Thyroid and Thymic Carcinomas: Where Are We Know?

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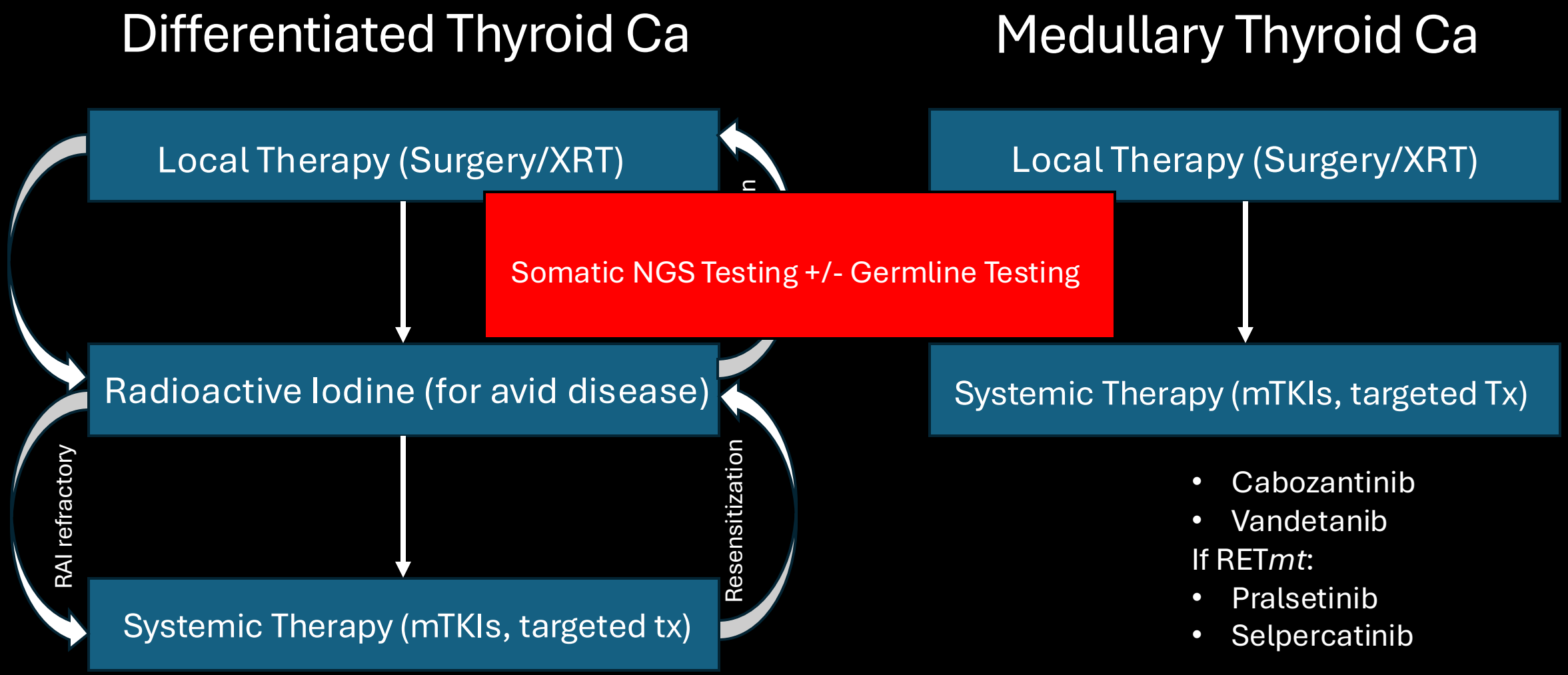
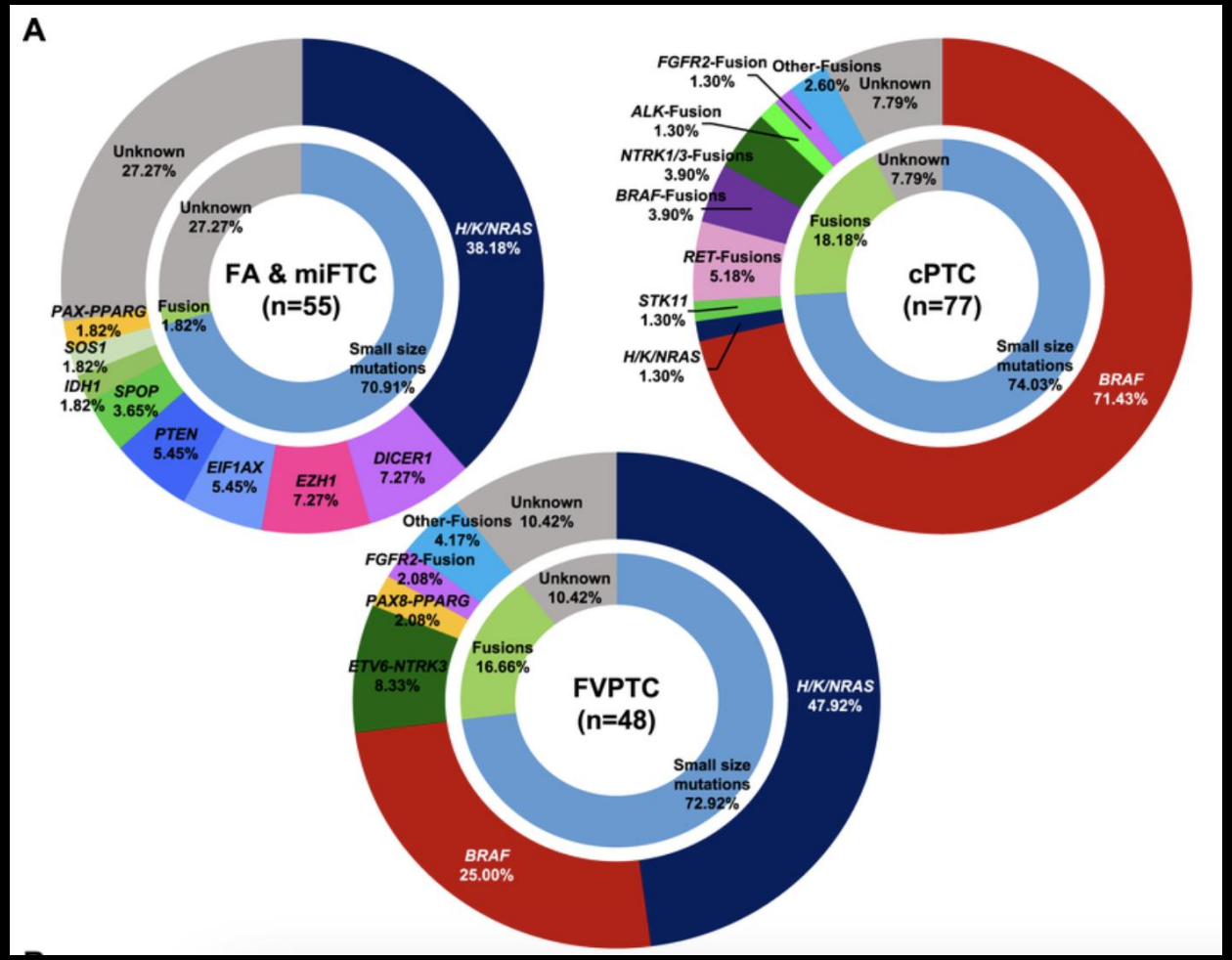
Multi-Disciplinary Management of Thyroid Cancer



Mutational Landscape of Differentiated Thyroid Cancer



NCCN Guidelines Version 4.2024
Thyroid Carcinoma – Papillary Carcinoma

TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY

Structurally persistent/recurrent locoregional or distant metastatic disease not amenable to RAI therapy

- Continue to suppress TSH with levothyroxine[l]
- For advanced, progressive, or threatening disease, somatic testing to identify actionable mutations (including *ALK*, *NTRK*, *BRAF*, and *RET* gene fusions), mismatch repair deficiency (dMMR), microsatellite instability (MSI), and tumor mutational burden (TMB)
- Consider clinical trial

Unresectable locoregional recurrent/ persistent disease

Soft tissue metastases (eg, lung, liver, muscle) excluding central nervous system (CNS) metastases (see below)

Bone metastases (PAP-11)

CNS metastases (PAP-12)

- Consider systemic therapy for progressive and/or symptomatic disease
  - Preferred Regimens
    - ◊ Lenvatinib (category 1)[kk]
  - Other Recommended Regimens
    - ◊ Sorafenib (category 1)[kk]
  - Useful in Certain Circumstances
    - ◊ Cabozantinib (category 1) if progression after lenvatinib and/or sorafenib
    - ◊ Larotrectinib or entrectinib or repotrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
    - ◊ Selpercatinib[oo] or pralsetinib for patients with *RET* gene fusion-positive tumors
    - ◊ Pembrolizumab for patients with tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options
    - ◊ Dabrafenib/trametinib[nn] for patients with *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options
    - ◊ Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[ll,mm]
- Consider resection of distant metastases and/or RT[q] or other local therapies[jj] when available to metastatic lesions if progressive and/or symptomatic (See treatment of locoregional recurrence PAP-9)
- Disease monitoring is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis[kk] (PAP-7)
- Best supportive care, see NCCN Guidelines for Palliative Care

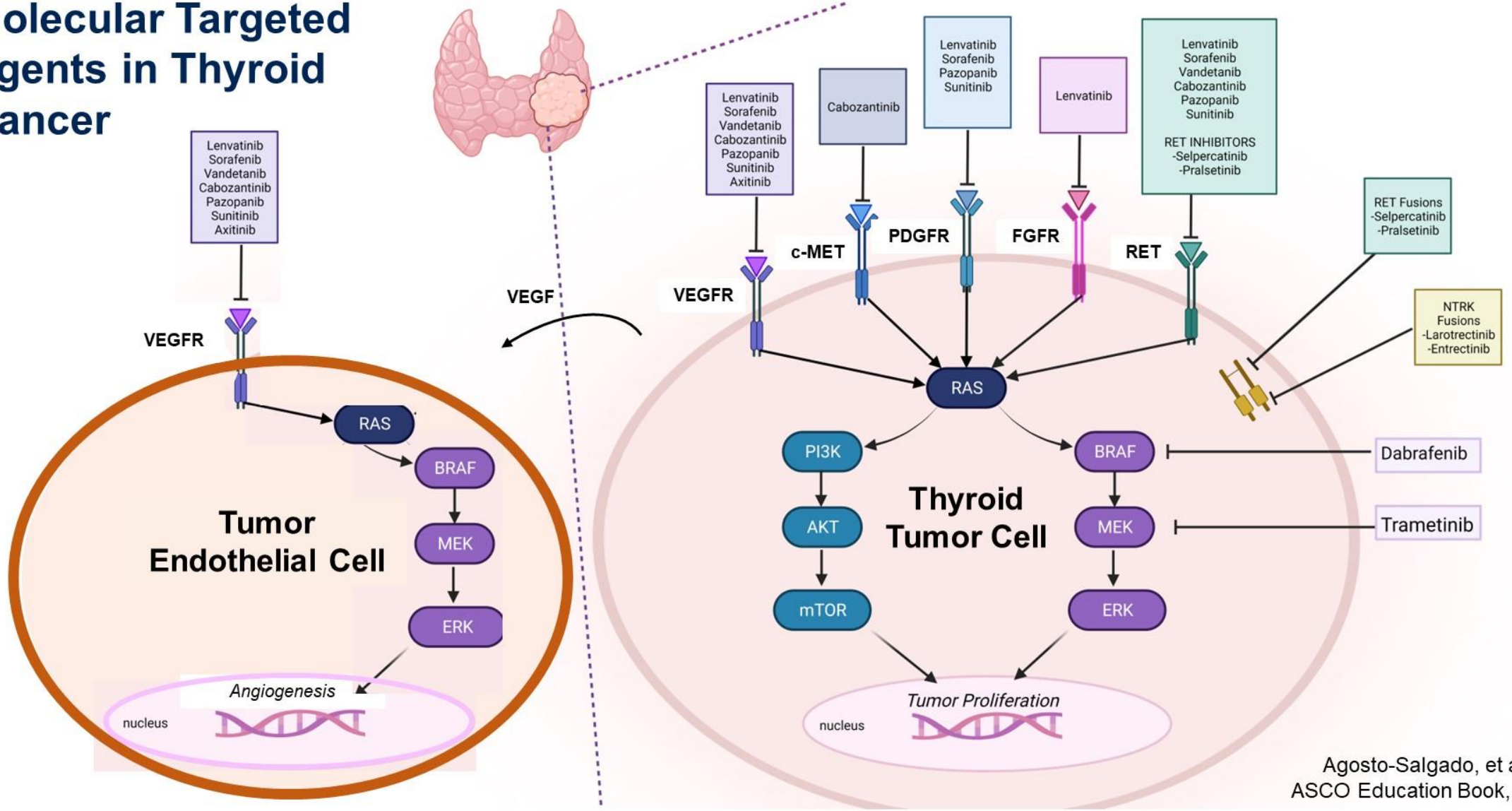
Radioactive Iodine (RAI) Refractory Differentiated Thyroid Cancer (DTC)

PRESENTED BY: Christine H. Chung, MD

When to start the systemic therapy?

- Symptomatic from disease burden but cannot be managed with a local therapy
  - Example: Short of breath from multiple lung nodules
- Clinically significant disease burden
  - Example: Progressive disease with doubling tumor size or developing new lesions within 6 months or progressive disease by RECIST within 13 months
- Tumors that threaten organ or limb function but cannot be managed with a local therapy
  - Example: Growing weight bearing bone metastasis even after radiation

Molecular Targeted Agents in Thyroid Cancer

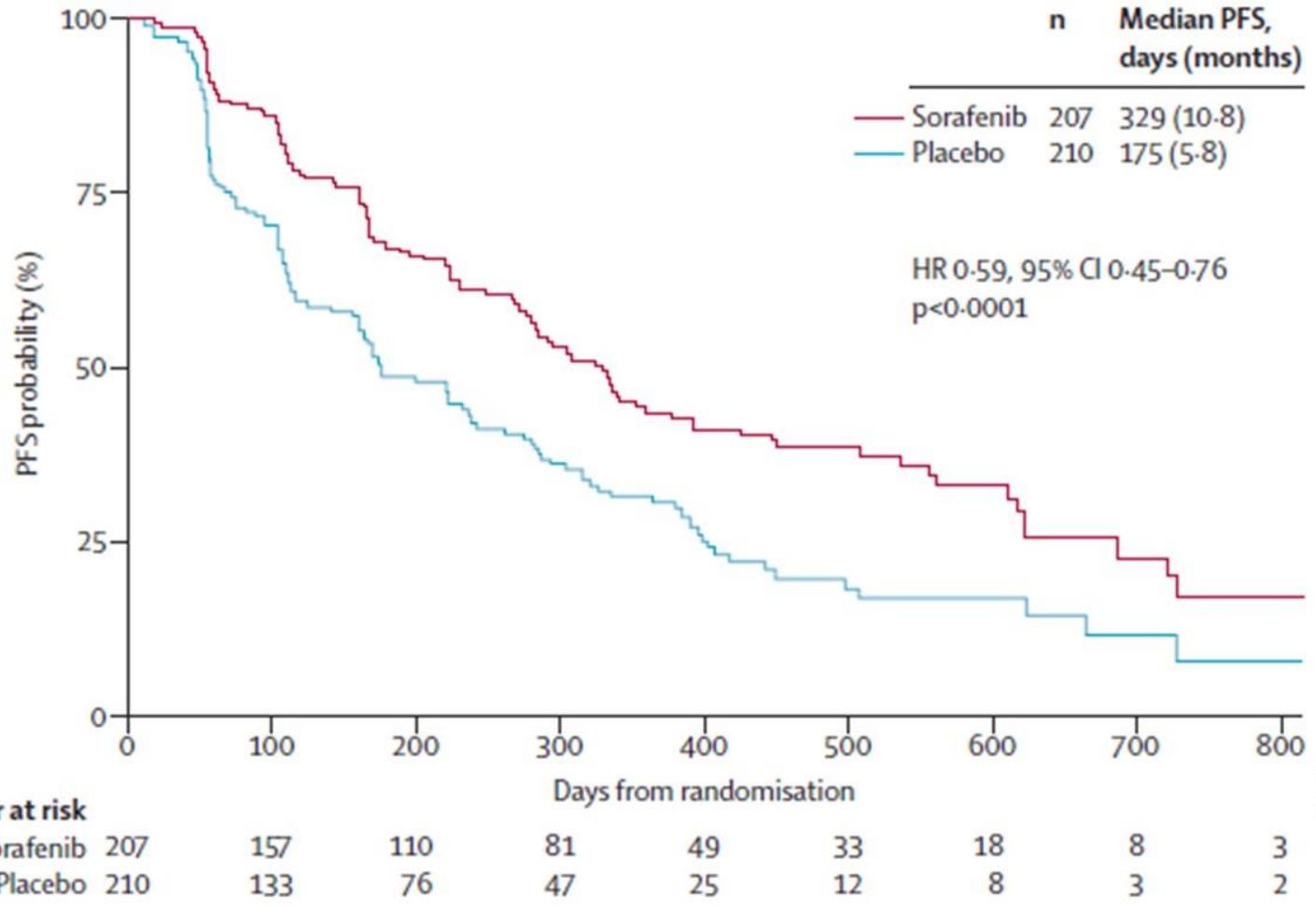


Agosto-Salgado, et al.
ASCO Education Book, 2023

Sorafenib in DTC

DECISION trial: Randomized Phase III Study (N=417)
Primary Endpoint: PFS → Median PFS 10.8 mos

- Targets: VEGFR-1, -2, and -3, RET, weak RAF (including $BRAF^{V600E}$), and PDGFR
- Locally advanced or metastatic RAIR DTC
- 1st line: No prior kinase inhibitor or chemotherapy

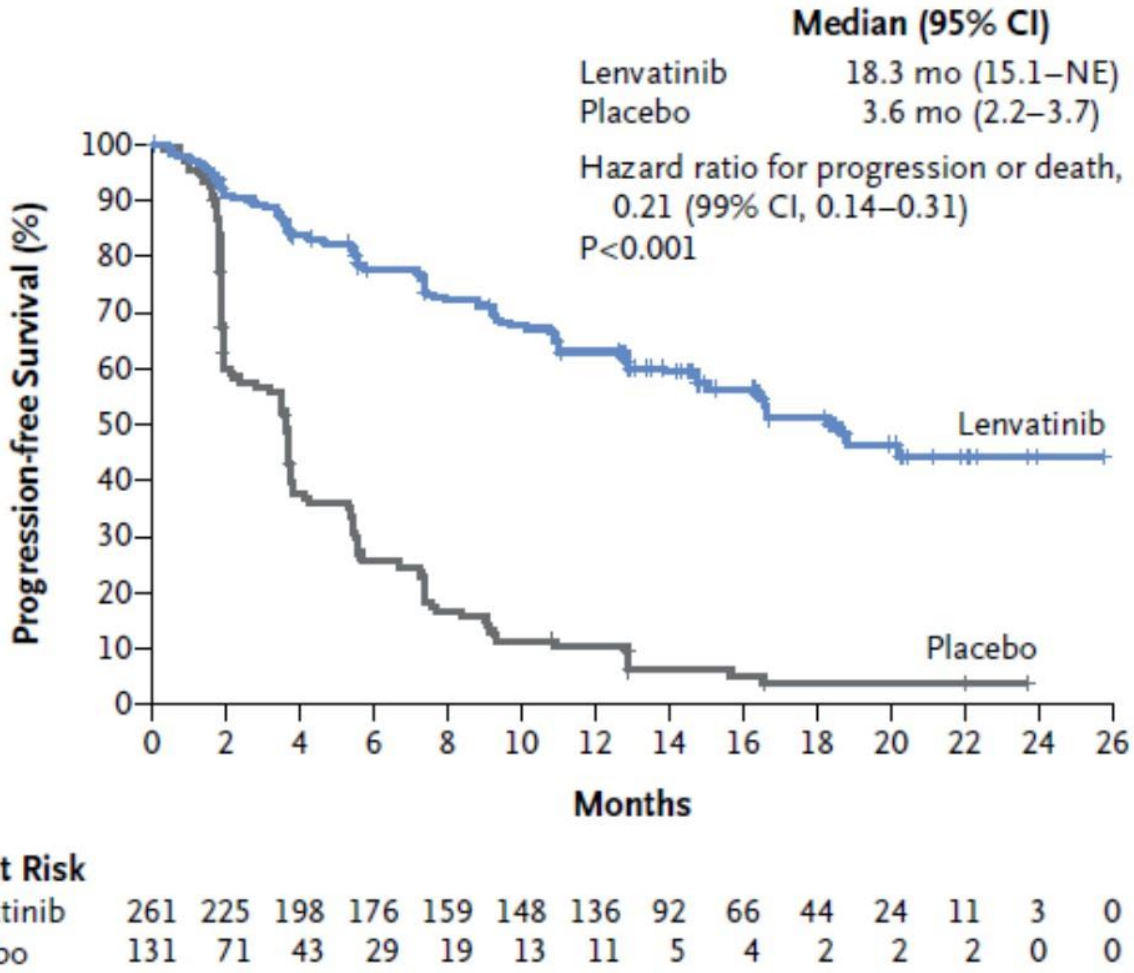


Brose M, *Lancet* 2014; 364:39-328

Lenvatinib in DTC

SELECT trial: Randomized Phase III Study (N=392)
Primary Endpoint: PFS → median PFS 18.3 mos

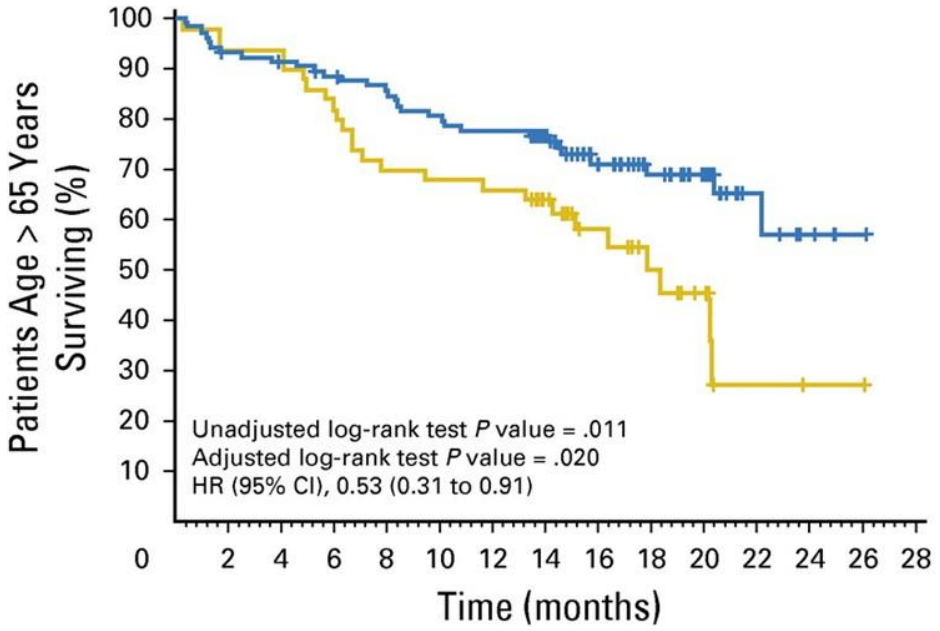
- Targets: VEGFR1–3, FGFR 1–4, PDGFRα, RET, and c-Kit
- Locally advanced or metastatic RAIR DTC
- 1st and 2nd line:
  - No prior TKI
  - one prior TKI: 25.3% of the Lenvatinib arm



Schlumberger M et al. *New Engl J Med* 2015;372:621-630

Lenvatinib improves Overall Survival in patients with age above 65

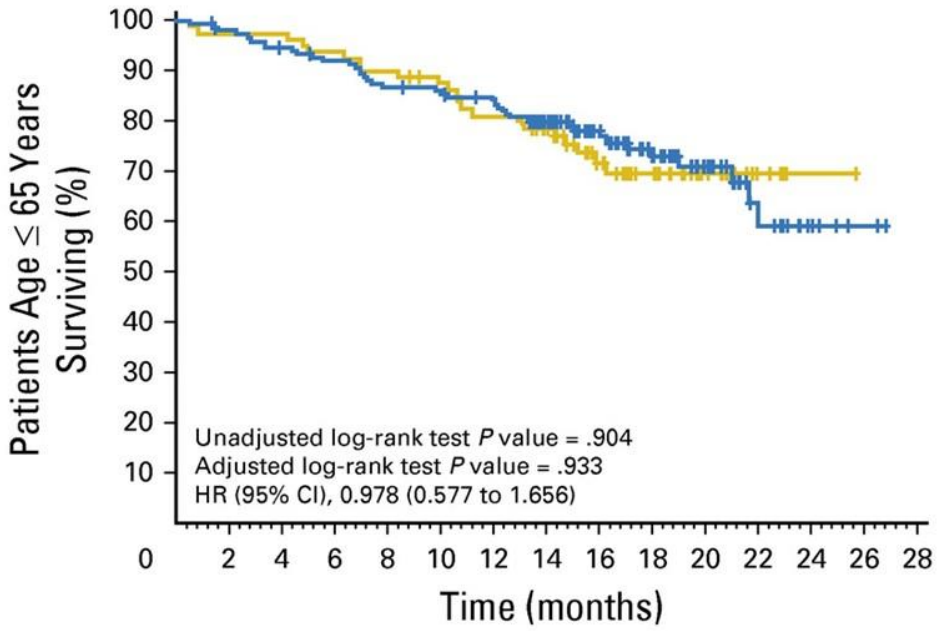
Treatment	Total	Treatment Failure	Censored	Median, months (95% CI)
Lenvatinib	106	31	75	NE (22.1 to NE)
Placebo	50	25	25	18.4 (13.3 to 20.3)



No. of patients at risk:

Lenvatinib	106	98	95	91	88	82	79	67	42	31	24	8	4	1	0
Placebo	50	47	47	42	35	34	33	26	16	11	7	2	1	1	0

Treatment	Total	Treatment Failure	Censored	Median, months (95% CI)
Lenvatinib	155	40	115	NE (22.0 to NE)
Placebo	81	22	59	NE (NE to NE)



No. of patients at risk:

Lenvatinib	155	150	144	139	131	129	124	102	70	47	31	14	6	2	0
Placebo	81	79	79	76	73	69	63	52	37	28	16	6	1	0	0

Brose MS. et al. et. al. J Clin Oncol. 2017;35(23):2692-9

Grade 3 or 4 (%) Toxicities

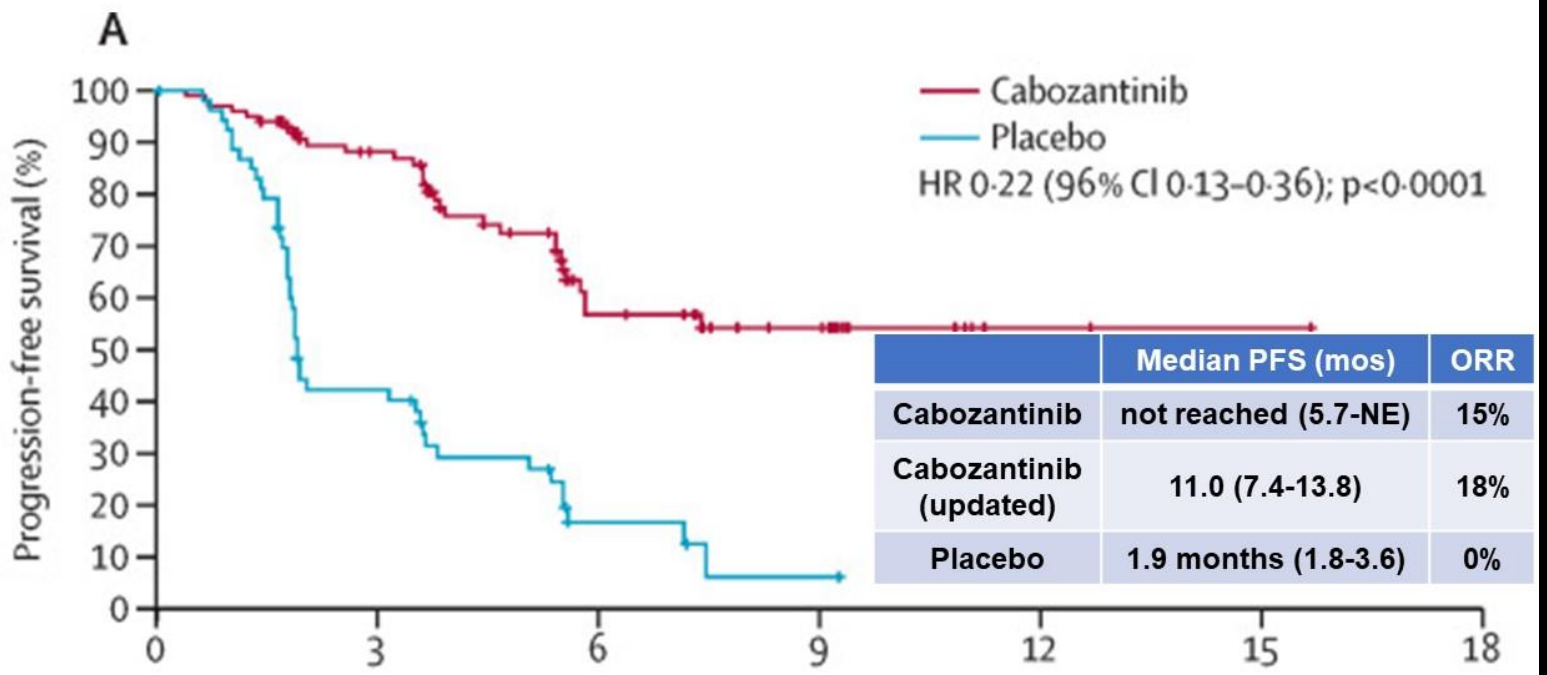
	Sorafenib (median FU: 16.2 mos)		Lenvatinib (median FU: 17.1 mos)	
Term	**Sorafenib**	**Placebo**	**Lenvatinib**	**Placebo**
Hypertension	10	2	42	2
Diarrhea	6	1	8	0
Fatigue/asthenia	6	1	9	2
Decreased appetite	2	0	12	0
Weight loss	6	1	10	0
Hand-foot	20	0	3	0
Proteinuria	0	0	10	0
Hypocalcemia	9	0	0	0
Headache	0	0	3	0
Dyspnea	5	2	0	0
Rash	5	0	0.4	0
Pulmonary embolism	1	0	1	1
Death attributed to drug by investigator	0.5%	1	2.3%	0

Brose MS et al, *Lancet* 2014; 364:39-328, Schlumberger M et al, *New Engl J Med* 2015;372:621-630

Cabozantinib (60 mg tablet) in DTC

COSMIC-311 trial: Randomized Phase III Study (N=227)
Primary Endpoint: ORR in the first 100 randomly assigned patients and PFS all patients

- **Targets: MET, VEGFR2, and RET**
- **Locally advanced or metastatic RAIR DTC**
- **2nd/3rdLine: previous lenvatinib or sorafenib and progressed during or after treatment with up to two VEGFR tyrosine kinase inhibitors**



	Median PFS (mos)	ORR
Cabozantinib	not reached (5.7-NE)	15%
Cabozantinib (updated)	11.0 (7.4-13.8)	18%
Placebo	1.9 months (1.8-3.6)	0%

Number at risk (number censored)							
Cabozantinib	125 (0)	69 (45)	26 (69)	15 (79)	2 (92)	1 (93)	0 (94)
Placebo	62 (0)	21 (11)	4 (17)	1 (18)	0 (19)	0 (19)	0 (19)

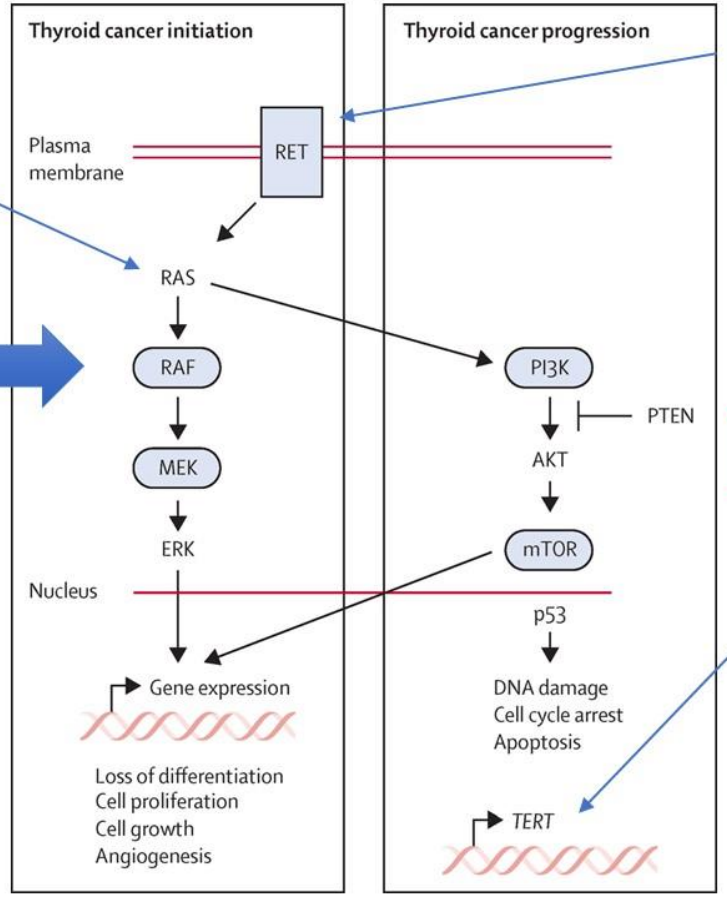
Brose MS et al. Lancet Oncol 2021; 22(8):P1126-1138
Cabozantinib package insert

Biology of Differentiated Thyroid Cancer

NRAS mutation (8.5%)
HRAS mutation (3.5%)

BRAF V600E: most common mutation in papillary thyroid cancers (~50-60%)

Generally low tumor mutation burden



RET fusion (6.3%)

Other fusions
- **BRAF (2.3%)**
- **PPARγ (1%)**
- **ALK (0.8%)**
- **NTRK1 (1%)**
- **NTRK3 (1.3%)**

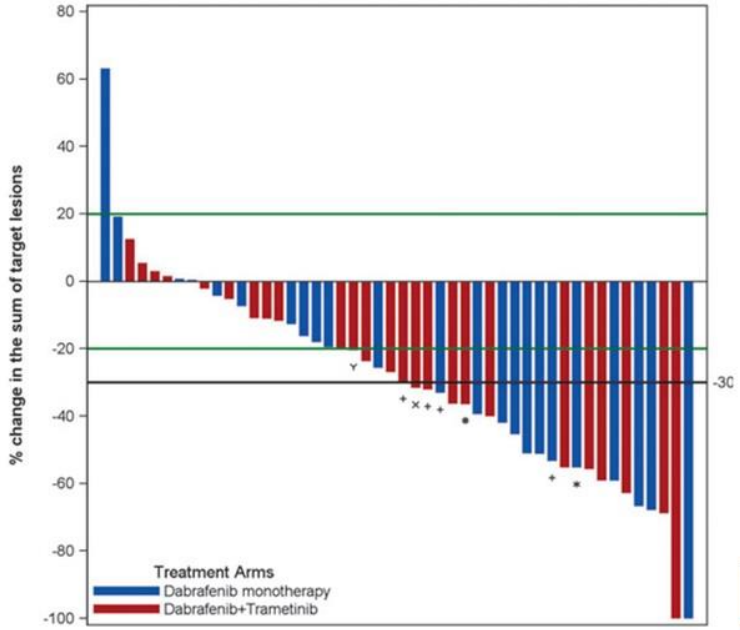
TERT promoter mutation (9.4%)

Cabanillas ME et al. *Lancet* 2016;388:2783-05

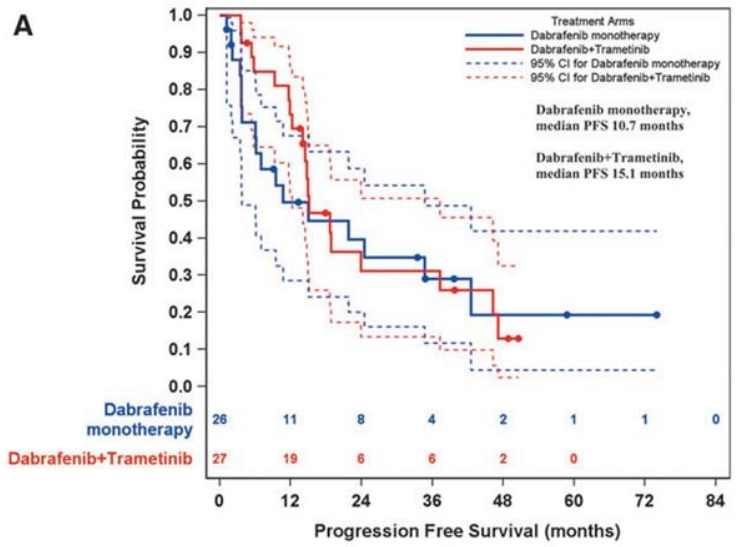
Global Anaplastic Thyroid Cancer Initiative (GATCI) medRxiv preprint doi: https://doi.org/10.1101/2023.04.10.23288365

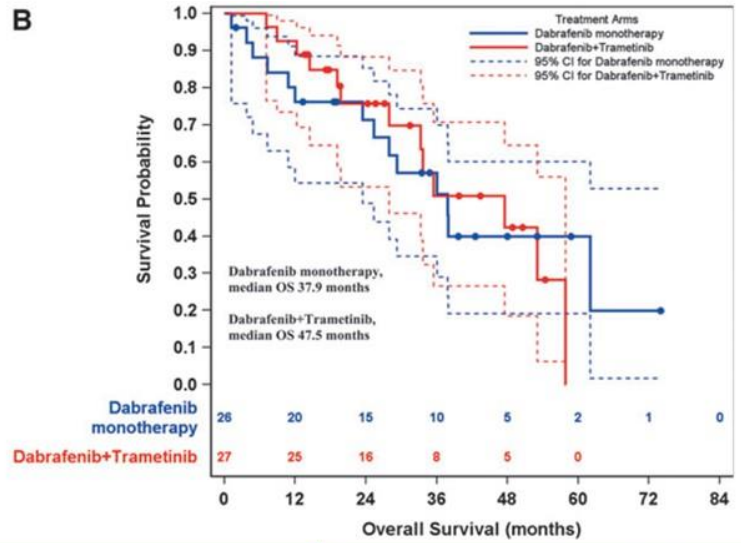
BRAF mutated RAI refractory Papillary Thyroid Cancer (~50-60%)

A multi-center, randomized phase 2 study with dabrafenib vs dabrafenib + trametinib



Busaidy NL et al. *Thyroid* 2022





	Median PFS (mos)	Partial response
Dabrafenib (N=26)	**10.7**	**35%**
Dabrafenib + Trametinib (N=27)	**15.1**	**30%**

Dabrafenib + Trametinib: The treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.

Grade 3 or 4 (%) Toxicities

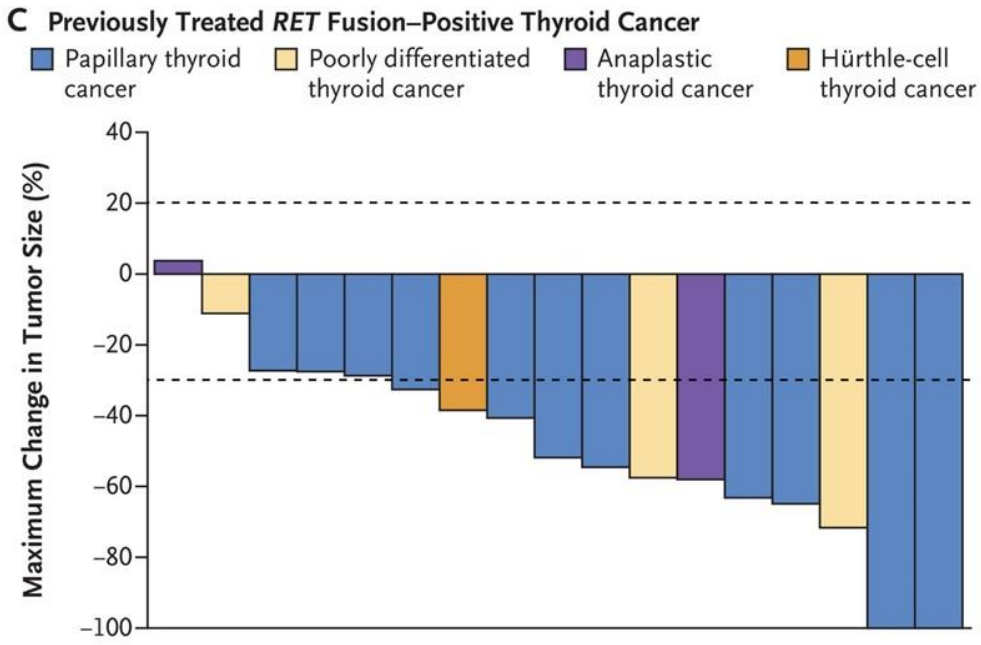
	Lenvatinib (median FU: 17.1 mos)		Cabozantinib (median FU: 6.2 mos)	
Term	Lenvatinib	Placebo	Cabozantinib	Placebo
Hypertension	42	2	9	3
Diarrhea	8	0	7	0
Fatigue/asthenia	9	2	10	0
Decreased appetite	12	0	3	0
Weight loss	10	0	1	0
Hand-foot	3	0	10	0
Proteinuria	10	0	1	0
Hypocalcemia	0	0	7	2
Headache	3	0	2	0
Dyspnea	0	0	3	4
Rash	0.4	0	0	0
Pulmonary embolism	1	1	2	0
Death attributed to drug by investigator	2.3%	0	0	0

	Dabrafenib + Trametinib (median FU: 25 mos)	
Term	Grade 3 (%)	Any grade (%)
Fever	4	59
Chills	0	52
Myalgia	0	22
Fatigue	4	52
Anorexia	0	33
Nausea	4	52
Vomiting	4	22
Diarrhea	0	26
Hypophosphatemia	11	41
Hyperglycemia	4	19
AST increase	4	37
ALT increase	4	30
Alk Phos increase	0	19

Schlumberger M et al, *New Engl J Med* 2015;372:621-630, **Brose MS et al.** *Lancet Oncol* 2021; 22(8):P1126-1138, **Busaidy NL et al.** *Thyroid* 2022

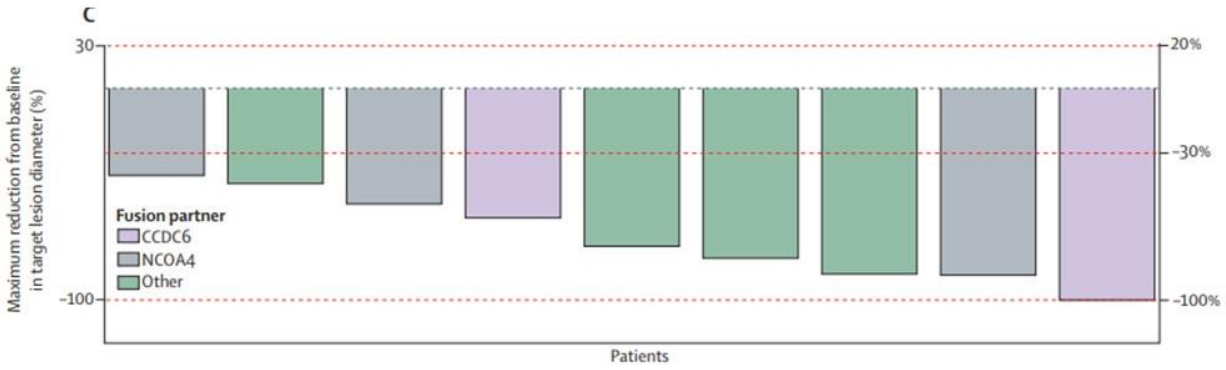
RET fusion positive thyroid cancer (~5-6%)

Selpercatinib (LOXO-292)
ORR 71% (N=19)



Wirth L et al. *New Engl J Med* 2020;383:825-835

Pralsetinib (BLU-667)
ORR 89% (N=9)

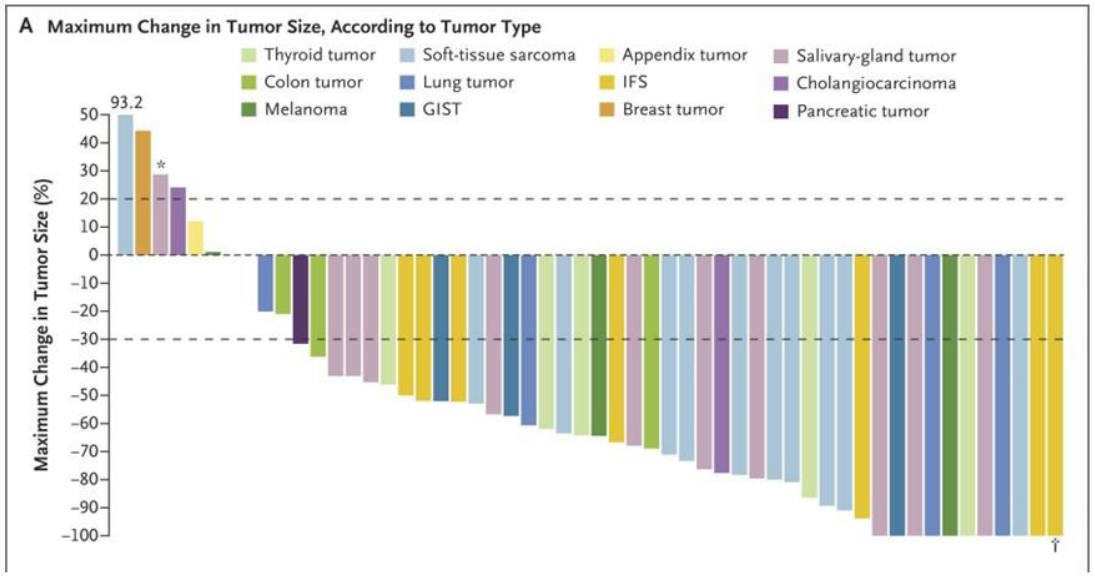


Subbiah V et al. *Lancet Diabetes Endocrinol* 2021;9:491–501

TRK fusion positive thyroid cancer (~1-2%)

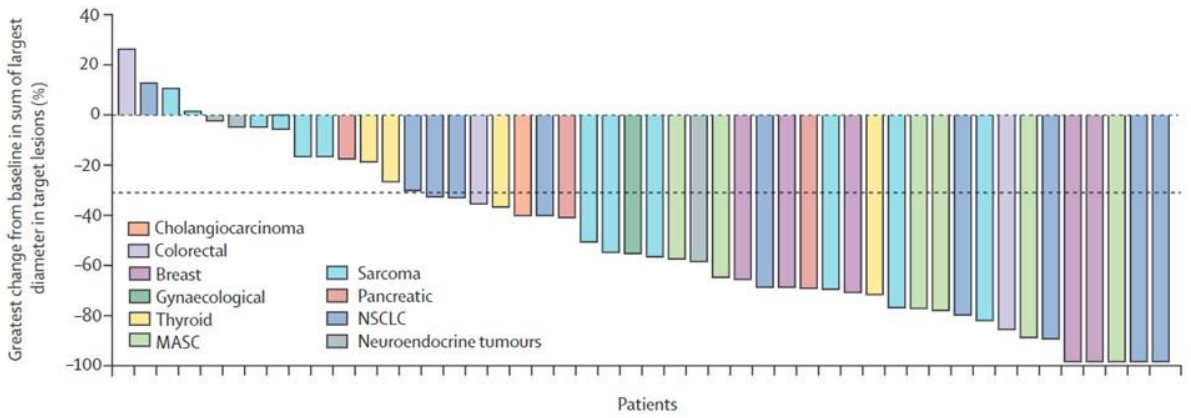
Targeting *ETV6-NTRK3*: Trk inhibitors

Larotrectinib (Thyroid N=5)



Drilon A et al. *New Engl J Med* 2018;378:731-739

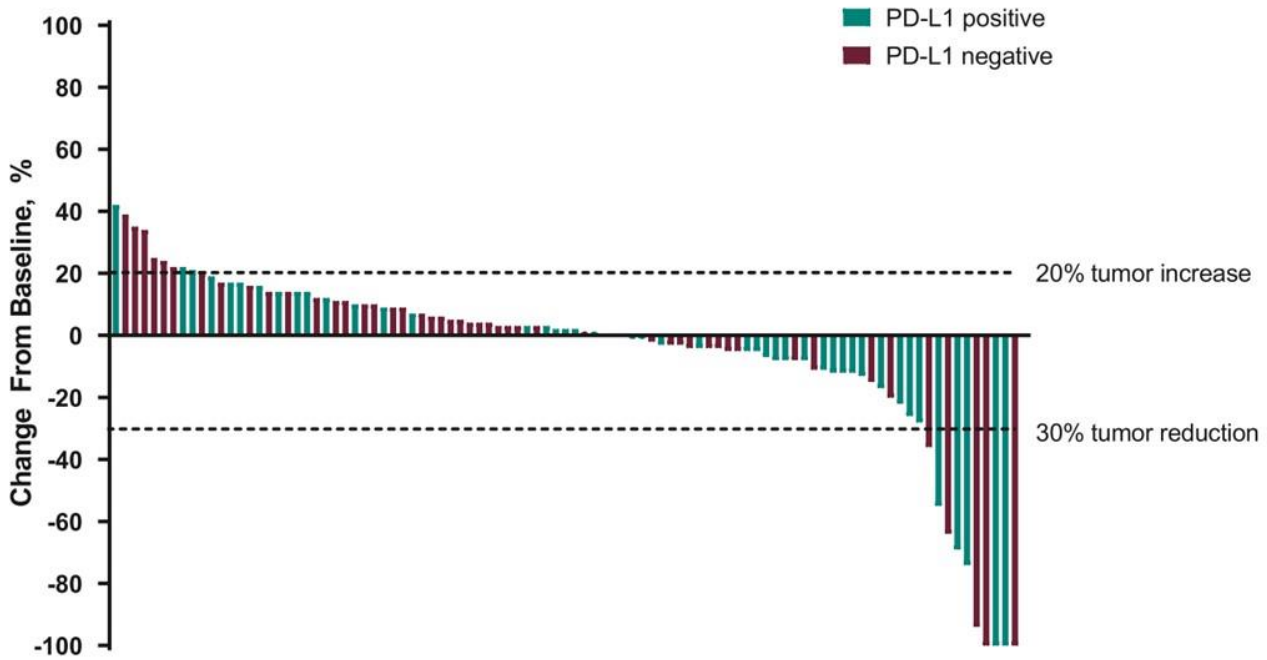
Entrectinib (Thyroid N=5)



Doebel RC et al. *Lancet Oncol* 2020

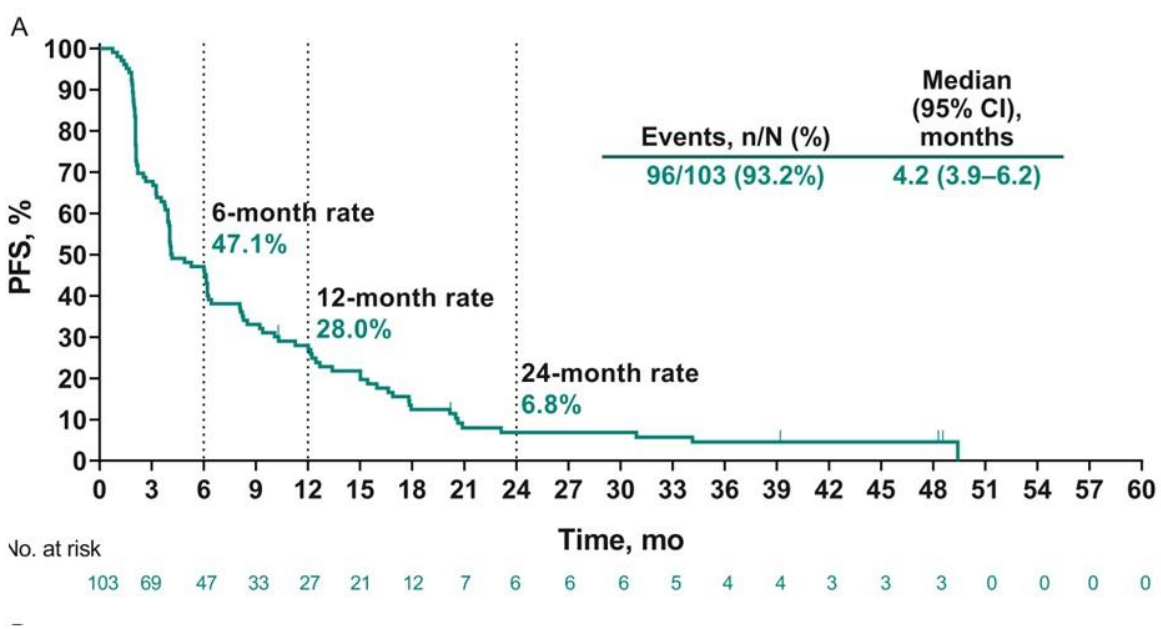
KEYNOTE-158 Phase II Pembrolizumab Differentiated Thyroid Cancer Cohort (N=103 PTC & FTC)

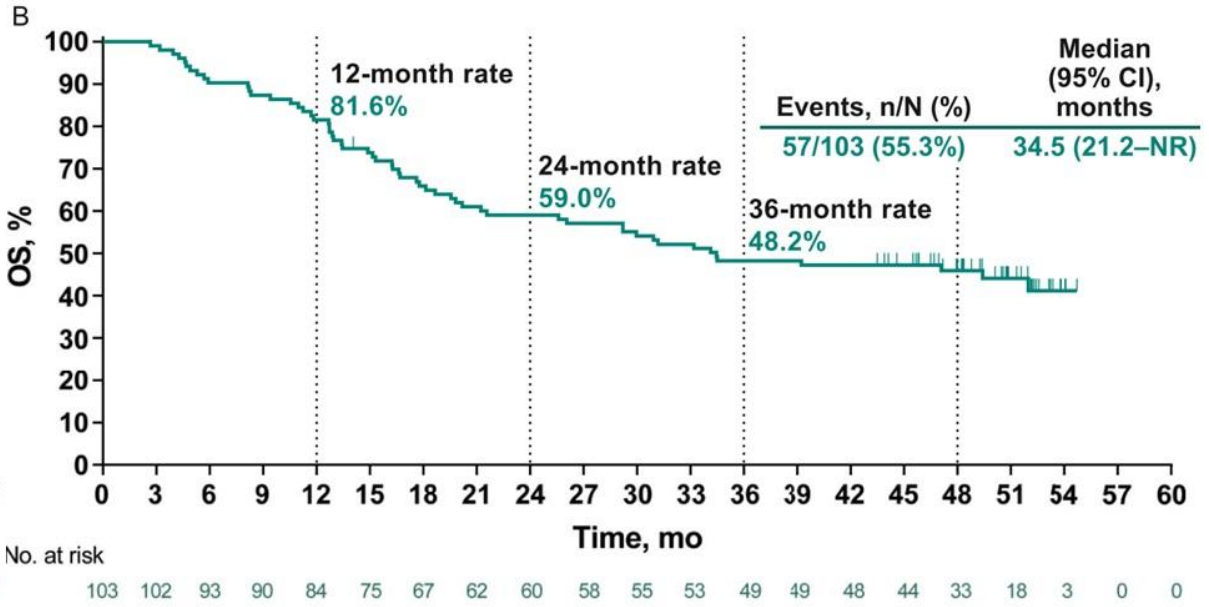
- Primary Endpoint: ORR
- Patients with progression on or intolerance to at least one prior line of standard treatment for metastatic and/or unresectable diseases
- **ORR 6.8% (2.8%-13.5%)**
- Programmed cell death ligand 1 (**PD-L1**) combined positive score **(CPS) ≥1** (n = 46): **ORR 8.7%** (2.4%-20.8%)
- **PD-L1 CPS <1: ORR 5.7%** (1.2%-15.7%)



Oh D-Y, et al. *Cancer* 2022

KEYNOTE-158 Phase II Pembrolizumab Differentiated Thyroid Cancer Cohort (N=103 PTC & FTC)





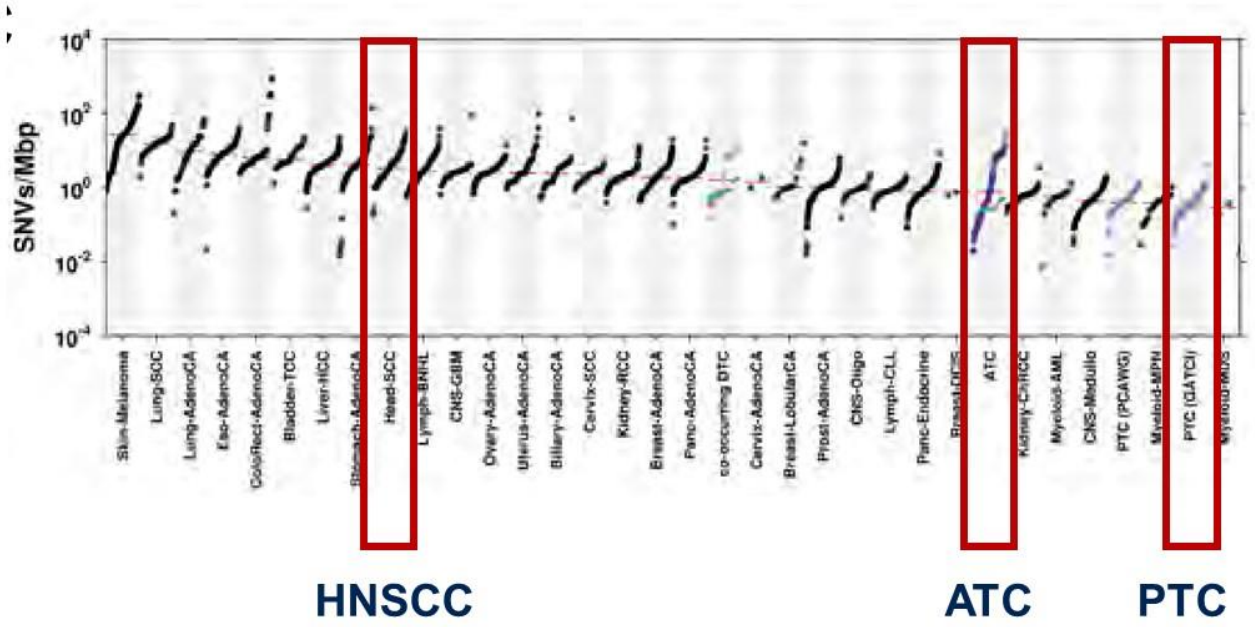
Oh D-Y, et al. *Cancer* 2022

Anaplastic thyroid cancer

PRESENTED BY: Christine H. Chung, MD

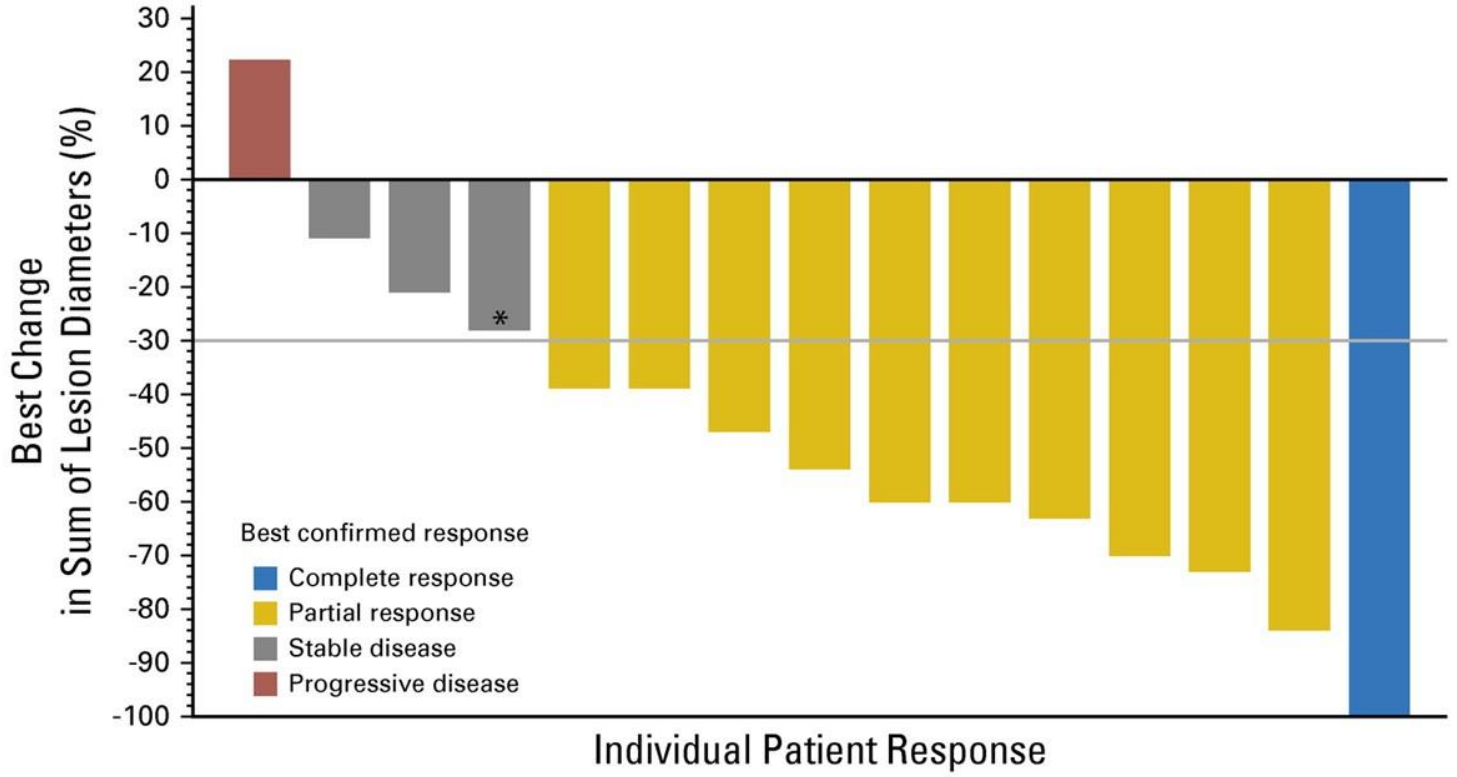
Common Genomic Alterations in ATC

	Study	ATC	DTC	PTC/HTC
TP53	GATCI	37%	21%	1%
	TCGA	N/A	N/A	0%
	Landa	70%	9%	N/A
	Pozdeyev	48%	8%	N/A
	Yoo	44%	20%	N/A
	Ganly	N/A	N/A	7%
	Gopal	N/A	N/A	13%
BRAF	GATCI	21% (11.4%)	50% (23.6%)	51% (30.0%)
	TCGA	N/A	N/A	59% (35.3%)
	Landa	45%	36%	N/A
	Pozdeyev	37%	59%	N/A
	Yoo	41%	27%	N/A
	Ganly	N/A	N/A	0%
	Gopal	N/A	N/A	3%



Global Anaplastic Thyroid Cancer Initiative (GATCI)
medRxiv preprint doi:
https://doi.org/10.1101/2023.04.10.23288365

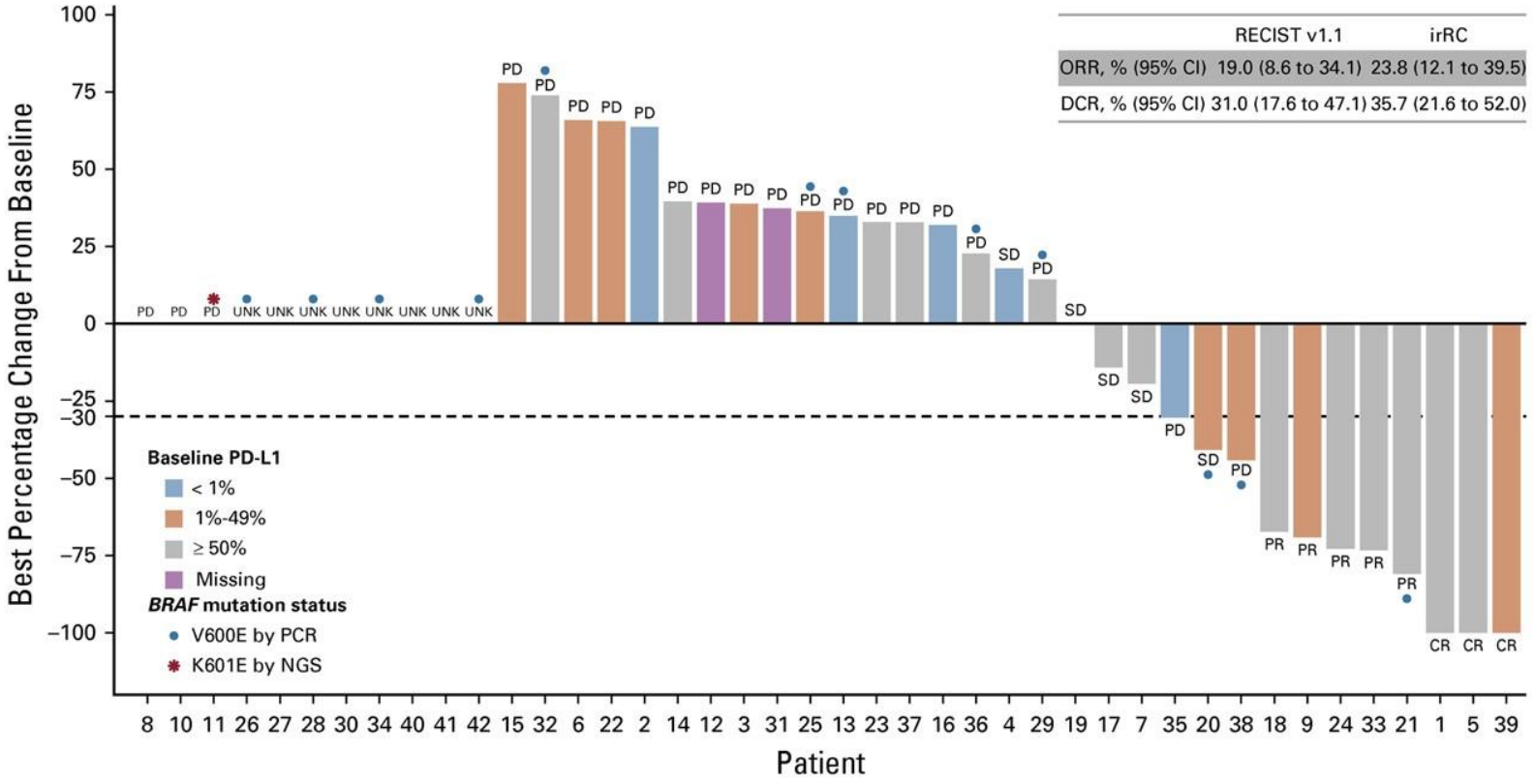
Dabrafenib + Trametinib for *BRAF* mutated ATC



- N=15
- ORR 63% (intent-to-treat)
- ORR 67% (*BRAF* V600E confirmed)

Subbiah V et al. *J Clin Oncol* 2018;36:7-13

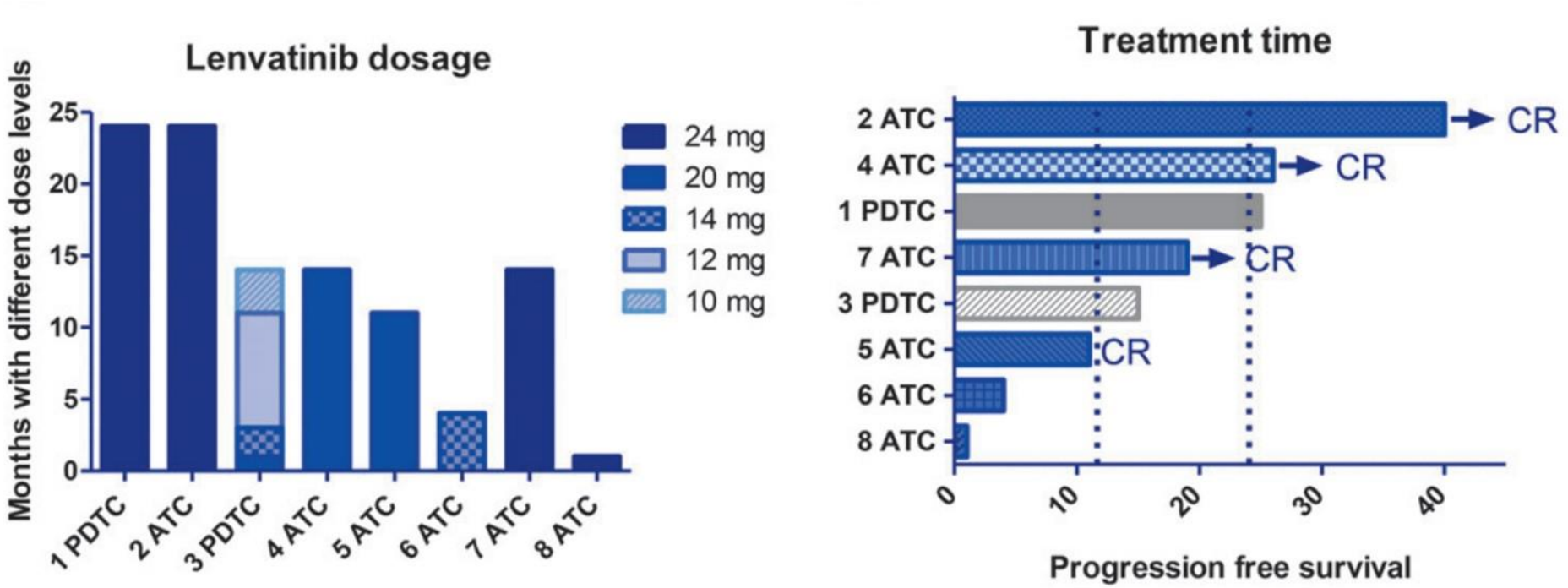
Spartalizumab (PDR001, anti-PD1 Ab) for ATC (N=42)



- ORR 19%
- DCR 31%

Capdevila J et al. *J Clin Oncol* 2020; 38:2620-2627

Combination of Lenvatinib and Pembrolizumab in Anaplastic and Poorly Differentiated Thyroid Cancer (N=8)



Dierks, et al. *Thyroid*, 2021

Conclusions/Take-Away

- Asymptomatic patients with DTC at a lower risk of progression: Watchful waiting
- Targeted therapy with MKIs are effective in treatment of DTC
  - Anti-angiogenic multi-kinase Inhibitors: Sorafenib, Lenvatinib, Cabozantinib
  - BRAF V600E targeting BRAF + MEK inhibitors: Dabrafenib + Trametinib
  - RET inhibitors: Selpercatinib, Pralsetinib
  - NTRK inhibitors: Larotrectinib, Entrectinib
- *BRAF* targeted therapy is effective in *BRAF* mutated ATC: dabrafenib+trametinib
- Immune checkpoint inhibitors +/- Lenvatinib may benefit a subset of ATC
- More research is needed to
  - Enhance activity of current therapy
  - Identify predictive biomarkers for response and toxicities
  - Understand underlying biology of resistance

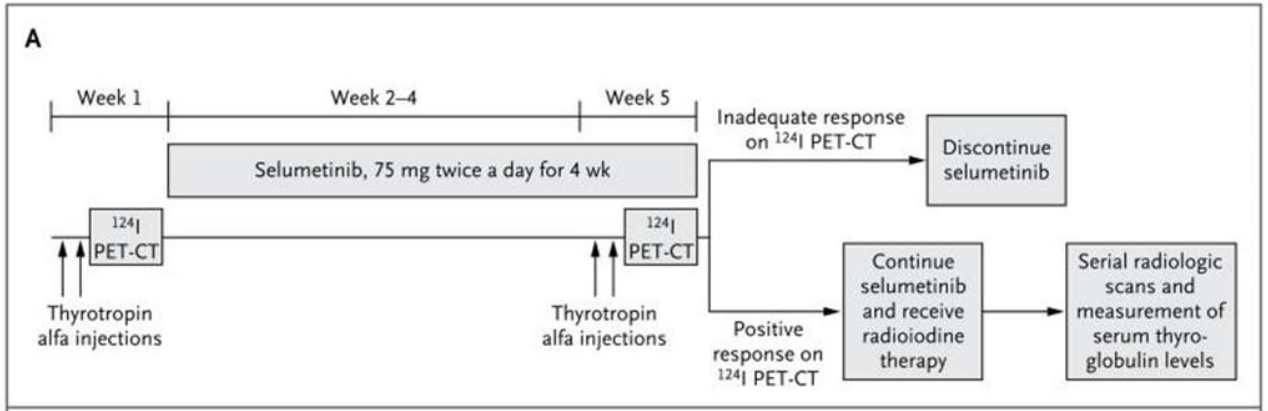
ORIGINAL ARTICLE

Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer

Alan L. Ho, M.D., Ph.D., Ravinder K. Grewal, M.D., Rebecca Leboeuf, M.D., Eric J. Sherman, M.D., David G. Pfister, M.D., Desiree Deandreis, M.D., Keith S. Pentlow, M.Sc., Pat B. Zanzonico, Ph.D., Sofia Haque, M.D., Somali Gavane, M.D., Ronald A. Ghossein, M.D., Julio C. Ricarte-Filho, Ph.D., José M. Domínguez, M.D., Ronglai Shen, Ph.D., R. Michael Tuttle, M.D., Steve M. Larson, M.D., and James A. Fagin, M.D.

TKI as a re-sensitization strategy for RAI

Selumetinib prior to RAI



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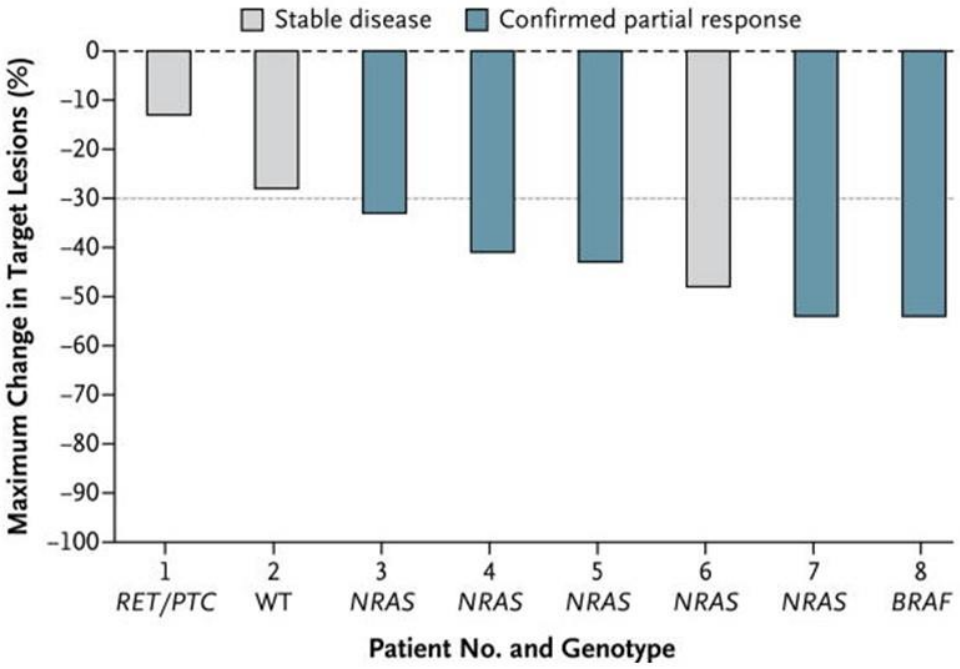
Tumor Genotype	Patients with Increased Iodine Uptake in a Lesion after Selumetinib	Patients Who Received Radioiodine
	no./total no. of patients	
BRAF	4/9	1/9
NRAS	5/5	5/5
RET/PTC	2/3	1/3
Wild-type	1/3	1/3
Total	12/20	8/20

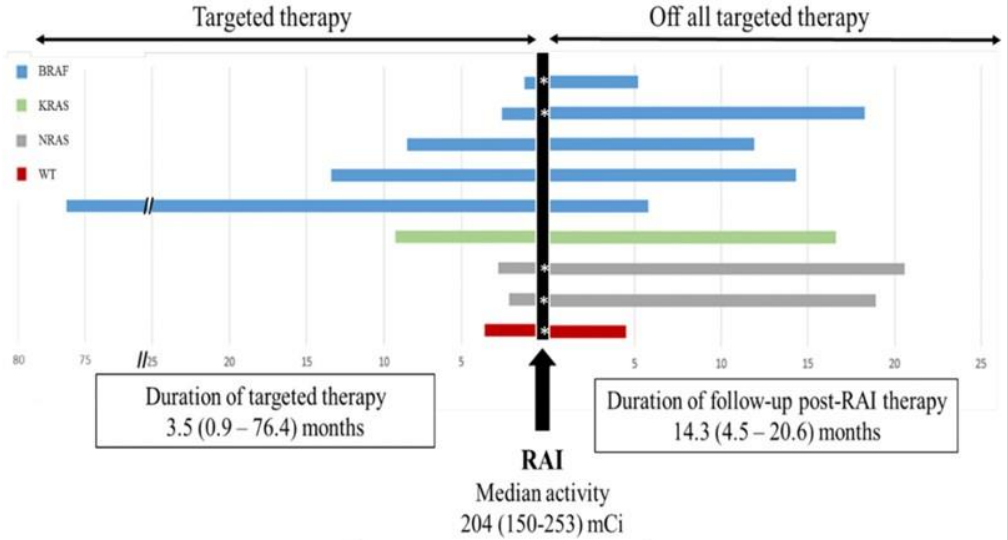


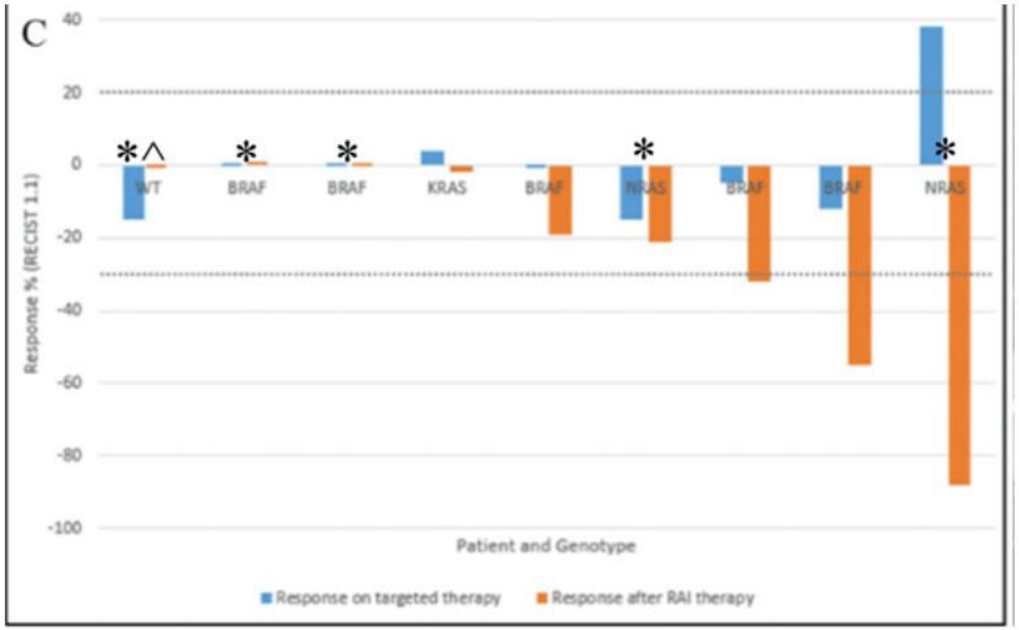
12 out of 20 patients had increased iodine uptake, 8 of whom reached prespecified dosimetric threshold (20 Gy with 300 mCi or less of RAI)

Ho AL et al. *New Engl J Med* 2013;368(7):623-632

TKI as a re-sensitization strategy for RAI

Dabrafenib/trametinib prior to RAI



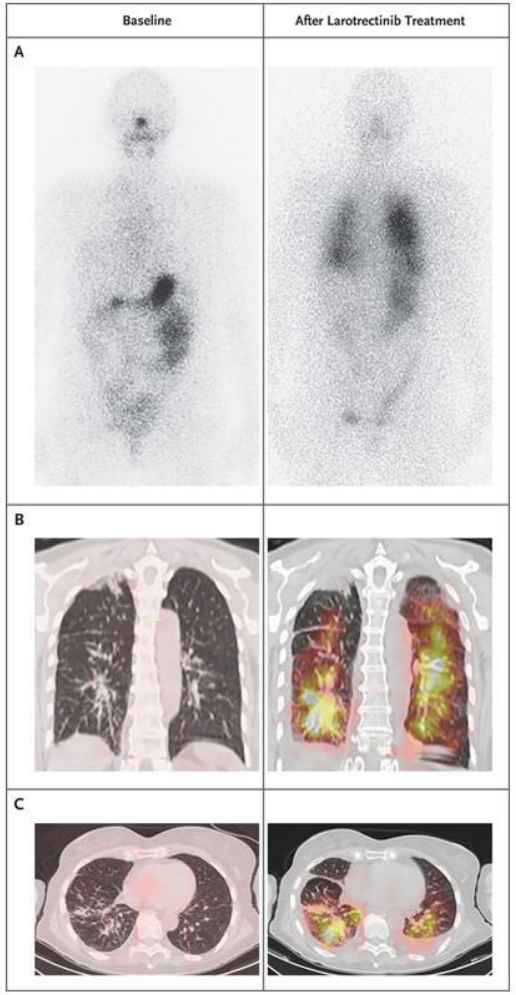


BRAFi/MEKi combo for BRAF mt
MEKi for NRAS or KRAS mt

8 out of 13 patients had clinically meaningful increased iodine uptake, and one additional treatment was treated with RAI despite no uptake

Jaber T et al. *J Clin Endocrinol Metab* 2018;103:3698-3705

TKI as a re-sensitization strategy for RAI



Larotrectinib prior to RAI

- 65 F with EML4-NTRK3 fusion positive papillary thyroid cancer
- 3 weeks after Larotrectinib, restoration of RAI uptake was noted on diagnostic scan

Groussin L et al. *New Engl J Med* 2020;383:1686-87

Medullary thyroid cancer

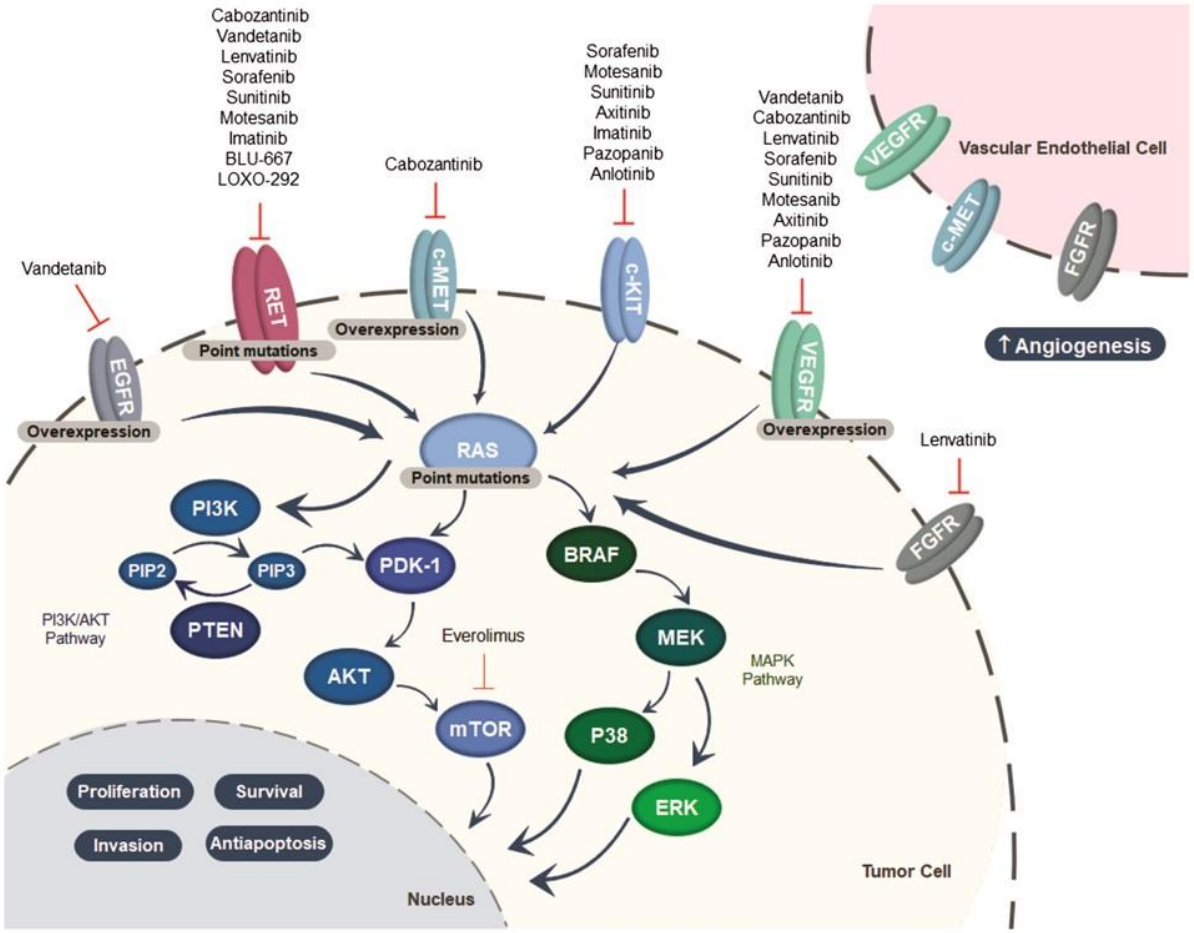
PRESENTED BY: Christine H. Chung, MD

Medullary Thyroid Cancers

- Rare cancer (2% of thyroid malignancy, 0.14 to 0.21 per 100,000)

- Can be hereditary
  - MEN2 syndrome (20-25%): germline *RET* mutation
  - Sporadic MTC (75-80%): 23-66% has *RET* M918T mutation

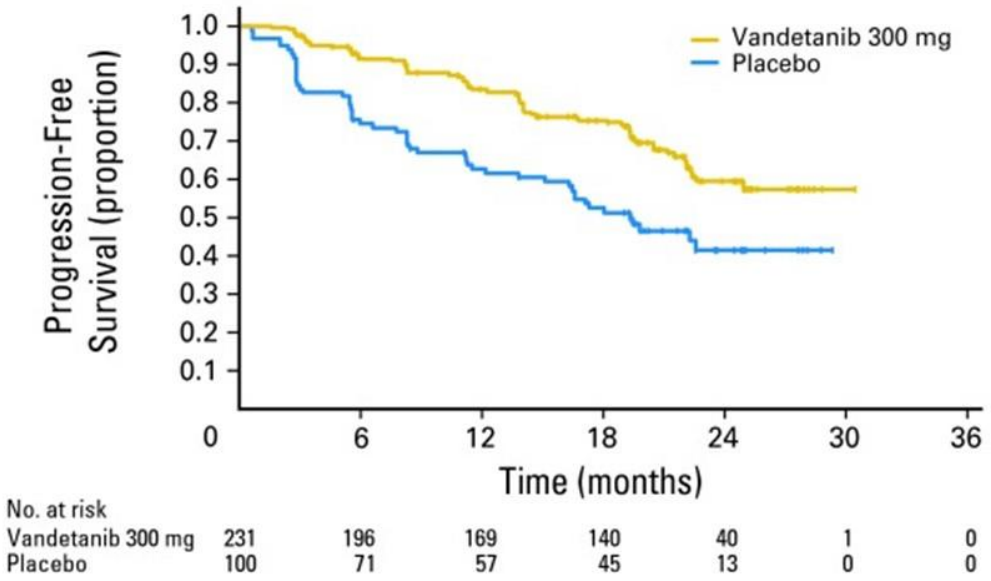
Biology of Medullary Thyroid Cancer

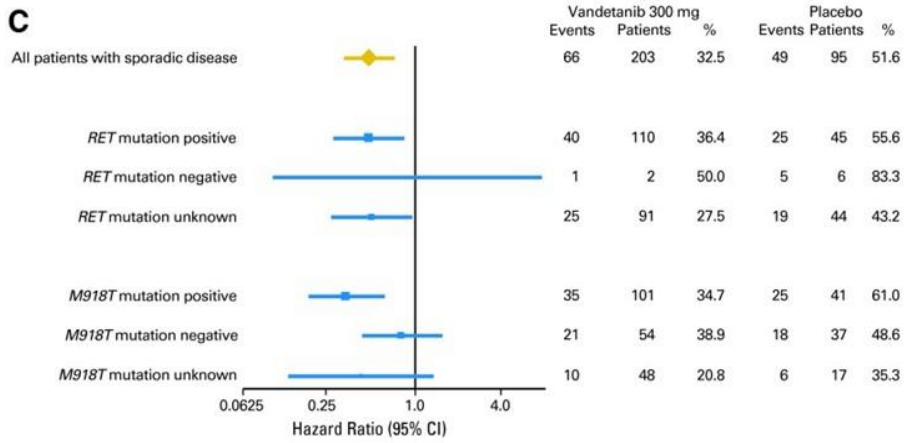


Ceolin L et al. *Endocrine-related Cancer* 2019;26: R499-518

Vandetanib in Medullary Thyroid Cancers

	Median PFS (mos)	ORR (%)
Vandetanib	30.5	45%
Placebo	19.3	13%

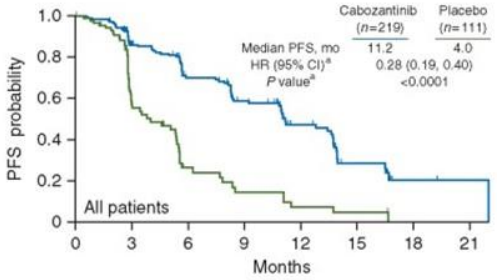




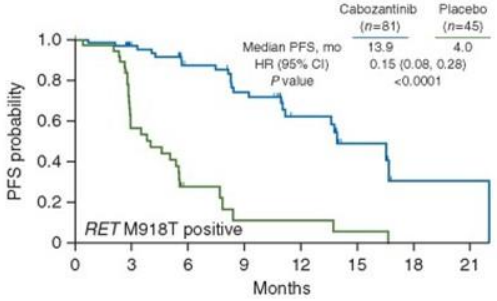
Wells SA et al. *J Clin Oncol* 2012;30:134-141

Cabozantinib (140mg capsule) in Medullary Thyroid Cancer (N=330)

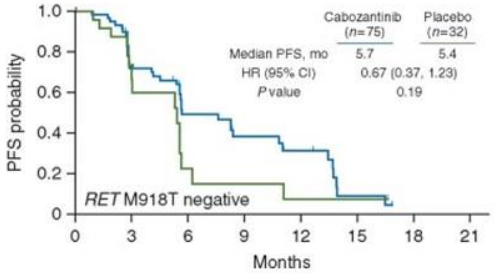
All population



RET M918T positive



RET M918T negative



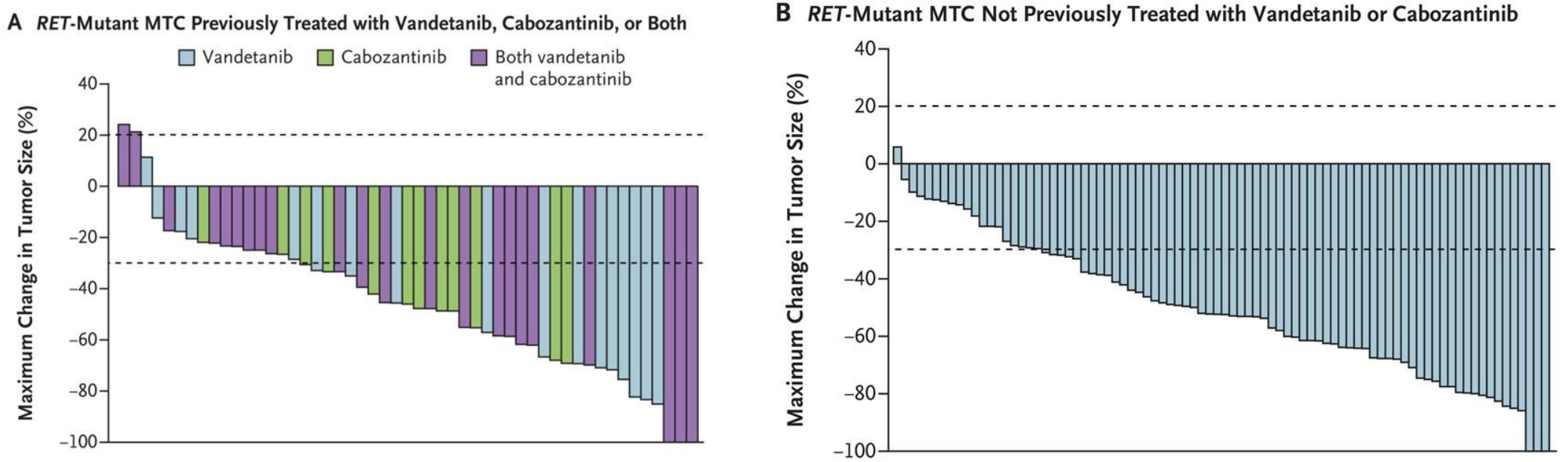
	Median PFS (mos): All	Median PFS (mos): RET M918T pos	Median PFS (mos): RET M918T neg	ORR (%)
Cabozantinib	**11.2**	**13.9**	**5.7**	**28%**
Placebo	**4.0**	**4.0**	**5.4**	**0%**

- 40% had prior anti-cancer therapy
- 21% had prior MKI

Schulmberger M et al. *Ann Oncol* 2017;28:2813-19

PRESENTED BY: Christine H. Chung, MD

Selpercatinib in *RET*-Mutant MTC

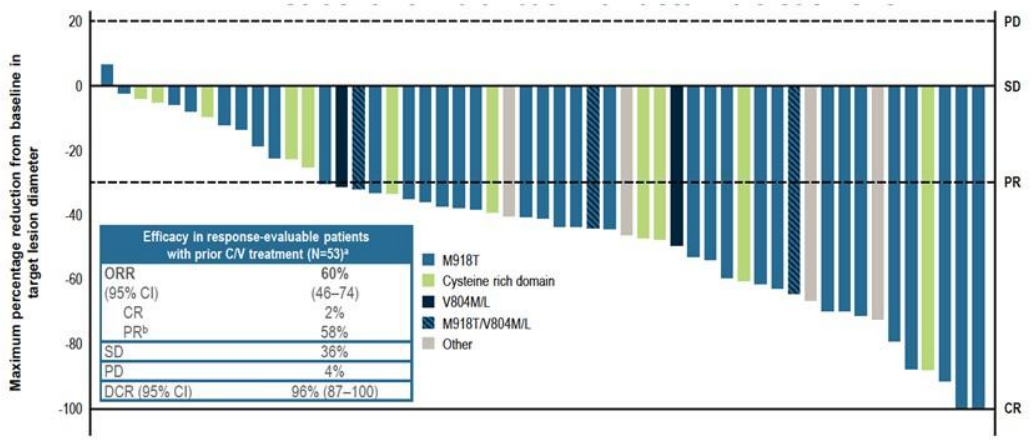


ORR 73% (TKI naïve MTC, n=88)
ORR 69% (TKI pre-treated MTC, n=55)

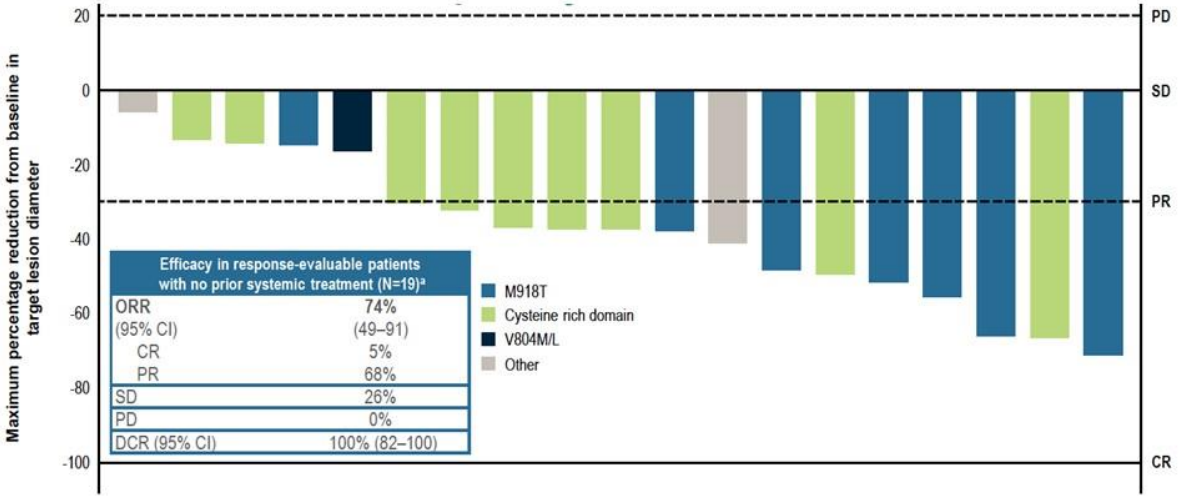
Wirth L et al. *New Engl J Med* 2020;383:825-835

Pralsetinib in *RET*-mutant MTC

RET-Mutant MTC previously treated with vandetanib or cabozantinib



RET-Mutant MTC not previously treated with vandetanib or cabozantinib



ORR 74% (in TKI naïve MTC, n=19)
ORR 60% (in TKI pre-treated MTC, n=53)

Hu M et al. ESMO Congress 2020

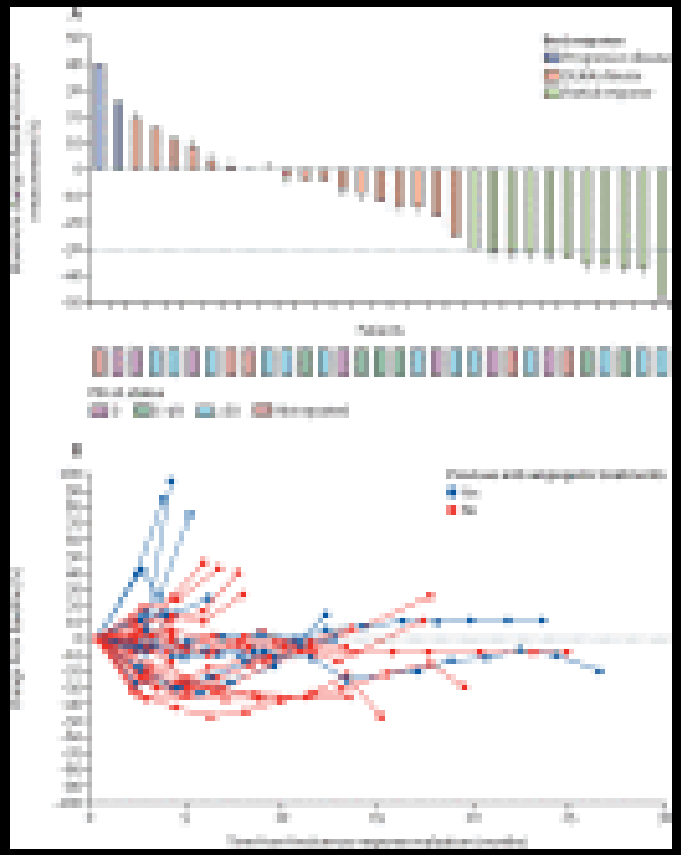
Thymic Carcinoma

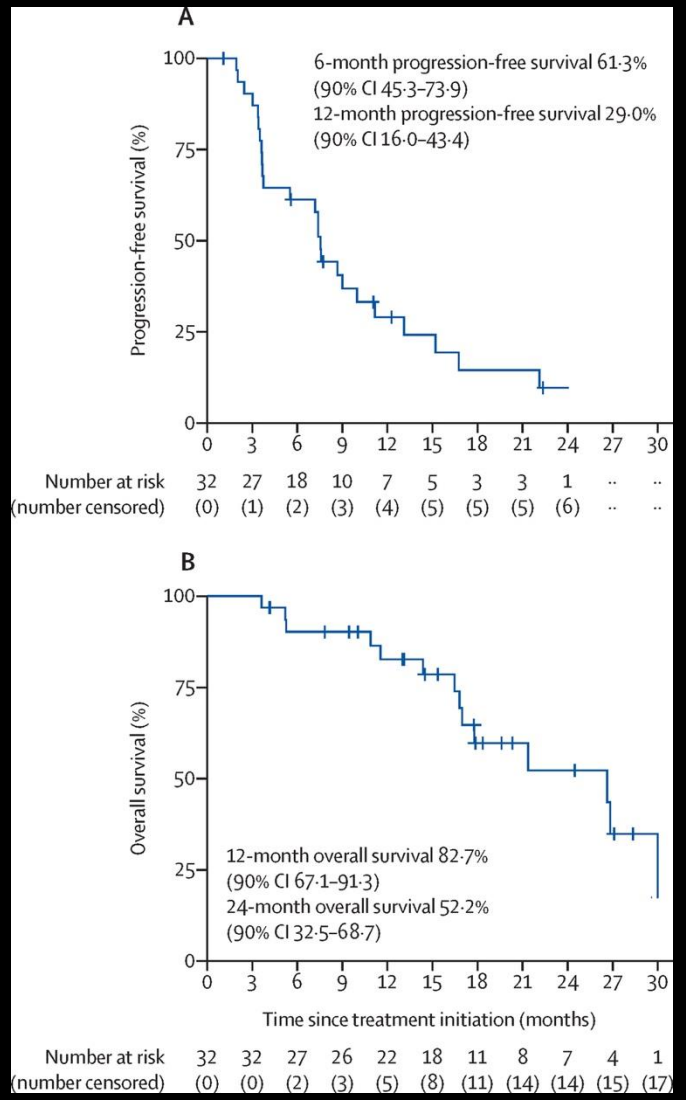
Avelumab plus axitinib in unresectable or metastatic type B3 thymomas and thymic carcinomas (CAVEATT): a single-arm, multicentre, phase 2 trial

Fabio Conforti [1], Paolo Andrea Zucali [2], Laura Pala [3], Chiara Catania [4], Vincenzo Bagnardi [5], Isabella Sala [5], Paolo Della Vigna [6], Matteo Perrino [7], Paola Zagami [8], Chiara Corti [8], Sara Stucchi [9], Massimo Barberis [10], Elena Guerini-Rocco [10], Benedetta Di Venosa [10], Fabio De Vincenzo [7], Nadia Cordua [7], Armando Santoro [2], Giuseppe Giaccone [11], Tommaso Martino De Pas [3]

Affiliations + expand

PMID: 36096156 DOI: 10.1016/S1470-2045(22)00542-3





Thank you!

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