Pharmacokinetic Models for First-in-Human (FIH) Dose Selection of Immune-Activating Products in Oncology

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Abbreviations

- bis-Ab: bispecific antibody
- BW(a): body weight, animal
- BW(h): body weight, human
- CL: clearance
- [C]: targeted plasma concentration
- DHOT: Division of Hematology Oncology Toxicology
- FIH: first-in-human
- FIH(SPM) dose: FIH dose using a simple PK model
- HNSTD: highest non-severely toxic dose
- IA: immune-activating
- mAb: monospecific antibody
- NOAEL: no observed adverse effect level
- MABEL: minimally anticipated biological effect level
- PAD: pharmacologic active dose
- PK: pharmacokinetics
- SPM: simple PK model
- STD10: severely toxic in 10% (of rodents)
- RHD: recommended human dose
- TMDD: target-mediated drug disposition

Disclaimer

This presentation is based on preliminary analysis of data collected in DHOT. Conclusions might change as we continue with the review and analyses.

FIH dose selection in oncology

- Small molecules: 1/10th STD10 or 1/6th HNSTD
- Biological products: a variety of approaches, e.g.
  - Based on PAD or NOAEL
  - Use of a MABEL approach (mainly for immune activating products)
    - Not a single approach: use of in vitro and/or in vivo data; based on activity or target occupancy; can include modeling (e.g. PK modeling)

FIH dose selection

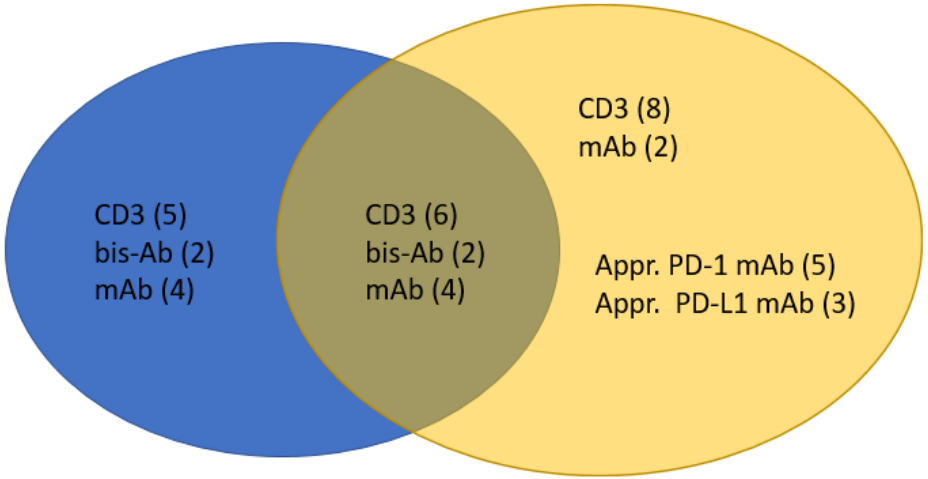
PK models

Cut-off for data collection: May 2023

IA products examined (41 products)

Review of sponsors' proposed PK models (23 products)

For estimation of FIH doses using a simple PK model ($FIH_{(SPM)}$ dose; 30 products)



Blue: The INDs were submitted with PK modeling; the models were reviewed
Yellow: Products used for FIH(SPM) dose estimation.
Appr.: approved; bis-Ab: bispecific antibody; CD3: CD3 multi-specific construct; mAb: monospecific antibody

Review of sponsors' PK models (23 INDs)

- The sponsors' PK models were diverse in methods, assumptions and use of variables, e.g.
  - single vs multi- compartment models
  - models including/ not including factors related to target-mediated drug disposition (TMDD)
  - clearance scaling exponent ranging from 0.75 to 0.9; human BW of 70 to 80 kg

- Allometric scaling for clearance using the NHP data was discussed in most models

- Safety margins (ratio of doses given to humans in clinical trials to PK-based proposed FIH doses)? 1- to 20,000-fold
  - ❖ 1-fold: CD3 construct
  - ❖ 20,000-fold: mAb

Use of a simple PK model for FIH dose selection (30 INDs)

Equation 1: $Clearance(h) = Clearance(a)\left(\frac{BW(h)}{BW(a)}\right)^{b}$

Equation 2: $FIH_{(SPM)}\ Dose = CL_h * [C] * tau$

a: animal; BW: body weight; CL: clearance; [C]: targeted plasma concentration; h: human; tau: dosing interval

BW(a)= 3 kg for cyno monkey; 25 g for mouse

1) B=0.85 and BW(h)= 70 kg
2) B=0.75 and BW(h)=60 kg

#1 was common in sponsors' PK models.
FIH doses using #1 are about 50% higher than those using #2, when scaling is based on NHP data

Impact of [C]: 2 sets of [C]

a) Those proposed by the sponsors (carefully selected; implied by justifications provided by the sponsors)
b) Mean EC50 from in vitro activity studies, irrespective of assay relevance or sensitivity

FIH(SPM) doses scaled from the NHP studies: CD3 constructs (14 INDs)

Description

- Green (safe approach): the FIH dose was at least 3-fold below the doses that have been given to humans and which had reasonable safety profile (e.g. no IND hold, no dose reduction).
- Red (unsafe approach): the FIH dose was at or above the dose that has been given to humans (with reasonable safety), or is too close to it (< 3-fold)
- Grey cells: FIH(SPM) dose could not be computed. [C] not found in the IND

FIH(SPM) doses: CD3 constructs (cont'd)

- Red (43%): mostly when mean EC50s were used irrespective of assay relevance or sensitivity
  - importance of selecting appropriate assays for [C]
- All products in the green zone when: b=0.75, BW(h)=60 kg, and appropriate [C] was used (i.e. sponsor's proposed [C]).
- 1 product in the red zone (b=0.85, BW=70 kg) even when [C] was based on a relevant/sensitive assay. This product was in the green zone when b=0.75 (60 or 70 kg BW)
  - Is the scaling factor of 0.85 appropriate for all CD3 constructs?
- Safety margins: 4- to 600-fold from human doses (using appropriate pharmacology studies for setting the [C])
  - *In comparison, 1- to 800-fold margins for sponsors PK-based models*

Results for mAbs (14 INDs)

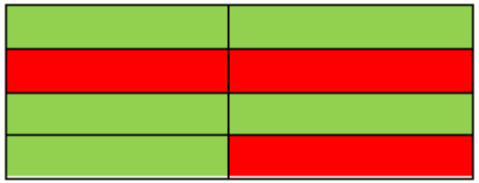
	b=0.75; BW(h)=60 kg	b=0.85; BW=70 kg
Sponsor's plasma conc		
Mean EC50		
Sponsor's plasma conc		
Mean EC50		
Sponsor's plasma conc		
Mean EC50		
Sponsor's plasma conc		
Mean EC50		
Sponsor's plasma conc		
Mean EC50		

- All green; not sensitive to the variables
- Large margins of safety (150-36,000) from doses given to humans.

Mouse data used for scaling

b=0.75 and $BW_{(h)}$=60	b=0.85 and $BW_{(h)}$=70 kg

NHP data used for scaling



Not enough data to make conclusions when the scaling was based on mouse data

Of the 22 products under INDs used for $FIH_{(SPM)}$ dose estimation, 7 products had PK data in both the NHP and the mouse:

- 4 x CD3 multi-specific constructs (red and green)
- 1 x monospecific antibody (green; data not shown)
- 2 x bispecific antibodies (green; data not shown)

Use of human data with closely related products in the model

- Has been occasionally proposed by the sponsors
- To evaluate this approach, we used approved mAbs (5 PD-1 inhibitors and 3 PD-L1 inhibitors)
  - Same targets, valency, format (IgG), size
  - n ≥ 3
  - Human data available and RHDs established

No closely related CD3 constructs (format, size, targets, valency) could be identified (n ≥ 3) at the cut-off date of this project

Use of human data with closely related products (cont'd)

Equation 1: $Clearance(h) = Clearance(a)\left(\frac{BW(h)}{BW(a)}\right)^{b}$

Equation 2: $FIH_{(SPM)}\ Dose = CL_h * [C] * tau$

(1) → Eq.1: As previously described (NHP to human)
Eq.2: use [C] of a closely related product from clinical studies conducted

(2) → Eq.1: Not relevant/ not needed
Eq.2: use $CL_{(h)}$ from a closely related product.
[C] is based on studies conducted with the investigational product

	*RHD (IV; adult; monotherapy)	CL(h) scaled from NHP and each product's EC50s	b=0.75; BW(h)= 60 kg; C_{trough} of a related product	b=0.85; BW(h)= 70 kg; C_{trough} of a related product	CL of a related product and each product's EC50s
PD-1 inhibitors					
cemiplimab	350 mg (Q3W)	54 mcg (Q3W)	170 mg Q3W)	255 mg (Q3W)	88 mcg (Q3W)
dostarlimab	Dose 1-4: 500 mg (Q3W)	904 mcg (Q3W)	188.4 mg (Q3W)	283 mg (Q3W)	1.3 mg (Q3W)
nivolumab	240 mg (Q2W); 480 mg (Q4W)	431 mcg (Q3W)	177 mg (Q3W)	266 mg (Q3W)	675 mcg (Q3W)
pembrolizumab	200 mg (Q3W)	263 mcg (Q3W)	163 mg (Q3W)	245 mg (Q3W)	448 mcg (Q3W)
retifanlimab	500 mg (Q4W)	51 mcg (Q3W)	304 mg (Q3W)	456 mg (Q3W)	46 mcg (Q3W)
PD-L1 inhibitors					
atezolizumab	840 mg (Q2W)	23 mcg (Q2W)	67 mg (Q2W)	101 mg (Q2W)	72 mcg (Q2W)
avelumab	800 mg (Q2W)	95 mcg (Q2W)	238 mg (Q2W)	357 mg (Q2W)	83 mcg (Q2W)
durvalumab	10 mg/kg (Q2W)	109 mcg (Q2W)	272 mg Q2W	408 mg (Q2W)	83 mcg (Q2W)

* Not all doses are shown

A 10-fold margin results in doses that are generally 2-4 artificial dose escalations (i.e., each of 3-fold) from recommended human doses (RHDs)

Using the C_{trough} of a related product (X), the $FIH_{(SPM)}$ doses are:

- In mg ranges
- Much higher than doses obtained when using the CL of a related product (X)
- In close proximity, such that a margin could be applied to all for FIH dose estimation

Summary

- The traditional approaches (NOAEL, HNSTD) for FIH dose selection may not be applicable to IA products
  - Use of modeling approaches has become common
- Sophisticated PK models are submitted by sponsors and vary in assumptions, methods, and assigned variables
- FIH dose selection of IA products is based on the totality of data.
  - PK models are submitted by the sponsors. The approach has been accepted by the FDA review teams for FIH dose estimation, but other data submitted to the IND are also considered.

Summary (cont'd)

- Use of a simple PK model in FIH dose selection was evaluated and was considered appropriate, recognizing that it may not result in optimal FIH doses. Safety margins:
  - 4- to 600- fold for CD3 constructs (using relevant and/or sensitive activity assays)
  - 150- to 36,000- fold for mAbs (using the mean EC50s)
- CD3 constructs were more sensitive than mAbs to changes in the model's variables
  - CL exponent of 0.85 resulted in FIH doses that were safe for mAbs
  - CL exponent of 0.75 resulted in FIH doses that were safe for CD3 constructs (when relevant activity assays were used)

Summary (cont'd)

- For mAbs, clinical data of closely related products may inform FIH dose selection.
  - Appropriate margins may be needed
- Could not make conclusions on the use of mouse data in the model due to insufficient number of products containing both the NHP and mouse data.

Future work

- More data on the use of mouse PK in the model
- If using the clinical concentration of a related mAb:
  - At what dose level of the related product?
  - Establishing an appropriate margin
- More data is needed with CD3 multi-specific constructs
- Better define critical elements in a model
  - Should CD3 constructs be further divided into subclasses?

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