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Clinical Trial Brief Report

Clinical Cancer Research

Activity and Safety of Palbociclib in Patients with Advanced Gastrointestinal Stromal Tumors Refractory to Imatinib and Sunitinib: A Biomarker-driven Phase II Study

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Abstract

Purpose: *CDKN2A* loss is frequent in gastrointestinal stromal tumors (GISTs) and associated with aggressive outcome. Palbociclib is a CDK4 inhibitor with preclinical antitumor efficacy in tumors with P16/CDKN2A loss.

Patients and Methods: This is a multicenter single-arm phase II clinical trial assessing safety and efficacy of palbociclib in patients with advanced GIST bearing *CDKN2A* gene loss. Adults with unresectable locally advanced or metastatic, refractory to at least imatinib and sunitinib, measurable and documented progressive disease (PD) as per RECIST 1.1, and *CDKN2A* deletion centrally assessed were eligible. Patients received palbociclib 125 mg orally daily on a 21 days on/7 days off dosing schedule, until PD or unacceptable toxicity. The primary endpoint was 4-month non-PD rate according to RECIST 1.1.

Results: As of May 2017, 71 patients had been included in the study, and 29 patients (40.3%) met the molecular eligibility requirement. Twenty-five patients (86.2%) had grade 1–2 adverse events (AEs) and 12 patients (41.4%) grade 3–4 AEs possibly related to the drug. The planned interim statistical analysis performed after central histologic and radiological review showed that 19 (86.4%) out of the first 22 evaluable patients had PD at 4 months. *CDKN2A* status had no impact either on overall survival or outcome on previous standard lines of treatment. Translational analysis suggested upregulation of *CCNE1* or downregulation of *CDKN1A/P21* or *LRRC3B* as potential mechanisms of resistance.

Conclusions: Palbociclib has no significant clinical activity as a single agent in *P16/CDKN2A*–deleted GIST refractory to imatinib and sunitinib.

Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors of the gastrointestinal tract characterized by somatic mutations in the gene encoding the KIT or the PDGFR alpha protein (1), and currently treated with oral tyrosine kinase inhibitors (TKI) of KIT and PDGFR such as imatinib, sunitinib, and regorafenib (2, 3). However, prognosis of patients in the metastatic setting remains poor with a need for new therapeutic strategies.

The "CINSARC" molecular signature is a validated predictor of metastasis in patients with GIST that comprises 67 genes involved in maintenance of chromosome integrity and mitotic control, with *AURKA* as the top-ranked overexpressed gene (4, 5). *CDKN2A* encodes two key tumor suppressor proteins, p16INK4a and the p14ARF, which regulate Rb and p53 restriction points, respectively. Normally, p16 prevents the CDK4/CCND1 complex from phosphorylating and inhibiting Rb. *CDKN2A* deletion is frequent in metastatic GIST, and associated with aggressive outcome (5). In the few cases of high-risk GIST lacking *CDKN2A* deletion, the *RB1* gene is deleted. This suggests an association between *CDKN2A* deletion, *RB1* deletion, *AURKA* expression, CINSARC score, and metastasis in GIST.

Palbociclib is a highly selective inhibitor of CDK4/CCND1 kinase activity that also inhibits CDK6, and results in strong suppression of Rb phosphorylation. Palbociclib is approved in

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Gastrointestinal stromal tumors (GISTs) are characterized by alterations in genes regulating cell cycle and particularly *p16/CDKN2A* deletions. We investigate here the prognostic and therapeutic impact of such alterations through a study assessing palbociclib, in p16/CDKN2A-deleted refractory to imatinib and sunitinib. We show here that palbociclib has only limited activity in p16/CDKN2A-deleted GIST patients refractory to imatinib and sunitinib and that this genomic alteration has nonprognostic value.

advanced breast cancer (6), and has also showed preclinical antitumor efficacy in tumors with P16/CDKN2A loss (7, 8). We hypothesized that palbociclib has activity in patients with imatinib and sunitinib refractory, unresectable, or metastatic GIST with *P16/CDKN2A* deletion.

Patients and Methods

CYCLIGIST is a multicenter single-arm phase II trial. Adults with metastatic or unresectable locally advanced, histologically confirmed malignant GIST, previously treated with at least imatinib and sunitinib, measurable and documented progression as per RECIST 1.1, and *CDKN2A* gene deletion centrally assessed by array-comparative genomic hybridization (CGH) were eligible for this study. A key exclusion criterion was *RB1* gene deletion centrally assessed by array-CGH. Patients received palbociclib 125 mg orally daily on a 21 days on/7 days off dosing schedule, after 2 weeks of wash out time from the previous treatment, and until progression of disease, unacceptable toxicity, death, or physician or patient decision. Tumor lesions were assessed according to RECIST v1.1 at baseline within 21 days before the first dose of palbociclib, at cycle 1 day 28, cycle 2 day 28, every 8 weeks until 6 months, and then every 12 weeks until disease progression or start of another treatment. All response had to be confirmed by repeating imaging > 4 weeks. Safety was monitored by assessing all adverse events (AE) continuously through the study. Palbociclib dose adjustment in case of AEs was planned in the protocol. This study was approved by the institutional ethics committee of Institut Bergonié (Comité de Protection des Personnes Sud-Ouest et Outre Mer III). All patients provided written informed consent before enrollment in the study. The corresponding author had full access to the data and had final responsibility for the decision to submit the manuscript for publication.

Statistical consideration

The primary endpoint was the 4-month nonprogression rate defined as the percentage of patients remaining alive and progression-free at 4 months after the first dose of palbociclib as per RECIST 1.1, and based on centrally reviewed radiological data.

A two-stage Simon design was used, (9) with 57 eligible patients needed to distinguish a favorable true 4-month

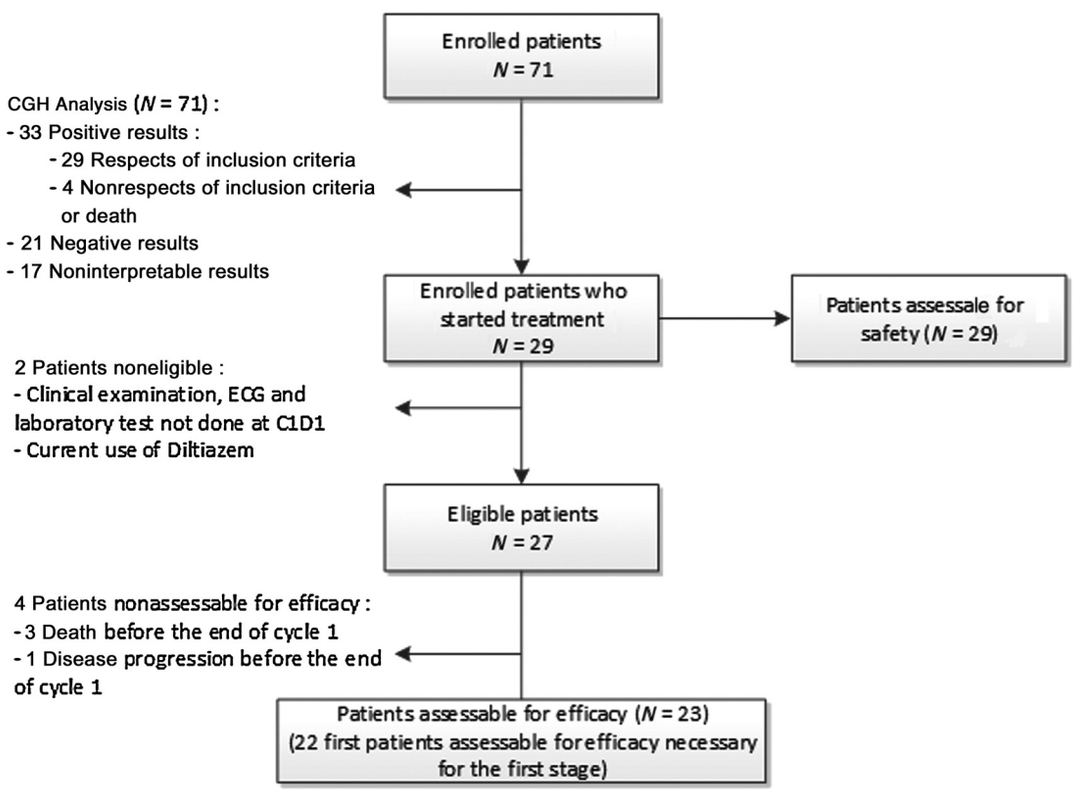

Figure 1.
Flowchart of patients ($N = 71$).

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nonprogression rate of 45% (H1) from a null rate of 25% (H0) with 90% power, and 5% type I error rate (10). Following the inclusion of the first 22 assessable patients, if ≤ 6 patients were progression-free [complete response (CR), partial response (PR), or stable disease (SD)] at 4 months, the study would be terminated early. Otherwise, the second group of 35 subjects would be recruited. If at the end of recruitment, ≥ 20 patients of the 57 assessable patients were progression-free at 4 months, palbociclib would be considered worth further testing in GIST. Secondary endpoints included Safety by CTCAE v4.0, Objective Response defined as CR or PR as per RECIST 1.1, 1-year progression-free survival (PFS), and 1-year overall survival (OS). PFS was defined from start of treatment to time of progression or death (from any cause). OS was defined from start of treatment to death (from any cause) or last patient contact. Patients alive and progression-free were censored at the date of last follow-up. All enrolled patients who received at least one dose of one of palbociclib were eligible for safety analyses. To be assessable for the primary efficacy endpoint, a subject had to meet eligibility criteria and had received at least one dose of palbociclib.

Results

Between February 2014 and July 2016, 71 patients were screened across 8 French Sarcoma Group centers–29 (41%) met the molecular eligibility criteria and started treatment, of whom 23 were assessable for the primary efficacy endpoint (Fig. 1). Baseline patient characteristics are listed in Table 1. Patients were heavily pretreated: 22 patients (76% of the enrolled population) had received more than two previous lines, with a median number of previous lines of four (min:2-max:6).

Seventeen patients (59%) completed at least two cycles. Four patients required treatment dose reduction to 100 mg and one a second dose reduction to 75 mg due to AEs. The most commonly observed toxicities were grade 1 or 2 fatigue (nine patients, 31%), nausea or vomiting (six patients, 21%), myalgia (four patients, 14%), platelet or neutrophil count decrease (four patients each, 14%), and mucositis (three patients, 10%). Grade 3 or 4 toxicities were observed in 12 patients, mainly neutrophil count decrease and anemia (Supplementary Table S2).

At the planned interim statistical analysis, out of the first 22 first patients eligible and assessable for efficacy, 19 (86.4%) had progressive disease (PD) at 4 months, indicating that palbociclib had not reached the primary endpoint for the first step of the study. Out of these 22 evaluable patients, 19 patients presented a tumor assessment during their follow-up, and no objective response was observed. Best response was stable disease (SD) for 14 patients (73.7%) and PD for five patients (26.3%; Fig. 2A). Three patients experienced tumor shrinkage: all of them were gastric GIST with KIT Exon 11 mutation. Median PFS was

Table 1. Patients characteristics ($N = 29$)

	Patients	%
Median age (min–max)	66	(40–81)
Gender		
Male	22	76%
Female	7	24%
Performance status		
0	7	24%
1	19	66%
2	2	3%
NA	1	7%
Location		
Gastric	15	52%
Small bowel	8	28%
Large bowel	2	7%
Other	4	13%
KIT mutational status		
Exon 11	22	76%
Exon 9	3	10%
Other	1	4%
No KIT/PDGFR mutation	3	10%
Number of previous lines of treatment		
2	7	24%
3	8	28%
≥4	14	48%
Previous treatments		
Imatinib	29	100%
Sunitinib	29	100%
Regorafenib	10	34%
Pazopanib	5	17%
Masitinib	4	14%
Sorafenib	4	14%
Nilotinib	3	10%
Dasatinib	1	3%
Dovitinib	1	3%
CDKN2A mutational status		
Homozygotous	18	62%
Heterozygotous	11	38%

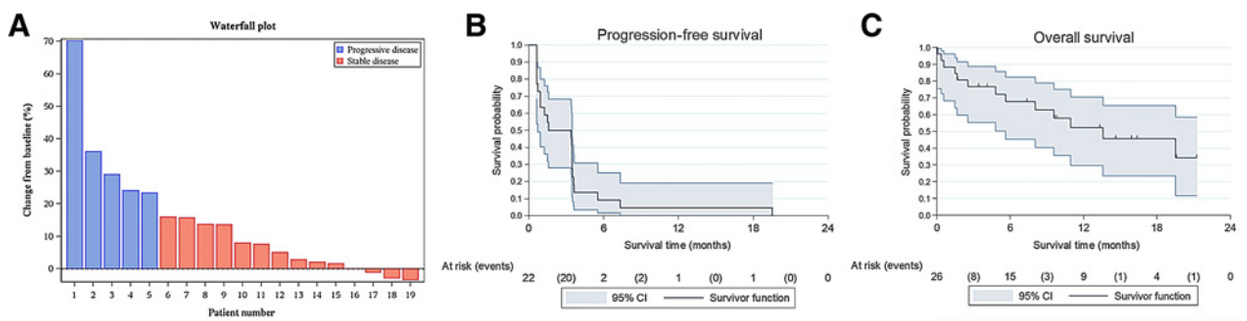

Figure 2.

Efficacy of palbociclib in patients with GIST. **A,** Waterfall plot of tumor change from baseline ($N = 19$). **B,** Kaplan–Meier curves for PFS for the first 22 patients eligible and assessable for efficacy. **C,** Kaplan–Meier curves for OS for the first 22 patients eligible and assessable for efficacy and the four patients withdrawn from study before completion of cycle 1 ($n = 26$).

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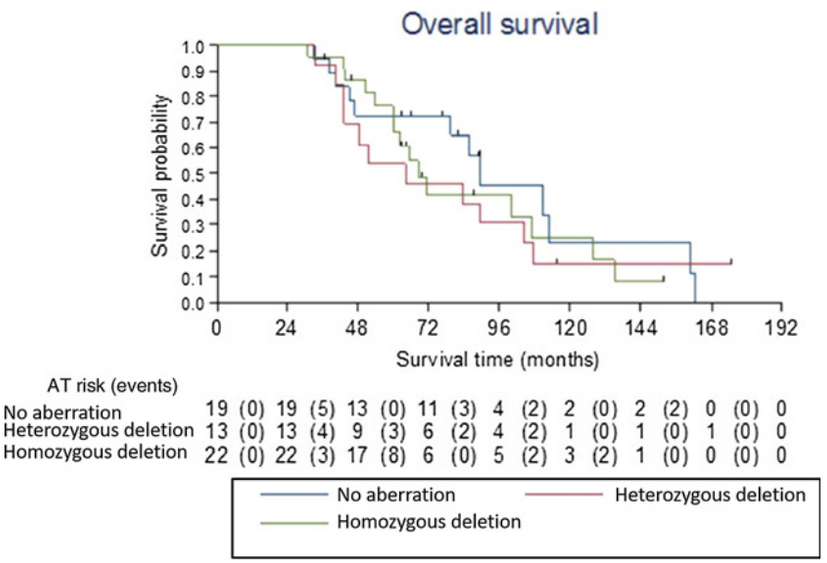

Figure 3.
OS according to *CDKN2A* status ($N = 54$ patients with interpretable results for the array-CGH analysis).

2.5 months (95% CI: 0.7–3.5; Fig. 2B). Nine patients died during the study, seven were still alive after 1-year follow-up and six were lost at follow-up. Median overall survival (OS) of the first 22 eligible patients and the four patients not evaluable for efficacy (study withdrawal before completion of cycle 1; Fig. 1) was 13.6 months (95% CI: 5.6–not reached; Fig. 2C). Among the 71 enrolled patients, 54 had interpretable array-CGH analysis results. Among them, 22 (41%) had homozygous deletion, 13 (24%) heterozygous deletion, and 19 (35%) no deletion of the p16/CDKN2A gene. In these 54 patients, there was no significant association between *KIT* and *CDKN2A* status (Fisher exact test, $P = 0.11$), nor between OS and *CDKN2A* status (log-rank test, $P = 0.38$; Fig. 3). In an exploratory analysis, there was no significant statistical association between previous TKI duration and *CDKN2A* status (nonparametric Kruskal–Wallis test, $P = 0.96$ for imatinib, and $P = 0.21$ for sunitinib, respectively).

Four patients consented to sequential tumor biopsies at baseline and at C2D1. Three of them had exploitable material for RNA-sequencing on paired samples. All three patients had *KIT* exon 11 deletions and *KIT* secondary mutations associated with resistance to KIT inhibitors (11, 12). RNA-sequencing confirmed the presence of alterations of *CDKN2A* and *RB1* showed on CGH at inclusion (Supplementary Table S3).

Using unsupervised clustering, we assessed differential gene expression profile between baseline and ontreatment samples for the three patients. We identified a common set of 25 genes differentially expressed in the three cases (Supplementary Table S4). Among these 25 genes, we found *LRRC3B* as one of the most strongly downregulated genes. We also assessed pharmacodynamics effects of palbociclib with supervised clustering of RNA-sequencing for pRB/E2F pathway target genes, combining sets of genes from previously published signatures (13–15). Patients No. 2 and No. 3, with heterozygous loss of *RB1*, had similar pRB/E2F pathway target genes expression profile variations on-treatment, including strong downregulation of numerous genes positively regulating cell-cycle progression, such as *KI67* and *AURKB*, but also of *CDKN1A/P21* (Supplementary File). Conversely, patient No. 1, who was the one with intact *PRB1* at inclusion, showed upregulation of a large set of E2F target genes on-treatment, including *AURKA*, *AURKB*, *KI67*, and *CCNE1*, together with increase of KI67 expression and also downregulation of *CDKN1A/P21* (Supplementary File).

Discussion

In this trial, we hypothesized that deletion of *CDKN2A* in the absence of homozygous *RB1* deletion in GIST could be a causative event leading to overexpression of CINSARC genes, chromosome instability, and poor prognosis, and that targeting this event by inhibition of CDK4/CCND1 activity could effectively inhibit tumor growth. With 86.4% of patients progressive at 4 months, this study is negative for its primary endpoint. Several factors can explain these results. First, patients were heavily pretreated, with a median of four previous lines of treatment. Second, stopping the KIT/PDGFR inhibition may have contributed to acceleration of tumor growth by releasing tumors clones that were still controlled by the previous TKI. Because no significant toxicity overlap is awaited between both drugs, combination of TKIs, such as imatinib or sunitinib and palbociclib, could be worth to assess. Finally, investigating the pharmacodynamics of palbociclib, we showed deregulation of genes that may play a role in resistance to CDK4/6 inhibition in GIST, such as downregulation of *LRRC3B* and *CDKN1A/P21* and upregulation of *CCNE1*. LRRC3B inhibits cell-cycle progression via downregulation of CCND1 and decreased MMP9 expression. Its downregulation is described in various tumors, most frequently through promoter methylation, and results in deregulation of cycle and proliferation (16, 17). Interestingly, *CCNE1* overexpression and loss of CDK inhibitor p21 have been reported as mechanisms of resistance to palbociclib in breast cancer (18).

Albeit negative, this study brings important new information. Detection of alterations of interest by CGH was highly feasible in the context of the clinical trial. Such techniques are becoming part of routine clinical care in rare tumors such as sarcomas (19). This study shows that it is possible to successfully conduct a study with patients recruited on a specific genomic alteration within a short time in a limited number of centers. It also

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allowed showing no prognostic value for *CDKN2A* deletion and identifying potential mechanism of resistance to CDK4/6 inhibition alone in GIST that can be exploited for documenting combinations trial rationales.

Conclusion

Palbociclib alone has limited efficacy in patients with unresectable locally advanced or metastatic *CDKN2A*–deleted GIST refractory to imatinib and sunitinib. *CDKN2A* deletion is frequent, but has no demonstrated prognostic impact. Better understanding of driver genomic events underlying alternative pathways activation in this patient population with dismal prognosis is warranted.

Disclosure of Potential Conflicts of Interest

J.-Y. Blay is a consultant/advisory board member for Novartis and Pfizer, and reports receiving commercial research grants from Novartis. O. Bouche reports receiving speakers bureau honoraria from Bayer and is a consultant/advisory board member for Novartis. O. Mir is an employee of and has ownership interests (including patents) at Amplitude Surgical and Transgene, reports receiving speakers bureau honoraria from Eli-Lilly, Roche and Servier, is a consultant/advisory board member for Amgen, Bayer, Blueprint Medicines, Bristol-Myers Squibb, Eli-Lilly, Lundbeck, MSD, Novartis, Pfizer, Roche, Servier, and Vifor Pharma. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: C. Lucchesi, A. Italiano
Development of methodology: C. Lucchesi, C.A. Bellera, A. Italiano
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Toulmonde, J.-Y. Blay, O. Bouche, O. Mir, N. Penel, N. Isambert, R. Boidot, A. Italiano
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Toulmonde, J.-Y. Blay, O. Mir, N. Penel, T. Esnaud, D. Geneste, F. Ghiringhelli, C. Lucchesi, C.A. Bellera, F.L. Loarer, A. Italiano
Writing, review, and/or revision of the manuscript: M. Toulmonde, J.-Y. Blay, O. Bouche, O. Mir, N. Penel, N. Isambert, F. Duffaud, R. Boidot, F. Ghiringhelli, C. Lucchesi, C.A. Bellera, F.L. Loarer, A. Italiano
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.-Y. Blay, F.L. Loarer, A. Italiano
Study supervision: A. Italiano
Other (inclusion of patients in the study): F. Duffaud

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Correction: Activity and Safety of Palbociclib in Patients with Advanced Gastrointestinal Stromal Tumors Refractory to Imatinib and Sunitinib: A Biomarker-driven Phase II Study

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In the original version of this article (1) as it was published online on April 12, 2019, the author order is incorrect. The HTML and PDF versions of this article were corrected on April 23, 2019, ahead of print. The publisher regrets this error.

Reference

1. Toulmonde M, Blay J, Bouche O, Mir O, Penel N, Isambert N, et al. Activity and safety of palbociclib in patients with advanced gastrointestinal stromal tumors refractory to imatinib and sunitinib: a biomarker-driven phase 2 study. Clin Cancer Res 2019;25:4611–15.

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