Update:

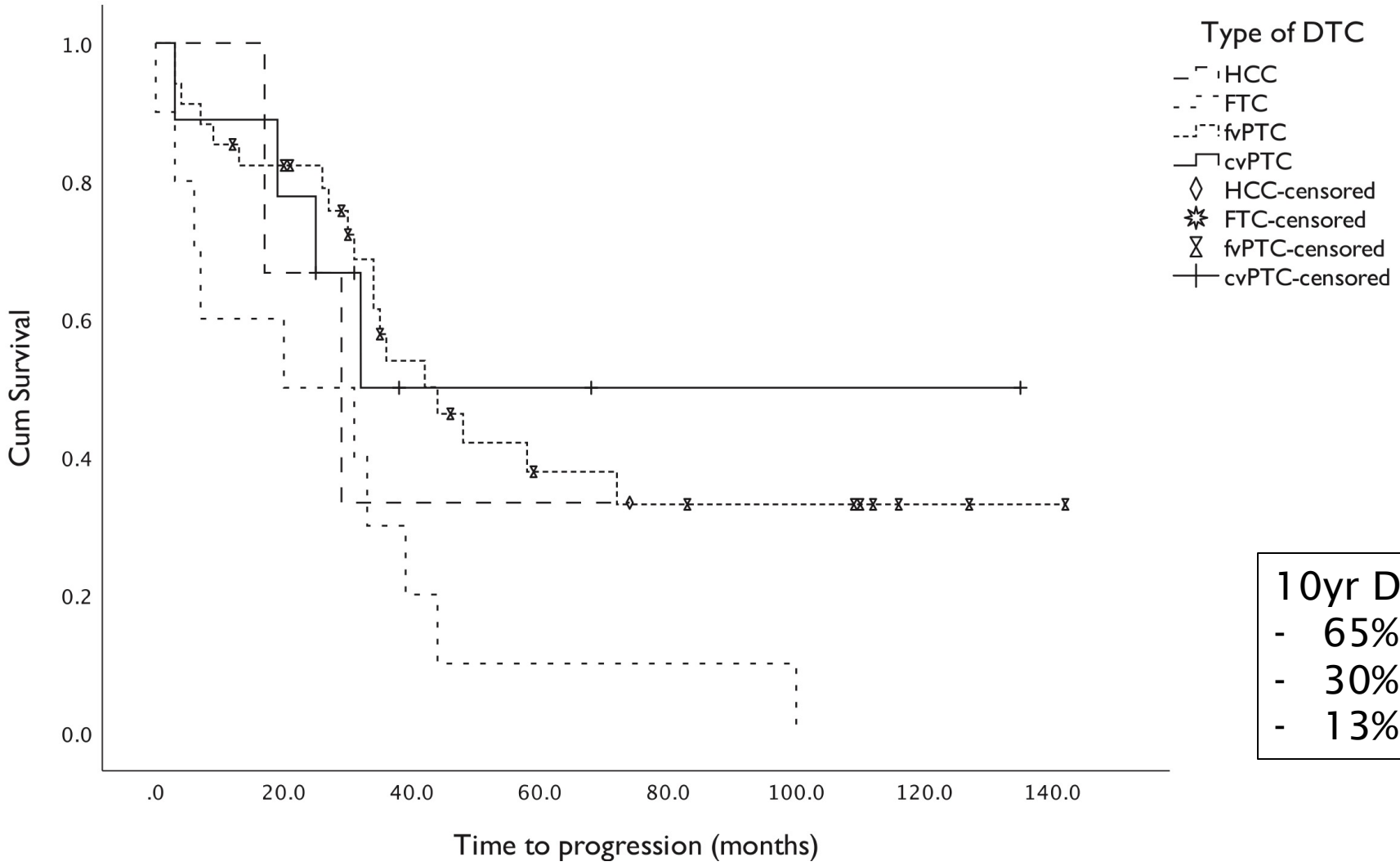
medikamentöse Therapie des Schilddrüsenkarzinoms

Markus Raderer

Division of Oncology & Neuroendocrine Tumor Unit

Medical University of Vienna

Radio-Jod Therapie bei Patienten mit DTC-Metastasen



10yr DSS
- 65% in PTC
- 30% in FTC
- 13% in HCC

Simoes-Pereira J et al, JCEM 2021;106:e3911-3922

Individualisierung des postoperativen Vorgehens: Selumetinib + RAI vs RAI + Placebo: ASTRA Trial

- High risk features: Tumor. > 4 cm

  T4 („Gross extension outside the thyroid“)

  N1a / N1b mit 1 LN > 1 cm oder > 5 LNN pos
- 2:1 Randomisierung Selumetinib 75 mg 2 x 1 vs Placebo für 5 Wochen
- 100 mCi / 3.7 Gbq am Tag 29 – 31 (nach rTSH Stimulation 0.9 mg)
- 233 pts: Selumetinib n = 155 / Placebo n = 78
- Primärer Endpunkt: CR-Rate nach 18 Monaten in der ITT Population (n = 400)

original reports

Selumetinib Plus Adjuvant Radioactive Iodine in Patients With High-Risk Differentiated Thyroid Cancer: A Phase III, Randomized, Placebo-Controlled Trial (ASTRA)

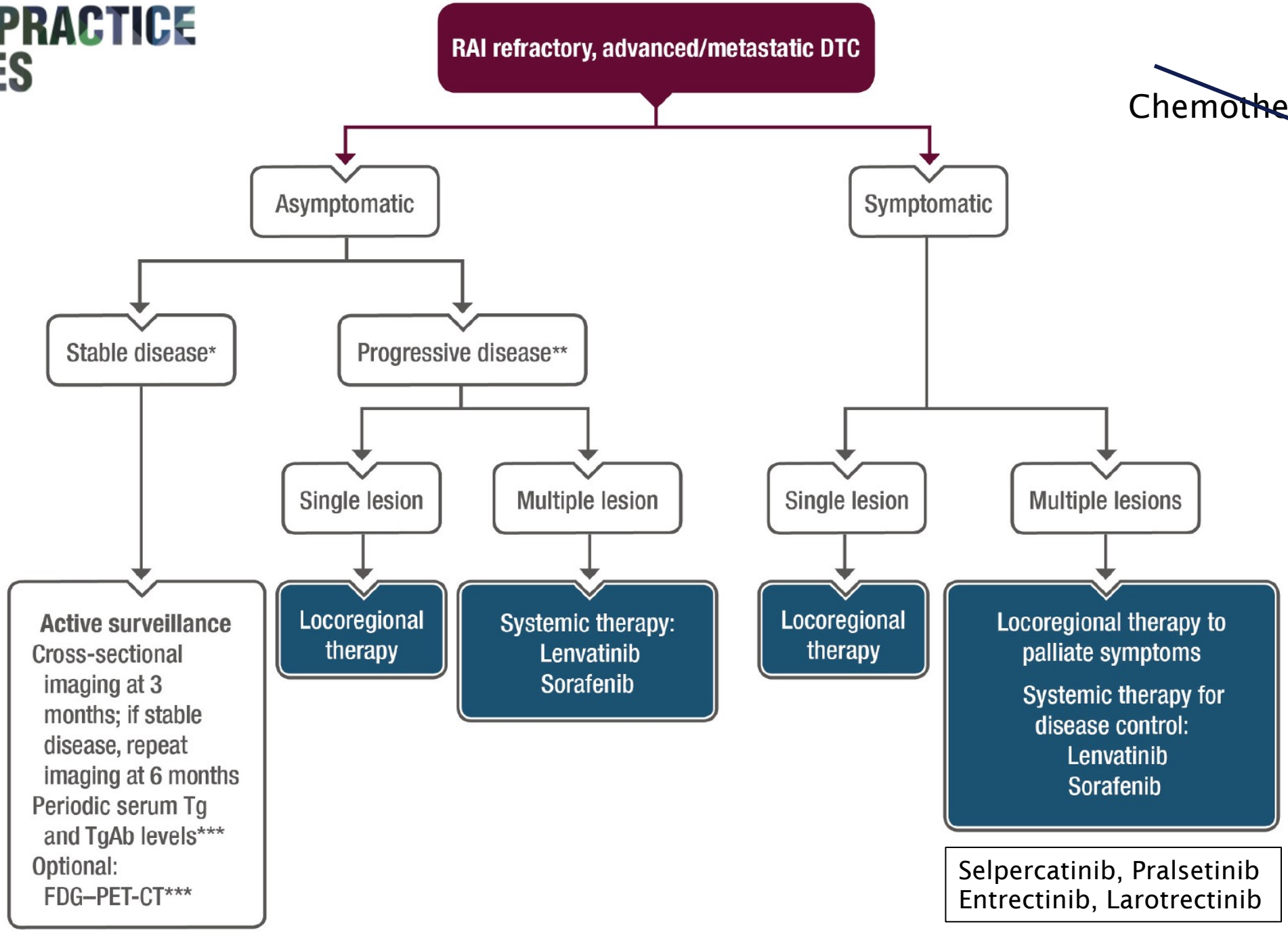
Alan L. Ho, MD, PhD[1]; Marek Dedecjus, PhD[2]; Lori J. Wirth, MD[3]; R. Michael Tuttle, MD[4]; William B. Inabnet III, MD[5,6]; Jan Tennvall, PhD[7]; Fernanda Vaisman, PhD[8]; Lars Bastholt, MD[9]; Andrew G. Gianoukakis, MD[10,11]; Patrice Rodien, PhD[12]; Ralf Paschke, PhD[13]; Rossella Elisei, MD[14]; David Viola, MD[14]; Karen So, MD[15]; Danielle Carroll, MD[15]; Tina Hovey, MSc[16]; Bhavana Thakre, MD[17]; and James A. Fagin, MD[4]; the ASTRA investigator group

TABLE 2. CR Rate at 18 Months (ITT and treatment-compliant analysis sets) and Reasons for Exclusion From CR Designation at 18 Months (ITT analysis set)

CR Rate	Selumetinib plus RAI	Placebo plus RAI
CR rate at 18 months, No. (%)	62/155 (40)	30/78 (38)
Full analysis set (primary analysis)	OR 1.07 (95% CI, 0.61 to 1.87); $P = .8205$	
Treatment compliant analysis set[a]	56/120 (47)	27/72 (38)
	OR 1.46 (95% CI, 0.81 to 2.67); $P = .2131$	

J Clin Oncol 2022

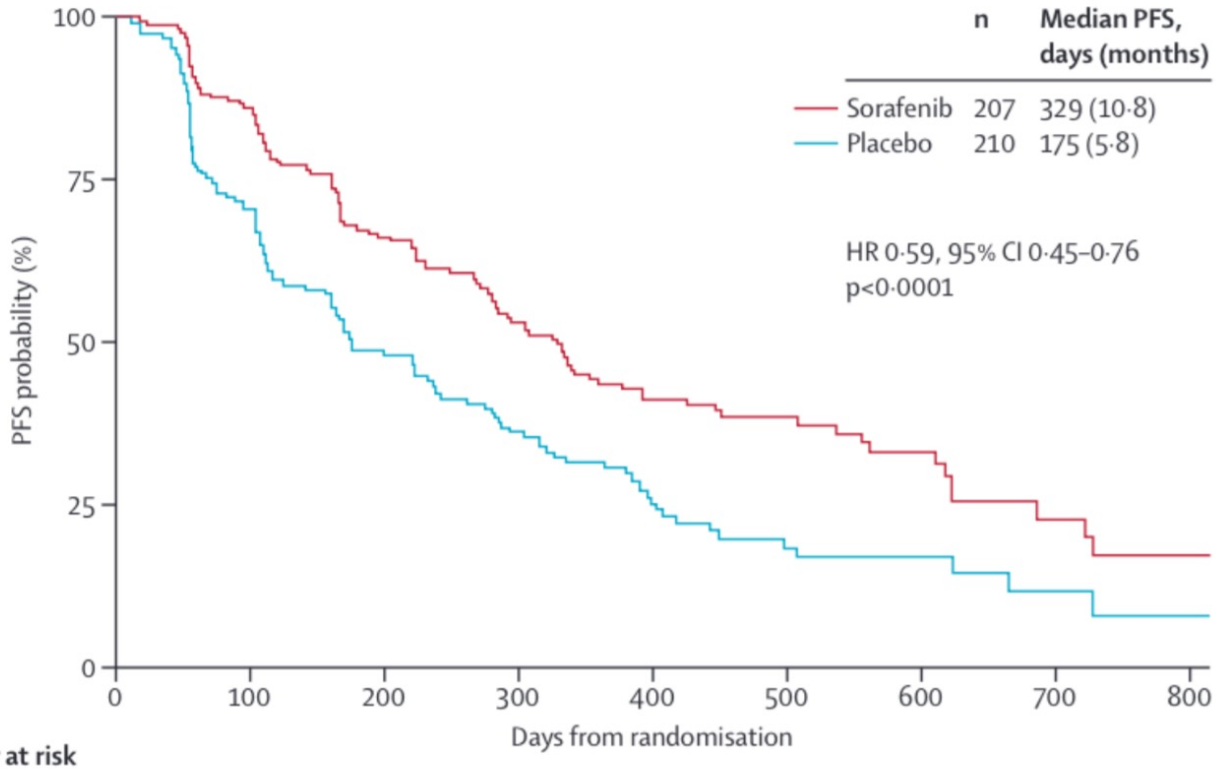
CLINICAL PRACTICE GUIDELINES



~~Chemotherapy?~~

Selpercatinib, Pralsetinib
Entrectinib, Larotrectinib

Sorafenib for RAI-DTC DECISION Study



Number at risk

Sorafenib	207	157	110	81	49	33	18	8	3
Placebo	210	133	76	47	25	12	8	3	2

ORR 12% vs 0.5%

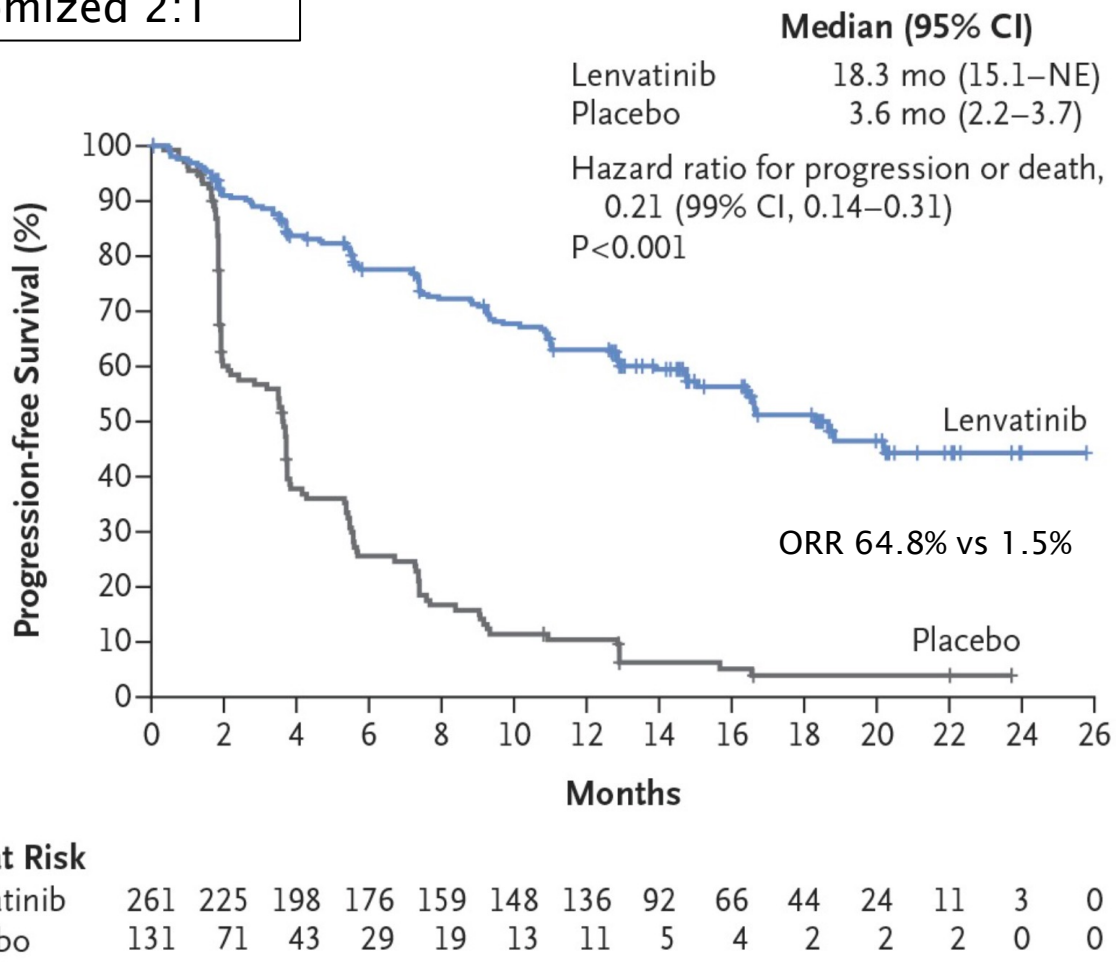
Brose M et al, Lancet 2014;9940:319-328

Lenvatinib for RAIR-DTC – Phase III SELECT Study

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)

Randomized 2:1



No. at Risk

Lenvatinib	261	225	198	176	159	148	136	92	66	44	24	11	3	0
Placebo	131	71	43	29	19	13	11	5	4	2	2	2	0	0

Schlumberger M et al, NEJM 2015;372:621-30

TKIs in der First-Line: Resultate

Signifikant verlängertes PFS

- Lenvatinib 18.3 mos versus 3.6 mos
- Sorafenib 10.8 mos versus 5.6 mos

Substantielle Rate objektiver Remissionen

- Lenvatinib ORR 65%

Indikation nur bei progedienter Erkrankung!

- SELECT: documented radiological progress <13 m
- DECISION: documented radiological progress <12 m

OS: bisher kein klarer OS-Vorteil (Cross-over!)

TOX: **Einfluss auf die QoL**

Substanz	**Lenvatinib**	**Sorafenib**
Studie	SELECT Phase III placebokontrolliert	DECISION Phase III placebokontrolliert
Targets	VEGFR-1–3, FGFR-1–4, PDGFRα, RET, KIT	VEGFR-1–3, RET, RAF, PDGFRβ
Einschlusskriterien	DTC, radiojodrefraktär, lokal fortgeschritten oder metastasiert	DTC, radiojodrefraktär, lokal fortgeschritten oder metastasiert
Primärer Endpunkt	PFS 3,6 m Placebo vs. 18,3 m Lenvatinib (HR 0,21, 95%-KI 0,14–0,31)	PFS 5,8 m Placebo vs. 10,9 m Sorafenib (HR 0,59, 95%-KI 0,45–0,76)
Toxizität CTCAE 3+ > 10 %	Hypertonie	Hand-Fuß-Syndrom

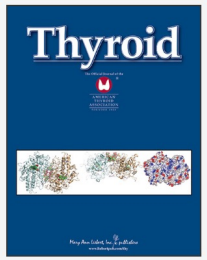
-> informed consent
-> drug holidays

Kiesewetter B , Raderer M, Universum Innere Medizin 02/21

Lenvatinib Compared with Sorafenib as a First-Line Treatment for Radioactive Iodine-Refractory, Progressive, Differentiated Thyroid Carcinoma: Real-World Outcomes in a Multicenter Retrospective Cohort Study

Mijin Kim, Meihua Jin, Min Ji Jeon, Eui Young Kim, Dong Yeob Shin, Dong Jun Lim, Bo Hyun Kim, Ho-Cheol Kang, Won Bae Kim, Young Kee Shong, Hee Kyung Kim, and Won Gu Kim

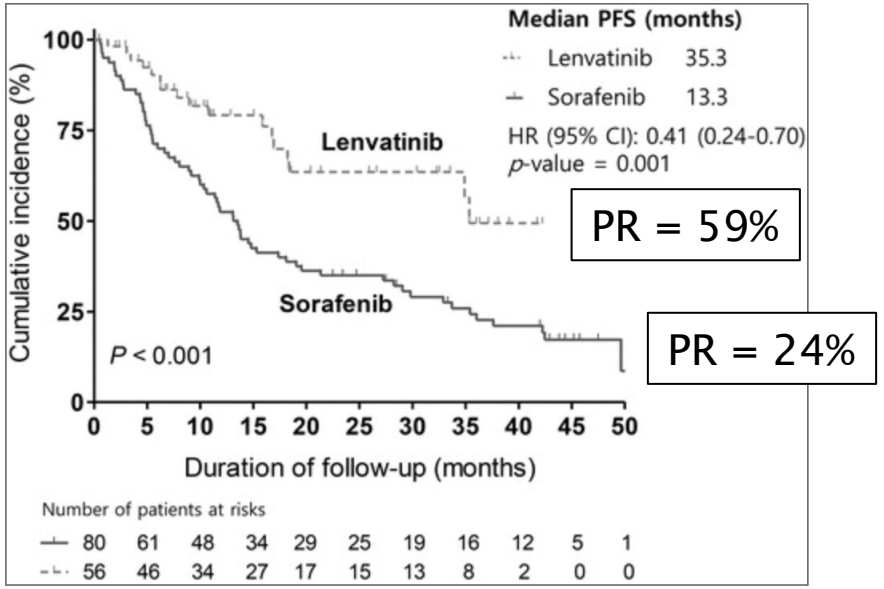
Published Online: 17 May 2022 | https://doi.org/10.1089/thy.2022.0054



Information

Response rate			
CR	0	0	
PR	19 (24%)	33 (59%)	<0.001
SD	55 (69%)	22 (39%)	
Durable SD[a]	33 (41%)	10 (18%)	
PD	6 (8%)	1 (2%)	
Objective response rate[b]	19 (24%)	33 (59%)	<0.001
Disease control rate[c]	74 (93%)	55 (98%)	0.276
Clinical benefit rate[d]	52 (65%)	43 (77%)	0.199

Fig. 1). Investigator-assessed PFS was significantly longer in the lenvatinib group than in the sorafenib group (HR = 0.41; CI, 0.24–0.70; p = 0.001, Table 2; Supplementary Table S1).



PR = 59%

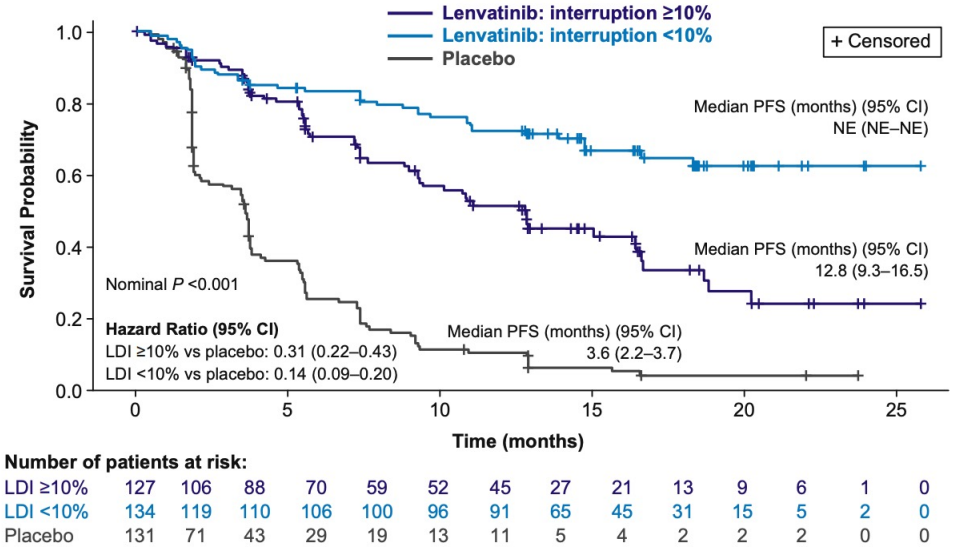
PR = 24%

FIG. 1. Kaplan-Meier plot of the progression-free survival of patients with progressive refractory DTC after treatment with first-line sorafenib or lenvatinib. DTC, differentiated thyroid carcinoma.

Impact of dose interruption on the efficacy of lenvatinib in a phase 3 study in patients with radioiodine-refractory differentiated thyroid cancer

Makoto Tahara [a,*], Marcia S. Brose [b], Lori J. Wirth [c], Takuya Suzuki [d], Hideaki Miyagishi [d], Katsuki Fujino [d], Corina E. Dutcus [e], Andrew Gianoukakis [f,g]

M. Tahara et al. / European Journal of Cancer 106 (2019) 61–68 65



Number of patients at risk:

LDI ≥10%	127	106	88	70	59	52	45	27	21	13	9	6	1	0
LDI <10%	134	119	110	106	100	96	91	65	45	31	15	5	2	0
Placebo	131	71	43	29	19	13	11	5	4	2	2	2	0	0

Fig. 1. Kaplan–Meier estimates of progression-free survival. CI, confidence interval; LDI, lenvatinib dose interruption (as percentage of total treatment duration); NE, not evaluable; PFS, progression-free survival.

Table 2
Multivariate analysis of patients randomised to lenvatinib in SELECT.

Parameter	Category	PFS HR	95% CI	Nominal *P* value
Dose interruption	<10% versus ≥10%[a]	0.467	0.307–0.712	0.0004
Age group (years)	≤65 versus >65	0.895	0.606–1.323	0.5781
Sex	Female versus male	0.780	0.529–1.150	0.2095
Region	Europe versus North America	1.381	0.868–2.197	0.3453
	Other versus North America	0.931	0.366–2.370	
Race	Nonwhite versus white	1.081	0.430–2.717	0.8684
BMI category (kg/m^2)	<25 versus ≥ 30	1.321	0.809–2.156	0.5054
	25–<30 versus ≥ 30	1.084	0.637–1.844	
ECOG PS score	0 versus ≥ 1	0.552	0.371–0.821	0.0034

Individualisierte Dosierung?

The Journal of Clinical Endocrinology & Metabolism, 2022, Vol. 107, No. 3, 776–787
https://doi.org/10.1210/clinem/dgab731
Clinical Research Article

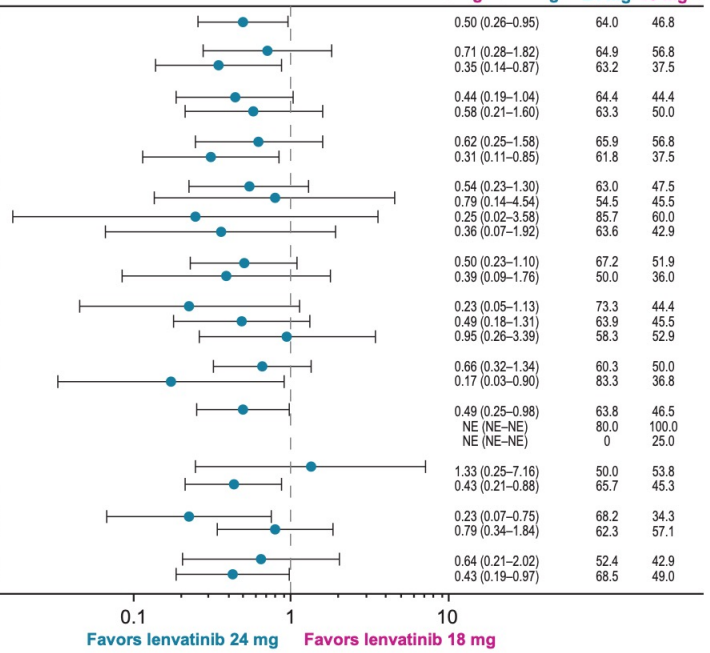
ENDOCRINE SOCIETY OXFORD

Clinical Research Article

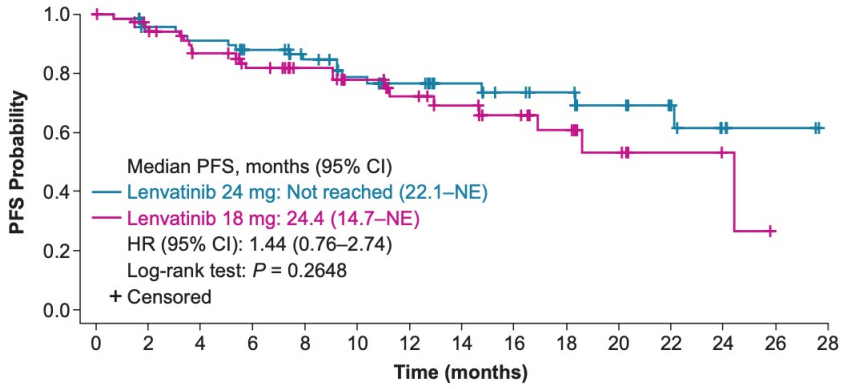
A Randomized Study of Lenvatinib 18 mg vs 24 mg in Patients With Radioiodine-Refractory Differentiated Thyroid Cancer

Marcia S. Brose,[1] Yury Panaseykin,[2] Bhavana Konda,[3] Christelle de la Fouchardiere,[4] Brett G. M. Hughes,[5] Andrew G. Gianoukakis,[6] Young Joo Park,[7] Ilia Romanov,[8] Monika K. Krzyzanowska,[9] Sophie Leboulleux,[10] Terri A. Binder,[11] Corina Dutcus,[11] Ran Xie,[12] and Matthew H. Taylor[13]

	Lenvatinib 24 mg n/n	Lenvatinib 18 mg n/n	Odds Ratio (95% CI) Lenvatinib 18 mg vs 24 mg	ORR (%) Lenvatinib 24 mg	ORR (%) Lenvatinib 18 mg
Overall	48/75	36/77	0.50 (0.26–0.95)	64.0	46.8
Age group					
≤ 65 years	24/37	21/37	0.71 (0.28–1.82)	64.9	56.8
> 65years	24/38	15/40	0.35 (0.14–0.87)	63.2	37.5
ECOG PS					
0	29/45	20/45	0.44 (0.19–1.04)	64.4	44.4
1 or 2	19/30	16/32	0.58 (0.21–1.60)	63.3	50.0
Sex					
Male	27/41	21/37	0.62 (0.25–1.58)	65.9	56.8
Female	21/34	15/40	0.31 (0.11–0.85)	61.8	37.5
Race					
White	29/46	19/40	0.54 (0.23–1.30)	63.0	47.5
Asian	6/11	5/11	0.79 (0.14–4.54)	54.5	45.5
Other	6/7	3/5	0.25 (0.02–3.58)	85.7	60.0
Missing	7/11	9/21	0.36 (0.07–1.92)	63.6	42.9
Previous VEGF					
0	41/61	27/52	0.50 (0.23–1.10)	67.2	51.9
1	7/14	9/25	0.39 (0.09–1.76)	50.0	36.0
Region					
Europe	11/15	12/27	0.23 (0.05–1.13)	73.3	44.4
North America	23/36	15/33	0.49 (0.18–1.31)	63.9	45.5
Other	14/24	9/17	0.95 (0.26–3.39)	58.3	52.9
Histology					
Papillary	38/63	29/58	0.66 (0.32–1.34)	60.3	50.0
Follicular	10/12	7/19	0.17 (0.03–0.90)	83.3	36.8
Baseline TSH (μIU/mL)					
≤ 0.5	44/69	33/71	0.49 (0.25–0.98)	63.8	46.5
> 0.5–2.0	4/5	2/2	NE (NE–NE)	80.0	100.0
> 2.0–5.5	0/1	1/4	NE (NE–NE)	0	25.0
Baseline weight kg					
< 60 kg	4/8	7/13	1.33 (0.25–7.16)	50.0	53.8
≥ 60 kg	44/67	29/64	0.43 (0.21–0.88)	65.7	45.3
Prior anticancer radiotherapy					
Yes	15/22	12/35	0.23 (0.07–0.75)	68.2	34.3
No	33/53	24/42	0.79 (0.34–1.84)	62.3	57.1
Previous anticancer medications					
Yes	11/21	12/28	0.64 (0.21–2.02)	52.4	42.9
No	37/54	24/49	0.43 (0.19–0.97)	68.5	49.0



The Journal of Clinical Endocrinology & Metabolism, 2022, Vol. 107, No. 3



”if all else fails.....”: Zweitlinientherapie ?

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

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Lenvatinib – SELECT
25% TKI pretreated

Sorafenib – DECISION
3% systemic pretreatment

The optimal sequence of MKIs in RAI-refractory DTC cannot be determined based on currently available evidence. Previous MKI therapy is not a contraindication for subsequent use of these drugs, but data on second-line efficacy are scarce [II, C].

Brose MS et al, Lancet Oncol 2021;22:1126-38

Recruited in >25 countries

Patient Population (N≈300)

Locally Advanced or Metastatic DTC

- RAI-refractory or -ineligible
- Radiographic progression during or after treatment with up to 2 prior VEGFR TKIs
- Prior TKI must include lenvatinib or sorafenib
- ECOG performance status 0–1
- Age ≥16 years

RECIST 1.1

2:1

Cabozantinib
60 mg QD

N=125

Crossover allowed at time of BIRC-confirmed progression per RECIST 1.1

N=62

Placebo
QD

Tumor assessment every 8 weeks for 12 months, then every 12 weeks per RECIST v1.1

Treatment until clinical benefit no longer experienced or intolerable toxicity

Stratification Factors
- Prior lenvatinib (yes/no)
- Age (≤65 vs >65 years)

Primary endpoints:
- ORR per RECIST v1.1 by BIRC [OITT, first 100 randomized pts]
- PFS per RECIST v1.1 by BIRC [ITT, all randomized pts]

BIRC, blinded independent radiology committee; ECOG, Eastern Cooperative Oncology Group; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; pts, patients

Objective response rate ITT population

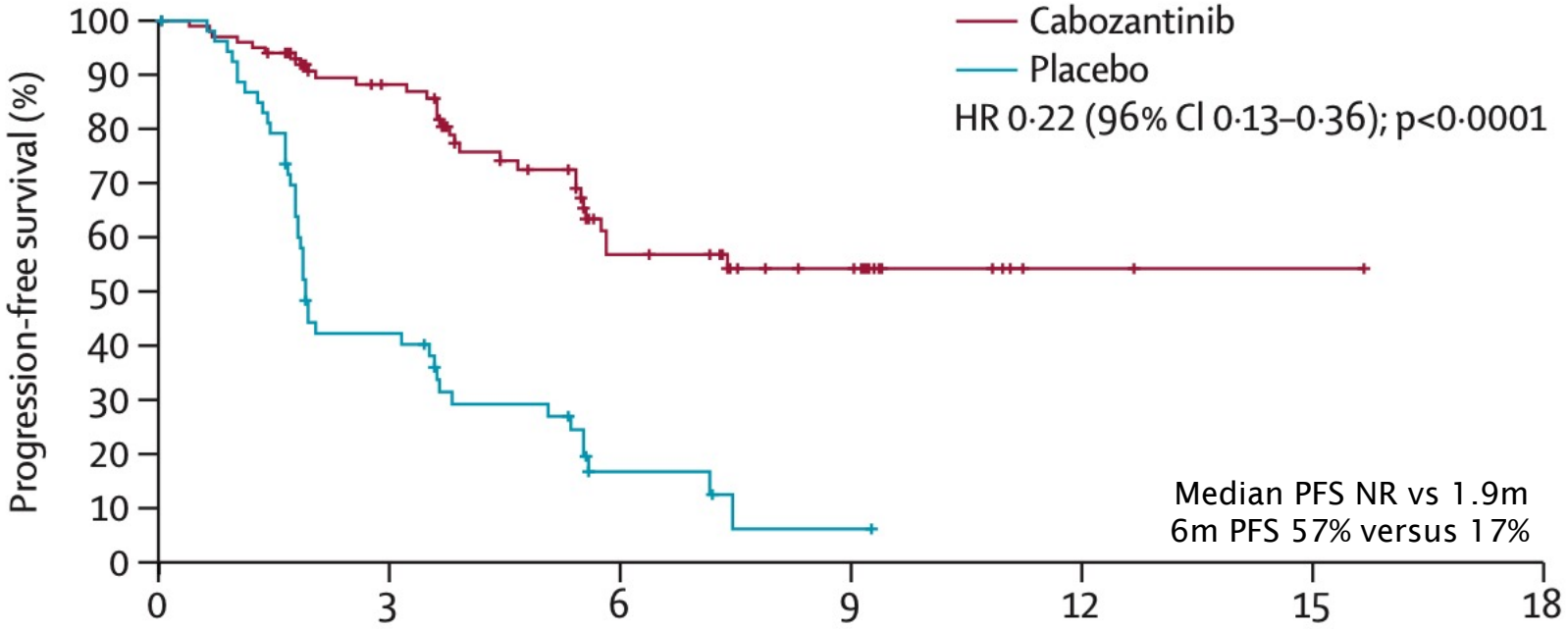
	Objective response rate intention-to-treat population		Intention-to-treat population	
	Cabozantinib group (n=67)	Placebo group (n=33)	Cabozantinib group (n=125)	Placebo group (n=62)
Objective response rate, %	15% (99% CI 5·8–29·3)	0 (99% CI 0–14·8)	9% (95% CI 4·5–15·2)	0 (95% CI 0–5·8)
p value*	0·028	..	0·017	..
Best overall confirmed response				
Complete response	0	0	0	0
Partial response	10 (15%)	0	11 (9%)	0
Stable disease	46 (69%)	14 (42%)	76 (61%)	21 (34%)
≥16 weeks	30 (45%)	9 (27%)	43 (34%)	10 (16%)
Progressive disease	4 (6%)	18 (55%)	8 (6%)	31 (50%)
Not evaluable	1 (1%)	1 (3%)	2 (2%)	1 (2%)
No disease	1 (1%)	0	1 (1%)	0
Missing	5 (7%)	0	27 (22%)	9 (15%)
Disease stabilisation rate, %†	60% (95% CI 47·0–71·5)	27% (95% CI 13·3–45·5)	43% (95% CI 34·4–52·4)	16% (95% CI 8·0– 27·7)
Duration of response, median, months	NR (95% CI 4·1–NE)	NA	NR (95% CI 4·1–NE)	NA
Time to response, median (IQR), months	2·5 (1·8–3·6)	NA	1·9 (1·8-3·6)	NA

ORR 15% versus 0% p=0.028
Not meeting prespecified level of <0.01

Median FUP 8.9m OITT

Brose MS et al, Lancet Oncol 2021;22:1126-38

Progression Free Survival in the Intention-to-Treat Population (BIRC)



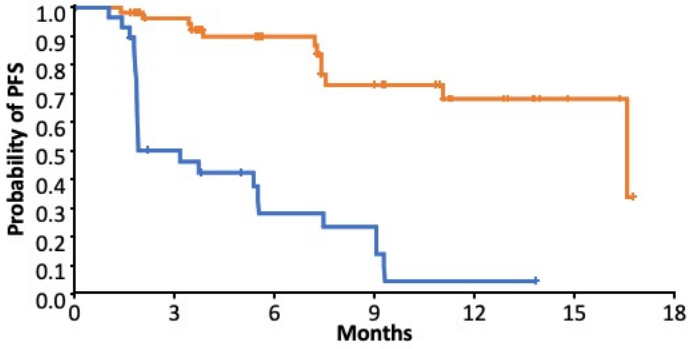
Number at risk (number censored)							
Cabozantinib	125 (0)	69 (45)	26 (69)	15 (79)	2 (92)	1 (93)	0 (94)
Placebo	62 (0)	21 (11)	4 (17)	1 (18)	0 (19)	0 (19)	0 (19)

Primary endpoint of PFS was met at planned interim analysis (critical p-value of 0.00036)

Median FUP 6.2m
N=19 (31%) crossover PD

Brose MS et al, Lancet Oncol 2021;22:1126-38

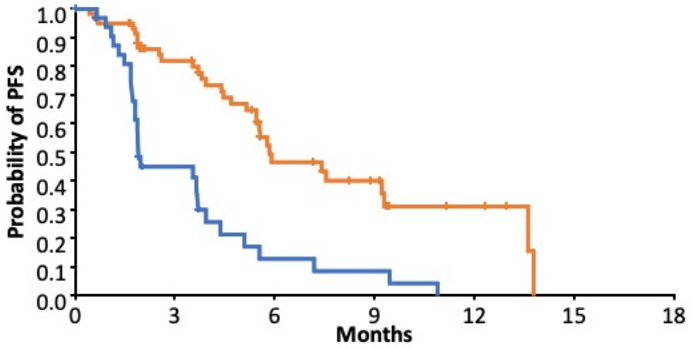
PFS by BIRC in prior therapy subgroups



Prior Sorafenib/No Lenvatinib

	N (events)	Median (95% CI), months
Cabozantinib	63 (12)	16.6 (11.0–NE)
Placebo	33 (24)	3.2 (1.9–5.5)

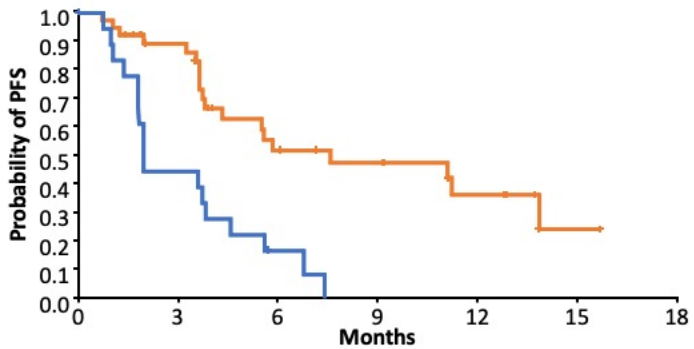
HR 0.13 (95% CI 0.06–0.26)



Prior Lenvatinib/No Sorafenib

	N (events)	Median (95% CI), months
Cabozantinib	68 (31)	5.8 (5.1–9.3)
Placebo	34 (28)	1.9 (1.7–3.7)

HR 0.28 (95% CI 0.16–0.48)



Prior Lenvatinib & Sorafenib

	N (events)	Median (95% CI), months
Cabozantinib	39 (19)	7.6 (3.8–13.8)
Placebo	21 (17)	1.9 (1.8–3.8)

HR 0.27 (95% CI 0.13–0.54)

Cabozantinib improved PFS versus placebo irrespective of prior exposure to sorafenib and/or lenvatinib

HR, hazard ratio; CI, confidence interval; NE, not estimable

2021 ESMO congress

Capdevila et al.

LIBRETTO-001 Selpercatinib for RET altered thyroid cancers

Study objectives

- To evaluate the longer term efficacy and safety of selpercatinib in patients with RET-altered thyroid cancer

Key inclusion criteria

- Advanced or metastatic RET-mutant medullary thyroid cancer, RET fusion-positive thyroid cancer
- QTc ≤470 msec
- ECOG PS 0–2

(n=531)

RET-mutant medullary thyroid cancer (n=315)

RET-fusion positive thyroid cancer (n=42)

Dose escalation
Selpercatinib orally 20 mg/day to 240 mg BID

Dose expansion
Selpercatinib orally 160 mg BID

Primary endpoint

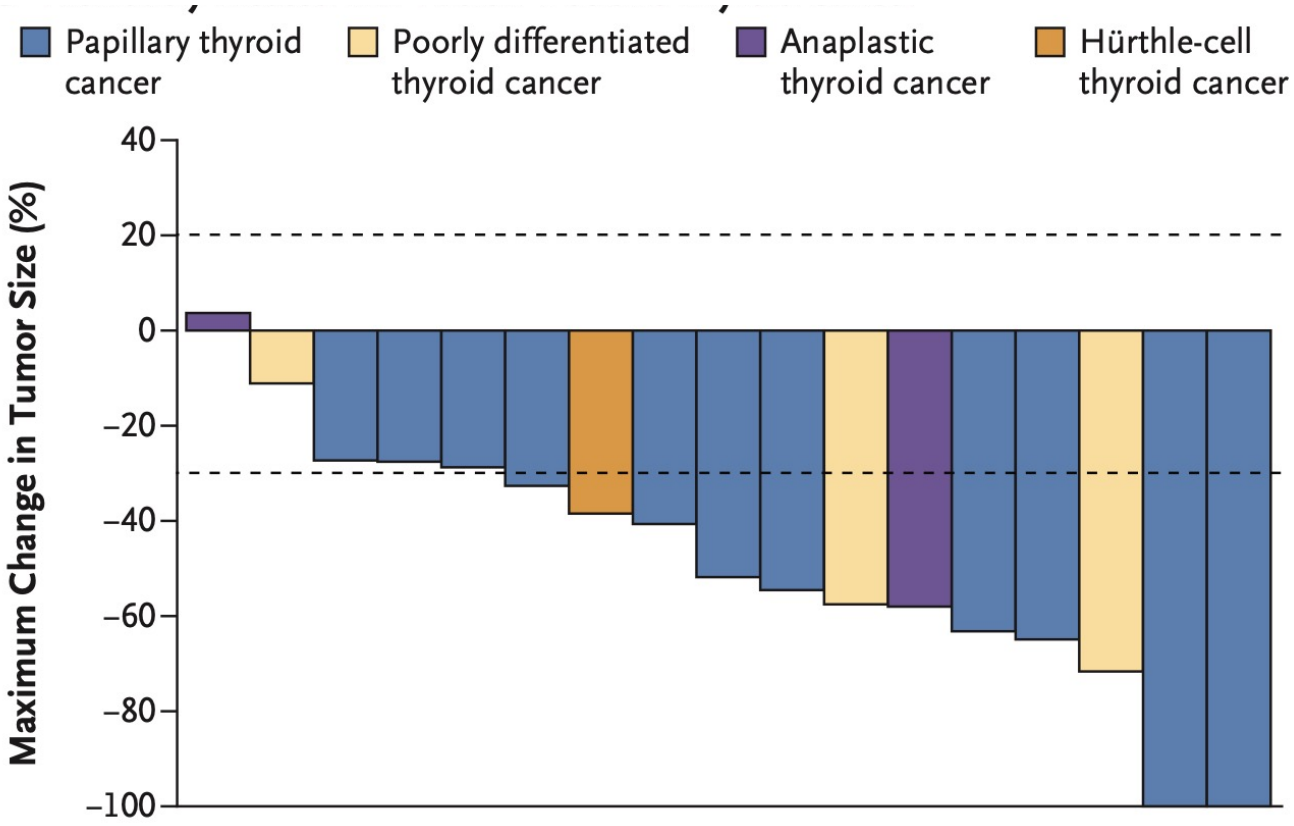
- ORR (RECIST v1.1, IRC)

Secondary endpoints

- DoR, PFS, CBR, safety

LIBRETTO-001 Selpercatinib Fusion-positive TC

Response	Previously Treated *RET* Fusion–Positive Thyroid Cancer	
	Independent Review (N=19)	Investigator Assessment (N=19)
Objective response — % (95% CI)	79 (54–94)	58 (34–80)
Best response — no. (%)		
Complete response	1 (5)	0
Partial response	14 (74)	11 (58)
Stable disease	4 (21)	7 (37)
Progressive disease	0	0
Could not be evaluated	0	1 (5)
Duration of response		
No. of patients with objective response	15	11
Data censored — no. (%)	9 (60)	8 (73)
Median (95% CI) — mo	18.4 (7.6–NE)	NE (9.5–NE)
Median follow-up — mo	17.5	17.5
Progression-free survival		
Data censored — no. (%)	11 (58)	12 (63)
Median (95% CI) — mo	20.1 (9.4–NE)	NE (10.0–NE)
Median follow-up — mo	13.7	19.3
Prevalence at 1 yr (95% CI) — %	64 (37–82)	61 (33–81)



Selpercatinib: EMA, 02. September 2022

European Commission > Live, work, travel in the EU >

Public Health - Union Register of medicinal products

Union Register support

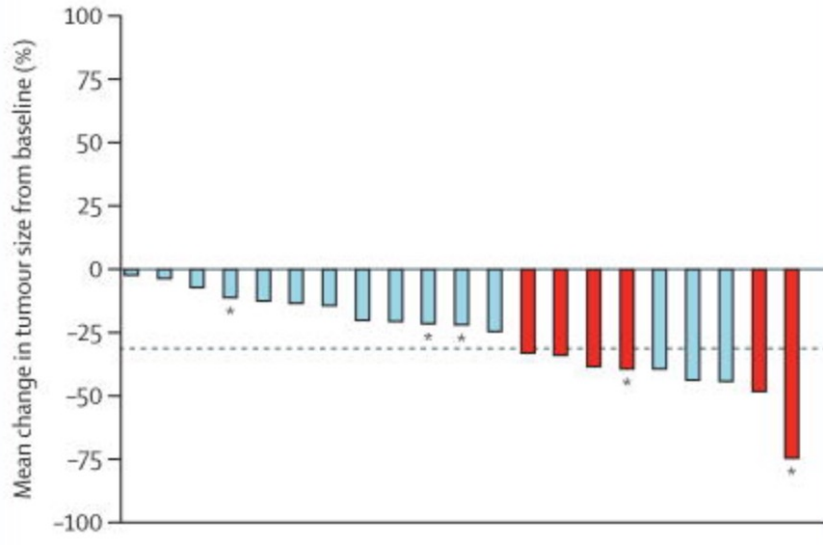
Union Register of medicinal products for human use

Product information

Product name:	Retsevmo ACTIVE
EU number:	EU/1/20/1527
Active substance:	selpercatinib
Indication:	Retsevmo as monotherapy is indicated for the treatment of adults with: – advanced RET fusion positive non small cell lung cancer (NSCLC) not previously treated with a RET inhibitor – advanced RET fusion positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET mutant medullary thyroid cancer (MTC).

Weitere molekulare Targets beim DTC (PTC)

BRAF V600E – Vemurafenib*



Phase II multicenter PTC, n=51 patients
- Cohort 1 untreated, Cohort 2 pretreated
- Cohort 1 ORR 38.5%, PFS 18.2m
- Cohort 2 ORR 27.3%, PFS 8.9m
- >60% SAEs, 27% SCC skin, 2 AE-related deaths

NTRK– Entrectinib, Larotrectinib

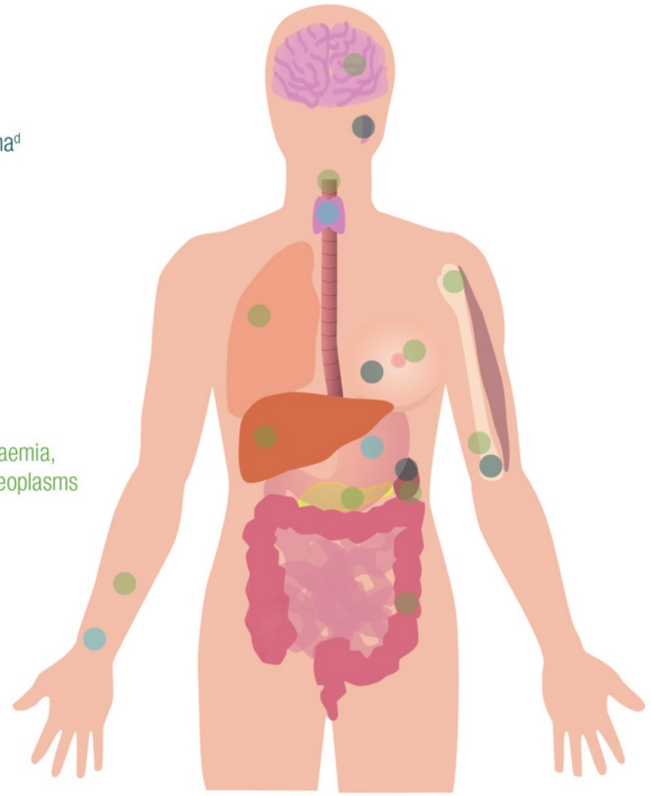
Cancers enriched for TRK fusions

Frequency >90%
MASC
Secretory breast carcinoma[b]
Cellular and mixed congenital mesoblastic nephroma[d]
Infanfile fibrosarcoma

Cancers harbouring TRK fusions at lower frequencies

Frequency 5% to 25%
Gastrointestinal stromal tumour (pan-negative)
Thyroid cancer[c]
Spitzoid tumours

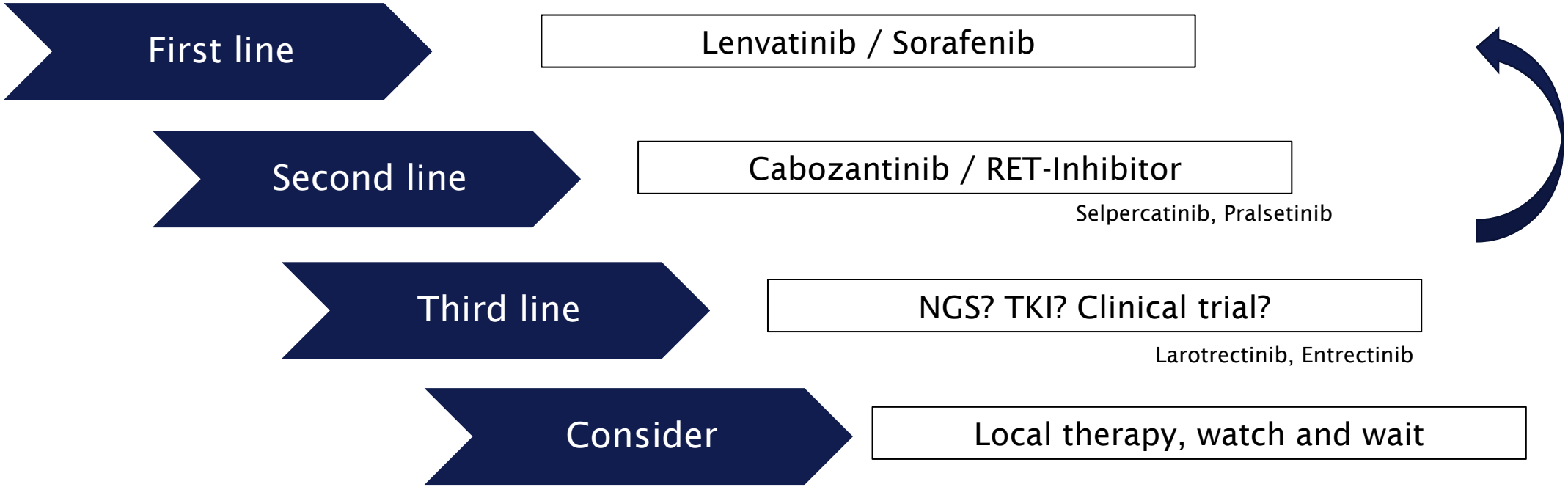
Frequency <5%
Acute lymphoblastic leukaemia, acute myeloid leukaemia, histiocytosis, multiple myeloma and dendritic cell neoplasms
Infantile sarcoma[d]
Breast cancer
Colorectal cancer
Cholangiocarcinoma
High-grade glioma[b]
Head and neck cancer
Lung cancer
Pancreatic cancer
Melanoma
Renal cell carcinoma[a]
Sarcoma



*not approved

Brose MS et al, Lancet Oncol 2016;17:1272-82
ESMO Oncology pro

Potential treatment sequence in DTC 2022



Open questions: value of rebiopsy, immunotherapy, imaging…