Lessons Learned from Oncology Dose Finding Workshops

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The Dose Optimization Issue

• High rate of dose reductions and discontinuations in clinical trials
• Adherence to therapy in the “real world”
• Redundant drug development process with inefficiencies
• More potential permutations of combinations than eligible patients
• Incomplete characterization of compounds and lack of full understanding of mechanisms of actions
• HIGHLY competitive and rapidly changing landscape
DFW: Part 1
Small Molecule Kinase Inhibitors

• Exposure response relationships are rarely defined nor interpatient variability adequately evaluated during early clinical development
  – Poor solubility and high variability of exposure
• AEs in Phase 2/3 clinical trials result in dose reductions, complicating study interpretation and determination of FDA-recommended dose
• Sponsor’s have to conduct additional dose optimization studies as PMRs
Broad target selectivity for many FDA-approved kinase inhibitors

1 μM kinase inhibitor profiled against 300 kinases in a biochemical enzymatic assay

Uitdehaag et al, PLOS one (2014)
General Considerations

- Interdisciplinary Communication
- Revisit and retest when signals emerge
- Purposeful selection of trial designs
DFW: Part 2
Large Molecules

• FIH dose selection (Saber et al Regul Toxicol Pharmacol 2016)
  – MABEL approach: Minimally Anticipated Biological Effect Level
  – Use receptor occupancy or pharmacologic activity to start
  – Use strategies such as Intra-patient dose escalation and n=1 escalation cohorts to minimize patients exposed to dose levels not expected to have biologic effects
Large Molecules

• RO and saturation may inform safe start dose, but % saturation may not equate to optimal dose
  – May be thought of as lower bound?
• PK-PD models may be informative
• E-R relationships
  – Contribution of disease status
Dose Adjustment: Challenges for E-R Relationship Estimation

- Exposure not constant over time
- Biased ER relationship

E-R: Exposure-Response; AE: Adverse Event

Courtesy of Chao Liu FDA
All Products and Combinations

• Systems pharmacology approaches may be informative
• Integration of multiple sources
• Consider time as a key factor
  – Dose adjustment Integrated E-R analysis
DFW: Part 2.5
Dose-Finding: IO Agents and Combinations

• Fixing dose and schedule of agents that are already approved or well characterized
• Safety attribution in combination studies
• Disease specificity for dose/schedule of combinations
• Benefits of larger sample sizes and randomized evaluation
DFW 2.75
AACR 2017

- Biomarkers and IO combination
  - SITC working group
  - Industry perspective
  - Use of biomarkers in modeling and simulation approaches

- How can you find the right dose if you cannot find the right patient?

- Is survival the only endpoint?
DFW 3!!
In an Ideal (?) World