Application of Machine Learning and Grid Search Approaches to Minimize Lucitanib Pharmacokinetic Variability Following Different Dosing Regimens

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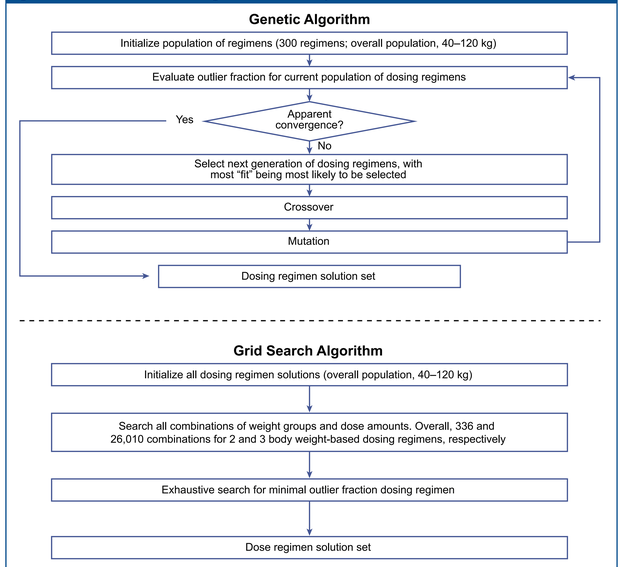
INTRODUCTION

- Lucitanib is an oral, potent tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor receptors 1, 2, and 3 (VEGFR1–3), platelet-derived growth factor receptors alpha and beta (PDGFRα/β), and fibroblast growth factor receptors 1, 2, and 3 (FGFR1–3)[1]; it is currently being evaluated in clinical trials[2,3]
- We sought to compare the variability of lucitanib exposure between weight-based dosing and fixed-dose regimens to inform the selection of an appropriate dosing regimen

METHODS

- Lucitanib pharmacokinetic (PK) profiles were simulated for 5000 virtual patients with a uniform distribution of body weight in 2 populations: overall (40–120 kg) and low weight (40–50 kg)
  - Patients received either a fixed dose (10 mg once daily) or body weight-based dosing (2 dose levels for 1 body weight cut point and 3 dose levels for 2 body weight cut points)
- Genetic and grid search algorithms were used to optimize the body weight-based dosing regimens (**Figure 1**). The fitness function (ie, the quantity to be optimized) for both algorithms was the fraction of outliers, which was to be minimized in this case
  - The fraction of outliers was defined as the percentage of patients for whom the predicted area under the curve during the dosing interval at steady state ($AUC_{tau,ss}$) was outside of the 5th and 95th prediction interval of the $AUC_{tau,ss}$ for 70-kg patients receiving the fixed dose
  - The search space parameters used for the optimization included the cut points for the weight ranges and the administered dose for each weight range
  - A genetic algorithm and a grid search algorithm were implemented using the genetic algorithm package and the grid search algorithm package in R version 3.5.1[5,6]
  - The genetic algorithm used a search space with continuous values of body weight and dose, whereas the grid search algorithm limited the search space to discrete values of body weight and dose (ie, 5-kg increments for body weight and 0.25-mg increments for dose)
- The optimized body weight-based dose regimens were compared to the fixed-dose regimen to reduce variability in exposure

Figure 1. Genetic and Grid Search Algorithms for Dose Optimization



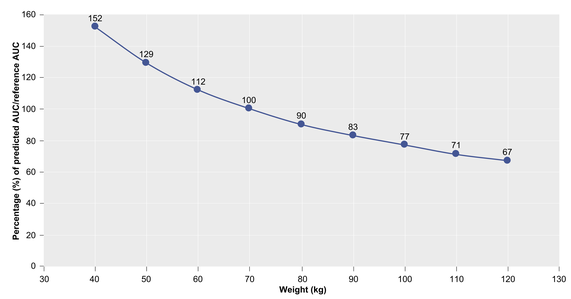
Crossover and mutation functions in the genetic algorithm are probabilistic operators that maintain diversity in a genetic algorithm from one generation to the next to provide solutions for the algorithm.[7]

- Derivative-based optimization algorithms (eg, quasi-Newton methods) required continuous derivatives in the search space of the objective function
  - For the present problem, the abrupt change in the fraction of outliers at the body weight cut points resulted in a discontinuity in the derivative, which would inevitably lead to difficulties with the minimization
  - This was avoided with the genetic algorithm in which the search was driven by crossovers and mutations instead of numeric derivatives

RESULTS

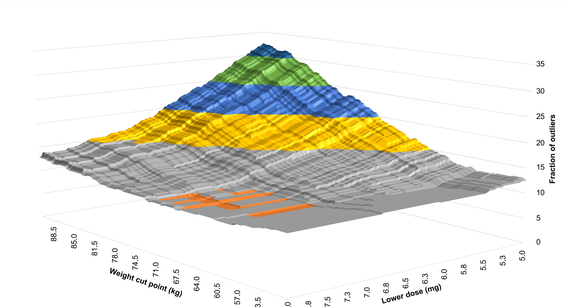
- The PK profile of lucitanib was described using a 2-compartment population PK model with first-order absorption and elimination (Data on file. Clovis Oncology, Inc.)
  - Body weight was a covariate on clearance and volume of distribution and influenced PK exposure
  - The population mean PK exposure was found to decrease with increasing weight in a fixed lucitanib dose regimen (**Figure 2**)
- Inter-individual variability for clearance (CL/F; $CL=a\times(WT)^{0.75}$) was estimated as 50.1%
- The relationship between dose level, weight cut point, and fraction of outliers is plotted in **Figure 3**

Figure 2. Population Mean Weight-Exposure Relationship for Lucitanib Based on an Established Population PK Model



AUC, area under the drug concentration curve; PK, pharmacokinetic; reference AUC, predicted mean AUC in patients weighing 70 kg.

Figure 3. Fraction of Outliers as a Function of Cut Point and Dose Adjustment (mg for Lower Dose) for the 2-Dose Problem



Dose Regimen Optimization Within the Overall Population

- The genetic and grid search algorithms identified similar and reasonable dosing regimens (**Table 1**) within the overall population (40–120 kg, with a uniform distribution across body weight to increase the influence of patients with either low or high weight; N=5000)
- Compared with the fixed dose, the use of 2 or 3 body weight-based dosing regimens decreased the fraction of outliers by ≈1% (2 dose groups), or ≈4% (3 dose groups) in the overall population

Table 1. Lucitanib Dosing Regimens and the Resulting Fraction of Outliers for 40–120-kg Patients[a]

Dosing regimens	Lucitanib dose groups by weight	Fraction of outliers[b] (%)	Decrease in outliers compared to the fixed-dose regimen (%)
Fixed dose	40–120 kg: 10 mg	14.1	-
Grid search algorithm: 2 dose groups	40–<55 kg: 7.25 mg 55–120 kg: 10 mg	13.1	1.0
Grid search algorithm: 3 dose groups	40–<55 kg: 7.25 mg 55–<85 kg: 10 mg 85–120 kg: 13.25 mg	10.4	3.7
Genetic algorithm: 2 dose groups	40–<56.1 kg: 7.3 mg 56.1–120 kg: 10 mg	12.9	1.1
Genetic algorithm: 3 dose groups	40–<56.1 kg: 7.3 mg 56.1–<88.1 kg: 10 mg 88.1–120 kg: 13.6 mg	10.2	3.9

[a]The reported results were based on simulated PK exposures for 5000 virtual patients from a previously established lucitanib population PK model, assuming the weight distribution being uniformly distributed across 40–120 kg.
[b]Outliers were defined as patients outside of the 5th and 95th prediction interval of $AUC_{tau,ss}$ for patients weighing 70 kg receiving the fixed 10-mg dose, 2.7 and 14.3 h × μg/mL, respectively.
$AUC_{tau,ss}$, predicted area under the curve during the dosing interval at steady state; PK, pharmacokinetic.

Low-Weight Population Using the Optimized Dose

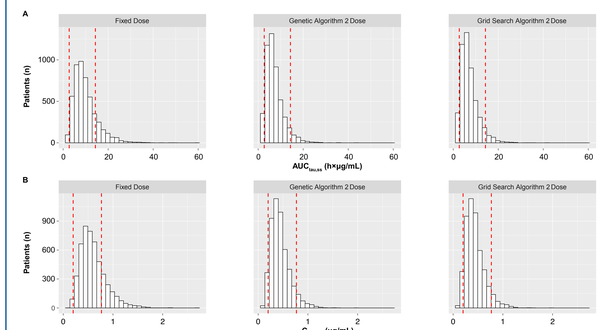
- We evaluated a low body-weight population (40–50 kg, uniform distribution; N=5000) by performing a weight-based dose adjustment (**Figure 3**), because patients with low body weight have the highest drug exposures and potential tolerability concerns with a fixed-dose regimen
- As presented in **Table 2**, body weight-based dosing regimens normalized exposures and decreased the total fraction of outliers (ie, >95th plus <5th percentiles)
  - The fraction of exposure >95th percentile was reduced by ≈10% for $AUC_{tau,ss}$, and ≈15% for the $C_{max,ss}$ compared with the fixed-dose regimen
  - The fraction of exposure <5th percentile increased to a lesser extent
- The relative outlier fractions for >95th or <5th percentiles are also presented in histogram plots (**Figure 4**) for the weight-based dosing regimens compared with the fixed-dose regimen

Table 2. Lucitanib Dosing Regimens and the Resulting Fraction of Outliers for Low-Weight Group (40–50 kg)[a]

Dosing regimens	Lucitanib dose	Fraction of $AUC_{tau,ss}$ outliers[b] (%)		Fraction of $C_{max,ss}$ outliers[c] (%)	
		>95th	<5th	>95th	<5th
Fixed dose	10 mg	16.4	1.2	21.7	0.9
Grid search algorithm	7.25 mg	5.3	4.9	6.0	4.4
Genetic algorithm	7.3 mg	5.5	4.8	6.2	4.1

[a]The reported results were based on simulated PK exposures for 5000 virtual patients from a previously established lucitanib population PK model, assuming the weight distribution being uniformly distributed across 40–50 kg.
[b]Outliers were defined as patients outside of the 5th and 95th percentile prediction interval of $AUC_{tau,ss}$ for 70-kg patients receiving the fixed 10-mg dose, 2.7 and 14.3 h × μg/mL, respectively.
[c]Outliers were defined as patients outside of the 5th and 95th percentile prediction interval of $C_{max,ss}$ for 70-kg patients receiving the fixed 10-mg dose, 0.2 and 0.77 μg/mL, respectively.
$AUC_{tau,ss}$, predicted area under the curve during the dosing interval at steady state; $C_{max,ss}$, maximum concentration at steady state; PK, pharmacokinetic.

Figure 4. $AUC_{tau,ss}$ and $C_{max,ss}$ Outliers for Low-Weight Group (40–50 kg)



Red dashed lines: 5th and 95th prediction interval of $AUC_{tau,ss}$ (A) and $C_{max,ss}$ (B) for patients weighing 70 kg receiving the fixed 10-mg dose, 2.7 and 14.3 h × μg/mL for $AUC_{tau,ss}$ and 0.2 and 0.77 μg/mL for $C_{max,ss}$.
Only 2 dose groups were presented because 3 dose groups had the same results at a low-weight range (40–50 kg).
$AUC_{tau,ss}$, predicted area under the curve during the dosing interval at steady state; $C_{max,ss}$, maximum concentration at steady state.

SUMMARY AND CONCLUSIONS

- **Lucitanib dosage optimization was tested using a previously developed population PK model and simulated patient population with a uniform body weight distribution**
- **The genetic algorithm provided similar results to the more computationally demanding method of grid searching**
- **Although the genetic algorithm provided more accurate results through continuous searching, the weight cut points and doses may need to be rounded for practical reasons**
  - **In contrast, the grid search algorithm evaluated preselected, clinically feasible weight cut points and dose levels**
- **Compared with a fixed-dose regimen, body weight-based regimens showed a small reduction in PK variability for lucitanib in the overall population, potentially due to the existing high interindividual variabilities in PK**
- **Body weight-based dosing provided limited benefits in decreasing the fraction of outliers in the simulated populations compared with a fixed-dose regimen for lucitanib**
- **Although the current analysis used an arbitrary benchmarking population weighing 70 kg where targeted ranges for PK profiles were set, with growing understanding of the targeted therapeutic range and exposure-response relationships, dose optimization for lucitanib will be further evaluated**

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