Application of Model-Informed Drug Development for Dose Optimization of Brigimadlin in Patients with Dedifferentiated Liposarcoma:

From First-in-human to Pivotal Trial

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Introduction

- The FDA has recently initiated Project Optimus to reform the dose optimization and selection paradigm in oncology drug development, emphasizing the need for greater attention to optimal efficacy and tolerability rather than selecting the maximum tolerated dose. Model-Informed Drug Development (MIDD) can support this effort by combining multiple sources of data to predict efficacy and safety outcomes in the overall population and in special patient populations.
- In this work, pharmacometric modeling was applied to leverage Phase I (various solid tumor patients), II (mainly biliary tract cancer [BTC] patients) and III (dedifferentiated liposarcoma [DDLPS] patients) data of brigimadlin, a highly potent, oral MDM2-p53 antagonist [1] (see **Figure 1**).

Objectives

The general aim was to support

- dose selection in Phase II and dose justification in Phase III
- clinical development of brigimadlin in patients with DDLPS
- discussion with health authorities and preparation of submission to health authorities

Methods

- During early clinical development, PK-PD models of longitudinal continuous dependent variables were implemented using brigimadlin plasma concentration, biomarker GDF-15, sum of longest diameters of target lesions (SLD), dropout, platelets, neutrophils and body weight.
- During later stage development, modelling was adapted to indication: used variables were brigimadlin plasma concentration, GDF-15, safety, from all patients; safety from BTC patients; SLD from DDLPS patients.
- With more mature data continuous endpoints were replaced by key clinical endpoints (categorical dependent variables): parametric time-to-event model for progression-free-survival (PFS) and the five most relevant safety endpoints: grade 3/4 thrombocytopenia, grade 3/4 neutropenia, grade 3/4, adverse events (AE), AE of special interest (AESI), and serious AE. With long term treatment, dose reductions were considered in modeling via a Markov model.
- NONMEM 7.4 [2] was used for all analyses including covariate search using the stepwise covariate model building procedure with adaptive scope reduction[3,4]. Simulations of the selected endpoints were performed to compare dose levels in groups of interest.

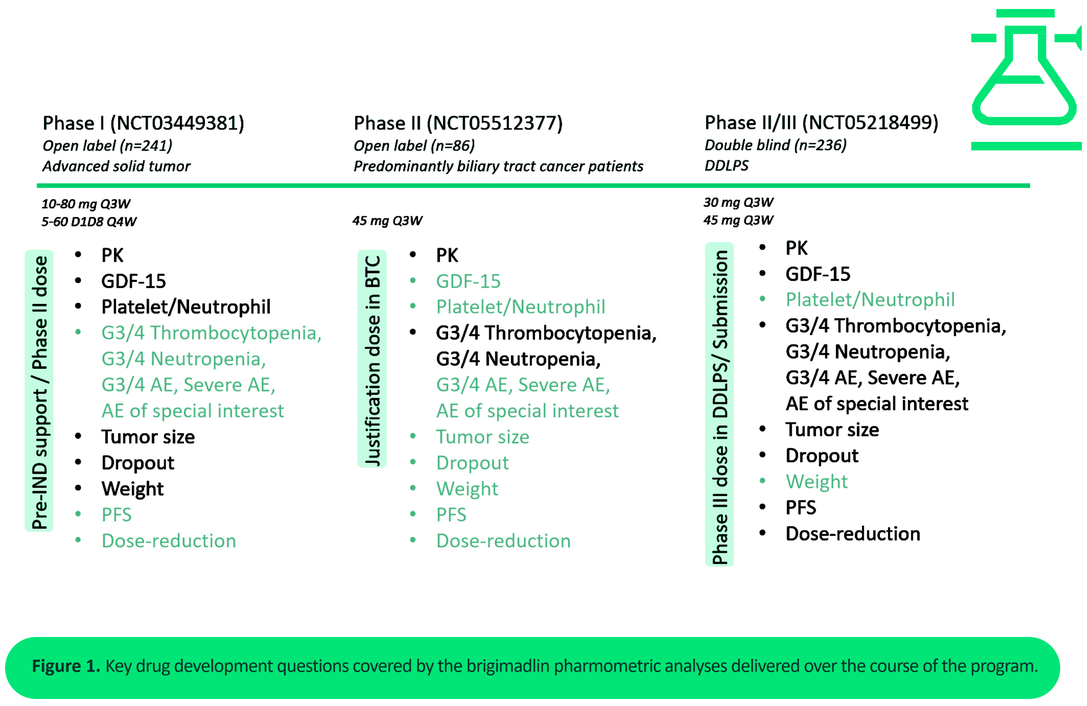

Figure 1. Key drug development questions covered by the brigimadlin pharmometric analyses delivered over the course of the program.

Conclusions

- This work showcases the application of MIDD approaches to dose optimization during an oncology drug development program, from early to late phase, in the Project Optimus era.
- The integrated model-based analysis utilizing clinical PK, efficacy, and safety data from several brigimadlin studies supported the selection of 45 mg q3w as the optimal dose in DDLPS patients.

Results

- In early clinical development:
  - PK/PD modeling confirming expected target engagement and predicted:
    - [biomarker] a >25% higher GDF-15 relative change from baseline at 72 h after 45 mg brigimadlin dosing compared to 30 mg.
    - [efficacy] stronger early tumor shrinkage for exposure associated with 45 mg vs 30 mg q3w.
    - [safety] lower body weight and higher total bilirubin associated with higher brigimadlin exposure, but impact not clinically relevant, and still supporting flat dosing.
- In later stage development:
  - [efficacy] stronger predicted tumor shrinkage after one year of treatment with 45 mg vs 30 mg q3w (-19.5% vs -9.86% relative change from baseline SLD) further supporting 45 mg
  - [efficacy] longer predicted PFS and higher predicted PFS rate of 45 mg compared to 30 mg q3w (≥2.55 months and 6.64%, respectively, after accounting for dose reductions via the developed dose reduction model, see **Figure 2**).
  - [safety] higher number of AE for higher exposures (class effect of MDM2-p53 antagonists for thrombocytopenia, neutropenia, AESI), and additional exposure-independent impact of “Asian race” on neutropenia, resulted in up to 16% higher predicted probability of grade 3/4 compared to non-Asian patients.

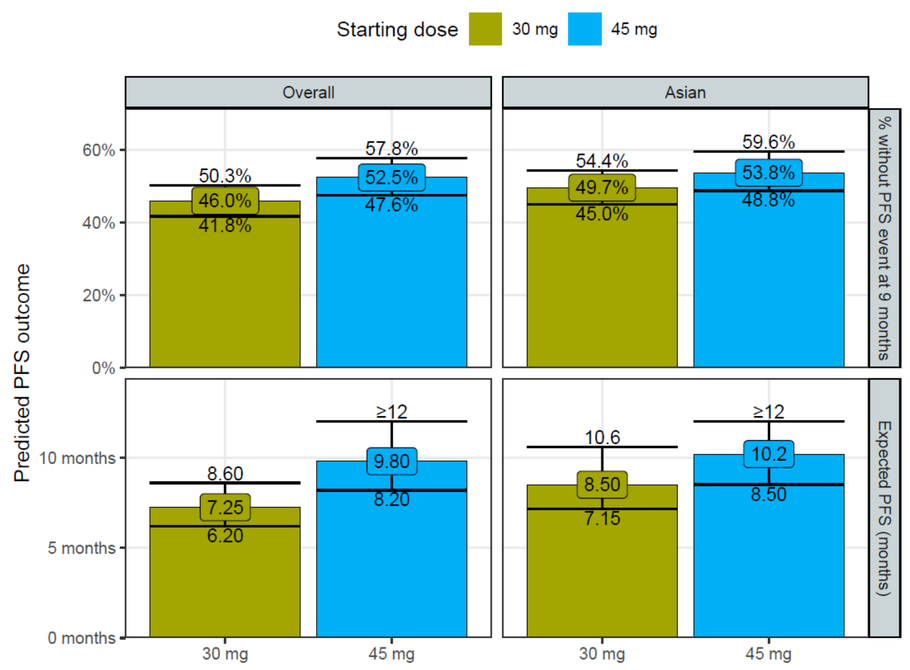

Figure 2. Simulated percentage of patients without a PFS event at 9 months (PFS rate; top panels) and expected PFS in months (bottom panels) by starting dose, for the overall population and for Asians only. Plots are stratified by population and colored by starting dose. The median and 90% CI across 1000 bootstrap replicates are shown by the bar height and error bar, respectively.

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