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Comprehensive Analysis of Serum Biomarkers and Tumor Gene Mutations Associated With Clinical Outcomes in the Phase 3 Study of (E7080) LEnvatinib in Differentiated Cancer of the Thyroid (SELECT)

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Background

- Lenvatinib is an oral, multikinase inhibitor of the VEGFR1–3, FGFR1–4, PDGFRα, RET, and KIT signaling pathways:
  - In the phase 3 **S**tudy of (**E**7080) **LE**nvatinib in Differentiated **C**ancer of the **T**hyroid (**SELECT**) for the treatment of RR-DTC, lenvatinib significantly prolonged median PFS by 14.7 months compared with placebo (HR 0.21; 99% CI, 0.14–0.31).
- To date, there are no established prognostic or predictive biomarkers for RR-DTC or its treatments:
  - Exploratory biomarker analyses in phase 2 trials of lenvatinib in RR-DTC have identified correlations between baseline Ang2 levels and genetic alterations in tumors (*RAS/RAF* mutations*)* with patient outcome
  - Ang2 regulates angiogenesis through Tie2.
- We present the results of the biomarker analyses of the placebo-controlled phase 3 **SELECT** trial.

Ang2, angiopoietin-2; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; RR-DTC, radioiodine-refractory differentiated thyroid cancer; VEGFR, vascular endothelial growth factor receptor

Patient Demographics

Parameter	ITT Population (N = 392)	Serum Biomarker Analysis Population (n = 387)	Tumor Gene Mutation Analysis Population (n = 183)
Age, mean (range)	61.9 (21, 89)	61.9 (21, 89)	61.3 (21, 85)
Sex, n (%)			
Female	192 (49)	189 (49)	80 (44)
ECOG Performance Status			
0–1	377 (96)	372 (96)	178 (97)
2–3	15 (4)	15 (4)	5 (3)
Histology			
Follicular, all	133 (33.9)	132 (34.1)	60 (32.8)
Hürthle cell	58 (14.8)	58 (15)	25 (13.7)
Papillary, all	259 (66.1)	255 (65.9)	123 (67.2)
Poorly differentiated	47 (12)	47 (12.1)	19 (10.4)
PFS HR* (95% CI)	0.20 (0.15–0.27)	0.20 (0.15–0.26)	0.19 (0.12–0.28)
P-value	$P < 0.001$	$P < 0.001$	$P < 0.001$

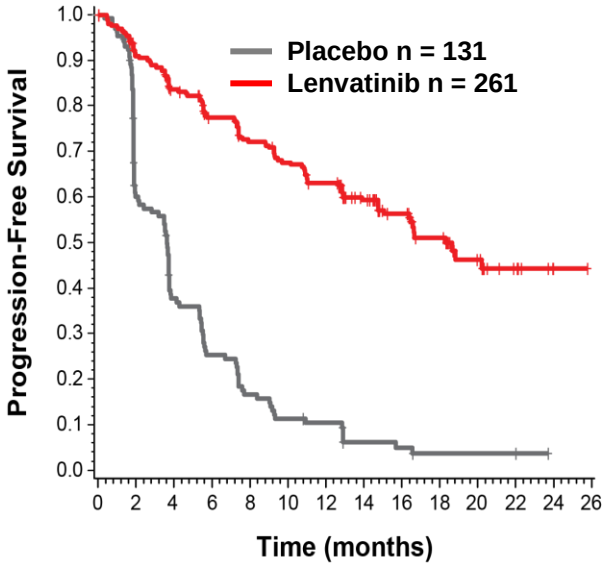
*Analyses are not stratified.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival;.

Analysis Groups and PFS

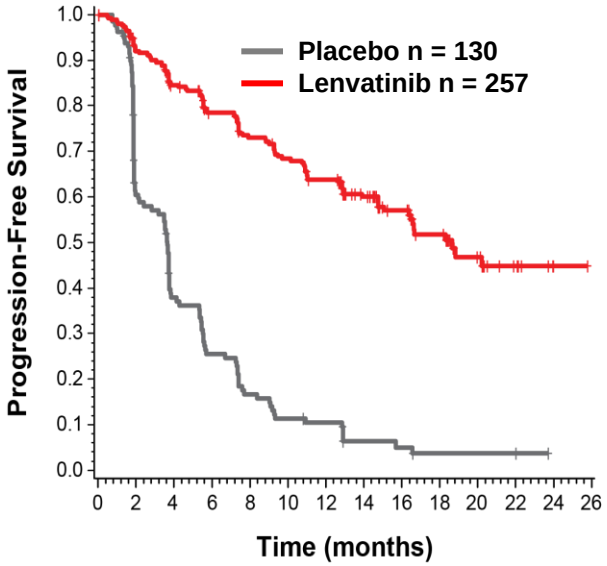
Overall

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)



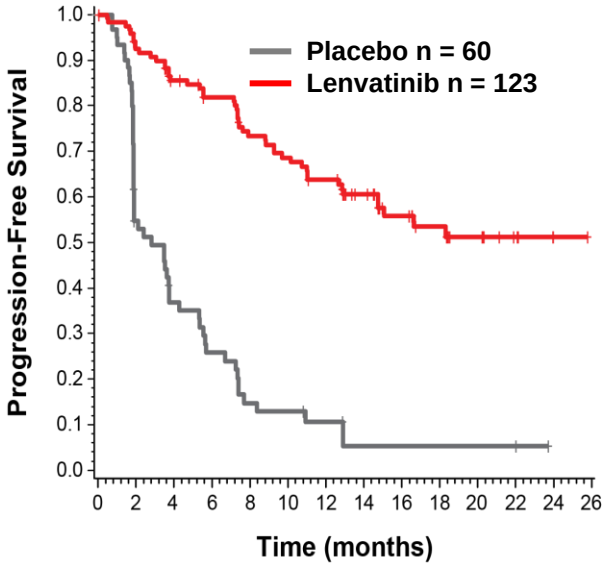
Serum biomarker

Placebo vs Lenvatinib
HR = 0.20 (95% CI 0.15–0.26), *P* < 0.001
3.6 mo (2.2–3.7) vs 18.7 mo (15.1–NA)



Tumor gene mutation

Placebo vs Lenvatinib
HR = 0.19 (0.12–0.28), *P* < 0.001
2.8 mo (1.9–3.7) vs NA (14.8–NA)



• PFS HRs (95% CI) in all groups were similar.

mo, months; NA, not available.

TUMOR MUTATIONS/ GENETIC BIOMARKERS

Genetic Biomarker Analysis in SELECT

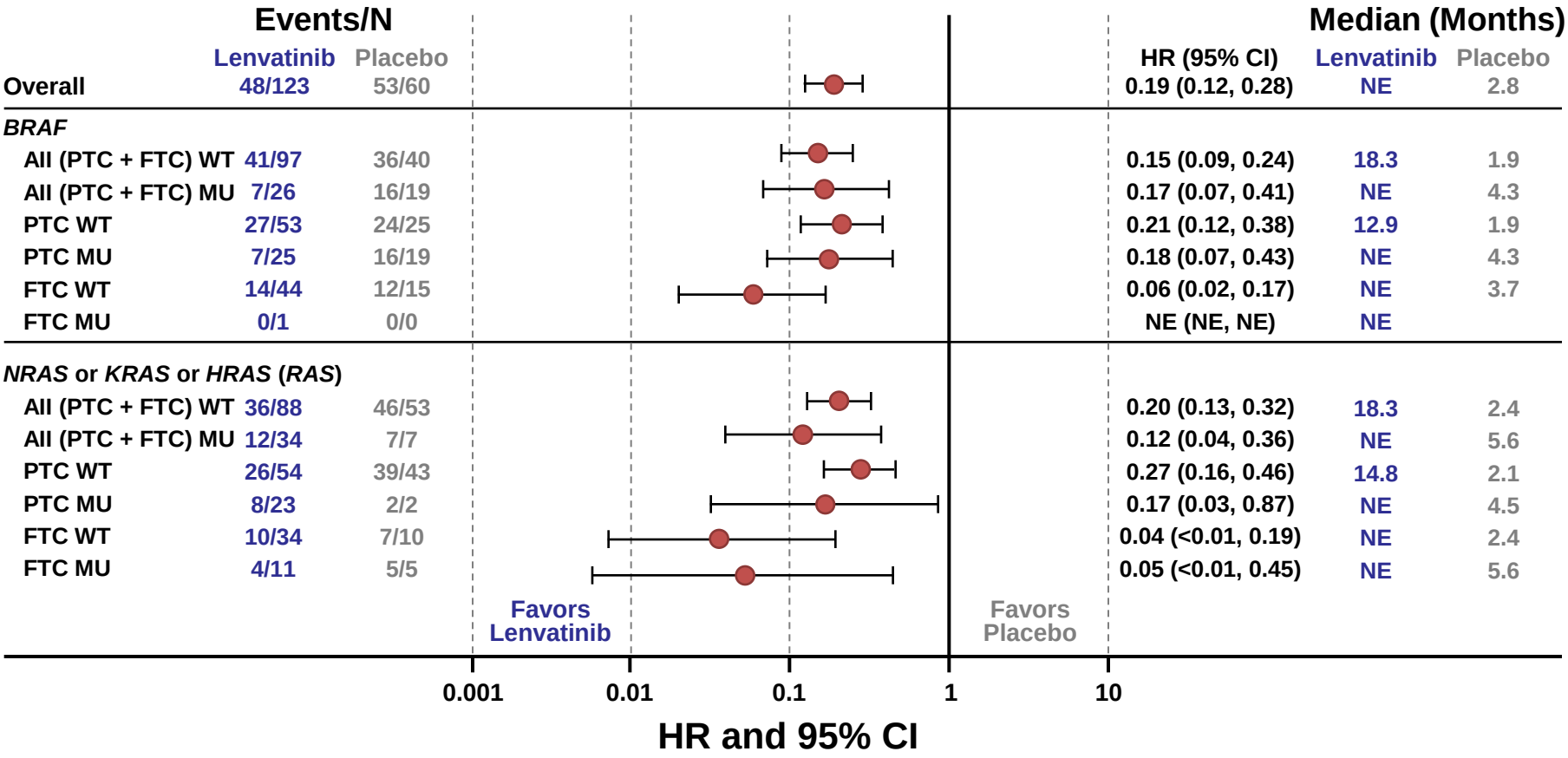
- Archival tumor tissues were obtained from 220 patients.
- 183 Samples were analyzed by amplicon sequencing by Ion Torrent PGM for:
  - *BRAF*: V600
  - *NRAS/KRAS/HRAS*: G12, G13, Q61
  - Mutation call criteria: > 500x coverage, > 5% frequency.

Gene	Cohort	All		Tumor Gene Mutation			
		Total	NA	n	WT	MU	Mutation (%)
RAS	All	392	210	182*	141	41	22.5
	Lenvatinib	261	139	122	88	34	27.9
	Placebo	131	71	60	53	7	11.7
BRAF	All	392	210	182*	137	45	24.7
	Lenvatinib	261	138	123	97	26	21.1
	Placebo	131	72	59	40	19	32.2

*1 Sample had no call.

MU, mutant; WT, wild type.

PFS Analysis: Tumor Mutations

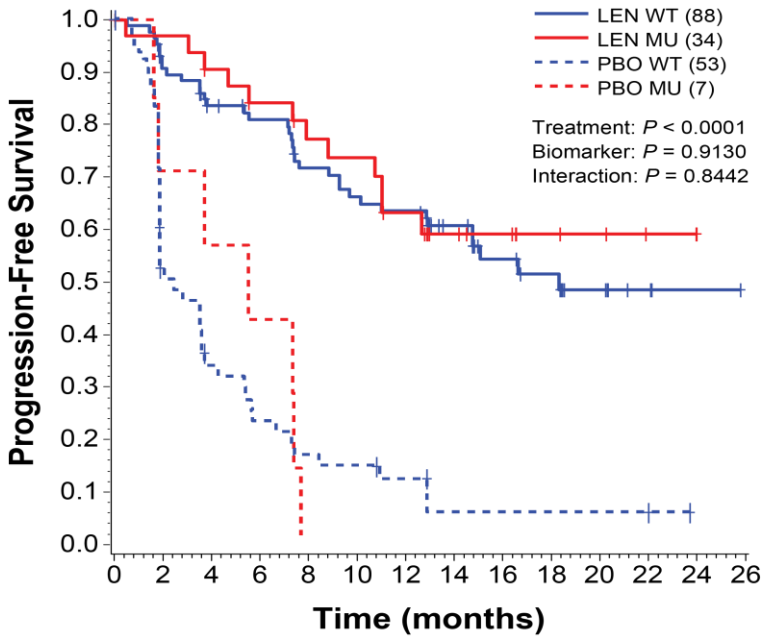


• In this placebo-controlled analysis, lenvatinib PFS benefit vs placebo was maintained regardless of *BRAF* or *RAS* mutation status.

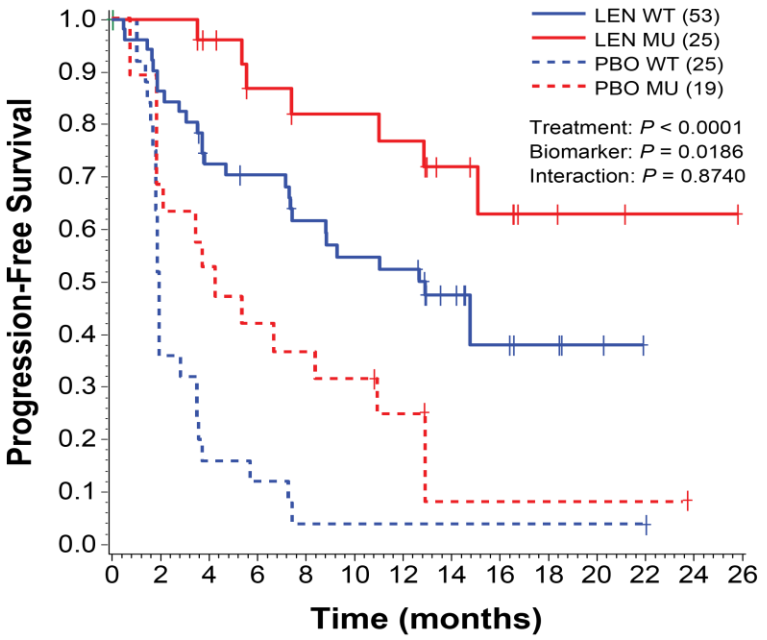
FTC, follicular thyroid carcinoma; NE, not evaluable; PTC, papillary thyroid carcinoma.

PTC Patients With *BRAF*^{WT} May Develop Rapidly Progressive Disease

PFS by *RAS* status



PFS by *BRAF* status, PTC only



- Lenvatinib PFS benefit vs placebo was maintained regardless of *RAS/RAF* mutation status:
  - Treatment * biomarker (response) interaction *P* = 0.844/0.874.
- *BRAF* mutation may be a prognostic factor for PFS in progressive metastatic PTC:
  - Univariate (placebo): *BRAF*^{WT} vs *BRAF*^{MU}: HR 0.48 (95% CI 0.25–0.92); Cox PH *P* = 0.027
  - Significance was maintained in a multivariate (placebo) analysis.

Cox PH, Cox proportional hazards; LEN, lenvatinib; PBO, placebo.

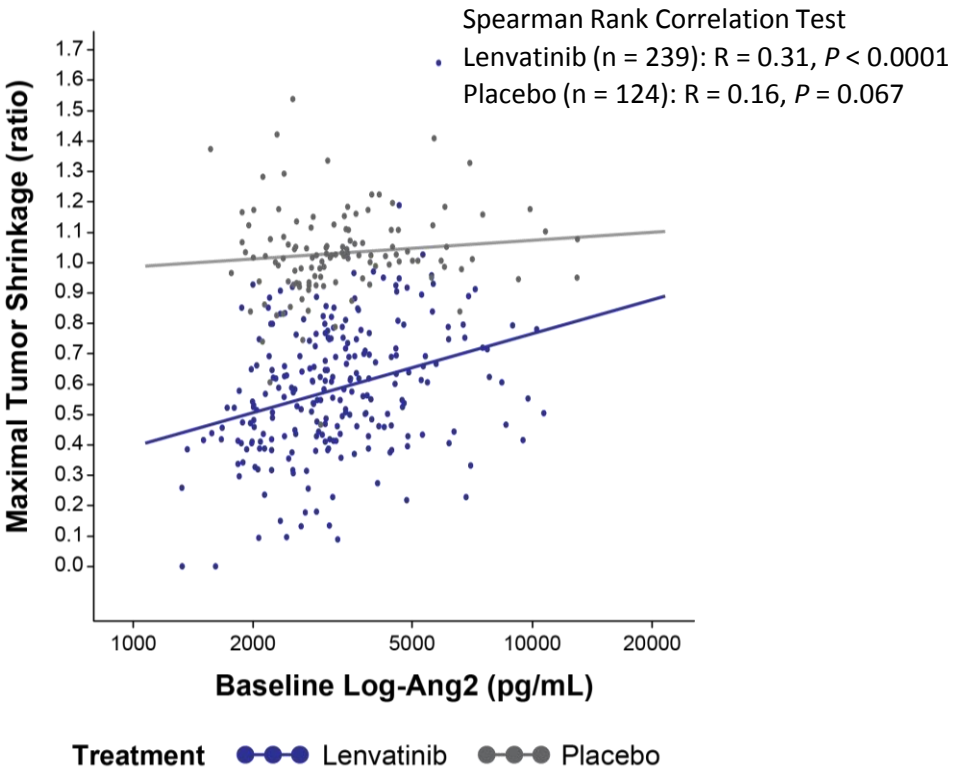
CIRCULATING SERUM BIOMARKERS

Serum Biomarker Analysis in SELECT

- Samples were collected at baseline, Cycle 1/Day 15, Day 1 of all subsequent treatment cycles until PD, and OT.
- Baseline serum samples were collected from 387 patients (98.7% of all randomized patients).
- Circulating CAFs were examined by ELISA:
  - VEGF, Ang2, soluble Tie2, TG

- **Baseline Ang2 levels were correlated with MTS and ORR in the lenvatinib arm.**
- **Baseline Ang2 was a predictive factor for MTS:**
  - **Treatment * biomarker (response) interaction *P* = 0.016.**

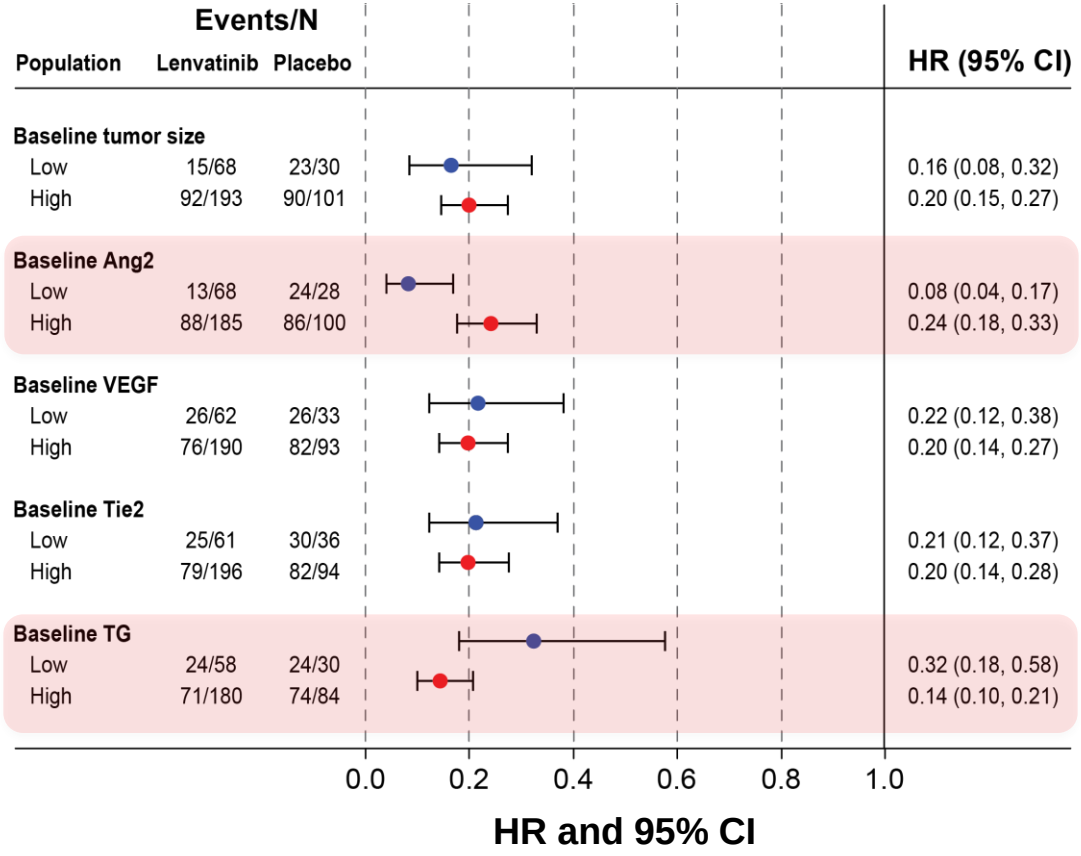
Correlation of baseline Ang2 with MTS



ELISA, enzyme-linked immunosorbent assay; MTS, maximum tumor shrinkage; ORR, overall response rate OT, off treatment; PD, progressive disease; TG, thyroglobulin.

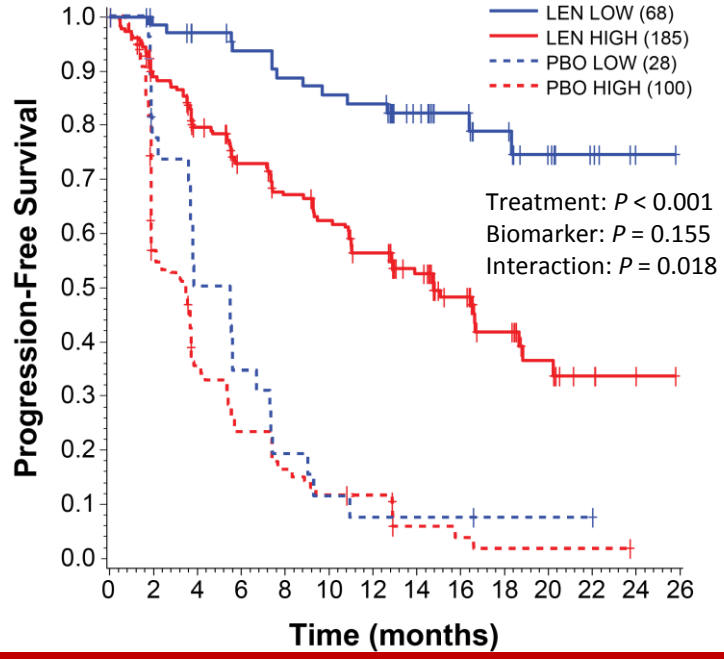
PFS Analysis: Dichotomized Subgroups of Baseline Serum Biomarker Levels

- Lenvatinib PFS benefit vs placebo was maintained regardless of baseline serum biomarker levels.
- Biomarkers were dichotomized into low (1st quartile) and high (all other quartiles) groups:
  - Kaplan-Meier curves of baseline Ang2 quartiles showed high PFS ratio (about 0.8 at 18 months) of the 1st quartile of the lenvatinib arm.
- HR in the low-baseline Ang2 subgroup (≤ 2556.06 pg/mL) was 3-fold lower than in the high subgroup.
- HR in the high Tg subgroup (> 159.5 ng/mL) was 2-fold lower than in the low subgroup.

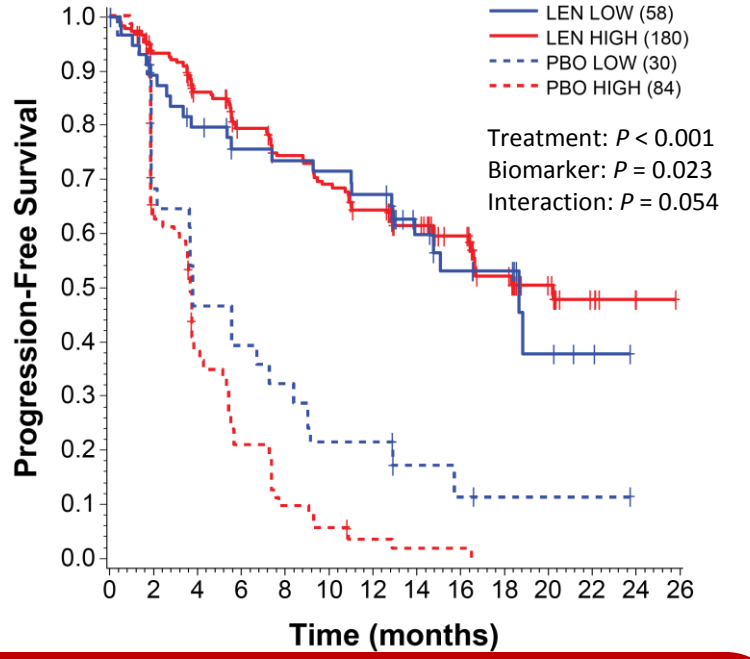


Baseline Biomarker Levels and Clinical Outcomes

PFS by baseline Ang2 levels



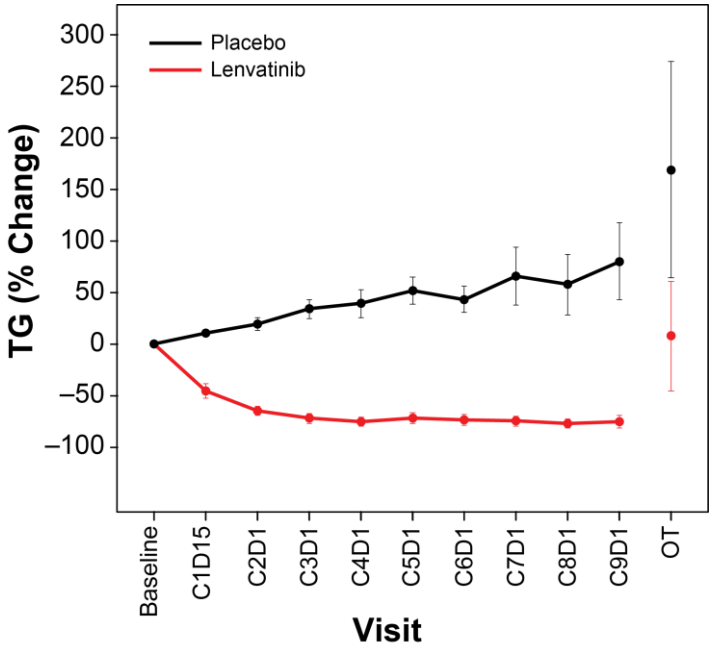
PFS by baseline TG levels



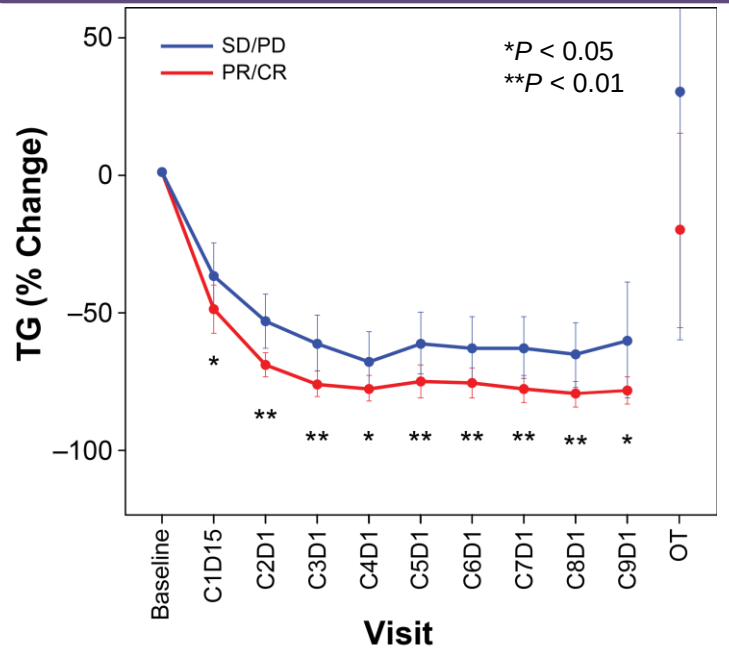
- **Low baseline Ang2 predicted PFS benefit from lenvatinib:**
  - **Univariate (lenvatinib arm): Low vs high Ang2 HR 3.40 (95% CI 1.90–6.10); Cox PH *P* <0.001**
  - **Significance was maintained in multivariate (lenvatinib arm) analysis**
  - **Treatment*biomarker (response) interaction *P* = 0.018.**
- **High baseline TG levels *may be* a prognostic factor for PFS:**
  - **Univariate (placebo arm): Low vs high TG HR 1.71 (95% CI 1.06-2.75); Cox PH *P* = 0.027.**

Change in TG Levels and Clinical Outcomes

Changes in TG levels



Changes in TG levels and ORR (lenvatinib arm only)

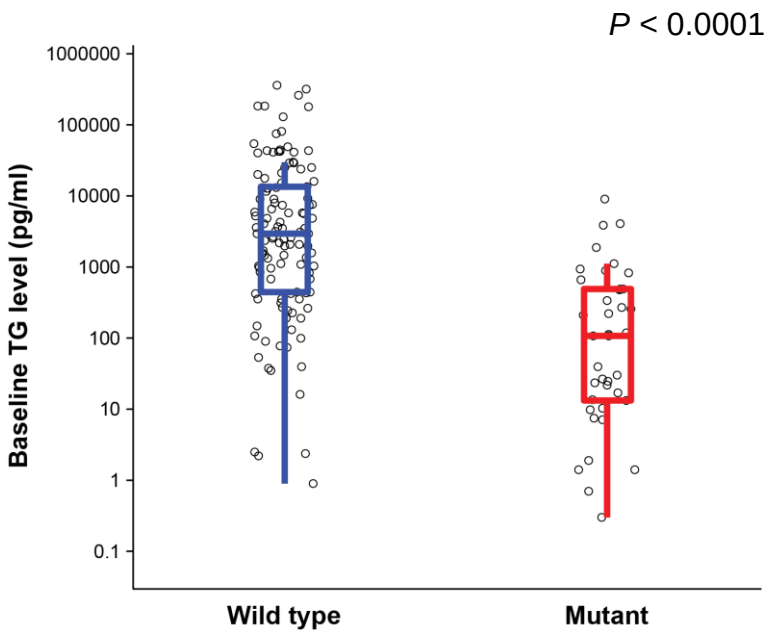


- **Mean serum TG levels rapidly decreased with lenvatinib treatment (by C1D15), and remained low during lenvatinib treatment.**
- **Mean serum TG levels increased from baseline in the placebo arm.**
- **Decreased levels of TG were associated with lenvatinib response (C1D15 and later).**

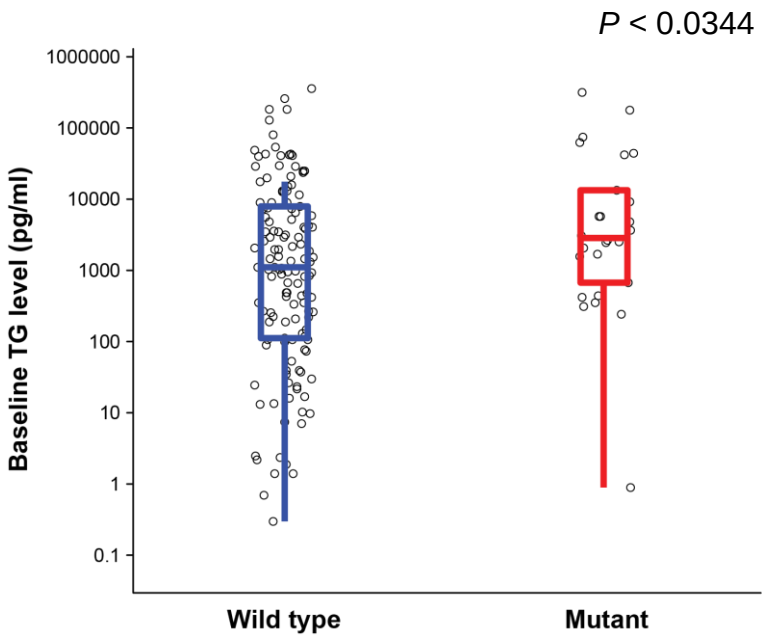
CR, complete response; C#D#, Cycle # Day #; PR, partial response; SD, stable disease.

Baseline Thyroglobulin and Tumor Mutations

BRAF status



NRAS status



- ***BRAF*^{MU} and *NRAS*^{MU} have significantly low and high baseline TG levels, respectively, vs WT.**

Conclusions

- Lenvatinib PFS benefit compared with placebo was maintained regardless of baseline circulating serum biomarker levels or *BRAF/RAS* mutational status.
- *BRAF*^{V600} may be a positive prognostic factor in PTC:
  - PTC patients with *BRAF*^{WT} may develop rapid disease progression.
- Baseline Ang2 levels were predictive for tumor size reduction and PFS in a subset of patients (lowest quartile, 0% to 25%) with lenvatinib treatment:
  - Ang2 may play a predictive role in defining sensitivity to lenvatinib.

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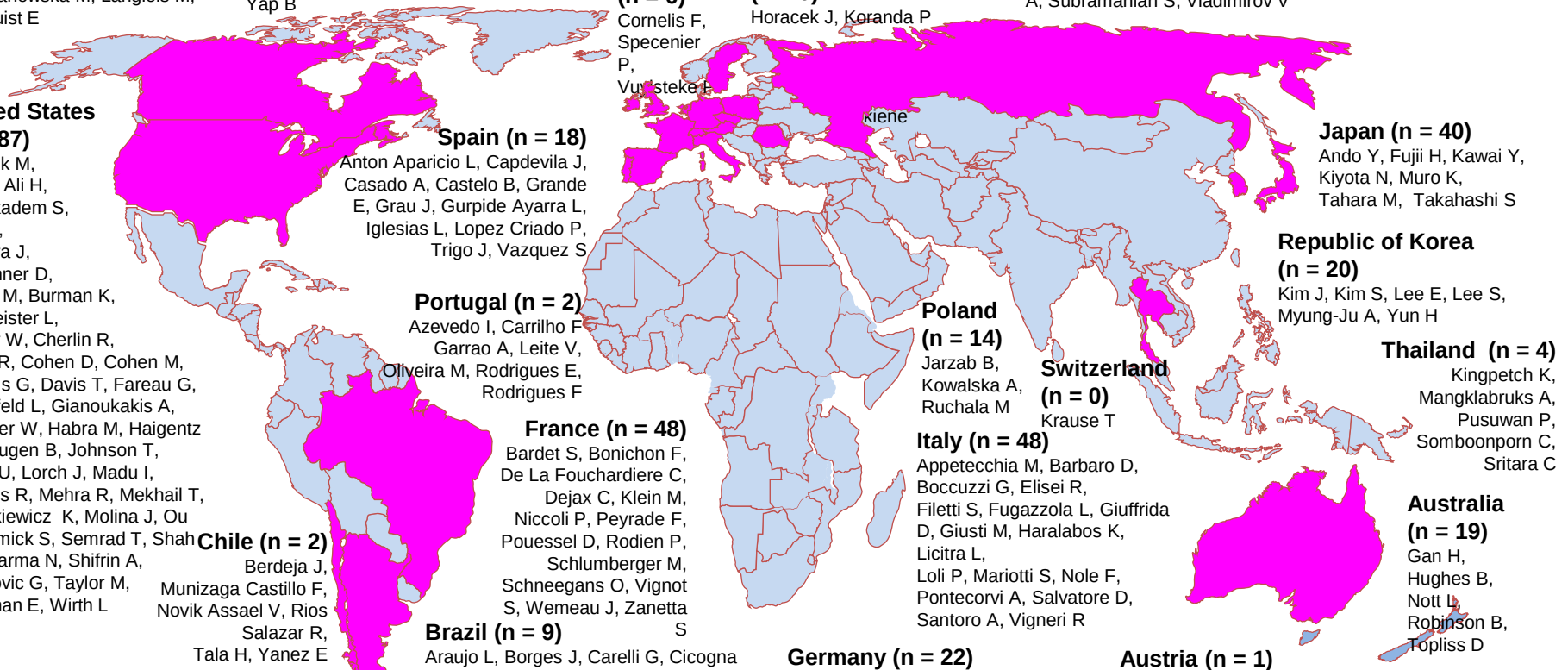

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Portugal (n = 2)
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