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

Study	Patients	Dose (mg/m^2)	Dosing schedule	ECG extraction and time-matched PK sampling*
C16001[1]	Advanced solid tumors	0.125–2.34	IV, Twice-weekly	Schedule A: Day 1: 0, 5 min Day 11: 0, 5 min, 1, 2, 24 h Schedule B: Day 1: 0, 10 min; Day 11: 0, 5 min
C16002[2]	R/R lymphoma	0.125–3.11	IV, weekly	Day 1 and 15: 0, 5 min
C16003[3]	R/R MM	0.24–2.23	PO, Twice-weekly	Day 1 and 11: 0, 0.5, 1, 4, 24 h
C16004[4]	R/R MM	0.24–3.95	PO, weekly	Day 1 and 15 : 0, 0.5, 1, 4 h and 24 h (only day 15)

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

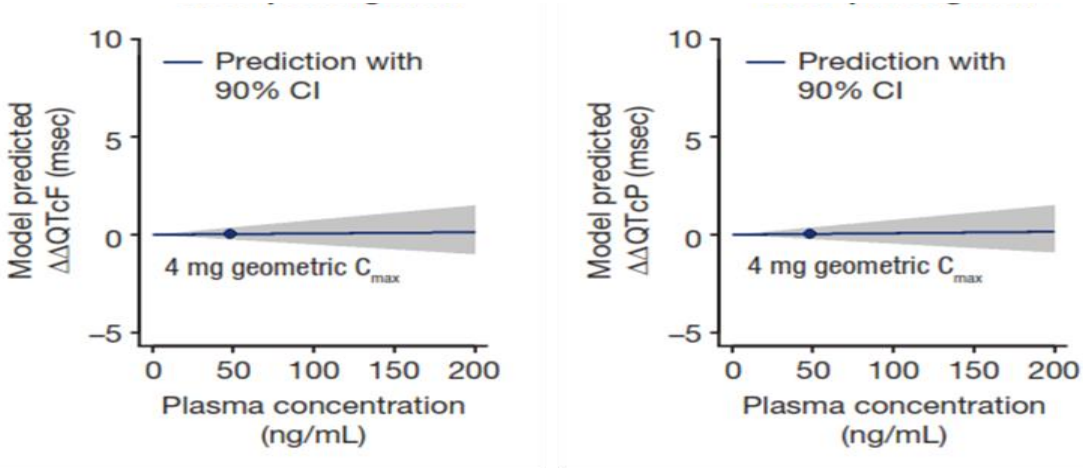
*All '0' time points are pre-dose unless otherwise stated; all other time points are post-dose; MM, multiple myeloma; Weekly- Days 1,8,15 in 28-day cycle; Twice-weekly- days 1,4,8,11 in 21-day cycle

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

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



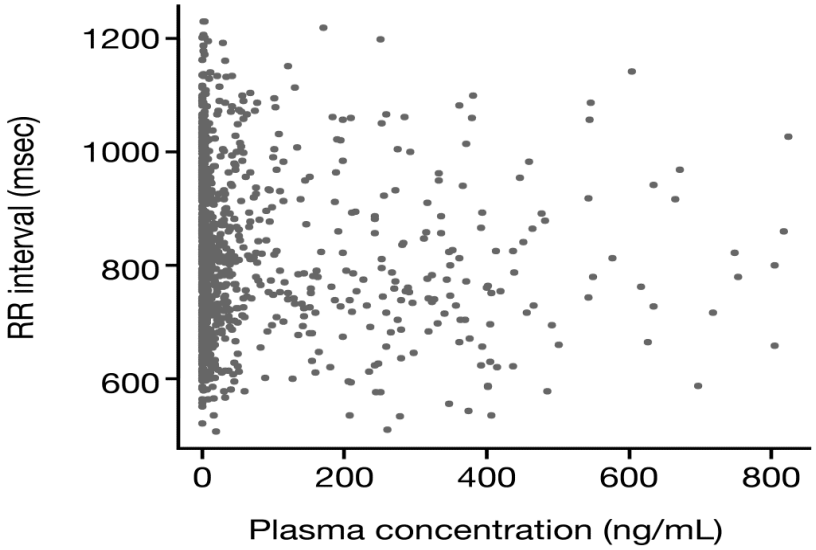
- Slope estimate for both QTcF and QTcP were not statistically significant.
- 90% Bootstrap CI also supports non-significance of drug-induced QTc prolongations.

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

β, 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



Linear Mixed Effects Model	Slope Estimation	SE	p value
	0.00790	0.0225	0.726

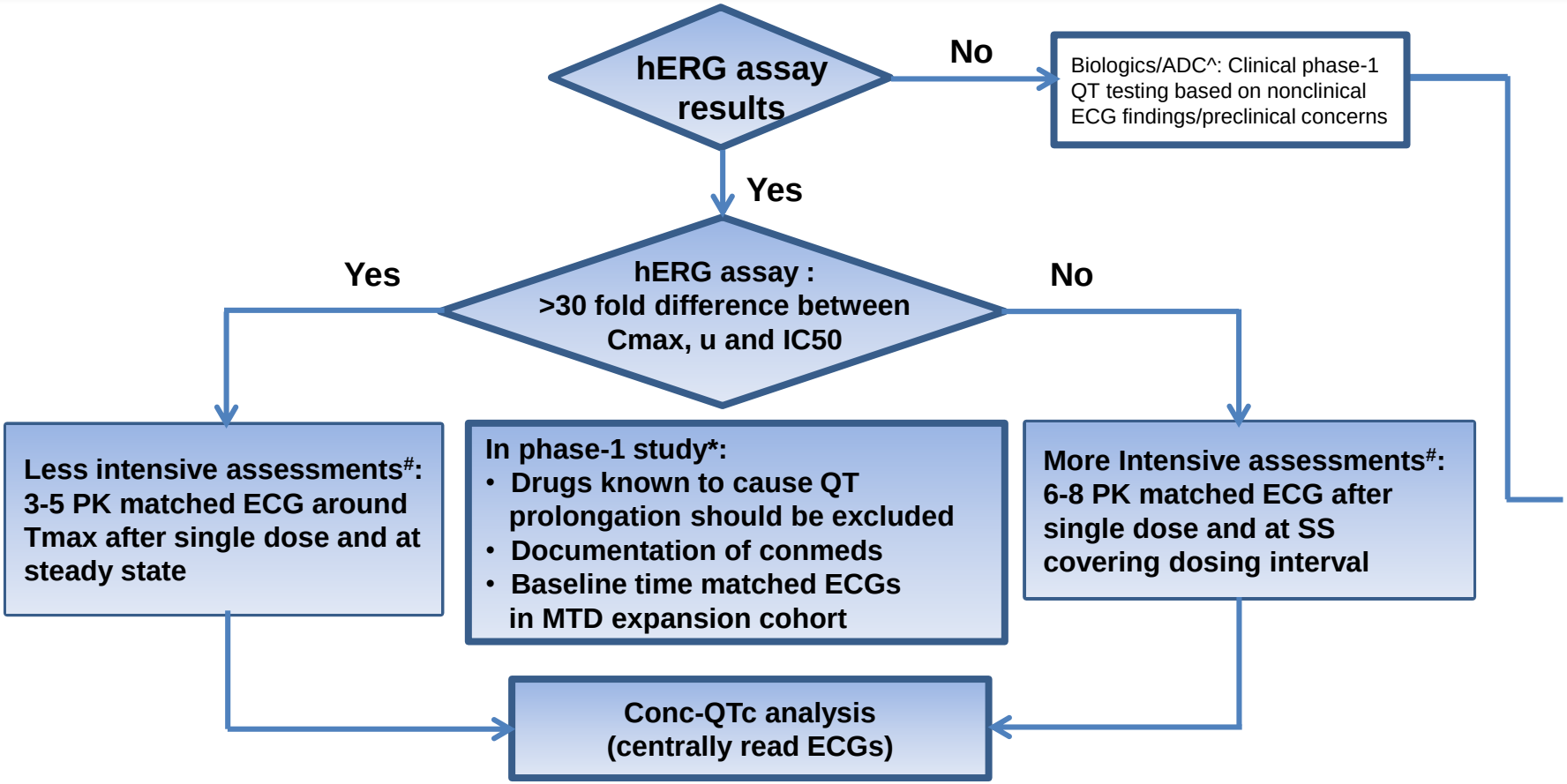
- Same model as the final model for concentration-QTc relationship
- Drug effect on heart rate appears to be not significant

LME Model for RR: $y_{ijk} = \beta^{(\mu)} + \eta_i^{(\mu)} + \beta^{(SI)} \cdot \{STUDY=I, I \neq C16001\} + \beta^{(F)} \cdot \{SEX = F\}$
$+ (\beta^{(Dj)} + \eta_i^{(Dj)}) \cdot \{Day=j, j \neq 1\} + \beta^{(Tk)} \cdot \{T=k, k \neq 0\} + \beta^{(C)} \cdot C_{ijk} + \varepsilon_{ijk}$

Conclusions: conc-QTc analysis

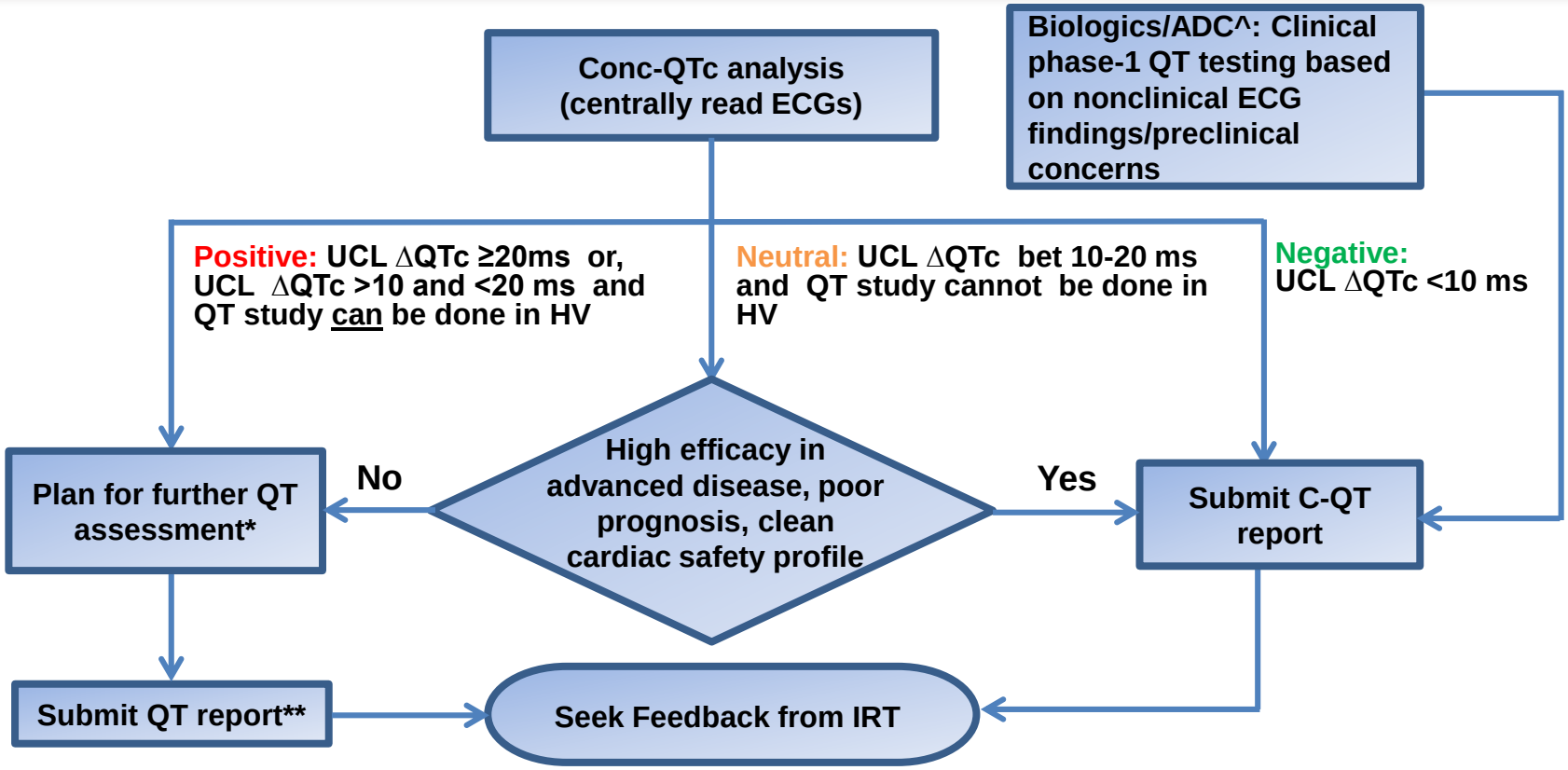
- Availability of IV data was a unique design feature
  - IV data resulted in supratherapeutic concentrations - 26% data greater than mean Cmax at 4 mg oral dose
- Ixazomib had no clinically meaningful effect on QTc based on model-predicted mean change in QTcF/QTcP from baseline
  - No QTc prolongation 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)



***Approaches may include:**
Dedicated QT study
QT assessment in a planned/ongoing clin pharm 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

ΔQTc 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

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