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

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

- 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</td>
<td>(-0.00440, 0.00679)</td>
<td>0.0612</td>
</tr>
<tr>
<td>QTcP</td>
<td>( \beta^{(C)} )</td>
<td>0.00123</td>
<td>(-0.00502, 0.00754)</td>
<td>0.0591</td>
<td>(-0.00485, 0.00694)</td>
<td>0.0520</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

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

LME Model for RR: $y_{ijk} = \beta^\mu + \eta_i^\mu + \beta^\text{STUDY} \cdot \{\text{STUDY}=l, l\neq C16001\} + \beta^\text{SEX} \cdot \{\text{SEX}=F\}$

+ $(\beta^\text{Day} + \eta_i^\text{Day}) \cdot \{\text{Day}=j, j\neq 1\} + \beta^\text{T} \cdot \{T=k, k\neq 0\} + \beta^\text{C} \cdot C_{ijk} + \epsilon_{ijk}$
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 Cmax 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)

**hERG assay results**

- **hERG assay**: 
  - >30 fold difference between Cmax, u and IC50

- **Yes**
  - Less intensive assessments#: 3-5 PK matched ECG around Tmax after single dose and at steady state
  - In phase-1 study*:  
    - Drugs known to cause QT prolongation should be excluded
    - Documentation of conmeds
    - Baseline time matched ECGs in MTD expansion cohort
  - Conc-QTc analysis (centrally read ECGs)

- **No**
  - More Intensive assessments#: 6-8 PK matched ECG after single dose and at SS covering dosing interval
  - Biologics/ADC^: Clinical phase-1 QT testing based on nonclinical ECG findings/preclinical concerns

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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)

- **Conc-QTc analysis (centrally read ECGs)**
  - Positive: UCL $\Delta$QTc $\geq 20$ ms or, UCL $\Delta$QTc $> 10$ and $< 20$ ms and QT study can be done in HV
  - Negative: UCL $\Delta$QTc $> 10$ and $< 20$ ms and QT study cannot be done in HV

- **Neutral: UCL $\Delta$QTc bet 10-20 ms**
  - High efficacy in advanced disease, poor prognosis, clean cardiac safety profile

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

- Plan for further QT assessment*
  - Submit QT report**
  - Seek Feedback from IRT

- **Submit C-QT report**

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

**QT report should consist of**
- 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

$\Delta$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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