OPTIMIZACIÓN DE LAS TERAPIAS SISTÉMICAS EN LA ENFERMEDAD yodorefractaria

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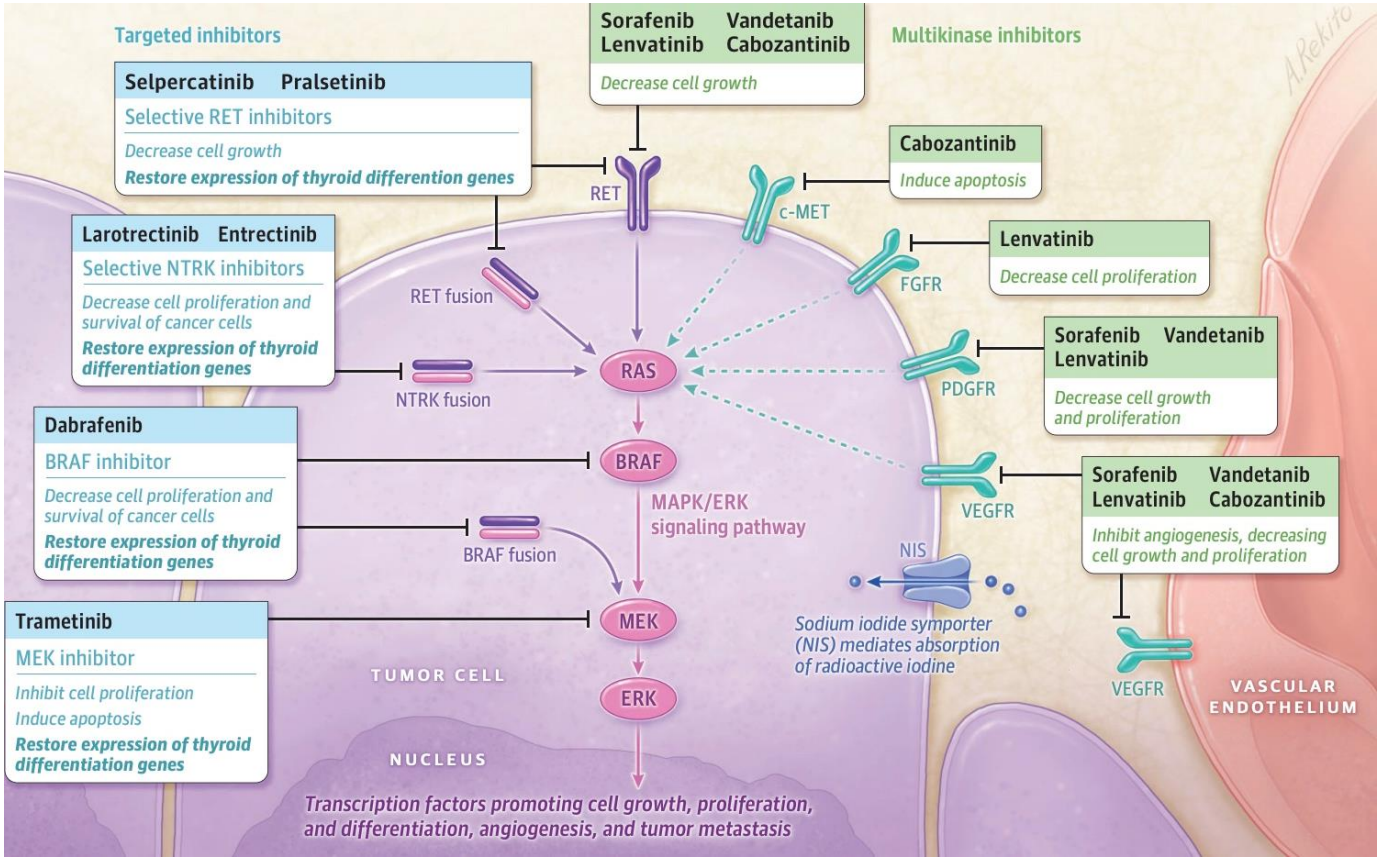
DISCLOSURES

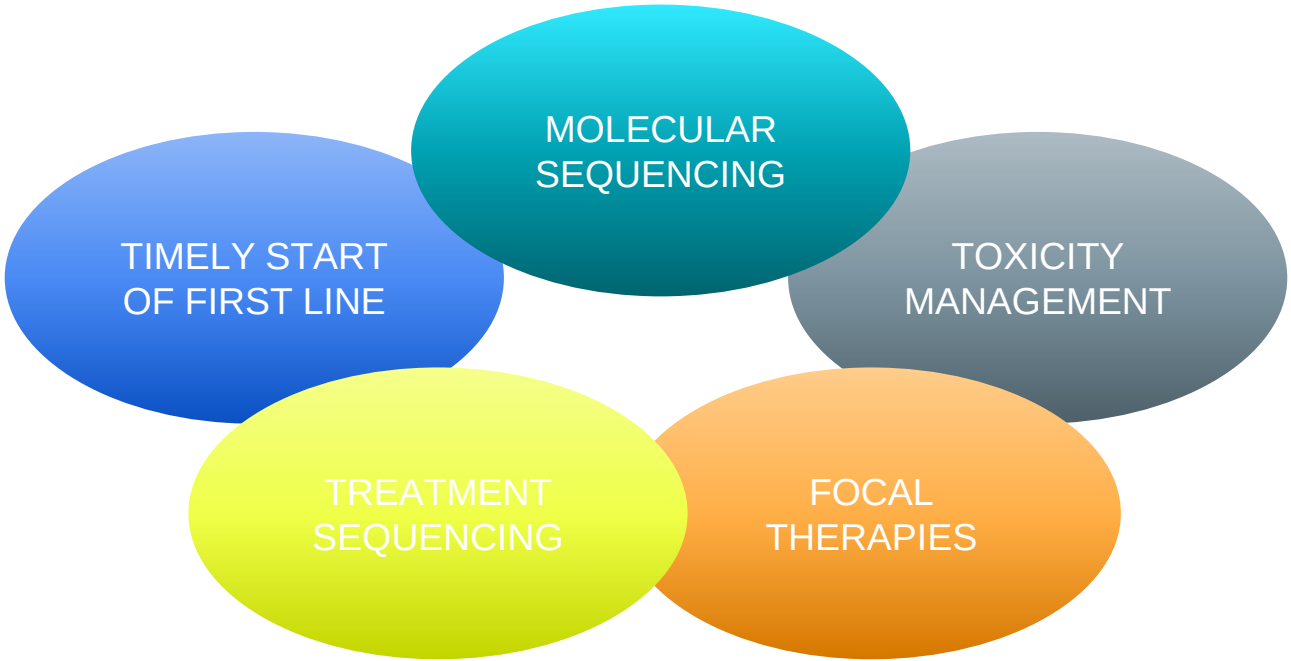
- He proporcionado asesoramiento científico a IPSEN, Roche, Bayer, Johnson & Johnson, Astellas, Eisai, Adacap, Lilly, MSD, Pfizer.

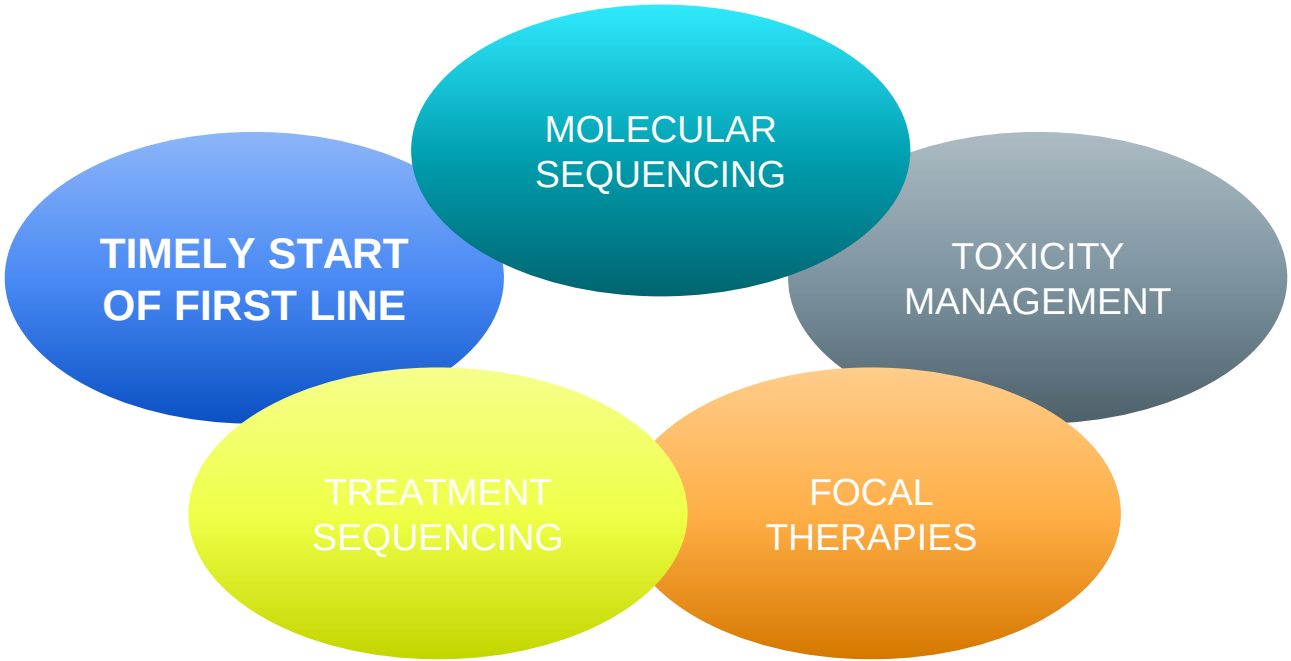
- He participado en reuniones médicas organizadas por IPSEN, Lilly, Bayer, Johnson & Johnson, Astellas, Eisai, Adacap.

- He recibido fondos para investigación de Roche, IPSEN, Pfizer, Janssen.



Boucai et al, JAMA 2024;331(5):425-435


MOLECULAR SEQUENCING
TIMELY START OF FIRST LINE
TOXICITY MANAGEMENT
TREATMENT SEQUENCING
FOCAL THERAPIES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TIMELY START OF SYSTEMIC THERAY

RAI DEFINITION	VS	TIMELY START OF SYSTEMIC THERAPY
Absence of RAI uptake Progressive decline in RAI uptake following RAI, Heterogeneity in uptake Progression after subsequent RAI. Other special situations: Uptake in 18FDG-PET Unresectable primary tumor Aggressive histologies		Timepoint at which the patient is deemed to be developing more rapidly progressive or symptomatic disease. Rate of progression Size or burden of disease Site of disease Symptoms Active surveillance vs Treatment initiation

Berdelou A, et al. Endocr Relat Cancer. 2018 Apr;25(4):R209-R223.

TIMELY START OF SYSTEMIC THERAY

SELECT

N = 392

- DTC, ^{131}I-refractory disease
- IRR evidence of progression within previous 13 months
- Up to 1 prior VEGF or VEGFR-targeted therapy
- mPFS = 19.4 vs 3.7 months (HR 0.24)

DECISION

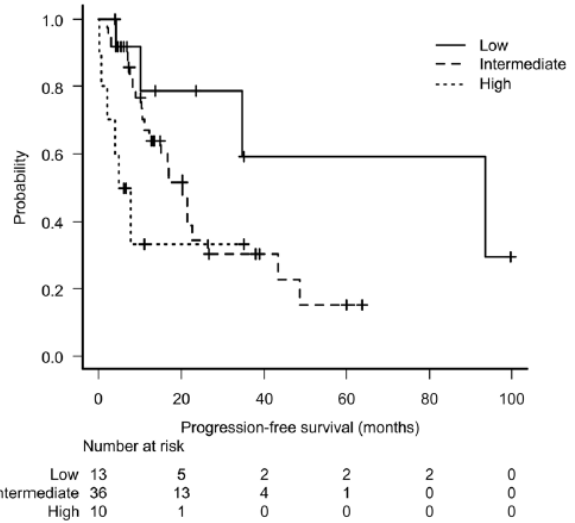
N= 417

- Locally advanced or metastatic, RAI-refractory DTC
- Progression (RECIST) within the previous 14 months
- mPFS = 10.8 vs 5.8 months (HR 0.59)

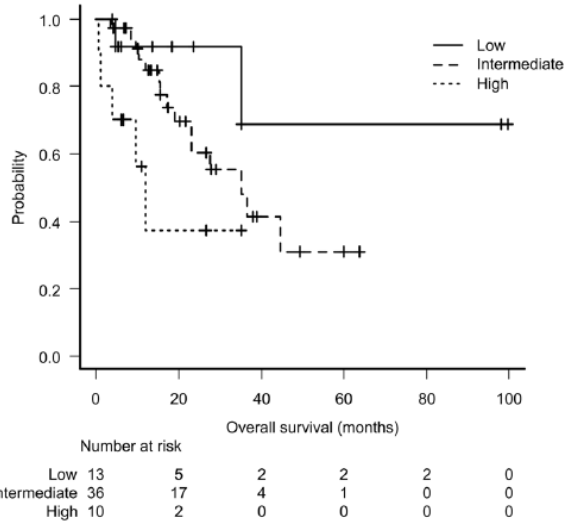
Schlumberger M, et al. N Engl J Med. 2015;372:621–630; Brose M, et al. Lancet. 2014;384:319-328; Brose MS, et al. Lancet Oncol. 2021 Aug;22(8):1126-1138.

CLINICAL SCORING SYSTEM PROPOSAL

Factors	Score
Age	
≤65 years	0
>65 years	1
Tumor-related symptom	
Asymptomatic	0
Symptomatic	1
Histological subtype	
Papillary thyroid cancer	0
Follicular thyroid cancer	1
Poorly differentiated thyroid cancer	1
Metastatic sites	
Pulmonary only	0
Extrapulmonary disease	1
Neutrophil-to-lymphocyte ratio	
≤3	0
>3	1
Size of lung metastasis	
<10 mm	0
≥10 mm	1
Baseline tumor size	
≤40 mm	0
>40 mm	1
Tumor-volume doubling time	
>1 year	0
≤1 year	1
Total score	MAX 8



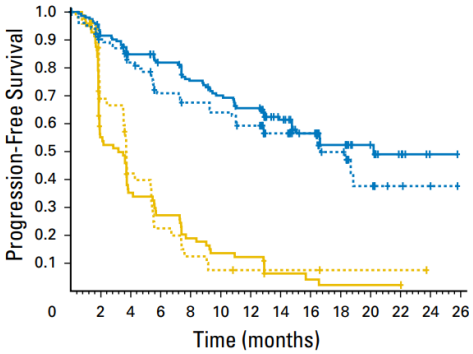
mPFS = 93.7 m (low) vs 20.3m (intermediate) vs 6.2m (high)(p < 0.02).



OS HR (high vs low) = 6.59, p < 0.03
OS HR (high vs intermediate) = 2.99, p <0.05)

Fukuda N, Toda K, Udagawa S, et al. Endocrine. 2022;10.1007/s12020-021-02963-z.

AGE > 65 years vs ≤ 65 years

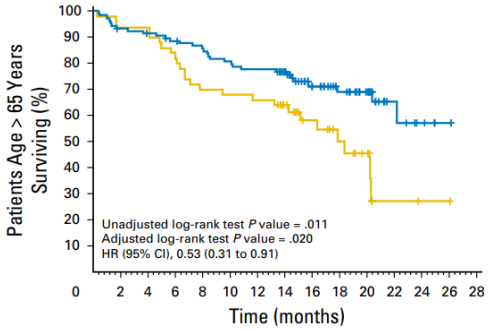


No. of patients at risk:

Age group: Patients age ≤ 65 years														
Lenvatinib	155	138	121	113	102	94	87	60	39	25	16	8	2	0
Placebo	81	42	26	20	14	10	9	3	2	1	1	1	0	0
Age group: Patients age > 65 years														
Lenvatinib	106	87	77	63	57	54	49	32	27	19	8	3	1	0
Placebo	50	29	17	9	5	3	2	2	2	1	1	1	0	0

Patients age ≤ 65 years Median, months (95% CI)	Patients age > 65 years Median, months (95% CI)
Lenvatinib 20.2 (14.8 to NE)	Lenvatinib 16.7 (11.0 to NE)
Placebo 3.2 (1.9 to 3.7)	Placebo 3.7 (3.5 to 5.4)
HR (95% CI), 0.19 (0.13 to 0.27) Log-rank test: *P* < .001	HR (95% CI), 0.27 (0.17 to 0.43) Log-rank test: *P* < .001

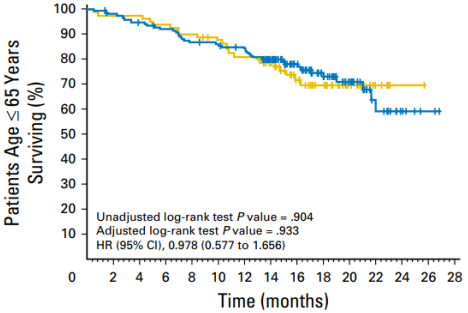
Treatment	Total	Treatment Failure	Censored	Median, months (95% CI)
Lenvatinib	106	31	75	NE (22.1 to NE)
Placebo	50	25	25	18.4 (13.3 to 20.3)



No. of patients at risk:

Lenvatinib	106	98	95	91	88	82	79	67	42	31	24	8	4	1	0
Placebo	50	47	47	42	35	34	33	26	16	11	7	2	1	1	0

Treatment	Total	Treatment Failure	Censored	Median, months (95% CI)
Lenvatinib	155	40	115	NE (22.0 to NE)
Placebo	81	22	59	NE (NE to NE)



No. of patients at risk:

Lenvatinib	155	150	144	139	131	129	124	102	70	47	31	14	6	2	0
Placebo	81	79	79	76	73	69	63	52	37	28	16	6	1	0	0

Brose M, et al. J Clin Oncol. 2017 Aug 10;35(23):2692-2699.

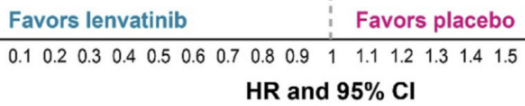
TUMOR RELATED SYMPTOMS

Factors	*PFS*			*OS*		
	HR	95% CI	*p*	HR	95% CI	*p*
Age (>65 years)	1.77	0.55–6.64	*ns*	3.06	0.74–20.56	*ns*
Gender (male)	1.50	0.40–5.00	*ns*	2.33	0.27–8.90	*ns*
Histology (follicular)	0.94	0.21–3.26	*ns*	1.17	0.25–4.47	*ns*
Tg doubling time	0.85	0.48–1.20	*ns*	1.02	0.61–1.41	*ns*
TL (other than lung)	1.37	0.39–4.66	*ns*	1.93	0.47–7.48	*ns*
Symptom present (yes)	5.39	1.40–35.5	<0.02	10.06	1.57–187.4	<0.01
Tumor size (>median)	1.20	0.37–3.86	*ns*	1.17	0.29–4.50	*ns*

Sugino K, et al. Endocr J. 2018 Mar 28;65(3):299-306.

SIZE OF METASTASES

Lung Metastases Size	Lenvatinib, n	Placebo, n[a]	HR (95% CI)	Median Survival Lenvatinib	Median Survival Placebo	*P*-Value
Overall Survival						
Any lung mets (target/non-target lesions)	226	124	0.76 (0.57–1.01)	43.2	34.0	0.0549
≥ 1.0 cm	**199**	**107**	**0.63 (0.47–0.85)**	**44.7**	**33.1**	**0.0025**
≥ 1.5 cm	150	84	0.63 (0.45–0.89)	44.1	22.3	0.0082
≥ 2.0 cm	94	58	0.65 (0.44–0.98)	34.7	19.3	0.0383
< 2.0 cm	105	49	0.63 (0.40–0.99)	49.2	38.6	0.0438
Progression-free Survival[b]						
Any lung mets (target/non-target lesions)	226	124	0.20 (0.15–0.27)	18.7	3.6	< 0.0001
≥ 1.0 cm	**199**	**107**	**0.20 (0.15–0.28)**	**20.2**	**3.7**	**< 0.0001**
≥ 1.5 cm	150	84	0.20 (0.14–0.29)	18.7	3.5	< 0.0001
≥ 2.0 cm	94	58	0.17 (0.11–0.28)	16.6	3.5	< 0.0001
< 2.0 cm	105	49	0.21 (0.13–0.34)	NE	3.7	< 0.0001



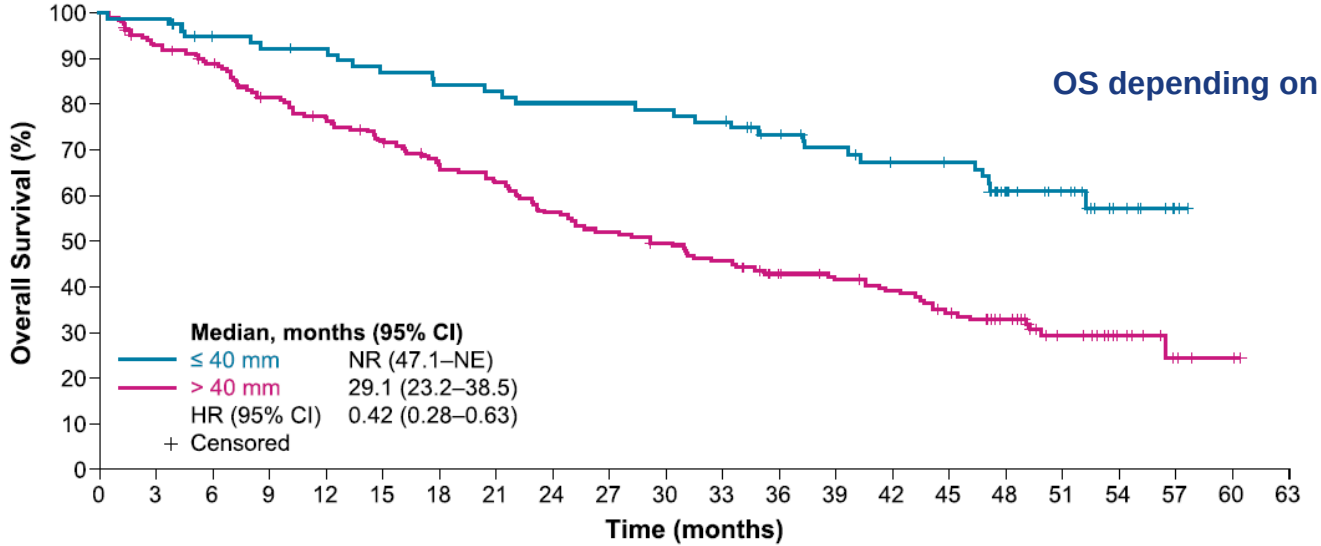
Treatment effect of lenvatinib may be greater **when lenvatinib is initiated in patients with a lower burden of disease**, rather than delaying initiation until a higher burden of disease is present

Delaying initiation of lenvatinib treatment may negatively impact a patient's prognosis.

Tahara et al. European Journal of Cancer, V147 (April 2021) 51-57

TUMOR BURDEN

OS depending on tumor burden



Number of patients at risk:

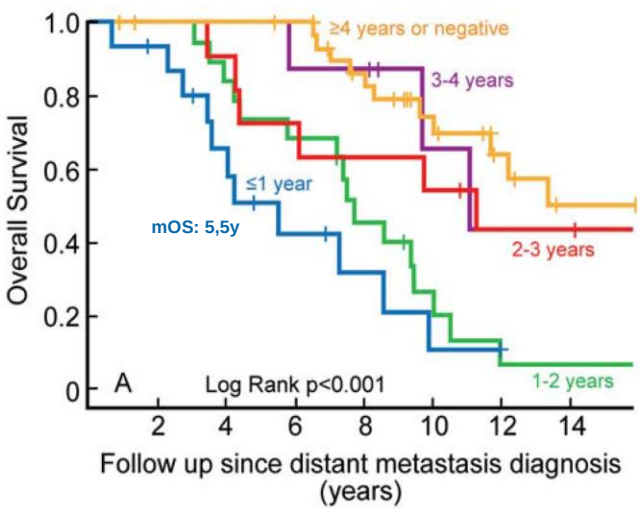
≤ 40 mm	79	78	73	70	69	65	63	62	60	60	59	57	51	47	43	42	26	19	9	2	0	0
> 40 mm	182	166	157	142	133	124	114	106	95	88	83	76	68	64	59	51	39	19	11	4	2	0

FIGURE 2. Overall survival by baseline tumor burden[a] (≤40 and >40 mm) in patients randomly assigned to the lenvatinib group
[a]Tumor burden was defined as the sums of diameters of target lesions per RECIST v1.1.
CI indicates confidence interval; NE, not estimable; NR, not reached; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Kiyota N et al. Cancer. 2022;128(12):2281-2287.

Tumor Volume Doubling Time (TVDT)

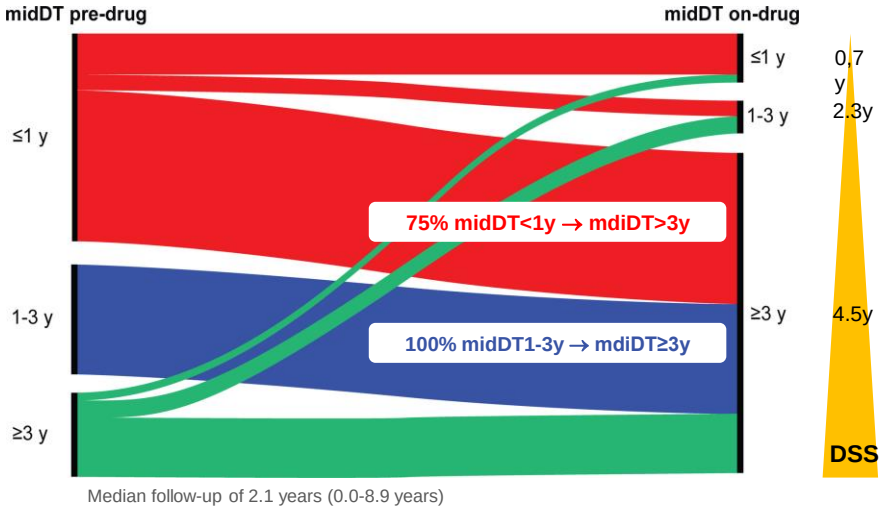
OS according to average TVDT (midDT) assorted in 5 groups[1]



Patients **midDT ≤1y** showed statistically **shorter OS** than the rest.

Systemic treatment

Change midDT after starting ST[2]



Median follow-up of 2.1 years (0.0-8.9 years)

Systemic Therapy statistically prolonged the TVDT in 69% of patients.

In RR-DTC patients achieving prolonged TVDT with ST, **Disease-Specific Survival** is statistically increased

Sabra MM, et al. Cancer. 2017;123(15):2955-2964.; Sabra MM, et al. Cancer. Clin Endocrinol (Oxf). 2019;90(4):617-622.

TIMELY START OF SYSTEMIC THERAY

Aggressive histologies. Poor response to first 131I dose.

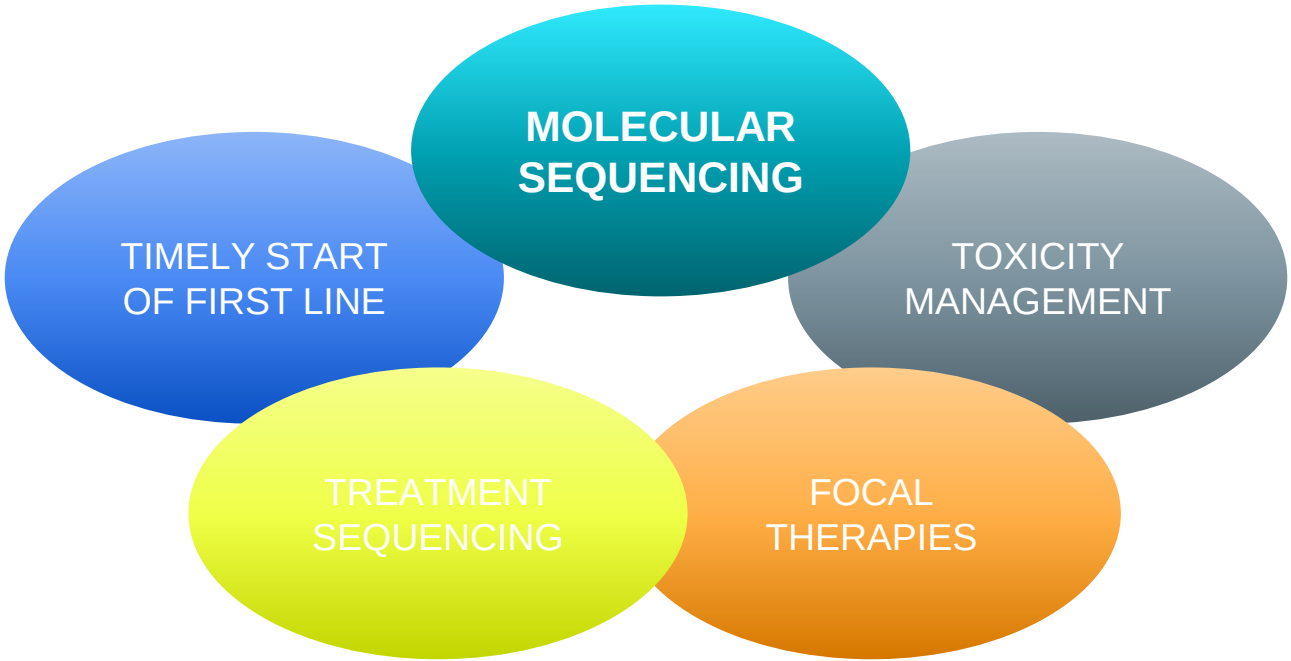
Metastatic tumor locations: Bone, Liver, Central nervous system, Soft tissue next to great vessels. Treated vs untreated, symptomatic vs asymptomatic CNS lesions.

Disease near critical structures: Immediate risk of invasion to carotid artery, mucosa of esophagus or bronchia or skin, bone soft tissue.

Risk factors related to poorer cancer treatment outcomes: Comorbidities, Obesity, Older age, Functional impairment, Multiple symptoms

Rising Tg not be the sole identifier of progressive disease, but surveillance for new metastases (e.g., brain, bone, liver)

Sugino K, et al. Endocr J. 2018 Mar 28;65(3):299-306.


MOLECULAR SEQUENCING
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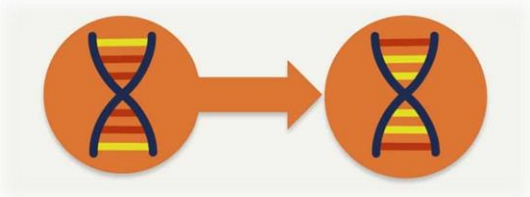
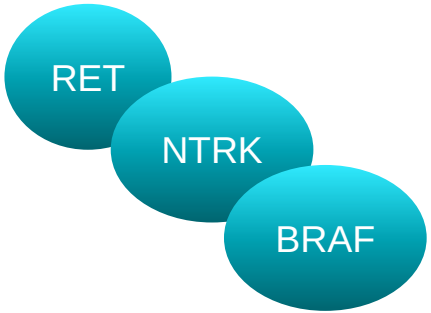
WHAT´S NEW THANKS TO MOLECULAR SEQUENCING





Genetic Alteration	Histology	Selective Kinase Inhibitor	Efficacy	FDA-Approved
BRAF V600E	DTC	Dabrafenib (n = 26)[20]	ORR 42%, median PFS 10.7 months	No
		Vemurafenib (n = 51)[21]	ORR 38%, median PFS 18.2 months (TKI-naïve); ORR 27%, median PFS 8.9 months (pretreated)	No
	ATC	Dabrafenib/trametinib (n = 36)[45]	ORR 56%, median PFS 6.7 months, OS 14.5 months	Yes
RET alteration				
RET fusion	All	Pralsetinib (n = 9)[24]	ORR 89%, DOR > 12 months in 86% (pretreated)	Yes
		Selpercatinib (n = 27)[22]	ORR 100%, DOR > 6 months in 75% (TKI-naïve)	Yes
			ORR 79%, DOR 18.4 months (pretreated)	
RET mutation	MTC	Selpercatinib (n = 193)[44]	ORR 69.4%, 12-month PFS 86.8% (TKI-naïve)	Yes
NTRK fusion	All	Entrectinib (n = 13)[27]	ORR 53.8%, median PFS 19.9 months	Yes
		Larotrectinib (n = 20 DTC;[25] n = 7 ATC)[46]	ORR 86%, 24-month PFS 84%, and OS 92% (DTC); ORR 14%, median OS 8.8 months (ATC)	Yes
ALK fusion	DTC	Alectinib[32,33]	Case reports	No
		Crizotinib[30,31]	Case reports	No
		Lorlatinib[31]	Case reports	No
ROS1 fusion	DTC	Entrectinib[34,35]	Case reports	No

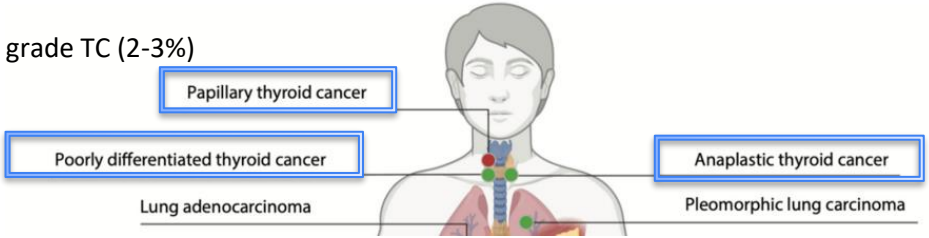
Yun KM, et al. JCO Oncol Pract. 2024 Jul;20(7):899-906.

WHAT´S NEW THANKS TO MOLECULAR SEQUENCING

RET ALTERED THYROID CANCER PATIENTS

Papillary thyroid cancer (5%–10%):
RET/CCDC6 or RET/NCOA4

High grade TC (2-3%)



Parimi V, et al. j Precision Oncology (2023) 7:10
Desilets A, et al. Cancers 2023, 15(16), 4146.
Rosella E, et al. Endocrine. 2023 Aug;81(2):206-215.
Shirali AS, et al. J Endocr Soc. 2024 Apr 24;8(6):bvae048
Wirth L, et al. Presented at ESMO 2023

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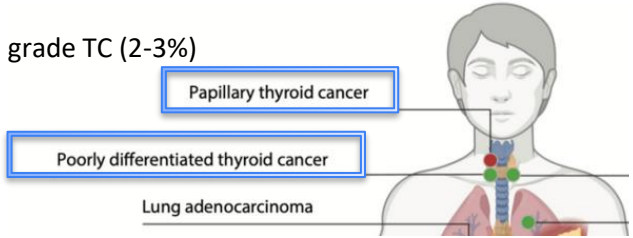


***RET* fusion-positive TC efficacy population (N=65) including:**

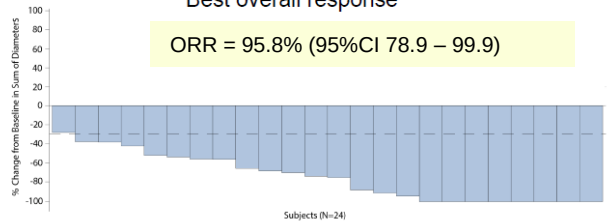
Treatment naïve (n=24)
Pre-treated patients (n=41)

Indicación EMA

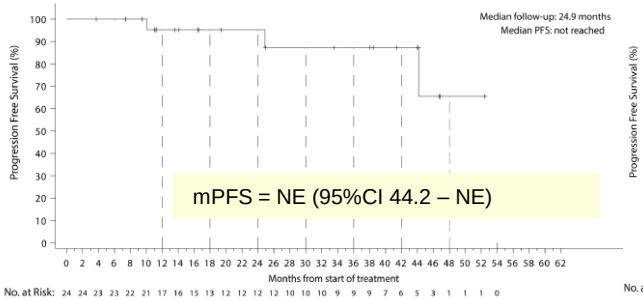
Treatment Naïve Patients with *RET* Fusion-positive TC

Best overall response

ORR = 95.8% (95%CI 78.9 – 99.9)



Progression Free Survival



mPFS = NE (95%CI 44.2 – NE)

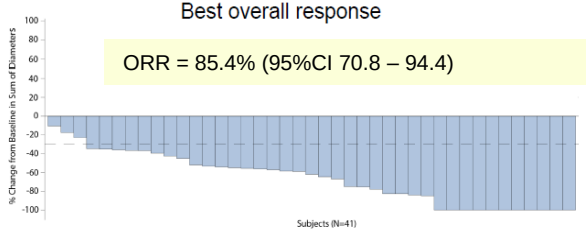
Top: Waterfall Plot Based on IRC Assessments. Best change in tumor size was defined as the ratio of smallest post-baseline tumor size compared to the baseline assessment by IRC. Bottom: Kaplan-Meier plot based on IRC assessments. + = Censored.

Indicación AEMPS

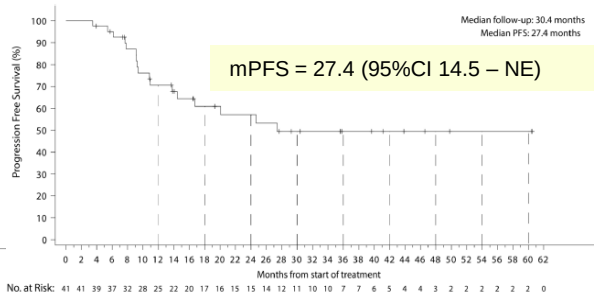
Pre-treated Patients with *RET* Fusion-positive TC

Best overall response

ORR = 85.4% (95%CI 70.8 – 94.4)



Progression Free Survival



mPFS = 27.4 (95%CI 14.5 – NE)

Topt: Waterfall Plot Based on IRC Assessments. Best change in tumor size was defined as the ratio of smallest post-baseline tumor size compared to the baseline assessment by IRC. Bottom: Kaplan-Meier plot based on IRC assessments. + = Censored.

Parimi V, et al. j Precision Oncology (2023) 7:10
Desilets A, et al. Cancers 2023, 15(16), 4146.
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Shirali AS, et al. J Endocr Soc. 2024 Apr 24;8(6):bvae048
Wirth L, et al. Presented at ESMO 2023

WHAT´S NEW THANKS TO MOLECULAR SEQUENCING

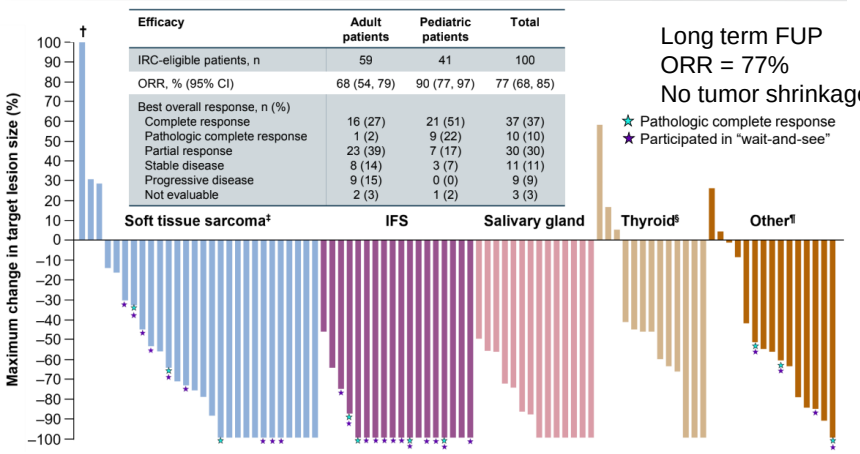
NTRK ALTERED THYROID CANCER PATIENTS

Annals of Oncology (2024) 35 (suppl_2): S482-S535
Cabanillas M, et al. J Clin Oncol 2023; 41 (16); 6091
Waguespack SG, et al. EJE 2022; 186 (6): 631-643
Bowles DM, et al. 44th Annual Meeting of the European Thyroid Association, 2022

ORR = 63% for all patients.
ORR DTC = 78% (13% CR)
ORR ATC = 14% (0% CR)
Median time to response = 1.9 months

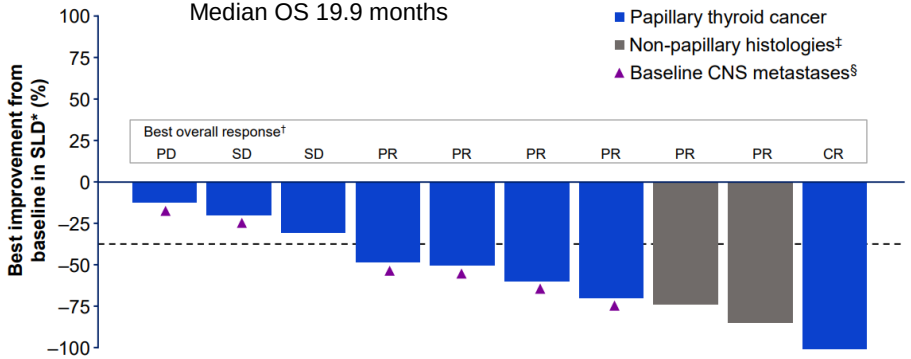
LAROTRECTINIB (TRKA/B/C)
Phase I
Phase I/II (SCOUT)
Phase II basket NAVIGATE
N=30 patients →17 patients

ENTRECTINIB (TRKA/B/C, ROS1, ALK)
STARTRK-2 Ph II basket study
(data cut-off 31 Aug 2020)
N= 13 patients (NTRK1/NTRK3: N=4 /N= 9)



Long term FUP
ORR = 77%
No tumor shrinkage in ATC

ORR = 54% (8%CR)
DoR 13.2 (7.9–NE)
Median OS 19.9 months

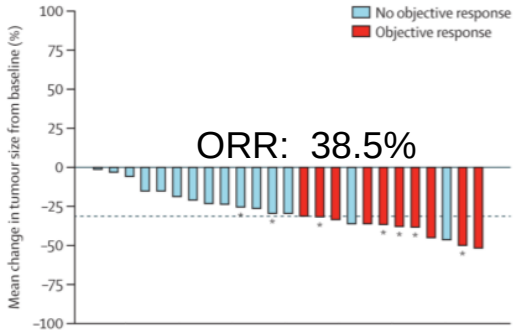


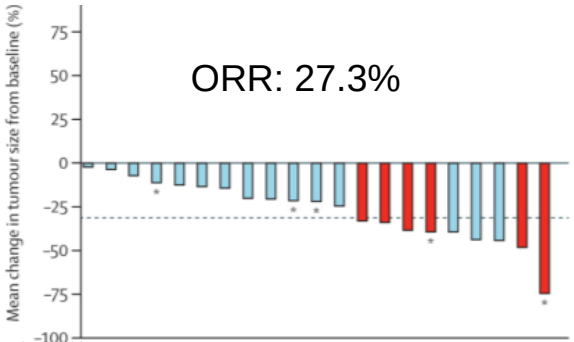
Adultos y pediátricos de ≥12 años con tumores sólidos fusión NTRK, quienes tienen enfermedad localmente avanzada, metastásica o donde es probable que una resección quirúrgica provoque una morbilidad severa, y quienes no tienen opciones terapéuticas satisfactorias

WHAT´S NEW THANKS TO MOLECULAR SEQUENCING

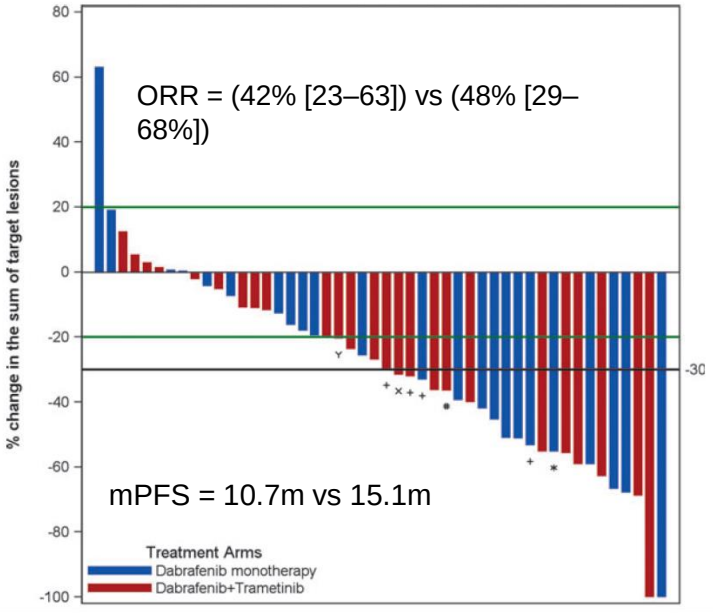
EFFICACY FROM BRAF +/- MEK INHIBITORS

VEMURAFENIB[1]:
Cohort 1 (treatment naive) > ORR: 38.5% and PFS: 18.2m
Cohort 2 (pre-treated) > ORR: 27.3% and PFS: 8.9m



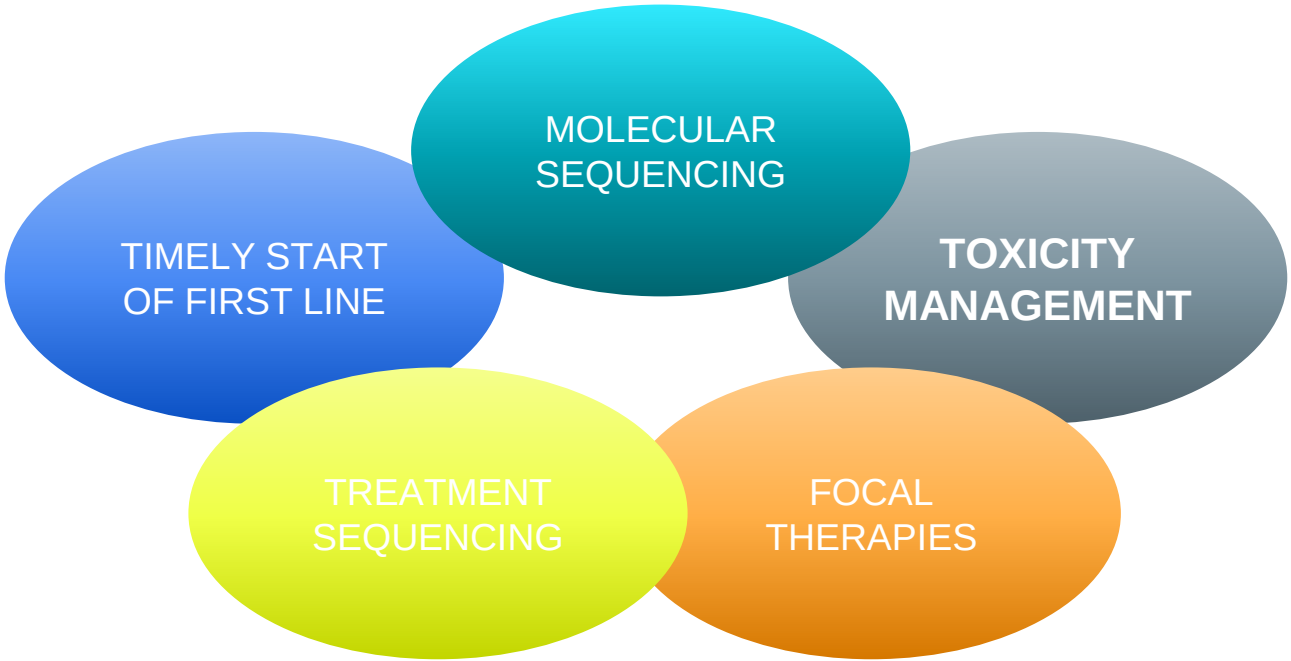


DABRAFENIB +/- TRAMETINIB[2]:
Phase II randomized
N=53 patients (26 D vs 27 D+T) with RR-DTC BRAF mut

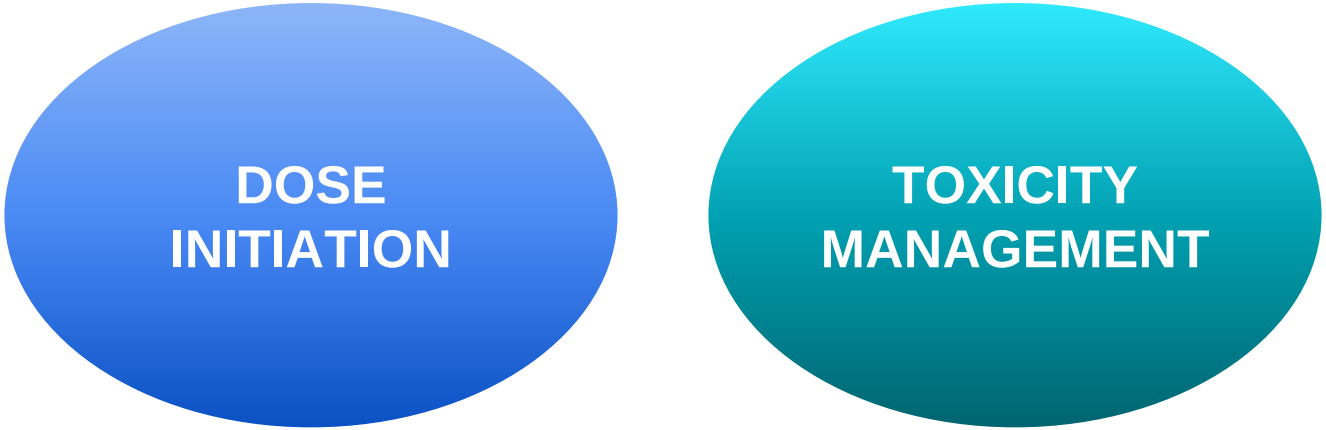


1. Brose M, et al. Lancet Oncol. 2016 September; 17(9): 1272–1282.

2. Shah MH, et al. J Clin Oncol (2017) 35(15 Suppl):6022


MOLECULAR SEQUENCING
TIMELY START OF FIRST LINE
TOXICITY MANAGEMENT
TREATMENT SEQUENCING
FOCAL THERAPIES

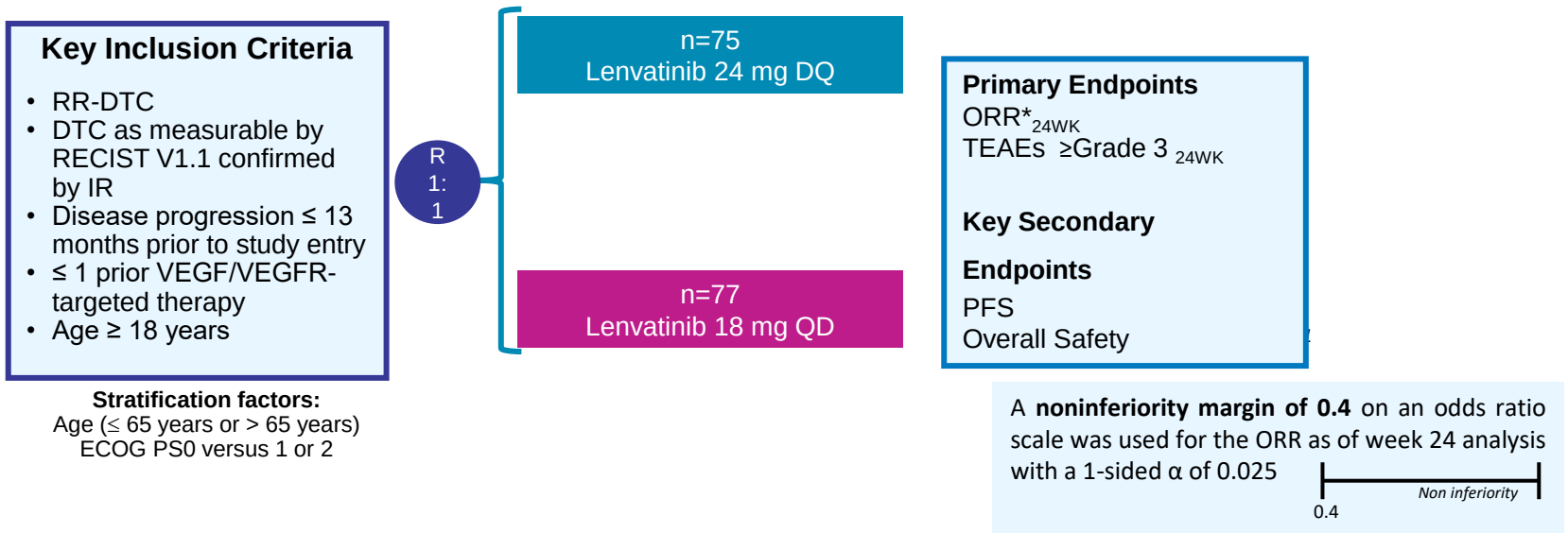
TREATMENT OPTIMIZATION UNDER THERAPY



DOSE INITIATION

Phase 2 (Study 211)

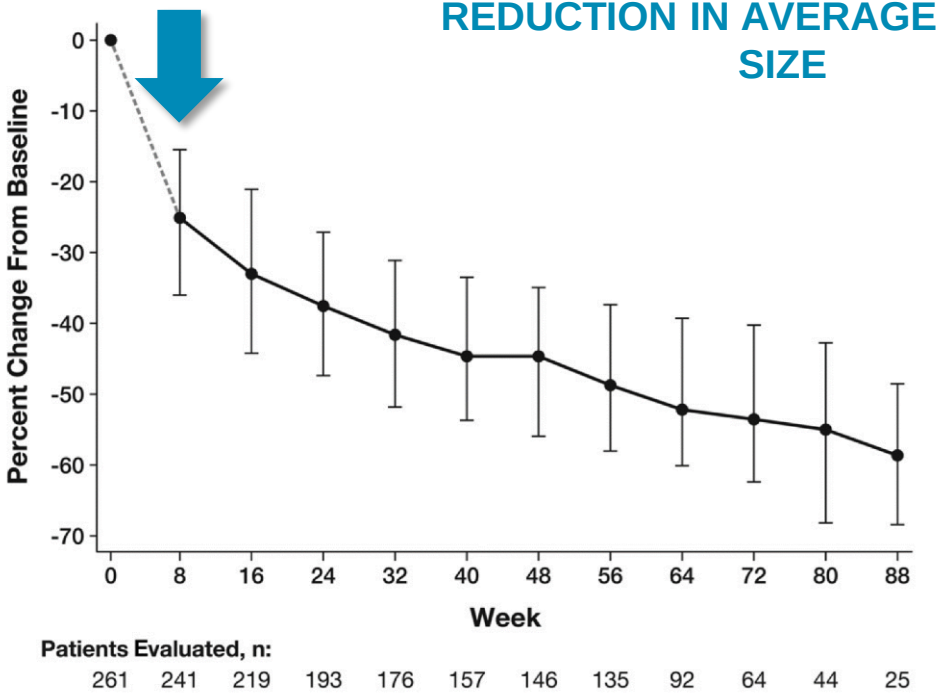
Randomized, double-blind, multicenter trial to evaluate whether **18mg starting dose** of LENVIMA® provides **comparable efficacy with a better safety profile than a 24mg** starting in RAI-R DTC patients



Brose MS, et al. J Clin Endocrinol Metab. 2022 Feb 17;107(3):776-787

DOSE INITIATION

REDUCTION IN AVERAGE TUMOUR SIZE



A rapid initial decline in average tumour size (−25.2%; median −25.0%) was observed by 8 weeks followed by a slower, continuous decrease at an average rate of −1.3% per month. Tumour regression continued throughout the course of the treatment.

Robinson B, et al. J Clin Endocrinol Metab. 2016;101:4103–4109

TOXICITY MANAGEMENT -> Before MKI initiation

Preparing patients for treatment

- Blood pressure
- ECG
- Baseline N-terminal proBNP and echocardiogram if concerns about cardiac status
- Review of medications, e.g. concomitant drugs that may lead to QTc prolongation
- Bloods - full blood count (FBC), renal, liver and bone profile, magnesium (Mg), thyroid function tests (TFTs), BNP
- Thyroglobulin (Tg)
- Urinalysis for protein

Wadsley J, et al. Clinical Oncology 2023; 35: 57 - 64

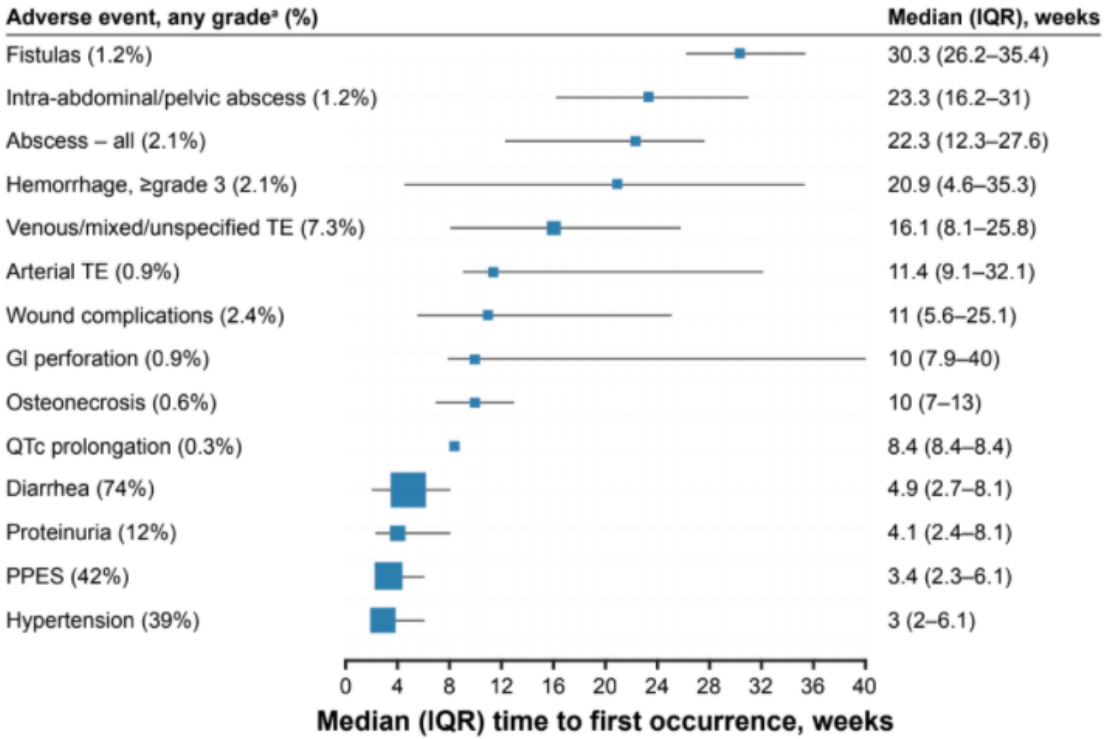
TOXICITY MANAGEMENT

RELATIVE CONTRAINDICATIONS TO MKI

- Poor cardiac function or recent myocardial infarction
- Uncontrolled HTN
- Large, unhealed wounds
- History of colitis, diverticulitis, intestinal perforation, recent bowel surgery
- Tumor invading trachea/esophagus/great vessels (endoscopic evaluation)
- Hemoptysis or use of anticoagulants
- Very low body weight (BMI: 18 – 21 kg/m2)

These relative contraindications should prompt a discusión with the patient regarding the risks and possibly a lower starting dose (considering the possible correlation between the dose of TKI and tumor shrinkage) or alternate drug choice.

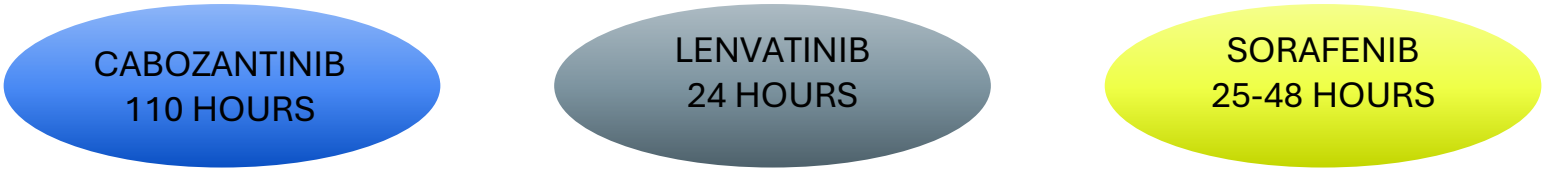
TOXICITY MANAGEMENT – Time to AE onset



Gerendash BS, et al. OncoTargets and Therapy 2017

TOXICITY MANAGEMENT -> Time to toxicity resolution for reintroduction

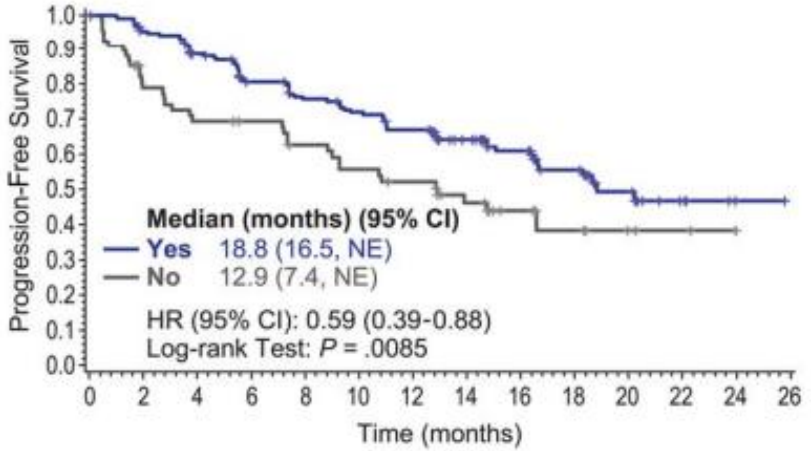
PLASMA HALF-LIFE



Tahara M, et al. European Journal of Cancer 2019

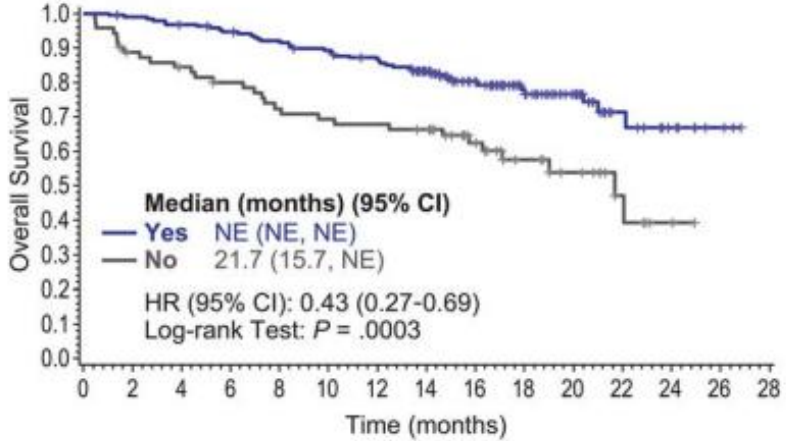
TOXICITY MANAGEMENT -> Predictive biomarkers?

LENVATINIB (SELECT TRIAL) AND HTN DEVELOPMENT



Number of patients with TE-HTN:

Yes	190	175	154	135	123	116	107	71	53	37	20	8	3	0
No	71	50	44	41	36	32	29	21	13	7	4	3	0	0



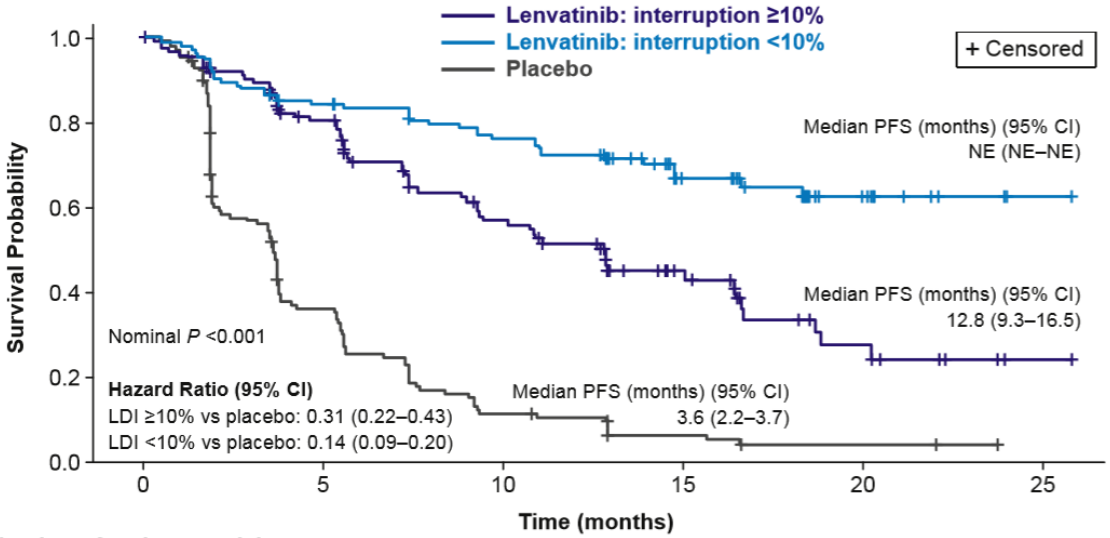
Number of patients with TE-HTN:

Yes	190	187	182	177	171	165	158	126	85	59	42	16	8	3	0
No	71	61	57	53	48	46	45	43	29	19	13	6	2	0	0

Wirth LJ, et al. Cancer 2018;124:2365-72.

TOXICITY MANAGEMENT -> MKI exposure

LENVATINIB (SELECT TRIAL) AND TREATMENT INTERRUPTION

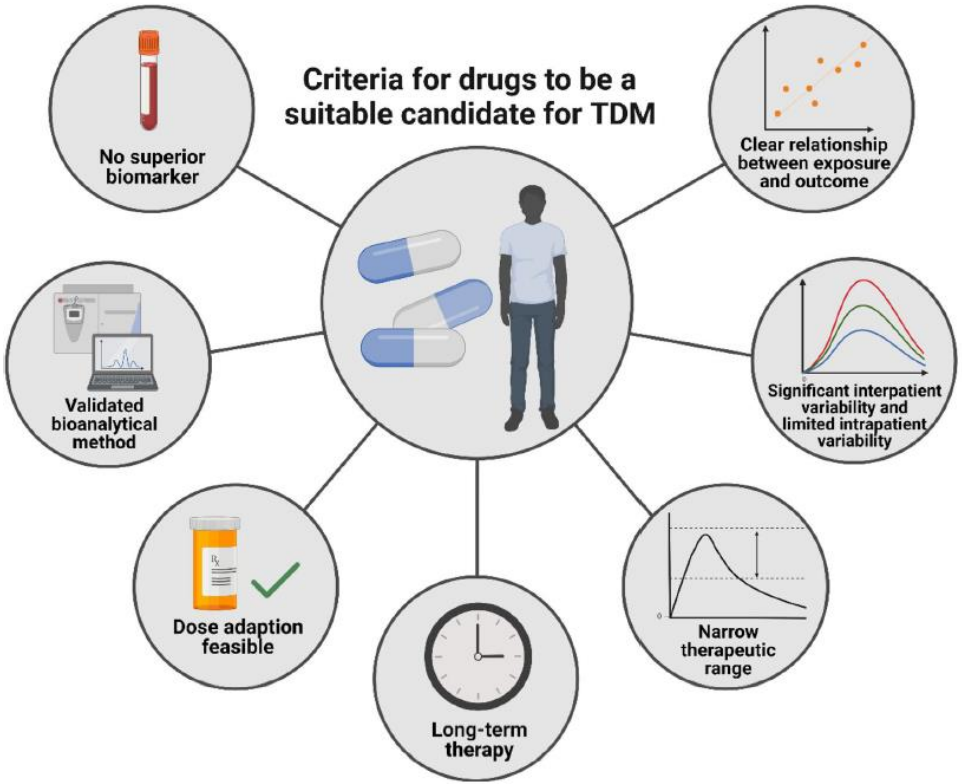


Number of patients at risk:

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

Tahara M, et al. European Journal of Cancer 2019

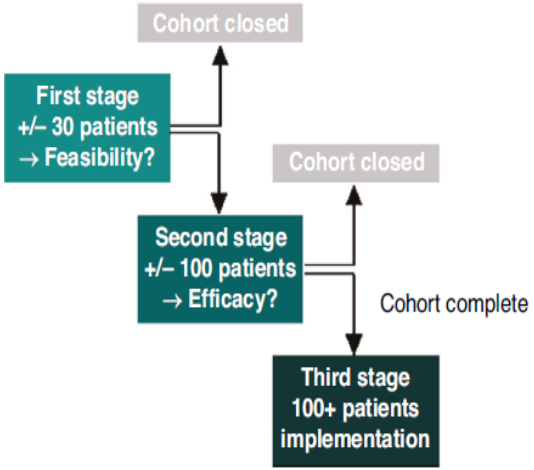
TOXICITY MANAGEMENT -> MKI exposure



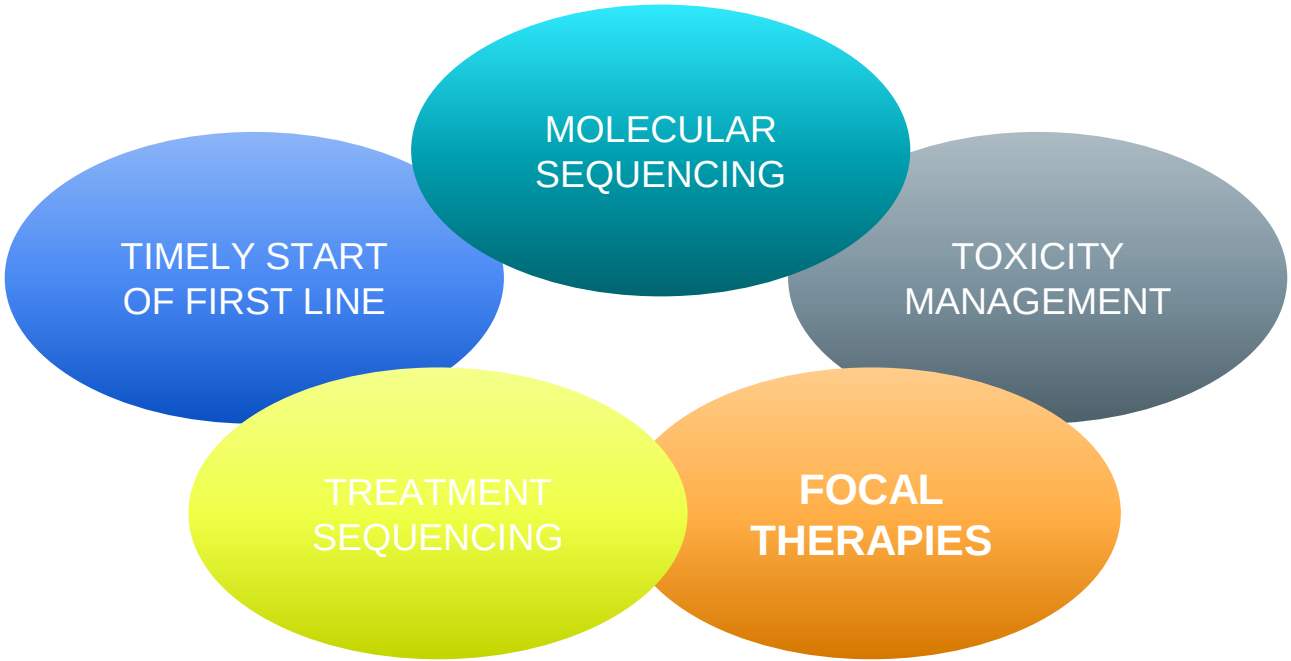
Van Der Kleij MBA, et al. Clinical Pharmacokinetics (2023) 62:1333–1364

TOXICITY MANAGEMENT -> MKI exposure

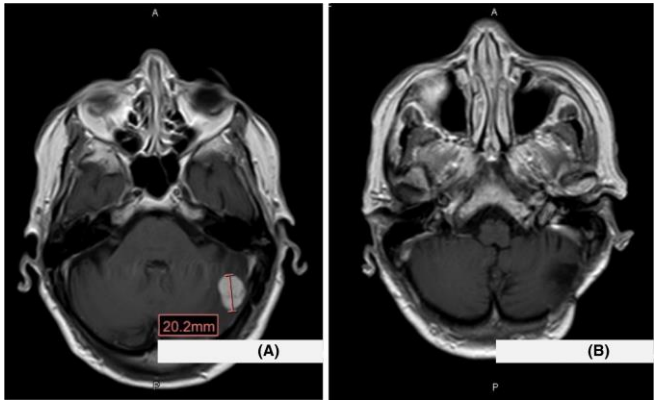
Drug	Pk parameter	Safety	Efficacy
Axitinib	AUC at 4 weeks from treatment start Css,trough	>6.6 ng/ml associated with ≥G2 hypothyroidism. >7.1 ng/ml associated with ≥G2 asthenia	>300 ng h/ml: better OS and PFS 154-620 ng h/ml better OS and PFS >5 ng/ml associated with longer OS
Pazopanib	Css,trough	≥ 15 mg/ml associated with higher rate of HTN	>15 mg/ml associated with PR/SD <15 mg/ml associated with PD ≥ 20.5 mg/ml longer PFS and greater tumor shrinkage
Sunitinib	Css,trough AUCss	≥ 100 ng/ml higher toxicity rate >2150 ng/ml/h higher grade 3-4 toxicity	Optimal concentration between 50 and 100 ng/ml (preclinical data) <100 ng/ml associated with longer PFS and TTF >100 ng/ml associated with worse outcomes Lower in PD patients compared with AUCss at treatment start.
Cabozantinib	Css,trough	≥ 617.7 ng/ml a 63.3% sensitivity and a 65.3% specificity to detect relevant toxicity (i.e. G3-4 toxicities and G2 toxicities determining a dose reduction or a drug discontinuation	< 536.8 ng/ml, 64.3% sensitivity and a 73.5% specificity to detect disease progression.



Van Der Kleij MBA, et al. Br J Cancer. 2024 Sep;131(5):843-851.
Cerbone L, et al. ESMO Open. 2021; 6 (6)

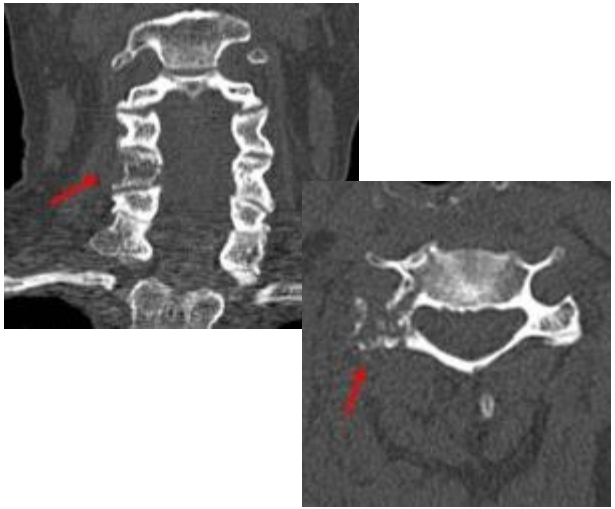

MOLECULAR SEQUENCING
TIMELY START OF FIRST LINE
TOXICITY MANAGEMENT
TREATMENT SEQUENCING
FOCAL THERAPIES

CNS metastases



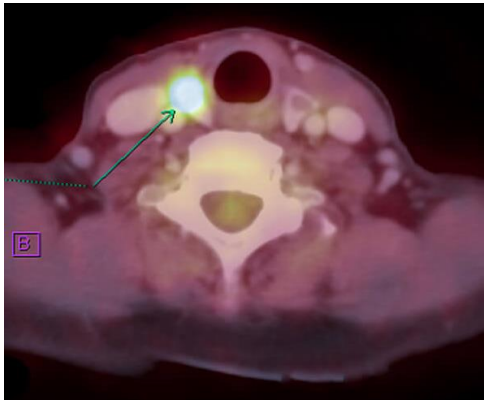
Focal therapy: SRS, Surgery, *WBRT*
Selective inhibitors may change treatment approach

Bone lesions



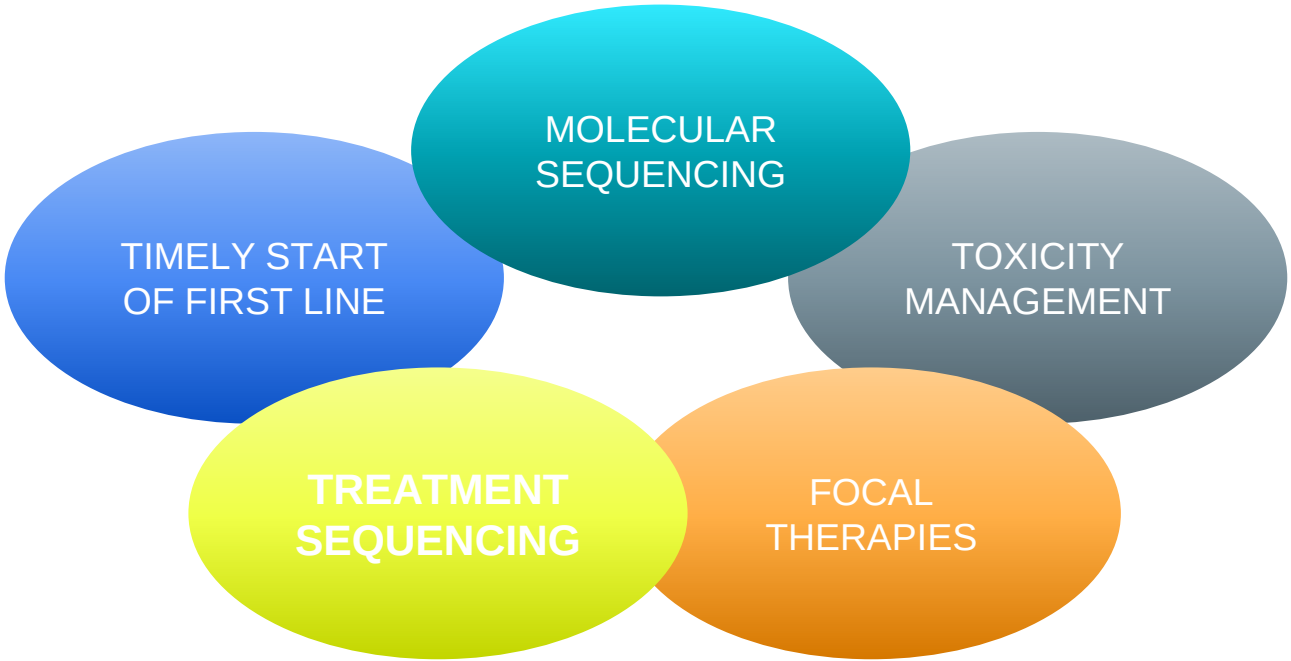
Focal therapy + Antiresorptive drugs, such as zoledronic acid or denosumab

Treatment beyond progression



Solitary lesions progressing in the setting of other stable lesions. Different techniques are currently available → MTD

Prinzi A, et al. Thyroid. 2024 Oct;34(10):1194-1204.


MOLECULAR SEQUENCING
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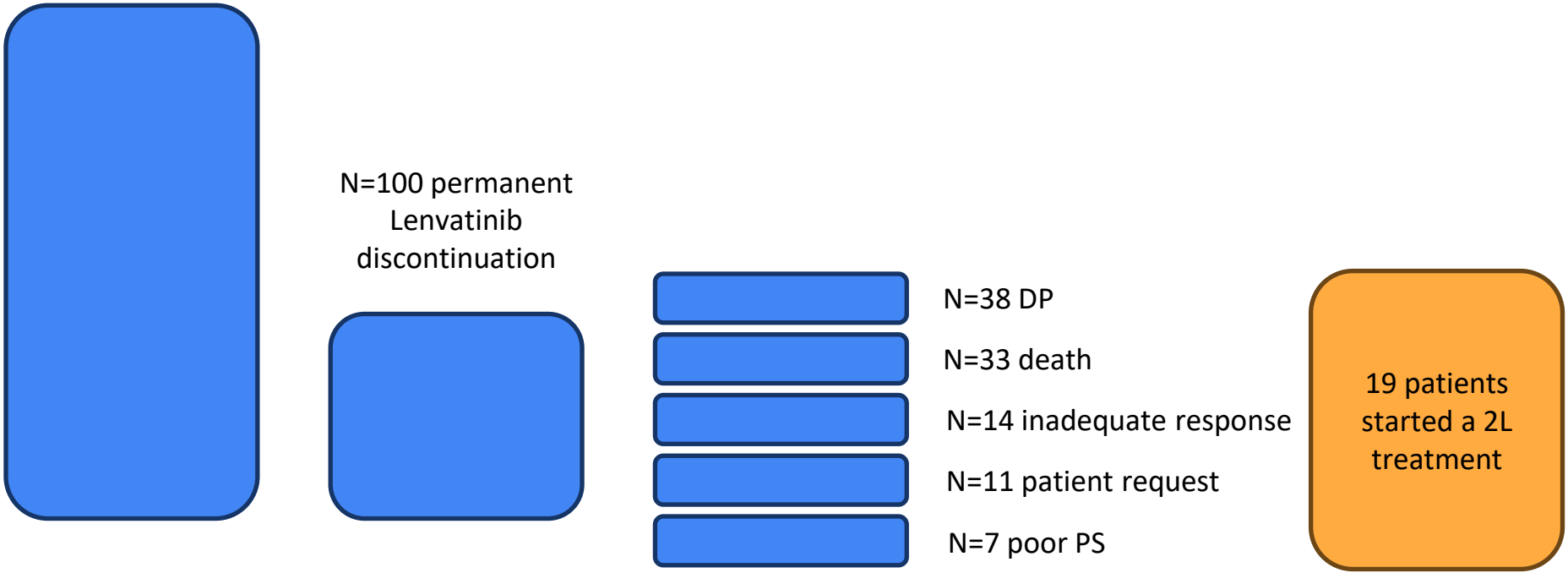
FOCAL THERAPIES

SUBSEQUENT TREATMENT LINES

N=308 RAI-R DTC (ORR=72,4%; mPFS=49m; mOS=NR)



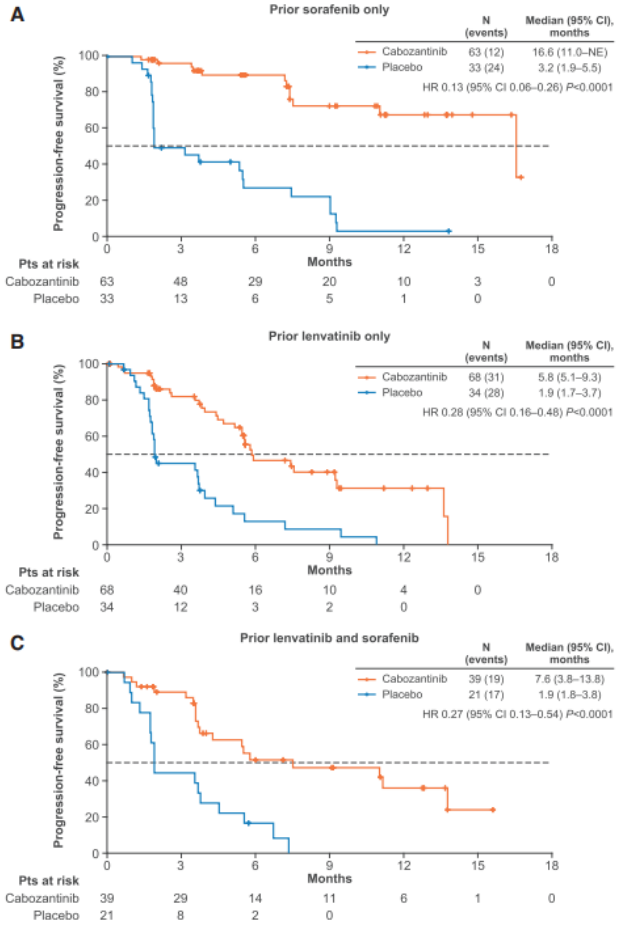
Worden F, et al. Endocrine 2024 May;84(2):663-669.

TREATMENT SEQUENCING

COSMIC 311

N=258

- Locally advanced or metastatic, RAI-refractory or ineligible DTC
- Progression during or after up to 2 prior VEGFR TKIs
- Prior TKI must include Lenvatinib or sorafenib
- mPFS = 11.0 vs 1.9 months (HR 0.22).
- ORR = 11.0% vs 0%



Capdevila J, et al. Thyroid. 2024 Mar;34(3):347-359.

TREATMENT SEQUENCE

SELPERCATINIB

ORR = 85.4% (95%CI 70.8 – 94.4)

mPFS = 27.4 (95%CI 14.5 – NE)

2-y PFS = 57.1% (95%CI 38.6 - 71.8)

mDOR = 26.7 months (12.1 - NE)

LAROTRECTINIB

ORR = 78% (13% CR)

DoR rate at 24 months was 81%

OS rate at 24 months was 92%

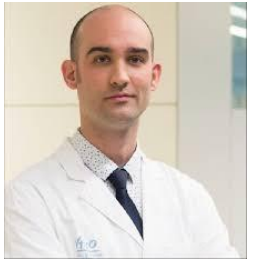
ENTRECTINIB

ORR = 54% (8%CR)

DoR 13.2 (7.9–NE)

Median OS 19.9 months

Schlumberger M, et al. N Engl J Med. 2015;372:621–630; Brose M, et al. Lancet. 2014;384:319-328; Brose MS, et al. Lancet Oncol. 2021 Aug;22(8):1126-1138.



Advanced RAI-R DTC

RAI-R evaluation
Optimal moment to start systemic treament
Molecular testing (BRAF mutations, RET fusions, NTRK fusions)

Rapidly progressive	**Moderately progressive**	**Indolent disease**
Symptomatic Aggresive histology Risk of death Bulky disease	Threat to vital structures Risk of clinical worsening Radiological progression	Asymptomatic Low volume, slow progression
1st line Lenvatinib (early start)	**1st line** Lenvatinib	Consider W&W **1st line** Sorafenib/Lenvatinib
RET: Selpercatinib[A] *NTRK:Entrectinib/Larotrectinib[B]*	RET: Selpercatinib[A] *NTRK:Entrectinib/Larotrectinib[B]*	RET: Selpercatinib[A] *NTRK: Entrectinib/Larotrectinib[B]*

Alonso-Gordoa T, et al. Clin Transl Oncol 2024

Advanced RAI-R DTC

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Optimal moment to start systemic treament
Molecular testing (BRAF mutations, RET fusions, NTRK fusions)

Rapidly progressive
Symptomatic
Aggresive histology
Risk of death
Bulky disease

1st line
Lenvatinib (early start)

RET: Selpercatinib[A]
NTRK:Entrectinib/Larotrectinib[B]

2nd line
Cabozantinib
NTRK:
Entrectinib/Larotrectinib
RET: Selpercatinib

Moderately progressive
Threat to vital structures
Risk of clinical worsening
Radiological progression

1st line
Lenvatinib

RET: Selpercatinib[A]
NTRK:Entrectinib/Larotrectinib[B]

2nd line
Cabozantinib
NTRK :
Entrectinib/Larotrectinib
RET: Selpercatinib

Indolent disease
Asymptomatic
Low volume, slow progression

Consider W&W
1st line
Sorafenib/Lenvatinib

RET: Selpercatinib[A]
NTRK: Entrectinib/Larotrectinib[B]

2nd line
Lenvatinib/Cabozantinib[C]
NTRK :
Entrectinib/Larotrectinib
RET: Selpercatinib

3rd line
Cabozantinib[C]/Lenvatinib
NTRK :
Entrectinib/Larotrectinib
RET: Selpercatinib

Alonso-Gordoa T, et al. Clin Transl Oncol 2024

Advanced RAI-R DTC

RAI-R evaluation
Optimal moment to start systemic treament
Molecular testing (BRAF mutations, RET fusions, NTRK fusions)

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NTRK:Entrectinib/Larotrectinib[B]

2nd line
Cabozantinib
NTRK:
Entrectinib/Larotrectinib
RET: Selpercatinib

Moderately progressive
Threat to vital structures
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Radiological progression

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NTRK:Entrectinib/Larotrectinib[B]

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NTRK :
Entrectinib/Larotrectinib
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Indolent disease
Asymptomatic
Low volume, slow progression

Consider W&W
1st line
Sorafenib/Lenvatinib

RET: Selpercatinib[A]
NTRK: Entrectinib/Larotrectinib[B]

2nd line
Lenvatinib/Cabozantinib[C]
NTRK :
Entrectinib/Larotrectinib
RET: Selpercatinib

3rd line
Cabozantinib[C]/Lenvatinib
NTRK :
Entrectinib/Larotrectinib
RET: Selpercatinib

Further lines
Clinical trials
BRAF: Dabrafenib +/- Trametinib[B] (early lines in case of high expected toxicity with approved drugs)
Chemotherapy
Other MKI supported by phase II clinical trials (i.e. pazopanib, sunitinib, axitinib)[B]
Best supportive care

Alonso-Gordoa T, et al. Clin Transl Oncol 2024

CONCLUSIONS

Molecular knowledge in thyroid cancer has demonstrated diagnostic and therapeutic implications.

Clinical (tumor-related and patient-related), metabolic and molecular factors should be considered in treatment decision.

Optimal management in DTC-RAR involves MTD teams from the beginning and through treatment administration.