2025 City of Hope Multidisciplinary Thyroid Cancer Symposium

Medical Therapy for Advanced Differentiated Thyroid Carcinoma

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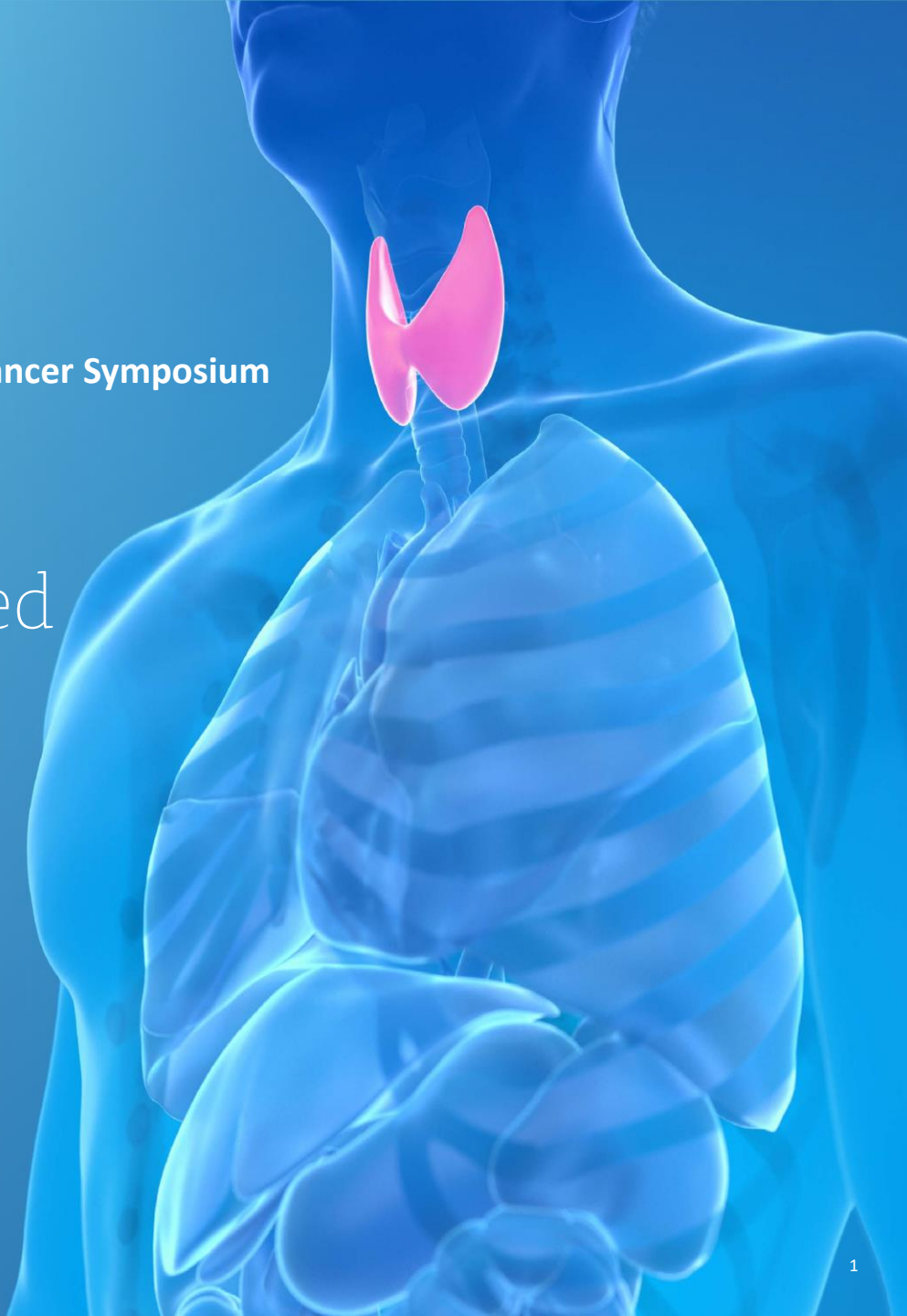
City of Hope



Disclosures

- Consultant for Genentech, Inc., and Novartis.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

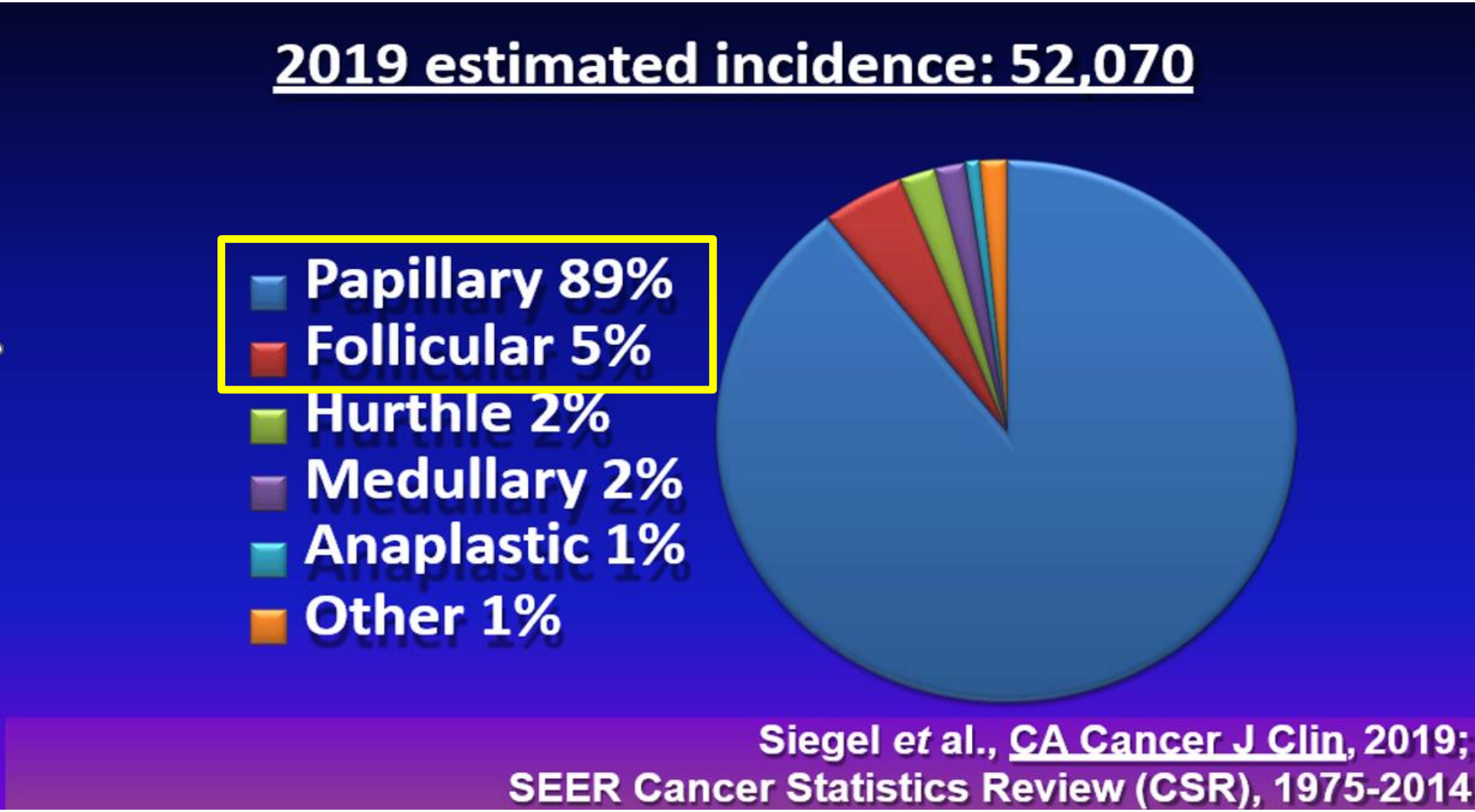
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

Outline

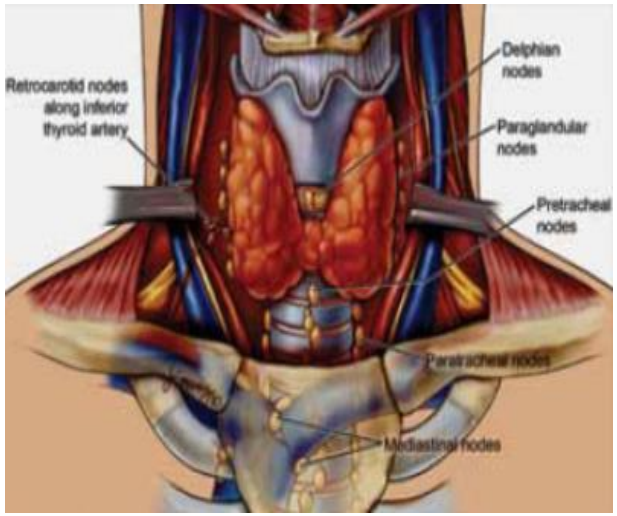
- Spectrum of differentiated thyroid carcinoma genetic signaling
- RAI-refractory advanced differentiated thyroid carcinoma
  - Treatments:
    - Targeted therapies, selective, and nonselective
    - Re-differentiation
    - Neoadjuvant therapy
- Medullary thyroid carcinoma, systemic therapies

Thyroid cancer subtypes



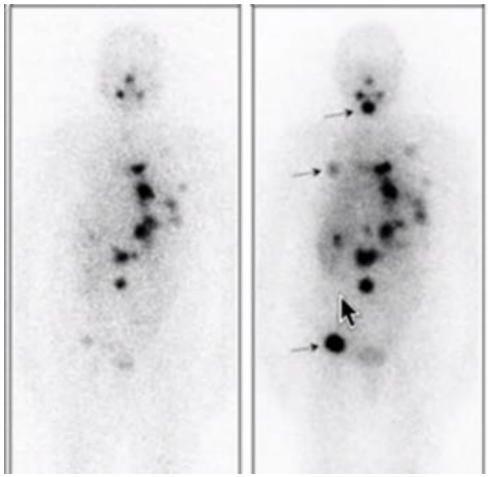
- **DTC refers to a malignant tumor that has a histologic appearance of cell types found in the thyroid**

DTC Initial Treatment



Surgery +/- LND

TSH suppression



Radioactive iodine

- DTC: > 90% will have long term survival when Dx in early stages
- 10-30% experience progression, recurrence, or mets
- 15% develop distant metastases, in which about 33% not have RAI uptake in metastatic sites (RAI-R)

EL. Mazzaferri, RT Loos, JCEM, 2001. Durante, Schlumberger et al, JCEAM, 2006

Metastatic DTC, Overall Survival and RAI

- Radioactive Iodine Refractory DTC
- Survival in RAI I-131 uptake VS no uptake in metastatic DTC

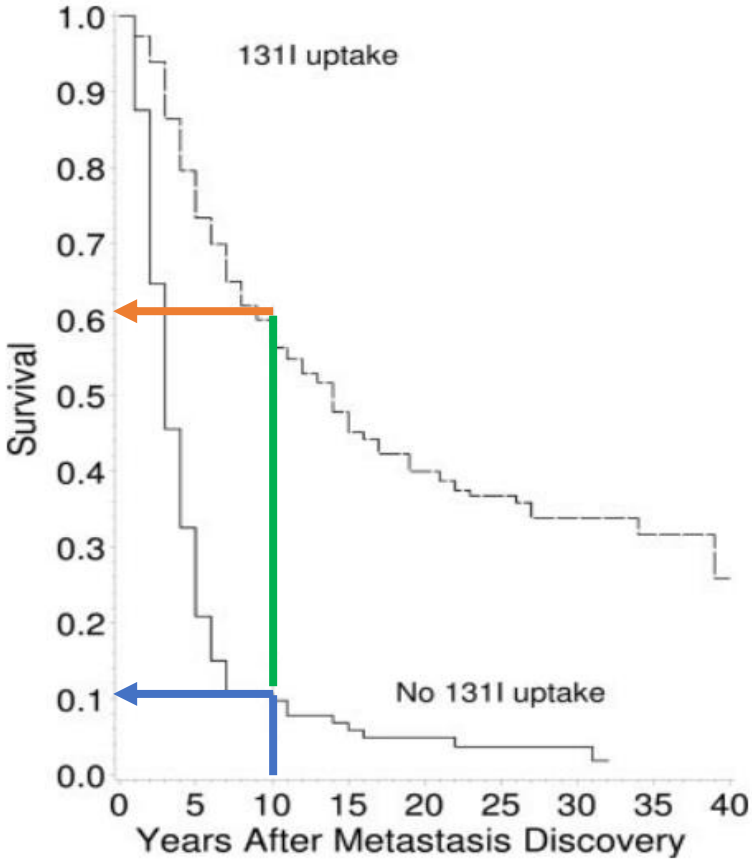
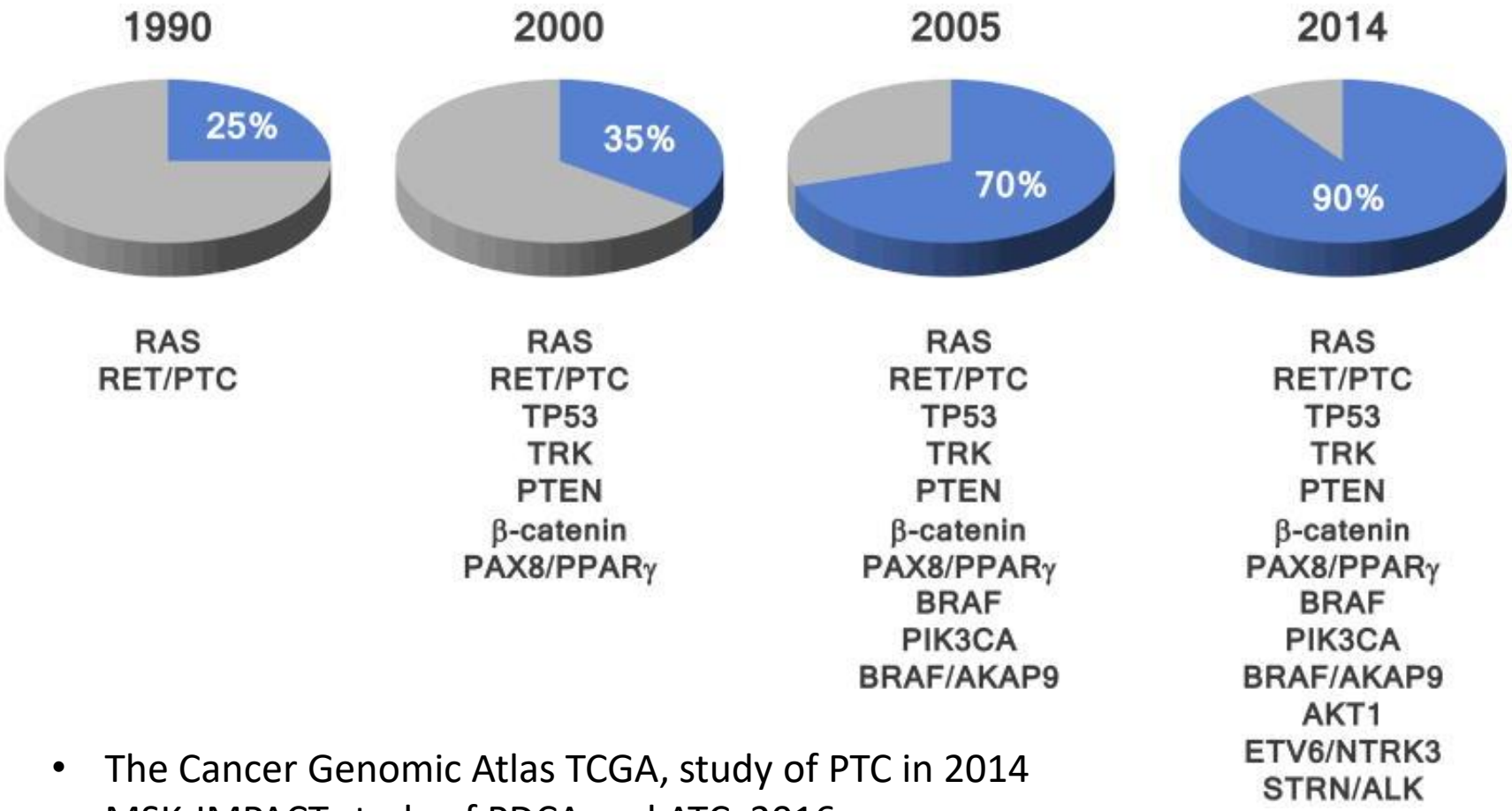


FIG. 1. Survival after the discovery of metastases according to the presence or absence of ^{131}I uptake in the metastases.

Durante et al, Outcome of 444 Patients with Distant Metastases, France, JCEM, 2006

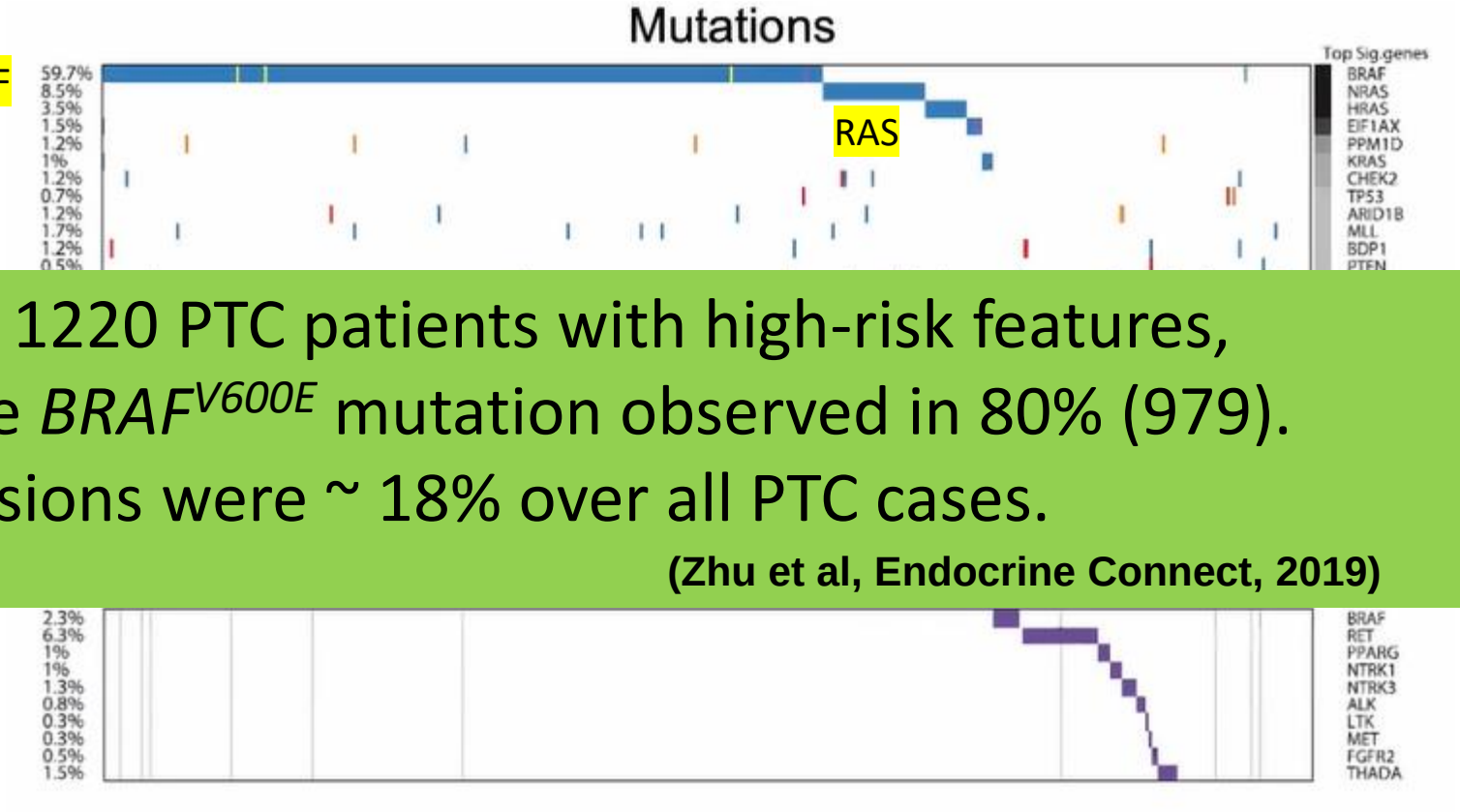
Progress in identifying genetic alterations in thyroid cancer



- The Cancer Genomic Atlas TCGA, study of PTC in 2014
- MSK-IMPACT study of PDCA and ATC 2016
- Pan-Cancer Atlas Project of TCGA 2018

Nikiforav et al, Endocrine –Related Cancer 2014

Thyroid Cancer Genomic Atlas, TCGA



In 1220 PTC patients with high-risk features, the *BRAF*^{V600E} mutation observed in 80% (979). Fusions were ~ 18% over all PTC cases.

(Zhu et al, Endocrine Connect, 2019)

- PTC driver genetic alterations are mutually exclusive
- These driver mutations or fusions are biologically so dominant that almost always only one happens

TCGA 2014

Systemic therapy, DTC

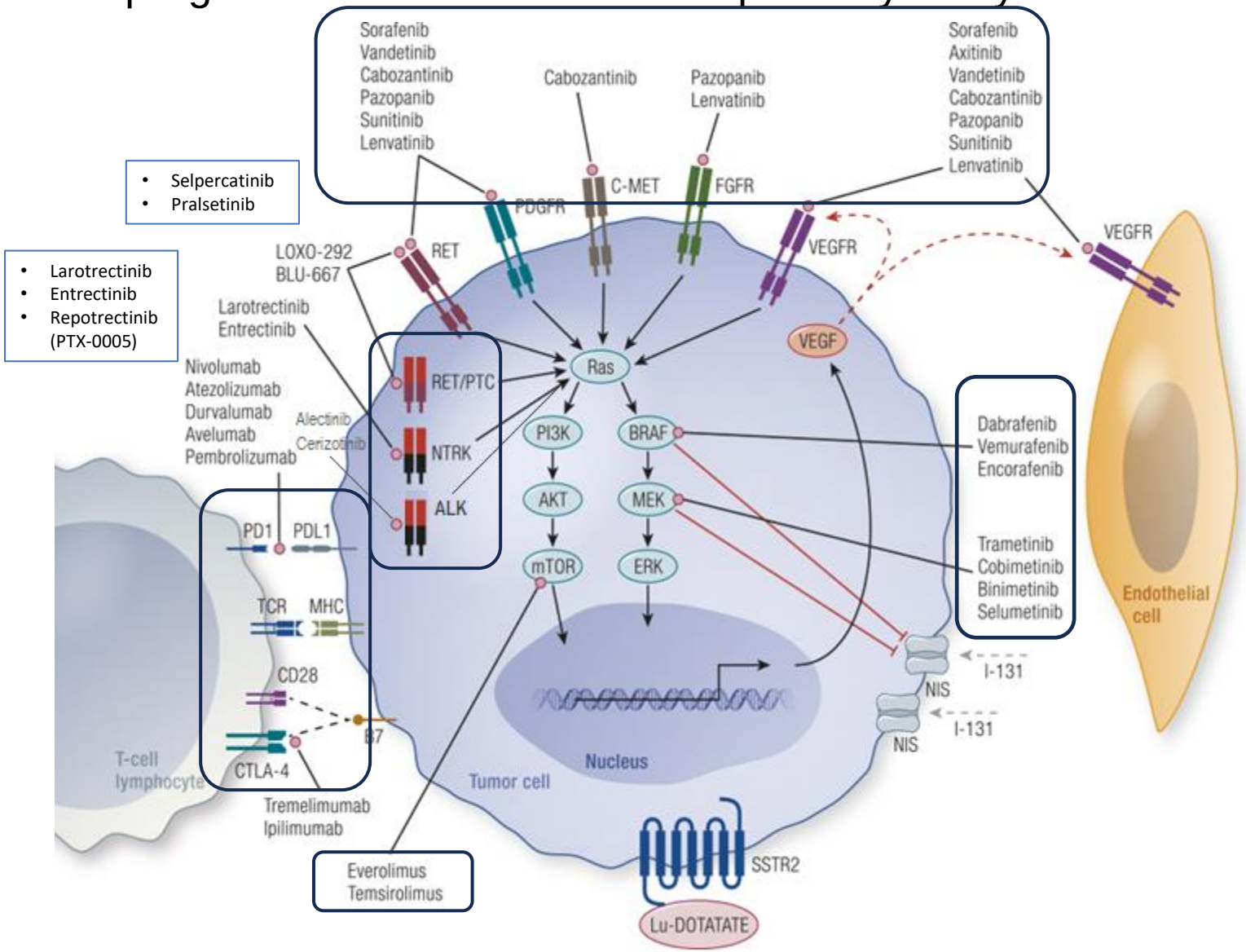
- A Multidisciplinary team approach for metastatic RAI-R

- ATA Guidelines : REC. 96-ATA 2015

  - Kinase inhibitor therapy should be considered in RAI-Refractory DTC patients with metastatic, rapidly progressive, symptomatic and or imminently threatening disease not otherwise amenable to local control using other approaches.
  - Patients who are candidates for kinase inhibitor therapy should be thoroughly counselled on the risks and benefits of this therapy as well as alternative therapeutic approaches including best supportive care.

Consider clinical trials when available

Upregulation of the MAPK / PI3K pathway in thyroid cancers

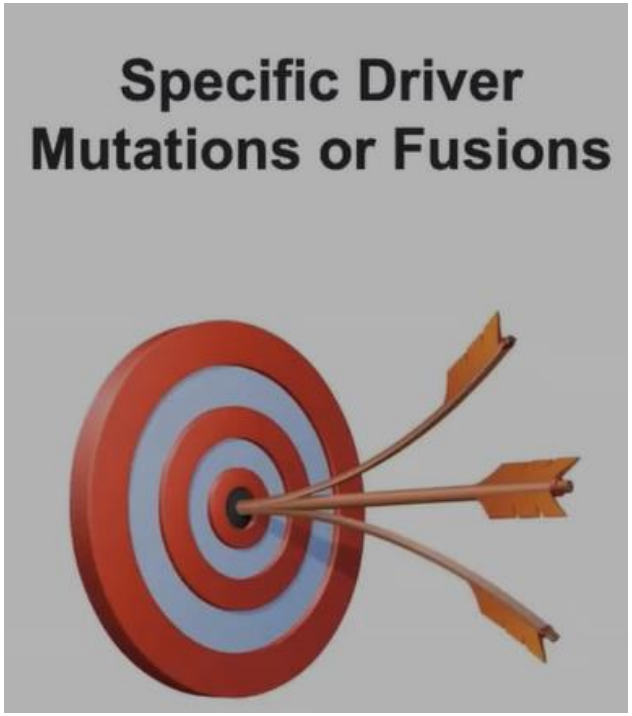


- **VEGFR, FGFR, C-MET, PDGFR, MHC, NIS, SSTR2**
- **RAS, RET, PIK3K, AKT, mTOR, BRAF, MEK, ERK, RET fusion, NTRK fusion, ALK fusion**
- **PD1, PDL1, CTCLA-4**

Adapted by S Fazeli 2023, Endocrine Reviews, 2019

Systemic therapies in metastatic RAI-R DTC

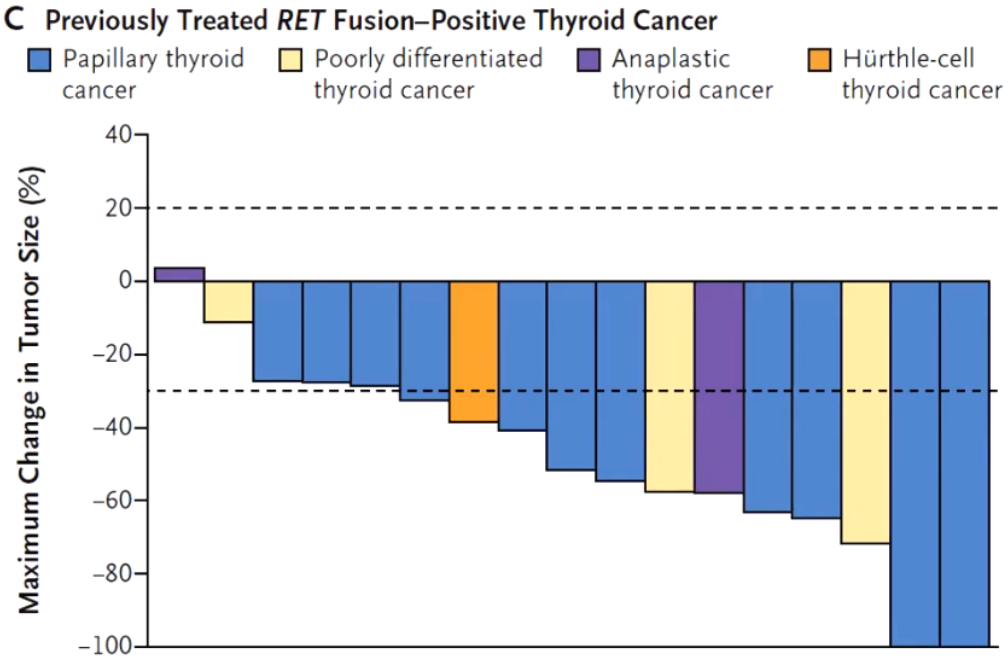
- Selective targeted therapies
  - Fusions: RET, ALK, NTRK
  - BRAF mutation: BRAFi+/- MEKi
- Nonselective targeted therapies: MKI
- Second-line therapies
  - MKI second-line
  - Immunotherapy
- Re-differentiation therapy



Selective Targeted Therapies, DTC

- **RET fusions**
  - Selpercatinib
  - Pralsetinib
- **NTRK fusions**
  - Larotrectinib
  - Entrectinib
  - Repotrectinib
- **ALK fusions**
  - Crizotinib
  - Alectinib
- **BRAF mutations**
  - Dabrafenib / Trametinib
  - Vemurafenib / Cobimetinib
  - Encorafenib / Binimetinib
- **BRAF fusions**
  - Has no selective treatment

Selpercatinib: RET fusion-positive DTC 6/2024 AGE 2 and Older



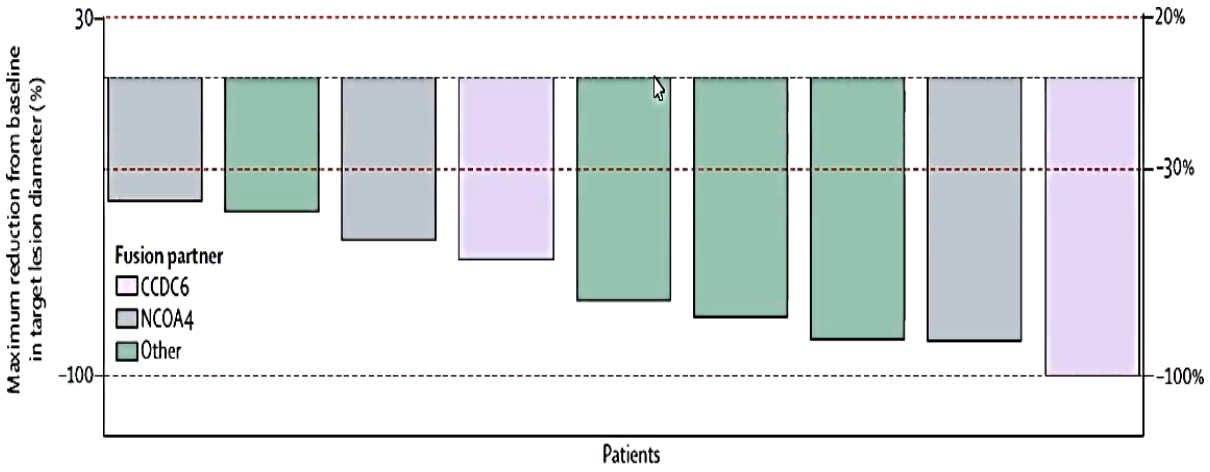
Response	Previously Treated *RET* Fusion–Positive Thyroid Cancer	
	Independent Review (N=19)	Investigator Assessment (N=19)
Objective response — % (95% CI)	79 (54–94)	58 (34–80)
Best response — no. (%)		
Complete response	1 (5)	0
Partial response	14 (74)	11 (58)
Stable disease	4 (21)	7 (37)
Progressive disease	0	0
Could not be evaluated	0	1 (5)
Duration of response		
No. of patients with objective response	15	11
Data censored — no. (%)	9 (60)	8 (73)
Median (95% CI) — mo	18.4 (7.6–NE)	NE (9.5–NE)
Median follow-up — mo	17.5	17.5
Progression-free survival		
Data censored — no. (%)	11 (58)	12 (63)
Median (95% CI) — mo	20.1 (9.4–NE)	NE (10.0–NE)
Median follow-up — mo	13.7	19.3
Prevalence at 1 yr (95% CI) — %	64 (37–82)	61 (33–81)

Selpercatinib:

- Papillary thyroid carcinoma
- Poorly differentiated thyroid carcinoma
- Anaplastic thyroid carcinoma
- Hurthle cell thyroid carcinoma

Wirth et al. NEJM 2020

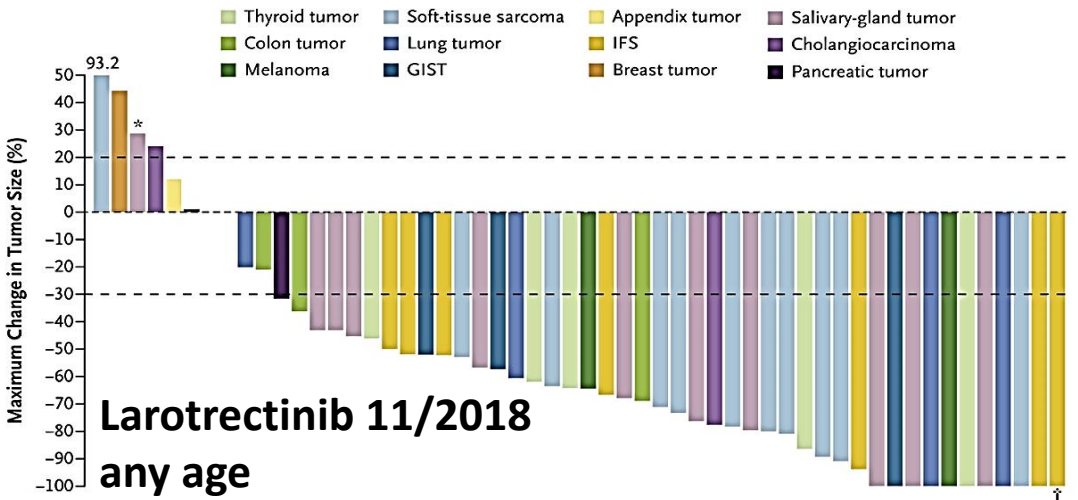
Pralsetinib: RET fusion positive DTC



	RET fusion-positive thyroid cancer group
	All (n=9)
Overall response rate	8 (89%); (52–100)
Best overall response	
Complete response	0
Partial response	8 (89%)
Stable disease	1 (11%)
Progressive disease	0
Disease control rate†	9 (100%); (66–100)
Clinical benefit rate‡	8 (89%); (52–100)
Median time to first response,§ months	1·9 (IQR 1·8–2·8)
Median duration of response,§ months	NR (NE–NE)
6 months	100% (100–100)
12 months	86% (60–100)

Lancet Diabetes Endocrinol 2021

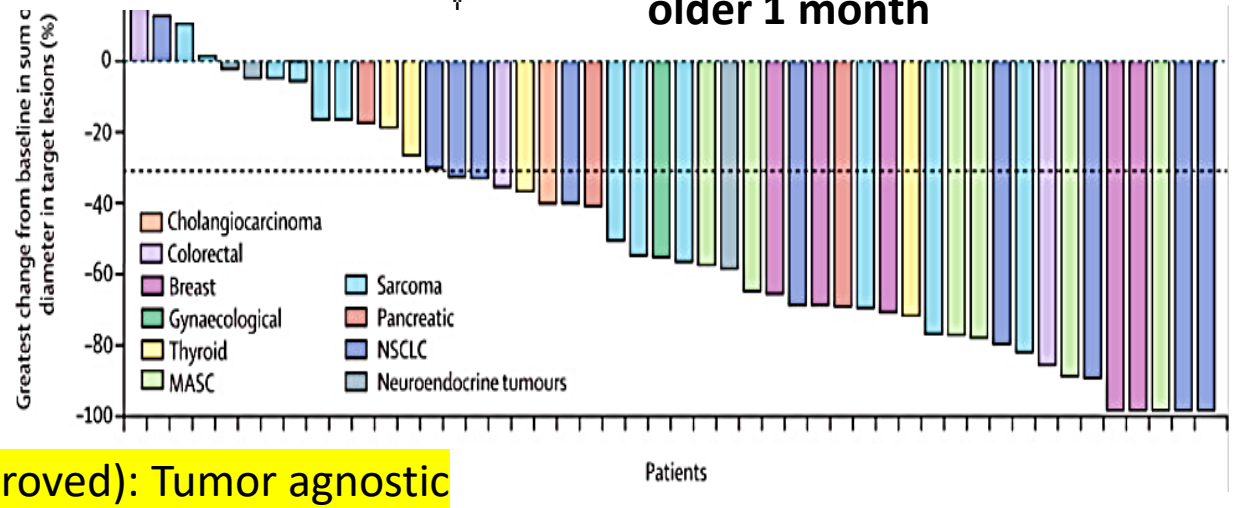
NTRK fusion positive DTC



Larotrectinib 11/2018
any age

ORR 86% DTC
ORR 29% ATC

Entrectinib 8/2019
older 1 month



- NTRK inhibitors (FDA approved): Tumor agnostic
- Very well-tolerated, watch for transaminitis,
- Watch for resistant mutations solvent front NTRK3 and NTRK1

Drilon et al. NEJM 2018

Doebele et al. The Lancet Oncology 2019

NTRK fusion positive tumors Repotrectinib

- **Repotrectinib, a new NTRK inhibitor 6/14/2023**
  - Adult and pediatrics from age 12
  - ORR 58% (TKI naïve), 50% (TKI prior)
  - Duration of response NR (naïve) and 9.9 months (prior)

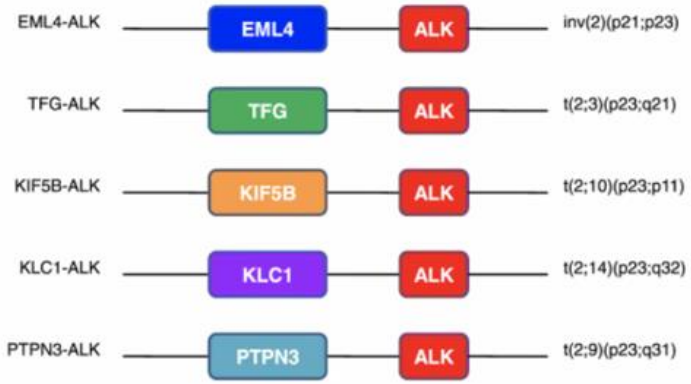
- In case of progression on NTRK inhibitor, a new biopsy is needed

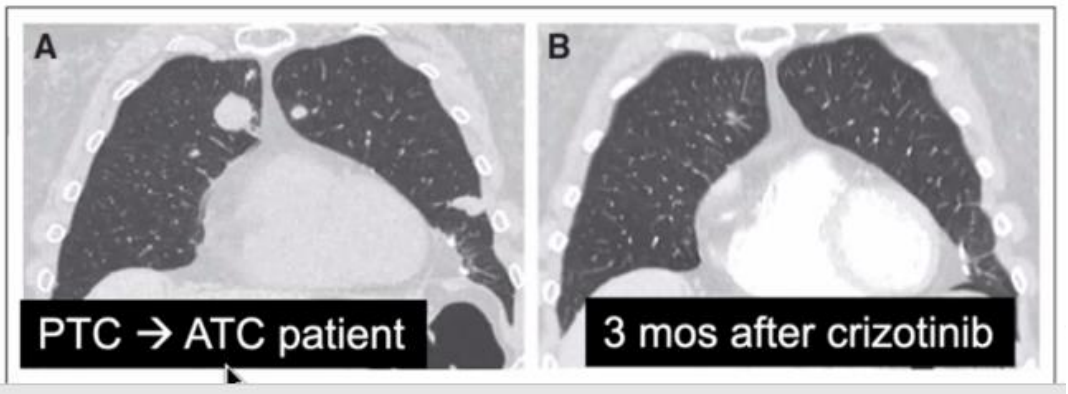
Drilon et al. NEJM 2018

Doebele et al. The Lancet Oncology 2019

ALK fusions

- *ALK* fusions: PTC (1-3%)[1], PDTC (4%)[2], ATC (rarely)[3], MTC[4]
- ALK inhibitors (FDA approved for NSCLC):
  - Crizotinib (1st gen)
  - Alectinib
  - Brigatinib
  - Ceritinib
  - Entrectinib
  - Lorlatinib



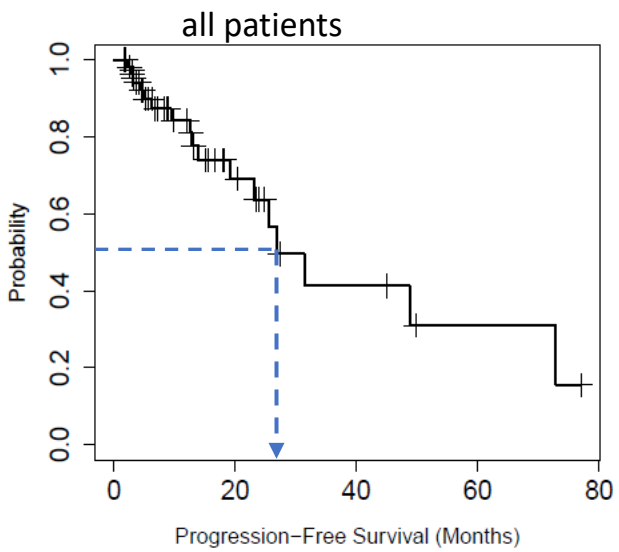


Leroy et al.
Thyroid 2020

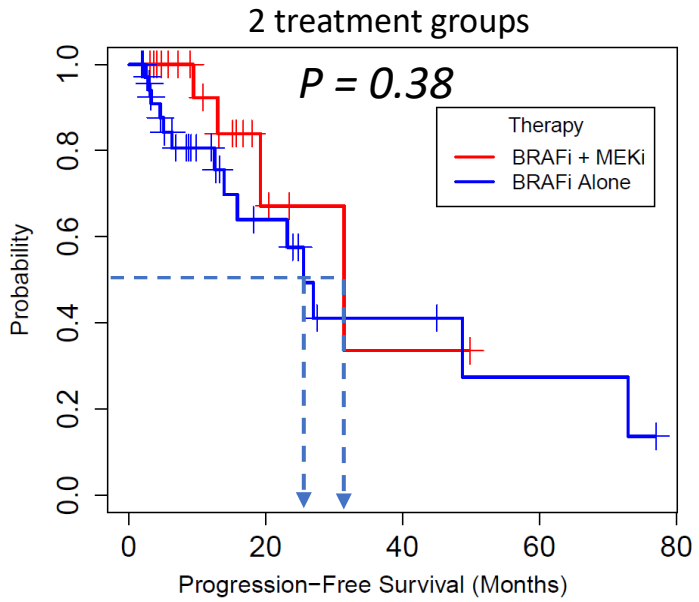
(1) Panebianco et al, ERC epub 9/2019, (2) Landa et al. JCI 2016, (3) Godbert et al JCO 2015, (4) Ji et al, PloS 2015

BRAF Inhibitor in BRAF Mutated DTC

BRAFi + MEKi vs BRAFi alone in all patients (n=56)



PFS months, median (95% CI) **27** (23.1-NR)

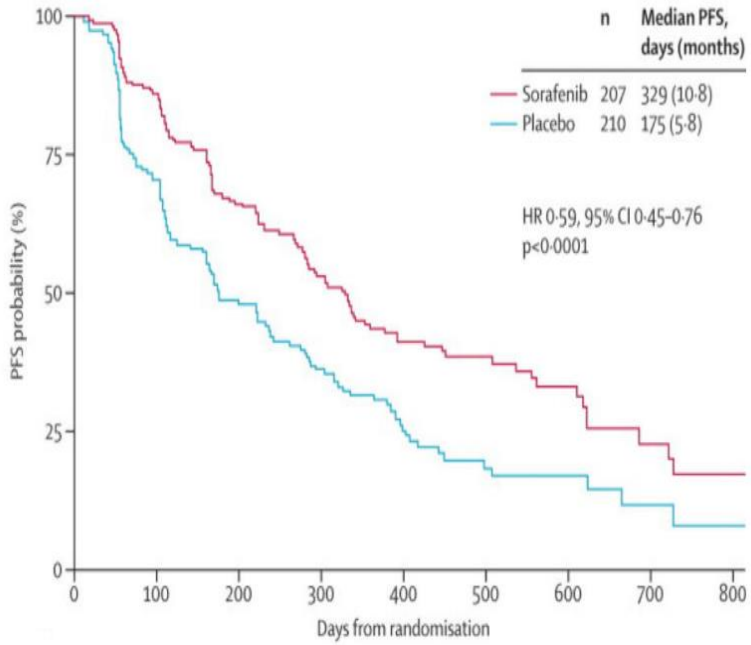


	BRAFi (n=36)	BRAFi + MEKi (n=20)
PFS months, median (95% CI)	**27** (21.1-NR)	**31.4** (19.2-NR)

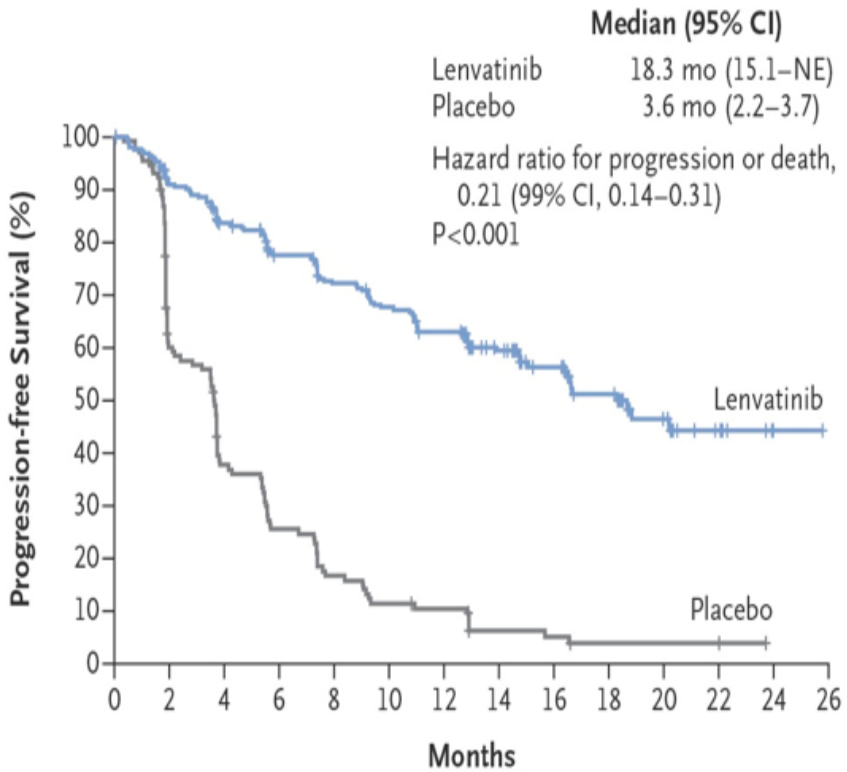
- **ORR 57%, with PFS 27-31 months**
- **FDA grants accelerated approval to dabrafenib+trametinib for unresectable or metastatic solid tumors, as Tumor Agnostic, June 22, 2022**

Fazeli et al. ATA 2022

Nonselective: Sorafenib and Lenvatinib, DTC



DECISION trial, 11/22/2013
Sorafenib approval for DTC-R



SELECT trial, 02/15/2015
Lenvatinib approval for DTC-R

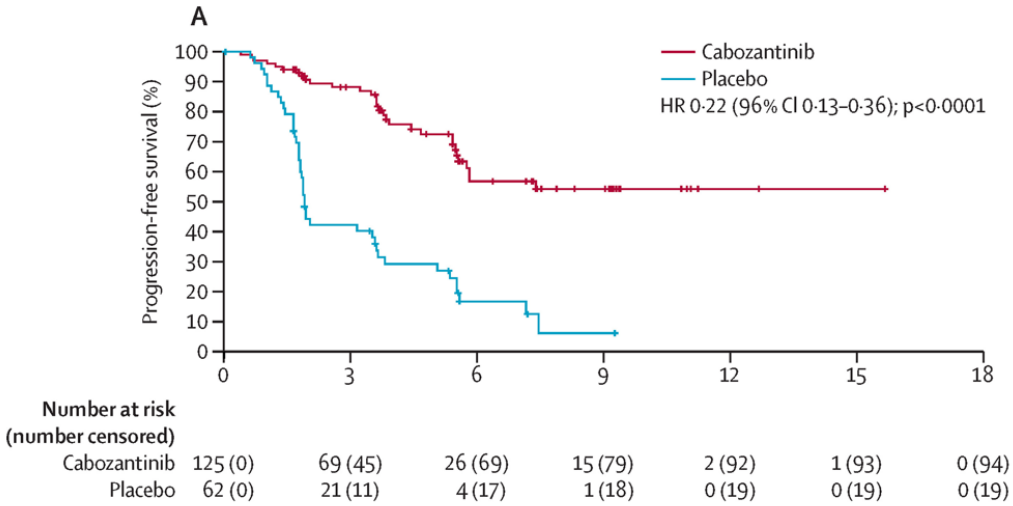
	Sorafenib	Lenvatinib
PFS months	10.8 m VS 5.8	18.3 VS 3.6 m

NCCN recommendation: Lenvatinib over Sorafenib

Schmidt et al. Arch Endocrinol Metab 2017

Second line therapy, metastatic, DTC-R

- **Cabozantinib, very good response in patients who failed other systems,** Phase 3
- **Median f/u up to 10.5 months**
- **ORR was 15% vs 0%**
- **PFS was NR vs 1.9 months**

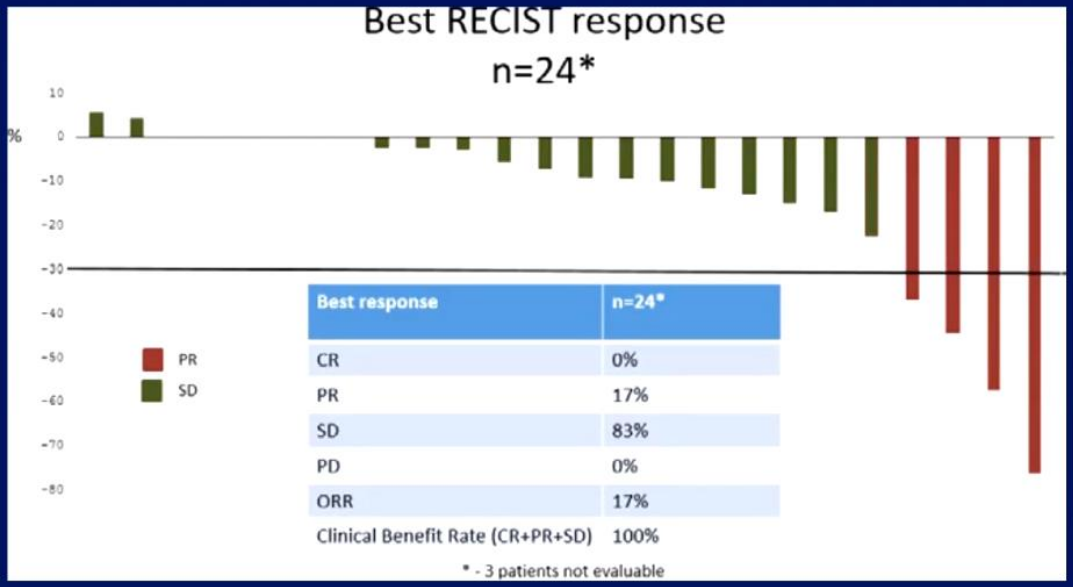


- **Cabozantinib** – On 9/17/2021, FDA approved as 2nd line therapy for progressive DTC

Brose et al. Lancet Oncology 2021

Second Line Therapy, DTC: Immunotherapy Combination

[Pembrolizumab slavage add-on therapy to Lenvatinib]



Best response	n=24*
CR	0%
PR	17%
SD	83%
PD	0%
ORR	17%
Clinical Benefit Rate (CR+PR+SD)	100%

* - 3 patients not evaluable

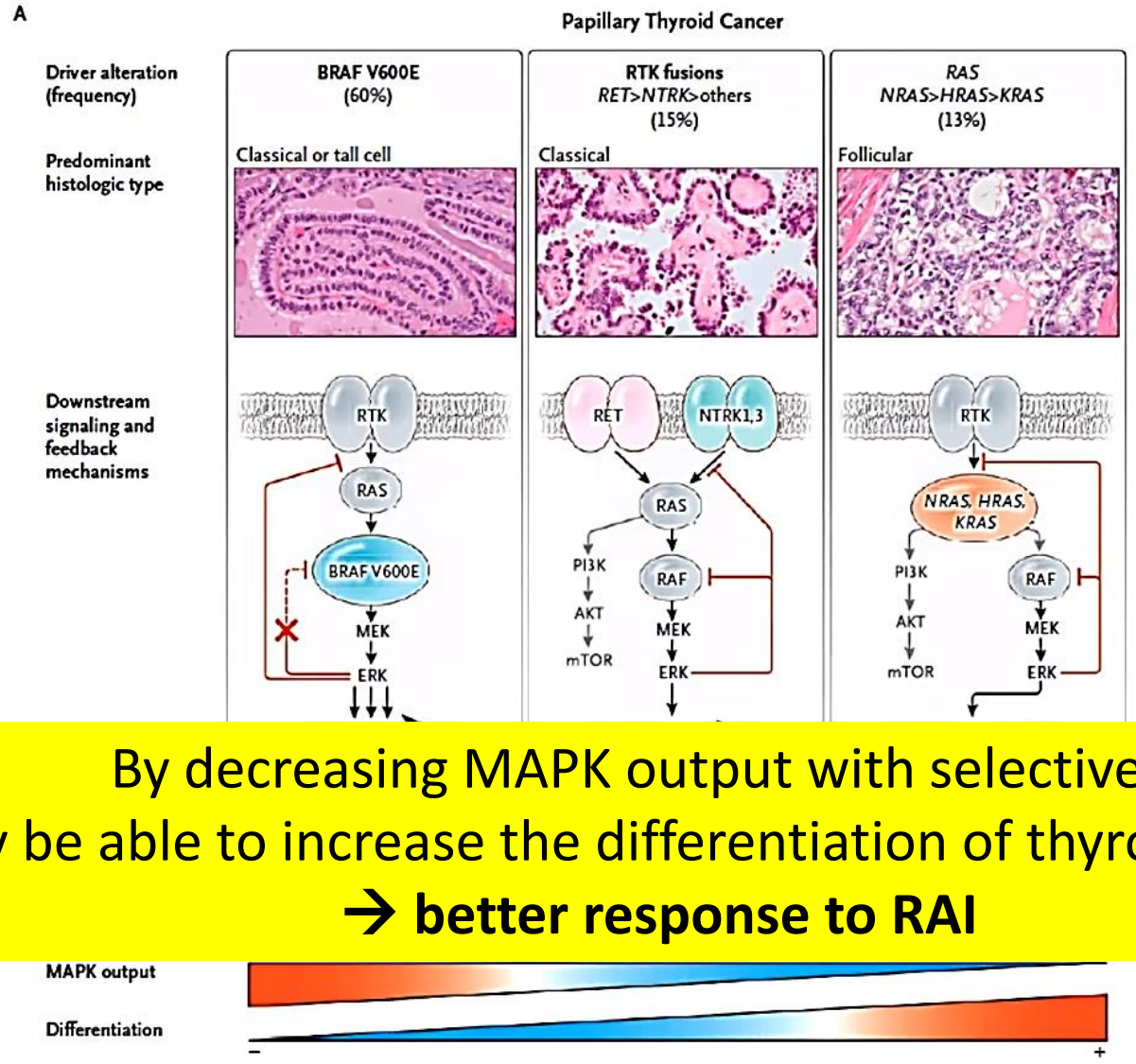
- **Summary/Conclusions**
- ORR for pembrolizumab salvage add-on therapy to lenvatinib (DTC progression) was 17%
- Clinical Benefit Rate (CBR) was 100%
- The median PFS on combination therapy was 11.0 months
- Pembrolizumab add-on therapy to lenvatinib was well-tolerated (44% grade 3 AE and no grade 4 AE)
- The addition of pembrolizumab to patients progressing on lenvatinib has a high CBR and favorable PFS in patients with RAIR DTC

Resensitization to RAI (Redifferentiation Strategy)

Neoadjuvant Targeted Therapy to Optimize Surgical Resection

Thomas Rowlandson, 'Amputation' (1793), Wellcome Library, London

Differentiation & Re–differentiation, DTC

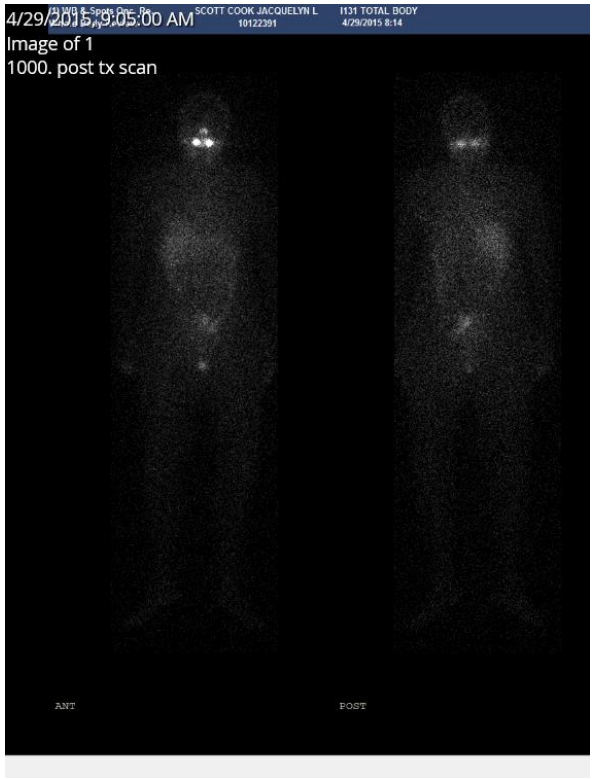


By decreasing MAPK output with selective blockers,
we may be able to increase the differentiation of thyroid cancer cells
→ **better response to RAI**

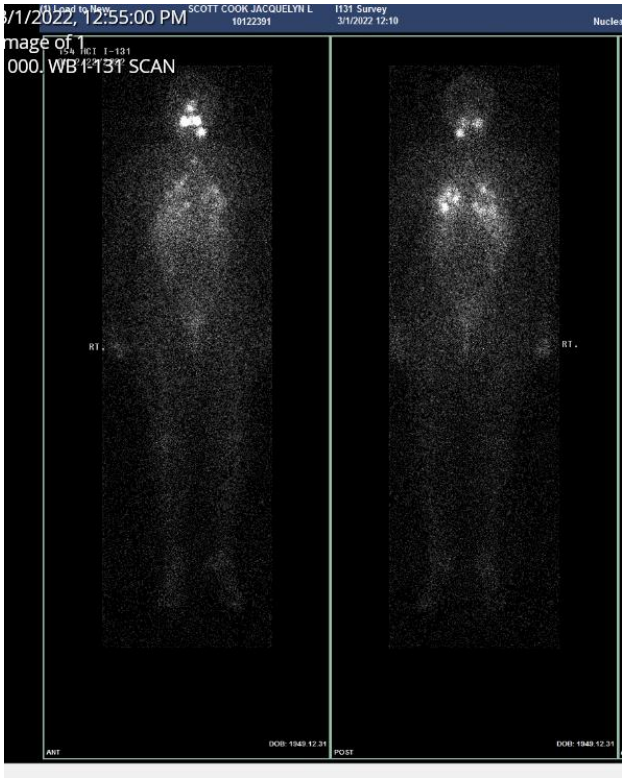
Fagin et al. NEJM 2016

Re-differentiation therapy, BRAF mutated DTC, COH patient

- Whole body scan after 225 mCi I-131 (2020)



- 6 weeks dabrafenib→ 150 mCi I-131 (2022)



Fazeli Patient 2022

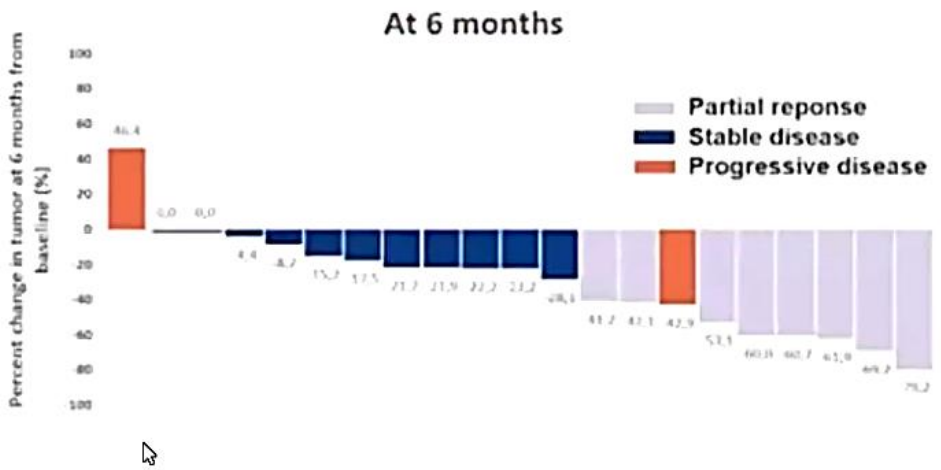
Re-Differentiation therapy, BRAF mutated DTC

- 8 French centers, 24 patients were treated
- Patients treated with dabrafenib (150 mg bid) and trametinib (2 mg QD) for 42 days followed by RAI 150 mCi

MERAIODE - Results: 6 months RECIST v1.1

	6 months RECIST evaluation (central review) N (%)
Complete Response	0
Partial Response	**8 (38.1%)**
Stable Disease	**11 (52.4%)**
Progressive Disease	**2 (9.5%)**
Not evaluable	0

Disease control Rate (CR + PR + SD): 90.5%



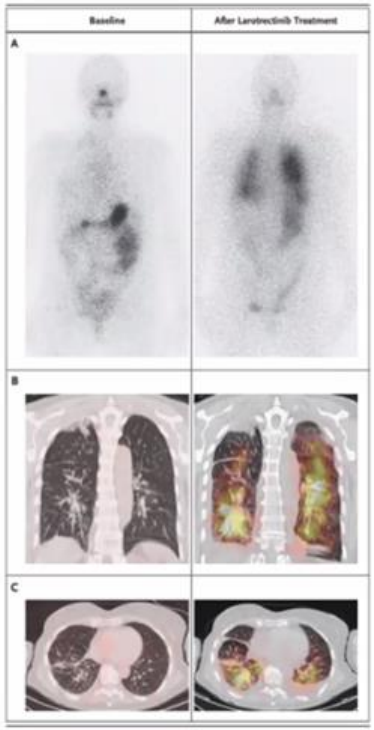
Median follow-up : 15.1 months, range [0.8 ; 25.9]

At last follow-up, 8 patients still in PR, **median duration of response : 13.2 months, range [6.0 ; 25.9]**

Leboulleux et al. Journal of the Endocrine Society, 2021

Redifferentiation with Inhibitors Targeting *NTRK* or *RET* Fusions

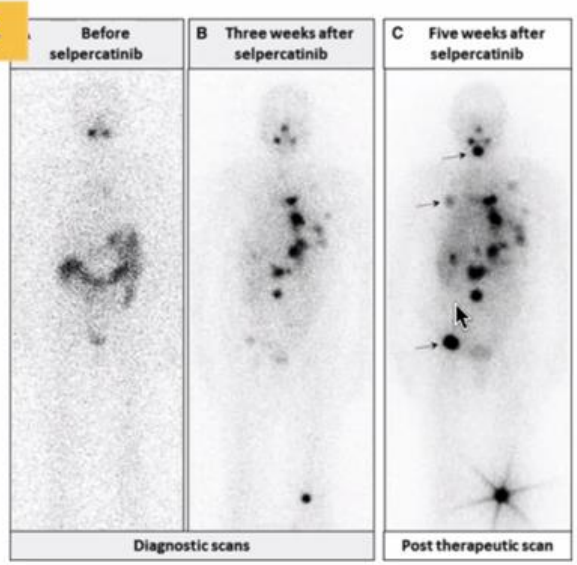
A



EML4-NTRK3 PTC

- no RAI on lenvatinib
- larotrectinib x3 weeks

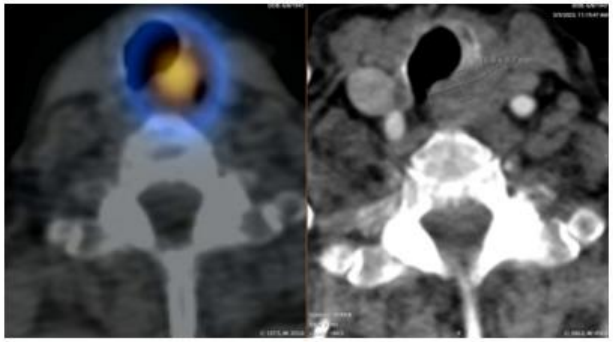
B



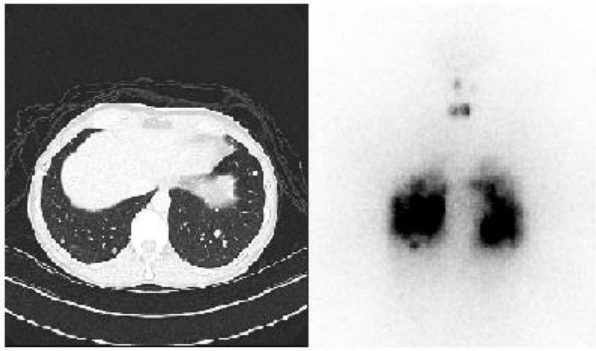
NCOA4-RET PTC

- no RAI baseline
- increased uptake w/ selpercatinib
- 131I RAI given, cont'd selper

A. Groussin L, et al. NEJM, 383(17), 2020.
B. Groussin L, et al. Thyroid, 31(10), 2021.
C. Lee YA, et al. J Clin Invest, 131(18), 2021.
D. Waguespack SG, et al. JCO Precis Oncol, April 2022

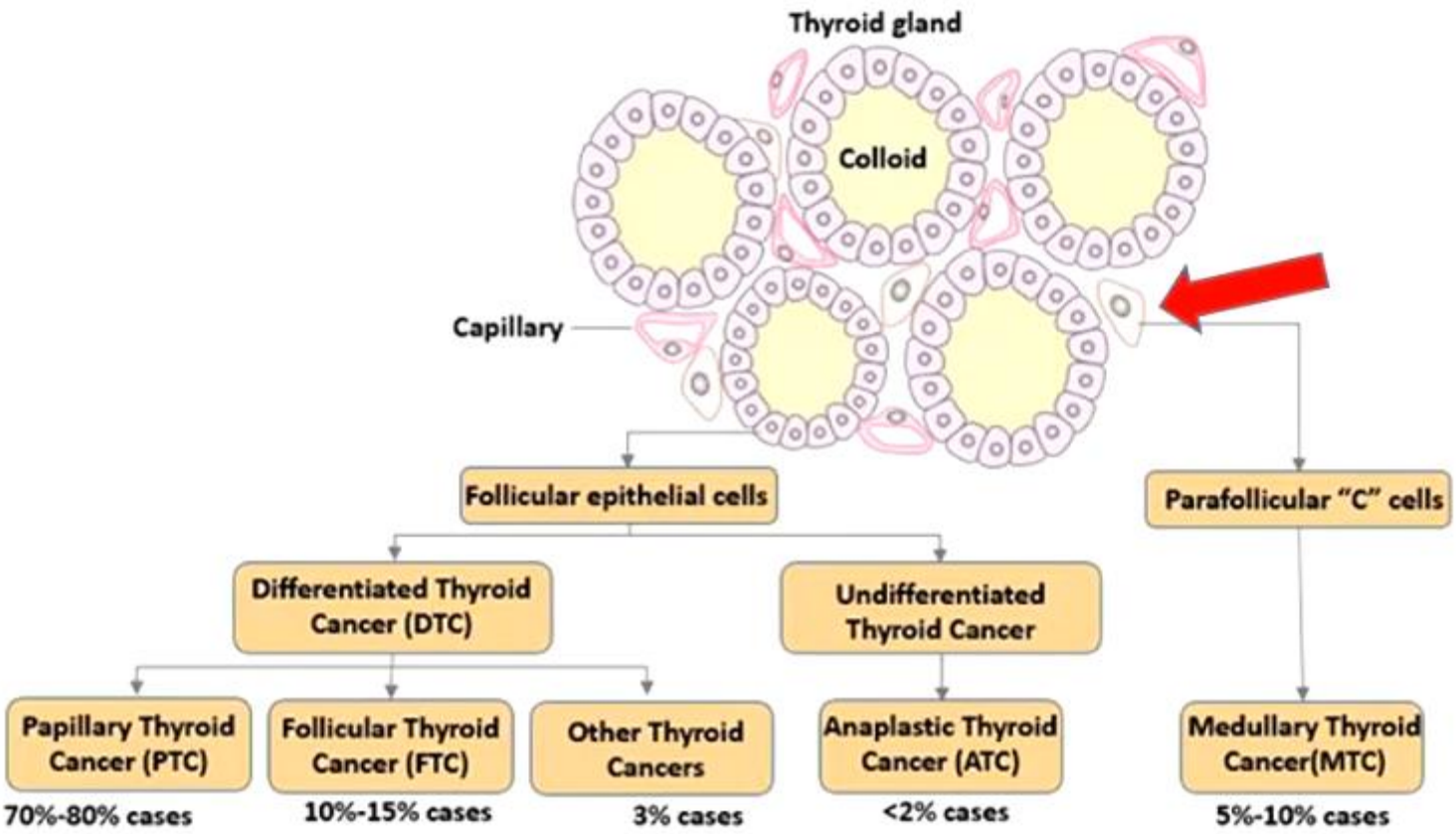


76 YO F, RET/PTC patient post 6 weeks selpercatinib Fazeli patient, 2023



53 YO F, ETV6-NTRK3 patient post 2 months Larotrectinib, Fazeli patient 2023

Medullary Thyroid Carcinoma, MTC



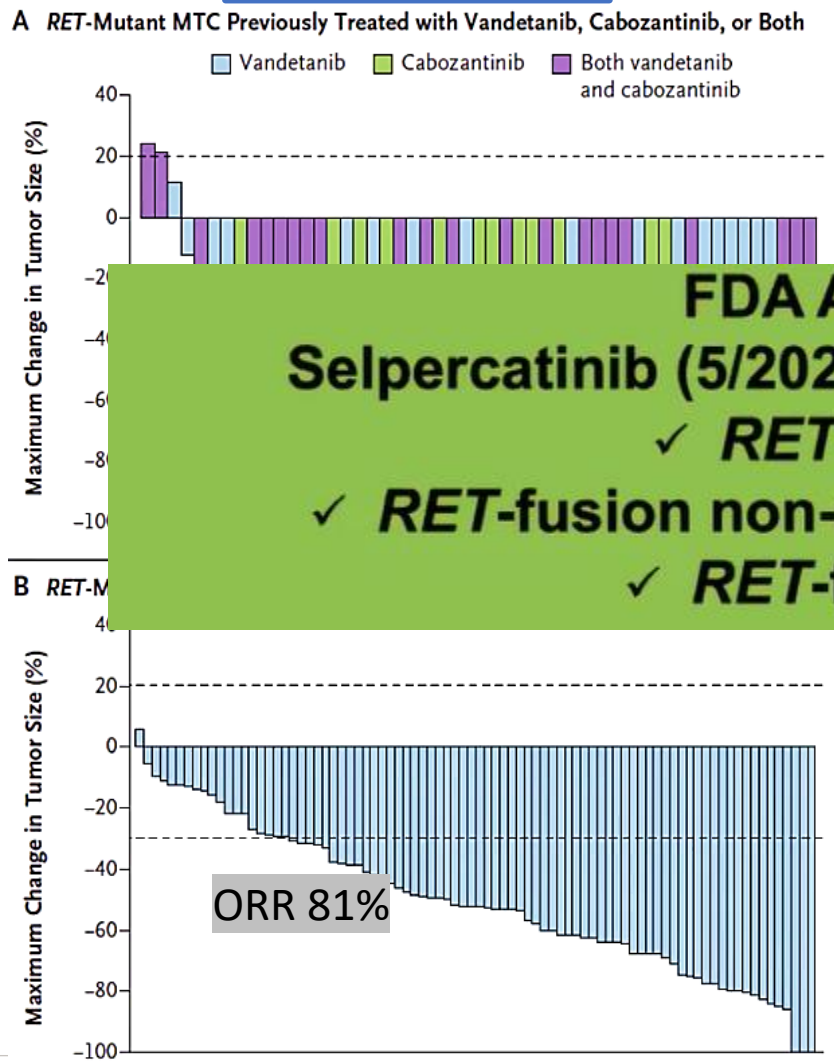
Medullary Thyroid Carcinoma, MTC

- Genetics:
  - 25% are hereditary and 75% Sporadic (65% have somatic RET)
  - Total RET mutation in MTC: 25% + 50% (75% x 0.65) = 75%
- Systemic Therapy, genetic driven
  - Nonselective
  - Selective, RET mutation inhibitors

Surg Oncol Clin N Am 2023

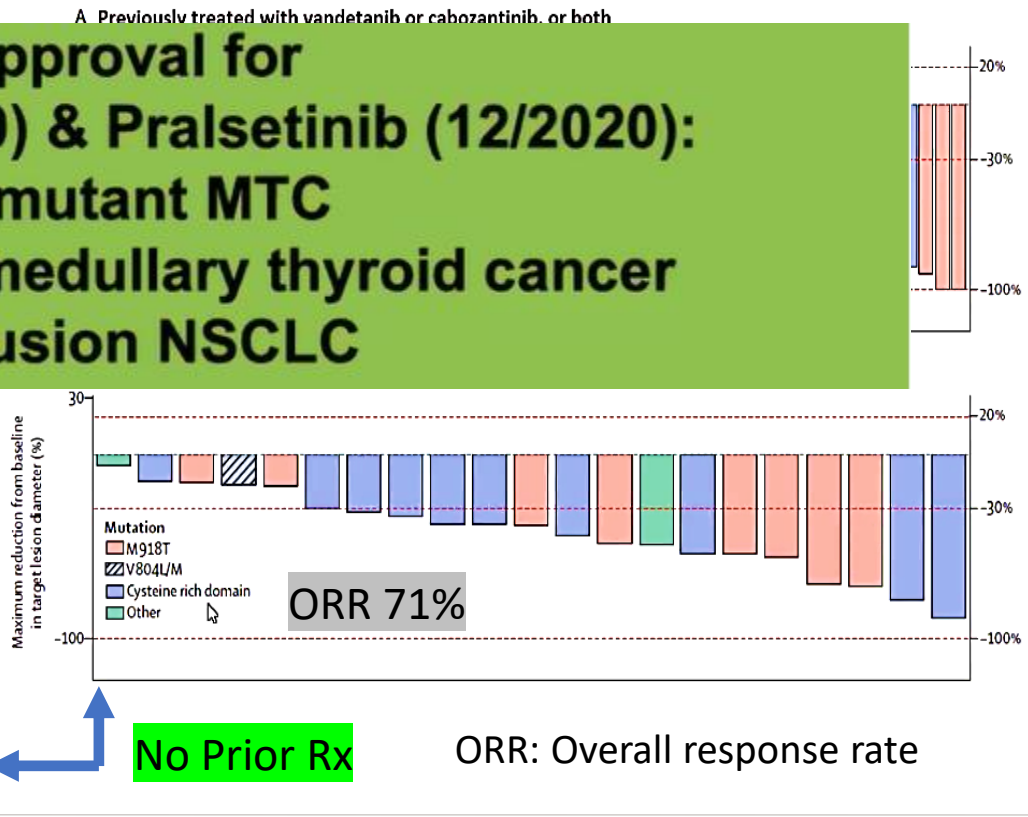
MTC, RET specific inhibitors, selective

Selpercatinib



Prior Rx

Pralsetinib



FDA Approval for
Selpercatinib (5/2020) & Pralsetinib (12/2020):
✓ ***RET*-mutant MTC**
✓ ***RET*-fusion non-medullary thyroid cancer**
✓ ***RET*-fusion NSCLC**

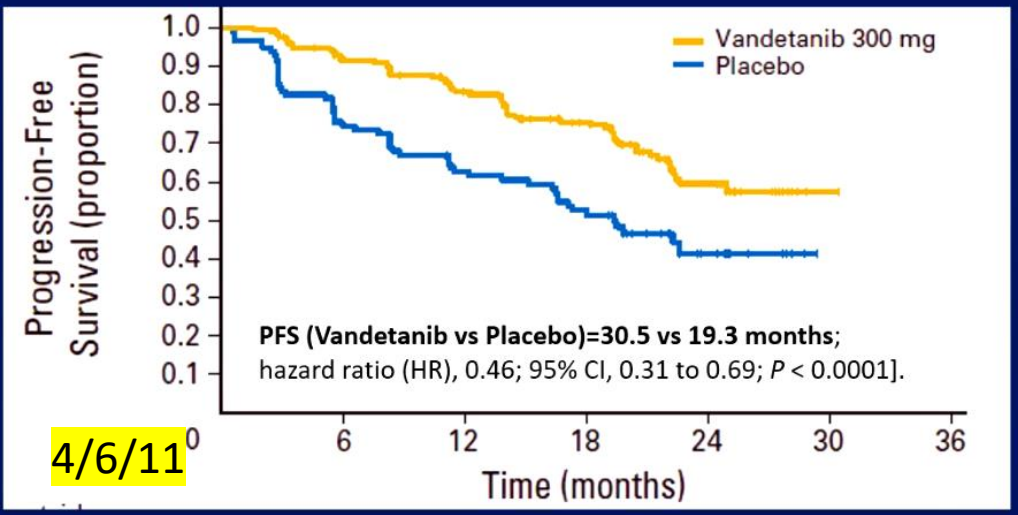
No Prior Rx

ORR: Overall response rate

NEJM 2020→ ESMO 2022

Lancet Diabetes Endocrinol 2021→ hu et al ATA 2022

MTC, Vandatinib vs Cabozantinib, MKI



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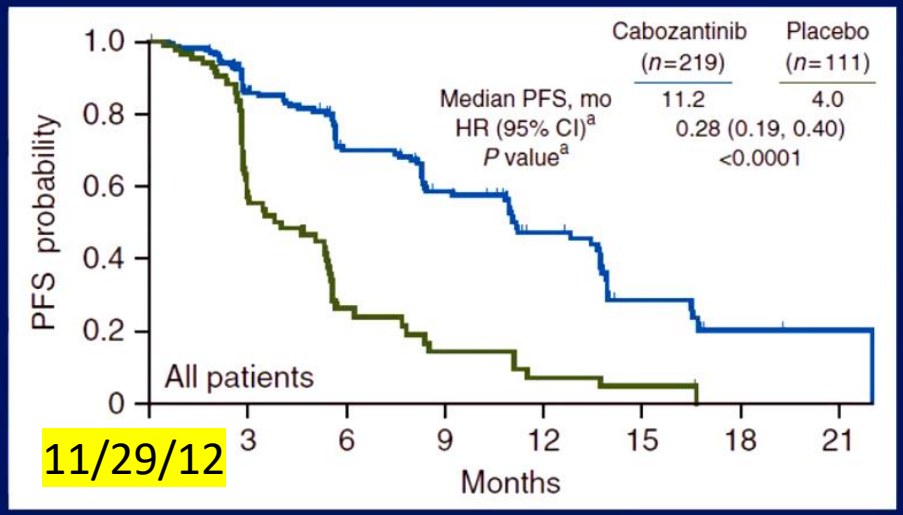

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- Vandetanib is the first medication approved by the FDA for the treatment of advanced and progressive and/or symptomatic MTC.
- Vandetanib is a multi-tyrosine kinase inhibitor (TKI) that blocks EGF, RET, VEGF2, and VEGF3 receptors.

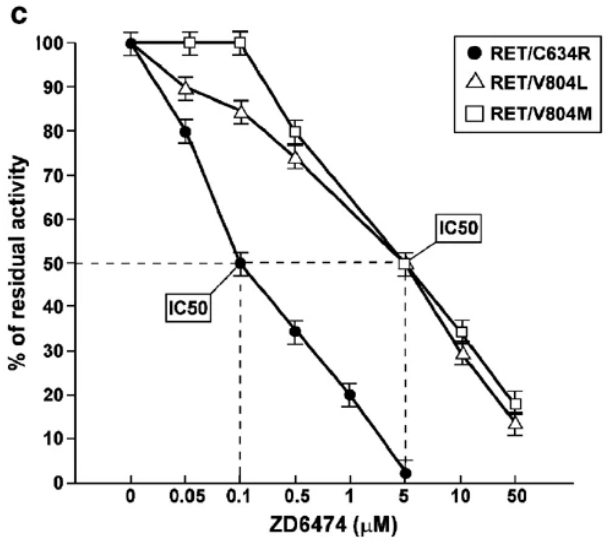
- Cabozantinib is a MKI that blocks the c-MET, RET, and VEGF2 receptors.
- Cabozantinib is a more potent antiangiogenic drug than vandetanib.

- **Vandatinib trial did not need progression prior, however, Cabozantinib needed progression.**
- Placebo groups were different in the 2 groups
- Cabozantinib is considered to be more effective
- Watch for QT prolongation with vandetanib

J Clin Oncol 2011

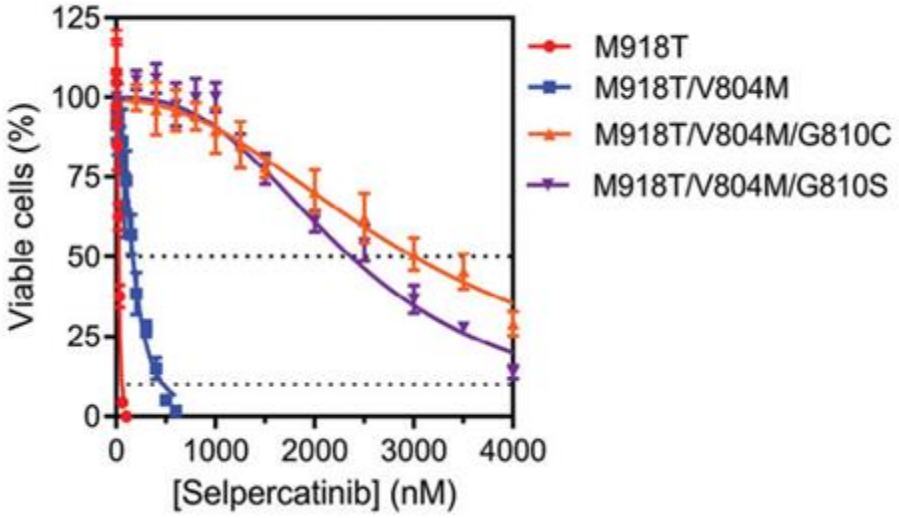
J Clin Oncol 2013

RET *V804* Gatekeeper mutations
Resistance to Vandetanib & Cabozantinib



[vandetanib]

RET *V810* Solvent Front
RET *Y806* Hinge mutations
Resistance to selective RET inhibitor



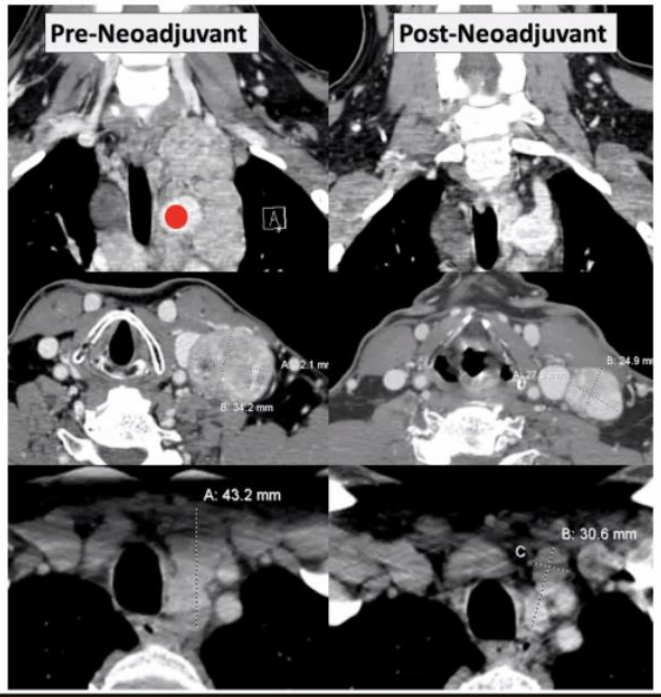
- RET 804 do not cause resistance to selective RET inhibitors

- **Trial phase ½: EP0031** Next generation RET inhibitor. NCT05443126 (Ellipses Pharma)
- Cover RET solvent front and gatekeeper

Carlomagno, et al., Oncogene 2004 Italy

Subbiah, et al., Ann Oncol 2021

Neoadjuvant Therapy with RETi or MKI



Phase II trial with neoadjuvant selpercatinib for *RET*-altered thyroid cancer
(NCT04759911; Co-PIs: Drs. Zafereo, Cabanillas, Hu)

- Phase II, open label, multicenter trial (NCT04321954; PI: Dr. G. Randolph)
- **Lenvatinib** in locally advanced thyroid cancer with extrathyroidal extension and/or locally invasive disease
- Excludes:
  - ATC and MTC
  - Intraluminal airway tumor
  - Complete carotid encasement/infiltration
  - Prior radiotherapy to neck, anticoagulation/antiplatelet therapy
  - Prior anti-VEGFR therapy
- Primary outcome: Overall R0/R1 resection rate

R0: no residual tumor
R1: microscopic residual tumor

Differentiated Thyroid Carcinoma

Name generic	Half-life (hours/days)	Metabolism	Target(s)	Dose
Dabrafenib	8 h	Hepatic (CYP2C8, CYP3A4)	B-RAF	150 mg BID
Vemurafenib	57 h	Hepatic (CYP3A4)	B-RAF	960 mg BID
Encorafenib	3.5 h	Hepatic (CYP3A4)	B-RAF	450 mg QD
Trametinib	4- 5 days	Unknown	MEK	2 mg QD
Cobimetinib	44 h	Hepatic (CYP3A4)	MEK	60 mg QD
Binimetinib	3.5 h	Hepatic (glucuronidation, CYP1A2, CYP2C19)	MEK	45 mg BID
Selumetinib	6.2 h	Hepatic (CYP3A4)	MEK1, MEK2	75 mg BID
Sorafenib	25-48 h	Hepatic (CYP3A4)	RAF (C-RAF, B-RAF), RET, VEGFR, PDGFR, RET/PTC	400 mg BID
Sunitinib	40-60 h	Hepatic (CYP3A4)	VEGFR, PDGFR, FGFR, CSFR, FLT3, RET	50 mg QD
Lenvatinib	28 h	Hepatic (CYP3A4)	VEGFR, PDGFR, FGFR, C-KIT, RET	24 mg QD
Pazopanib	31 h	Hepatic (CYP3A4, CYPA2, CYP2C8)	VEGFR, PDGFR, FGFR, C-KIT	800 mg QD
Axitinib	2.5-6.1 h	Hepatic (CYP3A4, CYPA2, CYP2C19)	VEGFR	5 mg BID
Vandetanib	19 days	Hepatic (CYP3A4)	VEGFR, EGFR, RET, BRK	300 mg QD
Cabozantinib	55 h	Hepatic (CYP3A4)	C-MET, RET, VEGFR	60-140 mg QD
Everolimus	30 h	Hepatic (CYP3A4)	mTOR	10 mg QD
Larotrectinib	2.9 h	Hepatic (CYP3A4)	TRK1, TRKB, TRKC	75-100 mg BID
Entrectinib	20 h	Hepatic (CYP3A4)	TRK1, TRKB, TRKC	500-600 mg QD
Repotrectinib	61 h	Hepatic (CYP3A4)	TRK1, TRKB, TRKC	160 mg QD (14 d) – 160 BID
Alectinib	33 h	Hepatic (CYP3A4)	ALK (2nd Generation), RET	600 mg BID
Crizotinib	42	Hepatic (CYP3A4)	ALK (1ST Generation), HGFR, c-MET, ROS1	250 mg BID
Selpercatinib	32 h	Hepatic (BCRP/ABCG2, CYP2CA, CYP3A4)	RET mutation, RET fusion VGFR (small)	160 mg BID 120 mg BID<50kg
Pralsetinib	15 h	Hepatic (CYP3A4)	RET mutation, RET fusion	400 mg QD
Pembrolizumab IV	22 days	Protein degradation	PD-1	200 mg Q3W

Summery

- **Molecular analysis** in thyroid cancers shows tumor behavior, helps guide systemic therapies
- **Systemic therapy Start**: metastatic, progressive, non-surgical, no focal therapies, threatening
- **Most common actionable genetic alterations DTC:**
  - DTC: BRAFV600E >>> RET fusion >> NTRK fusion > ALK fusion
- **In DTC, re-differentiation** therapy is experimental, and can be used selectively
- **DTC, systemic therapies:**
  - ALK, NTRK, RET fusions, BRAF mutation → MKI → and **second-line therapy**
  - **Immunotherapy:** MKIs or BRAF/MEKi + IO
- **MTC, RET inhibitors** first line for RET mutation-positive, watch for resistance
- **Neoadjuvant therapy for all tumor types**, particularly less differentiated
- **Unmet needs:** RAS mutated tumors, combating resistance, bone and brain metastasis

Thank you!!

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