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Evaluation of Palbociclib and Combinatorial Chemotherapy Pharmacokinetics in Pediatric Patients with Recurrent or Refractory Solid Tumors

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Objective

To evaluate the pharmacokinetics (PK) of palbociclib, temozolomide, irinotecan, cyclophosphamide, and topotecan in pediatric patients when given in combination.

Conclusions

- Palbociclib exhibited dose-proportional PK over the range of 55-95 mg/m^2 QD and comparable exposure across the chemotherapy combinations.
- Palbociclib and combinatorial chemotherapy had similar exposure as reported in previous studies indicating a lack of drug-drug interaction between them.
- Palbociclib exposure at the 75 mg/m^2 QD was similar to that observed in adult participants at the approved 125 mg QD dose suggesting appropriate body surface area-based dosing and attainment of expected target exposure in pediatric population.

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Background

- Irinotecan (IRN)/Temozolomide (TMZ) and Cyclophosphamide (CTX)/Topotecan (TOPO) are used in pediatric, adolescent or young adult patients with relapsed or refractory solid tumors, but outcomes remain poor.
- Non-clinical and clinical data suggest aberrations in cyclin-dependent- kinases (CDK)4/6 pathway can drive the growth of pediatric tumors.
- Palbociclib is a highly selective, reversible, small molecule inhibitor of CDK 4 and 6, administered orally.
- Hence, the objective of this study was to evaluate the PK of palbociclib, TMZ, IRN, CTX, and TOPO in pediatric patients when given in combination in a Phase 1 study.

Materials and Methods

- In an open-label, multicenter, non-randomized Phase 1 portion of the study (ClinicalTrials.gov ID: NCT03709680) palbociclib was given in combination with either IRN/TMZ or TOPO/CTX in children, adolescent, and young adult patients with recurrent/refractory solid tumors.
- Palbociclib was administered orally QD on Days 1 to 14 followed by 7 days off in both combinations (doses of 55, 75, and 95 mg/m^2 with IRN/TMZ and 75 mg/m^2 with CTX/TOPO).
- TMZ was administered QD at 100 mg/m^2, IRN was administered IV at 50 mg/m^2 over 90 minutes, CTX was administered IV at 250 mg/m^2 over 30-60 minutes, and TOPO was administered IV at 0.75 mg/m^2 over 30 minutes, all on Days 1 to 5.
- PK samples were collected as detailed in Table 1. PK parameters were calculated for each analyte, each participant and treatment, using noncompartmental analysis.

Table 1: PK sample collection timepoints

Drug	Study Visit (Cycle and Day) and Sampling time (hr) Post-Dose													
	C1D2	C1D5							C1D6	C1D14	C2D5			C2D14
	Pre-dose	Pre-dose	Post-infusion	1	2	4	6	8	24	Pre-dose	Pre-dose	Post-infusion	1	Pre-dose
Palbociclib (Oral)	X	X			X	X	X	X	X	X	X			X
Irinotecan (IV)	X	X	X			X		X	X		X	X		
Temozolomide (Oral)		X		X		X		X			X		X	
Temozolomide (IV)		X	X			X		X			X	X		
Topotecan (IV)	X	X	X			X		X	X		X	X		
Cyclophosphamide (IV)	X	X	X			X		X	X		X	X		

Results

- Palbociclib exposure increased proportionally with dose. Palbociclib exposure on C1D5 (75 mg/m^2 dose) when dosed with IRN/TMZ was similar to that observed when dosed with CTX/TOPO (Table 2)
- Palbociclib steady state exposure in pediatric participants based on AUC_τ and C_{max} (Table 2) was similar to exposure in adult participants following 125 mg QD dosed as monotherapy (Day 1 to Day 21 followed by 7 days off) on C1D21 (mean AUC_τ = 1733 hr·ng/mL and C_{max} = 97.4 ng/mL)[1]. Palbociclib exposure on C1D5 in pediatric participants following 75, or 95 mg/m^2 QD doses in combination with IRN + TMZ or TOPO + CTX in this study (Table 2) were similar to those observed on C1D21 when palbociclib was administered alone in pediatric participants (mean C_{max} = 139.9 ng/mL (Palbociclib 75 mg/m^2)and 190 ng/mL (Palbociclib 95 mg/m^2.)[2].
- Exposure of IRN/SN-38 (mean IRN C_{max} = 629.3, 595.5, 1033 ng/mL, mean SN-38: C_{max} = 7.386, 8.746, 11.32 ng/mL for 55, 75, and 95 mg/m^2 palbociclib dose combination, respectively), TMZ (mean C_{max} = 3930, 3960, 4404 ng/mL for 55, 75, and 95 mg/m^2 palbociclib dose combination, respectively), CTX (mean CL=3.772 L/hr/m^2), and TOPO (mean AUC_τ = 49.27 hr·ng/mL) were also generally consistent with exposure/parameters observed in published studies [3,4,5,6] (mean IRN C_{max} = 726 ng/mL, SN-38 C_{max} = 13 ng/mL; mean TMZ C_{max}= 3510 ng/mL; mean CTX CL = 2.14 L/h/m^2; mean TOPO AUC_τ = 42.8 h·ng/mL).

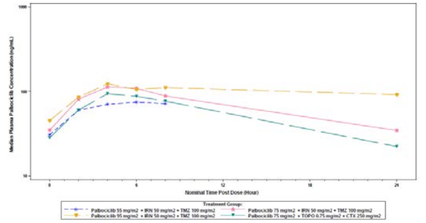
Table 2: Palbociclib Steady-State PK Parameter Summary

Parameter	Palbociclib 55 mg/m^2 + IRN/TMZ (N=4)		Palbociclib 75 mg/m^2 + IRN/TMZ (N=20)		Palbociclib 95 mg/m^2 + IRN/TMZ (N=6)		Palbociclib 75 mg/m^2 + TOPO/CTX (N=26)	
	n	Value	n	Value	n	Value	n	Value
AUC_τ (hr·ng/mL)	3	1161 (7)	14	1538 (49)	6	2082 (38)	20	1290 (59)
CL/F (L/hr/m^2)	3	47.31 (8)	14	48.75 (49)	6	45.61 (39)	20	58.12 (59)
C_{max} (ng/mL)	3	80.44 (21)	15	113.2 (49)	6	127.9 (44)	23	91.45 (58)
C_{trough} (ng/mL)	3	30.42 (7)	15	36.01 (50)	6	44.75 (54)	23	23.98 (81)
T_{max} (hr)	3	6.03 (2.02-6.08)	15	4.17 (1.85-6.47)	6	5.02 (2.07-8.05)	23	4.05 (1.97-24.0)

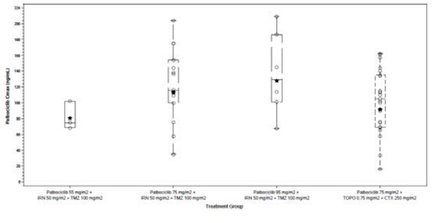
N = Total number of participants in the treatment group in the indicated population. n = number of participants contributing to the summary statistics. Geometric mean (geometric %coefficient of variation) for all except median (range) for T_{max}. Summaries include parameters derived from profiles that meet steady state criteria. Patients with reported vomiting events are excluded in summaries. Make-up visits are included only if Cycle 1 Day 5 is not available/reportable.

Figure 1: Palbociclib Plasma Concentrations Time Profiles, C_{max} and C_{trough} values by Treatment

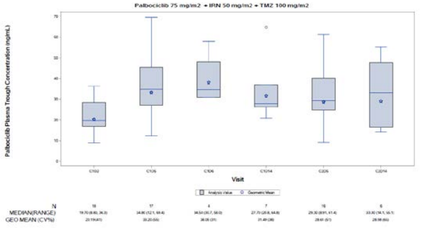
A. Median Plasma Steady-State Palbociclib Concentration-Time Profiles by Treatment (C1D5)



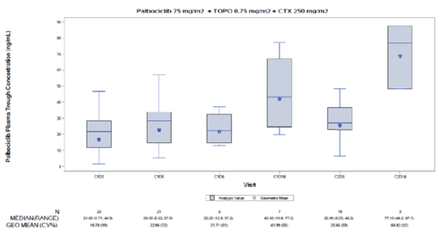
B. Palbociclib Steady State C_{max} Values by Treatment (C1D5)



C. Palbociclib C_{trough} Values by Visit for Palbociclib 75 mg/m^2 + IRN +TMZ



D. Palbociclib C_{trough} Values by Visit for Palbociclib 75 mg/m^2 + TOPO + CTX



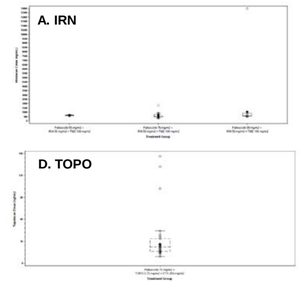


Figure 2: Combinatorial Chemotherapy C_{max} Values on C1D5 by Treatment

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