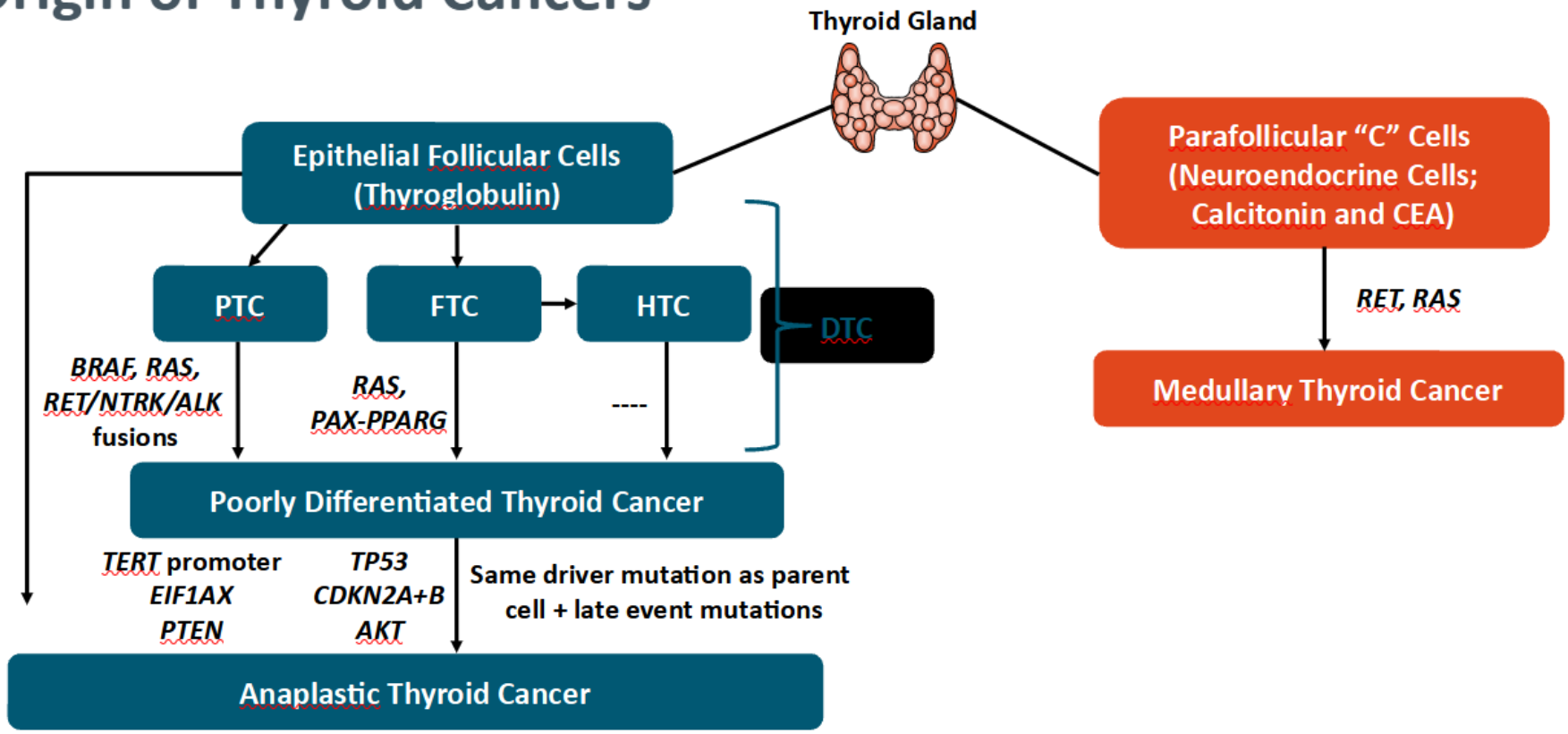
Carcinoma tiroideo iodio-refrattario, avanzato o metastatico : novità terapeutiche

Dr Vincenzo Ricci

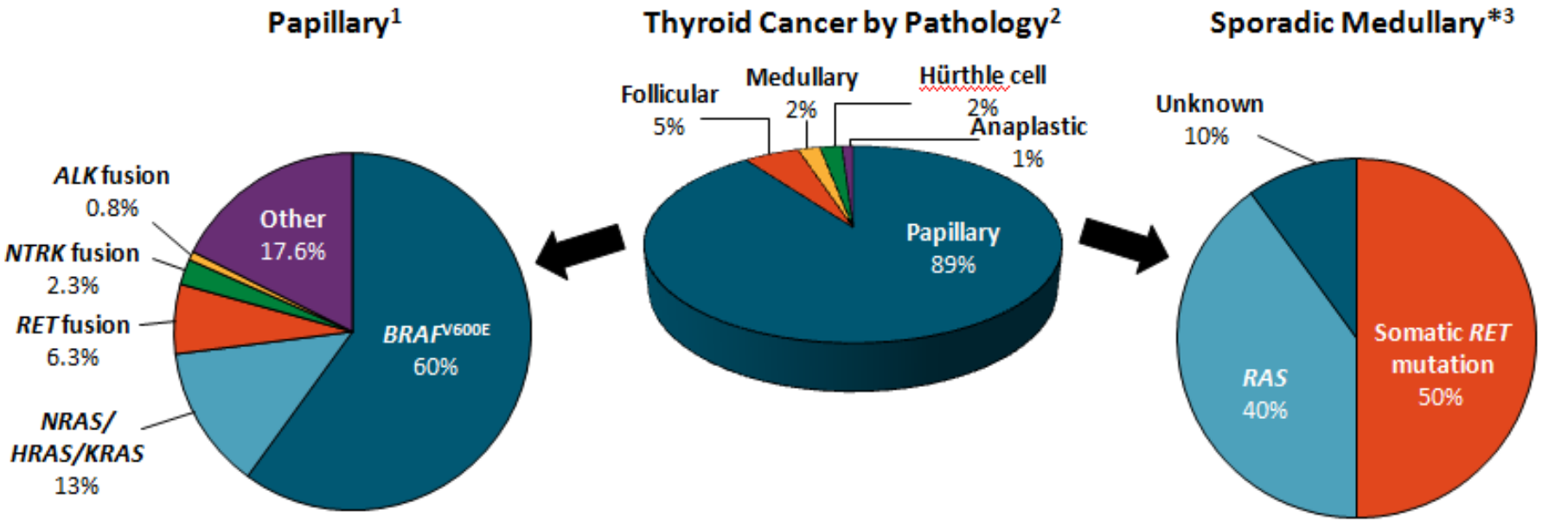
Agenda

- **Targeted tyrosine kinase inhibitors (TKIs)**
- **Target : BRAF, NTRK, RET**
- **Immunotherapy**

Origin of Thyroid Cancers



Mutation Spectrum in Thyroid Cancer



*Familial MTC: 100% germline *RET* mutation.

- Thyroid cancers are rich in druggable targets

1 Agarwal. Cell. 2014;159:676. 2. SEER. SEER cancer statistics review (CSR) 1975-2014.
3. Raue. Clin Cancer Res. 2016;22:5012.

Slide credit: clinicaloptions.com

CARCINOMA DIFFERENZIATO TIROIDEO IODO-REFRATTARIO

• Rappresenta un’entità clinica indipendente con una prognosi sfavorevole

• I tassi di sopravvivenza a 10 anni sono del 10% ed il tempo di sopravvivenza mediano è di 2.5-3.5 anni.

• Fino a pochi anni fa il carcinoma differenziato iodo-refrattario veniva trattato unicamente con polichemioterapia o monochemioterapia, impiegando regimi contenenti antracicline (cisplatino-doxorubicina) o taxani (carboplatino-paclitaxel), ottendendo una percentuale di risposte obiettive variabile dal 5 al 15%.

Targeted tyrosine kinase inhibitors (TKIs)

Targeted tyrosine kinase inhibitors (TKIs)—including vascular endothelial growth factor receptor inhibitors—that lead to the inhibition of tumor cell growth pathways, have shown activity in the treatment of progressive RR-DTC.

The National Comprehensive Cancer Network (NCCN) recommend **lenvatinib** or **sorafenib** (2 distinct TKIs) as systemic therapy for progressive and/or symptomatic RR-DTC

cabozantinib for patients must have received previous lenvatinib or sorafenib and progressed during or after treatment with up to two VEGFR tyrosine kinase inhibitors

Phase III DECISION trial

Patients were randomly allocated on a 1:1 basis to sorafenib or placebo.

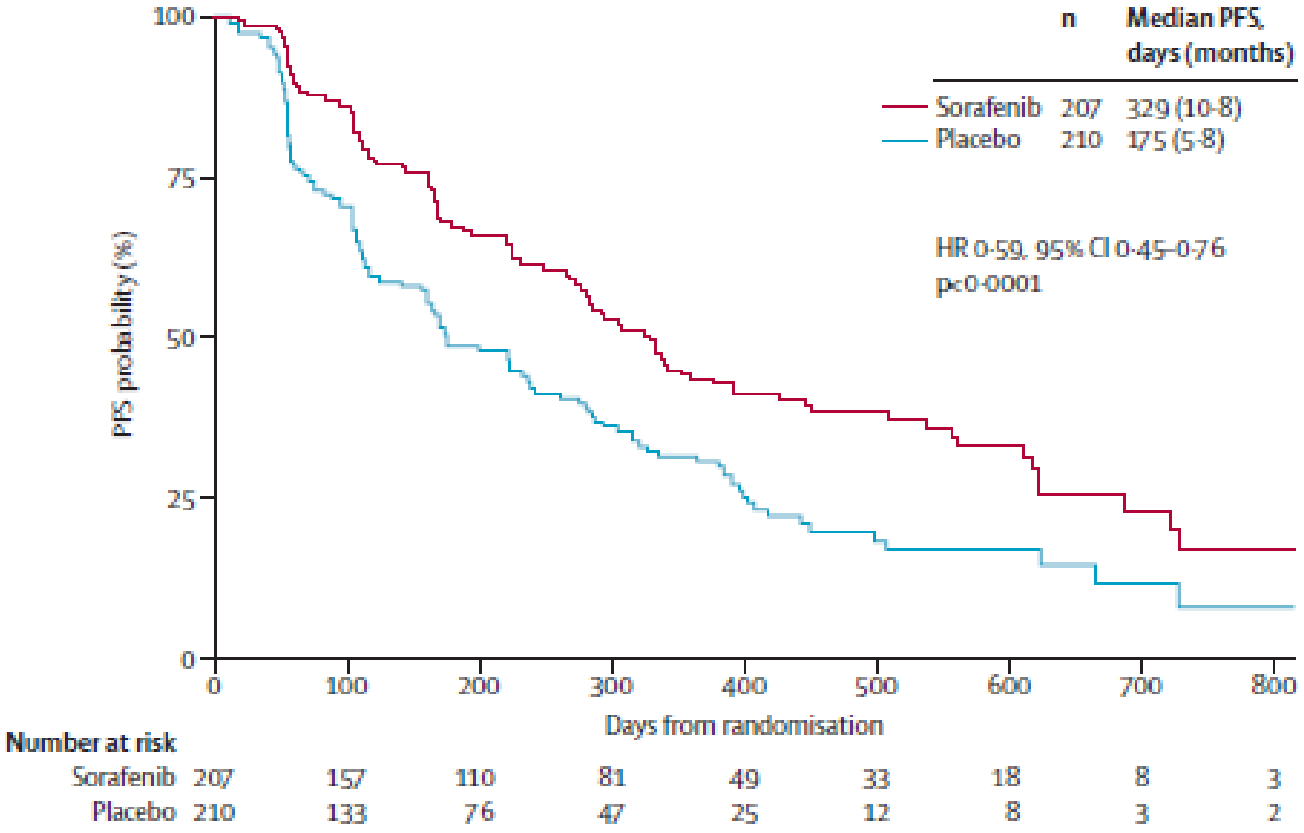
The intention-to-treat population comprised 417 patients (207 in the sorafenib group and 210 in the placebo group) and the safety population was 416 patients (207 in the sorafenib group and 209 in the placebo group).

Median progression-free survival was significantly longer in the sorafenib group (10·8 months) than in the placebo group (5·8 months; hazard ratio [HR] 0·59, 95% CI 0·45–0·76; $p<0·0001$).

Progression-free survival improved in all prespecified clinical and genetic biomarker subgroups, irrespective of mutation status

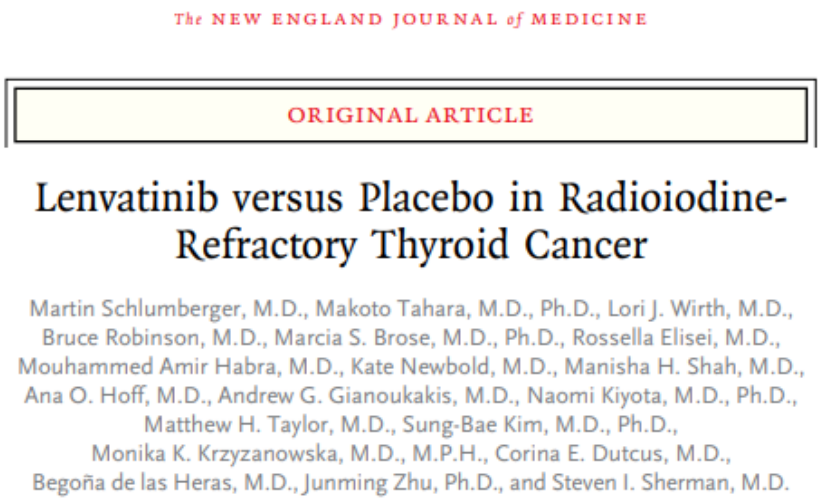
Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial

*Marcia S Brose, Christopher M Nutting, Barbara Jarzab, Rossella Elisei, Salvatore Siena, Lars Bastholt, Christelle de la Fouchardiere, Furio Pacini, Ralf Paschke, Young Kee Shong, Steven I Sherman, Johannes W A Smit, John Chung, Christian Kappeler, Carol Peña, István Molnár, Martin J Schlumberger, on behalf of the DECISION investigators**



Lancet 2014; 384: 319–28
Published Online
April 24, 2014
http://dx.doi.org/10.1016/S0140-6736(14)60421-9

LEnvatinib in Differentiated **C**ancer of the **T**hyroid (SELECT TRIAL)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer

Martin Schlumberger, M.D., Makoto Tahara, M.D., Ph.D., Lori J. Wirth, M.D., Bruce Robinson, M.D., Marcia S. Brose, M.D., Ph.D., Rossella Elisei, M.D., Mouhammed Amir Habra, M.D., Kate Newbold, M.D., Manisha H. Shah, M.D., Ana O. Hoff, M.D., Andrew G. Gianoukakis, M.D., Naomi Kiyota, M.D., Ph.D., Matthew H. Taylor, M.D., Sung-Bae Kim, M.D., Ph.D., Monika K. Krzyzanowska, M.D., M.P.H., Corina E. Dutcus, M.D., Begoña de las Heras, M.D., Junming Zhu, Ph.D., and Steven I. Sherman, M.D.

- Lenvatinib, an oral inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, fibroblast growth factor receptors 1 through 4, platelet-derived growth factor receptor α, RET, and KIT
- Phase 3, randomized, double-blind, multicenter study involving patients with progressive thyroid cancer that was refractory to iodine-131
- 261 patients randomized to received lenvatinib (at a daily dose of 24 mg per day in 28-day cycles) and 131 patients to received placebo

LEnvatinib in Differentiated **C**ancer of the **T**hyroid (SELECT TRIAL)

Table 1. Baseline Characteristics in the Intention-to-Treat Population.*

Variable	Lenvatinib (N=261)	Placebo (N=131)
Median age — yr	64	61
Male sex — no. (%)	125 (47.9)	75 (57.3)
Region — no. (%)		
Europe	131 (50.2)	64 (48.9)
North America	77 (29.5)	39 (29.8)
Other†	53 (20.3)	28 (21.4)
ECOG performance status — no. (%)‡		
0 or 1	248 (95.0)	129 (98.5)
2 or 3	13 (5.0)	2 (1.5)
One prior treatment regimen with a tyrosine kinase inhibitor — no. (%)§	66 (25.3)	27 (20.6)
Histologic subtype of differentiated thyroid cancer — no. (%)¶		
Papillary	132 (50.6)	68 (51.9)
Poorly differentiated	28 (10.7)	19 (14.5)
Follicular, not Hürthle cell	53 (20.3)	22 (16.8)
Hürthle cell	48 (18.4)	22 (16.8)
Metastatic lesions — no. (%)		
With bony metastases	104 (39.8)	48 (36.6)
With pulmonary metastases	226 (86.6)	124 (94.7)

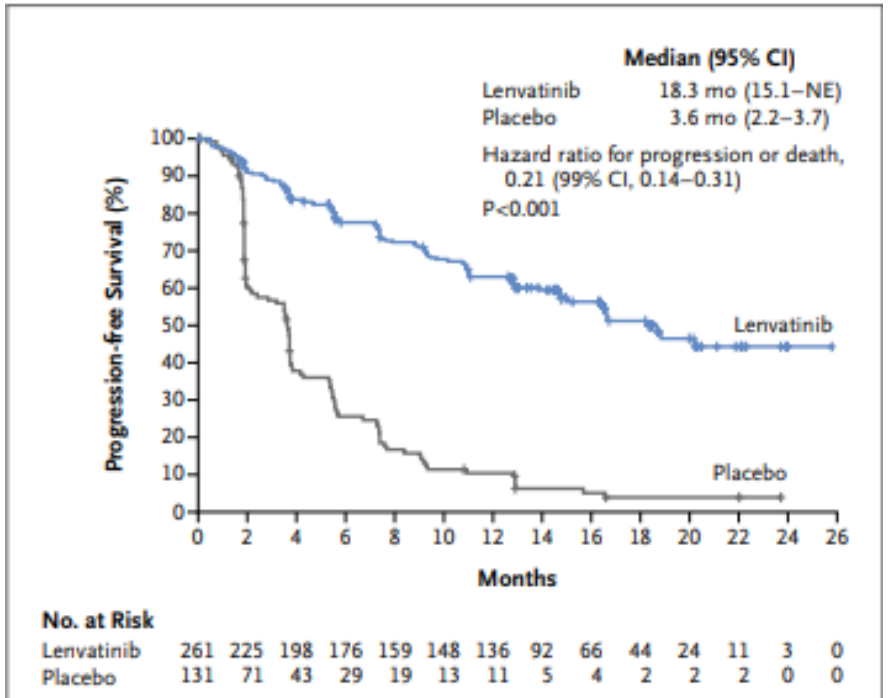


Figure 2. Kaplan–Meier Estimate of Progression-free Survival in the Intention-to-Treat Population.

Tumor responses were assessed with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and were confirmed by independent centralized radiologic review. Tumor responses were calculated as the maximum percentage change from baseline in the sum of the diameters of target lesions. CI denotes confidence interval, and NE not estimable.

The **median progression-free survival** was 1**8.3 months** in the lenvatinib group **and 3.6 months** in the placebo group (hazard ratio for progression or death, 0.21; 99% confidence interval, 0.14 to 0.31; P<0.001). A progression-free survival benefit associated with lenvatinib was observed in all prespecified subgroups. **The response rate** was **64.8%** in the lenvatinib group (4 complete responses and 165 partial responses) and **1.5%** in the placebo group (P<0.001). The median overall survival was not reached in either group.

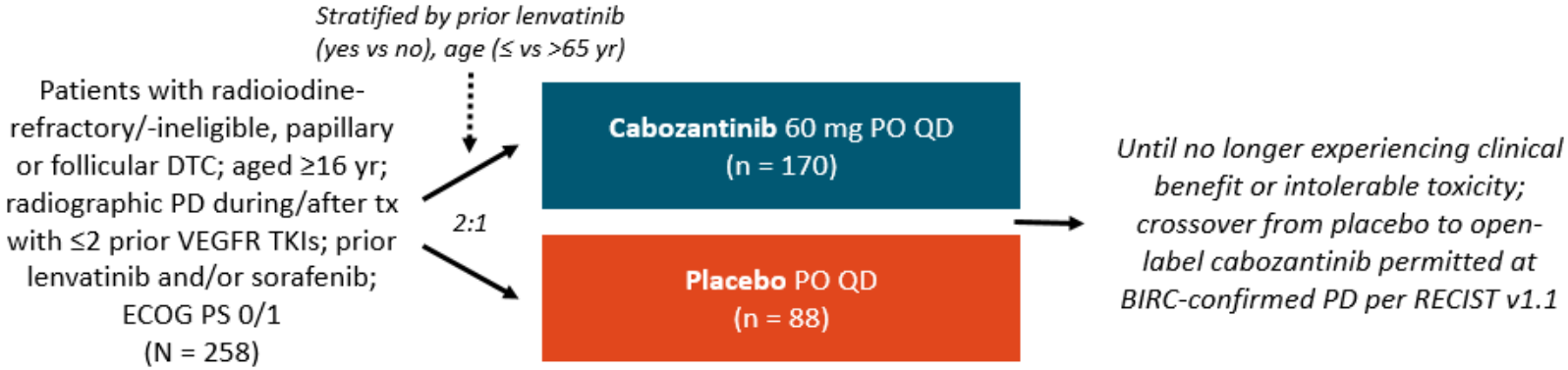
LEnvatinib in Differentiated **C**ancer of the **T**hyroid (SELECT TRIAL)

Table 3. **Adverse Effects.**

Effect	Lenvatinib (N=261)		Placebo (N=131)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any treatment-related adverse effect — no. of patients (%)	254 (97.3)	198 (75.9)	78 (59.5)	13 (9.9)
Adverse effect developing during treatment — no. of patients (%)				
Serious*				
Total	130 (49.8)		30 (22.9)	
Treatment-related	79 (30.3)		8 (6.1)	
Fatal				
Total†	20 (7.7)		6 (4.6)	
Treatment-related	6 (2.3)		0	
Treatment-related adverse effect of any grade in ≥10% of patients, of grade ≥3 in ≥2%, or both — %				
Hypertension	67.8	41.8	9.2	2.3
Diarrhea	59.4	[illegible]	8.4	0
Fatigue or asthenia	59.0	9.2	27.5	2.3
Decreased appetite	50.2	5.4	11.5	0
Decreased weight	46.4	9.6	9.2	0
Nausea	41.0	2.3	13.7	0.8
Stomatitis	35.6	4.2	3.8	0
Palmar–plantar erythrodysesthesia syndrome	31.8	[illegible]	0.8	0
Proteinuria	31.0	10.0	1.5	0
Vomiting	28.4	[illegible]	6.1	0
Headache	27.6	2.7	6.1	0
Dysphonia	24.1	1.1	3.1	0
Arthralgia	18.0	0	0.8	0
Dysgeusia	16.9	0	1.5	0
Rash	16.1	0.4	1.5	0
Constipation	14.6	0.4	8.4	0
Myalgia	14.6	1.5	2.3	0
Dry mouth	13.8	0.4	3.8	0
Upper abdominal pain	13.0	0	3.8	0
Abdominal pain	11.5	0.4	0.8	0.8
Peripheral edema	11.1	0.4	0	0
Alopecia	11.1	0	3.8	0
Dyspepsia	10.0	0	0	0
Oropharyngeal pain	10.0	0.4	0.8	0
Hypocalcemia	6.9	2.7	0	0
Pulmonary embolism	2.7	2.7	1.5	1.5

COSMIC-311 Final Analysis: Study Design

- Final analysis of international, randomized, double-blind phase III trial (data cutoff: February 8, 2021; median follow-up: 10.1 mo)
  - Per IDMC recommendation, enrollment stopped with last patient enrolled on February 4, 2021



- **Coprimary endpoints:** PFS by BIRC in ITT population; ORR per RECIST v1.1 by BIRC in ITT population (first 100 randomized patients)

Capdevila. ESMO 2021. Abstr LBA67. NCT03690388.

Slide credit: clinicaloptions.com

COSMIC-311 Final Analysis: Baseline Characteristics

Characteristic, n (%)	Cabozantinib (n = 170)	Placebo (n = 88)
Median age, yr (range)	65 (31-85)	66 (37-83)
Female, n (%)	87 (51)	49 (56)
Race, n (%)		
▪ White	121 (71)	59 (67)
▪ Non-white	37 (22)	25 (28)
▪ Unknown	12 (7)	4 (5)
Geographic region, n (%)		
▪ Europe	82 (48)	39 (44)
▪ Asia	24 (14)	19 (22)
▪ USA and Canada	15 (9)	12 (14)
▪ Rest of world	49 (29)	18 (20)
ECOG PS 0/1, n (%)	74 (44)/ 95 (56)	43 (49)/ 45 (51)
Histologic subtype: papillary/follicular, n (%)	96 (56)/ 78 (46)	54 (61)/ 35 (40)

Characteristic, n (%)	Cabozantinib (n = 170)	Placebo (n = 88)
Prior sorafenib/ lenvatinib		
▪ Only sorafenib	63 (37)	33 (38)
▪ Only lenvatinib	68 (40)	34 (39)
▪ Both sorafenib and lenvatinib	39 (23)	21 (24)
No. prior VEGFR TKI: 1/2	126 (74)/ 43 (25)	65 (74)/ 23 (26)
Metastatic sites, n (%)		
▪ Bone	51 (30)	21 (24)
▪ Liver	25 (15)	9 (10)
▪ Lung	121 (71)	61 (69)
▪ Other	127 (75)	70 (80)

Capdevila. ESMO 2021. Abstr LBA67.

Slide credit: clinicaloptions.com

COSMIC-311 Final Analysis: PFS, ORR

Outcome	Cabozantinib (n = 170)	Placebo (n = 88)	HR
Median PFS by BIRC, mo	11.00	1.9	0.22 (96% CI: 0.15-0.32; *P* <.0001)
Median OS, mo	19.4	NE	0.76 (95% CI: 0.45-1.31)
ORR by BIRC, %	11*	0	--

*Includes 1 CR.

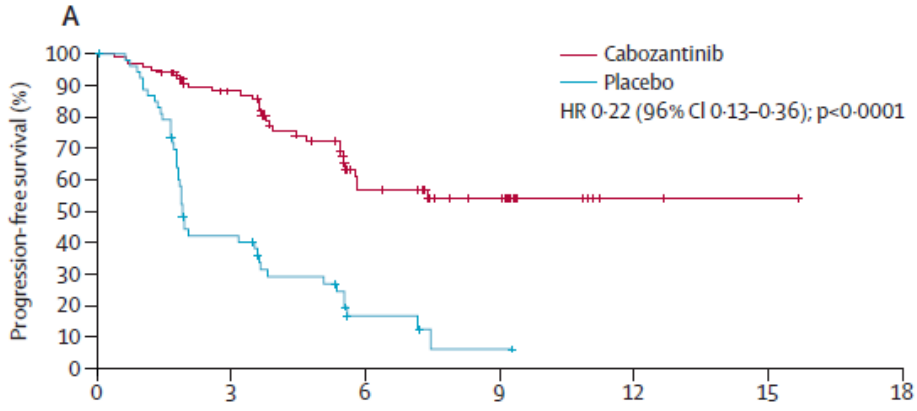
- Trial continued to demonstrate significant improvement in primary endpoint of median PFS with cabozantinib vs placebo (*P* <.0001)

Capdevila. ESMO 2021. Abstr LBA67.

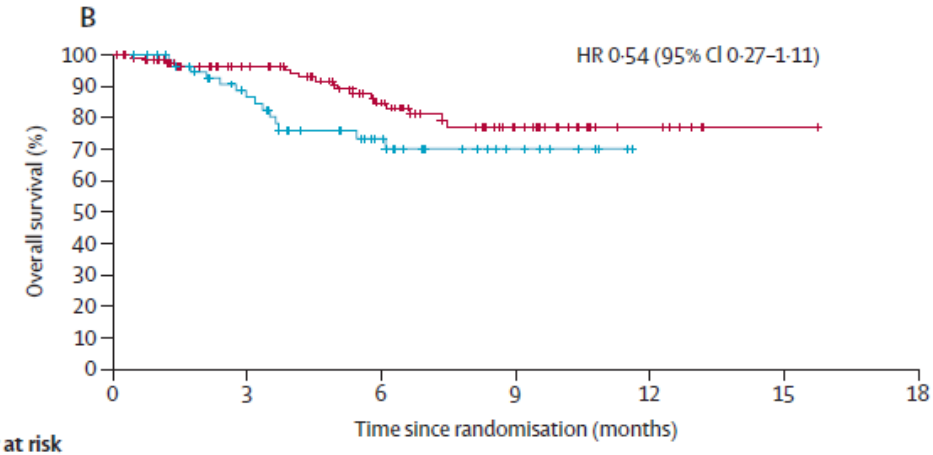
Slide credit: clinicaloptions.com

Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial

Marcia S Brose, Bruce Robinson, Steven I Sherman, Jolanta Krajewska, Chia-Chi Lin, Fernanda Vaisman, Ana O Hoff, Erika Hitre, Daniel W Bowles, Jorge Hernando, Leonardo Faoro, Kamalika Banerjee, Jennifer W Oliver, Bhumsuk Keam, Jaume Capdevila



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)



Number at risk (number censored)							
Cabozantinib	125 (0)	90 (31)	54 (58)	24 (84)	7 (101)	1 (107)	0 (108)
Placebo	62 (0)	42 (13)	24 (25)	9 (39)	0 (48)	0 (48)	0 (48)

Lancet Oncol 2021; 22: 1126–38

Published Online
July 5, 2021
https://doi.org/10.1016/
S1470-2045(21)00332-6

COSMIC-311 Final Analysis: PFS by Prior Therapy

Median PFS, Mo	Cabozantinib	Placebo	HR (95% CI)
Prior sorafenib/no lenvatinib	n = 63 16.6	n = 33 3.2	0.13 (0.06-0.26)
Prior lenvatinib/no sorafenib	n = 68 5.8	n = 34 1.9	0.28 (0.16-0.48)
Prior lenvatinib and sorafenib	n = 39 7.6	n = 21 1.9	0.27 (0.13-0.54)

- PFS improvement with cabozantinib vs placebo consistent across subgroups defined by prior exposure to sorafenib and/or lenvatinib

Capdevila. ESMO 2021. Abstr LBA67.

Slide credit: clinicaloptions.com

COSMIC-311 Final Analysis: Safety

AEs in ≥15% of Patients, %	Cabozantinib (n = 170)		Placebo (n = 88)	
	Any Gr	Gr 3/4	Any Gr	Gr 3/4
Any	98	62	85	28
Diarrhea	62	8	3	0
Hand-foot skin reaction	47	10	1	0
Hypertension	32	12	3	2
Decreased appetite	31	3	13	0
Fatigue	29	9	8	0
Nausea	28	2	2	0
ALT increase	25	1	2	1
AST increase	25	0	2	0

- Dose reductions due to AEs: cabozantinib, 67%; placebo, 5%
- No grade 5 TRAEs

AEs in ≥15% of Patients, %	Cabozantinib (n = 170)		Placebo (n = 88)	
	Any Gr	Gr 3/4	Any Gr	Gr 3/4
Hypocalcemia	25	8	3	2
Weight decrease	22	2	2	0
Vomiting	18	2	8	0
Stomatitis	18	4	2	0
Asthenia	17	2	14	0
Mucosal inflammation	17	2	0	0
Hypomagnesemia	16	1	3	0
Proteinuria	16	2	2	0

- Treatment discontinuations due to AEs unrelated to DTC: cabozantinib, 8.8%; placebo, 0%

Capdevila. ESMO 2021. Abstr LBA67.

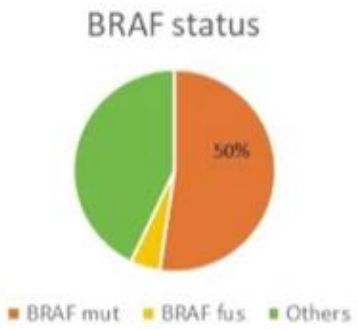
Slide credit: clinicaloptions.com

COSMIC-311 Final Analysis: Conclusions

- In this final analysis of the COSMIC-311 trial, cabozantinib maintained significantly improved PFS vs placebo in patients with radioiodine-refractory/-ineligible DTC with PD after prior VEGFR TKI
  - Median PFS: 11.0 vs 1.9 (HR: 0.22; 96% CI: 0.15-0.32; *P* <.0001)
  - PFS improvement maintained across subgroups defined by prior lenvatinib and/or sorafenib
- Coprimary endpoint of ORR was not met
- No new safety signals observed with cabozantinib

Anti-BRAF strategies in RAI-R DTC

	Vemurafenib naïve (n=26)	Vemurafenib prev tx (n=22)	Dabrafenib (n=22)	Dabrafenib + trametinib (n=24)
Response Rate	39%	27%	35%	30%
Median PFS (months)	18.2	8.9	10.7	15.1
Median OS (months)	NR	14.4	37.9	47.5



Dabrafenib/trametinib: accelerated approval for BRAF mutated solid tumors with no alternatives in US

Brose M, Lancet Oncol 2016; Busaidy NL, Thyroid 2022

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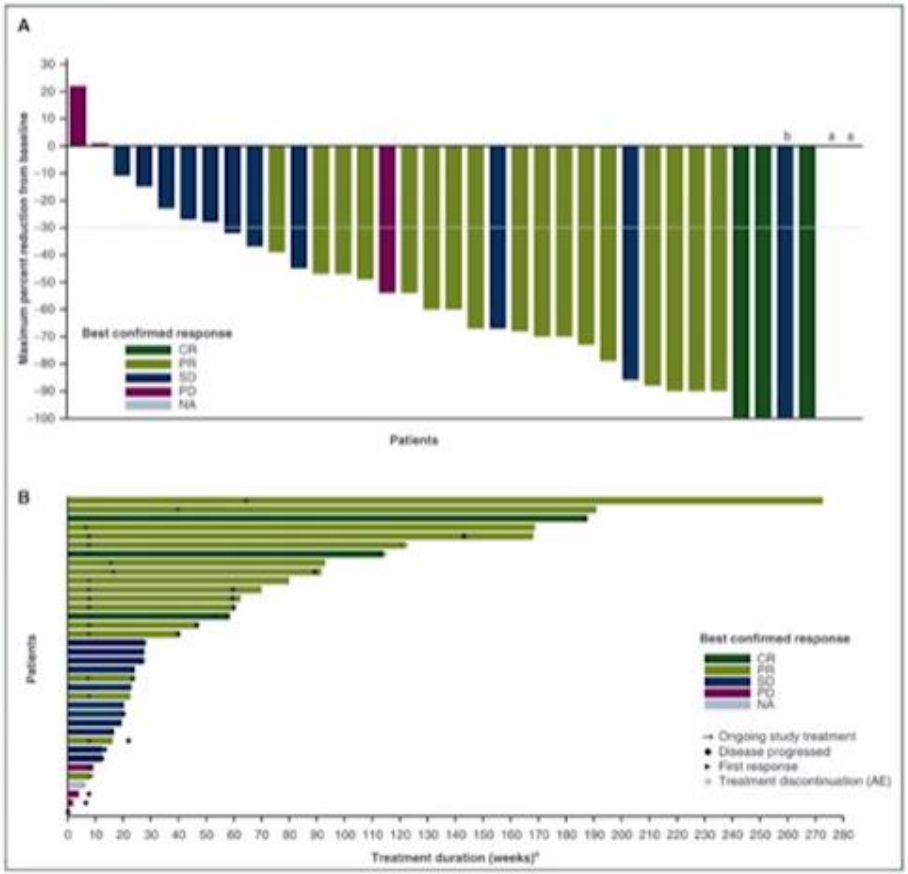
Dabrafenib and Trametinib in Anaplastic Thyroid Carcinoma

Table 3. ORRs per investigator and independent assessment

Response, *n* (%)	Investigator assessment		Independent assessment	
	ITT Assessable (*n* = 36)	*BRAF* V600E Assessable* (*n* = 33)	ITT Assessable (*n* = 36)	*BRAF* V600E Assessable* (*n* = 33)
ORR	20 (56)	20 (61)	19 (53)	19 (58)
95% CI	38.1-72.1	42.1-77.1	35.5-69.6	39.2-74.5
CR	3 (8)	3 (9)	2 (6)	2 (6)
PR	17 (47)	17 (52)	17 (47)	17 (52)
SD	11 (31)	8 (24)	8 (22)	6 (18)
PD	4 (11)	4 (12)	8 (22)	7 (21)
NA	1 (3)	1 (3)	1 (3)	1 (3)

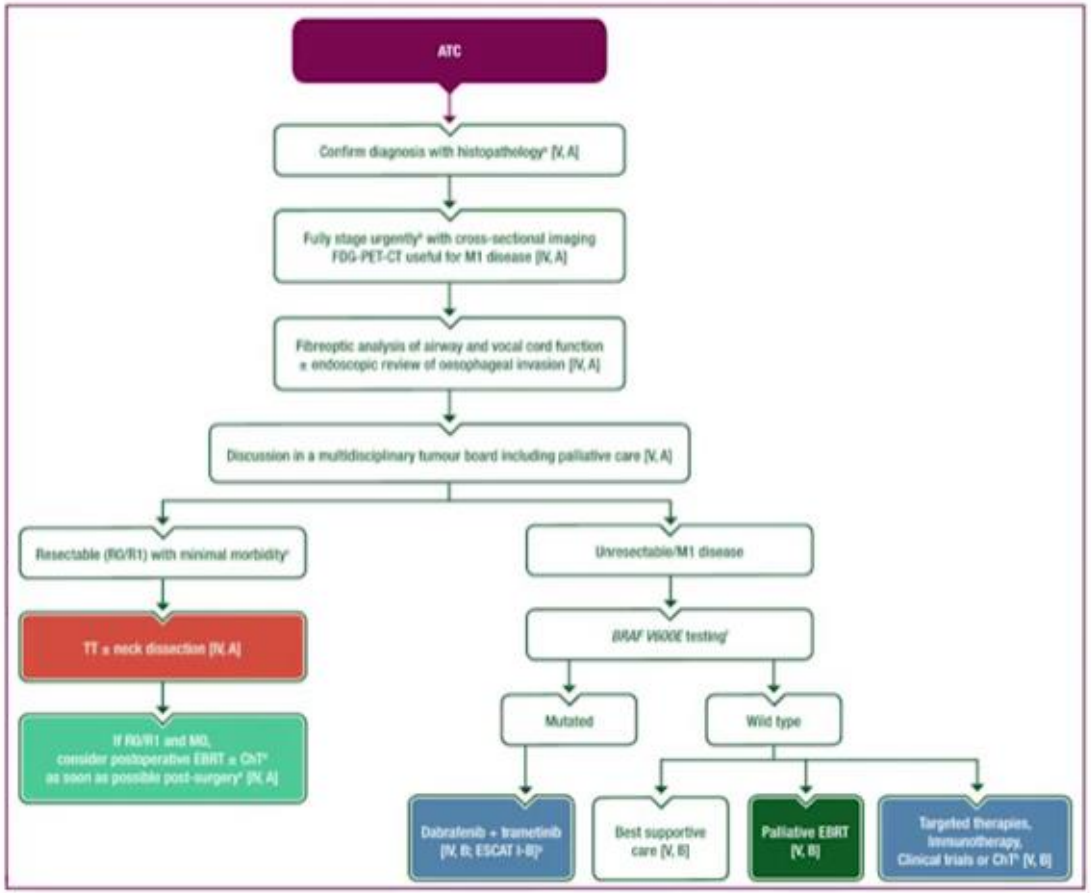
CI, confidence interval; CR, complete response; ITT, intent-to-treat; NA, not assessable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
*Includes patients with centrally confirmed *BRAF* V600E-mutant disease.

Median PFS 6.7 months (95% CI 3.7-12.9)
12-month PFS 43.2% (95% CI 26.6-58.8)
12-month OS 51.7% (95% CI 33.6-67.1)

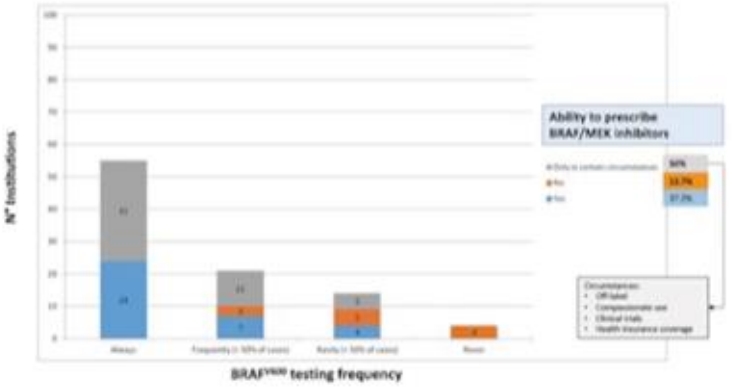


Subbiah V, Ann Oncol 2022

ESMO guidelines 2022: Anaplastic Follicular derived Thyroid Carcinoma



European picture of the anti-BRAF agents use



Locati LD et al., submitted

Filetti S et al, Ann Oncol 2022

<u>NEWS - legge 1996 / 648</u> : trattamento dei pazienti affetti da carcinoma anaplastico della tiroide, localmente avanzato o metastatico, con mutazione BRAF V600E

GAZZETTA UFFICIALE
DELLA REPUBBLICA ITALIANA

AGENZIA ITALIANA DEL FARMACO

DETERMINA 1 marzo 2023

Inserimento dei medicinali «Dabrafenib» e «Trametinib» nell'elenco istituito, ai sensi della legge 23 dicembre 1996, n. 648, per il trattamento del carcinoma anaplastico della tiroide. (Determina n. 2
Generale n.55 del 06-03-2023)

Vista la delibera di approvazione del consiglio d'amministrazione di AIFA del 23 gennaio 2023, n. 4;

Ritenuto, pertanto, di includere i medicinali «Dabrafenib» e «Trametinib» nell'elenco dei medicinali erogabili a totale carico del Servizio sanitario nazionale, ai sensi della legge 23 dicembre 1996, n. 648, per il trattamento del carcinoma anaplastico della tiroide;

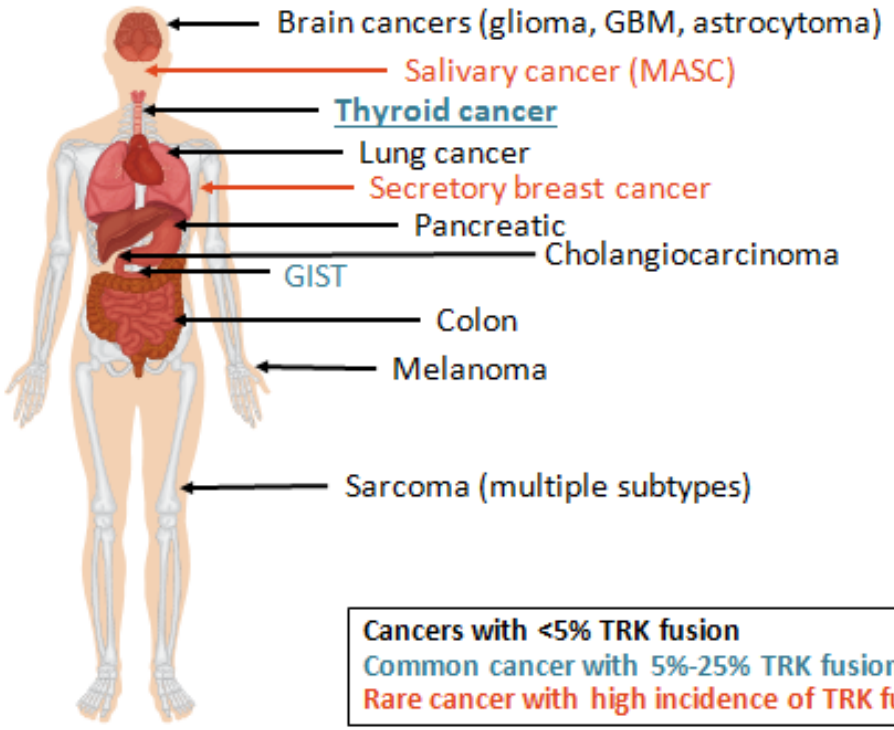
Determina:

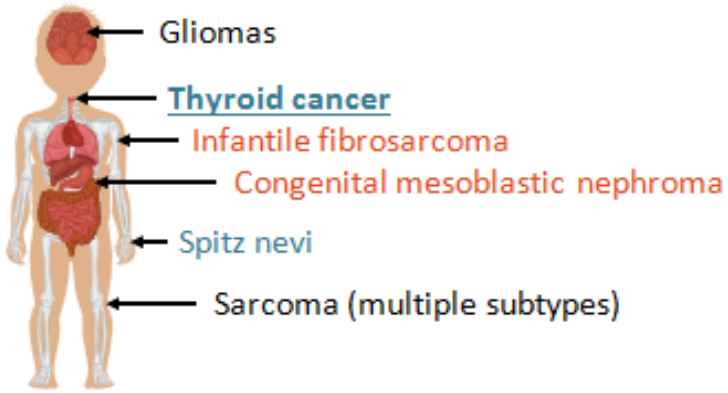
Art. 1

I medicinali DABRAFENIB e TRAMETINIB sono inseriti ai sensi dell'art. 1, comma 4, del decreto-legge 21 ottobre 1996, n. 536, convertito dalla legge 23 dicembre 1996, n. 648, nell'elenco istituito col provvedimento della Commissione unica del farmaco, per l'indicazione terapeutica di cui all'art. 2.

In data 6 marzo 2023, è stato pubblicato in Gazzetta Ufficiale l'inserimento di dabrafenib e trametinib nell'elenco istituito ai sensi della legge 1996 / 648, per il trattamento dei pazienti affetti da carcinoma anaplastico della tiroide, localmente avanzato o metastatico, con mutazione BRAF V600E, sottoposti a un precedente trattamento chirurgico, radioterapico e/o chemioterapico

NTRK Fusions Are Rare Events: 0.27% Across >11,000 Patients With Tumors of All Types





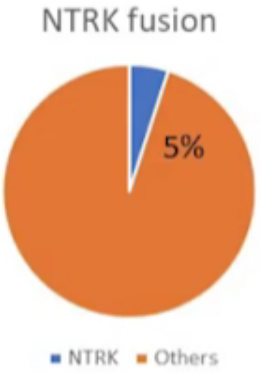
Cancers with <5% TRK fusion
Common cancer with 5%-25% TRK fusions
Rare cancer with high incidence of TRK fusions (>90%)

Cocco. Nat Rev Clin Oncol. 2018;15:731. Gatalica. AACR-NCI-EORTC 2017. Abstr A047.

Slide credit: clinicaloptions.com

Entrectinib and Larotrectinib in papillary thyroid carcinoma with *NTRK* fusion

	Entrectinib	Larotrectinib
	Prior TKI 77%	**Prior TKI 55%**
N°	13	22
ORR (95% CI)	**54% (25, 88)**	**86% (64, 97)**
CR	**8%**	**10%**
DCR (CR, PR, SD)	68%	100%
mDOR, mos (95% CI)	13.2 (7.9, NE)	-
mPFS, mos (95% CI)	19.9 (6.5, 33.8)	-
mOS, mos (95% CI)	19.9 (14.5-NE)	-
≥ G3 tox	76%	**7%**



Waguespack SG, Eur J End 2022; Bowels DW et al. ETA 11 sept 2022 OP-03-14

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Larotrectinib (laro) long-term efficacy and safety in patients (pts) with tropomyosin receptor kinase (TRK) fusion thyroid carcinoma (TC).

The gene fusions involved NTRK1 (n =14; 47%) or NTRK3 (n =16; 53%).

Larotrectinib was administered at 100 mg twice daily to most pts;

ORR was 63% (95% confidence interval [CI] 44–80): **three (10%) complete response**, 16 (53%) partial response (PR), five (17%) stable disease, four (13%) progressive disease, and two (7%) not evaluable.

For pts classified as **differentiated TC (DTC**; n = 23), the **ORR was 78%** (95% CI 56–93). For pts classified as **anaplastic TC** (ATC; n = 7), **the ORR was 14%** (95% CI 0–58). All four pts with CNS metastases at baseline had a PR.

Median time to response was 1.9 months, and median duration of response (DoR) was 43.3 months (95% CI 21.6–not estimable [NE]) at a median follow-up of 32.3 months.

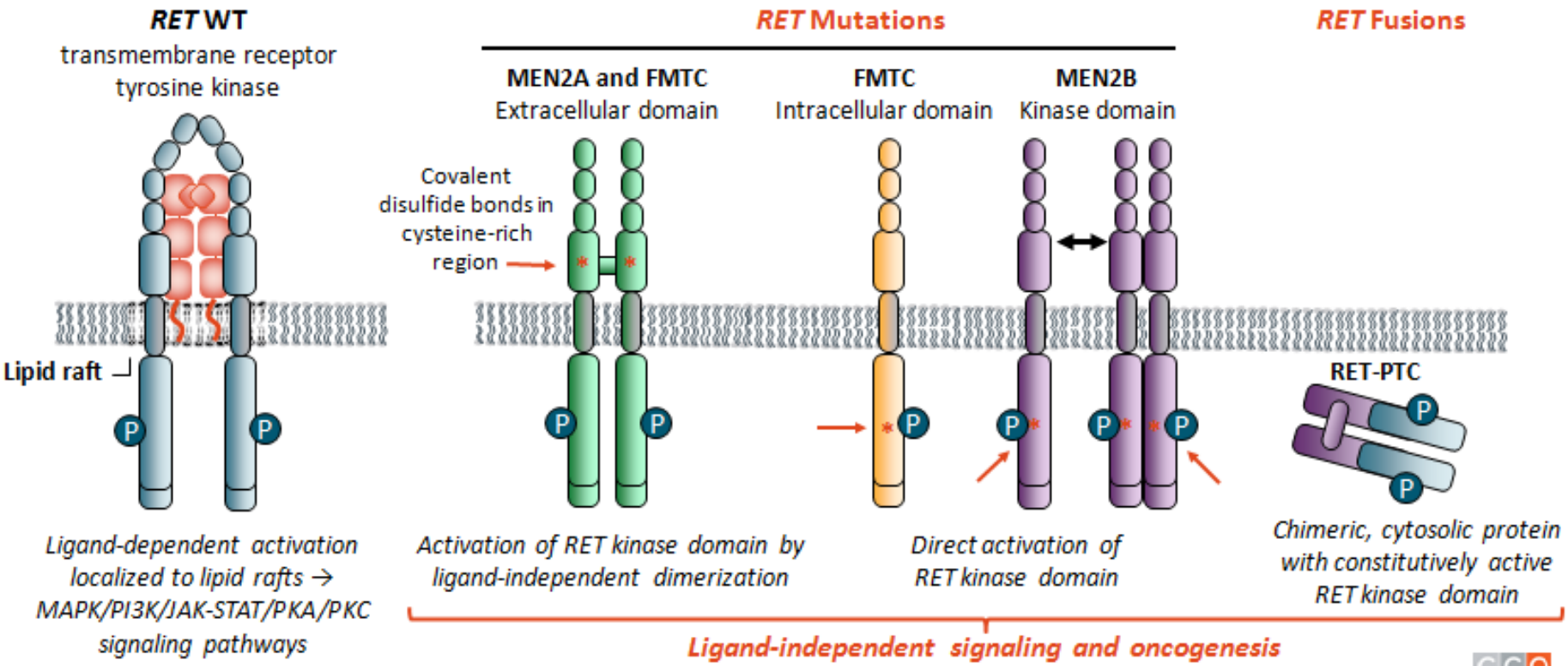
Median progression-free survival was 35.5 months (95% CI 23.4–NE) at a median follow-up of 34.0 months.

Median overall survival (OS) was not reached (NR; 95% CI 48.7–NE) at a median follow-up of 46.4 months; **the 48-month OS rate was 71%** (95% CI 54–88).

Median OS was NR (95% CI 48.7–NE) in DTC and 8.8 months (95% CI 2.6–NE) in ATC.

J Clin Oncol 41, 2023 (suppl 16; abstr 6091)

2 Major Mechanisms of *RET* Proto-Oncogene Activation in Thyroid Cancer: *RET* Mutations and *RET* Fusions

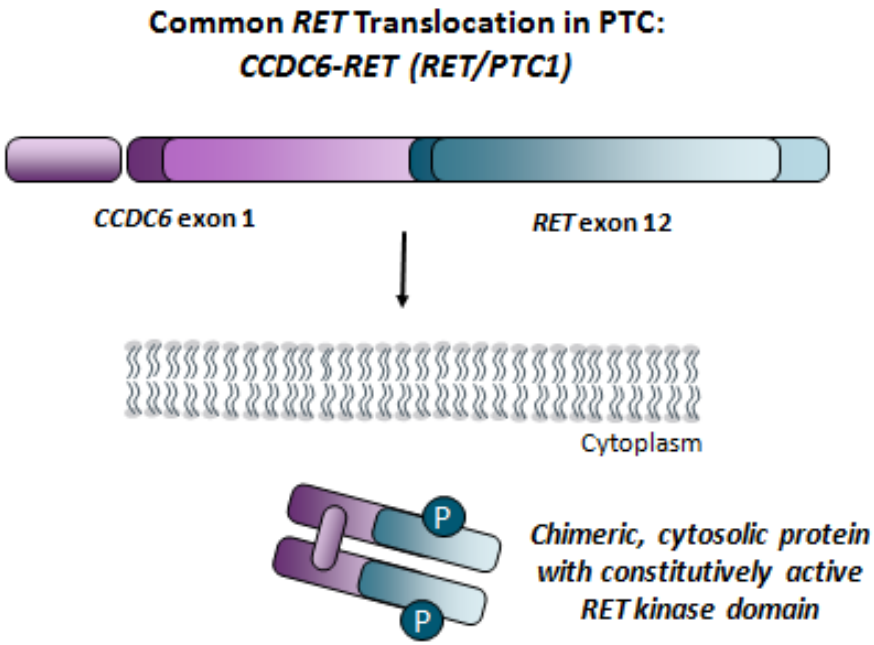


Subbiah. Cancer Discov. 2020;10:498. Drilon. Nat Rev Clin Oncol. 2018;15:510.

Slide credit: clinicaloptions.com

RET Fusions in Papillary Thyroid Carcinoma

- *RET* fusions found in <10% of PTCs
  - More frequent in pediatric and AYA patients: ~30%
  - 58% in pediatric Chernobyl-induced cancers
- 90% accounted for by *CCDC6-RET (RET/PTC1), NCOA4-RET (RET/PTC3)*
  - >20 5' fusion partners described
- Also can be present in PDTC, ATC

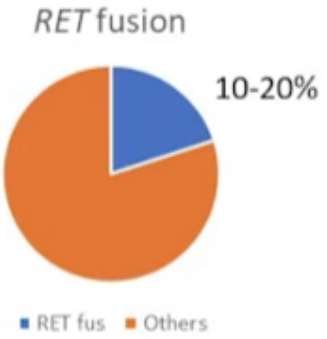


Agrawal. Cell. 2014;159:676. Thein. Trends Cancer. 2021;7:1074. Santoro. Genes (Basel). 2020;11:424. Saldarriaga. Front Oncol. 2019;9:1303. Ricarte-Filho. J Clin Invest. 2013;123:4935.

Slide credit: clinicaloptions.com

Pralsetinib and Selpercatinb in DTC with *RET* fusion

	Pralsetinib	Selpercatinib	Selpercatinib
	Prior RAI/ Sor/ Lenv 12Apr21	Prior RAI/ Sor/ Len June 2021	Naive
N°	19	22	12
ORR (95% CI)	**89.5% (67, 99)**	**77% (55, 92)**	**92% (62, 100)**
CR	**10.5%**	**9%**	**33%**
DCR (CR, PR, SD)	100%	100%	100%
mTTR, mos	1.8	-	-
mDOR, mos (95% CI)	17.5 (11.2, NE)	18.0 (10, NE)	NE (15, NE)
Ongoing w response at 1 yr	71.3%	-	-
Median follow-up, mos	13	20.3	9.1
mPFS, mos (95% CI)	19.4 (13, NE)	-	-
12-mo PFS (95% CI)	**74.4% (55, 94)**	**69% (43, 85)**	**100% (100, 100)**
Drug interruption for side effects	**5%**	**4.1%**	



Sherman EJ ASCO 2021; Mansfield ASCO 2022

Medullary thyroid cancer (MTC)

• MTC originates from the parafollicular C cells of the thyroid gland and represents 5% of all thyroid cancers

• MTC is a relatively indolent tumor, and the 10-year overall survival (OS) rate is approximately 75% to 80%

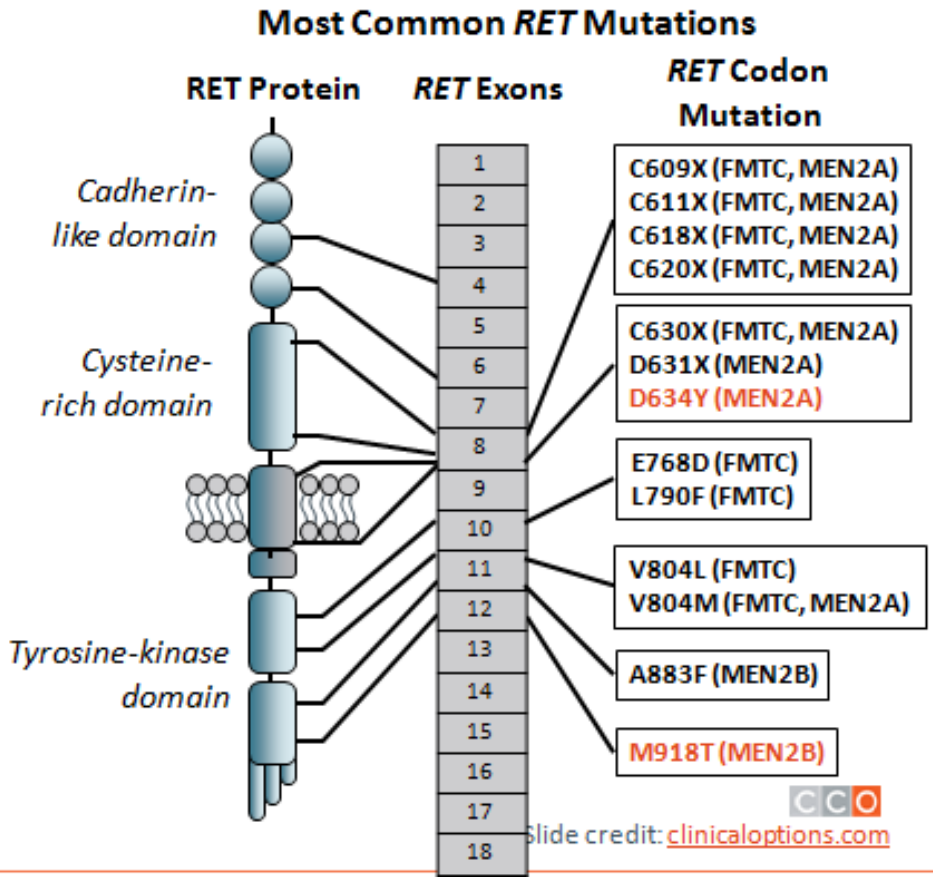
• Patients with unresectable, locally advanced or metastatic MTC have limited therapeutic options, and their 10-year OS rate is reported to be 40% or less

• **Vandetanib** (300mg/die) is the most widely used TKI for advanced MTC, targeting the *RET* oncogene, vascular endothelial growth factor receptor (VEGFR), and epidermal growth factor receptor (EGFR) (ZETA trial)

•**Cabozantinib** (140mg/die) improves PFS and response rates in patients with progressive metastatic MTC, including those previously treated with TKIs

RET Mutations in Medullary Thyroid Carcinoma

- *RET* gain-of-function mutation is main oncogenic driver in MTC
  - >100 reported
- Sporadic or nonfamilial MTC (70%-80%)
  - ~50% with somatic *RET* mutations
    - *RET* M918T most common
- Hereditary MTC (20%-30%)
  - >90% with germline *RET* mutation
    - MEN2B: *RET* M918T most common
    - MEN2A: *RET* C634X most common



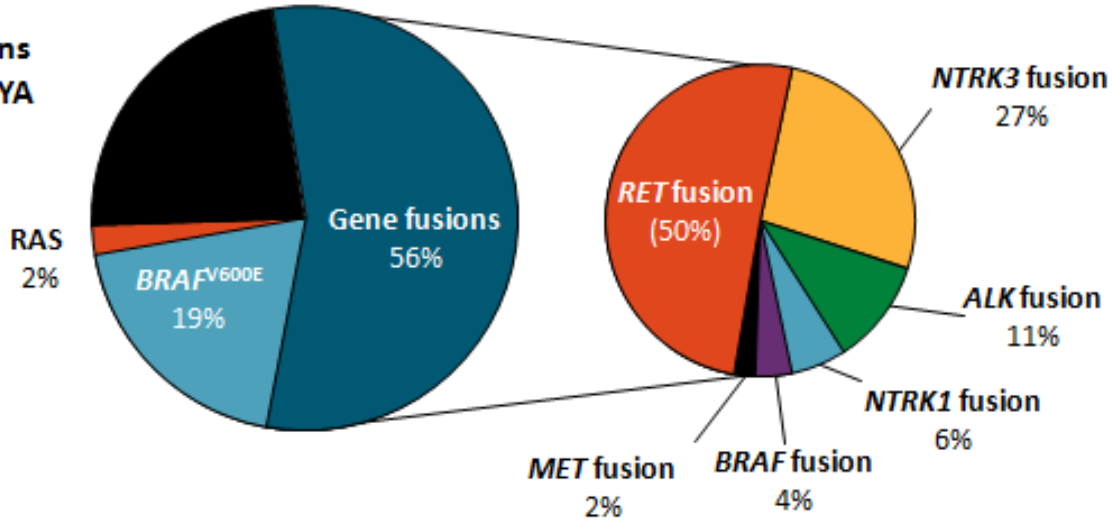
Santoro. Cold Spring Harb Perspect Biol. 2013;5:a009233. Wells. Thyroid. 2015;25:567.

Slide credit: clinicaloptions.com

Gene Fusions Are More Common in Pediatric and Young Adult Thyroid Cancers

- In 93 patients aged 6-20 yr with PTC, 56% harbored fusions
  - *RET* fusions most common; *NTRK* second most common
  - Multiple 5' fusion partners seen

Genetic Alterations in Pediatric and AYA PTC (N = 93)



Select Fusion Partners

RET	*CCDC6/RET*
	NCOA4/RET
	SQSTM1/RET
	RASAL2/RET
	RUFY2/RET
	PRKAR1A/RET
	TPR/RET
	ACBD5/RET
	BBIP1/RET
	IKBKG/RET
NTRK3	*ETV6/NRTK3*
	RBPMS/NRTK3
	EML4/NRTK3
	SQSTM1/NRTK3
ALK	*STRN/ALK*

Pekova. Thyroid. 2020;30:1771.

Pralsetinib and Selpercatinb in MTC with *RET* mutation (80-90% of cases with R/M MTC)

	Pralsetinib	Selpercatinib	Pralsetinib	Selpercatinib
	Prior C/V 12Apr21	Prior C/V 15 June 2021	C/V Naïve 12Apr21	C/V Naïve 15Jun21
N°	61	151	72	115
ORR (95% CI)	54% (41,67)	73.5% (66, 80)	76% (65, 86)	83.5% (75, 90)
CR	2%	9.3%	10%	17.4%
DCR (CR, PR, SD)	93%	94%	93%	95.7%
mTTR, mos	3.7	-	5.6	-
mDOR, mos (95% CI)	21.7 (18, NE)	NE (27.2 , NE)	34 (24, 34)	NE [31.3-NE]
Ongoing w response at 1 yr	84%	-	88%	-
Median follow-up, mos	24	27.6	12.7	23.9

LIBRETTO-531 (NCT04211337) is a multicenter, open-label, randomized, controlled, phase III trial comparing selpercatinib to cabozantinib or vandetanib in patients with advanced/metastatic *RET*-mutant MTC

- ONGOING -

Molecular Screening for *RET* Mutations in MTC

- All patients with MTC should have **germline testing**
  - Germline *RET* mutations lead to MEN2, a hereditary cancer syndrome with a high risk for developing MTC
  - Identification of hereditary MTC should prompt genetic counseling and cascade testing in family members
    - If germline *RET* mutation found, prophylactic thyroid removal is standard of care
- All patients with **sporadic** recurrent/persistent locoregional or metastatic MTC incurable by surgery should have **tumor somatic testing**
  - ~50% will have a somatic *RET* mutation
  - Exception: *RET* mutation already identified by germline testing
- If somatic *RET* mutation identified, **germline testing** for *RET* mutations also should be performed
  - Even in "apparent" sporadic cases w/o a family history, 7% will have a germline *RET* mutation

Thomas. Curr Oncol. 2019;26:338. NCCN clinical practice guidelines in oncology: thyroid carcinoma v3.2020. nccn.org.
Santoro. Cold Spring Harb Perspect Biol. 2013;5:a009233. Wells. Thyroid. 2015;25:567.

AGENZIA ITALIANA DEL FARMACO

DETERMINA 3 agosto 2022

Riclassificazione del medicinale per uso umano «Retsevmo», ai sensi dell'articolo 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 568/2022). (22A04622)

Art. 1

Classificazione ai fini della rimborsabilita'

Il medicinale RETSEVMO (selpercatinib) nelle confezioni sotto indicate e' classificato come segue.

Indicazioni terapeutiche oggetto della negoziazione:

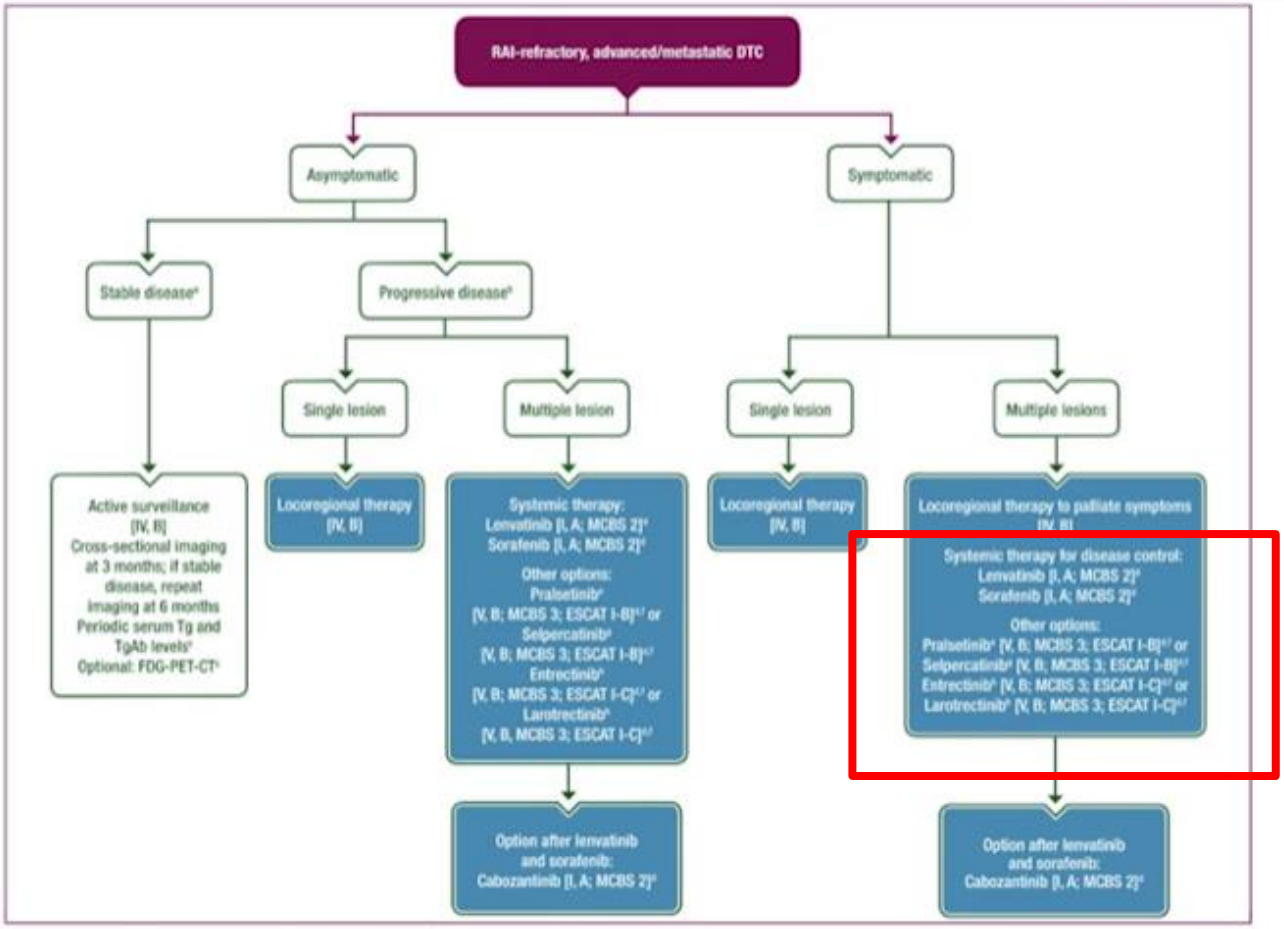
«Retsevmo» come monoterapia e' indicato nel trattamento di adulti con:

cancro del polmone non a piccole cellule (NSCLC) avanzato RET fusione-positivo che richiede terapia sistemica dopo precedente trattamento con immunoterapia e/o chemioterapia a base di platino;

cancro della tiroide avanzato RET fusione-positivo che richiede terapia sistemica dopo precedente trattamento con sorafenib e/o lenvatinib.

«Retsevmo» come monoterapia e' indicato per il trattamento di adulti e adolescenti di eta' pari o superiore a 12 anni con cancro midollare della tiroide (MTC) avanzato con mutazione di RET che richiede terapia sistemica dopo precedente trattamento con cabozantinib e/o vandetanib.

ESMO guidelines 2022: RAI Resistant Differentiated Thyroid Cancer



Filetti S et al, Ann Oncol 2022

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Thyroid Carcinoma – Papillary Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

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, genomic testing to identify actionable mutations (including *ALK*, *NTRK*, and *RET* gene fusions), DNA mismatch repair (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-10)

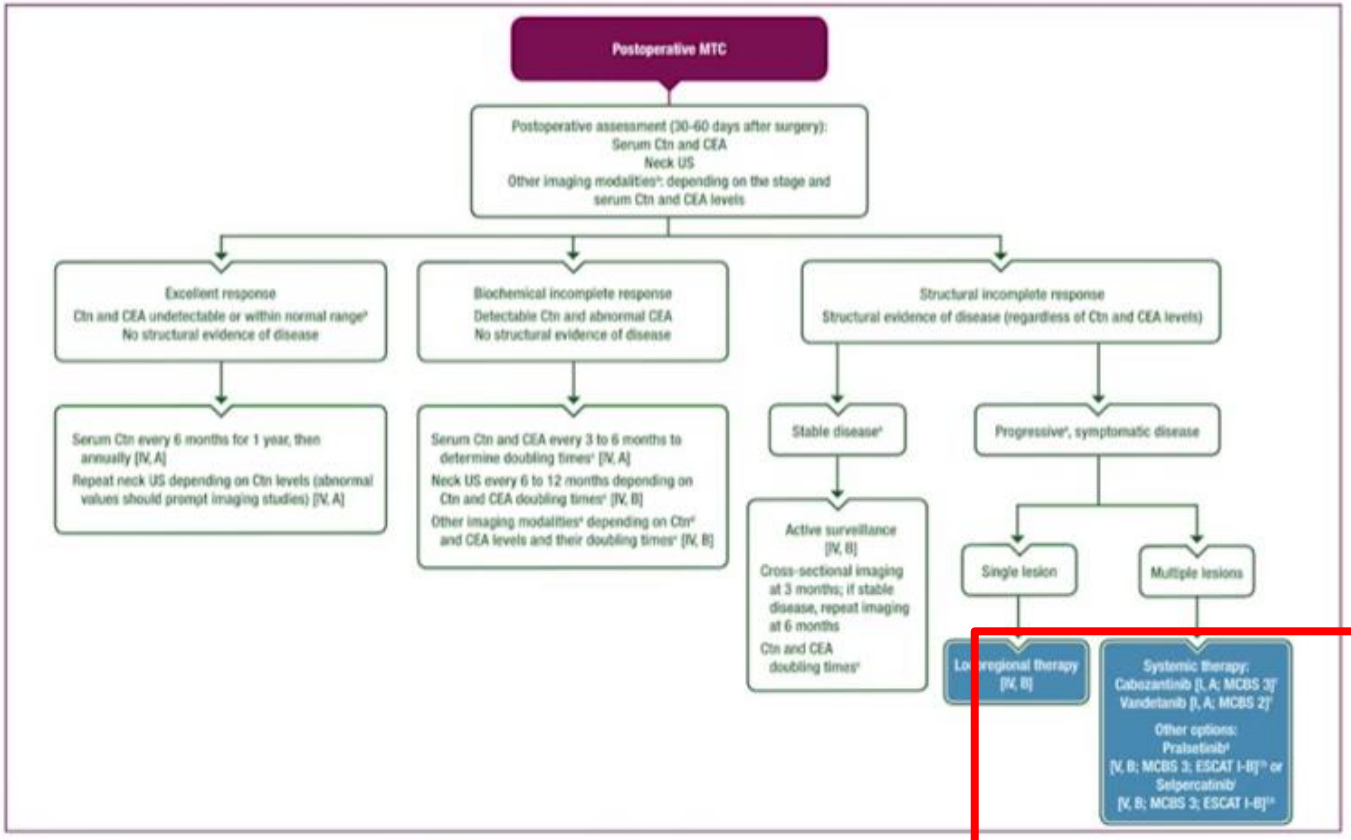
CNS metastases (PAP-11)

- Consider systemic therapy for progressive and/or symptomatic disease
  - Preferred Regimens
    - ◊ Lenvatinib (category 1)[dd]
  - Other Recommended Regimens
    - ◊ Sorafenib (category 1)[dd]
  - Useful in Certain Circumstances
    - ◊ Cabozantinib (category 1) if progression after lenvatinib and/ or sorafenib
    - ◊ Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
    - ◊ Selpercatinib or pralsetinib for patients with *RET*-fusion positive tumors
    - ◊ Pembrolizumab for patients with tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors
    - ◊ 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[ee,ff]
- Consider resection of distant metastases and/or EBRT (SBRT/ IMRT[n])/other local therapies[cc] when available to metastatic lesions if progressive and/or symptomatic (Locoregional disease PAP-8)
- Disease monitoring is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis[dd] (PAP-7)
- Best supportive care, see the NCCN Guidelines for Palliative Care

[l] Principles of TSH Suppression (THYR-A).
[n] Principles of Radiation and RAI Therapy (THYR-C).
[cc] Ethanol ablation, cryoablation, RFA, etc.
[dd] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. Principles of Kinase Inhibitor Therapy (THYR-B).

[ee] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], or dabrafenib [*BRAF* positive] [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[ff] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

ESMO guidelines 2022: Medullary Thyroid Carcinoma



Filetti S et al, Ann Oncol 2022

Cancer

ORIGINAL ARTICLE | Open Access

Efficacy and safety of pembrolizumab monotherapy in patients with advanced thyroid cancer in the phase 2 KEYNOTE-158 study

Do-Youn Oh MD, PhD, Alain Algazi MD, Jaume Capdevila MD, PhD, Federico Longo MD, Wilson Miller Jr. MD, PhD, Jerry Tan Chun Bing MD, Carlos Eduardo Bonilla MD, Hyun Cheol Chung MD, Tormod K. Guren MD, PhD, Chia-Chi Lin MD, PhD, Daniel Motola-Kuba MD, Manisha Shah MD, Julien Hadoux MD, PhD, Lili Yao PhD, Fan Jin MD, Kevin Norwood MD, Loïc Lebellec MD
... See fewer authors

First published: 07 February 2023 | https://doi.org/10.1002/cncr.34657

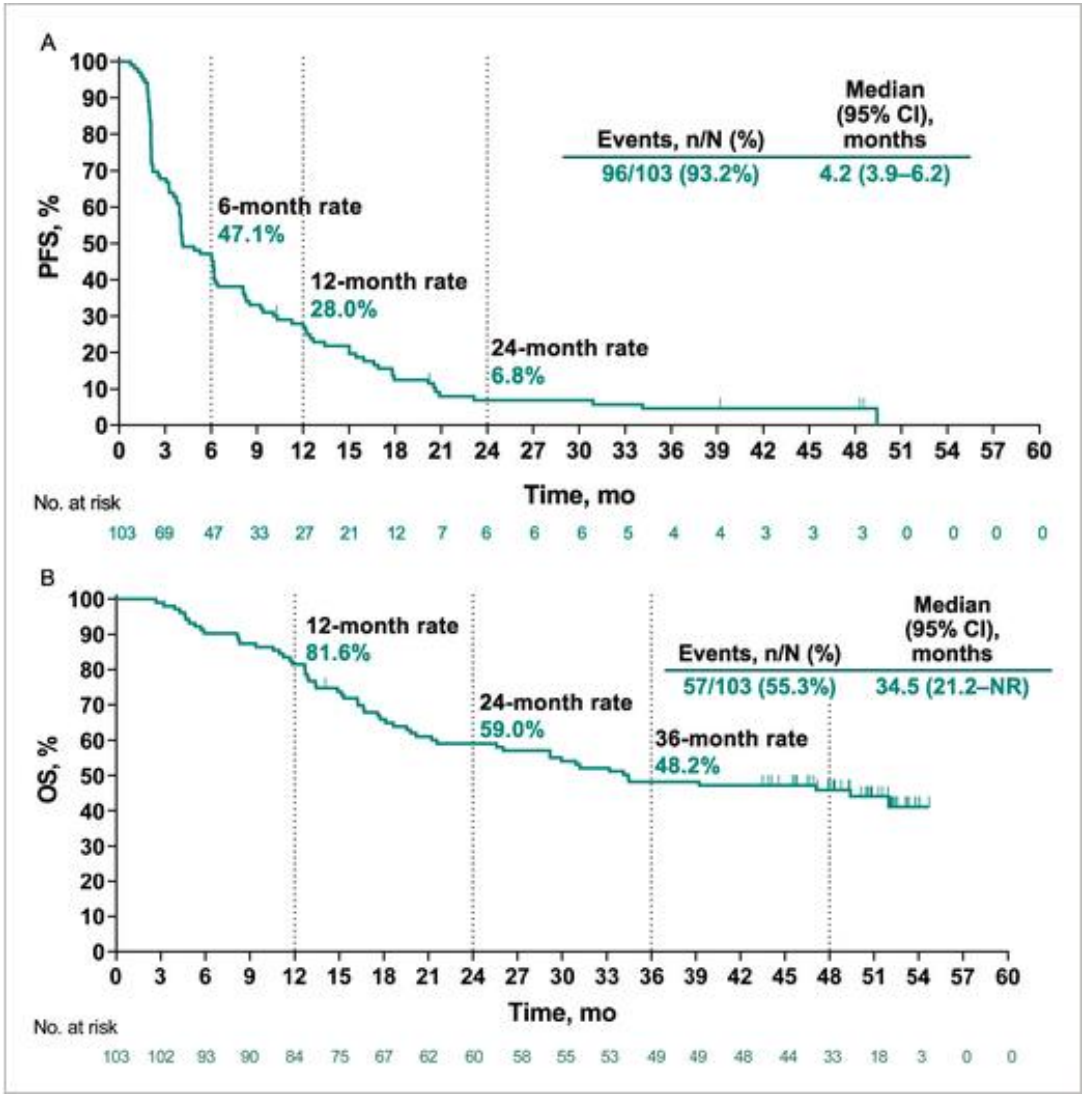
The trial registration is ClinicalTrials.gov, NCT02628067.

103 patients were enrolled and received pembrolizumab.

ORR was **6.8%**

ORR was 8.7% among patients with programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥1 (*n* = 46) and 5.7% (95% CI, 1.2%–15.7%) among patients with PD-L1 CPS <1 (*n* = 53).

Median **overall survival** and **progression-free survival** were **34.5** (95% CI, 21.2 to not reached) and **4.2** (95% CI, 3.9–6.2) months, respectively



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A multicenter, single-arm phase 2 study of surufatinib plus toripalimab for patients with locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer.

The open-label, multi-cohort, single-arm phase 2 study was performed to evaluate surufatinib (a small-molecule inhibitor of VEGFR 1-3, FGFR1 and CSF-1R) in combination with toripalimab (an anti-PD-1 antibody) in pts with RAIR-DTC

Eligible pts were with locally advanced or metastatic RAIR-DTC who were not amenable for surgery or external beam radiotherapy, with a radiologically confirmed disease progression within 12 months before treatment, and with ≥6 months since last radioiodine treatment. Enrolled pts received surufatinib 250 mg orally, QD, plus toripalimab 240 mg IV, Q3W, until disease progression or reaching the maximum treatment duration with toripalimab of 24 months

The confirmed **ORR was 33.3%** (5 PRs) and **DCR was 93.3%**.

mDoR was 8.34 months. mPFS (95%CI) was 10.91 months (4.01, NA).

mOS was not reached, and 12-month OS rate was 100%.

J Clin Oncol 41, 2023 (suppl 16; abstr 6089)

Phase II ATLEP trial: Final results for lenvatinib/pembrolizumab in metastasized anaplastic and poorly differentiated thyroid carcinoma

Phase II trial (ATLEP, Anaplastic Thyroid Carcinoma Lenvatinib Pembrolizumab, EudraCT No. 2017-004570-3) involving 27 ATC pts and 8 PDTC pts

Lenvatinib was started with 20 mg per day, and pembrolizumab (200 mg) was given i.v. every 3 weeks for up to two years.

The primary endpoint was defined as ORR of > 10% after 3 months of treatment

The primary endpoint **ORR at 3 mo** was achieved, and **was 34.3%** (12/35 PR) for all patients.

For ATCs the BOR (best overall response) within two treatment years was 51.9% PR (14/27) and 44.4% SD (12/27).

For PDTCs, BOR was 75% PR (6/8) and 25% SD (2/8).

The **Clinical Benefit Rate (CBR) was 96.3% for ATC** (26/27) and 100% for PDTC (8/8). For ATCs, the **median PFS was 9.5 mo** and the **OS 10.25 mo**. 25.9% of the ATC patients survived more than 2 years (7/27)

SUMMARY

- Several new tailored drugs have been incorporated in the update ESMO guidelines, best therapeutic
- Higher rate of objective response, prolonged PFS, favourable safety profile are the main characteristics
  of new tailored drugs, even if data on OS are not yet available
- NGS DNA and RNA to select patients for new therapeutic options