

Anaplastic Thyroid Cancer

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Professor & Faculty Director of Clinical Trials

Endocrine Neoplasia & Hormonal Disorders

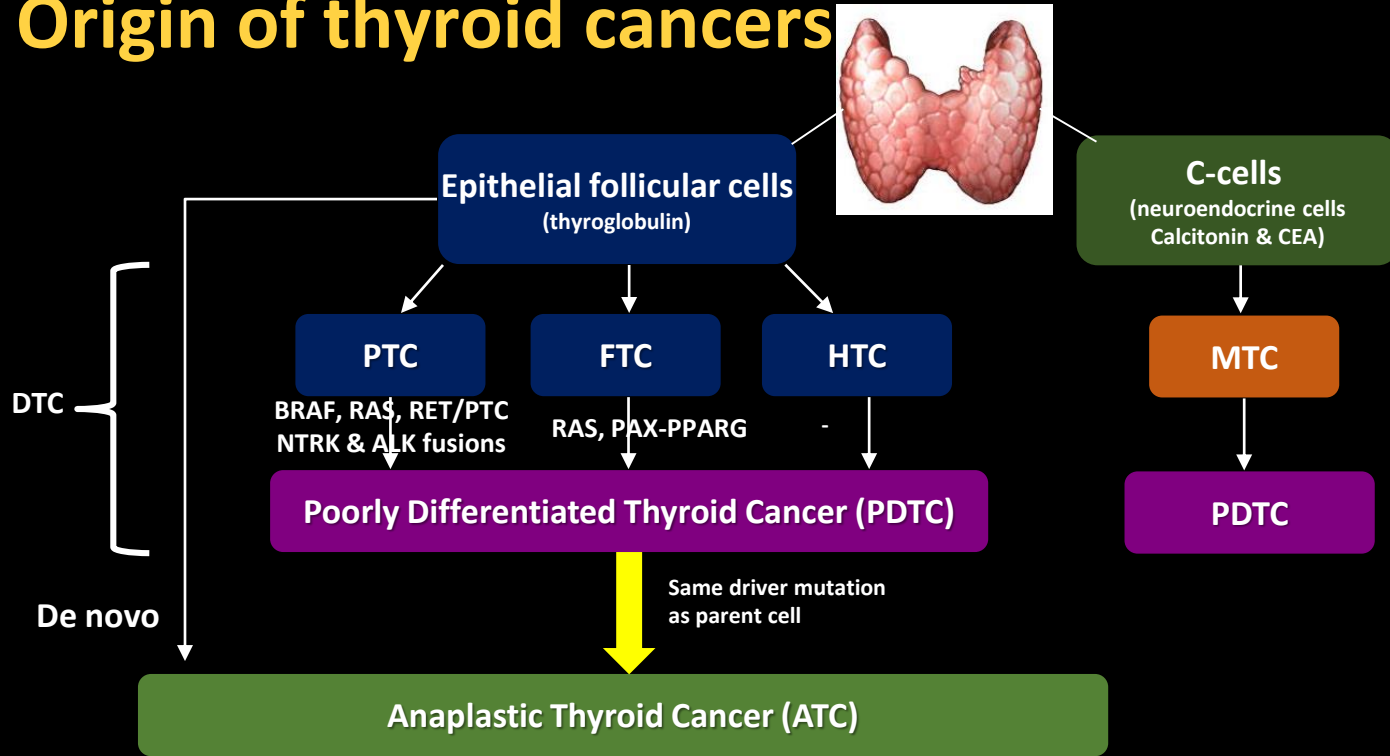
The University of Texas MD Anderson Cancer Center

Houston, Texas, USA

Disclosures

- Grant funding: Eisai, Exelixis, Genentech, Merck and Kura
- Advisory boards: Blueprint, Ignyta, Bayer and LOXO

Origin of thyroid cancers

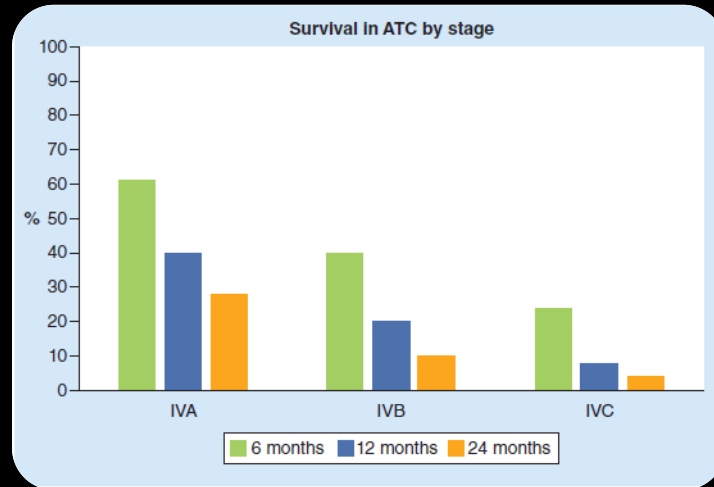


DTC=differentiated thyroid cancer
PTC=papillary thyroid cancer
FTC=follicular thyroid cancer
HTC=Hurthle cell thyroid cancer

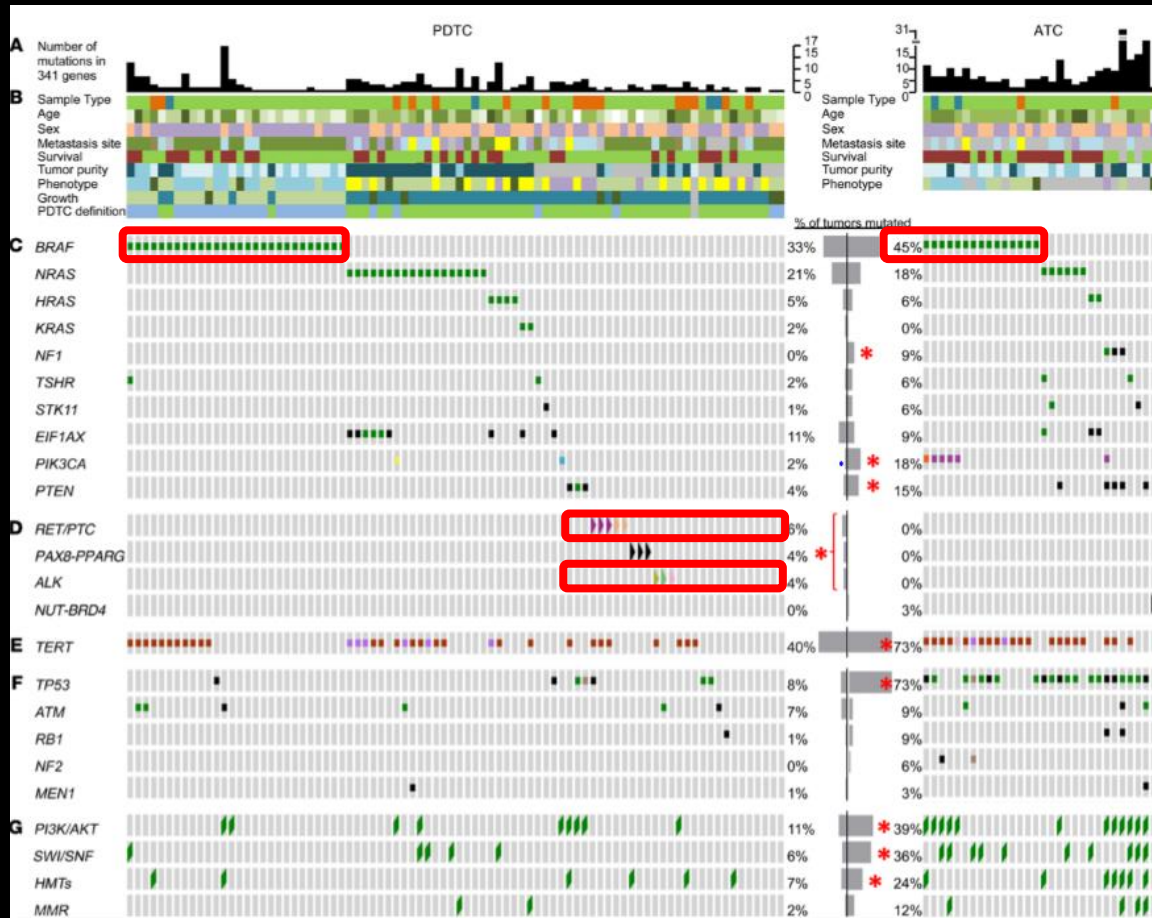
PDTC=poorly differentiated thyroid cancer
MTC=medullary thyroid cancer

Background

- Anaplastic thyroid cancer (ATC) is the deadliest of all thyroid cancers
 - Historical 12-month overall survival of < 30% for patients with stage IVB and IVC disease
- Rare disease (~1000 cases/year in the U.S.)
- Most patients cannot be meaningfully resected at diagnosis
- Half metastatic at diagnosis



Mutations in PDTC & ATC



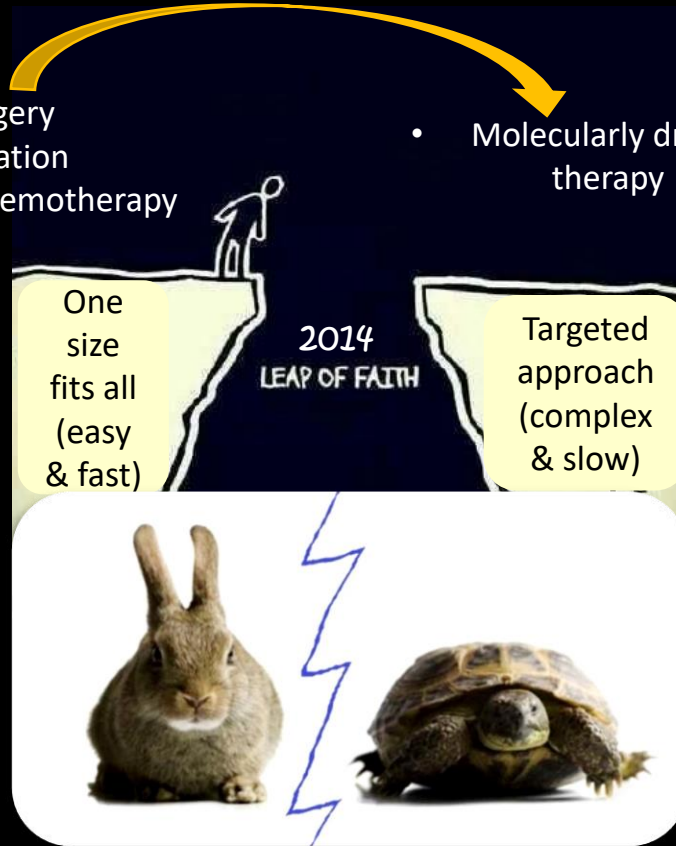
**NTRK* and *RET* fusions are also seen in ATC

Landa et al, JCI, 2016

Personalizing ATC Treatment

- Surgery
- Radiation
- Cytotoxic chemotherapy

- Molecularly driven therapy

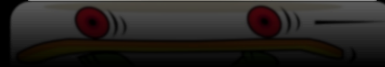
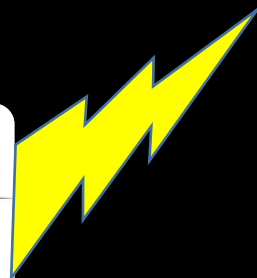


Limitations:

- Molecular testing is too slow for a rapidly fatal disease
- Would gene-specific targeted therapy work for a tumor with multiple mutations?



Rapid Tumor Genotyping



Molecular testing must be done at “ATC pace”

- Two faster tests:

- BRAF by immunohistochemistry (IHC)

- Liquid biopsy: circulating cell-free DNA (cfDNA) are small DNA fragments found circulating in plasma



BRAFV600E by IHC

- Must have surgical, core or FNA *cell block* specimen because FNA smears can give false positive results Smith A *et al*, Cancer Cytopathology, 2018

BRAFV600E by IHC

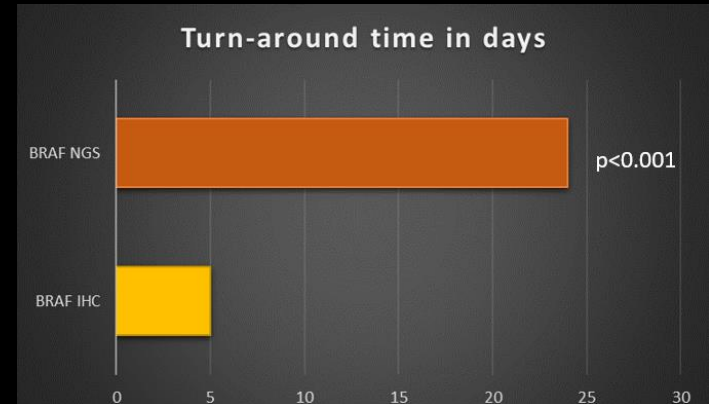
- Must have surgical, core or FNA *cell block* specimen because FNA smears can give false positive results Smith A *et al*, Cancer Cytopathology, 2018

	NGS BRAF V600E Positive	NGS BRAF V600E Negative
IHC BRAF V600E Positive	39	1
IHC BRAF V600E Negative	0	77
Sensitivity= 100%, Specificity= 99%, Positive predictive value= 98%, Negative predictive value= 100%		

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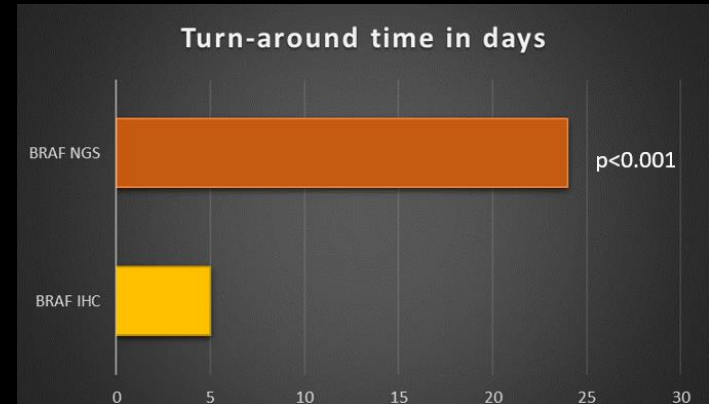
Limitations:

- Necrotic tissue (7% were inconclusive)
- Single gene test

Advantages:

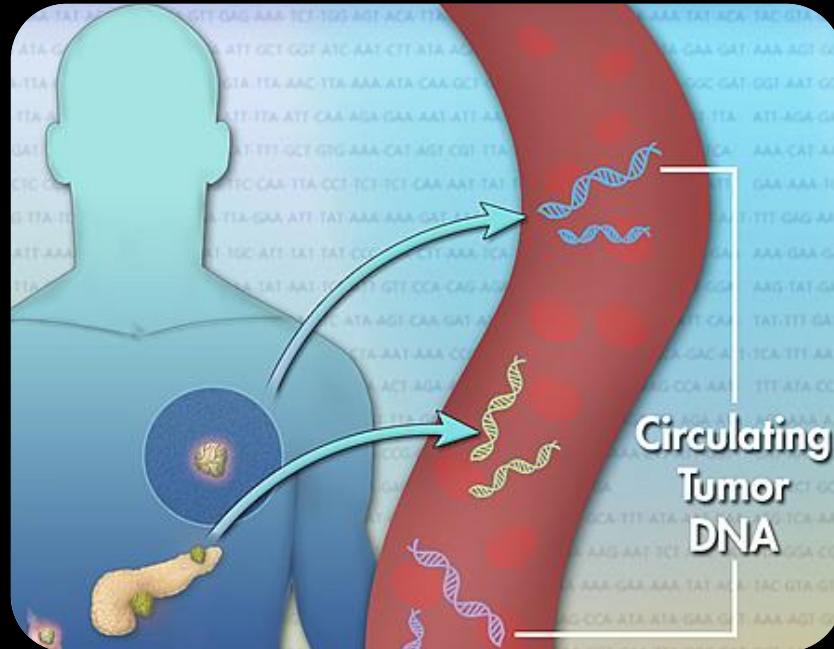
- Rapid turn around time
- Inexpensive test

Conclusion: should be performed by pathologist as routine test on all ATC diagnostic specimens



cfDNA “liquid biopsy”

Cell-free DNA are DNA fragments shed by the tumor and released into bloodstream



Liquid Biopsy

- 100% concordance for *BRAF*V600E between Guardant 360 cfDNA liquid biopsy and tissue NGS in patients with large volume, untreated disease (Sandulache *et al*, Thyroid 2016)

Group		Untreated Patients (n=12)											
Patient		3	7	8	9	11	12	14	15	19	20	21	23
BRAF	Tumor	+	+			+	+	+			+	+	
	Plasma	+	+			+	+	+			+	+	
NRAS	Tumor				+				+				+
	Plasma				+				+				+
KRAS	Tumor												
	Plasma												
HRAS	Tumor												
	Plasma												
PIK3CA	Tumor		+		+			+			+		
	Plasma		+		+			+					
TP53	Tumor	+			+			+					+
	Plasma	+	+	+	+			+					+

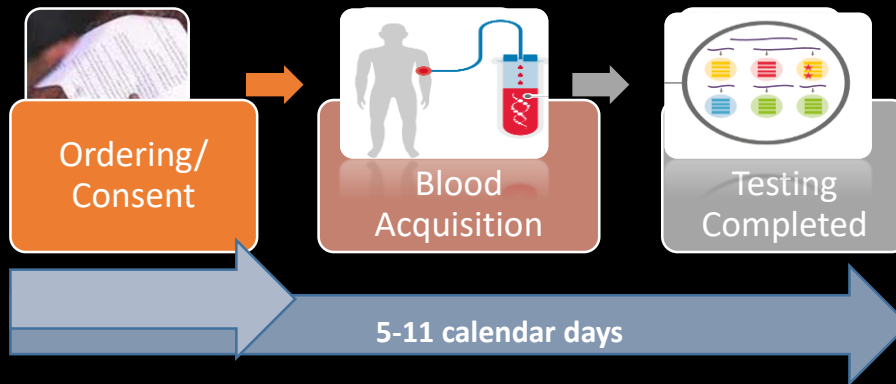
- Expanded data in 23 patients was concordant in 93% of *BRAF* mutated tissues (Qin Y *et al*, ATA 2018; submitted to Thyroid)

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BRAF	Tumor	■	■			■	■	■			■	■	
	Plasma	■	■			■	■	■			■	■	
NRAS	Tumor				■				■				■
	Plasma				■				■				■
KRAS	Tumor												
	Plasma												
HRAS	Tumor												
	Plasma												
PIK3CA	Tumor		■		■			■			■		
	Plasma		■		■			■					
TP53	Tumor	■			■			■					■
	Plasma	■	■	■	■			■					■

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	Plasma												
PIK3CA	Tumor		■		■			■			■		
	Plasma		■		■			■					
TP53	Tumor	■			■			■					■
	Plasma	■	■	■	■			■					■

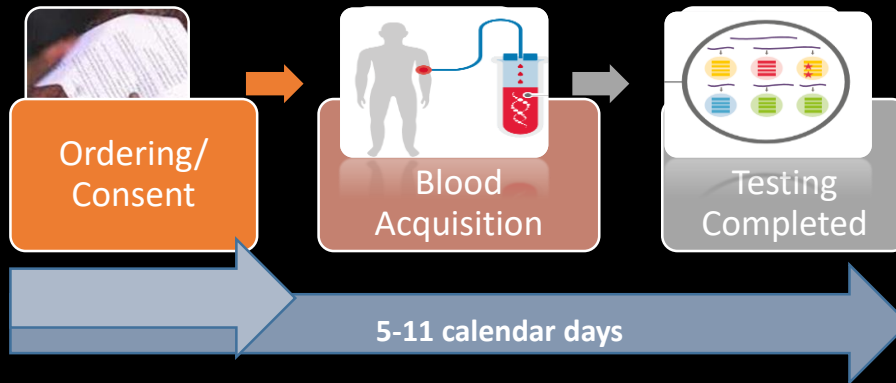
- Expanded data in 23 patients was concordant in 93% of *BRAF* mutated tissues (Qin Y *et al*, ATA 2018; submitted to Thyroid)

Limitations:

- Works best on untreated patients
- Reimbursement/cost
- Fairly slow → newer approaches underway
- Fusions are not included on all panels (ie, NTRK3 not included on Guardant360)

Advantages:

- Includes large number of genes/fusions

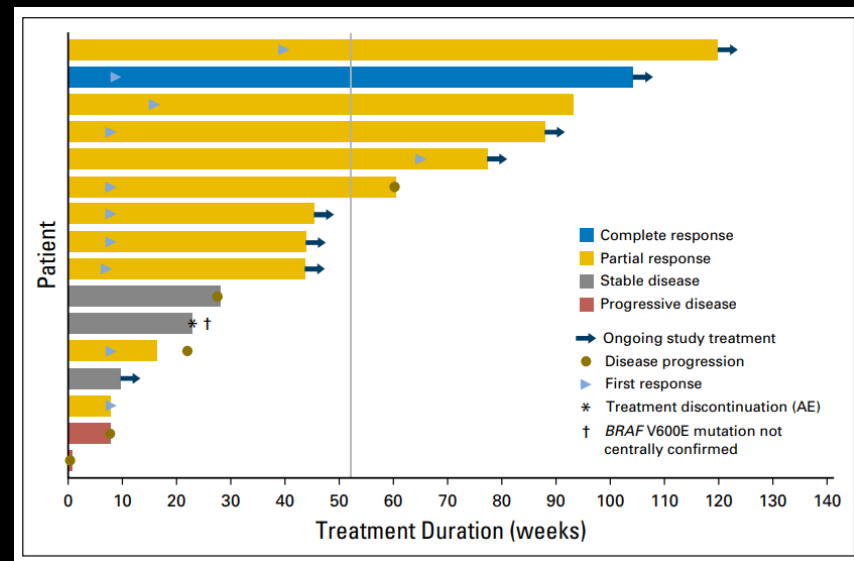
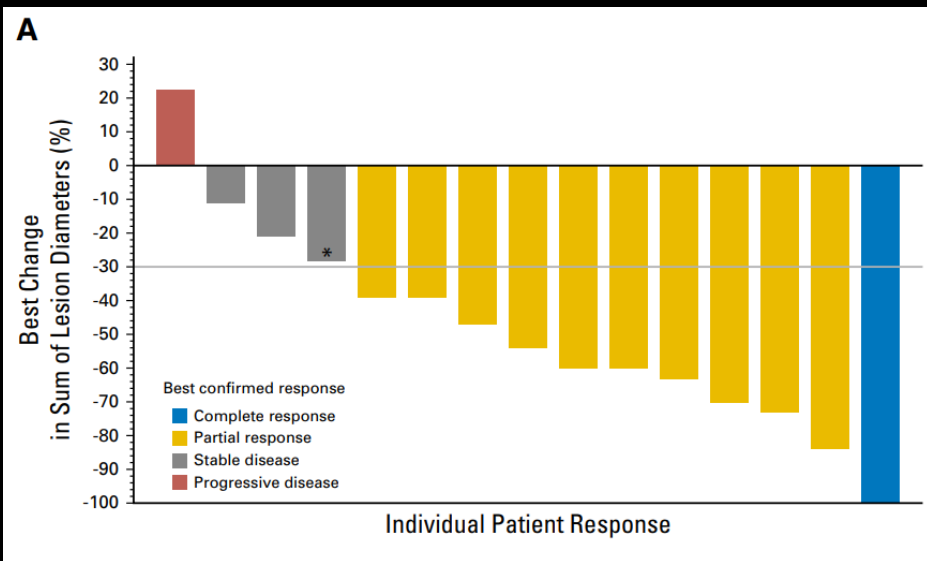




Molecularly Targeted Clinical Trials and Novel Approaches

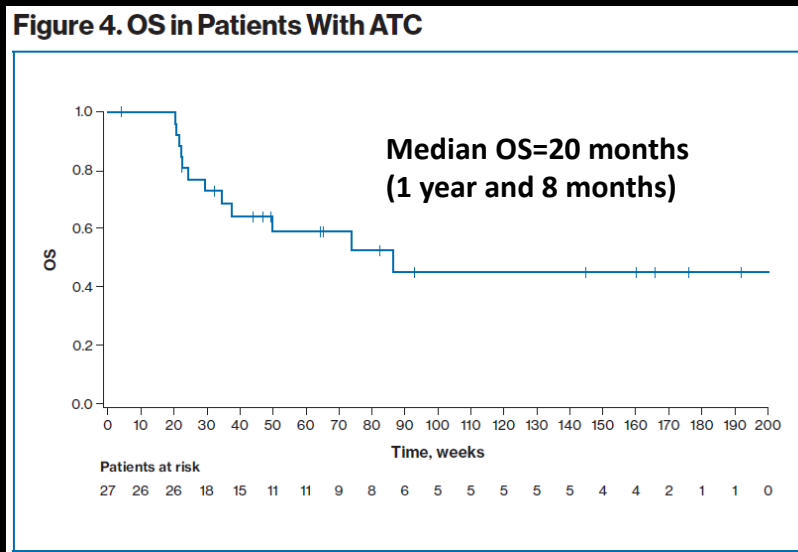
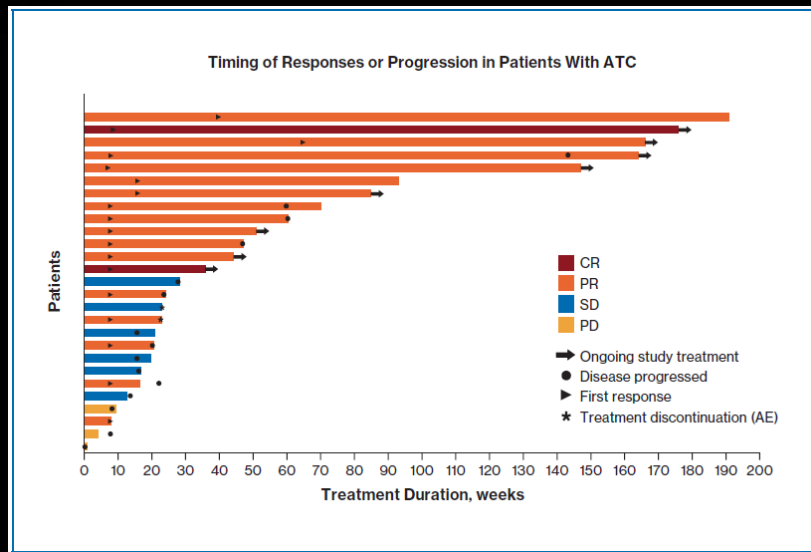
ATC: Dabrafenib (BRAFi) + trametinib (MEKi) basket trial

- 16 *BRAF*V600E mutated ATC patients
- Key entry criteria: Good PS, ability to swallow and normal organ function, chemoRT wash-out 14 days
- 69% response rate; OS 80% at 1 year



Updated Efficacy and Safety Data of Dabrafenib and Trametinib (“DT”) in Patients With BRAF V600–Mutated ATC

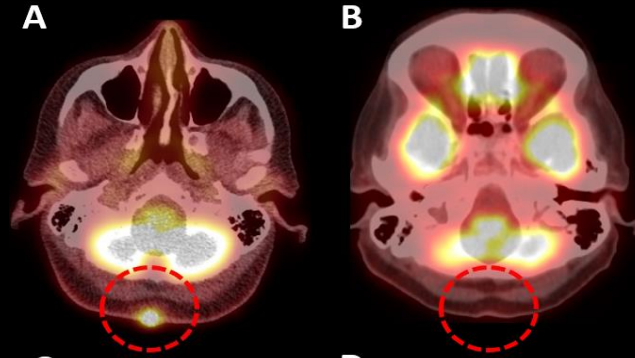
- 28 *BRAF*V600E mutated ATC patients
- Response rate 67% (includes 2 CRs)
- Median OS 86 weeks (95%CI, 35 weeks-NE)
- Response to therapy associated with better patient-reported outcome scores



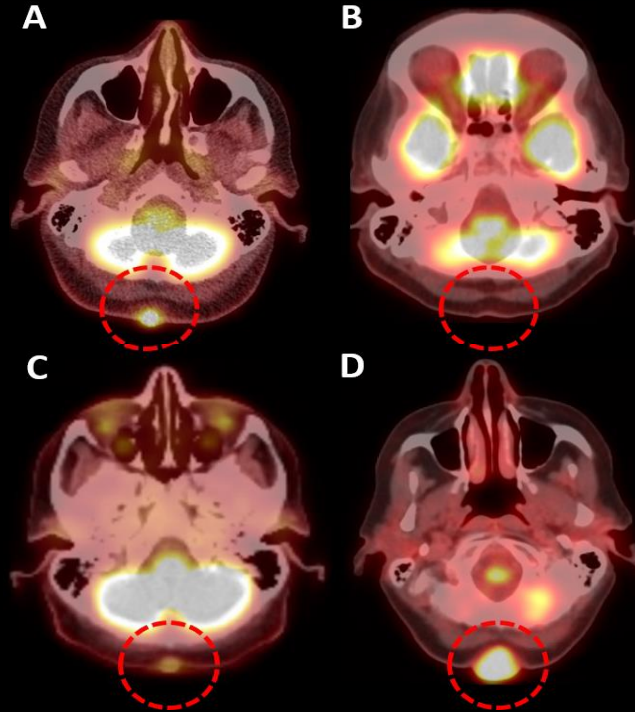
BRAF-mutated ATC after 4 weeks of dabrafenib/trametinib



Acquired resistance is the Achilles heel of kinase inhibitors

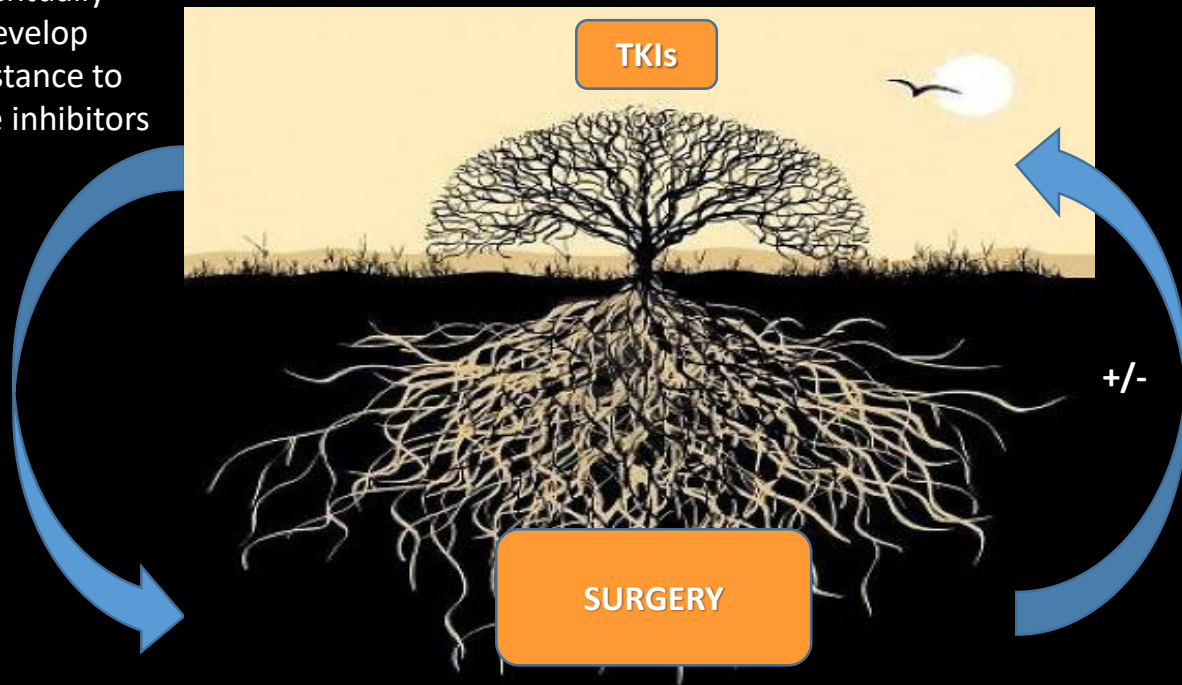


Acquired resistance is the Achilles heel of kinase inhibitors



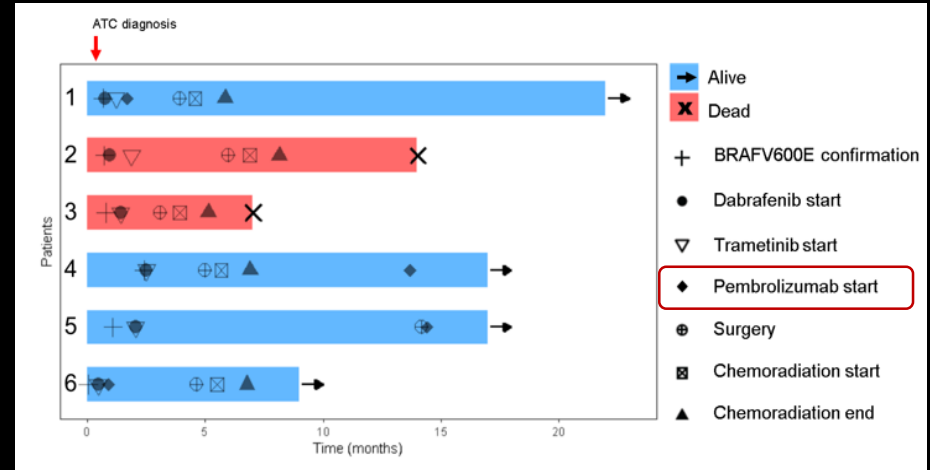
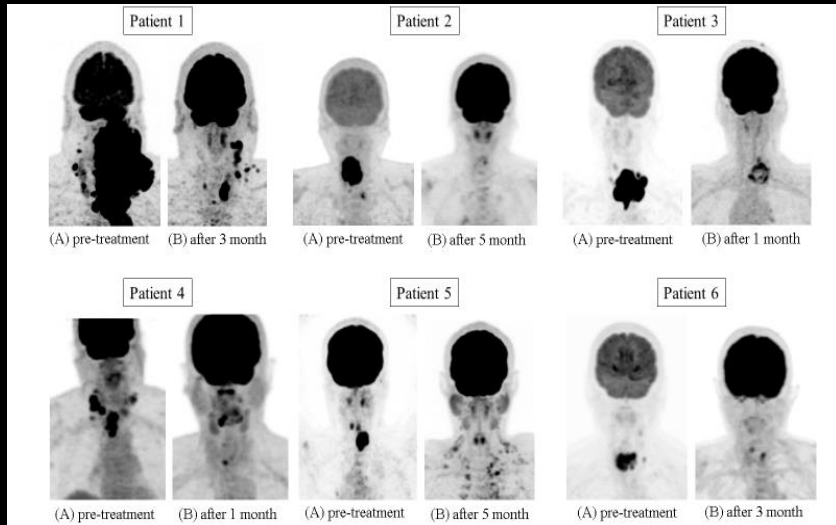
Neoadjuvant* BRAFi (MDA Standard of Care)

All patients eventually develop resistance to kinase inhibitors



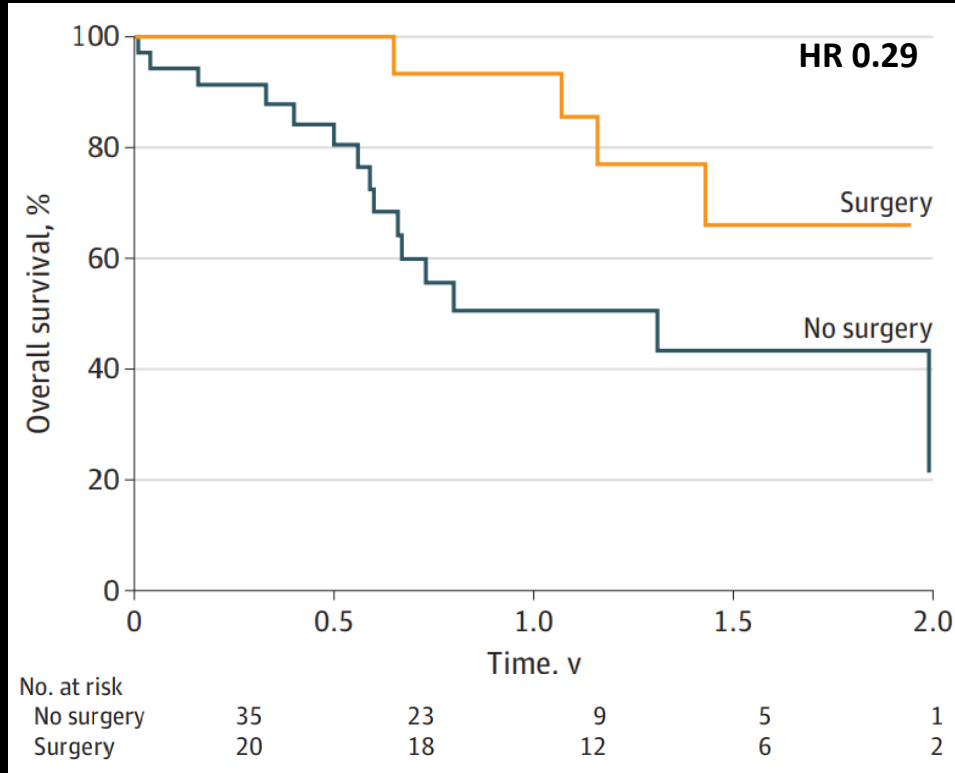
*The administration of a therapeutic agent(s) given as a first step to shrink a tumor before a surgical resection

Complete surgical resection following neoadjuvant dabrafenib plus trametinib in *BRAFV600E*-mutated ATC



- 6 inoperable ATC patients
- Utilization of dabrafenib with trametinib in a neoadjuvant setting facilitated surgical resection (+/- pembrolizumab)
- Median follow up time was 15.5 months; 12 month survival was 83.3%, 18 month survival 62.5% (only 2 patients have died)

Neoadjuvant therapy followed by surgery in $BRAF^{V600E+}$ patients (N=55)

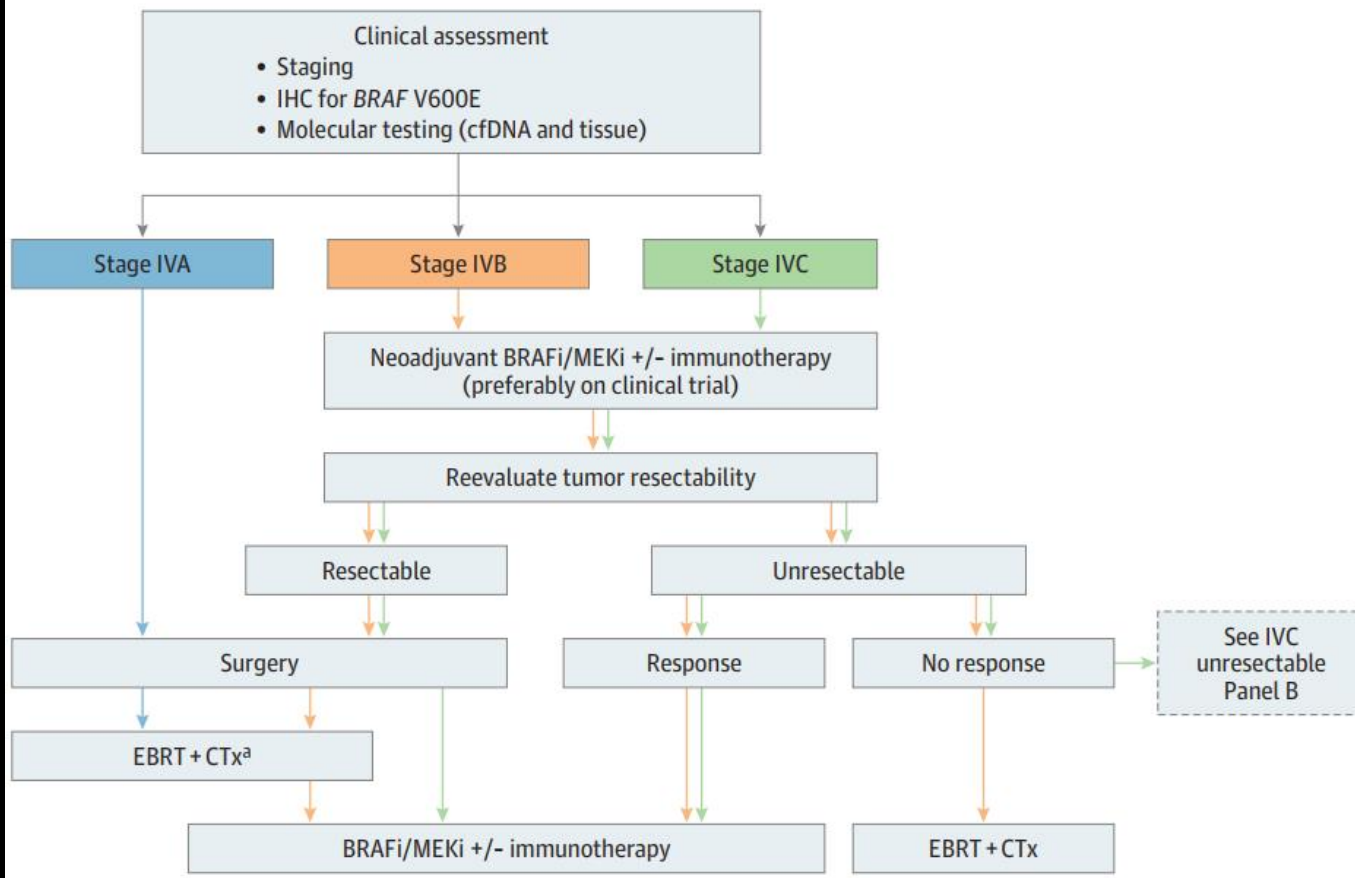


Median survival:

Surgery=not reached (1-year 94%)

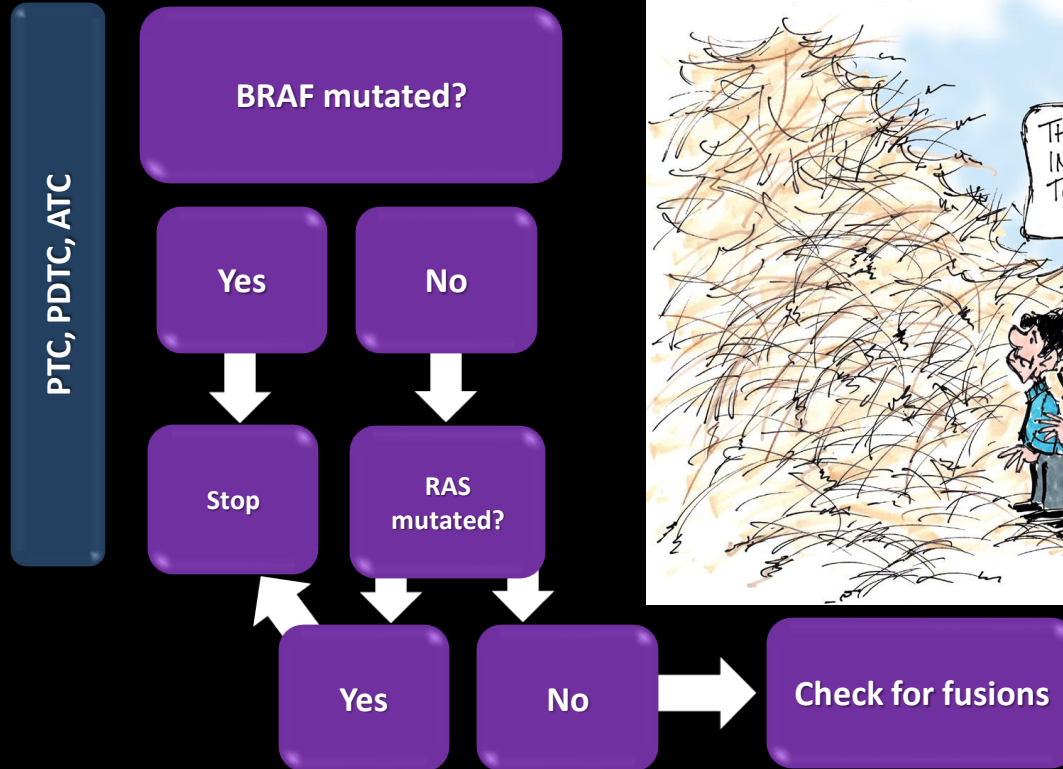
No surgery=0.8 years (1-year 52%)

A BRAF V600E variant ATC

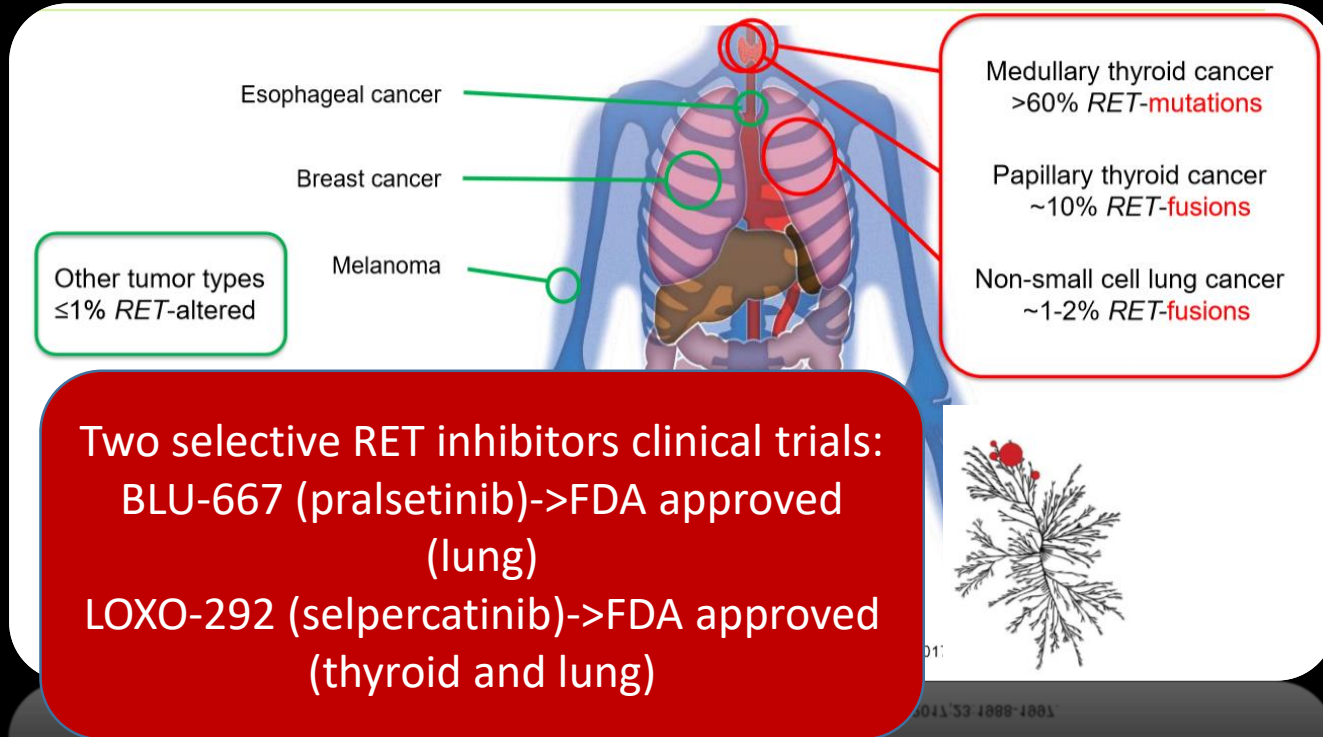


Non-BRAF mutated ATC

NTRK, ALK and RET fusions in PTC/ATC are Rare



RET is a driver in multiple cancers: mutations and fusions



Selpercatinib (LOXO-292) in *RET* fusion thyroid cancer

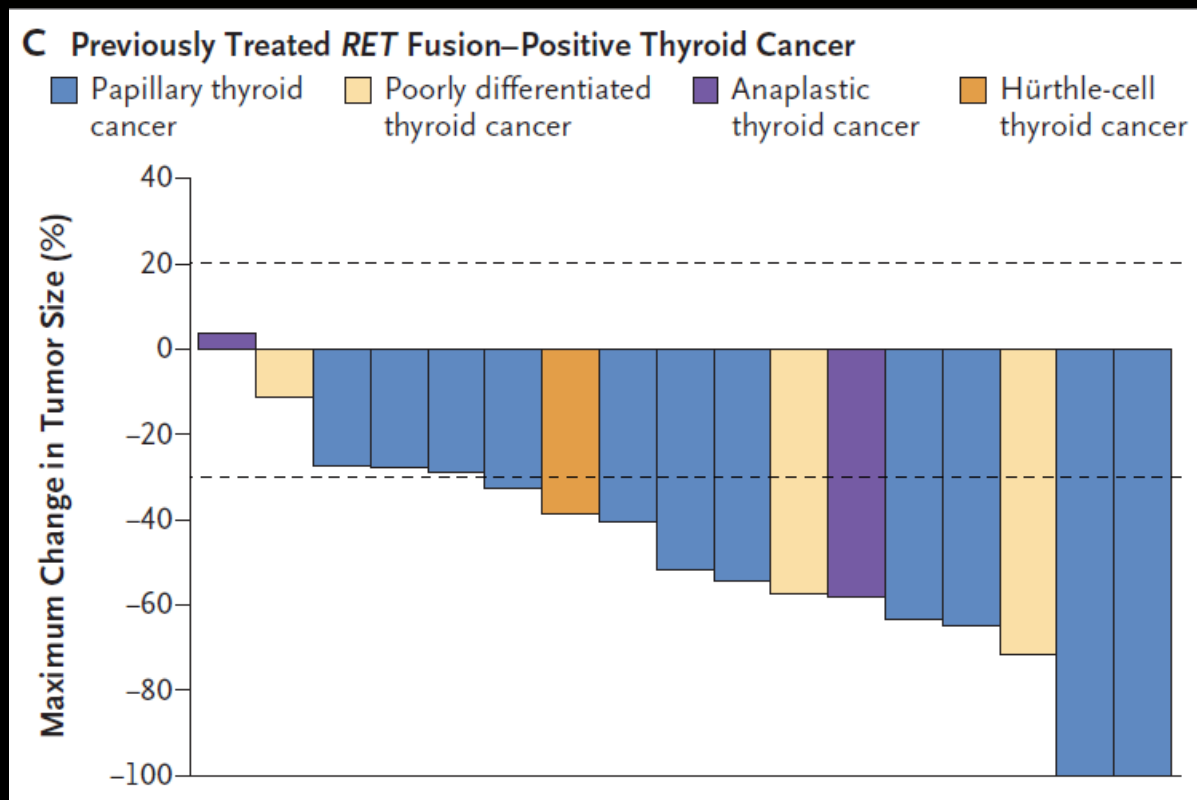
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Selpercatinib in *RET*-Altered Thyroid Cancers

L.J. Wirth, E. Sherman, B. Robinson, B. Solomon, H. Kang, J. Lorch, F. Worden,
M. Brose, J. Patel, S. Leboulleux, Y. Godbert, F. Barlesi, J.C. Morris,
T.K. Owonikoko, D.S.W. Tan, O. Gautschi, J. Weiss, C. de la Fouchardière,
M.E. Burkard, J. Laskin, M.H. Taylor, M. Kroiss, J. Medioni, J.W. Goldman,
T.M. Bauer, B. Levy, V.W. Zhu, N. Lakhani, V. Moreno, K. Ebata, M. Nguyen,
D. Heirich, E.Y. Zhu, X. Huang, L. Yang, J. Kherani, S.M. Rothenberg, A. Drilon,
V. Subbiah, M.H. Shah, and M.E. Cabanillas

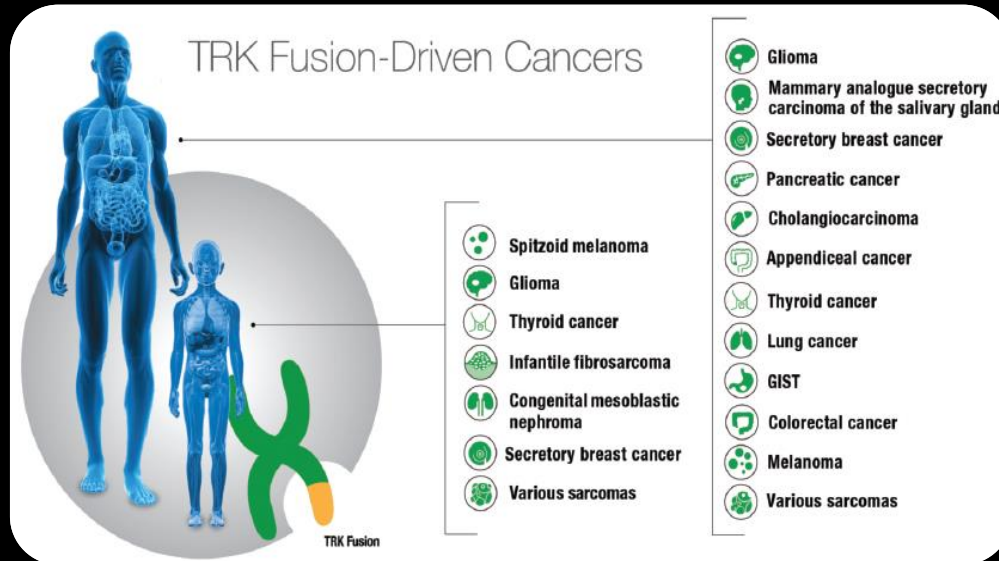
Selpercatinib in *RET* Fusion Thyroid Cancer



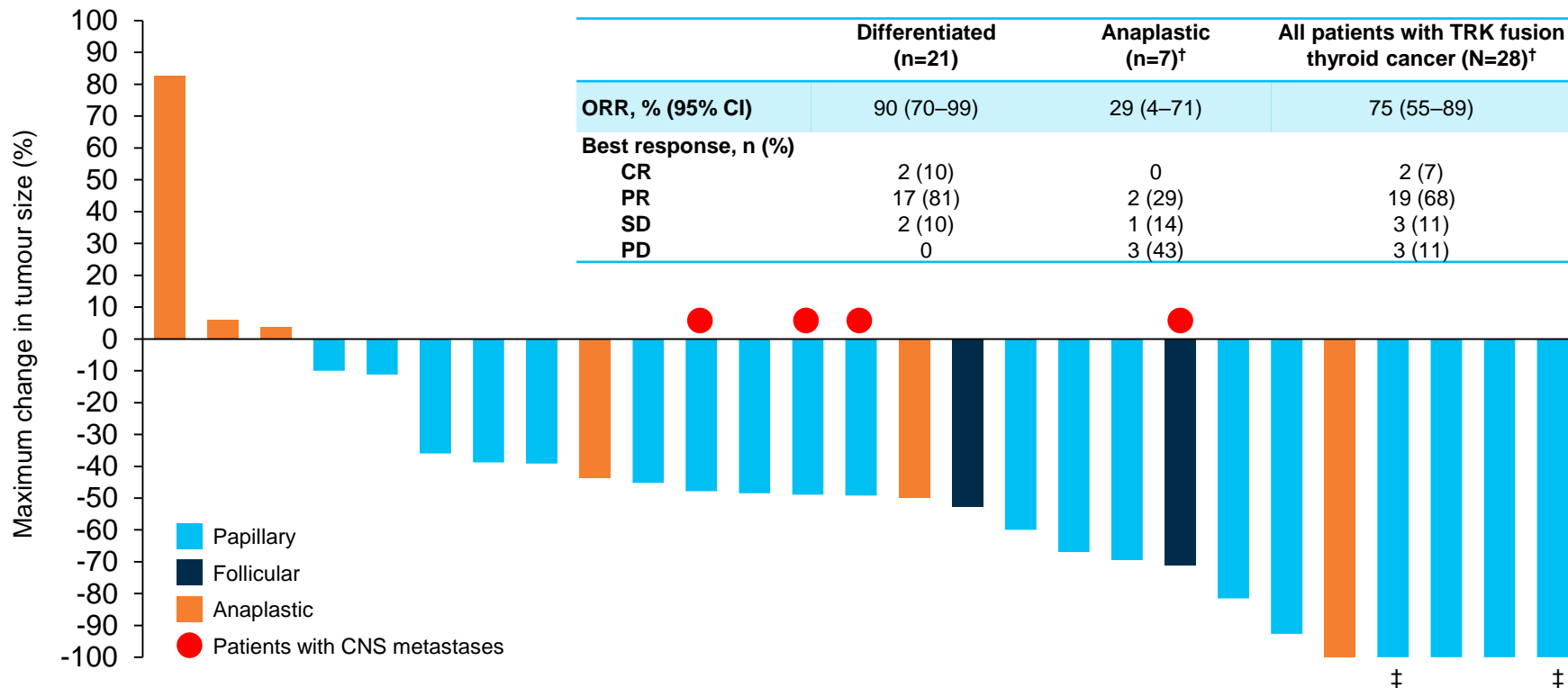
Of 2 patients with anaplastic thyroid cancer who were treated, 1 had a response for 18 months, with the response ongoing

NTRK fusions

- *NTRK* fusions are rare in PTC and very rare in ATC
- Entrectinib and larotrectinib are NTRK inhibitors (both are FDA approved—agnostic indication)



Best response to larotrectinib



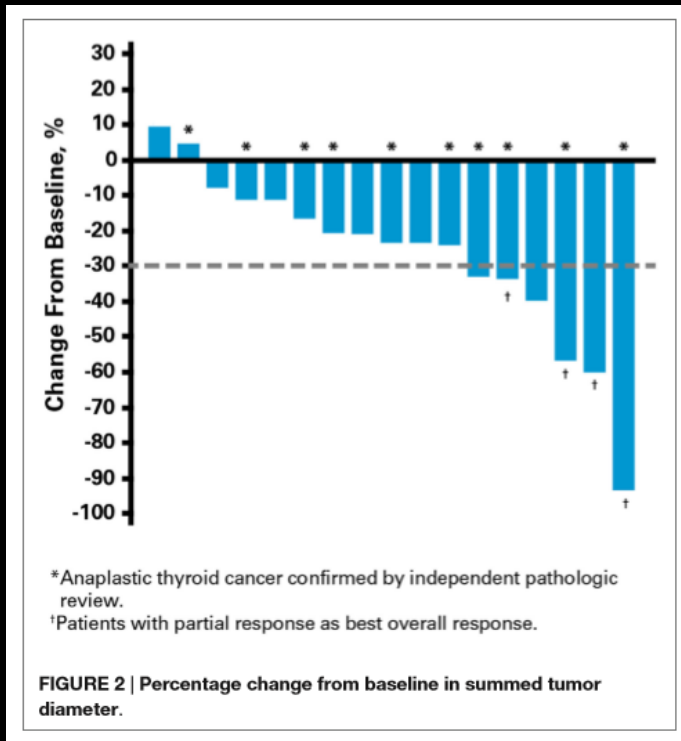
[†]One patient with anaplastic thyroid cancer had clinical disease progression prior to the first tumour response assessment. [‡]Paediatric patients (<18 years old).

CI, confidence interval; CNS, central nervous system; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TRK, tropomyosin receptor kinase.



Non-molecularly targeted
approaches

Lenvatinib Trial in ATC (Japan)



Tahara et al, 2017

ATC cohort (n=17)	
Median progression free survival (months)	7.4
Median overall survival (months)	10.6
Partial response (%)	4 (24%)
Stable disease (%) --all with regression	12 (71%)
Progression (%)	1 (6%)

Warning:

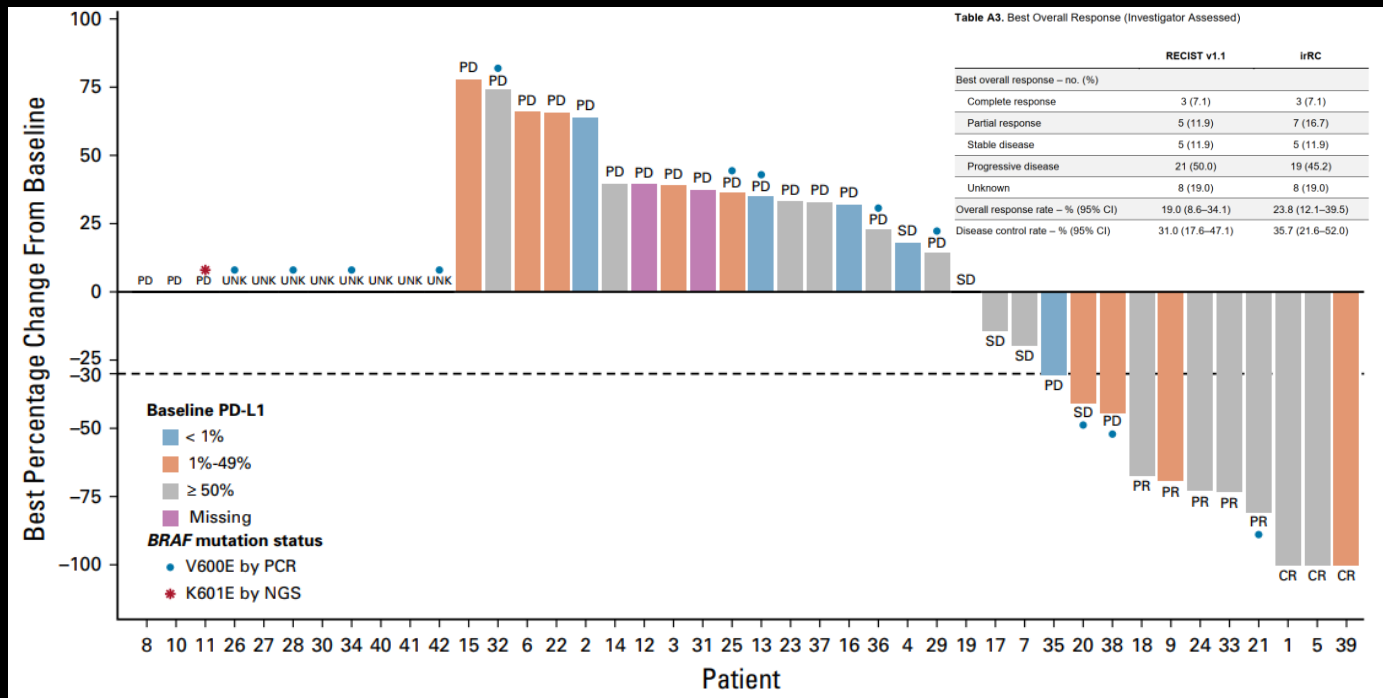
Lenvatinib in ATC trial in the U.S.: closed early due to futility (Endo 2020 abstract)

Beware of risk of bleeding/fistulas



Immunotherapy in Anaplastic Thyroid Cancer

Spartalizumab (anti-PD1/PD2) in ATC

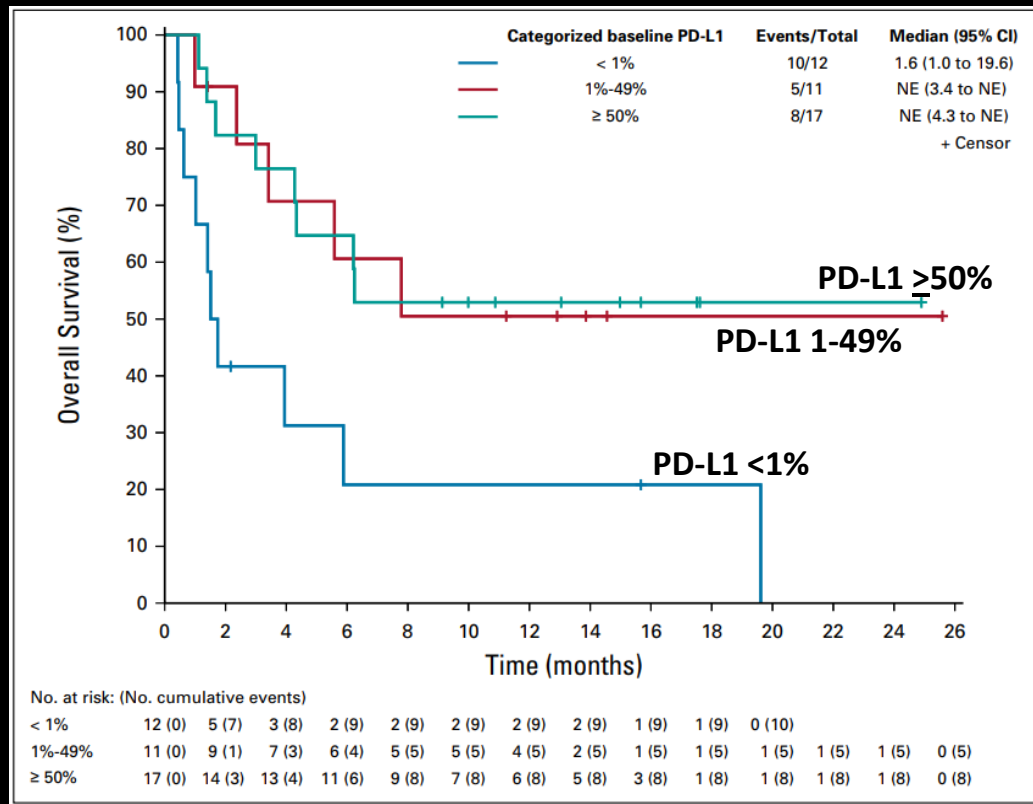


- 42 ATC patients
- Response rate was 19% (8/41) by RECIST 1.1 and 24% by irRC; 3 CRs
- Only one PR in BRAF mutated (8% response rate in BRAFV600E mutated)

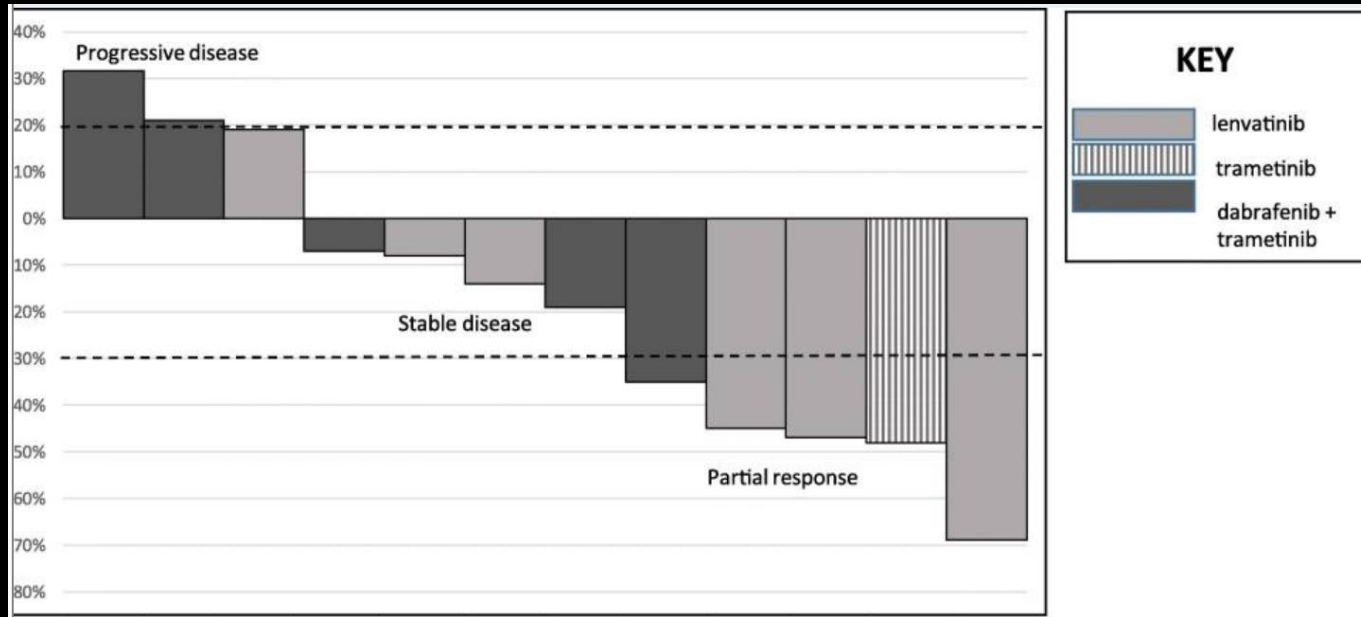
Spartalizumab (anti-PD1/2) in ATC

- Median PFS was 1.7 months
- Median OS was 5.9 months with 40% of patients alive at 1 year
- In patients with high PD-L1, 52% alive at 1 year (RR 29%)
- Median TMB was low at 3.78 mutations/Mb (range, 0-13.87 mutations/Mb)

Biomarker status	ORR – % (n/N) [95% CI]
PD-L1-positive cells by IHC	
<1%	0 (0/12) [0, 26.5]
1–49%	18.2 (2/11) [2.3, 51.8]
≥50%	35.3 (6/17) [14.2, 61.7]
Missing	0 (0/2) [0, 84.2]

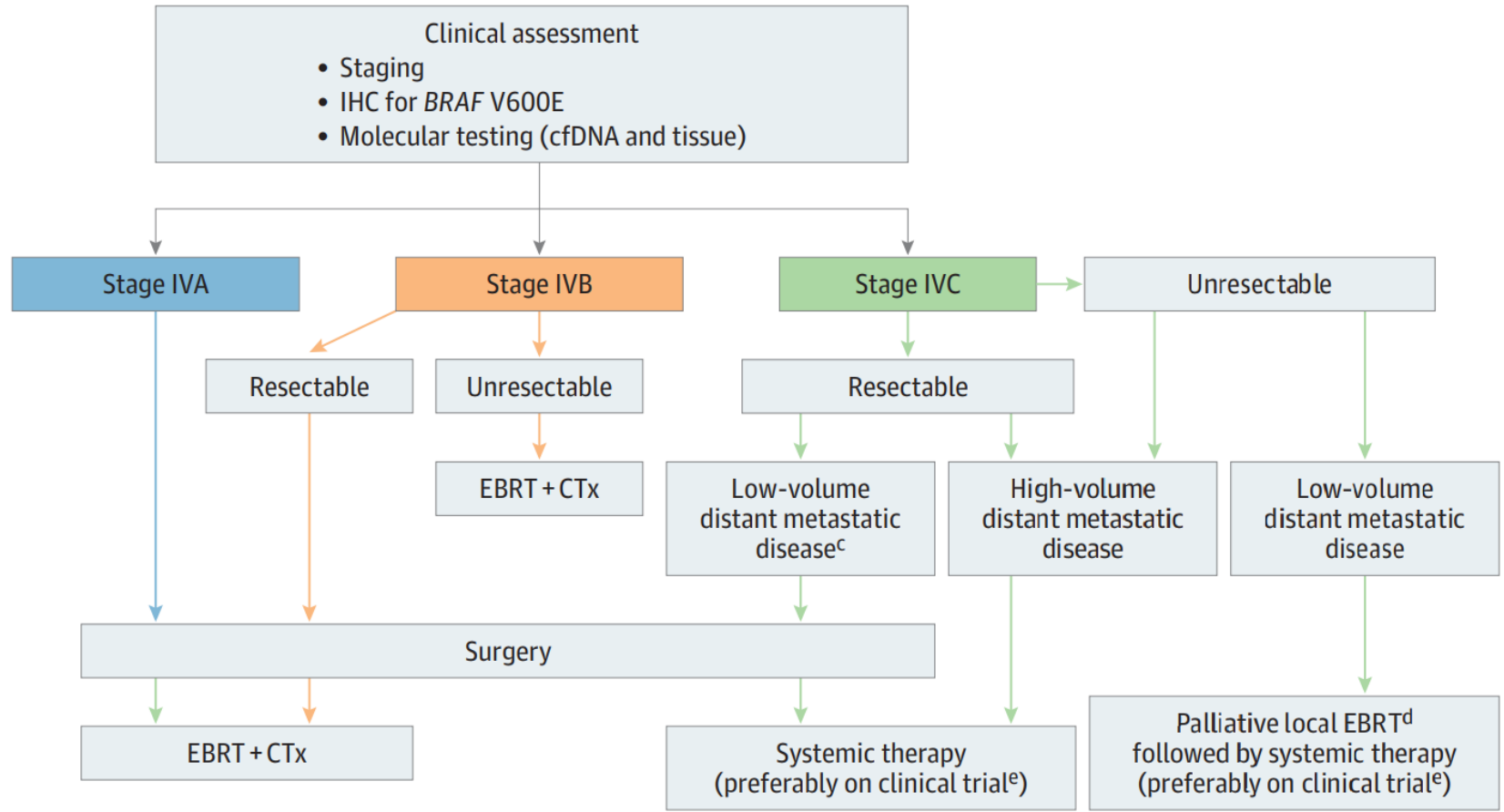


ATC: Addition of immunotherapy to targeted therapy (at progression)



partial response: 5/12 (42%)
stable disease: 4/12 (33%)
progressive disease 3/12 (25%)

B Non-*BRAF* V600E variant ATC and no actionable fusion^b



Summary

- Molecularly targeted therapy and immunotherapy (in PDL1 expressing) are efficacious in ATC
- Rapid evaluation of *BRAF* mutation status is critical to delivering treatment before patient is too ill
 - BRAF by IHC (should become standard pathology test for ATC)
 - Liquid biopsy
- Resistance to targeted therapy is inevitable, thus, when feasible, neoadjuvant approach is warranted
- Future work:
 - Adjuvant therapy (not discussed) to delay relapses and development of new distant metastasis after initial treatment in stage IVA/B patients
 - Better molecularly targeted therapy for non-BRAF/fusion ATC desperately needed
 - Professional guidelines to update and adopt some of the newer strategies for treatment (ATA guidelines forthcoming)

Thank you



Anaplastic Thyroid Cancer ("FAST") Team:
It takes a village!!