DEVELOPMENT OF SPARSE SAMPLING STRATEGIES DURING FIRST-IN-HUMAN ONCOLOGY STUDIES: A POTENTIAL APPROACH TO MINIMIZE CONFINEMENT AND FACILITATE ENROLLMENT OF CANCER PATIENTS

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ABSTRACT

Background: Dose-escalation studies in oncology are typically performed to assess safety, tolerability, and pharmacokinetics (PK) and ultimately determine the maximum tolerated dose (MTD). The majority of studies fail to meet enrollment timelines due to the well know difficulties associated to the recruiting of cancer patients. Extensive blood sampling required for PK assessment and the associated confinement of patients remain an important challenge for recruiting patients. A retrospective analysis was performed to determine whether sparse sampling strategies may be developed as part of a dose-escalation trial to optimize PK, minimize confinement and facilitate enrollment of cancer patients.

Methods: Dose-escalation studies involving ≥6 cohorts, ≥15 blood samples per patient and confinement ≥24 hours were included in the analysis. Sparse sampling strategies were developed following accrual of PK data from each cohort. Precision and bias of the area under the curve (AUC) and maximum concentrations (Cmax) derived with rich and sparse samplings were calculated using trial simulations. Relative standard error (RSE) on AUC and Cmax derived with sparse sampling was deemed acceptable. Modeling and simulations were performed using NONMEM (version 7.2) Optimal sampling strategies were developed with WinPOPT.

Results: For drugs with simple PK behavior (e.g., 1-compartment model, linear elimination), population PK models based on rich samples in Cohort 1-2 resulted in acceptable prediction of AUC and Cmax based on sparse samples collected in Cohorts 3-6. For drugs with more complex PK behavior (e.g., 2 or 3-compartment model), rich PK data in Cohort 1-3 resulted in acceptable prediction of PK based on sparse samples in Cohorts 4-6. For drugs with non-linear or target-mediated elimination, rich PK data in Cohort 1-4 may be required to minimize bias.

Conclusion: The above results suggest that sparse sampling strategies may be developed to optimize PK, facilitate enrollment of cancer patients and accelerate completion of dose-escalation studies.

Background

Operational Challenges of Phase I Oncology Studies

- Western markets are saturated: Patient enrollment and retention is more challenging than ever (scarce subjects)
- The majority of studies fail to meet enrollment timelines due to the well know difficulties associated to the recruiting of cancer patients.
- Extensive blood sampling required for PK assessment and the associated confinement of patients remain an important challenge for recruiting patients.

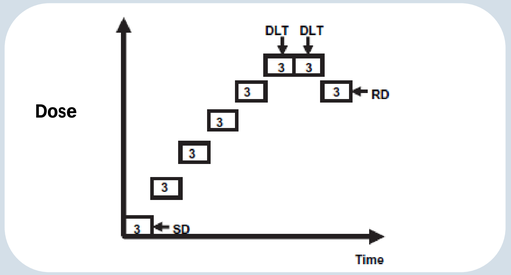
Opportunity

- Perform PK modeling based on data from first 3 cohorts, develop a sparse sampling strategy and apply in subsequent cohorts (e.g., 4, 5, 6…)
- The sparse sampling strategy will remove burden on patient and facilitate patient enrollment
- This will allow to reach MTD faster, and ultimately complete the trial earlier.

METHODS

Modeling and simulations (M&S) may be used in Phase I to develop sparse sampling strategies and minimize blood sampling burden The following framework was developed to optimize the PK component of Phase I oncology studies.

Figure 1: Modeling and Simulations Framework: Sparse Sampling to Facilitate Enrollment of Cancer Patients in Phase I



Sparse sampling strategies were developed following accrual of PK data from each cohort. Modeling and simulations were performed using NONMEM (version 7.2). Optimal sampling strategies were developed with WinPOPT.

Population precision and bias of PK parameters (CL, V, …), of the area under the curve [AUC] and maximum concentrations [Cmax]) derived with rich and sparse samplings were compared. Relative standard error (RSE) on PK parameters were those estimated with NONMEM and the RSE of AUC and Cmax were derived using trial simulations. The bias was calculated with the following equation:

$$\text{Bias}=\frac{PK_{sparse}-PK_{alldata}}{PK_{alldata}}$$

Where $PK_{alldata}$ are parameters derived with the rich data and PK_{sparse} are parameters derived with the sparse dataset

RESULTS

For drugs with simple PK behavior (e.g., 1-compartment model, linear elimination), population PK models based on rich samples in Cohort 1-2 resulted in acceptable prediction of AUC and Cmax based on sparse samples collected in Cohorts 3-10.

Table 1. Relative Standard Error and Bias of PK Parameters for a Tyrosine Kinase Inhibitor Based on Rich and Sparse sampling - Drug with Long Half-Life, 1-Compartment Model

Population PK Parameters	Relative Standard Error| Bias									
	Reference: 10 cohorts with Rich Sampling (N=64)	First Two Cohorts with Rich Sampling (N=6)		First Two Cohorts with Rich Sampling + 2 cohorts with sparse sampling (N=16)		+ 4 cohorts with sparse sampling (N=24)		+ 6 cohorts with sparse sampling (N=49)		+ 8 cohorts with sparse sampling (N=64)	
Ka (h^{-1})	9.7%	36.8%	-40.2%	24.0%	3.9%	18.9%	9.0%	12.5%	13.7%	11.4%	5.3%
CL (L/h)	**10.2%**	**16.5%**	**-10.9%**	**20.8%**	**7.2%**	**15.2%**	**0.6%**	**10.2%**	**-2.4%**	**9.2%**	**-3.6%**
Vc (L)	8.7%	8.3%	-8.6%	8.2%	-14.1%	9.6%	-13.3%	8.4%	-10.8%	6.8%	-9.0%
$Cmax_{SS}$	8.2%	17.9%	11.6%	23.9%	0.3	14.7%	2.8%	9.0%	4.5%	8.5%	5.3%
AUC_{SS}	9.0%	18.8%	14.6%	21.2%	-1.9%	16.5%	0.9%	10.1%	3.0%	9.5%	4.5%

RSE: Derived from NONMEM for the typical values (CL, Vc, Ka) and exposure derived with trial simulation (Cmax, AUC)

Optimal sampling strategy: predose, 2 and 9 h postdose

Table 2. Relative Standard Error and Bias of PK Parameters for a Small Molecule with Potent Multi-kinase Inhibitor Activity Based on Rich and Sparse Sampling – Drug with Short Half-Life, 2-Compartment Model

Population PK Parameters	Relative Standard Error| Bias						
	Reference: 5 cohorts with Rich Sampling (N=71)	First 2 with Rich Sampling (N=10)		First Two Cohorts with Rich Sampling + 2 cohorts with sparse (N=22)		+ 4 cohorts with sparse (N=71)	
Ka (h-1)	9.6%	55.1%	-41.3%	41.5%	-69.8%	26.7%	-73.2%
Lagtime (h)	0.1%	1.9%	18.9%	1.0%	-0.4%	1.4%	1.2%
CL/F (L/h)	**5.9%**	**12.4%**	**1.9%**	**10.2%**	**-13.0%**	**6.3%**	**2.8%**
Vc/F (L)	9.4%	14.2%	-0.7%	15.1%	15.5%	10.4%	4.0%
Q/F (L/h)	17.1%	16.4%	-16.6%	38.8%	-66.1%	22.2%	-31.6%
Vp/F (L)	9.3%	17.5%	-19.7%	24.3%	-42.2%	10.0%	-17.4%
CmaxSS –QD	6.4%	15.4%	3.0%	14.4%	5.7%	8.5%	5.5%
CmaxSS –BID	6.3%	23.4%	1.6%	22.2%	6.2%	8.0%	3.6%
AUCSS –QD	6.0%	13.3%	-0.2%	10.4%	16.0%	6.5%	-2.6%

RSE: Derived from NONMEM for the typical values (Ka, Lagtime, CL/F, Vc/F, Q/F, Vp/F) and derived with trial simulation for drug exposure (Cmax, AUC)

Optimal sampling strategy: predose, 0.5, 4 and 12 h postdose

Table 3. Relative Standard Error and Bias of PK Parameters for an Oral Drug that Induces Apoptosis Based on Rich and Sparse Sampling – Drug with Long Elimination Half-Life, 2-Compartment Model

Population PK Parameters	Relative Standard Error| Bias						
	Reference: 5 cohorts with rich sampling (N=37)	First 2 with rich (N=6)		First Two Cohorts with Rich Sampling + 2 cohorts with sparse (N=13)		+ 4 cohorts with sparse (N=37)	
CL (L/h)	7.0%	12.1%	39.1%	10.7%	31.5%	8.2%	-6.5%
Vc (L)	5.0%	5.4%	-7.0%	5.1%	3.6%	4.1%	-1.1%
Q (L/h)	10.3%	21.8%	-35.9%	19.5%	-34.9%	16.2%	-1.0%
Vp (L)	10.9%	24.4%	-8.1%	19.5%	-10.2%	14.6%	-6.3%
CmaxSS	6.4%	14.2%	-7.3%	12.8%	-15.3%	7.7%	-5.0%
AUCSS	6.9%	12.9%	-27.4%	10.9%	23.6%	8.5%	-6.1%

RSE: Derived from NONMEM for the typical values (Ka, Lagtime, CL/F, Vc/F, Q/F, Vp/F) and derived with trial simulation for drug exposure (Cmax, AUC)

Optimal Sampling Strategy: predose, 1, 96 and 240 h postdose

CONCLUSION

The above modeling and simulations suggests that sparse sampling strategies may be developed to optimize PK analysis in Phase I oncology studies.

The proposed sparse sampling strategies were shown to be robust for a wide varieties of products, with different ranges of half-lives (i.e., short and long)

The sparse sampling strategy may facilitate enrollment of cancer patients and accelerate completion of dose-escalation studies.

Protocols may be designed to prospectively allow a reduction of blood sampling for PK in later cohorts during the study.

The implementation of M&S in Phase I oncology studies may also be used to integrate PK/PD knowledge for decision making (Aarons et al. Eur J Pharm Sci. 2001. 13(2):115-22)