BiblioGETNE

Nº12 - marzo 2024

ÍNDICE:

GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos

Estimados compañeros y compañeras,

en la newsletter de este mes os enviamos dos presentaciones destacadas del último congreso europeo ENETS 2024, celebrado en Viena los pasados 13, 14 y 15 de marzo.

Pudimos ver una actualización de la cohorte de pacientes con carcinoma medular de tiroides del estudio DUTHY de GETNE. La combinación de *durvalumab* y *tremelimumab* presentó una PFS a 6 meses del 38% con una tasa de respuestas del 10%.

Por otro lado, vimos nuevos datos del estudio NETTER-2, esta vez la comparación de la revisión central y local (22 vs 8 meses en ambos casos), con un 82% de pacientes que presentaron cualquier grado de reducción en el brazo de PRRT frente al 34% del brazo octreotide doble dosis.

Esperamos que estas diapositivas sean de vuestro interés y os resulten de utilidad. Si queréis hacer un repaso de todas las novedades de ENETS 2024, **os invitamos a la reunión online post-ENETS el próximo 22 de abril.**

ACCEDE AL

PROGRAMA II JORNADA POST-ENETS

Más información e inscripciones en:
getne@getne.org

NETTER-2

[^{177}Lu]Lu-DOTA-TATE in Newly Diagnosed Patients with Advanced Grade 2 and Grade 3, Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors: Primary Analysis of the Phase 3 Randomized NETTER-2 Study

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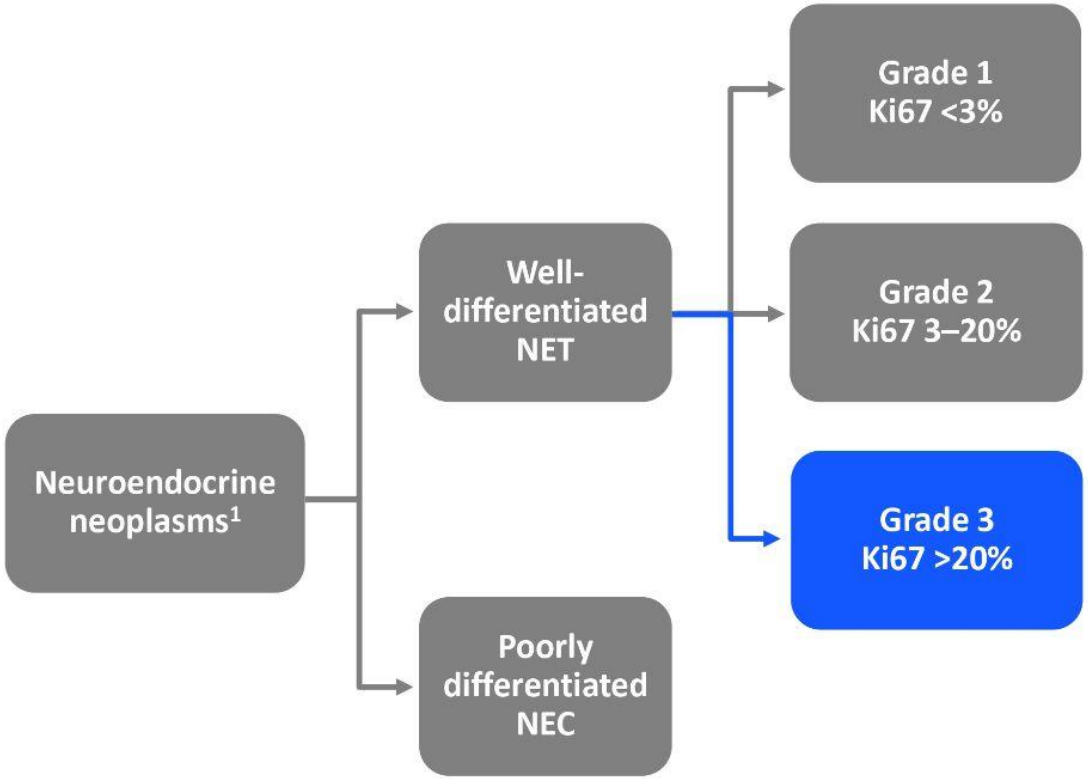
Standard of care is undefined for newly diagnosed advanced high Grade 2 and 3 GEP-NETs

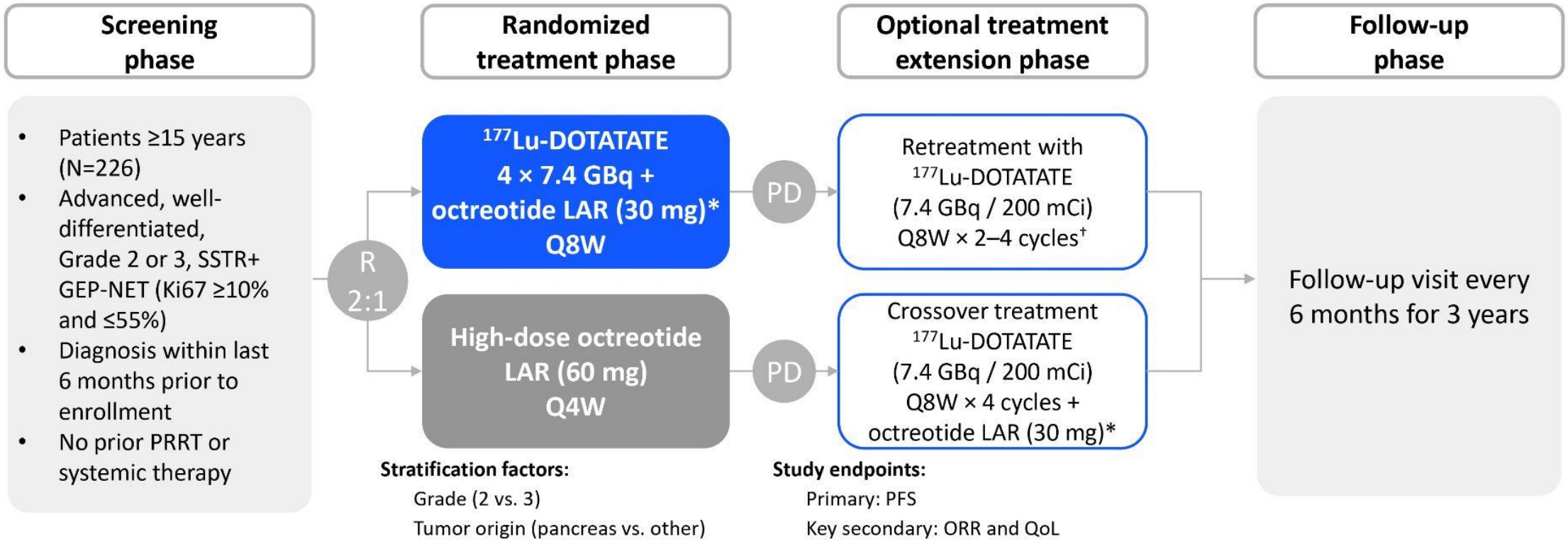


- No randomized studies have investigated the most appropriate first-line treatment strategy for advanced high Grade 2 and 3 GEP-NETs[2,3]

GEP-NET, gastroenteropancreatic neuroendocrine tumor; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

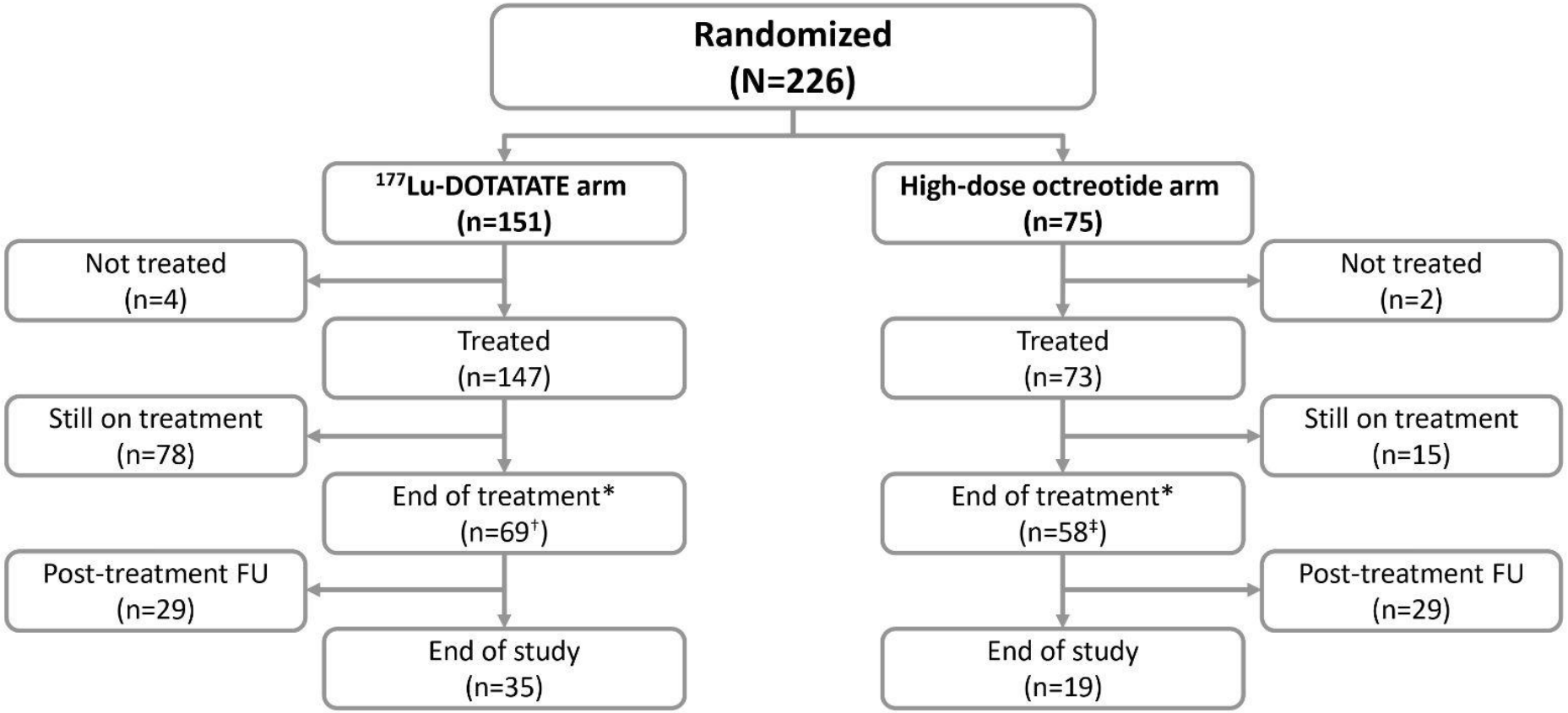
1. Nagtegaal ID, et al. Histopathology 2020;76:182–88; 2. Del Rivero J, et al. J Clin Oncol 2023;41:5049–67; 3. Eads JR, et al. Endocr Relat Cancer 2023;30:e220206.

NETTER-2 (NCT03972488) is the first randomized trial to evaluate radioligand therapy in a first-line metastatic setting for any solid tumor



*Q8W during ^{177}Lu-DOTATATE treatment and then Q4W; †Octreotide LAR in retreatment phase is at the investigator's discretion.
GEP-NET, gastroenteropancreatic neuroendocrine tumor; LAR, long-acting repeatable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; Q#W, every # weeks; QoL, quality of life; R, randomization; SSTR, somatostatin receptor.

Patients (N=226) were randomized in a 2:1 ratio to the ^{177}Lu-DOTATATE arm or high-dose octreotide arm



*End of treatment occurred upon disease progression or treatment discontinuation for other reasons; †Includes 5 patients still on retreatment with ^{177}Lu-DOTATATE; ‡Includes 10 patients still on crossover treatment with ^{177}Lu-DOTATATE.
FU, follow-up.

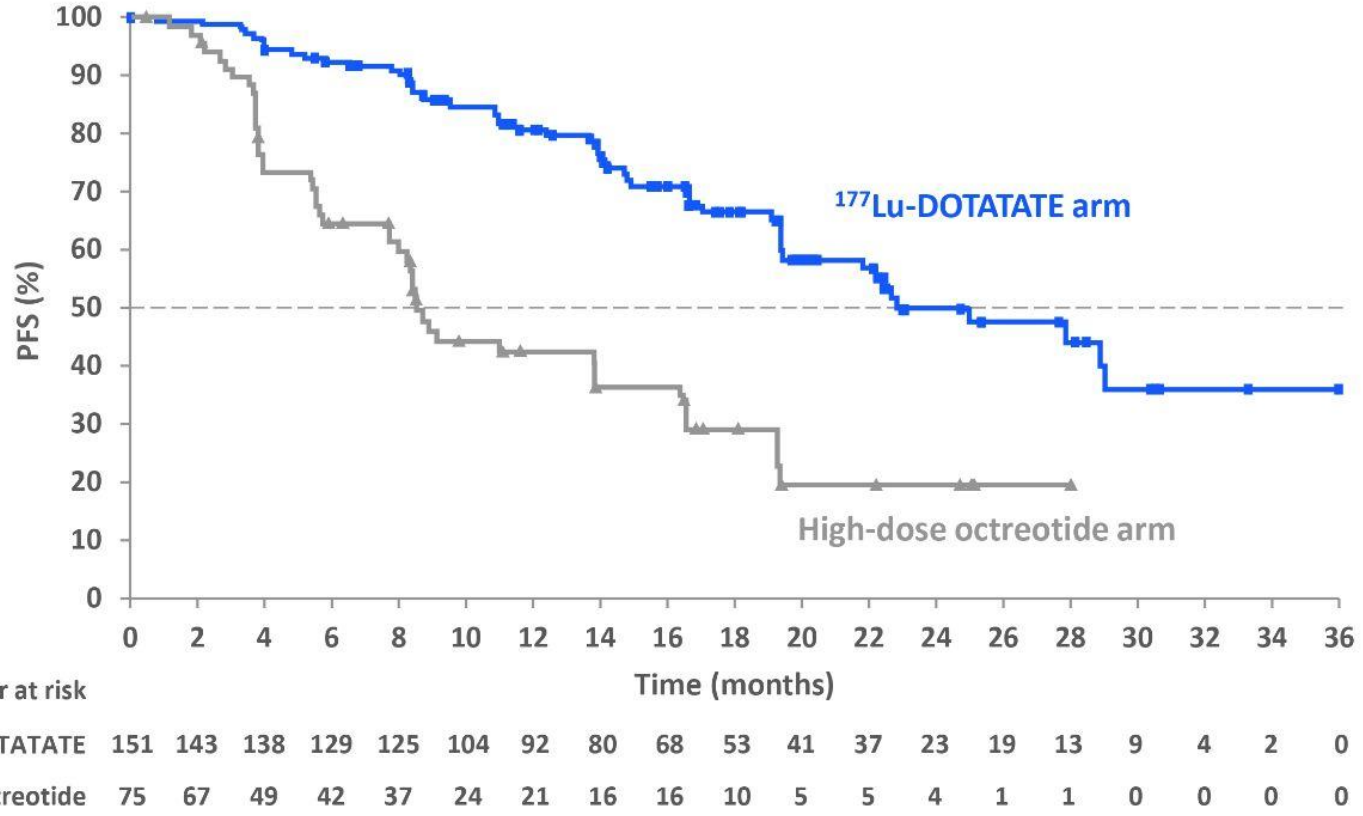
Treatment arms were well balanced

Patient characteristics	^{177}Lu-DOTATATE arm (n=151)	High-dose octreotide arm (n=75)
Age median (range), years	61 (23–88)	60 (34–82)
Sex, n (%)		
Male	81 (54)	40 (53)
Female	70 (46)	35 (47)
Race, n (%)		
White	115 (76)	50 (67)
Asian	23 (15)	11 (15)
Other	13 (9)	14 (19)
Karnofsky PS at BL, n (%)		
60	0	1 (1)
70–80	28 (19)	10 (13)
90–100	123 (81)	64 (85)

Tumor characteristics	^{177}Lu-DOTATATE arm (n=151)	High-dose octreotide arm (n=75)
Primary tumor site, n (%)		
Pancreas	82 (54)	41 (55)
Small intestine	45 (30)	21 (28)
Other	24 (16)	13 (17)
Site of metastases, n (%)		
Bone	37 (25)	18 (24)
Liver	134 (89)	69 (92)
Lymph nodes*	101 (67)	34 (45)
Peritoneum	26 (17)	9 (12)
NET grade at diagnosis, n (%)		
Grade 2	99 (66)	48 (64)
Grade 3	52 (34)	27 (36)
Ki67 index median (range), %	17 (10–50)	16 (10–50)

*Distant plus regional combined.
BL, baseline; NET, neuroendocrine tumor; PS, performance status.

^{177}Lu-DOTATATE demonstrated significant improvement in the primary PFS endpoint (central review)

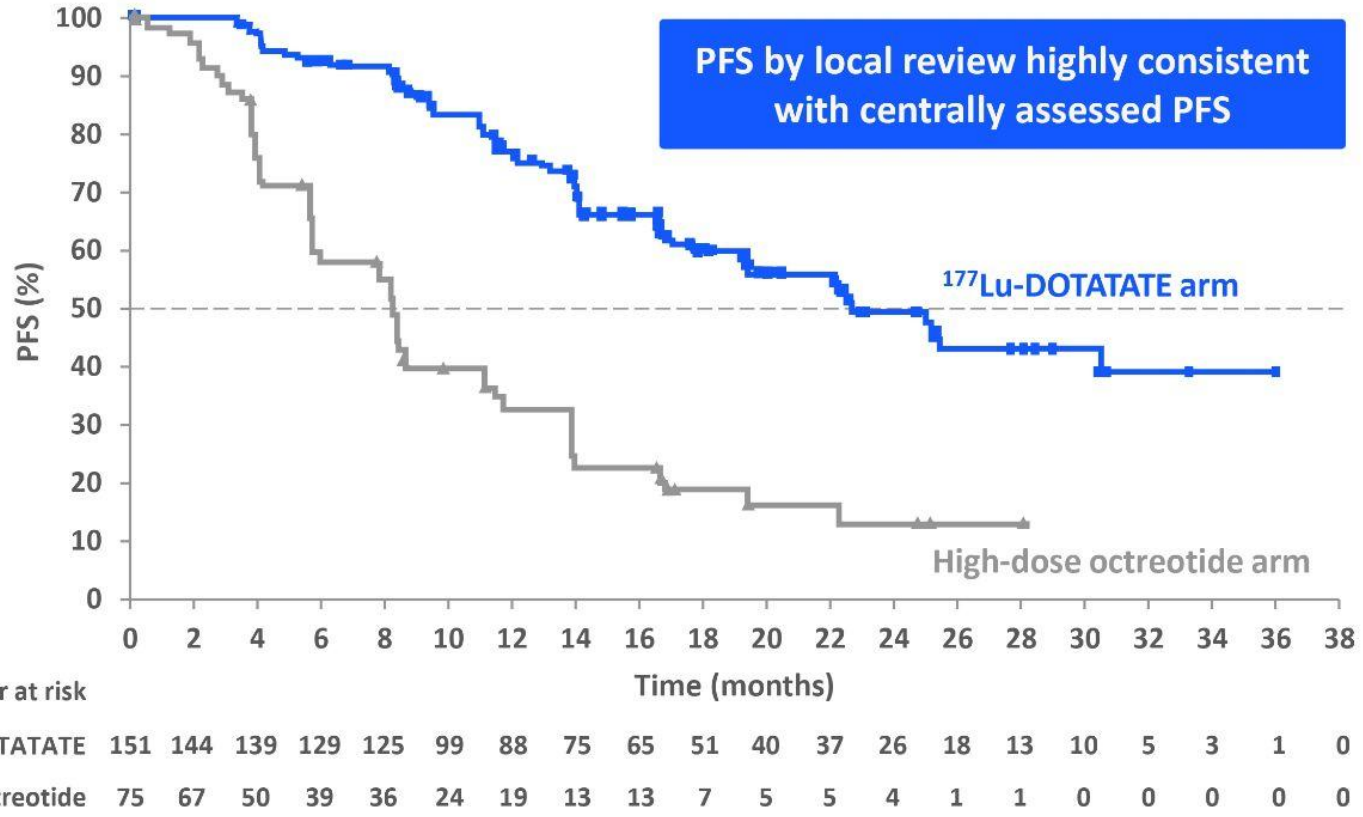


	^{177}Lu-DOTATATE arm (n=151)	High-dose octreotide arm (n=75)
PFS median, months (95% CI)	22.8 (19.4, NE)	8.5 (7.7, 13.8)
Stratified HR (95% CI)	0.276 (0.182, 0.418)	
p-value	<0.0001	
Number of events, n (%)	55 (36)	46 (61)
Progression	47 (31)	41 (55)
Death	8 (5)	5 (7)

72% reduction in the risk of disease progression or death in the ^{177}Lu-DOTATATE arm versus the high-dose octreotide arm

PFS assessed according to RECIST 1.1.
CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

^{177}Lu-DOTATATE showed significant improvement in the primary PFS endpoint (local review)

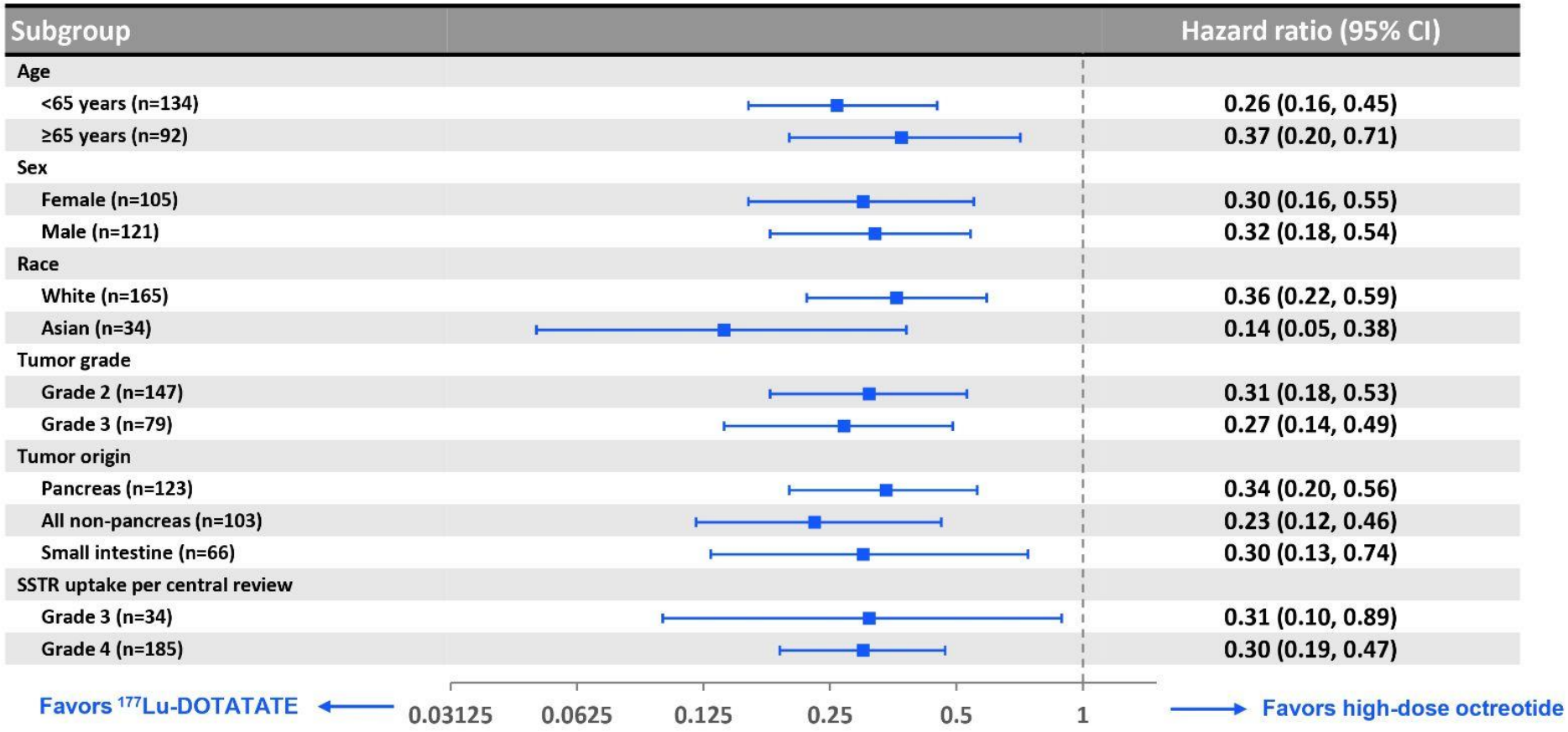


	^{177}Lu-DOTATATE arm (n=151)	High-dose octreotide arm (n=75)
PFS median, months (95% CI)	22.6 (17.7, NE)	8.2 (5.6, 11.1)
Stratified HR (95% CI)	0.234 (0.158, 0.347)	
p-value	<0.0001 (nominal)	
Number of events, n (%)	59 (39)	55 (73)
Progression	51 (34)	50 (67)
Death	8 (5)	5 (7)

77% reduction in the risk of disease progression or death in the ^{177}Lu-DOTATATE arm versus the high-dose octreotide arm

PFS assessed according to RECIST 1.1.
CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

PFS benefit was consistent across prespecified subgroups (central review)



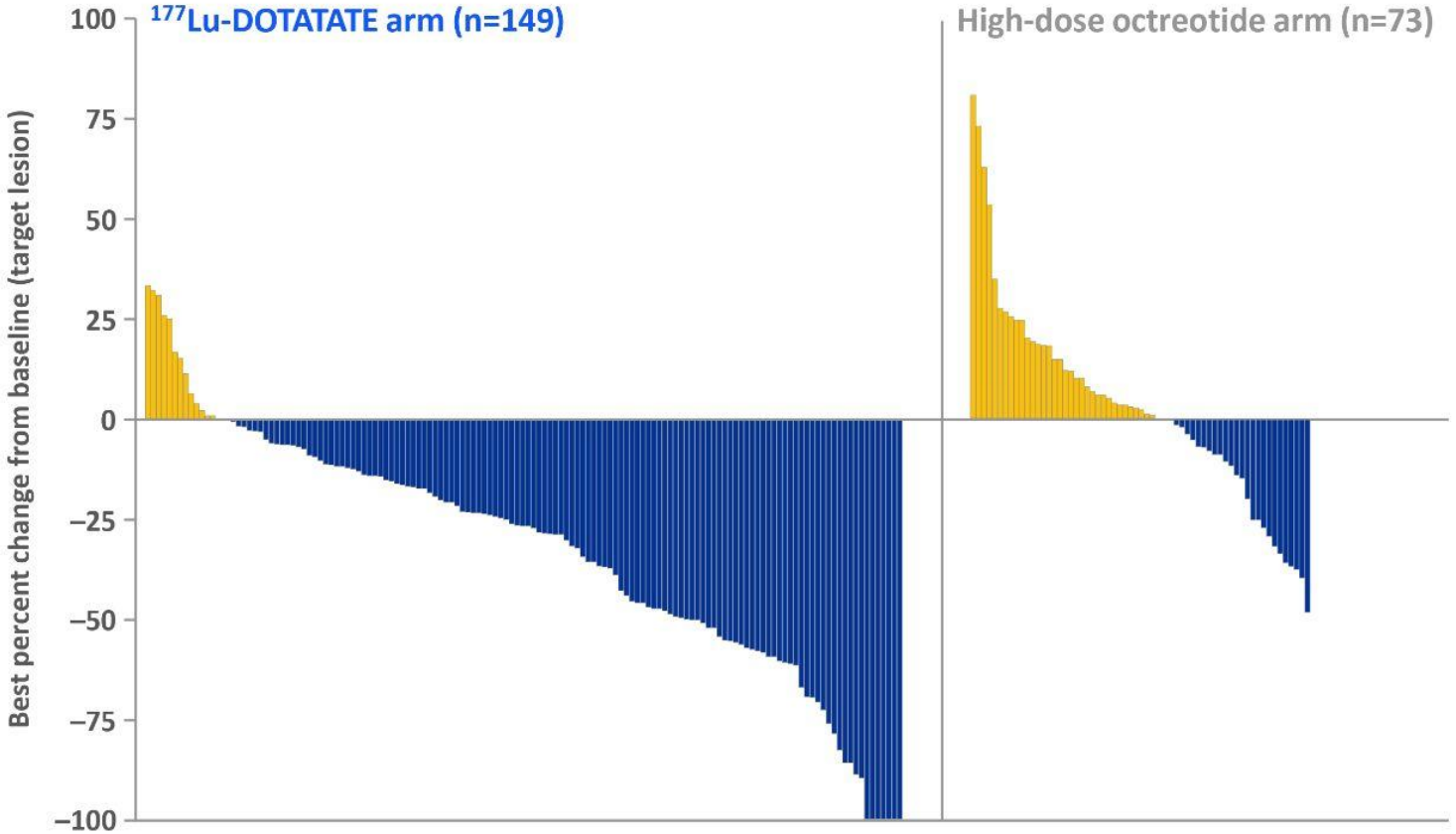
CI, confidence interval; PFS, progression-free survival; SSTR, somatostatin receptor.

ORR was significantly higher for ^{177}Lu-DOTATATE

	Central review		Local review	
	^{177}Lu-DOTATATE arm (n=151)	High-dose octreotide arm (n=75)	^{177}Lu-DOTATATE arm (n=151)	High dose octreotide arm (n=75)
Best overall response, n (%)				
CR	8 (5.3)	0	2 (1.3)	1 (1.3)
PR	57 (37.7)	7 (9.3)	68 (45.0)	7 (9.3)
SD	72 (47.7)	42 (56.0)	65 (43.0)	42 (56.0)
Non-CR / non-PD	0	1 (1.3)	0	0
PD	8 (5.3)	14 (18.7)	8 (5.3)	16 (21.3)
Unknown	6 (4.0)	11 (14.7)	8 (5.3)	9 (12.0)
ORR*, n (%)	65 (43.0)	7 (9.3)	70 (46.4)	8 (10.7)
95% CI	35.0, 51.3	3.8, 18.3	38.2, 54.6	4.7, 19.9
Stratified odds ratio (95% CI)	7.81 (3.32, 18.40)		7.22 (3.25, 16.05)	
p-value	<0.0001		<0.0001 (nominal)	
Responders, n	65	7	70	8
Duration of response, median (95% CI), months	23.3 (18.4, NE)	NE (2.3, NE)	19.9 (13.4, NE)	16.6 (2.3, NE)

*Key secondary endpoint: CR + PR (RECIST 1.1; confirmation of response was not required).
CI, confidence interval; CR, complete response; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Overall, 83% of patients receiving ^{177}Lu-DOTATATE had some degree of tumor shrinkage at primary analysis



	^{177}Lu-DOTATATE arm (n=149)	High-dose octreotide arm (n=73)
Decrease in best percent change from baseline	82.6%	34.2%
Increase / no change in best percent change from baseline	10.7%	50.7%
Percent change not available	5.4%	12.3%
Percent change contradicted by overall lesion response = progressive disease	1.3%	2.7%

Only patients with measurable disease at baseline included.

Safety was in line with the known profiles of ^{177}Lu-DOTATATE and octreotide LAR

Randomized treatment phase*	^{177}Lu-DOTATATE arm (n=147)	High-dose octreotide arm (n=73)
Any AE / AE related to treatment (all grades), n (%)	136 (92.5) / 101 (68.7)	69 (94.5) / 43 (58.9)
Any AE / AE related to treatment (Grade ≥3), n (%)	52 (35.4) / 23 (15.6)	20 (27.4) / 3 (4.1)
Most common all grade AEs (>20%), n %		
Nausea	40 (27.2)	13 (17.8)
Diarrhea		25 (34.2)
Abdominal pain		20 (27.4)
Most common Grade ≥3 AEs (>3%)		
Lymphocyte count decreased	8 (5.4)	0
GGT increased	7 (4.8)	2 (2.7)
Small intestinal obstruction	5 (3.4)	0
Abdominal pain	4 (2.7)	3 (4.1)
Secondary hematologic malignancies, n (%)	1 (0.7)	0

In the ^{177}Lu-DOTATATE arm, Grade ≥3 leukopenia (n=3), anemia (n=1), and thrombocytopenia (n=3) were observed

*Time from randomization up to the last randomized study treatment date + 30 days.
AE, adverse event; GGT, gamma-glutamyl transferase; LAR, long-acting repeatable.

Conclusions of the primary analysis

- ✓ **NETTER-2 is the first randomized trial to evaluate a radioligand therapy in the first-line metastatic setting in patients with well-differentiated Grade 2 and 3, SSTR+ GEP-NETs**
- ✓ NETTER-2 met its primary endpoint by reducing the risk of progression or death by 72%
  - Median PFS was significantly prolonged in the ^{177}Lu-DOTATATE arm (22.8 months) versus the control arm (8.5 months) (central review)
- ✓ PFS results per local review were highly consistent with centrally assessed PFS
- ✓ Improved response rates were observed with ^{177}Lu-DOTATATE
  - ORR (secondary endpoint) was significantly higher in the ^{177}Lu-DOTATATE arm (43.0%) versus the control arm (9.3%)
- ✓ Safety findings were consistent with the known safety profile for ^{177}Lu-DOTATATE. No new safety concerns emerged in this patient population
- ✓ **These data have clinical practice changing implications and support the use of radioligand therapy in the first-line setting for advanced, well-differentiated, Grade 2 and 3, SSTR+ GEP-NETs**

GEP-NET, gastroenteropancreatic neuroendocrine tumor; ORR, objective response rate; PFS, progression-free survival; SSTR, somatostatin receptor.

DUTHY TRIAL

GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos

Durvalumab Plus Tremelimumab for the Treatment of Patients With Progressive, Advanced Medullary Thyroid Carcinoma (MTC) - DUTHY (GETNE-T1812) Trial

Alejandro García-Álvarez [1], Javier Molina-Cerrillo, Beatriz Castelo, Maria Plana, Lara Iglesias, Alberto Carmona-Bayonas, Ricardo Yaya Tur, Sofia Ruiz, Neus Baste, Isabel Lorenzo-Lorenzo, Teresa Alonso-Gordoa, Jaume Capdevila [1]

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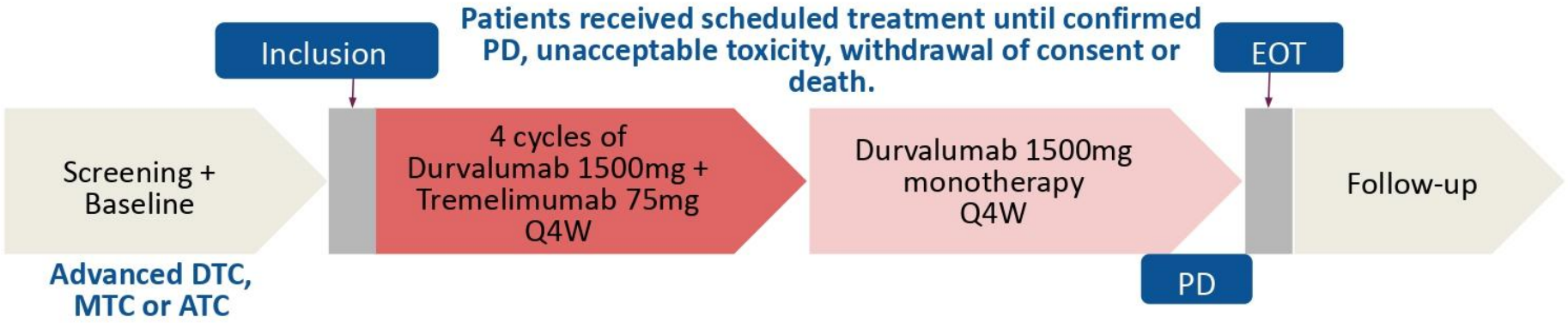
Background & study design

- Single targeting of PD-L1 has proven limited efficacy in advanced thyroid cancer patients [1].
- Dual targeting of PD-L1 and CTLA-4 was used in different cancer types [2,3] to overcome resistance.
- The DUTHY trial evaluated durvalumab plus tremelimumab efficacy and safety in advanced thyroid cancers.



1. Paz-Ares L, et al. The Lancet 394:1929–1939, 2019 // 2. Wolchok JD, et al. N Engl J Med 377:1345–1356, 2017 // 3. Motzer RJ, et al. N Engl J Med 378:1277–1290, 2018.

Objectives & endpoints

- **Primary outcome measure:**
  - 6-months progression-free survival (PFS) rate by RECIST 1.1

- **Secondary outcome measures:**
  - Overall response rate (ORR) by RECIST
  - Duration of response by RECIST 1.1
  - Median PFS according to RECIST.
  - Median overall survival (OS) time.
  - Safety profile of D+T in this patients.

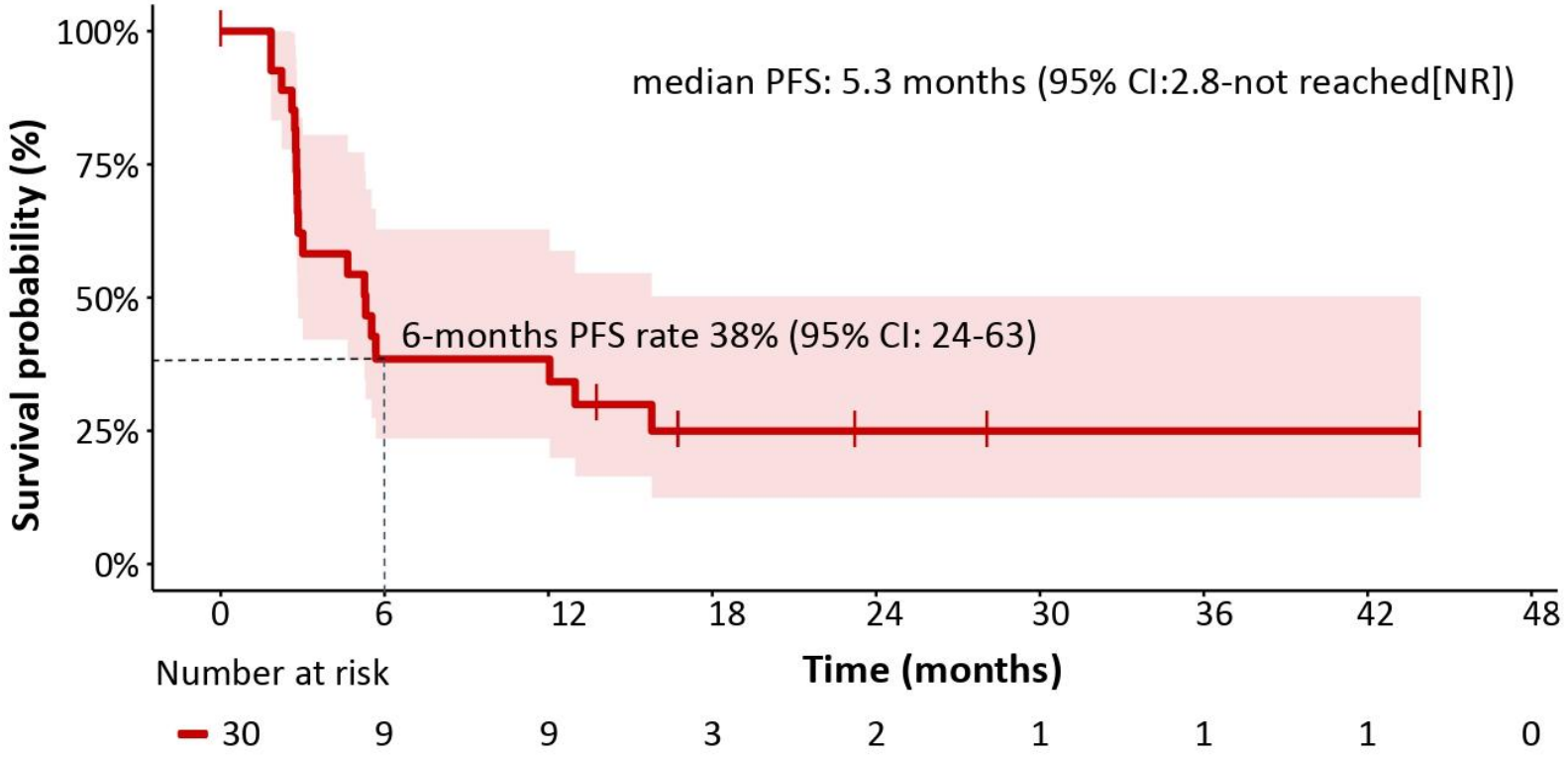
- Here we present data from the MTC cohort. The expected accrual in MTC cohort was 37 patients, using a Simon II design with H0 of 25% 6-m PFS rate and H1 of 45% (α=0.05, β=0.2).

Baseline characteristics

Characteristic	N=30
Median age (range), years	58 (32-76)
Gender; n (%)	
Male	20 (66.7)
Female	10 (33.3)
ECOG; n (%)	
0	13 (43.3)
1	17 (56.7)
M Stage; n (%)	
M0	21 (70.0)
M1	9 (30.0)
Metastasis locations; n (%)	
Lymphatic nodes	13 (36.1)
Liver	5 (13.9)
Bone	4 (11.1)
Lung	3 (8.3)
Other locations	6 (16.7)

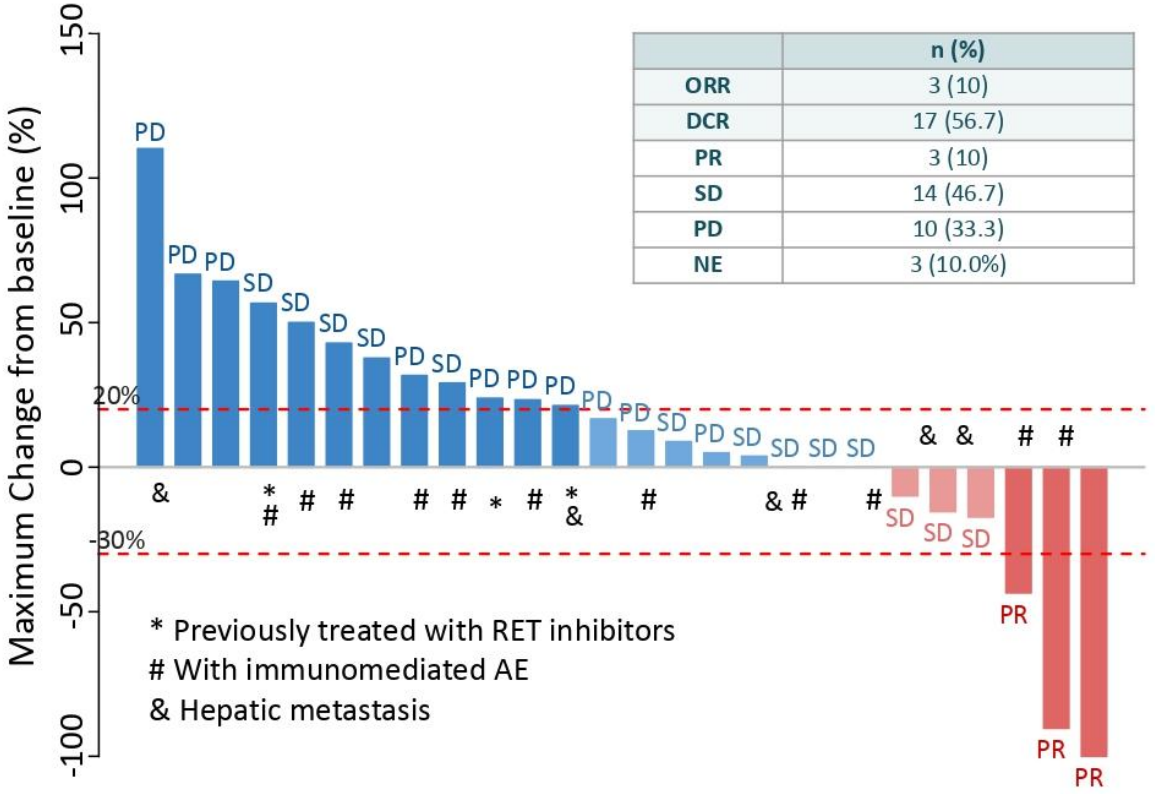
Characteristic	N=30
Number of previous treatments; n (%)	
1	15 (50.0)
≥2	8 (26.7)
≥3	7 (23.4)
Previous systemic treatments; n (%)	
Vandetanib	30 (100)
Cabozantinib	7 (23.3)
RET inhibitors	3 (10)
Chemotherapy	5 (16.7)

Efficacy: PFS (Primary Endpoint)

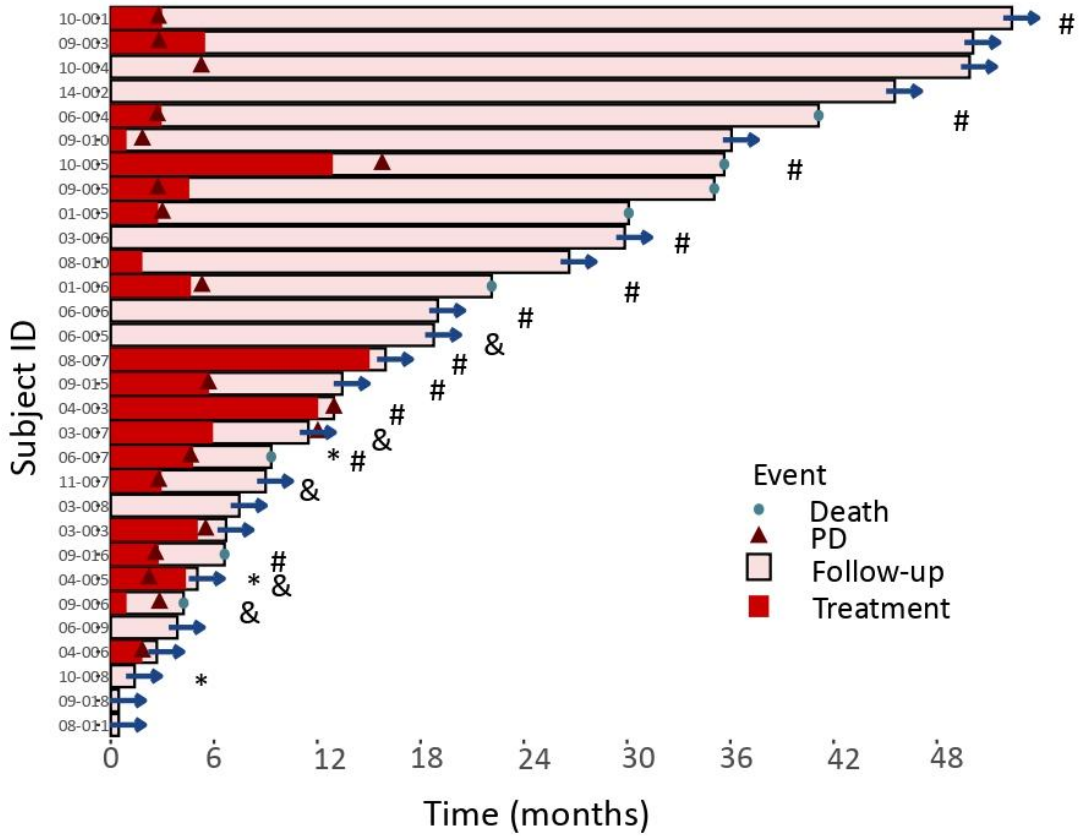


Median follow-up of 14.7 m (95% CI: 7.5-29.9)

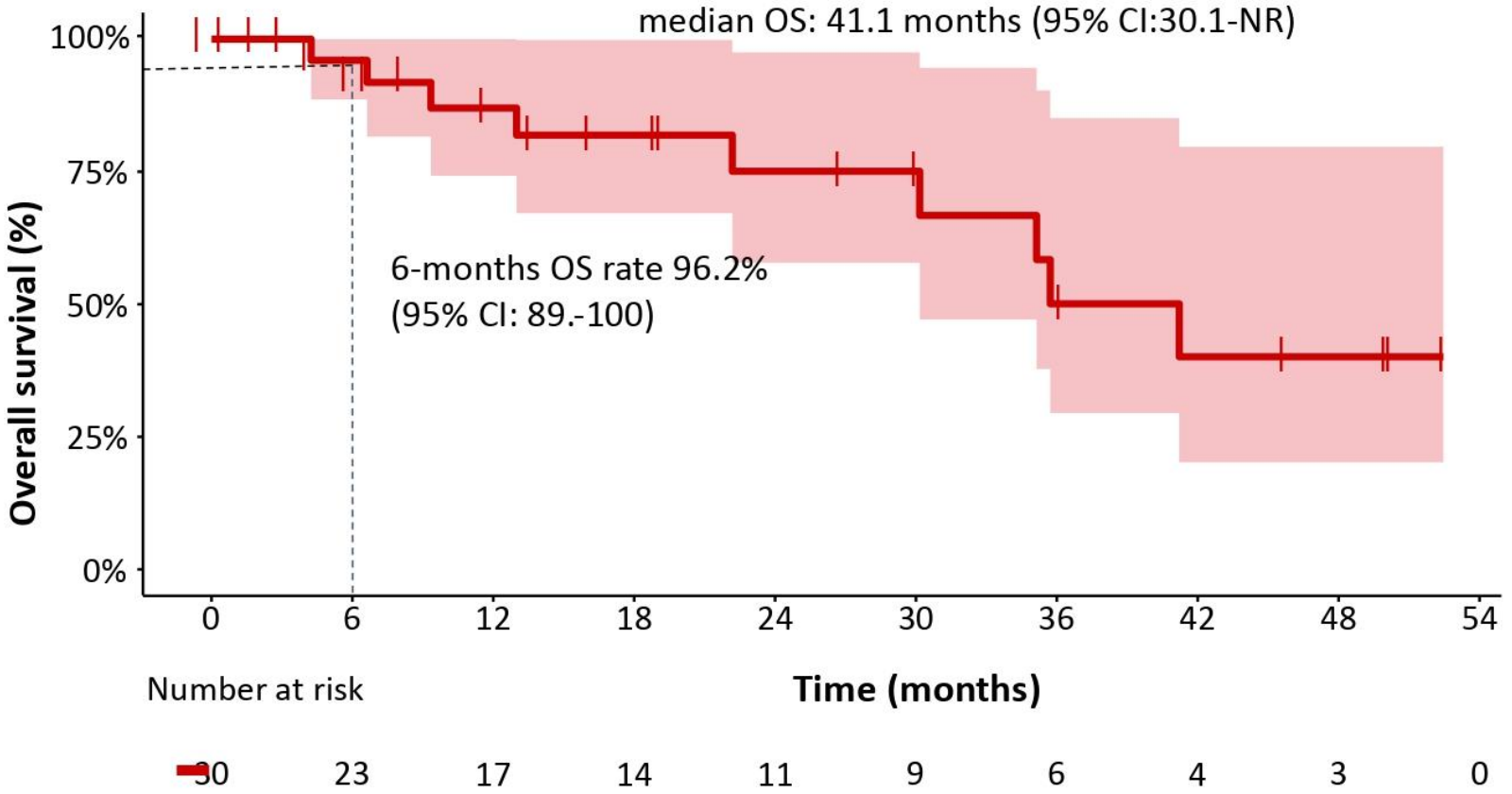
Efficacy: ORR



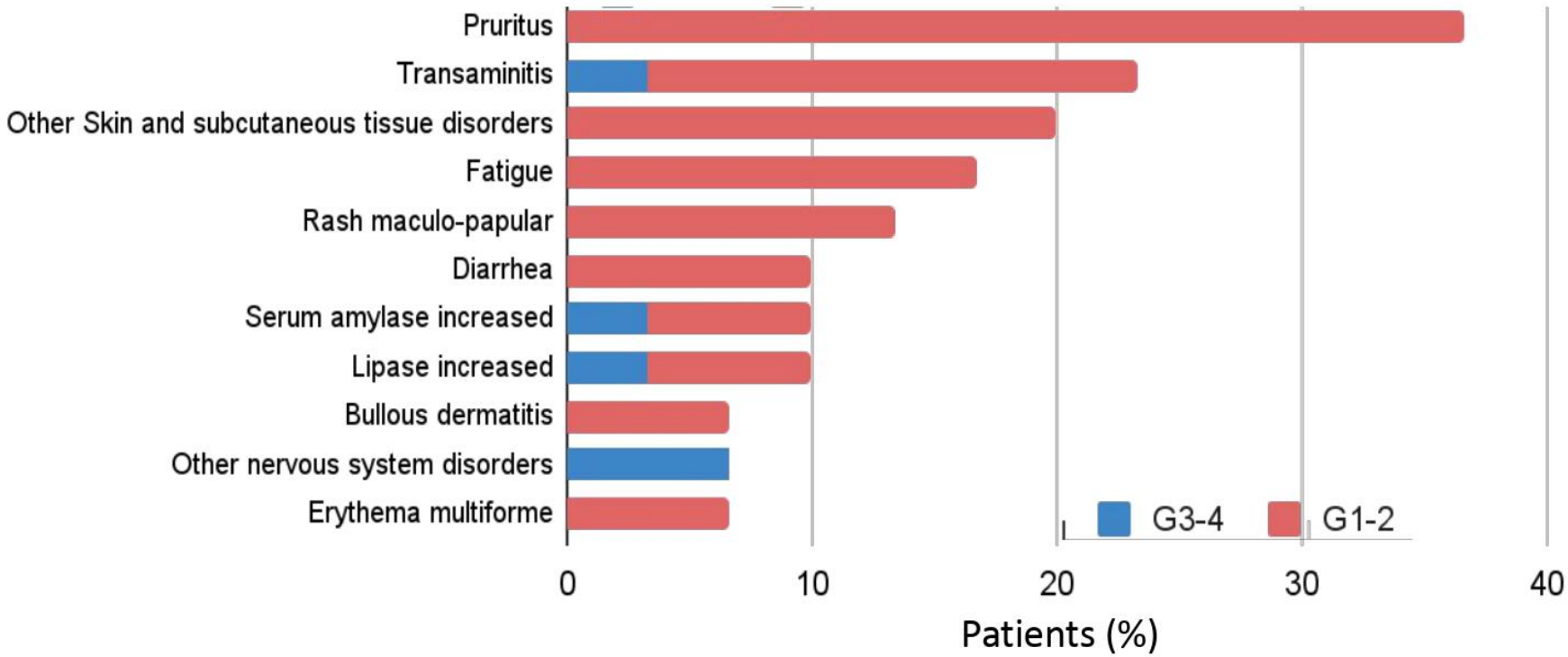
	n (%)
ORR	3 (10)
DCR	17 (56.7)
PR	3 (10)
SD	14 (46.7)
PD	10 (33.3)
NE	3 (10.0%)



Efficacy: OS


median OS: 41.1 months (95% CI:30.1-NR)
6-months OS rate 96.2%
(95% CI: 89.-100)
Overall survival (%)
100%
75%
50%
25%
0%
0
6
12
18
24
30
36
42
48
54
Time (months)
Number at risk
30
23
17
14
11
9
6
4
3
0

Safety



Treatment was discontinued in 73%, mainly due to progression (50%) and unacceptable toxicity (17%).
Grade ≥3 toxicities were reported in 5 (17%) patients, including 2 (7%) encephalitis.

Conclusions

- DUTHY is the 1st prospective study with immunotherapy in advanced MTC, showing tolerable toxicity and promising activity in heavily pretreated patients.

FUTURE PERSPECTIVES

- Exploratory objectives are ongoing with the aim to:
  - Evaluate the predictive value of baseline tumor and blood biomarkers and their association with efficacy endpoints.

Acknowledgement

Patients, their families, investigators, and study teams

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