Population Pharmacokinetics and Pharmacodynamics (PK/PD) Modeling of Mirdametinib in Patients With Neurofibromatosis Type 1-Related Plexiform Neurofibromas

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Introduction

- Plexiform neurofibromas (PNs) are nerve sheath tumors that develop in ~40% of patients with neurofibromatosis type 1 (NF1)[1,2]
- Substantial morbidities and complications are associated with PNs, such as severe pain, disfigurement, reduced quality of life, and malignant transformation[1-3]
- Mirdametinib is an investigational, oral MEK inhibitor that was evaluated in the Neurofibromatosis Clinical Trials Consortium Phase 2 NF106 clinical trial (NCT02096471) in adults and adolescents ≥16 years of age (n=19)[1]
  - Mirdametinib was dosed at 2 mg/m^2 twice per day on an intermittent dosing schedule (3 weeks on followed by 1 week off)
  - Mirdametinib treatment was associated with a 42% partial response rate in adolescents and adults with NF1 and inoperable PN that were either progressive or causing significant morbidity[1]
  - Study limitations included a small sample size, single capsule dose availability, and lack of dose optimization before study initiation

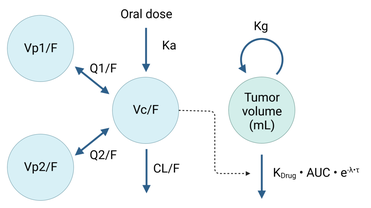
Objectives

- Develop a population PK/PD model for mirdametinib using data from Phase 2 NF106 clinical trial in adolescents and young adults.
- Explore the exposure-response relationship of mirdametinib by clinical trial simulations with the developed population PK/PD model

Methods

- Mirdametinib PK model developed from Phase 1 and 2 clinical data in adults was refined with data incorporated from patients in the NF106 trial (Figure 1)
  - Adult PK model parameters were scaled to the adolescent population by incorporating allometrically scaled body weight.
  - The PK model was optimized for the NF106 data by re-estimating PK Parameters using NONMEM (ver. 7.5).
- An integrated PK/PD model was developed to describe the drug effect on tumor growth dynamic using a tumor growth inhibition (TGI) model.

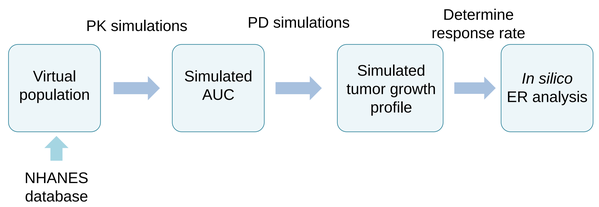
Figure 1. PK-TGI model structure



F: bioavailability:
CL: clearance
Vc: central volume of distribution
Q: intercompartmental clearance
Vp: peripheral volume of distribution
ka: absorption rate constant
Kg: tumor growth rate
K_{Drug}: drug-induced tumor shrinkage rate
AUC: mirdametinib area-under the concentration-time curve
λ: resistance development/tumor regrowth
τ: time

Methods (cont'd)

Figure 2. Flowchart of clinical trial simulations and *in silico* ER analysis



Results

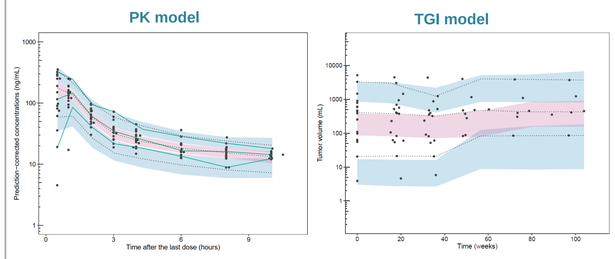
Table 1. Final PK/PD model parameter estimates

Parameters	Estimates	RSE (%)	IIV (%)
PK model			
Ka	2.12 (Fixed)	–	ND
CL/F	5.49	3.40	9.40
Q1/F	4.58	6.30	ND
Q2/F	2.56	13.9	ND
Vc/F	8.68	25.1	77.7
Vp1/F	24.5	11.0	ND
Vp2/F	29.2 (Fixed)	–	ND
TGI model			
K_g	0.00106	62.5	116.6
K_{Drug}	0.0271	24.6	22.4
λ	0.205	24.1	ND
Residual error			
Proportional PK	27.5%	9.60	–
Proportional PD	5.00%	16.1	–

RSE: relative standard error, IIV: inter-individual variability, Fixed: the parameter was fixed to the reference model value, ND: not determined.

- The final TGI model parameter estimate of tumor growth rate (0.00106/week; 5.53% growth/year) was consistent with previously reported natural growth rates[4]
- The TGI model adequately captured the observed tumor growth dynamics of the NF106 trial (R^2 for model-based prediction, 0.994)

Figure 3. Visual predictive check for the final PK-TGI models



Dotted lines represent the median, 5th, and 95th percentiles of observed data. Green solid lines indicate 5th, and 95th percentiles of simulation data. Shaded regions represent the 95% confidence interval of median, 5th, and 95th percentiles of simulation data.

Results (cont'd)

Figure 4. Simulated tumor growth profiles for different dosing regimens

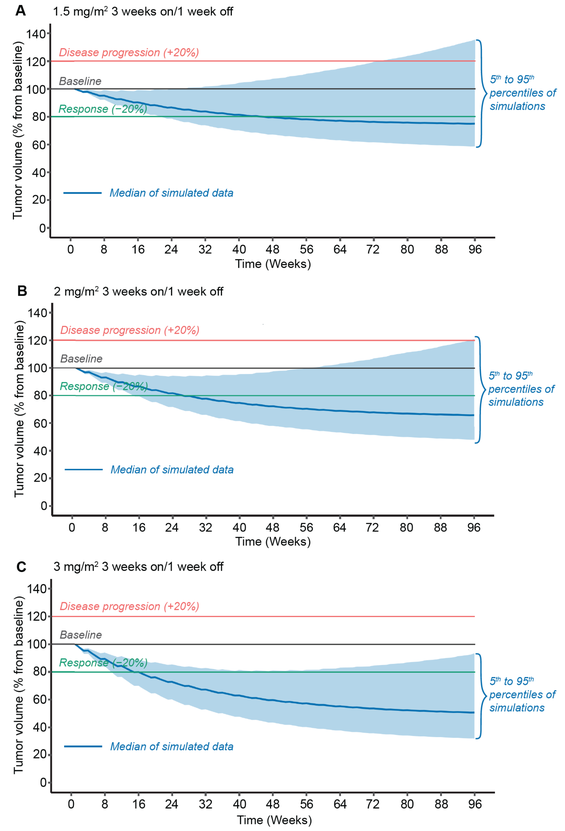
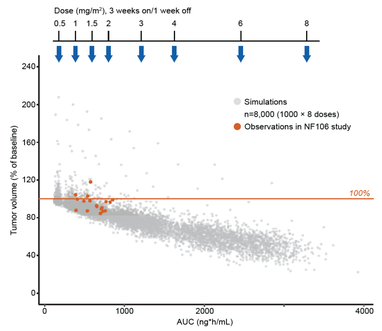
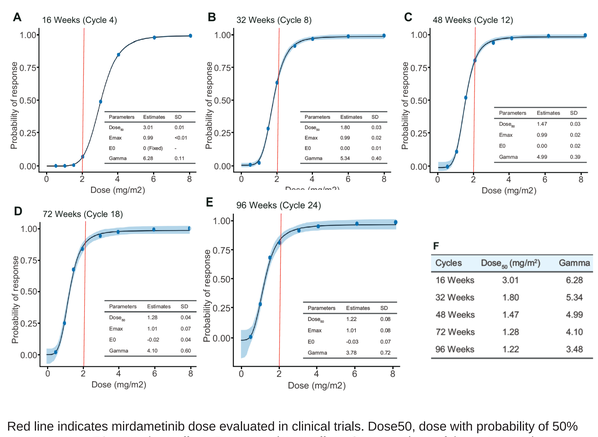


Figure 5. Association of Simulated Steady-State AUCs with Tumor Volume at Cycle 4 (Week 16).



Results (cont'd)

Figure 6. Relationship between dose and probability of response at each cycle



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Cycles	$Dose_{50}$ (mg/m^2)	Gamma
16 Weeks	3.01	6.28
32 Weeks	1.80	5.34
48 Weeks	1.47	4.99
72 Weeks	1.28	4.10
96 Weeks	1.22	3.48

Red line indicates mirdametinib dose evaluated in clinical trials. Dose50, dose with probability of 50% response rate; E0, zero-dose effect; Emax, maximum effect; Gamma, slope of the concentration-effect relationship.

Conclusions

- A mirdametinib PK-TGI model was developed in adolescent and young adult patients with NF1-related PNs.
- The observed tumor volume data in the NF106 study were well captured by the clinical trial simulations using the final model.
- At the mirdametinib dose level evaluated in clinical trials (2 mg/m^2 for 3 weeks-on 1 week-off), approximately 80% of patients in the simulation analysis reached a clinical response (≧20% tumor reduction) after 96 weeks (24 cycles) of treatment.
- Mirdametinib safety, tolerability, and maximization of time on treatment should be considered when determining the optimal dose and regimen.

Acknowledgements

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References

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