16:05 - 17:05h	**MESA 1 | TUMORES NEUROENDOCRINOS AVANZADOS: LA CIRUGÍA LLEVADA AL LÍMITE** Moderadores: Dra. Ana Custodio - Oncología Médica. Hospital Universitario La Paz, Madrid Dra. Virginia Pubul - Medicina Nuclear. Complexo Hospitalario Universitario de Santiago de Compostela
16:05 - 16:25h	**Neoadyuvancia en los TNE-GEP: opciones y realidades** Dra. Paula Jiménez Fonseca - Oncología Médica. Hospital Universitario Central de Asturias, Oviedo
16:25 - 16:45h	**Cirugía de debulking para potenciar los tratamientos sistémicos** Dra. Elena Martín - Cirugía. Hospital Universitario de La Princesa, Madrid
16:45 - 17:05h	**Trasplante hepático en TNE: indicaciones y resultados** Dra. Andrea Boscà-Robledo - Cirugía Hepatobiliopancreática y Trasplante. Hospital Universitari i Politècnic La Fe, Valencia
17:05 - 17:25h	*Pausa café*

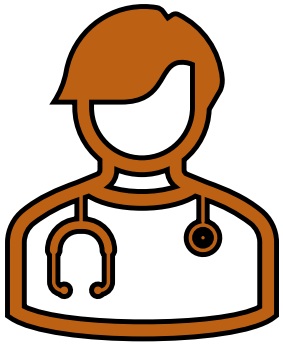
ÍNDICE: Tratamiento neoadyuvante en TNE-GEP IV

INTRODUCCIÓN

TERAPIA NEOADYUVANTE

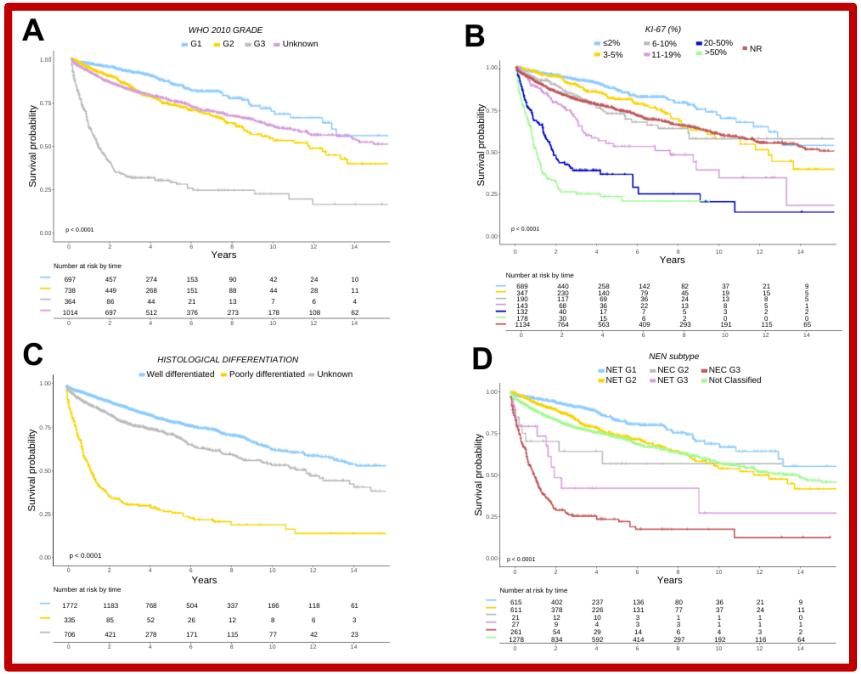
RESECCIÓN R0

SELECCIÓN
Tumor
Paciente



SELECCIÓN
Tratamiento
↑↑↑ ORR

Selección de tumores para tratamiento neoadyuvante



Histología:
TNE G1-2
Bien diferenciados

Histología:
CNE G3
Indiferenciados

Nuñez-Valdovinos B, Carmona-Bayonas A, Jimenez-Fonseca P, et al. Oncologist. 2018;23(4):422-32

Selección de tumores para tratamiento neoadyuvante

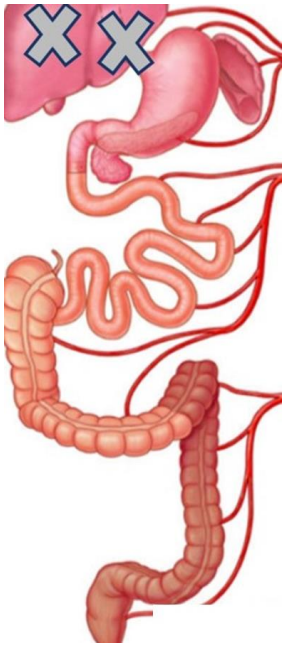
	N/n	Median	Overall survival (years) HR (95% CI)	% at 5 years (95% CI)	
Primary tumor site					
Pancreas	975/271	12.0	Ref.	70.2	66.6- 73.7
Esophagus	14/9	0.9	6.02 (3.09- 11.74)	29.2	3.32- 55.0
Stomach	298/78	14.3	1.11 (0.86- 1.43)	70.8	64.5- 77.0
Duodenum	104/20	15.8	0.64 (0.41- 1.02)	86.6	79.1- 94.0
Jejunum-ileum	518/109	12.9	0.71 (0.56- 0.88)	83.4	79.4- 87.3
Appendix	277/27	NC	0.32 (0.21- 0.47)	90.5	85.9- 95.0
Colon	153/57	11.9	1.58 (1.19- 2.11)	60.5	51.4- 69.5
Rectum	173/51	10.8	1.26 (0.93- 1.70)	63.0	53.9- 72.0
Enteric NOS	22/7	2.0	2.91 (1.37- 6.19)	50.0	16.8- 83.1
Hepatobiliary	34/15	5.5	2.19 (1.30- 3.68)	53.6	34.7- 72.4
Tumor of unknown primary origin	245/113	4.3	2.29 (1.84- 2.86)	47.3	39.5-55.2

Localización:

- Páncreas
- Intestino delgado
- Estómago
- Colorrectal

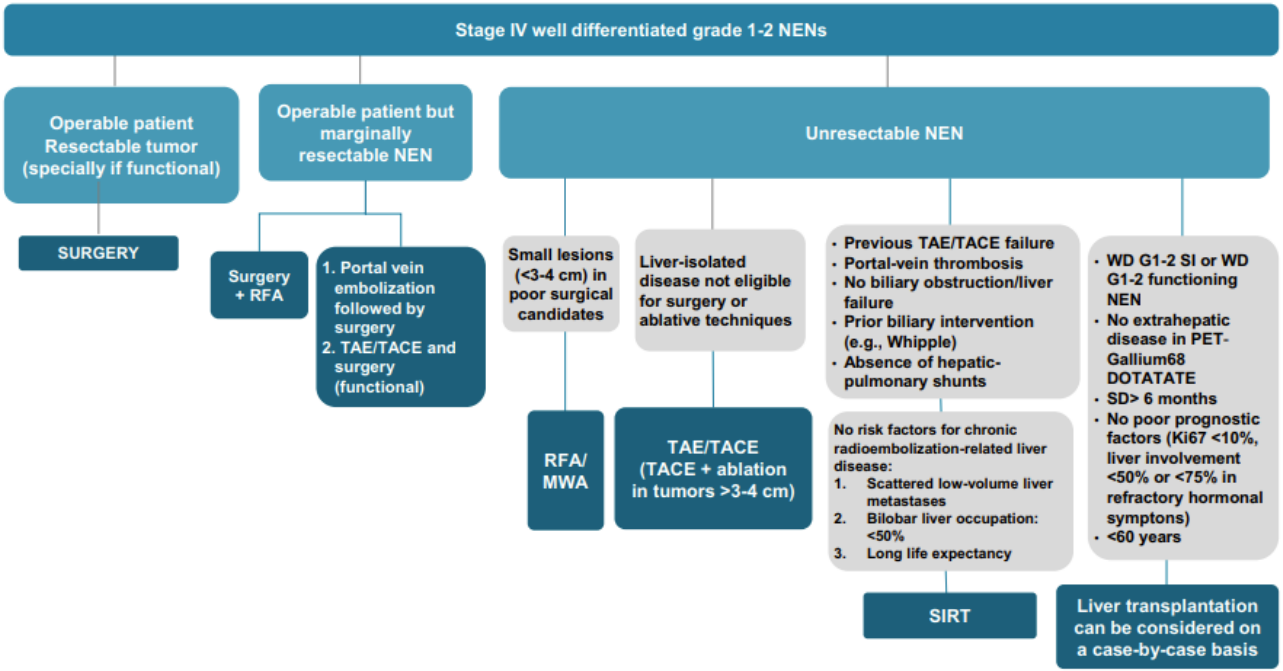
Localización:

- Esófago
- Hepatobiliar
- Primario desconocido



Nuñez-Valdovinos B, Carmona-Bayonas A, Jimenez-Fonseca P, et al. Oncologist. 2018;23(4):422-32

Selección de tumores para tratamiento neoadyuvante



Resecable:

- **<10-20% tumor residual**
- **Metástasis en otras localizaciones resecables**
- **Posibilidad de combinar con otros tratamientos sistémicos**

Irresecables

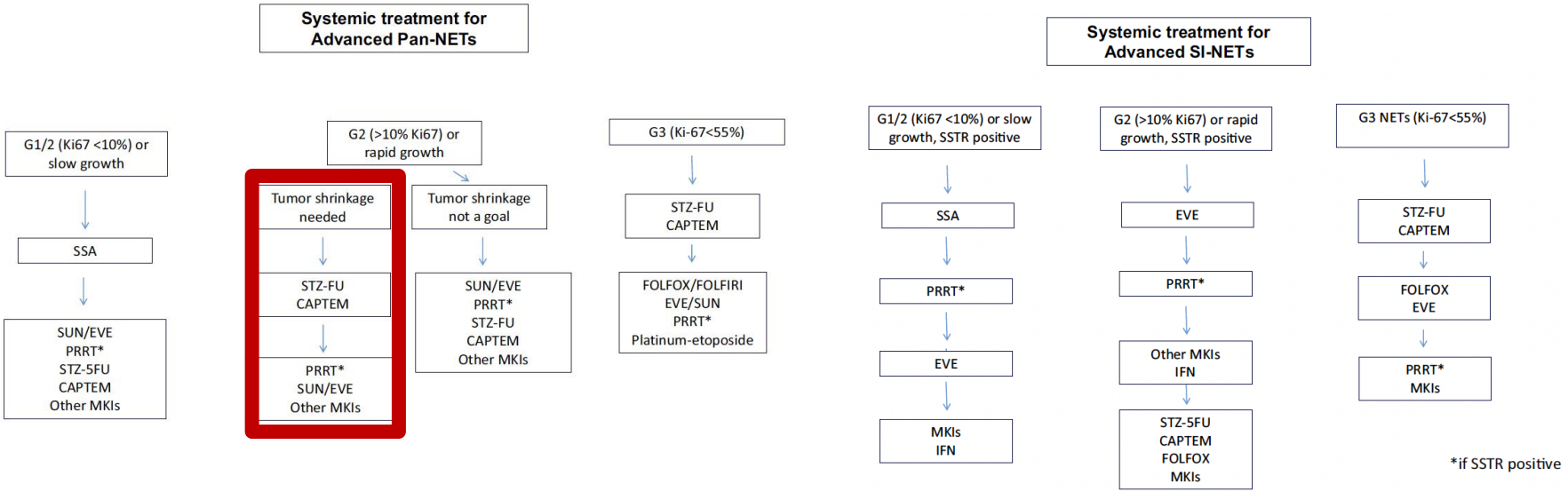
Capdevila-Castillón J, et al. SEOM-GETNE clinical guidelines for neuroendocrine neoplasms (NENs) (2022). Clin Transl Oncol. 2023 May 19.

Selección de pacientes para tratamiento neoadyuvante

1. **Evaluación multidisciplinaria**
2. **Estado funcional adecuado**
3. **Buena función de los órganos involucrados**
4. **Ausencia de comorbilidades significativas**
5. **Síndrome funcionante controlado**
6. **Motivación y aceptación del paciente**
7. Intervalo libre de recurrencia suficiente
8. Posibilidad de recibir terapia neoadyuvante

?

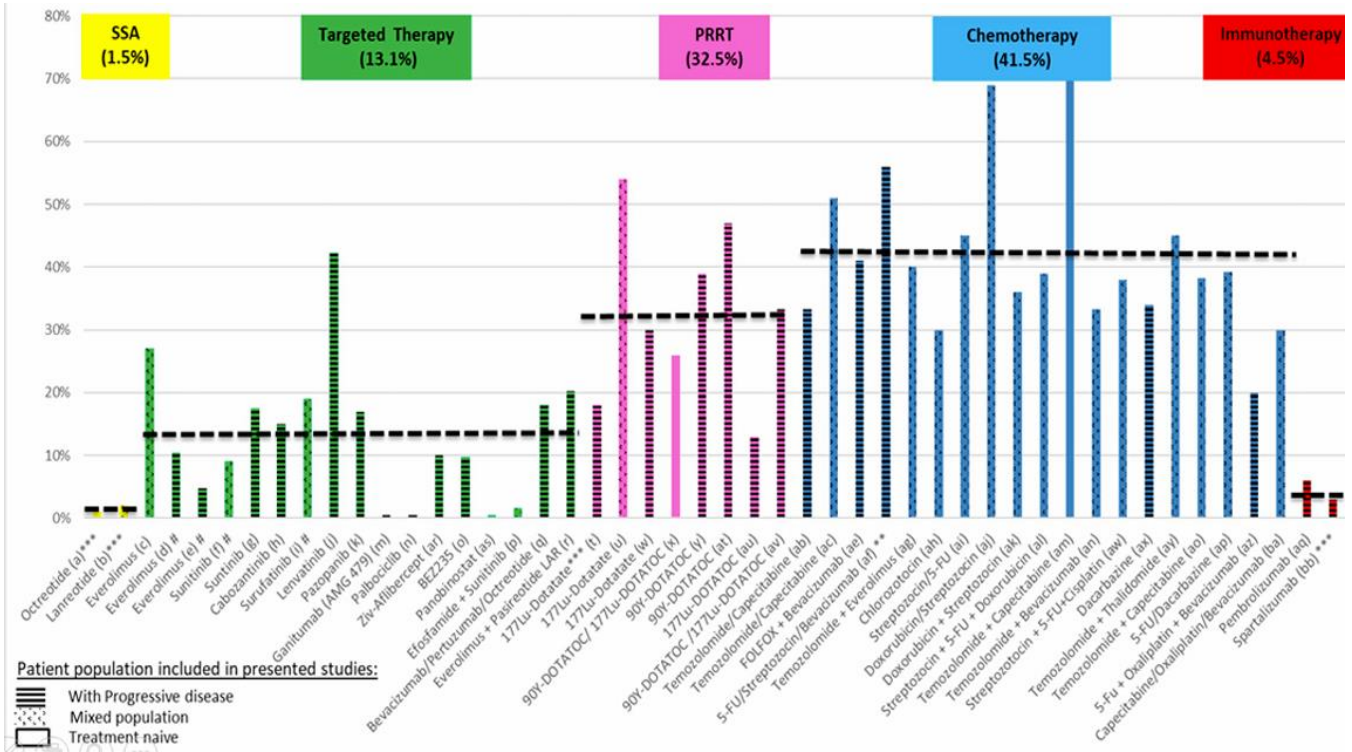
¿Qué dice la guía española SEOM 2023?



Capdevila-Castillón J, et al. SEOM-GETNE clinical guidelines for neuroendocrine neoplasms (NENs) (2022). Clin Transl Oncol. 2023 May 19.

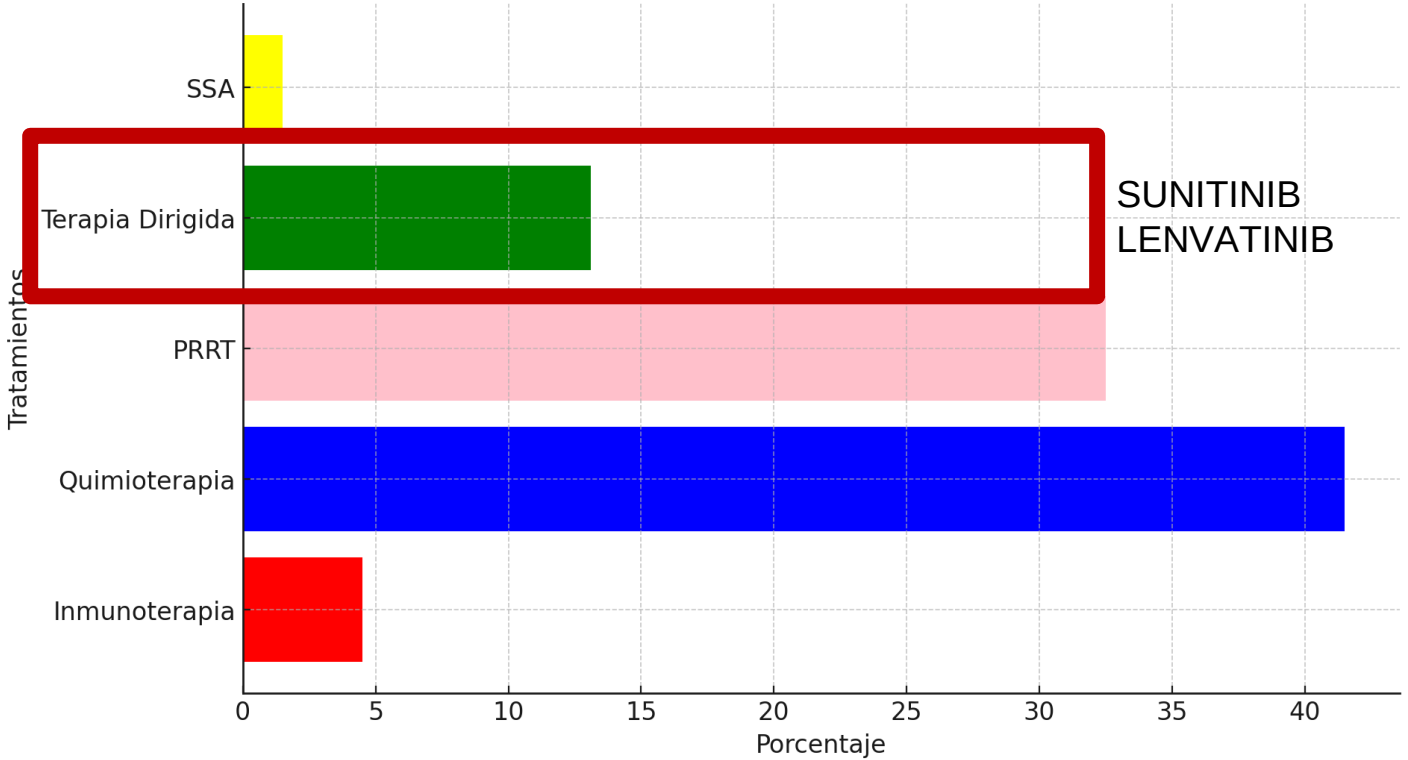
Selección de tratamiento neoadyuvante

ORR

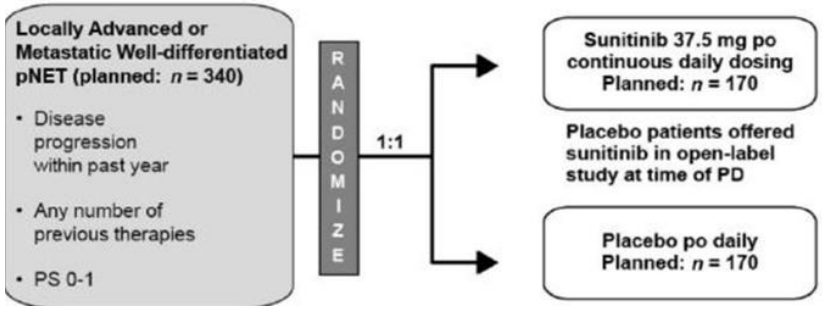


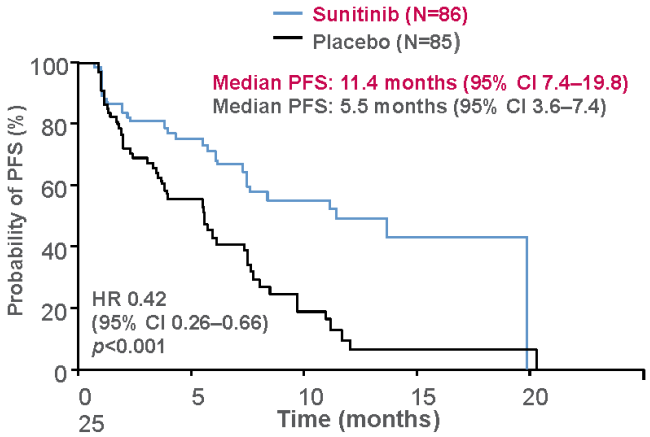
Megdanova-Chipeva VG, Lamarca A, PanNETs. Cancers (Basel). 2020 Jul 21;12(7):1988.

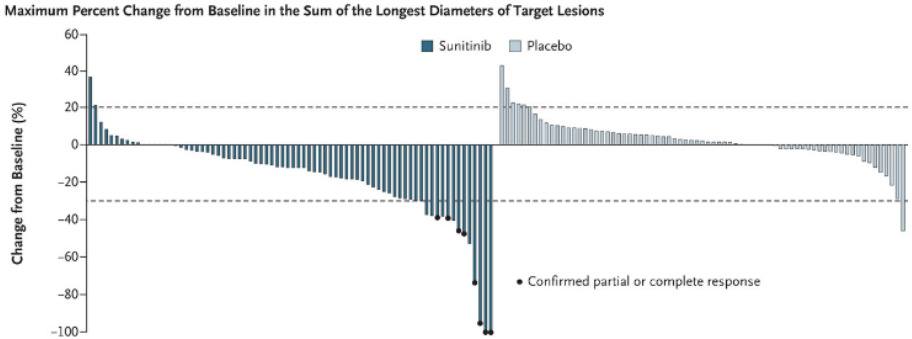
Selección de tratamiento neoadyuvante



Sunitinib-TNEp: ensayo fase 3 SUN 111





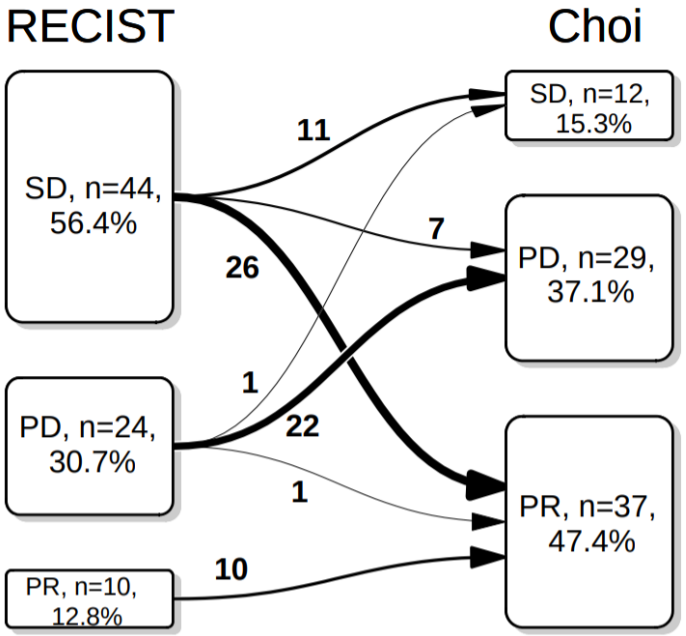


Outcome	Sunitinib (N=86)	Placebo (N=85)	P Value
Best observed RECIST response — no. (%)			
Complete response	2 (2)	0	
Partial response	6 (7)	0	
Stable disease	54 (63)	51 (60)	
Progressive disease	12 (14)	23 (27)	
Could not be evaluated	12 (14)	11 (13)	
Objective response rate — %	9.3	0	0.007

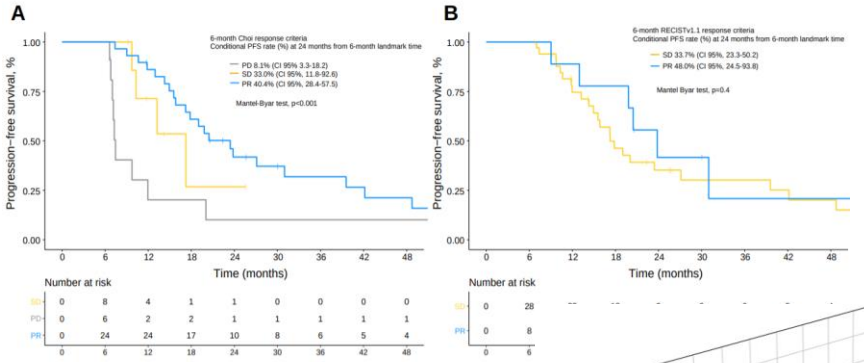
ORR: 9%

Raymond E. N Engl J Med. 2011;364(6):501-13

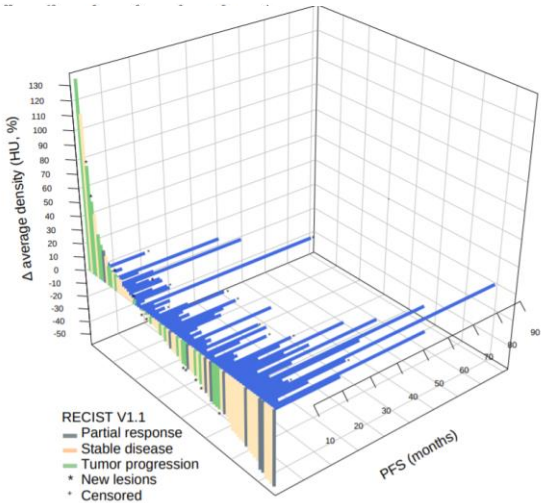
Sunitinib-TNEp: estudio CRIPNET_GETNE 1504



CHOI detecta mejor las **progresiones**.
RECIST estimó **mal la respuesta** en **49.6%**



ORR: 47%

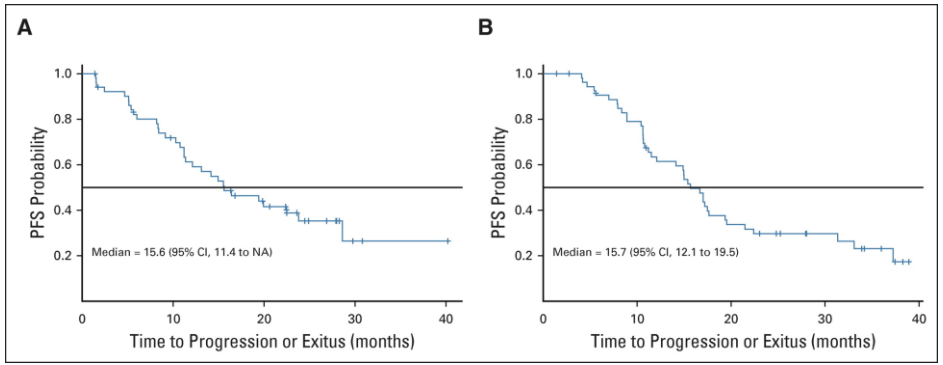


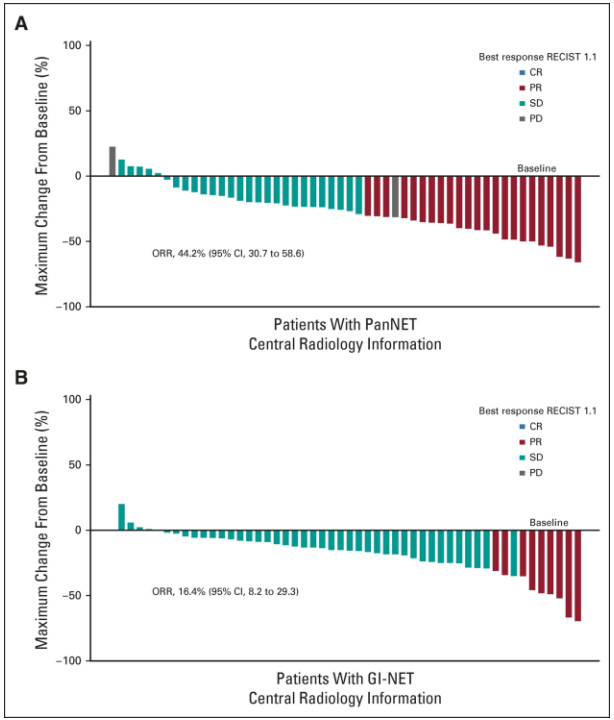
Solis P. CRIPNET-GETNE. Br J Cancer. 2019 Oct;121(7):537-544.

Lenvatinib: ensayo fase 2 TALENT_GETNE 1509

TABLE 2. Treatment Efficacy

Efficacy Parameter	panNETs (n = 55)	GI-NETs (n = 56)	Total (N = 111)
Patients with tumor assessment, No. (%)	52 (94.6)[a]	55 (98.2)[a]	107 (96.4)[a]
Best overall response, No. (%)			
Complete response	0	0	0
Partial response	23 (44.2)	9 (16.4)	32 (29.9)
Stable disease	27 (51.9)	42 (76.4)	69 (64.5)
Progressive disease	2 (3.9)	1 (1.8)	3 (2.8)
Not evaluable	0	3 (5.5)[b]	3 (2.8)[b]
Overall response rate (95% CI)	44.2% (30.7 to 58.6)	16.4% (8.2 to 29.3)	29.9% (21.6 to 39.6)
Disease control rate	96.2% (85.7 to 99.3)	92.7% (81.6 to 97.6)	94.4% (87.7 to 97.7)
Median duration of response, months (range)	19.9 (8.4-30.8)	33.9 (10.6-38.3)	21.5 (8.4-38.3)



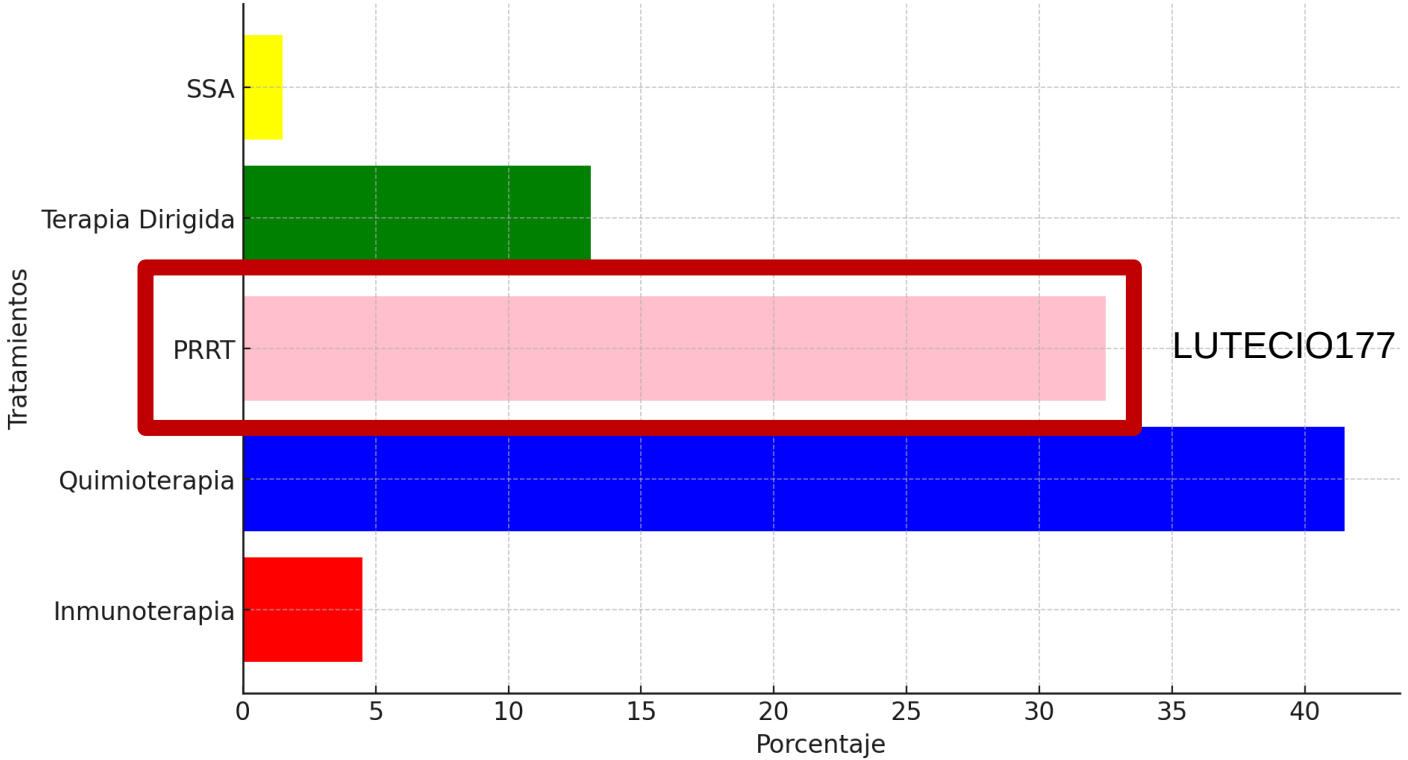


ORR TNEp: 44%

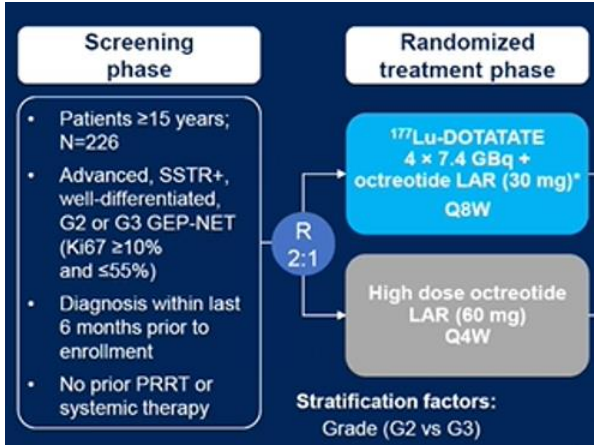
ORR TNEgi: 16%

Capdevila J. Clin Oncol. 2021;39(20):2304-2312.

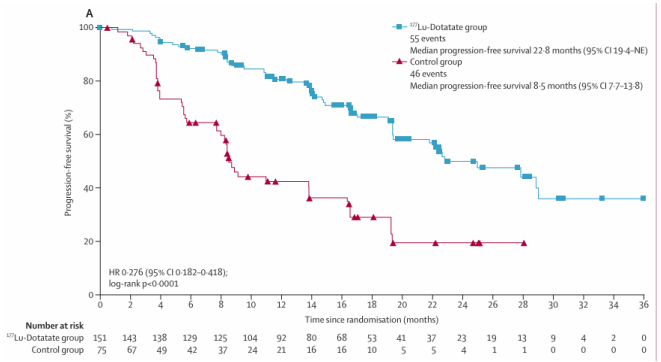
Selección de tratamiento neoadyuvante



Lutecio177-TNEgep G2-3: ensayo fase 3 NETTER-2



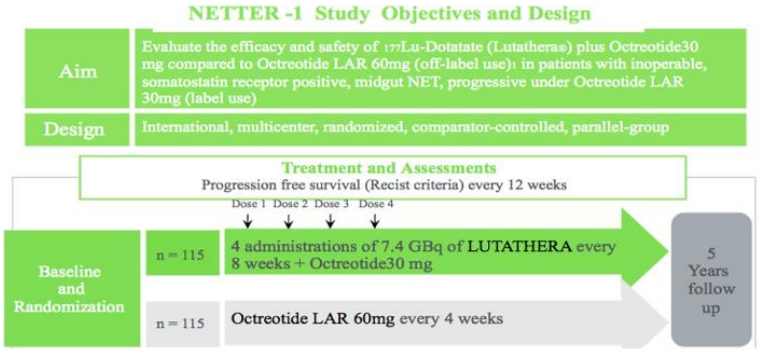
	^{177}Lu-Dotatate plus octreotide 30 mg LAR (n=151)	High-dose octreotide 60 mg LAR (control group; n=75)
Best overall response		
Complete response	8 (5%)	0
Partial response	57 (38%)	7 (9%)
Stable disease	72 (48%)	42 (56%)
Non-complete response or non-progressive disease	0	1 (1%)
Progressive disease	8 (5%)	14 (19%)
Unknown*	6 (4%)	11 (15%)
Objective response rate	65 (43·0%; 95% CI 35·0–51·3)	7 (9·3%; 95% CI 3·8–18·3)

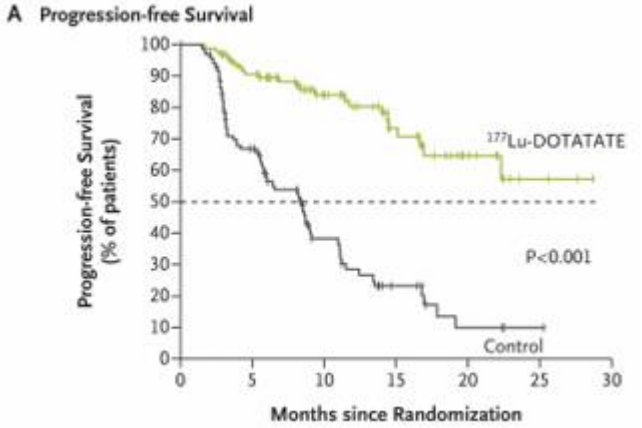


ORR TNEgep G2-3 (Ki67 ≥10% - ≤55%): 43%

Singh S, et al. Lancet. 2024;403(10446):2807-17

Lutecio177-TNEi G1-2: ensayo fase 3 NETTER-2





Response Category	^{177}Lu-Dotatate Group (N = 101)	Control Group (N = 100)	P Value†
Complete response — no. (%)	1 (1)	0	
Partial response — no. (%)	17 (17)	3 (3)	
Objective response			
No. with response	18	3	
Rate — % (95% CI)	18 (10–25)	3 (0–6)	<0.001

ORR TNEgi G1-2: 18%

Strosberg JR. Lancet Oncol. 2021 Dec;22(12):1752-63

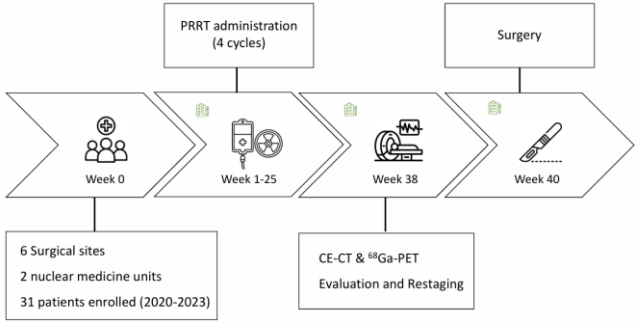
Ensayo fase 2, no aleatorizado. Vita-Salute San Raffaele University, Milan.
Objetivo: eficacia y toxicidad 177Lu-DOTATATE neoadyuvante panNEN IV G2-3 resecable de alto riesgo

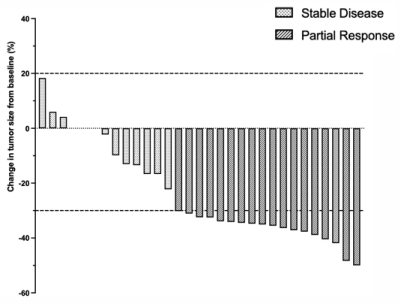
Inclusion criteria:

- >18 years old,
- Morphological (MR or CT scan) and cytological/histologically confirmed **sporadic resectable NF-PanNETs,**
- Positive ^{68}Ga-DOTATOC PET

and at least one of the following "**High-Risk features**":

- Radiological tumor size > 40 mm,
- Well differentiated G2 NF-PanNETs with Ki67 > 10%,
- Presence of nearby organs involvement,
- Vascular invasion (excluding SMV/PV > 180° and/or CT/SMA invasion),
- Mesenteric and/or portal and/or splenic vein thrombosis,
- Presence of a single resectable liver metastasis,
- Presence of enlarged hypervascularized lymph nodes at imaging, positive at ^{68}Ga-DOTATOC PET





Variables	*n* (%)
Final number of PRRT cycles performed	
1 cycle	0 (0)
2 cycles	2 (6)
3 cycles	3 (10)
4 cycles	26 (84)
Cause of therapy suspension	
AEs	3 (10)
Patient preferences	1 (3)
Unsafe absorbed dose	1 (3)
Post-PRRT CE-CT tumor size, mm§	42.4 (±22.6)
RECIST criteria	
Progressive disease	0 (0)
Stable disease	13 (42)
Partial response	18 (58)
Complete response	0 (0)
Post-PRRT SUV MAX ^{68}Gallium PET-DOTA*	44.5 (23.9–52.7)
Time PRRT-Surgery, days*	119 (113–142.5)

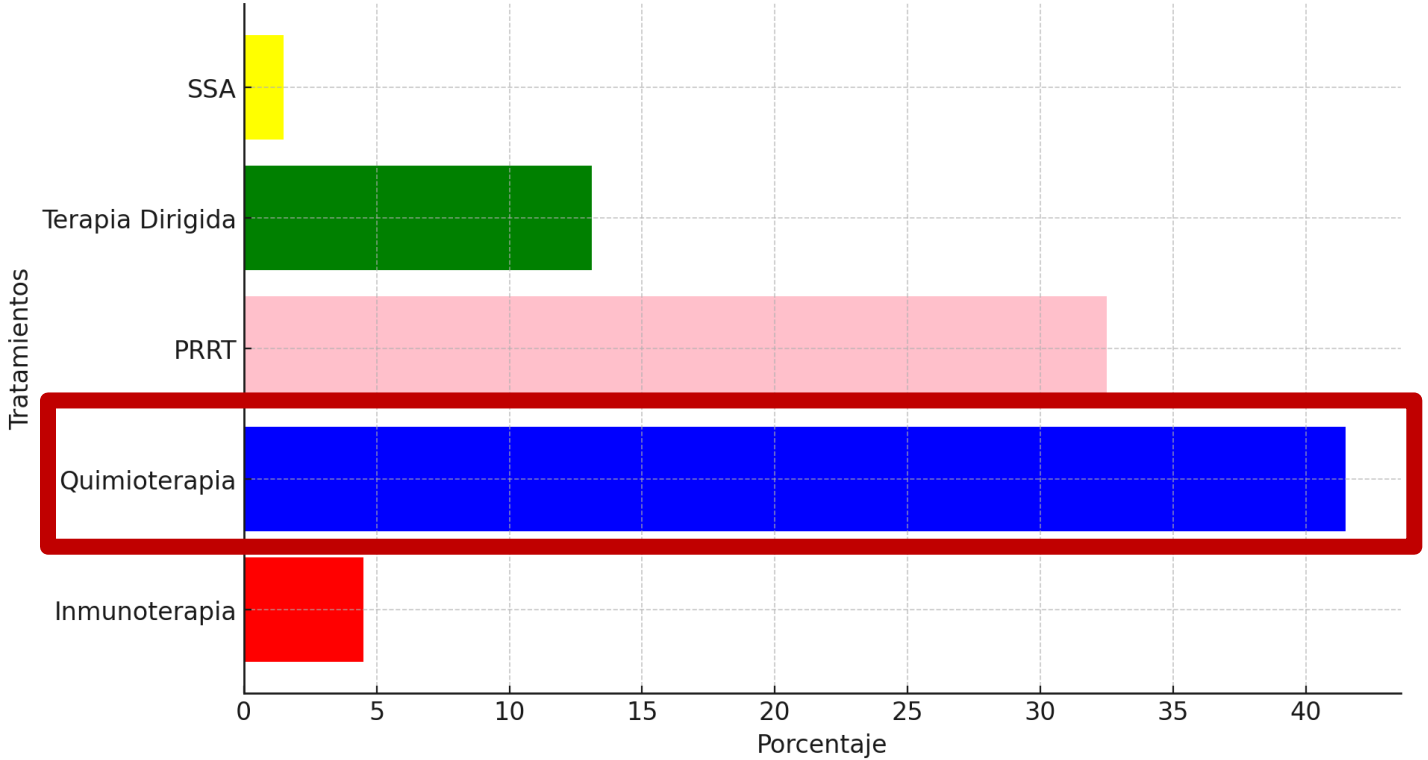
Variables	*n* (%)
Resectable disease	28 (97)
Type of surgery	
Total pancreatectomy	2 (7)
Pancreatoduodenectomy	11 (38)
Distal pancreatectomy	11 (38)
Enucleation	2 (7)
Others	3 (10)
Type of surgical approach	
Open	26 (90)
Laparoscopic	3 (10)
Operative time, minutes§	333.3 (±127.9)
Intra-operative bleeding, mL*	350 (100–750)

§ expressed as mean (±SD)
* expressed as median (IQR)

Neoadjuvant PRRT demonstrated to be a **safe** and **effective** therapeutic option for patients with high-risk NF-PanNETs.

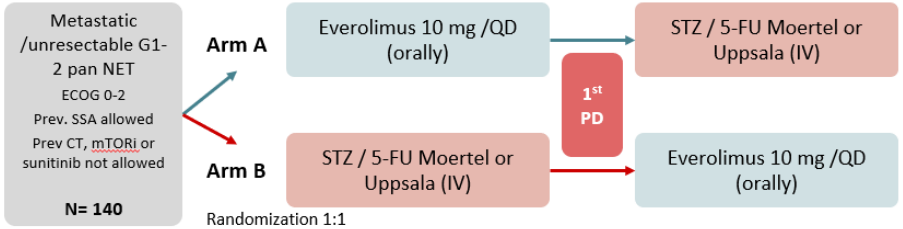
Partelli S, Milan. ESMO 2023

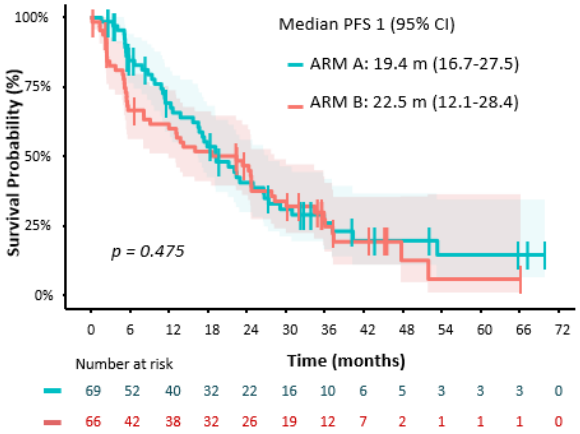
Selección de tratamiento neoadyuvante

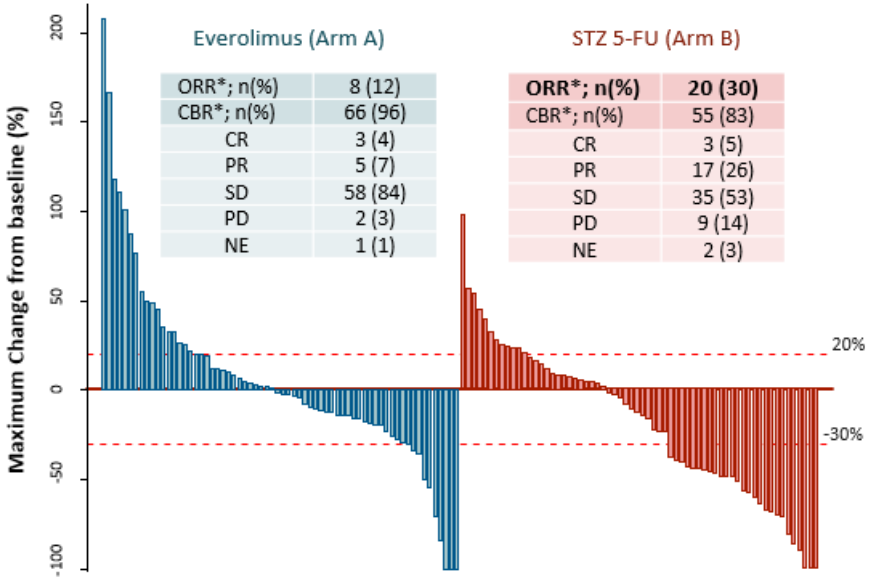


TNE páncreas
Stz-5FU +- Dox
TEMCAPE

Stz + 5FU-TNEp G1-2: ensayo fase 3 SEQTOR-GETNE 1206



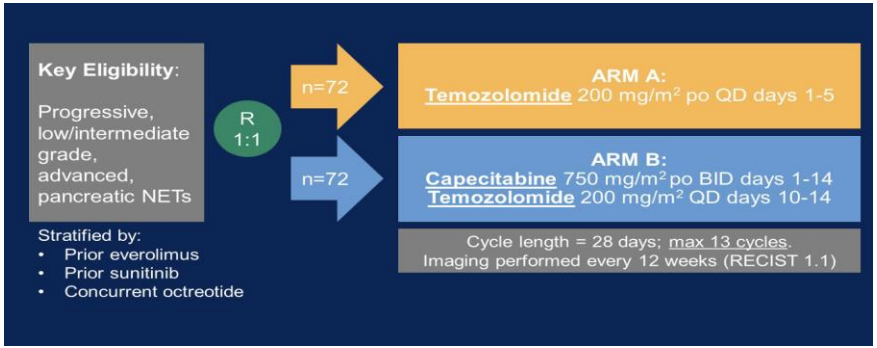


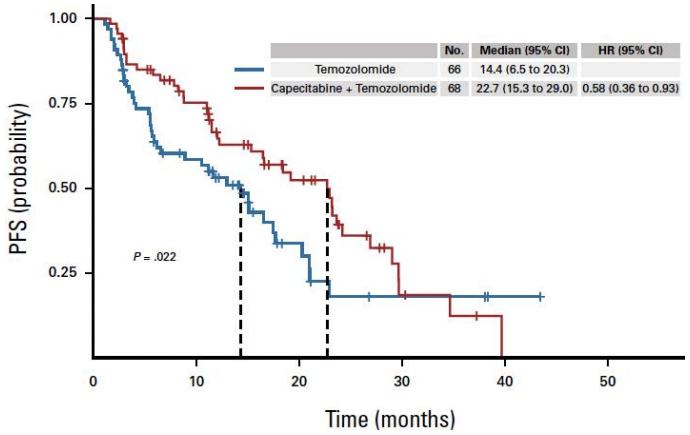


ORR TNEp G1-2:
QT 30%, EVE: 12%

Salazar R. ESMO 2024.

CAPTEM-TNEp G1-2: ensayo fase 2 ECOG-ACRIN Group (E2211)





	Temozolomide n = 65	Capecitabine/Temozolomide n = 68
Best Response		
Complete response	1 (2%)	1 (2%)
Partial response	21 (32%)	26 (38%)
Stable disease	26 (40%)	30 (44%)
Progressive disease	12 (19%)	9 (13%)
Unevaluable	5 (8%)	2 (3%)
Response Rate (CR+PR)	22 (34%)	27 (40%)*
Disease Control Rate (CR+PR+SD)	48 (74%)	57 (84%)
Response Duration (median)	12.6 mo	16.6 mo

ORR TNEp G1-2: 40%

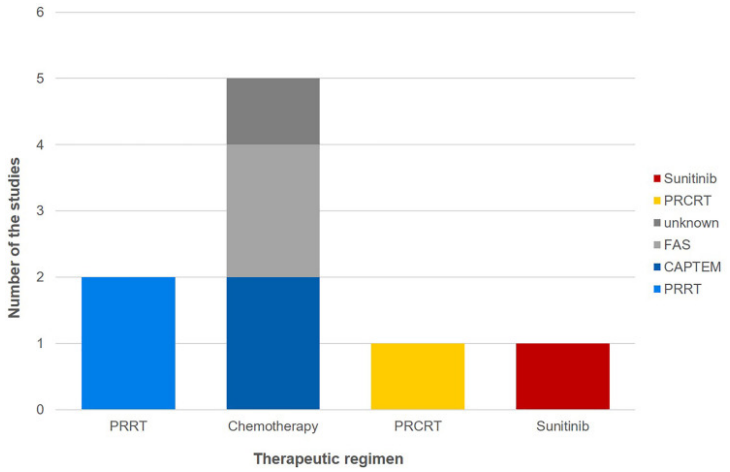
Kunz PL, et al. J Clin Oncol 2023.

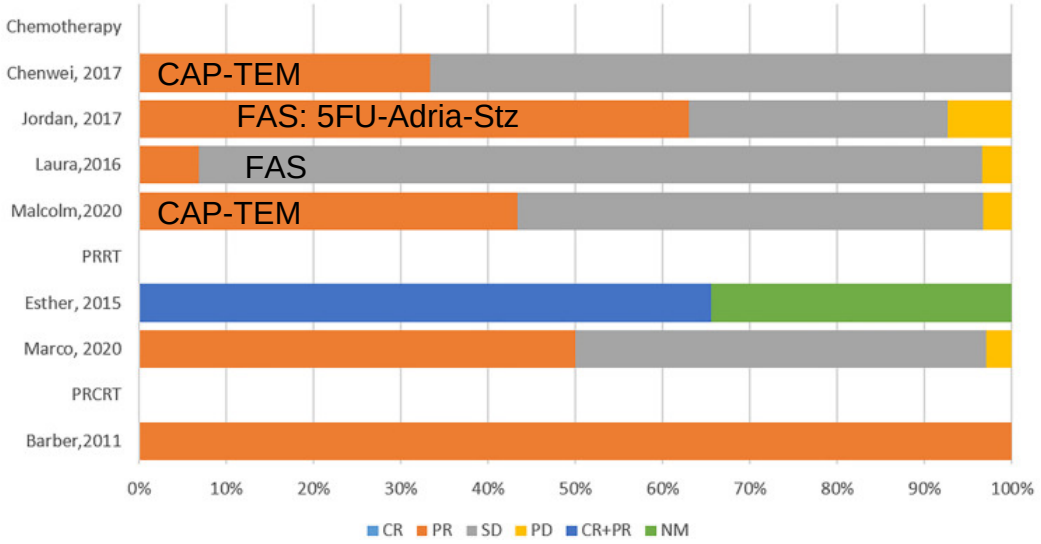
QT-TNEp G1-2: ensayos fase 2-3

Tratamiento	Fase	No. de pacientes	Tasa de respuesta (%)	mOS (mos)	PFS (mos)	Año
Estudios prospectivos						
STZ + 5 FU	3	42	63	26	-	1980[1]
STZ	3	42	36	16.4	-	
STZ + DOX	3	36	69	26.4	-	1992[2]
STZ + 5 FU	3	33	45	16.8	-	
Chlorozotocin	3	33	30	18	-	
Dacarbazine	2	50	34	19.3	-	2001[3]
TEM + thalidomide	2	11	45	NR	NR	2006[4]
TEM + bev	2	15	33	41.7	14.3	2012[5]
TEM + everolimus	1/2	24	35	-	-	2010[6]

Valle JW. Cancer Treat Rev. 2014;40(3):376-89

Revisión: 9 estudios retrospectivos de neoadyuvancia





Valle JW. Cancer Treat Rev. 2014;40(3):376-89

Revisión: 9 estudios retrospectivos de neoadyuvancia

	Resection rate	R0 resected
Total [95%CI]	65.7% [45.6, 85.8] I^2=97.12 %, P<0.001 (n=297)	58.4% [51, 65.7] I^2=0 %, P=0.67 (n=166)
Chemotherapy [95%CI]	79.3% [61.9, 96.7] I^2=90.29 %, P<0.001 (n=134)	61% [51.6, 70.3] I^2=0 %, P=0.451 (n=101)
CAPTEM [95%CI]	88.5 % [78.2, 98.7] I^2=0 %, P=0.592 (n=36)	Data deficient
FAS [95%CI]	74 % [25.1, 123] I^2=96.3 %, P<0.001 (n=56)	68.4 % [54.2, 82.6] I^2=0 %, P=0.695 (n=41)
PRRT [95%CI]	65 % [-0.6, 130.6] I^2=98.18 %, P<0.001 (n=53)	54.9 % [38.2, 71.7] I^2=0 %, P=0.374 (n=33)

	Neoadjuvant therapy	Median overall survival time (95% CI) (months)	
		Surgery	No surgery
Jordan, 2017	FAS	108.2 (73.2-143.2)	59.6 (42.5-76.8)
Laura, 2016	FAS	112 (104-120)	41 (16-66)
Yoshiki, 2021	Sunitinib	>72*	36.7

In conclusion, neoadjuvant therapies, such as chemotherapy and PRRT, could reduce the volume and stage of some borderline resectable or unresectable pNENs, and gave some patients the chance of radical resection. However, the current study was not able to identify differences in efficacy between different treatment regimens. Next, it is necessary to conduct prospective clinical studies on the role of neoadjuvant therapy in pNENs, which should include clear definitions and criteria for tumor resectability.

Li Y. Neoadjuvant therapy in pNEN: A systematic review and meta-analysis. Front Oncol. 2022;12:98157

CONCLUSIÓN

TERAPIA NEOADYUVANTE

RESECCIÓN R0

SELECCIÓN
Tumor
Paciente
Tratamiento

↑↑↑ ORR