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Development of a Population Pharmacokinetic Model for Binimetinib with Subsequent Exposure-Response Analyses in *NRAS* Mutant Melanoma

Lance Wollenberg[1], Mathilde Marchand[2], Henri Merdjan[2], Kevin Litwiler[1]

[1]Array BioPharma, Boulder, CO; [2]Certara Strategic Consulting, Paris, France

ABSTRACT

Objectives

To develop a population pharmacokinetic (PK) model for single-agent binimetinib to assess relevant covariates and exposure-response relationships of overall response rate (ORR) and progression-free survival (PFS) in an *NRAS* mutant melanoma population.

Methods

The PK analysis dataset was constructed by merging data collected in 6 clinical trials (4 Phase 1 studies, 1 Phase 2 study and 1 Phase 3 study) in a total of 75 healthy subjects and 526 patients. Population PK modeling was conducted using Phoenix NLME v.1.3. The exposure-response analysis was conducted using Kaplan-Meier plots and Cox regression for PFS and logistic regression for ORR using R v.3.1.3.

Results

The population PK model for the parent drug was a 2-compartment linear disposition model with first-order oral absorption with lag time, and a log-additive error model. The base population PK model was used to derive individual exposure parameter estimates in cancer patients. These values served as input for exposure-response analysis. The final population PK model with relevant covariates on clearance (Cl/F) and volume of distribution (V/F) is described with the following functional form:

$$Cl/F\ (L/h) = 20.6 \cdot \left(\frac{Age_i}{59\ y}\right)^{-0.020} \cdot \left(\frac{Bilirubin_i}{8.55\ \mu mol/L}\right)^{-0.207} \cdot e^{-0.197\ Mild\ RI} \cdot e^{-0.419 \cdot Moderate\ RI} \cdot e^{-0.159 \cdot female} \cdot e^{0.277 \cdot healthy}$$

$$V/F\ (L) = 107 \cdot \left(\frac{Weight_i}{78\ kg}\right)^{0.683} \cdot \left(\frac{Age_i}{59\ y}\right)^{-0.292} \cdot \left(\frac{Albumin_i}{43\ g/L}\right)^{-1.07} \cdot e^{-0.201 \cdot female}$$

where *Mild RI* and *Moderate RI* represent mild or moderate renal impairment, respectively. In the final covariate model, moderate renal impairment was the most important characteristic to explain variability on Cl/F. Binimetinib exposure-efficacy relationships were assessed based on data from the pivotal Phase 3 study NEMO (CMEK162A2301) in 266 patients with advanced unresectable or metastatic *NRAS* positive melanoma. The ORR probability did not significantly ($p>0.05$) increase with any of the binimetinib steady state exposure metrics. The hazard for PFS significantly decreased with increasing binimetinib exposures (Cmax,ss [p=0.00614], AUCtau,ss [p=0.0237]).

Conclusion

Overall these analyses support the well behaved pharmacokinetic behavior and positive exposure response relationship of binimetinib in a single agent setting.

INTRODUCTION

Binimetinib (or MEK162) is a potent and selective allosteric, ATP uncompetitive inhibitor of MEK1/2 that is active in inhibiting pERK and growth of *BRAF* mutant cancer cells in the low nanomolar range. Binimetinib is currently being investigated as a single agent and in combination with other chemotherapeutic agents in patients with selected advanced or metastatic solid tumors, including biliary cancer, colorectal cancer, and melanoma.

Patients with advanced cancer and healthy subjects have received or are currently receiving single and multiple doses of single-agent binimetinib in doses from 5 to 80 mg in the following studies: [CMEK162X2201] (183 patients with *NRAS* or *BRAF* metastatic melanoma), [CMEK162X1101] (21 Japanese patients with advanced solid tumors), [ARRAY-162-111] (93 patients with advanced biliary or colorectal cancer), [CMEK162X2101J] (37 healthy subjects), [CMEK162A2301] (269 patients with *NRAS* mutant melanoma) and [ARRY-162-0602] (38 healthy subjects).

The population PK analysis presented here was instrumental in the assessment of binimetinib (45 mg BID), in combination with encorafenib (450 mg QD), in the treatment of *BRAF* mutant metastatic melanoma. Combination approval of both of these agents by the Food and Drug Administration was granted June 2018.

METHODS

The PK analysis data set was constructed by merging rich and sparse data collected in a total of 6 clinical trials across a range of doses and regimens from the raw data collected from these studies and are described below in **Table 1**.

Table 1. Number of Subjects and Patients (N) Included in the PK Analysis, Stratified by Study and Dose Cohort

ARRAY-162-111		ARRY-162-0602		CMEK162X1101		CMEK162A2101J		CMEK162X2201		CMEK162X2301 (NEMO)		
Dose cohort	N	Dose cohort	N	Dose cohort	N	Dose cohort	N	Dose cohort	N	Dose cohort	N	Total
		5 mg QD	6									6
		10 mg QD	6									6
		20 mg QD	4									4
		20 mg BID	6									6
30 mg BID	4			30 mg BID	6							10
		40 mg QD	6									6
45 mg BID	40			45 mg BID	15	45 mg	37	45 mg BID	129	45 mg BID	266	487
60 mg	39	60 mg QD	6					60 mg BID	23			68
80 mg BID	4	80 mg	4									8
Study total	87	Study total	38	Study total	21	Study total	37	Study total	152	Study total	266	601

BID: twice-daily; N: sample size in binimetinib arms after data exclusion; QD: once-daily. Note: where no regimen is noted, a single dose was administered.

Datasets, exploratory evaluation and graphs for the population analyses were performed using R® Version 3.1.3 or higher. Descriptions of the population characteristics are presented in **Table 2** and **Table 3**. The population analyses were performed with a validated version of Phoenix NLME v.1.3.

An exploratory graphical screening was initially performed to detect which covariate effects were to be tested in a model-based analysis. The exploratory covariate screening suggested the following effects should be tested in the covariate analysis including creatinine clearance category, age, body weight, sex, total bilirubin, total protein, and NCI score on CL/F and body weight, sex, albumin, and age on V/F. All covariates were found to be significant in a univariate stepwise addition. Backward elimination at the $p<0.001$ level resulted in the dropping of the following covariate effects due to lack of significance on Cl/F: NCI score, total protein, and body weight.

PFS was explored as a function of binimetinib exposure (AUCtau,ss, and Cmax,ss). Model development was supported by exploratory analyses of the data using Kaplan-Meier plots by quartiles of exposure and p-values were assessed by Cox regression versus exposure as a continuous variable. Logistic regression of the probability of objective response or the following adverse events (grade 3 or higher creatinine phosphokinase or any grade retinal event) vs exposure metrics was performed using a general linearized model function with an underlying assumption of a binomial distribution.

Objectives

- To develop a population PK model for binimetinib.
- To predict binimetinib exposures from a sparsely sampled Phase 3 Study (CMEK162A2301 (NEMO).
- To assess exposure-response of PFS, ORR and adverse events of interest in patients with advanced unresectable or metastatic *NRAS* mutation-positive melanoma.

RESULTS

Subject Characteristics at Baseline

Table 2. Count and Frequency of Relevant Categorical Covariates of Subjects in the Population PK Model Dataset

Covariate	N (%) (Overall N = 601)	
Sex	Female: 387 (64)	Male: 214 (36)
Race	Caucasian: 515 (86) Black: 22 (3.7) Asian: 32 (5.3)	Native American: 4 (0.67) Other: 28 (4.7)
Tumor Type	Healthy: 75 (12) Other: 107 (18)	-*NRAS* melanoma: 58 (9.7) +*NRAS* melanoma: 361 (60)
ECOG Score	Unknown: 1 (0.17) 0: 430 (72)	1: 157 (26) 2: 13 (2.2)
Renal Impairment Category	Normal: 383 (64) Mild: 168 (28)	Moderate: 50 (8.3)
Formulation	Capsule: 22 (3.7) Suspension: 16 (2.7)	Array Tablet : 279 (46) Novartis Tablet : 284 (47)
Smoking	Yes: 60 (10)	Unknown: 2 (0.33) No: 539 (90)

ECOG: Eastern Cooperative Oncology Group.

Table 3. Statistics (Mean [CV%]) of Relevant Continuous Covariates for Subjects in the Population PK Model Dataset

Covariate	Mean (CV%)	Covariate	Mean (CV%)
Age (y)	57.2 (27)	Bilirubin (µmol/L)	9.18 (55.7)
Body weight (kg)	80 (22.6)	CRCL (mL/min)	107 (37.4)
Albumin (g/L)	42.1 (11.5)	LDH (U/L)	316 (96.2)
AST (U/L)	25.5 (63.8)	Total Protein (U/L)	71.5 (8.02)
ALT (U/L)	24.6 (73.6)		

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRCL: creatinine clearance; CV%: coefficient of variation; LDH: lactate dehydrogenase; N: sample size.

Final Model Parameter Estimates

Overall, the final population PK model for the parent drug was a 2-compartment linear disposition model with first-order oral absorption with lag time, and a log-additive error model. The final model included the following covariate effects:

- Effects on Cl/F: creatinine clearance category, age, sex, total bilirubin, and health status.
- Effects on V/F: body weight, sex, albumin, and age.

The typical population PK parameters of parent drug in the final population PK model are presented in **Table 4**.

Table 4. Typical Values of Final Structural and Covariate Model Parameter Estimates

Structural Parameters	Fixed Effects			Random effects			
Parameter	Est.	SE	RSE (%)	SE	RSE (%)	IIV%	Shrink.
Ka (1/h)	2.51	0.221	8.8	0.191	9.9	139	32
V/F (L)	107	3.06	2.9	0.0123	22.2	24	57
V2/F (L)	185	13.5	7.3	0.108	15.8	83	57
Cl/F (L/h)	20.6	0.437	2.1	0.00864	8.0	33	16
Cl2/F (L/h)	14.1	0.716	5.1	0.0430	26.1	41	63
Tlag (h)	0.164	0.00142	0.9				
log-additive error	0.499	0.00560	1.1				

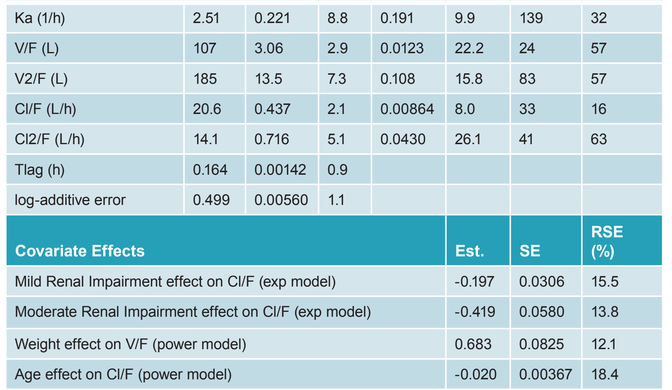
Covariate Effects	Est.	SE	RSE (%)
Mild Renal Impairment effect on Cl/F (exp model)	-0.197	0.0306	15.5
Moderate Renal Impairment effect on Cl/F (exp model)	-0.419	0.0580	13.8
Weight effect on V/F (power model)	0.683	0.0825	12.1
Age effect on Cl/F (power model)	-0.020	0.00367	18.4
Female effect on V/F (exp model)	-0.201	0.0302	15.0
Female effect on Cl/F (exp model)	-0.159	0.0219	13.8
Bilirubin effect on Cl/F (power model)	-0.207	0.0243	11.7
Age effect on V/F (power model)	-0.292	0.0404	13.9
Albumin effect on volume (power model)	-1.07	0.135	12.6
Healthy effect on Cl/F (exp model)	0.277	0.0349	12.6
-2LL: 10181			

Note: -2LL: objective function; Cl/F: apparent oral clearance; Cl2/F: apparent distributional clearance; Est: estimate; IIV: inter-individual variability; Ka: absorption rate constant; RSE: Relative Standard Error; SE: Standard Error; Shrink: shrinkage; Tlag: absorption lag; V/F: apparent volume of distribution of the central compartment; V2/F: apparent volume of distribution of the peripheral compartment.

Final Model Visual Predictive Check of Oncology Patients at Steady State

Steady-state evaluation of model performance was evaluated using a visual predictive check in **Figure 1**. At steady-state, the visual predictive check (VPC) well captured the median of observations and their associated 5th and 95th percentiles in the three studies where the sample size allowed meaningful VPC over the course of therapy (ARRAY-162-111, CMEK162X2201 and CMEK162X2301).

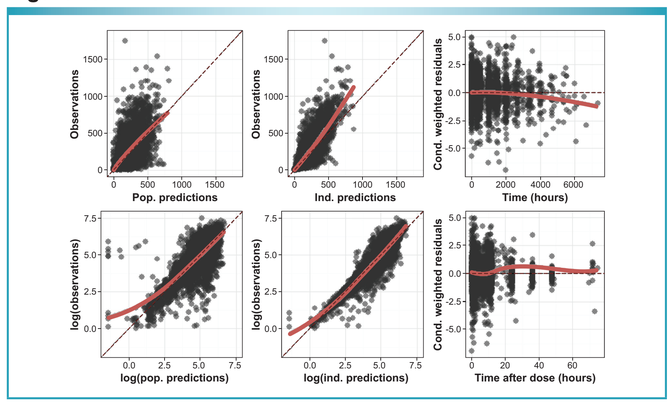
Figure 1.



Final Model Goodness-of-Fit Plots

Goodness-of-fit plots are presented in **Figure 2** including plots of observed concentrations with individual (ind.) and population (pop.) predictions of concentrations in linear and log space. Evaluation of the diagnostic plots indicate tight grouping of predictions and observations along the identity line. Conditional weighted residuals were homogeneously distributed around 0.

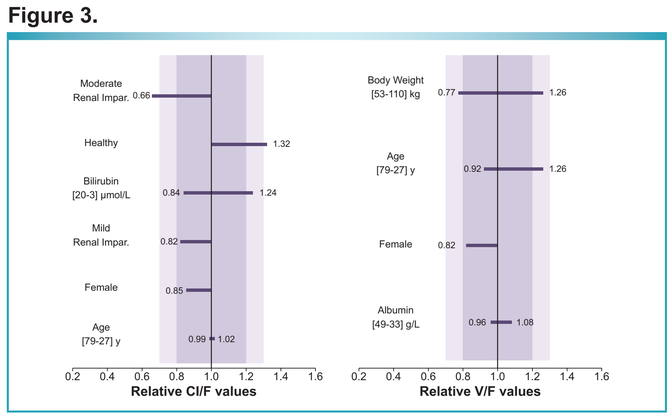
Figure 2.



Magnitude of Covariate Effects

Tornado plots are presented in **Figure 3** and are provided to describe the relative magnitude of covariate effect in a typical subject defined as a 59-year old male patient with normal renal function, and with a total bilirubin level of 8.55 µmol/L for Cl/F, and in a 59-year old male, weighing 78 kg, and with an albumin level of 43 g/L for V/F. Light and dark grey areas represent ±30% and ±20% changes from the reference, respectively. Covariate effects are plotted from top to bottom from the most to least influential. For each covariate effect, a horizontal segment is shown. The left and right ends of each segment represent the effects at the 5th and 95th percentiles, presented as a range in the figure, of each continuous covariate distribution taken from the population.

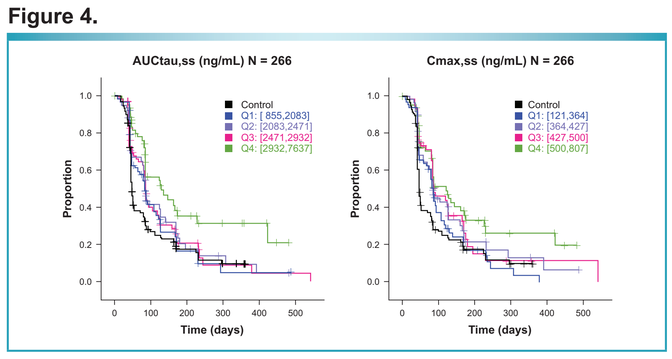
Figure 3.



Exposure-Response Analysis

PFS from the binimetinib arm in Study NEMO (CMEK162A2301) was analyzed in an exposure-response analysis (266 patients, 176 events). The hazard for progression or death decreased with increasing binimetinib exposure, with significant relationships with AUCtau,ss (p=0.0237) and for Cmax,ss (p = 0.00614) by Cox regression. Kaplan-Meier plots of PFS distributions by quartiles of Cmax,ss and AUCtau,ss are shown in **Figure 4** with the distribution in the control group (dacarbazine). The ORR probability did not significantly ($p>0.05$) increase with any of the binimetinib steady state exposure metrics. Analysis of exposure metrics and probability of an adverse event suggested increasing binimetinib Cmax,ss was associated with significantly higher probabilities of any grade retinal events (p=0.00476) or grade 3 or higher creatinine phosphokinase increases (p=0.000981). Increasing total binimetinib exposure (AUCtau,ss) was associated with significant increases in the probability of grade 3 or higher creatinine phosphokinase increases (p=0.00468).

Figure 4.



CONCLUSIONS

- Binimetinib PK obeys a two-compartment linear disposition model with first order absorption.
- Cl/F is influenced by moderate renal impairment, health status, total bilirubin, mild renal impairment, sex, and age. V/F was influenced by body weight, age, sex, and albumin.
- The hazard for progression or death decreased with increasing binimetinib exposure with significance for Cmax,ss and AUCtau,ss.
- Logistic regression analysis indicated significant exposure-response relationships between increased probabilities of grade 3 or higher creatinine phosphokinase elevations or any grade retinal events and increasing binimetinib exposure. No significant relationship between increasing binimetinib exposure and ORR was found.

REFERENCES

1. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/, 2014.

DISCLOSURES

Lance Wollenberg and Kevin Litwiler are employees of and are stockholders of Array BioPharma.
The authors have no other relevant conflicts to disclose.

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