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Population Pharmacokinetic Modeling of Palbociclib in Pediatric Patients with Recurrent or Refractory Tumors

Mark Hadigol[1], Charvi Nanavati[2], Kimberly Lee[3], Justin T. Hoffman[2], Diane Wang[4]

[1] Pfizer, Clinical Pharmacology, Oncology R&D, Collegeville, PA (at the time of the conduct of the study)
[2] Pfizer, Clinical Pharmacology, Oncology R&D, La Jolla, CA
[3] Pfizer, Clinical Bioanalytics, Groton, CT.
[4] Pfizer, Clinical Pharmacology, Oncology R&D, La Jolla, CA (at the time of the conduct of the study)

Objective

To characterize palbociclib pharmacokinetics (PK) using population PK modeling and to identify the covariates that impact palbociclib PK in pediatric patients with recurrent or refractory tumors as a monotherapy and in combination with chemotherapy.

Conclusions

- A 2-compartment model with 1st order absorption and absorption lag time characterized palbociclib PK in pediatric patients well.
- Population PK analysis indicates that BSA-based dosing of palbociclib across various pediatric age ranges is appropriate.
- Formulations (capsule vs oral solution) or treatment combinations (monotherapy vs combination (with IRN/TMZ or TOPO/CTX)) were not found to be a significant covariate for palbociclib PK
- Impact of dexamethasone on palbociclib CL/F in pediatric participants was consistent with moderate CYP3A induction by dexamethasone.

Presenting Author: Charvi Nanavati

Email for more information

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References: 1. Sun et al., The Journal of Clinical Pharmacology2017, 57(9) 1159–1173

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Contact the author at charvi.nanavati@pfizer.com for permission to reprint and/ or distribute.

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Introduction

- Palbociclib, an oral inhibitor of cyclin-dependent kinases 4/6, is approved for the treatment of adult patients with HR+, HER2- advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy or in combination with fulvestrant in patients with disease progression following endocrine therapy, at the recommended dose of 125 mg once daily for 21 consecutive days followed by 7 days off treatment.
- Palbociclib has been evaluated in pediatric participants with recurrent or refractory tumors as monotherapy (NCT02255461; Phase1 study PBTC-042) and in combination with either irinotecan (IRN) and temozolomide (TMZ) or topotecan (TOPO) and cyclophosphamide (CTX) (NCT03709680; Phase 1/2 study A5481092). Palbociclib was administered orally QD (50, 75, or 95 mg/m^2) for 21 days followed by 7 days off treatment (in study PBTC-042) or QD (55, 75, or 95 mg/m^2) on Days 1 to 14 followed by 7 days off treatment (in study A5481092).
- Population PK analysis was conducted to describe the population PK of palbociclib, identify significant covariates that affect palbociclib PK, and support the dosing approach in paediatric patients based on pooled data from Study PBTC-042 and Study A5481092.

Materials and Methods

- A 2-compartment model with first-order absorption and Alag similar to the model described in (Sun et al., JCP, 2017), for adult patients with advanced cancers served as the initial base model.
- Allometric scaling of CL/F, Q/F, KA, Vc/F, and Vp/F via baseline body weight (BWT) and baseline body surface area (BBSA) was explored during base model development to include the effect of body size on PK parameters. The effect of dosing related vomiting during the study on F and KA was evaluated during the base model development due to high rate of vomit events in Study A5481092.
- Based on the mechanistic rationale, literature research and visual inspection of individual ETAs versus covariates, covariates such as sex, race, formulation (capsule vs. oral solution), treatment (monotherapy vs. combination with chemotherapy), concomitant medications (dexamethasone, proton pump inhibitors, H2 receptor antagonists, CYP3A inhibitors), baseline bilirubin, baseline creatinine clearance were selected and tested for significance.
- PopPK modeling as well as SCM were performed using the NONMEM software version 7.4.3. PsN 4.9.0 was used for VPC and R 4.2.1 was used for pre- and post-processing and for summarizing and plotting results.

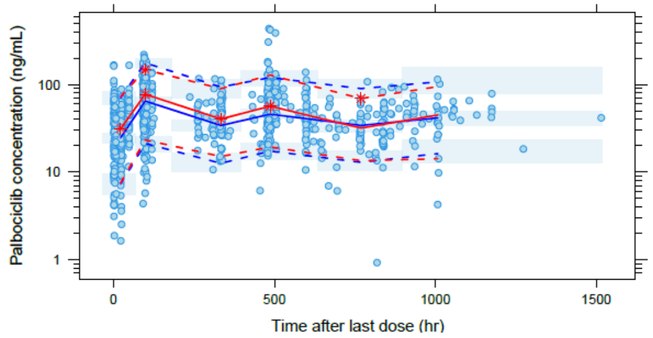
Results

- The pooled clinical data consisted of 1214 PK observations from 139 participants (age range 1-21 years).
- A 2-compartment model with first order absorption and lag time described the PK data for palbociclib in pediatric participants well.
- The final model included the effect of BBSA on CL/F, Q/F, KA, and Vc/F.
- Dexamethasone use was found to be a significant covariate on the CL/F, with an estimated increase of approximately 41% compared to pediatric participants not receiving dexamethasone. This can likely be attributed to dexamethasone-mediated induction of CYP3A for which palbociclib is a substrate. No other covariates were found to be significant.
- Simulations conducted using a palbociclib dosing of 75 mg/m^2 QD following a 2/1 schedule indicated comparable palbociclib exposure across different pediatric age groups and confirmed the appropriateness of BSA-based dosing for palbociclib in pediatric participants.

Table 1: PK Parameter Summary for Palbociclib Final Population Model in Pediatric Participants

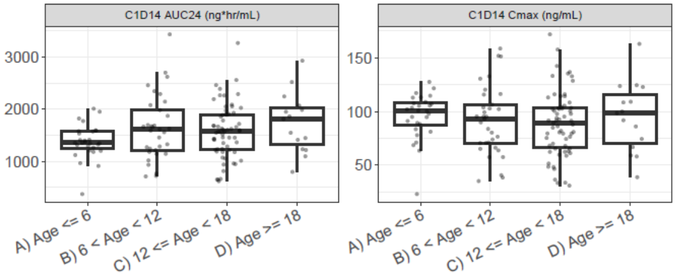
Parameter	Estimate	SE	RSE (%)	CV (%)	Bootstrap median [95% CI]
θ_CL/F (L/hr)	25.615	4.198	16.39	-	25.686 [9.188 – 41.689]
θ_Vc/F (L)	201.001	23.530	11.71	-	201.083 [158.394 – 259.295]
θ_Q/F (L/hr)	41.595	5.818	13.99	-	41.595 [24.55 – 60.743]
θ_Vp/F (L)	129277.0	27353.5	21.16	-	129408.5 [63160.25 – 283923.6]
θ_KA (hr^{-1})	0.061	0.002	3.63	-	0.061 [0.057 – 0.066]
θ_Fk	1.000	FIX	FIX	-	1 [1 – 1]
θ_Alag (hr)	0.444	0.012	2.77	-	0.444 [0.407 – 0.467]
σ (Additive)	0.463	0.023	5.00	-	0.461 [0.41 – 0.507]
Exp BBSA KA	-0.412	0.066	16.04	-	-0.42 [-0.602- -0.294]
Exp BBSA Q/F	1.356	0.228	16.79	-	1.344 [0.696- 2.207]
Exp BBSA Vc/F	1.441	0.288	19.97	-	1.437 [0.773-2.084]
Exp BBSA CL/F	0.395	0.143	36.27	-	0.424 [-0.06-1.037]
DEX effect CL/F	0.409	0.124	30.35	-	0.409 [0.14-0.977]
$\omega^2_{CL/F}$	0.354	0.103	29.18	59.53	0.351 [0.105-0.829]
$\omega_{Q/F}\omega_{CL/F}$	-0.390	0.097	24.79	62.42	-0.378 [-0.593 – -0.12]
$\omega^2_{Q/F}$	0.847	0.197	23.24	92.05	0.821 [0.406 – 1.46]
$\omega_{Vc/F}\omega_{CL/F}$	-0.316	0.184	58.31	56.22	-0.306 [-0.778 – 0.098]
$\omega_{Vc/F}\omega_{Q/F}$	0.499	0.187	37.42	70.64	0.493 [0.122 – 1.026]
$\omega^2_{Vc/F}$	1.135	0.190	16.78	106.56	1.124 [0.811 – 1.535]

Figure 1: Prediction- and Variance-Corrected Visual Predictive Check For Final Palbociclib Model in Pediatric Participants



Observed concentration data points, represented by blue scatter points. The red lines represent the median (solid line), 5th percentile (lower dash line) and 95th percentile (upper dash line) of the observed data. The median, 5th percentile and 95th percentile of simulated concentration values are presented by blue lines. 95% confidence intervals for simulated median and each percentile are shown by light blue shaded areas.

Figure 2: Simulated Palbociclib Exposure Metrics by Age Groups



Individual posthoc PK parameters were used and palbociclib dosing of 75 mg/m^2 QD, following a 2/1 schedule was assumed for simulations.AUC24=area under the concentration-time curve for 24 hours; C1D14=Cycle 1 Day 14; Cmax=maximum concentration.