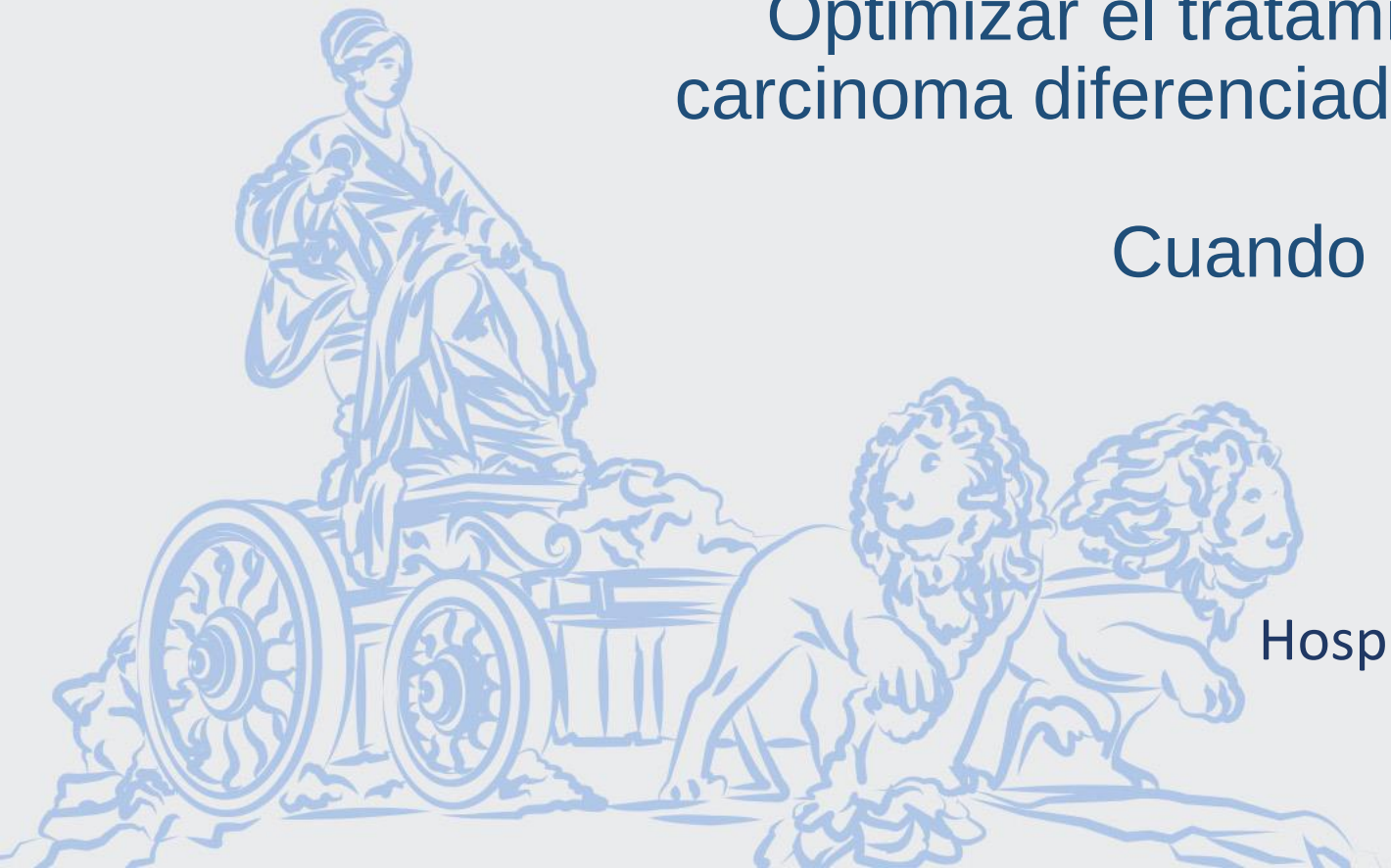
XXIV

Simposio de Revisiones en Cáncer

"Tratamiento médico del cáncer en el año 2022"



Optimizar el tratamiento en primera linea del carcinoma diferenciado de tiroides iodorefractario.

Cuando iniciar importa.

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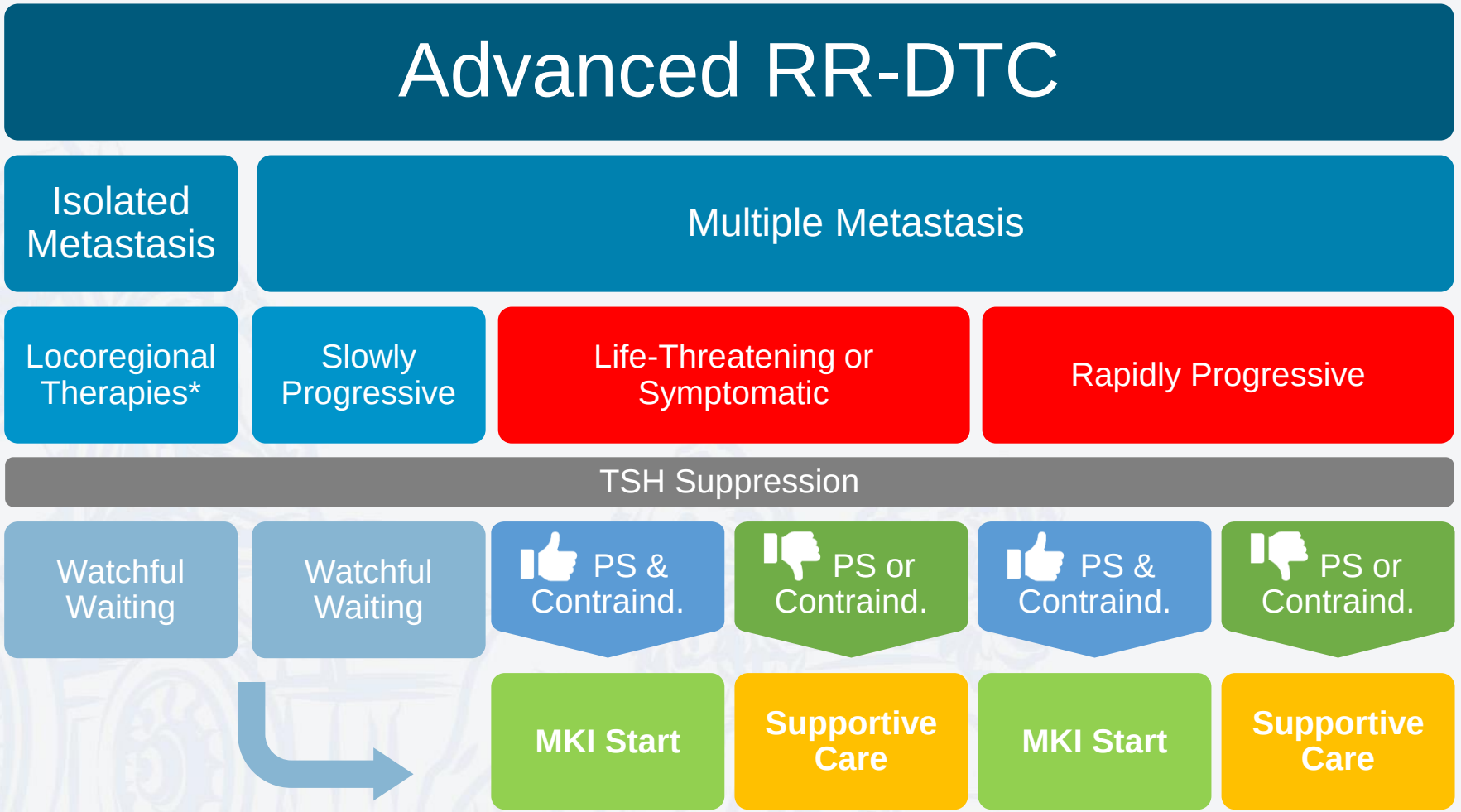
ARÁN

Decision Path in RR-DTC



Initial non-candidates may become MKI candidates upon **change in disease progression pace**

*Most commonly used include but are not limited to: surgery, external beam radiation (EBRT), radiofrequency ablation (RFA), ethanol ablation, and laser ablation.
RR-DTC=radioiodine refractory differentiated thyroid cancer; PS=performance status; MKI=multikinase inhibitor.
Adapted from Jin Y, et al. Crit Rev Oncol Hematol. 2018;125:111-120.

Systemic Therapy MUST be Started if…

Symptomatic Disease — MKI Start

⚠ **The presence of symptoms is associated with poor prognosis**, and treatment with **MKI should therefore be started even if radiological progression has not been confirmed**[1]

Asymptomatic Disease — MKI Start

High Tumour Burden | Rapidly Progressive | Life-Threatening

⚠ **Large, multiple tumors greater than 1-2 cm in size** that are rapidly progressing according to **RECIST (<6-12 months)** or **Tumour Volume Doubling Time (<3 years)**[2]

⚠ **Presence of tumor foci near the respiratory–digestive axis or large vessels** may be an indication to initiate MKI treatment before the trachea or esophagus are invaded or encasement of great vessels contraindicate its use, **even if radiological progression has not been confirmed**[2]

MKI=multikinase inhibitor.

1. Capdevila J, et al. Cancer Treat Rev. 2018;69:164-176. **2.** Schmidt A, et al. Arch Endocrinol Metab. 2017;61(1):81-89.

• Definition of RAI Refractoriness

ATA[1]

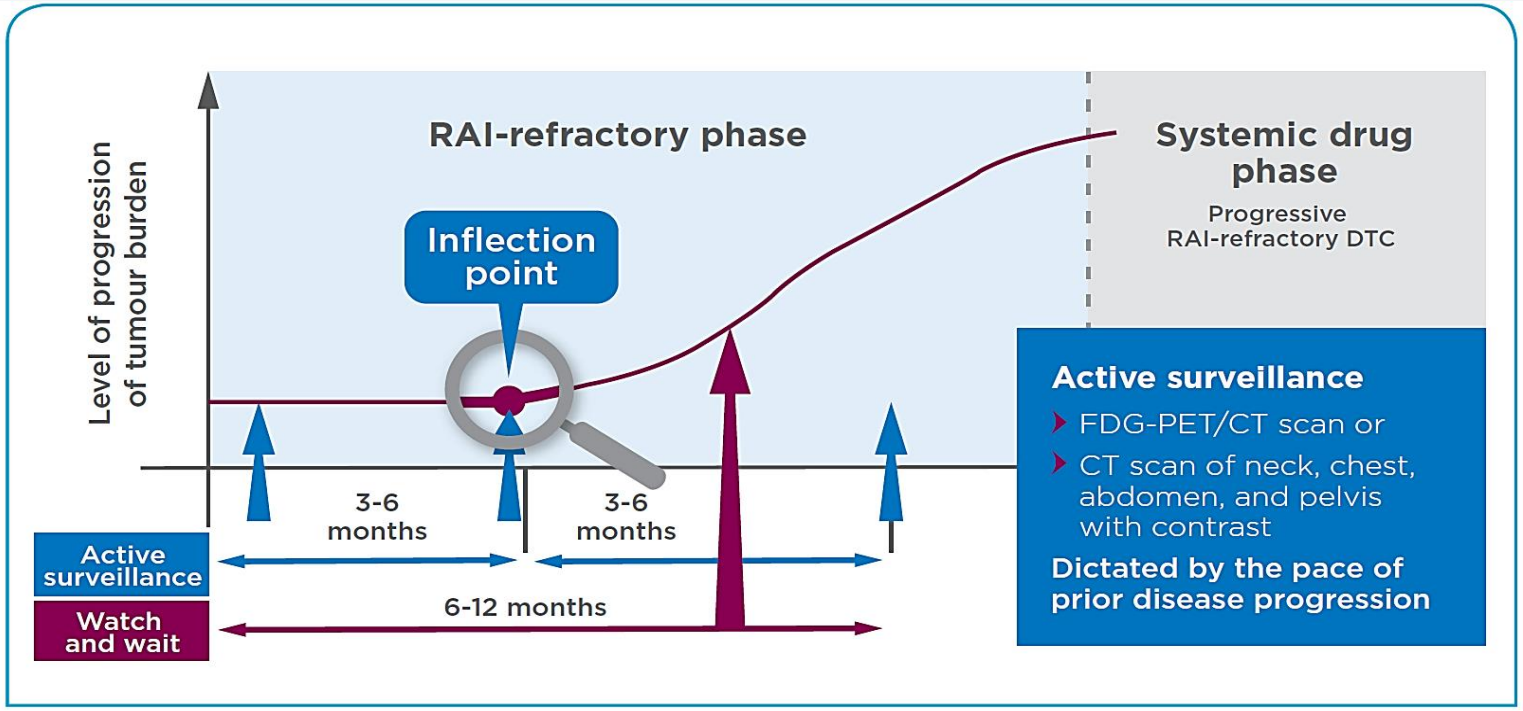
- The **malignant or metastatic tissue does not ever concentrate RAI** (no uptake outside the thyroid bed at the first therapeutic WBS).
- The tumor tissue **loses the ability to concentrate RAI after previous evidence of RAI-avid disease** (in the absence of stable iodine contamination)
- RAI is concentrated in **some lesions but not in others**
- Metastatic disease **progresses despite significant concentration of RAI**
- *Cumulative 131I **activities above 500–600 mCi** are associated with a significant increase in risk*

GETHI/SEEN[2]

- **No uptake of RAI** at the initial diagnosis of distant metastases or locoregional recurrence
- **Progressive loss of RAI uptake** after several sessions of RAI therapy
- Evidence of different metastases, **some of them with RAI uptake and others without RAI** uptake on the body scan
- **Tumor progression after adequate RAI treatment** even with previous RAI uptake
- Total cumulative doses of **RAI over 600 mCi**
- **Unresectable primary tumors of DTC**

1. Haugen BR, et al. Thyroid. 2016;26(1):1-133. **2.** Capdevila J, et al. Clin Transl Oncol. 2017;19(3):279-287.

Vigilancia activa del CDT-RYR:



FDG-PET=fluorodeoxyglucose-positron emission tomography; CT=computed tomography.

- Las guías de NCCN y ATA recomiendan la vigilancia activa para los pacientes con CDT-RYR
- Los expertos clínicos recomiendan controles de seguimiento **cada 3-6 meses** para detectar precozmente la progresión de la enfermedad
- **La vigilancia activa permite adaptar el plan de tratamiento a cada tipo de paciente único**

Definition of Rapidly Progressive disease (MKI indicated)

- Describing Rapidly Progressive disease relies today on 2 options:
  - **Option 1:** Using **RECIST to define Progressive Disease** that must be observed in a given **(predefined) time frame**
  - **Option 2:** Using lung metastasis **Tumour Volume Doubling Time (TVDT)** and, while still debated, systemic **Thyroglobulin Doubling Time (TgDT) without a predefined time frame**

Sabra MM, et al. Cancer. 2017;123(15):2955-2964.

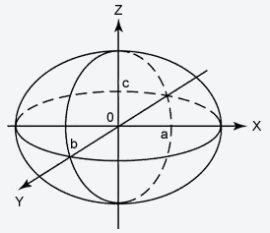
Definition of Rapidly Progressive disease (MKI indicated)

- Most National and International Treatment Guidelines do not provide a time frame for RECIST to define *Rapidly Progressive disease*…
  - **GETHI-SEEN (Spain):** Candidates to receive MKI should have **RECIST-determined Rapidly Progressive** RAI-R disease **without providing a time frame**[1]
  - **SIE (Italy):** Candidates to receive MKI should have **RECIST-determined Rapidly Progressive** RAI-R disease **without providing a time frame**[2]
  - **NCCN (US):** Candidates to receive MKI should have **RECIST-determined Rapidly Progressive** RAI-R disease **without providing a time frame**[3]
  - **ATA (US):** Candidates to receive MKI should have **RECIST-determined Rapidly Progressive** RAI-R disease **over a 6 month period**[4]
  - **SELECT & DECISION registration trials:** Candidates to receive MKI should have **RECIST-determined Progressive** RAI-R disease **over a 12 months period**[5,6]

GETHI=grupo estapañol de tumores huérfanos e infrecuentes; SEEN=sociedad española de endocrinología y nutrición; SIE=società italiana di endocrinologia; NCCN= . national comprehensive cancer network; ATA=american thyroid association; RAI-R=radioiodine-refractory.

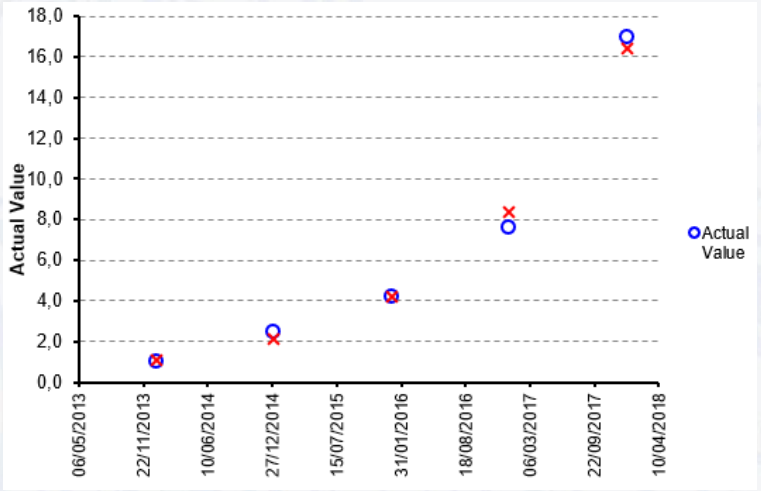
Definition of Tumour Volumen Doubling Time(MKI indicated)

- To work out the TVDT of a target lesion some assumptions must be made[1]
  - Tumours are, **in general ellipsoid in shape**, so their volume can be calculated with this formula:

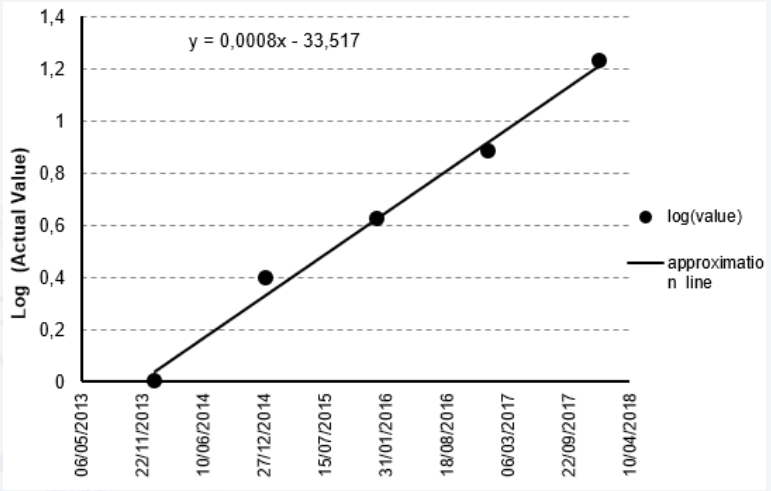


$$TV = \frac{\pi}{6} abc$$

  - Tumours generally grow **with exponential rate that remains constant over time** until large volumes are achieved, so TVDT can be found applying logarithm to Volume axis:



Log of Volumen



$$log(\mathrm{TV}) = \log(a) + b\mathrm{t}$$

$$\mathrm{TV} = tumour\ volume\ (mm^3)$$

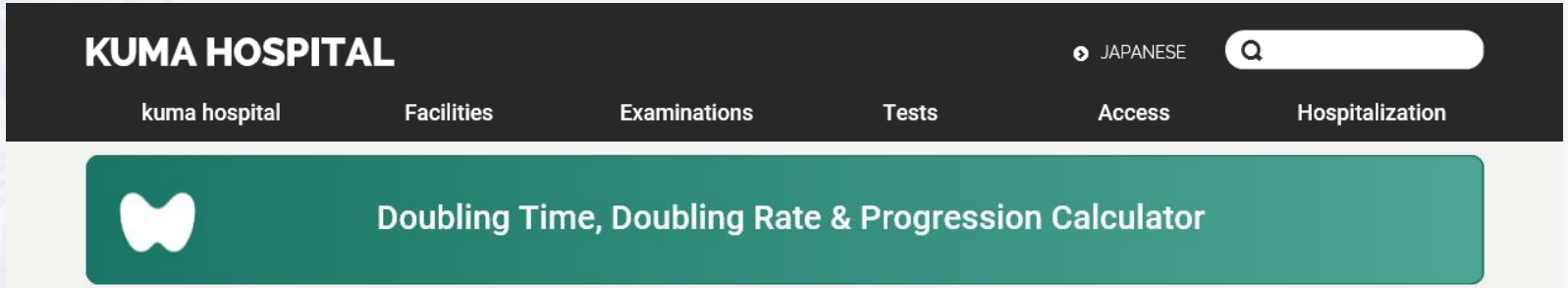
$$\mathrm{t} = time\ after\ initial\ CT\ (years)$$

$$\mathrm{TVDT} = Log(2)/b$$

1. Sabra MM, et al. Cancer. 2017;123(15):2955-2964. **2.** Available at: https://www.kuma-h.or.jp/english/

Definition of Tumour Volumen Doubling Time(MKI indicated)

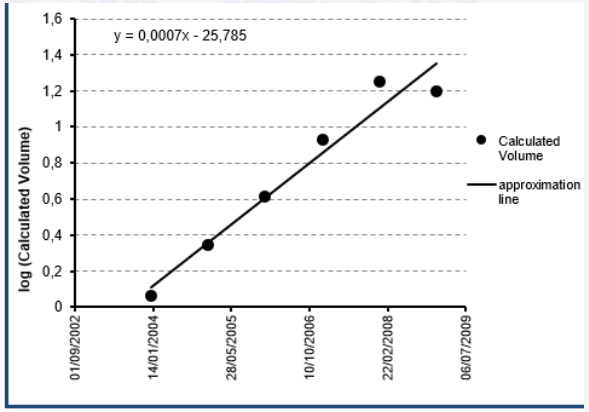
- To make things **EASIER** during the patient visits, various **free online biomarker calculators like the one from KUMA Hospital (JP),** very quickly gives the TVDT if at least 4 consecutive tumour measures are input[2]



Doubling Time	Doubling Rate
442 days	0,00 /day
14,7 months	0,07 /month
1,21 years	0,83 /year

① ②

Date	Major axis	Minor axis	Thickness
01/01/2004	1,1	2,0	1,0
01/01/2005	2,1	2,0	1,0
01/01/2006	3,9	2,0	1,0
01/01/2007	8,1	2,0	1,0
01/01/2008	17,0	2,0	1,0
01/01/2009	5,0	2,0	3,0

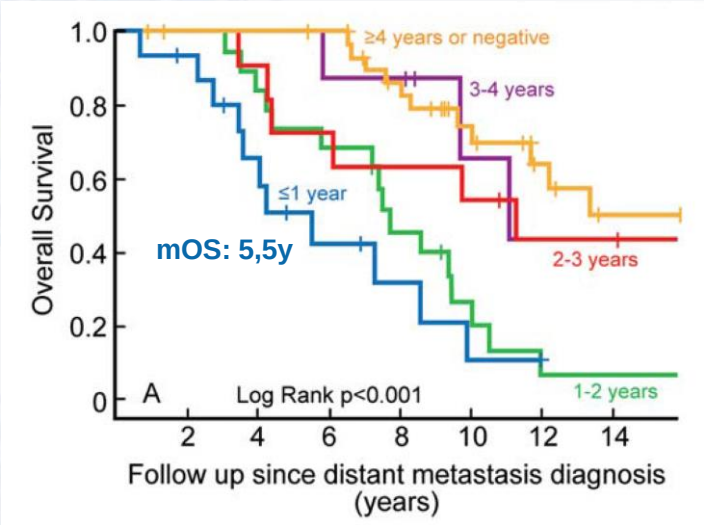


1. Sabra MM, et al. Cancer. 2017;123(15):2955-2964. **2.** Available at: https://www.kuma-h.or.jp/english/

Impact of TVDT on aDTC's Overall Survival (MKI indicated)

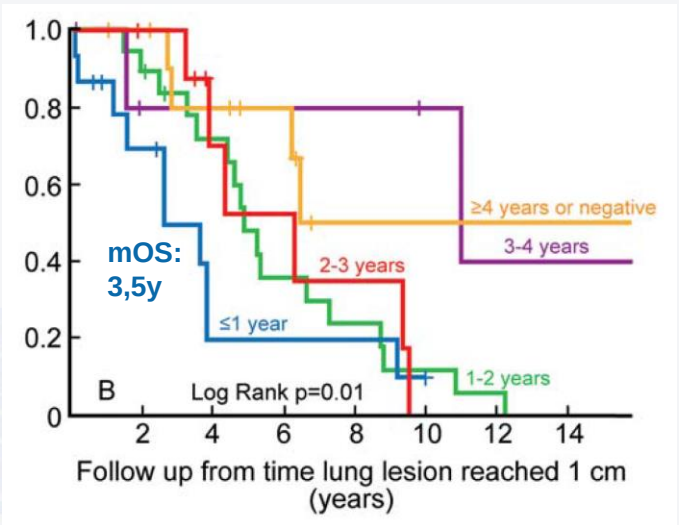
- When OS was plotted from the time lungs metastases reached ≥ 1cm, it became even shorter* for all midDT groups:

midDT (aDTC diagnosis)



After metastases reached ≥ 1cm

midDT (aDTC ≥ 1cm)



For patients with aDTC midDT ≤1y and lung lesions ≥ 1cm, **MKI therapy must be initiated without delay!**

Median follow-up from diagnosis of aDTC: 8.5 years (0.7-29.4 years)

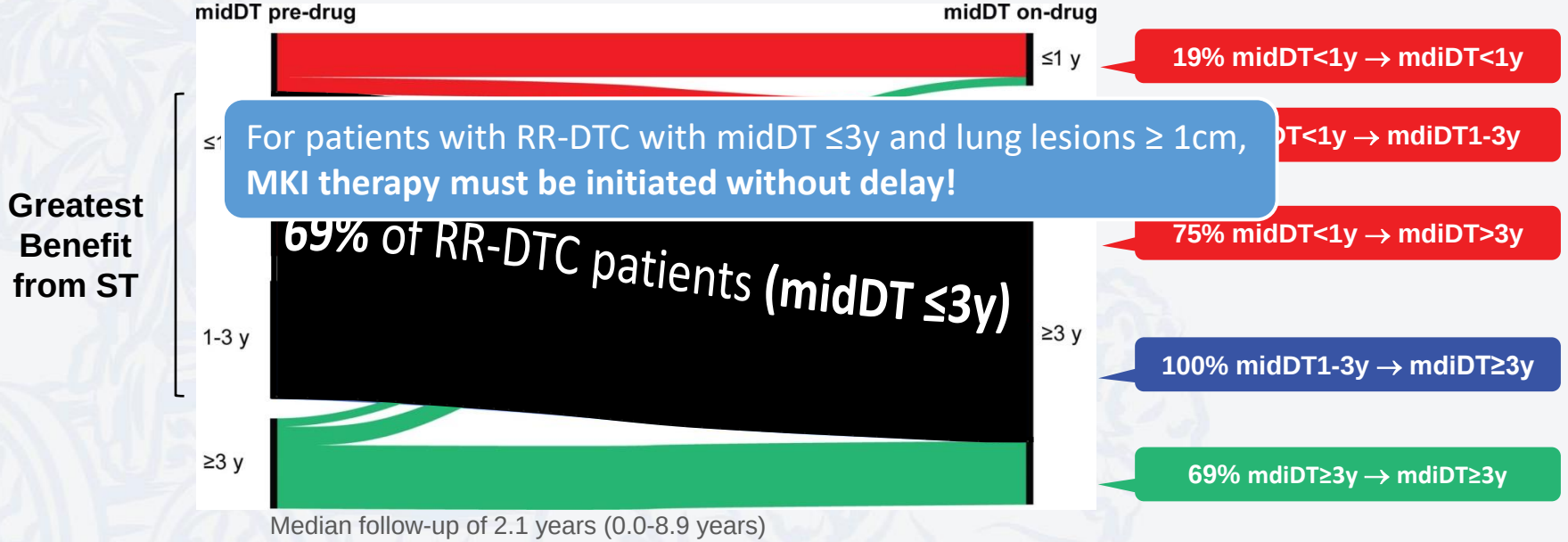
aDTC=advanced DTC; TVDT=tumour volumen doubling time; midDT=average tumour volume doubling time;

*The 5-y OS rate from the 1 cm time point was 20% for midDT≤1y, 50% for midDT 1-2y, 53% for 2-3y, 80% for 3-4y, 86% for ≥4y, and 52% for negative midDT.

Sabra MM, et al. Cancer. 2017;123(15):2955-2964.

- From a series of 62 RR-DTC patients* with lung metastases and baseline midDT ≤1y, 1-3y, and ≥3y, their change of midDT was registered after starting ST†

Change midDT after starting ST



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

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

RR-DTC=radioiodine-refractory advanced DTC; TVDT=tumour volumen doubling time; midDT=average tumour volume doubling time; ST=sytemic therapy.

*These 62 patients had metastatic pulmonary lesions measured in at least 4 consecutive CT scans both at baseline and during follow-up.

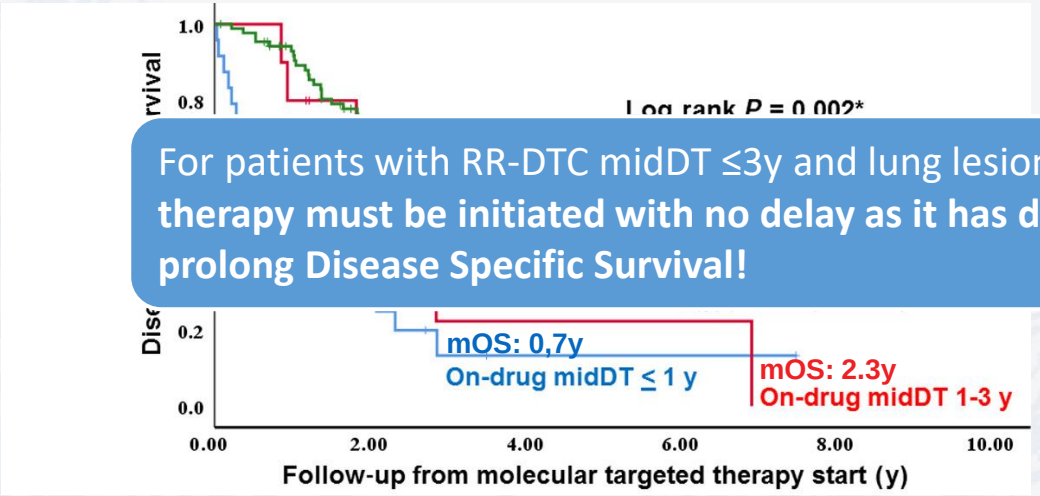
†Patients were treated with ≥1 ST during their follow-up. These included either aflibercept, sorafenib, pazopanib, lenvatinib, sorafenib/ everolimus, sorafenib/ temerolimus, everolimus alone, temsirolimus alone, dabrafenib alone or in combination with lapatinib, vemurafenib, fostamatinib, axitinib, sunitinib, vandetanib or cabozantinib.

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

Impact of TVDT on aDTC's Overall Survival (MKI indicated)

- In 122 RR-DTC patients* with lung metastases treated with ST, DSS was followed in 3 groups according to their achieved on-ST midDT

DSS according to ST-achieved midDT†



For patients with RR-DTC midDT ≤3y and lung lesions ≥ 1cm, **MKI therapy must be initiated with no delay as it has demonstrated to prolong Disease Specific Survival!**

DSS was **statistically increased in** …**tients achieving** compared to **midDT 1-3y** or **≤1y**

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

ST-achieved midDT prolongation is associated with statistically longer DSS!

TVDT=tumour volumen doubling time; DSS=disease-specific survival; midDT=average tumour volume doubling time; ST=systemic therapy.

*These 122 patients included the previous 62 plus 60 more with clinical features of disease progression without exactly having 4 CT baseline and follow-up scans.

†midDT was derived as the average TVDT calculated for the tumour dimensions of two index metastatic pulmonary lesions measured in at least 4 consecutive CT scans.

Sabir M, et al. Cancer Clin Endocrinol Oncol. 2019;90(4):617-622.

Impact of TVDT on aDTC's Overall Survival (MKI indicated)

- In addition, from the previous results authors also conclude that:

1. Any drug that can significantly prolong midDT of lung metastasis, is expected to prolong the Disease-Specific Survival of patients with RR-DTC

2. The duration of therapy and so the duration of midDT prolongation are crucial to influence survival

3. In fact, patients who can have sustained midDT prolongation for more than 1 year, fare better than those who lasted on drug <6 months

RR-DTC=radioiodine-refractory advanced DTC; TVDT=tumour volumen doubling time; midDT=average tumour volume doubling time; ST=systemic therapy.

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

Conclusions

1. In patients with symptomatic disease, MKI therapy must be started with no delay regardless of radiological evidence of disease progression[1]
2. Waiting for high tumor burden or for the onset of symptoms can compromise patient survival[1]
3. In patients with asymptomatic disease, MKI therapy must be started if there is a large tumour burden[1,2], disease is rapidly progressive[2,] or life-threatening[2,3] upon progression
4. In RR-DTC patients achieving prolonged TVDT with targeted therapy, Disease-Specific Survival is statistically increased[3,4]
5. This benefit is more likely when duration of systemic therapy treatment is of > 1 year[3,4]

MKI=multikinase inhibitor; TVDT=tumour volume doubling time.

1. Capdevila J, et al. Clin Transl Oncol. 2017;19(3):279-287. **2.** Schmidt A, et al. Arch Endocrinol Metab. 2017;61(1):81-89. **3.** Sabra MM, et al. Cancer. 2017;123(15):2955-2964. **4.** Sabra MM, et al. Cancer. Clin Endocrinol (Oxf). 2019;90(4):617-622.

Right Selection of Candidate Patients for Systemic Therapy

Is early initiation of lenvatinib treatment beneficial for patients who have lung metastases of ≥1.0 cm?

Impact of Lung Metastasis on Overall Survival in the Phase 3 SELECT Study With Lenvatinib in Patients With Radioiodine-Refractory Differentiated Thyroid Cancer (RR-DTC)

Makoto Tahara[1], Naomi Kiyota[2], Ana O. Hoff[3], Corin Badiu[4], Taofeek K. Owonikoko[5], Corina E. Dutcus[6], Takuya Suzuki[7], Min Ren[6], Soamnauth Misir[8], Lori Wirth[9]

[1]National Cancer Center Hospital East, Kashiwa, Japan; [2]Cancer Center, Kobe University, Kobe, Japan; [3]Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil; [4]National Institute of Endocrinology, Bucharest, Romania; [5]Emory University, Atlanta, GA, USA; [6]Eisai Inc., Woodcliff Lake, NJ, USA; [7]Oncology Business Group, Eisai Co. Ltd., Tokyo, Japan; [8]Formerly of Eisai Inc., Woodcliff Lake, NJ, USA; [9]Massachusetts General Hospital Cancer Center, Boston, MA, USA

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

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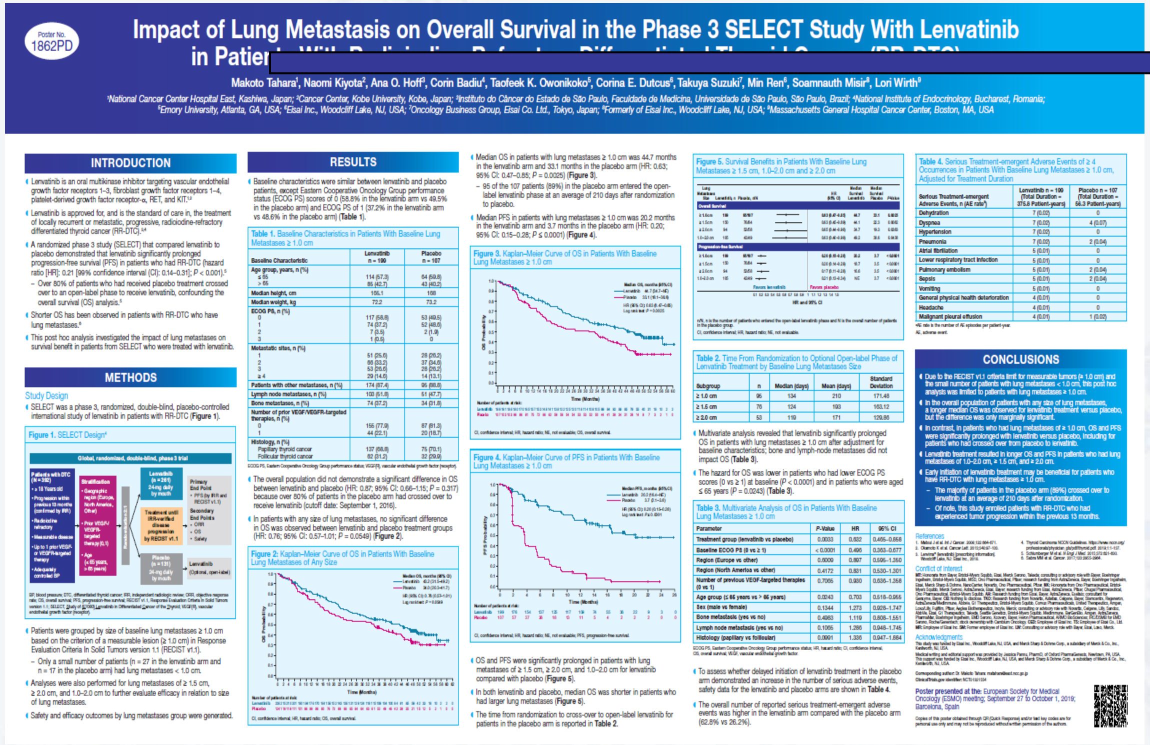
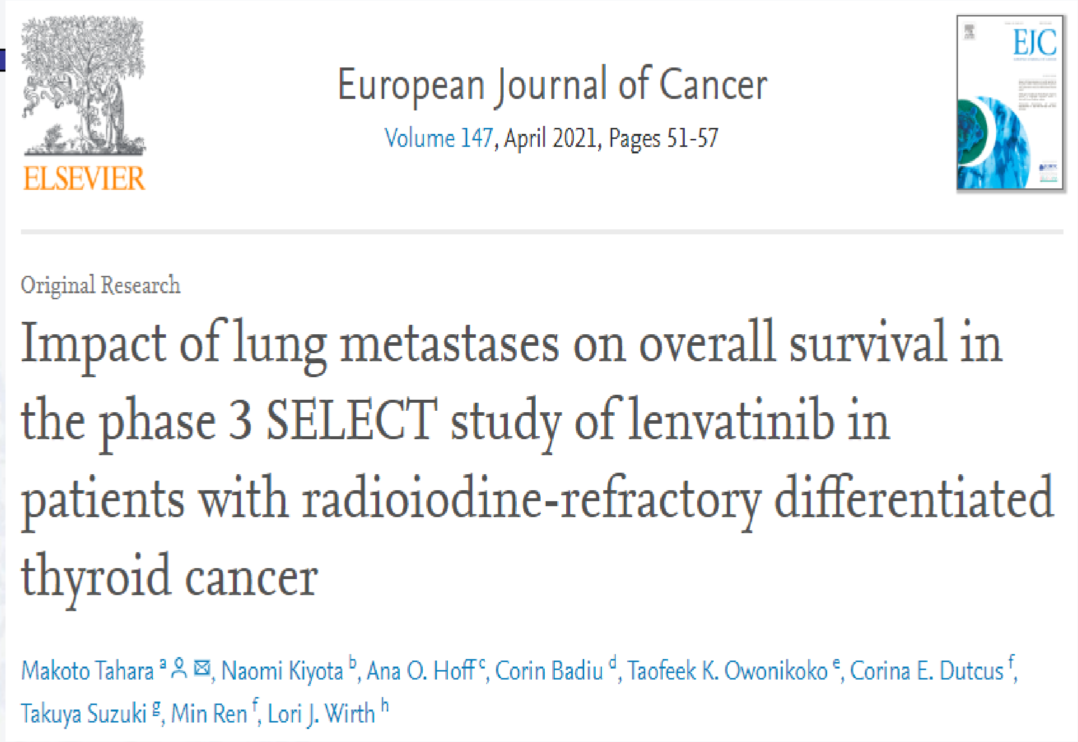
"Tratamiento médico del cáncer en el año 2022"

Impact of Lung Tumour Burden in the OS of Patients treated with Lenvatinib

ESMO 2019



EJC 2021



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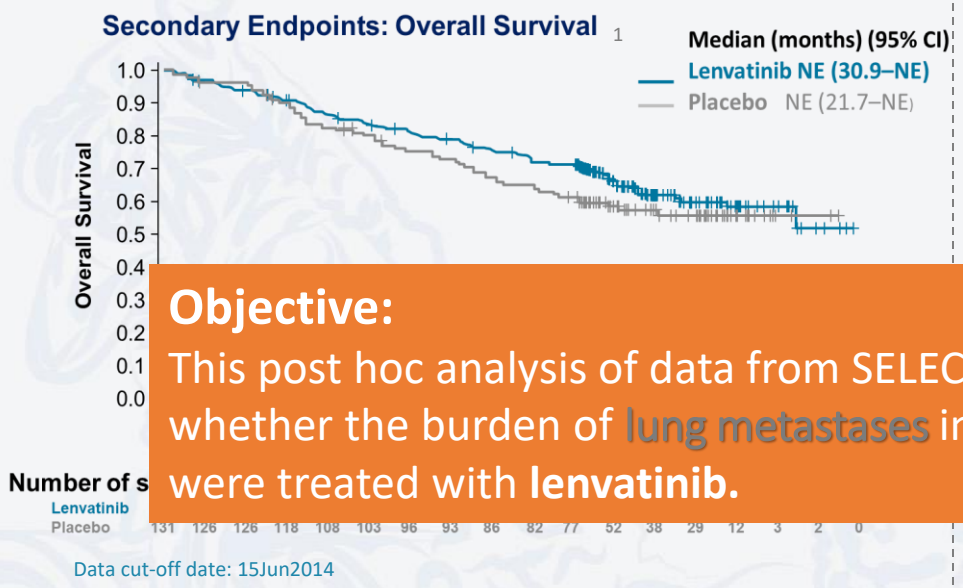
Rationale & Objective



Data cut-off date: 15Jun2014

83% of patients from placebo group crossed over to receive lenvatinib

Objective:
This post hoc analysis of data from SELECT was conducted to evaluate whether the burden of lung metastases influenced survival in patients who were treated with **lenvatinib.**

- Research has demonstrated a correlation between the presence of lung metastases in patients with RR-DTC and shorter survival

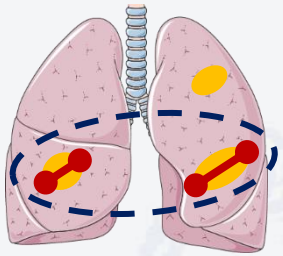
...es found ...only ...ourable survival outcomes compared to those with extrapulmonary metastases

1. Schlumberger M, et al. N Engl J Med. 2015;372:621–630

Methodology

SELECT

Post-hoc



- **Patients with any lung metastases (target/ non-target lesions) that could be classified as measurable based on the RECIST v1.1 criterion**
- **Patients were grouped by the size of their metastasis**
  - ≥1 cm
  - ≥1.5 cm
  - ≥2 cm
  - <2.0 cm

- *Safety and efficacy outcomes with the exception of PFS data by lung-metastases size group were generated using an updated data cut-off date of 1st September 2016.*
- *The data cut off used to evaluate PFS was 15th November 2013.*

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Baseline characteristics

Baseline characteristics in patients with any baseline lung metastases and lung metastases of >1.0 cm.

Category	Any Lung Metastases (target/non-target lesions)			
	Lenvatinib N = 226	Placebo N = 124		› n = 107
Age group, n (%)				
≤65 years	132 (58.4)	75 (60.5)		8)
>65 years	94 (41.6)	49 (39.5)		2)
Median height, cm	165.4	168.0		
Median weight, kg	73.8	74.0		
ECOG PS, n (%)				
0	128 (56.6)	66 (53.2)		5)
1	88 (38.9)	56 (45.2)		6)
2	9 (4.0)	2 (1.6)		
3	1 (0.4)	0		
Metastatic sites, n (%)				
1	52 (23.0)	29 (23.4)		2)
2	81 (35.8)	42 (33.9)		6)
3	61 (27.0)	38 (30.6)		2)
≥4	32 (14.2)	15 (12.1)		1)
Patients with any metastases other than lung metastases, n (%)	174 (77.0)	95 (76.6)		8)
Lymph node metastases	119 (52.7)	60 (48.4)		7)
Bone metastases	83 (36.7)	45 (36.3)		8)
Number of prior VEGF/VEGFR-targeted therapies, n (%)				
0	174 (77.0)	99 (79.8)		3)
1	52 (23.0)	25 (20.2)		7)
Histology, n (%)				
Papillary thyroid cancer	153 (67.7)	86 (69.4)	137 (68.8)	75 (70.1)
Follicular thyroid cancer	73 (32.3)	38 (30.6)	62 (31.2)	32 (29.9)

ECOG PS, Eastern Cooperative Oncology Group performance status; VEGF(R), vascular endothelial growth factor (receptor).

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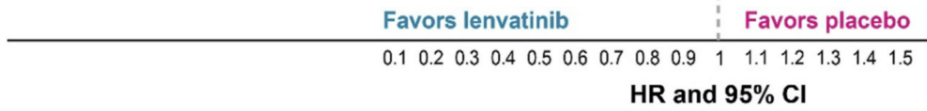
OS and PFS results

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



Transition to open-label lenvatinib

n	Median (days)	Mean (days)	Standard Deviation	
95	134	210	171.48	89%
76	124	193	163.12	90%
53	119	171	129.86	91%
42	185	260	203.70	85%

[a]The number of patients who entered the open-label lenvatinib phase from the placebo arm per baseline lung metastases subgroup were: any lung mets (target/nontarget lesions), n=115; lung metastases of ≥1.0 cm, n=95; ≥1.5 cm, n=76; ≥2.0 cm, n=53, and <2.0 cm, n=42.
[b]Progression-free survival was assessed by investigator review per RECIST version 1.1.

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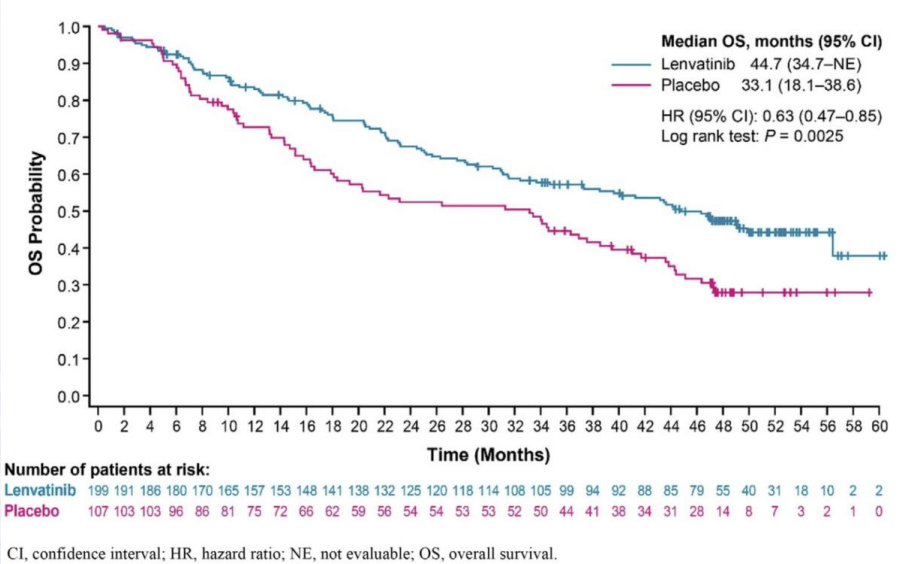
Efficacy in patients with lung metastases ≥1cm

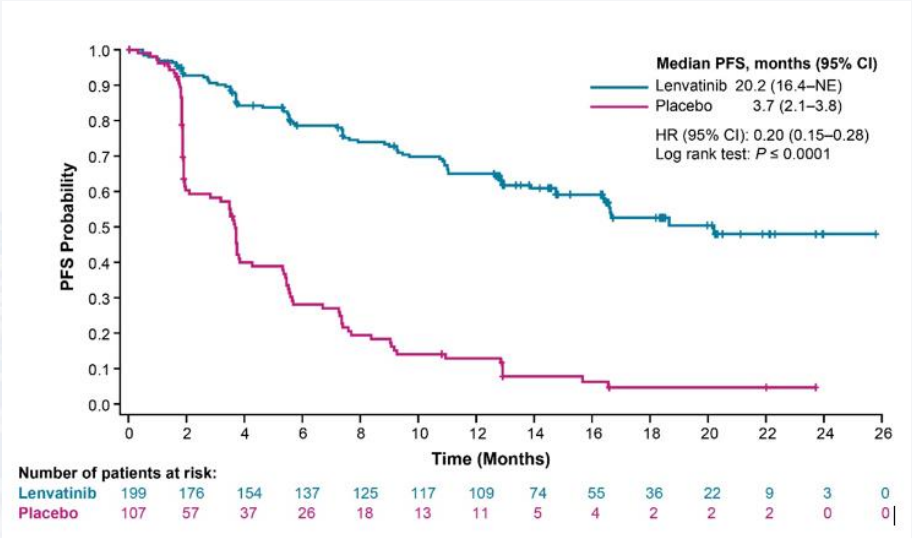
89% cross-over at 210 days

Overall Survival



CI, confidence interval; HR, hazard ratio; NE, not evaluable; OS, overall survival.

Progression Free Survival



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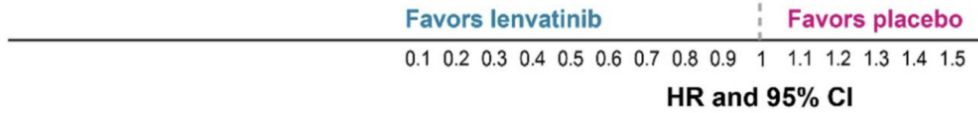
< 2.0 cm	105	49	0.63 (0.40–0.99)	49.2	38.6	0.0438
Progression-free Survival[b]						
Any lung mets (target/non-target lesions)	226	124	0.20 (0.15–0.27)	18.7	3.6	< 0.0001
≥ 1.0 cm	**199**	**107**	**0.20 (0.15–0.28)**	**20.2**	**3.7**	**< 0.0001**
≥ 1.5 cm	150	84	0.20 (0.14–0.29)	18.7	3.5	< 0.0001
≥ 2.0 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



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

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

[a]The number of patients who entered the open-label lenvatinib phase from the placebo arm per baseline lung metastases subgroup were: any lung mets (target/nontarget lesions), n=115; lung metastases of ≥1.0 cm, n=95; ≥1.5 cm, n=76; ≥2.0 cm, n=53, and <2.0 cm, n=42.
[b]Progression-free survival was assessed by investigator review per RECIST version 1.1.

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Multivariate analysis: Factors impacting OS

Table 3
Multivariate analysis of OS in patients with baseline lung metastases of ≥1.0 cm.

Parameter	*P*-value	HR	95% CI
Treatment group (lenvatinib versus placebo)	0.0033	0.632	0.465–0.858
Baseline ECOG PS (0 versus > 1)	<0.0001	0.496	0.363–0.677
Region (Europe versus other)	0.6009	0.897	0.595–1.350
Region (North America versus other)	0.4172	0.831	0.530–1.301
Number of previous VEGF-targeted therapies (0 versus 1)	0.7065	0.930	0.636–1.358
Age group (≤ 65 years versus > 65 years)	0.0243	0.703	0.518–0.955
Sex (male versus female)	0.1344	1.273	0.928–1.747
Bone metastasis (yes versus no)	0.4983	1.119	0.808–1.551
Lymph node metastasis (yes versus no)	0.1065	1.286	0.948–1.745
Histology (papillary versus follicular)	0.0991	1.336	0.947–1.884

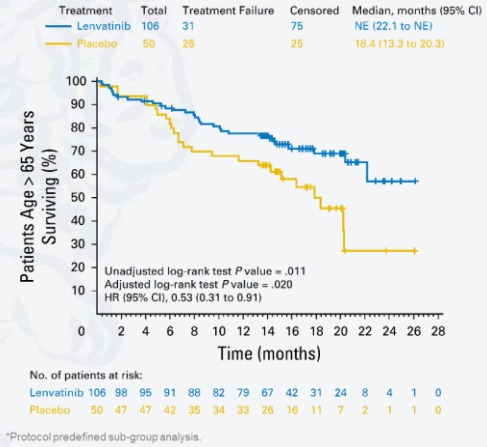
ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; CI, confidence interval; OS, overall survival; VEGF, vascular endothelial growth factor.

- Lenvatinib treatment significantly prolonged OS after adjustment for baseline characteristics

ECOG 0 vs ECOG 1	
OS	HR 0.42 [95% CI: 0.26–0.69]; P=0.0004
PFS	HR 0.52 [95% CI: 0.35–0.77]; P=0.001)
ORR	OR 3.51 [95% CI: 2.02–6.10]; P<0.0001

1

2



1. Matthew H. Taylor et al., Thyroid Feb 2021. Abstract available at https://doi.org/10.1089/thy.2020.0779; 2. Brose MS, et al. J Clin Oncol. 2017;10;35(23):2692-2699.

Safety

Lenvatinib Dose Intensity per Day	Any Lung Mets (target/nontarget)	Lung Mets of ≥1.0 cm	≥1.5 cm	≥2.0 cm	<2.0 cm
• Dose Intensity					
n	226	199	150	94	105
Mean (SD)	16.0 (5.35)	15.8 (5.36)	15.8 (5.16)	16.3 (5.26)	15.4 (5.44)
Median	15.2	14.9	15.0	15.1	14.6
Min, Max	5, 25	5, 25	5, 25	5, 24	6, 25

- TEAEs

The overall number of reported serious treatment-emergent adverse events was higher in the lenvatinib arm versus the placebo arm (62.8% versus 26.2%) in patients with baseline lung metastases of ≥1.0 cm.

Table 4
Serious TEAEs with ≥4 occurrences in patients with baseline lung metastases of ≥1.0 cm in both treatment arms, adjusted for treatment duration.[a]

Serious TEAEs, n (AE rate[b])	Lenvatinib (n = 199; total duration = 375.8 patient-years)	Placebo (n = 107; total duration = 56.3 patient-years)
Dehydration	7 (0.02)	0
Dyspnoea	7 (0.02)	4 (0.07)
Hypertension	7 (0.02)	0
Pneumonia	7 (0.02)	2 (0.04)
Atrial fibrillation	5 (0.01)	0
Lower respiratory tract infection	5 (0.01)	0
Pulmonary embolism	5 (0.01)	2 (0.04)
Sepsis	5 (0.01)	2 (0.04)
Vomiting	5 (0.01)	0
General physical health deterioration	4 (0.01)	0
Headache	4 (0.01)	0
Malignant pleural effusion	4 (0.01)	1 (0.02)

AE, adverse event; TEAEs, treatment-emergent adverse events.
[a] This analysis does not include the optional open-label phase.
[b] AE rate is the number of AE episodes per patient-year.

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Tahara Final remarks

- Patients with **non-target lung metastases** from SELECT were not evaluated as a separate subgroup because the sizes of the non-target lesions were either **not measurable** or not measured.
- The impact of **the number** of lung metastases on efficacy were **not considered** in this study.

- In patients who had baseline **lung metastases of ≥ 1.0 cm, both OS and PFS were significantly prolonged with lenvatinib treatment vs placebo.** (The placebo arm also included the 89% of patients who had crossed over to lenvatinib)
- Multivariate analysis demonstrated that an ECOG and age were independent predictors of OS.
- 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.
- **Early initiation of lenvatinib treatment may be beneficial for patients who have lung metastases of ≥1.0 cm**.

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Conclusions

1. In patients with symptomatic disease, MKI therapy must be started with no delay regardless of radiological evidence of disease progression[1]

2. Waiting for high tumor burden or for the onset of symptoms can compromise patient survival[1]

3. In patients with asymptomatic disease, MKI therapy must be started if there is a large tumour burden[1,2], disease is rapidly progressive[2,] or life-threatening[2,3] upon progression

4. In RR-DTC patients achieving prolonged TVDT with targeted therapy, Disease-Specific Survival is statistically increased[3,4]

5. This benefit is more likely when duration of systemic therapy treatment is of > 1 year[3,4]

6. In patients who had baseline lung metastases of ≥ 1.0 cm, both OS and PFS were significantly prolonged with lenvatinib treatment vs placebo. Early initiation of lenvatinib treatment may be beneficial for patients who have lung metastases of ≥1.0 cm[5]

MKI=multikinase inhibitor; TVDT=tumour volume doubling time.

1. Capdevila J, et al. Clin Transl Oncol. 2017;19(3):279-287. **2.** Schmidt A, et al. Arch Endocrinol Metab. 2017;61(1):81-89. **3.** Sabra MM, et al. Cancer. 2017;123(15):2955-2964. **4.** Sabra MM, et al. Cancer. Clin Endocrinol (Oxf). 2019;90(4):617-622. 5.Tahara M, et al. European Journal of Cancer, V147 (April 2021) 51-57

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