Management of Refractory Thyroid Cancer

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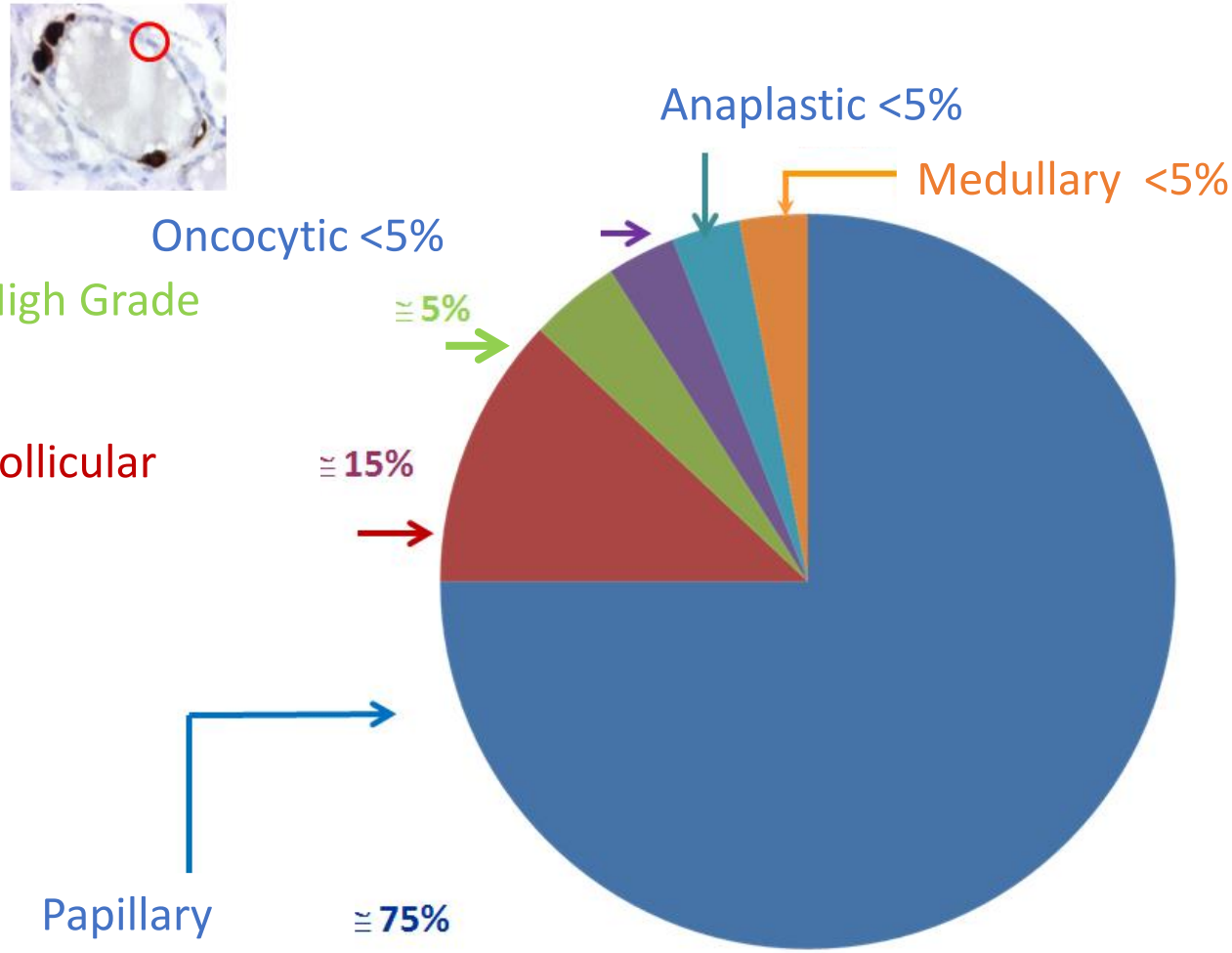
27th March 2024

Honoraria for lectures, advisory boards

- Bayer
- EISAI
- Lilly

Thyroid Cancer



95% of all TC are follicular-cell derived TC with an excellent prognosis

- 5 year Survival : 98.3%
- Specific Mortality : 0,4/100 000 habitants

Advanced TC are rare

RAIR Metastatic /locally advanced TC
Anaplastic TC
Metastatic MTC

WHO 2017 https://seer.cancer.gov/statfacts/html/thyro.html

OMS 2022: Follicular cell derived neoplams

Low risk neoplasms

NIFTP

TUMP: Tumors with unknown malignancy potential

Trabecular hyalinizing tumor

Treatment : Surgery

Malignant Neoplasmes

Papillary Carcinoma (with subtypes)

Follicular Carcinoma

Oncocytic Carcinoma

Invasive encapsulated follicular variant papillary carcinoma

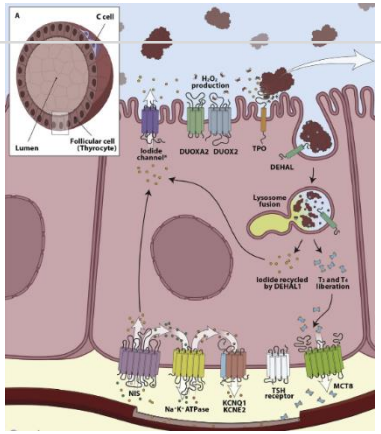
High grade Carcinoma

Differentiated Carcinoma High grade (mitosis ≥5/2mm2 or necrosis)

Poorly differentiated (mitosis ≥3/2mm2 and/or nécrosis)

A Tumor marker : Thyroglobulin

Treatment : Surgery, RAI according to prognostic factors, **Systemic treatment in case of advanced disease**



Carvalho *et al*. 2017

Anaplastic Thyroid Carcinoma

Treatment : - Surgery if R0 (R1?) is possible, Radio-chemotherapy +/- TKI Imunitherapy
- No Tg, NO RADIOACTIVE IODINE

OMS 2022

Molecular alterations in Thyroid Cancer

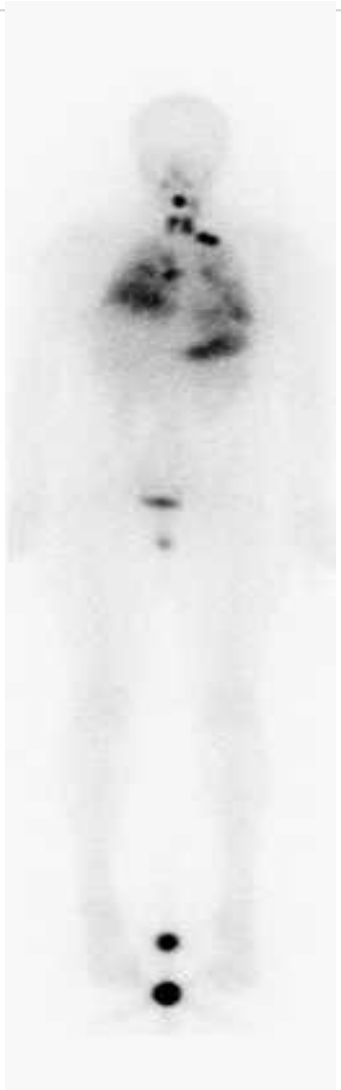
All patients with advanced disease need to have a molecular testing

	Radioactive Iodine Refractory TC	Anaplastic TC	Medullary TC
Mutation burden	Very low	Low	Very Low
BRAF alterations	**33%**	45%	-
RAS mutation	28%	24%	-
RET fusion	**6%**	**<1%**	**-**
RET mutation	**-**	**-**	**60-90%**
NTRK fusions	**≈ 1%**	**≈ 1%**	**-**
ALK mutation/translocation	≈ 1%	≈ 1%	-
PIK AKT mTOR pathway	10%	35%	-
C MET	< 1%	-	1-5%

Fagin NEJM 2016, Bonhomme 2017 Thyroid 2012, Prasad Cancer 2016, Pozdeyev CCR 2018, Hadoux, 2018, Iñiguez-Ariza 2020

Follicular- derived thyroid cancer with distant (except anaplastic)

- **In less than < 10% of the patients**
- Present at initial diagnosis (synchronous) : 50%
- Lung and Bone ++
- Have RAI uptake in 2/3 des cas



Durante et al. 2006

Treatment of distant metastases with radioactive

- **If the first post therapeutic Whole Body Scan shows Iodine in the distant metastases :**
  - Repeat treatment every 6 months for 2 years

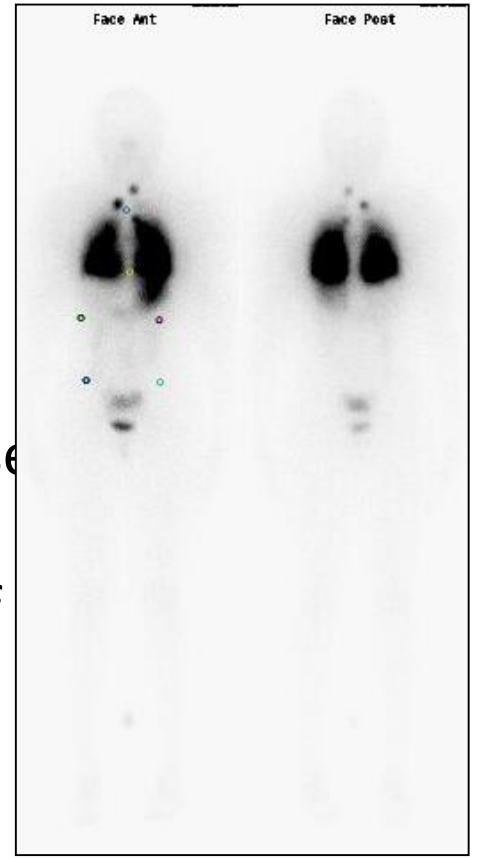
    As long as

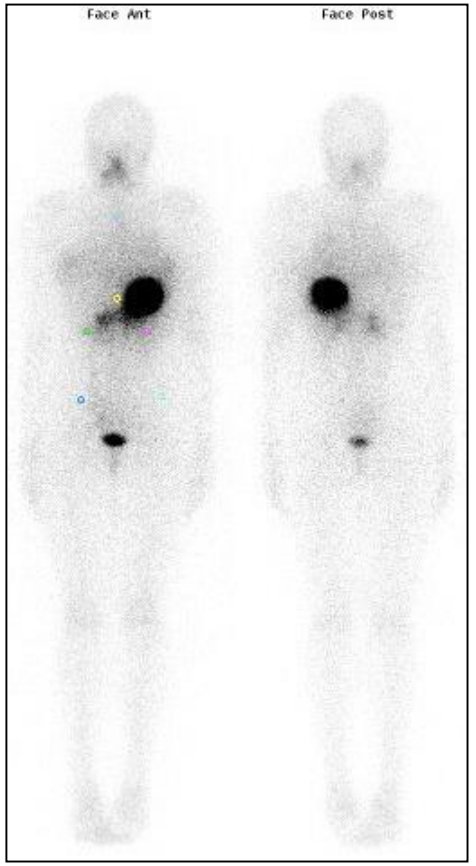
    *abnormal uptake on the WBS persists

    * conventionnal imaging shows a tumor response

- TSH goal is <0.1mUI/L between RAI administrations, if well tolerated

1/3 of the all patients with distant mets are cured with ^{131}I

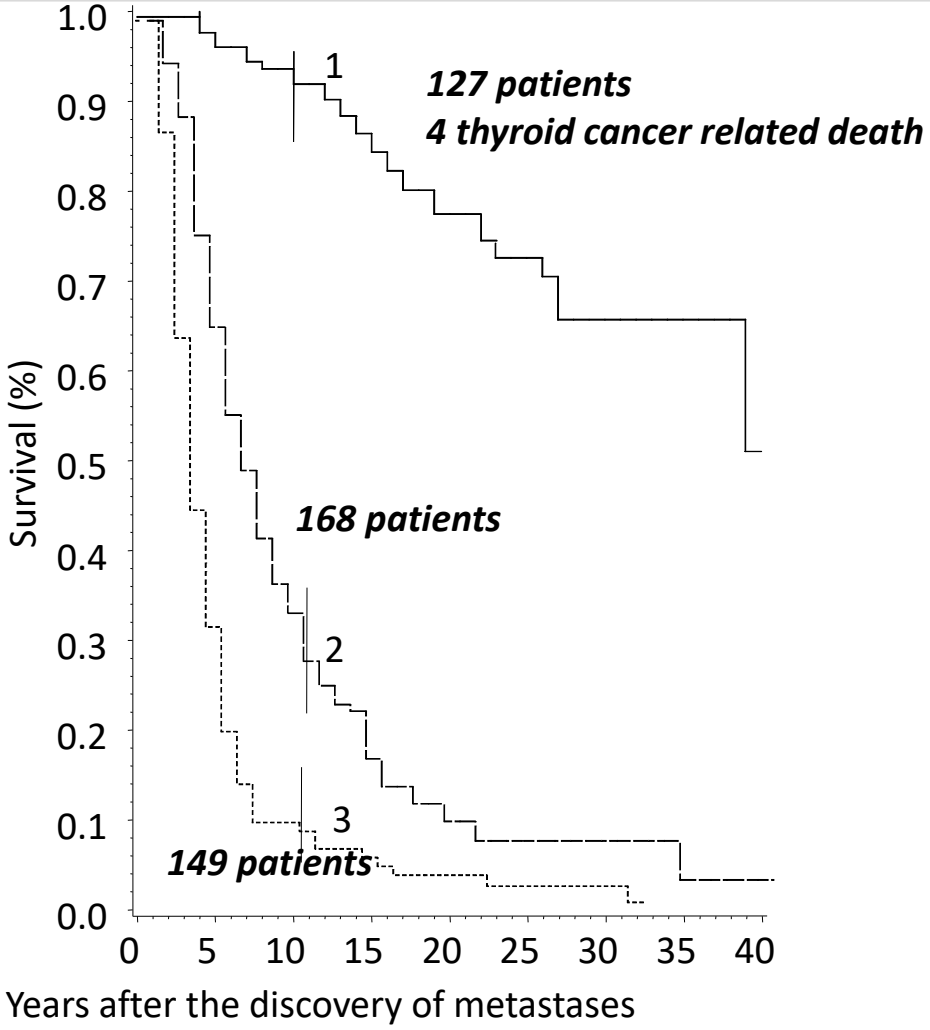




After 4 treatment with 100 (3.7 GBq) I-131

Durante et al. 2006.

Overall Survival in patients with distant metastases treated with RAI



- Group 1: patients cured with ^{131}I :

RAI uptake in the distant metastases → Complete Response

  - Age < 40 years
  - Well differentiated thyroid Cancer
  - Small Size lesion

- Groups 2 and 3 : not cured with ^{131}I

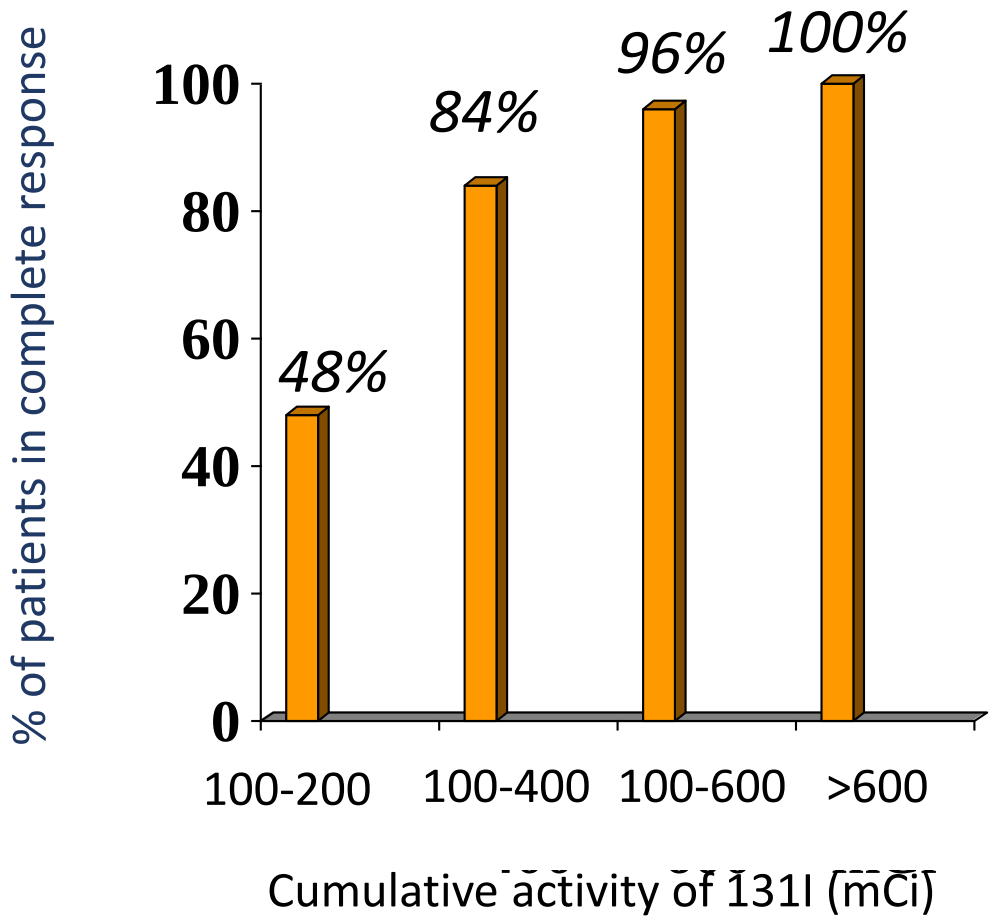
Iodine uptake in all, some or no lesions

  - Older age
  - Bigger size

Durante et al. J Clin Endocrinol Metab. 2006;91:2892-2899.

Complete response according to the cumulative RAI administered

444 patients with distant metastases
→ 127 achieved complete response
Rates of cure according to the cumulated activity of RAI



Durante et al. J Clin Endocrinol Metab. 2006;91:2892-2899.

Definition of RAI refractoriness

- Absence of RAI uptake in any of the lesions : at initial diagnosis or during after treatments
- Absence of RAI uptake in one of the lesion
- Tumor progression (Morphologic) within 12 months of a RAI treatment
- Discussed criteria : the persistence of disease after the administration of a cumulated activity ≥ 600 mCi

Schlumberger M et al. Lancet Diabetes & Endocrinol, 2014

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

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*

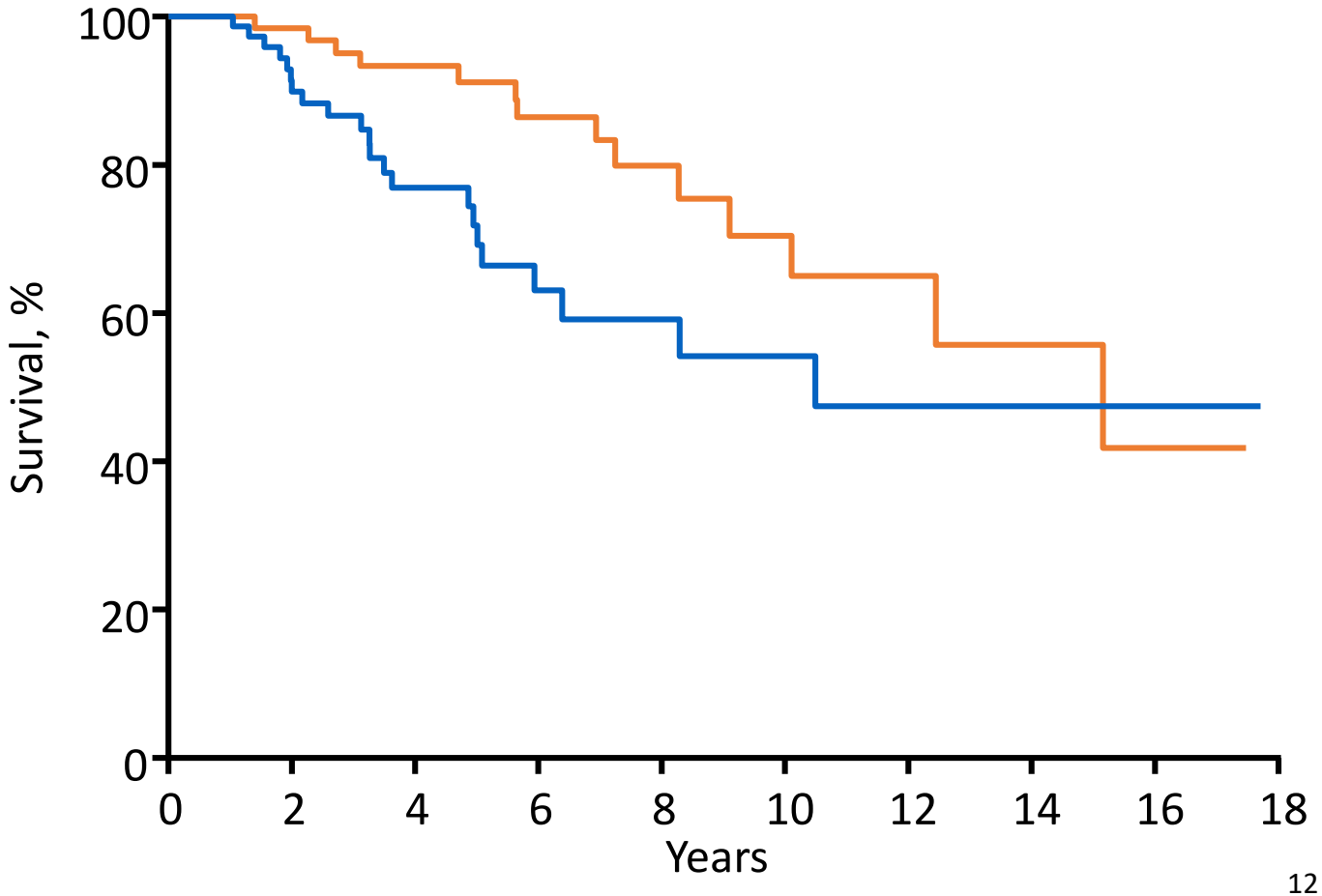
Volume 33 ■ Issue 7 ■ 2022

Treatment of RAIR DTC

- Goal of L-T4 treatment : TSH < 0.1 mU/L

n=450

	Median	
	all	**> 45 yr**
TSH suppressed	**15 yr**	**10 yr**
TSH unsuppressed	**11 yr**	**6 yr**
	p < 0.01	**p < 0.005**



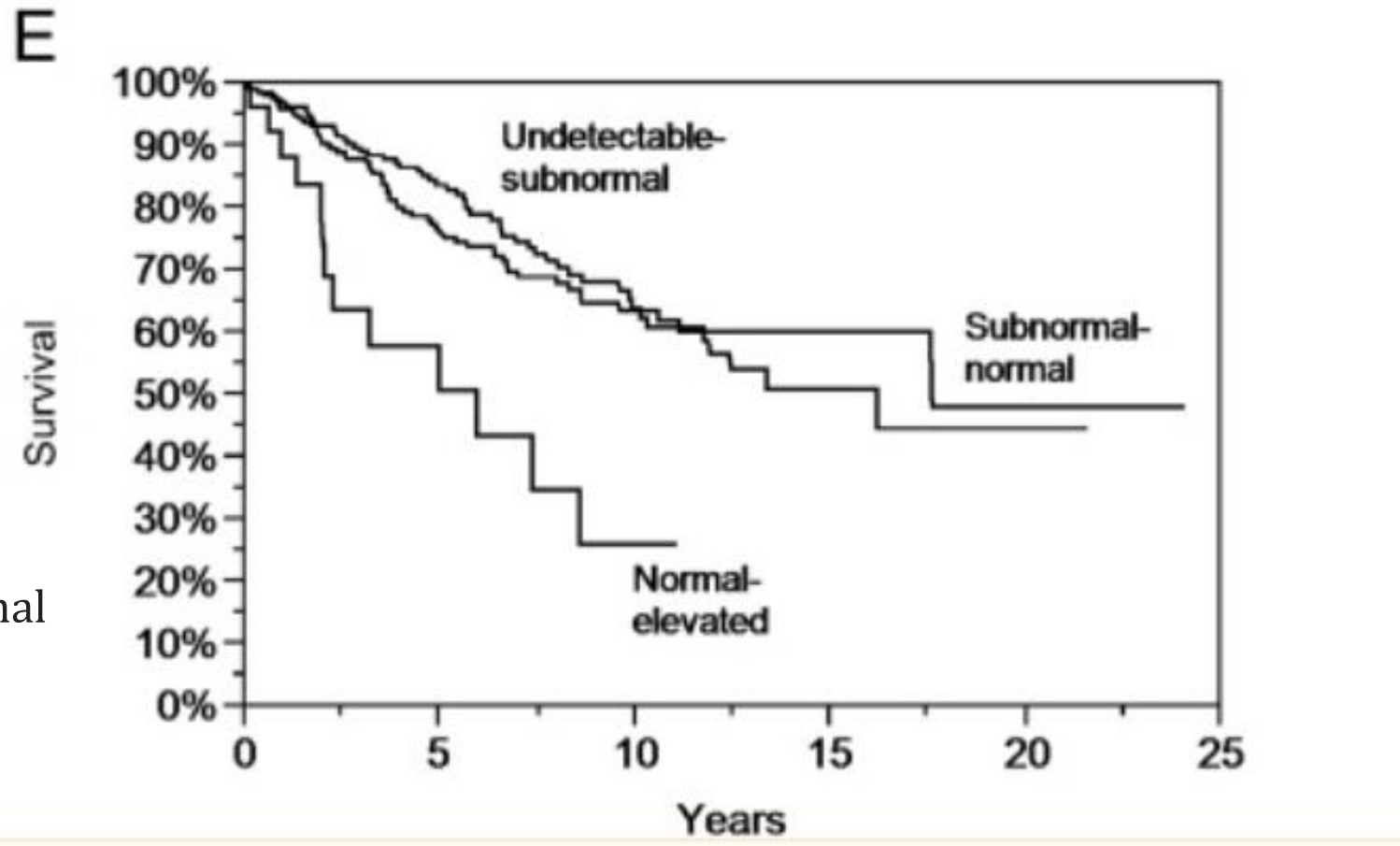
Jonklaas et al. Thyroid 2006;16:1299

TSH levels and OS in patients with distant metastases

- Goal of L-T4 treatment : TSH < 0.4 mU/L

TSH undetectable (TSH score = 1),
TSH subnormal but detectable (TSH score = 2),
TSH normal (TSH score = 3),
TSH elevated (TSH score = 4).

Mean TSH score :
* 1.0–1.99 : undetectable to subnormal (<0.1)
* 2.0–2.99 : moderate THST (subnormal to normal TSH levels); (TSH <0.1-0.4)
* 3.0–4, (TSH 0.4-4) nonsuppressed THST : (normal to elevated TSH levels)



Carhill et al 2015

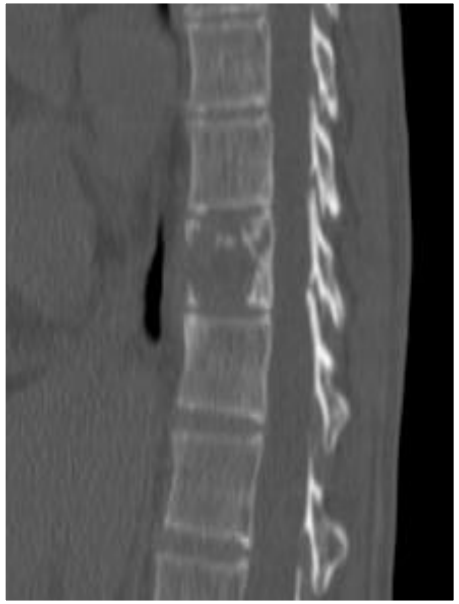
Treatment of RAIR DTC

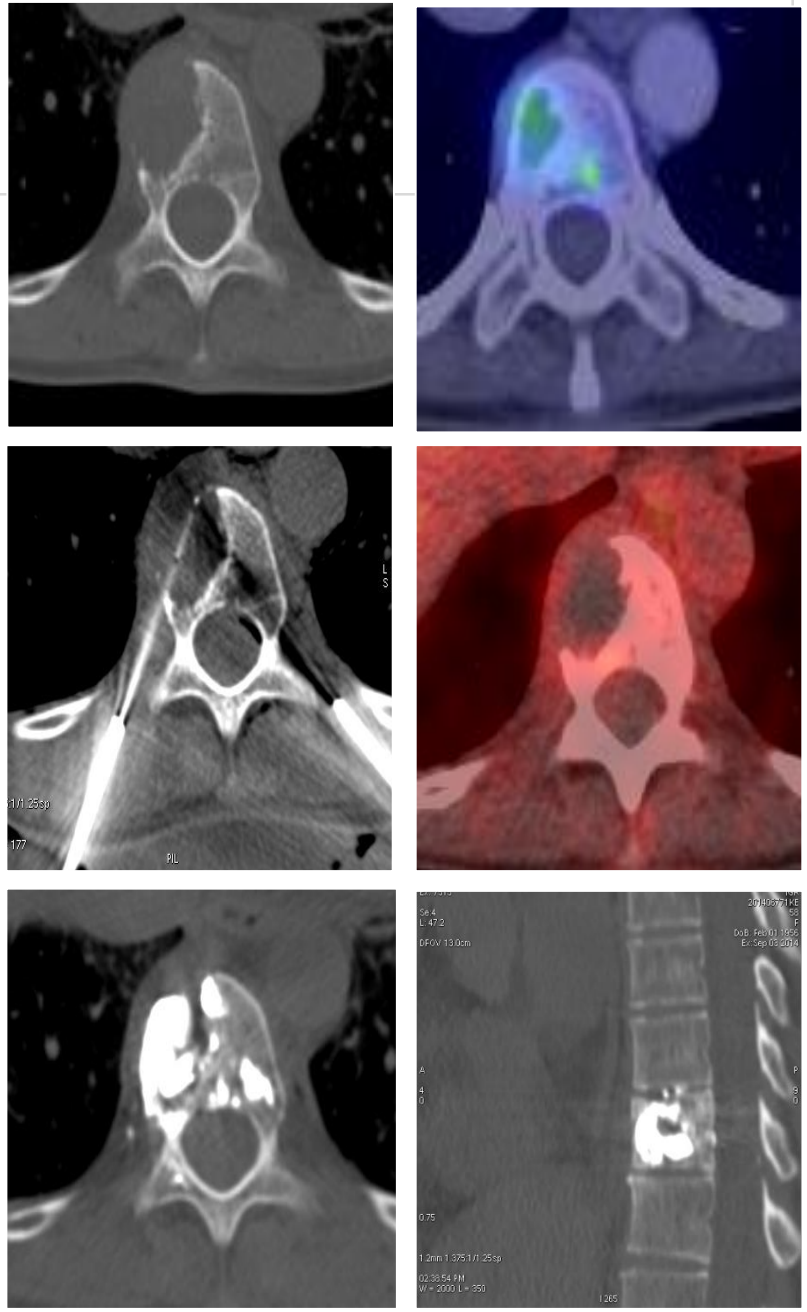
- Goal of L-T4 treatment : TSH < 0.1 mU/L

- Always consider local treatment first within a multidisciplinary board
  : surgery, external beam radiation, radiofrequency, cryo-ablation

Is a local treatment necessary ?

Is the lesion threatful for a critical organ?
Is the patient oligometastatic?
How many lesions are progressive?





Cryoablation + Cimentoplasty
= Local control and consolidation

F Deschamps, Gustave Roussy

Treatment of RAIR DTC

- Goal of L-T4 treatment : TSH < 0.1 mU/L

- Always consider local treatment first within a multidisciplinary board
  : surgery, external beam radiation, radiofrequency, cryo-ablation

- Imaging every 6 months
  - If stable: monitoring
  - If progression (RECIST criteria: 20% in 6-15 months): Need for systemic treatments (Targeted therapies)

Tumor mass
Rate of tumor growth
Symptoms
Location of the Metastasis
Age
Co-morbidities

Treatment of advanced MTC

- ~~Goal of L-T4 treatment : TSH < 0.1 mU/L~~ Search for hereditary MTC : take in charge pheo and hyperparathyroidism if necessary

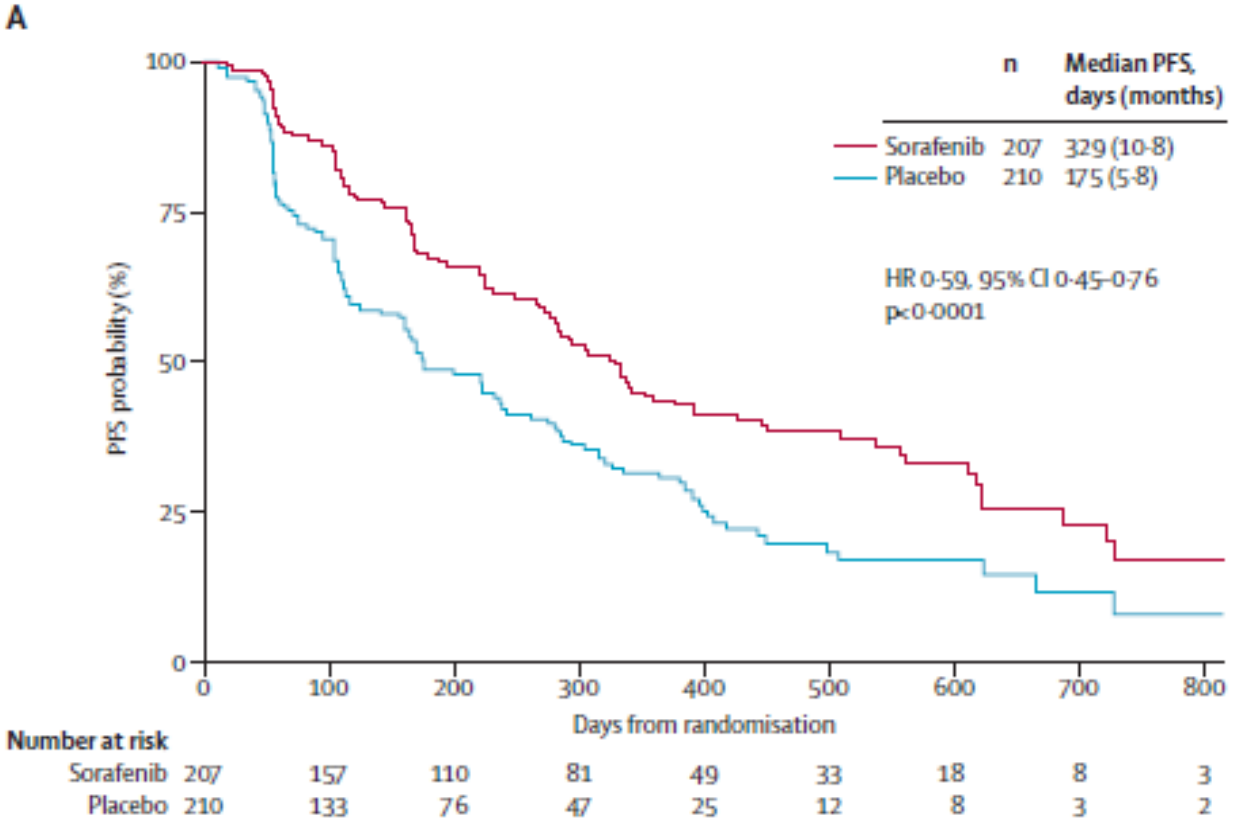
- Always consider local treatment first within a multidisciplinary board
  : surgery, external beam radiation, radiofrequency, cryo-ablation

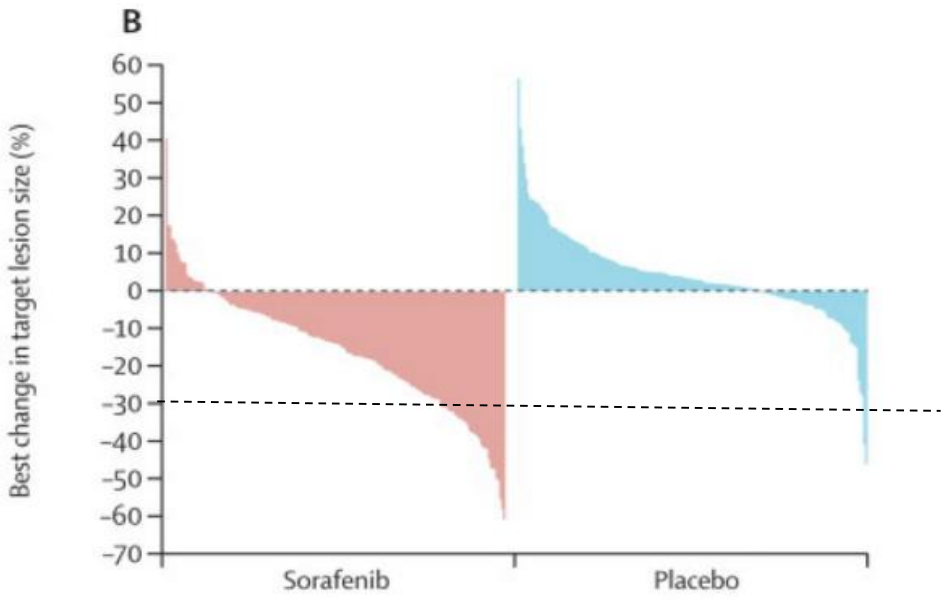
- Imaging every 6 months
  - If stable: monitoring
  - If progression (RECIST criteria: 20% in 6-15 months): Need for systemic treatments (Targeted therapies)

Tumor mass
Rate of tumor growth
Symptoms
Location of the Metastasis
Age
Co-morbidities

Sorafenib improves Progression-Free Survival (PFS) in DTC

- 417 radioactive iodine refractory DTC patients
- Phase III trial, placebo vs sorafenib 1:1; 800mg/d with cross over
- Mutations on 256 samples: BRAF: 30%; RAS: 20%



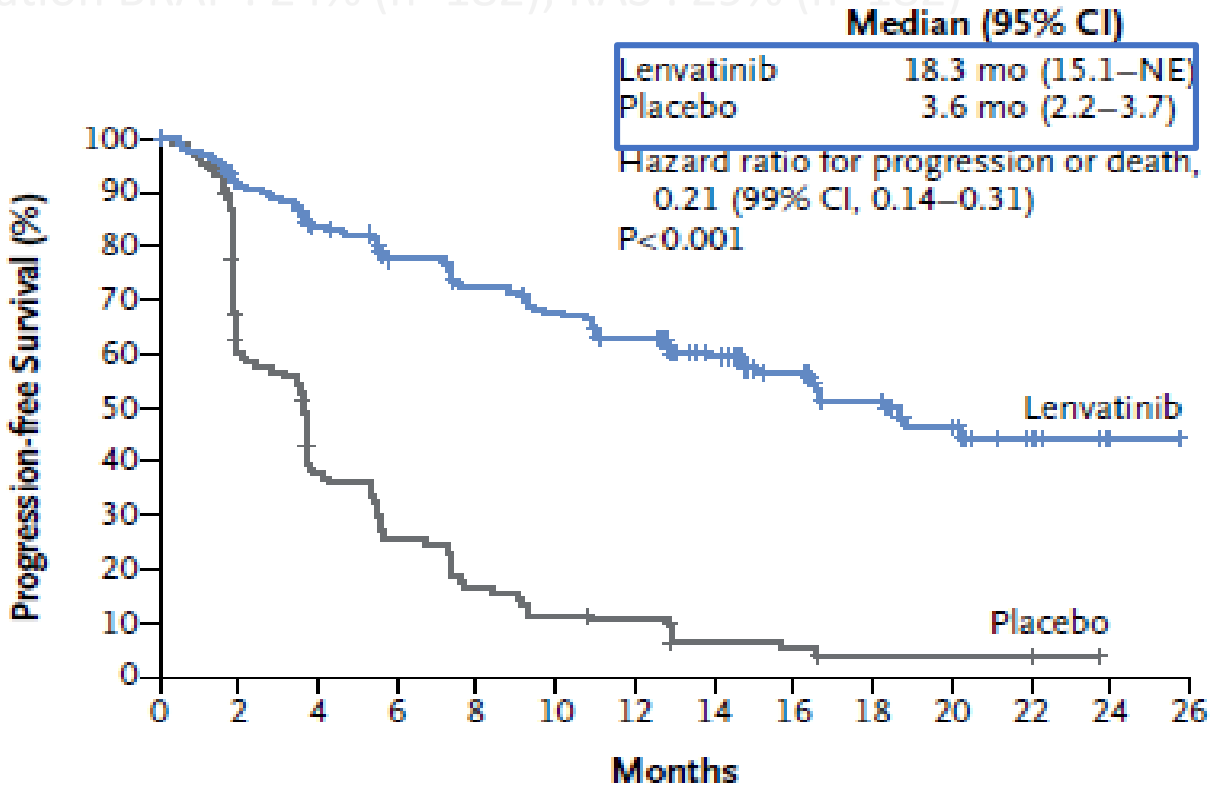


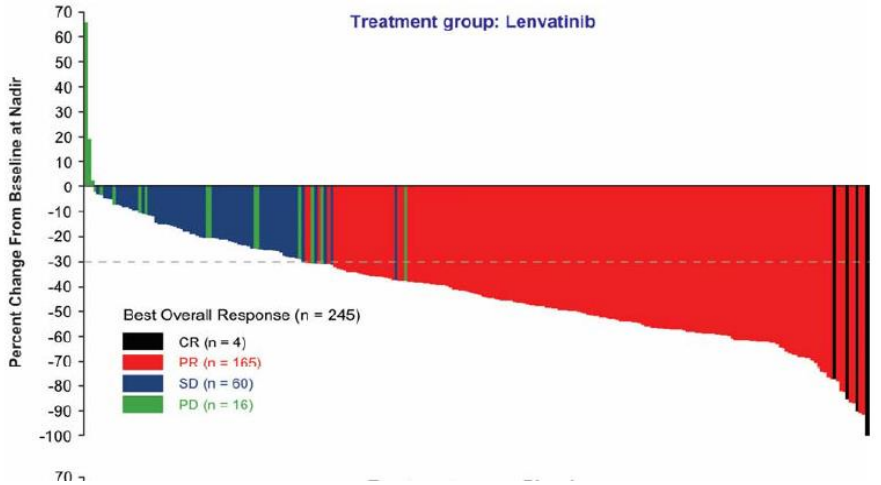
Response rate : 12%, length : 16.4 months

Brose et al. 2014

SELECT: lenvatinib improves PFS in DTC

- 392 radioactive iodine refractory DTC patients
- Phase III trial, placebo vs lenvatinib 2:1; 24 mg/d with cross over
- Mutation BRAF : 24% (n=182); RAS : 29% (n=182)



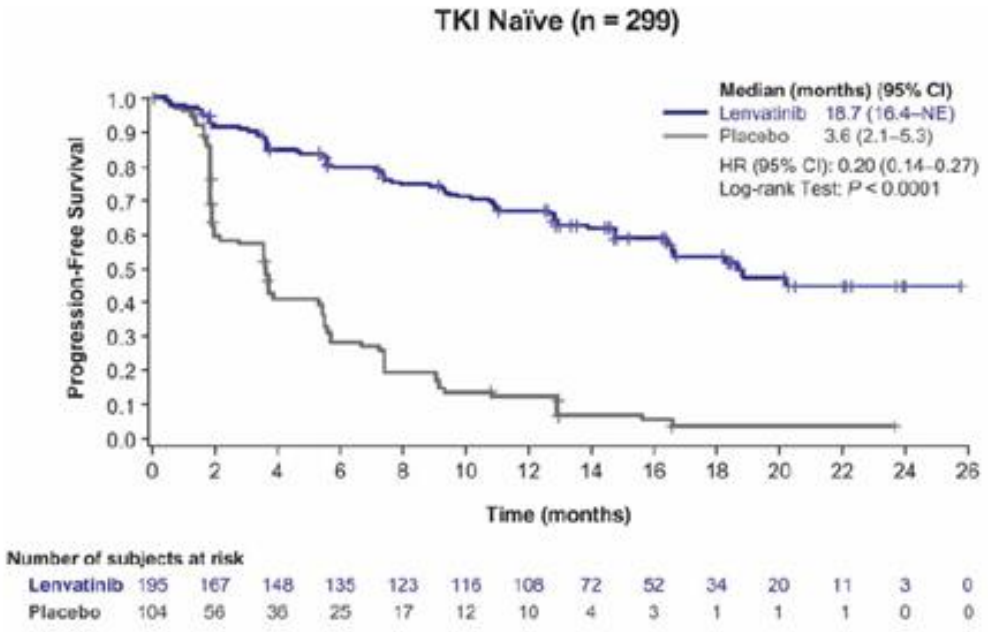


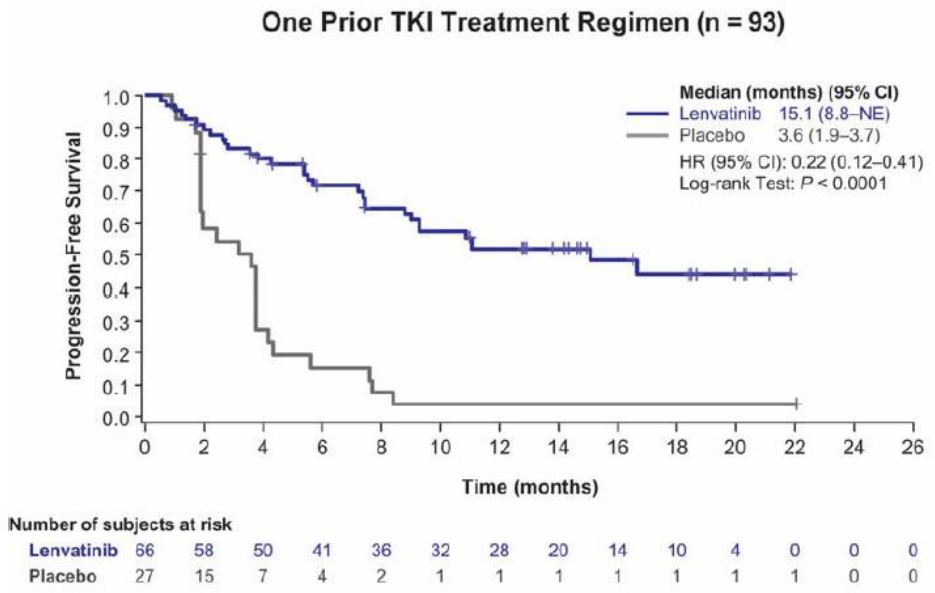
Response rate = 65%

Schlumberger et al., 2015

Lenvatinib improves PFS in TKI naïve & TKI pre-treated patients

	TKI naive		Other prior TKI treatment	
	lenvatinib	placebo	lenvatinib	placebo
PFS (months)	16.7	3.6	15.1	3.6





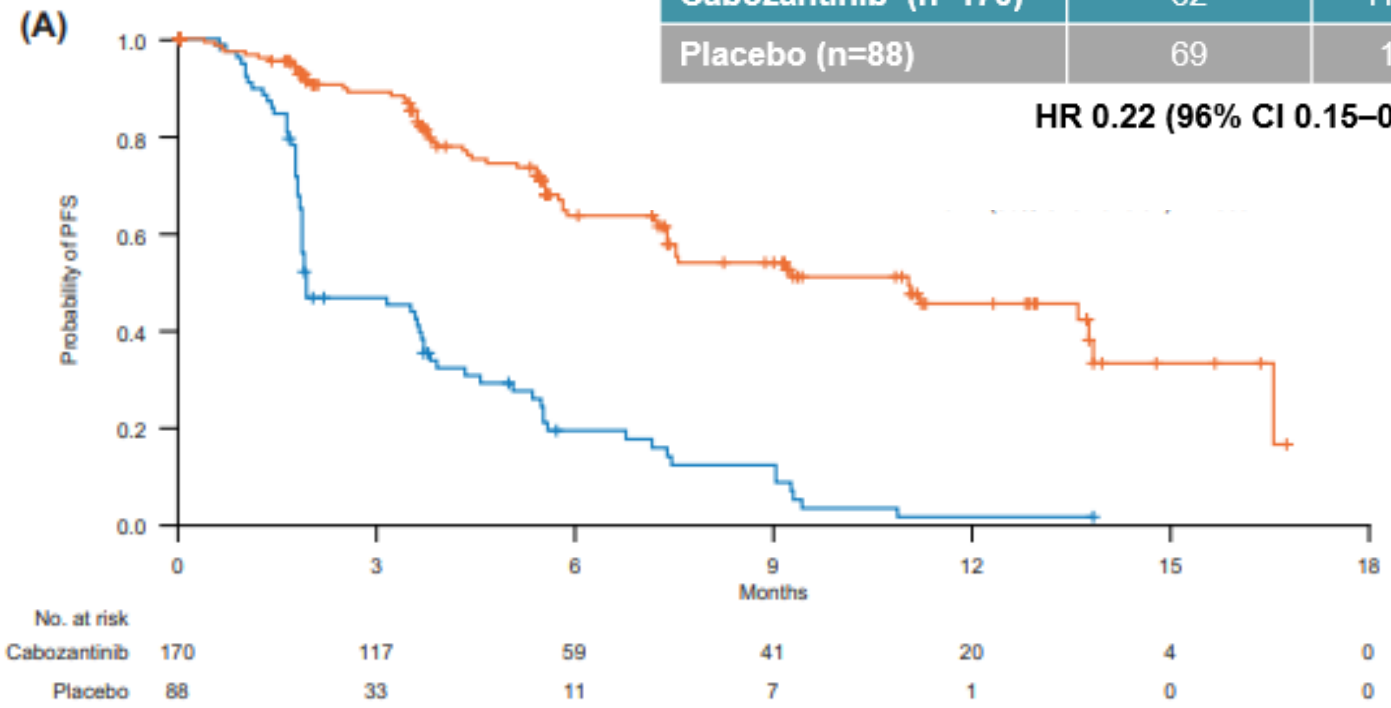
Schlumberger et al., 2015

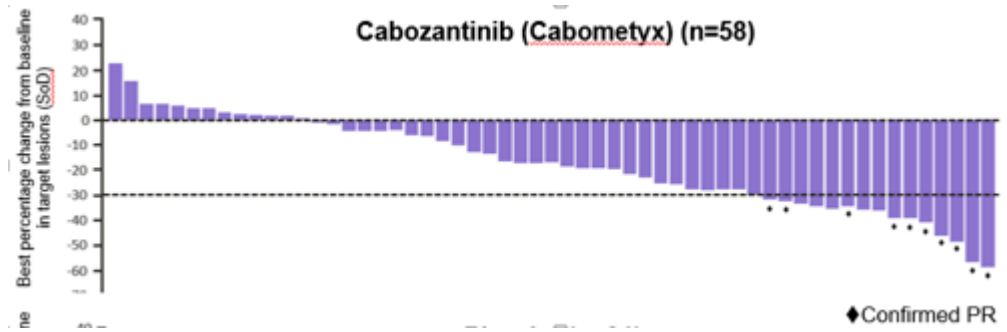
Cabozantinib : Improvement in PFS as 2nd line treatment

COSMIC : Placebo Randomized trial with Anti VEGFR 2nd line: Cabozantinib vs placebo after progression on a previous TKI.

	Events	Median (96% CI), months
Cabozantinib (n=170)	62	11.0 (7.4–13.8)
Placebo (n=88)	69	1.9 (1.9–3.7)

HR 0.22 (96% CI 0.15–0.32); p<0.0001



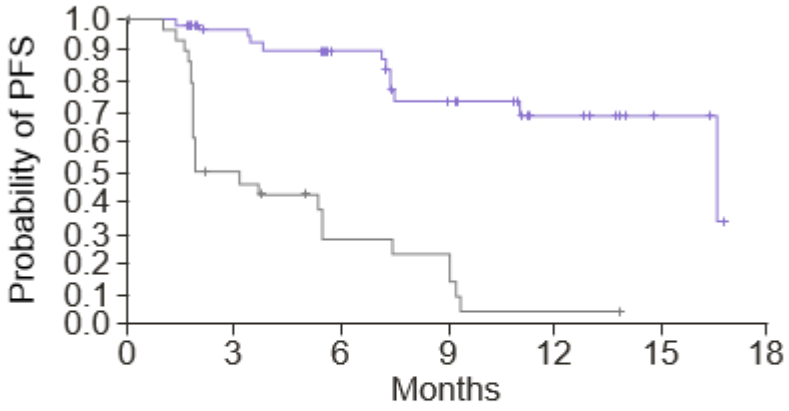


Response rate : 11%, length : 16.4 months

Brose et al. 2021 Lancet Oncol; Brose Cancer 2022

Cabozantinib : Improvement in PFS according to previous line

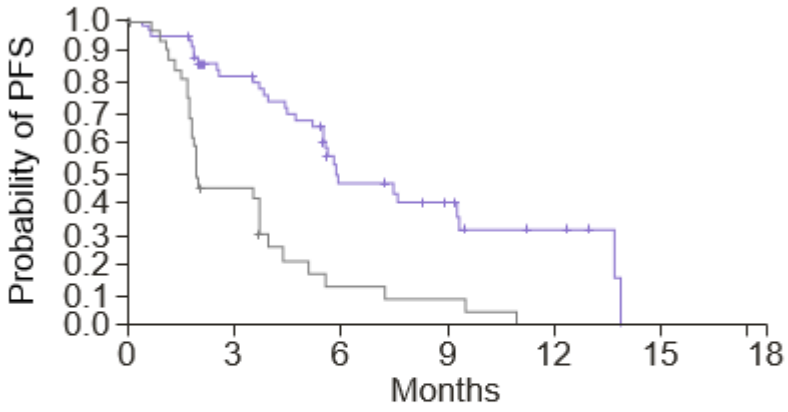
Prior sorafenib/no lenvatinib



	Events	Median (96% CI), months
Cabozantinib (n=63)	12	16.6 (11.0–NE)
Placebo (n=33)	24	3.2 (1.9–5.5)

HR 0.13 (95% CI 0.06–0.26)

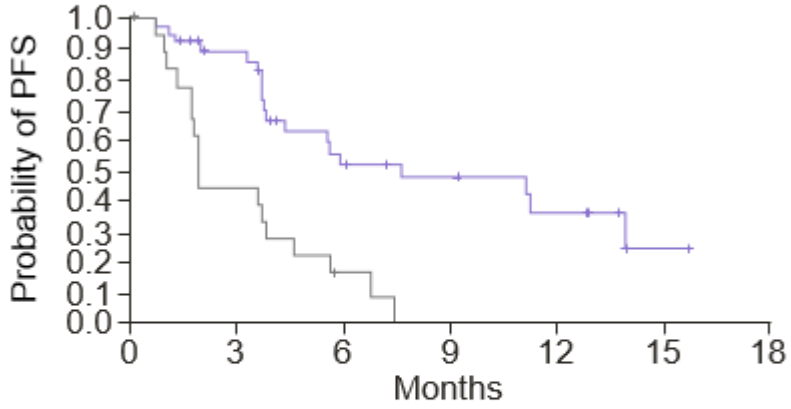
Prior lenvatinib/no sorafenib



	Events	Median (96% CI), months
Cabozantinib (n=68)	31	5.8 (5.1–9.3)
Placebo (n=34)	28	1.9 (1.7–3.7)

HR 0.28 (95% CI 0.16–0.48)

Prior lenvatinib and sorafenib



	Events	Median (96% CI), months
Cabozantinib (n=39)	19	7.6 (3.8–13.8)
Placebo (n=21)	17	1.9 (1.8–3.8)

HR 0.27 (95% CI 0.13–0.54)

Capdevila J, *et al*. Presented at ESMO 2021. Abstract LBA67.

Lenvatinib for RAIR TC from prospective data to real life

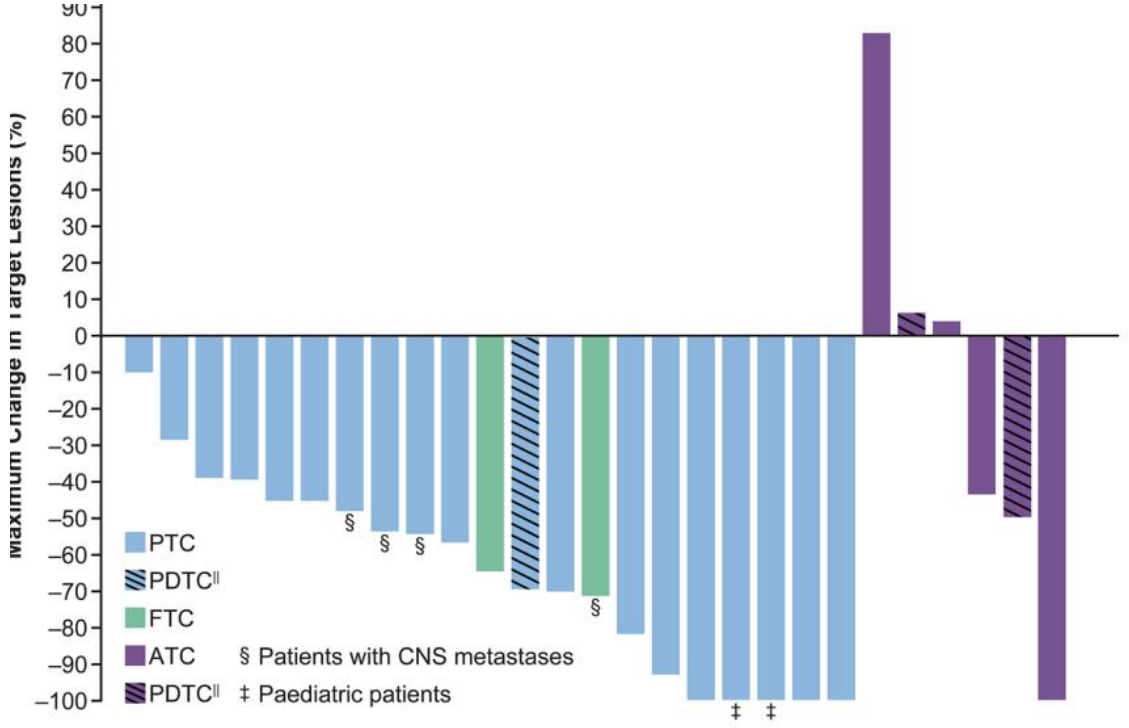
		Patients N	Response Rate %	Median PFS (months)	
Schlumberger et al, 2015		**392**	**65%**	**18.3**	
					Did not fulfill SELECT criteria %
Berdelou et al, 2018	France	75	31	10	77
Locati et al, 2019	Italy	94	36	19.2	43
Aydermili et al, 2020	Dutch	39	38	9.5	67
Jerkovich et al, 2020	Argentina	22	36	13.7	
Masaki et al 2020	Japan	42	60	13.8	
Song et al 2020	Korea	43	42	21.8	
Porcelli et al, 2021	Italy	23	26	25	
Koehler et al 2021	Germany	53	68	12	

Anti NTRK efficacy in tumors with NTRK rearrangement

		n	Complete Response Rate %	Partial Response Rate %	Median duration response (months)
Larotrectinib	Drilon, 18	155 (all cancer)	16	63	35.2
Entrectinib	Doebele 20	54 (all cancer)	7	50	10

DTC with NTRK rearrangement : efficacy of larotrectinib

	PTC/FTC (n=22)*	ATC (n=7)	All patients with TRK fusion-positive TC (N=29)
Evaluable patients, n	21	7	28
ORR, % (95% CI)	86 (64–97)	29 (4–71)	71 (51–87)
Best response, n (%)†			
Complete response	2 (10)	0	2 (7)
Partial response	16 (76)	2 (29)	18 (64)
Stable disease	3 (14)	1 (14)	4 (14)
Progressive disease	0	3 (43)	3 (11)
Not determined	0	1 (14)¶	1 (4)



Based on Data on 200 patients in all cancer types → approval was given

Waguespack et al. 2022

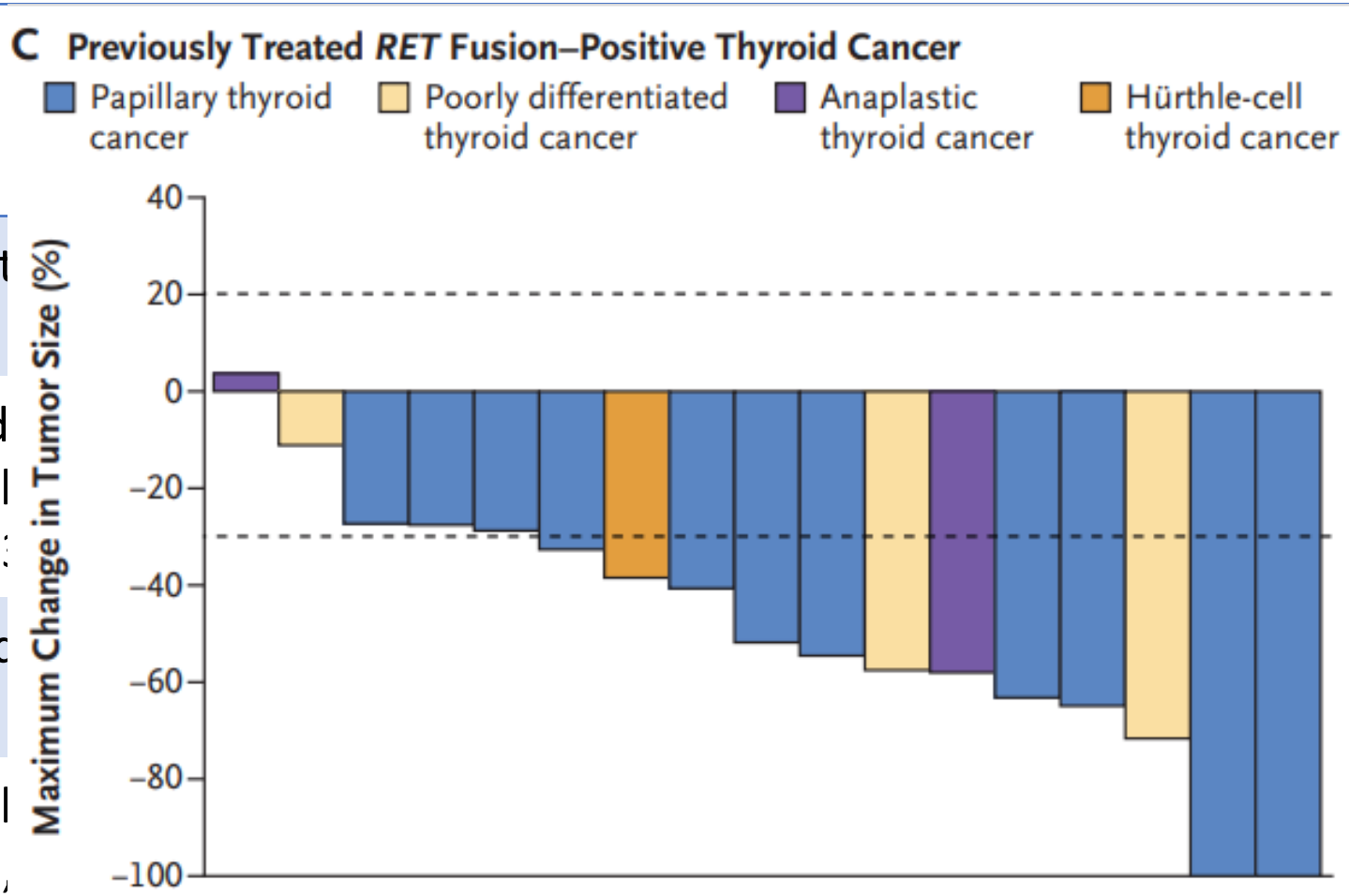
Anti NTRK in tumors with with NTRK rearrangement

		FDA approval	EMA approval	HAS
Larotrectinib VITRAKVI (100mg 2/day in adult)	Anti NTRK	Adult and pediatric with NTRK fusion (2018)		2021: restriction to sarcomas
Entrectinib ROZLYTREK (600 mg 1/day in adult)	Anti NTRK	Adults and adolescents aged ≥12 years with NTRK fusion (2020)		2021: unfavorable

Follicular cell derived thyroid cancer with RET fusion

		n	Complete Response %	Partial Response %	Median duration response (months)
Selpercatinib	Wirth, 20	19 **previously treated**	5	74	18
	Update Subbiah 2023	22 **previously treated**	14	77	24
Selpercatinib	Bradford, 21	8 **treatment naive**	12.5	88	Not reached
Pralsetinib	Subbiah, 21 Kim, 21	9 previously treated	0	89	Not reached

Follicular cell derived thyroid cancer with RET fusion



		dian duration response (months)
Selpercatinib	Wirt	18
	Upd Subl 202	24
Selpercatinib	Brac	Not reached
Pralsetinib	Subl Kim,	Not reached

EMA approval : Adults with RET fusion-positive thyroid cancer in adults previously treated with sorafenib or lenvatinib or both (2021)

BRAF mutated TC : anti BRAF and anti MEK

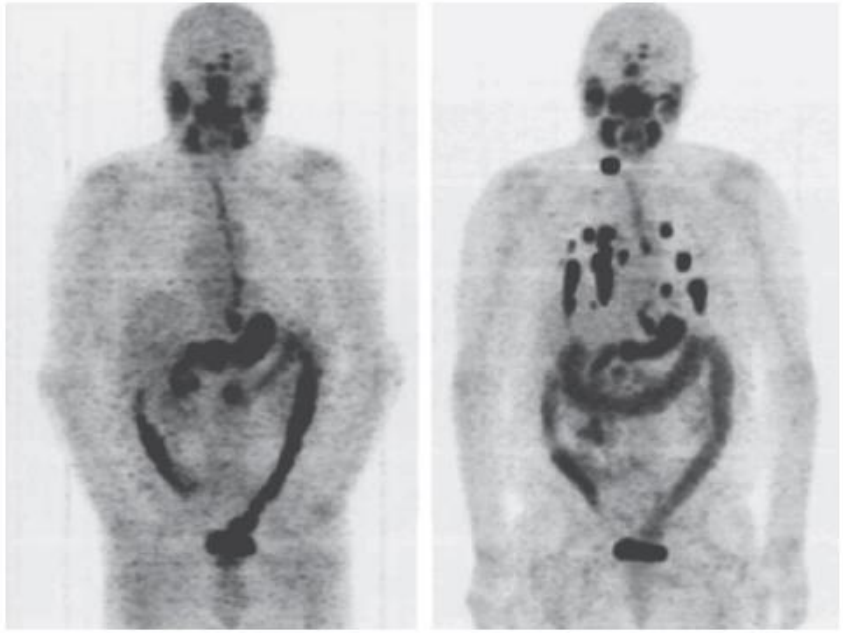
		Line	n	Complete Response %	Partial Response %	Median Duration of response (months)	Median PFS (months)
Busaidy 2022 Randomized Phase 2	Dabrafenib	>2	26	0	35	18.3	24.5
	Dabrafenib & Trametinib	>2	27	0	30	15.4	15.1
Tahara 2014 Phase 2	Encorafenib + binimetinib	>1	17	0	47	NR	NR

Phase III trial dabrafenib-trametinib or placebo vs. placebo (second line) - NCT04940052

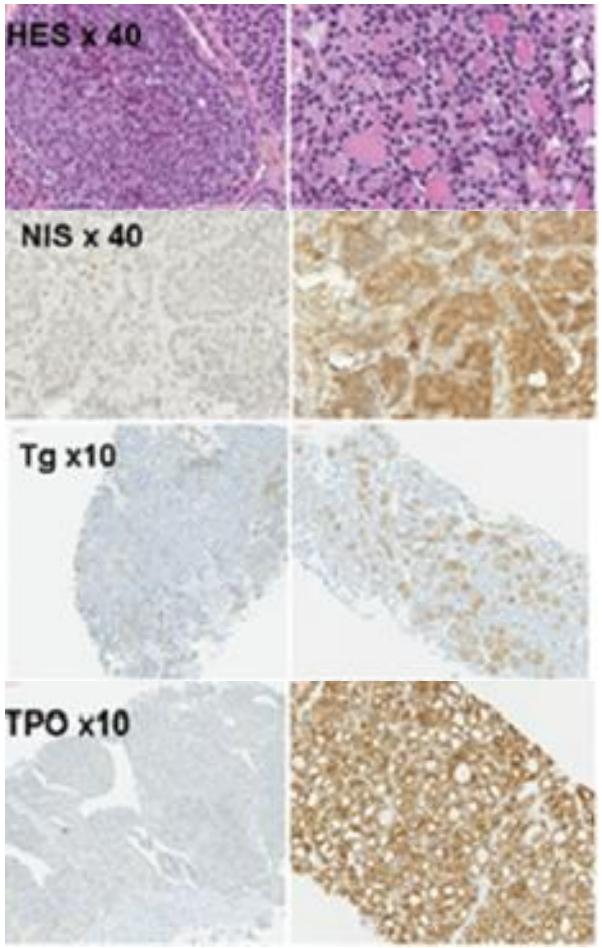
Redifferentiation is overcoming insensitivity to RAI

Redifferentiation is defined the re expression of genes involved in iodine metabolism

Redifferentiation is the appearance / re appearance of RAI uptake



Baseline After Selumetinib



Baseline **After dabra-trame**

Leboulleux et al. Thyroid 2019; Ho et al NEJM 2013

Redifferentiation in RAIR TC with a BRAF mutation

		N	Genetics	Increase of RAI uptake (according to)	Ttt with RAI	CR	Partial Response
Ho, 2012	Selumitinib +/- Iode 131	9	*BRAFV600E*	4 (60%) (^{124}I PET-CT)	1	0	**11% (best PR)**
Rothenberg, 2015	Dabrafenib +/- Iode 131	10	*BRAF V600E*	6 (60%) (Dc ^{131}I WBS)	6	0	**20% (best PR)**
Dunn, 2018	Vemurafenib +/- Iode 131	12	*BRAF V600E*	4 (40%) (Dc ^{131}I WBS)	4	0	**25% (best PR)**
Tchekmedyian, 2022	Vemurafenib + anti-ErbB3mAbCDX-337 +/- Iode 131	6	*BRAF V600E*	5 (80%) (^{124}I PET-CT)	5	0	**33% (6 months PR)**
Weber, 2022	Dabrafenib + Trametinib +/- Iode 131	6	*BRAF V600E*	2 (33%) (^{124}I PET-CT)	6	0	**17%**
Leboulleux, 2023	Dabrafenib + Trametinib +/- Iode 131	21	*BRAF V600E*	20 (95%) (post-T ^{131}I WBS)	21	1	**38% (6 months PR)**

Redifferentiation in RAIR TC with a RAS mutation

		N	Genetics	Increase of RAI uptake (according to)	Ttt with RAI	CR	PR
Ho, 2012 NEJM	Selumitinib +/- Iode 131	5	*RAS*	5 (100%) (^{124}I PET-CT)	5	0	80% (best PR)
Leboulleux, 2023 Thyroid	Trametinib +/- Iode 131	10	*RAS*	6 (60%) (post-T WBS)	10	0	20% (6 months PR)
Burman, 2022 ASCO	Trametinib +/- Iode 131	25	*RAS*	22 (88%) (^{124}I PET-CT)	15	0	32% (6 months PR)

Academic Promising,
No randomized trials
No Phase 3 Trial

Adapted from Leboulleux et al, Exp Opinion on Inv Drugs, 2022

Redifferentiation in real life

		RAI restoration	Best RECIST tumor response	
			Complete Response	Partial Response
Oncogenic driver	BRAF	37% (7/18)	0	6% (1/18)
	RAS	92% (11/12)	0	8% (1/12)
	RET	25% (1/ 4)	1 (25%)	0

Toro-Tobon et al. 2023

RAIR Follicular cell derived TC : Pembrolizumab

	RAIR DTC (n=27)	ATC (n=16)
CR % (n)	0%	6% (1)
PR % (n)	**11% (3)**	**19% (3)**
SD % (n)	19% (5)	6% (1)
PD % (n)	63% (17)	56% (9)
NE	7% (2)	13% (2)
Median PFS (months)	2.6	2.6

Leboulleux, ASCO 2021

RAIR Follicular cell derived TC : Lenvatinib-Pembrolizumab

	RAIR DTC	
	Treatment naive (n=28)	Pembro added after lenvatinib failure (n=24)
CR % (n)	0%	0
PR % (n)	64%	17%
SD % (n)	32% (4)	83%
PD % (n)		0
Median PFS (months) (95%CI)	NE (16.1-NE)	11 (7.1-NE)

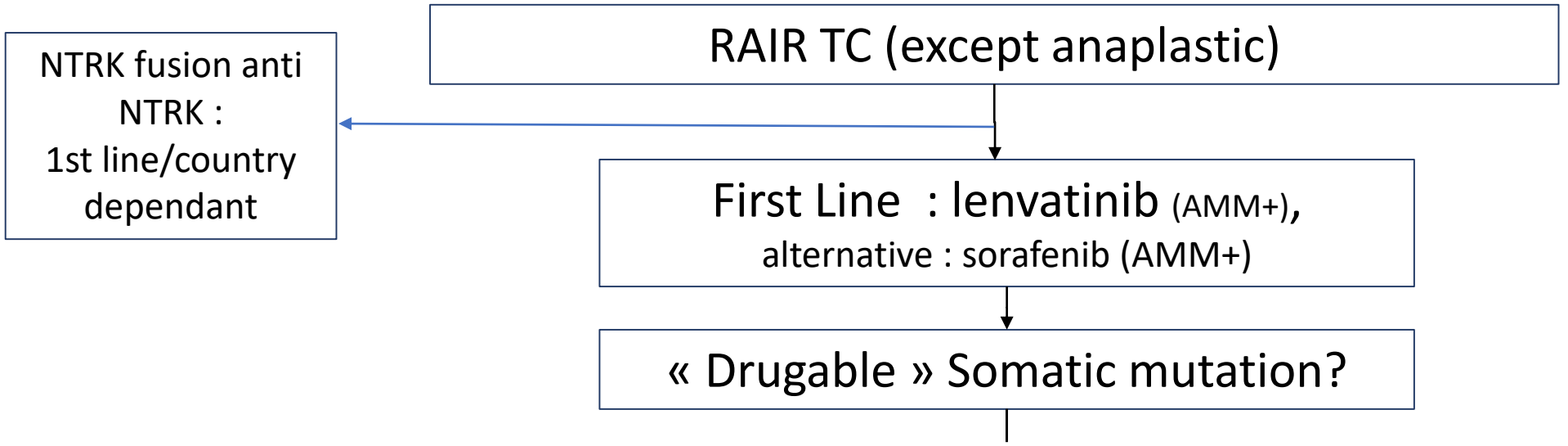
Trials : REGOMUNE : regorafenib + avelumab : a single-arm, open-label, phase II trial

Haugen, ASCO 2020, Haugen ESMO 2020

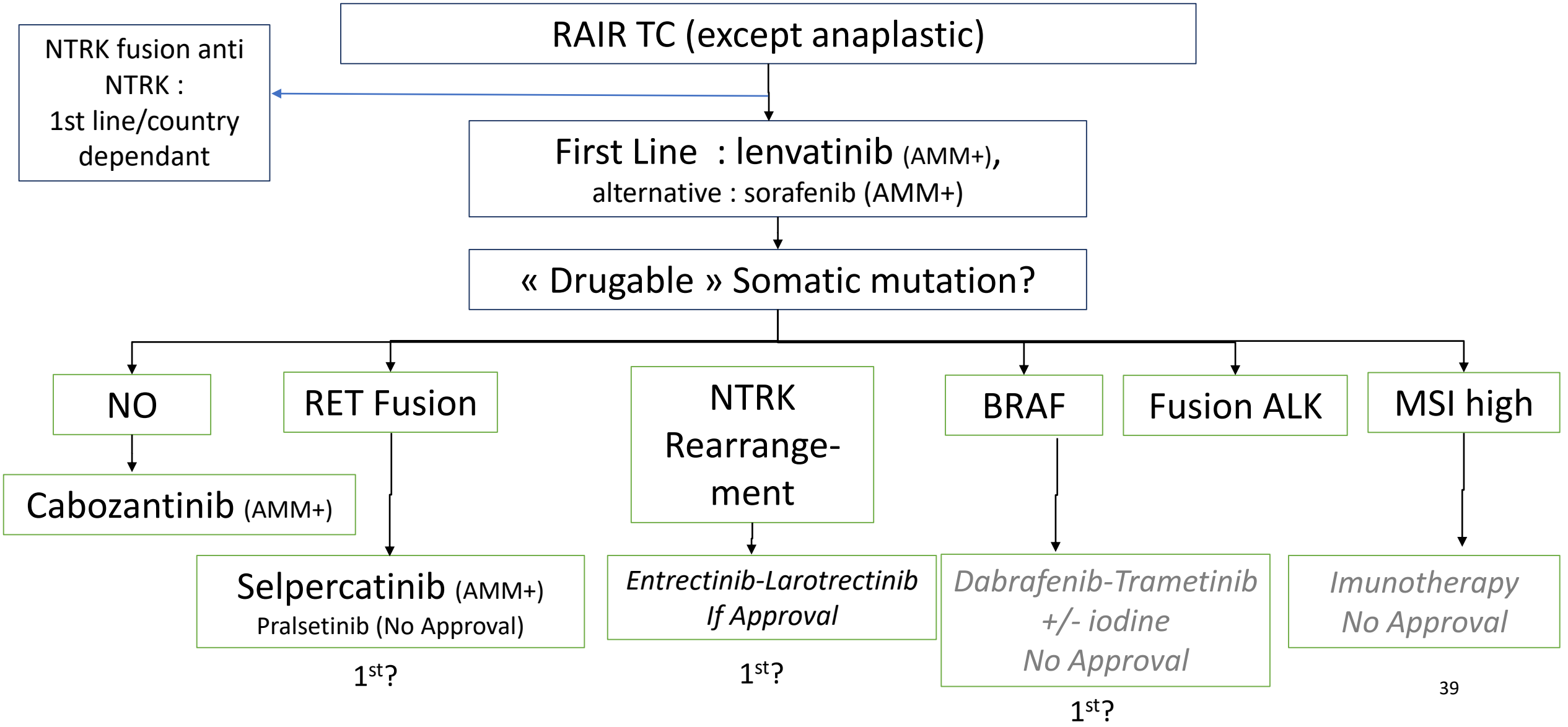
RAIR Follicular cell derived TC : **PIK,AKT,MTOR PATHWAY**

		Line	n	Complete Response %	Partial response %	Duration of Response	PFS (median, months)
Schneider, 2017	Everolimus	>1	28	**0**	**0**	-	9
Hanna, 2018	Everolimus	>1	33	**0**	**3**	-	12.9
Borson-Chazot, 2018	Buparlisib	>1	43	**0**	**0**	-	na

Sytemic therapy



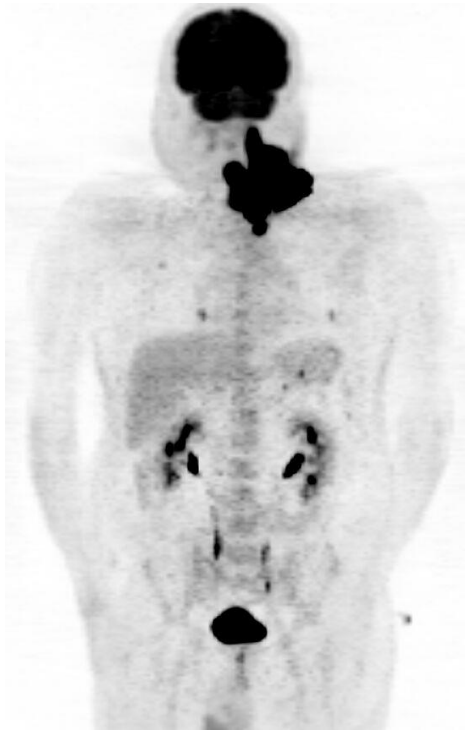
Sytemic therapy

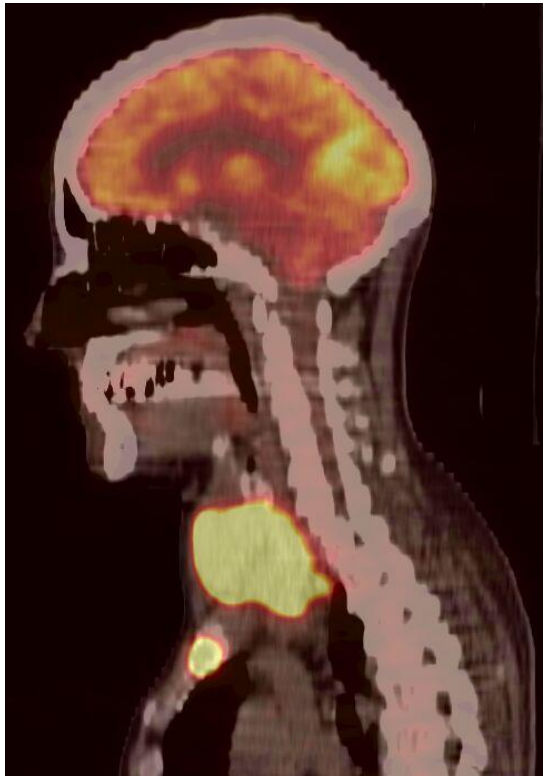


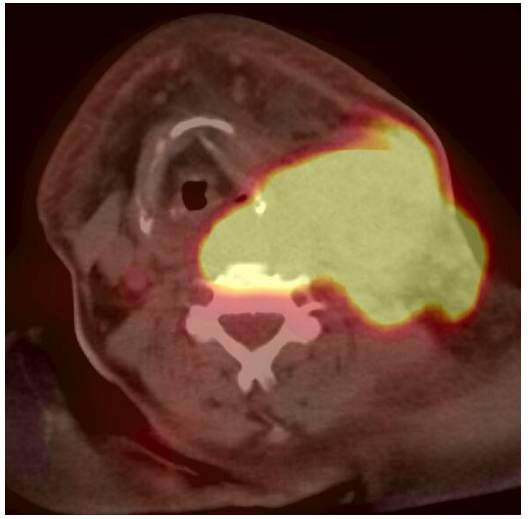
RAIR Follicular cell derived TC : Access to systemic therapy

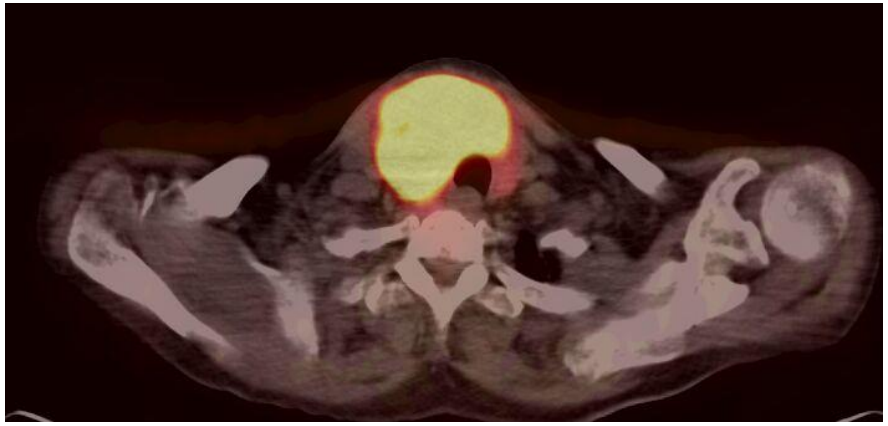
		FDA approval	EMA approval
Anti VEGFR	Sorafenib	Patients with locally recurrent or metastatic, progressive, RAI DTC (2013 & 2014)	
	Lenvatinib	Patients with locally recurrent or metastatic, progressive, RAI DTC (2015)	
	Cabozantinib	Patients with locally recurrent or metastatic, progressive, RAI DTC, **second line** (2021, 2022)	
Anti NTRK	Larotrectinib	Adult and pediatric with NTRK fusion (2018)	
	Entrectinib	Adults and adolescents aged ≥12 years with NTRK fusion (2020)	
Anti RET	Selpercatinib	**Adult and pediatric ≥12 years** of age with advanced/ metastatic RET fusion-positive thyroid cancer (2020)	Adults with RET fusion-positive thyroid cancer in adults **previously treated with sorafenib or lenvatinib or both (2021)**
	Pralsetinib	**Adult and pediatric ≥12 years** of age with advanced/ metastatic RET fusion-positive thyroid cancer (2020)	No

Anaplastic Thyroid Carcinoma: An Emergency









THYROID
Volume 31, Number 3, 2021

DOI: 10.1089/thy.2020.0944

SPECIAL ARTICLES

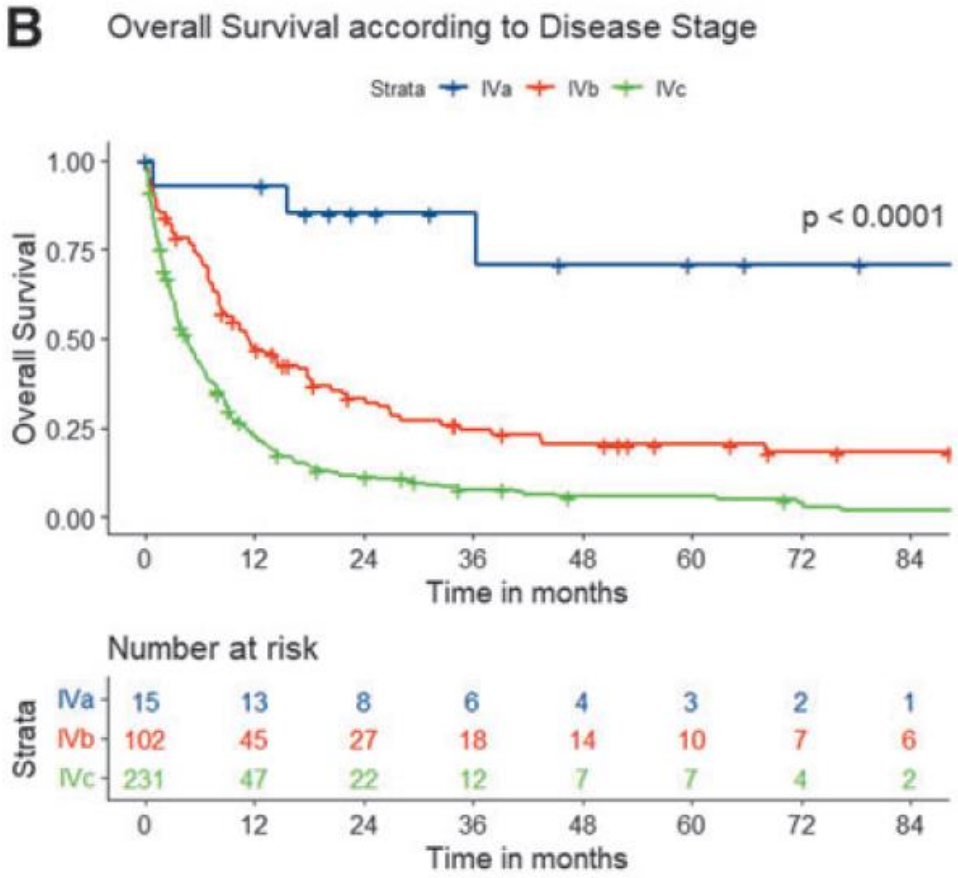
2021 American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer

American Thyroid Association Anaplastic Thyroid Cancer Guidelines Task Force

Keith C. Bible,[1] Electron Kebebew,[2] James Brierley,[3] Juan P. Brito,[4] Maria E. Cabanillas,[5] Thomas J. Clark Jr.,[6] Antonio Di Cristofano,[7] Robert Foote,[8] Thomas Giordano,[9] Jan Kasperbauer,[10] Kate Newbold,[11] Yuri E. Nikiforov,[12] Gregory Randolph,[13] M. Sara Rosenthal,[14] Anna M. Sawka,[15] Manisha Shah,[16] Ashok Shaha,[17] Robert Smallridge,[18] and Carol K. Wong-Clark*

Anaplastic carcinoma: a very poor prognosis

Kebebew et al. 2005, Registre SEER 516 patients : Median Survival : 3 months



	Stage	Median OS	12-months-OS
IVa	Intra-thyroïdal T1-T3a, N0, M0	**NR**	93%
IVb	Extra-thyroid extension pT3b, pT4, ou N1, M0	**11.4**	11.4%
IVc	IVC: All T, all N, M1	**4.6**	4.6%

Janin et al. Thyroid 2023

Treatment Principals

- Chemotherapy (Partial Response Rate ≈ 10%)

Treatment	Protocols and Dose
Chemotherapy	Every 3 or 4 weeks Doxorubicin (60 mg/m^2) + Cisplatin (120 mg/m^2) every 4 weeks Paclitaxel (175 mg/m^2) + Carboplatin (AUC 5) every 3 weeks Docetaxel (60 mg/m^2) + Doxorubicin (60 mg/m^2) every 3–4 weeks Paclitaxel (135–200 mg/m^2) every 3–4 weeks Doxorubicin (60–75 mg/m^2) every 3 weeks Every week Paclitaxel 50–100 mg/m^2 + Carboplatin AUC2 Docetaxel (20 mg/m^2) + Doxorubicin (20 mg/m^2) Paclitaxel (30–60 mg/m^2) Docetaxel (20 mg/m^2)

- External Beam Radiation

Bifractionated

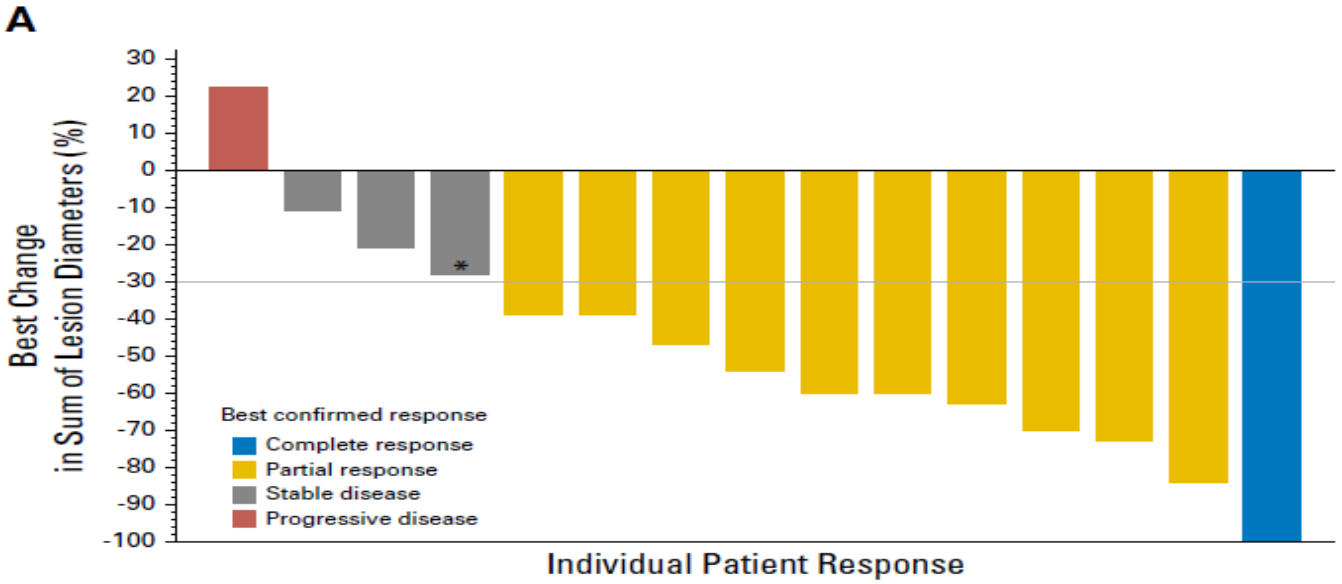
- Best Supportive Care

Except in case of drugable somatic mutation : BRAF

Janin et al. Cancers 2022

Dabrafenib-Trametinib for BRAF mutated ATC

	n	Median RR	12-month Kaplan-Meier estimate of duration of response
Subbiah et al, *2018*	15	67%	**90%.**
Subbiah et al, 2022	36	53%	**42%**

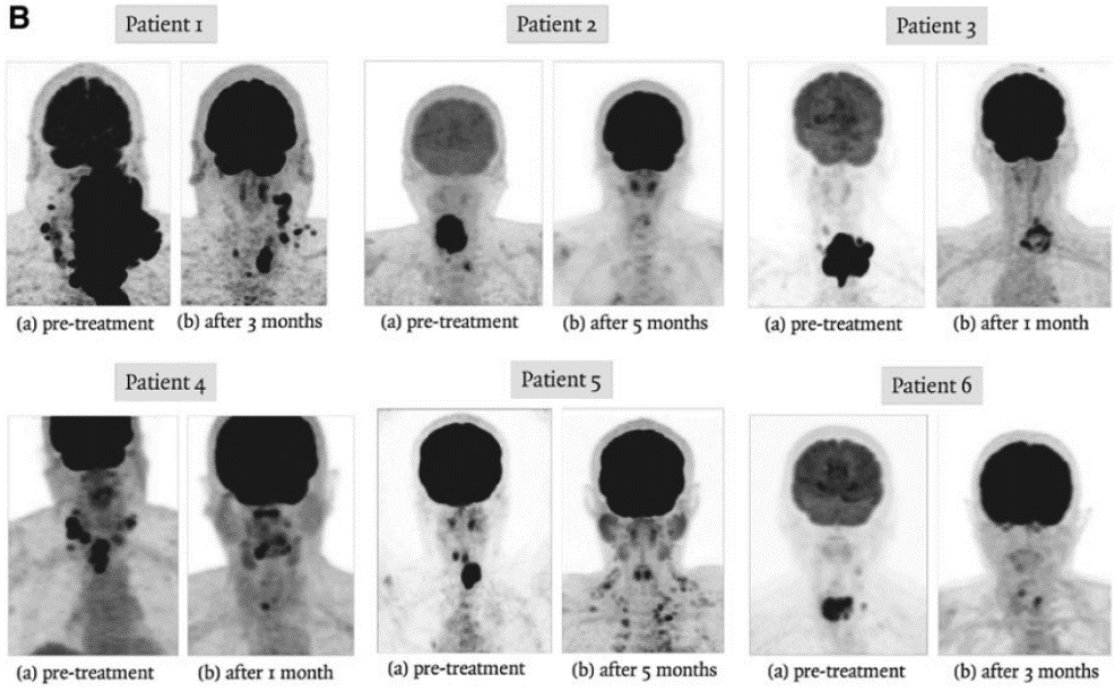


FDA approved

Dabrafenib-Trametinib for BRAF mutated ATC: from prospective data to real life

	n	Median RR	12-month Kaplan-Meier estimate of duration of response	Median OS
Subbiah et al, *2018*	15	67%	**90%.**	
Subbiah et al, 2022	36	53%	**42%**	
		Median RR	**Median PFS**	**Median OS**
Iyer et al, 2018	6	50%	5.2 months	9.3 months
Lorimer et al , 2023	17	88%	4.7 months	6.9 months
Bueno et al , 2023	5	60%	5 months	

Neo-adjuvant treatment with Dabrafenib-Trametinib



- High response rate
- Short length of response
- Neoadjuvant treatment for 2-4 months…monthly CT evaluation: rechallenge surgeons after each CT scan

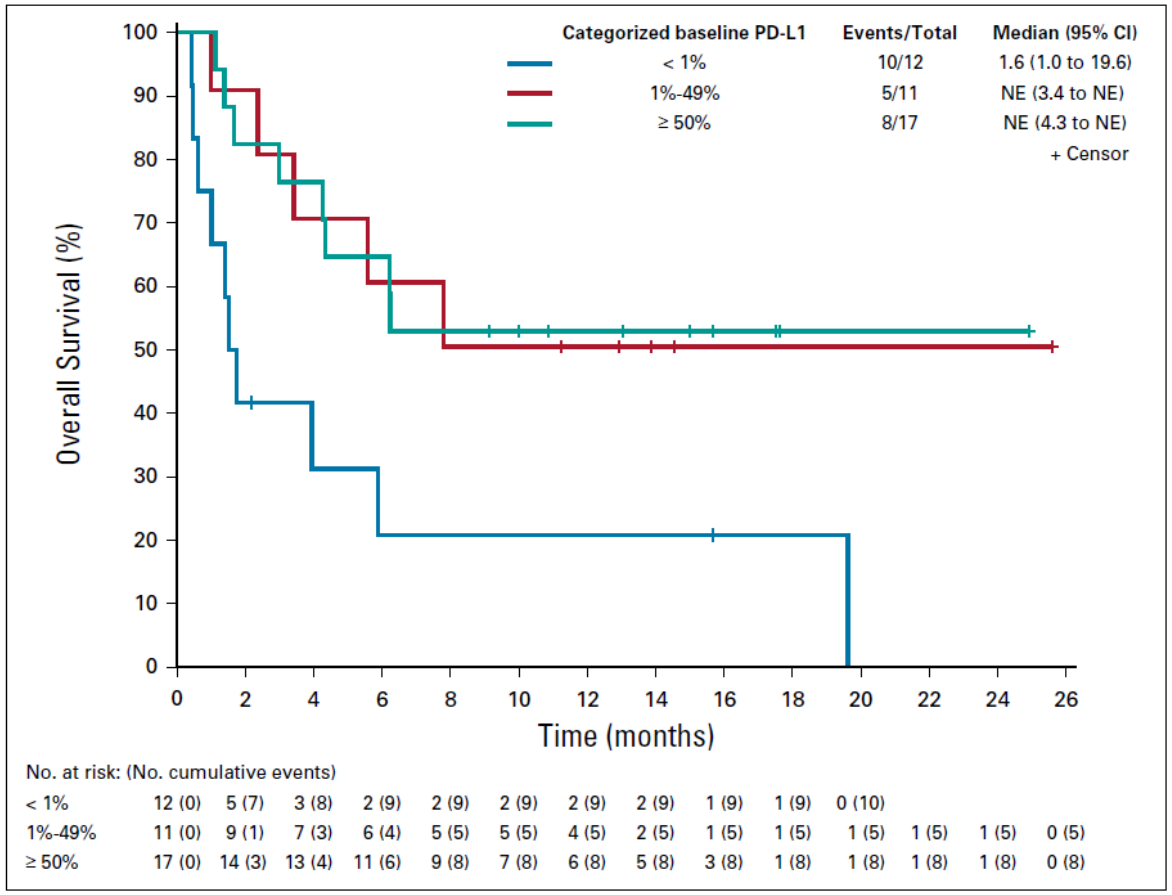
Wang *et al.* 2019

ATC et Anti PD1 Spartalizumab

	ATC (n=42)	
	RECIST 1.1	irRECIST
ORR (95%CI)	**19% (9-34)**	**24% (12-39)**
CR % (n)	7% (3)	7% (3)
PR % (n)	12% (5)	17% (7)
Median duration of response (months) (95%CI)	NE	NE
Median PFS (months) (95%CI)	1.7 (1.2-1.9)	1.7(1.2-2)

Capdevila *et al* JCO 2020

Overall Survival increased if PDL-1 is expressed

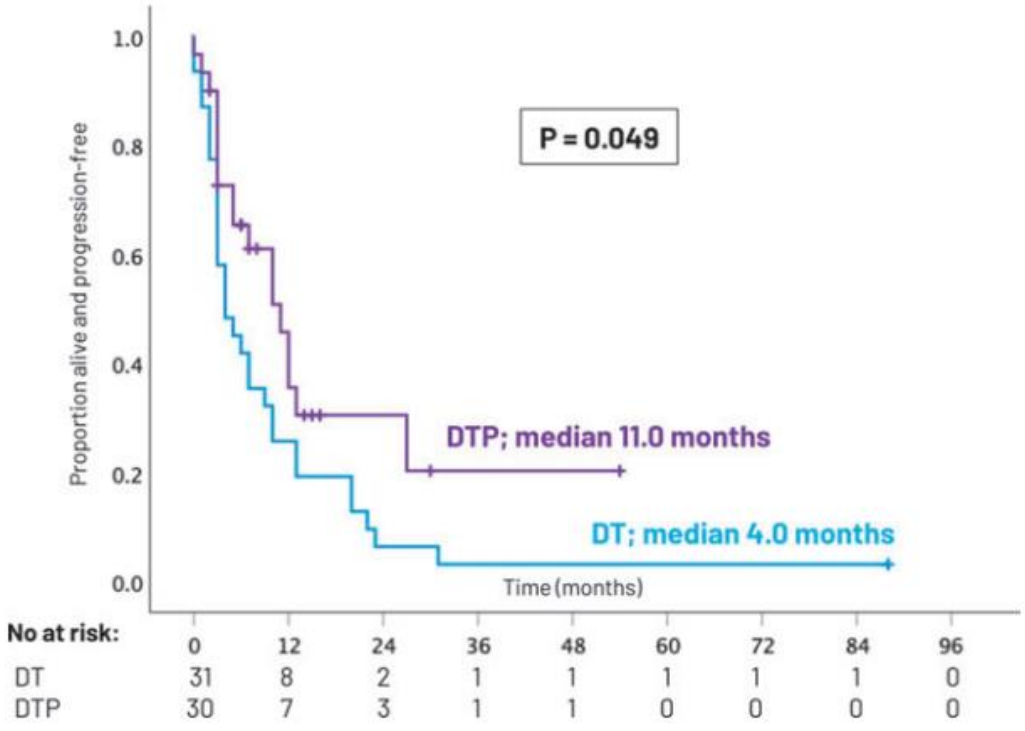


	PDL1 neg <1%	PDL1 1-49%	PDL1 ≥ 50%
1 year PFS	0%	20%	29%
Median OS	1.6	NR	NR

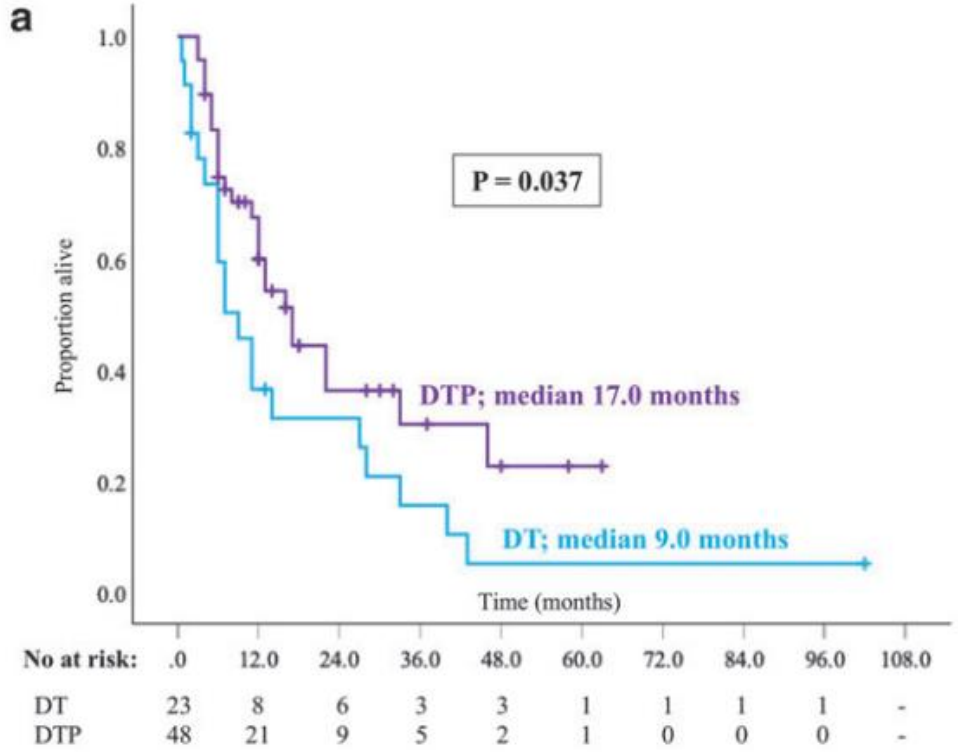
Capdevila *et al* JCO 2020

ATC : **Combination** of dabra-trame + pembrolizumab

Retrospective single-center study of patients with BRAFm-ATC treated with first-line BRAF-directed therapy
Dabra-trame vs. dabra-trame and pembrolizumab



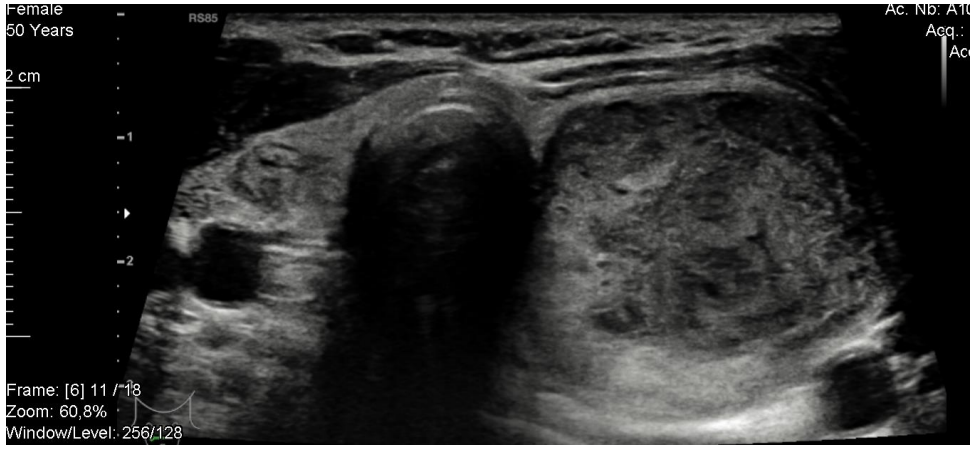
PFS



OS

Hamidi et al. 2024

A 50-year-old woman with a 4 cm EU TIRADS 5 thyroid nodule- Bethesda VI undergoes a total thyroidectomy with central neck dissection.



Pathology shows a 3.8 cm intra thyroid with 2 components;
papillary thyroid cancer component : 65%
anaplastic thyroid cancer (35%)

Mutations in RB1, DNMT3, PTEN, HNF1A, ATRX et TP53
No mutation in NRAS, BRAF, TERT.

Postoperative neck and chest CT scan shows two 5 mm lung nodules.

What would you do ?

A. Start levothyroxine treatment to obtain a TSH level of 0.1 mUI/L
B. Administer ^{131}I (3.7GBq, 100 mCi) after TSH stimulation
C. Obtain a postoperative Tg level and decide ^{131}I administration based on Tg level
D. Start chemotherapy and external beam radiation.
E. A lung biopsy and start tyrosine kinase treatment

OMS 2022: C cell derived carcinoma

<u>Medullary Thyroid Carcinoma :</u> <u>Endocrine Tumor</u>

International MTC Grading System :

High-grade MTC : at least 1 of the 3 criteria :

- Mitotic Index ≥ 5 per 2 mm^2
- And/or proliferative index Ki67 ≥ 5%,
- And/or tumor necrosis

Tumor marker : calcitonin

Hereditary in 1/3 of the cases : proto-oncogène RET mutation : Autosomic dominant transmission

Multiple endocrine neoplasia : phéochromocytoma +/- hyperparathyroïdism

OMS 2022, Xu et al. 2020 JCO

Genetic Alterations in MTC

Hereditary Forms : RET mutation RET : 100%

NEM2 : CMT +/- pheochromocytoma-hyerparathyroïdism

Sporadic

Author	N Tumor	RET+ RAS-	RET+ RAS+	RET- RAS+	Other mutations (%)
Moura, 2011	65	**60**	2%	26	Na
Boichard, 2012	50	**68**	0	26	Na
Agrawal 2013	57	**75**	0	16	MDC1 :5%
Ciampi 2013	188	**43**	0	10	Na
Simbolo 2014	20	**65**	0	20	STK11 (5%)
Ji, 2015	71	**51**	0	24	STK 11 (13%), MLH1 (5%), MET
Heilman 2016	30	**87**	0	10	CCND1 (9%) CDKN2A (9%), FGF19 (9%), VHL (6%)
Romei 2016	70	**91.4%**	-	8.6%	none

Hadoux *et al* 2018

Genetic Alterations in MTC

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Hadoux *et al* 2018

MTC : Anti VEGFR: Randomized phase III trials

	n	CR %	PR %	Duration of R (median, months)	PFS (median, months)
Vandetanib Wells 2011	331	0	45	Not reached	> 30 (V) vs 19.3 (P)
Cabozantinib Elisei 2013	330	0	28	14.6	4 (C) vs 11.2 (P)

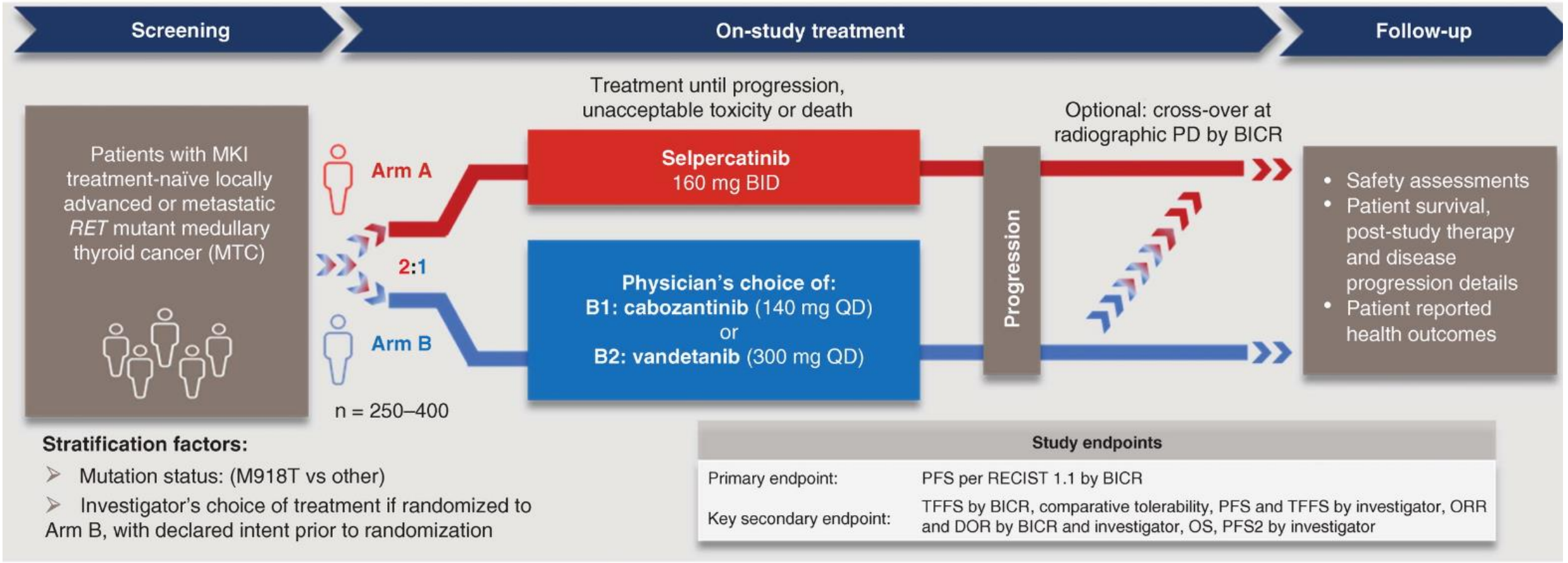
MTC WITH RET MUTATION: Selpercatinib: (LIBRETTO- 001) (Retsevmo ®)

	Patients with MTC and RET mutation	
	Previously treated (n=55)*	Treatment naive (n=88)
ORR (95%CI)	**69% (55-81)**	**71% (60-80)**
CR % (n)	9% (5)	11% (10)
PR % (n)	60% (33)	61% (54)
SD % (n)	25% (14)	23% (20
PD % (n)	2% (1)	2% (2)
Median duration of response (months) (95%CI)	NE	23.6 (NE-NE) (subject to changes, on less than 10% of the events)

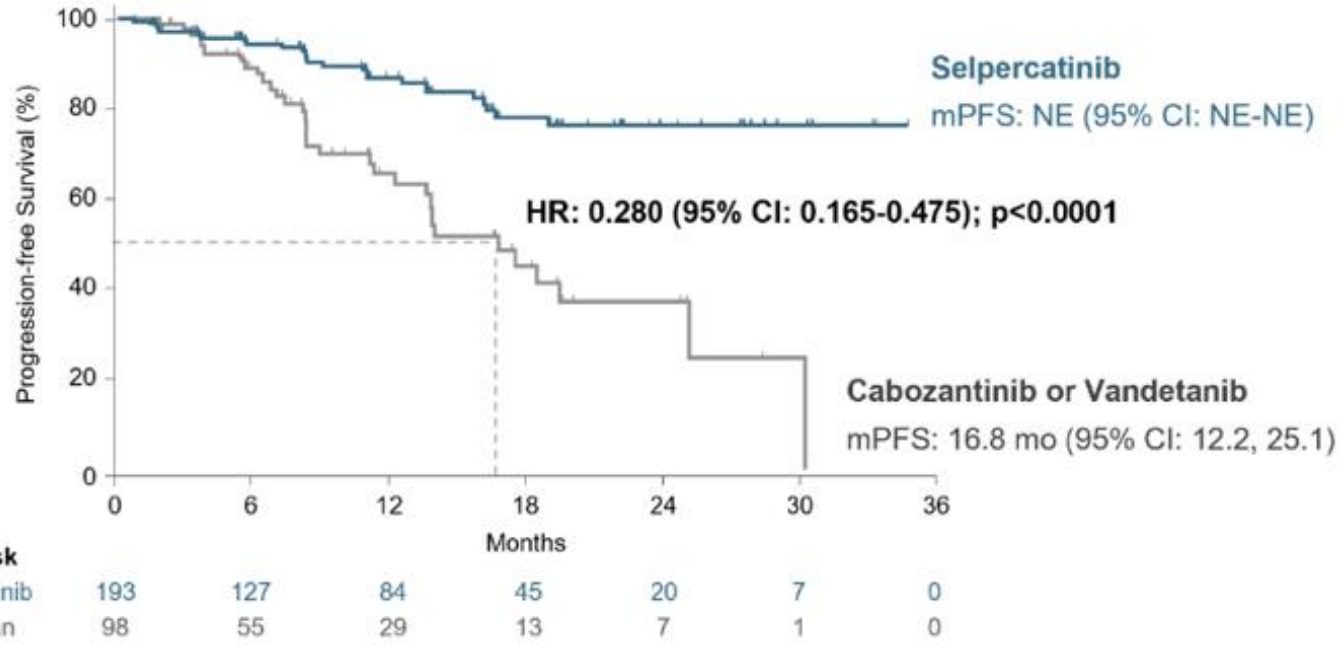
*: central review

Wirth *et al*, NEJM 2020, Update Sherman, ASCO 2021

Selpercatinib Phase III: 1st vs 2nd ligne of treatment in MTC a Phase 3 Trial: Libretto



Progression Free Survival (Blinded Independent Central Review)



NE

16.8 months

Selpercatinib demonstrated a statistically significant improvement in PFS

- Median follow-up of 12 months
- Investigator-assessed PFS was similar with a hazard ratio of 0.187 (95% CI: 0.109-0.321); p<0.0001[1]
- The study was considered positive for PFS if the two-sided p-value was <0.0033; therefore, this trial met its primary endpoint for evidence of efficacy

Hadoux *et al*, NEJM 2023

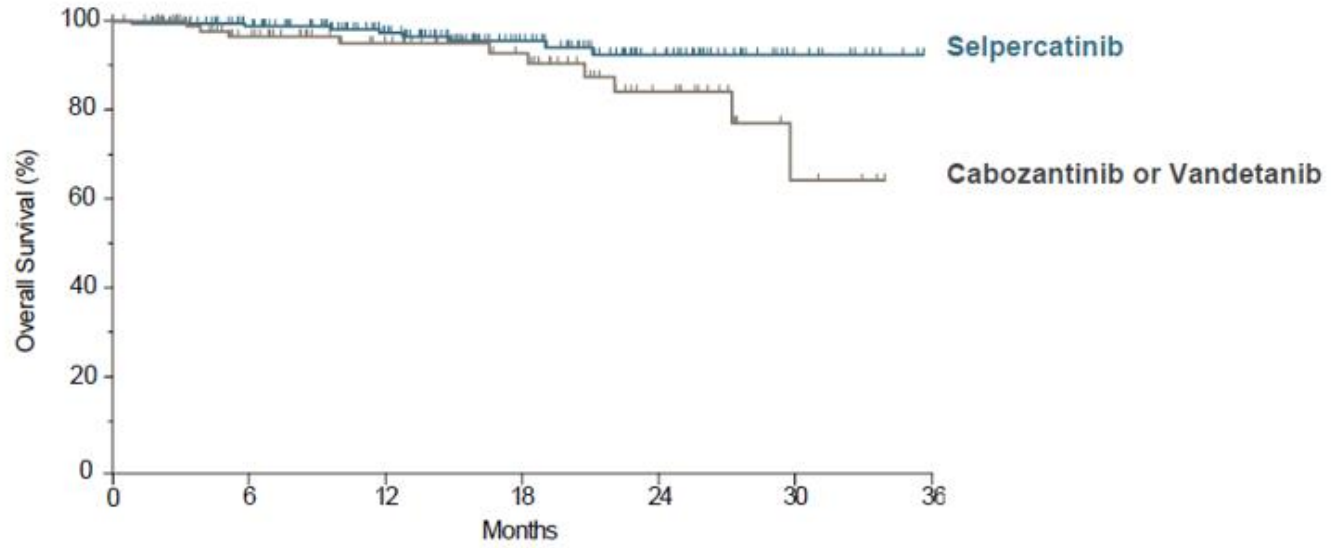
Overall Response Rate

Outcomes	Selpercatinib (N= 193)	Cabozantinib or Vandetanib (N= 98)
ORR, % (95% CI)[1]	69.4 (62.4, 75.8)	38.8 (29.1, 49.2)
Best overall response, no. (%)		
Complete response	23 (11.9)	4 (4.1)
Partial response	111 (57.5)	34 (34.7)
Median DOR, mo (95% CI)	NE (NE, NE)	16.6 (10.4, NE)

Overall response rate by RECIST 1.1 was higher and responses were more durable with selpercatinib

Hadoux *et al*, NEJM 2023

Overall Survival



- At the time of the interim analysis, 18 deaths (8 deaths on selpercatinib, 10 deaths on cab or van) were observed at median follow-up of 15 months
- 94.8% of patients were alive on selpercatinib and 85.7% on control arm
- 24 patients (77.4% of those eligible to crossover) elected to receive selpercatinib; 19 of whom remained on treatment at the data cutoff date
- HR: 0.374 (95% CI, 0.147 to 0.949); p=0.0312[1]

[1] Nominal value

Approval in first line pending

What should we give after progression on selpercatinib?

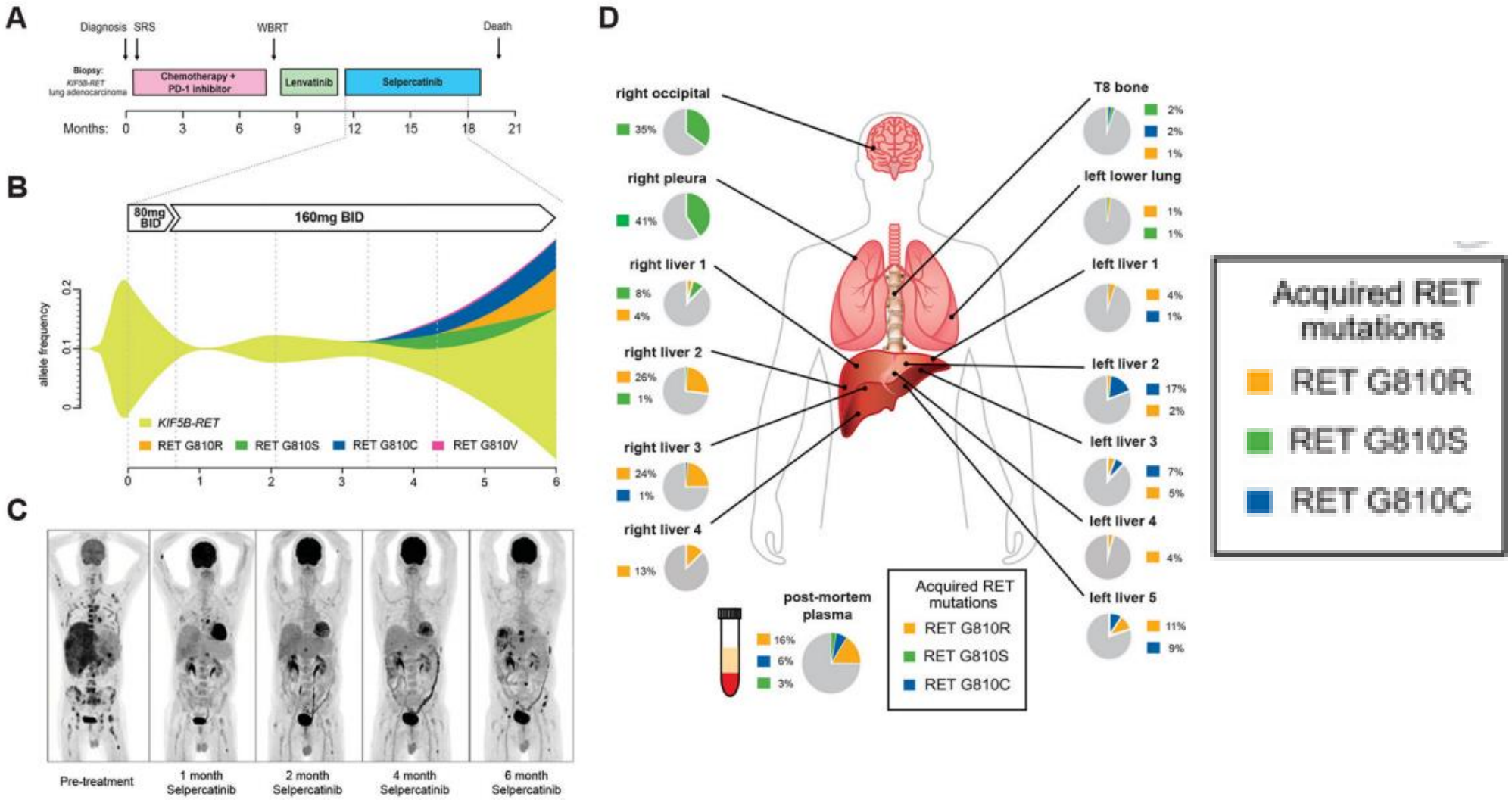
	Selpercatinib	Cabozantinib or vandetanib
12 months PFS	86.8 %	65.7%
24 months PFS	76.4%	37.2%

Two main mechanisms of resistance to selective RET inhibitors

- on-target mutations impairing drug binding : solvent front
- activation of alternative signaling pathways allowing bypass of RET inhibition
  - acquired KRAS, HRAS, NRAS and BRAF mutations
  - KRAS amplifications
  - MET and FGFR1 amplifications

Hadoux *et al*, NEJM 2023

Multiple Solvent front mutations in a patients with SCLC treated with selpercatinib



Solomon, et al 2021

On target mutations

Table 3. Mechanisms of resistance and IC_{50} (μM) for each drug.

Mutation Status		Cabozantinib [112]	Vandetanib [112]	Lenvatinib [112]	Ponatinib [112]	Selpercatinib [109]	Pralsetinib [109]
Gatekeeper	V804M	4.26	5.83	5.42	0.0339	0.0559	0.0168
	V804L	3.22	6.10	10.60	0.43 [60]	0.0172	0.0018
Solvent front	G810A	0.22	2.76	0.11	0.008 [60]	-	-
	G810R	-	-	-	-	2.744	2.650
	G810S	1.05	5.47	0.67	-	0.8802	0.3906
	G810C	-	-	-	-	1.227	0.6417
Other	S904F	-	0.908 [98]	-	-	-	-
	Y806C	-	0.933 [113]	-	-	0.1744	0.2958
	Y806N	4.76	5.86	1.93	-	0.1498	0.2925
	V738A	1.20	1.05	2.35	-	0.2388	0.1775

The IC_{50} values are mean (95% confidence interval). In red: resistant; in green: non-resistant. Values refers to BaF3 cell line, exception for Vandetanib Y806C value obtained in HEK 293.

Fancelli et al 2021

Mechanism of resistance : activation of alternative signaling pathways more frequent than solvent front?

Among 26 MTC patients treated with RETi,

<u>14 patients with pre and post selpercatinib molecular profile</u>

→ **By pass mechanism of resistance in 75% of the case**

RAS gene mutations (50%),
FGFR2 fusion
ALK fusions

→ solvent front mutation: 25%

MYC p.P44L. RET solvent front
hinge region mutations

<u>6 patients with tumor samples from initial thyroidectomy, pre- and post-RETi</u>

→ increase of the mean Ki 67-index of 7%, 17% and 40%
Hadoux, et al 2023

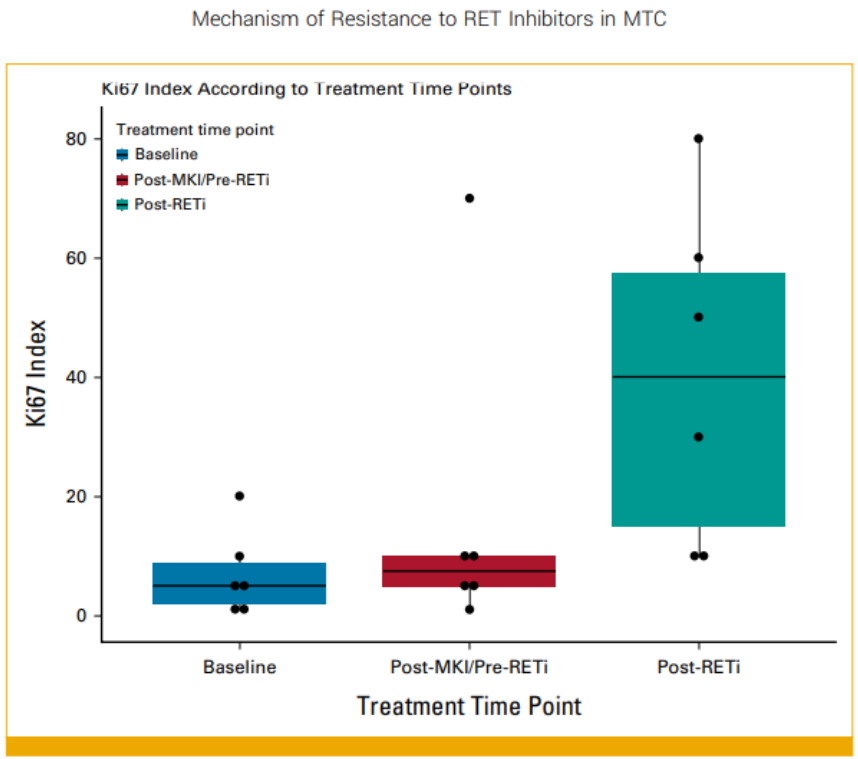


FIG A1. Box plot of Ki67 index in MTC tumor sampled at diagnosis, after MKI/before RETi, and after RETi. MKI, multikinase inhibitor; MTC, medullary thyroid carcinoma; RET, rearranged during transfection; RETi, selective RET inhibitor.

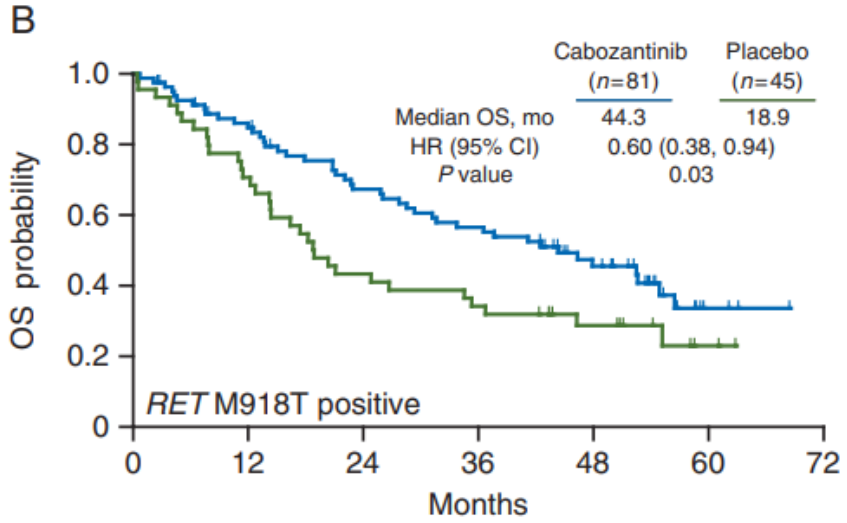
To assess the efficacy of vande /cabo after progression under selpercatinib

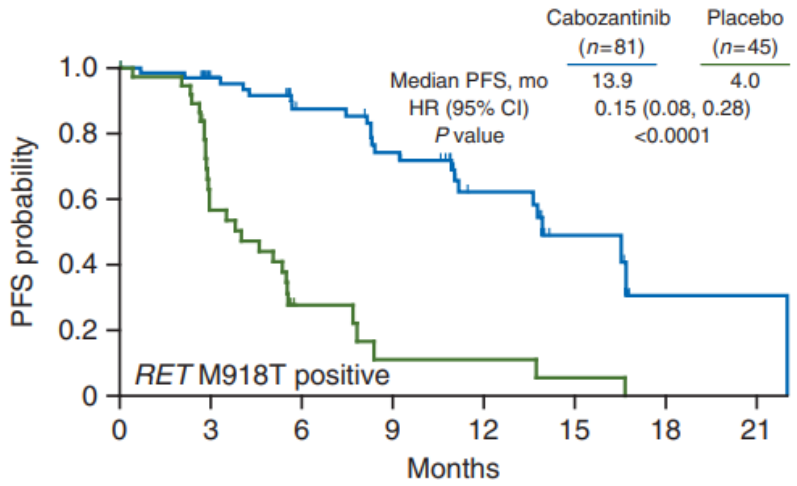
Longer follow-up data from the LIBRETTO 531 study
Efficacy according to the type of resistance mechanism

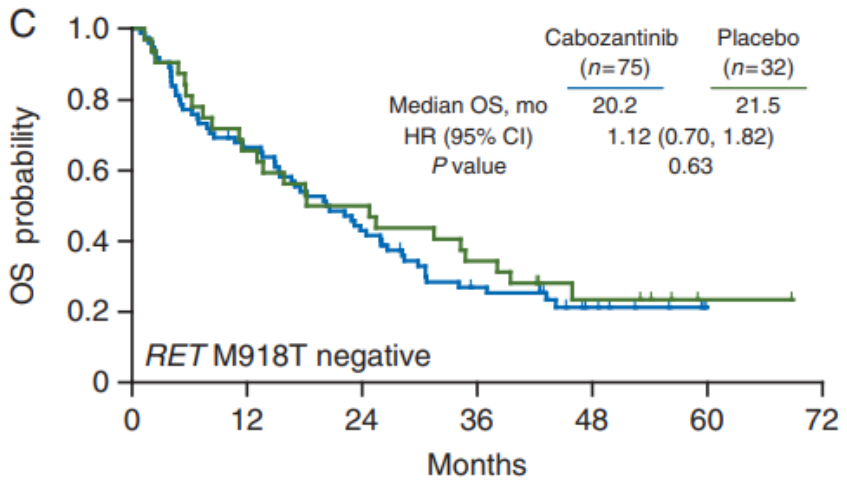
Patients without RET mutations

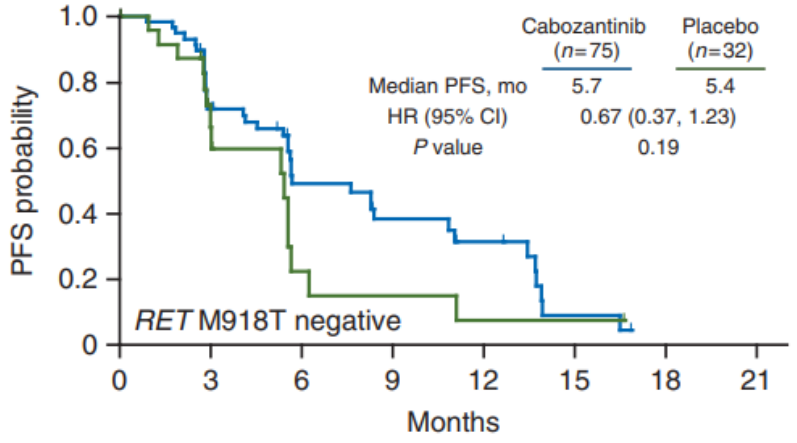
Author	N Tumor	RET+ RAS- %	RET+ RAS+ %	**RET- RAS+ %**	**Other mutations (%)**
Moura, 2011	65	60	2%	**26**	Na
Boichard, 2012	50	68	0	**26**	Na
Agrawal 2013	57	75	0	**16**	MDC1 :5%
Ciampi 2013	188	43	0	**10**	Na
Simbolo 2014	20	65	0	**20**	STK11 (5%)
Ji, 2015	71	51	0	**24**	STK 11 (13%), MLH1 (5%), MET
Heilman 2016	30	87	0	**10**	CCND1 (9%) CDKN2A (9%), FGF19 (9%), VHL (6%)
Romei 2016	70	91.4	-	**8.6**	none

Effect of cabozantinib on OS et PFS according to the RET status : the EXAM trial









Schlumberger, et al 2017

Chemotherapy in MTC

Drugs	n	Partial Response	
CVD	7	2	Averbuch et al 1988
CVD	9	1	Deutschbein et al
Dacarbazine +5FU	5	3	Orlandi et al 1994
Dacarbazine +5FU / 5FU streptozotocine	20	3	Schlumberger et al 1995
Dacarbazine +5FU / Doxo- streptozotocine	20	3	Nocera et al 2000
Dacarbazine +5FU	4	3	Marchand et al 2016
Capecitabine-Temozolomide	1	1	Lacin et al 2015

Refractory Thyroid Cancer

Rares Tumors

Include : DTC that are RAIR, All ATC and MTC with residual disease

Network of healthcare expertise
Data bases
TRIALS FOR UNMET NEEDS

DTC : **LT4**
Local treatments
Systemic treatments in case of progressive disease- high tumor burden
Mostly anti VEGFR -→ Rare actionable somatic mutations that need to be searched

Anaplastic thyroid carcinomas: **Urgent treatment**
Chemo-Radiation
Rare actionable mutations, that need to be searched

MTC : **Hereditary and sporadic forms: RET mutation**
Local treatments
Systemic treatments in case of progressive disease- high tumor burden
Anti RET: 1st line treatment…

Thanks for your attention