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Leveraging a Pharmacokinetic/ Pharmacodynamic (PK/PD) Model to Guide Dose Optimization of Palbociclib in Combination With Vepdegestrant

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Objective

- To leverage a PK/PD model to simulate palbociclib exposure and rate of neutropenia, taking into consideration the dose modification and management for hematologic toxicities provided in the palbociclib prescribing information[1]

Key Findings

- The PK/PD model simulation demonstrates that a reduced 100 mg starting dose of palbociclib in combination with vepdegestrant would produce both a similar incidence of grade 4 neutropenia and a comparable and adequate average palbociclib exposure compared with standard palbociclib dosing without vepdegestrant
- In comparison, a reduced 75 mg starting dose of palbociclib in combination with vepdegestrant results in a lower incidence of grade 4 neutropenia, but a lower average palbociclib exposure compared with standard palbociclib dosing without vepdegestrant

Conclusions

- The PK/PD model simulation allows for relative comparison of grade 4 neutropenia incidence and average palbociclib exposure between the planned reduced starting doses of palbociclib (100 mg and 75 mg) in the context of increased exposure relative to standard palbociclib dosing (125 mg), i.e., without vepdegestrant
- Based on the simulation, a reduced 100 mg starting dose of palbociclib, with a resulting 49% increase in exposure (mimicking that observed in the phase 1b combination study of vepdegestrant and palbociclib), provides a similar degree of grade 4 neutropenia and similar exposure as standard palbociclib dosing without vepdegestrant
- This simulation provides support for the study lead-in of the phase 3 VERITAC-3 study (NCT05909397) evaluating the combination of vepdegestrant 200 mg with 2 doses of palbociclib (100 mg or 75 mg) in patients with estrogen receptor (ER)+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer

References

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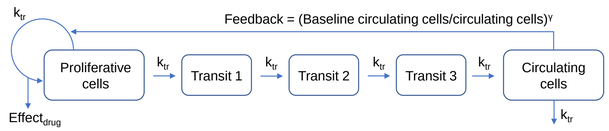
Background and Rationale

- Vepdegestrant is a potent, selective, orally bioavailable PROteolysis TArgeting Chimera (PROTAC) ER degrader that directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation[2]
- The recommended starting dose of palbociclib, a cyclin-dependent kinase 4/6 inhibitor, is 125 mg once daily for 3 weeks followed by 1 week off treatment for each 28-day cycle when combined with aromatase inhibitors or fulvestrant[1]
  - In the registrational trials of palbociclib, PALOMA-2 and PALOMA-3, neutropenia is the most frequently reported adverse event, with an incidence of ≈80% (grade 3/4, 66%)[1]
- When palbociclib (administered according to the recommended starting dose) was co-administered with vepdegestrant in a phase 1b cohort of a first-in-human phase 1/2 study in heavily pretreated patients with ER+/HER2- advanced breast cancer (NCT04072952):
  - Preliminary results showed robust clinical activity for the combination based on clinical benefit rate (rate of confirmed complete response, partial response, or stable disease ≥24 weeks)[3]
  - A 46% to 58% increase in palbociclib exposure was observed relative to historical palbociclib PK data[1] and was accompanied by a higher incidence of grade 3/4 neutropenia compared with prior palbociclib and endocrine therapy combination studies,[4,5] which was managed by monitoring and standard palbociclib dose modifications[3]
  - Please see poster PS15-03 presented by EP Hamilton, et al, to view the findings of the phase 1b study
- The global phase 3 VERITAC-3 study will evaluate the combination of vepdegestrant and palbociclib in participants with ER+/HER2- advanced/metastatic breast cancer (NCT05909397)
  - A study lead-in will explore reduced starting doses of palbociclib (100 mg and 75 mg) to mitigate increased rates of grade 4 neutropenia while maintaining adequate palbociclib exposure when combined with vepdegestrant
  - Please see poster PO2-20-03 presented by S Wander, et al, to view further information on the VERITAC-3 study lead-in

Methods

- A Monte-Carlo simulation platform[6] was utilized to monitor absolute neutrophil count (ANC) in 1000 patients, with weekly monitoring over 4 cycles (112 days) of palbociclib administration
- Simulated ANC was determined using a semi-mechanistic model of chemotherapy-induced myelosuppression as previously described (**Figure 1**)[7]
- Palbociclib dose modification methods included both dose hold and reduction based on an individual's ANC and thresholds for grade 3 (<1000 mm^3) or grade 4 (<500 mm^3) neutropenia
- Simulated neutropenia and exposures from palbociclib starting doses of 100 mg and 75 mg in the presence of a 25%, 49%, and 67% increase in typical exposure were compared with a palbociclib starting dose of 125 mg in the absence of increased exposure (**Table 1**)
- Average palbociclib exposure is calculated as the cumulative area under the curve divided by the simulation duration

Figure 1: PK/PD model structure from Friberg, et al,[7] describing palbociclib impact on ANC



ANC=absolute neutrophil count; k_{tr}=neutrophil transition rate constant; PD=pharmacodynamic; PK=pharmacokinetic

Table 1: Overview of attributes for each set of simulations with varying percent increases in exposure at different palbociclib starting doses

	Reference Palbociclib Simulation	100 mg Starting Dose With Varying % Increases in Exposure	75 mg Starting Dose With Varying % Increases in Exposure
Starting dose	125 mg	100 mg	75 mg
Increase in palbociclib exposure, %	NA	25	25
		49	49
		67	67
Dose reductions	100 mg	75 mg	None
	75 mg		

NA=not applicable

Results

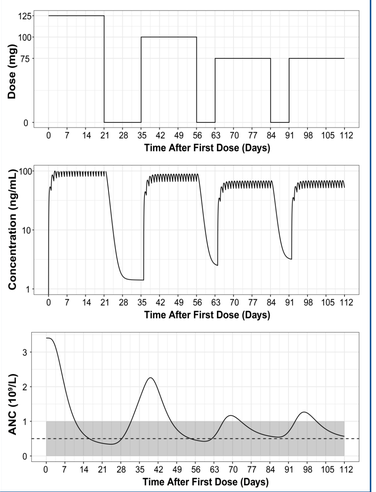
- The simulations provided a relative comparison of neutropenia incidence between different scenarios
- The 100 mg starting dose of palbociclib simulated across varying levels of increased exposure resulted in similar grade 4 neutropenia incidence and average exposure compared with the reference simulation (**Table 2**)
  - In the presence of a 49% increase in palbociclib exposure, a 100 mg starting dose results in similar grade 4 neutropenia incidence and achieves similar exposure compared with a 125 mg starting dose in the absence of increased exposure
- The 75 mg starting dose of palbociclib simulated across varying levels of increased exposure resulted in lower grade 4 neutropenia incidence as well as lower average exposure compared with the reference simulation (**Table 2**)
- The simulation platform is able to successfully adjust the palbociclib dose based on simulated ANC (**Figure 2**)
- Evaluation of a virtual patient with varying palbociclib starting doses as well as percent increases in typical palbociclib exposure highlights the impact of reduced starting doses on grade 4 neutropenia (**Figure 3**)

Table 2: 4-cycle simulation results comparing reduced starting doses of palbociclib in the presence of increased typical exposure to a reference standard palbociclib dosing in the absence of increased exposure

Palbociclib Starting Dose (mg)	Relative Increase in Palbociclib Exposure (%)	Relative Change in Grade 4 Neutropenia Incidence (%)	Relative Change in Average Palbociclib Exposure (%)
	25	-9.0	-7.8
100	49	5.6	2.6
	67	11.8	9.3
	25	-42.4	-31.7
75	49	-31.3	-23.8
	67	-25.7	-19.0

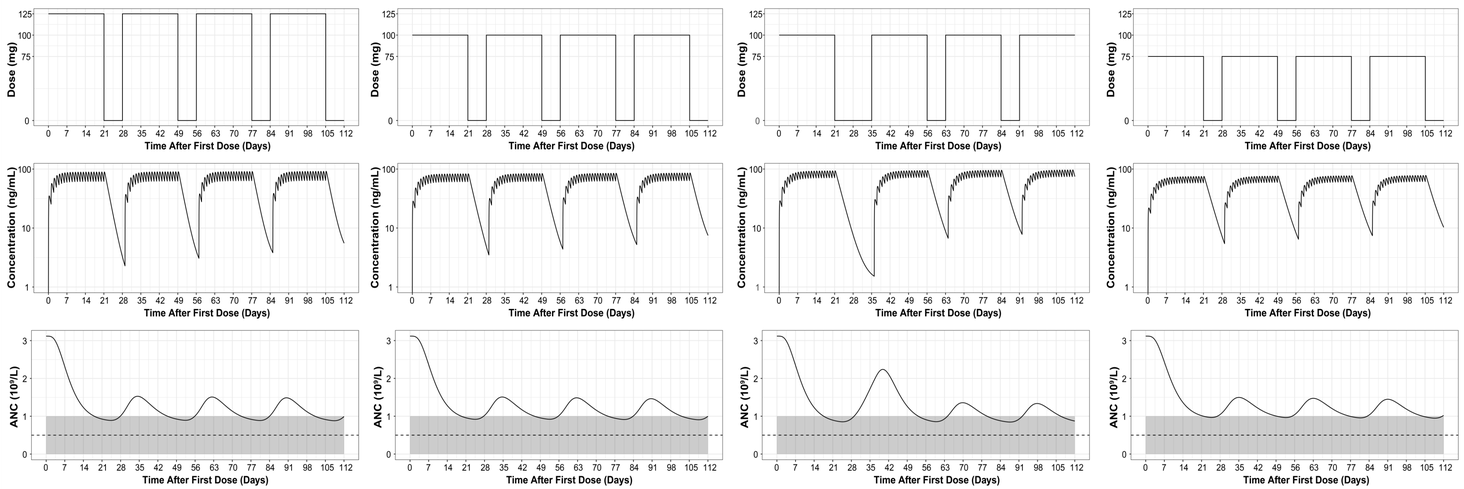
>10% difference (more favorable) | >10% difference (less favorable) | ≤10% difference (comparable)

Figure 2: Simulation result for a virtual patient from the reference palbociclib simulation requiring multiple dose reductions over 4 cycles



The grey shaded area highlights the region of grade 3 and grade 4 neutropenia, with the dotted line showing the cutoff for grade 4 neutropenia
ANC=absolute neutrophil count

Figure 3: Simulation results illustrating the impact of reduced palbociclib starting doses on grade 4 neutropenia in the same virtual patient under various percent increases of typical palbociclib exposure



The grey shaded area highlights the region of grade 3 and grade 4 neutropenia, with the dotted line showing the cutoff for grade 4 neutropenia
ANC=absolute neutrophil count