Concentration-QTc analysis to obviate the need for a dedicated QTc study in cancer patients: ixazomib, an oral proteasome inhibitor, as a case study

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Outline

• Concentration-QTc analysis to obviate the need for a dedicated QTc Study
  – Case study: ixazomib, an investigational proteasome inhibitor in patients with cancer

• Discuss framework to guide strategies for QTc assessment in oncology drug development
Ixazomib concentration–QTc analysis (N=245)

- Pharmacokinetic-matched triplicate ECGs were collected from four phase-1 studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Dose (mg/m²)</th>
<th>Dosing schedule</th>
<th>ECG extraction and time-matched PK sampling*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C16001</td>
<td>Advanced solid tumors</td>
<td>0.125–2.34</td>
<td>IV, Twice-weekly</td>
<td>Schedule A: Day 1: 0, 5 min Day 11: 0, 5 min, 1, 2, 24 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Schedule B: Day 1: 0, 10 min; Day 11: 0, 5 min</td>
</tr>
<tr>
<td>C16002</td>
<td>R/R lymphoma</td>
<td>0.125–3.11</td>
<td>IV, weekly</td>
<td>Day 1 and 15: 0, 5 min</td>
</tr>
<tr>
<td>C16003</td>
<td>R/R MM</td>
<td>0.24–2.23</td>
<td>PO, Twice-weekly</td>
<td>Day 1 and 11: 0, 0.5, 1, 4, 24 h</td>
</tr>
<tr>
<td>C16004</td>
<td>R/R MM</td>
<td>0.24–3.95</td>
<td>PO, weekly</td>
<td>Day 1 and 15: 0, 0.5, 1, 4 h and 24 h (only day 15)</td>
</tr>
</tbody>
</table>

- Mean age is 57 (range: 23-86) years
- Male/female: 140 (57%)/105 (43%)

*All ‘0’ time points are pre-dose unless otherwise stated; all other time points are post-dose; MM, multiple myeloma; Weekly- Days 1,8,15 in 28-day cycle; Twice-weekly- days 1,4,8,11 in 21-day cycle  
1: NCT00830869; 2: NCT00893464; 3: NCT00932698; 4: NCT00963820
Model predicted QTcF and QTcP (including 90% confidence intervals) following a 4 mg phase-3 dose

The relationships between concentration and QTcF or QTcP was best explained by linear mixed model

\[
y_{ijk} = \beta^{(\mu)} + \eta_{i}^{(\mu)} + \beta^{(Sl)} \cdot \{\text{STUDY}=l, l\neq C16001\} + \beta^{(F)} \cdot \{\text{SEX} = F\} \\
\quad + (\beta^{(D)} + \eta_{i}^{(D)} \cdot \{\text{Day}=j, j\neq 1\} + \beta^{(Tk)} \cdot \{T=k, k\neq 0\} + \beta^{(C)} \cdot C_{ijk} + \varepsilon_{ijk}
\]

- Slope estimate for both QTcF and QTcP were not statistically significant.
- 90% Bootstrap CI also supports non-significance of drug-induced QTc prolongations.

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameter</th>
<th>Estimation</th>
<th>90% CI</th>
<th>Model predicted ddQTc at Cmax</th>
<th>90% Bootstrap CI</th>
<th>Bootstrap predicted ddQTc at Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTcF</td>
<td>$\beta^{(C)}$</td>
<td>0.00148</td>
<td>(-0.00460, 0.00756)</td>
<td>0.0710 (-0.221, 0.363)</td>
<td>(-0.00440, 0.00679)</td>
<td>0.0612 (-0.211, 0.326)</td>
</tr>
<tr>
<td>QTcP</td>
<td>$\beta^{(C)}$</td>
<td>0.00123</td>
<td>(-0.00502, 0.00754)</td>
<td>0.0591 (-0.242, 0.361)</td>
<td>(-0.00485, 0.00694)</td>
<td>0.0520 (-0.233, 0.333)</td>
</tr>
</tbody>
</table>

$\beta$, fixed-effect parameter; CI, confidence interval
No relationship between ixazomib concentration and RR interval; no effect on HR

- The final model used for C-QT analysis was also used for C-RR analysis. There was no relationship between ixazomib concentration and RR interval, suggesting that ixazomib has no effect on HR.

![Graph showing relationship between plasma concentration and RR interval](image)

**Linear Mixed Effects Model**

<table>
<thead>
<tr>
<th>Slope Estimation</th>
<th>SE</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00790</td>
<td>0.0225</td>
<td>0.726</td>
</tr>
</tbody>
</table>

- Same model as the final model for concentration-QTc relationship
- Drug effect on heart rate appears to be not significant

LME Model for RR: \( y_{ijk} = \beta^{(\mu)} + \eta_{i}^{(\mu)} + \beta^{(SI)} \cdot \{STUDY=l, l \neq C16001\} + \beta^{(F)} \cdot \{SEX = F\} \)

\[ + (\beta^{(Dj)} + \eta_{i}^{(Dj)}) \cdot \{Day=j, j \neq 1\} + \beta^{(Tk)} \cdot \{T=k, k \neq 0\} + \beta^{(C)} \cdot C_{ijk} + \varepsilon_{ijk} \]
Conclusions: conc-QTc analysis

• Availability of IV data was a unique design feature
  – IV data resulted in supratherapeutic concentrations - 26% data greater than mean Cmax at 4 mg oral dose
• Ixazomib had no clinically meaningful effect on QTc based on model-predicted mean change in QTcF/QTcP from baseline
  – No QTc prolongation at ixazomib plasma concentrations that far exceed the clinically relevant range (i.e., 4 times the C_{max} at the 4 mg dose)
• There was no relationship between ixazomib concentration and RR, suggesting no effect on HR.
• No observed QTcF and QTcP values were >500 msec. Only one observation of ΔQTcP was >60 msec while none were observed for ΔQTcF.
Strategy for QTc assessment in oncology (1)

ECGs collection in triplicate, centrally read and always collect baseline triplicate ECG (time matched, if possible)

* Some drugs may be allowed for palliative care (if no other option available)

#Phase-1 dose escalation studies; timing/number of ECGs may vary based on time course of active metabolite, if applicable

^For ADC – toxin can be treated similar to small molecule
**Strategy for QTc assessment in oncology (2)**

- **Dedicated QT study**
- **QT assessment in a planned/ongoing clinical trial**
- **QT assessment in a Phase 3 trial**

**Biologics/ADC**: Clinical phase-1 QT testing based on nonclinical ECG findings/preclinical concerns

**Conc-QTc analysis (centrally read ECGs)**

- **Positive**: UCL \( \Delta \text{QTc} \geq 20 \text{ms} \) or, UCL \( \Delta \text{QTc} > 10 \text{ and } < 20 \text{ ms} \) and QT study can be done in HV

- **Neutral**: UCL \( \Delta \text{QTc} \) bet 10-20 ms and QT study cannot be done in HV

- **Negative**: UCL \( \Delta \text{QTc} < 10 \text{ ms} \)

- **High efficacy in advanced disease, poor prognosis, clean cardiac safety profile**

- **Seek Feedback from IRT**

**Plan for further QT assessment**

- **Submit QT report**

**Submit C-QT report**

**Approaches may include**:
- Dedicated QT study
- QT assessment in a planned/ongoing clinical pharmacology study
- QT assessment in a Phase-3 trial

**Central tendency and conc-QT analysis**
- Study reports, protocols, IB, CRF
- A data definition file
- Electronic data sets as SAS.xpt transport files and all the SAS codes used for the analyses

\( \Delta \text{QTc} \) is expressed as upper end of 95% confidence interval; ^For ADC – toxin can be treated similar to small molecule
Conclusions

• Concentration-QTc analysis is a viable approach that may obviate the need for a dedicated QTc Study
• A QTc assessment framework for development of new anti-cancer drugs was proposed
• The specifics of these approaches will require consideration of the overall nonclinical and clinical benefit vs. safety profile and can be guided by appropriate engagement with health authorities
Acknowledgements

• Patients and their families
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