Clinical and statistical considerations of bridging approaches to alternative dosing regimen or formulations

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- PK bridging approaches for dosing frequency
- PK bridging approaches for change in route of administration
Change in dosing schedule

Situation

- Fixed dose 100mg for indications A and B every 4 weeks (Q4W) as infusion, monotherapy
- One wants to explore a Q2W and Q6W dosing schedule
- Available data
  - Dose finding study (DF) exploring various body weight adjusted and fixed dosing for Q4W in indication A
  - Other Phase Ib, II and III studies in both indications A and B
Part A: Population PK (popPK) model

• **Questions to address:**
  – Linear pharmacokinetics (within data available)?
  – Disposition (compartment models) and elimination (x-order)
  – Covariates that are statistically significantly related to drug’s PK in popPK model (e.g. body weight, tumor burden, gender…)
  
  • Assess impact on exposure (relevant for interpolation / extrapolation to alternative schedules)

• **Model set-up (in short)**

"Usual" PK Studies
Dense sampling, N small

Population PK Studies
Sparse data, N large

The population, rather than the individual, is considered as a unit of analysis for estimating distribution of each parameter.
Part A: Population PK (popPK) model

Example

• Use fitted popPK model to simulate / predict hypothetical doses / schedules
• Key benchmarks are Cycle 1 and steady state exposure
• For the example drug, assume Ctrough drives efficacy, Cmax safety

<table>
<thead>
<tr>
<th>Regime</th>
<th>Cmax (ug/mL)</th>
<th>Ctrough (ug/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycle 1</td>
<td>Steady state</td>
</tr>
<tr>
<td>100mg Q4W</td>
<td>33</td>
<td>50</td>
</tr>
<tr>
<td>55mg* Q2W</td>
<td>18</td>
<td>34</td>
</tr>
<tr>
<td>165mg* Q6W</td>
<td><strong>55</strong></td>
<td><strong>62</strong></td>
</tr>
</tbody>
</table>

*Dose determined using target exposure (often Ctrough) established based on non-clinical studies

To ensure “at least” target exposure
Part B: Exposure-response (ER) model

- Questions to address
  - Impact of exposure (AUC, Cmax, Cmin) on efficacy and safety
  - Assess patient characteristics with respect to prognostic & predictive impact on endpoints

- Example

Percent change from baseline in first RECIST measurement versus vemurafenib exposure (Zhang, Heinzmann, Grippo, Clin Pharmacokinet 2017)
How much evidence needed?

• Assume Package = PopPK model plus substantial evidence on approved dose plus some sparse data on other doses.

• Sufficient? – Efficacy considerations
  – Maybe if no exposure-response relationship found for efficacy and safety within range one wants to extend dosing
  – Exposure achieved by approved dosing regime is in the flat or plateau part of the exposure-response curve
  – No impact on efficacy outcome expected as long as new dosing regimen achieved exposure greater than target concentration and within range of approved dose regime

• Sufficient? – Safety considerations
  – Cmax (AUC) – safety relationship (ER): No trend? Can one exclude increase in safety risk by higher Cmax with Q6W?
  – “Sparse data”: Is highest Cmax observed in some Phase I / II / III data (although likely only limited N)?
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PK bridging approaches for dosing frequency

PK bridging approaches for change in route of administration
Rationale for considering subcutaneous instead of IV administration

### Clinical activity
- Potential to provide comparable efficacy, pharmacokinetics and safety with subcutaneous administration, demonstrated in several clinical trials with other agents
  - Bortezomib subcutaneous\(^1,2\)
  - Alemtuzumab subcutaneous\(^3,4\)

### Patient needs
- Potential for greater patient preference and satisfaction, and reduced treatment burden with subcutaneous administration
  - Denosumab subcutaneous\(^5,6\)

### Healthcare professional needs
- Potential to optimise medical resource utilisation
  - Reduced administration time
  - No requirement for dedicated infusion suites/staff
  - No need for infusion bag preparation

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Herceptin SC development program

- **2010**
  - Robust evidence of clinical activity (efficacy, safety and PK)
  - Phase I CP2
  - Phase III HannaH

- **2011**
  - EMA Herceptin SC approval

- **2012**
  - CP2: Dose-finding/dose confirmation/fixed dose
  - HannaH: Comparability between Herceptin SC vial and IV

- **2013**
  - PrefHer (cross-over design)
    - Phase II PrefHer (cross-over design)
    - Preference study
    - Switching study
  - SafeHer – Safety study
    - Phase III SafeHer – Safety study
    - Safety Study

- **2014**

Patient preference and satisfaction
Healthcare professional preference and satisfaction
Medical resource utilisation
Phase I: popPK model to determine Herceptin SC dose

(1.) $C_{\text{min}}$ at least as high
(2.) Comparable AUC
(3.) Dose such that no loading dose required

Quartino et al, 2015, Cancer Chemother Pharmacol
Phase III: Optimal population and endpoint

• Guiding principle: Sensitivity
  – The idea is to study Herceptin SC in the population of patients with an endpoint such that *if there is a difference between Herceptin SC and Herceptin IV* – that difference will most likely be detected

• Extensive analyses show that this is satisfied by:
  – **Population:** Neoadjuvant
  – **Endpoint:** pathologic Complete Response (pCR)

  – **REF:** Jackisch, Scappaticci, Heinzmann et al 2015, Future Oncol. « Neoadjuvant breast cancer treatment as a sensitive setting for trastuzumab biosimilar development and extrapolation»
HannaH: Phase III, non-inferiority trial

**Co-primary endpoints**

**PK:** Observed $C_{\text{trough}}$ at pre-dose cycle 8 (non-inferiority)

**pCR:** Pathological complete response in the breast (non-inferiority)
HannaH: Phase III, non-inferiority trial

PK hypotheses confirmed by non-inferior efficacy

Objective (1.)
$C_{\text{min}}$ at least as high

Objective (2.)
Comparable AUC
prefHER study: Patient preference, Time and motion

Vial cohort

HER2-positive EBC (N=200)

R

1:1

SC vial every 3 weeks x 4

Intravenous every 3 weeks x 4

Herceptin

Intravenous cycles to complete 18 cycles in total

SC vial every 3 weeks x 4

Remaining Herceptin cycles to complete 18 cycles in total

• Primary objective: Assess patients' preference for Herceptin subcutaneous vs intravenous administration in patients with HER2-positive early breast cancer
• Secondary objectives: HCP satisfaction, safety, efficacy and immunogenicity
Alternative designs?

- Done: Comparative trial IV vs SC (non-inferiority)
- Alternative: 3 arm design with testing superiority of IV and SC versus SoC

### Scenario *

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Alpha</th>
<th>Sample size (events/pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-inferiority</td>
<td>2.5% one-sides</td>
<td>~631 / 814</td>
</tr>
<tr>
<td>Superiority</td>
<td>2.5% two-sided for both tests</td>
<td>~338 / 446 (three arms)</td>
</tr>
</tbody>
</table>

*Assuming TTE endpoint, median TTE in SoC arm 8 mo, target median in experimental 12 mo with 80% power, non-inferiority margin HR=1.25, target HR for superiority 0.67, accrual 22 mo, similar event/patient ratio and trial duration*
Summary

• Dose schedule changes
  – M&S sufficient?
  – If data on alternative dosing schedules needed, how much data?

• Changes of administration route
  – Same active substance, similar efficacy and safety
  – What type of Phase III needed (non-inferiority, or alternative a three arm superiority trial)?

• Open item: Switching
  – What data needed to support switch between dose schedules & formulations?
  – If switching study is needed, what endpoints to look at?
Doing now what patients need next