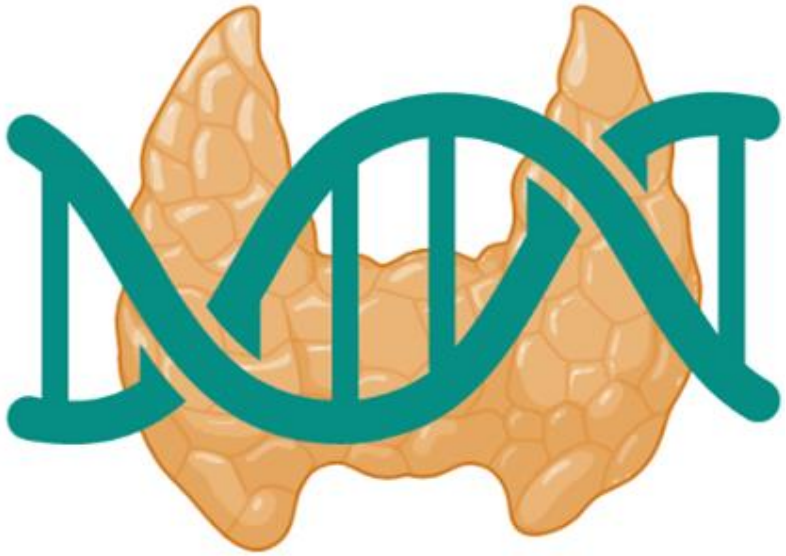
FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI



Studio del profilo molecolare del carcinoma tiroideo: perché farlo?

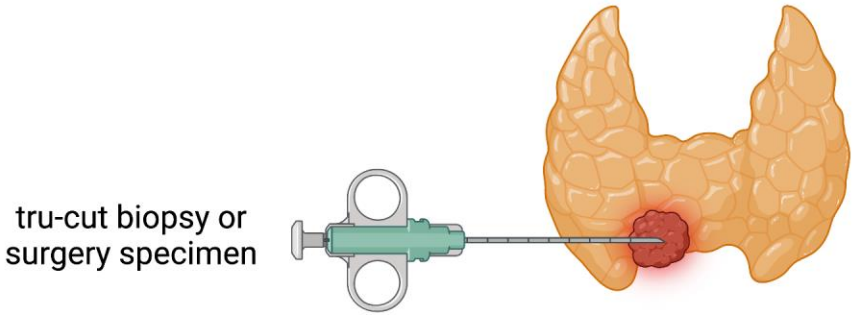
Elena Colombo
S.C. Oncologia Medica 3 – Tumori di Testa e Collo
Molecular Tumor Board
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano

Disclosures

I have no potential conflicts of interest to report

Outline

1. Molecular profiling of Thyroid Carcinoma: optional or necessary?
2. International Guidelines and the Atlantic gap
3. From theory to reality: the experience of TC profiling at INT
4. Future directions

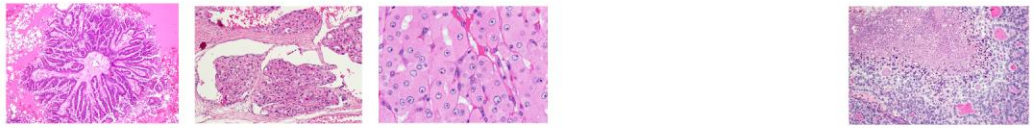


♀ 10/100.000

♂ 3/100.000

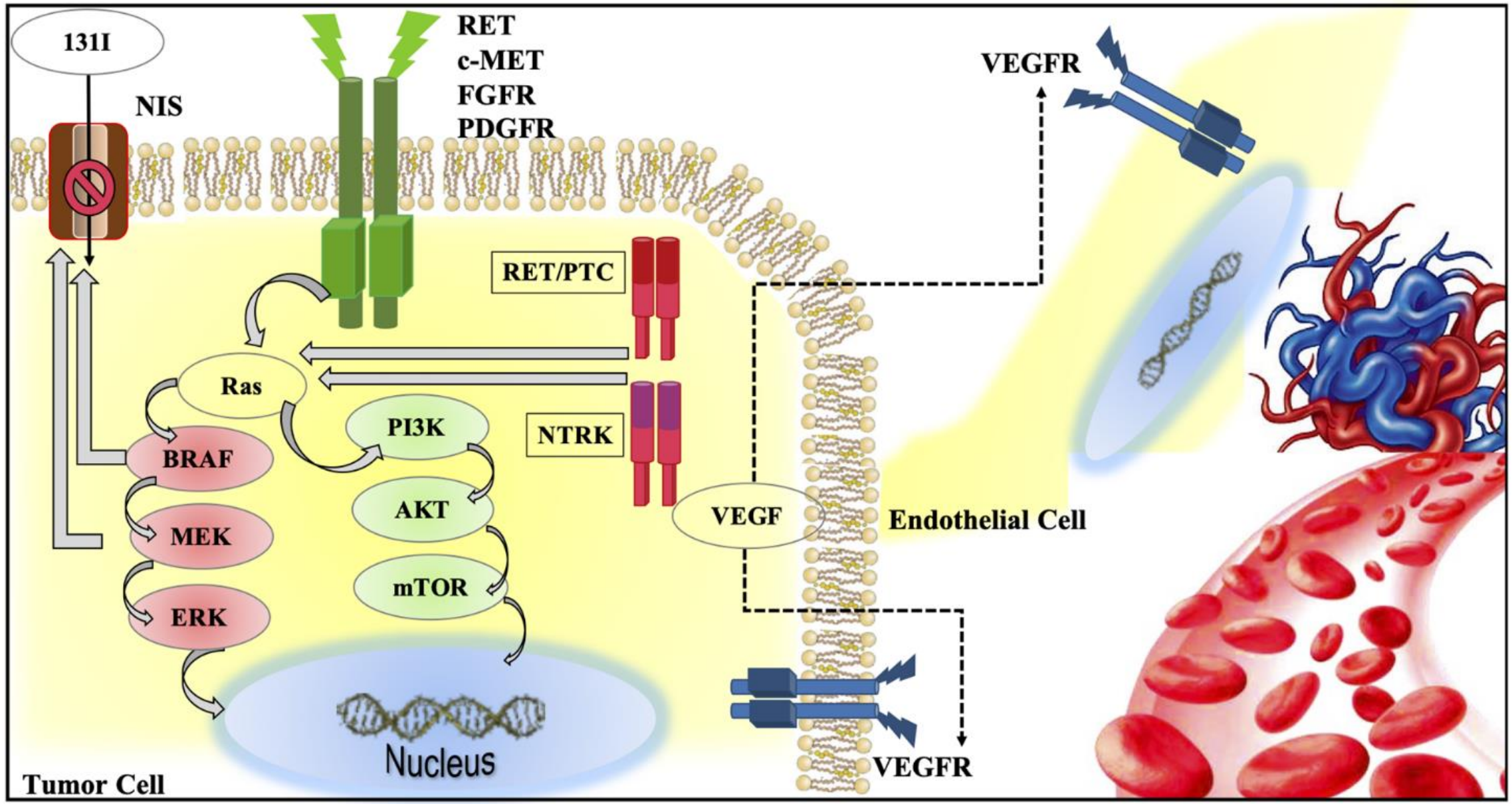
Thyroid Cancers (TC) from the follicular cells/thyreocytes

differentiation



Papillary PTC >80%	Follicular FTC 10%	Oncocytic OTC 4%	Poorly Differentiated PDTC 3-5%	Anaplastic ATC 2%
Radioiodine therapy Multikinase inhibitors: Lenvatinib (SSN), Cabozantinib (L.648/96)				Taxane-based chemo
BRAF *NTRK* *RET* *ALK*	NRAS HRAS KRAS PIK3CA	RAS CDKN2A	RAS BRAF TMB-H *NTRK, RET*	BRAF RAS TMB-H *ALK* *NTRK*
selective RET inhibitors Selpercatinib	**NTRK inhibitors** Entrectinib Larotrectinib	**BRAF/MEK inhibitors** Dabrafenib/ Trametinib	**Immunotherapy** for TMB-H solid tumors	**Clinical Trials**

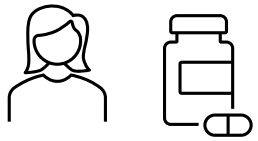
Colombo E., created with BioRender



Lorusso L. et al, *Int. J. Mol. Sci.* 2021

Valid reasons to offer molecular profiling of TC

PATIENT

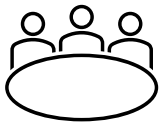


- ✓ Performance status
- ✓ Swallowing function/gastrostomy
- ✓ Clinical trials feasibility
- ✓ Contraindications to VEGFi
- ✓ Intolerance to VEGFi
- ✓ Failure to VEGFi

HYSTOLOGY

- ✓ Anaplastic TC (BRAF)
- ✓ Papillary TC
- ✓ PDTC, Oncocytic TC, FTC

SETTING



- ✓ Advanced R/M **ATC**
- ✓ Advanced R/M **RAIR DTC**
- ✓ Borderline resectable **ATC** (U.S.A.)
- ✓ Re-biopsy after targeted therapy

Expand the therapeutic options with targeted therapy/immunotherapy

Multidisciplinary Team ⟷ **Molecular Tumor Board**

International Guidelines: Europe

ESCAT = systematic framework to rank molecular targets based on evidence available supporting their value as clinical targets

SPECIAL ARTICLE *Annals of Oncology*, 2022

ESMO Clinical Practice Guideline update on the use of systemic therapy in advanced thyroid cancer

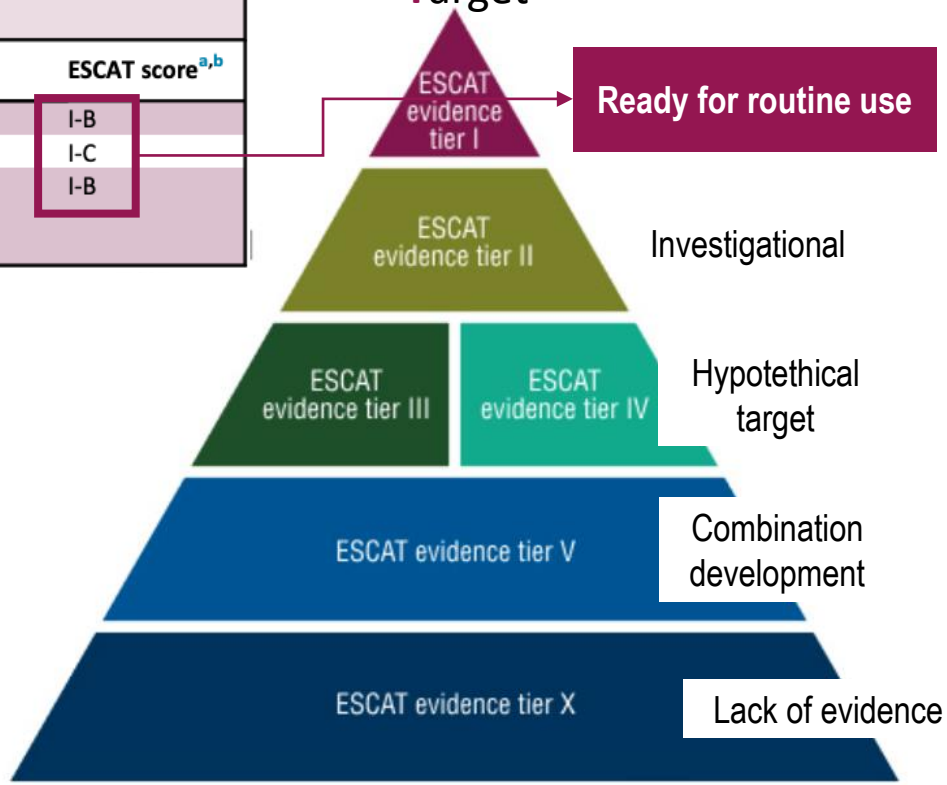
S. Filetti[1], C. Durante[2], D. M. Hartl[3,4], S. Leboulleux[5,6], L. D. Locati[7,8], K. Newbold[9], M. G. Papotti[10] & A. Berruti[11], on behalf of the ESMO Guidelines Committee[*]

Table 9. Biomarkers and molecular targets for precision medicines and corresponding ESCAT scores

Biomarker or genomic alteration	Method of detection	Drug match	ESCAT score[a,b]
BRAF mutations[23,24]	Sanger sequencing or NGS	*BRAF* inhibitors (e.g. dabrafenib)	I-B
NTRK fusions[12,13]	Sanger sequencing or NGS	*NTRK* inhibitors (e.g. entrectinib, larotrectinib)	I-C
RET mutations in medullary thyroid cancer and RET fusions in thyroid cancers[9,11]	Sanger sequencing or NGS	*RET* inhibitors (e.g. pralsetinib, selpercatinib)	I-B

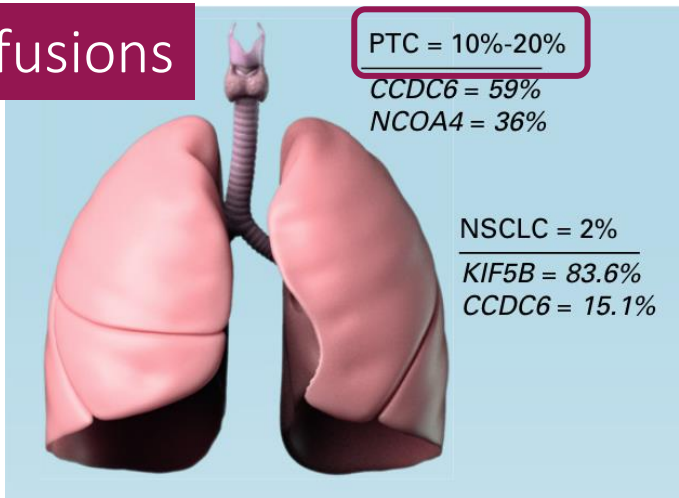
ESCAT evidence tier	Required level of evidence	Clinical value class	Clinical implication
I: Alteration-drug match is associated with improved outcome in clinical trials	I-A: prospective, randomised clinical trials show the alteration-drug match in a specific tumour type results in a clinically meaningful improvement of a survival end point	Drug administered to patients with the specific molecular alteration has led to improved clinical outcome in prospective clinical trial(s)	Access to the treatment should be considered standard of care
	I-B: prospective, non-randomised clinical trials show that the alteration-drug match in a specific tumour type, results in clinically meaningful benefit as defined by ESMO MCBS 1.1		
	I-C: clinical trials across tumour types or basket clinical trials show clinical benefit associated with the alteration-drug match, with similar benefit observed across tumour types		

ESMO
Scale of
Clinical
Actionability of molecular
Target



Response and survival benefit for patients with actionable TC

RET fusions

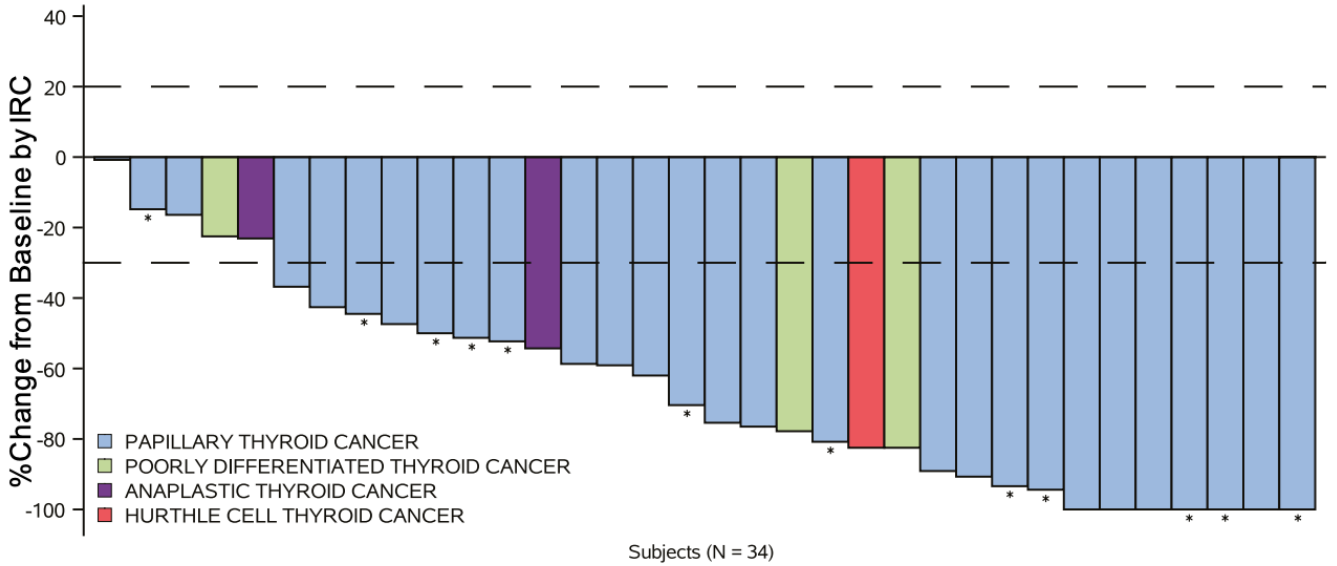


Phase 1/2 **LIBRETTO-001 trial (Cohort 1)**

- N=42 pts with R/M **RET fusion-positive** TC
  - N=22 pre-treated with MKI (>1L)
  - N=12 MKI-naïve (1L)
- **Selpercatinib** 160 mg orally twice daily
- Median follow-up of **20.3** months

Sherman et al, *#6073 ASCO* 2021

	>1L	1L
ORR (%)	**77**	**92**
CR (%)	9	33
PR (%)	68	58
mDoR (months)	18 (10-NE)	NE (15 – NE)
1-yr PFS (%)	69	100



Response and survival benefit for patients with actionable TC

NTRK fusions

prevalence of NTRK fusion?

Phase 1/2 single arm trials (STARTRK-1/2 + 5) pooled analysis

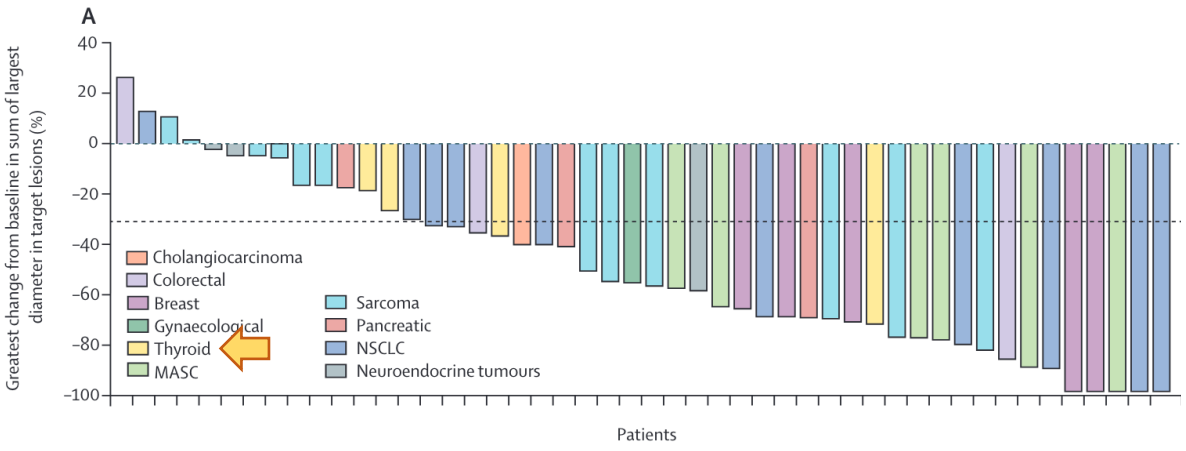
- **Entrectinib** 600 mg orally daily (single arm trials)
- **ORR** = **57%**
- **Median DoR** = **10.4** months
- **Median PFS** = **11** months

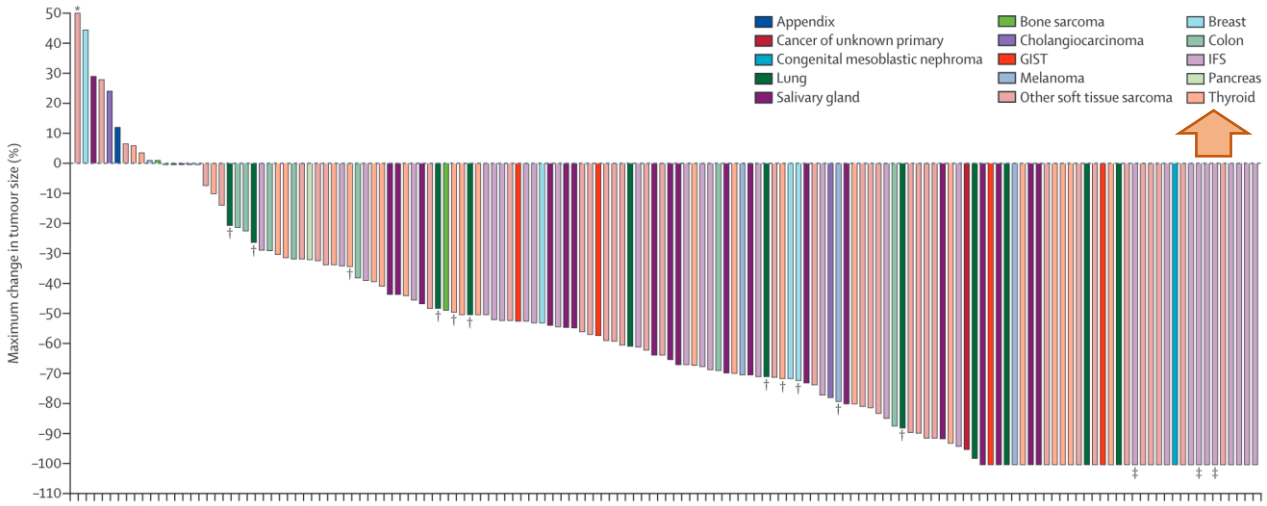
Doebele et al, *Lancet Oncology* 2020

Phase 1/2 single arm **trials** (SCOUT, NAVIGATE + 3) pooled analysis

- **Larotrectinib** 100 mg orally twice daily
- **ORR** = **79%**
- **Median DoR** = **35.2** months
- **Median PFS** = **28.3** months

Hong DS et al, *Lancet Oncology* 2020



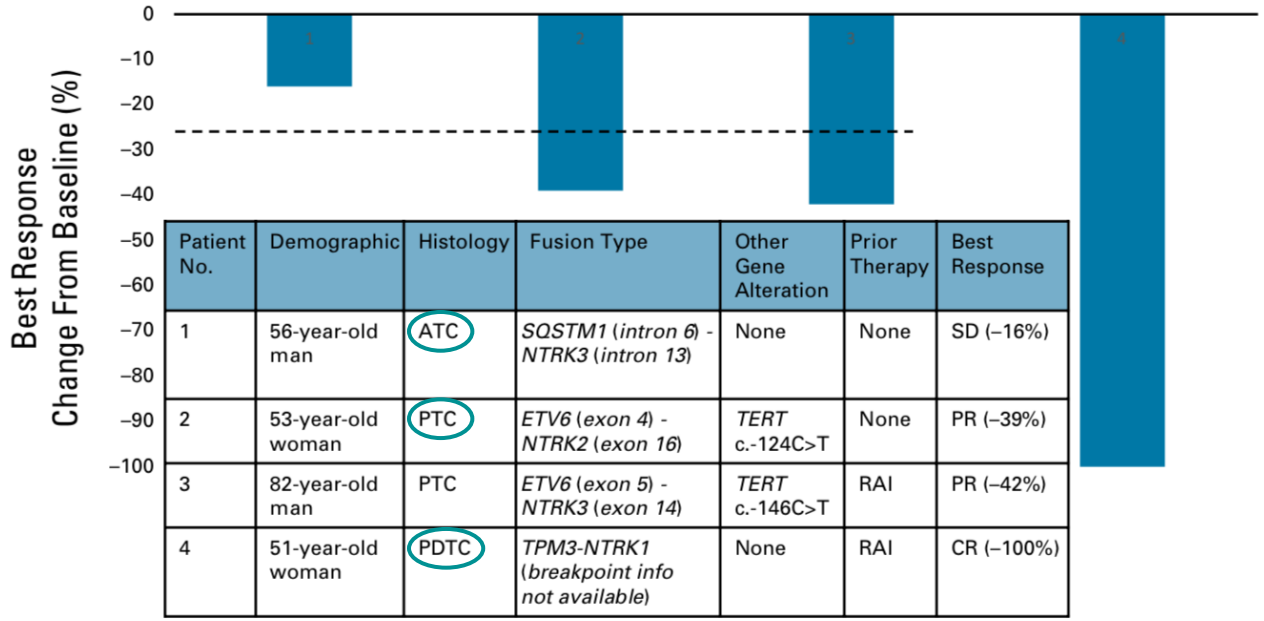


NTRK fusions

Real-World Experience of *NTRK* Fusion–Positive Thyroid Cancer

Jong Chul Park, MD[1]; Arya Ashok, PhD[2]; Chienying Liu, MD[3]; and Hyunseok Kang, MD, MPH[3]

JCO Precis Oncol 6:e2100442. © 2022 by American Society of Clinical Oncology



Patient No.	Demographic	Histology	Fusion Type	Other Gene Alteration	Prior Therapy	Best Response
1	56-year-old man	ATC	*SQSTM1 (intron 6) - NTRK3 (intron 13)*	None	None	SD (−16%)
2	53-year-old woman	PTC	*ETV6 (exon 4) - NTRK2 (exon 16)*	*TERT* c.-124C>T	None	PR (−39%)
3	82-year-old man	PTC	*ETV6 (exon 5) - NTRK3 (exon 14)*	*TERT* c.-146C>T	RAI	PR (−42%)
4	51-year-old woman	PDTC	*TPM3-NTRK1 (breakpoint info not available)*	None	RAI	CR (−100%)

FIG 1. Baseline clinicopathologic characteristics of four patients with *NTRK* fusion harboring thyroid cancer who were treated with larotrectinib, and waterfall plot for best response. ATC, anaplastic thyroid cancer; CR, complete response; PDTC, poorly differentiated thyroid cancer; PR, partial response; PTC, papillary thyroid cancer; RAI, radioactive iodine; SD, stable disease.

Types and frequencies of NTRK gene alterations

- **2.362** TC specimens identified in 3 U.S.A. databases (the AACR Genie, TCGA and Tempus)
- **51 patients** (2.2%) with NTRK1/NTRK3 fusion
- No NTRK2 fusions identified

- **10 different 5' fusion partner genes identified. Most frequent fusions:**
  - 43% ETV6-NTRK3
  - 18% TPM3-NTRK1
  - 14% TPR-NTRK1

- **Most frequent coalterations found**
  - **29%** pTERT mutation
  - **8%** TP53 mutation

NTRK fusions

Article

NTRK Fusion Genes in Thyroid Carcinomas: Clinicopathological Characteristics and Their Impacts on Prognosis

Pekova B et al, *Cancers*, 2021

- **259** thyroid tissue samples analysed: 205 PTCs, 16 sporadic MTCs, 13 FTCs, 9 ATCs, 6 PDTCs, and 10 HCCs
- **Samples positive for the *BRAF*, *HRAS*, *KRAS*, *NRAS*, *RET*, *RET/PTC* or *PAX8/PPARg* mutation were excluded from the further analyses**; samples with *TERT* or *TP53* mutations were included in further testing for NTRK fusion.

NTRK fusion gene in 59 patients with TC:
- 57/846 (**6.7%**) patients with PTC
- 2/10 (**20.0%**) patients with PDTC

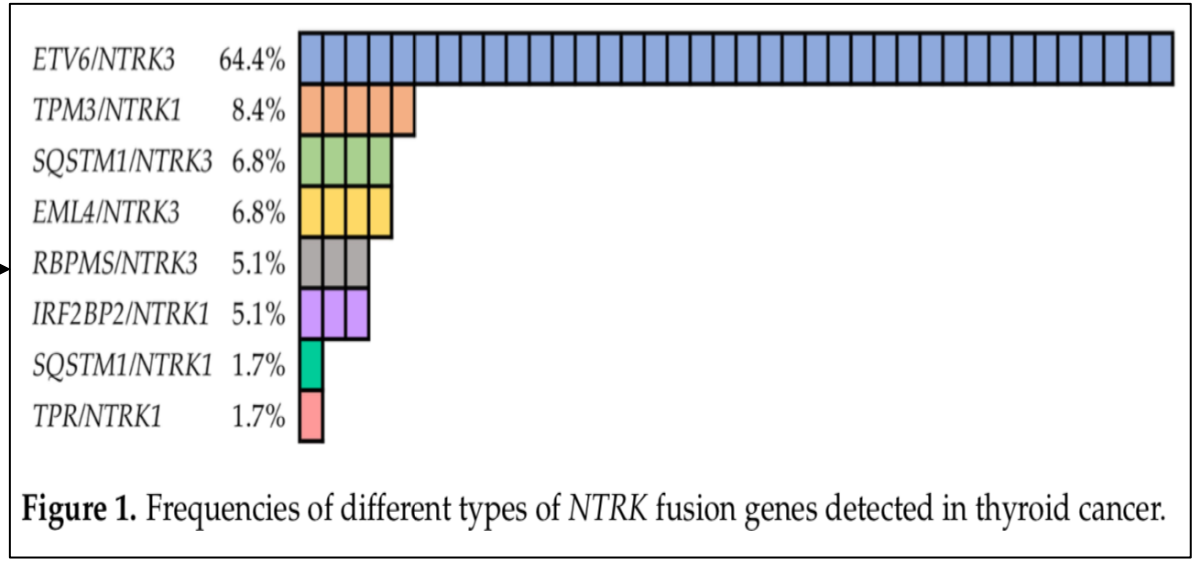


Figure 1. Frequencies of different types of *NTRK* fusion genes detected in thyroid cancer.

→ **With a better selection of cases, the prevalence of NTRK fusion in thyroid carcinomas is higher than 2.2%**

Response and survival benefit for patients with actionable TC

BRAF mutation in ATC

Phase 2 ROAR basket trial (NCT02034110)

- **36** pts with R/M **BRAF mutant ATC**
- **Dabrafenib** 150 mg BID **+ Trametinib** 2 mg QD
- Primary endpoint: ORR; secondary: PFS, DoR, safety

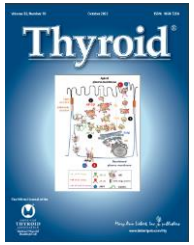
At a median follow-up of 11.1 months:

- **ORR** = **56%** (3 complete responses)
- **Median duration of response** = **12** months
- **Median overall survival** = **15** months
- **24-months OS rate** = **31.5%**

Subbiah V. et al, *Annals of Oncology* 2022

BRAF mutation in DTC

Targeted therapy for BRAF-mutant DTC not mentioned in the ESMO Guidelines 2022

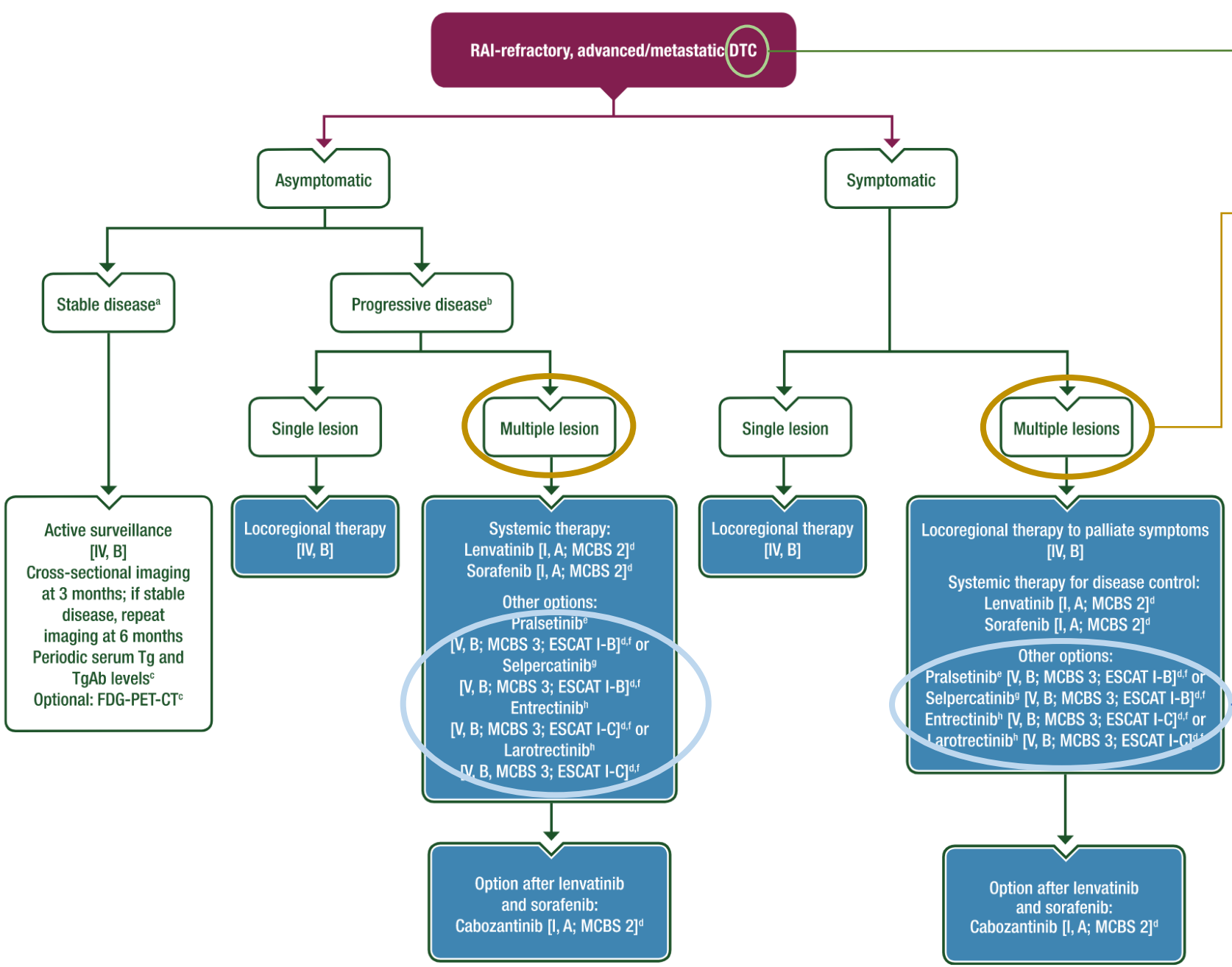


Dabrafenib Versus Dabrafenib + Trametinib in *BRAF*-Mutated Radioactive Iodine Refractory Differentiated Thyroid Cancer: Results of a Randomized, Phase 2, Open-Label Multicenter Trial

- **53 patients**
- **2 cohorts:**
  (1) **Dabrafenib** 150 mg BID (n=26)
  (2) **Dabrafenib** 150 mg BID + **Trametinib** 2 mg QD (n=27)
- **ORR within the first 24 weeks of tx:**
  - (1) **42%** (95%CI 23 – 63%)
  - (2) **48%** (95%CI 29 – 68%)

  p = 0.67

Busaidy et al, *Thyroid*, 2022



HYSTOLOGY

✓ DTC or PDTC

PATIENT

✓ With multiple RAIR lesions
- Symptomatic
- Asymptomatic in progression

SETTING

✓ Advanced/Metastatic RAIR TC

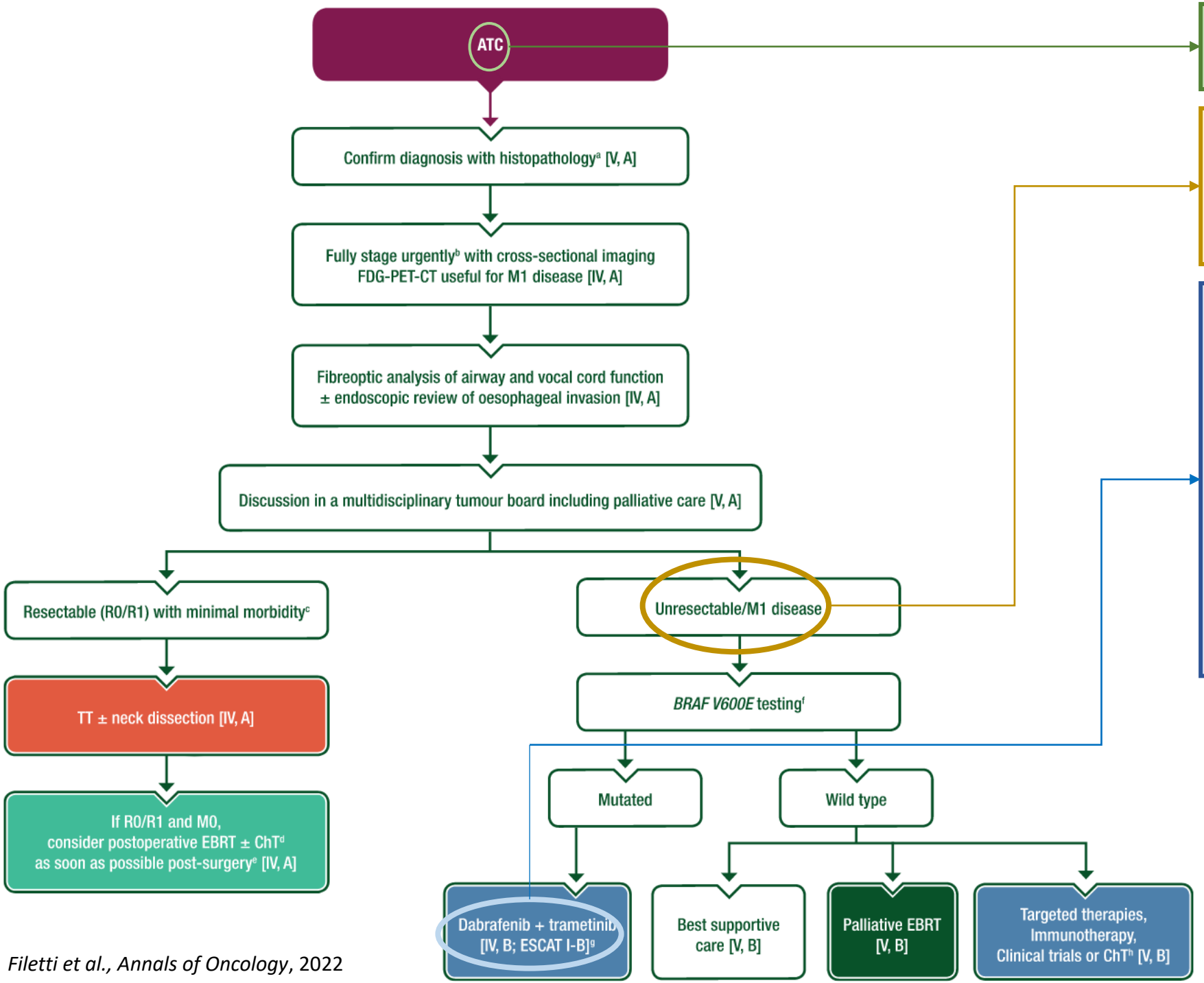
✓ **≥1** Line: **NTRK** inhibitors
- **Entrectinib**
- **Larotrectinib**

✓ **>1** Line after TKI: **RET** inhibitors
- **Selpercatinib**

Other targets? → **NGS** for **Clinical Trials**

Recommendations

If a systemic therapy of advanced/metastatic DTCs is planned, a genetic test targeting actionable cancer mutations should be considered to individualise therapy. Next-generation sequencing (NGS) analysis is the preferred approach, if available [III, C].



HYSTOLOGY

✓ ATC

PATIENT

✓ BRAF status should be promptly assessed (with IHC, RT-PCR) at diagnosis

SETTING

✓ R/M ATC

✓ **BRAF-mutant** → 1 Line: Dabrafenib + Trametinib

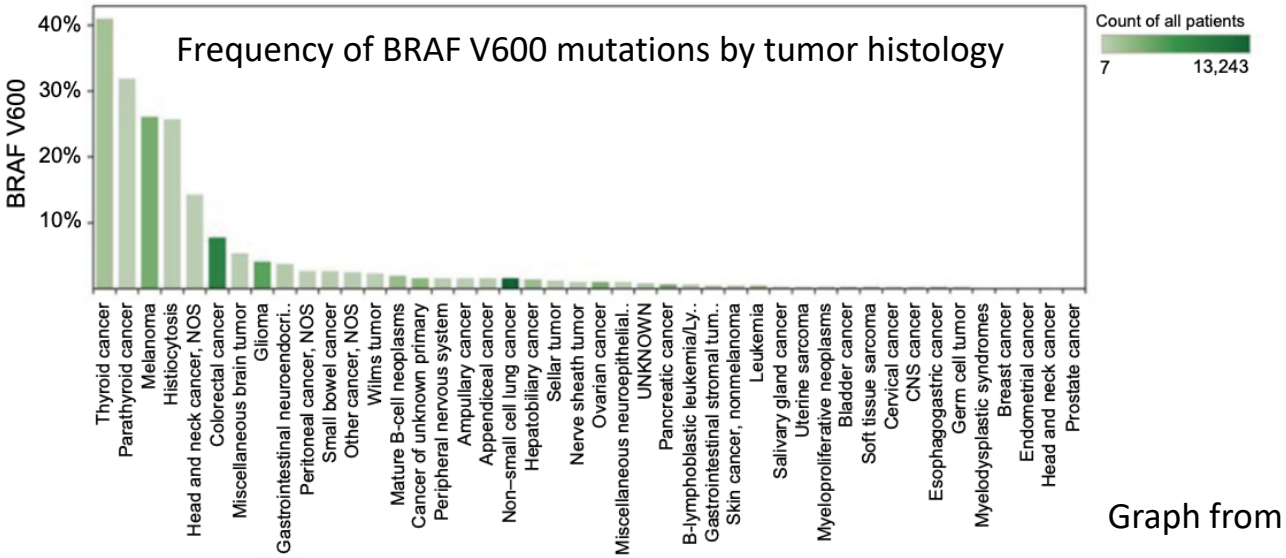
✓ **BRAF wild-type → ChT + NGS profiling in targeted therapy clinical trials screening** (including assessment of NTRK/RET/ALK fusions!)

Filetti et al., Annals of Oncology, 2022

The “Atlantic gap” for targeted therapy in TC

updated at February 2023

Molecular alterations	Drugs	FDA	EMA	AIFA
BRAF^{V600E} mutation	Dabrafenib plus Trametinib	(since June 2022) approved for R/M **solid tumors** in PD to standard treatment and without satisfactory treatment options	Not approved for thyroid cancer	• L.648 for **ATC**? (approved in June 2020 and suspended for compassionate use program ongoing) • Compassionate use program for BRAF-mutant solid tumors closed since 15 Dec 2022



Graph from Adashek et al, *Molecular Cancer Therapeutics* 2022

The “Atlantic gap” for targeted therapy in TC

updated at February 2023

Molecular alterations	Drugs	FDA	EMA	AIFA
BRAF^{V600E} mutation	Dabrafenib plus Trametinib	(since June 2022) approved for R/M solid tumors in PD to standard treatment and without satisfactory treatment options	Not approved for thyroid cancer	• L.648 for **ATC**? (approved in June 2020 and suspended for compassionate use program ongoing) • Compassionate use program for BRAF-mutant solid tumors closed since 15 Dec 2022
RET fusion	Selpercatinib Pralsetinib	in **≥1** Line in **≥1** Line	• Selpercatinib approved in **>1 Line** (after at least 1 line of MKI lenvatinib/sorafenib in DTC) • Pralsetinib not approved for TC (the company withdrew EMA application on November 2022)	
NTRK fusion	Entrectinib Larotrectinib	in **≥1** Line in **≥1** Line	Approved for advanced solid tumors expressing NTRK fusion and without satisfactory treatment options	

From theory to reality: TC profiling at INT

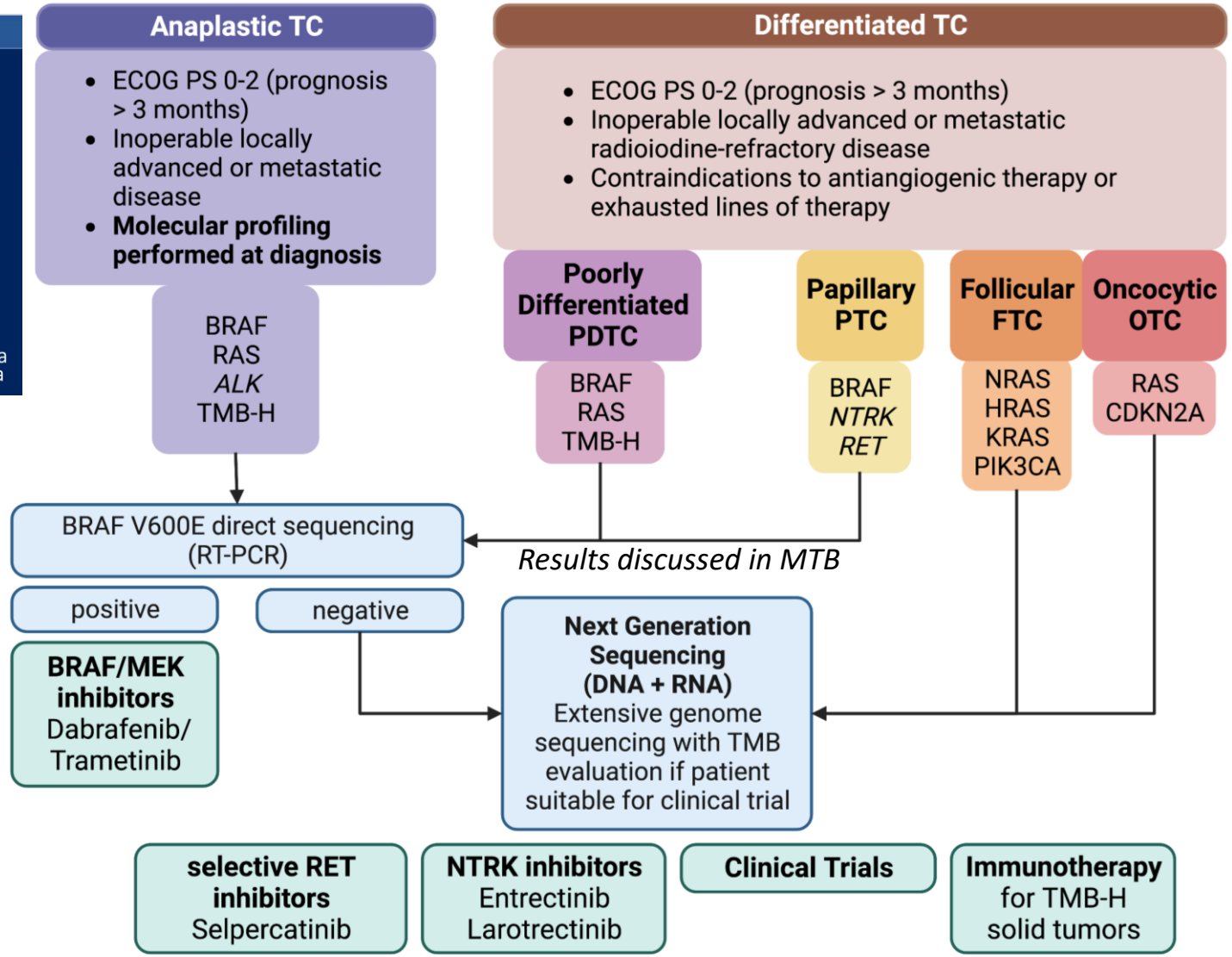
AIOM22 ONCOLOGIA e COMPLESSITÀ

UNIVERSITÀ DEGLI STUDI DI MILANO

FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

Sequential molecular profiling of advanced thyroid cancers for precision oncology: flowchart from an Italian referral center

Elena Colombo, Arianna Ottini, Francesca Caspani, Cristiana Bergamini, Carlo Resteghini, Salvatore Alfieri, Stefano Cavalieri, Imperia Nuzzolese, Matteo Duca, Biagio Paolini, Andrea Vingiani, Elena Tamborini, Federica Perrone, Giancarlo Pruneri, Laura D. Locati, Lisa Licitra

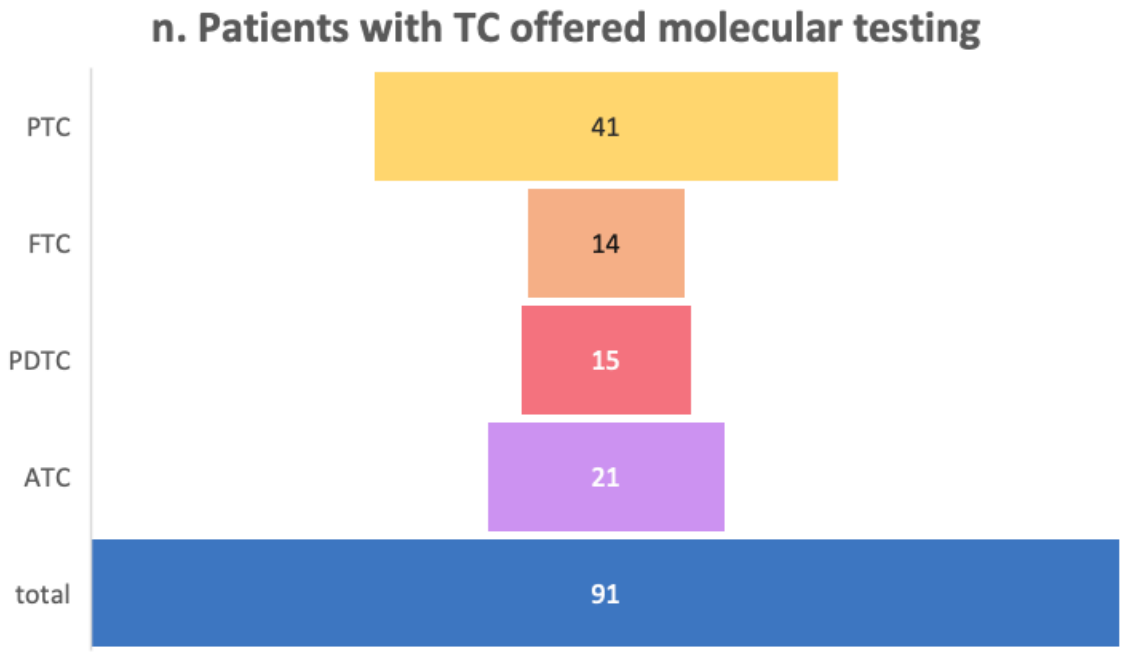


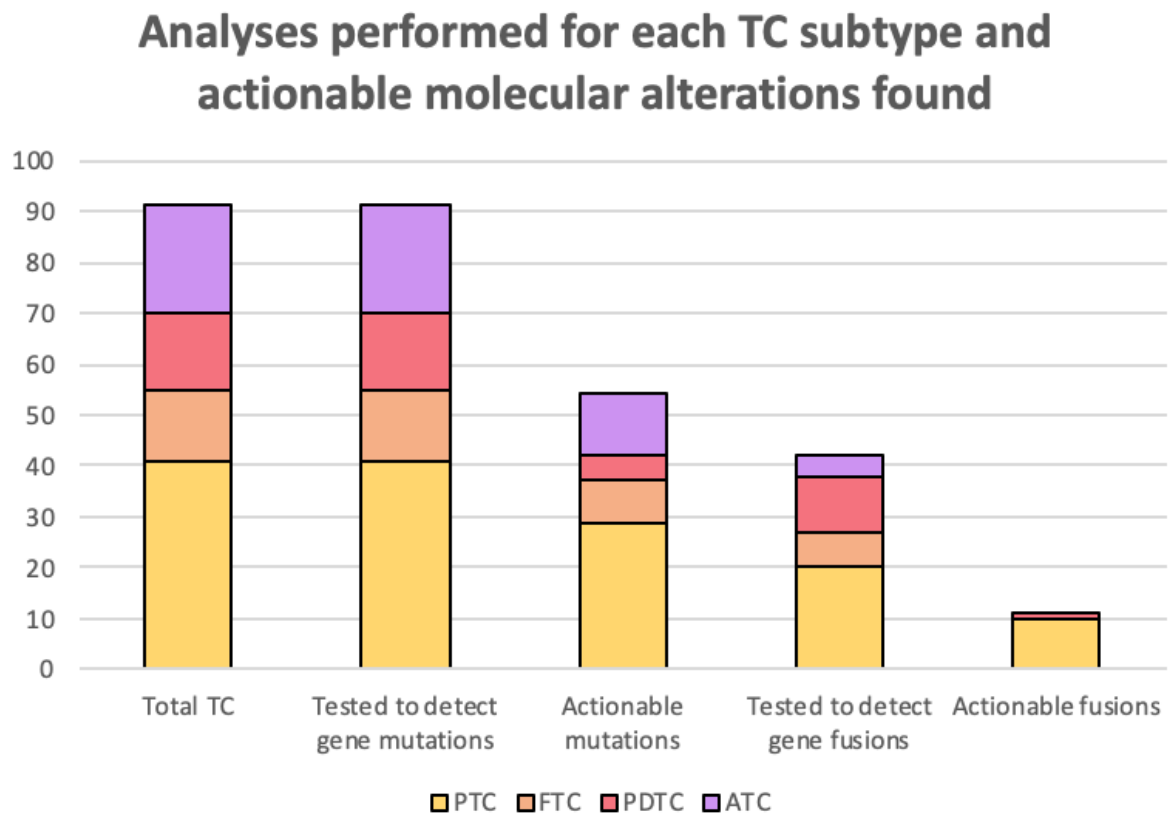
From theory to reality: TC profiling in FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

From January 2020 to April 2022, **91** patients with TC received at least one molecular test:

- 60/91 (65.9%) **before starting 1st line therapy**
- 31/91 (34%) **after 1st line**

F = 51 (56%)
M = 40 (44%)

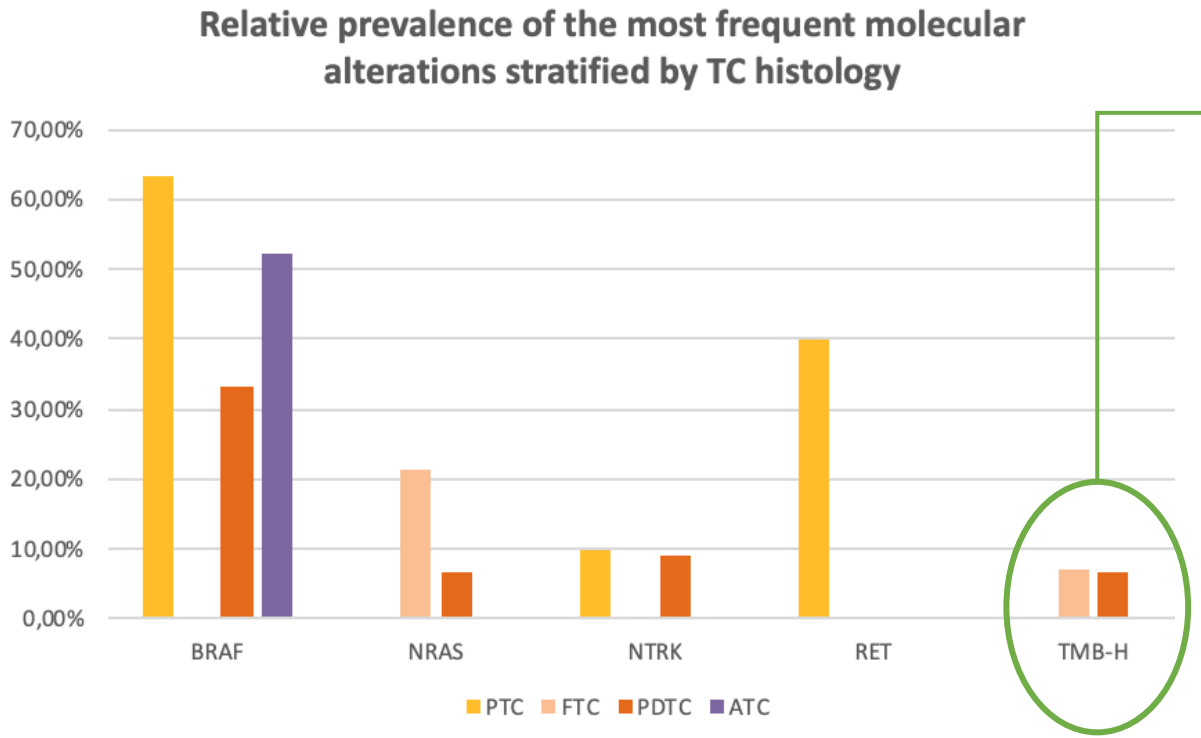




From theory to reality: TC profiling in FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

Most frequent molecular alterations found

- **mutations**
  - **44% BRAF^{V600E}**
  - **9.9% NRAS**
- **fusions**
  - **21.6% RET**
  - **7.3% NTRK**



Tumor mutational burden was assessed in 5 cases: 2 had TMB > 10 Mut/Mb

Overall, **69.2%** of this cohort had **at least one molecular target** potentially allowing access to targeted therapies in compassionate use programs/clinical trials

Future directions for molecular profiling in TC

1. Move targeted therapy to **early stage disease** for *neoadjuvant* strategy

→ Already feasible in the USA for **borderline resectable** $BRAF^{V600E}$-mutant **ATC**

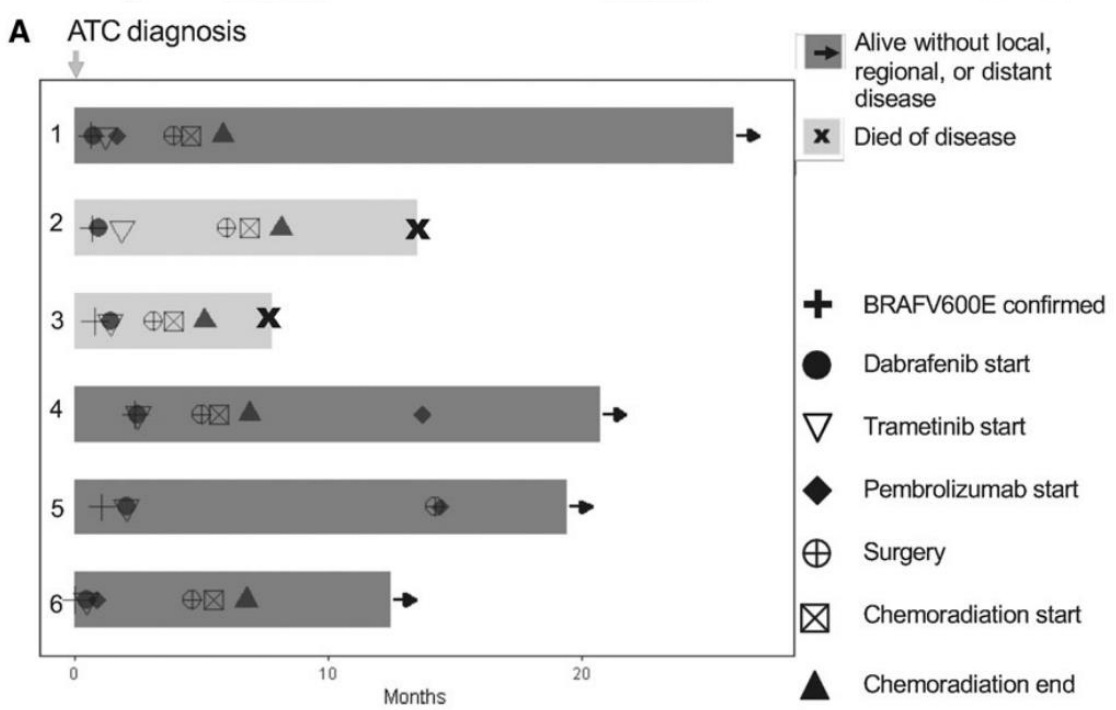
- The successful use of **neoadjuvant dabrafenib plus trametinib** with or without immunotherapy has been described in a series of 6 patients.
- **BRAF-directed therapy required continuation after surgery**, to maintain control of the disease.
- All but one pts received **adjuvant CTRT** after surgery

Outcomes:

✓ **12-months OS= 83%**

✓ **Locoregional control rate = 100%**

Bible et al. *Thyroid* 2021



Wang JR et al. *Thyroid* 2019

Future directions for molecular profiling in TC

1. Move targeted therapy to **early stage disease** for *neoadjuvant* strategy
2. Associations of **targeted therapy + immunotherapy**

Meeting Abstract | 2020 ASCO Annual Meeting I

HEAD AND NECK CANCER

Atezolizumab combinations with targeted therapy for anaplastic thyroid carcinoma (ATC).

Maria E. Cabanillas, Ramona Dadu, Renata Ferrarotto, Suyu Liu, Bryan M. Fellman, Neil D. Gross, Maria Gule-Monroe, Charles Lu, Horiana Grosu, Michelle D. Williams, Dzifa Yawa Duose, Saradhi Mallampati, Shannon Dervin, Edward Francis Mckenna, Rui Jennifer Wang, Mark Zafereo, Naifa Lamki Busaidy

The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD

28% of patients were able to undergo complete tumour resection after response to systemic therapy (n=7 in cohort 1; n=1 in cohort 2)

Phase II – single institution
Study population:
Cohort 1 = $BRAF^{V600E}$ mutant ATC
→ **Atezolizumab + Vemurafenib + Cobimetinib**
Cohort 2 = $BRAF^{WT}$ + RAS/NF1/NF2-mutant ATC
→ **Atezolizumab + Cobimetinib**

Female [N (%)]	17 (50%)	
Age, in yrs [median (range)]	66 (44-74)	
	N	Median OS in mos (95%CI)
Cohort 1	17	Not reached
Cohort 2	14	18.23 (4.47-NE)

Future directions for molecular profiling in TC

1. Move targeted therapy to **early stage disease** for *neoadjuvant* strategy
2. Associations of **targeted therapy + immunotherapy**

Clinicaltrials.gov Identifier	Title	Phase	N	Population	Treatment Arms	Primary Endpoint
NCT04061980 DTC	Encorafenib/Binimetinib With or Without Nivolumab for Patients With Metastatic BRAF V600 Mutant Thyroid Cancer.	II	40	Histologically (or cytologically) confirmed diagnosis of metastatic, radioiodine (RAI) refractory, BRAFV600E/M mutant differentiated thyroid cancer (DTC)	Arm I: Encorafenib + Binimetinib Arm II: Encorafenib + Binimetinib + Nivolumab.	ORR
NCT04675710 ATC	Pembrolizumab in Combination With Dabrafenib and Trametinib as a Neoadjuvant Strategy Prior to Surgery in BRAF-Mutated Anaplastic Thyroid Cancer.	II	30	BRAFV600E mutation-positive anaplastic thyroid carcinoma surgically resectable.	Dabrafenib + Trametinib + Pembrolizumab.	Complete gross surgical resection (R0 or R1 resection) and OS

Gracia-Alvarez et al., *Frontiers in Endocrinology* 2022

Future directions for molecular profiling in TC

1. Move targeted therapy to early stage disease
2. Associations of targeted therapy + immunotherapy
3. Enhance **radioiodine re-uptake**?

The NEW ENGLAND JOURNAL of MEDICINE

Groussin et al, NEJM 2020

Larotrectinib-Enhanced Radioactive Iodine Uptake in Advanced Thyroid Cancer

- 64 year-old female patient
- 34-year history of PTC with synchronous lymphnode and lung metastases
- After 8 RAI treatments (cumulative dose of 1405.4 mCi), long-term control of the cancer was maintained for 12 years.
- At PD with hight tumor burden, patient started **Lenvatinib** (partial response, but G3-G4 adverse events despite dose adjustments)
- NGS: ***EML4-NTRK*** fusion detected
- **Larotrectinib** (100 mg BID) → PR

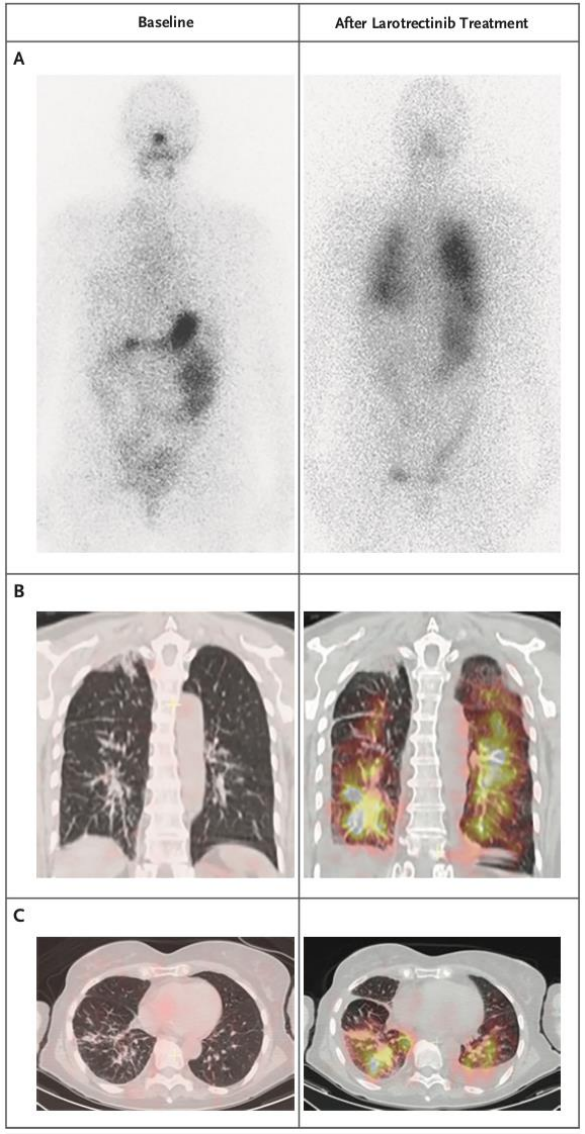


Figure 1. Diagnostic Scans Obtained before and after Larotrectinib Treatment.

Images were obtained with the use of iodine-131 (300 to 370 MBq [8 to 10 mCi]) before treatment with larotrectinib and 3 weeks after the initiation of treatment. Anterior images of whole-body scans show restored iodine uptake after administration of larotrectinib in almost all lung metastases that had previously shown no uptake (Panel A). Substantially increased iodine uptake after larotrectinib treatment can also be observed in fused frontal (Panel B) and axial (Panel C) chest images.

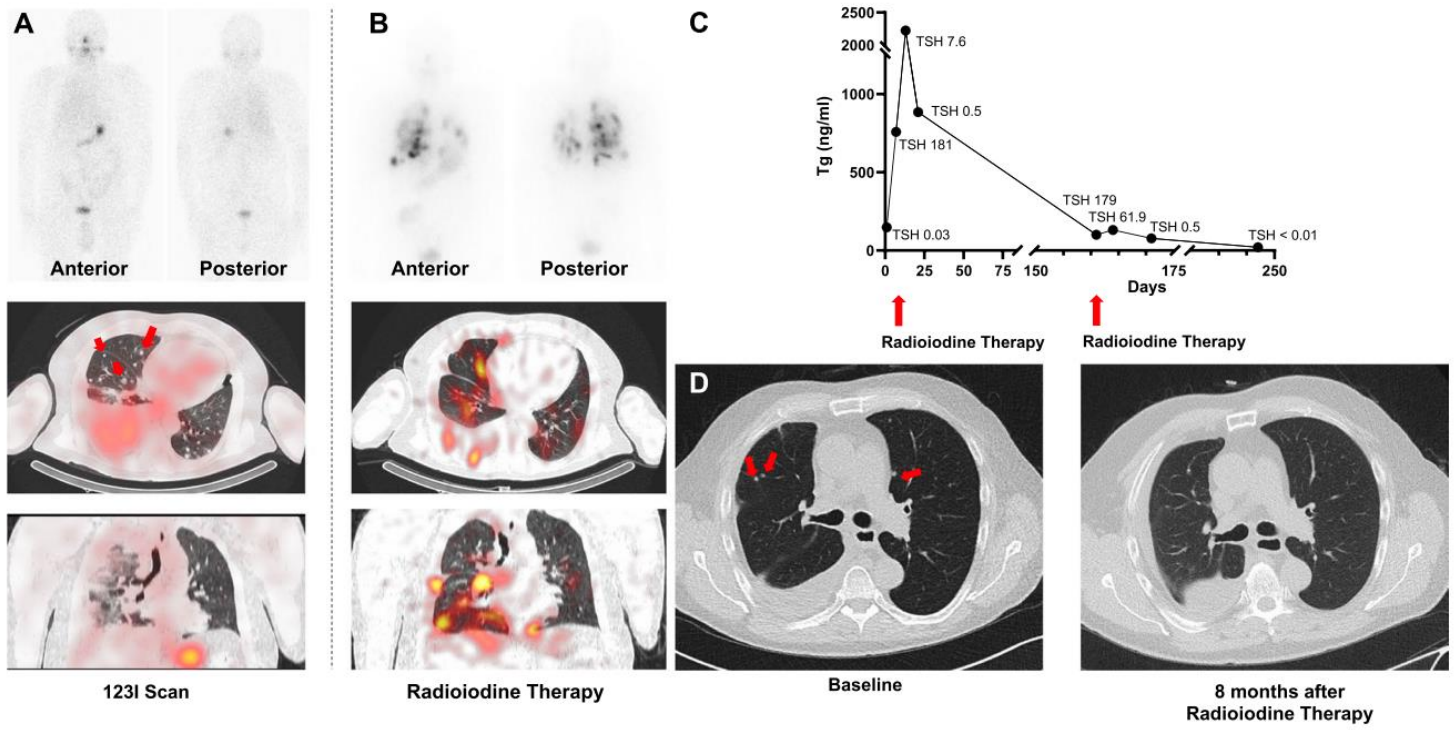
Future directions for molecular profiling in TC

1. Move targeted therapy to early stage disease
2. Associations of targeted therapy + immunotherapy
3. Enhance **radioiodine re-uptake**?

Successful combination of selpercatinib and radioiodine after pretherapeutic dose estimation in RET-altered thyroid carcinoma

Werner RA et al, *European J of Nuclear Medicine and Mol Imaging* 2022

- **RET-rearranged PTC → thyroidectomy + RA**I
- Follow-up ^{123}I scan: no uptake in lung nodules identified on CT scan = **RAIR DTC** (A)
- **Selpercatinib** (15 months)
- **Diagnostic whole-body ^{131}I:** intense radiotracer accumulation in sites of disease
- **RAI with 9.4 GBq →** previously negative nodules showed radiotracer accumulation on post-therapeutic scan (B).
- 13 days after RAI, a **peak of Tg** of 2.224 ng/ml was observed, followed by rapid decline (C)
- 8 months after RAI, **Tg dropped** from baseline 148 ng/ml under TSH suppression to 21 ng/ml with CT demonstrating reduction of lung nodules (D)



Rebiopsy for 2nd generation TKI

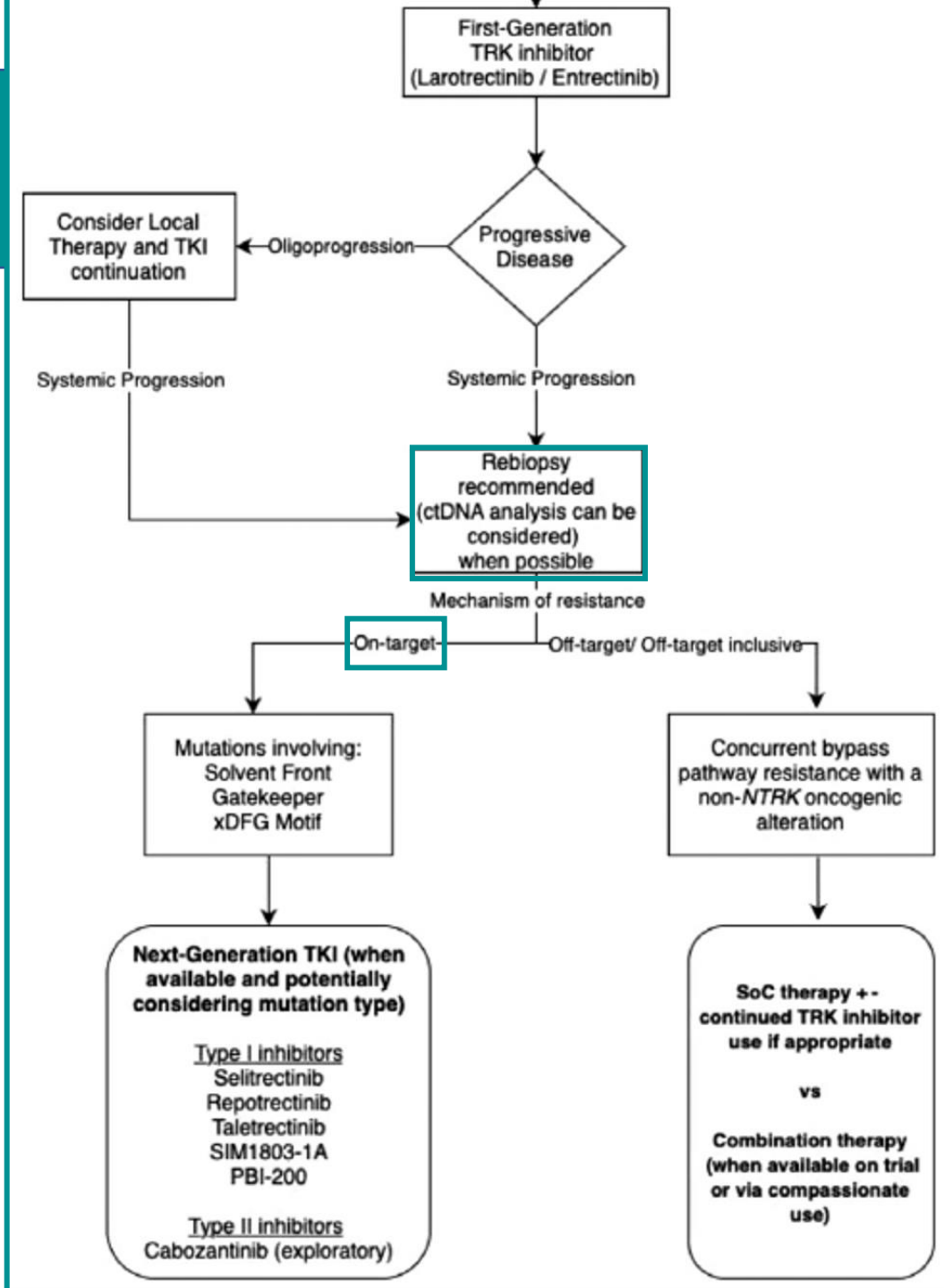
Besse et al, *Mol Cancer Therapeutics - AACR* 2021

Update on dose-escalation phase I/II clinical trial TRIDENT-1
With repotrectinib for TrkA/B/C – ROS1 – ALK rearranged solid tumors

in TRK TKI–naïve cohort
ORR 63% mDoR 1.9–7.4+ months
In TRK TKI-pretreated cohort
ORR 47% mDoR 1.9–15.1+ months

*Early interim data led to Fast Track designation by the FDA for **Repotrectinib in TRK TKI-pretreated patients***

Harada G and Drilon A, *Cancer Genetics* 2022



Highlights

- **RET and NTRK inhibitors** are now standard-of-care in the advanced setting: **NGS RNA** molecular profiling can significantly improve the prognosis of patients with TC harboring these actionable targets.

- Multidisciplinary Team (MDT) and Molecular Tumor Board (MTB) are pivotal to optimize decisions on the **timing, methodology** and **results** of the molecular profiling for each patient

- Targeted therapy is now approved for unresectable/metastatic TC, but clinical trials are ongoing to evaluate the impact of targeted therapy in **early-stage disease** (neoadjuvant setting)

thank you!

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