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.

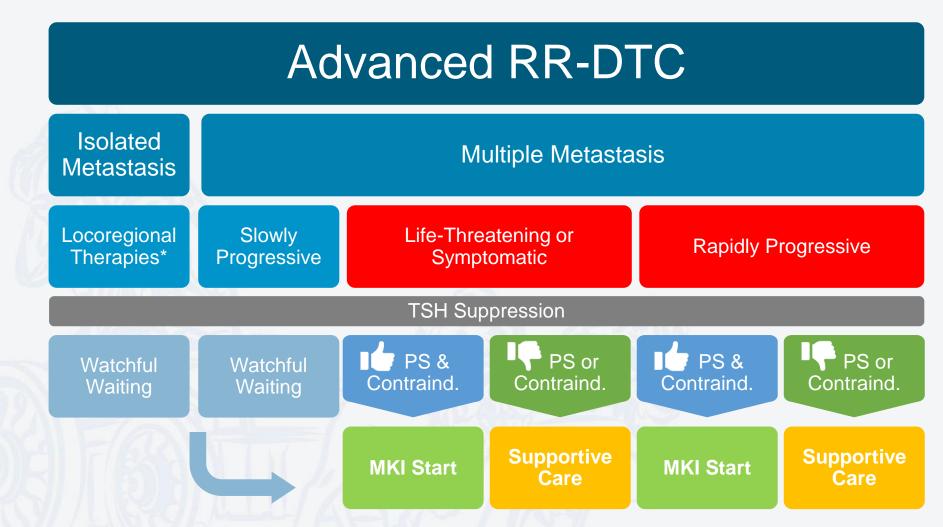
Angel Agustin Segura Huerta. Servicio Oncologia Medica. Hospital Universitari i Politecnic La Fe. Valencia

NRÁN



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

The presence of symptoms is associated with poor prognosis, and treatment with MKI should therefore be started even if radiological progression has not been confirmed¹

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 confirmed²

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

ATA¹

- 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 1311 activities above 500–600 mCi are associated with a significant increase in risk

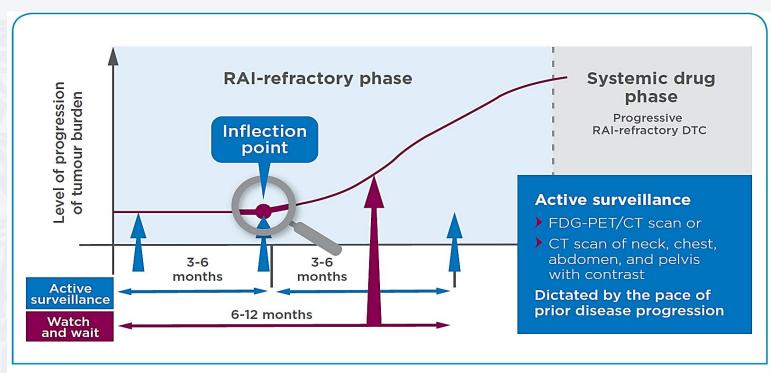
GETHI/SEEN²

- 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.



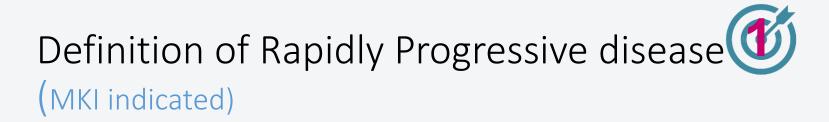
Vigilancia activa del CDT-RYR:



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 <u>cada 3-6 meses</u> para detectar precozmente la progresión de la enfermedad
 - La vigilancia activa permite adaptar el plan de tratamiento a cada tipo de paciente único





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



"Tratamiento médico del cáncer en el año 2022"



- Most National and International Treatment Guidelines do not provide a time frame for RECIST to define *Rapidly Progressive disease*...
 - <u>GETHI-SEEN (Spain)</u>: Candidates to receive MKI should have RECISTdetermined Rapidly Progressive RAI-R disease <u>without providing a</u> <u>time frame</u>¹
 - <u>SIE (Italy)</u>: Candidates to receive MKI should have RECIST-determined Rapidly Progressive RAI-R disease without providing a time frame²
 - <u>NCCN (US)</u>: Candidates to receive MKI should have **RECIST-determined** Rapidly Progressive RAI-R disease <u>without providing a time frame</u>³
 - <u>ATA (US)</u>: Candidates to receive MKI should have RECIST-determined Rapidly Progressive RAI-R disease over a 6 month period⁴
 - <u>SELECT & DECISION registration trials</u>: Candidates to receive MKI should have RECIST-determined Progressive RAI-R disease <u>over a 12</u> <u>months period</u>^{5,6}

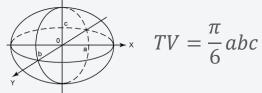
GETHI=grupo estapañol de tumores huérfanos e infrecuentes; SEEN=sociedad española de endocrinología y nutrición; SIE=società italiana di endocrinologia; NCCN= . national comprehensive cancer network; ATA=american thyroid association; RAI-R=radioiodine-refractory.



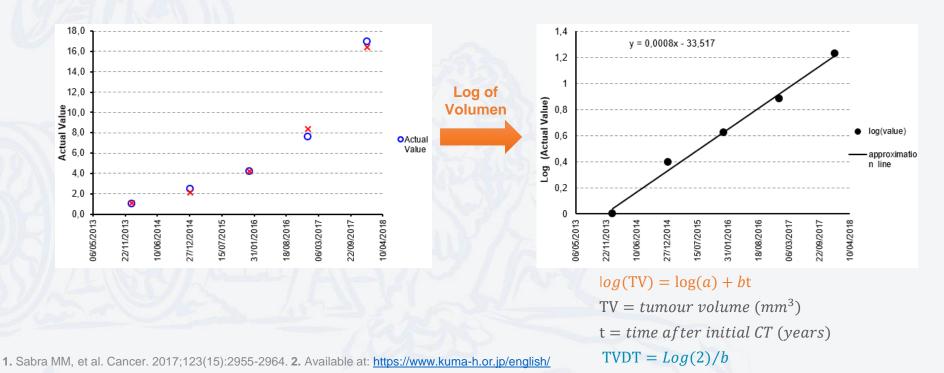


8

- To work out the TVDT of a target lesion some assumptions must be made¹
- Tumours are, in general ellipsoid in shape, so their volume can be calculated with this formula:



• 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:







 To make things <u>EASIER</u> 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 input²

KUMA HOSPI	ΓAL		JAPANESE	a 📄		
kuma hospital	Facilities	Examinations	Tests	Access	Hospitalization	
	Doubling Time, Doubling Rate & Progression Calculator					

Calculater

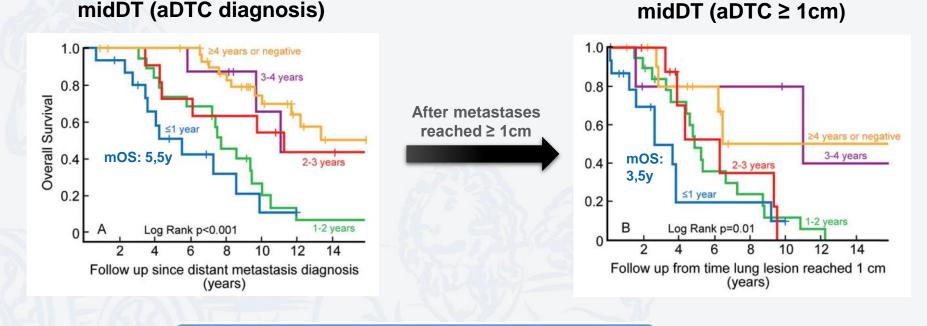
Doublin	ig Time	Doublin	ig Rate
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14,7	' months	0,07 /month	
1,	,21 years	0,83 /year	
	-	↑ _	-
1		2	
	-	Minor axis	
01/01/2004	1,1	2,0	1,0
01/01/2005	2,1	2,0	1,0
01/01/2006	3,9	2,0	1,0
01/01/2007	8,1	2,0	1,0
01/01/2008	17,0	2,0	1,0
01/01/2009	5,0	2,0	3,0

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:



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

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

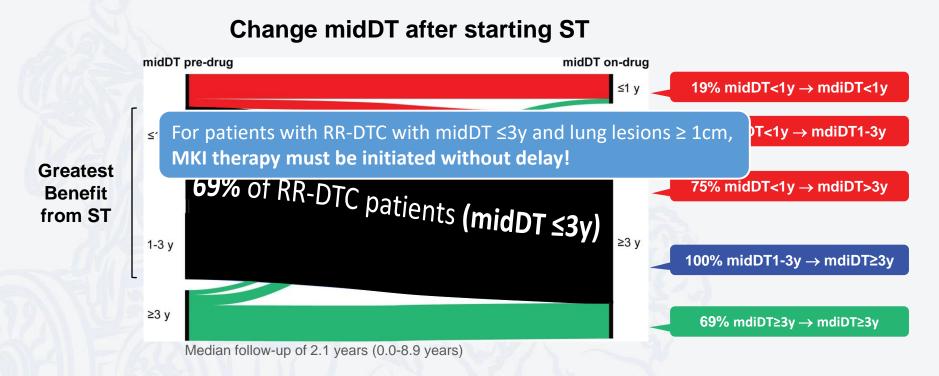
aDTC=advanced DTC; TVDT=tumour volumen doubling time; midDT=average tumour volume doubling time;

*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 \geq 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⁺



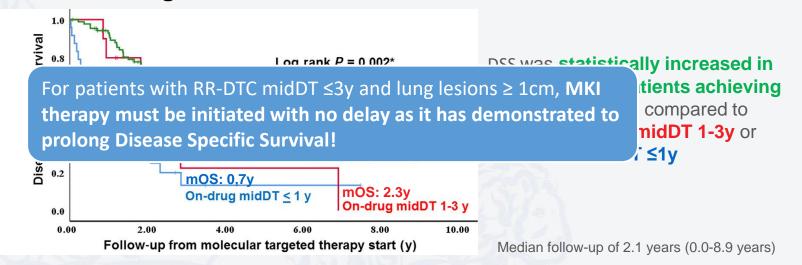
Systemic Therapy statistically prolonged the TVDT in 69% of patients!

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.



 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⁺



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.

Sabrial MWwas ale Grandes (Glander Barder Barde



- In addition, from the previous results authors also conclude that:
- 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</p>

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



Conclusions



- 1. In patients with symptomatic disease, MKI therapy must be started with no delay regardless of radiological evidence of disease progression¹
- 2. Waiting for high tumor burden or for the onset of symptoms can compromise patient survival¹
- 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}
- 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 Tahara¹, Naomi Kiyota², Ana O. Hoff³, Corin Badiu⁴, Taofeek K. Owonikoko⁵, Corina E. Dutcus⁶, Takuya Suzuki⁷, Min Ren⁶, Soamnauth Misir⁸, Lori Wirth⁹

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



Poster No. 1862PD

Impact of Lung Tumour Burden in the **O**S of Patients treated with Lenvatinib

ESMO 2019

Impact of Lung Metastasis on Overall Survival in the Phase 3 SELECT Study With Lenvatinib

Makoto Taharai, Naorri Kiyotai, Anao Q. Hoff, Corin Badiri, Tanfeek K. Owenikokof, Corina E. Dukazi, Takuya Sazaki, Min Ren¹, Saannaadi Minir¹, Lini Winth¹ Natoral Garoor Center Hospital Est, Karlina, Japan, "Caroor Carler, Kolo University, Kolo, Japan, "Institute of Caroor do Sato Pada, Sao Fada, Sao Pada, S

INTRODUCTION	RESULTS	Median OS in patients with lung metastases ≥ 1.0 cm was 44.7 months in the lervatinib arm and 33.1 months in the placebo arm (HR: 0.63; 96% CI: 0.47-0.85; P = 0.0025) (Figure 3).	Figure 5. Survival Benefits in Patients With Baseline Lung Metastases ≥ 1.5 cm, 1.0–2.0 cm and ≥ 2.0 cm	Table 4. Serious Treatment-emergent Adverse Events of ≥ 4 Occurrences in Patients With Baseline Lung Metastases ≥ 1.0 cm, Adjusted for Treatment Duration		
Lenvatinib is an oral multikinase inhibitor targeting vascular endothelial growth factor receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor-o, RET, and KIT. ¹⁹	 Baseline characteristics were similar between lervatinib and placebo patients, except Eastern Cooperative Oncology Group performance status (EOOG PS) scores of 0 (58.8% in the lervatinib arm vs 49.5% 	 95 of the 107 patients (89%) in the placebo arm entered the open- label lenvatinb phase at an average of 210 days after randomization to placebo. 	Log Rode Rode Reates To Londol, 1 Pools, 41 (55, 1) Londol Pools Pool (1974)	Adjussed for interment Lucence Serious Treatment-emergent Adverse Events, n (AE right) 375.6 Potient-event) 61.0 Patient-event		
Lervatinib is approved for, and is the standard of care in, the treatment	in the placebo arm) and ECOG PS of 1 (37.2% in the lervatinib arm		1100 19 807 HILLS 47 21 582	Dehydration 7.0.02 0		
f locally recurrent or metastatic, progressive, radiciodine-refractory	vs 48.6% in the placebo arm) (Table 1).	Median PFS in patients with lung metastases ≥ 1.0 cm was 20.2 months	atten 10 Mas 00166448 41 23 000	Dyspnea 7 (0.02) 4 (0.07)		
Rerentiated thyroid cancer (RR-DTC).14		in the lervatinib arm and 3.7 months in the placebo arm (HR: 0.20;	#10cm ## 058 605#4480 #7 93 600	Hostension 7/0.02 0		
	Table 1. Baseline Characteristics in Patients With Baseline Lung	95% Cl: 0.15-0.28; P ≤ 0.0001) (Figure 4).	(billion (2) (24) (24) (25) (25) (25) (25) (25) (25) (25) (25			
andomized phase 3 study (SELECT) that compared lervatinib to	Metastases ≥ 1.0 cm		Premarkan has kerdent	Preumonia 7 (0.02) 2 (0.04)		
sebo demonstrated that lervatinib significantly prolonged	Lenvatinb Placebo	Figure 3. Kaplan-Meier Curve of OS in Patients With Baseline	215m 10 007 atm 1010.0420 02 17 right	Abrial fibrillation 5 (0.01) 0		
gression-free survival (PFS) in patients who had RR-DTC (hazard	Baseline Characteristic n = 100 n = 107	Lung Metastases > 1.0 cm	atten 19 344 - 1004 9409 97 15 attes	Lower respiratory tract infection 5 (0.01) 0		
[HR]: 0.21 [99% confidence interval (CI: 0.14-0.31]; P < 0.001).5	Age group, years, n (%)		allen H 060 0176/1428 86 35 1001	Putmonary embolism 5 (0.01) 2 (0.04)		
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ter OS has been observed in patients with RR-DTC who have	ECOG P8, n (%)	17 Ligranking P+1005				
	0 117 (58.8) 53 (49.5)		oN, t is the number of patients who entered the open-label investing phase and N is the overall number of patients	Malignant pieural effusion 4 (0.01) 1 (0.02)		
metastases.*	1 74 (37.2) 52 (48.6) 2 70.5 2 11.9	a month	In the placebo group. CI, confidence internal HII, heard ratio NE, not evaluable.	vkä min is the number of AE opinodes per patient-year. AE, advanse senet.		
post hoc analysis investigated the impact of lung metastases on	2 r (0.6) 2 (1.6) 3 1(0.5) 0		CI, confidence Hamai, HII, facilieri nelle, NE, not evaluates.	K, abera met.		
ival benefit in patients from SELECT who were treated with lervatinib.	Motastatic stas. n //J	2 M				
inal benefit in patents non occcor who were neared with envalue.	Modastatic stres, n (%) 1 51 (25.0) 28 (25.2)	° 11				
	2 66 (33,2) 26 (70,2)		Table 2. Time From Randomization to Optional Open-label Phase of	CONCLUSIONS		
	2 66 (312) 37 (34.6) 3 53 (26.6) 28 (26.7)		Lerivatinib Treatment by Baseline Lung Metastases Size			
METHODS	2 4 29 (14.0) 14 (13.1)	0	Standard	I Due to the RECIST v1.1 ortigita limit for measurable tumors (> 1.0 orti) and		
INETTIODO	Patients with other metastases, n (%) 174 (87.4) 95 (93.8)	**************************************	Subgroup n Median (days) Mean (days) Deviation	the small number of patients with lung metastases < 1.0 cm, this post hoc		
Desian	Lymph node metastases, n (%) 103 (51.8) 51 (47.7)		2 1.0 cm 96 134 210 171.48	analysis was limited to patients with lung metastases > 1.0 cm.		
	Bone motastases, n (%) 74 (07.2) 34 (01.8)	Time (Manda)		In the overall population of patients with any size of lung metastases,		
CT was a phase 3, randomized, double-blind, placebo-controlled	Number of prior VEGF/NEGFR-targeted	LAND SERVICED CONTRACTORS CONTRACTORS AND A A A A A A A A A A A A A A A A A A	2 1.5 cm 75 124 193 163.12	a longer median CS was observed for lenvisitnib treatment versus placebo, but the difference was only marginally significant.		
national study of lervatinib in patients with RR-DTC (Figure 1).	Therapies, n (%)	Res 171118 8 1 1 1 8 1 8 1 8 1 8 1 8 1 8 1	2 20 cm 53 119 171 129.86	but the difference was only marginally significant.		
	0 155 (77.9) 87 (91.3)			In contrast, in patients who had jung metastases of a 1.0 cm, OS and PFS		
ure 1. SELECT Design*	1 44 (22.1) 20 (18.7)	CI, confidence internal; HE, hazand natio; NE, not evaluable; CS, overall survival	Multivariate analysis revealed that lervatinits significantly prolonged	were significantly prolonged with lenvalinib versus placebo, including for		
are noticed of brough	Histology, n (%)		OS in patients with lung metastases ≥ 1.0 cm after adjustment for	caterits who had crossed over from clacebo to lenvelinib.		
	Papillary theroid cancer 127 (08.8) 75 (70.1)		baseline characteristics: bone and lymph-node metastases did not	 Lervelinb treatment resulted in longer OS and PFS in patients who had lung 		
Global randomized, double-blind, phase 3 trial	Folikular thyroid cancer 62 (31.2) 32 (29.9)	Figure 4, Kaplan-Meier Curve of PFS in Patients With Baseline	impact OS (Table 3).	 Lerivating dearners resulted in longer US and H-S in patents who had long metastasias of 10-20 cm. a 1.5 cm. and a 2.0 cm. 		
	5000 PS, Eastern Cooperative Oncology Group performance status; VSGF(R), vascular endothelial growth factor (receptor)	Lung Metastases ≥ 1.0 cm				
Leavebild			The hazard for OS was lower in patients who had lower ECOG PS	Early initiation of lematinitio treatment may be beneficial for patients who		
	The overall population did not demonstrate a significant difference in OS		scores (0 vs ≥ 1) at baseline (P < 0.0001) and in patients who were aged	have RR-DTC with lung metastases > 1.0 cm.		
13 Yours old + Canyyeptic 24-ng duty End Poline	between lervatinib and placebo (HR: 0.87; 95% CI: 0.66-1.15; P = 0.317) 10 Biolect/W1, norths \$15(0) (c) (c) (c) (c) (c) (c) (c) (c) (c) (c)	≤ 65 years (P = 0.0243) (Table 3).	 The majority of patients in the placebo arm (89%) crossed over to 		
synesion within Ingian (Curson, 7	because over 80% of patients in the placebo arm had crossed over to			krivalinib at an average of 210 days after randomization.		
Note 13 months North America, and America	receive lervatinib (cutoff date: September 1, 2016).	64 HE (00 C2	Table 3. Multivariate Analysis of OS in Patients With Baseline	 Of note, this study enrolled patients with RR-OTO who had 		
	In patients with any size of lung metastases, no significant difference	07 lag mit Bet Publikt	Lung Metastases ≥ 1.0 cm	experienced tumor progression within the previous 13 months.		
ACOTA PROVIDENT A COR		Eul to Strange		adversion of the burgle state of the burgles of the state		
Corp. programin + 08	in OS was observed between lervatinib and placebo treatment groups		Parameter P-Value HR 95% CI			
aprelis doese Tagend by REDST v1.1 - Subay	(HR: 0.76; 95% CI: 0.57-1.01; P = 0.0549) (Figure 2).	1 m m m m m m m m m m m m m m m m m m m	Treatment group (ienvatinit) vs placebol 0.0033 0.632 0.455-0.858	References Media J di di M / Gener 200 (10 MBA7) A Threat Carterine XCD Solidana Merchanis remain		
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Plants Plants	Figure 2: Kaplan-Meier Curve of OS in Patients With Baseline	E		Lamine* demained: presenting internation(Loberts/organited and All Deal 2015 (2016):466 Loberts MM & all Carport 2017 (2016):5694		
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			Hard M. Later December Decise State entering data 18 heard alls Discutions interi-	ACHTOWNEOUTHETES The study was facility of Dial Inc., Neutod Fluie, NJ, USA, and Marck Starp & Colors Cop., a subsidiary of Warck & Co., Inc., Tableted NJ, USA.		
uation Criteria In Solid Turnors version 1.1 (RECIST v1.1).	11.		ECOS/HJ, Eastern Cooperative Drocking Group performance status; HII, hauard ratio; CI, confidence internel; CS, cound survive; VEGE, vascular endotholial growth factor.	Medical-writing and editorial suggest and provided by Jensite Parry, PlannC, of Oxford Phermalianesis, Navforn, PA, USA, This suggests has been by liase for, Woodshif Lake, NJ, USA, and Wend Share & Oxford Cost, a subsetter of Merick & Go, Inc.		
Inly a small number of patients (n = 27 in the lervatinib arm and		OS and PFS were significantly prolonged in patients with lung		This support wile Randon by Enail Inc., Weskeld Lake, NJ, USA, and Wordt Sharp & Detroise Corp., a subsidiary of Merck & Co., Inc. Earthroph. NJ, USA.		
= 17 in the placebo arm) had lung metastases < 1.0 cm.		metastases of ≥ 1.5 cm. ≥ 2.0 cm. and 1.0-2.0 cm for lervatinib	To assess whether delayed initiation of lervatinib treatment in the placebo	Commendation authors D. Match. Many methanolised wat on its		
	<i>u</i> -	compared with placebo (Figure 5)	arm demonstrated an increase in the number of serious adverse events.	Convegending safeet D. Malob Tahara mabhanalised no: gr.gr Closes/Trols was identifier NCT1000152		
lyses were also performed for lung metastases of ≥ 1.5 cm,			safety data for the lervatinib and placebo arms are shown in Table 4.			
10 cm, and 1.0-2.0 cm to further evaluate efficacy in relation to size	Time (double)	In both lervatinib and placebo, median OS was shorter in patients who	salety data for the lenvatino and placedo arms are shown in Table 4.	Poster presented at the: European Society for Medical Oncology (ESMO) meeting: September 27 to October 1, 2019; September 27 to October 20 to Octobe		
ung metastases.	Lanating and the second s	had larger lung metastases (Figure 5).	The overall number of reported serious treatment-emergent adverse	Oncology (ESMO) meeting: September 27 to October 1, 2019; SST 1944 Barbelona. Spain		
	Rado DISTRICT DI SI	The time from randomization to cross-over to open-label lenvatinib for	events was higher in the lervatinib arm compared with the placebo arm	A#462		
afety and efficacy outcomes by lung metastases group were generated.	CI, confidence internal, HPI, haparti ratio, CG, ownall survival.		(62.8% vs 26.2%).	Copies of this poster obtained through GR (Saich Response) and/or test key codes are for periodic are only and that not be reproduced without writing or the authors.		
		patients in the placebo arm is reported in Table 2.	(02.079 ¥3.20.276).	perioral use only and may not be reproduced without within permission of the authors.		



European Journal of Cancer Volume 147, April 2021, Pages 51-57

EJC 2021

Original Research

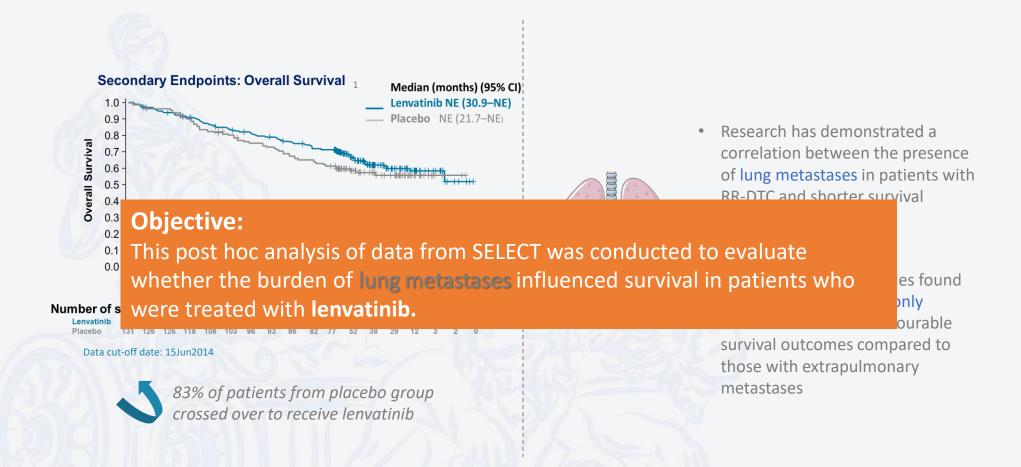
Impact of lung metastases on overall survival in the phase 3 SELECT study of lenvatinib in patients with radioiodine-refractory differentiated thyroid cancer

Makoto Tahara ^a \approx \boxtimes , Naomi Kiyota ^b, Ana O. Hoff^c, Corin Badiu ^d, Taofeek K. Owonikoko ^e, Corina E. Dutcus ^f, Takuya Suzuki ^g, Min Ren ^f, Lori J. Wirth ^h



Rationale & Objective





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



Methodology



<2.0 cm

Patients with any lung metastases (target/non-target lesions) that could be classified as measurable based on the RECIST v1.1 criterion Post-hor SELECT Post-hor Post-hor</td

- 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.

STATE Characteristics



Category	Any Lung Metastases (tar	get/non-target lesions)		
	Lenvatinib $N = 226$	Placebo N $= 124$		o n =
Age group, n (%)				
\leq 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-targ	geted 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).





Lung Metastases Size I	.envatinib, n	Placebo,	nª	HR (95% CI)	Median Survival Lenvatinib	Median Survival Placebo	<i>P-</i> Value					
Overall Surviv	al							Т	ransition to	o open-	label lenv	<i>v</i> atinib
Any lung mets (target/non-targe lesions)	226 t	124		0.76 (0.57–1.01)	43.2	34.0	0.0549	n		Mean (days)	Standard Deviation	. 5
≥ 1.0 cm	199	107		0.63 (0.47-0.85)	44.7	33.1	0.0025	9	5 134	210	171.48	89%
≥ 1.5 cm	150	84	- _	0.63 (0.45-0.89)	44.1	22.3	0.0082	7		193	163.12	90%
≥ 2.0 cm	94	58	•	0.65 (0.44-0.98)	34.7	19.3	0.0383	5		171	129.86	91%
< 2.0 cm	105	49		0.63 (0.40-0.99)	49.2	38.6	0.0438	4	2 185	260	203.70	85%
Progression-f	ree Survival	Ь										
Any lung mets (target/non-targe lesions)	226 t	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					
		F	avors lenvatinib	Favors placebo								
		0	0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9	1 1.1 1.2 1.3 1.4 1.5								
			HR and	1 95% CI								

^aThe 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 \geq 1.0 cm, n=95; \geq 1.5 cm, n=76; \geq 2.0 cm, n=53, and <2.0 cm, n=42.

^bProgression-free survival was assessed by investigator review per RECIST version 1.1.

Efficacy in patients with lung metastases ≥1cm

"Tratamiento médico del cáncer en el año 2022"



89% cross-over at 210 days







Lung Metastases Size Ler	nvatinib, n	Placebo, nª			HR (95% CI)	Median Survival Lenvatinib	Median Survival Placebo	<i>P-</i> Value	Delaying initiation of lenvatinib treatment may
Overall Survival									negatively impact a
Any lung mets (target/non-target lesions)	226	124		•	0.76 (0.57–1.01)	43.2	34.0	0.0549	patient's prognosis.
≥ 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	e Survival ^ı	2							
Any lung mets (target/non-target lesions)	226	124			0.20 (0.15–0.27)	18.7	3.6	< 0.0001	Treatment effect of lenvatinib may be greater when lenvatinib is initiated in patients with a lower burden of diseas
≥ 1.0 cm	199	107	—		0.20 (0.15-0.28)	20.2	3.7	< 0.0001	rather than delaying initiation until a
≥ 1.5 cm	150	84 -	- -		0.20 (0.14-0.29)	18.7	3.5	< 0.0001	higher burden of disease is present
≥ 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	

HR and 95% CI

^aThe 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 \geq 1.0 cm, n=95; \geq 1.5 cm, n=76; \geq 2.0 cm, n=53, and <2.0 cm, n=42.

^bProgression-free survival was assessed by investigator review per RECIST version 1.1.



Multivariate analysis: Factors impacting OS

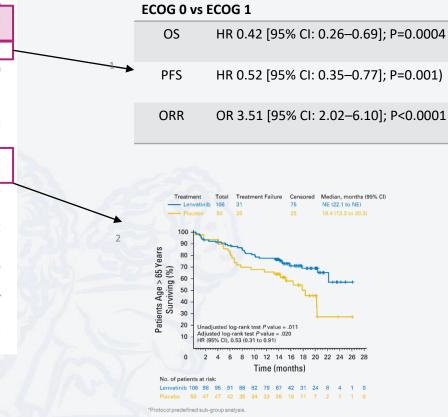


Table 3

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	0.4172	0.831	0.530 - 1.301
versus other)			
Number of previous VEGF-	0.7065	0.930	0.636-1.358
targeted therapies (0 versus 1)			
Age group (≤ 65 years versus > 65	0.0243	0.703	0.518 - 0.955
years)			
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	0.1065	1.286	0.948 - 1.745
(yes versus no)			
Histology (papillary versus	0.0991	1.336	0.947 - 1.884
follicular)			

Lenvatinib treatment significantly prolonged OS after adjustment for baseline characteristics



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

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 • D	Any Lung Mets (target/nontarget) OSE Intensity	Lung Mets of ≥1.0 cm	≥1.5 cm	≥2.0 cm	<2.0 cm
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 \geq 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	Lenvatinib	Placebo
(AE rate ^b)	(n = 199; total)	(n = 107; total)
	duration = 375.8 patient-years)	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.

Tahara Final remarks



"Tratamiento médico del cáncer en el año 2022"



- 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.



Conclusions



- In patients with symptomatic disease, MKI therapy must be started with no delay regardless of radiological evidence of disease progression¹
- 2. Waiting for high tumor burden or for the onset of symptoms can compromise patient survival¹
- 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 cm⁵

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





