Modeling & Simulation Approaches To Support Development of Immuno-Oncology Drugs

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Goals of M&S in the Development of I-O Drugs

- Characterize clinical pharmacology profile
- Inform go/no-go decisions and dose selection
- Inform assessments of benefit-risk
- Support dose-optimization

*Pharmacometric analyses should account for the unique attributes of I-O agents*
Mechanism of Action of I-O Agents: Ipilimumab and Nivolumab

- Ipilimumab: fully human aCTLA-4 IgG1 mAb
- Nivolumab: fully human aPD-1 IgG4 mAb

**I-O agents enable and enhance the ability of the immune system to recognize and eliminate tumor cells**
- **Ipilimumab increases the number of activated T-cells**
- **Nivolumab prevents inactivation, and promotes re-activation of T-cells**

Characteristics of tumor-response to I-O Agents

- **Patients who do not progress tend to have durable disease control**
- **Unconventional responses: reduction in target tumor burden despite appearance of new lesions**
- **Distinct patterns of response particularly evident with combination therapy**


Onset and Durability of I-O Agent Induced Tumor Responses: Metastatic Melanoma

Treatment Duration and Tumor Response: Advanced Melanoma Patients Treated with Nivolumab

- Tumor responses are maintained, despite discontinuation of therapy
- The immune response may be self-sustaining

Long-Term Survival: Ipilimumab in Metastatic Melanoma

- **Delayed separation of OS curves relative to non-IO agents**
- **Median survival may not fully reflect clinical benefit**

Model-Predicted* Tumor Growth Dynamics Following Treatment with I-O Agents (Ipilimumab and Nivolumab)

*Nonlinear mixed-effects mixture-model of TGD is based on structural model proposed by Wang et al, CPT (2009)

*Mixture model of TGD describes patterns of tumor response
Utility of I-O Agent Induced Tumor Response to Predict Overall Survival: Ipilimumab in Advanced Melanoma

External Validation of Prognostic Variables and Tumor Shrinkage Measures to Predict OS

- **OS model developed with data from Ph2 studies was validated with data from a Ph3 study**
- **I-O agent induced tumor shrinkage is predictive of OS**
Pharmacokinetics of Nivolumab and Ipilimumab in Combination: Effects of Covariates on CL and VC*

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Nivolumab Effect Value (95% CI)</th>
<th>Ipilimumab Effect Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA (3rd Gen Assay)</td>
<td>125 (116, 134)</td>
<td>106 (96.5, 115)</td>
</tr>
<tr>
<td>Positive / Negative (N=237/1918)</td>
<td></td>
<td></td>
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<tr>
<td>ADA (1st Gen Assay)</td>
<td>110 (98.3, 133)</td>
<td>129 (100, 162)</td>
</tr>
<tr>
<td>Positive / Negative (N=46/1318)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADA (2nd Gen Assay)</td>
<td>134 (105, 146)</td>
<td></td>
</tr>
<tr>
<td>Positive / Negative (N=42/1318)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipilimumab 3 mg/kg</td>
<td>135 (127, 143)</td>
<td>92.5 (80, 107)</td>
</tr>
<tr>
<td>3 mg/kg no lpi (N=462/1430)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipilimumab 1 mg/kg</td>
<td>102 (78.6, 124)</td>
<td>101 (97.8, 106)</td>
</tr>
<tr>
<td>1 mg/kg no lpi (N=16/1430)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline eGFR 80 (46.5 – 115) [ml/min/1.73m2]</td>
<td>106 (103, 109) 92 (88.3, 95.7)</td>
<td>128 (122, 135) 90.1 (88.4, 91.9)</td>
</tr>
<tr>
<td>ECOG &gt;0=0 (N=783/1125)</td>
<td>122 (117, 128)</td>
<td></td>
</tr>
<tr>
<td>Baseline Body Weight 80 (53.4 – 114) [kg]</td>
<td>130 (126, 134) 74.2 (71.9, 76.7)</td>
<td>125 (122, 130) 77.3 (74.5, 79.8)</td>
</tr>
<tr>
<td>GENDER Male / Female (N=1239/678)</td>
<td>112 (109, 116)</td>
<td></td>
</tr>
<tr>
<td>Baseline Body Weight 80 (53.4 – 114) [kg]</td>
<td>.124 (121, 126) 78.6 (76.7, 80.7)</td>
<td>127 (124, 129) 76.5 (74.8, 78.3)</td>
</tr>
</tbody>
</table>

**CL: Clearance, VC: Central compartment volume of distribution**

*CL: Clearance, VC: Central compartment volume of distribution

**Nivolumab and ipilimumab exhibit linear PK**
- **CL and VC increase with increasing body weight**
- **CL is associated with disease severity (ECOG and LDH)**

Statkevich P, et al, ASCPT (2016) [Poster PC-17 and PI-126]
Exposure-Response of Safety (AEs DC/D)*: Nivolumab and Ipilimumab in Advanced Melanoma

**Covariate**

- PD-L1 Status (positive:negative): 571:972
- M Stage (M0/M1A/M1B:M1C): 942:601
- Line of Therapy (≥2nd line:1st line): 257:1286
- ECOG (≥1:0): 424:1119
- Sex (Male:Female): 561:982
- Baseline LDH [xULN]: 1 (0.584 – 3.44)
- Body Weight [kg]: 80 (55.5 – 112)
- Age [yr]: 65 (34 – 79)

**Risk of AEs DC/D is higher with combination therapy (relative to NIVO 3 mg/kg)**

- Nivo Cav1 (Nivo 1/Ipi 3) [ug/mL]
  - Nivo:28.4 (4.96 – 10.3)
  - Ipi:0 (15.4 – 30.3)
- Nivo Cav1 (Nivo 3 mTx) [ug/mL]
  - Nivo:28.4 (20.1 – 37.5)

**Hazard Ratio (95% CI)**

- PD-L1 Status (positive:negative): 1.07 (0.864, 1.32)
- M Stage (M0/M1A/M1B:M1C): 1.05 (0.839, 1.31)
- Line of Therapy (≥2nd line:1st line): 0.748 (0.492, 1.13)
- ECOG (≥1:0): 1.24 (0.979, 1.57)
- Sex (Male:Female): 1.2 (0.949, 1.52)
- Baseline LDH [xULN]: 1.41 (1.11, 1.8)
- Body Weight [kg]: 1.18 (0.964, 1.44)
- Age [yr]: 1.18 (1.06, 1.33)

*AEs leading to discontinuation or death

Nivolumab Dose/Exposure-Response of OS in Patients with 2L RCC

Kaplan-Meier of OS, Dose Level (Randomized Ph2 Study of NIVO Q3W)

Kaplan-Meier of OS, by Exposure Quartiles (Ph3 Study of NIVO 3 mg/kg Q2W)


The modest dose-response is not consistent with the apparent exposure-response
Functional Form of Cavgss and CL Relationship to Risk of Death

- **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**
Another Example of the Association Between CL and OS: Tremelimumumab Patients with Metastatic Melanoma

Kaplan-Meier of OS, by Exposure Quartiles (Ph3 Study of TREME 15 mg/kg Q90D)

**Magnitude of the effect of CL cannot be explained by lower exposure**

**OS of 15 mg/kg Q90D was better than 10 mg/kg Q28D (in Ph2 study)**

**Association between CL is independent of other risk factors**

Potential Reasons for the Association Between CL of Anti-Cancer mAbs and Efficacy

• CL of anti-cancer mAbs is associated with factors related to disease-severity (and poor prognosis)
• Observed prognostic factors only explain a portion of the higher risk
• CL may be a surrogate for unobserved risk factors
Potential Confounding Effect of CL on Exposure-Response of Efficacy (OS) in NSQ-NSCLC (1/2)

Effect of Covariates on Hazard of OS in NSQ-NSCLC
(Full Model without CL)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Prior Maintenance Therapy (Yes:No)</td>
<td>1.11 (0.829, 1.5)</td>
</tr>
<tr>
<td>EGFR (Wild Type:Mutant)</td>
<td>0.757 (0.503, 1.14)</td>
</tr>
<tr>
<td>Smoker (Never:Current/Former)</td>
<td>0.942 (0.654, 1.36)</td>
</tr>
<tr>
<td>PD-L1 status (&gt;=1%:&lt;1%)</td>
<td>0.661 (0.48, 0.911)</td>
</tr>
<tr>
<td>Line of Therapy (&gt;2nd Line:2nd Line)</td>
<td>1.5 (1.08, 2.08)</td>
</tr>
<tr>
<td>Sex (Male:Female)</td>
<td>1.17 (0.863, 1.58)</td>
</tr>
<tr>
<td>ECOG (&gt;=0:&lt;0)</td>
<td>1.52 (1.09, 2.1)</td>
</tr>
<tr>
<td>Baseline Tumor Size [cm]</td>
<td>0.871 (0.64, 1.18)</td>
</tr>
<tr>
<td>Baseline Albumin [g/dL]</td>
<td>1.07 (0.922, 1.24)</td>
</tr>
<tr>
<td>Baseline Body Weight [kg]</td>
<td>0.722 (0.595, 0.874)</td>
</tr>
<tr>
<td>Age [yr]</td>
<td>1.59 (1.21, 2.1)</td>
</tr>
<tr>
<td>Baseline LDH [xULN]</td>
<td>0.823 (0.62, 1.09)</td>
</tr>
<tr>
<td>Cavqss [μg/mL]</td>
<td>1.16 (0.936, 1.43)</td>
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<td>1.07 (0.863, 1.33)</td>
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<td></td>
<td>0.923 (0.719, 1.19)</td>
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<td>1.9 (1.48, 2.43)</td>
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<td>0.624 (0.519, 0.749)</td>
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<td>0.508 (0.384, 0.672)</td>
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<td>1.69 (1.36, 2.1)</td>
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Predictions of model without CL are not consistent with the observed data

Feng Y et al, ASCPT (2016) [Poster PC-10 and PI-098]
Potential Confounding Effect of CL on Exposure-Response of Efficacy (OS) in NSQ-NSCLC (2/2)

Effect of Covariates on Hazard of OS in NSQ-NSCLC
(Full Model with CL)

- Prior Maintenance Therapy (Yes:No) (N=190:164)
- EGFR (Wild Type:Mutant) (N=191:50)
- Smoker (Never:Current/Former) (N=68:286)
- PD-L1 status (>=1%<1%) (N=133:122)
- Line of Therapy (>2nd Line:2nd Line) (N=100:254)
- Sex (Male:Female) (N=187:167)
- ECOG (<=0:0) (N=256:98)
- Baseline Tumor Size [cm] (7.6 (2.1 – 19))
- Baseline Albumin [g/dL] (4 (3.1 – 4.63))
- Baseline Body Weight [kg] (70.2 (49 – 98.5))
- Age [yr] (62 (44.7 – 77))
- Baseline LDH [xULN] (1 (0.557 – 2.21))
- Clearance [mL/h] (8.4 (4.75 – 14.4))
- Cav1 [ug/mL] (27.9 (14.9 – 90))

Hazard Ratio (95% CI):
- 0.981 (0.725, 1.33)
- 0.763 (0.506, 1.15)
- 0.971 (0.674, 1.4)
- 0.67 (0.485, 0.926)
- 1.52 (1.09, 2.13)
- 0.98 (0.722, 1.33)
- 1.42 (1.02, 1.97)
- 0.756 (0.557, 1.03)
- 1.14 (0.987, 1.33)
- 0.823 (0.659, 1.01)
- 1.32 (0.982, 1.78)
- 0.54 (0.396, 0.735)
- 1.59 (1.26, 2)
- 1.11 (0.885, 1.38)
- 0.891 (0.691, 1.15)
- 1.84 (1.44, 2.35)
- 0.638 (0.532, 0.764)
- 2.59 (2.33)
- 0.637 (0.281, 0.482)
- 0.982 (0.68, 1.42)
- 1.01 (0.829, 1.23)

Predictions of model with CL are consistent with observed data

Feng Y et al, ASCPT (2016) [Poster PC-10 and PI-098]
Summary

• I-O agents have unique attributes
  - Tumor growth may be controlled without achieving objective response (PR or CR) by RECIST criteria
  - Efficacy may be maintained long after drug wash-out

• CL of mAb agents may be associated with efficacy, independent of exposure
  - Subjects who have more severe disease may have higher CL
  - Exposure-response relationships determined with data from just a single dose level may show an artefactual relationship
  - Dose-response studies are recommended to generate data that can estimate the effects of both CL and exposure
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