Translational and Clinical Pharmacology Perspectives of Cancer Immunotherapy

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Learning Objectives

• What covariates should be assessed on PK parameters of anti-cancer mAbs?
• What is the association between disease severity and PK
• How should the effect of ADA be assessed?
• What measures of exposure should be utilized in exposure-response analyses
• How can E-R analyses be leveraged to address data gaps and inform drug development and regulatory decisions
• Considerations for FIH dose selection
Clinical Pharmacology Profiling of Ipilimumab

- Ipilimumab is a fully human α-CTLA4 mAb
- First immune-checkpoint inhibitor to demonstrate clinical benefit
- Dosing regimen: 3 mg/kg Q3W (4 doses)
- Ipilimumab PK is linear (T-half ~15 days)
- Approx 80% of steady-state is achieved by the 4th dose
- PK data available for clinical pharmacology profiling
  - Intensive PK (N=15): 10 mg/kg
  - Sparse PK (N=713): 0.3, 3, and 10 mg/kg

Effect of Covariates on Ipilimumab PK

- CL was higher in patients who were: previously treated, male, ECOG>0, lower serum albumin, higher GFR, higher BWT, higher LDH
- VC was higher in patients who were: male, higher BWT

**Magnitudes of the covariate-effects are not considered to be clinically relevant**

Feng Y, et al. (2014) *Br J Clin Pharm*
Assessment of Organ Dysfunction on Ipilimumab Exposure (3 mg/kg Q3W)

Neither renal nor hepatic impairment have a clinically relevant effect on exposure

Feng Y, et al. (2014) Br J Clin Pharm

*As defined in: Ramalingam SS (2010), J Clin Oncol
Subjects with higher ipilimumab exposure have better efficacy and worse safety

Model-Based Evidence of Ipilimumab Efficacy in Previously Untreated Advanced Melanoma

- In 2011, 3 mg/kg IPI monotherapy was approved in the US and EU
  - US: for advanced (metastatic unresectable stage III/IV) melanoma
  - EU: for previously treated advanced melanoma
- A Ph3 study of 10 mg/kg IPI in previously untreated advanced melanoma in combination with dacarbazine (DTIC) showed that
  - IPI 10 mg/kg + DTIC was more efficacious than DTIC alone
  - Toxicity of 10 mg/kg IPI + DTIC was markedly higher than IPI 3 mg/kg monotherapy (mTx)

How can the understanding of E-R be leveraged to obtain approval for 3 mg/kg mTx in previously untreated advanced melanoma patients without a RCT?
Challenge: Demonstrate efficacy of 3 mg/kg IPI mTx in Previously Untreated Advanced Melanoma Patients

• Available data
  • PK and OS data from 4 Ph2 studies of IPI mTx (mostly previously treated patients), and 1 Ph3 study (previously untreated patients)
  • OS data from 2 observational studies in previously untreated patients with IPI 3 mg/kg

• Approach:
  • Compare OS in observational studies with virtual historical controls generated by the Korn meta-analysis
  • Quantify effect of prior treatment on OS by exposure-response analysis
External Validation of Meta-Analysis Model

Observed and Predicted OS of Previously Untreated Advanced Melanoma Patients Receiving Only DTIC (CA184024)

The OS of previously untreated patients receiving DTIC is similar to that of the Korn model predicted historical OS

Feng Y, et al. (2014) ESMO
Evidence that 3 mg/kg Ipilimumab Confers a Survival Benefit to Previously Untreated Advanced Melanoma (2/2)

The OS of previously untreated patients receiving IPI is better than that of the Korn model generated historical controls

Feng Y, et al. (2014) ESMO
E-R Analysis of OS in Advanced Melanoma Patients

**Hazard Ratio of OS (Pooled Ph2 and Ph3 Clinical Studies)**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Hazard Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTIC Yes:No (N=491:516)</td>
<td>1.13 (0.762, 1.67)</td>
</tr>
<tr>
<td>M stage M1c:M0, M1a, or M1b (N=564:443)</td>
<td>1.35 (1.15, 1.57)</td>
</tr>
<tr>
<td>ECOG status 0-1:2 (N=315:692)</td>
<td>1.74 (1.49, 2.04)</td>
</tr>
<tr>
<td>Prior systemic anti-cancer therapy</td>
<td>1.21 (0.862, 1.71)</td>
</tr>
<tr>
<td>Previously treated: Previously untreated (N=438:569)</td>
<td></td>
</tr>
<tr>
<td>Cminss (3 mg/kg) [μg/mL]</td>
<td></td>
</tr>
<tr>
<td>0 (5.62 – 38.9)</td>
<td>0.668 (0.58, 0.769)</td>
</tr>
<tr>
<td>Cminss (10 mg/kg+DTIC) [μg/mL]</td>
<td>0.62 (0.486, 0.781)</td>
</tr>
<tr>
<td>0 (19.7 – 91.9)</td>
<td>0.902 (0.857, 0.946)</td>
</tr>
<tr>
<td>Cminss (10 mg/kg) [μg/mL]</td>
<td>0.309 (0.205, 0.466)</td>
</tr>
<tr>
<td>0 (18.6 – 113)</td>
<td>0.824 (0.77, 0.882)</td>
</tr>
<tr>
<td>LDH [IU/L]</td>
<td>2.71 (2.23, 3.28)</td>
</tr>
<tr>
<td>203 (129 – 837)</td>
<td>0.729 (0.687, 0.775)</td>
</tr>
</tbody>
</table>

- **The model-based analyses provided key supportive evidence for the EU approval of 3 mg/kg IPI mTx in previously untreated advanced melanoma**

- **Yervoy SmPC: “OS was independent of prior systemic anti-cancer therapy, and increased with higher ipilimumab Cminss”**
Confirmation of Ipilimumab E-R of OS in Adv Melanoma

OS in Advanced Melanoma: Ph3 Study of Ipilimumab 3 vs 10 mg/kg Q3W (4-doses)

Long-term efficacy of ipilimumab does not depend upon maintenance of drug in circulation

Confirmation of Ipilimumab E-R of OS in Adv Melanoma

PFS and OS in Advanced Melanoma: Ph3 Study of Ipilimumab 3 vs 10 mg/kg Q3W (4-doses)

- PFS was similar, but OS was better with 10 mg/kg
- Long-term efficacy of ipilimumab does not depend upon maintenance of drug in circulation

External Validation of a TGD-OS Model

TGD-OS model developed with nivolumab predicts OS with ipilimumab

Nivolumab Dose Selection: Preliminary E-R of Efficacy in Melanoma, NSCLC, and RCC

- Exposure-response appears to have an increasing trend
- Observed response rate is maximal at 3 mg/kg Q2W

Agrawal S, et al. (2016) *J Immunotherapy Cancer*
Nivolumab Exploratory E-R of Efficacy (Melanoma)

Subjects with higher CL have lower probability of responding

Exploratory Nivolumab E-R of OS in RCC

Martingale Residuals versus Cavgss in 2L RCC, by Nivolumab Dosing Regimen

Martingale Residuals versus CL in 2L RCC, by Nivolumab Dosing Regimen

- Relationship of Cavgss to risk of death is not consistent across dose regimens
- Relationship of CL to risk of death is consistent across dose regimens

Roy A (2016) ASCPT Pre-Conference Meeting
Discovery of Time-Varying Nivolumab CL

Liu C, et al. (2016) *CPT*
Association of CL and Efficacy (Best Overall Response): Melanoma, RCC, and NSCLC

Wang Y, et al. (2016) CPT
Covariate Effects on Nivolumab PK

- CL was higher in patients who were: male, ECOG>0, lower serum albumin, higher BWT, higher LDH
- VC was higher in patients who were: male, higher BWT

- Covariates that affect nivolumab PK are similar to those of ipilimumab
- Nivolumab CL may vary with tumor type

Temporal changes in CL correspond to temporal changes in covariates that are associated with disease

Comparison of Nivolumab CL in Adjuvant and Advanced Melanoma

Nivolumab CL in adjuvant melanoma is constant, and consistently lower than in advanced melanoma

Hamuro L, et al. (2018) ASCPT Meeting
### Covariate-Effects on Ipilimumab PK (in Combination with Nivolumab)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Effect Value (95% CI)</th>
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<tbody>
<tr>
<td>Tumor Type</td>
<td></td>
</tr>
<tr>
<td>SCLC: MEL (n = 170:1372)</td>
<td>93.8 (87.6, 100)</td>
</tr>
<tr>
<td>RCC: MEL (n = 438:1372)</td>
<td>101 (91.4, 112)</td>
</tr>
<tr>
<td>NSQ NSCLC: MEL (n = 275:1372)</td>
<td>96.8 (81.9, 101)</td>
</tr>
<tr>
<td>SQ NSCLC: MEL (n = 99:1372)</td>
<td>103 (92.4, 115)</td>
</tr>
</tbody>
</table>

### Serum concentrations of mAb drugs << endogenous IgG

### Linear component of mAb CL unlikely to be affected by combination therapy with another mAb

### DDI assessment focused on effect of treatment, rather than concentration of interacting drug

### Enables assessment of potential DDI due to both PK and PD related effects

### E-R analyses of safety was performed by time-to-event analysis using time-varying exposure

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**Clin Pharm Profiling of IO mAbs in Combination**

- Serum concentrations of mAb drugs << endogenous IgG
- Linear component of mAb CL unlikely to be affected by combination therapy with another mAb
- DDI assessment focused on effect of treatment, rather than concentration of interacting drug
- Enables assessment of potential DDI due to both PK and PD related effects
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**Covariate**

- Continuous = Reference
- Categorical = Comparator: Reference

**Nivolumab Dosing Regimen**

- 3 mg/kg Q3W: MONO (n = 248:891)
- 3 mg/kg Q3W: MONO (n = 269:891)
- 1 mg/kg Q3W: MONO (n = 603:891)
- 3 mg/kg Q2W: MONO (n = 38:891)
- 0.3 mg/kg Q2W: MONO (n = 14:891)

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**VC**

- BLDH: 206 (128:729) U/L
- BLDW: 50 (53.2-111) kg
- BBWT: 50 (53.2-111) kg

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**Notes**


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**Graphs**

- Graphs showing the effect of various covariates on Ipilimumab PK in combination with Nivolumab.
Assessment of Effect of Anti-Drug Antibodies (ADA) on CL

Effect of ADA on Elotuzumab CL (Estimated by PPK Analysis)

Assessment of ADA on PK should account for the time-varying nature of this covariate

Model-Based Dose Optimization of Nivolumab

- Compare nivolumab exposures with 240 mg Q2W and 480 mg Q4W with that of 3 mg/kg Q2W and 10 mg/kg Q2W
  - 240 mg Q2W is equivalent to 3 mg/kg for an 80 kg patient (~ median weight)
  - 480 mg Q4W is expected to achieve the same Cavgss as that of 240 mg Q2W
  - Utilize a population pharmacokinetic (PPK) model to predict exposures
  - Quantify differences in summary measures of exposure

- Assess the impact of differences in exposure
  - Safety margin with respect to 10 mg/kg Q2W, shown to be safe and tolerable in Ph1 study
  - E-R of efficacy: Objective response rate (ORR), and overall survival (OS)
  - E-R of safety: Adverse events leading to discontinuation or death (AE-DC/D), Gr3+ AEs, and immune-mediated AEs
  - E-R of biomarkers: Intratumoral receptor occupancy (RO)

Roy A (2017) ACCP Meeting
Comparison of Conc-Time Profiles, by Dosing Regimen

240 mg Q2W vs 3 mg/kg Q2W

• Exposures are slightly more variable with flat dosing
• Q4W dosing results in higher peak concentrations and lower trough concentrations than Q2W dosing

Assessment of Dosing Regimen on OS (Melanoma)

E-R of OS in Advanced Melanoma (Visual Predictive Check)

Predicted OS in Previously Untreated Adv Melanoma, by Dosing Regimen

Translational Considerations for FIH Dose Selection

• Safety of subjects is a priority, but need to also consider the opportunity for clinical benefit for patient studies

• Identify risks and factors that mitigate risks: Consider the totality of the data
  – Mechanism-of-action:
    • Agonist/antagonist
    • Knowledge of the safety/activity of compounds with similar MoA
  – Relevance of animal model
  – Potential for adverse immune-reactions
    • Minimal anticipated biologically active level (MABEL)
    • Cytokine release assay

*FIH dose selection should be based on the totality of the data*

Saber H, et al. (2016) *Reg Tox Pharm*
Determination of Maximum Recommended Starting Dose

- **MSRD** is determined based on both NOAEL and MABEL
- **MABEL** based MSRD is not expected to provide any clinical benefit

Muller PY, et al. (2009) *Curr Opin Biotech*
Translational PK-PD To Select FIH Starting Dose: Case Study with anti-OX40 mAb

Targeting $AUC_{\text{ref week}}$ of 100 µg·day/mL for human efficacious dose projection

Values in plots are the doses studied
Dosing regimens:
- Exp 1 & 2: every 6 days × 2
- Exp 3: every 7 days × 2
- Exp 4: every 4 days × 2

Targeting $C_{\text{max first week}}$ of 25 µg/mL for human efficacious dose projection

TGI: Tumor Growth Inhibition

Human efficacious dose projected to be 1 mg/kg based on target AUC and Cmax

Huang C, et al. (2017) SITC Meeting
## Comparison of Starting Dose Selected by Alternative Criteria

<table>
<thead>
<tr>
<th></th>
<th>PK/PD-based FIH starting dose</th>
<th>Toxicology-based FIH starting dose (one-sixth monkey HNSTD)</th>
<th>No effect level in dry-coat cytokine release assay(^a)</th>
<th>Minimal vaccine-induced T-cell response in monkeys</th>
<th>Clinically tolerated exposure with previously reported anti-OX40 agonist(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose, mg/kg</strong></td>
<td>0.25</td>
<td>17-20</td>
<td>1.3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td><strong>C(_{\text{max}}), \mu g/mL</strong></td>
<td>6.3</td>
<td>425-500</td>
<td>33</td>
<td>78</td>
<td>80</td>
</tr>
<tr>
<td><strong>C(_{\text{max}}) margin (vs PK/PD-based FIH starting dose)</strong></td>
<td>NA</td>
<td>68-80(^x)</td>
<td>5.3(^x)</td>
<td>13(^x)</td>
<td>2.5(^x)</td>
</tr>
</tbody>
</table>

*NA = not applicable*

\(^a\) Drug concentration in the dry-coat cytokine release assay was approximated using the incubation volume (0.3 mL), and the human dose was calculated by multiplying the no-effect drug level by the plasma volume of 40 mL/kg.

\(^b\) Margin was calculated after normalization with differences in the binding EC\(_{50}\) values.

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**FIH starting dose of aOX40 agents already in clinical development was ~10-fold lower**

Huang C, et al. (2017) *SITC Meeting*
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• What is the association between disease severity and PK
• How should the effect of ADA be assessed?
• What measures of exposure should be utilized in exposure-response analyses
• How can E-R analyses be leveraged to address data gaps and inform drug development and regulatory decisions
• Considerations for FIH dose selection
Summary

• Clearance of I-O mAbs is associated with disease severity
  – Higher in patients with worse disease
  – Decreases with improvement of patient status
• Assessment of ADA should account for time-varying nature of covariate
• Exposure-response can inform regulatory decisions
  – Randomized dose-ranging studies are needed for robust characterization of E-R
  – Select early measure of exposure to avoid confounding of E-R relationship
  – TTE analyses are needed for endpoints affected by censoring
• Translational PK-PD modeling can inform FIH dose selection
  – Prioritize safety and consider the desire for potential clinical benefit
  – Identify potential risks and consider factors that mitigate risk
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References (1/2)


References (2/2)


