Cabozantinib plus Atezolizumab in Patients with Advanced and Progressive Neuroendocrine Neoplasms (NEN): A Prospective Multi-cohort Basket Phase II Trial (CABATEN / GETNE-T1914)

Jorge Hernando[1], Javier, Molina-Cerrillo[2], Enrique Grande[3], Marta Benavent Viñuales[4], Rocio Garcia-Carbonero[5], Alex Teule[6], Ana Custodio[7], Paula Jimenez-Fonseca[8], Cinta Hierro[9], Carlos López[10], Isabel Sevilla[11], Marta Llanos[12], Alberto Carmona-Bayonas[13] , Vicente Alonso[14], Javier Gallego[15] , Inmaculada Gallego Jiménez[4], Alberto Orta[3], Fabio Franco[3], Alejandro García-Álvarez[1], Jaume Capdevila[1]

[1] Medical Oncology Department, Vall Hebron University Hospital, Vall Hebron Institute of Oncology (VHIO), Barcelona, Spain [2] Medical Oncology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain [3] Medical Oncology Department, MD Anderson Cancer Center Madrid, Madrid, Spain [4] Medical Oncology Department, University Hospital Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS), Seville, Spain [5] Medical Oncology Department, Hospital Universitario 12 de Octubre, Imas12, UCM, Madrid, Spain [6] Medical Oncology Department, Institut Català d´Oncologia (ICO) - IDIBELL, L´Hospitalet de Llobregat, Spain [7] Medical Oncology Department, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain [8] Medical Oncology Department, Hospital Universitario Central de Asturias, ISPA, Oviedo, Spain [9] Medical Oncology Department, Catalan Institute of Oncology (ICO-Badalona) Germans Trias i Pujol University Hospital, Badalona, Spain [10] Medical Oncology Department, Hospital Universitario Marqués de Valdecilla, IDIVAL, UNICAN, Santander, Spain [11] Medical Oncology Department, Investigación Clínica y Traslacional en Cáncer / Instituto de Investigaciones Biomédicas de Málaga (IBIMA) / Hospitales Universitarios Regional y Virgen de la Victoria de Málaga, Spain [12] Medical Oncology Department, Hospital Universitario de Canarias, San Cristobal de la Laguna, Spain [13] Medical Oncology Department, Hospital General Universitario Morales Meseguer, UMI. IMIB. Murcia, Spain [14] Medical Oncology Department, Hospital Universitario Miguel Servet, Zaragoza, Spain [15] Medical Oncology Department, General Universitario de Elche Hospital, Alicante, Spain.

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P108

BACKGROUND

- Treatments with immune-checkpoint inhibitors (ICI) as single agents in NEN show limited response rates [1-2].
- Angiogenesis plays a key role in development and progression of NEN and synergism has been observed when antiangiogenics are combined with ICI [3-5].
- We aimed to assess the efficacy and safety of cabozantinib (Cabo) plus atezolizumab (Atezo) in advanced and progressive NEN.

METHODS

- CABATEN is an academic, prospective, multicenter, phase II single arm basket trial that recruited patients with neuroendocrine & endocrine neoplasms in 6 cohorts.

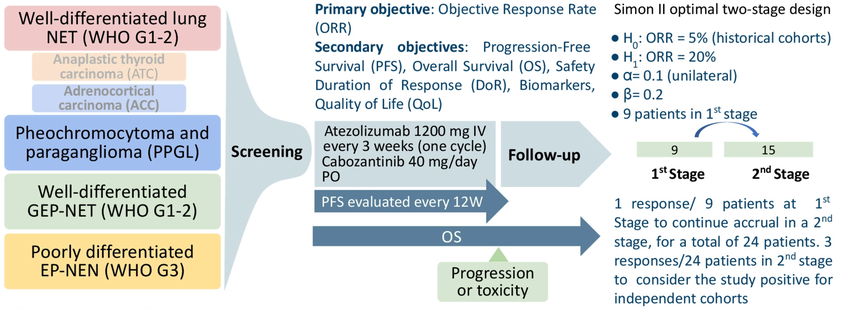


Figure 1. CABATEN Design

- Patients received Atezolizumab 1200 mg every 3 weeks and cabozantinib 40 mg/day until confirmed disease progression, or unacceptable toxicity.
- Primary endpoint was Overall Response Rate (ORR) by RECIST 1.1. The study had a Simon-II design.
- Here we present a subgroup analysis of efficacy for 4 NEN cohorts: well-differentiated lung NET (G1-2), Pheochromocytoma and paraganglioma (PPGL), well-differentiated GEP-NET (WHO G1-2) and Poorly differentiated extrapulmonary (EP)-NEN (WHO G3) (**Figure 1**) and a Landmark analysis to assess the impact of cabozantinib dose reduction in efficacy.

Table 1. Baseline characteristics

Characteristics		Lung NET N = 9	PPGL N = 13	G1-2 GEP-NET N = 24	G3 EP-NEN N = 9
Age, years	Median (range)	63 (31-81)	48 (36-67)	60 (31-77)	62 (38-73)
Gender, n (%)	Male	5 (55.6)	10 (76.9)	13 (54.2)	6 (66.7)
WHO grade, n (%)	1	1 (11.1)	-	7 (29.2)	0 (0)
	2	8 (88.9)	-	17 (70.8)	0 (0)
	3	0 (0)	-	0 (0)	9 (100)
Number of metastasis sites, n (%)	0	2 (22.2)	1 (7.7)	1 (4.2)	0 (0)
	1	0 (0)	4 (30.8)	6 (25)	1 (11.1)
	≥ 2	7 (77.8)	8 (61.5)	17 (70.8)	8 (88.9)
Metastasis locations, n (%)	Liver	6 (66.7)	4 (30.8)	20 (83.3)	9 (100)
	Nodes	5 (55.6)	2 (15.4)	11(45.8)	6 (66.7)
	Bone	2 (22.2)	6 (46.2)	6 (25.0)	2 (22.2)
	Lung	3 (33.3)	3 (23.1)	2 (8.3)	1 (11.1)
Previous treatments, n (%)	0	0 (0)	1 (7.7)	0 (0)	0 (0)
	1	2 (22.2)	4 (30.8)	9 (37.5)	3 (33.3)
	≥ 2	7 (77.8)	8 (61.5)	15 (62.5)	6 (66.7)
Previous treatment type, n (%)	SSA	7 (77.8)	4 (33.3)	20 (83.3)	0 (0)
	Chemotherapy	5 (55.6)	7 (58.3)	7 (29.2)	9 (100)
	TKIs	7 (77.8)	2 (16.7)	11 (45.8)	0 (0)
	PRRT	1 (11.1)	3 (25.0)	4 (16.7)	0 (0)
	Mitotane	0 (0)	1 (8.3)	0 (0)	0 (0)
	Other	1 (11.1)	0 (0)	0 (0)	0 (0)

RESULTS

From october 2020, a total 55 patients were enrolled in 4 NEN cohorts. See **Table 1** for baseline characteristics. ORR were 15.4% (95%CI:1.9-45.5) in PPGL and 16.7% (95%CI:4.7-37.4) in GEP-NET. LungNETs and G3 EP-NEN had no responses (**Figure 2**). Duration of response (DoR) were 12.2m (5.5-19.0) and 15.8m (10.6 - 20.2) in PPGL and GEP-NET cohorts, respectively. LungNET, PPGL, GEPNET and G3 EP-NEN presented a median PFS (m, 95% CI) of 8.4 [7.7-NR], 8.4 [5.7-NR], 13 [11.2-NR] and 2.7 [2.6-NR] respectively (**Figure 3**).
Cabozantinib was reduced to 20 mg/day in 58,2% of patients. In Landmark analysis of relative dose intensity (RDI) 3-month interval, the 12-m PFS was 50% (95%CI: 29.6-84.4) RDI<81% vs 55.6% (95%CI: 39.7-77.9) RDI≥81% (p=0.9). The 12-m OS was 86.7% (CI 95%: 71.1-100) RDI<81% vs 84.7% (CI 95%: 72.0-99.7) RDI≥81% (p=0.6) (Cox) (**Figure 4**). PFS>12m subgroup had a trend towards better ECOG. PFS>15m GEP-NET presented a non-significant trend towards a lower Ki67 index and less previous treatment (no chemotherapy).

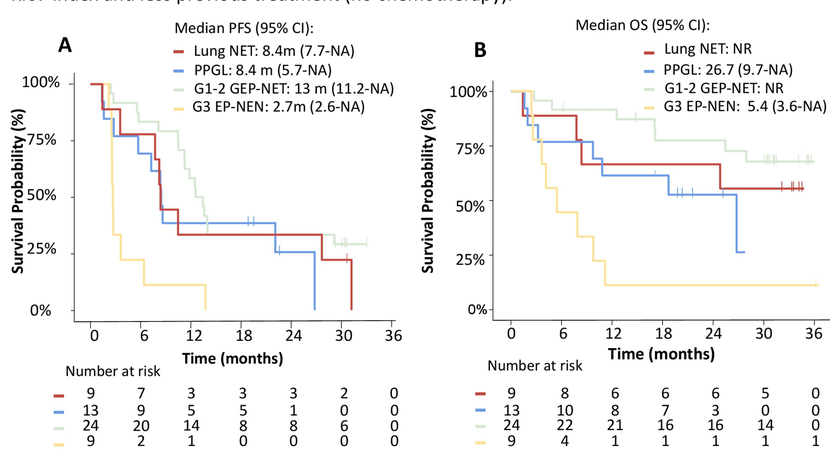


Figure 3. Efficacy (Kaplan Meier) in NEN cohorts. A) Progression-free survival. B) overall survival.

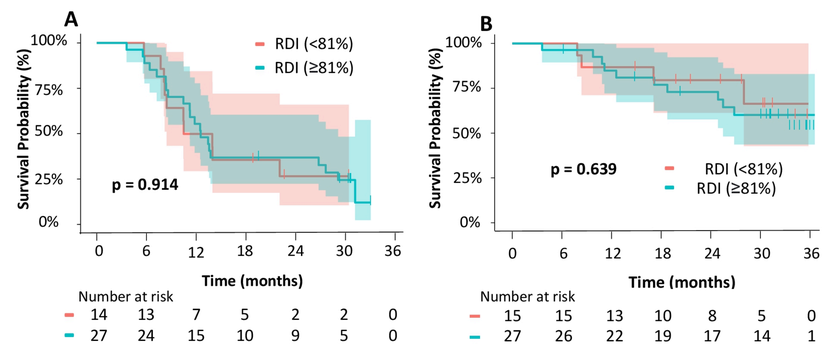
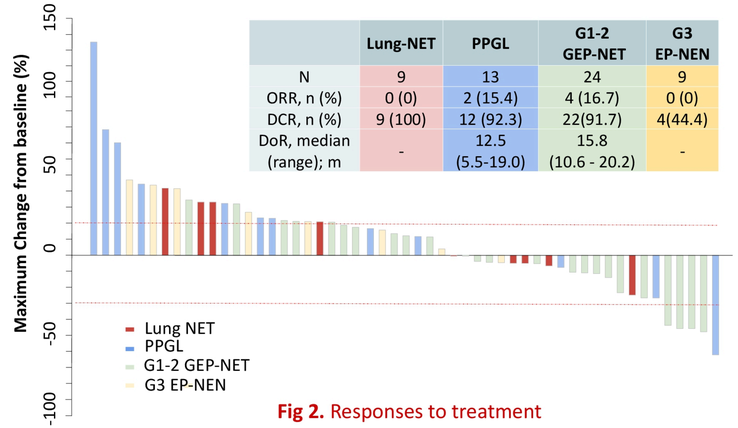


Fig 4. Efficacy by Landmark analysis. Progression-free survival (A) and overall survival (B)

CONCLUSIONS

- The combination of cabozantinib and atezolizumab showed limited efficacy in the CABATEN NEN cohorts.
- Responses were observed in PPGL and GEP-NET cohorts, but not in LungNET nor in G3 EP-NEN, regardless of cabozantinib dose intensity.
- No differences in PFS and OS were found regardless cabozantinib dose intensity by Landmark analyses.
- Cabozantinib and Atezolizumab showed limited activity but achieved prolonged disease control in a small group of patients with PPGL and GEPNET but not in LungNET and G3 EP-NEN.



	Lung-NET	PPGL	G1-2 GEP-NET	G3 EP-NEN
N	9	13	24	9
ORR, n (%)	0 (0)	2 (15.4)	4 (16.7)	0 (0)
DCR, n (%)	9 (100)	12 (92.3)	22(91.7)	4(44.4)
DoR, median (range); m	-	12.5 (5.5-19.0)	15.8 (10.6 - 20.2)	-

Fig 2. Responses to treatment

FUTURE PERSPECTIVES

Future drug combination research with multikinase and ICIs in neuroendocrine and endocrine fields should optimize the dose/schedule of the potentially more toxic compound to ensure compliance and long-term efficacy.

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Correspondence to: jhernando@vhio.net // **Presented at:** ASCO 2024 Annual ,Symposium //
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