PK and PKPD considerations for dose selection in the development of pembrolizumab

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Disclosure Information

Dinesh de Alwis, Ph.D.

I have the following financial relationships to disclose:

• I am an Employee and Stockholder of MSD
Outline

• Dose finding in oncology – A “historical” perspective
  – Why we hope focus on MTD is historical?

• Keytruda

MTD: Maximum Tolerated Dose
Traditional Dose Finding in Oncology

All focus on finding MTD!
3+3, CRM, mCRM, TITE-CRM, accelerated titration, ...

What about efficacious dose?
Deserves more attention

Ph1: Dose escalation

MTD/MAD

Perceived benefit: Fast to registration

MTD: Maximum Tolerated Dose
MAD: Maximum Administered Dose
Historically oncology has performed relatively poorly in identifying “optimal” doses in the pre-market setting.

FDA can issue post-marketing commitments/requirements to study optimal dose considering safety and efficacy.

**Table 1.** Dose interruptions and reductions in initial registration trials for small-molecule KIs approved for oncology indications with PMC or PMR to study alternate doses (percentage of patients on registration studies)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose interruption</th>
<th>Dose reduction</th>
<th>Dose interruption or delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>62%</td>
<td>19%</td>
<td>NA</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>47%</td>
<td>49%</td>
<td>80%</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>NA</td>
<td>79%</td>
<td>86%</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>66%</td>
<td>52%</td>
<td>74%</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>69%</td>
<td>59%</td>
<td>71%</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>NA</td>
<td>34%</td>
<td>53%</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>56%</td>
<td>68%</td>
<td>90%</td>
</tr>
</tbody>
</table>
MTD/MAD ≠ Optimal dose/regimen

Oncology Early Phase Dose Selection needs Significant Improvement

Roughly 2/3rd (48/77) of the compounds are approved at doses lower than MTD
Roughly 1/3rd (25/77) are approved at less than MTD/2

For Targeted Therapies, Doses Reaching MTD Increase Toxicity Without Necessarily Improving Response in Phase I

Normalization to combine data from different trials:
- low-dose: ≤25% MTD of the trial
- High-dose: ≥75% MTD of the trial
- Medium-dose: 25-75%

24 trials treating 683 patients between Oct, 2004 - Jun, 2008, at MD Anderson Cancer Center

Clin Cancer Res 2010;16:1289-1297
Proper Dose Finding in Oncology – MTD/MAD and BED

All focus on finding MTD!
3+3, CRM, mCRM, TITE-CRM, accelerated titration, ...

Ph1: Dose escalation

What about efficacious dose?
Deserves more attention

MTD/MAD

Biologically Effective Dose (BED)
KEYTRUDA®
(MK-3475, pembrolizumab)
Case Study
Initiation of KEYTRUDA® Clinical Program

• Preclinical data suggested that KEYTRUDA® would have anti-tumor activity in multiple cancers

• US IND was opened on Jan 7, 2011
  – A Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinomas and Melanoma (Protocol 001)
    • Initial intent was to define DLT, characterize PK, and establish POC
Part A: FIH Dose Escalation and PK/PD Evaluation

- Part A-1 dose escalation study
  - Objectives:
    - To define DLT, MTD (Maximum Administered Dose), and characterize PK
  - Design:
    - Open label, non randomized traditional 3+3 dose escalation followed by a small expansion cohort n~32
      - 1mg/kg Q2W → 3 mg/kg Q2W → 10 mg/kg Q2W
  - Results
    - No DLT at tested doses
    - Objective response in 2 out of 3 first melanoma patients
      - First response at 3 mg/kg Q2W in melanoma
    - Based on a strong activity signal, amendment was issued to expand melanoma cohort
      - 10 mg/kg Q2W (MAD) selected as the first dose
PK profile support for Q3W dosing

- Pharmacokinetic profile is typical for a therapeutic mAb with low clearance (0.22 L/h), limited volume of distribution (3.7 L) and low variability (28 % CV on CL)
- 26 day half life (95% CI 24-28 days)
A Strong Data, from Cohort B1, Accelerated the Development Program

Objective Response Rates and Duration of Response based on Independent Radiology Review using RECIST 1.1 Criteria

<table>
<thead>
<tr>
<th></th>
<th>Objective Response</th>
<th>Complete Response</th>
<th>Duration of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N, 95% CI)</td>
<td>(N, 95% CI)</td>
<td>(days) Median (Range)</td>
</tr>
<tr>
<td>All MEL N=85</td>
<td>40%</td>
<td>3.5%</td>
<td>Not reached (28-240+)</td>
</tr>
<tr>
<td></td>
<td>(34‡; 29% - 51%)</td>
<td>(3; 0.7% - 10%)</td>
<td></td>
</tr>
<tr>
<td>IPI Naïve N=58</td>
<td>43.1%</td>
<td>3.4%</td>
<td>Not reached (30-240+)</td>
</tr>
<tr>
<td></td>
<td>(25; 30% - 57%)</td>
<td>(2; 0.4% - 11.9%)</td>
<td></td>
</tr>
<tr>
<td>IPI Treated N=27</td>
<td>33.3%</td>
<td>3.7%</td>
<td>Not reached (28-169+)</td>
</tr>
<tr>
<td></td>
<td>(9‡; 16% - 54%)</td>
<td>(1; 0.1% - 19%)</td>
<td></td>
</tr>
</tbody>
</table>

All patients dose at 10 mg/kg.

Includes all patients who received the first dose as of April 25, 2012. Centrally available response information as of Dec. 3, 2012.

‡ Confirmed objective response is defined as a complete response or partial response that is evident on two consecutive CT scans obtained at least 4 weeks apart.
Protocol 001 First in Human to Registration

From a small Phase 1-the study expanded to a 655-melanoma patient multi-part study

- 5 amendments, between Dec-2011 to Sep-2013, to answer emerging questions
- 4 “phase 2 study-like” parts including 3 randomized dose comparison sub-studies

Defining a dose range for the pivotal B2 cohort

• Part A-2 dose expansion study
  – Objectives:
    • To evaluate PK/PD of Q3W dosing schedule
    • Intra-patient dose escalation to explore PK PD of KEYTRUDA® in 0.005 to 10 mg/kg Q3W
      – Basis for translational PK/PD to define the efficacious dose of 2 mg/kg Q3W
    – Patients were escalated in 3 steps (at days 1, 8 and 22) from low (0.005 to 0.06 mg/kg) to high doses (2 and 10mg/kg)
    – Ex vivo IL-2 assay developed
      » No IL-2 release from lymphocytes with activated PD-1 pathway
      » SEB causes release, further enhanced by pembrolizumab effect on PD-1
Ex-vivo IL2 assay: Peripheral PK-PD in the Clinic to inform efficacious dose

• 95-% saturation level reached at ~1 mg/kg Q3W

• Simulations show, > 95% of the effect of Keytruda on the ex vivo IL-2 release is achieved at $C_{\text{trough}}$ reached with a dose regimen of ~1 mg/kg Q3W

• Therefore, 1 mg/kg Q3W is lower boundary for clinical efficacy

Keytruda Exposure is Associated with Complete Functional Blockade of PD-1 in the ex vivo IL-2 Release Assay at Doses of 1 mg/kg Q3W or Higher

J Elassaiss-Schaap, S Rossenu, A Lindauer, SP Kang, R de Greef, JR Sachs and DP de Alwis CPT:PSP, Jan 2017
PK-PD simulations to select BED

- PK-PD model was developed for simulations considering PK and PD variability
- At 1 mg/kg Q3W, the probability of achieving full target engagement is 64%. ≥ 2 mg/kg the probability is ≥ 90%.
  - Dose of 2 mg/kg falls likely near the plateau of the underlying exposure-response
- Proposed BED: 2 mg/kg Q3W
Can Translational PK-PD further inform our choice?

Semi-mechanistic tPKPD model

Step 1: Develop mouse model relating PK $\rightarrow$ Target binding $\rightarrow$ tumor growth inhibition

Step 2: Translation to human by adjusting PK and tumor growth parameters

Dose of 2 mg/kg every 3 weeks or more shows maximal response. Dose range of 2 - 10 Q3W determined for clinical trials

Model fit tumor data from mouse

A Lindauer, CR Valiathan, K Mehta, V Sriram, R de Greef, J Elassaiss-Schaap and DP de Alwis; CPT PSP. 2017
PK-PD modeling guides a critical decision on **KEYTRUDA®**

- Team discussion on what doses to take forward based on results **from non-randomized studies** (B1)
  - ORR ipi treated 10Q2: 56% > 10Q3: 27%
  - ORR ipi naïve 2Q3: 45%, 10Q3: 37%, 10Q2: 46%

**Based on the Translational modeling, ex-Vivo IL-2 data and observed clinical data, what dose or doses would you take forward into B2 pivotal cohort?**
PK-PD modeling guides a critical decision on **KEYTRUDA®** dose

- **Exposure-response** analysis: flat exposure-response between 2Q3, 10Q3, 10Q.
  - Key point: Tumor size change was used for modeling as response instead of conventional RECIST criterion
  - Change in Tumor size vs Exposure: no difference between 2Q3, 10Q3, 10Q2

The black line shows the (log)linear regression of change from baseline vs. AUC. Dashed reference lines indicate +20%, 0 and -30% change.
Tumor Response model Characterizes Growth Patterns and Overall Predictions with Dose

Relatively flat exposure-response relationships in efficacy [tumor size reduction] resulting in optimally efficacious dose of 2 mg/kg Q3W

MS Chatterjee, J Elassaiss-Schaap, A Lindauer, DC Turner, A Sostelly, T Freshwater, K Mayawala, M Ahamadi, JA Stone, R de Greef, AG Kondic and DP de Alwis; CPT:PSP, 2017
Flat exposure-AE relationship resulting in supporting optimally efficacious dose of 2 mg/kg Q3W

AEs (AEOSI; AEs of special interest)

Solid lines represent model estimated probability and shaded areas represent the 95% confidence intervals. P-values represent significance level of the exposure-response term when forced into the model.
PFS from randomized studies confirmed 2 mg/kg as an optimal dose

Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial

Ribas et al, Lancet 2015
PK/PD Findings supported Development and Approval

• Exposure-Response analysis was key to identifying optimal dose.
• A wide therapeutic range was established, based on Exposure-Response, Exposure-Safety analyses

• Approval of KEYTRUDA® based upon positive risk/benefit
  – Efficacy based on cohort B2 173 IPI-refractory patients, with 80 patients at the 2 mg/kg recommended dose
• Received Accelerated Approval on Sept 4, 2014
  • Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit.
  • Two confirmatory trials (P002 (IPI-treated) and P006 (IPI-naïve)) were conducted to confirm the safety and efficacy of KEYTRUDA
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