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

Sorafenib
400 mg orally twice daily

Randomization 1:1

Placebo
orally twice daily

Primary endpoint
- Progression-free survival

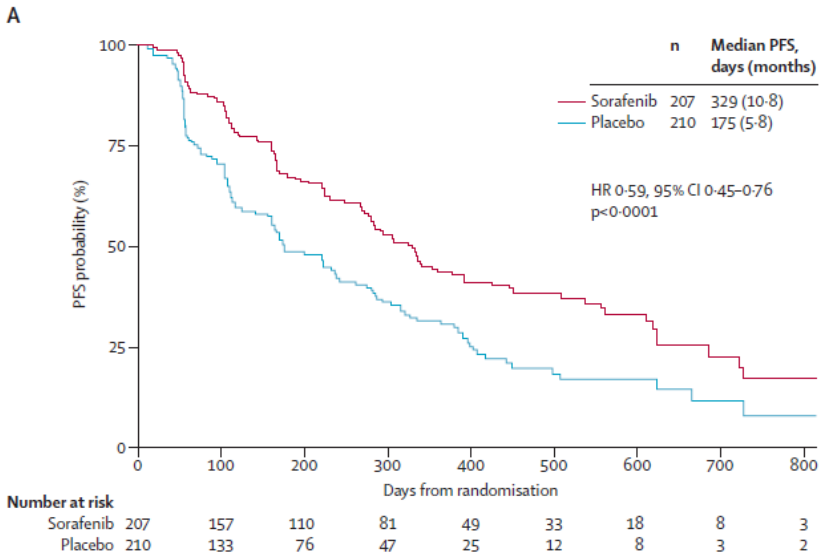
Secondary endpoints
Overall survival
Response rate
Safety
Time to progression
Disease control rate
Duration of response
Sorafenib exposure ($AUC_{0–12}$)

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

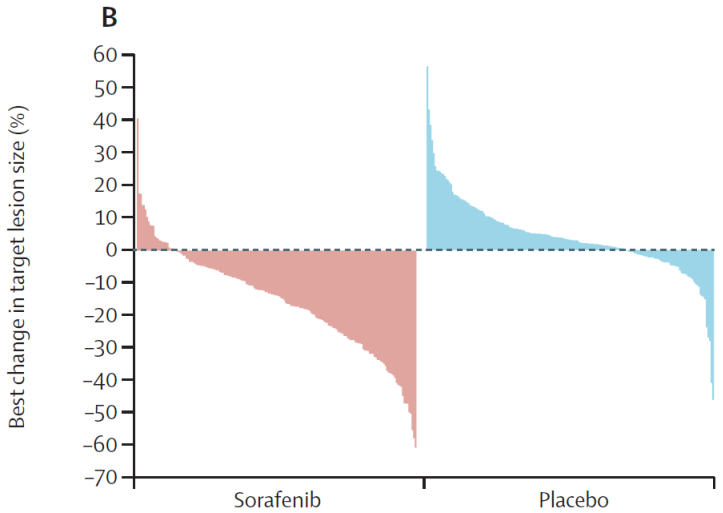
Brose M, et al. *Lancet*. 2014;384;319-328.

- DECISION: PFS (ICR) and Response

mPFS Primary Endpoint



Objective Response Rate

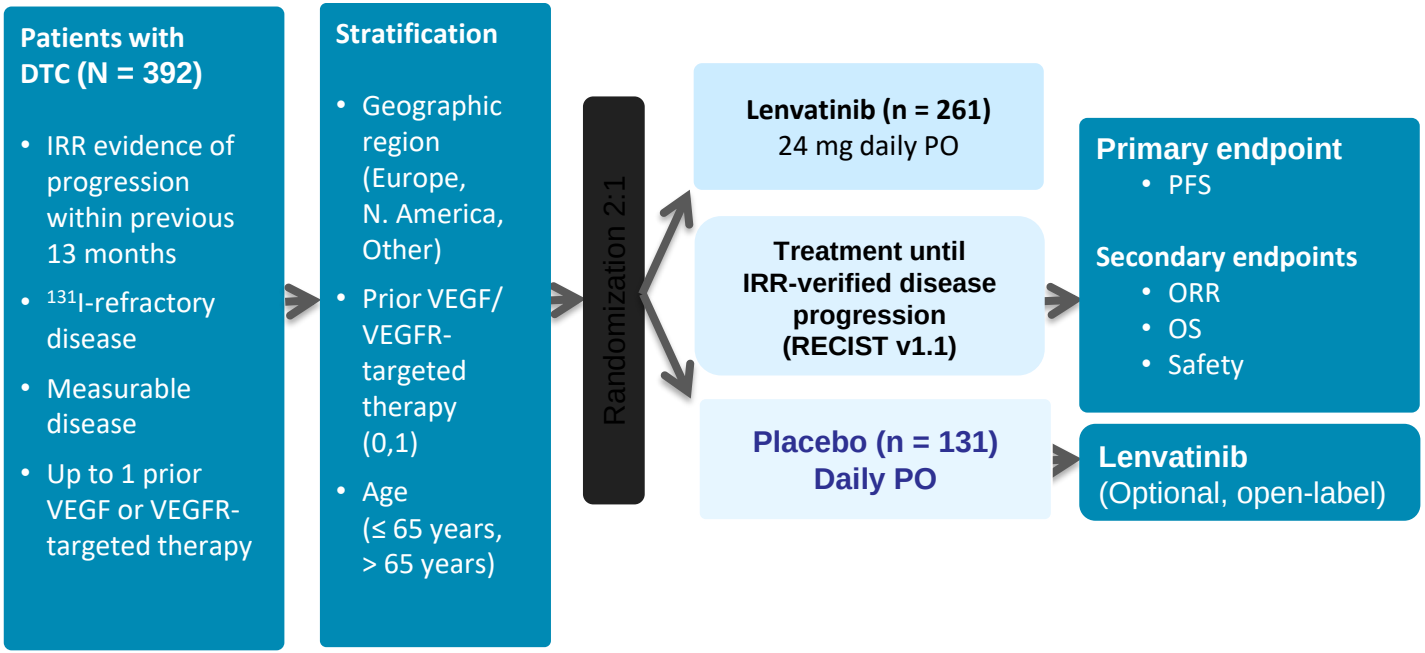


ORR

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

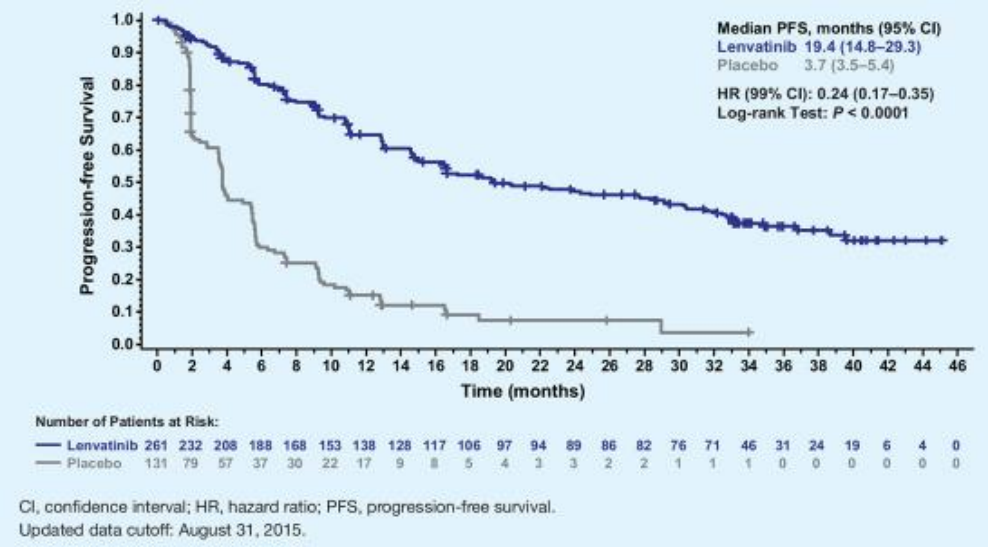
Brose M, et al. *Lancet*. 2014;384;319-328.

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

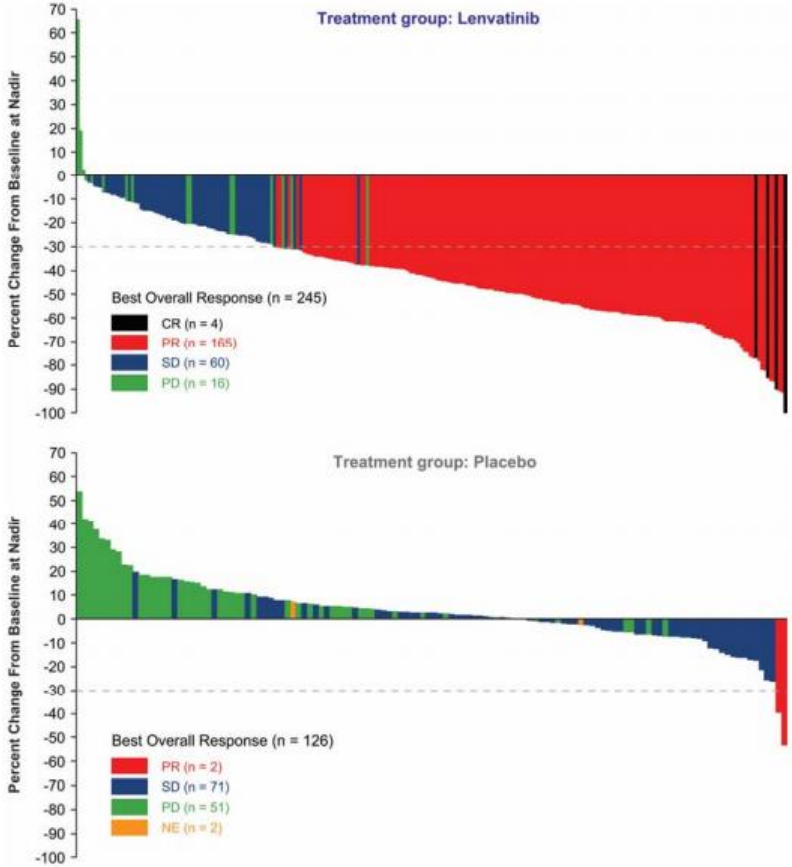


DTC, differentiated thyroid cancer; ^{131}I, radioiodine; IRR, independent radiologic review, ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; RECIST, response evaluation criteria in solid tumors; VEGF/VEGFR, vascular endothelial growth factor/receptor.

Schlumberger M, et al. *N Engl J Med*. 2015;372(7):621-630.



CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
Updated data cutoff: August 31, 2015.



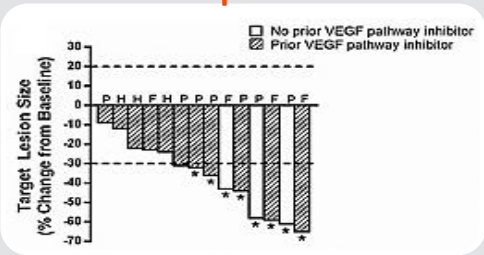
ORR (LEN vs PBO)
64.8% vs 1.5% ($P < .001$)
CR: 1.5% (n = 4) vs 0
PR: 63.2% vs 1.5%

1. Gianoukakis AG, et al. ASCO 2016. Abstract 6089. 2. Schlumberger M, et al. *N Engl J Med*. 2015;372:621-630.

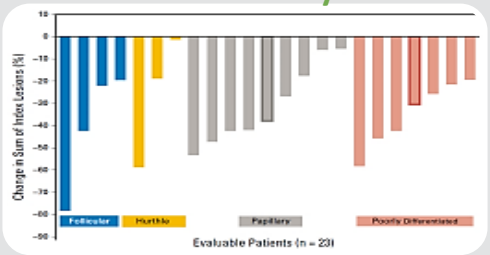
What's Next?

Clinical Activity in DTC Supports Further Development of Cabozantinib

Exelixis-Sponsored[1]



CTEP Study[2]



Investigator-Initiated[3]

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

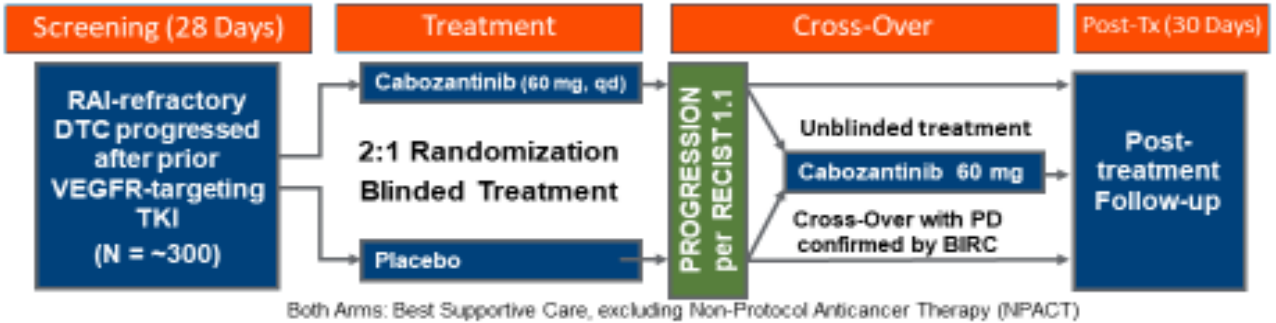
- **63% ORR**
- **34% SD**
- **mDOT: 40 weeks**
- **mPFS: NR**

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

1. Cabanillas ME et al. Thyroid 2014; 24(10): 1508-1514; 2. Cabanillas ME et al. J Clin Oncol 2017; 35(29): 3315-3321; 3. Brose MS et al. Presented at ASCO 2018.

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

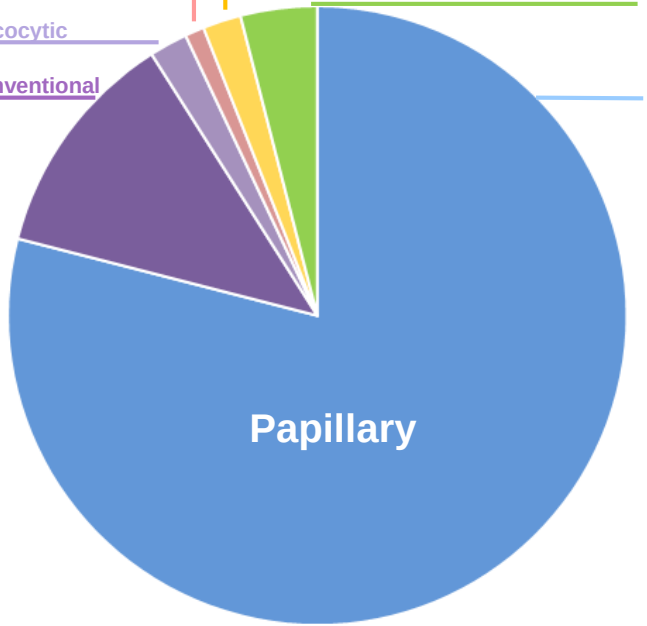
EXELIXIS

COSMIC

•Genetics of Differentiated Thyroid Cancer: aberrant intracellular signaling

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

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



Anaplastic

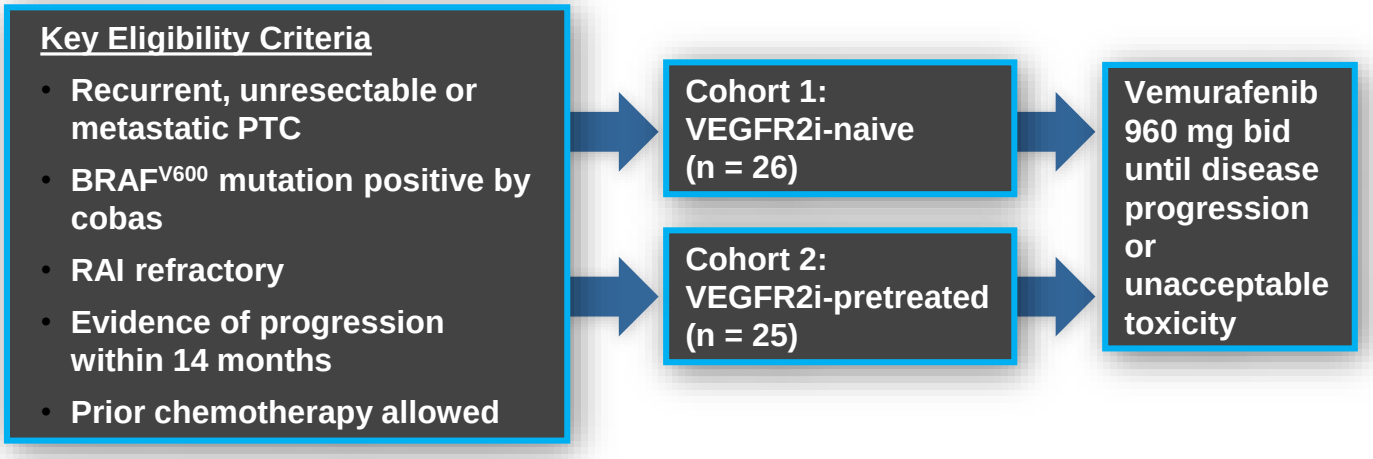
Medullary

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

DTC
- Papillary
- Follicular - Conventional
- Follicular - Oncocytic (Hürthle cell)
- Poorly differentiated
- Anaplastic
- Medullary

[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

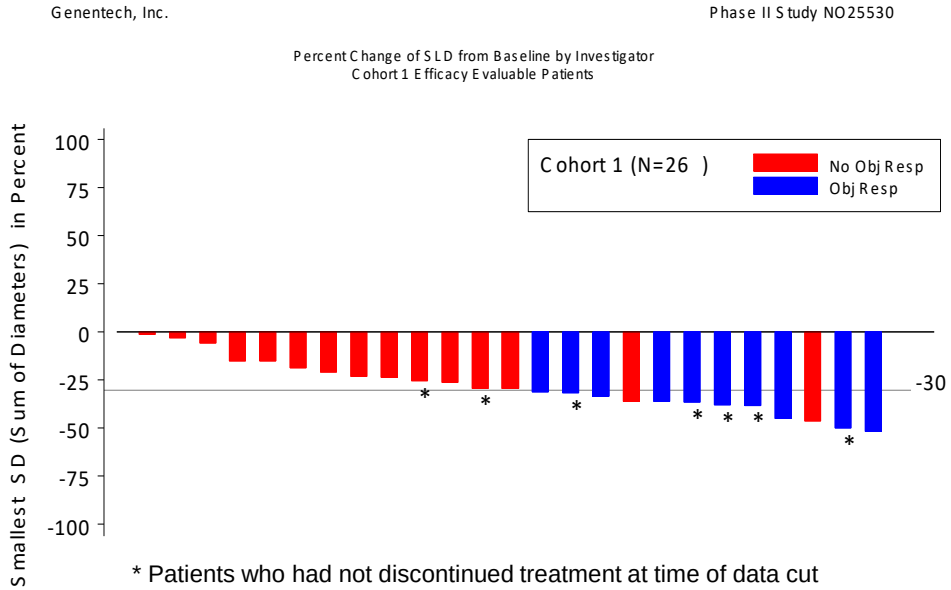


Primary end point: response rate per investigator in VEGFR2i-naive patients.

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

bid, 2 times a day; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; VEGFR, vascular endothelial growth factor receptor; VEGFR2i, vascular endothelial growth factor receptor 2 inhibitor.

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



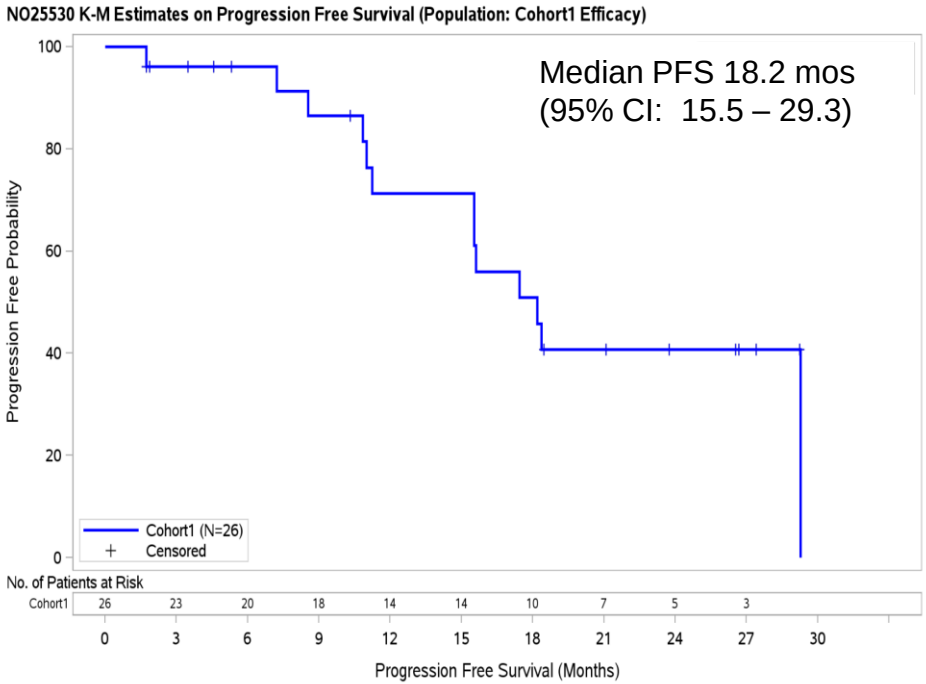
Source: Biostatistics (jkatzman) pgm(/onco/braf/no25530/pub2014/programs/g_waterfall)
Dbase(OPEN). Data as of 18APR14. Verified data and program. Datasets (atr as l ars)
pub2014 : Generated 28OCT14 14:34 Page 1 of 1

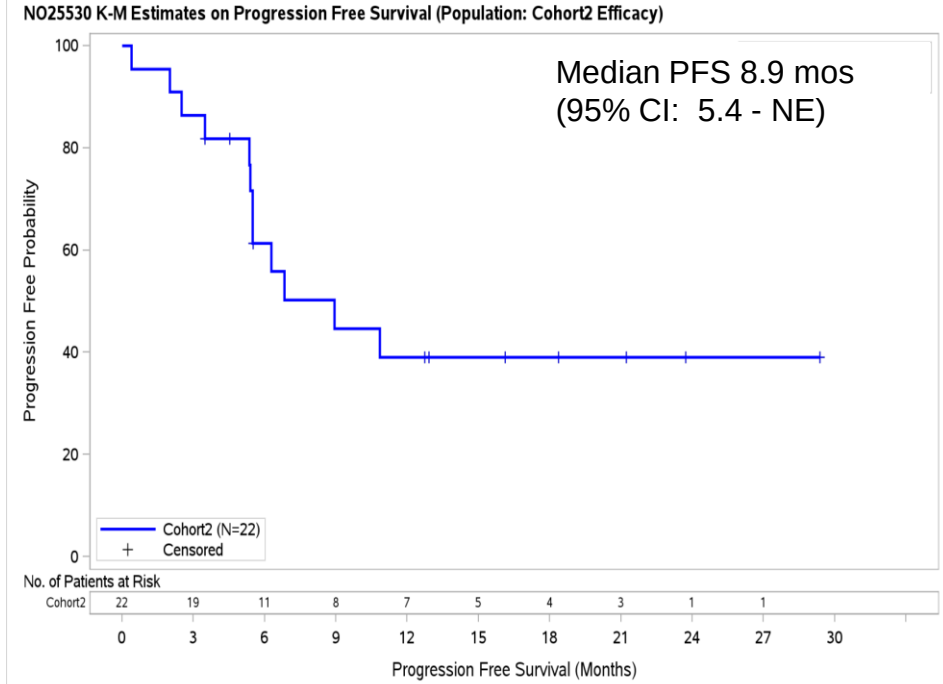
	Cohort 1 (Tki naïve)
	BORR-evaluable[1] N= 26
Objective Responders[2] **(Rate; 95% CI)**	10 (38.5%;0.20-0.59)
Best Response (confirmed)	
PR	10 (38.5%;0.20-0.59)
SD	15 (57.7%;0.37-0.77)
PD	1 (3.8%: 0.10-0.20)
Clinical Benefit Response (CR, PR, SD ≥ 6 mos)	19 (73.1%; 0.52-0.88)

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

Brose et al. *Lancet Oncol* 2016

PFS KM Curve: Cohort 1

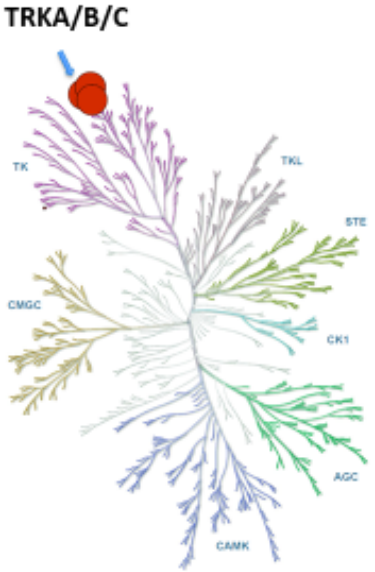




Brose et al. *Lancet Oncol* 2016

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

- Larotrectinib is a highly potent TRK inhibitor against TRKA, TRKB, TRKC (5–11 nM IC_{50} 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 targets[1]
- Larotrectinib is highly active against TRK fusion cancer with durable responses in both children and adults
- TRK fusions are extimated to be present in 5-25% of recurrent DTC

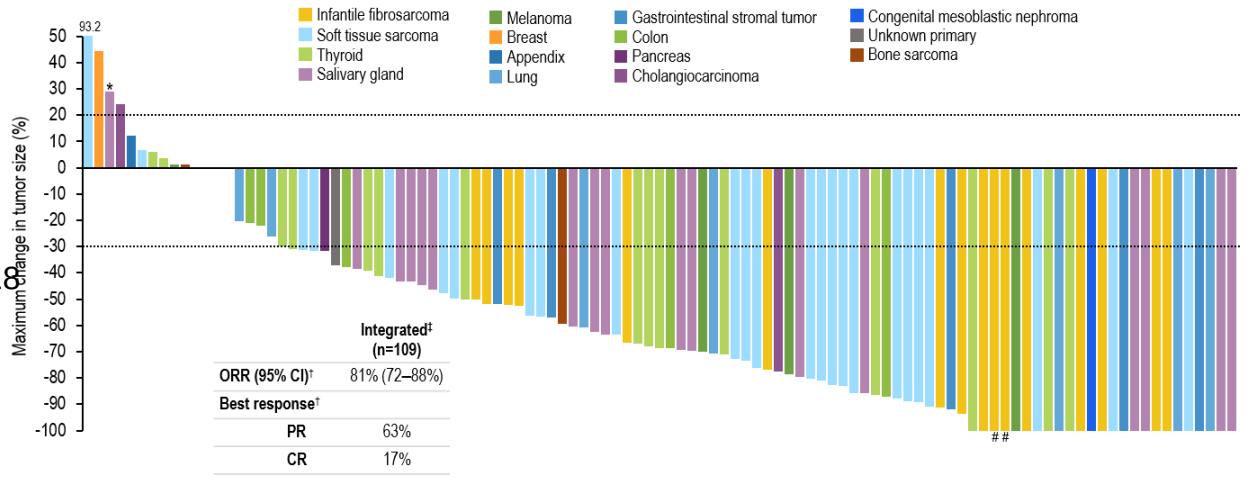


References 1. Doebele et al. *Cancer Discov.* 2015 Oct;5(10):1049-57. 2. Chartier et al. 2013 Kinome Render: a stand-alone and web-accessible tool to annotate the human protein kinome tree. *PeerJ* 1: e126.

Larotrectinib in TRK/Fusion Cancers

- Esmo 2018

Integrated dataset: Larotrectinib is efficacious regardless of tumor type

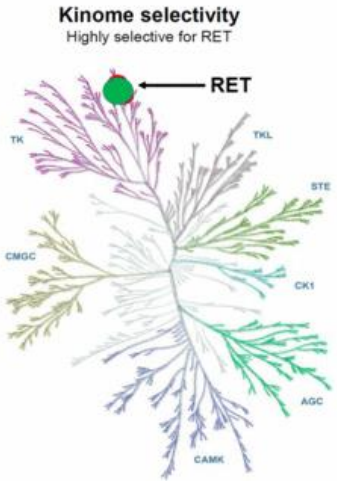


‡Includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment
*Patient had TRKC solvent front resistance mutation (G623R) at baseline due to prior therapy; #Surgical CR; †RECIST 1.1
Note: Two patients not shown here. These patients discontinued treatment prior to any post-baseline tumor measurements.
CR, complete response; ORR, objective response rate; PR, partial response

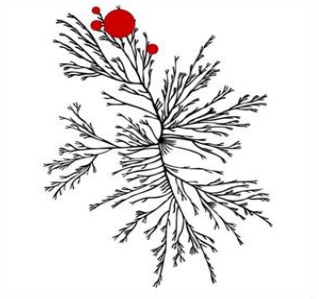
Investigator response assessments, as of 30 July 2018

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

Selpercatinib



Pralsetinib: High kinome selectivity for RET

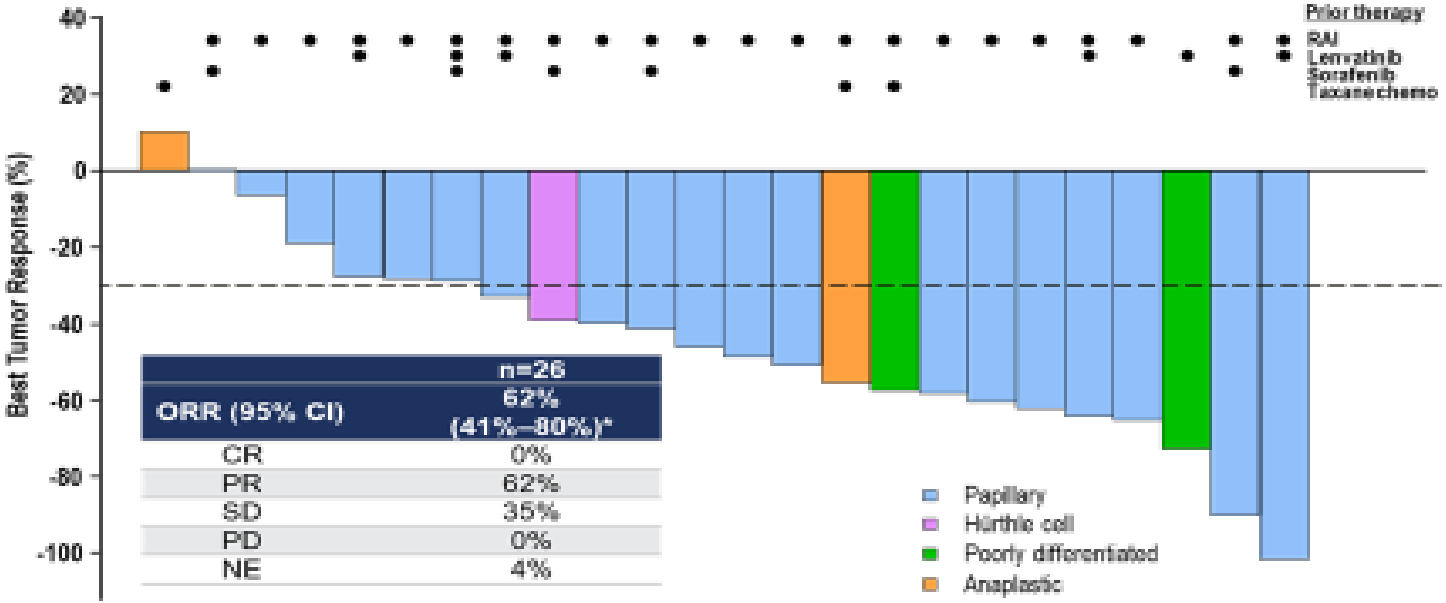


Pralsetinib vs. pharmacologically relevant kinases:

- ~90-fold more selective for RET than VEGFR2
- 20-fold more selective for RET than JAK1

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

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



	n=26
ORR (95% CI)	62% (41%–80%)*
CR	0%
PR	62%
SD	35%
PD	0%
NE	4%

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. 2 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 2 unconfirmed PRs awaiting confirmatory response assessments. NE=not evaluable, n=1 patient deemed not evaluable on study by the investigator; RAI=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.