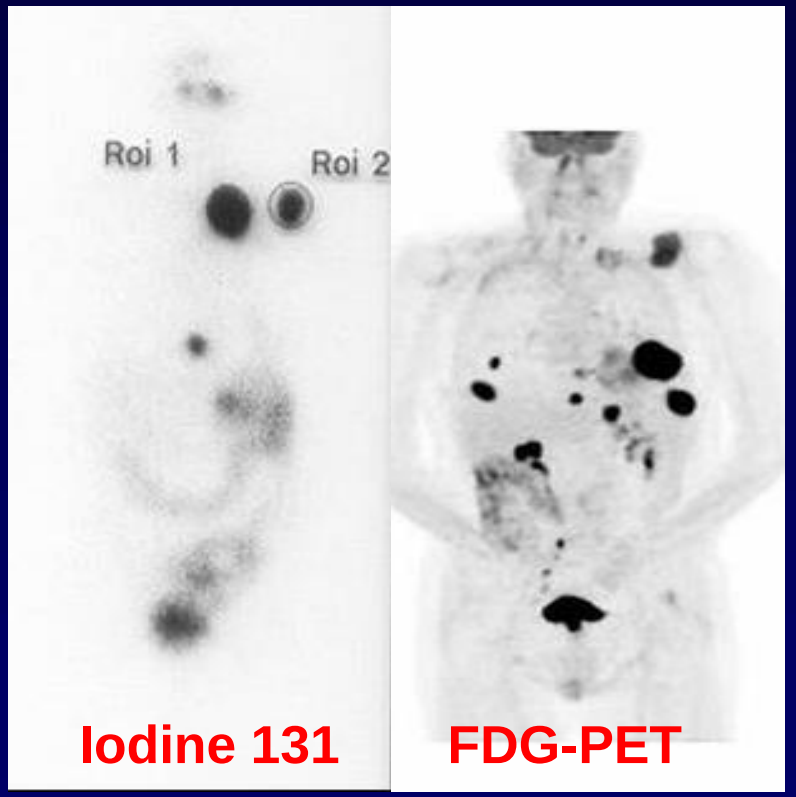
- In approximately 5%-15% of patients with thyroid cancer, the disease becomes refractory to RAI[1,2]
- Median survival for patients with RAI-refractory DTC and distant metastases is estimated to be 2.5 - 3.5 years[3,4]
- Patients often suffer multiple complications associated with disease progression
- There was no standard therapy for patients with RAI-refractory DTC prior to 2013

1. Xing M, et al. *Lancet.* 2013;381(98871):1058-1069; 2. Pacini F, et al. *Expert Rev Endocrinol Metab.* 2012;7(5):541-554; 3. Durante C, et al. *J Clin Endocrinol Metab.* 2006;91(8):2892-2899; 4. Robins RJ, et al. *J Clin Endocrinol Metab.* 2006;91(2):498-505.

Resistance to RAI Therapy

1. **No RAI uptake**
2. **RAI uptake in some lesions but not in others**
3. **Progression despite RAI uptake**



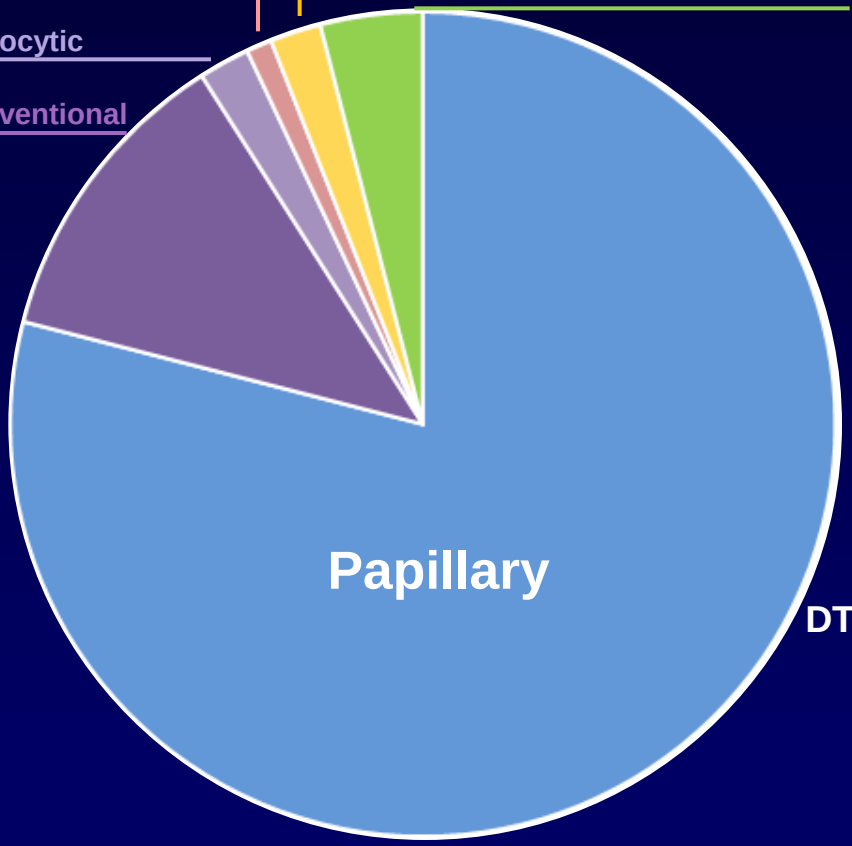


No place for RAI therapy
Patient candidate for alternative systemic therapy

Genetics of Thyroid Cancer: Rationale for Biomarker Analysis

Poorly differentiated
- ***RAS* (25–30%)**
- *TP53* (20–30%)
- *CTNNB1* (10–20%)
- ***BRAF* (10–15%)**

Follicular
Mutations identified in 70%-75%
- ***RAS* (40%-50%**; lower in oncocytic)
- *PAX8/PPARγ* (30%-35%; lower in oncocytic)
- *TP53* (21%)
- *PTEN* (8%)
- *PIK3CA* (7%)
- ***BRAF* (2%)**



Papillary
Mutations identified in ~70%
- ***BRAF*[a] (40%-50%)**
- ***RAS*[b] (7%-20%)**
- *RET/PTC* (clonal; 10%-20%)
- *EGFR* (5%)
- *TRK* (<5%)
- *PIK3CA* (2%)

[a]***BRAF* mutations are mostly *V600E*; 1%–2% are *K601E* and others**
[b]***RAS* includes *N-, H-,* and *K-RAS* (predominantly *NRAS* and *HRAS* codon 61)**

Nikiforov YE et al. *Arch Pathol Lab Med.* 2011;135(5):569-577; COSMIC database – Catalogue of Somatic Mutations in Cancer. Available at: http://cancer.sanger.ac.uk/cancergenome/projects/cosmic. Accessed 9 October 2014. Brose M, et al. *Eur J Cancer.* 2013;49(Suppl1): Abstract 3155.

DECISION Trial – Background and Study Rationale

- Sorafenib is a multikinase inhibitor targeting VEGFRs 1-3, PDGFRs, BRAF, RET, and c-Kit[1]
- Sorafenib is approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma
- Sorafenib has shown activity as monotherapy in phase II trial in patients with advanced refractory thyroid cancer[2-6]
- **DECISION** is a randomized, double-blind, placebo-controlled phase III trial designed to explore the efficacy and safety of sorafenib in patients with RAI-refractory DTC
  - stu**D**y of soraf**E**nib in lo**C**ally advanced and metastat**I**c patient**S** with radioactive **I**odine refractory thyr**O**id ca**N**cer

1. Wilhelm S, et al. *Nature Rev Drug Discovery.* 2006;5(10):835-844; 2. Gupta-Abramson V, et al. *J Clin Oncol.* 2008;26(29):4714-4719; 3. Kloos RT, et al. *J Clin Oncol.* 2009;27(10):1675-1684; 4. Lam ET, et al. *J Clin Oncol.* 2010;28(14):2323-2330; 5. Ahmed M, et al. *Eur J Endocrinol.* 2011;165(2):315-322; 6. Schneider TC, et al. *Eur J Endocrnol.* 2012;167(5):643-650

DECISION – Study Schema

417 patients randomized from Oct 2009 to July 2011

- Locally advanced or metastatic, RAI-refractory DTC
- Progression (RECIST) within the previous 14 months
- No prior chemotherapy, targeted therapy, or thalidomide

Sorafenib
400 mg orally twice daily

Randomization 1:1

Placebo
Orally twice daily

Primary Endpoint:

Progression-Free Survival

Secondary Endpoint:

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

Stratified by:

- Geographic region (North America or Europe or Asia)
- Age (<60 or ≥60 years)
- Progression assessed by independent central review every 8 weeks

At progression:

- Pts on placebo allowed to crossover at the investigastor's discretion
- Pts on sorafenib allowed to continue on open-label; sorafenib at the investigator's discretion

Brose MS, et al. *Lancet.* 2014;384(9940):319-328.

Key Inclusion and Exclusion Criteria

Inclusion

- Locally advanced or metastatic DTC (papillary; follicular, including Hürthle cell or poorly differentiated)
- RAI-refractory DTC
  - At least one target lesion without iodine uptake, or
  - Progression following treatment dose of RAI, or
  - Cumulative RAI treatment ≥600 mCi
- Progressive disease within the last 14 months (RECIST)
- Adequate TSH suppresion (0.5 mU/L)
- Not a candidate for surgery or radiotherapy with curative intent
- Adequate bone marrow, liver, and renal function
- Eastern Cooperative Oncology Group (ECOG) performace status (PS) 0-2

Exclusion

- Prior anticancer treatment with targeted therapy or chemotherapy

Brose MS, et al. *Lancet.* 2014;384(9940):319-328.

Patient Demographics

		Sorafenib (n = 207)	Placebo (n = 210)
Gender, %	Male	50.2	45.2
	Female	49.8	54.8
Age	Median (range)	63 (24-82)	63 (30-87)
	≥60 years, %	61.4	61.4
Region, %	Europe	59.9	59.5
	North America	17.4	17.1
	Asia	22.7	23.3
ECOG PS, %	0	62.8	61.4
	1	33.3	35.2
	2	3.4	2.9

Brose MS, et al. *Lancet.* 2014;384(9940):319-328.

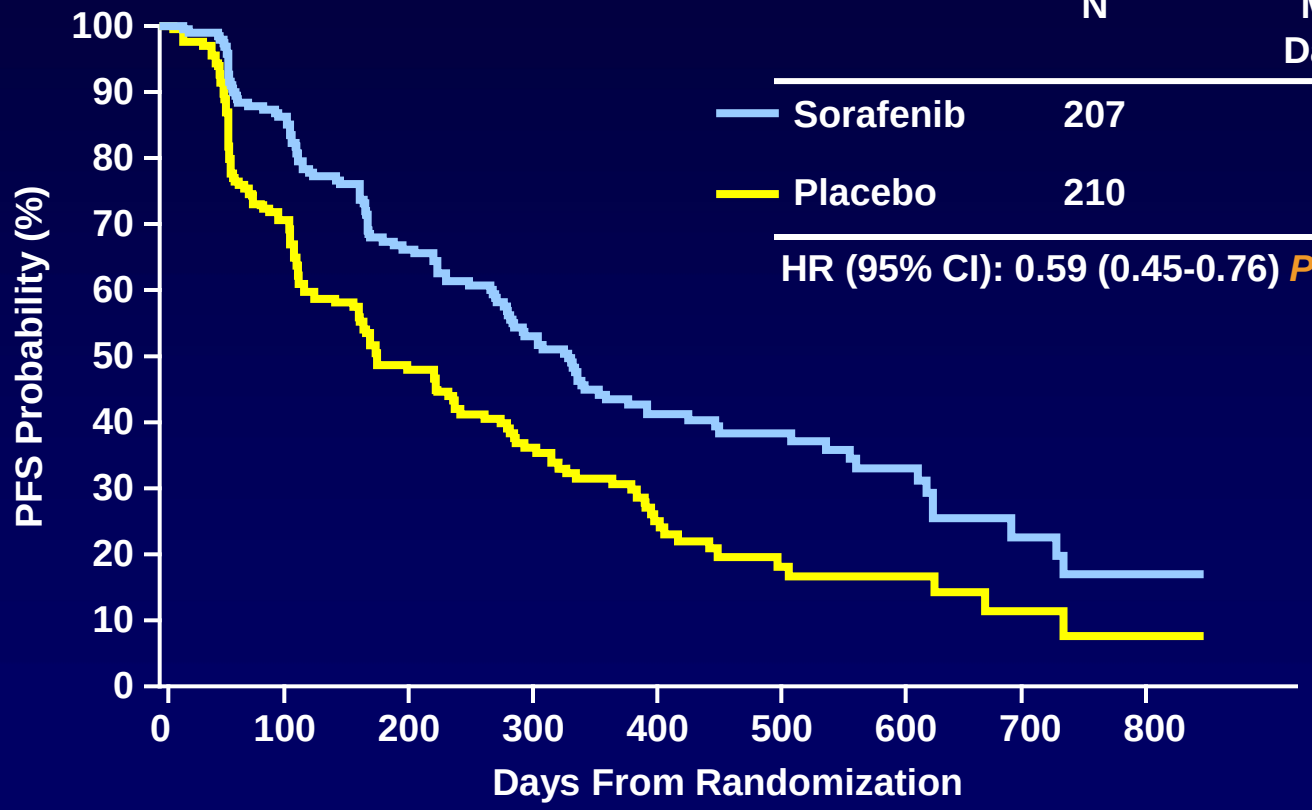
Baseline Disease Characteristics

		Sorafenib (n = 207)	Placebo (n = 131)
Histology, by central review*†, %	Papillary	57.0	56.7
	Follicular, oncocytic (Hürthle cell)	17.9	17.6
	Follicular, non-Hürthle cell	6.3	9.0
	Poorly differentiated	11.6	7.6
	Well differentiated	1.0	0.5
	Other	7.3	8.6
Metastases	Locally advanced	3.4	3.8
	Distant	96.6	96.2
Most common target/non-target lesion sites, %	Lung	86.0	86.2
	Lymph nodes (any)	54.6	48.1
	Bone	27.5	26.7
	Pleura	19.3	11.4
	Head and Neck	15.9	16.2
	Liver	13.5	14.3

*All patients had differentiated thyroid cancer according to investigator assessment. †Two patients in the sorafenib group and one in the placebo group were assigned two different histologies on the basis of multiple samples.

Brose MS, et al. *Lancet.* 2014;384(9940):319-328.

Progression-Free Survival
(By independent central review)

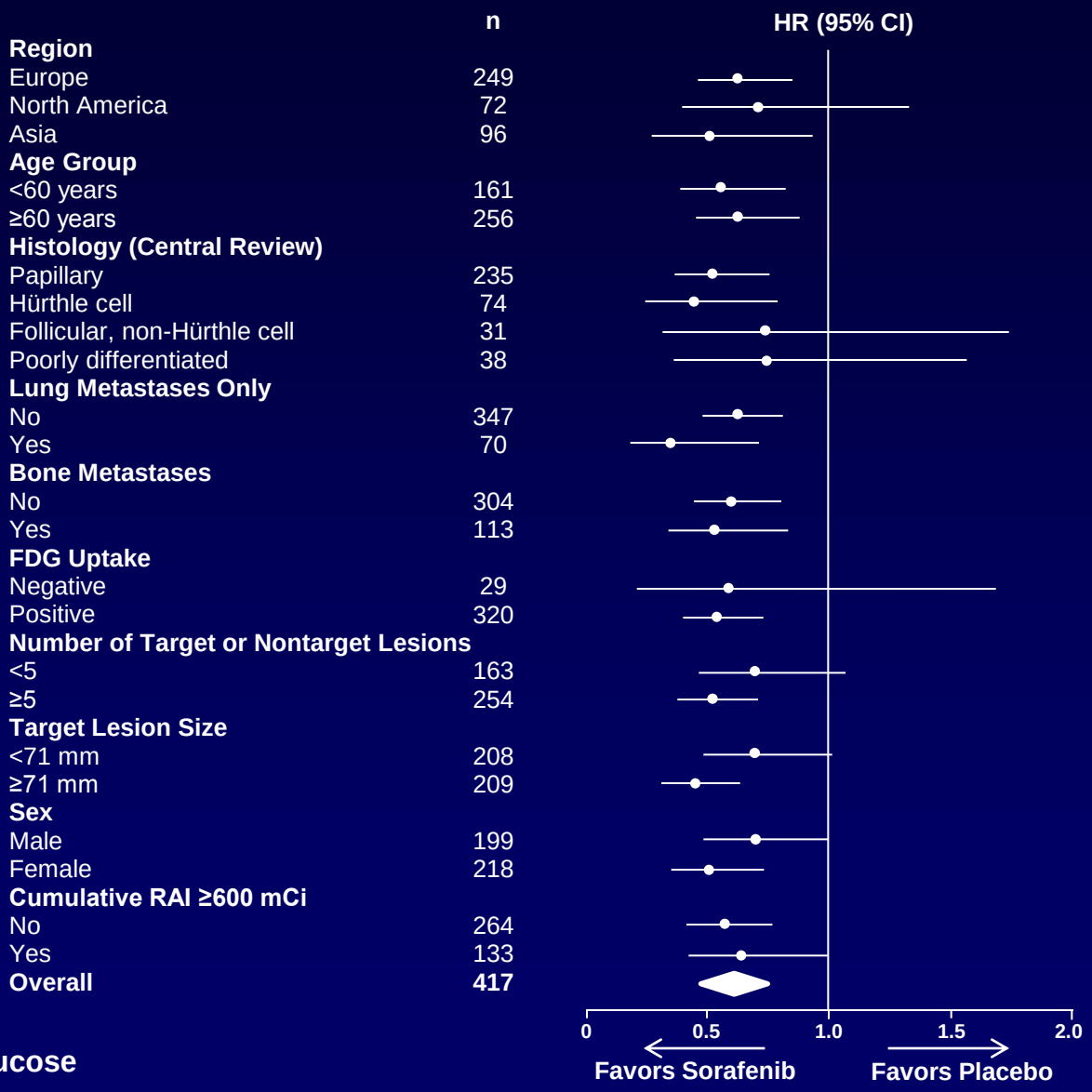


	N	Median PFS, Days (Months)
Sorafenib	207	329 (10.8)
Placebo	210	175 (5.8)

HR (95% CI): 0.59 (0.45-0.76) *P*<.0001

Brose MS, et al. *Lancet.* 2014;384(9940):319-328.

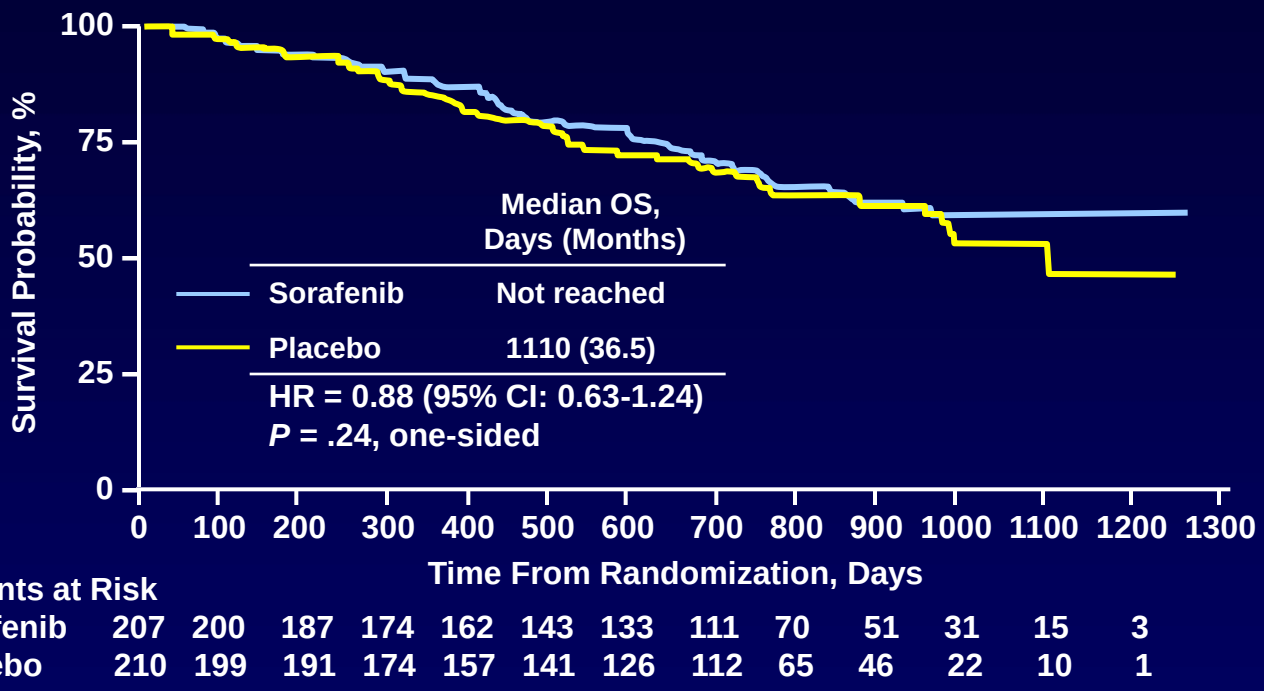
PFS in Predefined Subgroups



FDG, fluorodeoxyglucose

Brose MS, et al. *Lancet.* 2014;384(9940):319-328

Updated Analysis Overall Survival (Month 9)



Patients at Risk

Sorafenib	207	200	187	174	162	143	133	111	70	51	31	15	3
Placebo	210	199	191	174	157	141	126	112	65	46	22	10	1

Data cut-off 31 May 2013

- Median OS was still not reached with sorafenib, and median OS with placebo was 36.5 months (95% CI: 32.2-not estimable)
- There was no statistically significant difference between the treatment arms
  - (HR: 0.88 [95% CI: 0.63-1.24]; *P* = .24, one-sided)

Brose MS, et al. *J Clin Oncol.* 2014;32(5s): Abstract 6060.

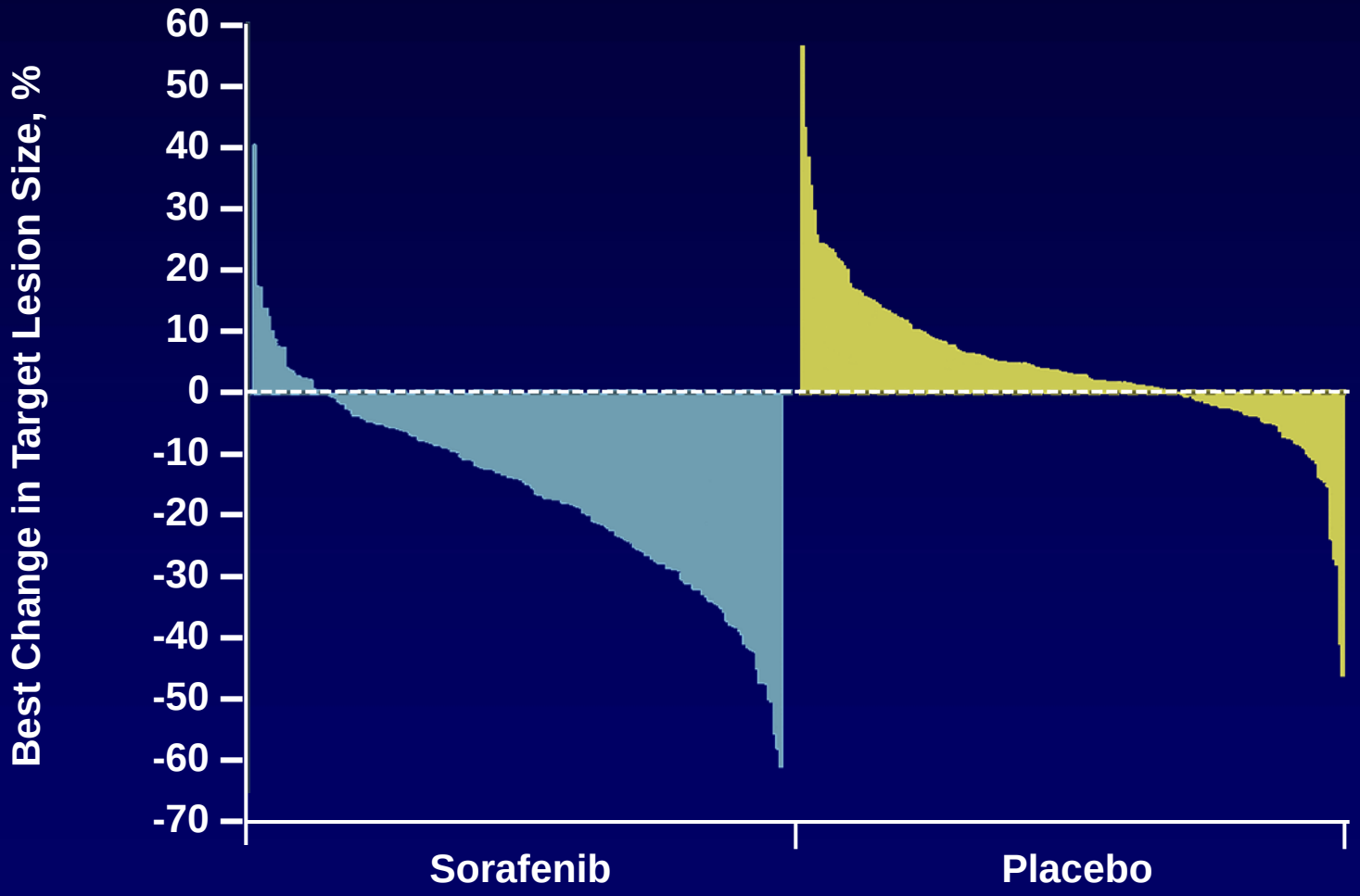
Other Secondary Efficacy Endpoints

	Sorafenib n (%)	Placebo n (%)	*P* value
Total evaluable patients	196	201	
Response rate	24 (12.2)	1 (0.5)	<.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)	<.0001
Median duration of response (PRs), months (range)	10.2 (7.4-16.6)	NA	-

CR, complete response; PR, partial response; SD, stable disease; NA, not assessed

Brose M, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 4.

Best Change in Target Lesion Size (Central Review)



Brose MS, et al. *Lancet.* 2014;384(9940):319-328.

Treatment and Dose Modifications (Double-Blind Period)

	Sorafenib n = 207	Placebo n = 209
Mean dose	651 mg	793 mg
Median (range) treatment duration	46.1 weeks (0.3-135.3)	28.3 weeks (1.7-132.1)
Dose modification due to AEs, %	77.8	30.1
Dose reduction	64.3	9.1
Dose interruption	66.2	25.8
Permanent discontinuation due to AEs, %	18.8	3.8

AE, adverse event

Brose M, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 4.

Most Common TEAEs in Sorafenib Group (Double-Blind Period)

	Sorafenib (n = 207)			Placebo (n = 209)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Hand-foot skin reaction	158 (76.3%)	42 (20.3%)	--	20 (9.6%)	0	--
Diarrhea	142 (68.6%)	11 (5.3%)	1 (0.5%)	32 (15.3%)	2 (1.0%)	0
Alopecia	139 (67.1%)	--	--	16 (7.7%)	--	--
Rash or desquamation	104 (50.2%)	10 (4.8%)	0	24 (11.5%)	0	0
Fatigue	103 (49.8%)	11 (5.3%)	1 (0.5%)	53 (25.4%)	3 (1.4%)	0
Weight loss	97 (46.9%)	12 (5.8%)	--	29 (13.9%)	2 (1.0%)	--
Hypertension	84 (40.6%)	20 (9.7%)	0	26 (12.4%)	5 (2.4%)	0
Anorexia	66 (31.9%)	5 (2.4%)	0	10 (4.8%)	0	0
Oral mucositis (functional/symptomatic)	48 (23.2%)	1 (0.5%)	1 (0.5%)	7 (3.3%)	0	0
Pruritis	44 (21.3%)	2 (1.0%)	--	22 (10.5%)	0	--

Data are n (%). Adverse events are reported according to National Cancer Institite Common Terminology Criteria for Adverse Events version 3.0.TEAE, treatment-emergent adverse event.

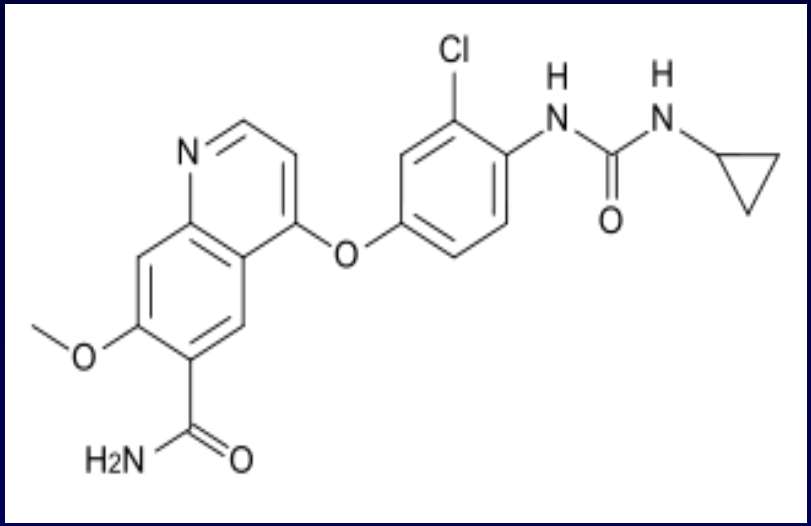
Brose MS, et al. *Lancet.* 2014;384(9940):319-328

Summary

- DECISION is the first phase III study of a targeted agent in RAI-refractory DTC
- Safety results are consistent with the known safety profile of sorafenib
  - Hand-foot skin reaction, diarrhea, alopecia, rash/desquamation, fatigue, and hypertension
- The DECISION study met its primary endpoint
  - 41% reduction in the risk of progression or death with sorafenib compared with placebo (HR: 0.587; 95% CI: 0.454-0.758; *P*<.0001)
- OS results remain immature
  - Median OS with sorafenib has still not been reached
  - Median OS with placebo was 36.5 months (95% CI: 32.2-not estimable)
  - As DECISION investigated first-line treatment, many patients received other subsequent therapies, which may confound the OS results

Brose M, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 4; Brose MS, et al. *J Clin Oncol.* 2014;32(5s): Abstract 6060

E7080: Lenvatinib



A synthetic, orally available inhibitor of VEGFR2 tyrosine kinase with potential antineoplastic activity.

E7080 blocks VEGFR2 activation by VEGF, resulting in inhibition of the VEGF receptor signal transduction pathway, decreased vascular endothelial cell migration and proliferation, and vascular endothelial cell apoptosis.

SELECT Trial – Study Rationale

- Until the approval of sorafenib for radioiodine-refractory (RR) DTC in the United States (2013) and Europe (2014), treatment options for these patients were limited
- The VEGF-signaling networks have been implicated in tumor angiogenesis and metastasis of thyroid cancer[1-4]:
- However, other molecular drivers of tumor growth and maintenance beyond VEGF-driven angiogenesis contribute to the pathogenesis of thyroid cancer
- Lenvatinib, an oral multityrosine kinase inhibitor of VEGFR1-3, FGFR1-4, PDGFRα, RET, and KIT demonstrated clinical activity in a phase II study of patients with RR DTC
- This phase III **S**tudy of (**E**7080) **LE**nvatinib in Differentiated **C**ancer of **T**hyroid (**SELECT**) was conducted to assess the PFS of patients with RR DTC treated with lenvatinib versus placebo

FGDR, fibroblast growth receptor; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; VEGF/VEGFR, vascular endothelial growth factor/receptors

1. Bergers G, et al. *Nat Rev Cancer.* 2008;8(8):592-603; 2. Ebos JM, et al. *Clin Cancer Res.* 2009;15(16):5020-5025;
3. Rivera M, et al. *Mod Pathol.* 2010;23(9):1191-1200; 4. Volante M, et al. *J Clin Endocrinol Metab*. 2009;94(12):4735-4741.

Schlumberger M, et al. *J Clin Oncol.* 2014;32(s): Abstract LBA6008.

SELECT – Study Schema

Global, randomized, double-blind, phase III trial

Patients with DTC (N = 392)
- IRR evidence of progression within previous 13 months
- ^{131}I-refractory disease
- Measurable disease
- Up to 1 prior VEGFR or VEGFR-targeted therapy

Stratification
- Geographic region (Europe, N America, other)
- Prior VEGF/VEGFR-targeted therapy (0,1)
- Age (≤65 years, >65 years)

RANDOMIZATION

2:1

Lenvatinib (n = 261)
24 mg daily PO

Placebo (n = 131)
24 mg daily PO

Treatment until disease progression confirmed by IRR (RECIST v1.1)

DTC, differentiated thyroid cancer; 131I, radioiodine; IRR, independent radiologic review; ORR, objective response rate; OS, overall survival; PO, by mouth; RECIST, response evaluation criteria in solid tumors

Schlumberger M, et al. *J Clin Oncol.* 2014;32(s): Abstract LBA6008.

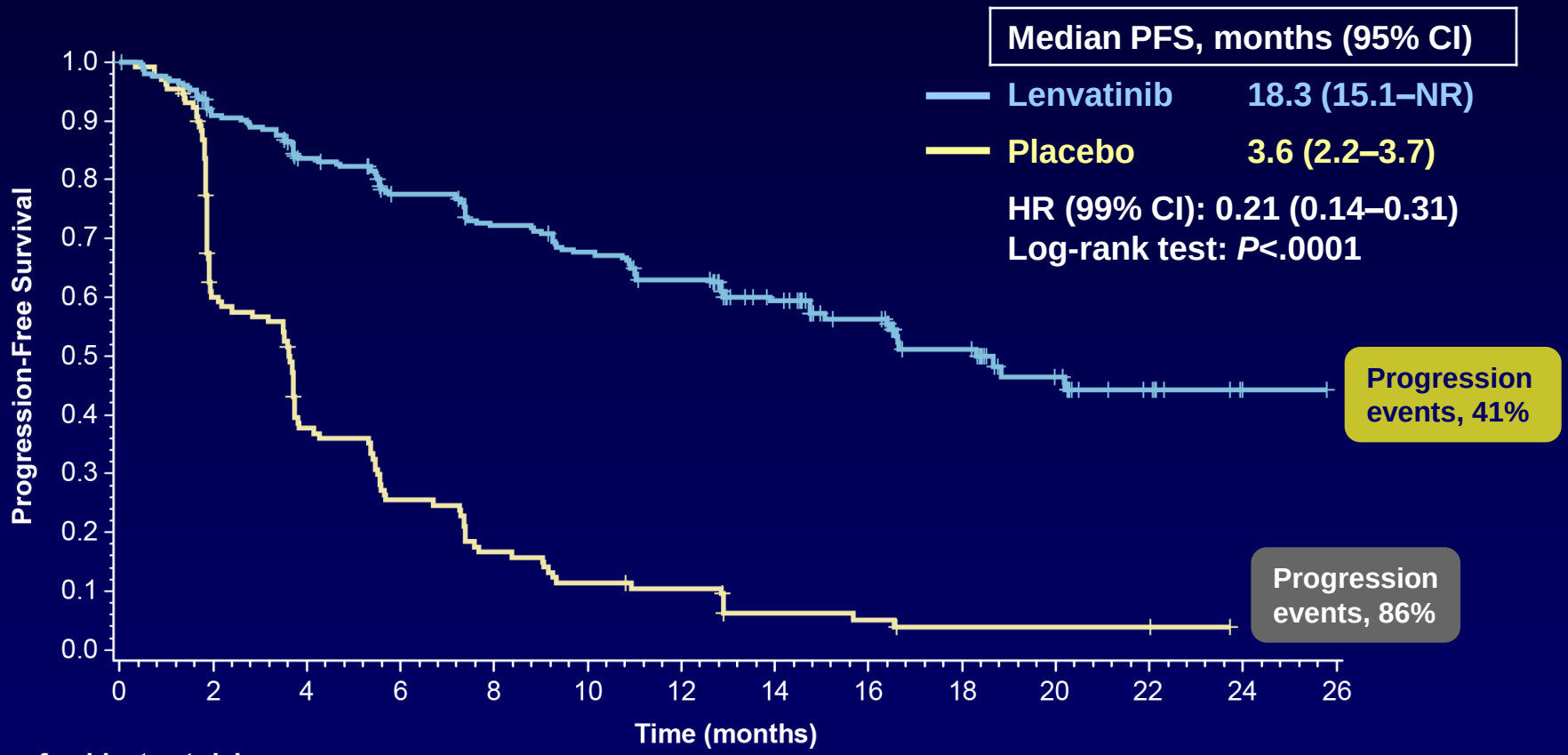
Patient Characteristics

		Lenvatinib (n = 261)	Placebo (n = 131)
Median age, years		64	61
Sex, n (%)	Female	136 (52)	56(43)
Region, n (%)	Europe	131 (50)	64 (49)
	North America	77 (30)	39 (30)
	Other	53 (20)	28 (21)
ECOG Performance status, n (%)	0-1	248 (95)	129 (98)
	2-3	13 (5)	2 (2)
Prior VEGF-targeted therapy, n(%)[a]	0	195 (75)	104 (79)
	1	266 (25)	27 (21)
Histology (investigator-assessed), n (%)	Papillary	141 (54)	71 (54)
	Poorly Differentiated	28 (11)	19 (15)
	Follicular	92 (35)	41 (31)
Metastatic lesions, n (%)	Only bone metastases	4 (2)	2 (2)[b]
	Pulmonary metastases	226 (87)	124 (95)

[a] Differeces in prior VEGF-targeted therapy were not significant (*P* = .305)
[b] Includes 1 patient with bone metastases and 1 patient with a malignant neck node

Schlumberger M, et al. *J Clin Oncol.* 2014;32(s): Abstract LBA6008.

Primary Endpoint: Kaplan-Meier Estimate of PFS

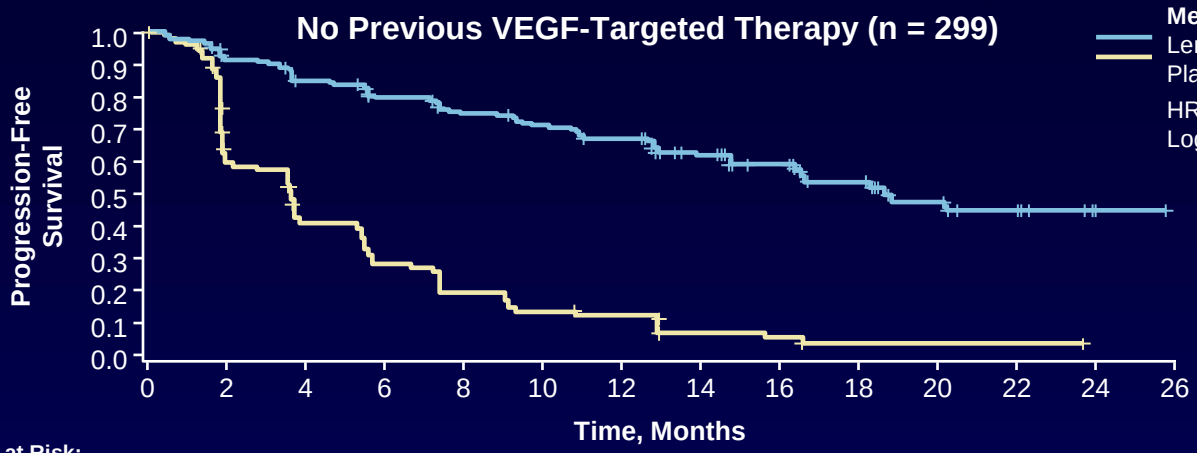


Number of subjects at risk:

Lenvatinib	261	225	198	176	159	148	136	92	66	44	24	11	3	0
Placebo	131	71	43	29	19	13	11	5	4	2	2	2	0	0

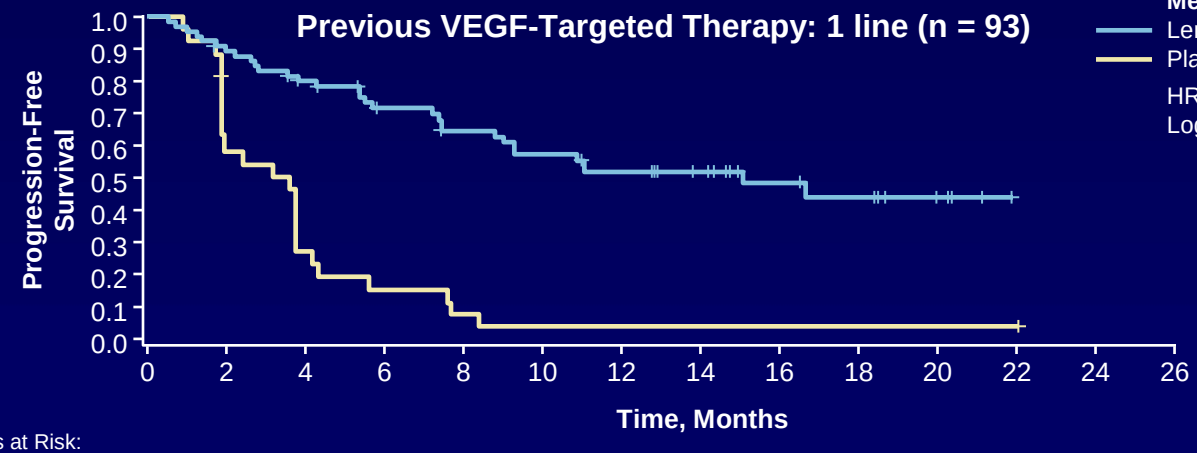
Schlumberger M, et al. *J Clin Oncol.* 2014;32(s): Abstract LBA6008.

PFS by Previous VEGF-Targeted Therapy



Number of Subjects at Risk:

Lenvatinib	195	167	148	135	123	116	108	72	52	34	20	11	3	0
Placebo	104	56	36	25	17	12	10	4	3	1	1	1	0	0



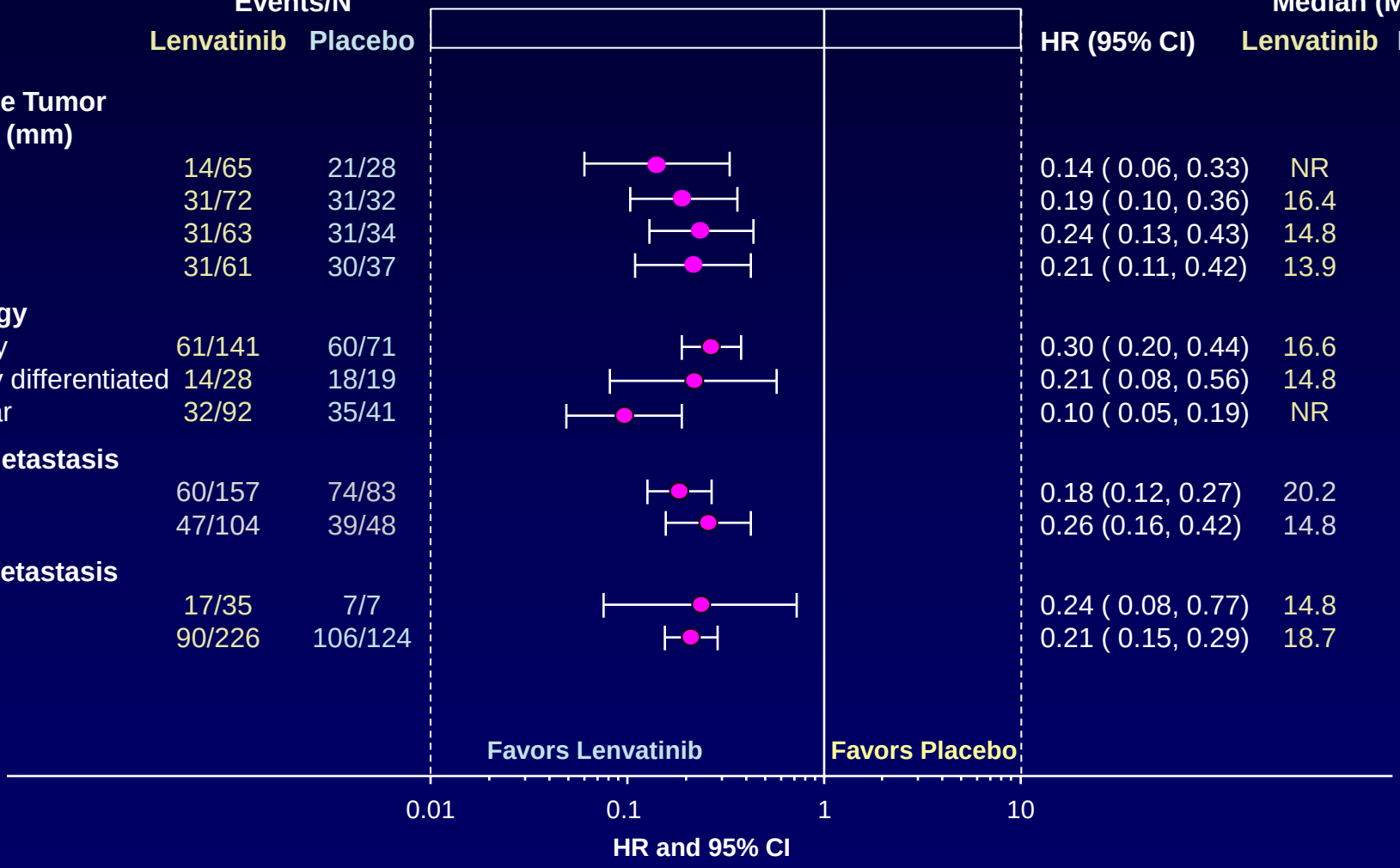
Number of Subjects at Risk:

Lenvatinib	66	58	50	41	36	32	28	20	14	10	4	0	0	0
Placebo	27	15	7	4	2	1	1	1	1	1	1	1	0	0

Schlumberger M, et al. *J Clin Oncol.* 2014;32(s): Abstract LBA6008.

PFS Subgroup Analyses

	Events/N			Median (Months)	
	Lenvatinib	Placebo	HR (95% CI)	Lenvatinib	Placebo
Baseline Tumor Burden (mm)					
≤35	14/65	21/28	0.14 (0.06, 0.33)	NR	5.6
35−60	31/72	31/32	0.19 (0.10, 0.36)	16.4	3.7
60−92	31/63	31/34	0.24 (0.13, 0.43)	14.8	3.6
>92	31/61	30/37	0.21 (0.11, 0.42)	13.9	2.4
Histology					
Papillary	61/141	60/71	0.30 (0.20, 0.44)	16.6	3.5
Poorly differentiated	14/28	18/19	0.21 (0.08, 0.56)	14.8	2.1
Follicular	32/92	35/41	0.10 (0.05, 0.19)	NR	3.7
Bone Metastasis					
No	60/157	74/83	0.18 (0.12, 0.27)	20.2	3.7
Yes	47/104	39/48	0.26 (0.16, 0.42)	14.8	2.1
Lung Metastasis					
No	17/35	7/7	0.24 (0.08, 0.77)	14.8	2.4
Yes	90/226	106/124	0.21 (0.15, 0.29)	18.7	3.6



CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

Schlumberger M, et al. *J Clin Oncol.* 2014;32(s): Abstract LBA6008.

Response Rates

N (%)	Lenvatinib (n = 261)	Placebo (n = 131)
ORR	169 (65%)	2
95% CI	59.0-70.5	0.0-3.6
P value	<.0001	
CR	2 (2%)	0
PR	165 (63%)	2 (2%)
SD ≥23 weeks	40 (15%)	39 (30%)
PD	18 (7%)	52 (40%)
Median time to objective response, months (95% CI)	2.0 (1.9-3.5)	-
Duration of responses, months, median (95% CI)	NR (16.8-NR)	-

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Patients With CRs

	Subject 1	Subject 2	Subject 3	Subject 4
Sex, age	F, 55	M, 48	F, 30	M, 64
Histologic subtype	Hürthle Cell	Insular	Clear Cell	Insular
Prior VEGF-targeted therapy	0	0	0	Sorafenib
Time since prior progression, months	1.5	3	0.7	0.5
Baseline tumor burden, mm	33.8	33.2	21.3	83
Number of target lesions	1	2	1	3
Location of target lesions	Oropharyngeal LN	Lung	Supra / Infraclavicular LN	Lung, Hilar LN
Time of PR, timepoint: week	8	8	8	8
Time of CR; timepoint: week	16	48	16	48
Last timepoint assessed, week	124, ongoing	98, ongoing	100, ongoing	84, ongoing

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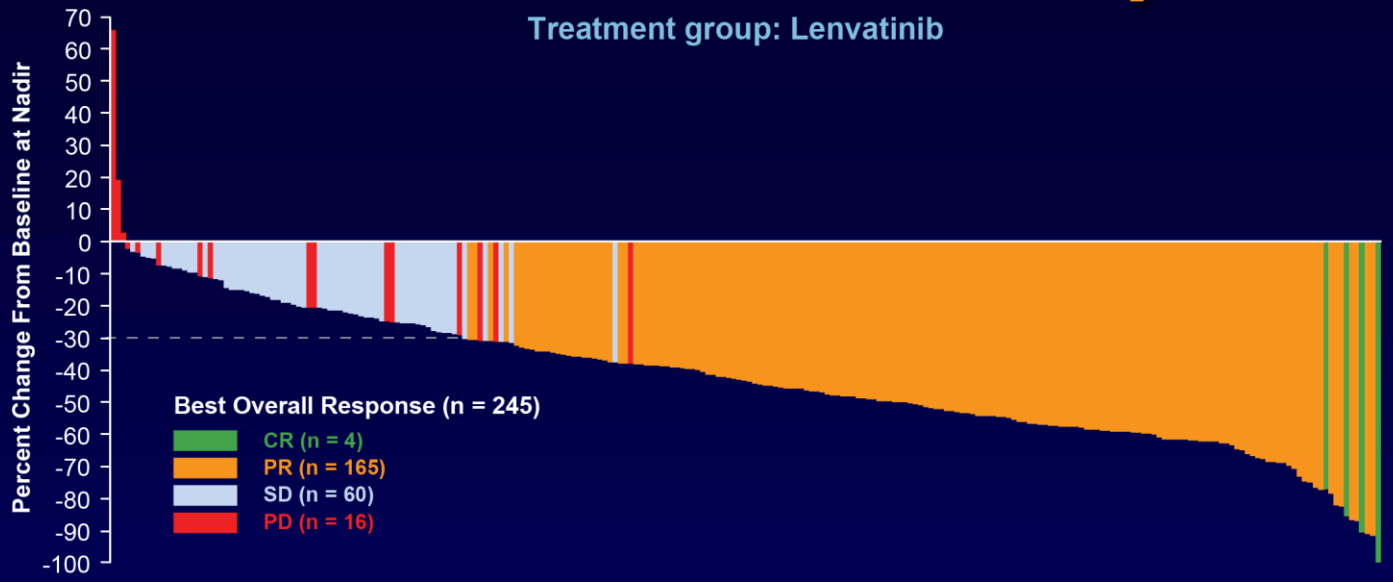
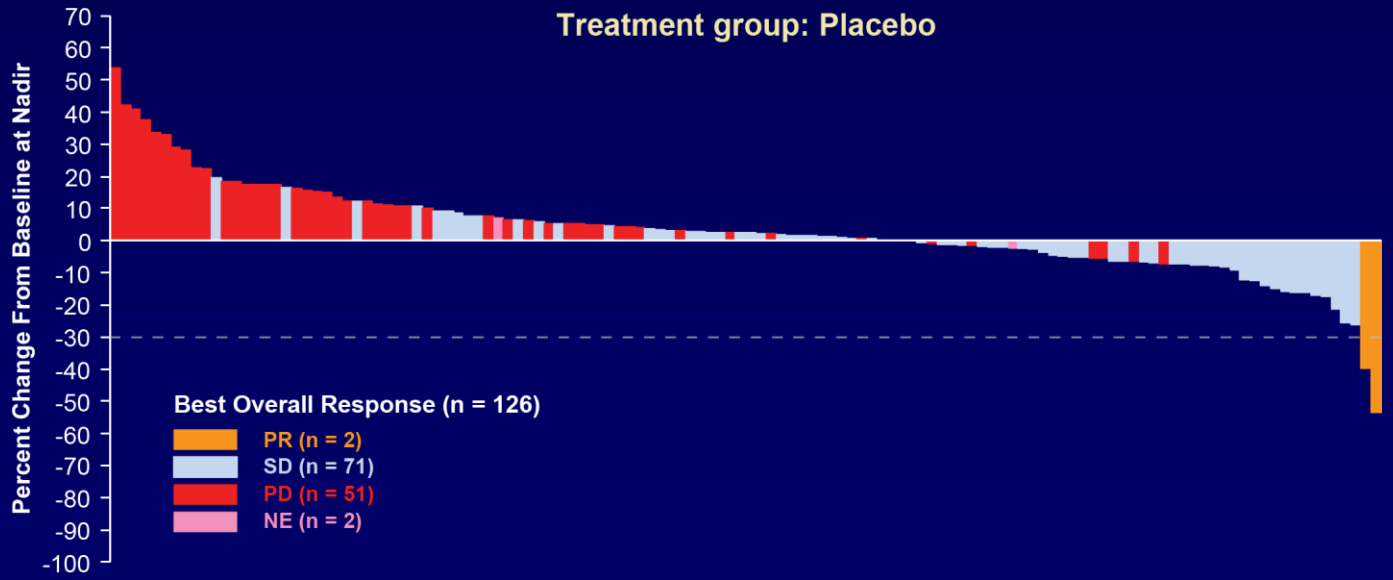
Best Tumor Response



Median tumor shrinkage for responders (range): -52% (-100%, -30%)



Median tumor shrinkage for all patients (range): +2% (-53%, +54%)

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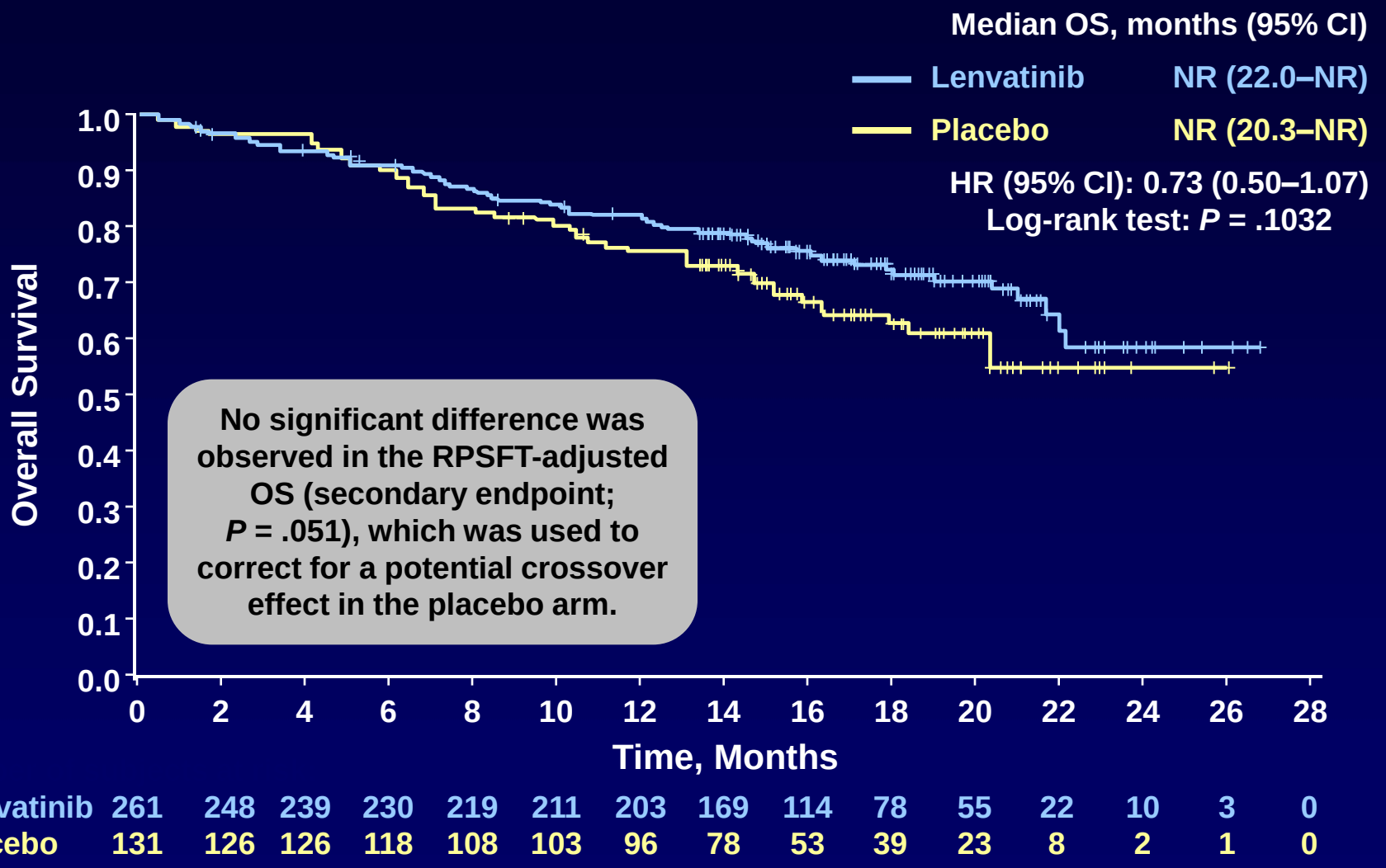
Overall Survival, ITT population



RPSFT, rank-preserving structural failure time

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Study Medication Exposure

	Lenvatinib n = 261	Placebo n = 131
Duration of treatment, months, median (range)	13.8 (0–27)	3.9 (0–24)
Dose intensity, mg/day - median (range)	16.8 (6–25)	24.0 (15–24)
Time to first dose reduction, months - median (95% CI)[a]	3.0 (2.0–3.2)	NR

[a] For patients who had dose reductions only (n = 223; 85.4%)
CI, confidence interval; NR, not reached.

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Treatment-Emergent Adverse Events (TEAEs)

N (%)	Lenvatinib n = 261	Placebo n = 131
TEAEs	260 (>99%)	118 (90%)
TEAE reported as treatment-related	254 (97%)	78 (60%)
Serious TEAEs	133 (51%)	31 (24%)
TEAE resulting in		
Dose reduction	177 (68%)	6 (5%)
Dose interruption	215 (82%)	24 (18%)
Discontinuation of treatment	37 (14%)	3 (2.3)
Fatal TEAE	20 (8%)	6 (5%)
Fatal TEAE reported by investigator as treatment-related	6 (2%)	0

6/20 lenvatinib treatment-emergent death were considered by investigator as treatment-related:
Pulmonary embolism (n = 1)
Hemorrhagic stroke (n = 1)
General health deterioration (n = 4)

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Most Frequent Treatment-Related Adverse Events (>20%)

	Lenvatinib n = 261		Placebo n = 131	
Adverse Event	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Hypertension	68	42	9	2
Diarrhea	60	8	8	0
Fatigue / asthenia	59	9	28	2
Decreased appetite	50	5	12	0
Nausea / vomiting	46	3	15	1
Decreased weight	46	10	9	0
Stomatitis	36	4	4	0
Palmar-plantar erythrodysesthesia syndrome	32	3	1	0
Proteinuria	31	10	2	0
Headache	28	3	6	0
Dysphonia	24	1	3	0

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TEAEs of Special Interest

Adverse Event, %	Lenvatinib n = 261		Placebo n = 131	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Hypertension[a]	73	44	15	4
Proteinuria	32	10	3	0
Venous TEs	5	4	5	2
Arterial TEs	5	3	2	1
Renal failure[b]	4	2	1	1
Hepatic failure	0.4	0.4	0	0
PRES	0.4	0	0	0

[a] Includes 'hypertension' and 'blood pressure increased'.
[b] Includes 'renal failure' and 'renal failure acute'.
PRES, posterior reversible encephalopathy syndrome; TE, thromboembolic event; TEAEs, treatment-emergent adverse events.

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Conclusions

- In patients with RR DTC, lenvatinib significantly prolonged median PFS by 14.7 months compared with placebo:
  - Lenvatinib median PFS: 18.3 months (95% CI 15.1-NR)
  - Placebo median PFS: 3.6 months (95% CI 2.2-3.7)
    - HR 0.21 (99% CI, 0.14-0.31)

- Response rates for lenvatinib and placebo, respectively, were:
  - ORR: 65% vs 2% (with CR; 2% vs 0%)
  - The median time to objective response for lenvatinib was 2.0 months (95% CI, 1.9-3.5 months)
  - The median duration of response for lenvatinib has not been reached
    - 75% of responders had an objective response >9.4 months

- Toxicities of therapy, although considerable, were managed with dose modification and supportive medications

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VERIFY Trial

- A Randomized, Double-Blind, Placebo-Controlled, Multi-Centre Phase III Study to Assess the Efficacy and Safety of Vandetanib 300 mg in Patients With Differentiated Thyroid Cancer That Is Either Locally Advanced or Metastatic Who Are Refractory or Unsuitable for Radioiodine (RAI) Therapy

- Primary Endpoint
  - Determination of the efficacy, as assessed by PFS of vandetanib
- Secondary Endpoints
  - Improvement in time to worsening of pain
  - Efficacy of vandetanib when compared to placebo in the patient population as assessed by efficacy variables:
    - Tumor size
    - Duration of response
    - Objective response rate
    - Overall survival
  - Pharmacokinetics of vandetanib
  - Safety and tolerability

- Expected results Q4 2017

National Institutes of Health. www. http://clinicaltrials.gov/show/NCT01876784. Accessed October 7, 2014.