Optimising Phase 1 oncology dosing schedule of an ATR inhibitor in real time using a model informed approach to predict myelosuppression


Abstract

Oncology phase 1 development is crucial to establish the recommended dose and schedule of novel agents and their combinations for phase 2 trials through dose escalation. Toxicities are important endpoints for phase 1 trials involving cytotoxic agents; it is essential to avoid exposing too many patients to sub-therapeutic doses while preserving safety, maintaining rapid accrual and if possible detect early signals of efficacy and toxicity. Here we utilize emerging data from the AZD6738 phase 1 program and model the relationship between drug exposure and patient safety of a novel oncology compound AZD6738. A quantitative understanding of duration and severity of myelosuppression is vital for dose-regimen optimization in this phase [1].

Introduction

- AZD6738 is a potent, highly specific ATR kinase inhibitor being tested in phase 1 clinical trials in patients with solid malignancies as monotherapy and in combination:
  - An AZ sponsored phase 1 study with a modular protocol:
    - Module 1, combining AZD6738 with chemotherapy, carboplatin
    - Module 2, combining with a PARP-1 inhibitor olaparib.
  - An externally sponsored research (ESR) phase 1 study (PATRIOT) to access AZD6738 as a single agent and in combination with palliative radiation therapy.
  - Thrombocytopenia and neutropenia are known adverse events with carboplatin monotherapy, hence the understanding of the relationship between AZD6738, carboplatin dose and exposure to platelet or neutrophil nadir is essential for selection of tolerated dose and schedule in combination.
  - As part of a model informed drug development [2], a PK-safety modelling approach was applied by integrating data across phase 1 studies to support dose-regimen selection.

Methods

1. Data

Emerging plasma concentration (PK), absolute platelet count (APC) and absolute neutrophil count (ANC) data from 2 phase 1 studies of AZD6738 dosed alone or in combination intermittent doses with carboplatin and olaparib were used.

ATR inhibitor (AZD6738)

<table>
<thead>
<tr>
<th>AUC 5 (21 days cycle)</th>
<th>1 study (n=33)</th>
<th>1 study (n=31)</th>
<th>4 studies (n=152)</th>
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<tbody>
<tr>
<td>Carboplatin</td>
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<td>300 mg BD continuous</td>
<td>100, 200 or 300 mg</td>
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2. Models

- **Dosage regimen**: 20mg, 40mg, 80mg or 200mg.
- **Drug effect**: Reduces proliferation, increases evasion and reduces the output of proliferative cells.
- **PK model**: Dose dependence, non-linear PK.
- **Safety models**: Mitigates the impact of hematologic toxicity by dose adjustments in future trials.

Conclusions

- The model simulations supported team decisions on dose and schedule and will minimize dose adjustments in future trials.
- Understanding single agent and combination safety profiles provided confidence for combination choices and differentiation strategy.

Reference

1. Berges et al PAGE 2017
5. Buil Bruna et al PAGE 2017

Acknowledgements

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