Nuevas Terapias em El Cancer de Tiroides

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Disclosures

- Research Support
  - Exelixis, Eli Lilly, Novartis
- *Steering Committee (Selpercatinib)*:
  - Eli Lilly (MTC)
- Advisory Board
  - Bayer, Eli Lilly, Knight
- ATA Guideline Committee (MTC)

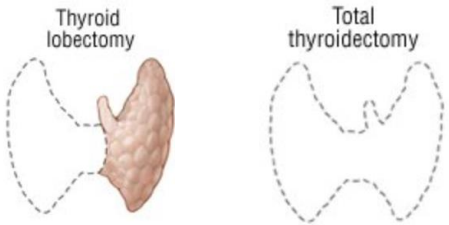
Differentiated Thyroid Cancer
Personalized Treatment – Minimizing treatment

Diagnosis

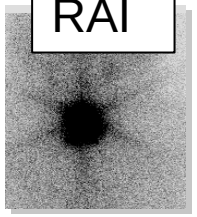
Personalized Treatment**

Differentiated Thyroid Cancer

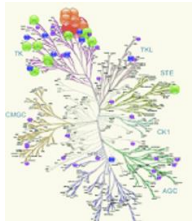
Active Surveillance

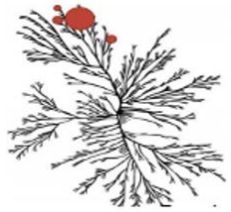


RAI



TSH Suppression





** Tailored to extent of disease and progression

Outcome:

- 80-85% - Excellent Response
- 20-25% - recurrence

Selection of Treatment Extent

- AJCC Staging
- ATA Risk Stratification System
- Age
- Co-morbidities
- ? Molecular profile

Haugen BR et al. THYROID Volume 26, Number 1, 2016

Anderson RT, et al. *Thyroid*. 2013;23(4):392-407.

Durante C, et al. *J Clin Endocrinol Metab.* 2006;91(8):2892-2899.

Personalized Treatment

Decision Based on Risk Stratification

LOW RISK + LOBECTOMY

- No RAI, TSH 0.5 – 2.0 mU/mL
- F/U: US, TSH, TG, anti-TG

LOW RISK + TT

- No RAI or low-dose RAI
- TSH 0.5-2.0 mU/mL
- F/U: US, TSH, TG, anti-TG

INTERMEDIATE RISK

- RAI: Up to 150 mCi for adjuvant treatment
- TSH 0.1-0.5 mU/mL
- F/U: US, TSH, TG, anti-TG

HIGH RISK

- RAI: Up to 150 mCi for adjuvant treatment
- Consider dosimetry for structural disease
- TSH < 0.1 um/mL
- F/U: US, TSH, TG, anti-TG, CT, PET/CT

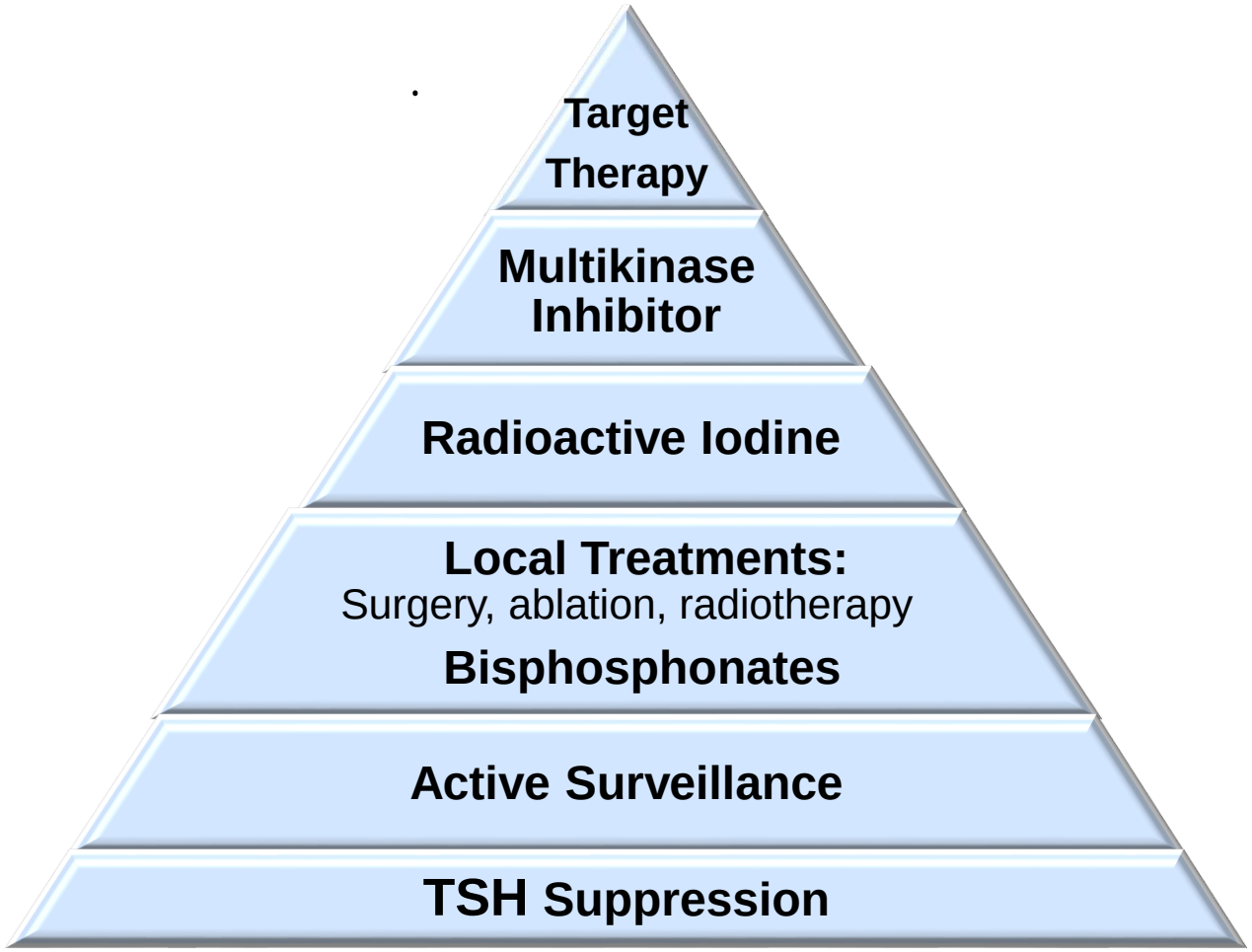
Haugen BR et al. THYROID Volume 26, Number 1, 2016

Management of Thyroid Cancer
Local and Distant Recurrences

Local Recurrence

- Surgery
- TSH Suppression
- Active Surveillance
- Ablation (RF, laser, cryotherapy) under investigation
- RAI, radiotherapy

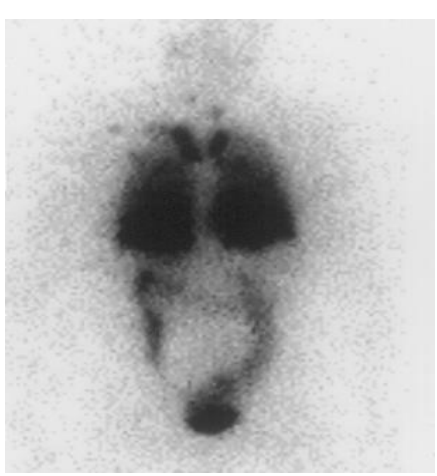
Distant Metastases

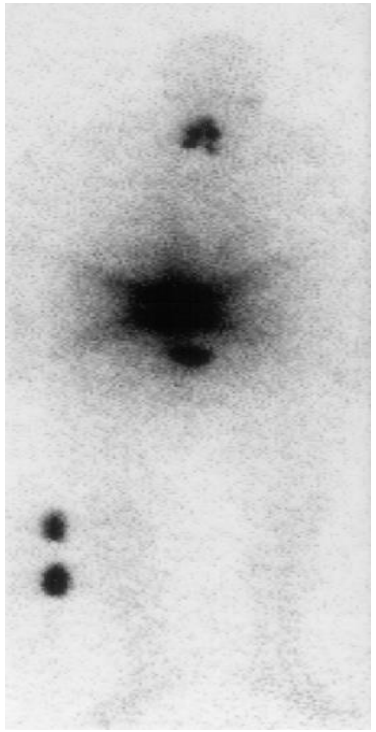


Haugen BR et al. THYROID Volume 26, Number 1, 2016

Treatment of Advanced Thyroid Cancer
Distant Metastatic Disease

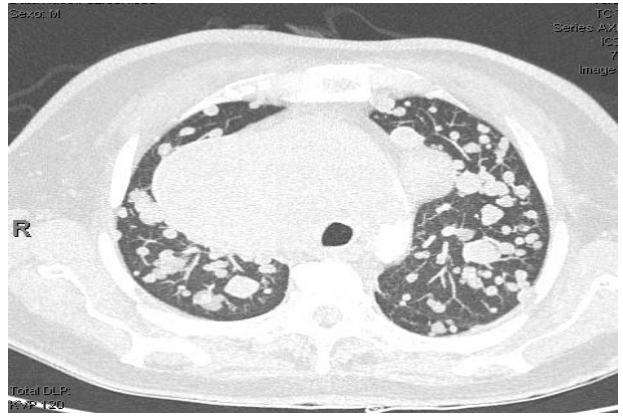
RAI: First-Line Therapy

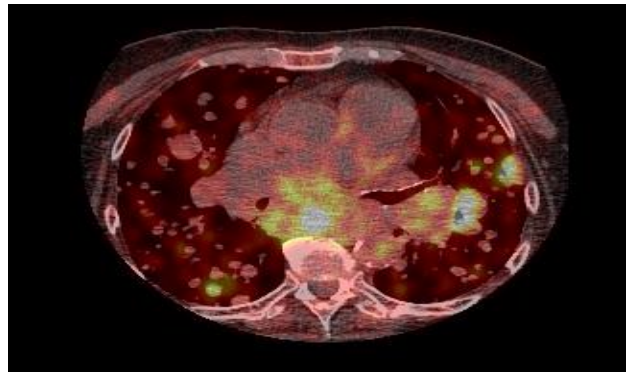




TSH Suppression

Iodine-Refractory DTC





Median survival estimated less than 3 years

Tumor load

+

Progression

Systemic Therapy

Anderson RT, et al. *Thyroid*. 2013;23(4):392-407.

Durante C, et al. *J Clin Endocrinol Metab.* 2006;91(8):2892-2899.

Metastatic RAIR DTC
Current and FutureTreatments

- Choice of treatment will be defined by
  - Presence or absence of contraindications to anti-angiogenics
  - Tumor Molecular profile
  - Potential for redifferentiation.

- Access to molecular testing and drugs

Antiangiogenics

- Lenvatinib*
- Sorafenib*
- Cabozantinib – 2nd Line

* Anvisa approved

Targeted Agents

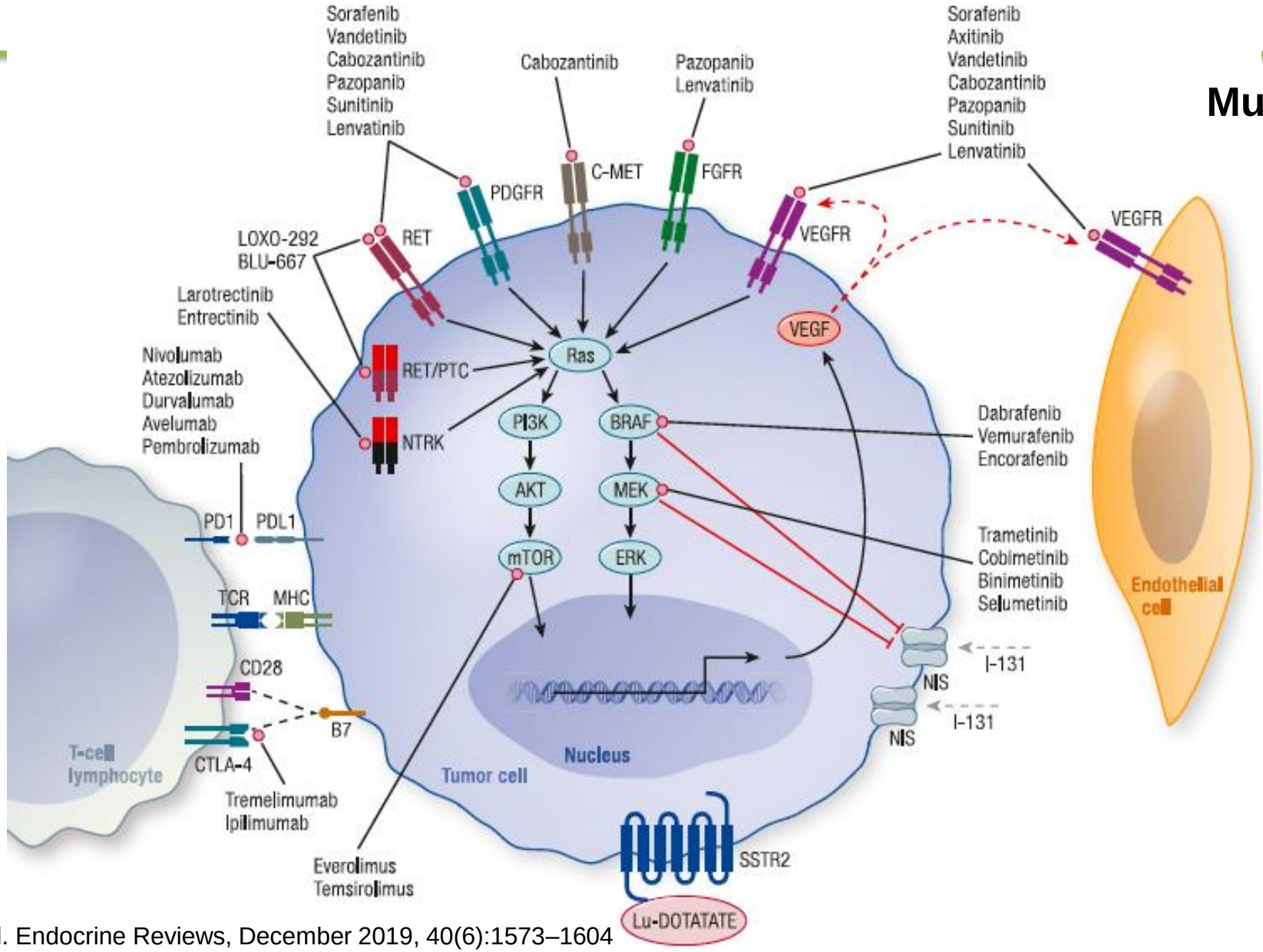
- ***NTRK inhibitors****
- ***RET inhibitors***
- ***BRAF inhibitors***
- ***Ros inhibitors***
- ***ALK inhibitors***

Redifferentiation agents

UNDER INVESTIGATION

- *BRAF inhibitors*
- *NTRK inhibitors*
- *RET inhibitors*

Targeted Therapies
Multi-kinase Inhibitors and Specific TK Inhibitors



Multi-kinase Inhibitors
Multiple targets

Specific Inhibitors
NTRK
RET
BRAF
ROS
ALK

Cabanillas et al. Endocrine Reviews, December 2019, 40(6):1573–1604

Phase III Trials in Differentiated Thyroid Cancer Multi-Kinase Inhibitors

Drug	Targets	Key Baseline Characteristics	N
Sorafenib (Brose 2014)	VEGFR, RET, BRAF, PDGFRβ	PTC, FTC, Hurthle cell cancer	417
Lenvatinib (Schlumberger 2015)	VEGFR, FGFR, PDGFRα, RET, c-kit, SCFR	PTC, FTC and poorly-differentiated 25% with prior TKI	392

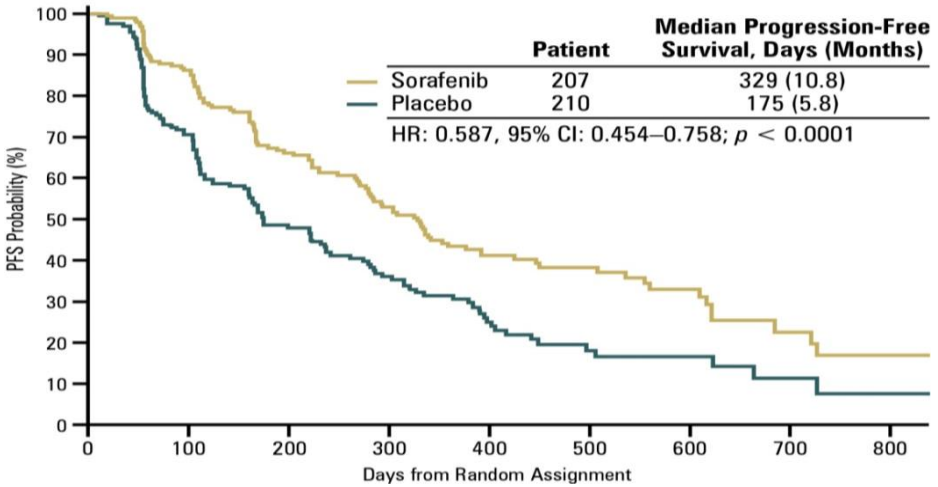
1ary endpoint:
Progression-free survival (PFS)

2ary endpoint:
Response Rate
Overall Survival
Safety

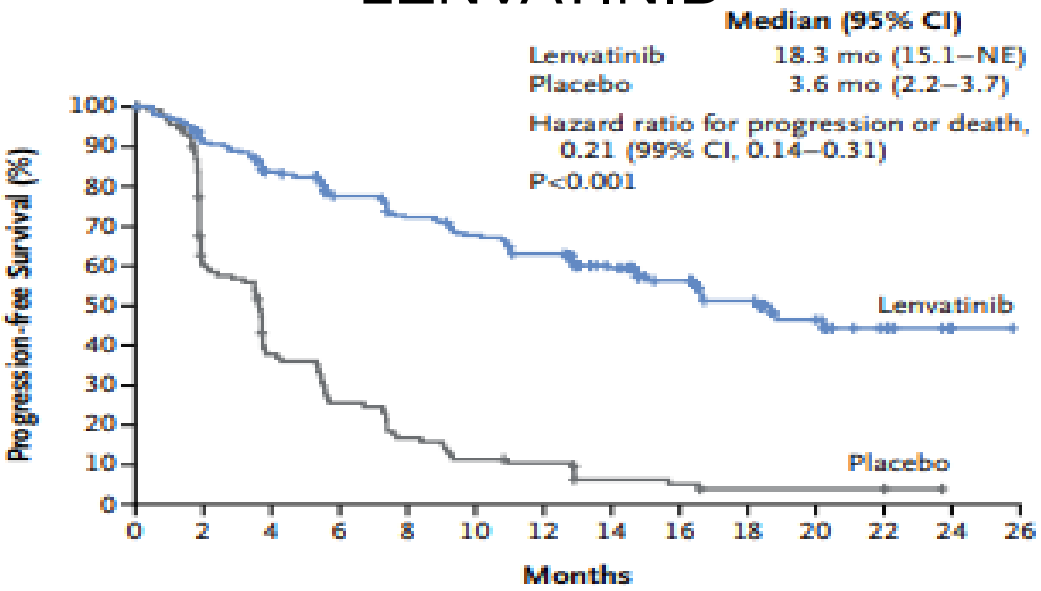
Brose MS et al Lancet. 2014 Jul 26;384(9940)
Schlumberger M, Hoff AO et al N Engl J Med 2015;372:621-30.

Progression Free Survival and Response Rate

SORAFENIB



LENVATINIB



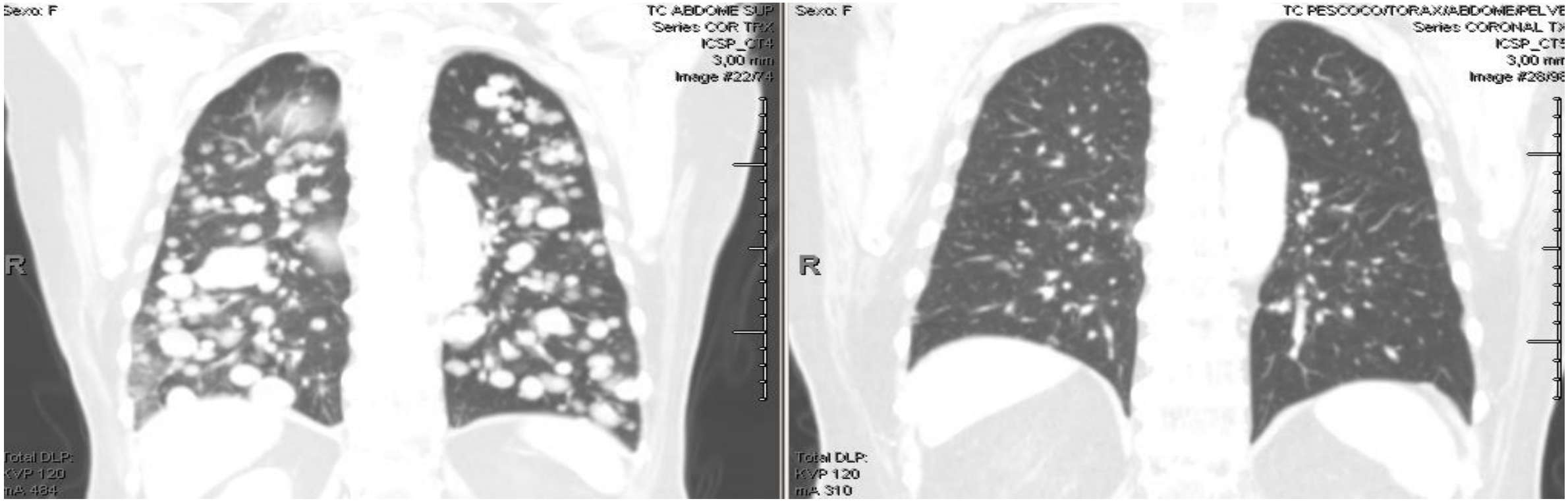
	CR	PR	SD	PD
Sorafenib	0	12%	42%	NR
Lenvatinib	2%	63%	15%	7%

Brose MS et al Lancet. 2014 Jul 26;384(9940)
Schlumberger M, Hoff AO et al N Engl J Med 2015;372:621-30.

Lenvatinib – Phase III Trial

74 year-old female with Follicular Thyroid Cancer

Cumulative activity of RAI: 800 mCi – progression of disease < 12 months
On oxygen therapy - room air O2 sat 78%



9/2013
24 mg

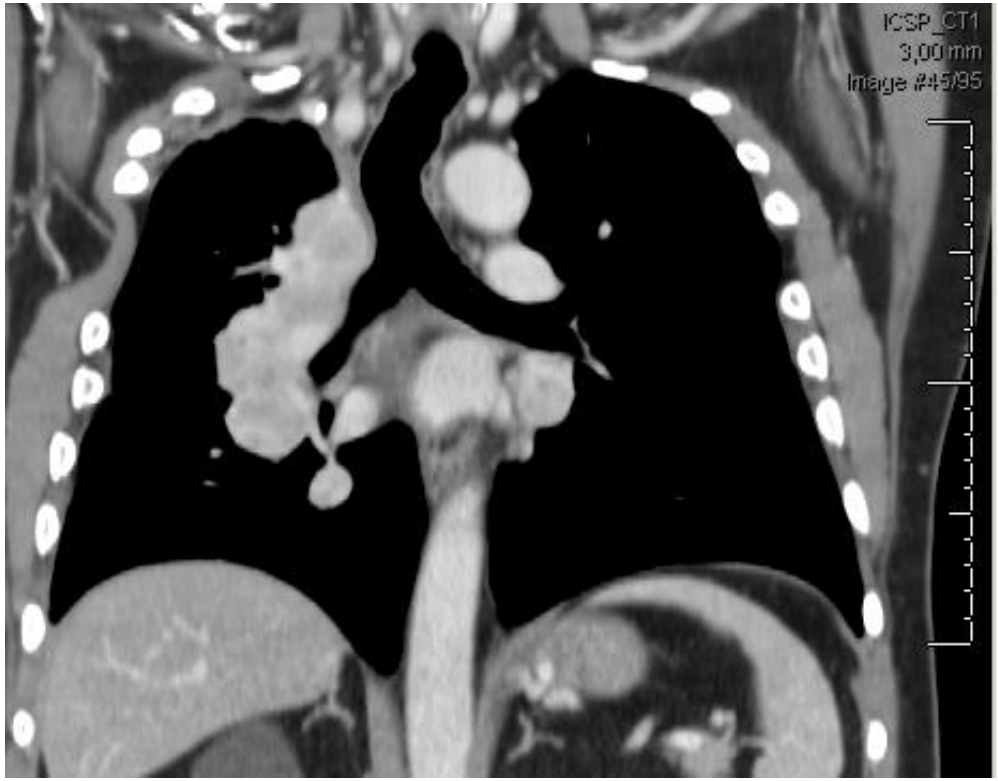
Hiypothyroidism, Severe HTN, TIA -01/2014 dose 4 mg

9/2017
4 mg

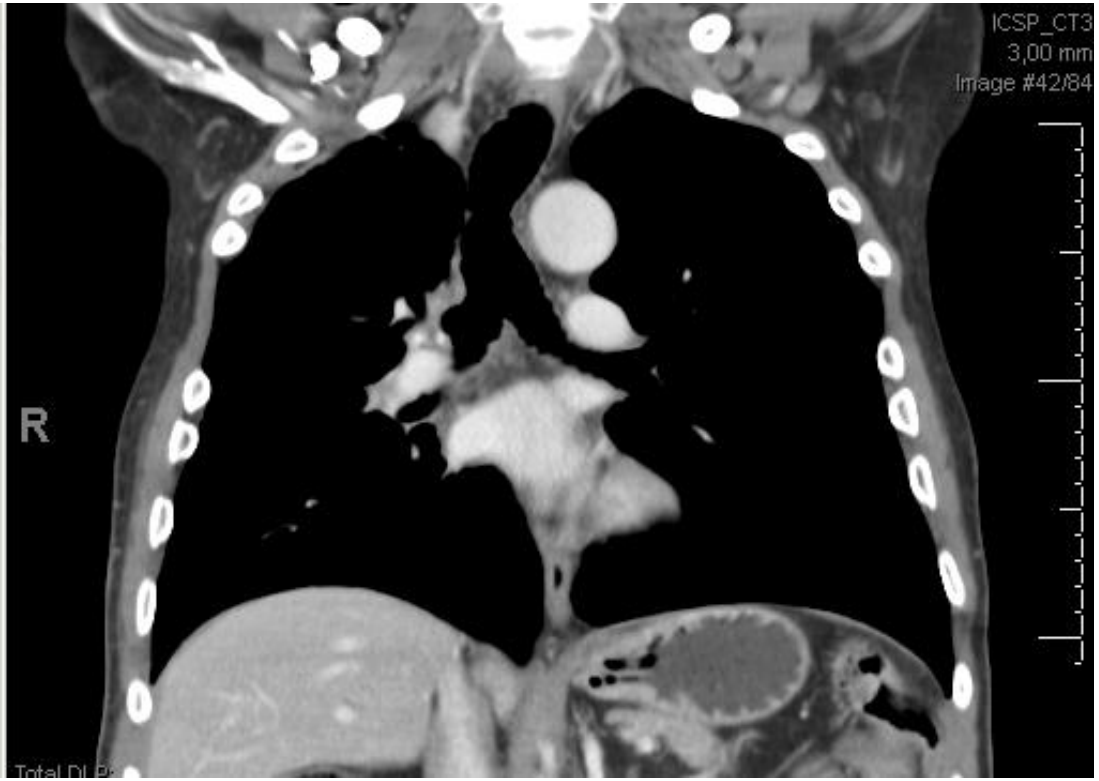
Schlumberger M, Hoff AO et al N Engl J Med 2015;372:621-30

Estudo SELECT
Fase III - LENVATINIBE

7/2012



7/2023



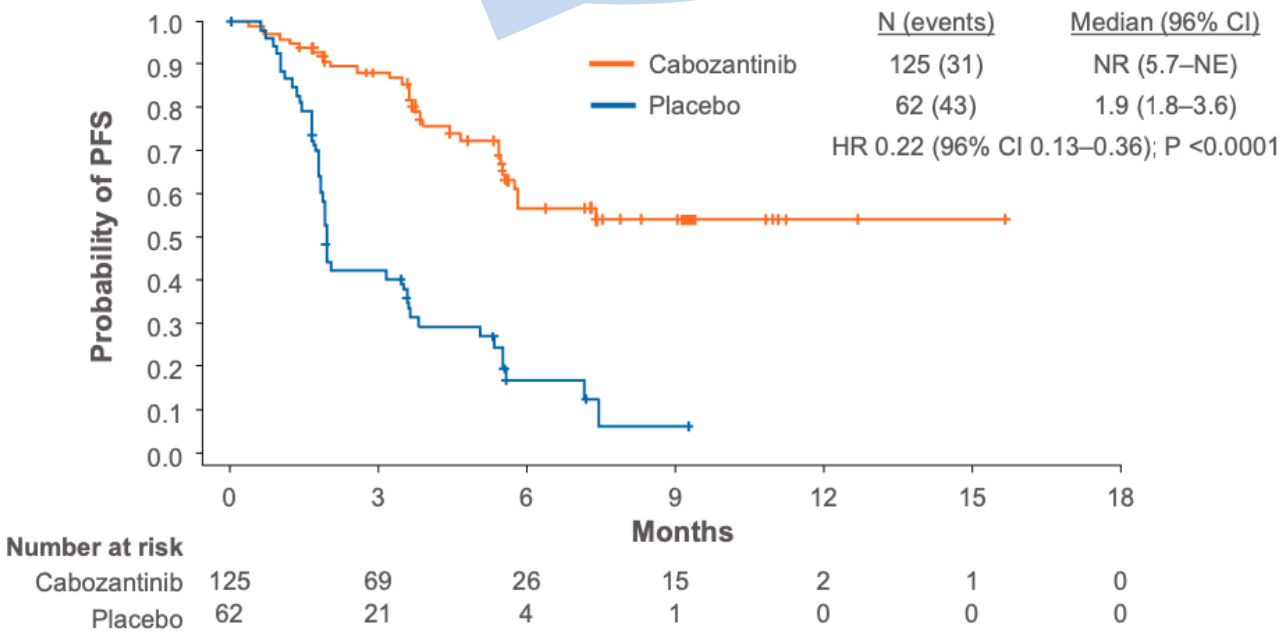
Currently on lenvatinb 10 mg/day

Schlumberger M, Hoff AO et al N Engl J Med 2015;372:621-30

Cabozantinib Versus Placebo in Patients With Radioiodine-Refractory Differentiated Thyroid Cancer Who Have Progressed After Prior VEGFR-targeted Therapy: Results From the Phase 3 COSMIC-311 Trial

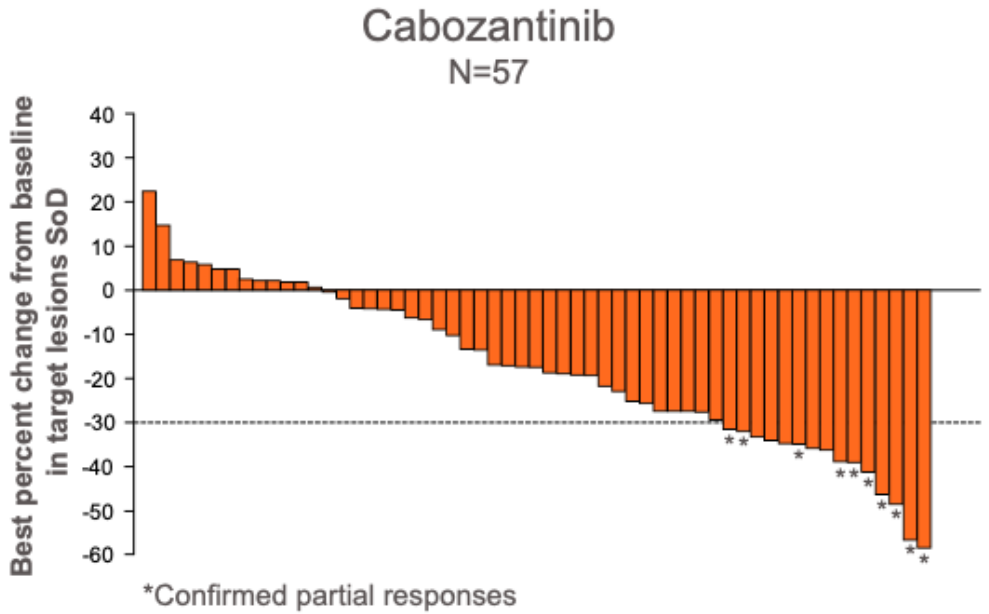
INSTITUTO DO CÂNCER DO ESTADO DE SÃO PAULO
OCTAVIO FRIAS DE OLIVEIRA

78% reduction in the risk of disease progression or death



Primary endpoint of PFS was met at planned interim analysis (critical p-value of 0.00036)

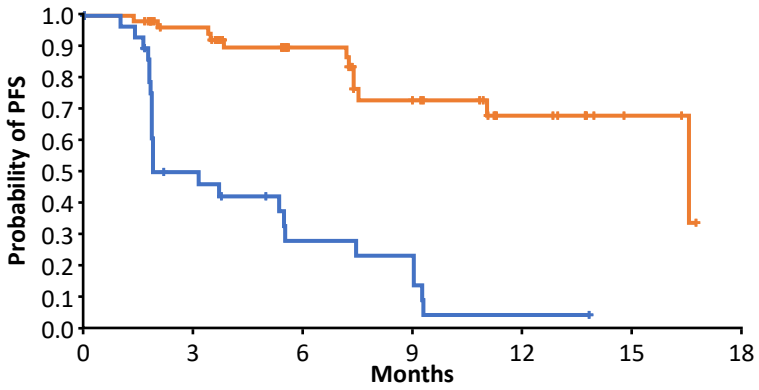
SECOND or THIRD LINE THERAPY



At 6 months minimum follow-up, any reduction in target lesions: 76% for cabozantinib vs 29% for placebo

Brose M, Vaisman F, Hoff AO, et al Lancet Oncology 2021

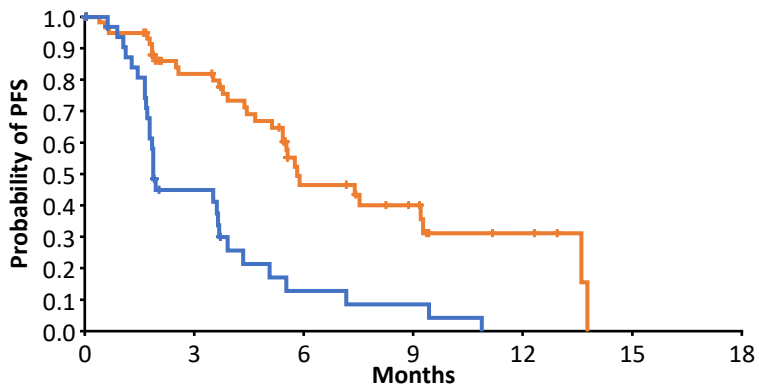
Progression-Free Survival by BIRC in Prior Therapy Subgroups



Prior Sorafenib (No Lenvatinib)

	N (events)	Median (95% CI), months
Cabozantinib	63 (12)	16.6 (11.0–NE)
Placebo	33 (24)	3.2 (1.9–5.5)

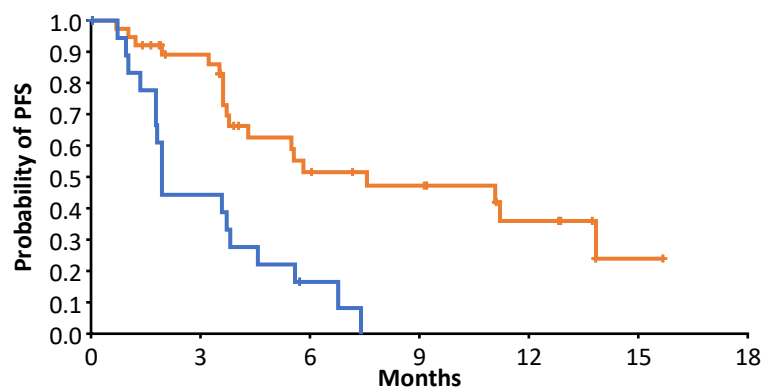
HR 0.13 (95% CI 0.06–0.26)



Prior Lenvatinib (No Sorafenib)

	N (events)	Median (95% CI), months
Cabozantinib	68 (31)	5.8 (5.1–9.3)
Placebo	34 (28)	1.9 (1.7–3.7)

HR 0.28 (95% CI 0.16–0.48)



Prior Lenvatinib & Sorafenib

	N (events)	Median (95% CI), months
Cabozantinib	39 (19)	7.6 (3.8–13.8)
Placebo	21 (17)	1.9 (1.8–3.8)

HR 0.27 (95% CI 0.13–0.54)

Cabozantinib improved PFS versus placebo irrespective of prior exposure to sorafenib and/or lenvatinib

BIRC, blinded independent radiology committee; CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival

Brose M, Waisman F, Hoff AO, Lancet Oncology 2021

Adverse Events

~ 90% of patients will develop at least 1 adverse event

SORAFENIB

	Adverse Event	All Grades
Sorafenib	Hand-foot skin reaction	76%
	Diarrhea	69%
	Alopecia	67%
	Fatigue	50%
	Weight Loss	47%
	Hypertension	41%
	Anorexia	32%

LENVATINIB

	Adverse Event	All Grades
Lenvatinib	Hypertension	68%
	Diarrhea	59%
	Fatigue	59%
	Anorexia	50%
	Weight Loss	46%
	N/V	46%
	Hand-foot skin reaction	32%

CABOZANTINIB

	Adverse Event	All Grades
Cabozantinib	Diarrhea	51%
	Hand-foot skin reaction	46%
	Hypertension	28%
	Fatigue	27%
	ALT Increased	24%
	Weight loss	18%
	Proteinuria	15%

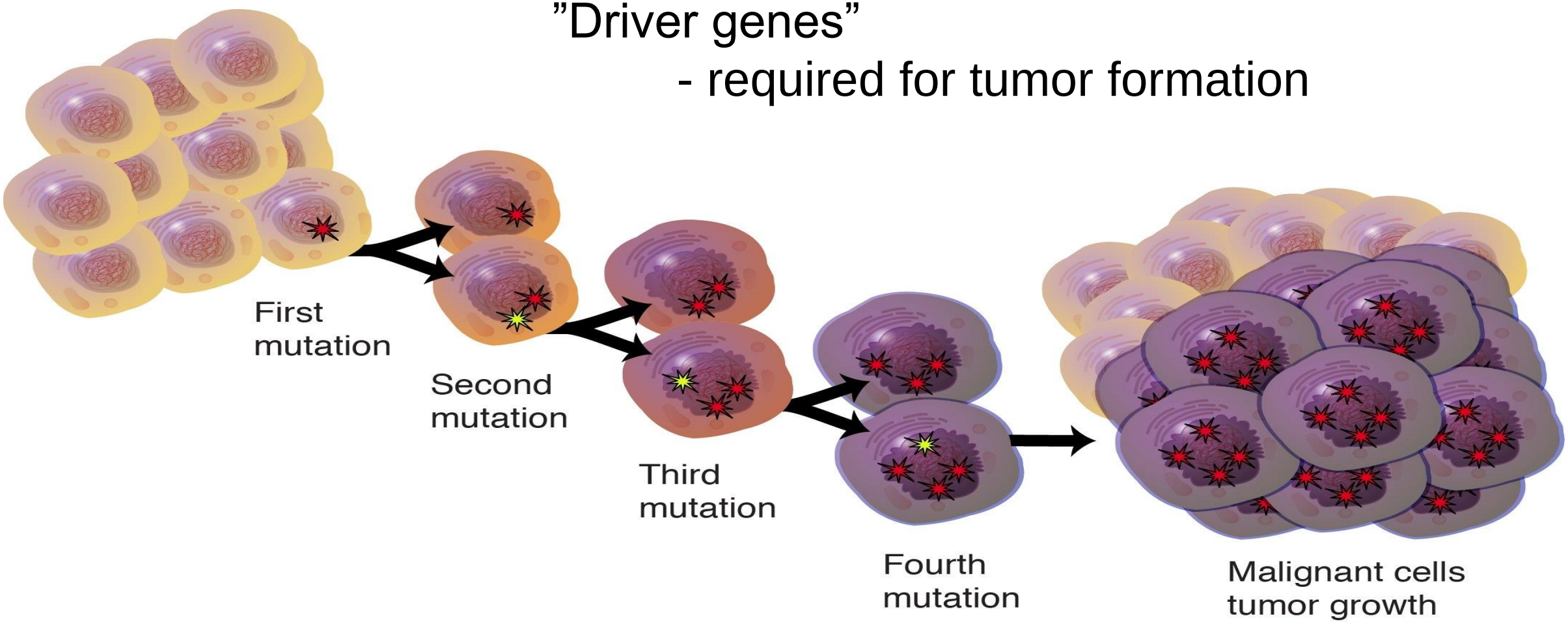
Brose MS et al Lancet. 2014 Jul 26;384(9940)
Schlumberger M, Hoff AO et al N Engl J Med 2015;372:621-30.

Brose M, Waisman F, Hoff AO, Lancet Oncology 2021

Cancer is a Disease Caused by Genetic Mutations

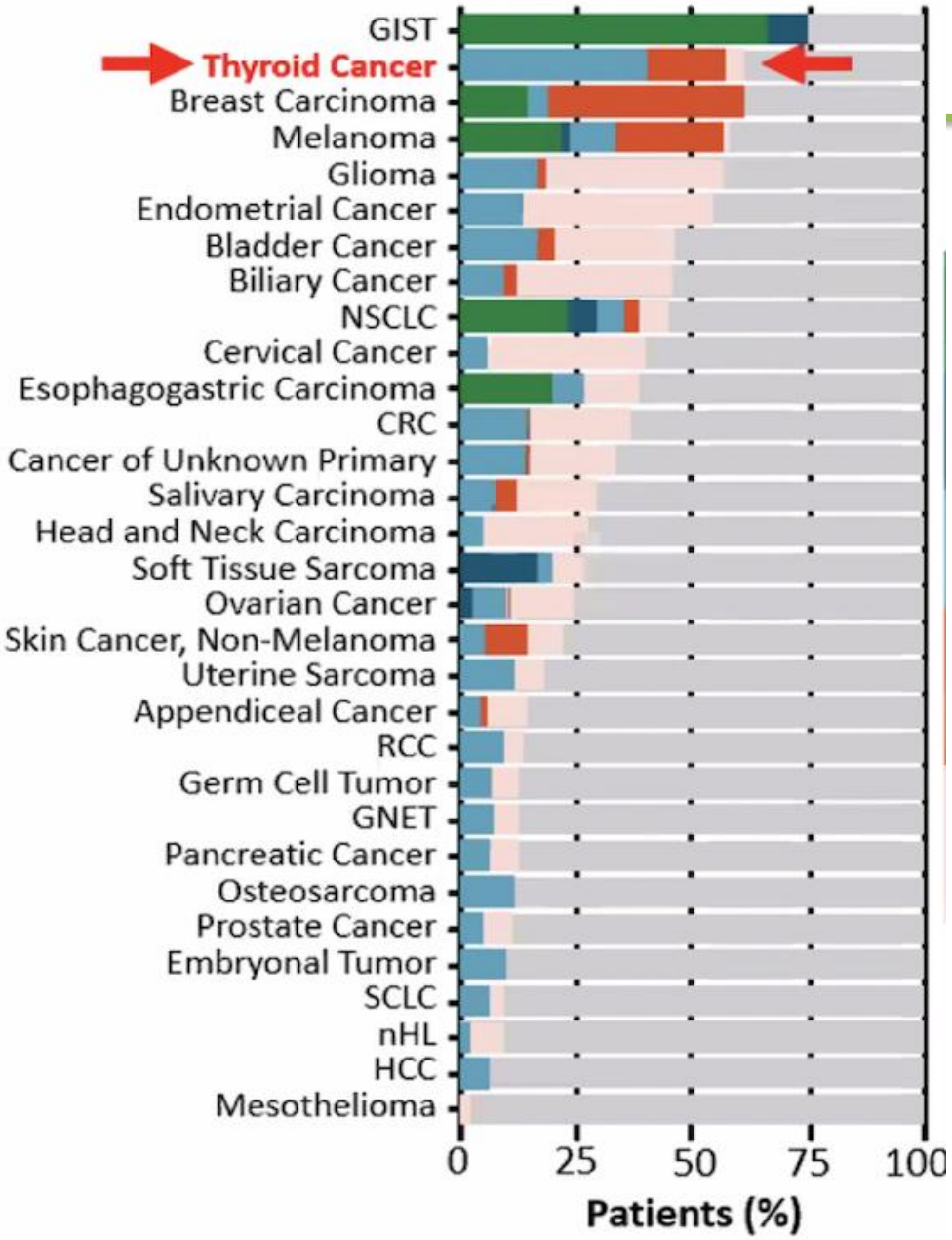
”Driver genes”

- required for tumor formation



Cell division: balance between proliferation and apoptosis – lost in carcinogenesis

Provided by Gilbert Cote



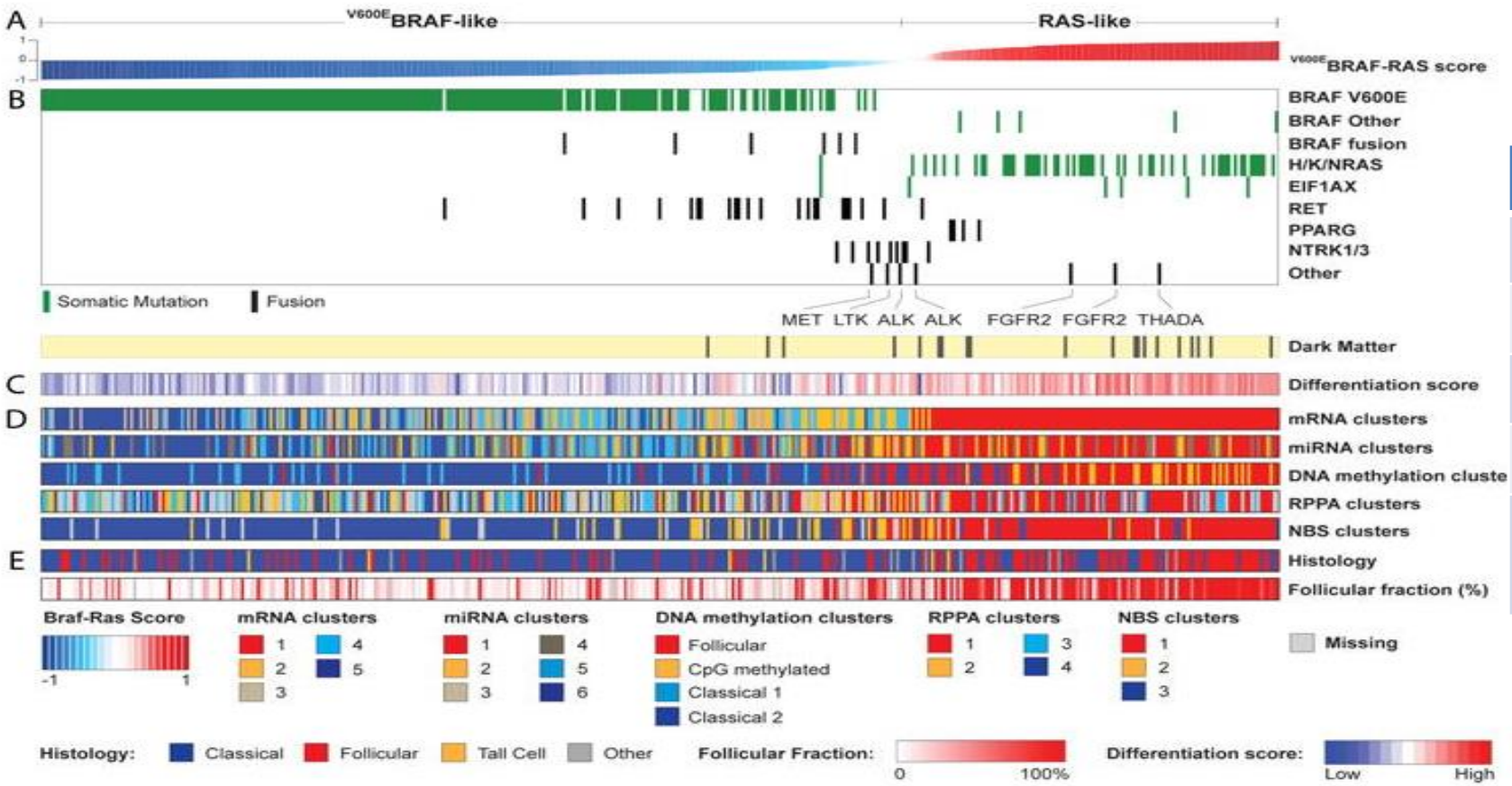
- Over the last decade, the application of clinical genomics to the diagnosis and treatment of different tumors has become a routine (lung cancer and melanoma)

- Thyroid Cancers harbor one of the HIGHEST rates of ACTIONABLE driver alterations of all malignancies

Zehir et al Nat Med. 2017 Jun;23(6):703-713

Tumor Molecular Profile
TCGA - PTC

The Cancer Genome Atlas (TCGA) project

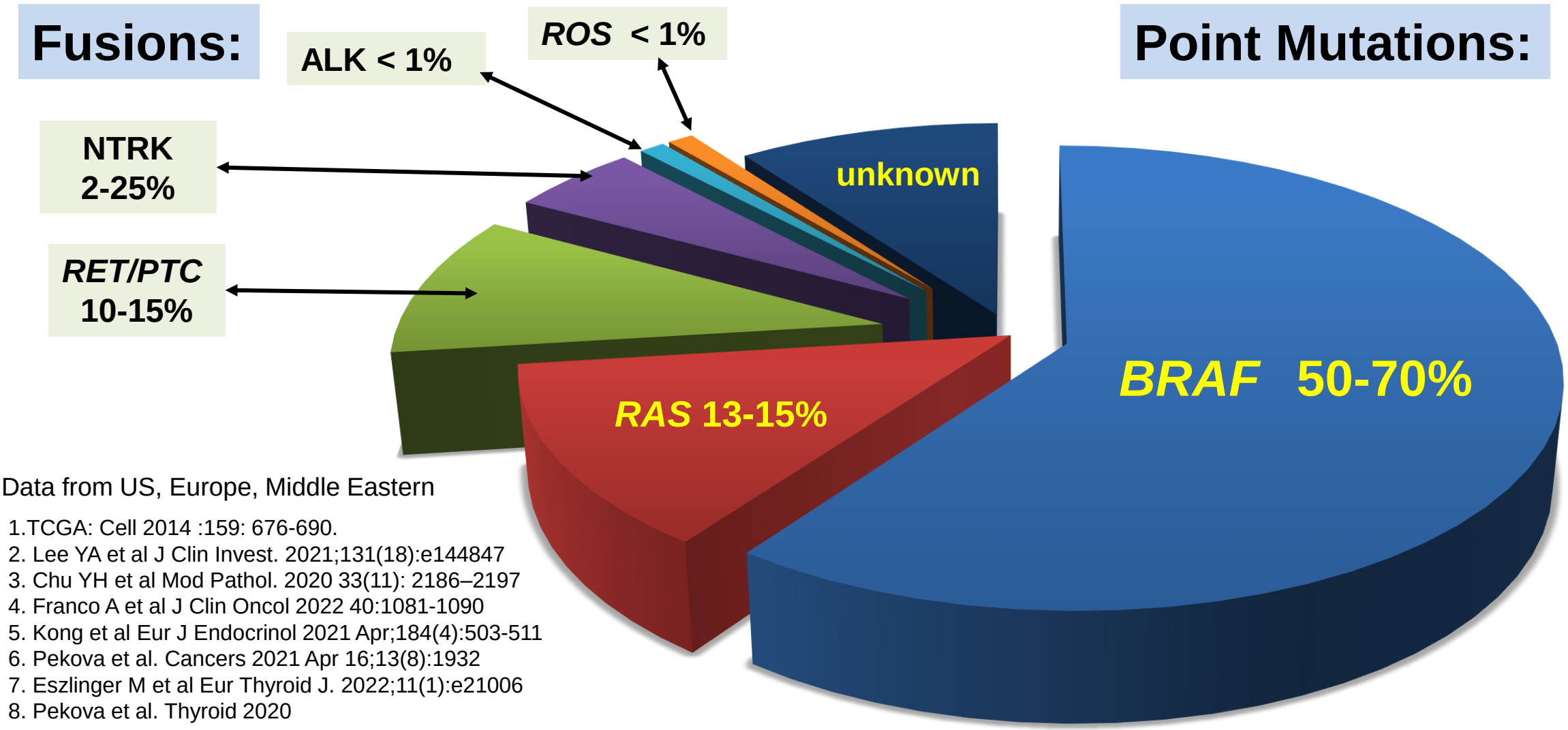


N=496
Papillary Thyroid Cancer

Mutations	
BRAF	248 (61.7%)
RAS	52 (12.9%)
RET/PTC	33 (6.8%)
BRAF fusions	13 (2.7%)
NTRK 3 Fusions	6 (1.2%)

Cell 2014 :159: 676-690.

Kinase Inhibitors Specific to Key Driver Mutations in Thyroid Cancer



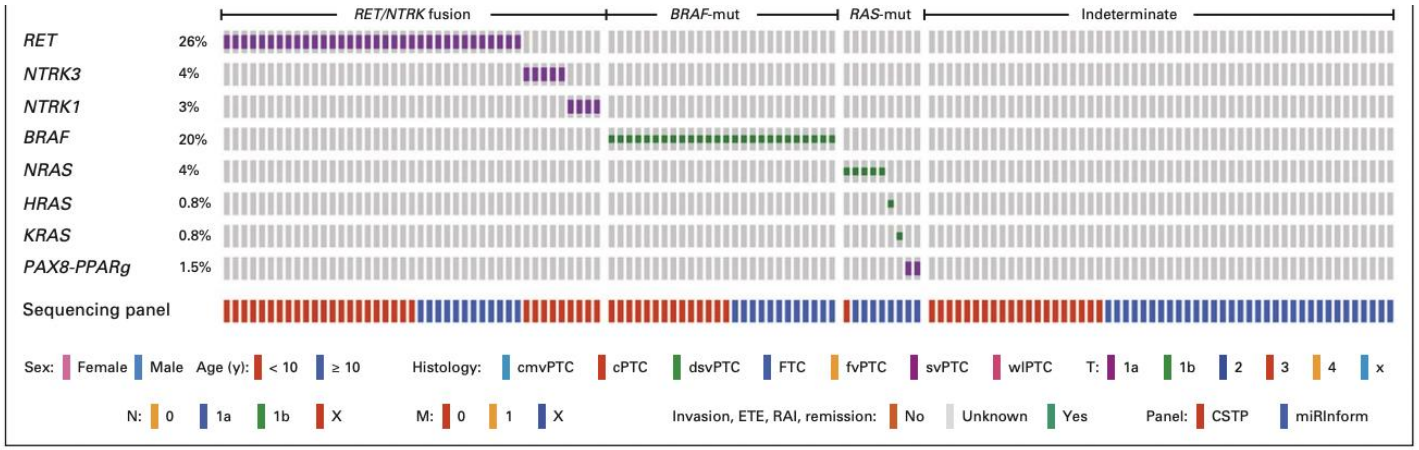
Data from US, Europe, Middle Eastern

1.TCGA: Cell 2014 :159: 676-690.
2. Lee YA et al J Clin Invest. 2021;131(18):e144847
3. Chu YH et al Mod Pathol. 2020 33(11): 2186–2197
4. Franco A et al J Clin Oncol 2022 40:1081-1090
5. Kong et al Eur J Endocrinol 2021 Apr;184(4):503-511
6. Pekova et al. Cancers 2021 Apr 16;13(8):1932
7. Eszlinger M et al Eur Thyroid J. 2022;11(1):e21006
8. Pekova et al. Thyroid 2020

NTRK and *RET*- Fusion Tumors are more aggressive and more frequent in pediatric DTC

Children's Hospital of Philadelphia

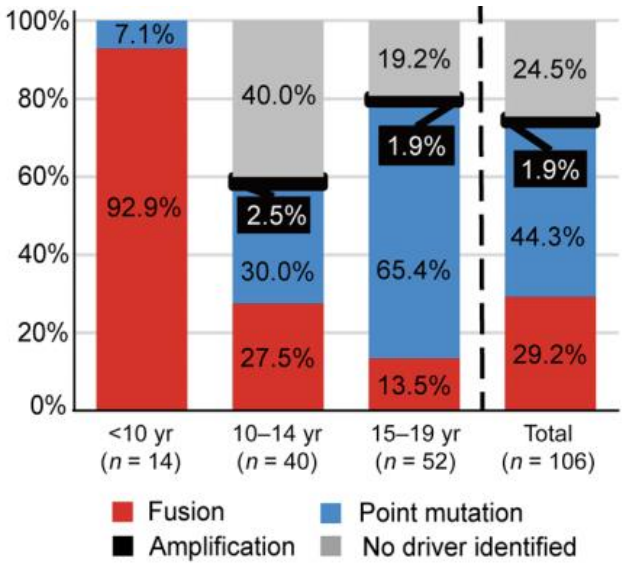
N: 131 DTC

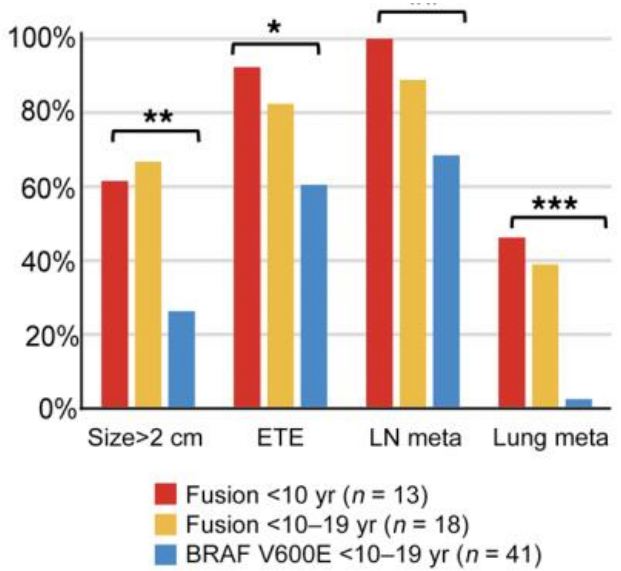


- ✓ Classic or diffuse sclerosing variants
- ✓ Significantly higher rates
  - ✓ Invasion
  - ✓ LN mets
  - ✓ N1 and M1 disease (lung)
- ✓ Lower rates of remission
- ✓ Not seen in FTC e FVPTC

Franco A et al J Clin Oncol 40:1081-1090, 2022

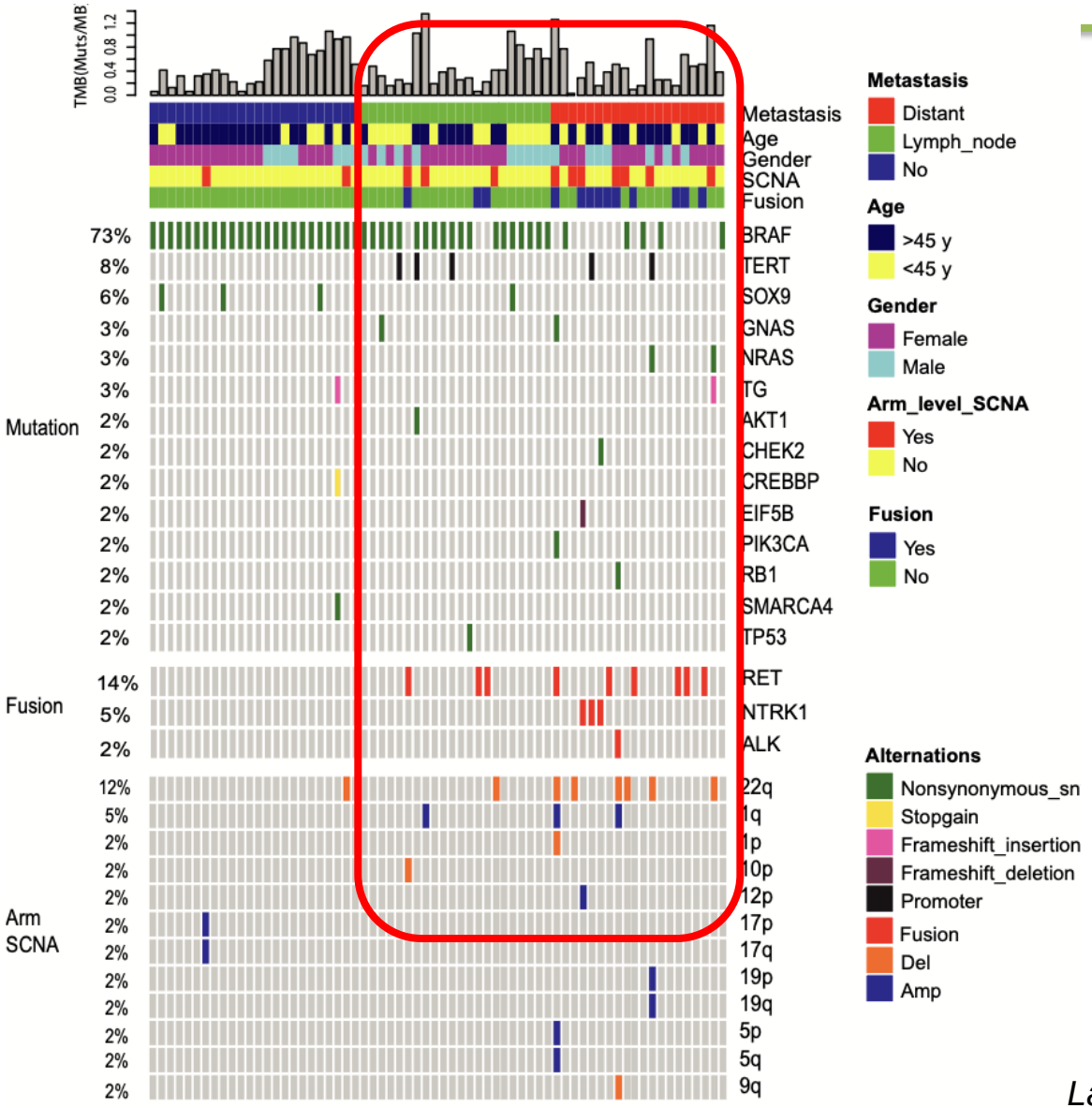
Korean Study (106 pediatric PTC)





A et al J Clin Invest. 2021;131(18):e144847

Genomic Landscape of Metastatic PTC reveals enrichment of fusions in metastatic disease



- 20 PTC with DM and 46 PTC without DM
  - whole exome sequencing
  - GeneseeqPrime (425 genes) panel sequencing

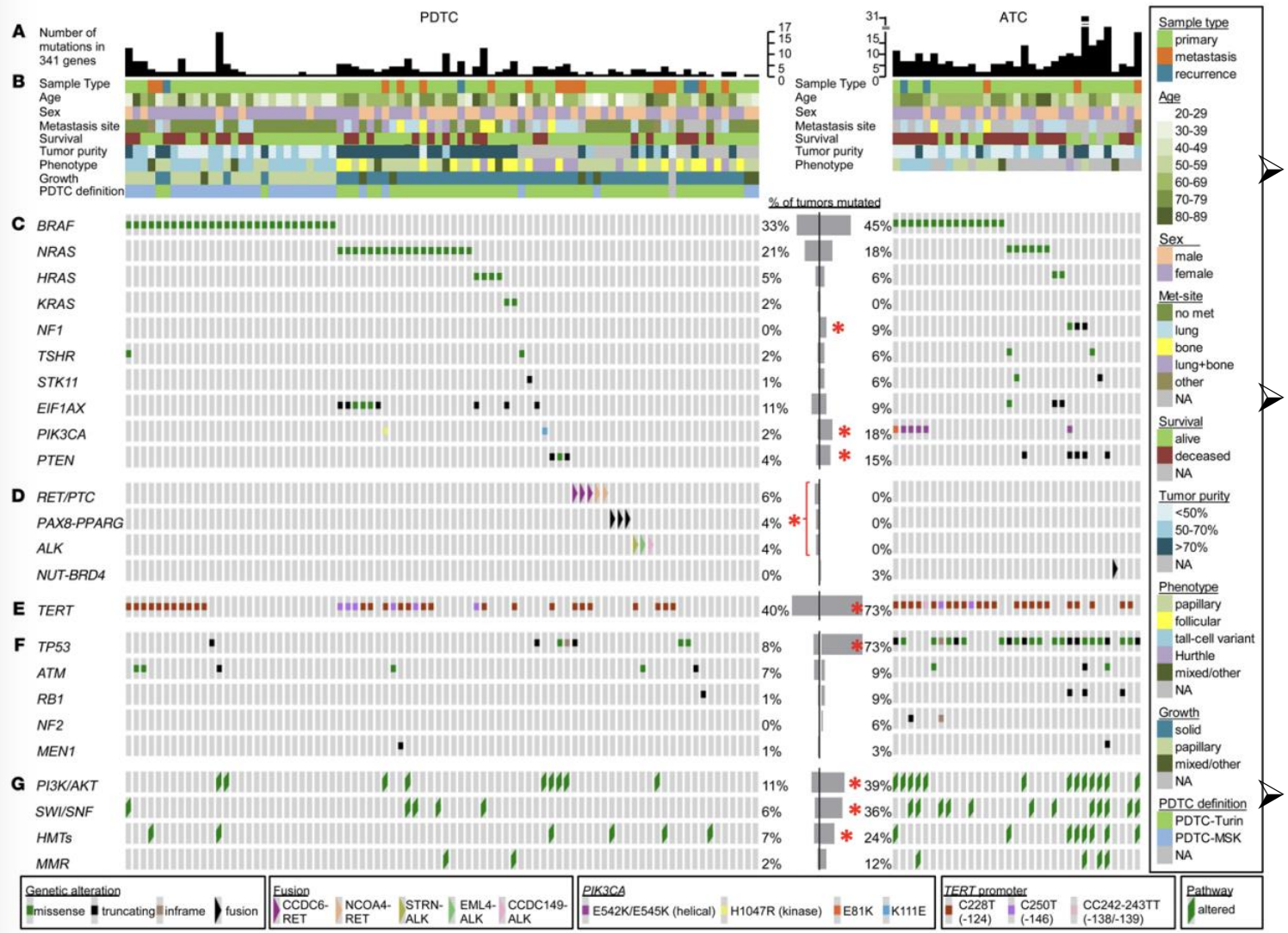
- *BRAF-V600E* in 73% of PTC, *RET* fusions (14%),NTRK1 (5%), ALK (2%)

- Gene fusions (*RET*, *ALK* or *NTRK1*) and chromosome 22q loss ($P < 0.01$) were independently associated with DM in both univariate and multivariate analyses.

DM: DISTANT METASTASES

Lan X et al. Cancer Science. 2020;111:2163–2173.

BRAF and *RAS* are the predominant drivers in PDTC and ATC but with addition of key genetic abnormalities



N: 84 PDTC
N: 33 ATC

- **Driver Mutations:**
  - BRAF 33% (PDTC) – 55% (ATC)
  - N/K/HRAS 28%(PDTC), 24%% (ATC)
  - ATC: NF1 (9%),PIK3CA (18%), PTEN(15%)
- **ATCs**
  - greater mutation burden
  - a higher frequency of mutations in TP53, TERT promoter, PI3K/AKT/mTOR pathway effectors, SWI/SNF subunits, and histone methyltransferases
- **Low-frequency of RET/PTC and NTRK fusions**

Landa I et al : J Clin Invest. 2016;126(3):1052–1066

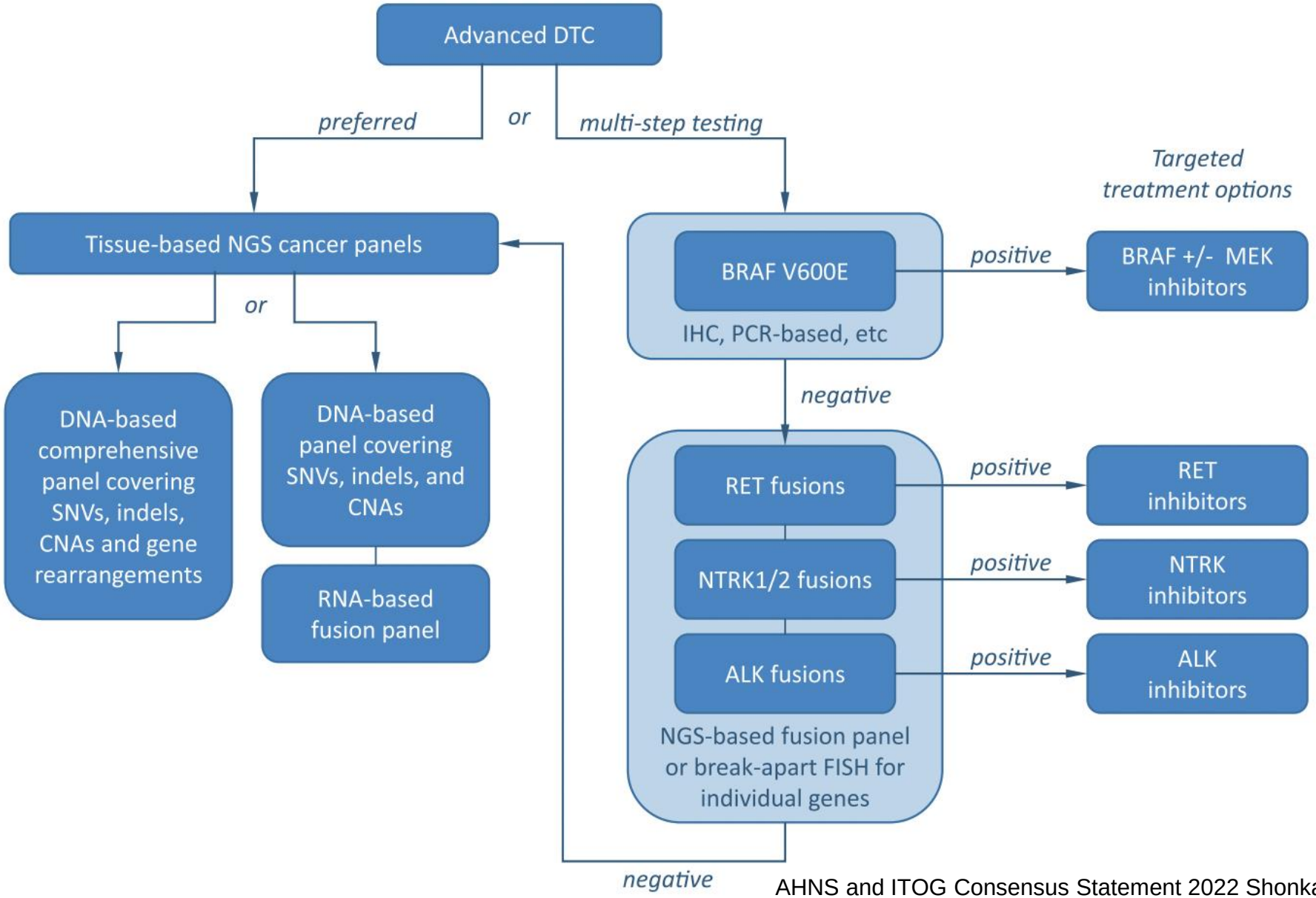
Tumor Molecular Testing

Somatic testing attempts to find mutations in the tumor

- Surgical block, core biopsy, FNA biopsy, or liquid biopsy
- NGS (DNA and RNA), IHC (BRAF, NTRK), blood cfDNA

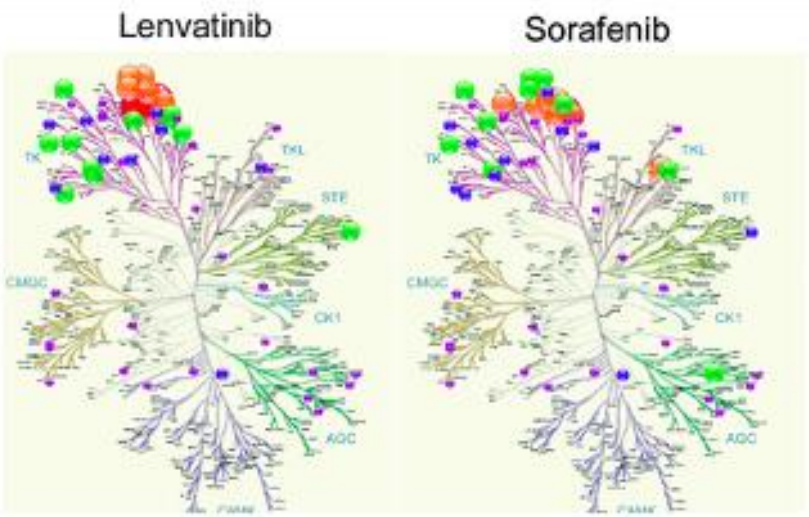
- Foundation One: entire coding sequence of 315 cancer-related genes
- Fleury – Foundation One e Painel expandido com análise de RNA, painel de fusões
- Thyroseq V3 - 112 thyroid-related genes including mutations, gene fusions, copy number alterations, and gene expression alterations,
- Afirma Xpression Atlas
- MirType

Somatic Mutational Testing – ITOG Recommendation

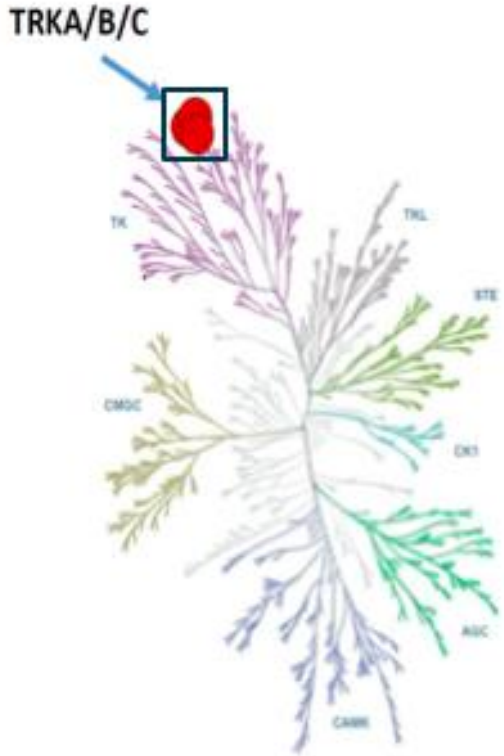


AHNS and ITOG Consensus Statement 2022 Shonka D et al Head & Neck 2022

Specific Inhibitors – Higher potency with less side-effects



Vandetanib



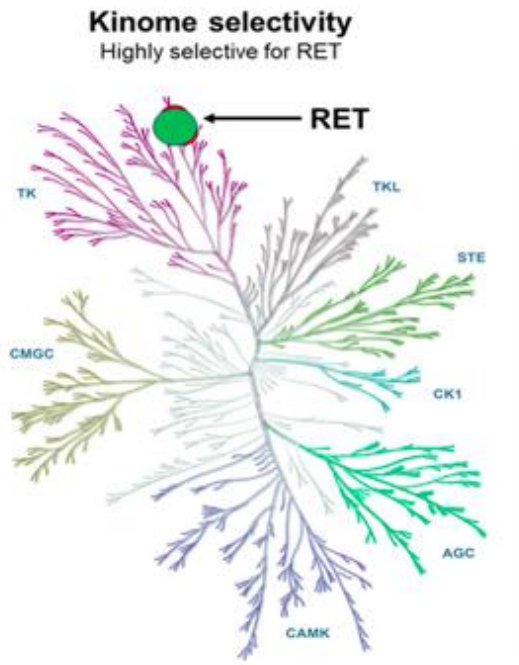
Larotrectinib

LOXO-292

BLU-667

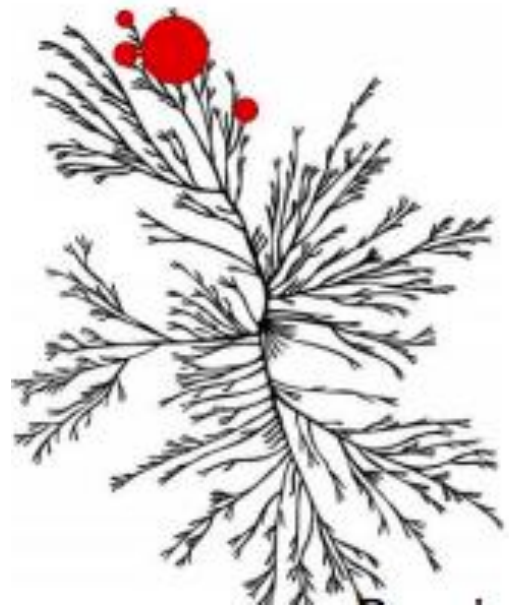
Drilon 2016; Frett 2015; Blueprint web site; Brandhuber 2016 Subbiah V et al Cancer discovery April 15th 2018

Selective RET Inhibitors



LOXO-292

SELPERCATINIB



BLU-667

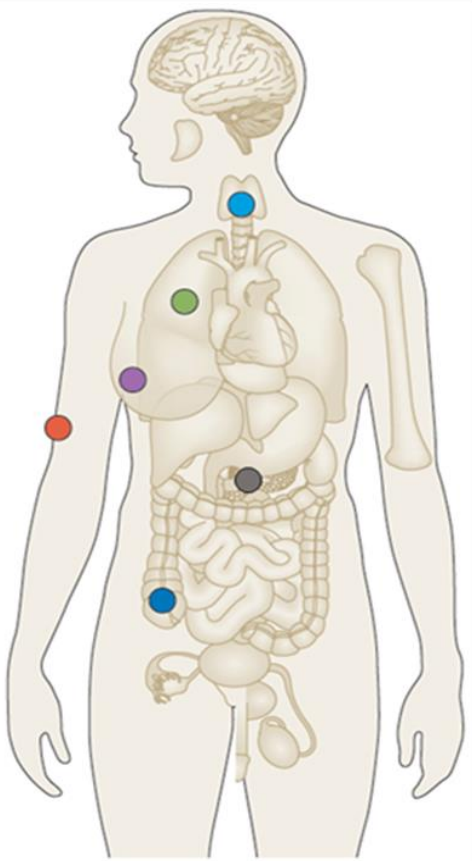
PRASELTINIB

Drilon 2016; Frett 2015; Blueprint web site; Brandhuber 2016

Subbiah V et al Cancer discovery April 15th 2018

RET is activated by two major mechanisms in cancer

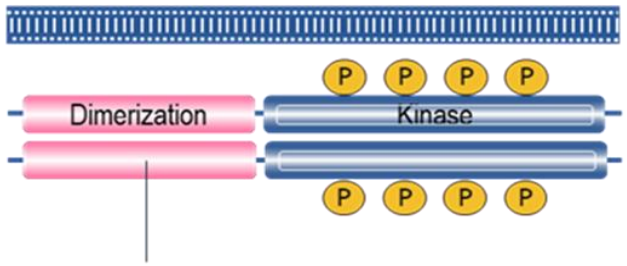
RET fusions



Non-small cell lung cancer (2%)

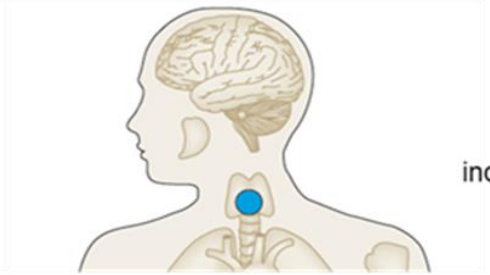
Papillary and other thyroid cancers (10–20%)

Pancreatic cancer (<1%)
Salivary gland cancer (<1%)
Spitz tumors (<1%)
Colorectal cancer (<1%)
Ovarian cancer (<1%)
Myeloproliferative disorders (<1%)
Many others (<1%)



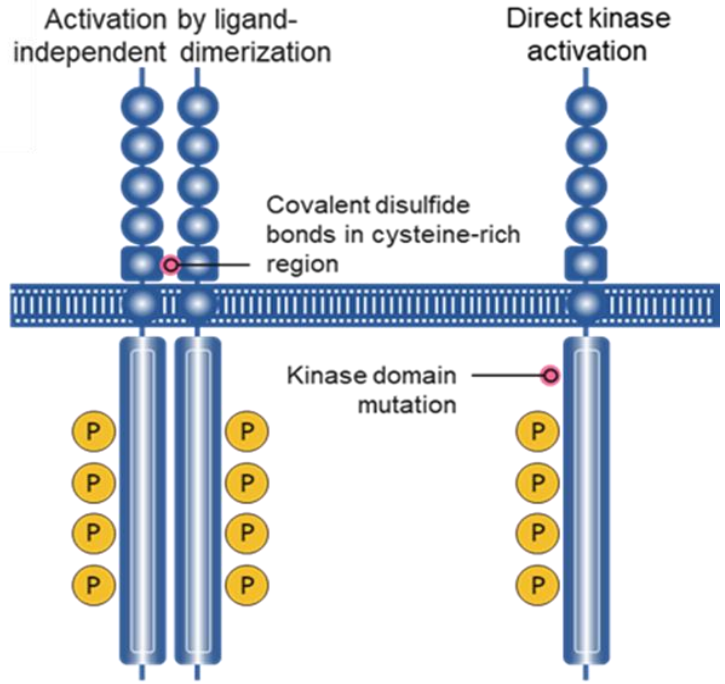
KIF5B (most common in lung cancer)
CCDC6 or NCOA4 (most common in thyroid cancer)

RET mutations



Medullary thyroid cancer

sporadic (>60%)
hereditary (>90%)



Common mutation: **RET M918T**

Drilon et al. Nat Rev Clin Oncol 2018;15:151–67; Kato et al. Clin Cancer Res 2017; 23:1988–97; Pietrantonio et al. Ann Oncol 2018;Mar 10; Su et al. PLoS One 2016;11(11)

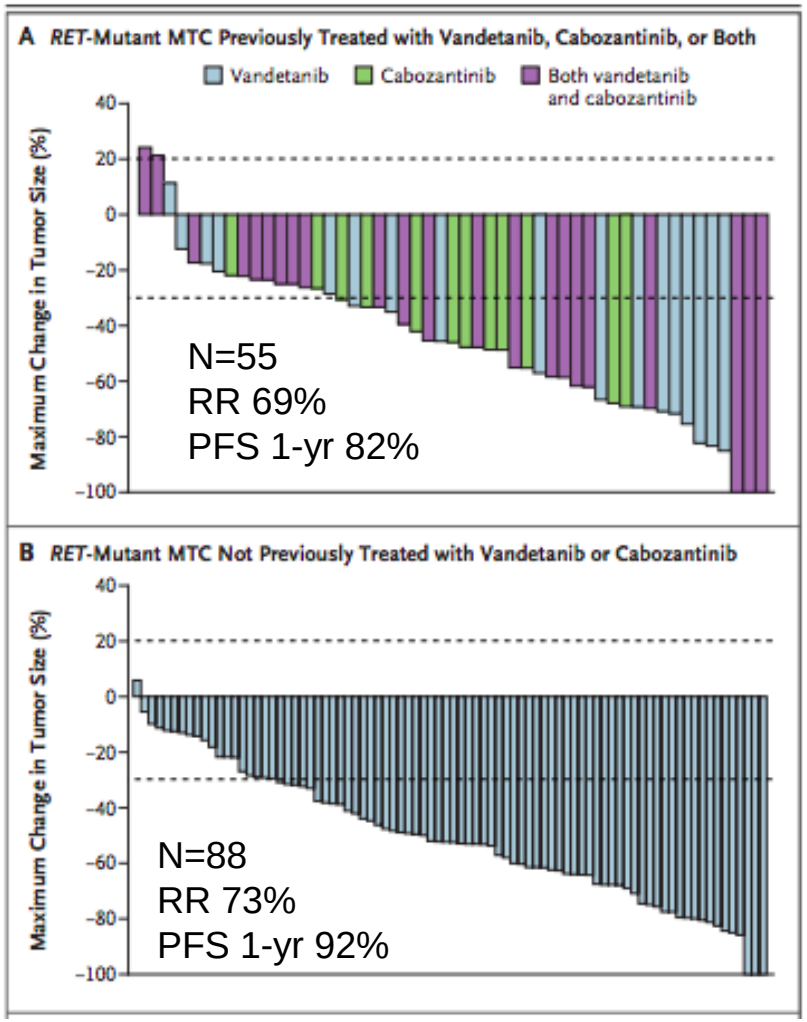
Wirth L et al ATA Presentation 2018

The NEW ENGLAND JOURNAL of MEDICINE

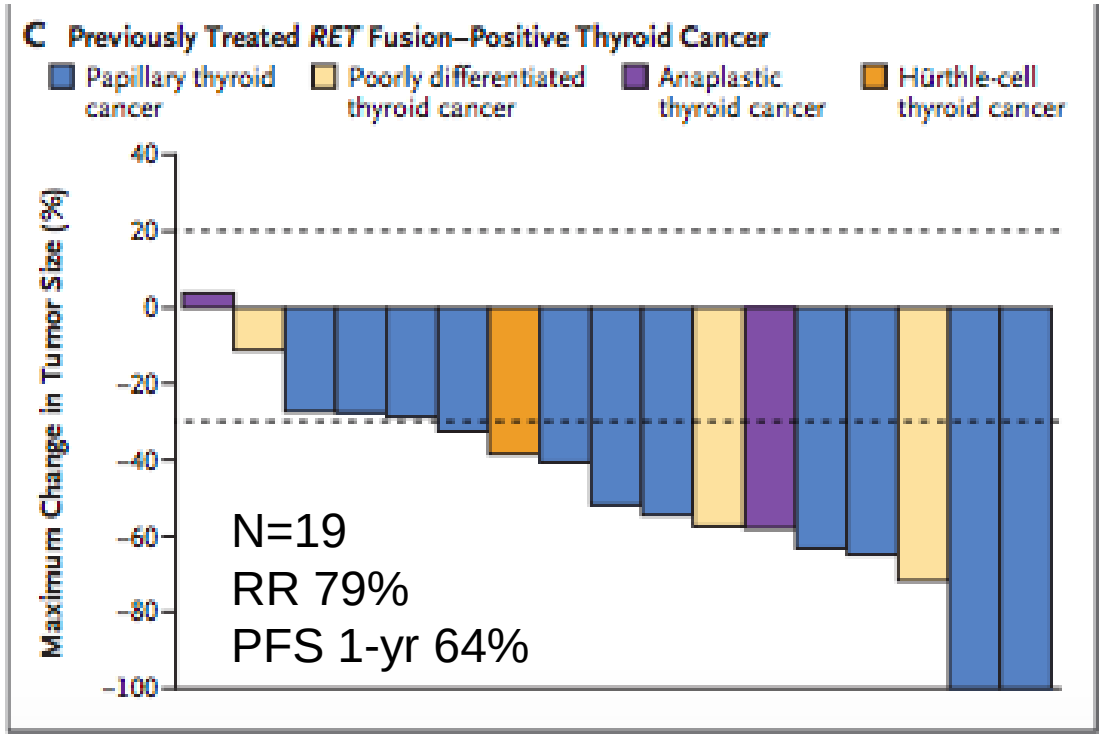
ORIGINAL ARTICLE

Efficacy of Selpercatinib in *RET*-Altered Thyroid Cancers

MTC



PTC – RET fusion



PTC: 13
Poorly-differentiated: 3
Hurthle cell cancer: 2
Anaplastic: 1

68% - previously treated with sorafenib, lenvatinib or both
6 patients (32%) – brain mets

Wirth L et al. N Engl J Med 2020;383:825-35

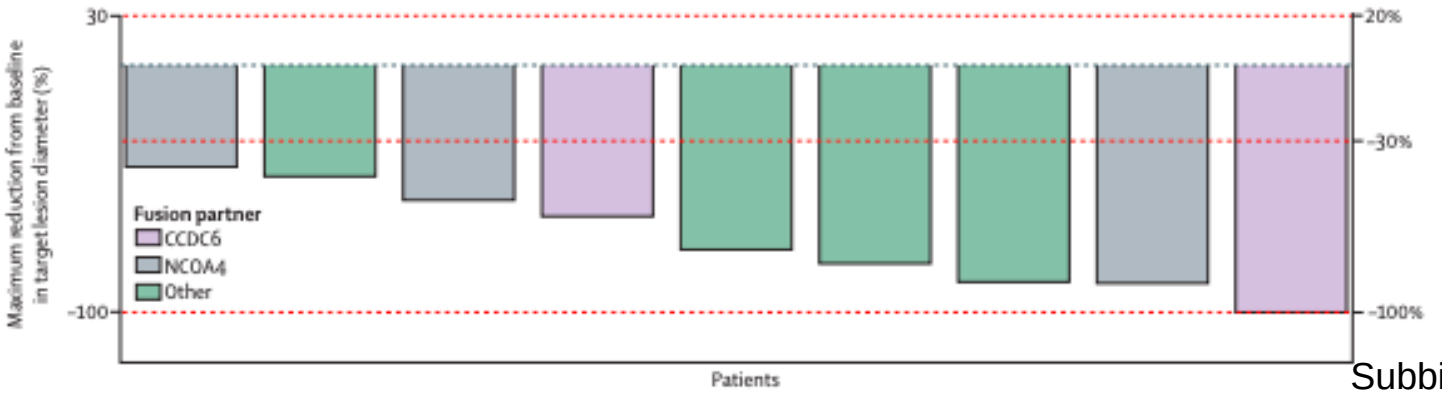
Pralsetinib
ARROW STUDY

Pralsetinib for patients with advanced or metastatic *RET*-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study

Vivek Subbiah, Mimi I Hu*, Lori J Wirth, Martin Schuler, Aaron S Mansfield, Giuseppe Curigliano, Marcia S Brose, Viola W Zhu, Sophie Leboulleux, Daniel W Bowles, Christina S Baik, Douglas Adkins, Bhumsuk Keam, Ignacio Matos, Elena Garralda, Justin F Gainor, Gilberto Lopes, Chia-Chi Lin, Yann Godbert, Debashis Sarker, Stephen G Miller, Corinne Clifford, Hui Zhang, Christopher D Turner, Matthew H Taylor*

11 DTC patients with RET/PTC Fusions:
- RAI refractory, 9 measurable disease
- 8 patients with previous TKI
- 5 patients with brain mets (45%)
- Median age 61 yrs (54-70)

ORR	8/9 (89%)
Best Overall response CR PR SD PD	 0 8 (89%) 1 (11%) 0
Disease Control Rate	9 (100%)
Median time for first response	1.9 months (1.8-2.8)
Median DOR	6 months: 100% 12 months: 89%

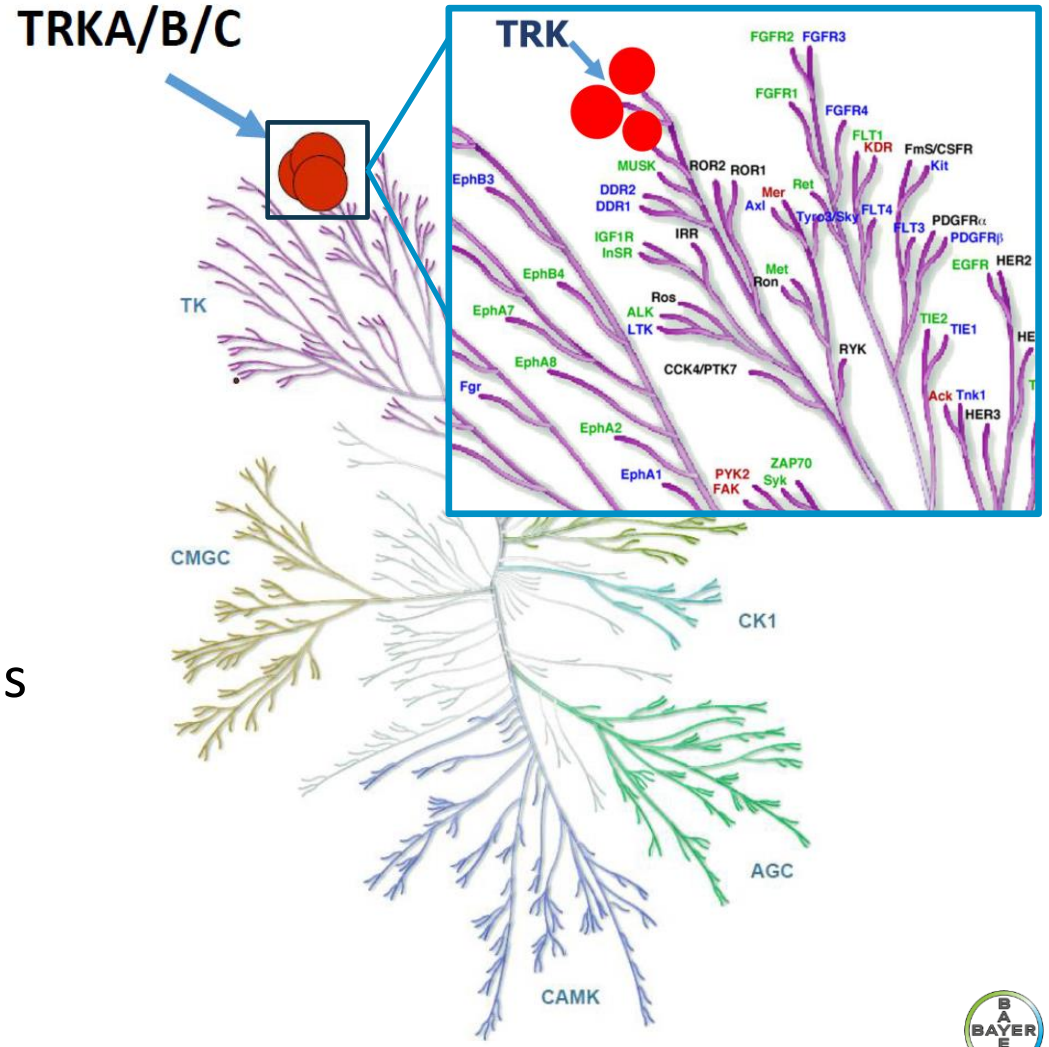


Subbiah V et al Lancet Diabetes Endocrinol 2021; 9: 491–501

Mechanism of Action of Larotrectinib

Larotrectinib is a Highly Selective TRK Inhibitor

- First-in-class selective TRK inhibitor[1]
- High potency against TRKA, TRKB, and TRKC[1]
- High selectivity[1,2]
  - Limited inhibition of other kinases
  - ≥100-fold selectivity versus 229 other kinases
- Larotrectinib is CNS active[3]



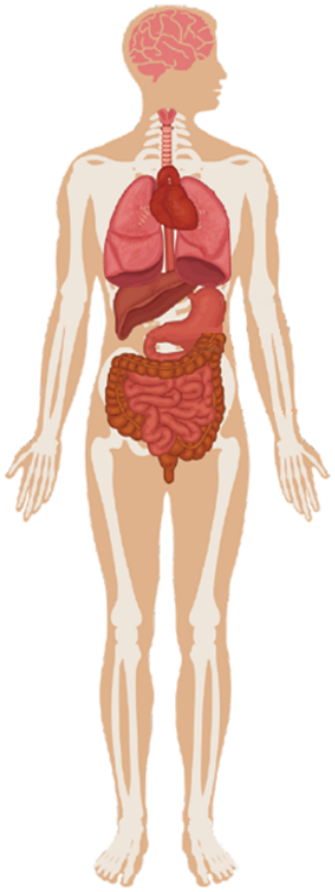
IC_{50}, half inhibitory concentration; $T_{½}$, plasma half-life

1. Hyman DM, *et al. J Clin Oncol.* 2017;35:LBA2501.
2. Drilon A, *et al. N Engl J Med.* 2018;378:731-739.
3. Ziegler et al. *British Journal of Cancer*. 2018;119:693-696

NTRK gene fusion incidence

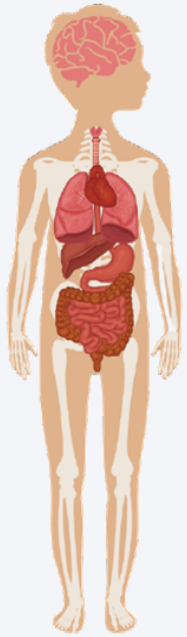
NTRK Gene Fusions Occur in a Range of Adult and Pediatric Tumor Types

Adult



- Brain cancers (0.4–3.1%)[1]
- Salivary (MASC; 90–100%)[1]
- Secretory breast cancer (92%)[2*]
- Pancreatic cancer (<1%)[3,4]
- Cholangiocarcinoma (3.6%)[1]
- Thyroid cancer (1.5–14.5%)[1]
- Lung cancer (0.2–3.3%)[1]
- GIST (3.2%)[5]
- Colon cancer (1.5%)[1]
- Melanoma (0.3%)[1,6]
- Sarcomas (1%)[6*]

Pediatric



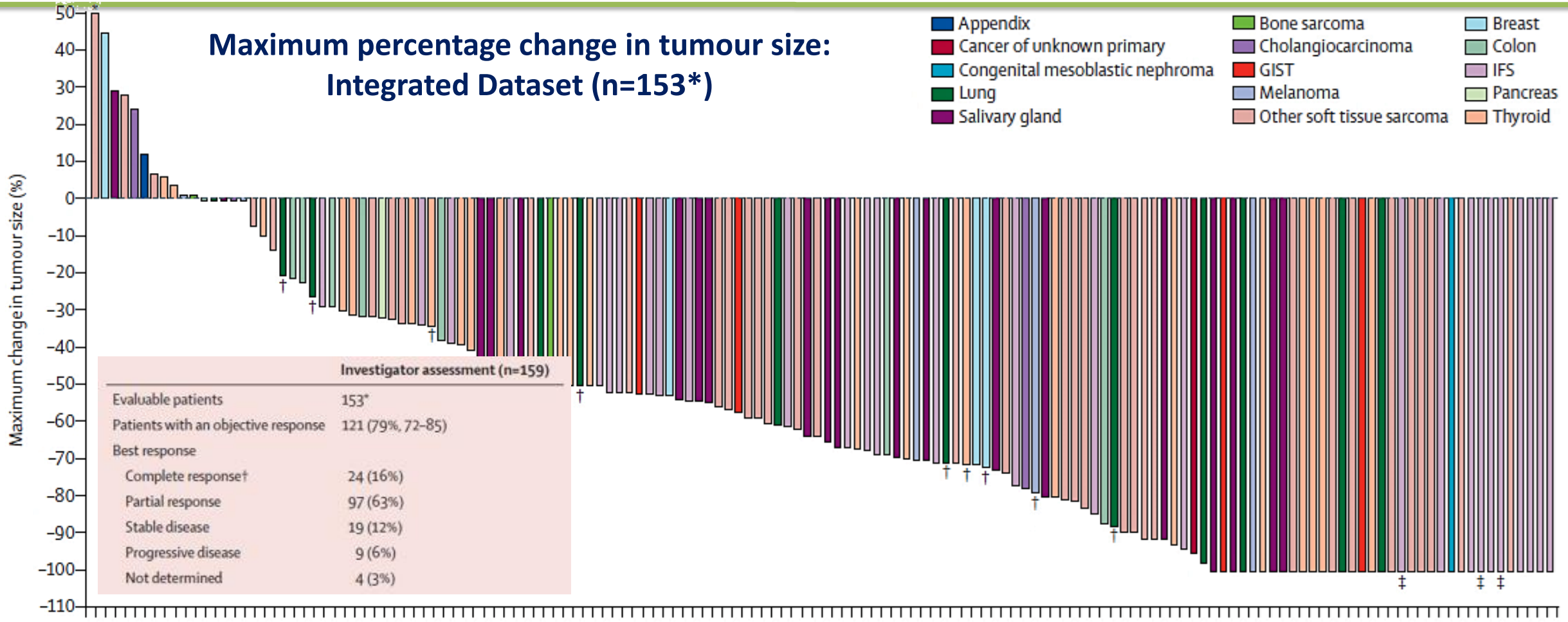
- Brain cancers (~10%)[7]
- Spitzoid neoplasms (16.4%)[8]
- Gliomas (7.1%)[1]
- Thyroid (9.4–25.9%)[9,10]
- Infantile fibrosarcoma (91–100%)[11]
- Congenital nephroma (83%)[1]
- Secretory breast cancer (92%)[2*]
- Sarcomas (1%)[6*]

*Frequency in adult vs. pediatric patients not specified; GIST, gastrointestinal stromal tumor; MASC, mammary analogue secretory carcinoma.

1. Vaishnavi A, Le A, Doebele RC. Cancer Discov. 2015;5:25-34. 2.Tognon C, et al. Cancer Cell. 2002;2:367-376. 3. Pishvaian MJ, et al. DOI: 10.1200/JCO.2018.36.4_suppl.521 Journal of Clinical Oncology 36, no. 4_suppl (February 1 2018) 521-521. 4. Cocco E, et al. Nat Rev Clin Oncol.2018 Oct 17. doi:10.1038/s41571-018-0113-0. 5. Brenca M, et al. J Pathol 2016;238:543-549. 6. Stransky N, et al. Nat Communications 2014;DOI: 10.1038/ncomms5846. 7. Wu G, et al. Nat Genet. 2014; 46(5): 444–450. 8. Wiesner T, et al. Nat Communications 2014;5:3116. doi:10.1038/ncomms4116. 8. Ricarte_Filho_JC, et al. J Clin Invest 2013;123:4935-4944. 9.Prasad ML, et al. Cancer 2016; DOI: 10.1002/cncr.29887. 10.Bourgeois JM, et al. Am J Surg Pathol 2000;24: 937–946.

Larotrectinib is a Highly Selective TRK Inhibitor Agnostic Treatment

Maximum percentage change in tumour size: Integrated Dataset (n=153*)



*149 shown

Figure 2: **Waterfall plot of the maximum percentage change in tumour size according to tumour type**

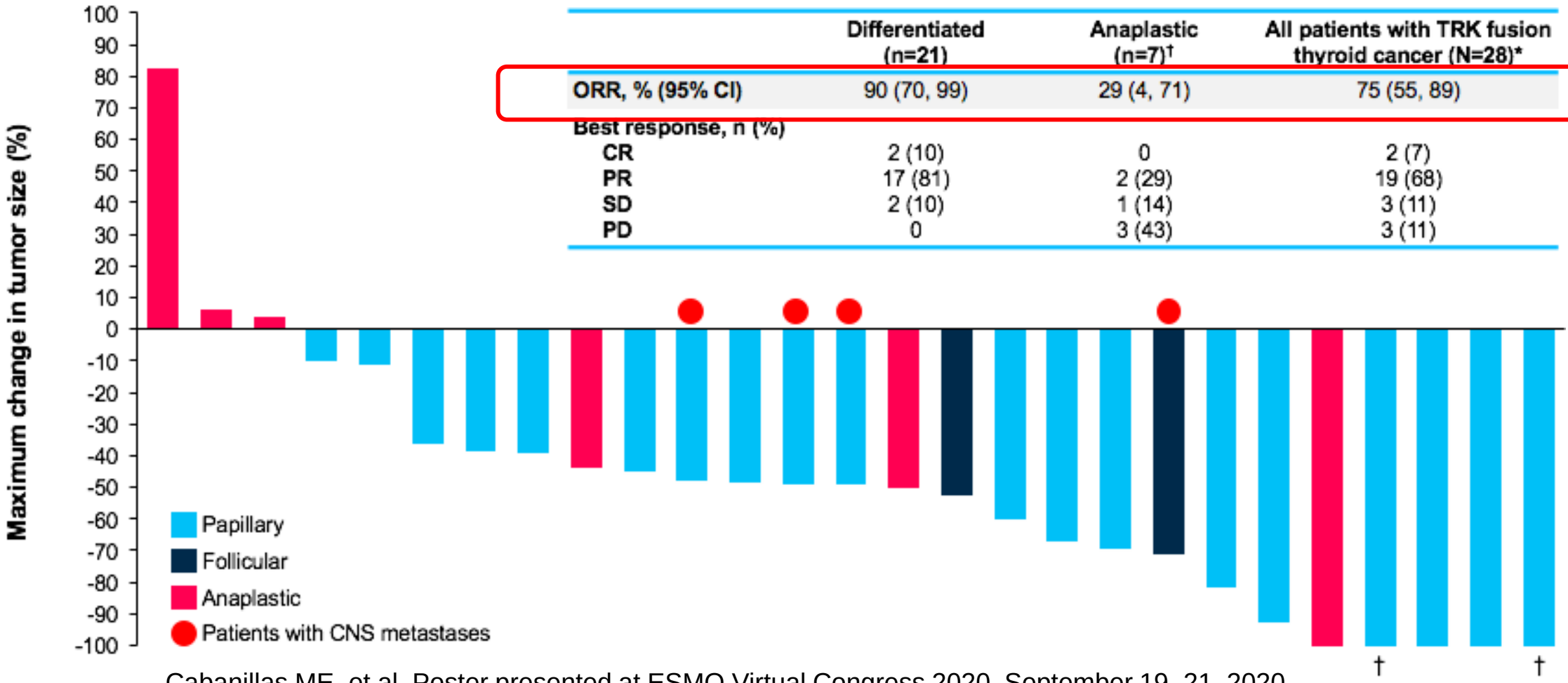
The waterfall plot excludes four patients who had clinical deterioration before an initial response assessment and six patients who were not evaluable due to insufficient time on therapy. GIST=gastrointestinal stromal tumour. IFS=infantile fibrosarcoma. *Maximum change in tumour size of 93% tumour growth. †Patients with brain metastases. ‡Patients with a pathological complete response.

Hong et al, Lancet Oncology 2020. https://doi.org/10.1016/S1470-2045(19)30856-3

Larotrectinib in Thyroid Cancer

Best response to larotrectinib

	Differentiated (n=21)	Anaplastic (n=7)†	All patients with TRK fusion thyroid cancer (N=28)*
ORR, % (95% CI)	90 (70, 99)	29 (4, 71)	75 (55, 89)
Best response, n (%)			
CR	2 (10)	0	2 (7)
PR	17 (81)	2 (29)	19 (68)
SD	2 (10)	1 (14)	3 (11)
PD	0	3 (43)	3 (11)

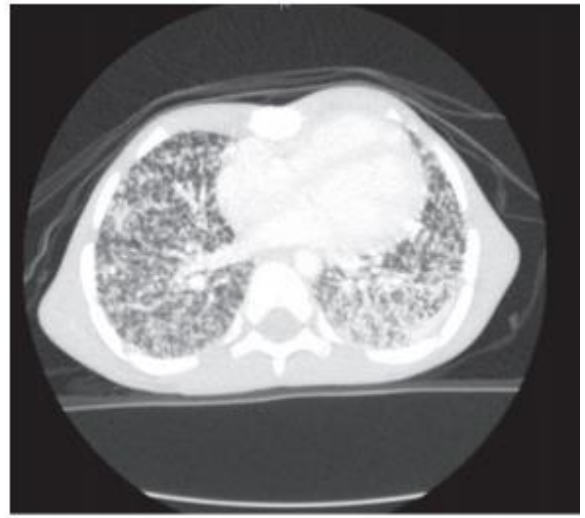


Cabanillas ME, et al. Poster presented at ESMO Virtual Congress 2020, September 19–21, 2020. Abstract 1916P

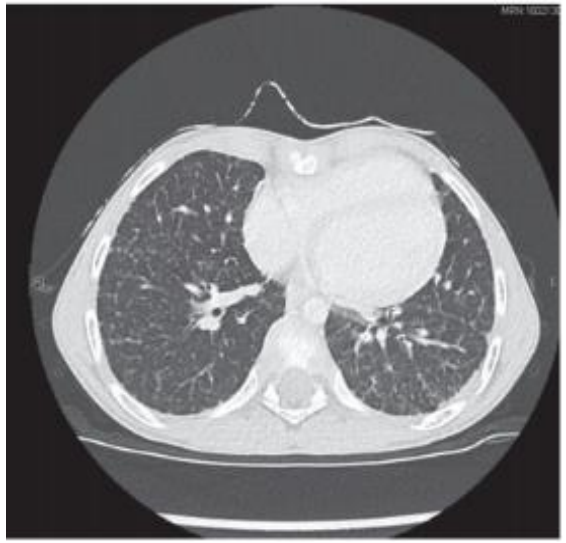
SQSTM1-NTRK1 fusion in PTC

- 5-year-old male with PTC and extensive regional lymph node and pulmonary metastases
- Prior therapies included thyroidectomy, lymph node dissection, and two 65 mCi doses of I-131
- Developed hypoxia, dyspnea at 7 years of age; received lenvatinib x 1 month; symptomatic improvement
- Discontinued lenvatinib when NGS results revealed *SQSTM1-NTRK1* fusion; enrolled in larotrectinib clinical trial
- As of 2/19/18, remains on larotrectinib without respiratory symptoms or limitation of activity

Baseline



After 2 cycles



Hawkins DS, *et al*. Poster presented at the Integrative Therapies Program for Children with Cancer; September 13, 2018. https://www.loxooncology.com/docs/presentations/ITPCC__Poster_2018.pdf. Accessed October 24, 2018

Response Rates

Study/Drug	CR	PR	SD	PD
Decision [1](Sorafenib) N= 417	0	12%	42%	NR
Select[2] (Lenvatinib) N= 392	2%	63%	15%	7%
Phase I/II Selpercatinib[3] N=19	1 (5%)	14 (74%)	4 (21%)	0
Phase I/II Arrow[4] (Pralsetinib) N=09	0	8 (89%)	1 (11%)	0
Phase I/II Larotrectinib[5] N=21 (DTC)	2 (10%)	17 (81%)	2 (10%)	0

1. Brose MS et al Lancet. 2014 Jul 26;384(9940). 2. Schlumberger M et al N Engl J Med 2015;372:621-30.
3. Wirth L et al. N Engl J Med 2020;383:825-35. 4. Subbiah V et al Lancet Diabetes Endocrinol 2021; 9: 491–501
5. Drilon A, *et al. N Engl J Med.* 2018;378:731-739.

Adverse Events

MKI and Selective Inhibitors

Sorafenib

Adverse Event	All Grades
Hand-foot skin reaction	76%
Diarrhea	69%
Alopecia	67%
Fatigue	50%
Weight Loss	47%
HTN	41%
Anorexia	32%

Lenvatinib

Adverse Event	All Grades
HTN	68%
Diarrhea	59%
Fatigue	59%
Anorexia	50%
Weight Loss	46%
N/V	46%
Hand-foot skin reaction	32%

Cabozantinib

Adverse Event	All Grades
Diarrhea	62%
Hand-foot skin reaction	47%
HTN	32%
Nausea	28%
Fatigue	27%
AL, AST Increased	25%
Weight loss	22%
Proteinuria	16%

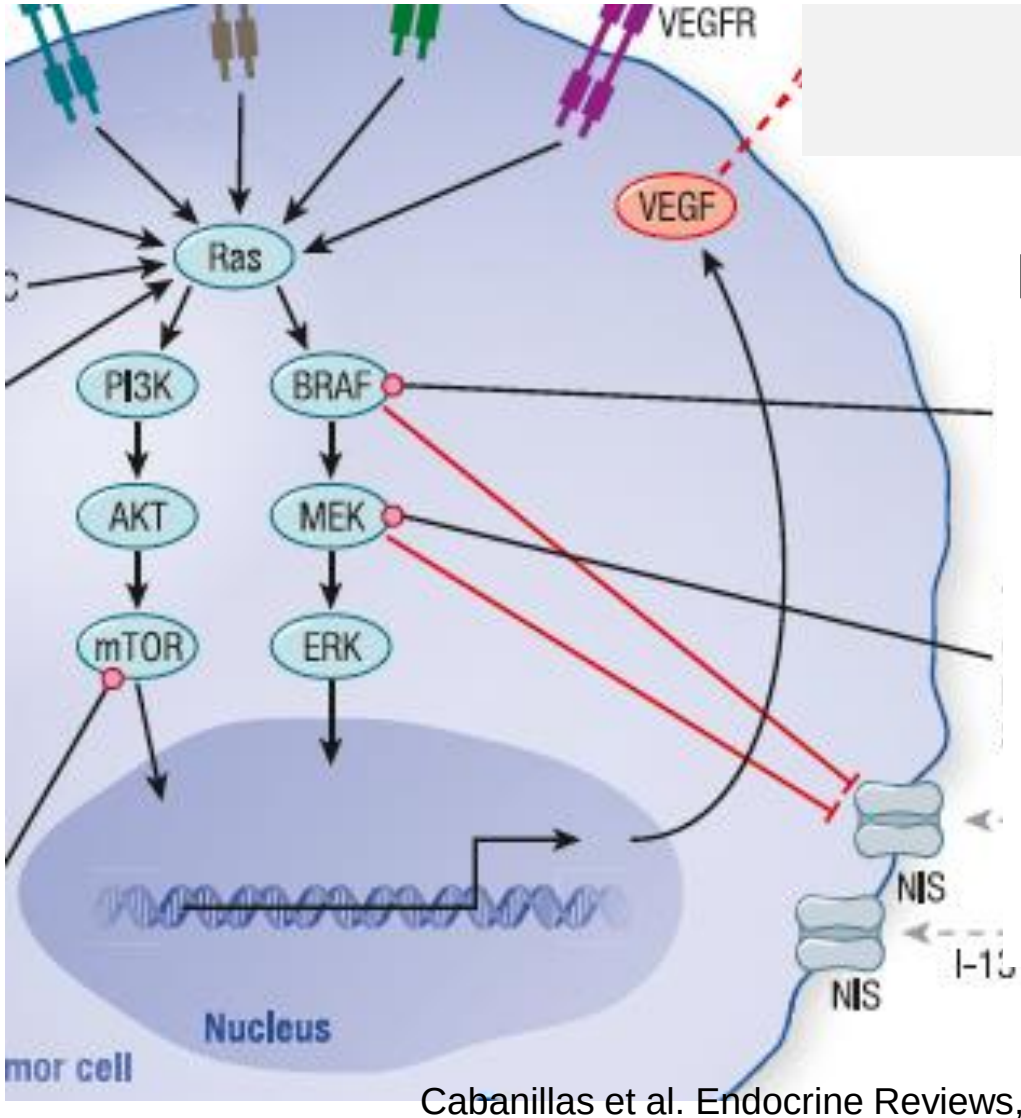
Selpercatinib

Adverse Event	All Grades
Dry Mouth	39%
HTN	30%
Increased SGOT/SGPT	28%
Fatigue	25%
Diarrhea	17%
Nausea	15%
Increased creatinine	14%
QT prolongation	13%

Larotrectinib

Adverse Event	All Grades
Fatigue	29%
Dizziness	29%
Increased SGOT/SGPT	29%
Leukopenia	18%
Constipation	18%
Peripheral edema	11%
Myalgia	11%
Nausea	7%

BRAF Inhibition
Inhibition of MAPK pathway



BRAF Inhibitors:

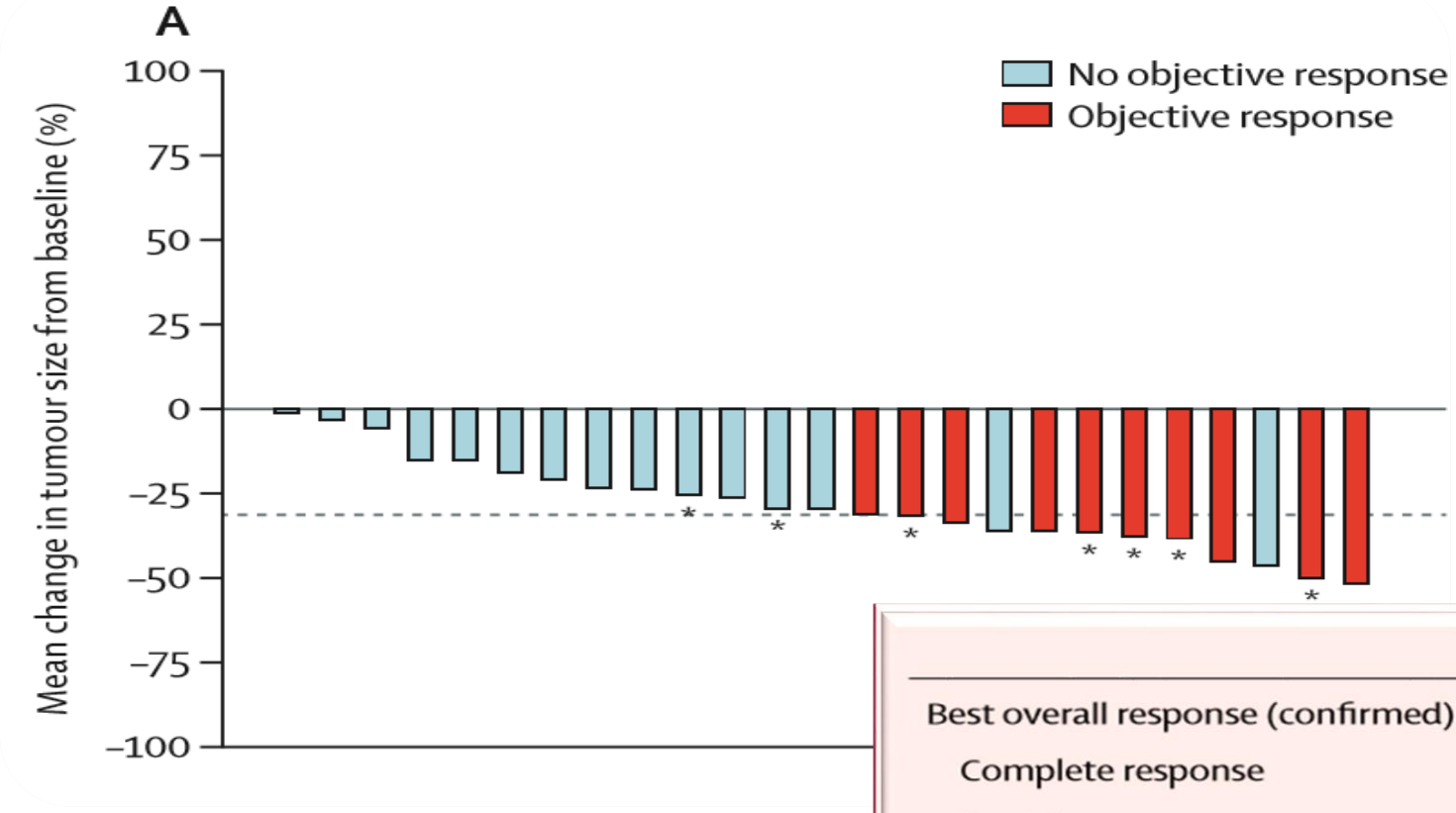
- Vemurafenib
- Dabrafenib
- Encorafenib

MEK Inhibitors:

- Trametinib
- Cobimetinib
- Binimetinib
- Selumetinib

Cabanillas et al. Endocrine Reviews, December 2019, 40(6):1573–1604

Vemurafenib (BRAF inhibitor) in BRAF-mutated PTC



- Median PFS= 18.2 months (95% CI 15.5–29.3)
- Median duration of response= 16.5 meses
- Median OS not reached

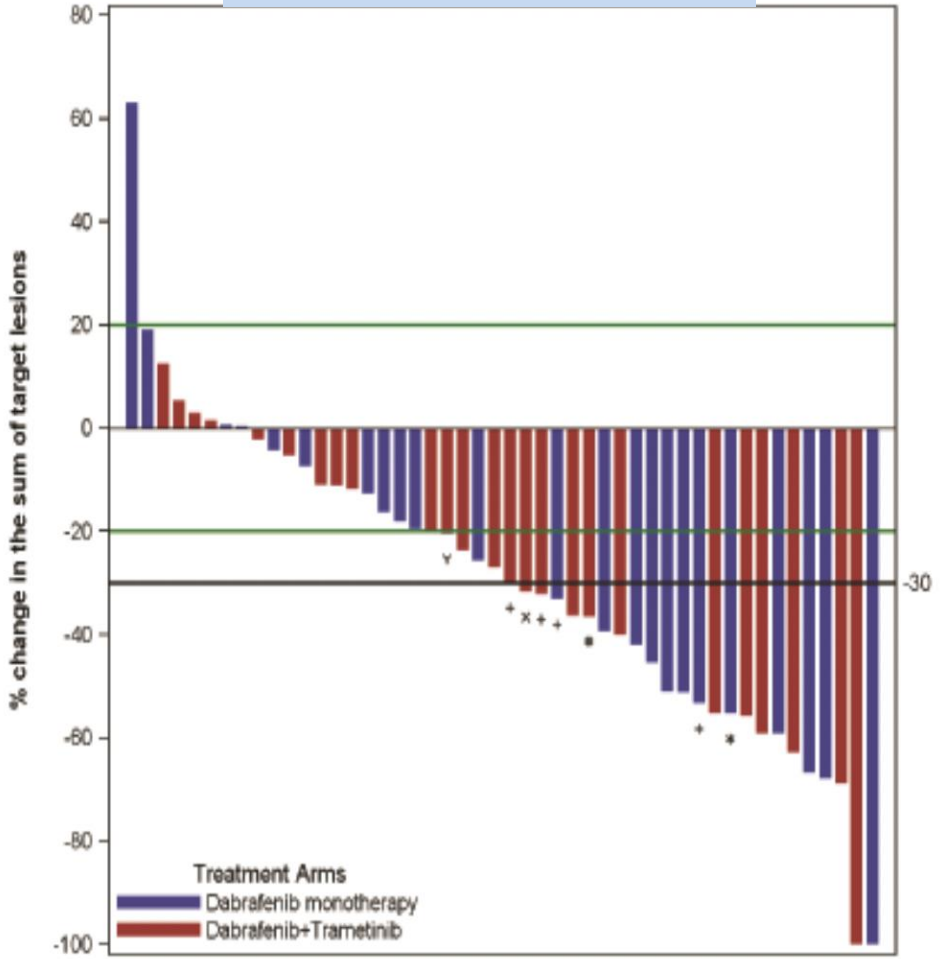
* Patients on therapy at time of publication

	Cohort 1 (n=26)
Best overall response (confirmed)	
Complete response	0
Partial response	10 (38·5%, 20·2–59·4)
Stable disease	15 (57·7%, 36·9–76·7)
Progressive disease	1 (3·8%, 0·1–19·6)
Unknown	0

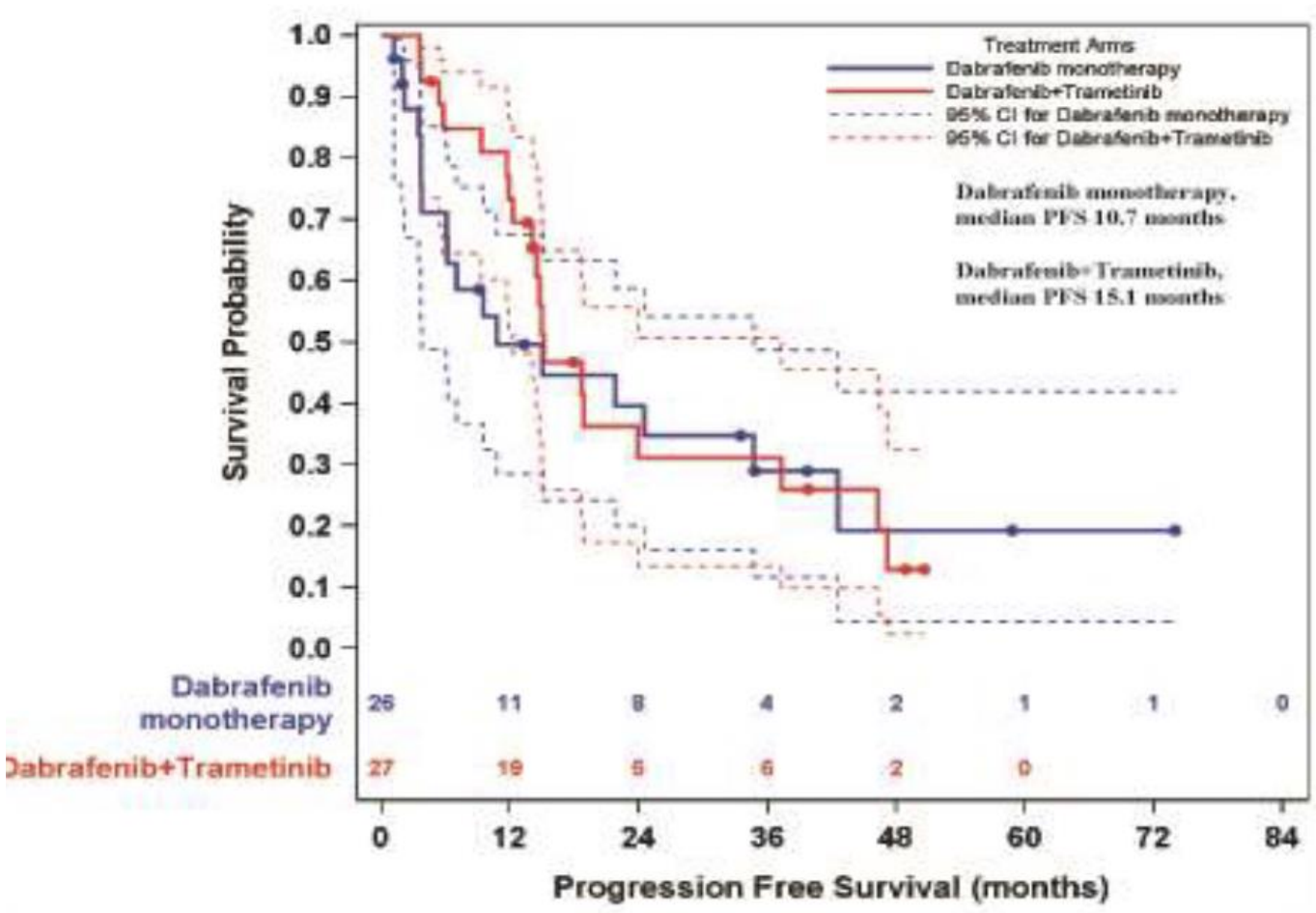
Brose MS, Cabanillas ME, Cohen EE, Wirth LJ, Riehl T, Yue H, Sherman SI, Sherman EJ, Lancet Oncology, 2016

Randomized phase II trial of **dabrafenib** versus **dabrafenib** plus **trametinib** in BRAF-mutated papillary thyroid carcinoma.

Tumor Response



Progression-free Survival



Busaidy N et al Thyroid, June 2022

Randomized phase II trial of **dabrafenib** versus **dabrafenib** plus **trametinib** in BRAF-mutated papillary thyroid carcinoma.

- ✓ 53 pts (median age 63 years, 38 females) were enrolled;
- ✓ 25% of pts had 1-3 prior therapy with multi-kinase inhibitors.

OUTCOME	Dabrafenib Alone (N=26)	Dabrafenib + Trametinib (N= 27)	P-value	Crossover (N=14)
Progressive Disease	2	0		2
Stable Disease	10	12		8
Median Objective Response (PR + minor resp)	11 (42%) (23-6)	13 (48%)	0.67	4 (29%)
Median Duration of Response	18.3 mo (5-NR)	17 mo (9.7-44.5)	0.99	16 mo (6.3-25.6)

- ✓ No difference between dabrafenib alone or in combination with trametinib.
- ✓ But, They observed activity of adding trametinib after dabrafenib failure

Busaidy N et al Thyroid, June 2022

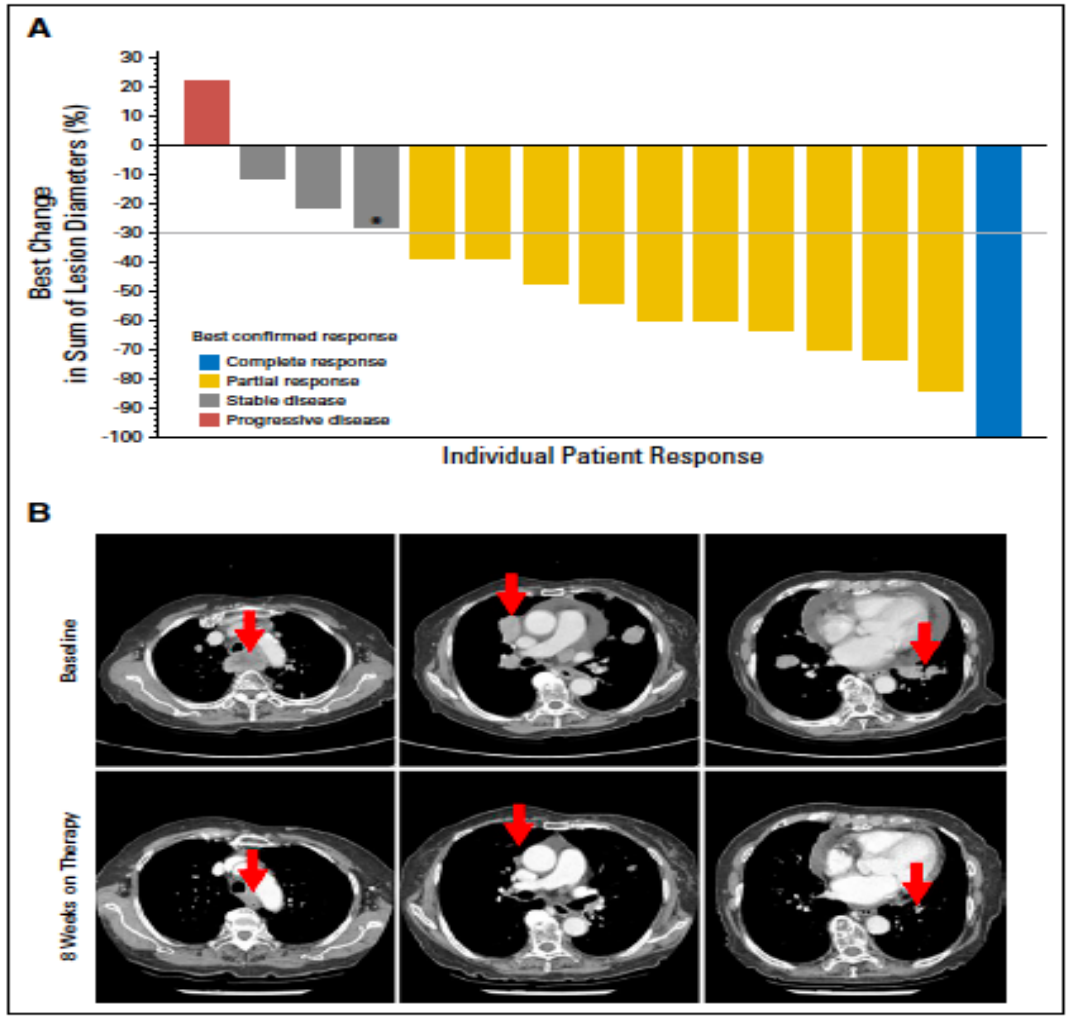
Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600–Mutant Anaplastic Thyroid Cancer

Phase II
Open-label

N=16 ATC BRAF +

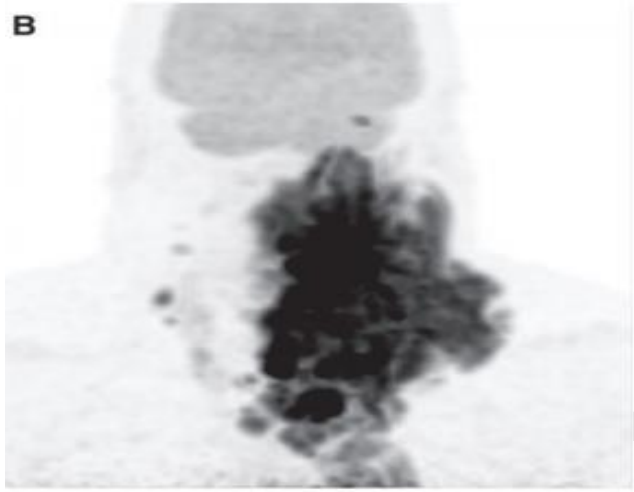
ORR 69% (11 of 16):
1 CR
10 PR

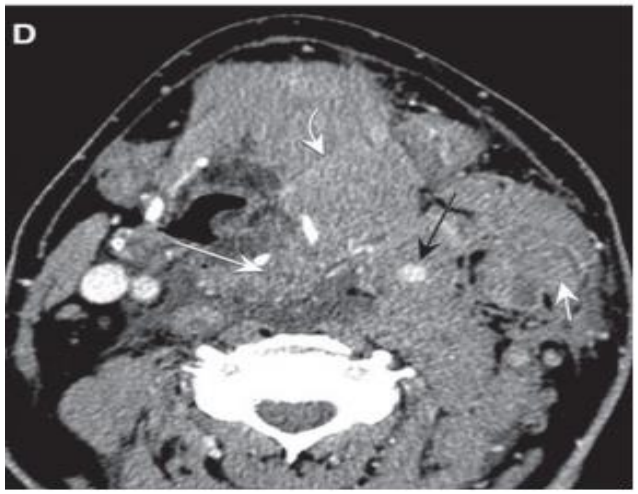
FDA approved 5/2018



Subbiah V et al J Clin Oncol 36:7-13, 2017

Neoadjuvant BRAF and Immune-Directed Therapy for Anaplastic Thyroid Carcinoma

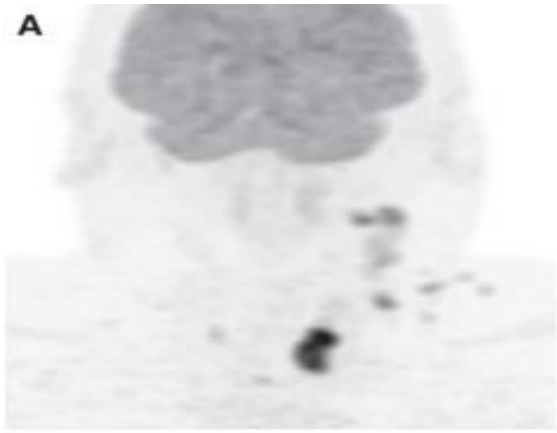


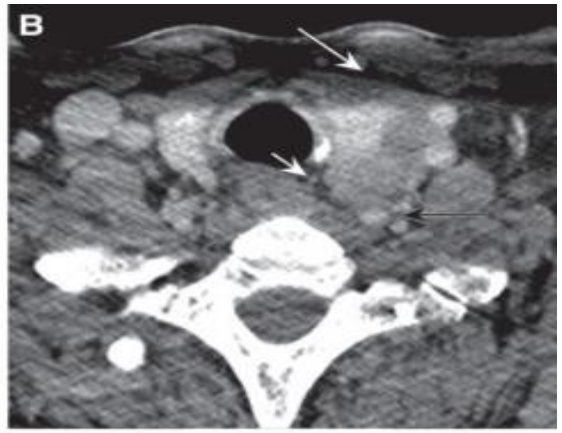


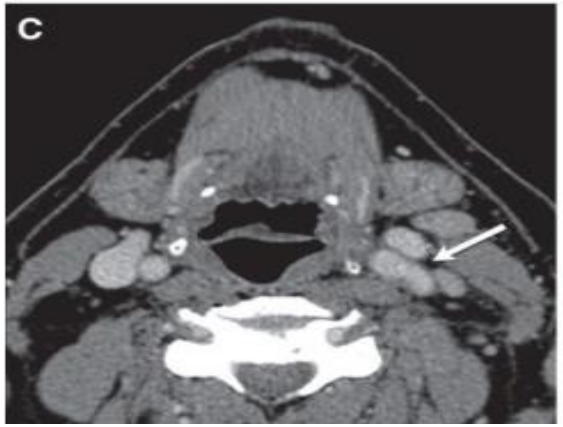
60 yr-old
BRAF +
ATC

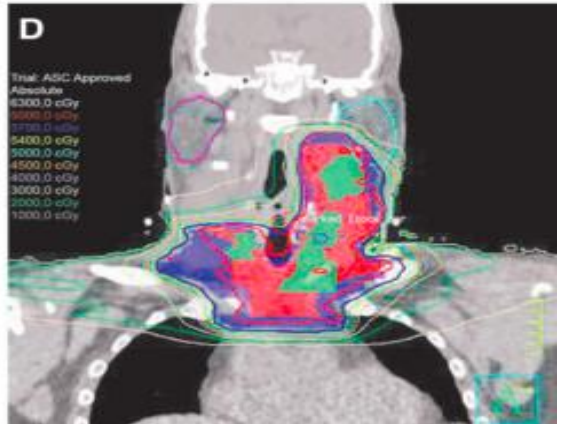
Dabrafenib + Trametinib

Pembrolizumab





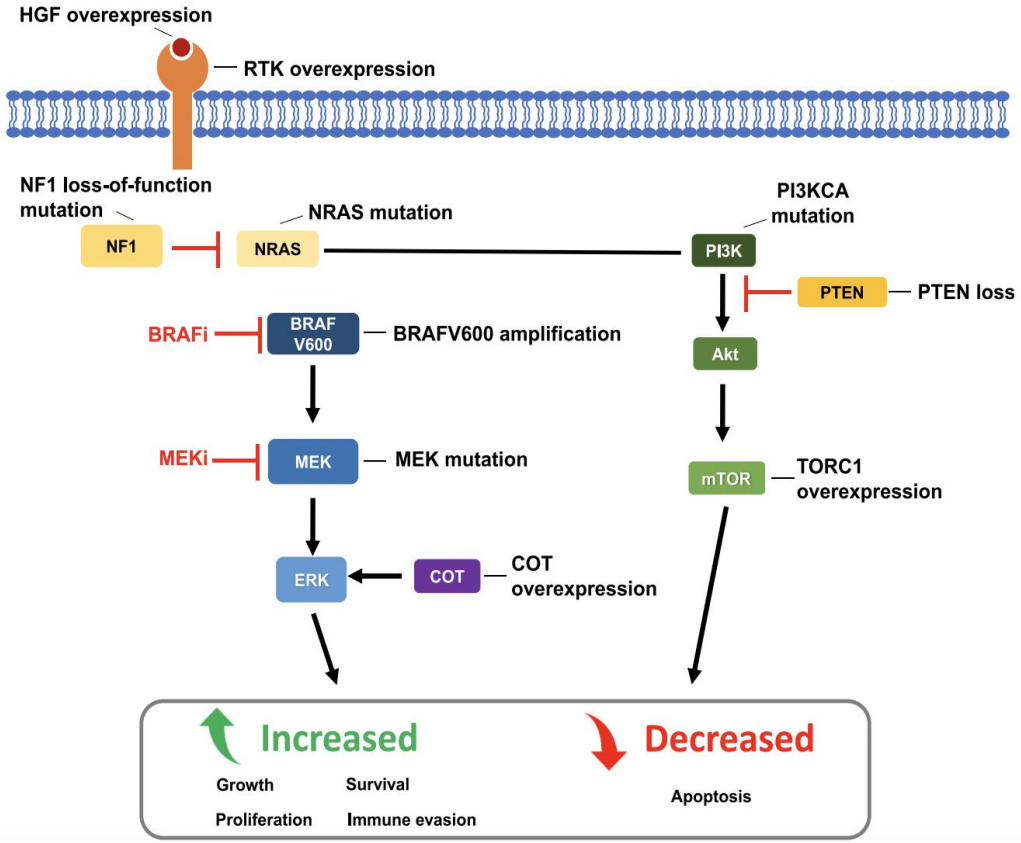




Cabanillas et al THYROID Volume 28, Number 7, 2018

Why Response to BRAF Inhibitors is not Similar to Other Specific Kinase Inhibitors?

- Adaptive feedback signaling upon treatment with BRAFi, leading to reactivation of the MAPK pathway (Oncogenic Addition)
  - Activation of Other TK receptors (VEGFR, EGFR, MET, Her 2, etc)
  - Development of resistant mutations



Emergence of *RAS* mutations

TABLE 1. OVERVIEW OF MISSENSE MUTATIONS IN BRAF^{V600E} POSITIVE SAMPLES AT BASELINE AND AT PROGRESSION UNDER BRAF INHIBITORS

	Mutations in baseline sample					*Mutations in resistant sample*				
Patient	*NCBI accession No.*	*Name*	*DNA change*	*Protein change*	*Variant allele frequency (%)*	*NCBI accession No.*	*Name*	*DNA change*	*Protein change*	*Variant allele frequency (%)*
1	NM_004333.4	BRAF	c.1799T>A	p.V600E	—	NM_004333.4	BRAF	c.1799T>A	p.V600E	—
						NM_004985.3	KRAS	c.35G>T	p.G12V	
2	NM_004333.4	BRAF[a]	c.1799T>A	p.V600E	26.4	NM_004333.4	BRAF	c.1799T>A	p.V600E	—
	NM_000546.5	TP53[a]	c.524G>A	p.R175H	22.3	NM_000546.5	TP53	c.524G>A	p.R175H	—
	NM_ 005228.4	EGFR[a]		p.G322S	1.6	—	—	—	—	—
						NM_002524.4	NRAS	c.181C>A	p.Q61K	—
						NM_005157.4	ABL1	c.740A>G	p.K247R	—
3	NM_004333.4	BRAF[a]	c.1799T>A	p.V600E	0.4	NM_004333.4	BRAF	c.1799T>A	p.V600E	—
	NM_000051.3	ATM	c.5956A>G	p.I1986V	—	NM_000051.3	ATM	c.5956A>G	p.I1986V	—
	NM_021960.4	MCL1	c.1051dupT	Nonsense	—	—	—	—	—	—
	NM_000546.5	TP53[a]		p.R273H	0.4	NM_004985.3	KRAS	c.35G>T	p.G12V	—
	NM_ 005228.4	EGFR[a]		p.R776H	0.2	NM_001626.4	AKT2	c.49G>A	p.E17K	—
	NM_001012331.1	NTRK1[a]		p.H571Y	0.6	NM_198253.2	TERT (promoter)	c.-124C>T	—	—
	NM_004958.3	MTOR[a]		p.V169I	0.3					
4	NM_004333.4	BRAF	c.1799T>A	p.V600E	—	NM_004333.4	BRAF[a]	c.1799T>A	p.V600E	0.3
						NM_002524.4	NRAS[a]	c.38G>A	p.G13D	0.3

[a]Indicates that the mutations were detected on liquid biopsy (cfDNA, Guardant 360).

Cabanillas M et al THYROID Volume 30, Number 9, 2020

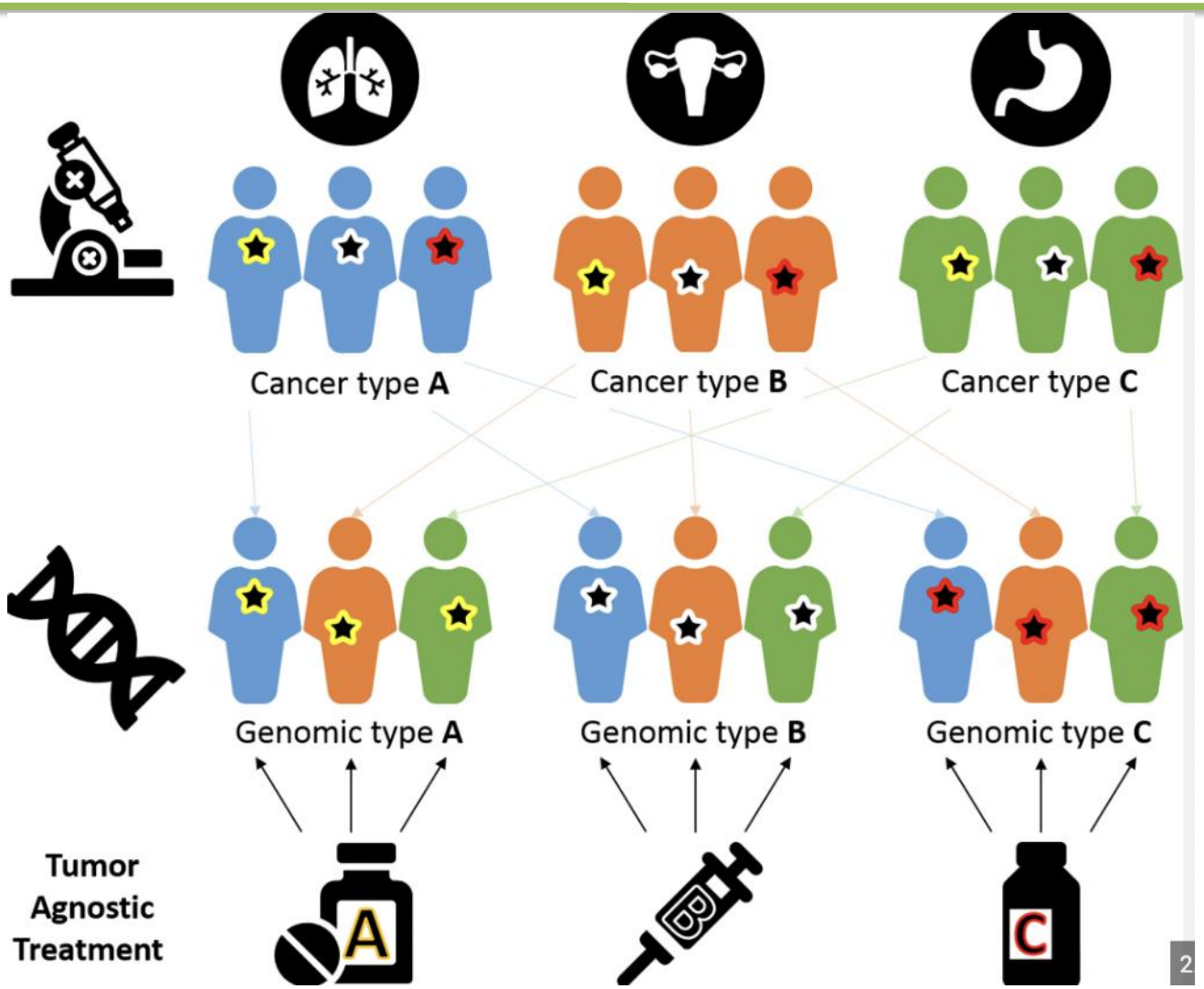
Subbiah V et al Trends in Cancer, September 2020, Vol. 6, No. 9

Which drug to start first?
What is evolving?

Iodine-refractory Metastatic DTC in progression

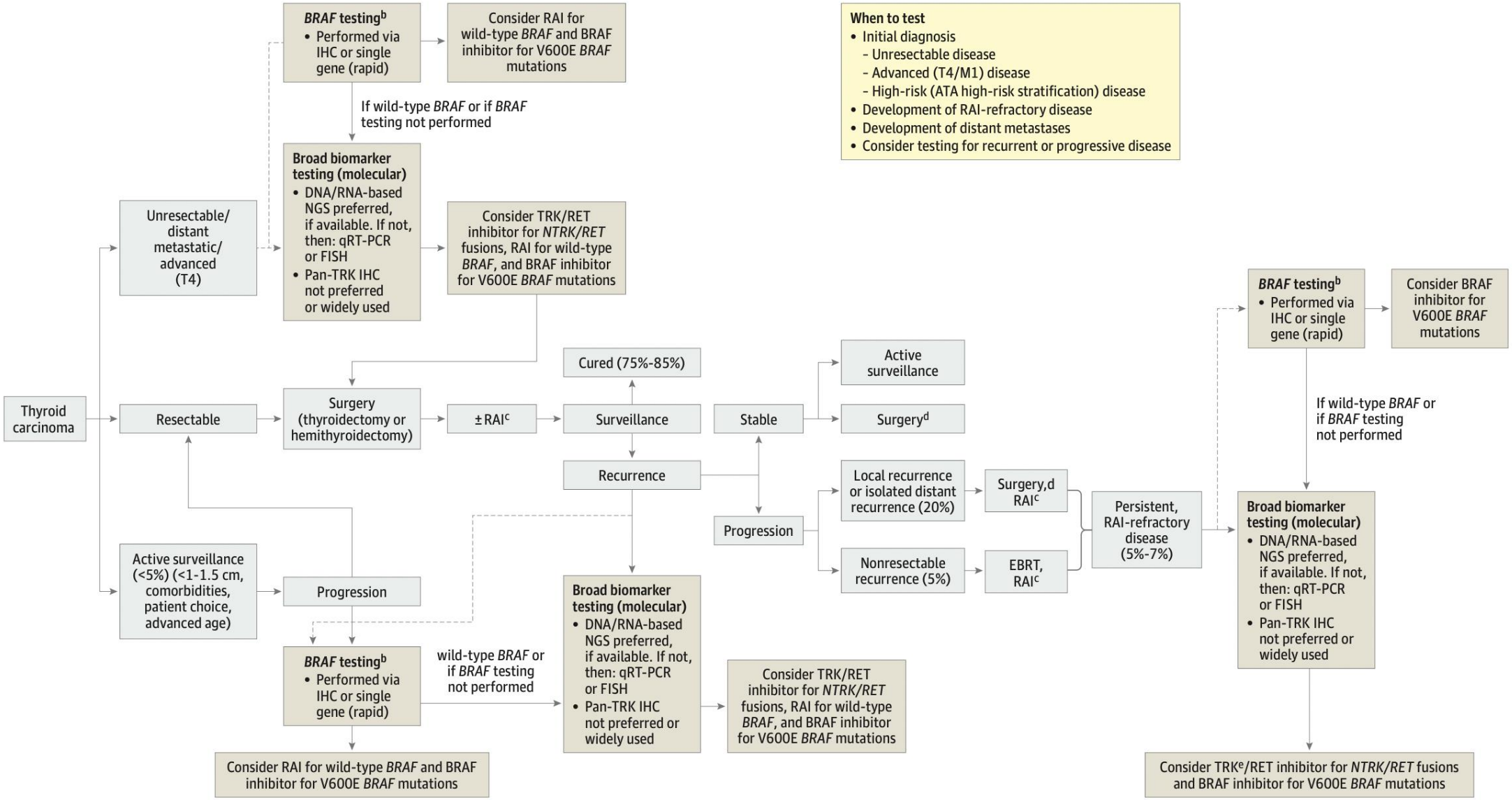
Tumor genetic profile available		Tumor genetic profile NOT available
NTRK →	Larotrectinib	Lenvatinib
RET/PTC →	Selpercatinib, pralsetinib	Sorafenib
BRAF →	Lenvatinib, sorafenib Trial Dabrafenib/tramentinib	Cabozantinib
RAS →	Lenvatinib, sorafenib	
No mutations		

Tumor-agnostic inhibitors in oncology: A new phase for precision medicine



Molecular Testing – When to test?

Haddad R, MD; Elisei R, MD; Hoff AO, Cabanillas M et al JAMA Oncology, June 2023



Tumor Profiling
When to do it?

- When considering specific kinase inhibitor
  - Metastatic and Progressive disease (RAI-refractory DTC) or MTC or ATC
    - To initiate specific kinase inhibitor
  - Metastatic Disease failing first or second line MKI (DTC, MTC, ATC)
  - Neoadjuvant treatment (DTC, MTC and ATC)
    - Unresectable,
    - T4 (locally advanced disease)
  - Prior to Radioactive Iodine for redifferentiation therapy (DTC)
    - Slowly progressive disease in Young patients with metastatic RAI refractory diseae
    - In patients on long-term MKI and good response - to attempt MKI discontinuation

Haddad R, MD; Elisei R, MD; Hoff AO, Cabanillas M et al JAMA Oncology, June 2023

Conclusions

- ✓ The in-depth knowledge of genetic drivers and the advent of genomic/agnostic therapy has completely changed the treatment scenario for thyroid cancer beyond radioactive iodine

- ✓ At this time, approved drugs include Sorafenib, Lenvatinib, Larotrectinib, Selpercatinib, Cabozantinib, Dabrafenib/Trametinib (ATC)

- ✓ The best time to perform tumor genetic analysis needs to be established in each country as identification of a genetic driver might lead to an effective, well tolerated but costly medication.

Thank You!

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INSTITUTO DO CÂNCER DO ESTADO DE SÃO PAULO
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ICESP/HC – Grupo Multidisciplinar em Câncer de Tireoide

Current Clinical Trials

Specific to Thyroid Cancer

- BRAF mutation (V600E) positive (PTC)
  - Dabrafenib and tramentinib Vs placebo in patients with RAIR metastatic DTC that failed first line therapy with TKI – **ClinicalTrials.gov Identifier: NCT04940052**
- RET positive MTC
  - **Libretto-531** – Selpercatinib. – first line therapy – MTC **ClinicalTrials.gov Identifier: NCT04211337**

Agnostic Therapy

- Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (**TAPISTRY**) Platform Study - **ClinicalTrials.gov Identifier: NCT04589845 - Nonrandomized**
  - **RET fusion-**positive tumors – pralsetinib
  - ROS1 **fusion-**positive- entrectinib NTRK1/2/3 **fusion-**positive tumors – entrectinib
  - ALK **fusion-**positive tumors – alectinib
  - AKT1/2/3 mutant-positive tumors – Ipatasertib
  - BRAF class II or III mutant or **fusion-**positive tumors – Belvarafenib
  - PIK3CA multiple mutant-positive tumors - Inavolisib