A rational approach to dose optimisation of pembrolizumab using cost analysis and pharmacokinetic modelling and simulation

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**BACKGROUND**

- Pembrolizumab (KEYTRUDA®) currently available in the UK as a 50 mg vial is licensed at a dose of 2mg/kg every three weeks. The cost per mg of pembrolizumab is £26.30.
- A population pharmacokinetic (PK) model based on two compartment first order elimination model was used to describe the PK of pembrolizumab.
- Dose banding or the standardisation of doses into a defined set of weight based ranges offers an alternative approach to body weight dosing.
- The aim of this work is to evaluate using a simulated study and data from 42 patients treated at one UK centre changes in cost, drug exposure and target engagement between different dosing strategies.

**DOsING STRATEGIES**

- **BODY WEIGHT** 2mg/kg
- **DOSE BAND ±10% Variance**
- **FIXED DOSE** 150mg
- **FIXED DOSE** 200mg
- **PK DERIVED**

**COST ANALYSIS – METHOD**

**BODY WEIGHT**

<table>
<thead>
<tr>
<th>Weight Range (kg)</th>
<th>Band</th>
<th>From</th>
<th>To</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 55 60 70 84 98 112 125</td>
<td>16% Saving</td>
<td>£844k</td>
<td></td>
</tr>
<tr>
<td>59 69 112 139 129</td>
<td>25% Saving</td>
<td>£822k</td>
<td></td>
</tr>
<tr>
<td>70 83 140 167 150</td>
<td>7% Cost</td>
<td>£11 Mil</td>
<td></td>
</tr>
<tr>
<td>84 97 168 195 175</td>
<td>18% Saving</td>
<td>£818k</td>
<td></td>
</tr>
</tbody>
</table>

**Dose and Weight of Patients identified on Cycle 1 (Baseline)**

<table>
<thead>
<tr>
<th>Body Weight Range (kg)</th>
<th>Band</th>
<th>From</th>
<th>To</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 50 55</td>
<td>100</td>
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<tr>
<td>50 60 112 139 129</td>
<td>50 150</td>
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<tr>
<td>70 83 140 167 150</td>
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<tr>
<td>84 97 168 195 175</td>
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<tr>
<td>98 111 196 222 200</td>
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<tr>
<td>112 124 223 249 225</td>
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<tr>
<td>125 137 250 274 250</td>
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<tr>
<td>150 165 300 330 300</td>
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</tbody>
</table>

**PHARMACOKINETICS – METHOD**

- A population PK model of plasma concentration-time profiles was developed with data from 476 subjects.
- Flat exposure-response relationship was observed for efficacy and safety between 2 mg/kg and 10mg/kg.
- Maximum target engagement at 10 mg/L has been demonstrated based on ex vivo stimulation ratio of clinical biomarker (IL2).
- Simulation studies (MATLAB) based on the population PK model was used to simulate 1000/250 random individuals to determine changes in exposure and probability of trough concentration achieving target level (10mg/L) required for maximum target engagement.

**REFERENCES**

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**CONCLUSION**

- Dose Banding offers a safe, effective and economical alternative to Body Weight dosing which could help to alleviate pressures on drugs budgets.
- Dose banding appears to be non-inferior to Body Weight dosing based on exposure (AUC) and probability of target engagement.
- The fixed dose of 200mg currently being investigated appears to overcompensate for majority of individuals.
- Vial size availability can have a direct impact on drug wastage cost.
- An optimal dosing strategy that takes into account vial size and effect of body size on PK eliminates waste and offers comparable results to Body Weight dosing in relation to AUC and probability of target engagement.

**Fig 3**: Scatter plots of probability of simulated individual mean trough concentration at different cycles against target level (10 mg/L) against body weight for the different strategies. The lines are locally weighted scatterplot smooth (smooth) lines through the data. The simulation was based on 250 individuals.

**Fig 1**: Boxplots of AUC over last two cycles (6 weeks) stratified by body weight (BW) for the different strategies. Median, 50%, 80%, 125% and 200% horizontal lines are based on the results of simulation for a typical individual (70kg) in the population that received a standard dose (2mg/kg).

**Fig 2**: Boxplots of AUC over last two cycles (6 weeks) stratified by body weight (BW) for the different strategies. Median, 50%, 80%, 125% and 200% horizontal lines are based on the results of simulation for a typical individual (70kg) in the population that received a standard dose (2mg/kg).