Application of tumor size modelling and simulations to support the dose selection of brigimadlin (BI 907828) for a Phase II study

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Objectives

To support the selection of a brigimadlin (BI 907828) dose for the Brightline-2 (BL-2) study (NCT05512377) in patients with locally advanced or metastatic, mouse double-minute 2 (MDM2) amplified, tumor protein 53 (p53) wild type biliary tract cancer (BTC), pancreatic cancer or other selected solid tumors [1].

CONCLUSIONS

- The developed models predicted that tumor shrinkage was higher in patients receiving higher doses and in patients with lower body weight (i.e., higher $C_{av,ss}$)
- These results, among assessment of other endpoints, contributed to selecting the 45 mg dose level as the initial dose in the BL-2 Phase II clinical study

Introduction

Brigimadlin is an MDM2-p53 antagonist that is being developed for the treatment of advanced solid tumors. Preliminary data have been encouraging in a variety of tumor types in the monotherapy Phase I clinical trial (NCT03449381) [2] and brigimadlin is now being further studied in patients with BTC in the BL-2 study [1]. Encouraged by the Food and Drug Administration to reform dose selection in Oncology [3], pharmacometric modeling was applied in this program to leverage the phase I data to support the dose selection of the Phase II BL-2 study [2].

Patients and Data

- 81 advanced or metastatic solid tumors patients in the Phase I study [2]
  - 45 Sarcoma of Soft Tissue and Bone, 2 BTC, 34 other tumor types
  - 54 MDM2 amplified, 21 MDM2 non-amplified, 6 unknown MDM2 amplification status
- 314 tumor size (TS) assessments (i.e., sum of longest diameters, SLD), recorded every 6, 8 or 12 weeks or until progressive disease (PD) according to RECIST 1.1 [4] during more than a year since start of brigimadlin treatment
- Brigimadlin treatment
  - oral administration of a film-coated tablet
  - 5-80 mg every third week (q3w)
  - 5-60 mg day 1 and day 8 every fourth week

Methods

Population modelling

NONMEM 7.4 [5]

TS (SLD)

- Derivation of exposure metrics $C_{av,ss}$, $AUC_{\tau,ss}$, $C_{max,ss}$, $C_{min,ss}$
- Claret TGI model [6]
- Exposure-response assessment
- Covariate analysis of patient- and tumor-specific covariates
- Model finalization and evaluation

Dropout from TS assessments

- Logistic regression model
- Covariate analysis of
  - TS-based variables and time
  - Patient-specific covariates
- Model finalization and evaluation

Simulations mrgsolve [7]

- 20, 30, 45 and 60 mg brigimadlin q3w during one year of treatment
- Three different body weights
- 10000 virtual patients with advanced or metastatic solid tumors
- Inter-individual variability included (not residual unexplained variability)
- TS assessments were performed every 6 weeks

Results

Simulations

- The relative decrease from SLD at baseline was larger for higher dose levels and for lower body weights, due to a higher $C_{av,ss}$ (Figure 1)
  - Median decrease (70 kg) after one year of treatment: 3.85% (20 mg), 8.04% (30 mg), 14.2% (45 mg) and 19.7% (60 mg)

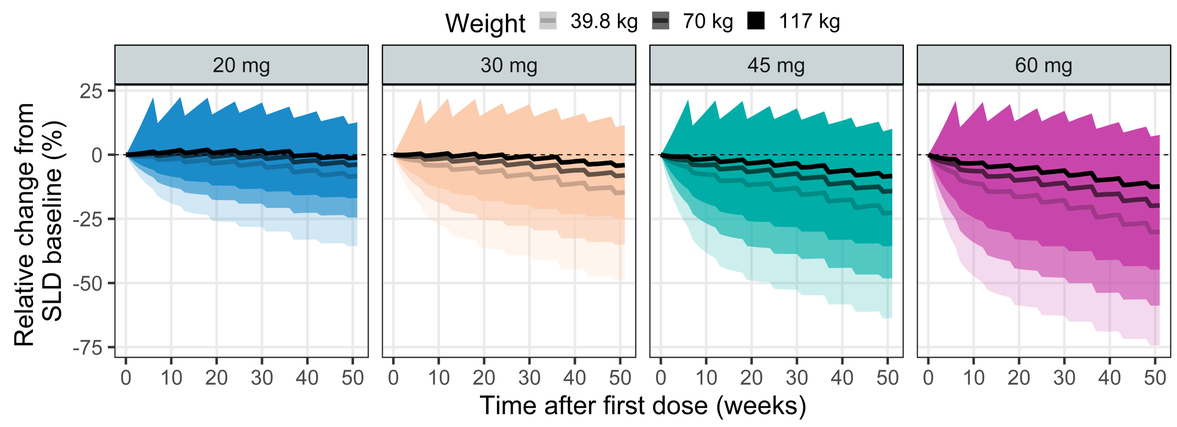

Figure 1. Simulation plots illustrating the effect of brigimadlin dose level (indicated by colors) on the relative change from SLD baseline. These simulations also show the impact of body weight (indicated by shadings of lines and areas). The solid lines and shaded areas display the median and the 90% prediction interval of the simulations, respectively.

Model development

- The final TGI model is described in the equations below

$$\frac{dSLD}{dt} = k_G \cdot SLD - k_D(t) \cdot C_{av,ss} \cdot SLD, \; SLD(0) = SLD_0$$
$$k_D(t) = k_{D,0} \cdot e^{-\lambda \cdot t}$$

- TS model qualified for simulations across different dose levels (Figure 2)
- None of the explored covariates (supplementary information) identified in the TGI model that impact exposure-response
- Probability to dropout from TS assessments increased at the occurrence of PD and decreased exponentially over time
- Model for dropout from TS assessments qualified for simulations (Figure 3)

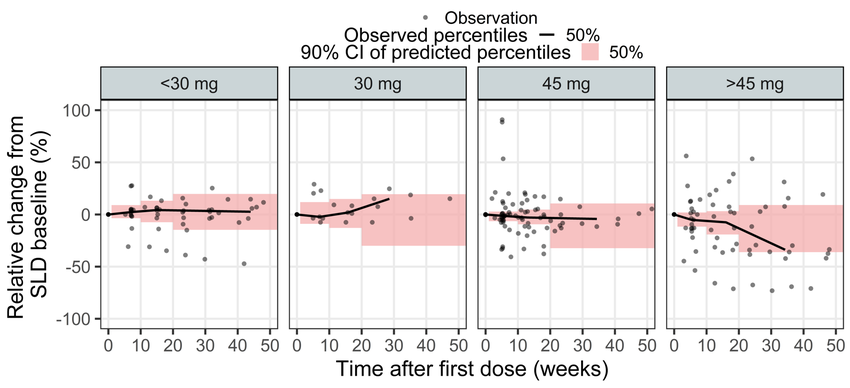

Figure 2. Visual predictive check (VPC) of relative change from SLD baseline versus time after first dose, for the final TS model together with the final TS dropout model, stratified by the assigned dose level. The figure is presenting data up to 50 weeks after first dose.

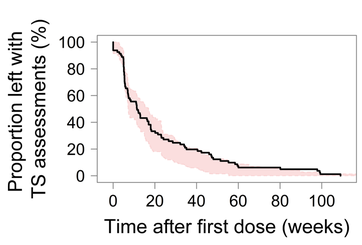

Figure 3. VPC of TS dropout based on Kaplan-Meier curve versus time after first dose, using the final TS dropout model. The black line represents the observed TS dropout data and the shaded red area represents the 95% confidence interval

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1. Brightline-2, Identifier NCT05512377. https://clinicaltrials.gov/ct2/show/NCT05512377; 2. Schoeffski P, et al. Presented at ESMO Congress 2022, Paris, France. Abstract 4520; 3. Fourie Zirkelbach J, et al. J Clin Oncol 2022;40, 30:3489-3500; 4. Eisenhauer EA, et al. Eur J Cancer 2009;Jan;45(2):228-47; 5. Beal SL, et al. NONMEM 7.4 Users Guides. (1989–2019); 6. Claret L, et al. J Clin Oncol 2009; Sep;27(25):4103-8; 7. Baron KT, et al. J Pharmacokinet Pharmacodyn. 2015;42(W-23):S84-5

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Supplementary information

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Supplementary Methods

Logistic regression model

The model for dropout from TS assessments without any predictors is described below:

$$\mathrm{LP}_{\mathrm{DO},0} = \mathrm{logit}(\mathrm{P}_{\mathrm{DO},0})$$

where $\mathrm{LP}_{\mathrm{DO},0}$ is the logit of base probability to dropout per time unit and $\mathrm{P}_{\mathrm{DO},0}$ is the base probability to dropout per time unit. $\mathrm{LP}_{\mathrm{DO},0}$ can be converted back to probability scale by:

$$\mathrm{P}_{\mathrm{DO},0} = \frac{e^{\mathrm{LP}_{\mathrm{DO},0}}}{1+e^{\mathrm{LP}_{\mathrm{DO},0}}}$$

The probability to dropout during a time interval between two TS assessments (P_{DO}) can then be calculated by:

$$\mathrm{P}_{\mathrm{DO}} = 1 - \left(1 - \mathrm{P}_{\mathrm{DO},0}\right)^{\Delta\mathrm{TIME}}$$

where ΔTIME is the time interval between two TS assessments

Covariate analysis

The stepwise covariate model building procedure (SCM) procedure with adaptive scope reduction (ASR) was used for the evaluation of covariate-parameter relationships in the TGI model and for the evaluation of predictors of dropout from TS assessments [1,2]. The forward selection and backward elimination p-values were, respectively, 0.01 and 0.001. Continuous covariate-parameter relationships were implemented as exponential models, while categorical covariate-parameter relationships were implemented as a fractional difference to the most common category.

Parameter-covariates evaluated in the TGI model

Parameters: SLD_0, k_G, and $k_{D,0}$
Covariates: sex, age, weight, race, ECOG and MDM2 amplification status

Predictors evaluated in the dropout from TS assessment model

Parameter: $\mathrm{LP}_{\mathrm{DO},0}$
TS-based predictors: absolute TS, absolute change from TS baseline and relative change from TS baseline over time, baseline TS and PD
Patient-specific predictors: sex, age, weight, race, ECOG and MDM2 amplification status

Model evaluation

Model evaluation was based on the inspection of relative standard errors plausibility of the parameter estimates, graphical diagnostics, including VPCs, as well as changes in the OFV provided by NONMEM

Derivation of exposure metrics

A population PK model, developed in the same population as the TGI model (1479 plasma concentrations in 78 patients), was used to derive exposure metrics that were assessed in the exposure-response relationship in the TGI model. Characteristics of the PK model is given below.

Characteristics of the PK model

The structure of the PK model is illustrated in Figure S1

- Covariate model: Allometric scaling on CL/F, Q/F, V_c/F and V_p/F with fixed allometric exponents (0.75 for CL/F and Q/F) and (1 for V_c/F and V_p/F)
- IIV model: exponential IIV on MAT, CL/F and V_c/F with correlation between etas related to CL/F and V_c/F
- RUV model: proportional RUV (implemented as additive on the log-scale) with an exponential IIV

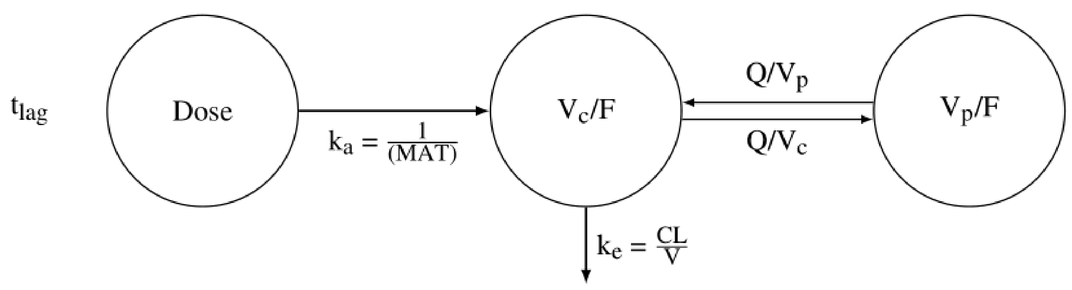

Figure S1. Schematic illustration of the PK model

Exposure metrics

- $\mathrm{AUC}_{\tau,ss} = \frac{\mathrm{Dose}}{\mathrm{CL}}$

  Dose is the last dose given and could vary over time for each dosing interval and CL was constant over time.

- $\mathrm{C}_{\mathrm{av},ss} = \frac{\mathrm{AUC}_{\tau,ss}}{\tau}$

- $\mathrm{C}_{\mathrm{max},ss}$ and $\mathrm{C}_{\mathrm{min},ss}$ - derived from the individual primary PK parameters, given the last administered dose, using mrgsolve. This dose could vary over time for each dosing interval.

Glossary

τ	dosing interval
λ	wash-out of drug-induced tumor shrinkage constant
ASR	adaptive scope reduction
$\mathrm{AUC}_{\tau,ss}$	area under the concentration-time curve during a dosing interval at steady state
BL-2	Brightline-2
$\mathrm{C}_{\mathrm{av},ss}$	average concentration during a dosing interval at steady state
$\mathrm{C}_{\mathrm{max},ss}$	maximum concentration during a dosing interval at steady state
$\mathrm{C}_{\mathrm{min},ss}$	minimum concentration during a dosing interval at steady state
CL/F	apparent clearance
ECOG	Eastern Cooperative Oncology Group Performance status
IIV	inter-individual variability
$k_D(t)$	drug-induced cell kill rate constant
$k_{D,0}$	baseline drug-induced cell kill rate constant
k_G	tumor growth rate constant
$\mathrm{LP}_{\mathrm{DO},0}$	logit of base probability to dropout per time unit
MAT	mean absorption time
MDM2	murine double minute 2
OFV	objective function value
P53	protein 53
$\mathrm{P}_{\mathrm{DO},0}$	base probability to dropout per time unit
P_{DO}	probability to dropout during a time interval between
PD	progressive disease
PK	pharmacokinetic
q3w	every third week
Q/F	apparent inter-compartmental clearance
RUV	residual unexplained variability
SCM	stepwise covariate model building procedure
SLD_0	baseline sum of longest diameters
SLD	sum of longest diameters
SS	steady state
t	time
TGI	tumor growth inhibition
t_{lag}	lag time
TS	tumor size
V_c/F	apparent central volume of distribution
V_p/F	apparent peripheral volume of distribution
VPC	visual predictive check

References

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