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Clinical Trial Results

The PALBONET Trial: A Phase II Study of Palbociclib in Metastatic Grade 1 and 2 Pancreatic Neuroendocrine Tumors (GETNE-1407)

Enrique Grande,[a] Alex Teulé,[b] Teresa Alonso-Gordoa,[c] Paula Jiménez-Fonseca,[d] Marta Benavent,[e] Jaume Capdevila,[f] Ana Custodio,[g] Ruth Vera,[h] Javier Munarriz,[i] Adelaida La Casta,[j] Juan José Díez,[k] Pablo Gajate,[c] Javier Molina-Cerrillo,[c] Ignacio Matos,[f] Eva María Cristóbal,[l] José C. Ruffinelli,[b] José Palacios,[m] Rocío García-Carbonero[n]

[a]Department of Medical Oncology, MD Anderson Cancer Center Madrid, Madrid, Spain; [b]Department of Medical Oncology, Catalan Institute of Oncology (Hospital Duran i Reynals), L'Hospitalet, Barcelona, Spain; [c]Department of Medical Oncology, University Hospital Ramón y Cajal, IRYCIS, CIBERONC, Madrid, Spain; [d]Department of Medical Oncology, University Hospital Central de Asturias, Oviedo, Spain; [e]Department of Medical Oncology, University Hospital Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS), Seville, Spain; [f]Department of Medical Oncology, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), CIBERONC, Barcelona, Spain; [g]Department of Medical Oncology, University Hospital La Paz, Centro de Investigación Biomédica en Red Cáncer CB16/12/00398, Madrid, Spain; [h]Department of Medical Oncology, Complejo Hospitalario de Navarra, IdisNA, Pamplona, Spain; [i]Department of Medical Oncology, University Hospital General de Castellon, Castellon, Spain; [j]Department of Medical Oncology, University Hospital Donostia, San Sebastián, Spain; [k]Department of Endocrinology, University Hospital Puerta de Hierro Majadahonda, Department of Medicine, Faculty of Medicine, Universidad Autónoma, Madrid, Spain; [l]Department of Pathology, University Hospital Ramón y Cajal IRYCIS, CIBERONC, Madrid, Spain; [m]Department of Pathology, University Hospital Ramón y Cajal, Departament of Medicine and Medical Specialties, Faculty of Medicine, University of Alcalá, IRYCIS, CIBERONC, Madrid, Spain; [n]Department of Medical Oncology, University Hospital 12 de Octubre, IIS imas12, UCM, CNIO, CIBERONC, Madrid, Spain

Trial Information

- **ClinicalTrials.gov Identifier**: NCT02806648
- **Sponsor**: GETNE
- **Principal Investigator**: Enrique Grande
- **IRB Approved**: Yes

Lessons Learned

- Palbociclib demonstrated no detectable activity in molecularly unselected and heavily pretreated patients with advanced grade 1/2 pancreatic neuroendocrine tumors.
- Predictive biomarkers that improve patient selection should be investigated in future studies of palbociclib.

Abstract

Background. Palbociclib, a CDK4/6 inhibitor, has shown in vitro activity in pancreatic neuroendocrine tumor (pNET) cell lines. Here we prospectively assessed the activity and safety of palbociclib in monotherapy in metastatic refractory pNETs.

Methods. This was a nonrandomized, open-label, phase II study of patients with metastatic grade (G)1/2 pNETs recruited from 10 centers in Spain. Palbociclib 125 mg was orally administered once daily for 21 of 28 days until disease progression or unacceptable toxicity.

Results. Twenty-one patients were included; 52.4% were men, and median age was 57.4 years (range, 37.4–73.4). Patients had previously received a median of three prior lines of systemic therapy (range, 1–10) for advanced disease (somatostatin analogues, 71.4%; sunitinib, 81.0%; everolimus, 47.6%; chemotherapy, 47.6%). Nineteen patients were evaluated for objective response rate (ORR), with a median follow-up of 12.4 months (range, 7.53–19.33). No objective and confirmed responses were observed (0%); 11 (57.9%) patients had stable disease, and 6 of them lasted more than 6 months; 8 (42.1%) patients had disease progression as best response. Median progression-free survival (PFS) was 2.6 months (95% confidence interval [CI], 0–14.4) and median overall survival (OS) was 18.7 months (95% CI, 7.4–29.9; Fig. 1). Most frequent toxicities of any grade were asthenia (76.2%), neutropenia (42.9%), diarrhea (33.3%), and nausea (33.3%). Five (23.8%) patients developed G3–4 neutropenia and two (9.5%) patients developed G3–4 thrombocytopenia.

Conclusion. Lack of activity was observed with palbociclib as a single agent in molecularly unselected and heavily pretreated patients with advanced G1/2 pNETs. ***The Oncologist*** 2020;25:745–e1265

Correspondence: Erique Grande, M.D., Ph.D., Department of Medical Oncology, MD Anderson Cancer Center Madrid, C/ Arturo Soria 270, Madrid, Spain 28033. Telephone: 34-917878600; e-mail: egrande@oncomadrid.com Received November 29, 2019; accepted for publication January 13, 2020; published Online First on February 11, 2020. http://dx.doi.org/10.1634/theoncologist.2020-0033

Discussion

The cyclin-dependent kinases (CDKs) regulating cell cycle progression have long been viewed as promising targets for cancer therapy. Third-generation CDK4/6 inhibitors are highly selective and present limited toxicity and potent in vivo activity and include palbociclib, ribociclib, and abemaciclib among others [1]. These drugs received US Food and Drug Administration and European Medicines Agency approval for the treatment of hormone receptor-positive and HER2-negative breast cancer in combination with either aromatase inhibitors or fulvestrant based on significant improvements in PFS [2]. In these studies, hazard ratios for PFS were similar for the three drugs and ranged between 0.46 and 0.58 for palbociclib, 0.55 and 0.59 for ribociclib, and 0.54 and 0.55 for abemaciclib when compared with the standard hormonal therapy [1]. Palbociclib has been also tested in monotherapy in phase II trials in a variety of solid tumors, such as gastric and esophageal cancer [3], advanced non-small cell lung cancer [4], well-differentiated or dedifferentiated liposarcoma [5, 6], urothelial carcinoma (ClinicalTrials.gov: NCT02334527), and epithelial ovarian cancer [7].

Patients included in our study had been diagnosed with well-differentiated G1-G2 pNETs (Ki-67 ≤ 20%) and presented advanced or metastatic disease that had progressed to at least one line of previous systemic treatment. However, although in approved indications CDK4/6 inhibitors are used in combination with aromatase inhibitors or letrozole, here we analyzed the efficacy and safety of palbociclib in monotherapy in molecularly unselected patients. Furthermore, in our study the patients were heavily pretreated, as the median time since initial diagnosis of the disease was 54.8 months and two-thirds of the patients (66.7%) had received at least two prior lines of systemic treatments, including 81% of patients who had been pretreated with sunitinib and 47% with everolimus. This may have selected a population of patients with poor prognosis because of a high tumoral burden and advanced progressive disease. In our study palbociclib did not meet the primary endpoint (ORR ≥5%), and median PFS was only 2.6 (95% CI, 0.0–14.4) months (Fig. 2). Although there were no objective responses, a proportion of patients (57.9%) presented disease stabilization, of which 54.5% lasted for ≥6 months. Current targeted therapies approved for pNETs include sunitinib, which showed a median PFS of 11.4 months versus 5.5 months of placebo [8], and everolimus, with a median PFS of 11.4 months versus 5.4 months of placebo [9]. Reported ORR in these trials were 9.3% versus 0% for placebo and 4.8% for everolimus versus 2% for placebo.

Clearly there is a need for predictive biomarkers that could allow better patient selection. No correlation between the clinical outcome and the expression of RB1, Ki-67, and p16 on the tumor tissue was observed [10].

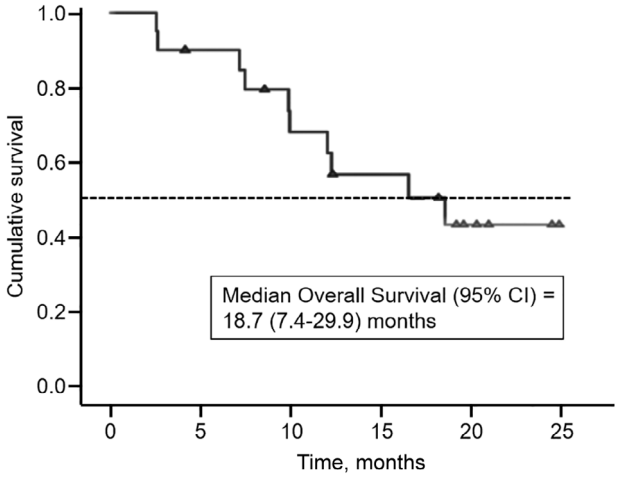

Figure 1. Kaplan-Meier curve for overall survival of patients treated with palbociclib (n = 20).
Abbreviation: CI, confidence interval.

Trial Information	
Disease	Neuroendocrine–pancreatic
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	More than 2 prior regimens
Type of Study – 1	Phase II
Type of Study – 2	Single Arm
Primary Endpoint	Overall response rate
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Toxicity
Secondary Endpoint	Time to progression
Secondary Endpoint	Duration of the response
Secondary Endpoint	Overall survival
Secondary Endpoint	Biomarker predictive value evaluation
Additional Details of Endpoints or Study Design	The primary endpoint was the ORR as assessed by RECIST 1.1 criteria. The evaluation of tumor disease response was made by computed tomography (CT) scans every 8 weeks until week 24, and then every 12 weeks, regardless dose delay or interruptions due to toxicity or other causes.

	The initial planned number of patients was 21 based on a two-stage Simon's phase II design in which palbociclib was considered as inactive in terms of ORR if <5% of patients responded and had a top 20% ORR. Patients received palbociclib until radiological progression was confirmed according to RECIST 1.1 criteria, unacceptable toxicity, noncompliance with the protocol, or patient withdrawal of informed consent or until the interruption of treatment (decision based on reaching the maximum benefit with acceptable tolerability). Dose reductions were permitted according to the labeling of the product.
Investigator's Analysis	Palbociclib as a single agent failed to demonstrate antitumor activity in pretreated metastatic pNETs.

Drug Information	
Drug 1	
Generic/Working Name	Palbociclib
Company Name	Pfizer
Drug Type	Small molecule
Drug Class	CDK
Dose	125 mg per flat dose
Route	p.o.
Schedule of Administration	125 mg per day for 21 days in cycles of 28 days

Patient Characteristics	
Number of Patients, Male	11
Number of Patients, Female	10
Stage	Unresectable locally advanced or metastatic well-differentiated G1 or 2 (Ki-67 ≤20%)
Age	Median (range): 57.4 (37.4–73.4)
Number of Prior Systemic Therapies	Median (range): 3 (1.0–10.0)
Performance Status: ECOG	0 — 9 1 — 11 2 — 3 — Unknown — 1
Other	Patients eligible for enrollment were 18 years of age or older and had histologically or cytologically diagnosed, unresectable locally advanced, or metastatic well-differentiated G1 or 2 pNET (Ki-67 ≤20%), which had progressed on at least one line of prior systemic therapy. Patients previously treated with somatostatin analogs (SSAs), chemotherapy, antiangiogenics, mTOR inhibitors, radionuclides, or interferon were permitted providing that toxicity had resolved to grade ≤1 and 4 weeks had passed after last administration. Concomitant treatment with SSAs was allowed. Additionally, eligible patients had documented progression of disease by CT scan, magnetic resonance imaging, or somatostatin receptor scintigraphy within 12 months of study entry; ECOG performance status <2; and a life expectancy >12 weeks.
Cancer Types or Histologic Subtypes	Pancreatic neuroendocrine

Primary Assessment Method	
Title	New assessment
Number of Patients Enrolled	21
Number of Patients Evaluable for Toxicity	21
Number of Patients Evaluated for Efficacy	19
Evaluation Method	RECIST 1.1
Response Assessment SD	*n* = 11 (57.9%)
Response Assessment PD	*n* = 8 (42.1%)
(Median) Duration Assessments PFS	2.6 months, CI: 0.0–14.4
(Median) Duration Assessments TTP	7.7 months, CI: 5.8–13.7
(Median) Duration Assessments OS	18.7 months, CI: 7.4–29.9
Outcome Notes	Of the 21 patients enrolled, 19 were evaluated for response, as one was lost to follow-up after the first cycle of treatment and another one interrupted treatment after 0.7 months due to overall health deterioration. Patients remained on treatment a median time of 2.0 months (range, 1.8–13.8) and the median follow-up was 12.4 months (range, 7.5–19.3). Of the 19 patients with follow-up, the reasons for study discontinuation were disease progression in 16 (84.2%) patients, adverse events (AEs) in 1 (4.8%) patient, death of 1 (4.8%) patient, and other causes (diarrhea unrelated to treatment) in 1 patient (4.8%). A total of 14 patients provided enough tumor tissue at the time of initial diagnosis for immunohistochemical evaluation (Table 1). An H-score >10 (at least 5% of cells with moderate nuclear staining) was seen in 13 (93%), 8 (57%), and 2 (14%) tumors for total pRB1, cyclin D1, and CDK4, respectively (Fig. 3). No statistical differences were observed in any of the biomarkers analyzed in patients with stable and progressive disease.

Adverse Events							
Of Special Interest, All Cycles							
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Generalized muscle weakness	23%	29%	24%	19%	5%	0%	77%
Neutrophil count decreased	52%	5%	14%	24%	5%	0%	48%
Diarrhea	66%	24%	5%	0%	5%	0%	34%
Nausea	66%	24%	10%	0%	0%	0%	34%
Edema limbs	71%	24%	5%	0%	0%	0%	29%
Abdominal pain	75%	10%	5%	10%	0%	0%	25%
Constipation	81%	14%	0%	5%	0%	0%	19%
Anorexia	85%	10%	5%	0%	0%	0%	15%
Anemia	85%	10%	0%	5%	0%	0%	15%
Proteinuria	90%	0%	10%	0%	0%	0%	10%
Platelet count decreased	80%	10%	0%	5%	5%	0%	20%

Abbreviation: NC/NA, no change from baseline/no adverse event.

AEs of any grade occurred in 100% of treated patients, and the number of AEs reported per patient ranged from 2 to 31. The most frequent AEs of any grade were asthenia (76.2% of patients), neutropenia (42.9%), diarrhea (33.3%), nausea (33.3%), and peripheral edema (28.6%). Temporary interruption of treatment because of AEs was reported for eight patients (38.1%), and four patients (19.0%) had to definitively discontinue study medication.

Serious Adverse Events	
Name	**Attribution**
Hypoglycemia	Unrelated
Febrile neutropenia	Probable
Cholangitis	Unrelated
Thrombopenia	Probable
Subarachnoid hemorrhage	Unrelated
Depression of level of consciousness	Unrelated
Lung abscess	Unrelated
Confusion	Unrelated
Tumor fever	Unrelated
Deep venous thrombosis	Unrelated
Thrombocytopenia	Probable
Escherichia coli infection	Unrelated
Acute coronary syndrome	Unrelated
Abdominal pain	Unrelated
Pneumonia	Unrelated
Diarrhea	Unrelated

A total of 19 serious AEs (SAE) were reported in 9 patients (42.9%).

Assessment, Analysis, and Discussion	
Completion	Study completed
Investigator's Assessment	Palbociclib as a single agent failed to demonstrate antitumor activity in pretreated metastatic pNETs

Palbociclib (PD0332991) is a small molecule with highly specific and reversible inhibitory activity against cyclin-dependent kinases (CDK) 4 (IC_{50}, 0.011 µmol/L) and CDK6 (IC_{50}, 0.016 µmol/L). It shows a potent antiproliferative activity in RB-positive tumor cells in vitro, inducing G1 arrest [5, 11–13] in pNET cell lines overexpressing CDK4 [14]. Studies have also demonstrated activity of palbociclib in colon cancer, glioblastoma, breast cancer, and prostate tumor xenografts [13, 15, 16]. Palbociclib (Ibrance, Pfizer) received accelerated approval in 2015 by the US Food and Drug Administration, in combination with letrozole, for the treatment of hormone receptor-positive, human epidermal growth factor receptor (HER2)-negative advanced breast cancer after endocrine-based therapy [17, 18]. On the basis of these findings, the aim of our study was to analyze the efficacy and safety of palbociclib in monotherapy in patients with well-differentiated (grade [G]1 or 2, Ki-67 ≤ 20%) advanced pNETs that had progressed on at least one line of previous systemic treatment.

However, we did not detect activity of palbociclib in molecularly unselected and heavily pretreated patients with advanced G1/2 pNETs. The adverse events observed were consistent with previous reports.

In our view, the development of predictive biomarkers for better patient selection is necessary if future palbociclib studies are considered. The emergence of somatic RB1 inactivating mutations has been observed in patients after exposure to palbociclib and ribociclib, suggesting that they developed under selective pressure of therapy [19]. The use of RB1 and p16 as predictive biomarkers of response to CDK4/6 inhibitors has not been studied in detail, mainly because most clinical trials avoided the inclusion of patients with RB1-negative disease [20]. Resistance to palbociclib has also been correlated with high levels of expression of the *CCNE1* gene encoding cyclin E1, suggesting that this is a potential biomarker of resistance to this drug [21]. Translational studies correlating palbociclib activity with Ki-67 proliferation index are ongoing.

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Disclosures

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures and Table

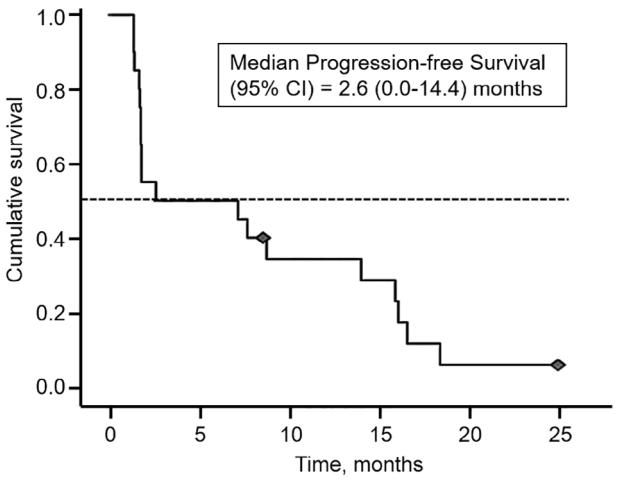

Figure 2. Kaplan-Meier curve for progression-free survival of patients treated with palbociclib (*n* = 20).
Abbreviation: CI, confidence interval.

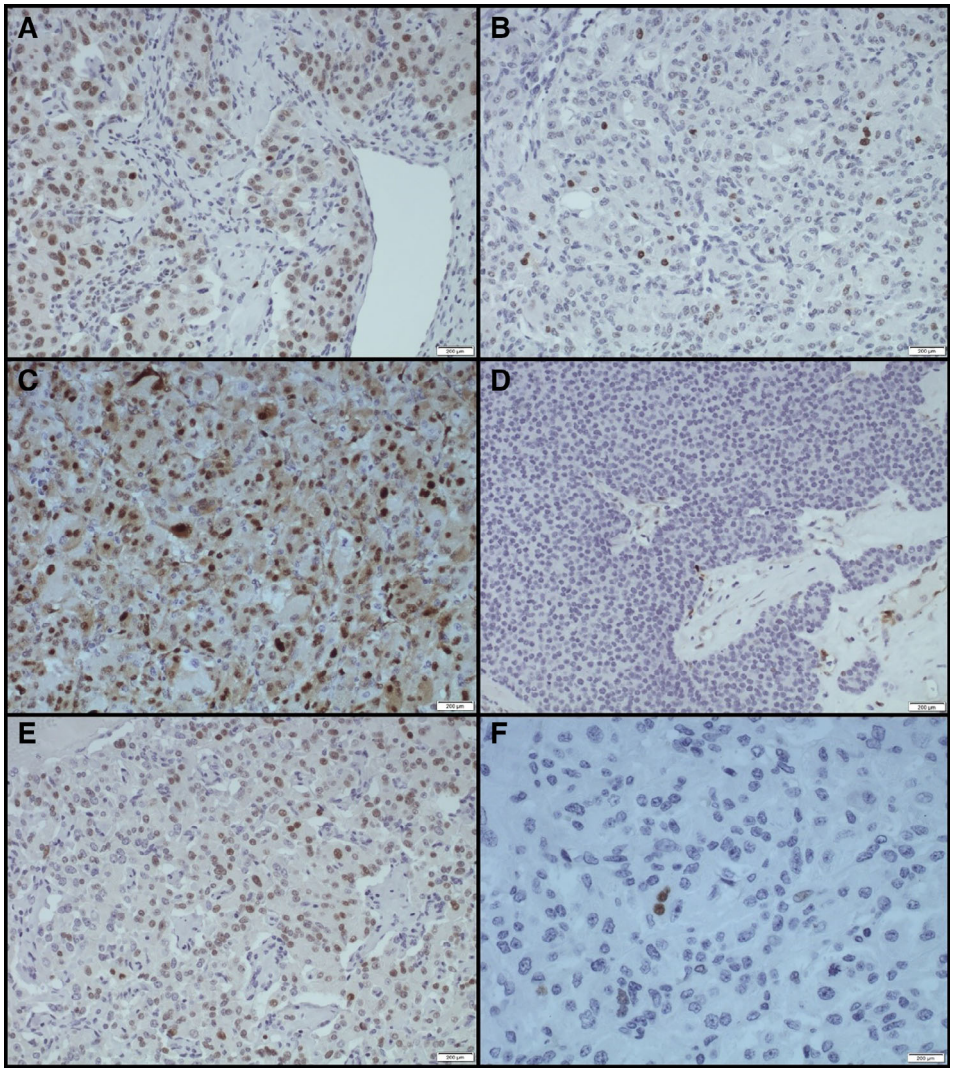

Figure 3. Differences in expression of total pRB, cyclin D1 and CDK4 among pancreatic neuroendocrine tumors. An H-score > 10 (at least 5% of cells with moderate nuclear staining) was seen in 13 (93%), 8 (57%), and 2 (14%) tumors for total pRB1 **(A, B)**, cyclin D1 **(C, D)**, and CDK4 **(E, F)**, respectively. No statistical differences were observed in any of the biomarkers analyzed in patients with stable and progressive disease.

Table 1. Immunohistochemical results

Patient	Cyclin D1, H-score	pRb1, H-score	CDK4, (H-score	p53	Ki-67, %	Response	PFS, mo
U03004	0	190	0	WT	1	SS	25.1
U06001	10	70	0	WT	20	SS	14.1
U05001	1	45	0	WT	20	SS	8.8
U05005	0	120	0	WT	1	SS	7.8
U07001	100	40	0	WT	10	SS	1.8
U04002	210	13	30	WT	3	SS	16.7
U05003	100	160	100	WT	3	SS	16.0
U01002	40	6	0	WT	8	PD	1.8
U07004	240	50	3	WT	3	PD	1.9
U08001	240	110	0	WT	15	PD	1.9
U03005	10	150	0	WT	15	PD	1.5
U07002	0	170	0	WT	3	PD	1.7
U05002	40	125	0	WT	3	PD	1.4
U05004	270	200	0	WT	3	PD	1.8

Abbreviations: PD, progressive disease; PFS, progression-free survival; SS, stable disease; WT, wild-type.