Targeted therapy for HNSCC
&
Thyroid Cancer

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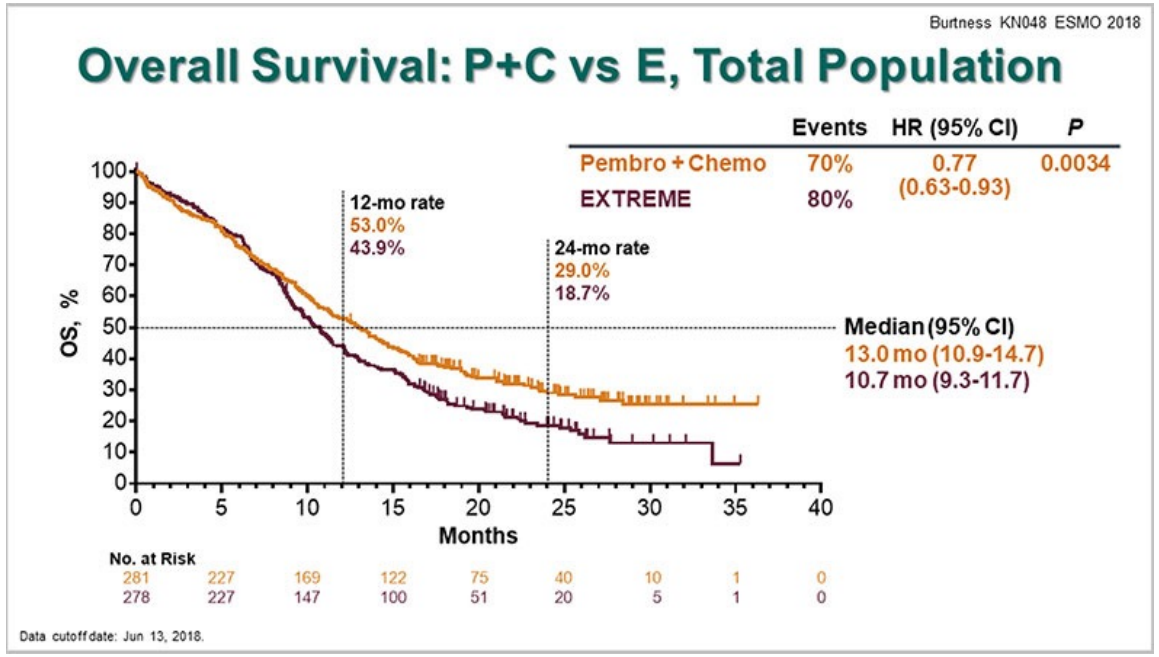
Head and Neck Cancer

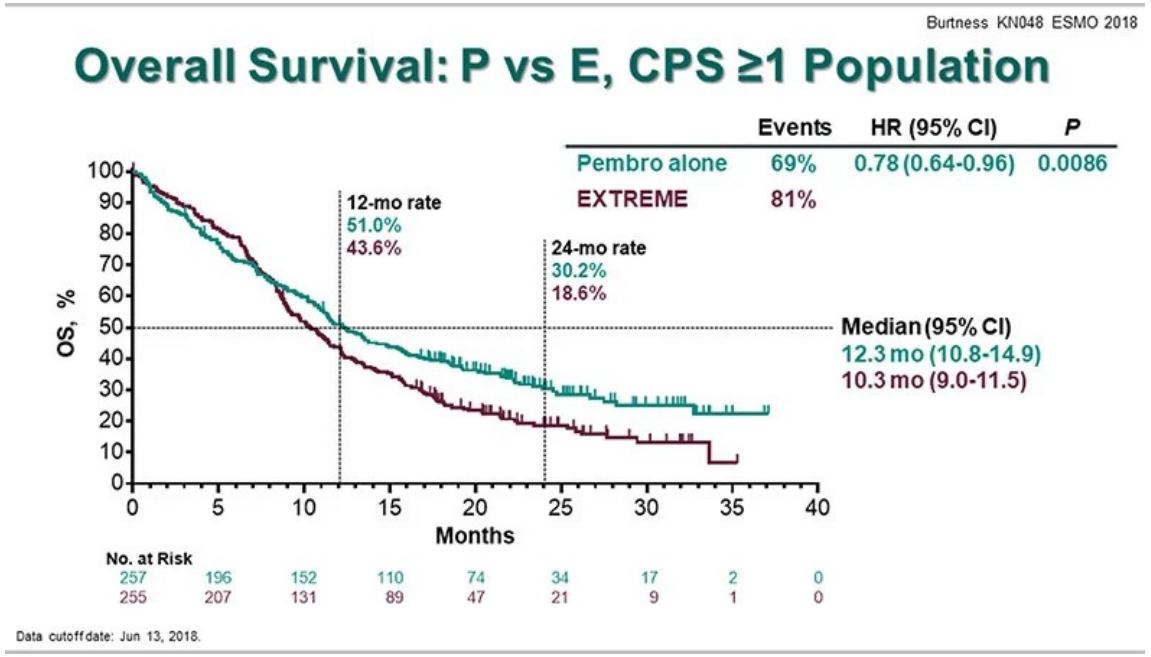
- About 4% of all cancers in the United States.
  - Estimated 66,630 people (48,740 men and 17,890 women) will develop head and neck cancer.

- Aprox. 14,620 deaths (10,640 men and 3,980 women) from head and neck a year in US

Head and Neck Cancer

A decade of advances, so much more to do…





Targeted Therapy???

Sledge 2005:

"A targeted therapy should attack a biologically important process (usually, though not necessarily, a single molecule), preferably one central to a hallmark of cancer"

→ Is **Methotrexate** a targeted therapy, since it only inhibits dihydrofolate reductase?

→ Are Aromatase inhibitors targeted therapies?

Peters GJ. *From 'Targeted Therapy' to Targeted Therapy.* Anticancer Res. 2019 Jul;39(7):3341-3345

Targeted Therapy???

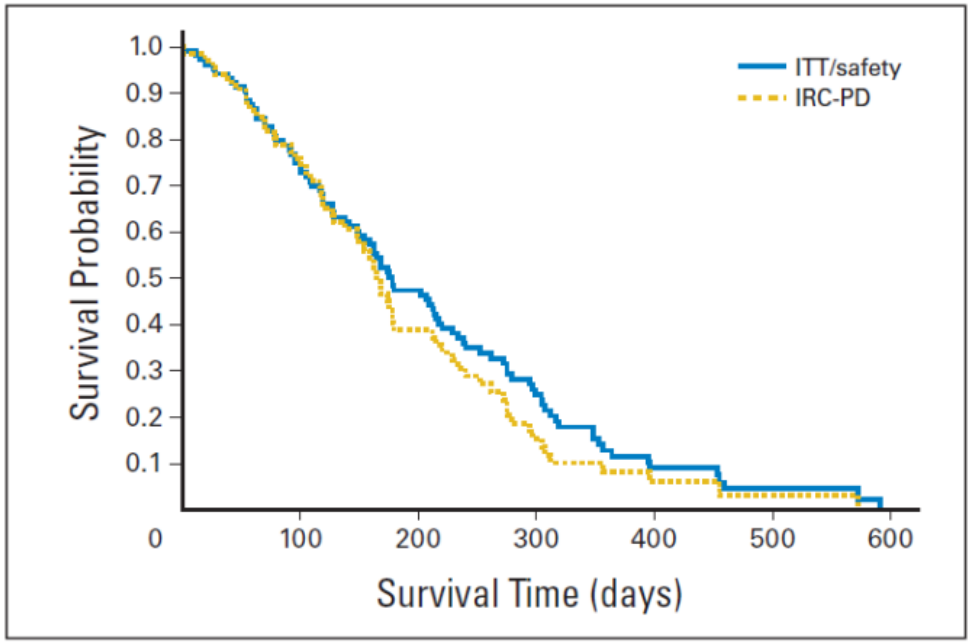
NCI…

"*Targeted therapies act on specific molecular targets, were designed to interact with their target, and are often cytostatic (block proliferation), while standard conventional chemotherapy is cytotoxic*"

Imatinib → first targeted therapy?

Head and Neck Cancer

A decade of advances, so much more to do…



- **Cetuximab is only "targeted therapy" currently approved for FDA**
- **Low single agent ORR and DOR**

Cetuximab in platinum-refractory SCCHN.

- ORR 13%

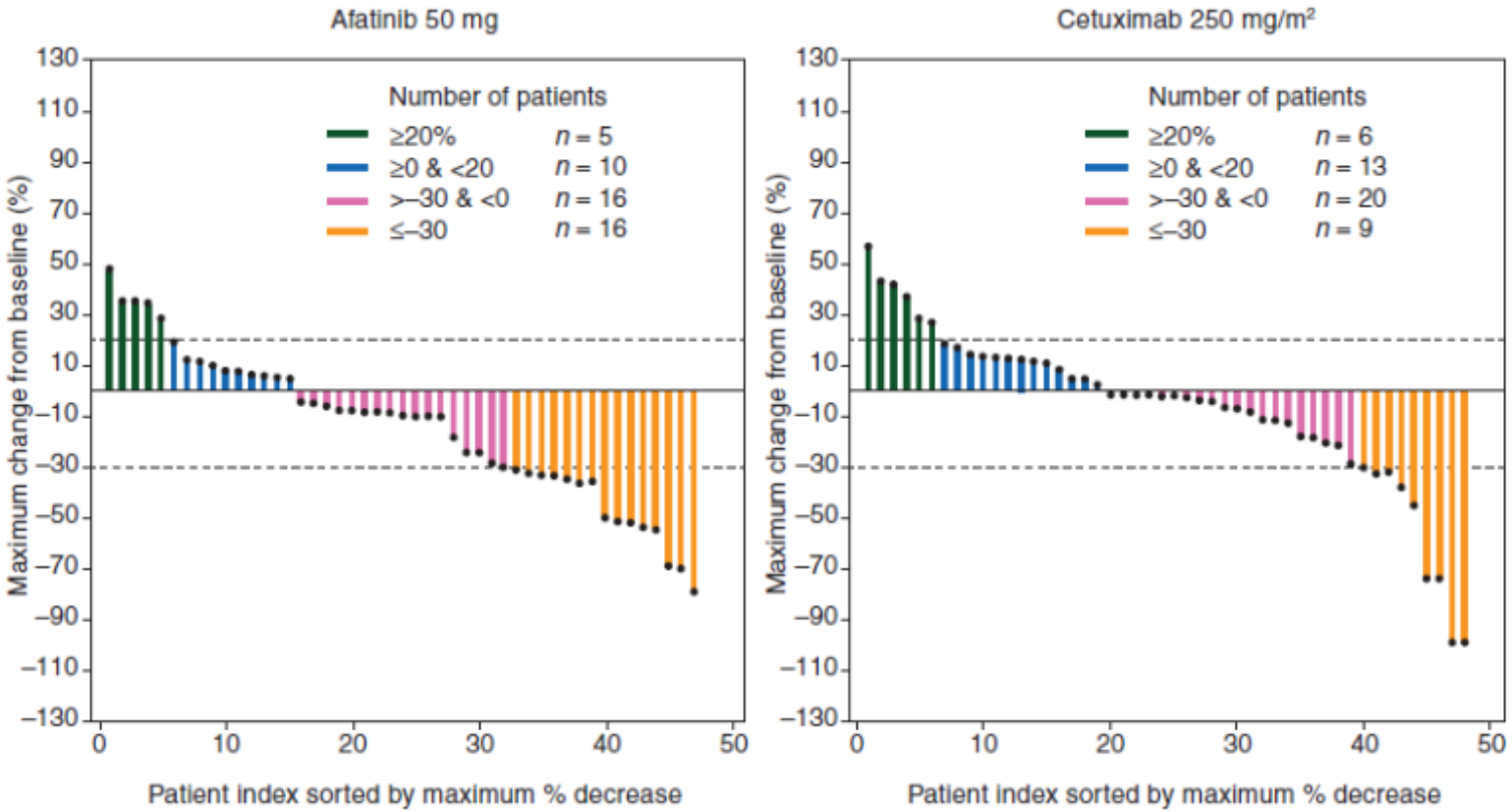
J Clin Oncol 2007 25:2171-2177.

Afatinib vs cetuximab in unselected R/M SCCHN

ORR 16.1% with Afat vs 6.5% with Cetux. (Investigator reported)

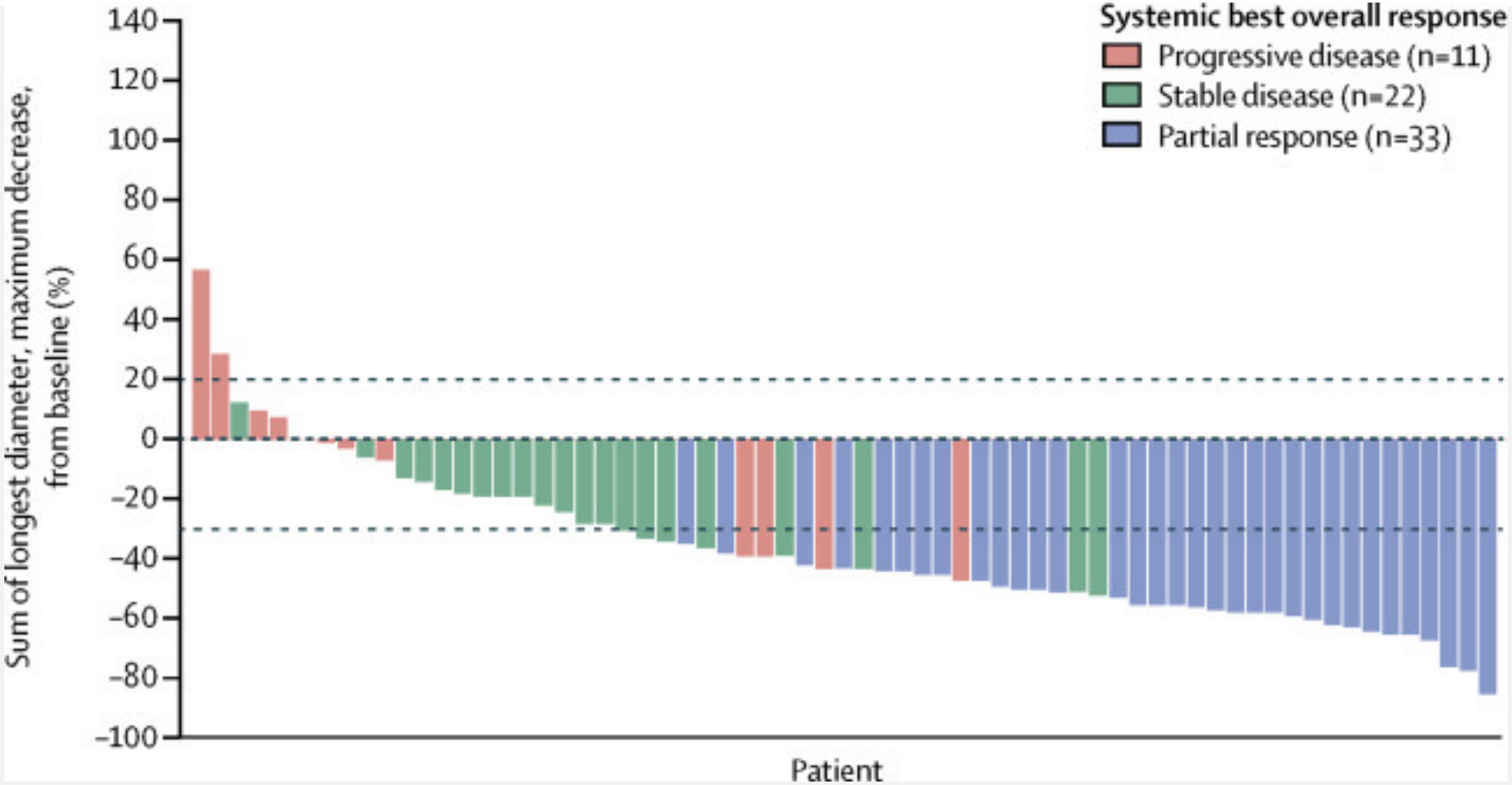
DRAEs leading to Tx discontinuation

23% with Afat vs 5% with Cetux



Annals of Oncology 25: 1813–1820, 2014

Targeted Therapy, to achieve good results, should have a predictive marker!



Shaw AT et al. Alectinib in crizotinib resistant ALK NSCLC – Lancet 2016

Head and Neck Cancer

So what are the targets?

- Primarly of tumors from the oral cavity (62%)
- Only 13% HPV-related
- Most male and heavy smokers

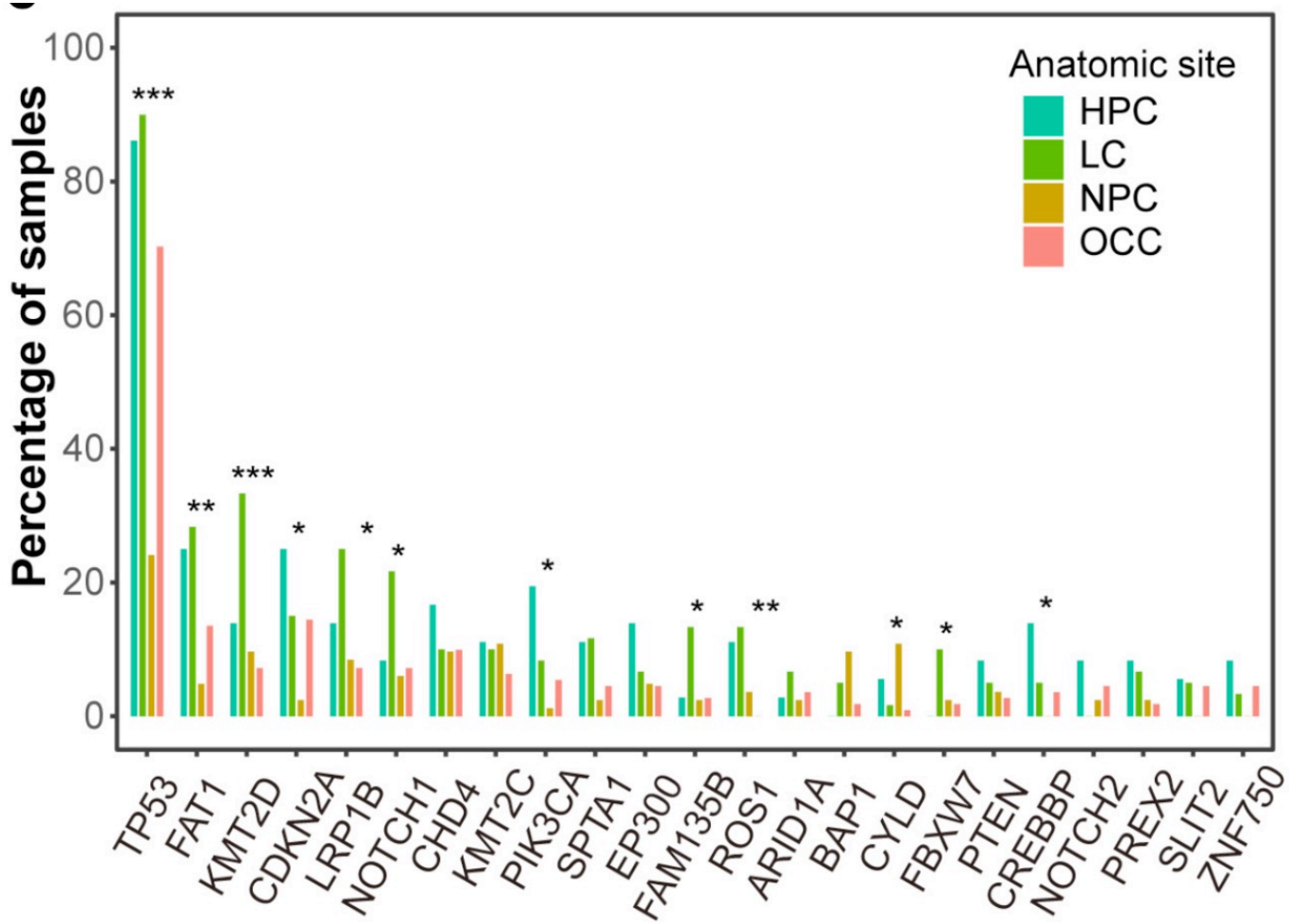
Results:

- TP53 (84%)
- CDKN2A (58%)
- CCDN1 (31%)

- ***HRAS 5%***
- ***PIK3CA (34%)***

The Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature* **517,** 576–582 (2015).

Genomic Landscape of Head and Neck Squamous Cell Carcinoma Across Different Anatomic Sites in Chinese Population



Front Genet 2021 Jun 14;12:680699

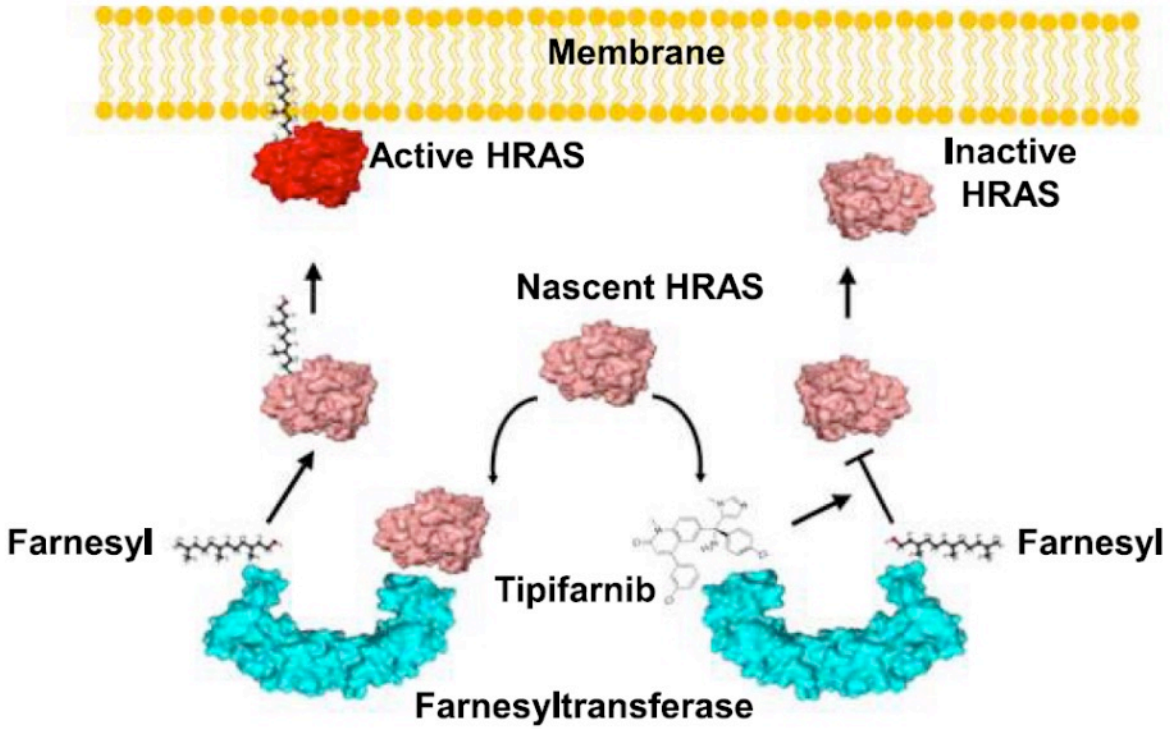
HRAS and Farnesyltransferase inhibitors in SCCHN

RAS proteins require posttranslational modifications to associate with intracellular membranes

HRAS is only dependent on farnesylation for its membrane localization

Overral 3-5% of SCCHN have HRAS mutation

Tipifarnib is a farnesyltransferase inhibitor (FTI)



Mol Cancer Ther 2020 Sep;19(9):1784-1796.

Tipifarnib in HRAS+ SCCHN

Stage 1

Patients with HRAS-mutant solid tumor

Cohort 1: Thyroid Cancer
13 patients dosed
11 evaluable
9 patients with SD
No PRs observed

Cohort 2: Solid tumors other than thyroid cancer
13 patients dosed
12 evaluable
7 patients with SD
2 PRs observed in 3 patients with HNSCC

Cohort 3: SCC other than HNSCC
Up to 20 patients

Stage 2

HNSCC only
Primary objective met with 5 PRs in a total of 9 patients with HNSCC

Cohort Expansion

Cohort expanded to further characterize safety and tolerability in indication(s) of interest

Total patients with HNSCC enrolled
(N = 31)
(30 from KO-TIP-001 and 1 expanded access)

HRAS VAF ≥ 20%
serum albumin ≥ 3.5g/dL or HRAS ≥ 35%
(n = 22)

HRAS VAF ≤ 20%
HRAS VAF 20%-35% with serum albumin ≤ 3.5g/dL
(n = 9)

Patients Received Treatment
(n = 22)

Patients evaluable for efficacy
(n = 20)
PR (n = 11)
SD (n = 9)

Patients not evaluable for efficacy
(n = 2)

Patients evaluable for efficacy
(n = 4)
SD (n = 2)
PD (n = 2)

Patients not evaluable for efficacy
(n = 5)

VAF, variant allele frequency

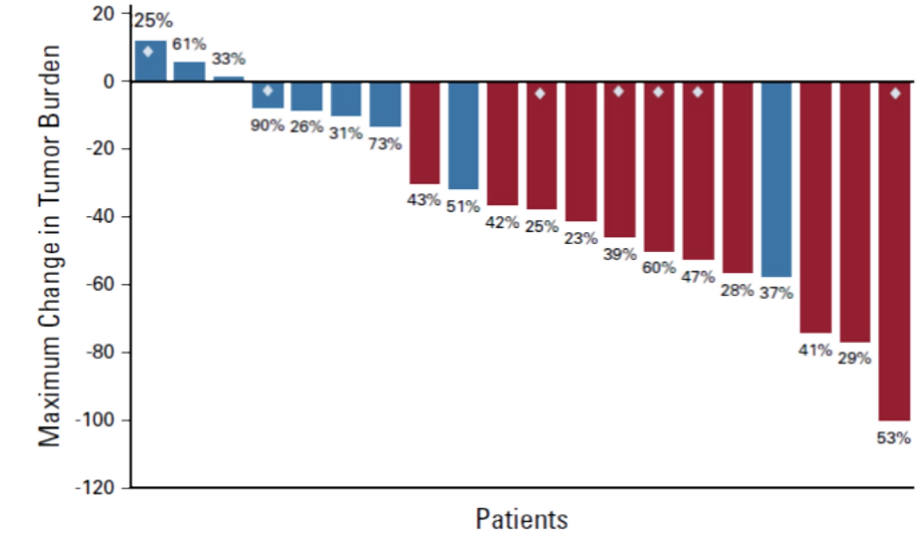
[1]Ho AL, Brana I, Haddad R, et al. Tipifarnib in Head and Neck Squamous Cell Carcinoma With *HRAS* Mutations. *J Clin Oncol*. 2021;39(17):1856-1864. doi:10.1200/JCO.20.02903.

Demographics of Patients with High-VAF HNSCC

Characteristic	%
Patients enrolled	22
Patients evaluable for efficacy	90.1%
Age (years), median (range)	63 (20-89)
Male	68.2%
Site of primary tumor	
Oral cavity	45.5%
Pharynx	18.2%
Larynx	13.6%
Other	22.7%
No. of prior anticancer regimens	
Median (min, max)	2 (0, 6)
Type of prior anticancer therapy	
Platinum	90.9%
Immunotherapy	63.6%
Cetuximab	50.0%
HPV status available	61.9%
HPV Positive (of 13)	30.7%
HPV Negative (of 13)	69.2%

Tipifarnib in Head and Neck Squamous Cell Carcinoma With HRAS Mutations

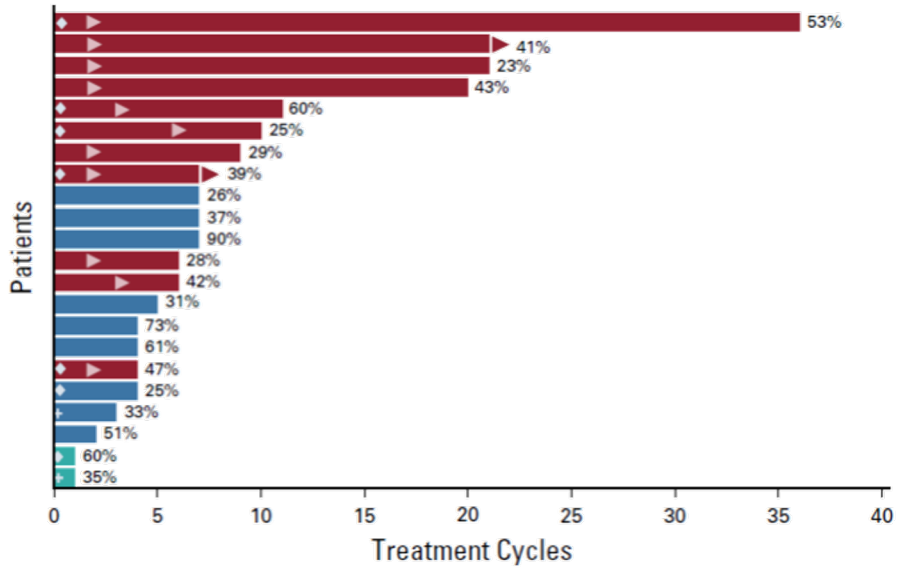
Maximal change in tumor size



PR
SD
Not evaluable for efficacy
Patient initiated treatment at 600 mg bid
Patient withdrew consent
Start of Response
Active treatment

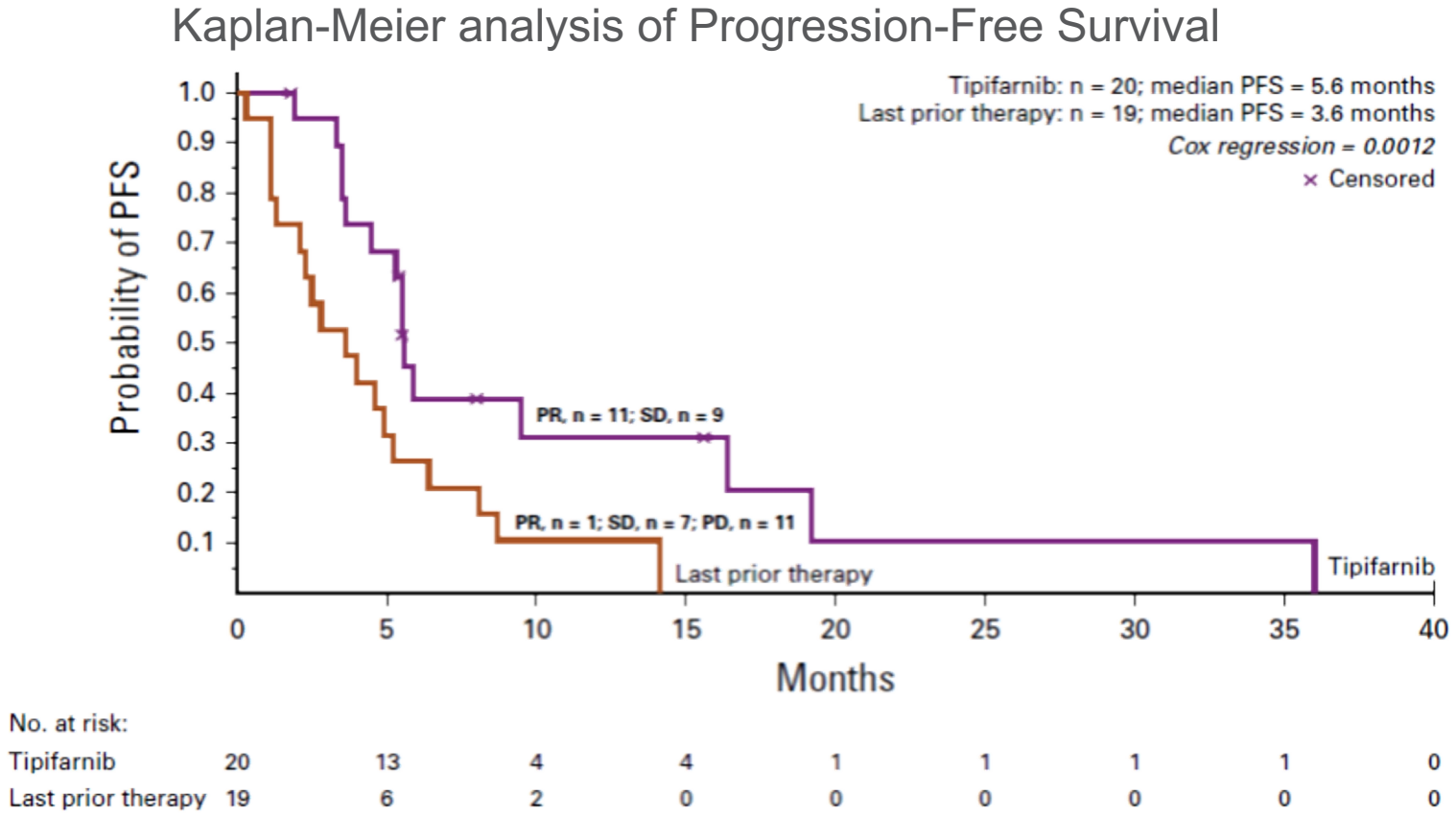
% Numbers at the end of bars represent VAF for each patient

Duration of response to treatment



ORR in pts VAF > 20: 55%

Tipifarnib in Head and Neck Squamous Cell Carcinoma With HRAS Mutations - PFS



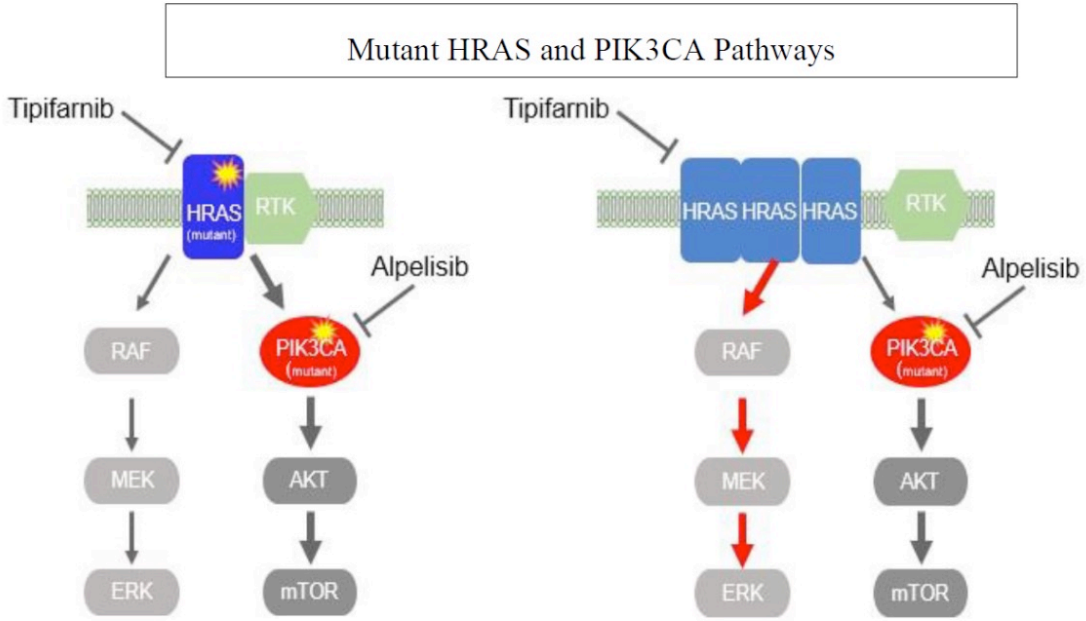
Ho AL, et al. Tipifarnib in Head and Neck Squamous Cell Carcinoma With *HRAS* Mutations. *J Clin Oncol*. 2021;39(17):1856-1864.

n = 30

Blood and lymphatic system disorders	15 (50%)	**Metabolism and nutrition disorders**	9 (30%)
• Anemia	11 (37%)	• Hypercalcemia	3 (10%)
• Neutropenia	3 (10%)	• Hypokalemia	3 (10%)
• Lymphopenia	4 (13%)	• Hypophosphatemia	3 (10%)
• Leukopenia	3 (10%)		
Respiratory, thoracic, and mediastinal disorders	9 (30%)	**Gastrointestinal disorders**	6 (20%)
• Pneumonia	3 (10%)	• Nausea	3 (10%)

Ho AL, et al. Tipifarnib in Head and Neck Squamous Cell Carcinoma With *HRAS* Mutations. *J Clin Oncol*. 2021;39(17):1856-1864.

A Phase 1/2 of tipifarnib and alpelisib in patients with HRAS overexpressing and/or PIK3CA-mutated and/or -amplified recurrent/metastatic head and neck squamous cell carcinoma (the Kurrent trial)



- Two cohorts:
  - PIK3CA mutant
  - HRAS overexpressed
- PIK3CA cohort ongoing

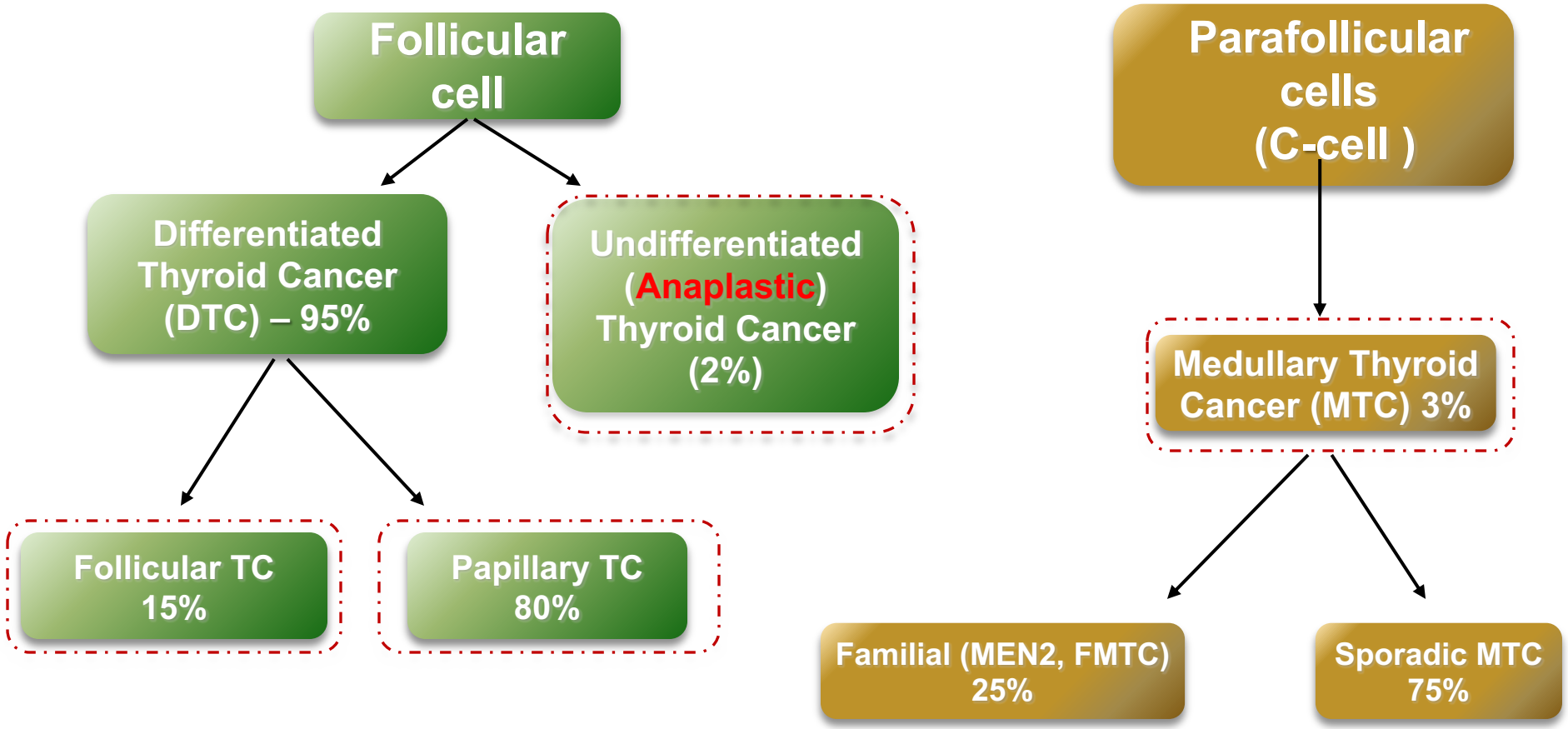
Simultaneous Dosing: 28 Day Cycle			
Week 1	Week 2	Week 3	Week 4
Tipifarnib	Rest	Tipifarnib	Rest
Alpelisib	Alpelisib	Alpelisib	Alpelisib

So whats going on at the Thyroid Cancer arena?

SARAH CANNON
Research Institute
at Florida Cancer Specialists

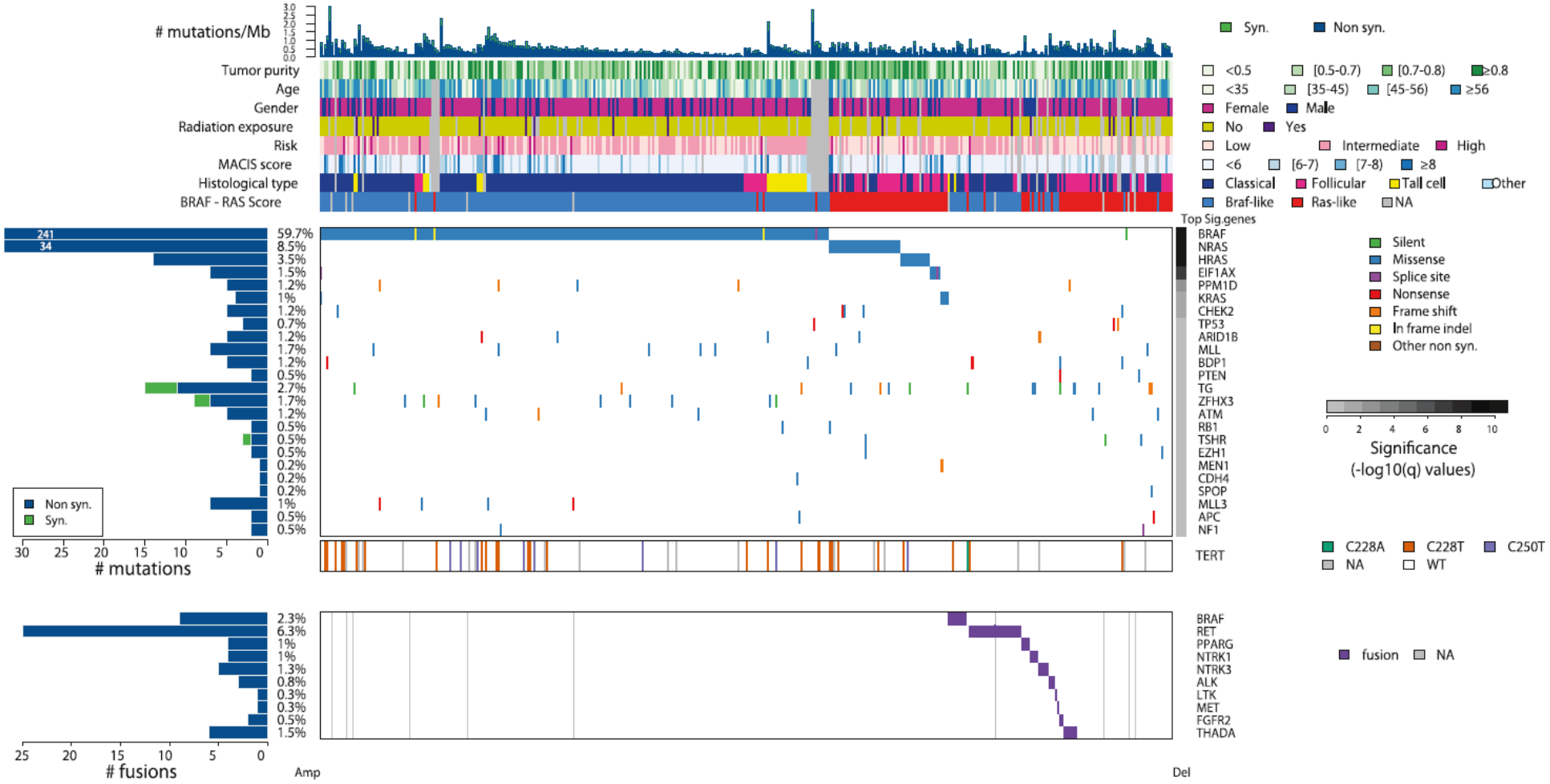
FLORIDA CANCER
SPECIALISTS
& Research Institute

Refractory Thyroid Cancer
Subtypes



Papillary Thyroid Cancer

Genomic characterization



Integrated genomic characterization of papillary thyroid carcinoma. Cancer Genome Atlas Research Network. Cell. 2014 Oct 23;159(3):676-90.

Recurrent Thyroid Cancer

Genomic characterization

Altered Gene	PTC	FTC	ATC	MTC
RET	-	-	-	80%
RET/PTC	6.3%	-	-	-
BRAF	59%	-	20%	-
HRAS	4%	18%	3%	
NTRK1,3	0.8%	-	-	-
B-catenin		-	-	-
PAX8:PPARγ		35%	-	-
TP53	1.2%	1.0%	65%	-
other	20%	20%	25%	19%

PTC: Papillary Thyroid Cancer
ATC: Anaplastic Thyroid Cancer

FTC: Follicular Thyroid Cancer
MTC: Medullary Thyroid Cancer

Clin Cancer Res 2018 Jul 1;24(13):3059-3068.

Refractory Thyroid Cancer

Medullary vs. Differentiated

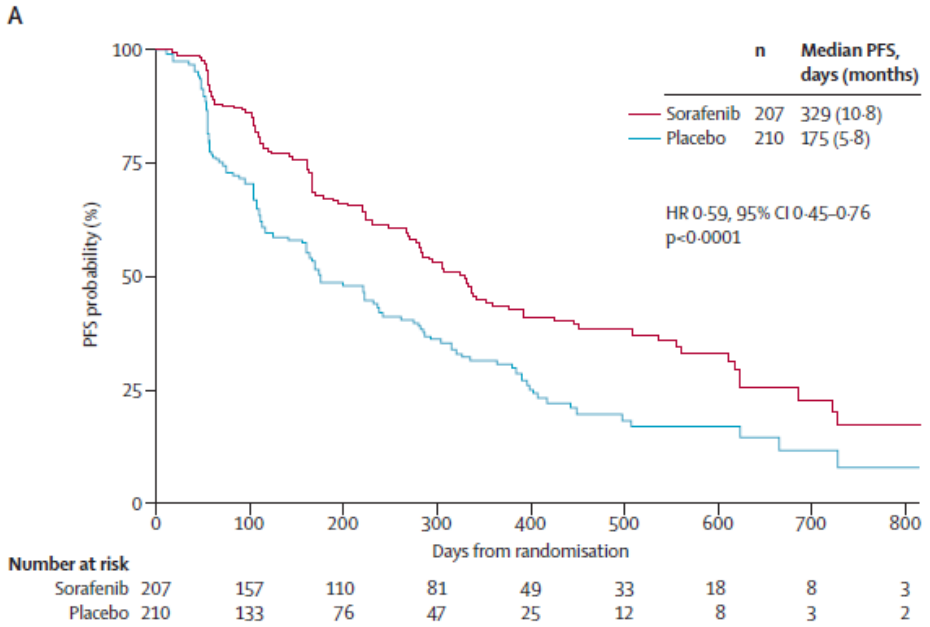
Medullary (3%)	Differentiated (95%)
RAI resistant	RAI-avid (initially)
+ RET Mutation	+ BRAF and RET/PTC
85% 10-year OS	95% 10-year OS
SM: CEA and Calcitonin	SM: Thyroglobulin

RAI Refractory Thyroid Cancer

RAI Refractory Differentiated Thyroid Cancer (DTC)
DECISION Trial

Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial

- Sorafenib → MKI of VEGFRs 1, 2, and 3, PDGFR β, Raf-1, RET, and BRAF
- 207 pts on sorafenib and 210 on placebo
- Crossover allowed at progression



- **PFS 10.8 vs 5.8 months**
- **ORR 20%, Clinical Benefit 54%**

Lancet. 2014 Jul 26;384(9940):319-28.

RAI Refractory Differentiated Thyroid Cancer (DTC)
SELECT Trial

ORIGINAL ARTICLE

Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer

- **Lenvatinib is an oral MKI of *VEGFRs* 1, 2, and 3, *FGFRs* 1 through 4, *PDGFR* α, *RET*, and *KIT***
- 261 pts in **lenvatinib**, 131 with placebo
- *Crossover allowed at progression*

N Engl J Med. 2015 Feb 12;372(7):621-30

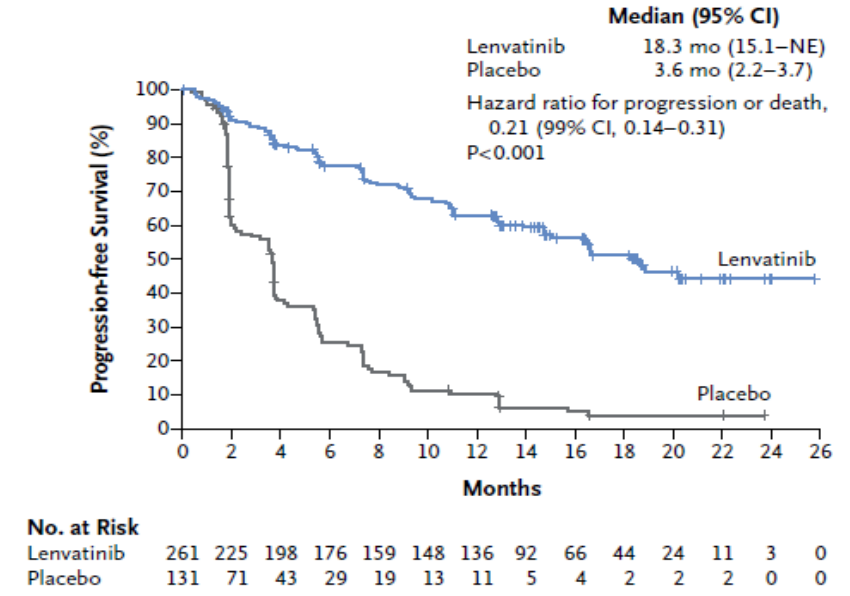


Figure 2. Kaplan–Meier Estimate of Progression-free Survival in the Intention-to-Treat Population.

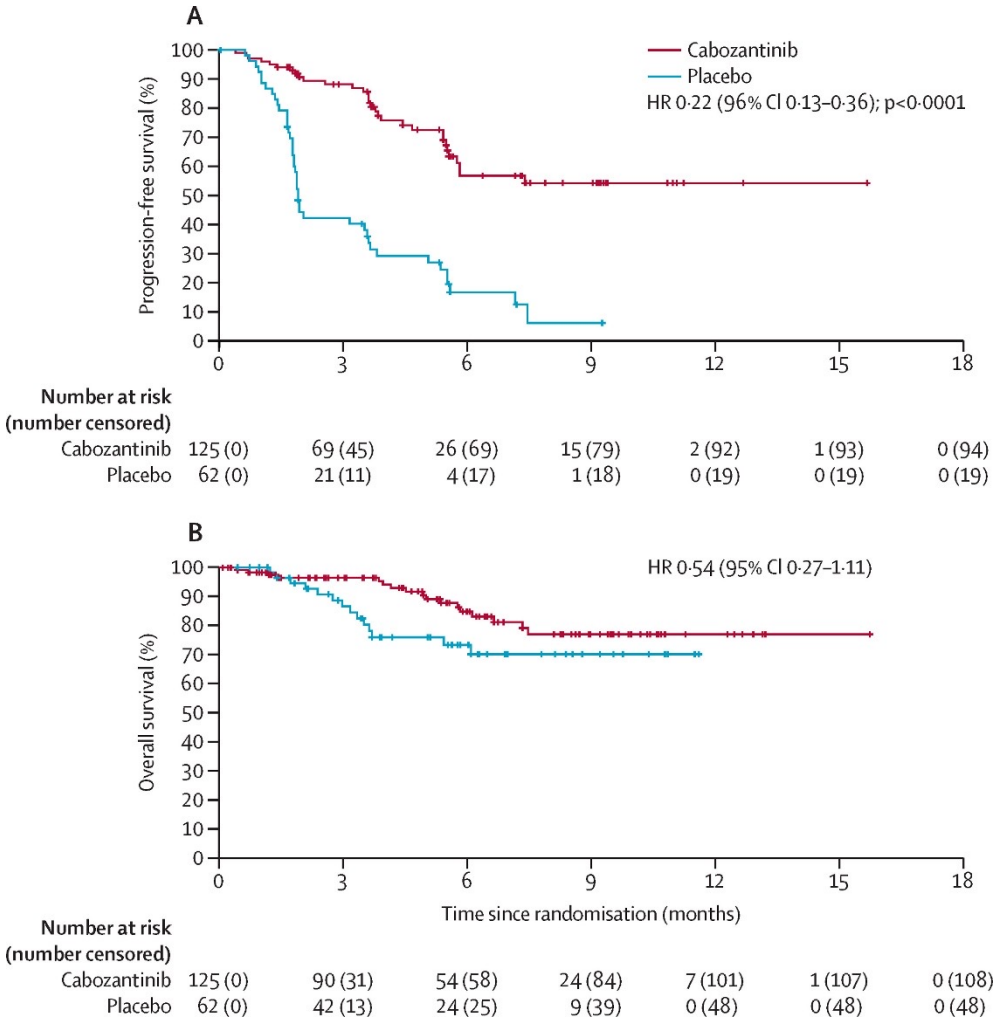
- **PFS 18.3 vs 3.6 months**
- **ORR 64.8%, Clinical Benefit 81%**

RAI Refractory Differentiated Thyroid Cancer (DTC)
SELECT and DECISION Trials

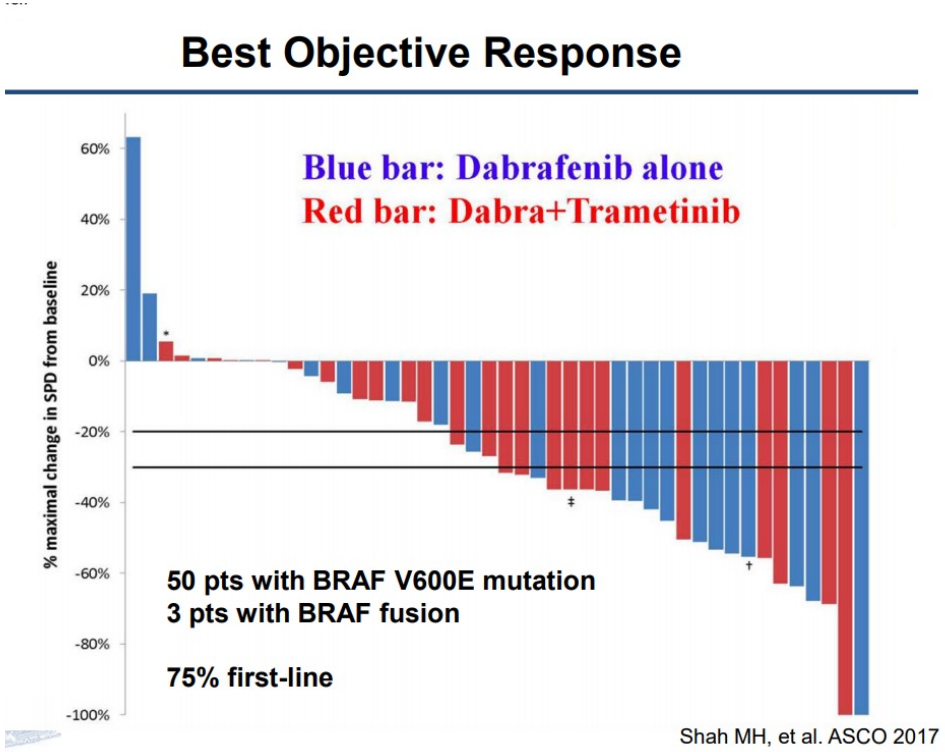
- ***Sorafenib***
  - Treatment-Related Serious AE's in 20% of pts
    - HTN, hand-foot syndrome, dyspnea, diarrhea
  - ORR 20%, PFS 11 months
  - FDA approved for RAI refractory DTC in ***Nov 2013***
- ***Lenvatinib***
  - Treatment-Related Serious AE's in 30%
    - HTN, proteinuria, QT prolongation (8%), diarrhea
  - ORR 65%, PFS 18.3 months
  - FDA approved for RAI refractory DTC in ***Feb 2015***

Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial

- RAI refractory pts (progressed on Lenvatinib or sorafenib) randomized 2:1 to cabozantinib (60 mg once daily) or matching placebo
- PFS significantly improved compared to placebo (96% CI 5.7–NE) vs. 1.9 months (1.8–3.6); HR 0.22
- ORR in the cabozantinib 15% (99% CI 5.8–29.3) of 67 patients in the cabozantinib group versus 0% (0–14·8) in the placebo (p=0·028)



Results of randomized phase II trial of dabrafenib versus dabrafenib plus trametinib in BRAF-mutated papillary thyroid carcinoma.
Journal of Clinical Oncology 35, no. 15_suppl 6022-6022.



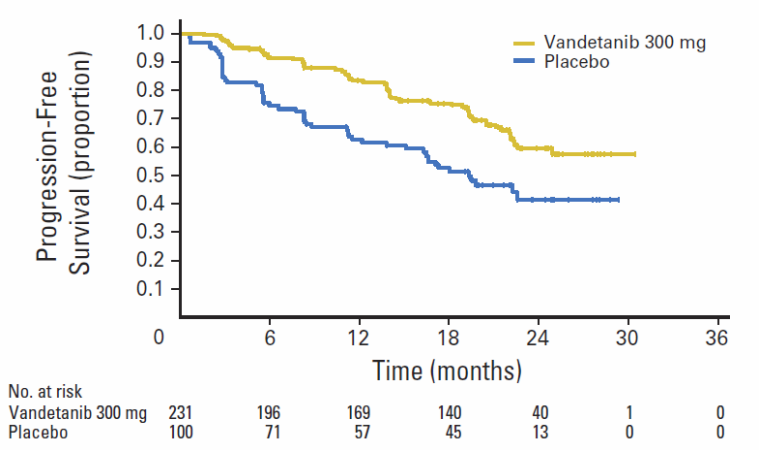
Metastatic Medullary Thyroid Cancer

Metastatic *Medullary* Thyroid Cancer
MTC - ZETA and EXAM Trials

VOLUME 30 · NUMBER 2 · JANUARY 10 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Vandetanib in Patients With Locally Advanced or Metastatic Medullary Thyroid Cancer: A Randomized, Double-Blind Phase III Trial

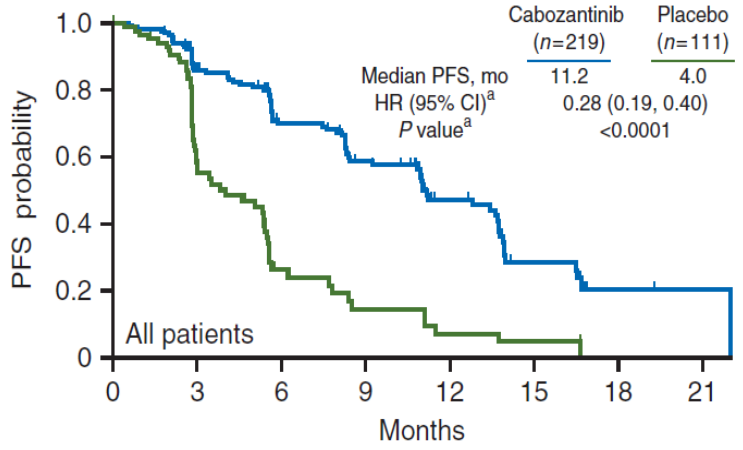
Samuel A. Wells Jr, Bruce G. Robinson, Robert F. Gagel, Henning Dralle, James A. Fagin, Massimo Santoro, Eric Baudin, Rossella Elisei, Barbara Jarzab, James R. Vasselli, Jessica Read, Peter Langmuir, Anderson J. Ryan, and Martin J. Schlumberger



VOLUME 31 · NUMBER 29 · OCTOBER 10 2013
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Cabozantinib in Progressive Medullary Thyroid Cancer

Rossella Elisei, Martin J. Schlumberger, Stefan P. Müller, Patrick Schöffski, Marcia S. Brose, Manisha H. Shah, Lisa Licitra, Barbara Jarzab, Viktor Medvedev, Michael C. Kreissl, Bruno Niederle, Ezra E.W. Cohen, Lori J. Wirth, Haythem Ali, Colin Hessel, Yifah Yaron, Douglas Ball, Barry Nelkin, and Steven I. Sherman



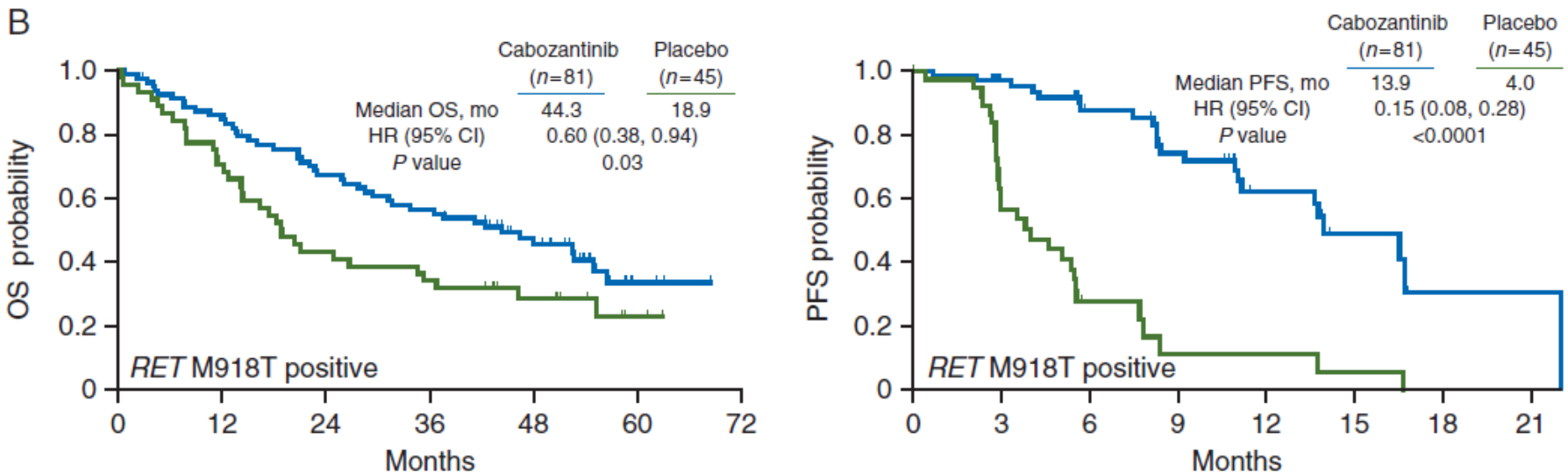
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 2813–2819, 2017
doi:10.1093/annonc/mdx479
Published online 22 September 2017

ORIGINAL ARTICLE

Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma

M. Schlumberger[1*], R. Elisei[2], S. Müller[3], P. Schöffski[4,5], M. Brose[6], M. Shah[7], L. Licitra[8,9], J. Krajewska[10], M. C. Kreissl[11†], B. Niederle[12], E. E. W. Cohen[13], L. Wirth[14], H. Ali[15], D. O. Clary[16], Y. Yaron[16], M. Mangeshkar[16], D. Ball[17], B. Nelkin[17] & S. Sherman[18]



Medullary Thyroid Cancer
MTC - ZETA and EXAM Trials

- Treatment only in patients with progression within 6 months

- Two drugs approved by FDA
  - Vandetanib
  - Cabozatinib
  - ✓ *Both with improved PFS*
  - ❖ *Severe AE's in 1-8%, AE's in 30-40%*

Medullary Thyroid Cancer

RET mutations

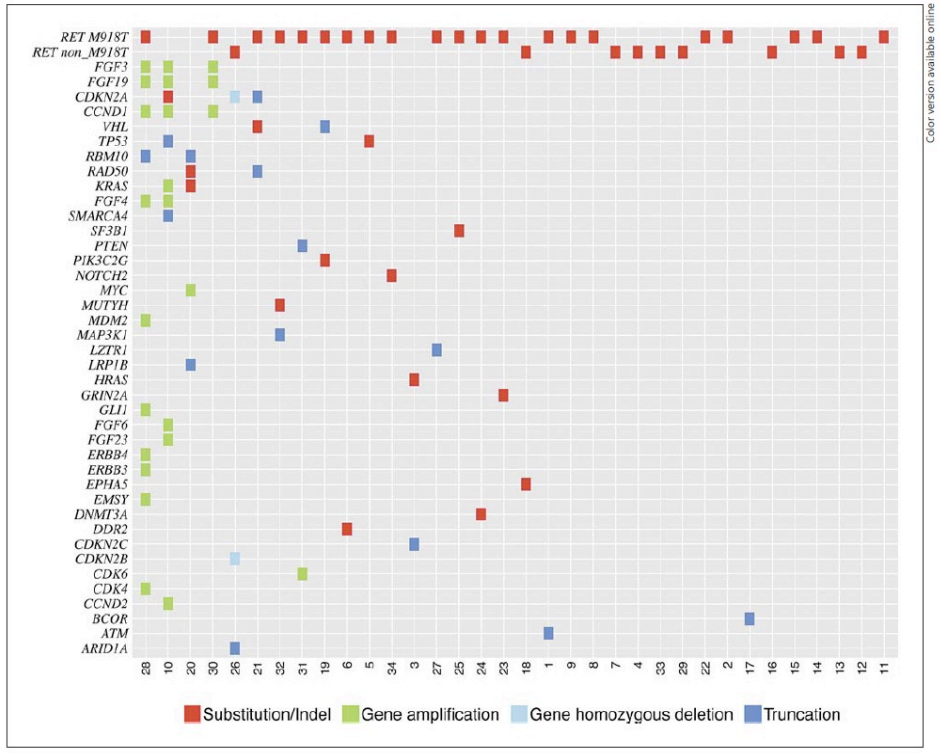
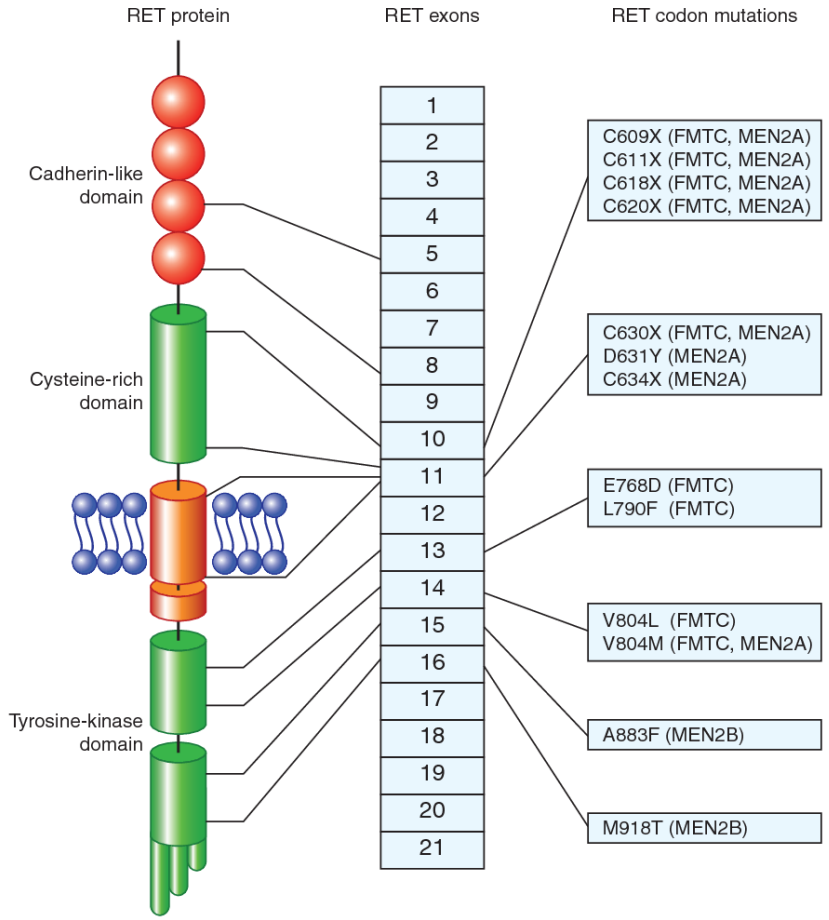


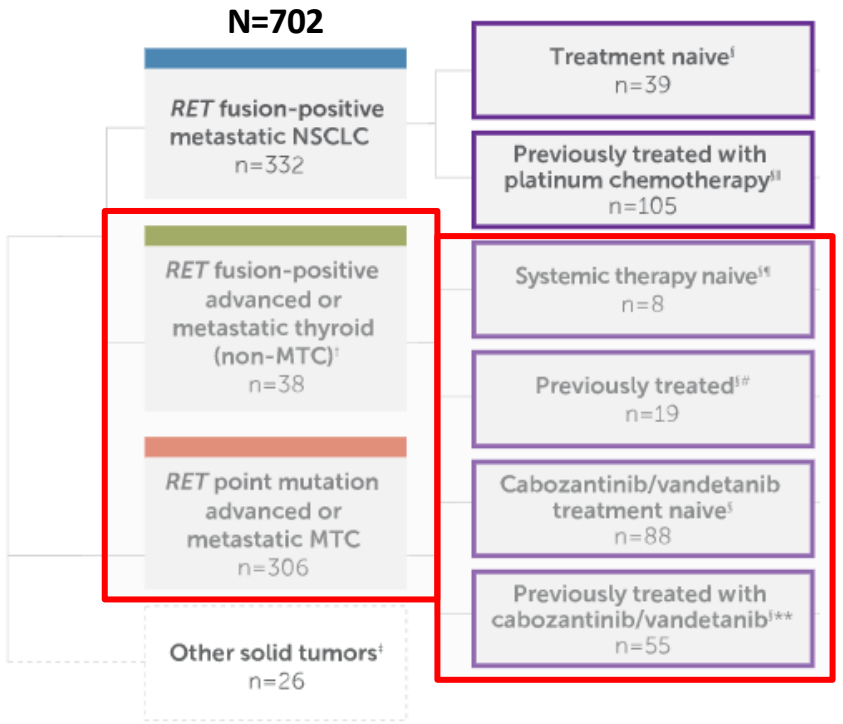
Fig. 1. Tile plot of genomic alterations identified by comprehensive genomic profiling in 34 cases of advanced MTC.



Andreas M. Heilmann AM et al. Comprehensive Genomic Profiling of Clinically Advanced Medullary Thyroid Carcinoma. Oncology 2016.

Phase I/II LIBRETTO-001: Selpercatinib in RET-Mutant MTC and RET Fusion–Positive Thyroid Cancer

- Adv/met solid tumor
- In need of systemic therapy
- RET fusion or mutation[a]
- ECOG PS 0-2
- Adequate organ function
- Normal QT interval (corrected for HR ≤ 470 msec)
- Any no. prior tx



- ***RET* alteration**
  - Determined by local CLIA (or similarly accredited) laboratories
- **Primary endpoint**
  - Objective response rate (RECIST 1.1)
- **Secondary endpoints**
  - Duration of response
  - Progression-free survival
  - Safety
- Treatment beyond progression permitted with continued benefit

- For this analysis, had to have either RET-mutant MTC or RET fusion(+) thyroid ca of any histology

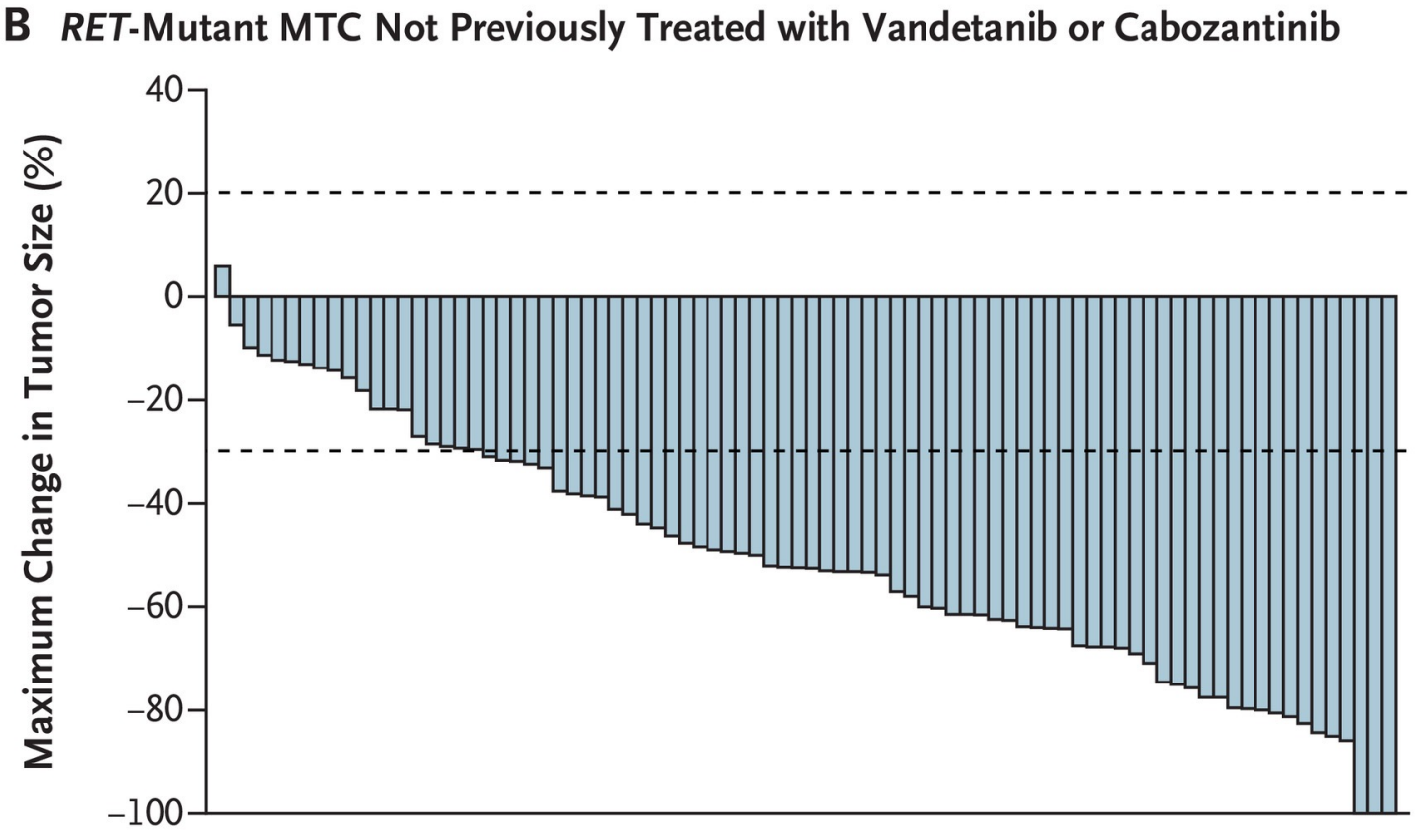
Wirth LJ, et al. *N Engl J Med*. 2020;383:825-835.

Phase I/II LIBRETTO-001: Efficacy

Response	RET-Mutant MTC Previously Treated	RET-Mutant MTC Not Previously Treated	Previously Treated RET Fusion–Positive Thyroid Cancer	Not Previously Treated RET Fusion–Positive Thyroid Cancer
	IND-REV (N=55)	IND-REV (N=88)	IND-REV (N=19)	IND-REV (N=8)
Objective response, no. (%)	38 (69)	64 (73)	15 (79)	8 (100)
CR	9	11	5	12.5
PR	60	61	74	88
SD	25	23	21	
Median DOR, mo (95% CI)	NE (19.1–NE)	22.0 (NE–NE)	18.4 (7.6–NE)	NE
mPFS, mo (95% CI)	NE (24.4–NE)	23.6 (NE–NE)	20.1 (9.4–NE)	--

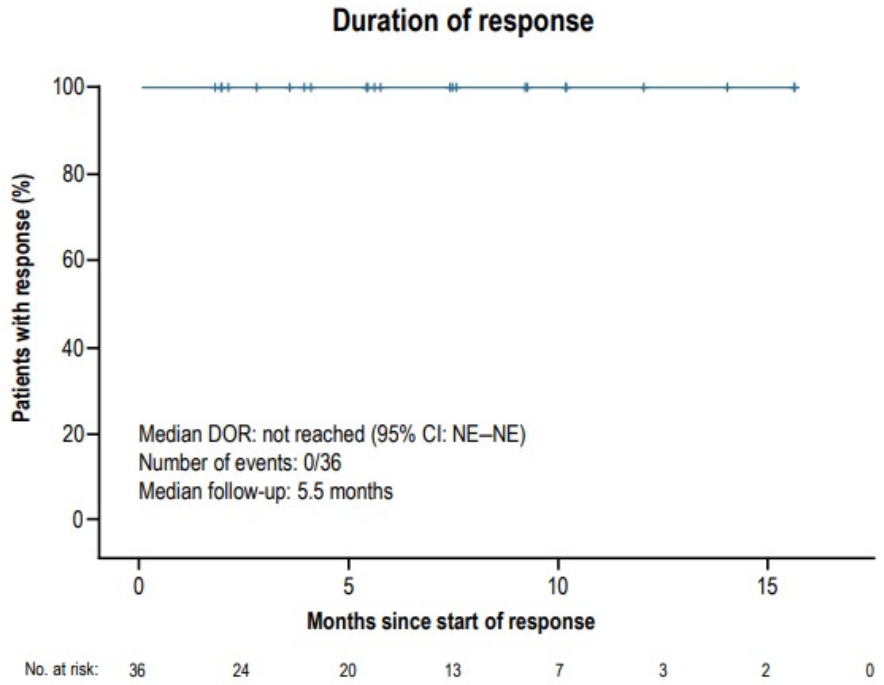
Wirth LJ, et al. N Engl J Med. 2020;383:825-835

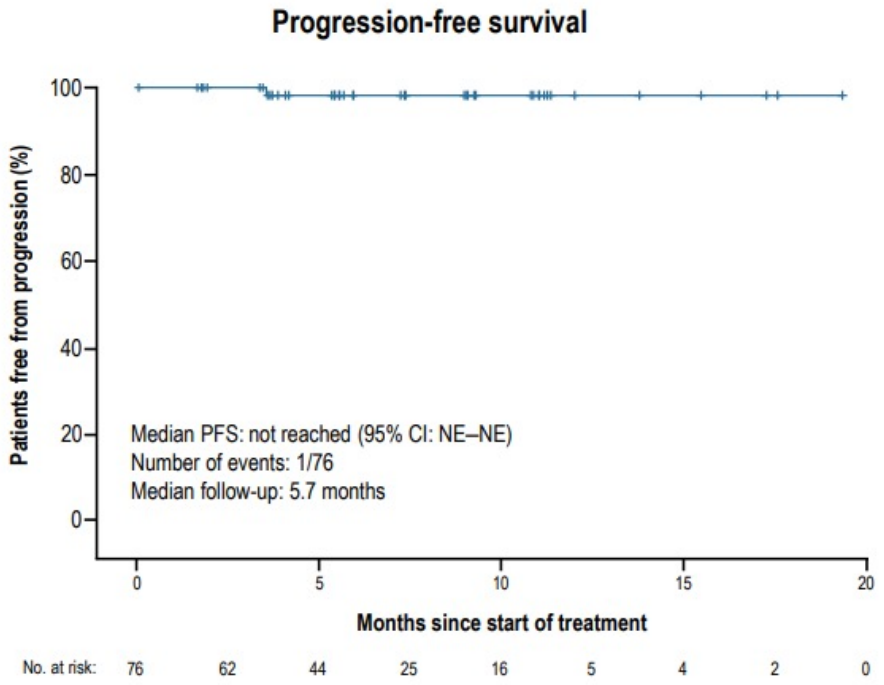
Phase I/II LIBRETTO-001: Tumor Response—RET Mutated, No Prior TKI



Wirth LJ, et al. N Engl J Med. 2020;383:825-835

Phase I/II LIBRETTO-001: Durability of Benefit—Cabozantinib-/Vandetanib-Naïve





BARCELONA 2019 ESMO congress

Data cutoff: June 17, 2019. No shading to show 95% confidence band due to a very low number of events.

Wirth LJ, et al. ESMO 2019. Abstract LBA93. Wirth LJ, et al. *N Engl J Med*. 2020;383:825-835.

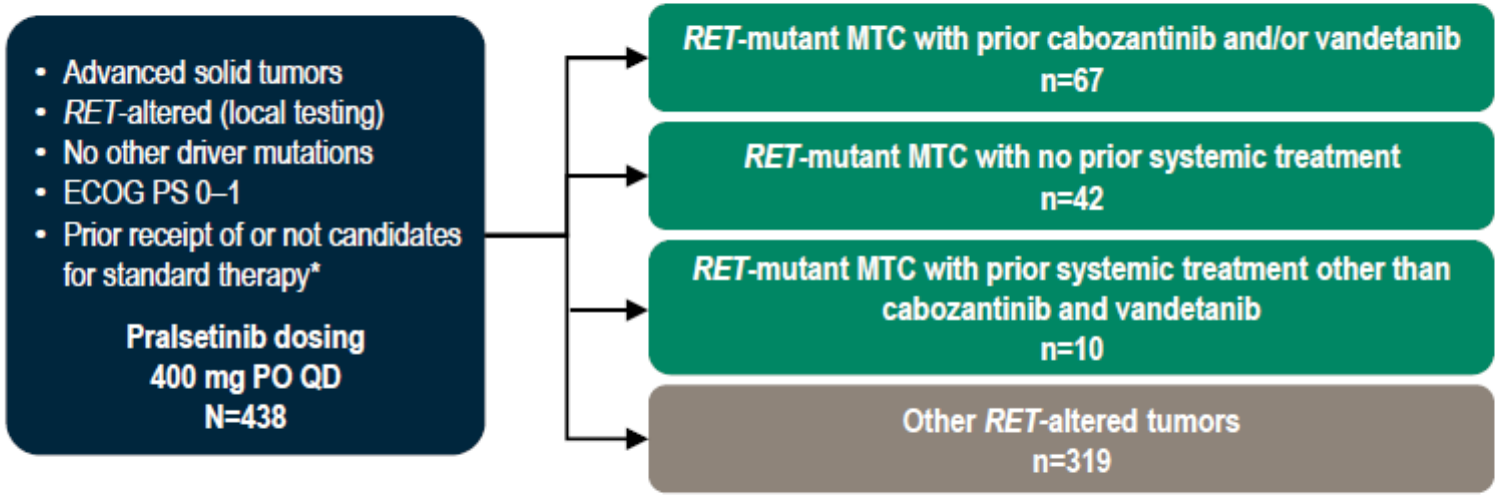
Phase I/II LIBRETTO-001: TRAEs in 162 Patients with RET-Mutant MTC or RET Fusion–Positive Thyroid Cancer Who Received Selpercatinib (≥15%)

AE	Treatment-Related AEs, N (%)		
	Grade 3	Grade 4	Any Grade
Any AE	45 (28)	3 (2)	153 (94)
Dry mouth	0	0	63 (39)
Hypertension	19 (12)	0	49 (30)
Diarrhea	4 (3)	0	27 (17)
Fatigue	1 (1)	0	41 (25)
Increased aspartate aminotransferase level	12 (7)	1 (1)	45 (28)
Nausea	0	0	25 (15)
Constipation	0	0	26 (16)
Increased alanine aminotransferase level	16 (10)	1 (1)	42 (26)
Peripheral edema	0	0	29 (18)

Of 531 patients who received selpercatinib:

- Dose reduction due to TRAE: 160 (30%)
- Discontinuation due to TRAE: 12 (2%); most common: elevated ALT (n = 2), drug hyper-sensitivity (n = 2)

Phase 1/2 ARROW Trial of Pralsetinib for RET-Mutant Medullary Thyroid Cancer—Study Design



Key endpoints

- **Blinded, independent central review ORR and DOR per RECIST v1.1**
- **Safety**

ARROW (NCT03037385) is an ongoing, international multicenter phase 1/2 study across 84 sites in 11 countries

*Until protocol amended in July 2019 to allow enrollment of treatment-naïve, standard therapy-eligible patients. Data cutoff February 13, 2020.
ECOG PS, Eastern Cooperative Oncology Group performance score; DOR, duration of response; NSCLC, non-small cell lung cancer; ORR, overall response; PO, orally; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Phase 1/2 ARROW: Efficacy in MTC

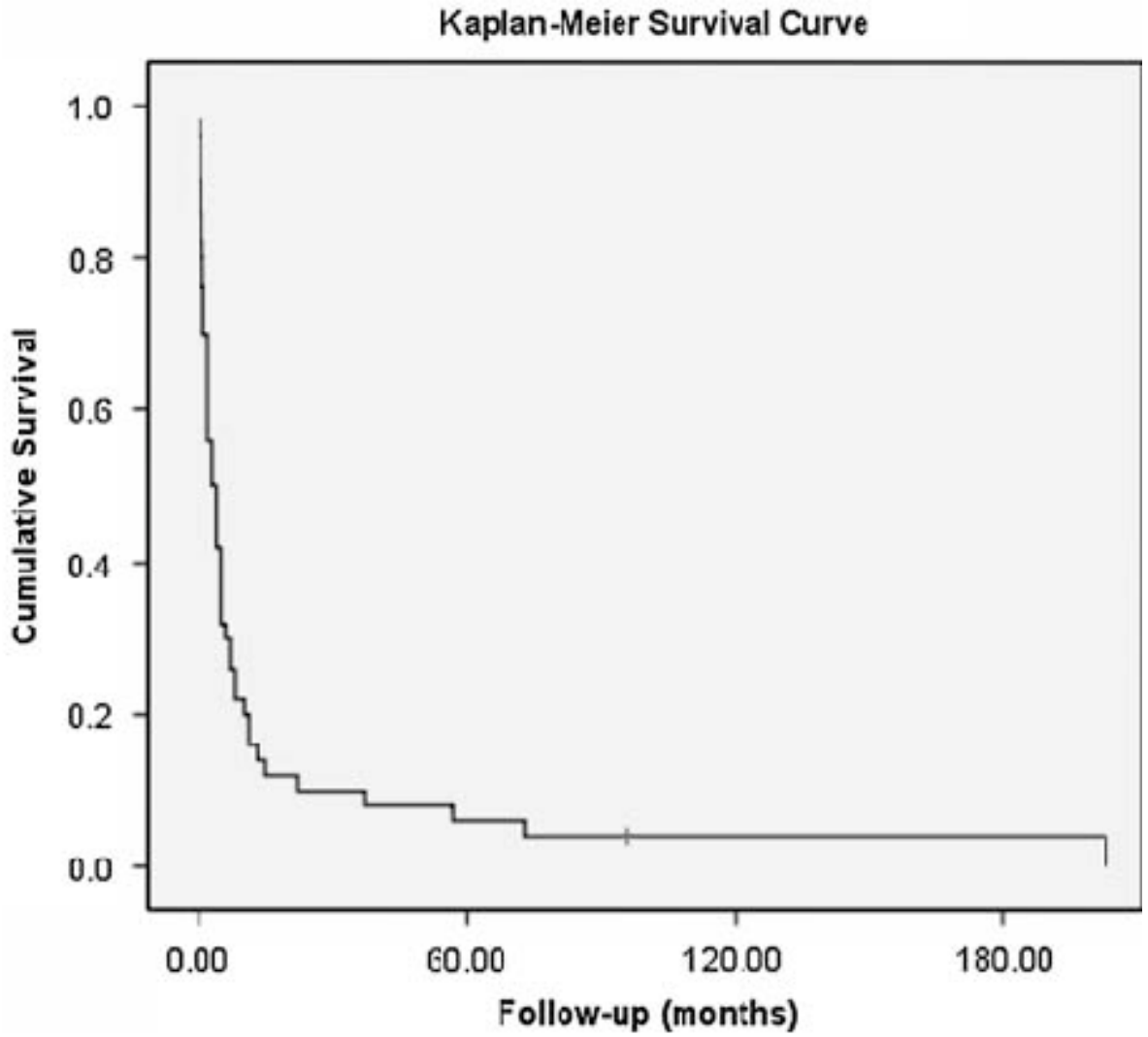
Efficacy	RET-Mutant MTC After CAB or VAN (N = 55)	CAB- and VAN-Naïve RET-Mutant MTC (N = 29)
ORR	60% (95% CI: 46-73)	66% (95% CI: 46-82)
Complete response	1.8%	10%
Partial response	58%	55%
Median DOR	NR (95% CI: 15.1 mo-NE) (n = 33)	NR (NE, NE) (N = 19)
DOR ≥ 6 mo[a]	79%	84%

a Calculated using the proportion of responders with an observed DOR ≥ 6 mo.
CAB, cabozantinib; DOR, duration of response; ORR, confirmed overall response rate by BICR; NE, not estimable; NR, not reached; VAN, vandetanib.
Pralsetinib. Prescribing Information. Blueprint. 2020.

Anaplatic (Undifferentiated) Thyroid Cancer

- All Considered Stage IV
- Chemo and RadioTx resistant
- 5-year relative survival rate around 7%
- **15-20% have BRAF mutation**

Anaplastic (Undifferentiated) Thyroid Cancer



Anaplatic (Undifferentiated) Thyroid Cancer – BRAFi

*Granted Accelerated approval by FDA on may 4th 2018

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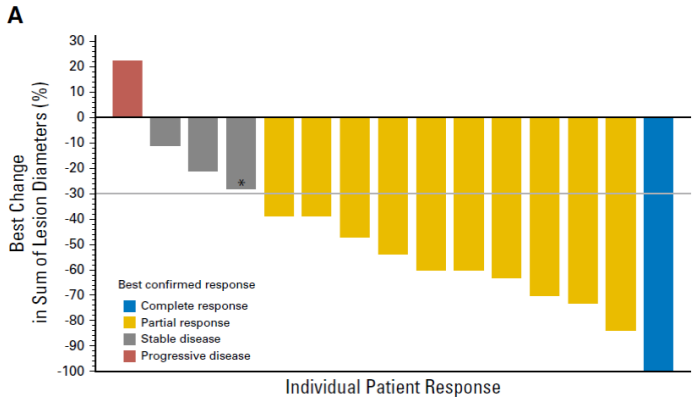
Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic *BRAF* V600–Mutant Anaplastic Thyroid Cancer

Vivek Subbiah, Robert J. Kreitman, Zev A. Wainberg, Jae Yong Cho, Jan H.M. Schellens, Jean Charles Soria, Patrick Y. Wen, Christoph Zielinski, Maria E. Cabanillas, Gladys Urbanowitz, Bijoyesh Mookerjee, Dazhe Wang, Fatima Rangwala, and Bhumsuk Keam

- ATC cohort of a 9-cohort trial (BRF117019) in patients with BRAF V600E mutation.
- 26 patient with ATC enrolled, median age was 70 years
- ORR in 23 evaluable patients 61%
- The duration of response was ≥ 6 months in 64% of responders.

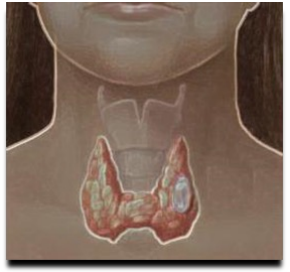


Updated results

Ann Oncol. 2022 Jan 10

- ***ORR 56%***
- ***12-month DOR 50%***
- ***OS 14.5***

Targeted therapy for thyroid cancer



- *All patients with thyroid cancer should have NGS done when RAI refractory, metastatic, progressive disease is seen (STAT for ATC)*
- *Lenvantinib is effective for 1st line RAI-refractory DTC*
- *Cabozatinib for second line DTC*
- *BRAF inhibitors could be used for BRAF positive DTC, good tolerability but maybe less ORR*

Targeted therapy for thyroid cancer

- ***Know the RET mutation status of your patient with MTC once metastatic!***

- ***Selpercatinib and Praseltinib are very effective in RET+ MTC***
-
- ***Vandetanib* and *Cabozatinib* are approved for refractory, progressive, unselected MTC**

- Dabrafenib/Trametinib effective in BRAF-mutant Anaplastic TC

Targeted Head and Neck Cancer

- HRAS and PIK3CA mutations/amplifications are potential targets
- Tipifarnib is promising for HRAS mutant SCCHN, moreover if VAF >20%
- PIK3CA mutations continue to be targeted, both with monotherapy with irreversible PIK3CAi as in combination with FTI
- **We might finally have a “targeted therapy” for SCCHN!**