The challenge of selecting the best treatment sequence in radio-iodine refractory thyroid cancer

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Disclosures

Laura D. Locati, MD, PhD

Financial Interests

Conference honoraria/Advisory Board: EISAI, MSD, IPSEN, Bayer, Johnson and Johnson

Funded to my Istitution: Novartis, Eisai, Takeda

Travel grant: MSD

Non-Financial Interests

ESMO Task Force for Thyroid Cancer and Salivary Gland Cancer Guidelines

EORTC Endocrine Task Force and Head & Neck group

Coordinator of the Italian Medical Oncology Association (AIOM) Guidelines in Thyroid Cancers

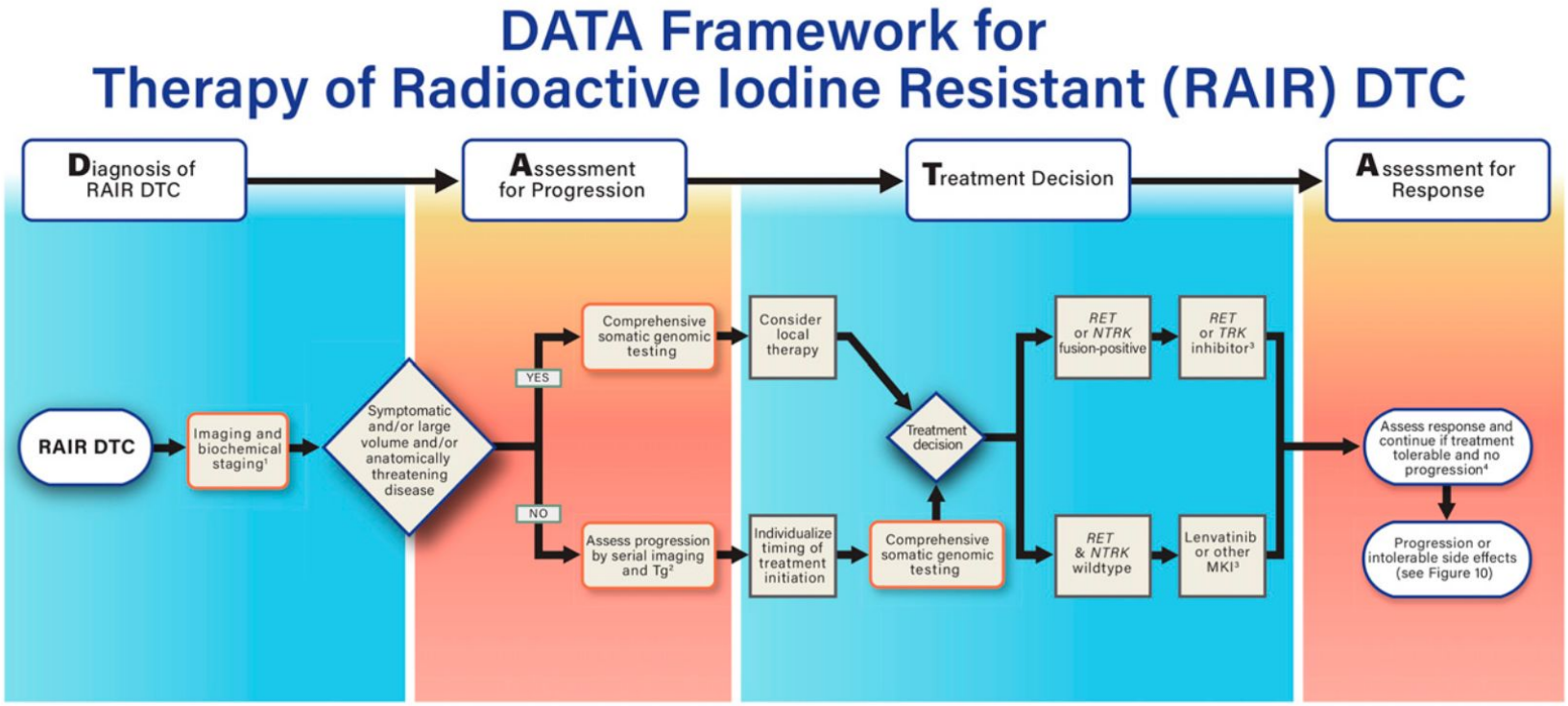
MSGS (Multidisciplinary Salivary Glands Society); ITOG (International Thyroid Oncology Group); AIOM (Italian Association of Medical Oncology); AIOCC (Italian Association of Head and Neck Oncology): affiliate member

Agenda

- **Current guidelines from US: ATA, ASCO and NCCN**

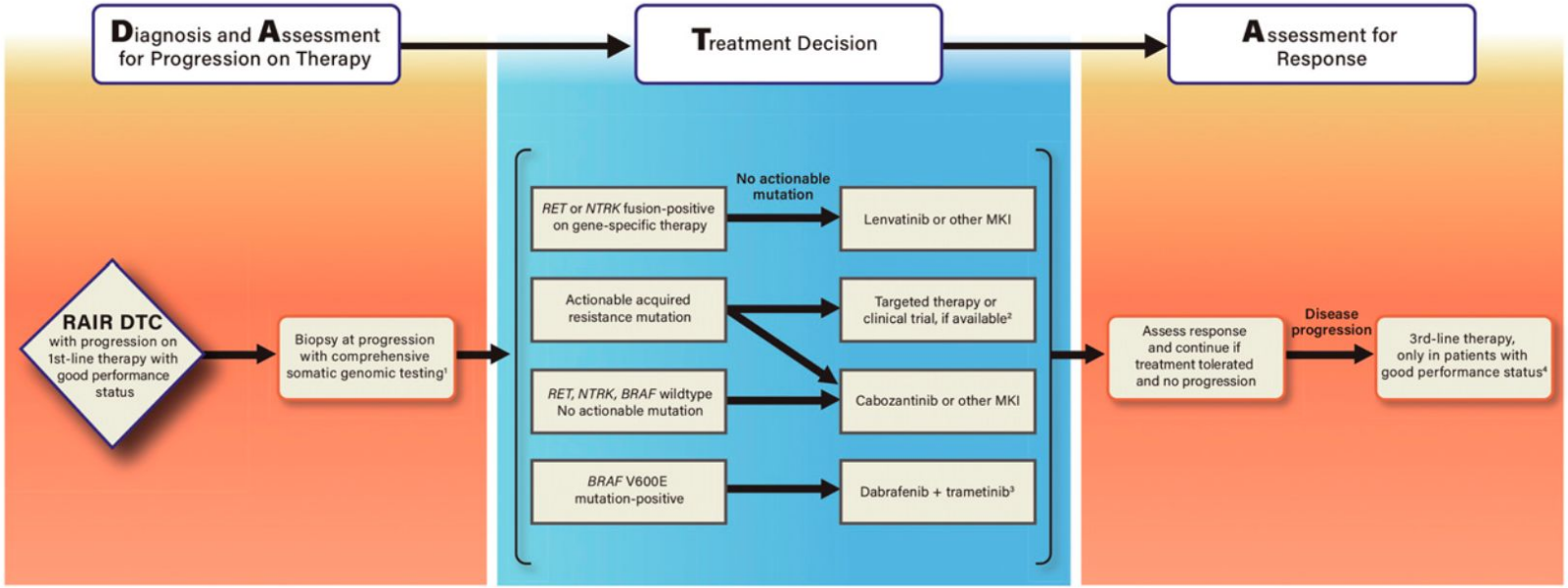
- Current clinical practice

ATA Guidelines 2025



Ringel MD et al. Thyroid 2025

DATA Framework for Second-line Therapy of RAIR DTC

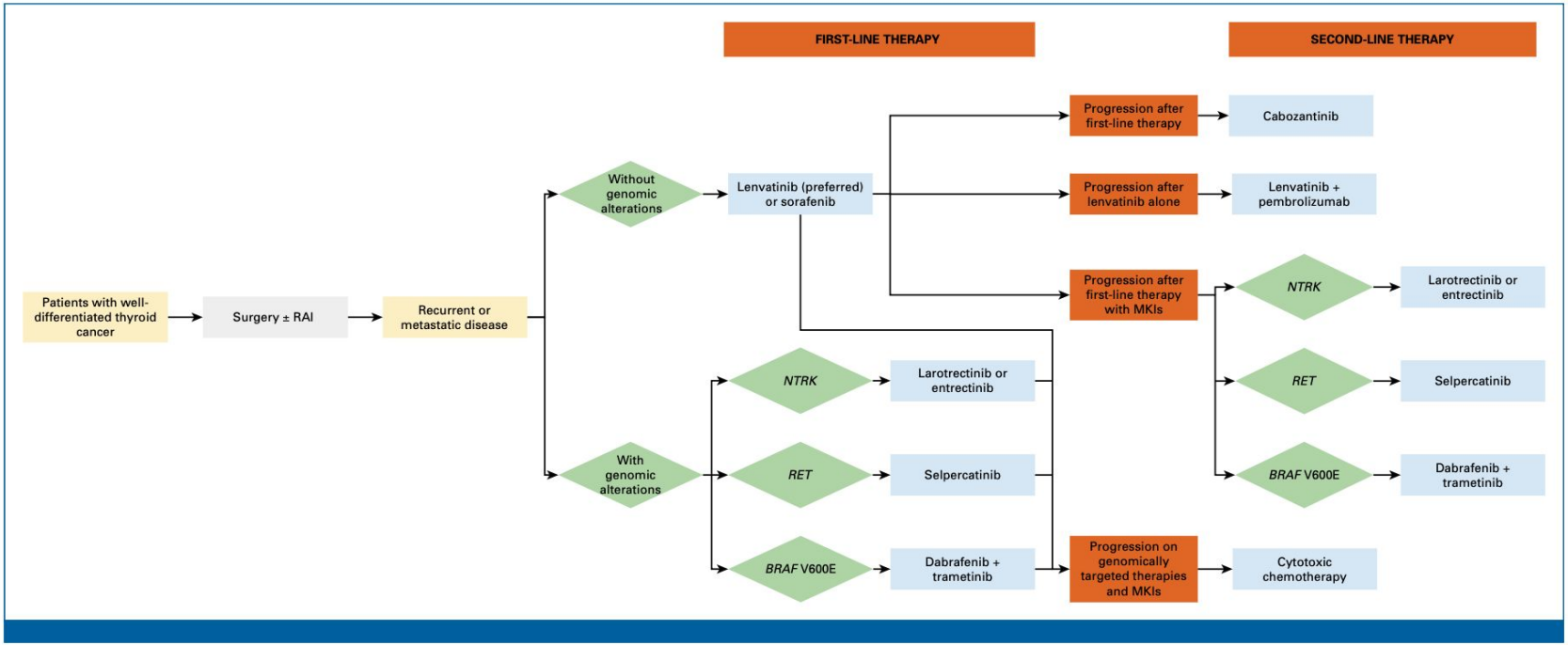


Ringel MD et al. Thyroid 2025

ASCO Guidelines

Systemic Treatment of Thyroid Cancer: ASCO Guideline

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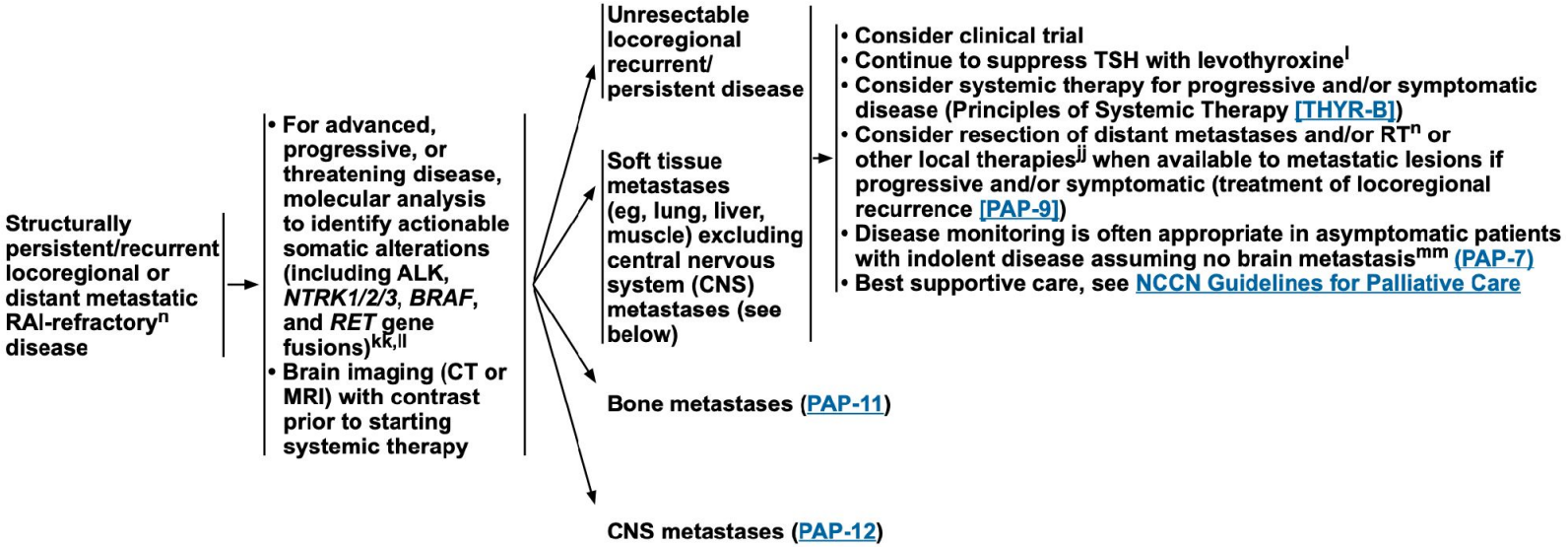
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NCCN Guidelines Version 2.2026
Thyroid Carcinoma – Papillary Carcinoma

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TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC RAI-REFRACTORY DISEASE



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Thyroid Carcinoma

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PRINCIPLES OF SYSTEMIC THERAPY

Differentiated Thyroid Cancer (Papillary, Follicular, or Oncocytic Carcinomas): Locoregionally Invasive, Rapidly Progressive and/or Symptomatic or Recurrent RAI-Refractory Locoregional or Distant Metastatic Disease[a,b]

Preferred	Useful in Certain Circumstances

• Lenvatinib (category 1)[c,d]
• *NTRK1/2/3* gene fusion-positive tumors
  ▸ Entrectinib
  ▸ Larotrectinib
  ▸ Repotrectinib
• *RET* gene fusion-positive tumors
  ▸ Pralsetinib
  ▸ Selpercatinib[e]
	• Sorafenib (category 1)[c,d]
	• Cabozantinib if progression after Lenvatinib and/or Sorafenib (category 1 for papillary carcinoma; category 2A for follicular carcinoma and oncocytic carcinoma)
	• Ipilimumab + Nivolumab (oncocytic carcinoma only)[1]
	• Carboplatin/Pemetrexed if disease progression following prior treatment
	• Dabrafenib/Trametinib[f] for *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options
	• Binimetinib/Encorafenib for *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options[2]
	• Lenvatinib + Pembrolizumab if disease progression on Lenvatinib
	• Pembrolizumab[g] for TMB-H (≥10 [mut/Mb]) or for MSI-high (MSI-H) or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options
	• Consider if clinical trials or other systemic therapies are not available or appropriate[h]:
	  ▸ Axitinib
	  ▸ Everolimus
	  ▸ Pazopanib
	  ▸ Sunitinib
	  ▸ Vandetanib
	  ▸ Dabrafenib (if *BRAF* V600E positive) (category 2B)
	  ▸ Vemurafenib (if *BRAF* V600E positive) (category 2B)

• Pembrolizumab and berahyaluronidase alfa-pmph subcutaneous injection may be substituted for IV pembrolizumab. Pembrolizumab and berahyaluronidase alfa-pmph has different dosing and administration instructions compared to IV pembrolizumab.


COMING
SOON
STAY TUNNED!

MTKi and RAI-R DTC

	1st line		2nd line	Prior sorafenib	Prior lenvatinib	Prior sorafenib/lenvatinib
Agent	**Lenvatinib 24 mg**	**Sorafenib 400 mg BID**	**Cabozantinib 60 mg**	**Cabozantinib 60 mg**	**Cabozantinib 60 mg**	**Cabozantinib 60 mg**
N°	392	417	258	99	102	60
Ph	3	3	3	3	3	3
ORR% CR	64.8 vs 1.5 4	12.2 vs 0.5 0	11 vs 0 1	21 vs 0	4.0 vs 0 1	8.0 vs 0
mPFS, months	18.3 vs 3.6	10.8 vs 5.8	11.0 vs 1.9	16.6 vs 3.2 **PFS1+2=27.4**	5.8 vs 1.9 **PFS1+2=24.1**	7.6 vs 1.9
TRAEs ≥ G3%	75.9 vs 9.9	SAEs 37.2 vs 26.3	62 vs 28	63	57	69
TEAEs G5%	5	6 vs 3	2 vs 1	4 vs 2	7 vs 3	3 vs 2
TRAEs G5%	2.3	0	0	0	0	0

Schlumberger M, NEJM 2015; Brose M, Lancet 2014; Brose M, Cancer 2022; Capdevila J, Thyroid 2024

Oncogene addicted RAI-R DTC: RET fusion

Agent	Selpercatinib (Libretto 001)		Pralsetinib (Arrow)
	Naïve	Previously treated	Previously treated
N°	24	41	24
Ph	1/2	1/2	1/2
Previous MKIs		Lenvatinib (63.4%); Sorafenib (22%); both (9.8%)	Lenvatinib, sorafenib or both 55%
ORR% CR% PR%	95.8 20.8 75.0	85.4 12.2 73.2	91.7 16.7 75
DoR, median, months	NE	26.7	NR
mPFS, months	NE	24.4	NR
mOS, months	NE	NE	NR (25.4- NE)
AEs G3%	71.2		68%

EMA approval:
Selpercatinib is indicated for the treatment of adults and adolescents 12 years and older, with advanced RET fusion-positive TC who are RAI-refractory (if RAI is appropriate)

FDA approval for pralsetinib

Subbiah V, ASCO 2026; Wirth L et al. JCO 2024

Oncogene addicted RAI-R DTC: NTRK fusion

Agent	Larotrectinib (long term data from NAVIGATE and SCOUT)	Entrectinib (ALKA-372-001 STARTRK-1; STARTRK-2	Repotrectinib (TRIDENT 1)
N°	24	150	144
Ph	1/2	1/2	1/2
Naïve Pretreated	50% 50% (> 1 line in 25%)	16	6 Thyroid ca (TKI naïve) 7 Thyroid ca
ORR% CR% PR%	79 13 67	62.5	100 (naïve); 29 (pre-treated)
DoR, median, months	35	13.2	Not reported
mPFS, months	44	NE	Not reported
mOS, months	NR	NE	Not reported
TRAEs G3%	16.7	TRAEs led to treatment discontinuation in 7.2%	Not reported

EMA approval: Adult and pediatric patients 12 years of age and older with NTRK fusion-positive locally advanced or metastatic solid tumours who have progressed following prior therapies or when standard therapies are not available.

Waguespack SG, Endocrine-related Cancer 2026;
Besse B et al, Nat Med 2026;
Krzakowski MJ et al JCO 2022

Original Reports | Precision Medicine

Larotrectinib Compared With Real-World Non–Tropomyosin Receptor Kinase Inhibitor Therapies in Patients With Tropomyosin Receptor Kinase Fusion Cancer

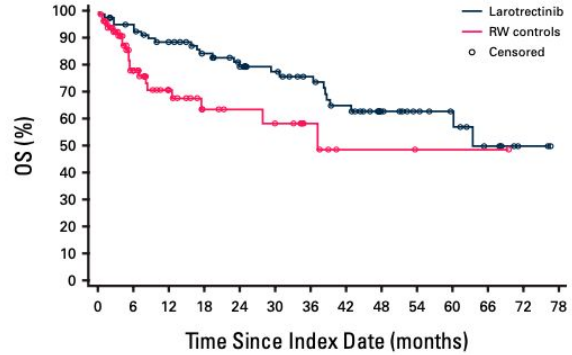
Marcia S. Brose, MD, PhD[1]; C. Benedikt Westphalen, MD[2,3,4]; Xiaoyun Pan, PhD, MS[5]; Vadim Bernard-Gauthier, PhD[6]; Milena Kurtinecz, DPhil[5]; Helen Guo, MSc[6]; Virginie Aris, PhD[5]; Neil R. Brett, PhD[7]; Abdelali Majdi, MD[8]; Vivek Subbiah, MD[9]; Nathan A. Pennell, MD, PhD[10]; Kenneth L. Kehl, MD, MPH[11,12]; and Alexander Drilon, MD[13,14]

DOI https://doi.org/10.1200/PO-24-00500

2025

A

KM Analysis/Population	Median OS (95% CI), Months	
	Larotrectinib (n = 82)	RWC (n = 82)
Overall, unweighted	63.4 (42.9-NE)	37.2 (17.4-NE)

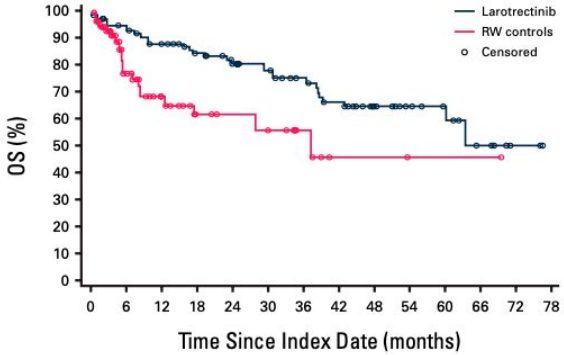


No. at risk:

Larotrectinib	82	74	66	56	48	42	36	29	19	14	11	6	2	0
RW controls	82	40	23	14	12	10	6	2	2	1	1	1	0	0

B

KM Analysis/Population	Median OS (95% CI), Months	
	Larotrectinib (n = 82)	RWC (n = 82)
Overall, weighted	Not reached (42.9-NE)	37.2 (12.5-NE)



No. at risk:

Larotrectinib	82	73	65	55	48	43	37	31	20	12	9	5	1	0
RW controls	81	39	22	14	12	9	6	2	2	1	1	1	0	0

TABLE 1. Attrition Table After Design Matching by Tumor Type and Line of Therapy Number

Characteristic	Larotrectinib (n = 82)	RW Controls (n = 82)
Tumor type, No. (%)		
CRC	17 (21)	17 (21)
NSCLC	15 (18)	15 (18)
Salivary gland	15 (18)	15 (18)
Soft tissue sarcoma	23 (28)	23 (28)
Thyroid	12 (15)	12 (15)
Index line of therapy number, No. (%)		
1	39 (48)	39 (48)
2	20 (24)	20 (24)
3	19 (23)	19 (23)
4	4 (5)	4 (5)

Abbreviations: CRC, colorectal cancer; NSCLC, non–small cell lung cancer; RW, real-world.

Oncogene addicted RAI-R DTC: BRAF

Drug, author	Phase	N°	ORR%	mPFS, months	mOS, months
Vemurafenib Naïve, Brose 2016	2	26	39	18.2	NR
Vemurafenib Pre tx, Brose 2016	2	22	27	8.9	14.4
Dabrafenib	2	22	35	10.7	37.9
Dabrafenib + trametinib, Busaidy 2022	2	24	30	15.1	47.5
Encorafenib + Binimetinib Tahara 2024	2	22 (5 ATC)	47.1	mPFS NR 12-monPFS 78.8%	NR
Dabrafenib + trametinib Gao M, 2026	3	153 (31% Lenvatinib; 69% other TKIs)	58 vs 4	12.8 vs 3.7	NR

D/T are indicated for the treatment of adult patients with locally advanced or metastatic differentiated thyroid cancer with a *BRAF* V600E mutation, refractory to or not eligible for radioactive iodine who have progressed during or after prior systemic therapy (EMA 2026)

MKIs activity is independent from BRAF status

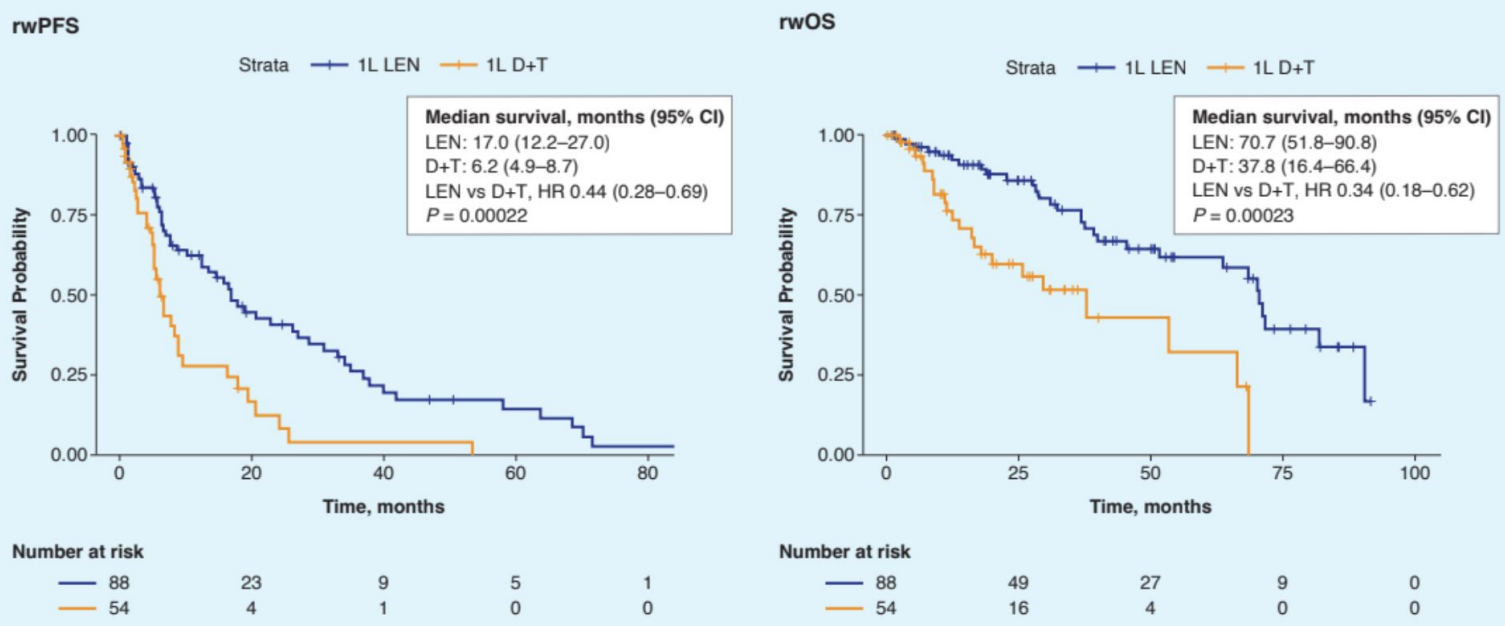
	mPFS BRAF+	mPFS BRAF-
Sorafenib (61.4% tumor mutation available)	20.5 vs 9.4 months	8.9 vs 3.8 months
Lenvatinib (46% tumor mutation available)	NE vs 4.3 months	18.3 vs 1.9 months
Cabozantinib (41% tumor mutation available)	9.2 vs 1.9 months	11.1 vs 1.9 months

Brose M, Lancet 2014; Schlumberger M, NEJM 2015; Brose M et al. Front Oncol 2026

Real-word data Lenvatinib vs D/T 1st line

N° 142; 88 Lenvatinib; 54 D/T

Figure 3. rwPFS and rwOS of Patients With *BRAF*-Mutated Tumors Who Received 1L Lenvatinib or D+T



1L, first-line; CI, confidence interval; D+T, dabrafenib plus trametinib; HR, hazard ratio; LEN, lenvatinib; rwOS, real-world overall survival; rwPFS, real-world progression-free survival.

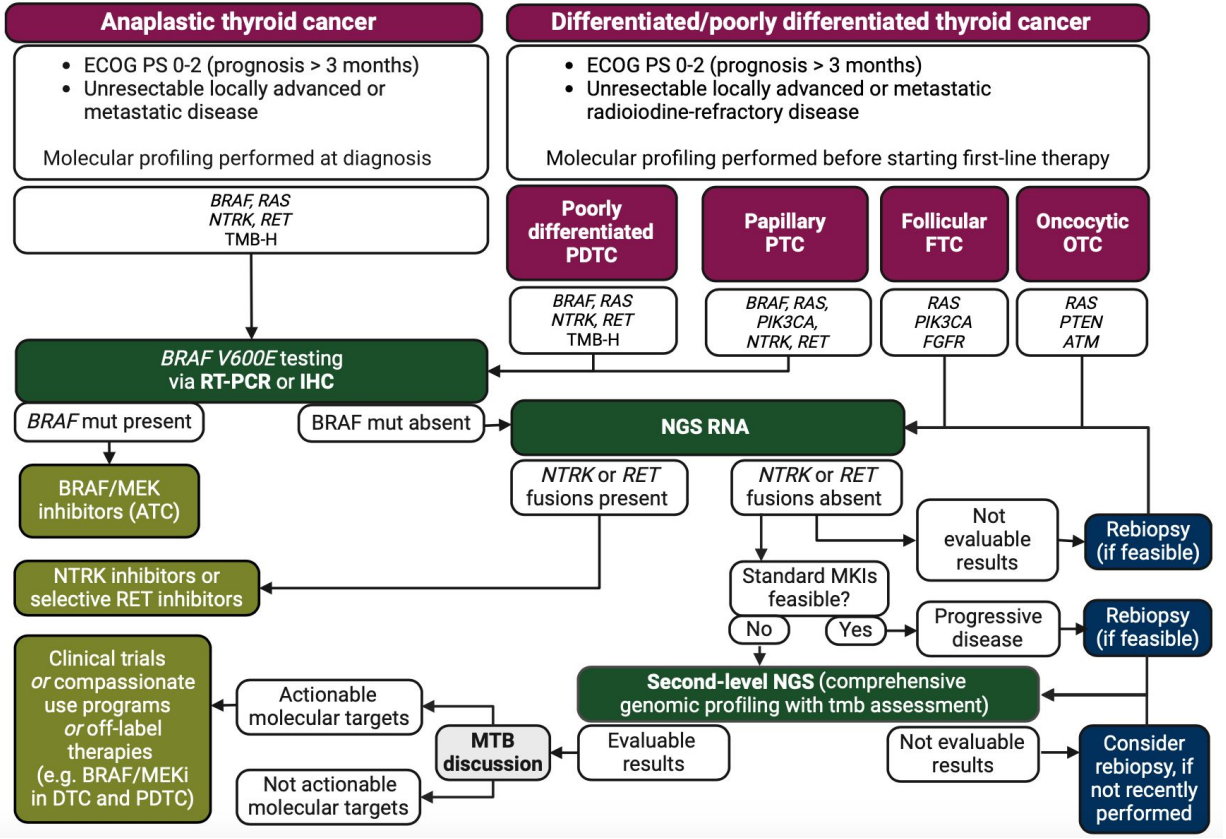
Ngai W, abs 6052 ASCO 2026

Agenda

- Current guidelines from US: ATA, ASCO and NCCN

- **Current clinical practice**

DIAGNOSIC ALGORYTHM



Colombo E et al ESMO Open 2025

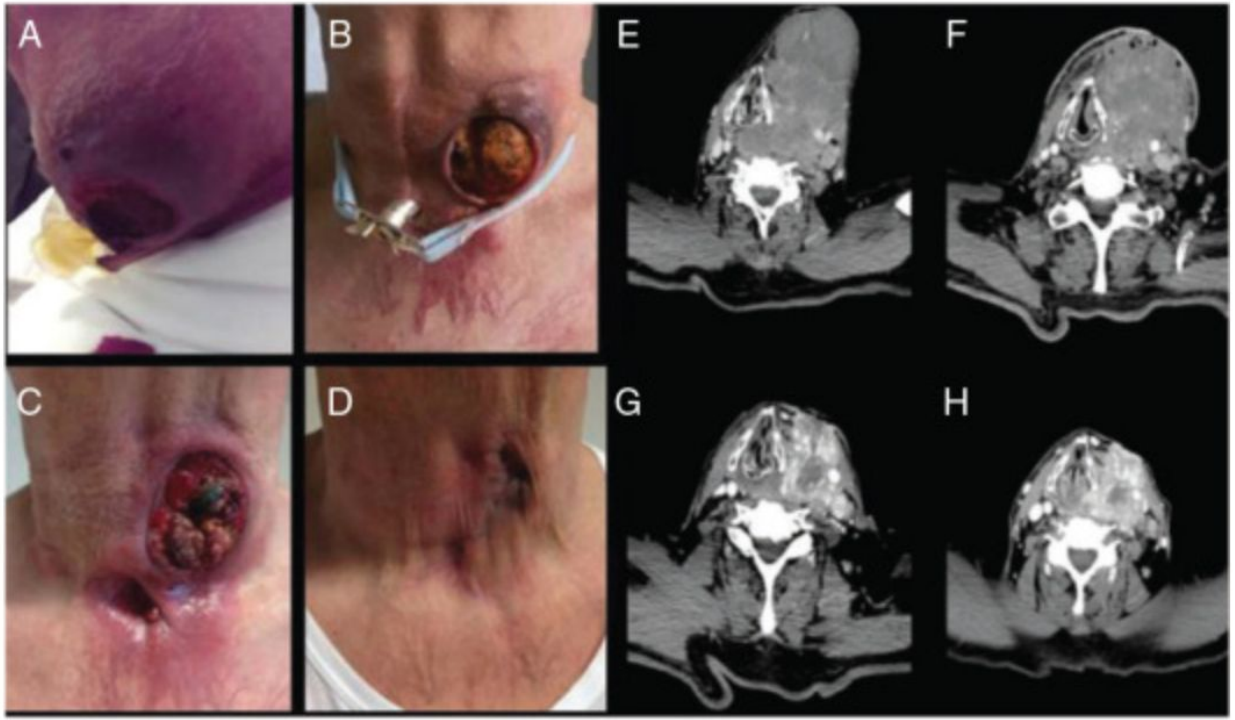
Evaluability of NGS results stratified for specimen age	Cases with specimens aged **< 5 years** /cases with performed NGS test	79	79/116 (68.1)
	DNA	71	70/105 (66.7)
	unevaluable results	2	2/71 (2.8)
	RNA	45	45/59 (76.3)
	unevaluable results	5	5/45 (11.1)
	Cases with specimens aged ≥ **5 years** /cases with performed NGS test	37	37/116 (31.9)
	DNA	34	34/105 (32.4)
	unevaluable results	11	11/34 (32.3)
	RNA	14	14/59 (23.7)
	unevaluable results	5	5/14 (35.7)
	Lower rate of not evaluable NGS in cases with specimens aged < 5 years vs ≥ 5 years		7/79 vs 16/37 *p = 0.0001*

Colombo E et al ESMO Open 2025

MKI vs selective inhibitors

	Anti-RET and anti-NTRK	Anti-BRAF
Higher response rate	X	?
Type of response (different pattern of shrinkage)	X	X
Better Toxicity profile	X	X
Age, comorbidities, performance status, scope of the treatment, site of tumor	X	X
Prolonged activity	X	?

Response from lenvatinib



Ann Oncol 2017

23 June 2022



Selpercatinib 80 mg x 2

F, 58 yrs old, PTC with *CCDC6-RET* fusion

6 July 2022



18 July 2022





April 2023



March 2024

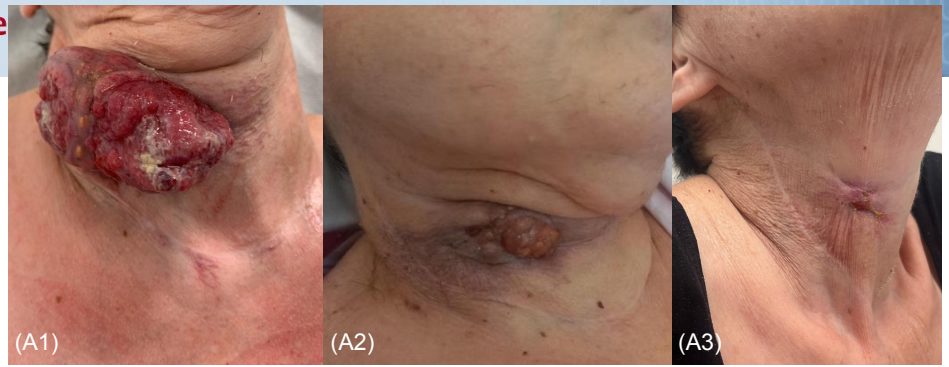
Which is the optimal sequence?

case reports

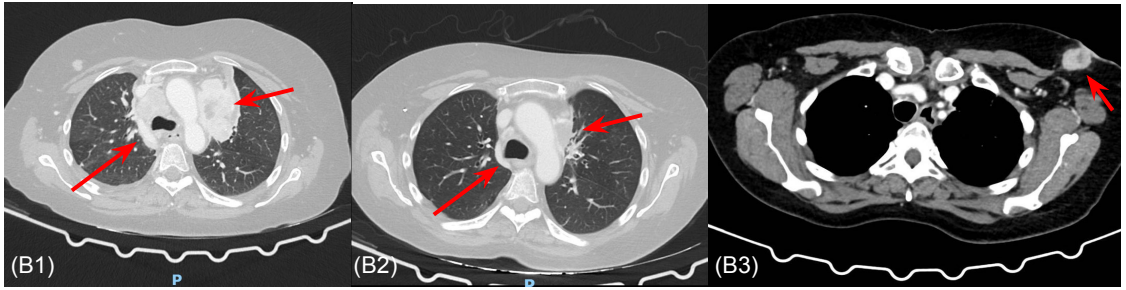
Response to Cabozantinib Following Acquired Entrectinib Resistance in a Patient With *ETV6-NTRK3* Fusion-Positive Carcinoma Harboring the *NTRK3*^{G623R} Solvent-Front Mutation

Dorothea Hanf, MD[1,2,3]; Christoph Heining, MD[1,2,3]; Karin Laaber, MSc[4,5]; Heiner Nebelung, MD[6]; Sebastian Uhrig, MSc[7,8,9]; Barbara Hutter, PhD[7,8,9]; Arne Jahn, MD[1,2,3,10,11,12]; Daniela Richter, PhD[1,2,3]; Daniela Aust, MD[13]; Friederike Herbst, PhD[4]; Stefan Fröhling, MD[9,14]; Hanno Glimm, MD[1,2,3,4]; and Gunnar Folprecht, MD[12,15]

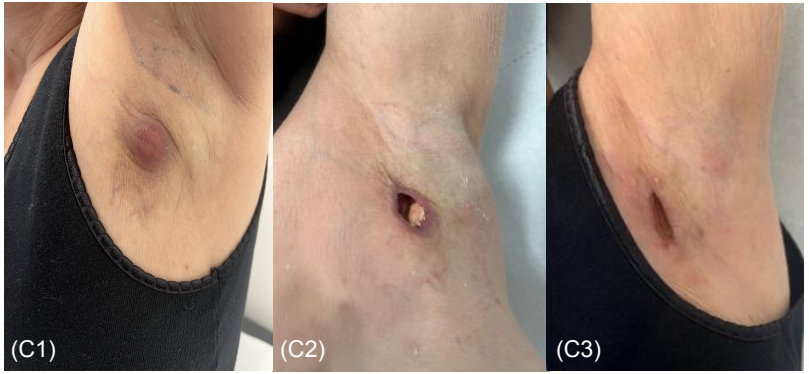
(A)



(B)



(C)





CONCLUSIONS

- NTRK and RET first line, BRAF second line
- MKI for non oncogene addicted
- Molecular test as early as possible
- NGS not for all
- Biopsy before the 2nd line to explore mechanism of resistance
- Optimal sequence is still a matter of debate
- Clinical trials





Premio Nobel per la Medicina, 1906



Thanks for your attention

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