Carcinoma de Tiroide: Teràpies Diana

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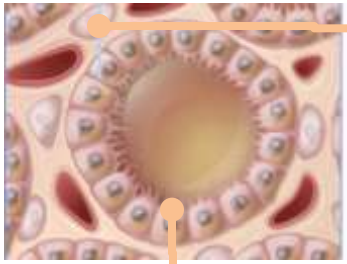
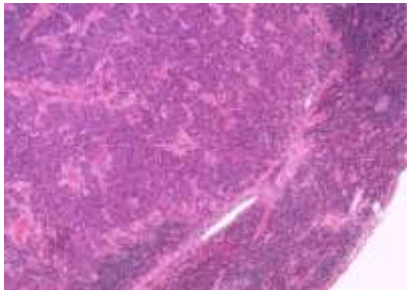
THYROID CANCER: CELL TYPE AND HISTOLOGY

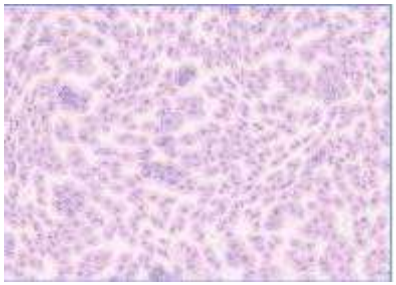


Parafollicular cells (3-5%) → **Medullary thyroid carcinoma (MTC)**



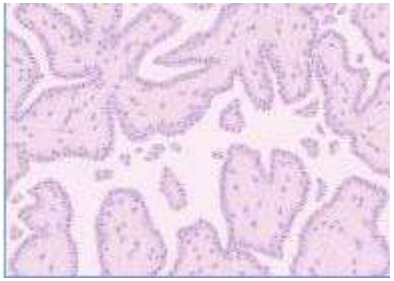
Follicular cells (90-95%)

Anaplastic

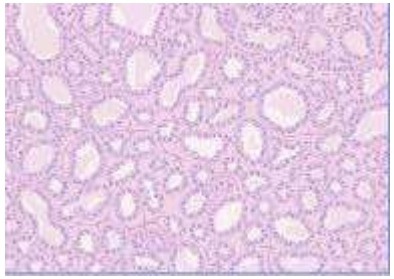


Differentiated

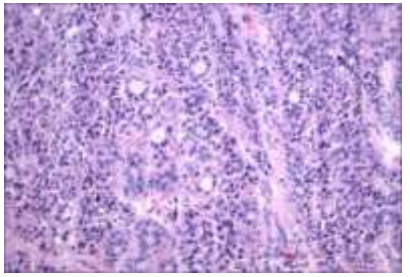
Papillary



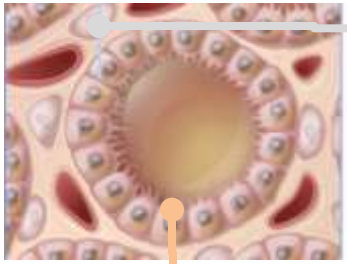
Follicular



Hürthle cell



THYROID CANCER: CELL TYPE AND HISTOLOGY



Parafollicular cells

(3-5%)

Medullary thyroid carcinoma (MTC)

Follicular cells (90-95%)

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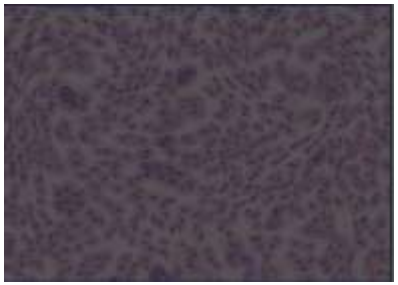

Differentiated

Papillary

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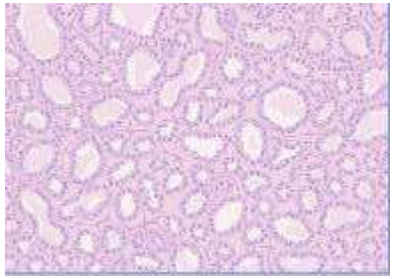
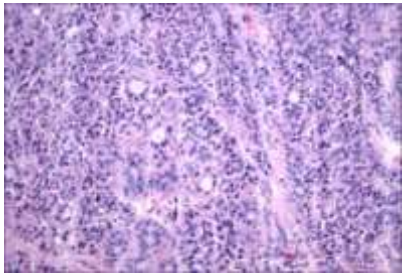


Hürthle cell



ADVANCES IN DTC

- Two new drugs for systemic therapy in RAI-refractory setting
  - SORAFENIB (FDA & EMA approval)
  - LENVATINIB (FDA & EMA submitted)
- Targeting MAPK pathway in DTC
  - BRAF inhibitors
  - Redifferentiation with MAPK inhibitors

DECISION: Study Design

417 patients randomized from November 2009 to August 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

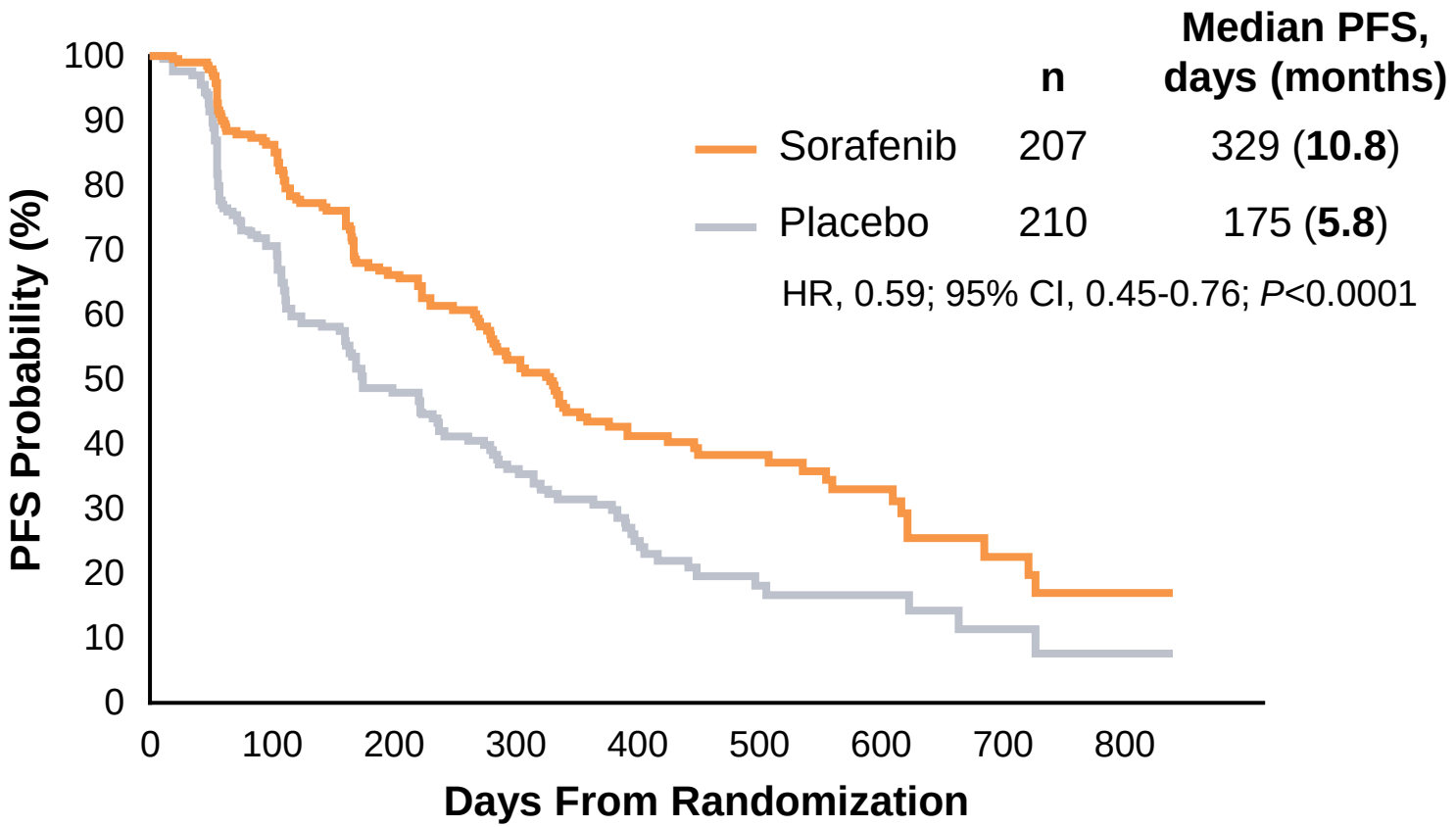
Primary endpoint
- Progression-free survival

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

- **Stratified by:**
  - **Geographical region (North America or Europe or Asia)**
  - **Age (<60 or ≥60 years)**
- Progression assessed by independent central review every 8 weeks
- At progression
  - Patients on placebo allowed to cross over at the investigator's discretion
  - Patients on sorafenib allowed to continue on open-label sorafenib at the investigator's discretion

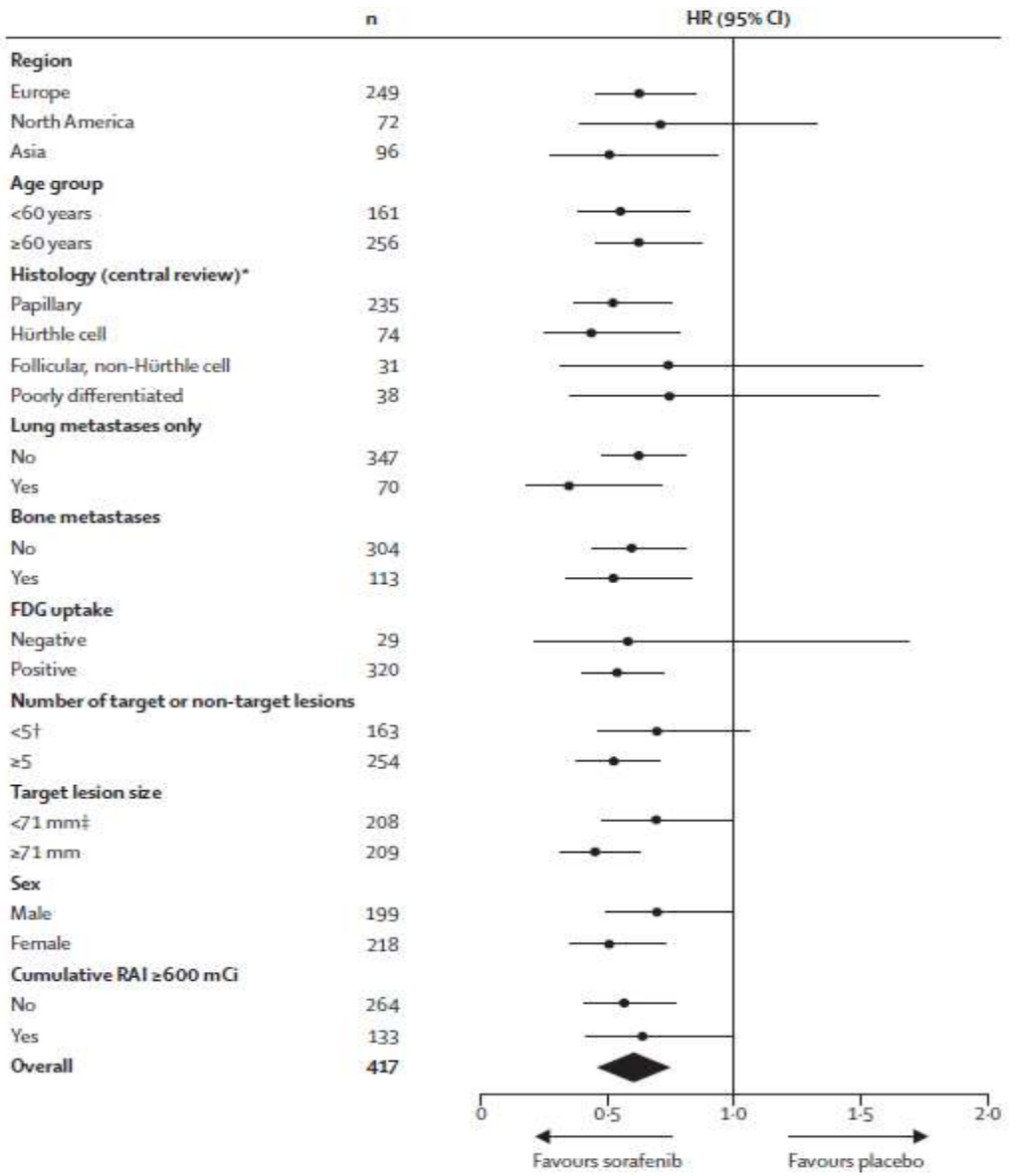
Brose M, et al. Lancet 2014

DECISION: Progression-free Survival (by Independent Central Review)



Brose M, et al. Lancet 2014

DECISION: PFS in Predefined Subgroups



Brose M, et al. Lancet 2014

Vall d'Hebron Hospital

DECISION: 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 (PRs) months (range)	10.2 (7.4-16.6)	NA	—

Brose M, et al. Lancet 2014

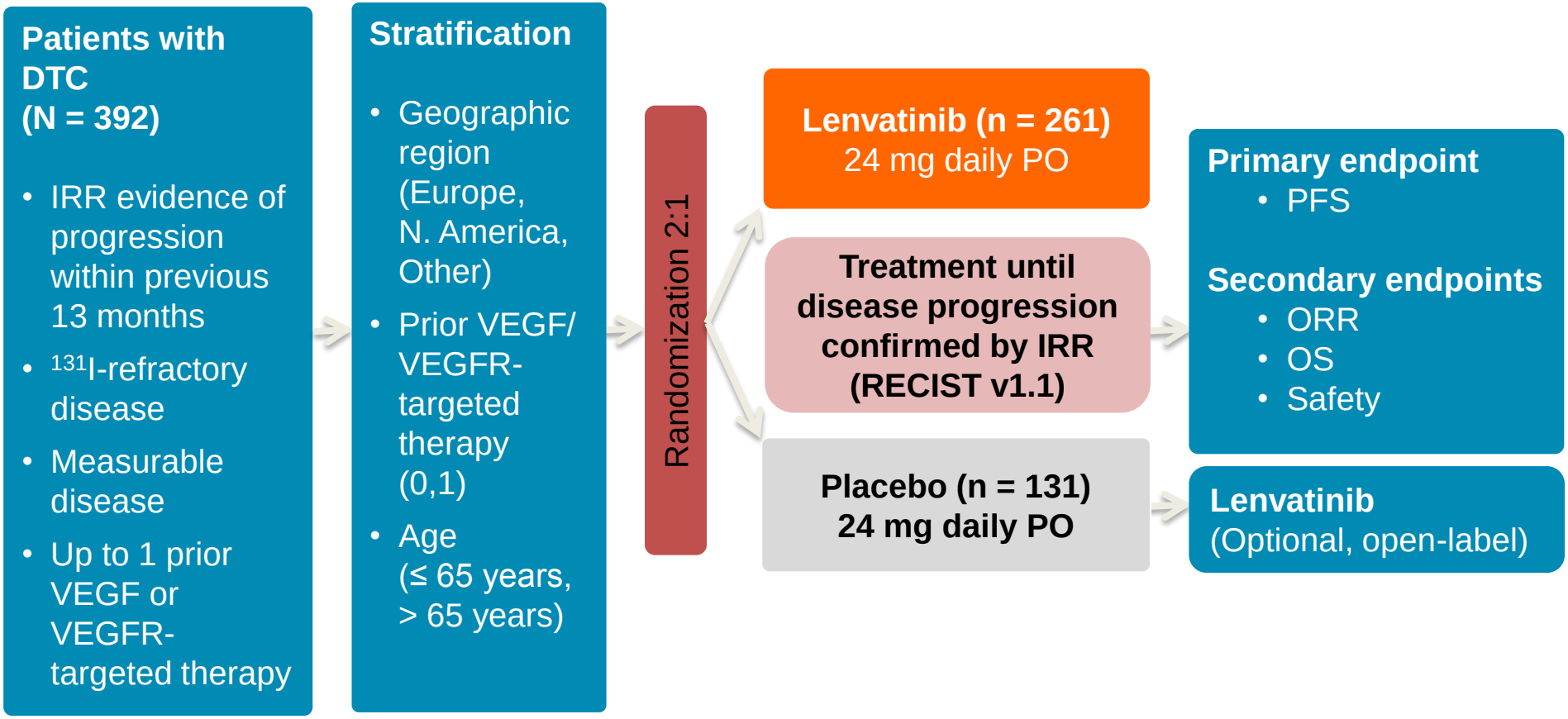
DECISION: Most Common TEAEs

AE*, %	Sorafenib (n = 207)		Placebo (n = 209)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hand-foot skin reaction	76.3	20.3	9.6	0
Diarrhea	68.6	5.8	15.3	1.0
Alopecia	67.1	0	7.7	0
Rash/desquamation	50.2	4.8	11.5	0
Fatigue	49.8	5.8	25.4	1.4
Weight loss	46.9	5.8	13.9	1.0
Hypertension	40.6	9.7	12.4	2.4
Metabolic – lab (other)†	35.7	0	16.7	0
Serum TSH increase†	33.3	0	13.4	0
Anorexia	31.9	2.4	4.8	0
Oral mucositis	23.2	1.0	3.3	0
Pruritus	21.3	1.0	10.5	0
Nausea	20.8	0	11.5	0
Hypocalcemia	18.8	9.2	4.8	1.5

Brose M, et al. Lancet 2014

Vall d'Hebron Hospital

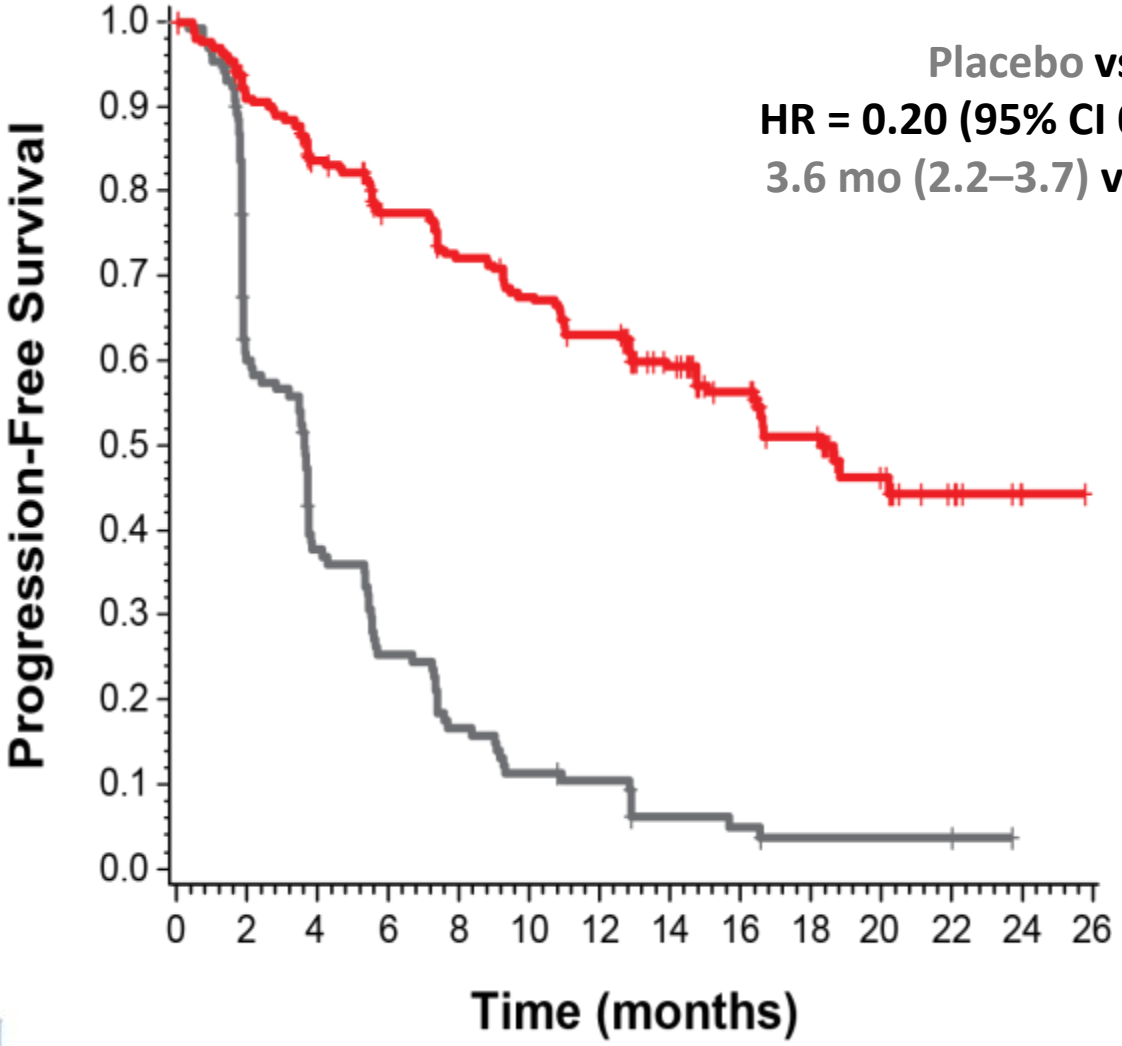
Study 303 (SELECT): Study Schema



DTC, differentiated thyroid cancer; ^{131}I, 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. ASCO 2014

Primary Endpoint: Kaplan-Meier Estimate of PFS



Placebo vs Lenvatinib

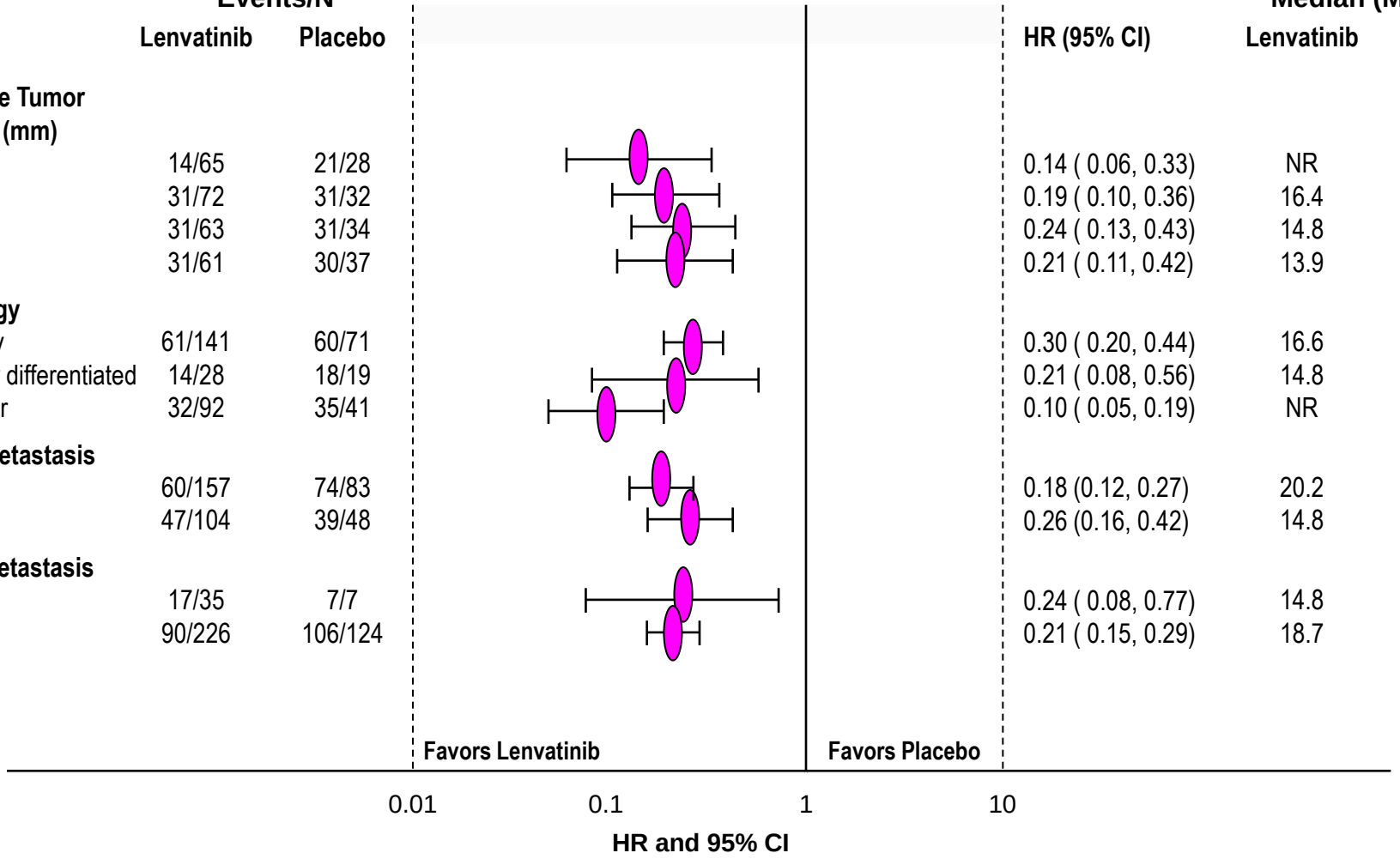
HR = 0.20 (95% CI 0.15–0.27), *P* < 0.001

3.6 mo (2.2–3.7) vs 18.3 mo (15.1–NA)

Schlumberger M, et al. ASCO 2014

PFS Subgroup Analyses

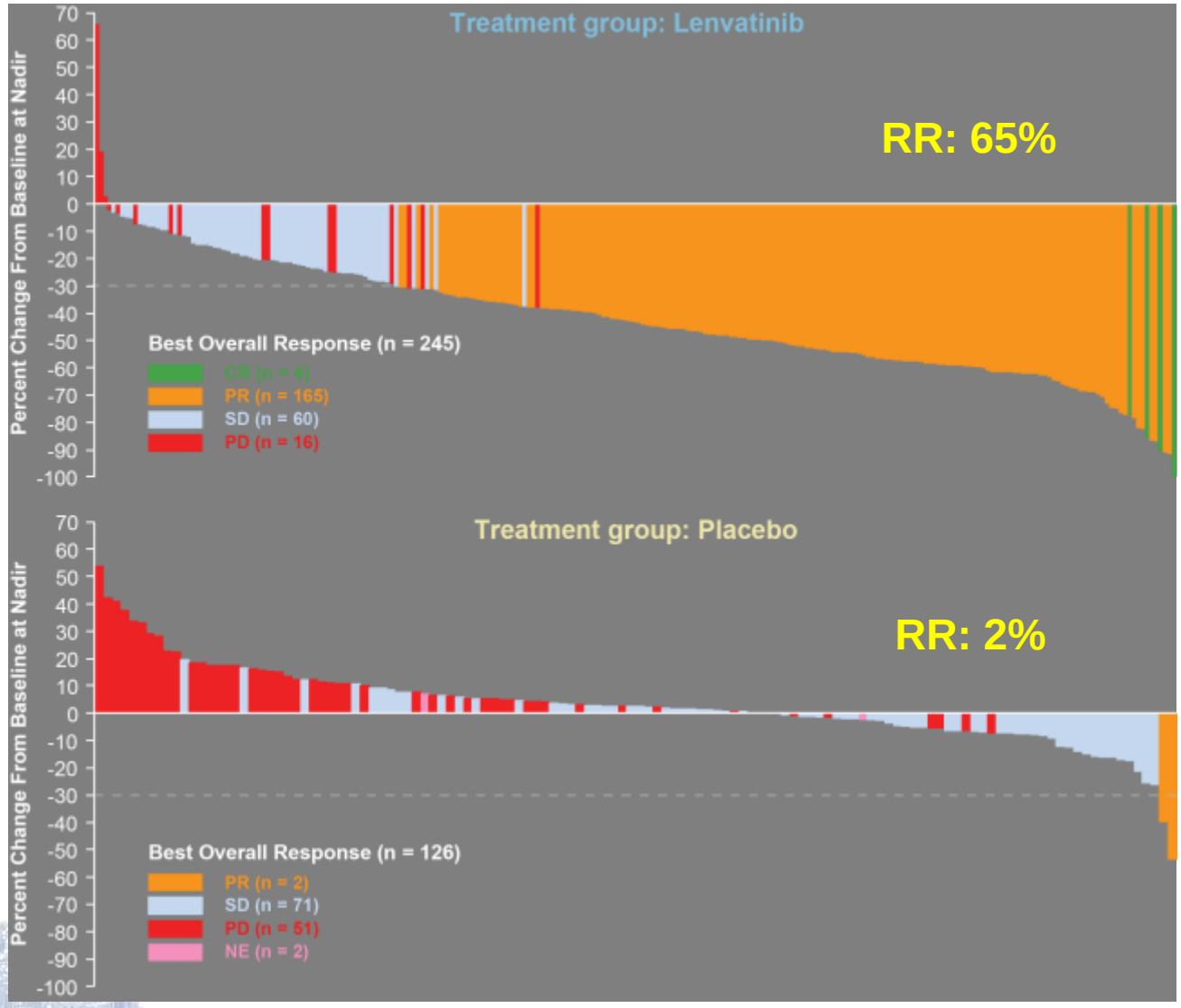
	Events/N			Median (Months)	
	Lenvatinib	Placebo	HR (95% CI)	Lenvatinib	Placebo
Baseline Tumor Burden (mm)					
≤35	14/65	21/28	0.14 (0.06, 0.33)	NR	5.6
35−60	31/72	31/32	0.19 (0.10, 0.36)	16.4	3.7
60−92	31/63	31/34	0.24 (0.13, 0.43)	14.8	3.6
>92	31/61	30/37	0.21 (0.11, 0.42)	13.9	2.4
Histology					
Papillary	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. ASCO 2014

Best Tumor Response



Median tumor shrinkage for <u>responders</u> (range): -52% (-100%, -30%)

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

Schlumberger M, et al. ASCO 2014

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

Adverse Event, %	Lenvatinib (n = 261)		Placebo (n = 131)	
	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

6/20 lenvatinib treatment-emergent deaths were considered by investigator as treatment-related:

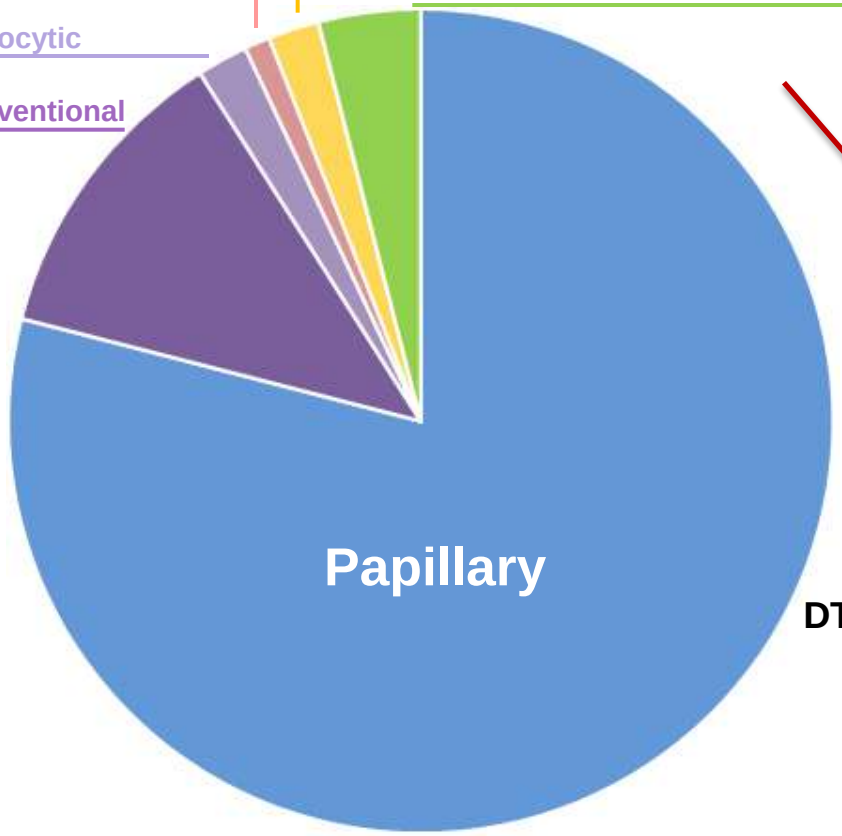
Pulmonary embolism (n = 1)
Hemorrhagic stroke (n = 1)
General health deterioration (n = 4)

Schlumberger M, et al. ASCO 2014

Genetics of Thyroid Cancer

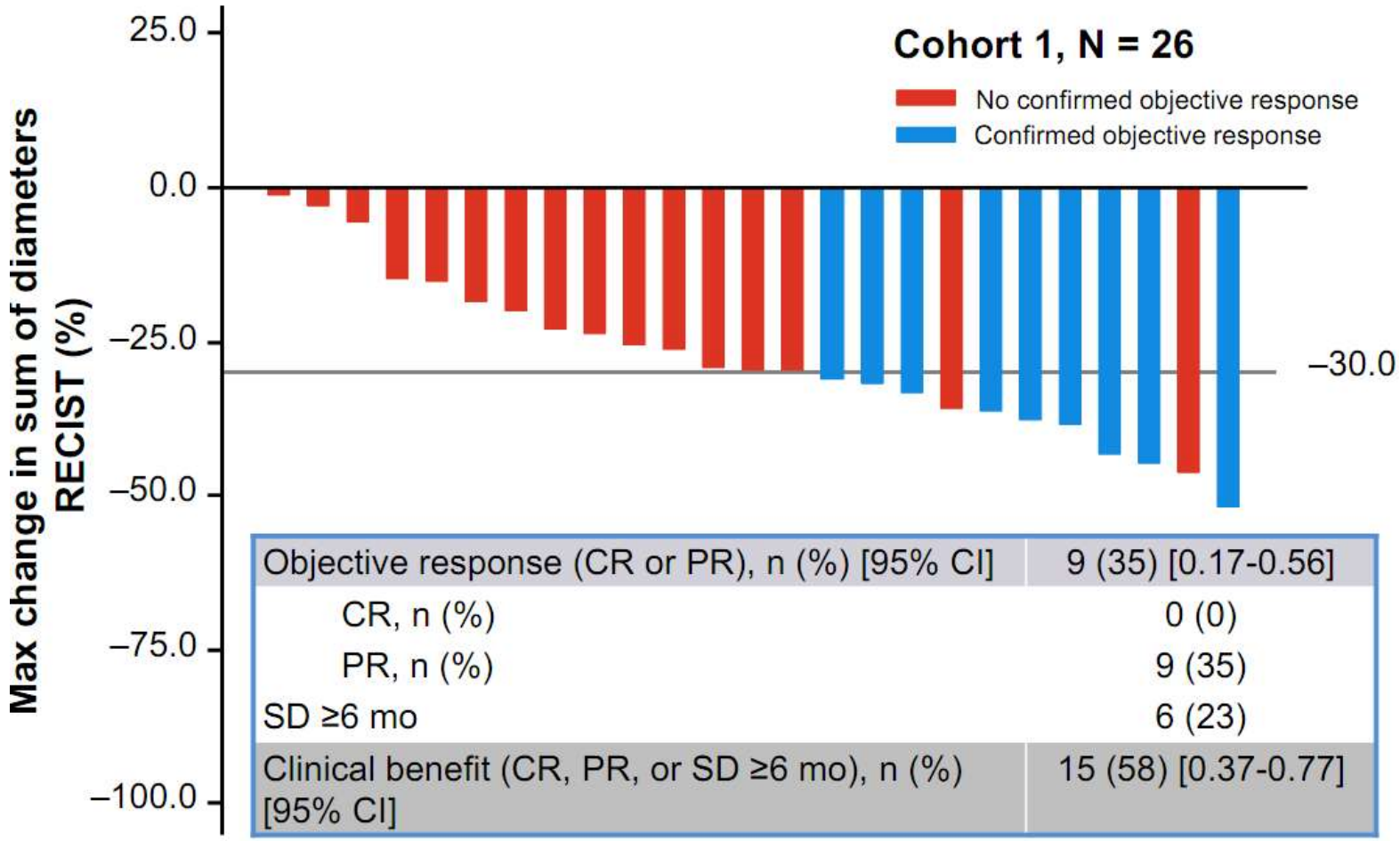
Poorly differentiated
- ***RAS* (25–30%)**
- *TP53* (20–30%)
- *CTNNB1* (10–20%)
- ***BRAF* (10–15%)**

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%)

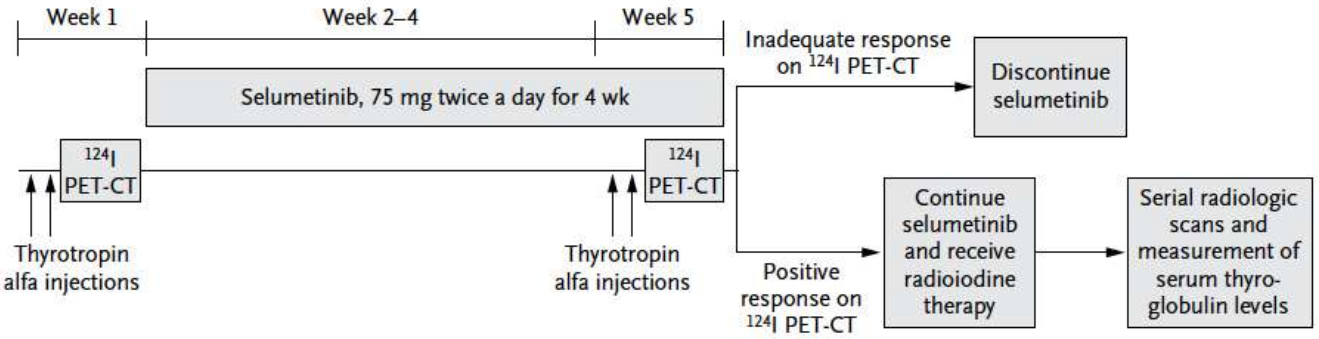
BRAF Inhibition in BRAF mutant DTC

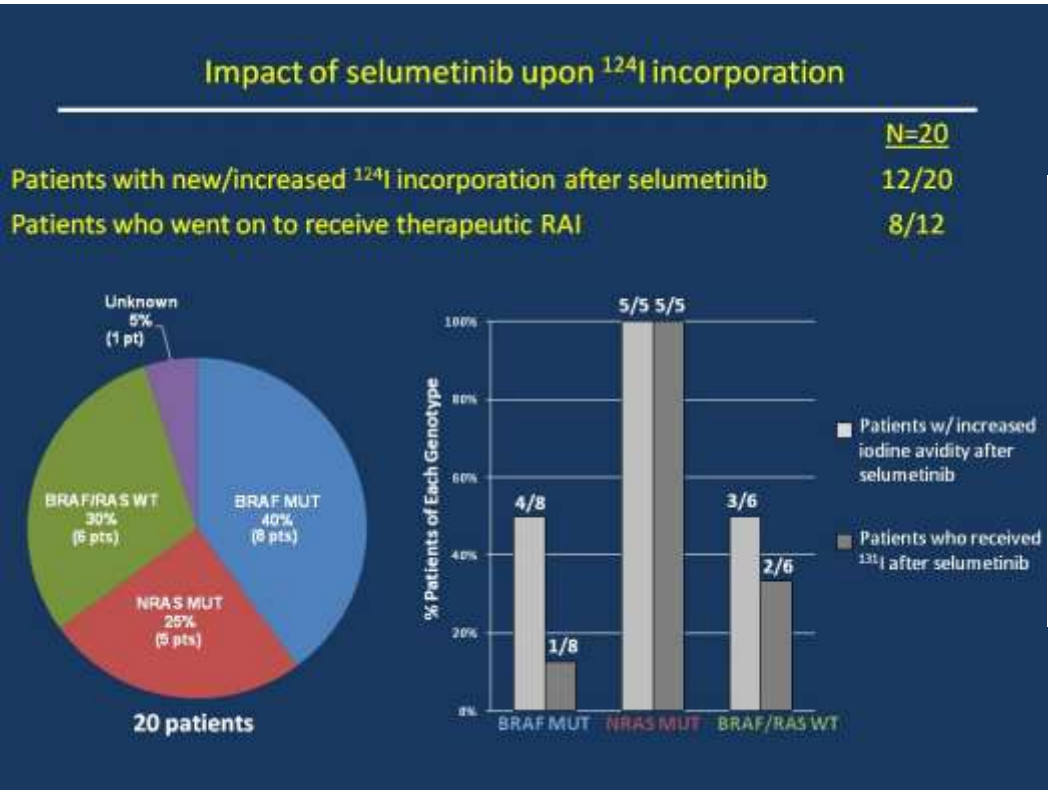


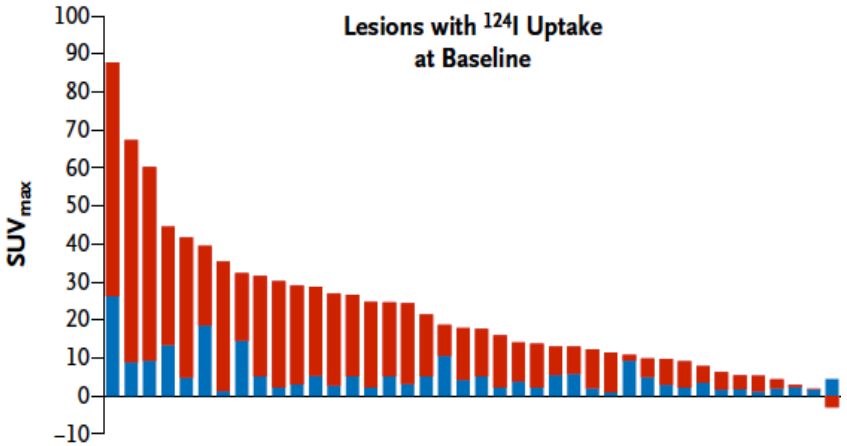
Objective response (CR or PR), n (%) [95% CI]	9 (35) [0.17-0.56]
CR, n (%)	0 (0)
PR, n (%)	9 (35)
SD ≥6 mo	6 (23)
Clinical benefit (CR, PR, or SD ≥6 mo), n (%) [95% CI]	15 (58) [0.37-0.77]

Brose M, et al. ESMO 2013

MAPK Inhibition "Resensitizes" DTC

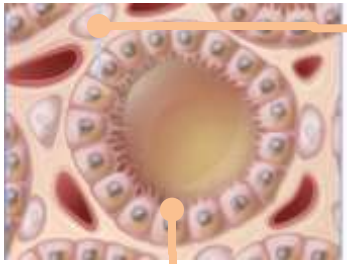






Ho AL, et al. N Engl J Med 2013

THYROID CANCER: CELL TYPE AND HISTOLOGY



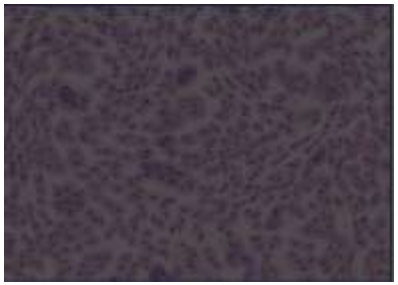
Parafollicular cells

(3-5%)

Medullary thyroid carcinoma (MTC)

Follicular cells (90-95%)

Anaplastic

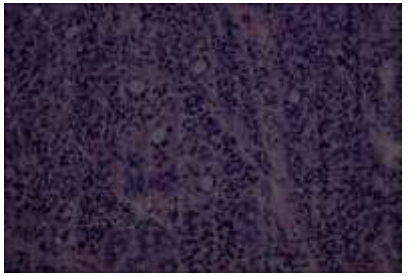


Differentiated

Papillary

Follicular

Hürthle cell



ADVANCES IN MTC

- Two new drugs for systemic therapy in advanced MTC
  - VANDETANIB (FDA & EMA approval)
  - CABOZANTINIB (FDA & EMA approval)

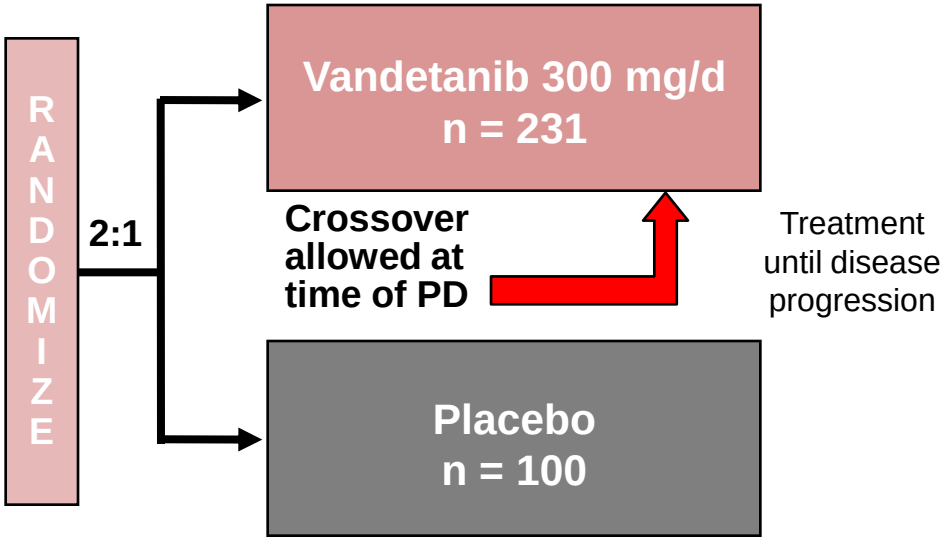
Vandetanib Pivotal Phase III Trial: The ZETA Study

Patients with locally advanced or metastatic MTC, N=331

- RET mutation positive or negative
- Prior antitumour therapy allowed
- WHO PS ≤2

Stratified by:

- RET mutation status
- Hereditary vs Sporadic
- Previous calcitonin and CEA
- Prior therapies
- Response to prior therapies



Multiphasic CT or MRI performed every 12 weeks

Primary Endpoint:

- PFS

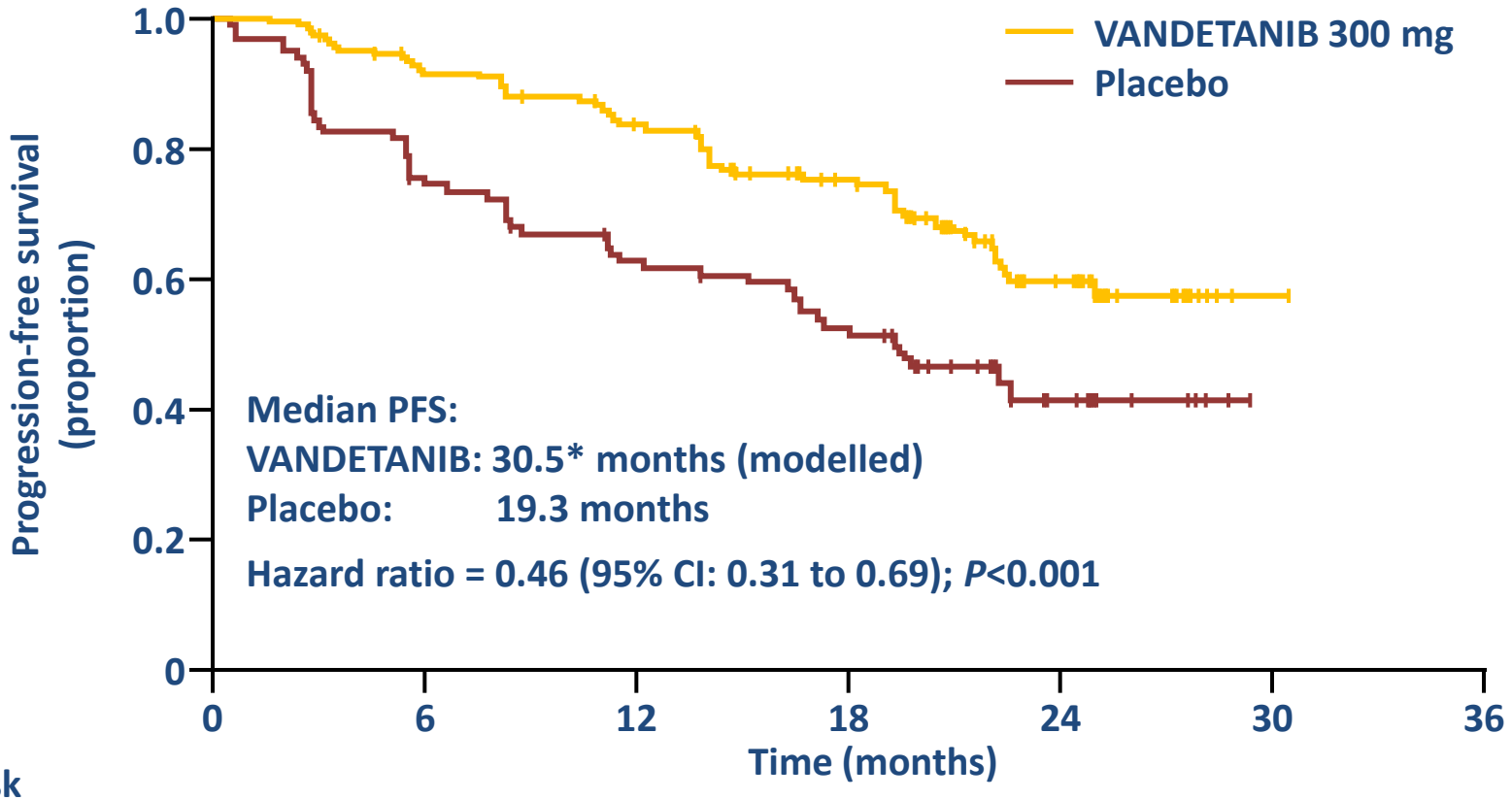
Secondary Endpoints:

- OS
- ORR
- DCR
- Biochemical response (calcitonin/CEA)
- Time to worsening of pain

Randomization: December 2006 to November 2007

Wells SA, et al. J Clin Oncol 2012

Vandetanib Significantly Prolonged PFS vs Placebo

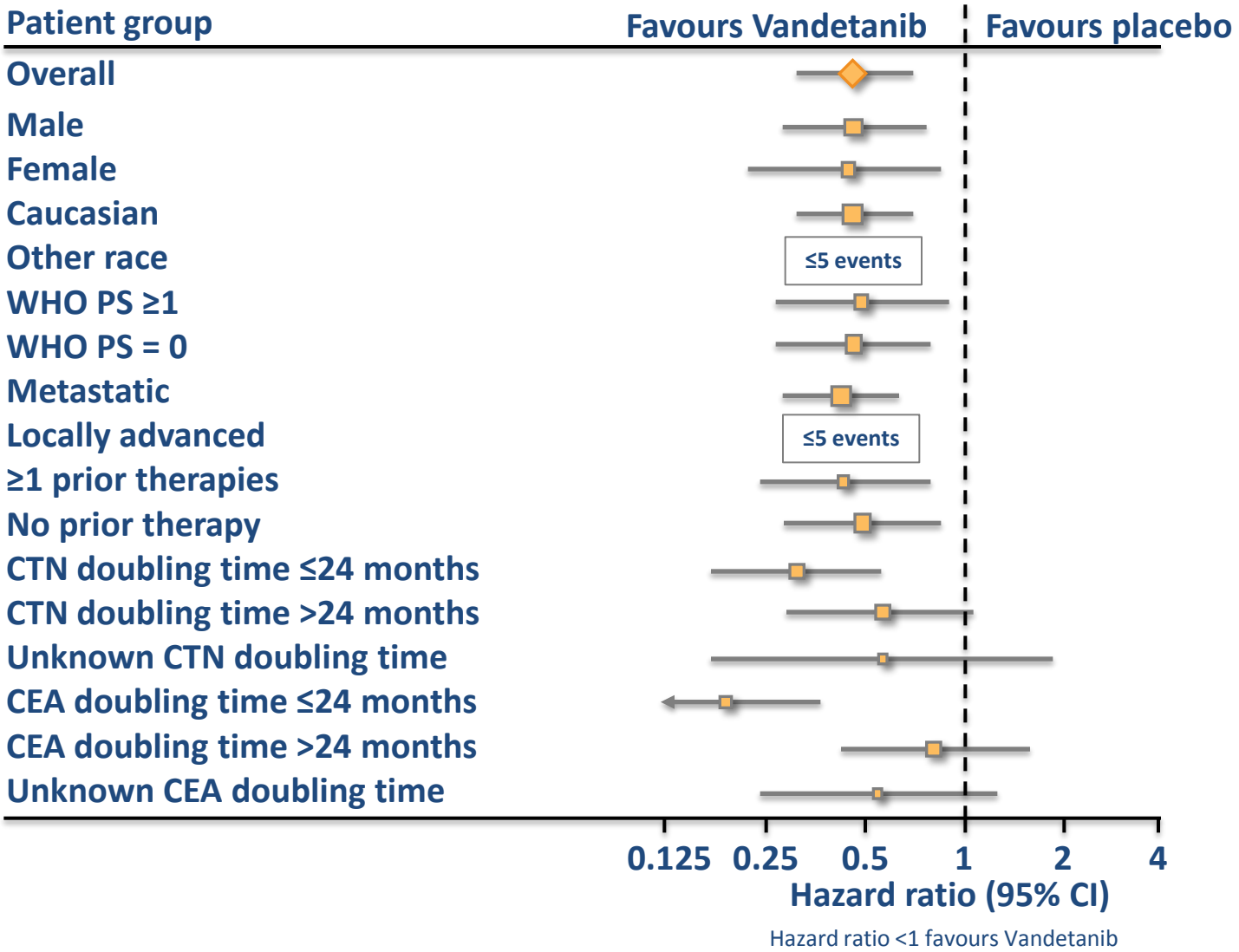


Number at risk							
VANDETANIB 300 mg	231	196	169	140	40	1	0
Placebo	100	71	57	45	13	0	0

*Not yet reached; predicted using a Weibull model. Weibull W. *J Appl Mech Trans* 1951;18:293–297

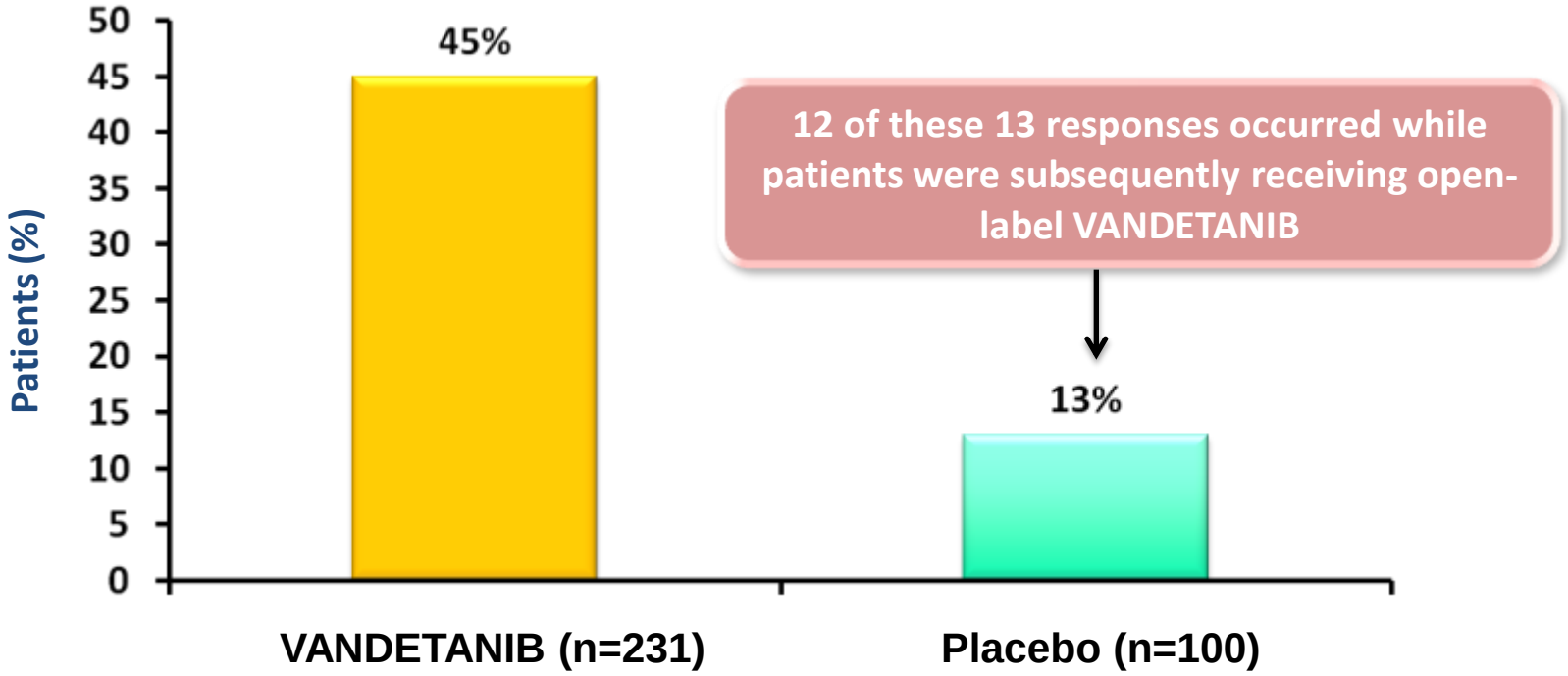
Wells SA, et al. J Clin Oncol 2012

PFS Subgroup Analyses



Wells SA, et al. J Clin Oncol 2012

Vandetanib Significantly Increased Objective Response Rate Versus Placebo



- **Odds ratio = 5.48 (95% CI: 2.99 to 10.79); *P*<0.001**
- **All responses were partial**
- **Responses were durable in patients receiving Vandetanib**
  - **Median duration of response had not been reached after 24 months of follow-up**

Wells SA, et al. J Clin Oncol 2012

AES of Any Grade (Incidence ≥10%)

AE	VANDETANIB 300 mg (n=231)	Placebo (n=99)
Diarrhoea	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%)

AE	VANDETANIB 300 mg (n=231)	Placebo (n=99)
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%)

*As reported by the investigator; defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3

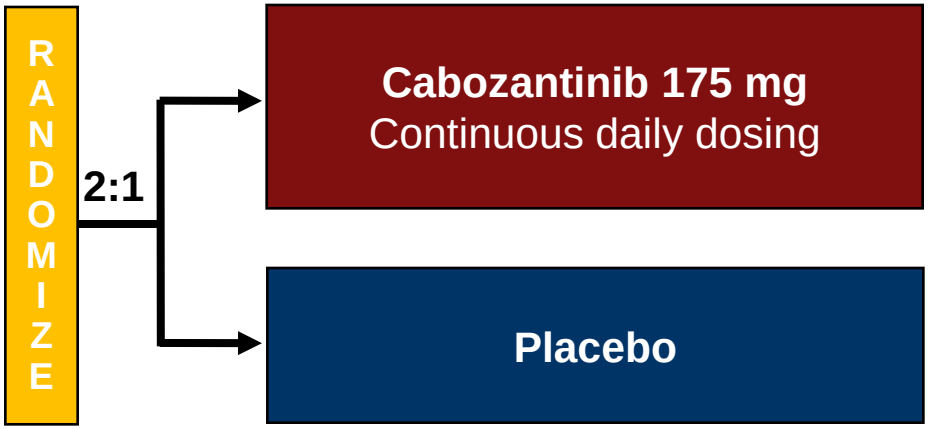
Wells SA, et al. J Clin Oncol 2012

Cabozantinib: EXAM Phase III Study

- Phase III randomized, placebo-controlled, double-blind trial

Locally advanced or metastatic MTC patients (n=315)

- Disease progression in past 14 months
- Not amenable to curative treatment
- One previous therapy with VEGFR inh allowed
- WHO PS ≤2



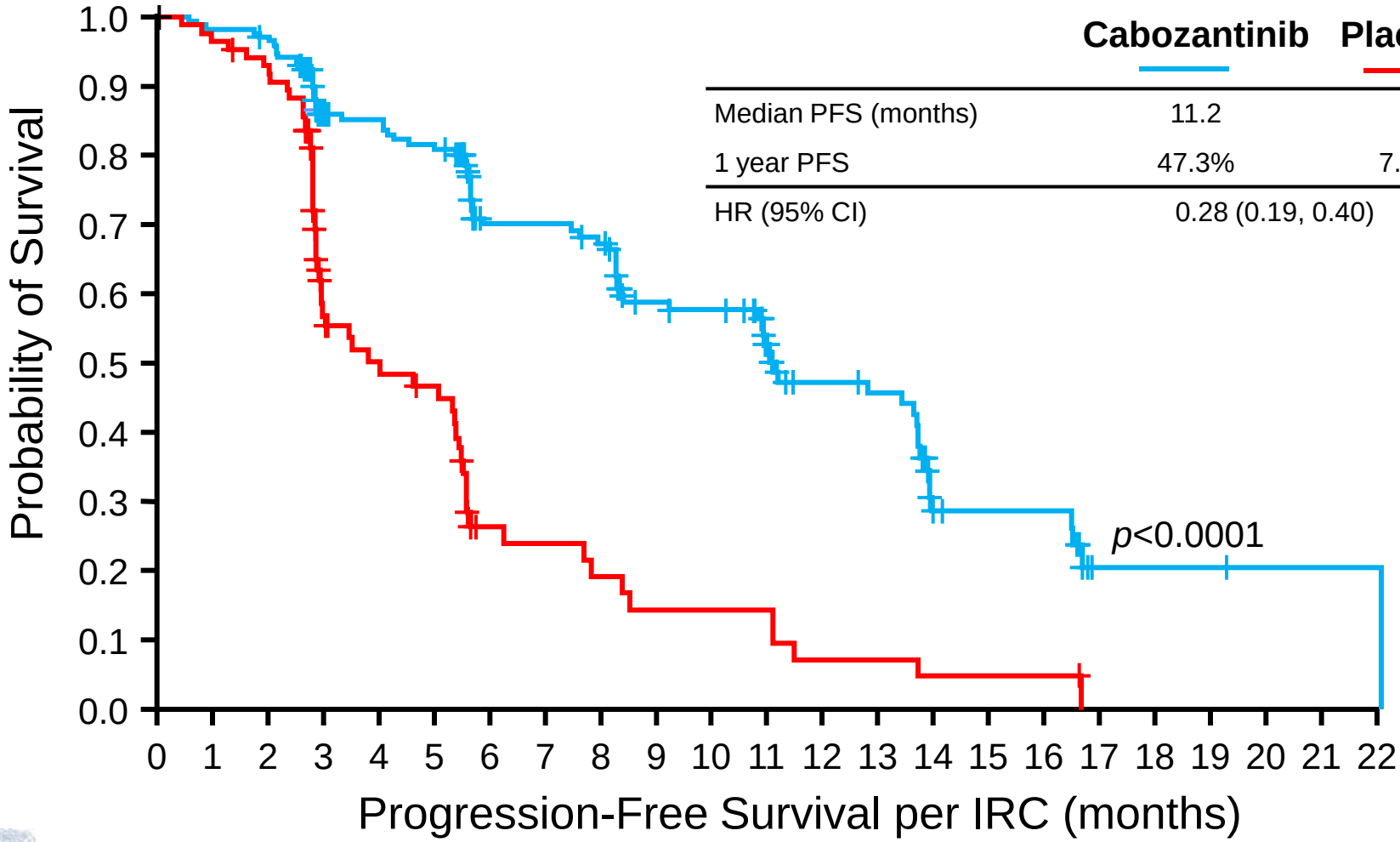
Primary Endpoint
- PFS

Secondary Endpoints
- OS
- ORR
- TTR
- Safety
- PK and PD data

* Recruitment completed in January 2011

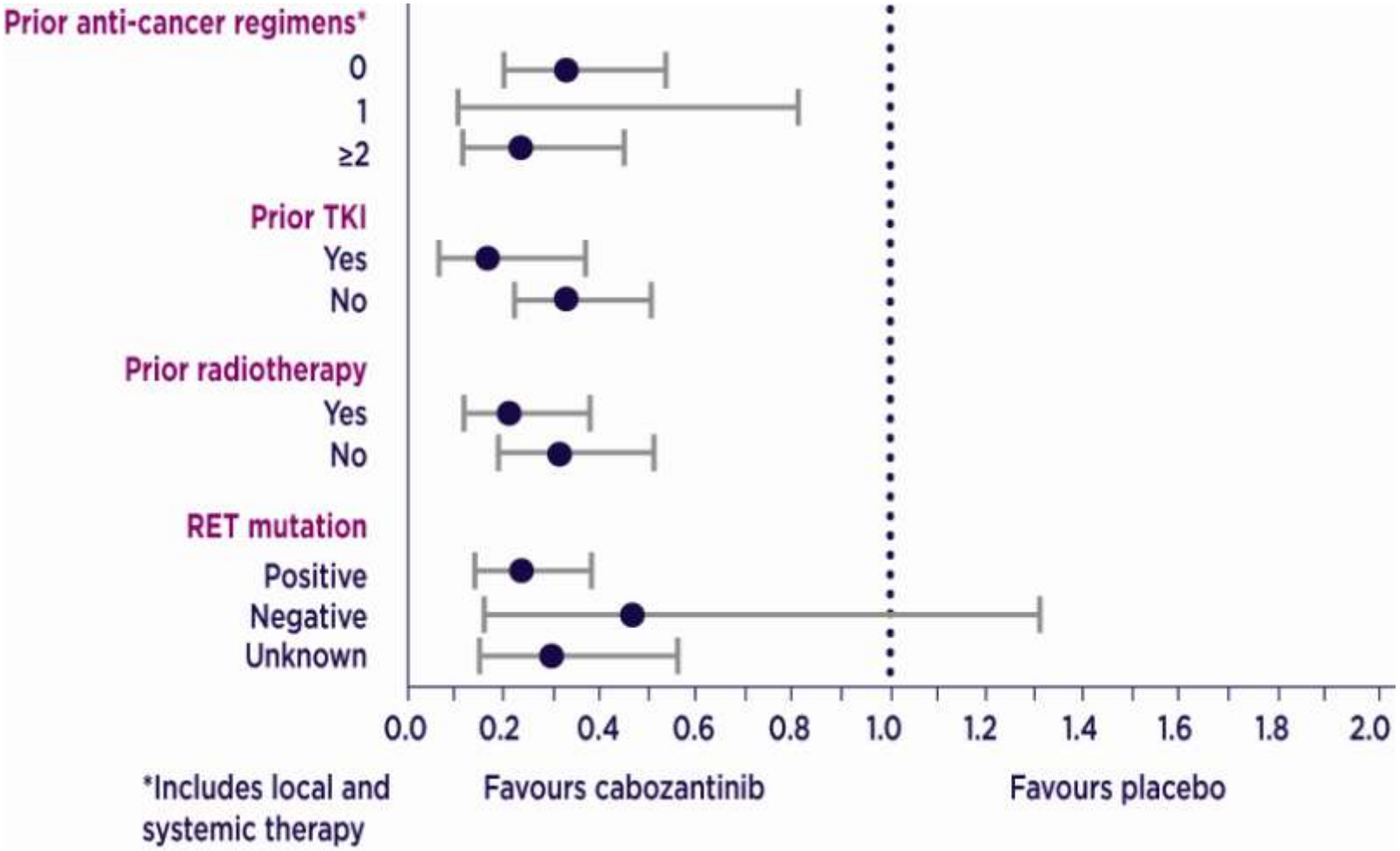
Elisei R, et al. J Clin Oncol 2013

EXAM: Progression-free Survival by IRC (Primary Endpoint)



Elisei R, et al. J Clin Oncol 2013

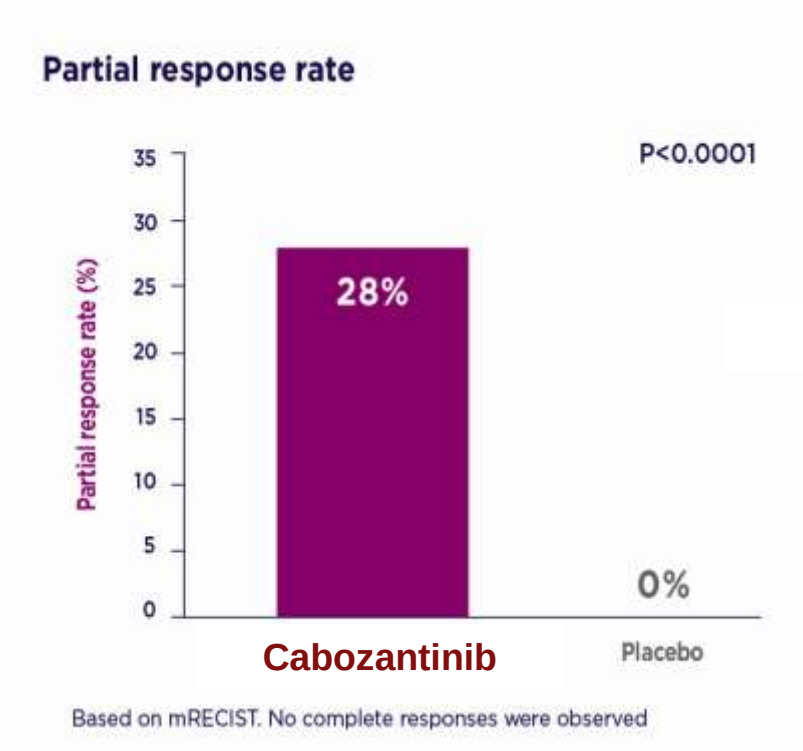
PFS Subgroup Analyses

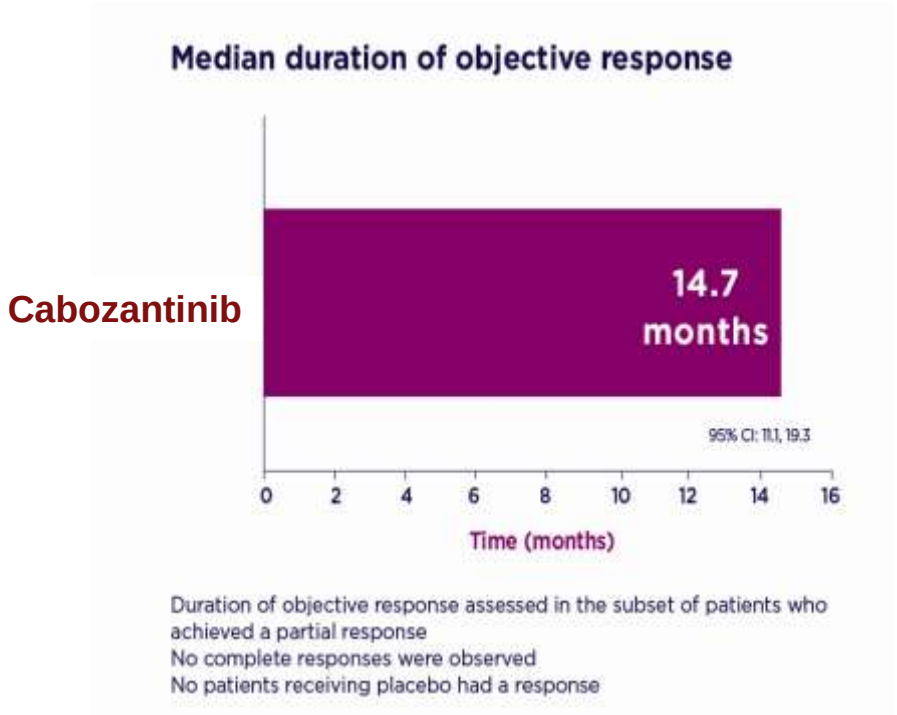


Elisei R, et al. J Clin Oncol 2013

Tumor Response Rate

- **Cabozantinib demonstrated a tumor response rate of 28% with a duration of 14.7 months in patients with progressive MTC**





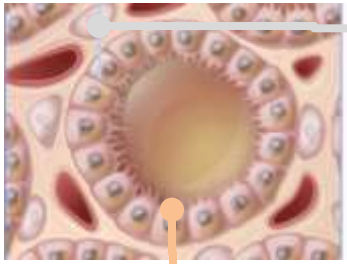
Elisei R, et al. J Clin Oncol 2013

Adverse Events > 25% Incidence

	All Grades n (%)		Grades 3-4 n (%)	
	Cabozantinib (n=214)	Placebo (n=109)	Cabozantinib (n=214)	Placebo (n=109)
Adverse event[a] (in order of decreasing frequency)				
Diarrhoea	63%	33%	16%	2%
Hand foot skin reaction	50%	2%	13%	0%
Decreased weight	48%	10%	5%	0%
Decreased appetite	46%	16%	5%	1%
Nausea	43%	21%	1%	0%
Fatigue	41%	28%	9%	3%
Dysgeusia	34%	6%	0.5%	0%
Hair colour changes	34%	1%	0.5%	0%
Hypertension[b]	33%	5%	8%	1%
Stomatitis	29%	3%	2%	0%
Constipation	27%	6%	0%	0%

Elisei R, et al. J Clin Oncol 2013

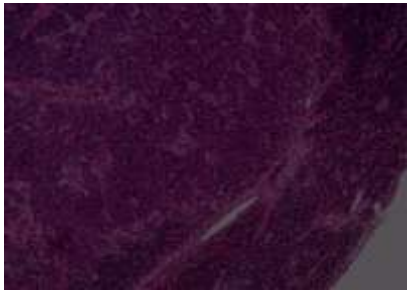
THYROID CANCER: CELL TYPE AND HISTOLOGY



Parafollicular cells

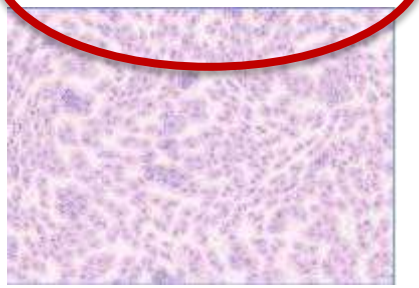
(3-5%)

Medullary thyroid carcinoma (MTC)



Follicular cells (90-95%)

Anaplastic

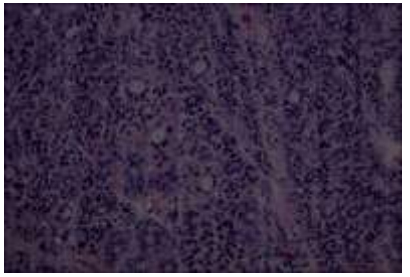


Differentiated

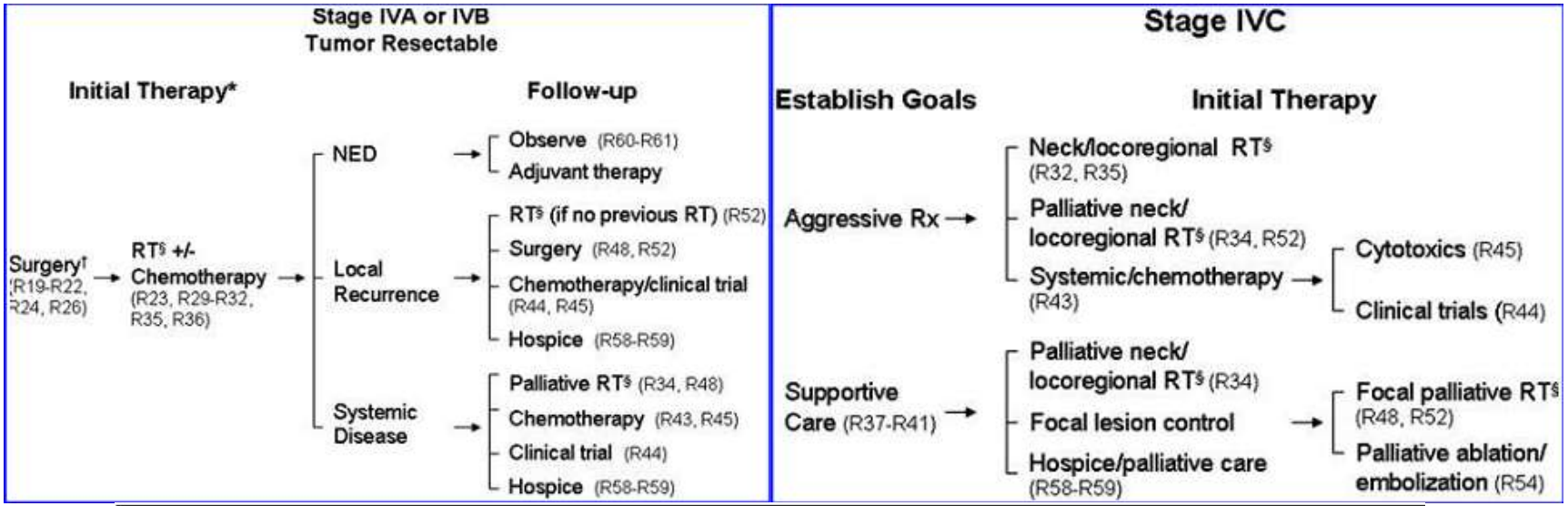
Papillary

Follicular

Hürthle cell



ANAPLASTIC THYROID CANCER



Regimen	*Agents/dosages*	*Frequency*
Paclitaxel/carboplatin	Paclitaxel 60–100 mg/m^2, carboplatin AUC 2 mg/m^2 IV	Weekly
Paclitaxel/carboplatin	Paclitaxel 135–175 mg/m^2, carboplatin AUC 5–6 mg/m^2 IV	Every 3–4 weeks
Docetaxel/doxorubicin	Docetaxel 60 mg/m^2 IV, doxorubicin 60 mg/m^2 IV (w/ pegfilgrastim) *or* Docetaxel 20 mg/m^2 IV, doxorubicin 20 mg/m^2 IV	Every 3–4 weeks Weekly
Paclitaxel	Paclitaxel 60–90 mg/m^2 IV	Weekly
Paclitaxel	Paclitaxel 135–200 mg/m^2 IV	Every 3–4 weeks
Doxorubicin	Doxorubicin 60–75 mg/m^2 IV	Every 3 weeks
Doxorubicin	Doxorubicin 20 mg/m^2 IV	Weekly

mOS: 3 months
One-year survival rates: <10%

ATA Guidelines Thyroid 2014

FACT trial: Fosbretabulin in Anaplastic Cancer of the Thyroid

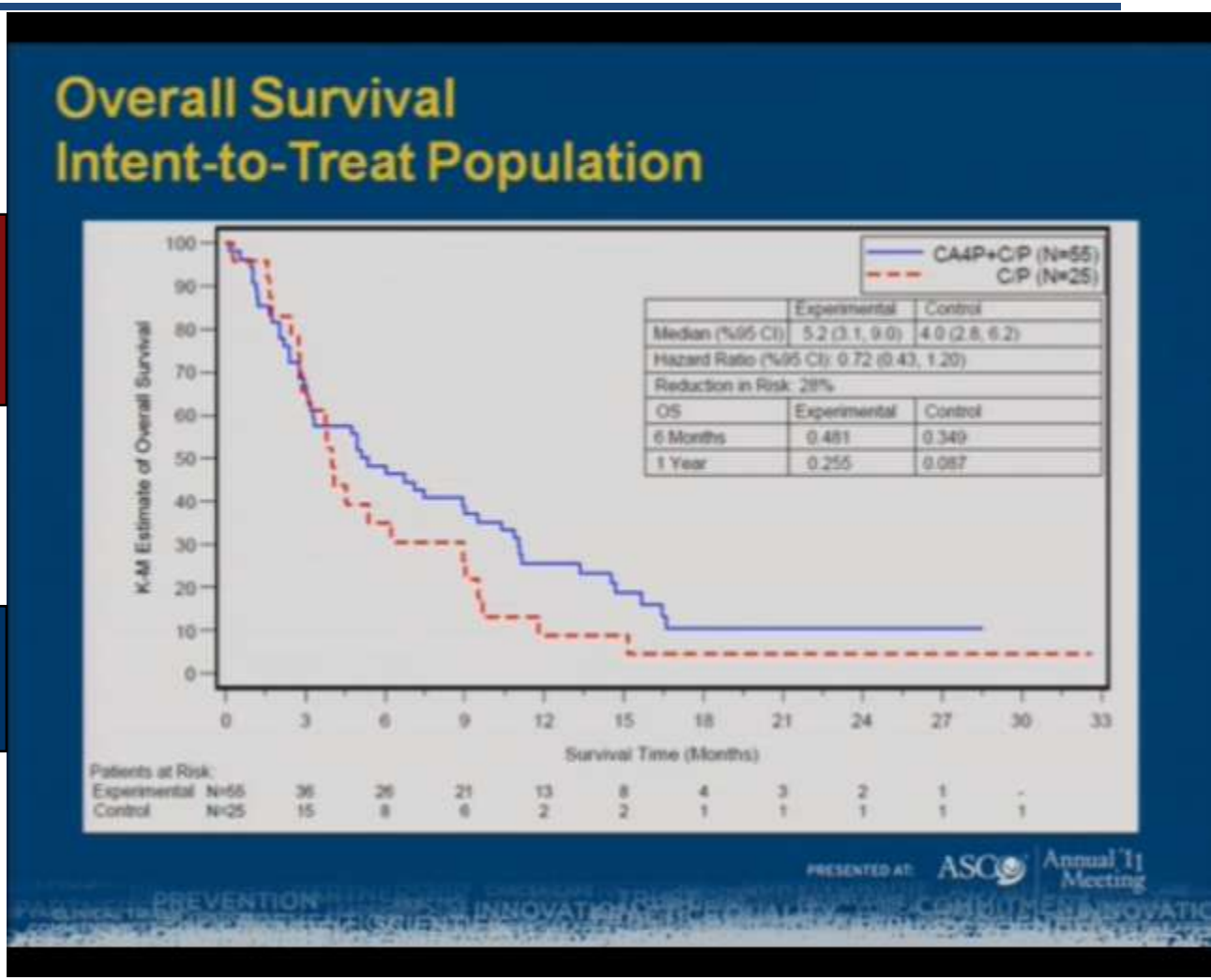
Open-label,
phase II/III Study

Paclitaxel 200 mg/m2
Carboplatin AUC 6
Fosbretabulin 60 mg/m2

RANDOMIZATION
2:1

Paclitaxel 200 mg/m2
Carboplatin AUC 6

N: 80 pts

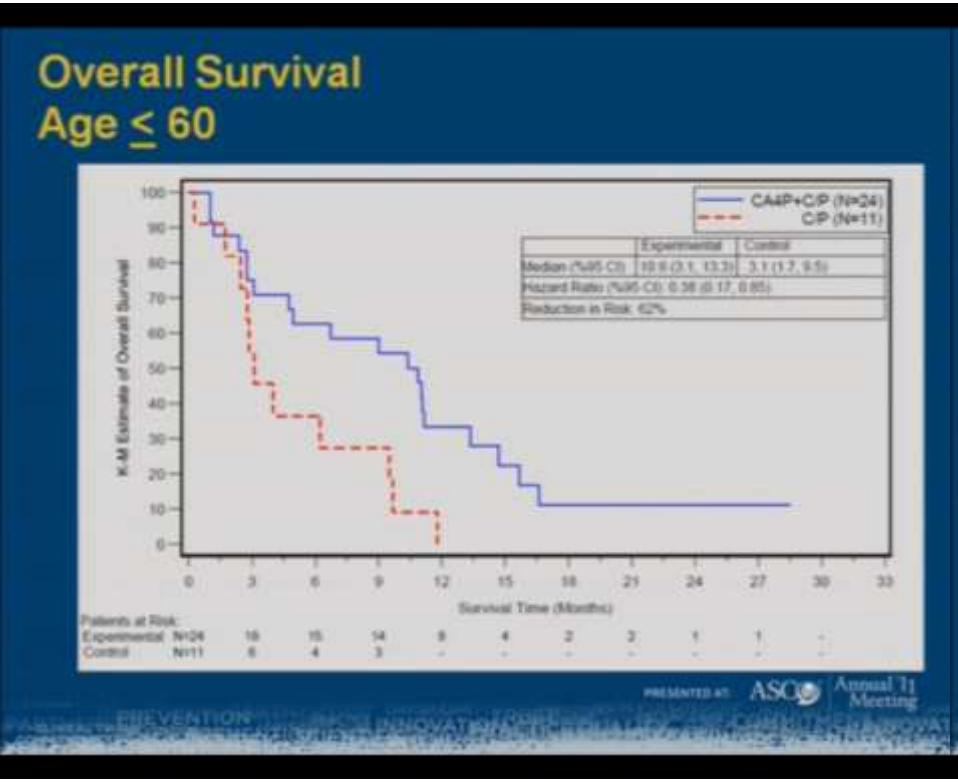


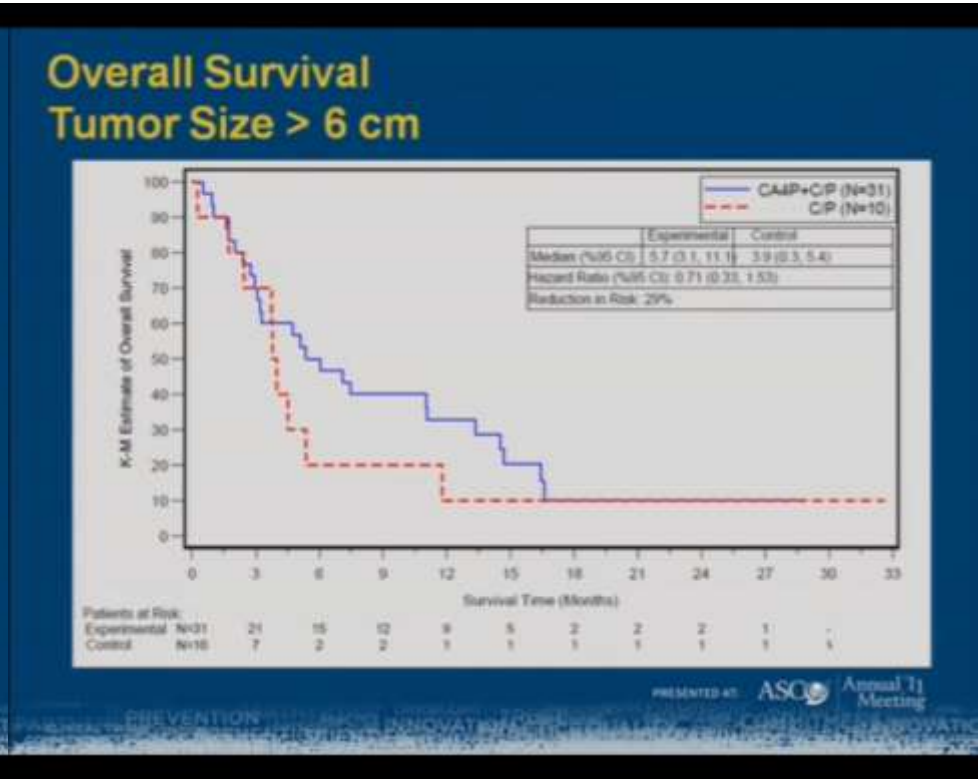
	Experimental	Control
Median (%95 CI)	5.2 (3.1, 9.0)	4.0 (2.8, 6.2)
Hazard Ratio (%95 CI): 0.72 (0.43, 1.20)		
Reduction in Risk: 28%		
OS	Experimental	Control
6 Months	0.481	0.349
1 Year	0.255	0.087

1-y survival rate: 26% vs 9%

Sosa JA, et al. Thyroid 2014

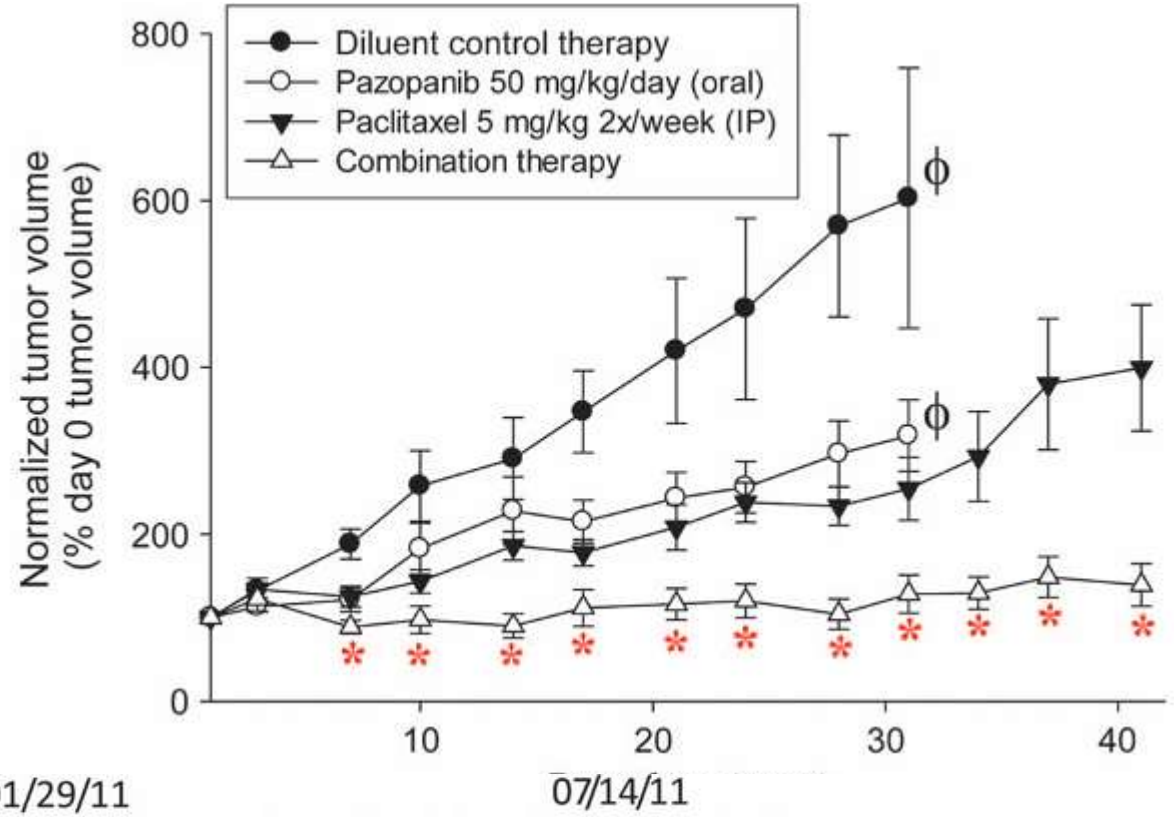
FACT trial: Fosbretabulin in Anaplastic Cancer of the Thyroid

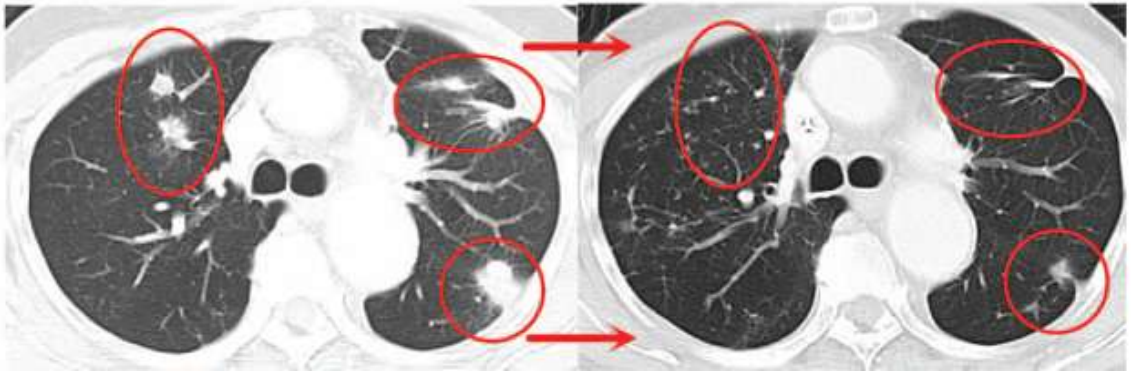




Sosa JA, et al. Thyroid 2014

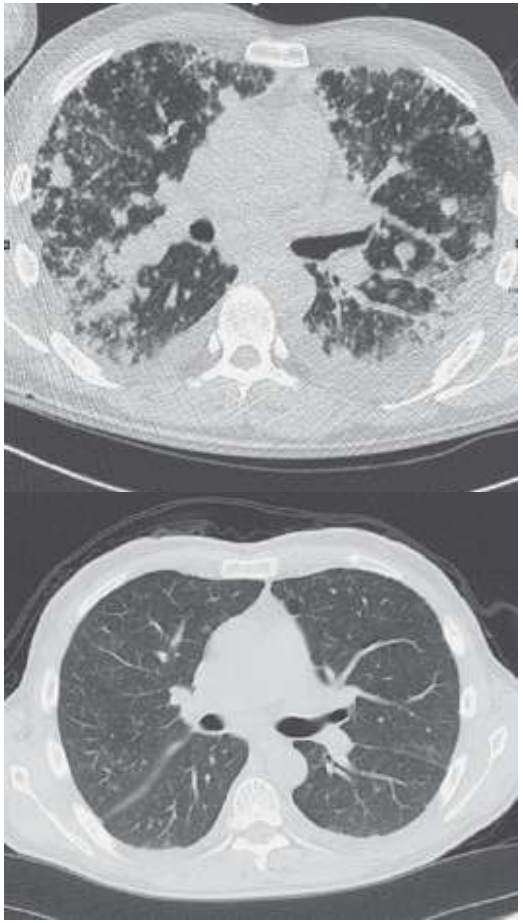
MTTs in Combination with CHT ?

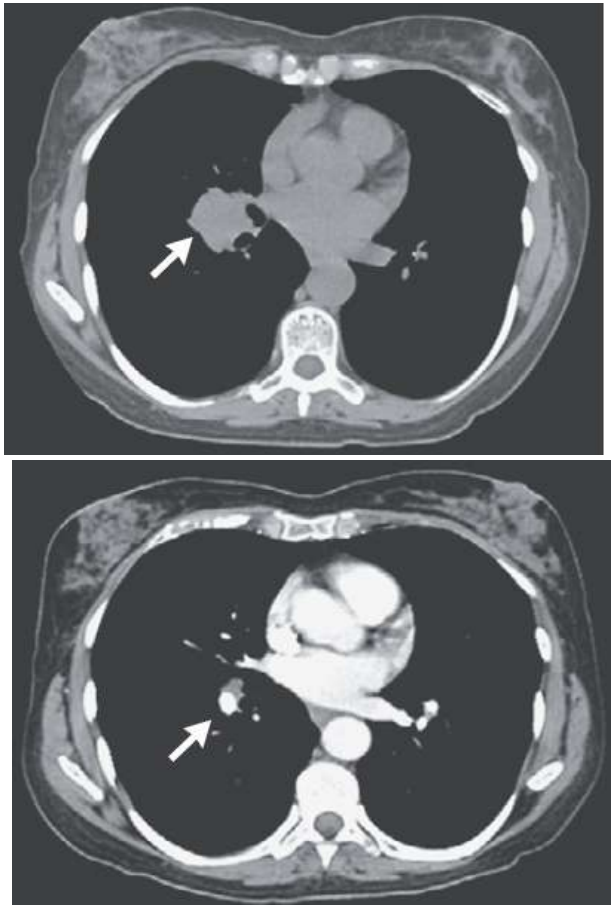


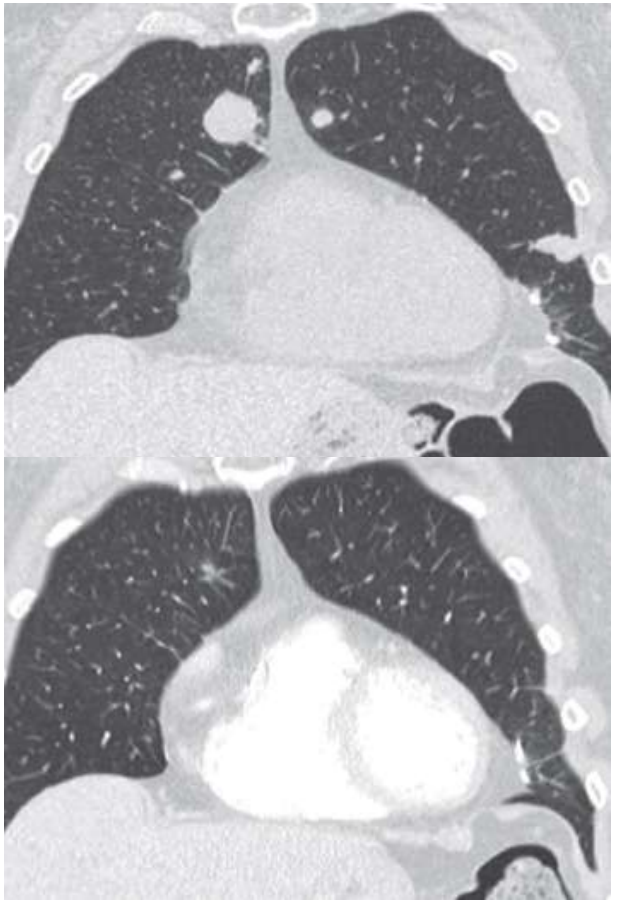


Isham CR, et al. Sci Transl Med 2013

Targeted Agents in Selected Population







V600E mutant: vemurafenib TSC2 mutant: everolimus ALK rearrangement: crizotinib

Rosove MH, et al. N Engl J Med 2013;

Wagle N et al. N Engl J Med 2014; Godberg Y, et al. J Clin Oncol 2014

Take Home Messages

- Two new drugs for systemic therapy in advanced DTC
  - SORAFENIB (FDA & EMA approval)
  - LENVATINIB (FDA & EMA submitted)
- Two new drugs for systemic therapy in advanced MTC
  - VANDETANIB (FDA & EMA approval)
  - CABOZANTINIB (FDA & EMA approval)
- Still waiting for active drugs in ATC… but promising results of personalized medicine in selected population

GRÀCIES PER LA VOSTRA ATENCIÓ

VHIO

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