

How to Manage RR-DTC Patients After Progression to Approved Therapies

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What are the Approved Therapies?

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

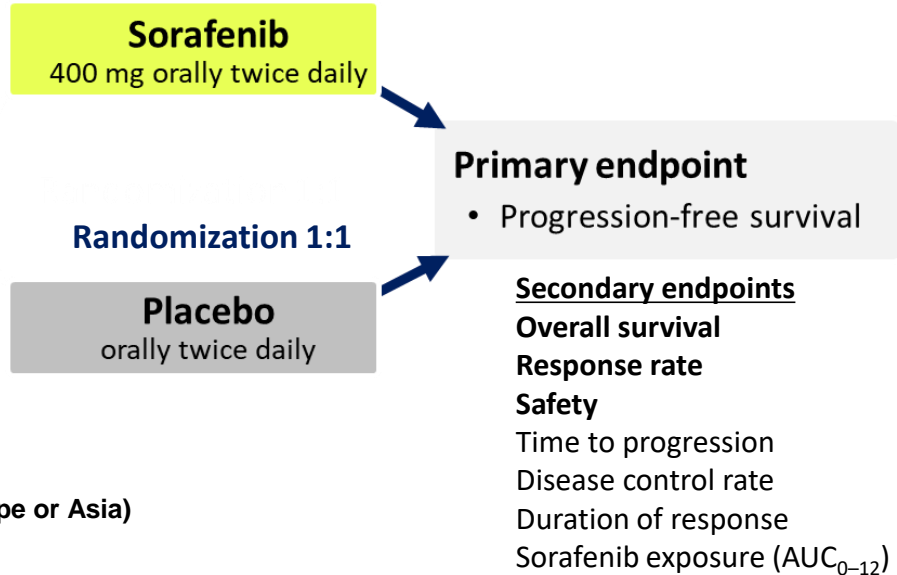
Stratified by:
geographical region (North America or Europe or Asia)
age (<60 or ≥60 years)

Progression assessed by ICR Q8WK
every 8 weeks

At progression:

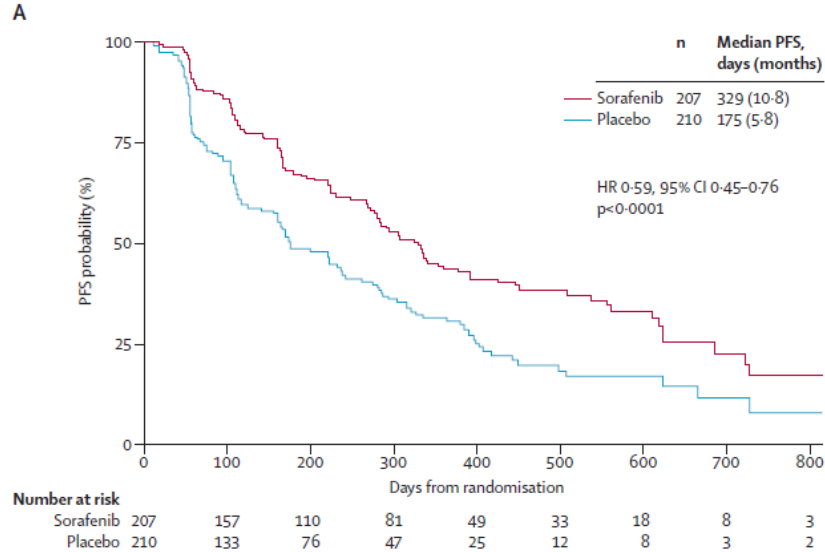
patients on placebo allowed to cross over at the investigator's discretion

patients on sorafenib allowed to continue on open-label sorafenib at the investigator's discretion

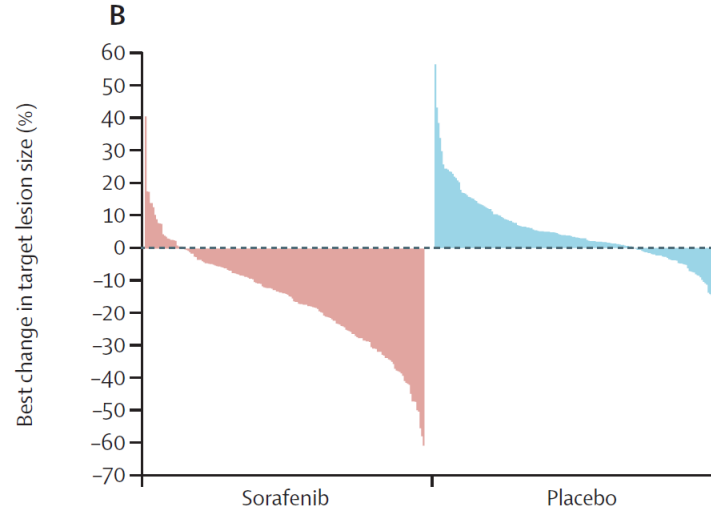


● **DECISION: PFS (ICR) and Response**

mPFS Primary Endpoint



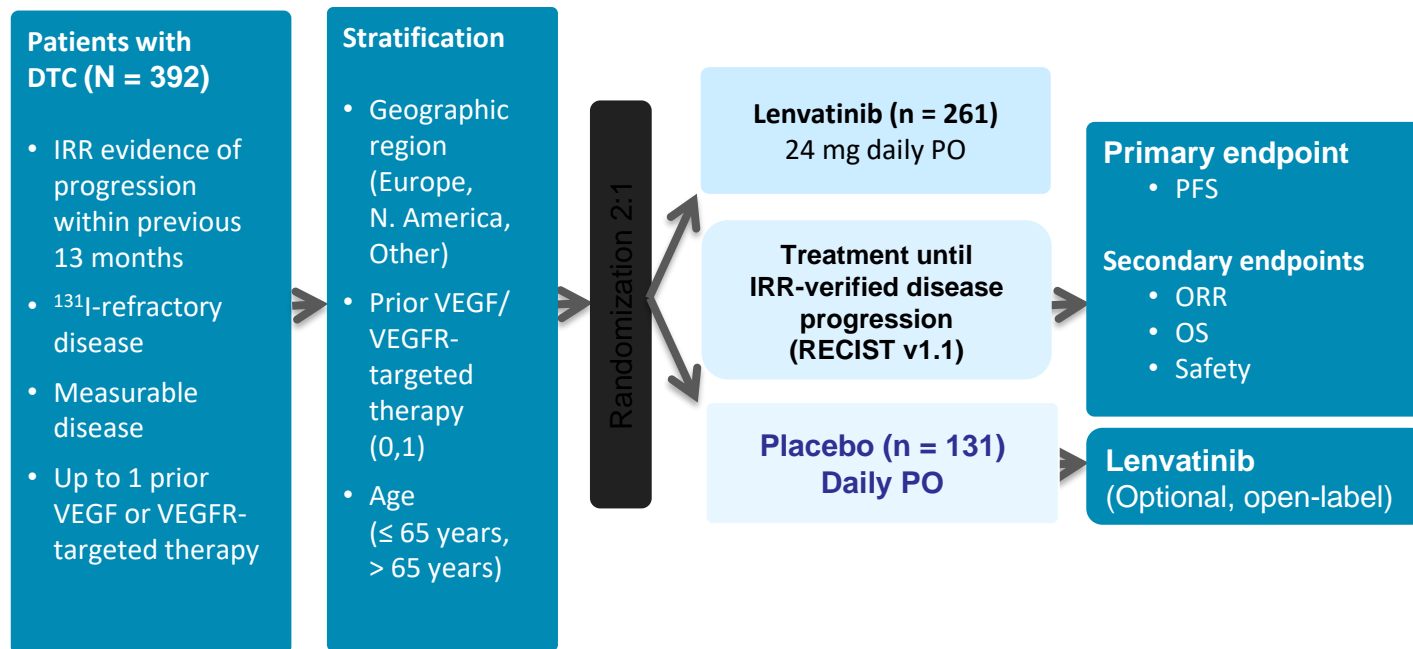
Objective Response Rate



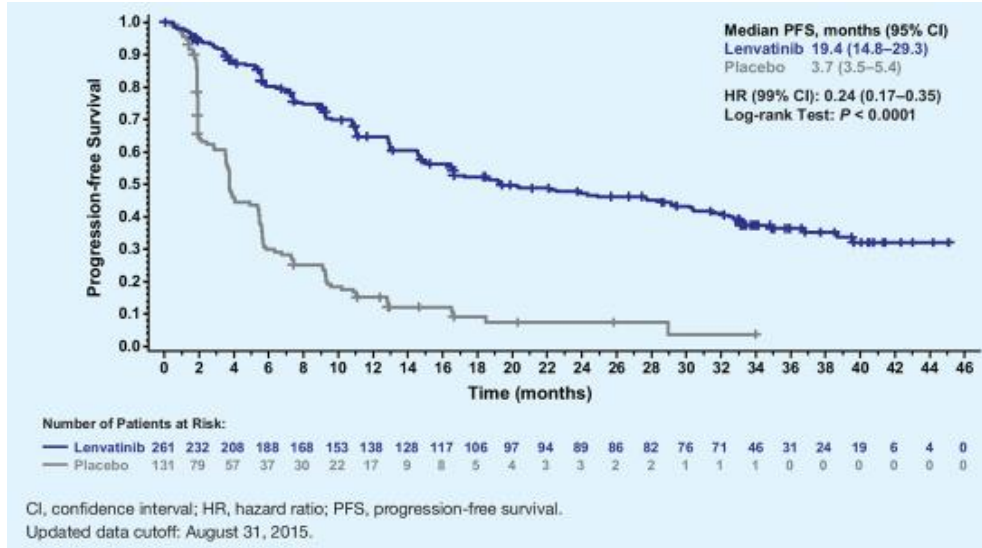
ORR

- **12.2% SOR vs 0.5% PBO**
- **$P < .0001$**

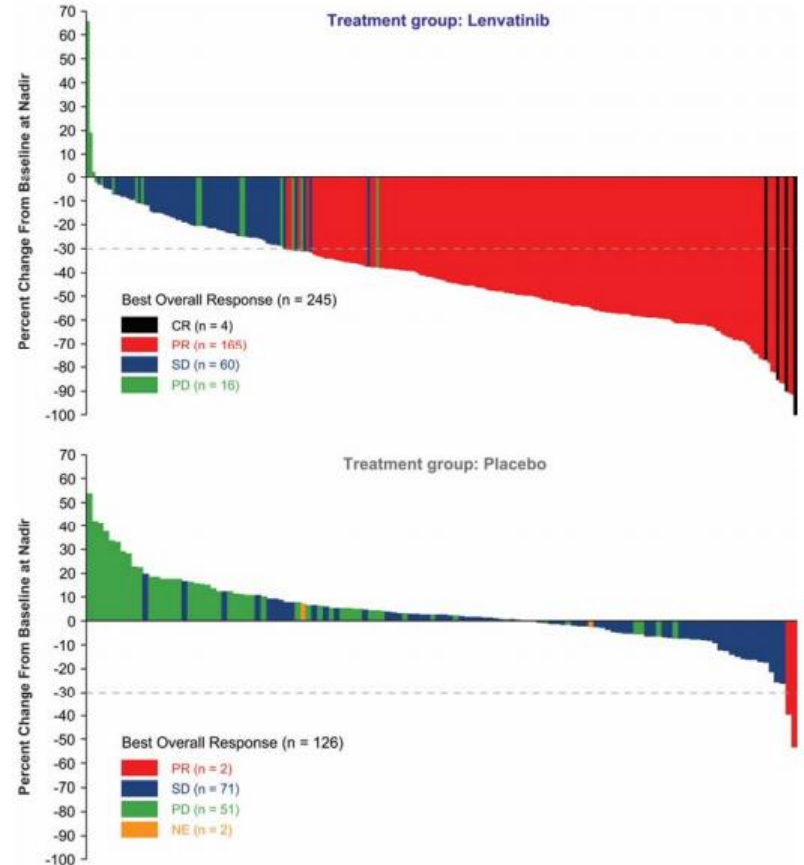
●Phase 3 Global, Randomized, Double-Blind SELECT Trial: Study Schema



DTC, differentiated thyroid cancer; ¹³¹I, radioiodine; IRR, independent radiologic review; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; RECIST, response evaluation criteria in solid tumors; VEGF/VEGFR, vascular endothelial growth factor/receptor.



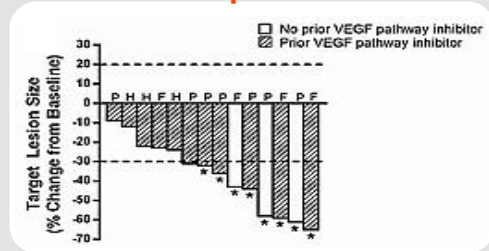
ORR (LEN vs PBO)
 64.8% vs 1.5% ($P < .001$)
 CR: 1.5% (n = 4) vs 0
 PR: 63.2% vs 1.5%



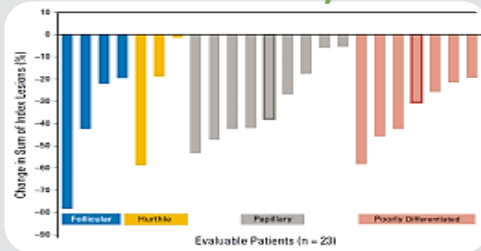
What's Next?

Clinical Activity in DTC Supports Further Development of Cabozantinib

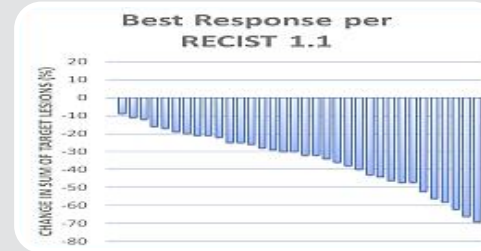
Exelixis-Sponsored¹



CTEP Study²



Investigator-Initiated³



Phase I DDI

- RAI-refractory
- 80% ≥ 1 prior systemic agent, N=15
- **53% ORR**
- **40% SD**
- **mDOR: NR (2.0 – 14.5m)**
- **mPFS: NR (10.3 - 17.0)**

Phase 2

- RAI-refractory
- 1-2 prior VEGFR-targeted therapy, N=25
- **40% ORR**
- **52% SD**
- **mDOR: 11.3 (10.3 - NR)**
- **mPFS: 12.7m (10.9 - 34.7)**

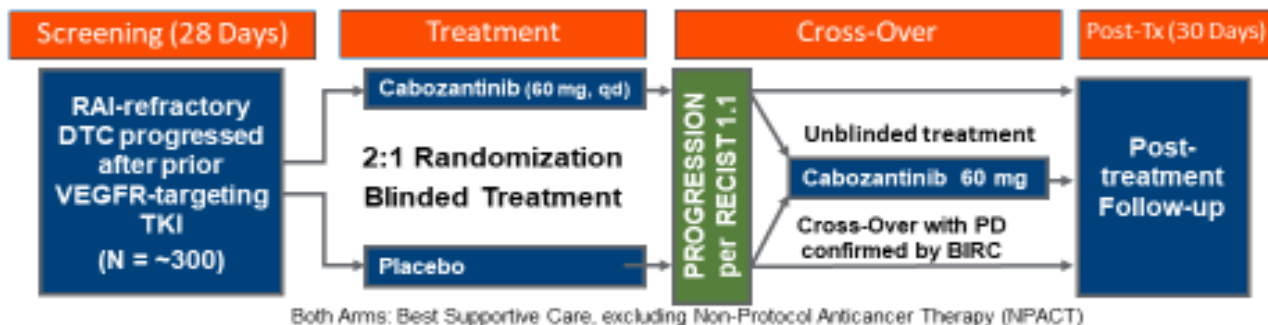
Phase 2

- RAI-refractory
- 1L DTC, N=35
- **63% ORR**
- **34% SD**
- **mDOT: 40 weeks**
- **mPFS: NR**

DDI: drug-drug interaction; DOR: duration of response; DOT: duration of therapy; NR: not reached; RAI: radioactive iodine.

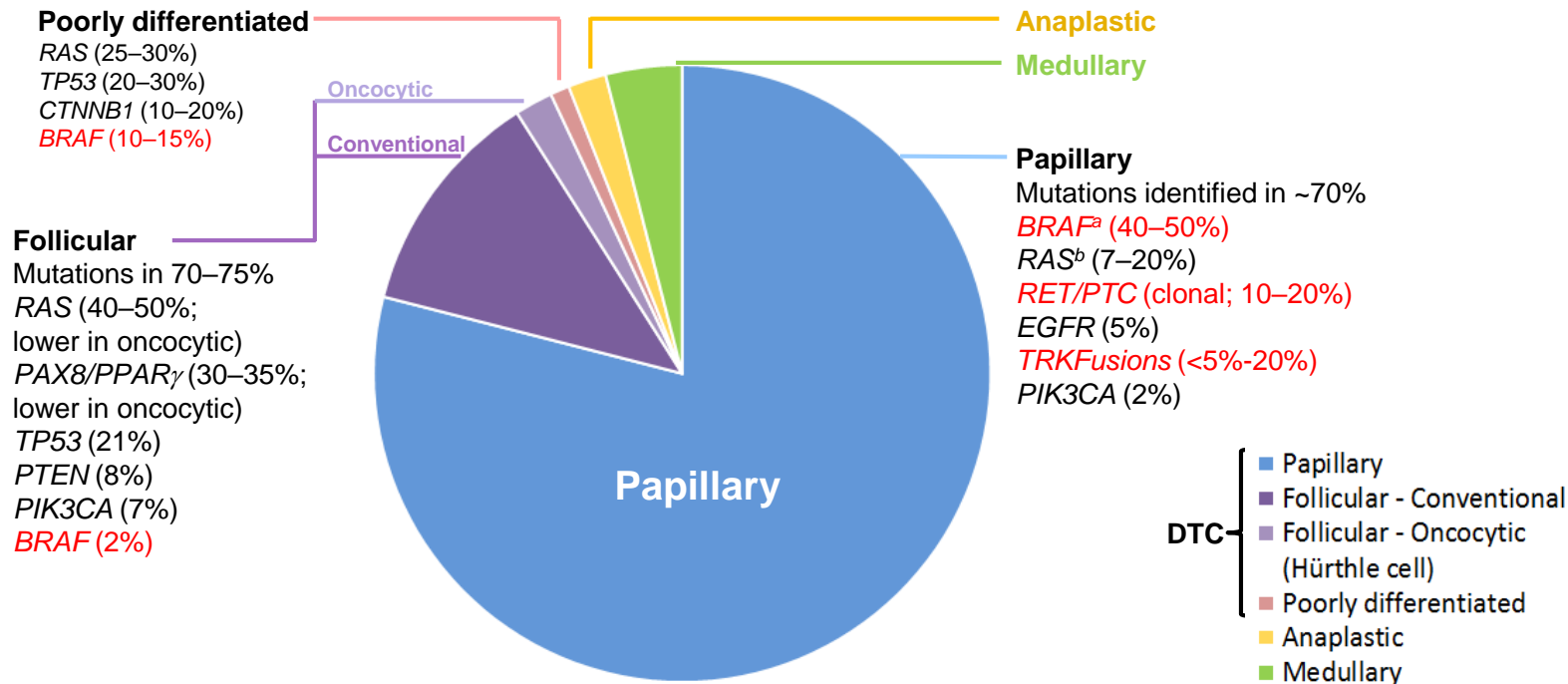
COSMIC-311 Study Schema

Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of cabozantinib in subjects with RAI-refractory DTC (who have progressed after prior VEGFR-targeted therapy), with treatment cross-over phase for placebo arm



- **Treatment Phase - Randomization to oral cabozantinib or placebo stratified by:**
 - Receipt of prior Lenvatinib (yes vs. no)
 - Age at informed consent (≤ 65 years vs. > 65 years)
- **Cross-Over Phase:**
 - Placebo Arm: Upon Blinded Independent Radiology Committee (BIRC)-confirmed disease progression, subjects randomized to placebo will have the opportunity to crossover to receive cabozantinib
 - Cabozantinib Arm: Unblinded subjects randomized to cabozantinib may continue on study treatment if the Investigator believes the subject is deriving clinical benefit

● Genetics of Differentiated Thyroid Cancer: aberrant intracellular signaling

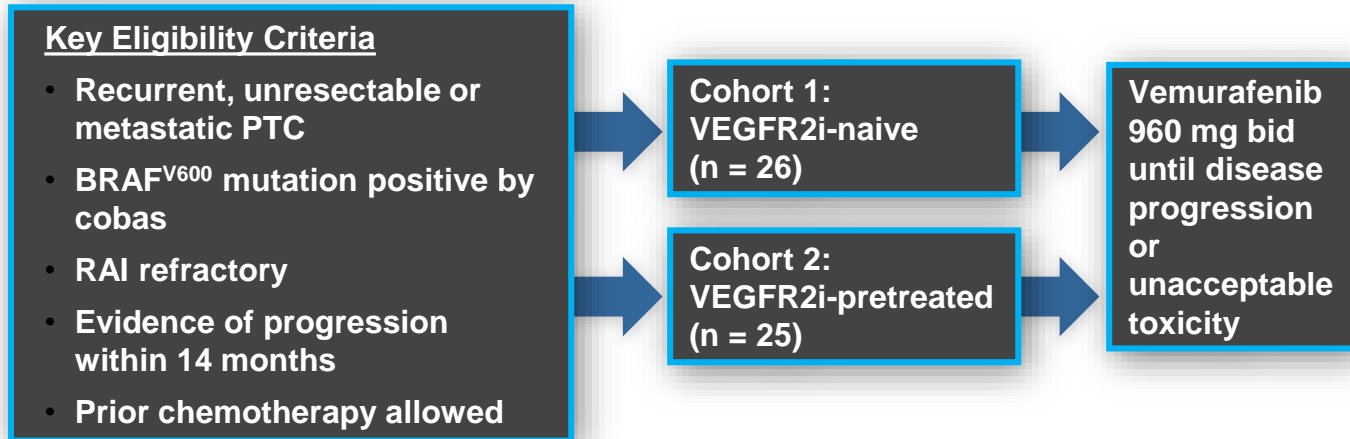


^a**BRAF** mutations are mostly V600E; 1–2% are K601E and others

^b**RAS** includes *N*-, *H*-, and *K*-RAS (predominantly *NRAS* and *HRAS* codon 61)

Nikiforov YE et al. Arch Pathol Lab Med 2011;135:569–77; COSMIC database – Catalog of Somatic Mutations in Cancer (as of February 22, 2013) <http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/>

UPCC 18310: NO25530 Vemurafenib in patients with Progressive PTC with BRAF V600E



Primary end point: response rate per investigator in VEGFR2i-naive patients.

Secondary end points: safety, duration of response, PFS, OS, PK, response rate in VEGFR2 inhibitor-pretreated patients

NO25530 Waterfall plot: Cohort 1 (TKI-naïve) Vemurafenib in BRAF V600E RR-DTC

Genentech, Inc.

Phase II Study NO25530

Percent Change of SLD from Baseline by Investigator
Cohort 1 Efficacy E evaluable Patients



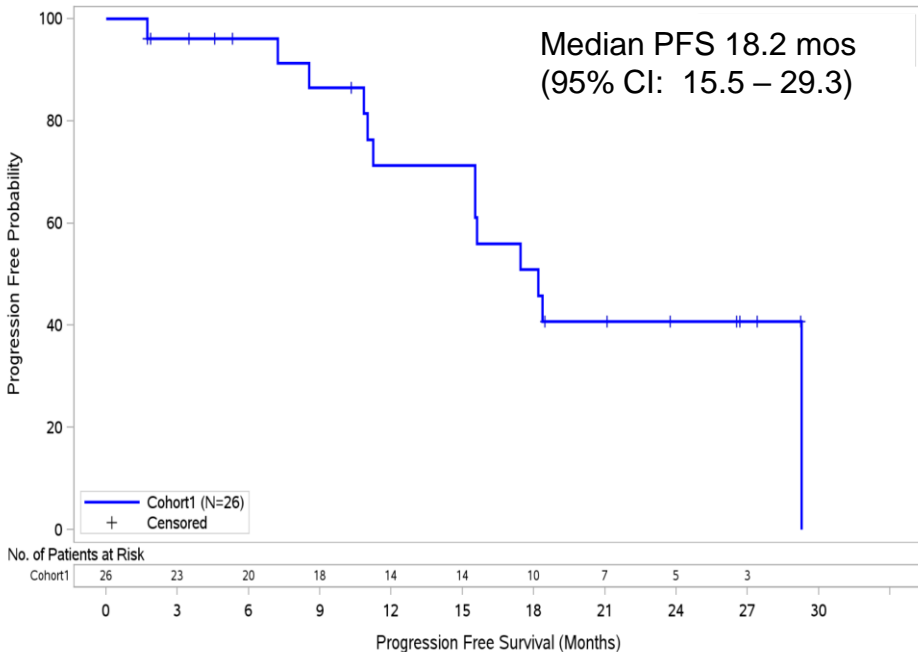
Source: Biostatistics (jkatzman) pgm/bnco/brav/no25530/pub2014/programs/g_waterfall
Dbase(OPEN). Data as of 18APR14. Verified data and program. Datasets (atraslars)
pub2014 : Generated 28OCT14 14:34 Page 1 of 1

	Cohort 1 (Tki naïve)
	BORR-evaluable¹ N= 26
Objective Responders² (Rate; 95% CI)	10 (38.5%;0.20-0.59)
Best Response (confirmed)	
PR	10 (38.5%;0.20-0.59)
SD	15 (57.7%;0.37-0.77)
PD	1 (3.8%: 0.10-0.20)
Clinical Benefit Response (CR, PR, SD ≥ 6 mos)	19 (73.1%; 0.52-0.88)
1 Patients with at least 2 post-BL tumor scan or PD/WD from for death or AE within first two cycles. 2 Confirmed PR/CR	



PFS KM Curve: Cohort 1

NO25530 K-M Estimates on Progression Free Survival (Population: Cohort1 Efficacy)

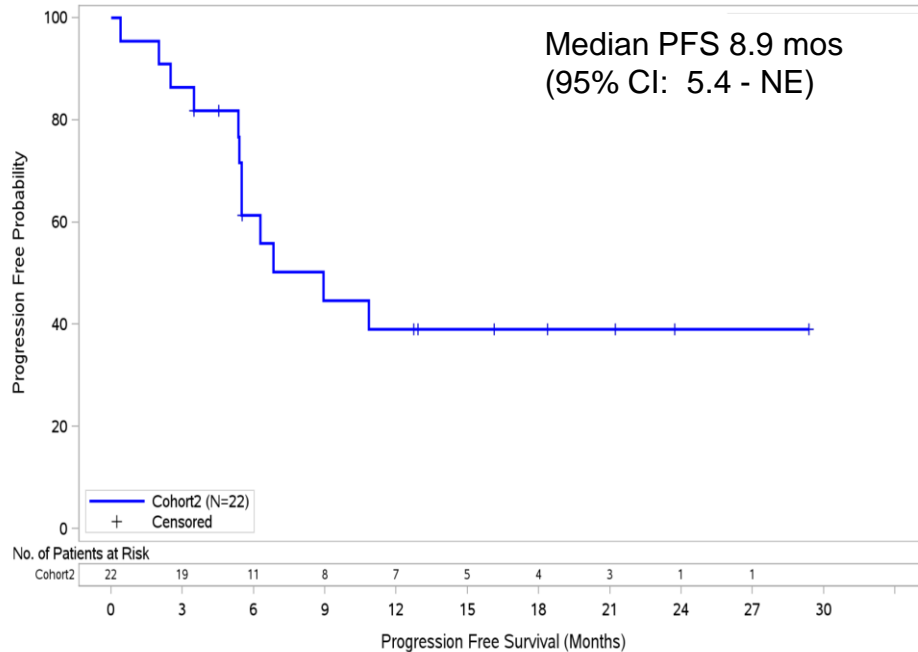


Cohort1=Sorafenib Naive.

Data as of 18APR14. Verified data and program.

Program: /onco/braf/no25530/pub2014/programs/g_km_pfs_cohort1.sas Output: /onco/braf/no25530/pub2014/results/g_km_pfs_cohort1.pdf 20OCT2014 11:59

NO25530 K-M Estimates on Progression Free Survival (Population: Cohort2 Efficacy)



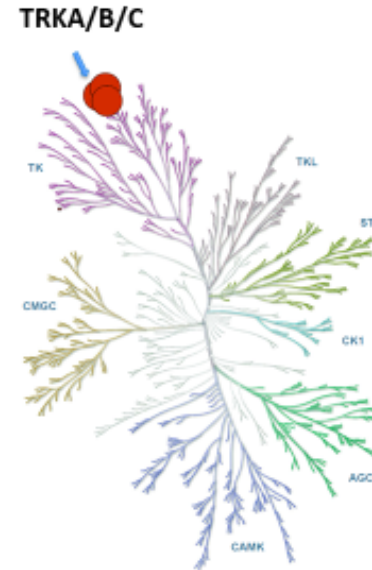
Cohort2= Prior Sorafenib.

Data as of 18APR14. Verified data and program.

Program: /onco/braf/no25530/pub2014/programs/g_km_pfs_cohort2.sas Output: /onco/braf/no25530/pub2014/results/g_km_pfs_cohort2.pdf 20OCT2014 12:01

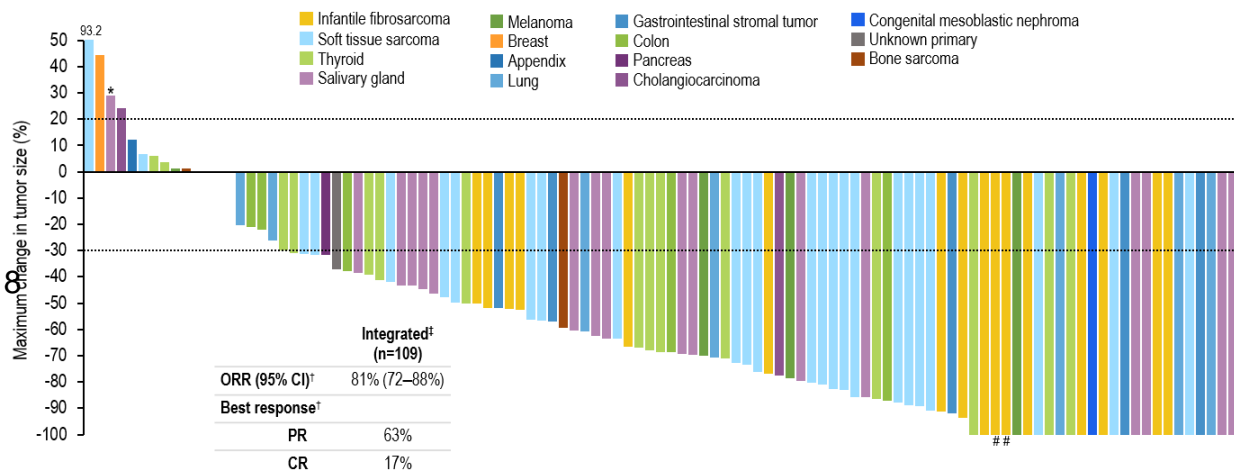
•Larotrectanib in TRK/Fusion positive cancer: FDA Approved November 2018

- Larotrectinib is a highly potent TRK inhibitor against TRKA, TRKB, TRKC (5–11 nM IC₅₀ in cellular assays)¹
- Highly selective, with little or no interaction with other kinase and non-kinase targets
 - limited inhibition of other kinases and >1,000x selective over other off targets¹
- Larotrectinib is highly active against TRK fusion cancer with durable responses in both children and adults
- TRK fusions are estimated to be present in 5-25% of recurrent DTC



•Larotrectinib in TRK/Fusion Cancers

Integrated dataset: Larotrectinib is efficacious regardless of tumor type



• Esmo 2018

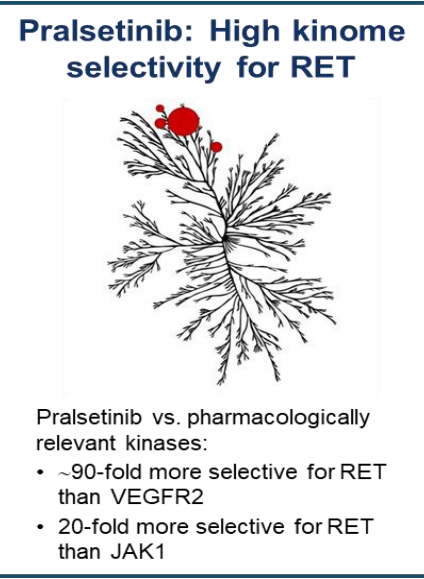
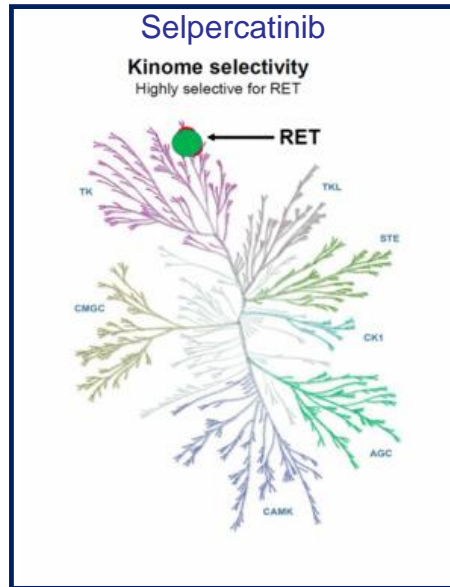
[‡]Includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment

^{*}Patient had TRKC solvent front resistance mutation (G623R) at baseline due to prior therapy; [#]Surgical CR; [†]RECIST 1.1

Note: Two patients not shown here. These patients discontinued treatment prior to any post-baseline tumor measurements.

CR, complete response; ORR, objective response rate; PR, partial response

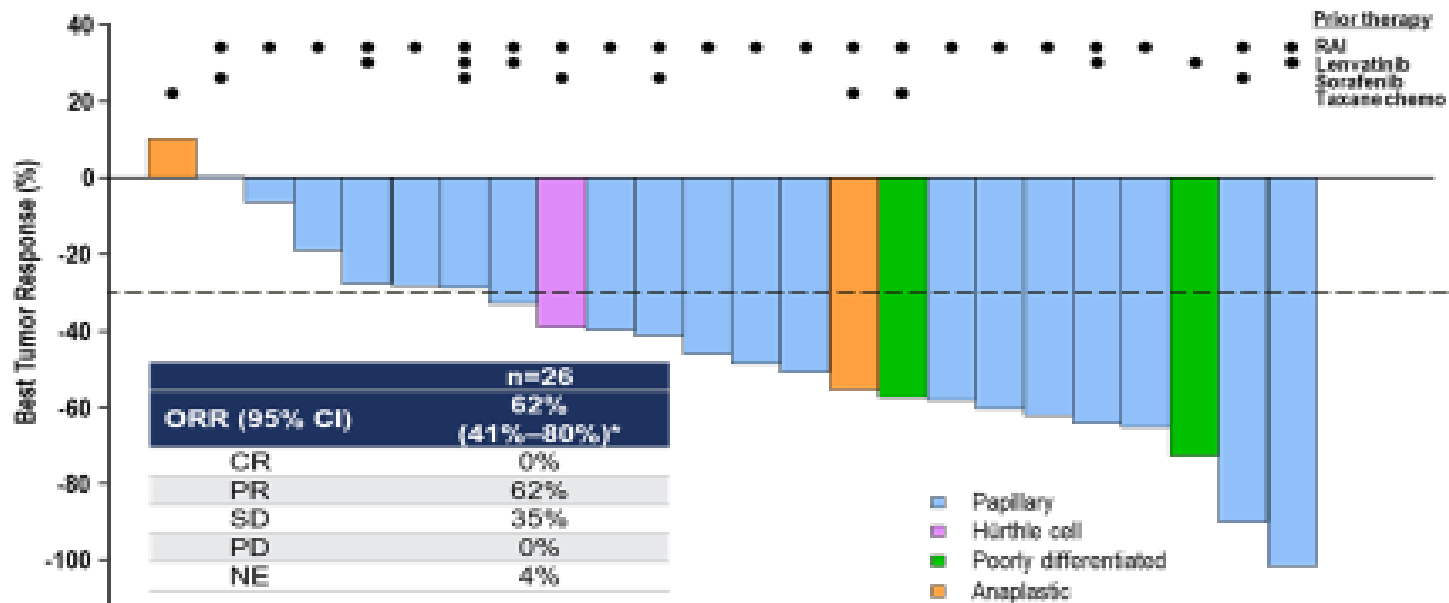
•New Selective RET inhibitors: pralsetinib (BLU-667) and selpercatinib (Loxo-292)





- LIBRETTO:Efficacy of Selpercatinib in RET/fusion cancers (DTC): FDA Approved May 2020

Activity of selpercatinib: *RET* fusion-positive thyroid cancer (n=26)



Investigator response assessments as of June 17, 2019. Total % may be different than the sum of the individual due to rounding. Data include patients with at least one evaluable post-baseline assessment and those who discontinued therapy prior to any post-baseline imaging assessment. 3 patients not shown in waterfall plot: 1 did not have measurable disease at baseline, and 1 deemed not evaluable on study by the investigator. *Includes 3 unconfirmed PRs awaiting confirmatory response assessments. NE—not evaluable, n=1 patient deemed not evaluable on study by the investigator; RA—radioactive iodine.



Summary: What Comes Next RAI refractory DTC 2020

- Sorafenib (FDA 2013) and lenvatinib (FDA 2015) were approved on the basis of randomized Phase III studies. Primary target VEGFR inhibition. Both can be used sequentially.
- A Phase III study of **cabozantinib** in the second or third-line setting is underway based on strong activity in three phase I and II studies.

Following these agents requires genetic characterization of the tissue for point mutations and gene fusions:

- BRAFV600E inhibitors **vemurafenib** and **dabrafenib** are not FDA approved but available per NCCN for BRAFV600E patients, usually used in second line any beyond after other FDA approved agents.
- **Larotrectinib** is FDA and EMA approved for patients with TRK/Fusion cancers – mostly adolescents with PTC (November 2018)
- **Selpercatinib** (Loxo-292, FDA May 2020) and **pralsetinib** (BLU-667, FDA pending) second generation RET inhibitors may have a roll for RET/PTC DTC and due to their improved toxicity profiles may be considered first in patients with RET/PTC, so get testing early.