PKPD analysis of soluble CD25 to characterize the concentration-effect relationship observed following the administration of Cergutuzumab Amunaleukin, a targeted immunocytokine for cancer immunotherapy

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Cergutuzumab Amunaleukin (CEA-IL2v) is a tumor-targeted immune cell growth factor

*Engineered Immunoglobulin-cytokine fusion protein*

CEA = Carcinoembryonic antigen, IL2=Interleukin 2, cytokine for cell signaling
Targeted IL2v Mechanism of Action

Growth factor for Natural Killer cells and Killer T-cells in the tumor

Step 1: Targeting
Target specific retention of compound in the tumor

Step 2: Activation
Providing activation and proliferation signals to immune cells on site
IL2v-IL2R interaction leads to immune activation and CD25 release

Amount of sCD25 in plasma is proportional to number of active immune cells

Assumption: sCD25 measured in periphery is a good reflection of immune activation in the tumor
IL2v-IL2R interaction is a pathway for drug elimination

CEA-IL2v binds to receptor

Activation and proliferation of immune cells

Internalization of drug-receptor complex is a pathway for elimination (TMDD)

Increased cell count lead to increased elimination capacity at next drug administration

Shedding of CD25 from the cell surface
Measured as sCD25 in plasma
Pharmacokinetic behavior is driven by TMDD and self induced clearance which lead to exposure reduction following multiple dosing.

PK work was presented by H.P. Grimm et al @ PAGE 2016 and by H.E. Silber Baumann et al @ PAGE 2017.
Team challenge and motivation for analysis

• Objective
  – To quantify the concentration-effect relationship of CEA-IL2v on sCD25
  – To support optimization of the dosing regimen of CEA-IL2v by investigating the impact of alternative dosing regimens on sCD25 through simulations

• Challenge for understanding concentration-effect relationship
  – Non-linear PK
  – Heterogeneous data

Population PKPD analysis provides a powerful methodology to analyze the full set of data while accounting for the actual dosing history and non-linearity in PK
sCD25 concentration-time data was collected from an EIH dose escalation trial in mixed population of solid tumors

sCD25 was measured up to 4 or 5 treatment cycles

- 106 patients
- Mixed regimens
  - weekly (QW) or bi-weekly (Q2W)
  - Intra-patient up-titration
- Doses 6-40 mg
An exposure-response relationship could be identified over multiple treatment cycles.

Smaller effect was observed at later cycles, likely due to reduced exposure.

AUC quartiles were calculated separately for each cycle.
An indirect response model with a drug effect on sCD25 production was used to describe the PKPD relationship.

The PKPD relationship remain constant, confirming that the drop in effect after multiple dose is driven by the drop in exposure.
Administration frequency and non-linear PK affects sCD25 profiles

The PKPD relationship is the same for the QW and Q2W regimens

With a Q2W regimen, a new steady-state is reached within a few treatment cycles.
Administration frequency and non-linear PK affects sCD25 profiles

The PKPD relationship is the same for the QW and Q2W regimens

- QW regimen initially leads to higher accumulation
- Non-linear PK results in lower plasma concentrations and smaller effect as a result
Different dosing strategies to optimize immune activation

*Induction/maintenance (QW -> Q2W) v.s. Q3W*

**Sustained activation** – frequent dosing (QW -> Q2W)
+ Initial strong activation
+ Predicted increased accumulation within the tumor micro-environment
- Cannot be maintained without multiple dose up-titration due to non-linear PK
- Must reduce dosing frequency due to tolerability

**Pulsatile activation** – less frequent dosing (Q3W)
+ Repeated activation with maintained magnitude, small impact of non-linear PK
+ Convenient
- Predicted limited accumulation within tumor micro-environment
The simulations indicate a clear difference in the impact of the schedule on IL-2R engagement.

Not clear if this translates into differential efficacy.
Conclusions

• An indirect response model was found to describe the observed concentration-time profile of sCD25 well
  – CEA-IL2v PK with a delay (effect compartment) was used to provide a drug effect on sCD25 production

• Reduced response with time was found to be due to non-linear PK and was more pronounced with a weekly regimen compared to bi-weekly regimen

• Simulations of alternative regimens were performed to investigate an induction-maintenance regimen and a 3-weekly regimen as alternatives that may be tolerable to patients while providing meaningful immune activation
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Thank you for listening!
Doing now what patients need next