Innovations for effective drug development

Promoting Effective Drug Development Programs: Opportunities and Priorities for FDA's Office of New Drugs

Martin Roessner
Corporate Vice President, Biostatistics
Parexel International
November 7, 2019

© 2019 Parexel International Corporation / CONFIDENTIAL

Agenda

- Innovative approaches to accelerate development
- Design options for dose escalation
- Seamless Phase I/II design
- Considerations for more effective drug development

© 2019 Parexel International Corporation / CONFIDENTIAL

Survey demonstrates impact of innovations - low adoption rates and barriers

THE INNOVATION IMPERATIVE: THE FUTURE OF DRUG DEVELOPMENT

Innovation Type	Reduction In Enrollment Time	Likelihood of Launch	Adoption rate
Adaptive Trials	↓ 4.2 Months	13% ↑	**0.6%**
Precision Medicine Trials	↓ 5.2 Months (Oncology) ↓ 0.9 Months (Neurology) ↓ 10.6 Months (Rare Diseases)	10% ↑	**5.2%**
Patient Centricity	↓ 3 Months	19% ↑	**13.7%**
Real-World Data Trials	↓ 1 Month	21% ↑	**0.3%**

Enablers
Advanced Data Analytics
Workforce Readiness
Collaborative Partnerships
Early Regulator, Payer, & Patient Involvement

Barriers for Adoption

Vast, New and Fragmented Data

Small or Inadequate Workforce

Negative Perceptions of Pharma

Cultural Barriers

https://druginnovation.eiu.com
Commissioned by Parexel

parexel

Dose Escalation Designs used in Oncology

- **Rule based**
  - Simple up and down, 3+3 type, **i3+3**, accelerated titration
- **Model Based**
  - Continual Reassessment Method (CRM) and modifications
  - Escalation with Overdose Control (EWOC)
  - Bayesian Optimal INterval (BOIN) Design
  - Modified toxicity probability interval design (mTPI , mTPI 2)
  - Toxicity and efficacy probability interval (TEPI)
- **Comparison Rule/Model based Trials**

N=172 trials*	Rule-based	Model-based
Duration of trials	36 mo	26 mo
# Patients below RP2D	40	31
Safety: DLTs	14%	13%

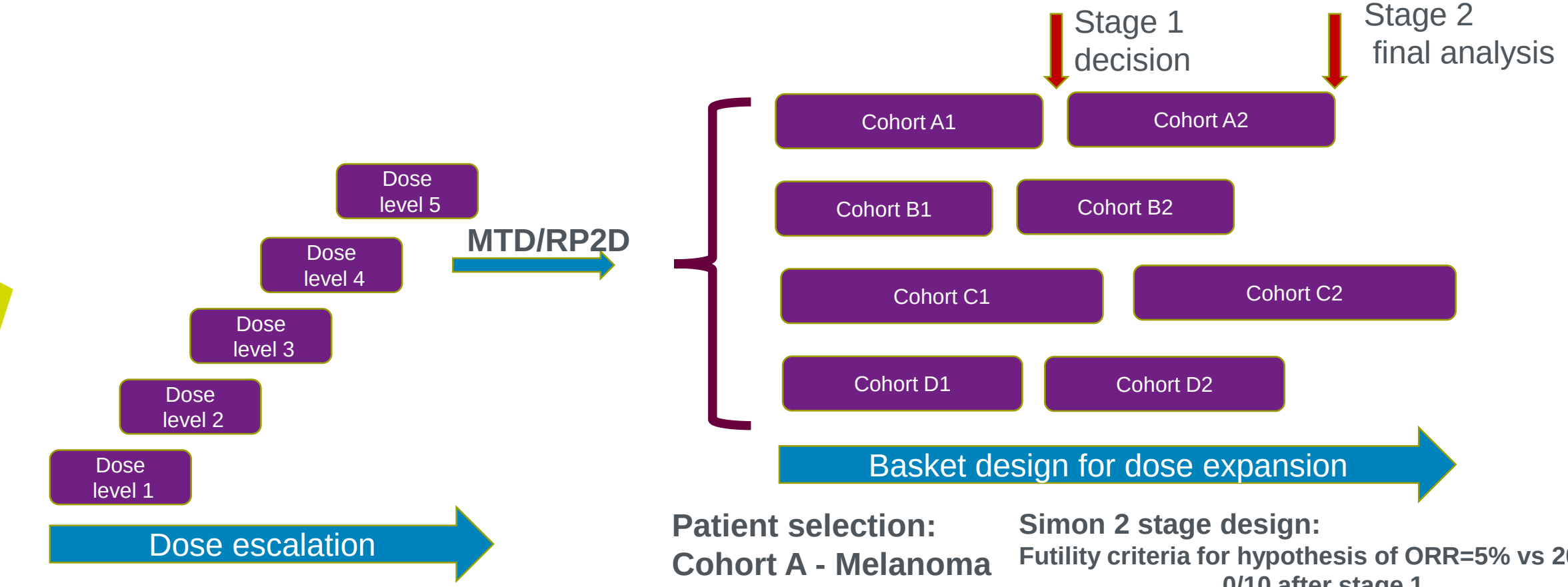
*van Brummelen et al, The performance of model-based versus rule-based phase I clinical trials in oncology, June 2016

© 2019 Parexel International Corporation / CONFIDENTIAL

parexel

Seamless Phase I/II Study

Combining Dose Escalation and dose expansion



Dose levels: 50 , 100, 200, 400, 600 mg QD

Patient selection:
Cohort A - Melanoma
Cohort B – NSCLC
Cohort C – H&N
Cohort D - Gastric

Simon 2 stage design:
Futility criteria for hypothesis of ORR=5% vs 20%:
0/10 after stage 1
3/29 after stage 2
Futility criteria for hypothesis of ORR=10% vs 25%:
2/18 after stage 1
7/43 after stage 2

© 2019 Parexel International Corporation / CONFIDENTIAL

Synthetic Control Arm

Real World Evidence to Support Development of Drugs and Biologics

Single arm Clinical Study (CS)

RWD collection

- Patient-level data in similar patients

Matching algorithm applied to RWD

- Create a matching cohort to CS cohort

Comparative analysis CS vs RWD cohorts

- Demonstrate superiority of CS treatment vs RWD control cohort

https://www.fdli.org/2018/08/update-fdas-historical-use-of-real-world-evidence/

© 2019 Parexel International Corporation / CONFIDENTIAL

Considerations for more effective drug development

Use more efficient study designs in early development

- Apply innovations –Adaptive trial designs, Precision medicine, Patient centricity, RWD
- Apply model based dose escalation designs and expansion designs to oncology and non-oncology studies
- Consider RWD to support development through synthetic control arms
  - Agree on acceptable methodology

© 2019 Parexel International Corporation / CONFIDENTIAL

Thank you

© 2019 Parexel International Corporation / CONFIDENTIAL