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Clinical Trial Results

Phase II Trial of Palbociclib in Patients with Advanced Esophageal or Gastric Cancer

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Trial Information

- **ClinicalTrials.gov Identifier**: NCT01037790
- **Sponsor**: Peter J. O'Dwyer
- **Principal Investigator**: Peter J. O'Dwyer
- **IRB Approved**: Yes

Lessons Learned

- Palbociclib monotherapy demonstrated minimal clinical activity in patients with previously treated gastroesophageal cancers.
- Further clinical evaluation of palbociclib monotherapy is not warranted in gastroesophageal cancers, but improved understanding of resistance mechanisms may permit rational combination approaches.

Abstract

Background. Dysregulation of the cell cycle is a hallmark of cancer. Progression through the G1/S transition requires phosphorylation of retinoblastoma (RB) by cyclin-dependent kinases (CDKs) 4 and 6, which are regulated by cyclins D and E. Amplifications of cyclin D loci and activating mutations in CDKs are frequent molecular aberrations in gastroesophageal malignancies. We conducted a phase II trial of the CDK4/6 inhibitor palbociclib as an initial test of efficacy.

Methods. Patients with previously treated metastatic gastroesophageal cancers with intact RB nuclear expression by immunohistochemistry were treated with 125 mg daily of palbociclib for days 1–21 of 28-day cycles. The primary endpoint was overall response rate.

Results. We screened 29 patients and enrolled 21 patients: 5 with gastric adenocarcinoma, 3 with gastroesophageal junction adenocarcinoma, 8 with esophageal adenocarcinoma, and 5 with esophageal squamous cell carcinoma. All 29 tumors screened had intact nuclear RB expression, and four treated patients tested positive for CCND1 overexpression. No objective responses were seen. Median progression-free survival was 1.8 months, and median overall survival was 3.0 months. All recurrent grade 3 or 4 toxicities were hematologic, with neutropenia in eight patients (38%), anemia in four patients (19%), and thrombocytopenia in two patients (10%).

Conclusion. Palbociclib has limited single-agent activity in gastroesophageal tumors. ***The Oncologist*** 2020;25:e1864–e1868

Discussion

Cell cycle dysregulation is a cancer hallmark, and alterations in the RB pathway controlling the G1 to S phase cell transition are among the most common in human cancer [1]. Palbociclib is a small molecule inhibitor of CDK4 and 6, which complex with cyclin D1 to phosphorylate RB [2]. Palbociclib improves overall survival in combination with hormonal therapy in metastatic breast cancer [3] and has demonstrated preclinical activity in a variety of tumor types [4].

Gastric and esophageal cancers display increased reliance on the RB pathway, with frequent overexpression of CCND1 and p16 loss [5, 6]. In this study, patients with advanced gastroesophageal cancer with at least one line of prior therapy were treated with palbociclib at standard doses until disease progression. Patients with HER2 overexpression were permitted to continue trastuzumab concurrently with palbociclib.

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Palbociclib monotherapy failed to demonstrate relevant activity in this heavily pretreated population of patients with gastroesophageal cancer. No objective responses were observed, and only two patients had stable disease lasting for more than 4 months: one was treated concurrently with trastuzumab, and both had subsequent progression before 6 months. Median progression-free survival was 1.8 months, and overall survival was similarly short, with a median of 3.0 months (Fig. 1).

The toxicity of palbociclib was as expected, with cytopenias being the only recurring grade 3 and 4 events, with neutropenia in eight patients (38%), anemia in four patients (19%), and thrombocytopenia in two patients (10%). One patient with grade 4 thrombocytopenia experienced upper gastrointestinal bleeding from the tumor in the setting of therapeutic anticoagulation, and palbociclib was stopped. No other patients discontinued therapy because of toxicity, but five patients interrupted treatment because of cytopenias, and four patients had their dose reduced to 100 mg. No patients experienced neutropenic fever or other infectious complications attributable to palbociclib.

Limited biomarker work performed as part of this study confirmed continued RB expression in all patients and CCND1 overexpression by fluorescent in situ hybridization in four patients whose outcomes were similar to the overall population. In the eight patients who had next-generation sequencing, the only gene mutated in more than one patient was *TP53*. No significant correlation was seen between any exploratory biomarker and disease outcome.

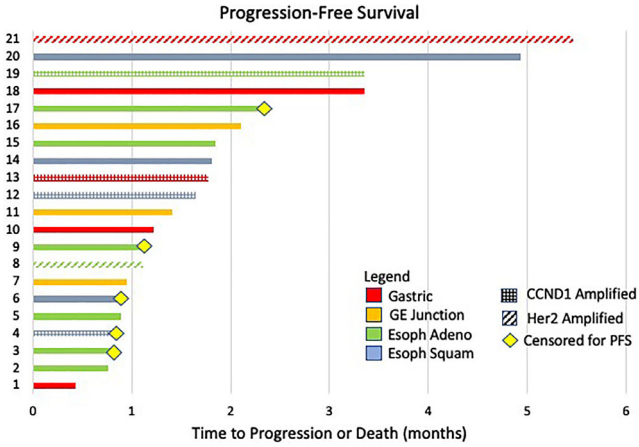

Figure 1. Swimmer plot: progression-free survival.
Abbreviations: Esoph Adeno, esophageal adenocarcinoma; Esoph Squam, esophageal squamous cell carcinoma; GE, gastroesophageal; PFS, progression-free survival.

Based on the limited efficacy demonstrated in this study, further exploration of palbociclib monotherapy in advanced gastroesophageal cancer is not warranted. The disconnect between preclinical activity and the lack of clinical benefit observed in this study and others [7–10] calls into question the validity of CDK4/6 pathway aberrations as broadly actionable targets for cancer therapy.

Trial Information	
Disease	Esophageal cancer
Disease	Gastric cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	No designated number of regimens
Type of Study	Phase II, single arm
Primary Endpoint	Overall response rate
Secondary Endpoints	Toxicity, progression-free survival, overall survival
Additional Details of Endpoints or Study Design	
The response rate of interest in this trial was 15%. If one response was observed in the first 15 subjects, an additional 15 subjects would be enrolled for a total of 30. Observing zero responses in the first 15 subjects would exclude response rates as low as 15% with a 90% one-sided upper confidence bound. If at least three responses were observed in a total of 30 evaluable patients, we would conclude that the drug is active and merited further study; if the true response rate was 15% or greater, three or more responses would be observed with a probability of at least 85%. If the true response rate was only 3%, three or more responses would be observed with a probability of only 6%. In addition to complete and partial responses, disease stabilization would be considered: if the proportion of patients with disease stabilization for 6 months exceeded 20%, we would conclude that the drug may warrant further investigation. With n = 30 subjects and a true response rate of 15%, the expected confidence interval width would be $\pm$10.7% around the estimated proportion. Moreover, we would have 90% power to detect any unforeseen adverse effect that occurred in at least 7% of cases.	
Investigator's Analysis	Level of activity did not meet planned endpoint

Drug Information	
Drug 1	
Generic/Working Name	Palbociclib
Trade Name	Ibrance
Company Name	Pfizer

Drug Type	Small molecule
Drug Class	CDK
Dose	125 milligrams (mg) per flat dose
Route	Oral (p.o.)
Schedule of Administration	Once daily for days 1–21 of a 28-day cycle

Patient Characteristics

Number of Patients, Male	15
Number of Patients, Female	6
Stage	IV
Age	Median (range): 64 years (42–85 years)
Number of Prior Systemic Therapies	Median (range): 2 (1–6)
Performance Status: ECOG	0 — 9 1 — 12 2 — 3 — Unknown —

Other

Eligible patients were aged least 18 years with previously treated locally advanced or metastatic esophageal, gastric, or gastroesophageal junction cancer. All patients had measurable disease per RECIST criteria and an Eastern Cooperative Oncology Group performance status of 0 or 1. Standard laboratory eligibility parameters were used. Tumors must have retained RB nuclear expression by immunohistochemistry. Patients could not have received cytotoxic chemotherapy within 3 weeks or investigational therapy within 4 weeks of the first dose of palbociclib, and prior toxicities of treatment must have returned to baseline or grade 1. Patients with uncontrolled intercurrent illness, human immunodeficiency virus, and untreated brain metastases were not permitted.

Cancer Types or Histologic Subtypes	Gastric adenocarcinoma, 5; gastroesophageal junction adenocarcinoma, 3; squamous cell carcinoma of the esophagus, 8; adenocarcinoma of the esophagus, 5.

Primary Assessment Method

Title	Overall Response Rate
Number of Patients Screened	21
Number of Patients Enrolled	21
Number of Patients Evaluable for Toxicity	21
Number of Patients Evaluated for Efficacy	17
Evaluation Method	RECIST version 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 0 (0%)
Response Assessment SD	*n* = 5 (29%)
Response Assessment PD	*n* = 12 (71%)
(Median) Duration Assessments PFS	1.8 months; confidence interval, 1.1–4.9
(Median) Duration Assessments OS	3.0 months; confidence interval, 1.9–6.6

Outcome Notes

Overall response rate and progression-free survival were assessed using RECIST criteria version 1.1. Subjects were assessed at baseline and approximately every 9 weeks (±4 days) from the first dose of palbociclib until documented progression or withdrawal from the study.

Adverse Events

All Cycles

Name	NC/NA, %	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades, %
Platelet count decreased	85	5	5	0	5	0	15
Neutrophil count decreased	57	0	5	24	14	0	43

Lymphocyte count decreased	81	0	0	14	5	0	19
White blood cell decreased	90	5	0	5	0	0	10
Anemia	67	0	14	14	5	0	33
Headache	95	0	0	5	0	0	5
Aspartate aminotransferase increased	95	0	0	5	0	0	5
Alanine aminotransferase increased	95	0	0	5	0	0	5
Gait disturbance	95	0	0	5	0	0	5
Thromboembolic event	90	0	10	0	0	0	10
Dysgeusia	95	0	5	0	0	0	5
Fatigue	86	0	14	0	0	0	14
Anorexia	90	5	5	0	0	0	10
Diarrhea	95	0	5	0	0	0	5
Rash maculopapular	95	0	5	0	0	0	5
Cough	95	5	0	0	0	0	5

Five patients required dose interruption and four patients required dose reduction to 100 mg of palbociclib because of thrombocytopenia and/or neutropenia. All nonhematologic toxicities were managed without modification of palbociclib dosage.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events

Name	Grade	Attribution
GI bleed	3	Possible
Small bowel obstruction	3	Unrelated
Esophageal obstruction	3	Unrelated
Confusion	3	Unrelated
Atrial fibrillation	3	Unrelated

Abbreviation: GI, gastrointestinal.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Level of activity did not meet planned endpoint

At the time this trial was developed, gastric and esophageal cancers were targeted based on near universal expression of retinoblastoma (RB), frequent overexpression of CCND1, and a positive feedback loop between CCND1 and apoptosis signal-regulating kinase 1 [5]. Later large-scale sequencing efforts through The Cancer Genome Atlas confirmed very low levels of RB pathway mutations, high levels of CCND1 amplification, and frequent epigenetic silencing of p16, all of which were expected to increase reliance on the cyclin-dependent kinase 4 and 6 (CDK4/6) pathway [6]. Importantly, p16 loss was later shown not to correlate with palbociclib sensitivity in breast cancer [11]. A more recent comprehensive mutational analysis of 551 esophageal adenocarcinoma samples demonstrated sensitizing mutations to CDK4/6 inhibitors in more than 50% of samples, with corresponding sensitivity to CDK4/6 inhibitors in cell culture and organoid models [12].

Despite this strong preclinical evidence suggesting a reliance of many gastroesophageal cancers on the CDK4/6 pathway, clinical activity with palbociclib was very limited in this study, a result similar to that seen with palbociclib in a variety of nonbreast tumor types [7–10]. Recent insights into the complex picture of the actions of CDK4/6 inhibitors in cancer may enhance mechanistic understanding and guide future rational combinations [1, 13]. One promising strategy is the combination of CDK4/6 inhibition and immune checkpoint blockade, with multiple publications showing synergy through effects on regulatory T cells, myeloid derived suppressor cells, antigen expression, and interferon production [14–16]. An ongoing trial of abemaciclib with the PD-1 inhibitor pembrolizumab in gastroesophageal cancers may allow for further clinical elucidation of relevant mechanisms of action and resistance (NCT03997448).

Disclosures

Thomas Benjamin Karasic: Pfizer (C/A); **Nevena Damjanov**: Merck (C/A, RF); **Peter J O'Dwyer**: Array, Genentech, (C/A), Pfizer, Genentech, Bristol-Myers Squibb, GlaxoSmithKline, Five Prime,

FortySeven, BBI, Novartis, Celgene, Incyte, Lilly/Imclone, Array, H3Biomedicine, Taiho, Pharmacyclics/Abbvie (RF), Eli Lilly & Co. (ET). The other authors indicated no financial relationships.

(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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