Advances in systemic treatment of thyroid cancer

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Head and Neck Symposium

4th November 2022

Systemic therapy in context

- Surgery mainstay of treatment
- +/- RAI, or EBRT (uncommonly)

- Small proportion develop incurable locally advanced or metastatic disease
- Prognosis after diagnosis of advanced disease can vary from weeks (anaplastic) to years (DTC/MTC)
- Goals of management
  - Manage symptoms of disease
  - Timing of interventions balanced against toxicity and likely rate of disease progression

Management strategies for of advanced thyroid cancer

- Depends on site of disease and symptoms
  - Surveillance
  - Localised therapy
    - Radiotherapy
    - Surgery (palliative eg symptomatic nodal disease, orthopaedic intervention)
  - Systemic therapy
    - Multi-kinase inhibitors (MKIs)
    - Targeted therapies (RET/NTRK inhibitors)
  - General supportive care
    - Analgesia
    - Anti-diarrhoea agents
    - Bisphosphonates/denosumab
    - Psychological support

Radioiodine refractory thyroid cancer

First line systemic therapy (radioiodine refractory DTC)

Lenvatinib – inhibitor of VEGFR, EGFR, PDGFRα, RET and KIT

Prolonged PFS 18.3 vs 3.6months, RR 65%, OS benefit in pts > 65yrs

Toxicity – **hypertension** (67%), diarrhoea (60%), fatigue (60%), anorexia/weight loss/nausea (40-50%), proteinuria (31%). Treatment discontinued in 14%

Oral administration - 24mg od

NICE approved 2018

SELECT trial

Lenvatinib vs placebo in radioiodine refractory thyroid cancer. *Schlumberger M et al. NEJM 2015; 372 621-630*

Sorafenib – inhibitor of VEGF, RET and RAF

Prolonged PFS 10.8 vs 5.8months, RR 12%

Toxicity – **hand/foot syndrome** (76%), diarrhoea (68%), alopecia (67%), rash or desquamation (50%), fatigue, hypertension (40%)

Oral administration – 400mg bd

NICE approved 2018

DECISION trial

Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial.
Brose MS, Nutting CM, Jarzab B et al. Lancet 2014;384:319-28

Second line option

Cabozantinib - inhibitor of MET, VEGF, RET, AXL, KIT, and FLT3

COSMIC-311 phase 3 study (cabozantinib vs placebo in patients with RAI refractory disease previously treated with lenvatinib or sorafenib)

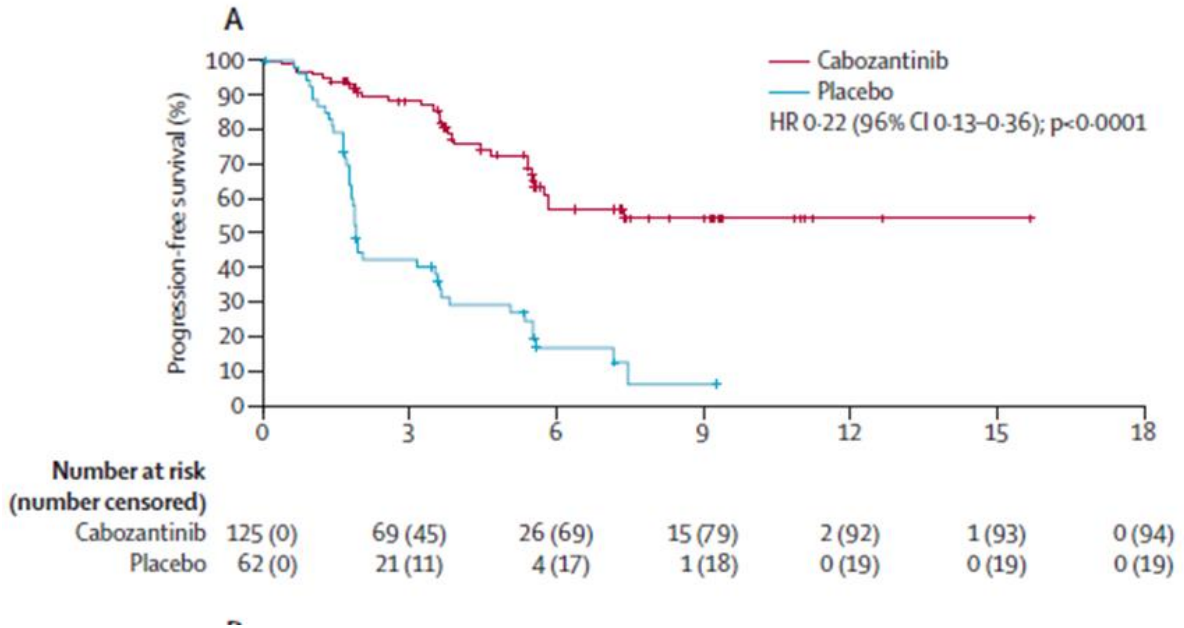
Interim analysis of PFS showed significant reduction in disease progression or death by 78% compared with placebo (HR 0.22, CI 0.13-0.36; p<0.0001)

Toxicity – treatment related adverse events of ≥ G3 in 62%, most commonly hypertension, hand and foot skin reaction, fatigue and diarrhoea

Treatment discontinued in 5%

Oral administration – 60mg od

Currently undergoing NICE appraisal for use in second line setting



Brose MSP, Robinson B, Sherman S et al. Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2021; 22: 1126–38

Medullary thyroid cancer

First line systemic therapy (MTC)

Cabozantinib – inhibitor of MET, VEGF, RET, AXL, KIT, and FLT3
Prolonged PFS 11.2 vs 4months, RR 30%
Toxicity – **diarrhoea** (63%), **hand foot syndrome** (50%), nausea (43%), fatigue (41%), hypertension (33%).
Treatment discontinued in 16%

Oral administration - 140mg od
NICE approved 2018

EXAM trial
Elisei R, Schlumberger MJ, Müller SP, Schöffski P, Brose MS, Shah MH, Licitra L, Jarzab B, Medvedev V, Kreissl MC, Niederle B, Cohen EE, Wirth LJ, Ali H, Hessel C, Yaron Y, Ball D, Nelkin B, Sherman SI. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol. 2013 Oct 10;31(29):3639-46.

Practical aspects of MKIs – starting treatment

- Timing
- Baseline investigations:
  - Blood pressure, ECG, consider echocardiogram
  - Review of concomitant medication (risk of QTc prolongation)
  - Bloods
  - Urinalysis for protein
  - CT brain, neck, thorax, abdomen, pelvis

- **Correct abnormalities prior to starting to avoid dose interruptions**

- Start at full dose

Practical aspects of MKIs – monitoring on treatment

- Pro-active identification and management of toxicity

- **Patients who have shorter dose interruptions gain more benefit than those with longer interruptions[1]**
  - Start anti-hypertensives early **(treatment emergent hypertension may predict improved outcomes)[2]**
  - Proteinuria (often associated with hypertension)
  - Skin – emollients, antibiotics if needed

- Radiological imaging after 3 cycles or sooner if not tolerating
- Monitor Tg or calcitonin
  - Changes in markers precedes morphological changes

1. Tahara M, Brose M, Wirth LJ et al. Impact of dose interruption on the efficacy of lenvatinib in a phase 3 study in patients with radioiodine-refractory differentiated thyroid cancer. European Journal of Cancer 2019; 106:61-68
2. Wirth LJ,Tahara M, Robinson B et al Treatment-Emergent Hypertension and Efficacy in the Phase 3 Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT). Cancer 2018; 12:2365-2372

Recent advances in systemic therapy (DTC and MTC)

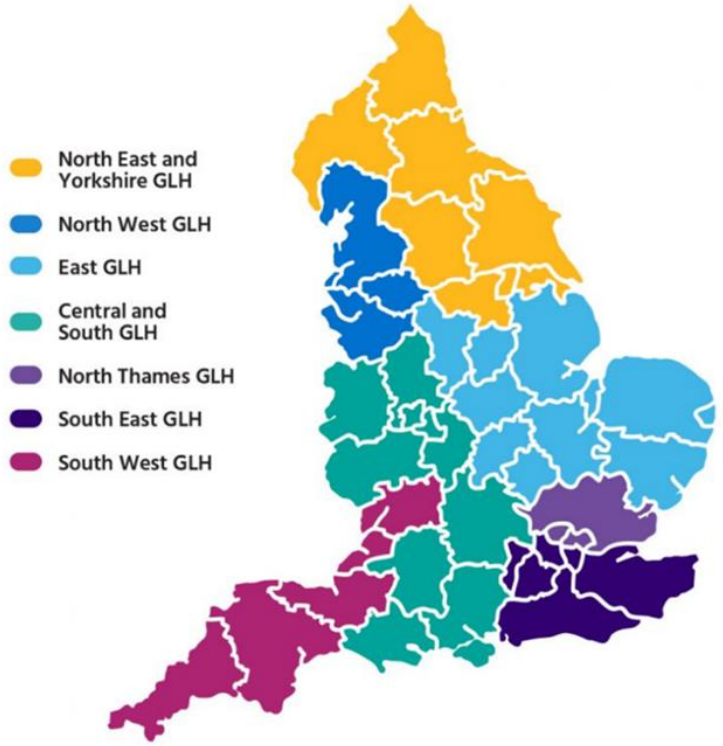
Newer developments – RET/NTRK inhibitors

Targeted treatment

- Some thyroid cancers harbour RET mutations/fusions or NTRK (Neurotrophin Tyrosine Receptor Kinase) fusions
- Oncogenic drivers – ie promote tumour growth/development
- Treatments available that specifically target cells with these alterations
- Currently reserved for second-line use in patients with confirmed gene alterations

Molecular testing

- Genomic Laboratory Hubs (7)
- Test tumour/biopsy for gene alterations
- Can use fresh or archived tissue
- Turnaround approx 2 weeks
- Similar service in Wales (All Wales Medical Genomics Service) and Scotland (Molecular Pathology Consortium)
- **Recommend testing at the point of diagnosis of advanced disease**



North East and Yorkshire GLH	Newcastle upon Tyne Hospitals NHS FT
North West GLH	Manchester University NHS FT
East GLH	Cambridge University Hospitals NHS FT
Central and South GLH	Birmingham Women's and Children NHS FT
North Thames GLH	Great Ormond Street Hospital for Children NHS FT
South East GLH	Guy's and St Thomas' NHS FT
South West GLH	North Bristol NHS Trust

RET alterations (DTC and MTC)

- Advanced RAI refractory DTC
  - 10-20% have RET fusion
- MTC
  - 75% sporadic – 50-60% have RET somatic mutation
  - 25% inherited – almost all have RET germline mutation

- RET specific inhibitors
  - Highly specific for RET
  - Less toxicity than MKIs due to less off-target effects (eg VEGF)

➢**Selpercatinib**
  - ➢Available in England via Cancer Drugs Fund in second line setting
  - ➢LIBRETTO-531 currently recruiting – first line for RET mutant MTC vs SOC

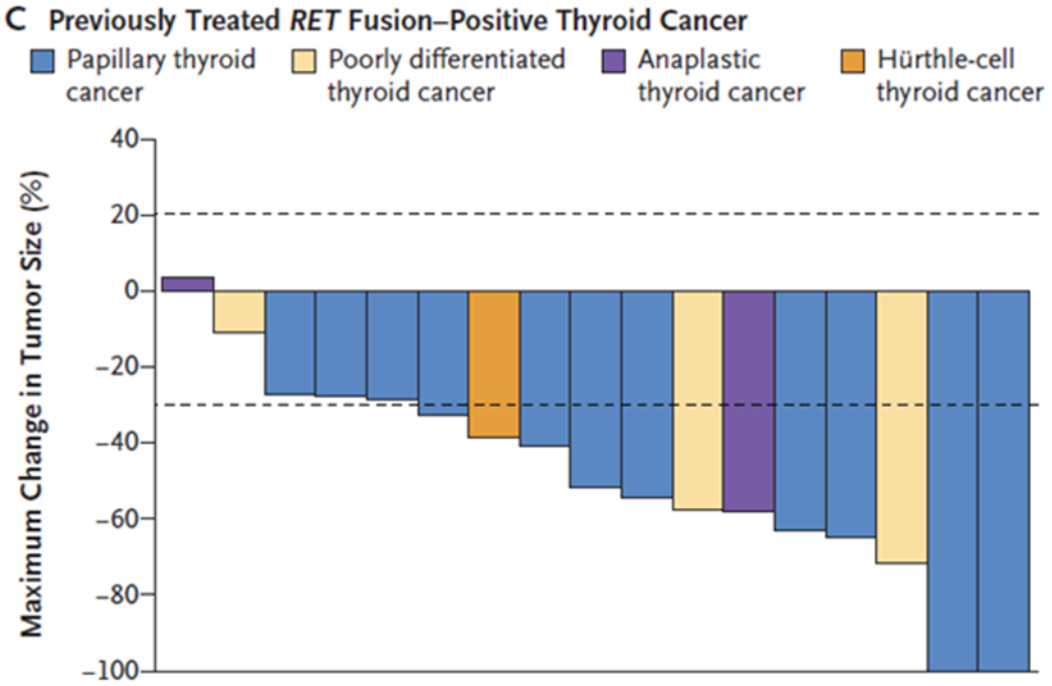
➢**Pralsetinib**
  - ➢Not currently licenced in UK

Selpercatinib

- LIBRETTO-001 phase I/II trial for patients with solid tumours with RET alterations, included 3 cohorts of thyroid cancer patients

	Previous treatment	Objective Response Rate	Patients progression free at 1 yr
MTC with RET mutation	Yes	69%	82%
	No	73%	92%
TC with RET fusion	Yes	79%	64%

- Toxicity – treatment related adverse events of ≥ G3 in 30%, most commonly hypertension and increase in ALT/AST. Treatment discontinued in 2%
- *Oral administration - 160mg bd or 120mg bd depending on body weight*
- *Available via CDF in England*
- Wirth LJ, Sherman E, Robinson B et al. Efficacy of selpercatinib in RET-altered thyroid cancers. N Engl J Med 2020; 383:825-35.



NTRK fusions (DTC)

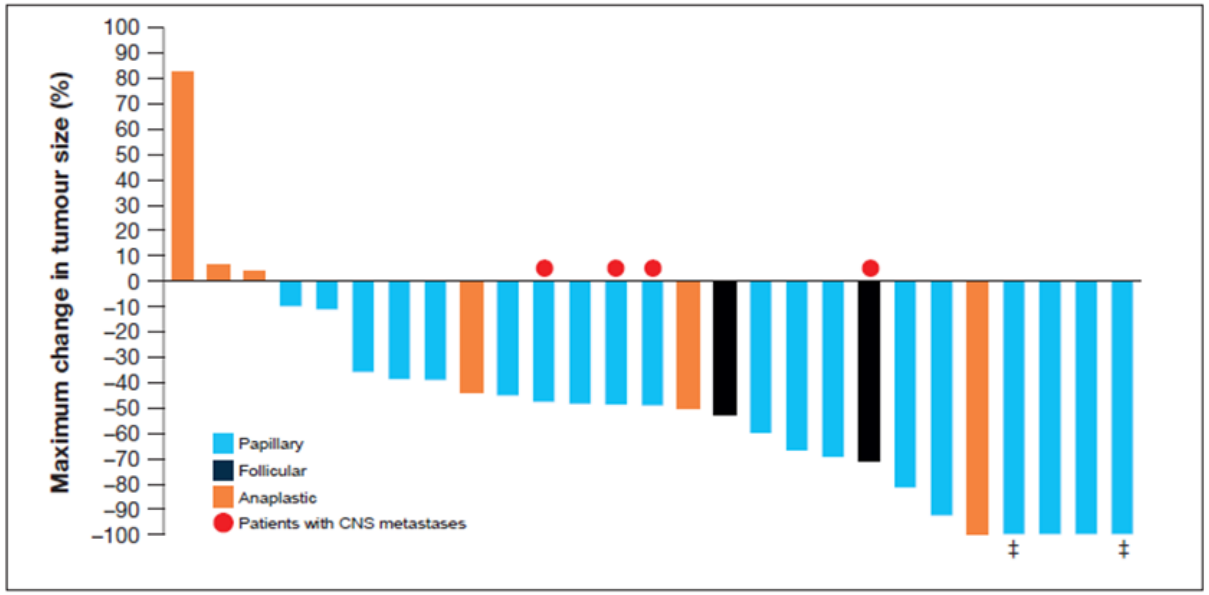
- Advanced RAI refractory DTC
  - 5-25% thyroid cancers have NTRK fusion

- NRTK inhibitors
  - NICE approved for patients who have no satisfactory alternative treatment options
  - ➢ **Larotrectinib**
  - ➢ **Entrectinib**

Larotrectinib

- 28 patients with NTRK fusion +ve thyroid cancer
- Overall response rate 75%
- *Responses seen in DTC but also ATC*
- PFS 86% (at 18 months)
- Toxicity mostly G1 or G2
- G3 toxicity in 32%
- Treatment discontinued 0%
- Raised liver enzymes, fatigue, constipation

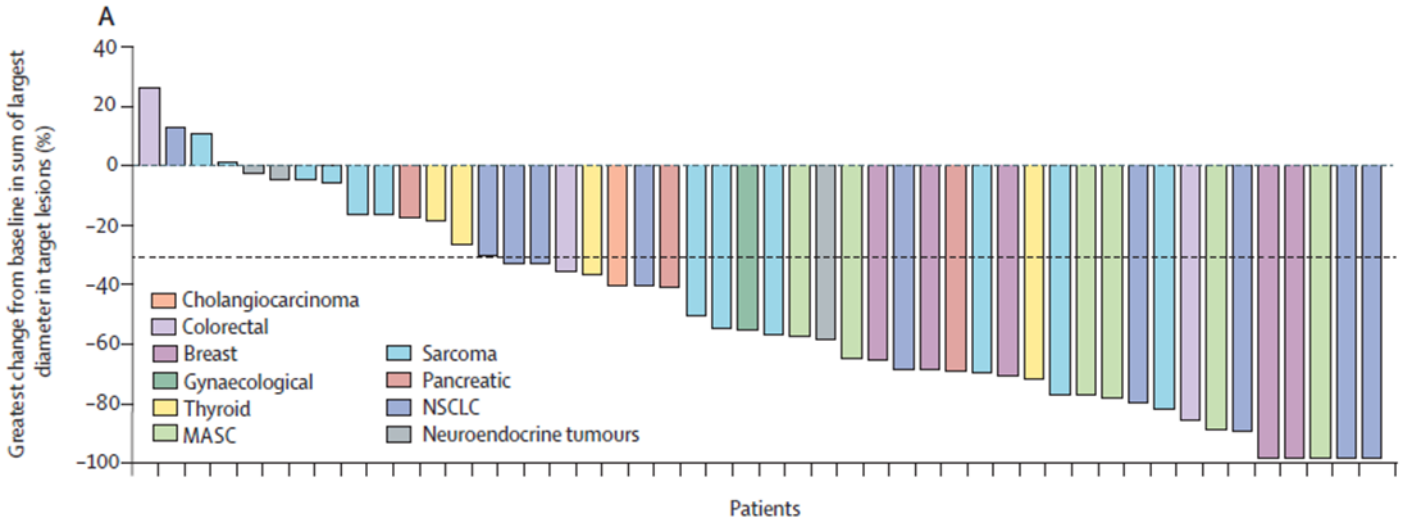
Figure 1. Best change in tumour size



Cabanillas ME, Drilon A, Farago AF et al. Larotrectinib treatment of advanced TRK fusion thyroid cancer. ESMO Virtual Congress 2020, 19–21 September 2020

Entrectinib

- Combined report of 3 phase 1 or 2 trials including 54 adults and children with solid tumours with NTRK fusions (including 5 patients with thyroid cancer)
- Overall response rate 57%
- Median duration of response 10 months
- Toxicity mostly G1 or G2
- Treatment discontinued in 4%



Doebele RC, Drilon A, Paz-Ares L et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials. Lancet Oncol 2020; 21: 271–82

Anaplastic thyroid cancer

Anaplastic thyroid cancer

- Very aggressive, often metastatic/inoperable at diagnosis
- Median survival around 7 months
- Historically limited options:
  - BSC
  - Pall chemo (eg Taxanes/Anthracyclines/Platinum)
  - Pall RT
- Mode of death often asphyxiation
- Needs early, open and frank discussions with patients and families to manage expectations and accommodate patient's wishes

New developments for ATC

- BRAF V600E mutation (reported in up to 20-50% ATC)
  Dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) combination

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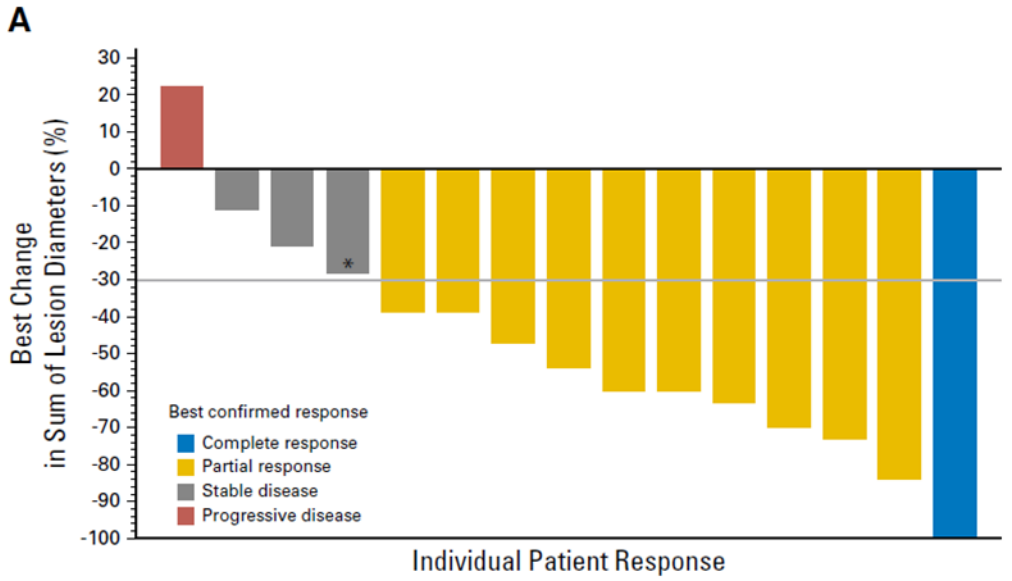
JOURNAL OF CLINICAL ONCOLOGY RAPID COMMUNICATION

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

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



- 16 patients
- Response rate 69%, often dramatic and rapid improvement
- Most common toxicities fatigue (44%), pyrexia (31%), nausea (31%)
- Events of ≥ G3 were seen in 42% patients

D&T in neoadjuvant setting

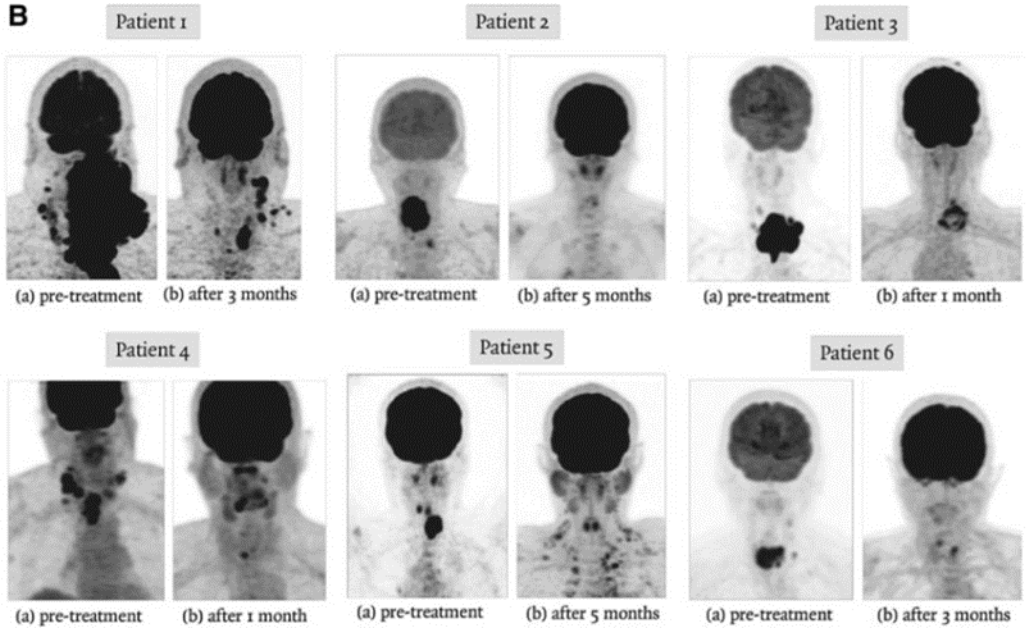
- 6 patients received D&T prior to surgery
- All 6 patients had complete resection of the thyroid tumour, and the resected specimens showed significant pathological response with reduction in ATC viability
- 2 patients died (8 and 14 months after diagnosis) from metastatic disease (no locoregional disease)
- The other 4 patients were alive and disease free at the time of last follow up (ranging from 12 to 26 months from diagnosis)
- Tumours develop resistance to the drugs, multimodality treatment is recommended

THYROID
Volume 29, Number 8, 2019
Mary Ann Liebert, Inc.
DOI: 10.1089/thy.2019.0133

SPECIAL ARTICLE

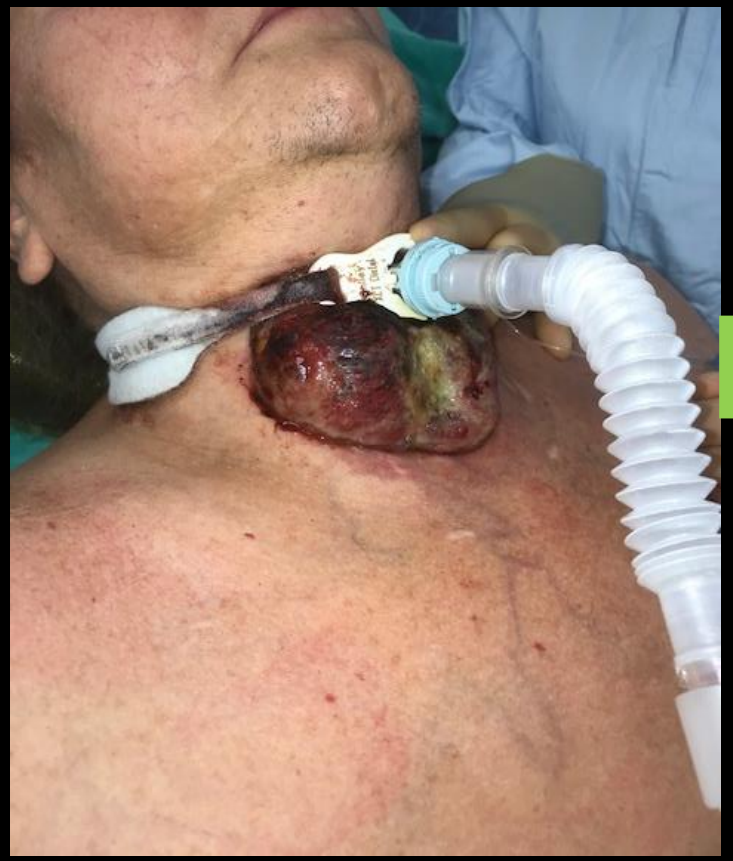
Complete Surgical Resection Following Neoadjuvant Dabrafenib Plus Trametinib in *BRAF*^{V600E}-Mutated Anaplastic Thyroid Carcinoma

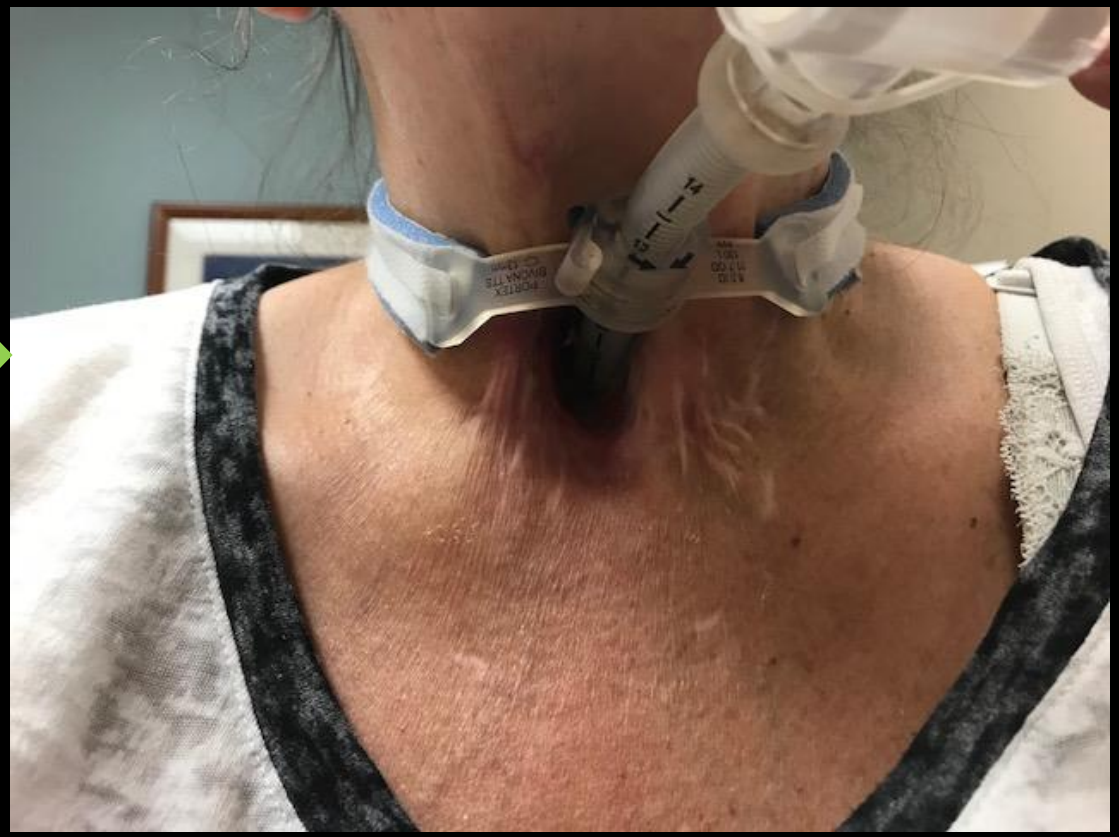
Jennifer R. Wang,[1,*] Mark E. Zafereo,[1,*] Ramona Dadu,[2] Renata Ferrarotto,[3] Naifa L. Busaidy,[2] Charles Lu,[3] Salmaan Ahmed,[4] Maria K. Gule-Monroe,[4] Michelle D. Williams,[5] Erich M. Sturgis,[1] Ryan P. Goepfert,[1] Neil D. Gross,[1] Stephen Y. Lai,[1,6] Gary Brandon Gunn,[6] Jack Phan,[6] David I. Rosenthal,[6] Clifton David Fuller,[6] William H. Morrison,[6] Priyanka Iyer,[2,7] and Maria E. Cabanillas[2]



Greater Manchester Cancer

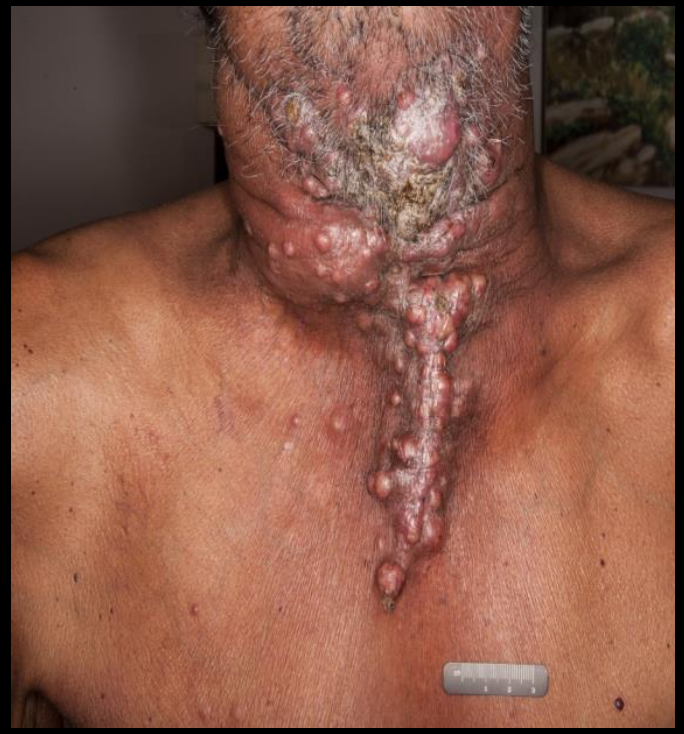
BRAF-mutated ATC after 4 weeks of dabrafenib/trametinib



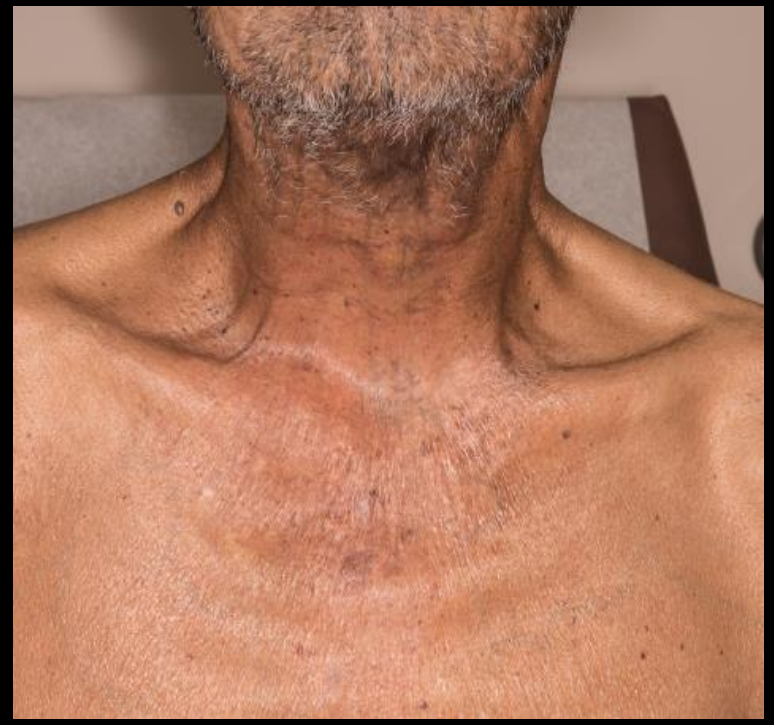


Courtesy of Prof Maria Cabanillas, MD Anderson

68 y/o BRAF V600E mutated ATC patient treated with dabrafenib + trametinib



Before treatment



5 weeks later

Courtesy of Prof Maria Cabanillas, MD Anderson

Dabrafenib and Trametinib in UK

- Oct 2022 – new NHSE clinical commissioning policy
  - Inoperable and/or metastatic
  - BRAF V600E mutation present
  - ECOG PS 0-2
- Need confirmation of BRAF V600E mutation – quickly
- UK outcome data collected from treated patients and accepted for publication
- Don’t forget iNATT, all patients with ATC can consent

iNATT

The *inter***N**ational **A**naplastic **T**hyroid Cancer **T**issue Bank and Database Project (***i*NATT**)

Summary

- Advanced/metastatic radioiodine refractory DTC and MTC
  - Period of surveillance often appropriate
  - Manage expectations and anxiety
  - Systemic therapy options available for progressive disease (MKI's, RET inhibitors, NTRK inhibitors)

- ATC
  - Needs quick decision re active treatment vs BSC
  - Prospect of longer term survival with targeted treatment for selected patients
  - Need fast confirmation of BRAF mutation status

Summary of systemic treatment options

	DTC		MTC		ATC	
1st line	Lenvatinib or Sorafenib		Cabozantinib		BRAF mutant D&T	BRAF wild-type Pall chemo
2nd line	*Cabozantinib*					
2nd line	RET fusion+ Selpercatinib	NTRK fusion+ Larotrectinib or Entrectinib	RET+ Selpercatinib	RET-		

Questions?