Challenges and Opportunities for Modeling and Simulation in Late Phase Oncology Development: Combinations, Cancer Immunotherapy, and More

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Modeling and Simulation in Oncology Development

- **Overview**
  - Today’s Anti-cancer Agents
  - M&S in Drug Development

- **Case Examples**
  - NME+SOC Combo Dose Selection – *Benefit-risk analysis*
  - Cancer Immunotherapy Dose Justification – *PK-tumor-survival*

- **Final Remarks**
Today’s Anti-Cancer Agents

**Vision:** Simultaneous inhibition of multiple targets to enhance activity in broader population with less resistance
- Multiple mechanism of action
- Multiple molecule types
- Combination therapy (NME+SOC, NME+NME)

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**Kinase Pathways**

**Cancer Immunotherapy**

- Priming and activation
- Cancer antigen presentation
- T cell granule content
- Inflammation

**Drug Targets**

NME: new molecular entity; SOC: standard of care

Chen & Mellman; Immunity 2013
Overview

Modeling and Simulation in Drug Development

Project Modeling (Molecule-specific)

**Phase I/II/III**
- Dose optimization: *translational & clinical PK/PD*
- Regimen and dosing schedule optimization: *longitudinal M&S*
- Effect of intrinsic factors: *PopPK, PBPK*
- Effect of extrinsic factors: *PopPK, PBPK*
- QT prolongation: *concentration-QT*
- Exposure and response at site of action: *biomarker PK/PD, PBPK/PD*
- Sampling optimization: *Trial simulation*

**Pre IND**
- Human dose projection: *translational PK/PD*
- Exposure and target engagement at site of action: *tissue PK/PD, PBPK/PD*

**Platform Modeling (Cross-molecules)**
M&S for molecule platform and/or disease platform: disease progression, prediction of outcome by early endpoints, literature meta-analysis, system pharmacology modeling (QSP), etc.
Case Examples

Modeling and Simulation in Drug Development

Phase I/II/III
- Dose optimization: translational PK/PD
- Regimen and dosing schedule optimization: longitudinal M&S
- Effect of intrinsic factors: PopPK, PBPK
- Effect of extrinsic factors: PopPK, PBPK
- QT prolongation: concentration-QT
- Exposure and response at site of action: biomarker PK/PD, PBPK/PD
- Sampling optimization: Trial simulation

Pre IND
- Human dose projection: translational PK/PD
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Clinical Pharmacology Characterization
- Decision making
- Label

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Chen & Mellman; Immunity 2013
Dose Selection for Ipatasertib

- The PI3K/AKT pathway is central for cancer cell growth and survival
- Ipatasertib (GDC-0068) is a potent, oral, ATP-competitive AKT inhibitor

Ipatasertib 2L mCRPC Phase 2 (A.MARTIN) Study Design

Randomize 240 pts 1:1:1 stratify:
- Prior treatment with enzalutamide (Y/N)
- Progression Factor (PSA only vs other)
- # prior chemotherapies for metastatic disease (1 vs >1)

n= 80/arm

Comparison 1
Abiraterone* + GDC-0068 400 mg QD

Comparison 2
Abiraterone* + GDC-0068 200 mg QD
Abiraterone* + Placebo (1:1 ratio to 400mg QD/placebo and 200mg QD/placebo groups)

Clinical Question: What is the recommended Ipatasertib dose for further development in mCRPC?

Clinical Question: How to account for the confounding effect of dose reduction in Phase 2?

DI Model 1: Prob(DI≥1) vs. Dose

DI Model 2: DI distribution in DI<1 population

Dose Selection: Exposure-Response

Exposure-Efficacy: radiographic PFS

Dose-rPFS projections from Cox regression model of exposure-rPFS coupled with dose intensity model

Exposure-Safety: Gr2+ Diarrhea

Dose-safety projections from logistic regression model of exposure-safety coupled with dose intensity model (Gr2+ diarrhea)

Similar analyses conducted for: Gr3+ diarrhea, Gr2+ rash, Gr 3+ rash

Dose Selection: Clinical Utility Index

Benefit-risk analysis via exposure-response and clinical utility index (CUI) approaches indicated that 400 mg QD Ipatasertib has the highest probability of achieving the minimal Product Profile (PP) with better benefit/risk balance than 200, 300, or 500 mg QD.

Impact: Overall, Ipatasertib 400mg QD dose was supported by M&S for further development in mCRPC.
Case Examples

Modeling and Simulation in Drug Development

Project Modeling (Molecule-specific)

- IND
- Ph Ia
- Ph Ib/II
- Ph III
- EOP2
- BLA/NDA
- Ph IV

Pre IND
- Human dose projection: translational PK/PD
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Chen & Mellman; Immunity 2013
Cancer Immunotherapy and Atezolizumab

Atezolizumab Case Example

Atezolizumab is a humanized engineered mAb that selectively targets PD-L1
- By inhibiting interactions with receptors PD-1 and B7.1, anti-cancer immunity can be reinvigorated and enhanced

Atezolizumab has demonstrated efficacy and safety in a broad range of cancer types, including mUC, NSCLC and RCC

The POPLAR study is an open-label, Phase 2 randomized controlled trial of atezolizumab compared to docetaxel in patients (n=297) with advanced NSCLC who progressed on post-platinum chemotherapy¹

- Median OS: Atezolizumab 12.6 months (95% CI: 9.7-16.4); Docetaxel 9.7 months (8.6-12.0)
- Hazard ratio: 0.73 (95% CI: 0.53-0.99, p=0.040)

Clinical Question: Is there any dose adjustment need for Atezolizumab due to loss of efficacy in patients with lower exposure, or increased safety risk in patients with higher exposure?

Exposure-response:
- OS is correlated with atezolizumab exposure
- Exposure-OS relationships are confounded with baseline prognostic factors

Bruno et al. ACoP 2016
Atezolizumab Case Example

Oncology Modeling Framework

Models-based tumor growth inhibition (TGI) metrics could be used as biomarkers to capture treatment effect and predict for OS benefit.

Q1: Can causality for exposure-response (via tumor growth inhibition) as a way to mitigate confounding by baseline prognostic factors?
Atezolizumab Case Example

Tumor Response Data from POPLAR

Atezolizumab
(1200 mg IV q3w)

Docetaxel
(75 mg/m² IV q3w)

All profiles in grey, 50 patients taken at random are colored

Bruno et al. ACoP 2016
Dose Justification for Atezolizumab in NSCLC

The bi-exponential Stein model: 

$$TS(t) = TS_0 \cdot [\exp(-KS \cdot t) + \exp(KG \cdot t) - 1]$$

Stein et al. CCR 17:907-17, 2011

- Slower tumor growth (KG) in atezolizumab arm
- KG correlated with atezolizumab exposure
- In the multivariate OS model, with baseline prognostic factors and KG capturing treatment effect, atezolizumab exposure is no longer significant
- The multivariate OS model was used to simulate exposure-response with OS after adjusting for prognostic

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<th>HR</th>
<th>CI</th>
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<td>0.62</td>
<td>(0.56,0.68)</td>
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</table>

AUCss tertiles=median, interval, [a, b); HR=Hazard ratio distribution over 1000 replicates; 95%PI=95% prediction interval, 5000 patients, 1000 replicates

Impact: Overall PK-TGI-OS M&S suggested no dose adjustment need due to loss of efficacy in patients with lower exposure, supporting the Atezolizumab dosing of 1200 mg q3w in 2L+ NSCLC patients.

Atezolizumab Case Example

Bruno et al. ACoP 2016
Models-based tumor growth inhibition (TGI) metrics could be used as biomarkers to capture treatment effect and predict for OS benefit.

Q2: Is this paradigm working for cancer immunotherapy?
Qualification of TGI~OS Model in POPLAR

The OS model appears to capture treatment effect of Atezolizumab in POPLAR study.

The POPLAR project suggested validity of TGI~OS paradigm for cancer immunotherapy. This approach is being further evaluated and validated for broader CIT development.
Final Remarks

- Identification of the “optimal dose” is one of the primary challenge and opportunity in today’s drug development
  - Challenge the MTD paradigm with today’s anti-cancer therapies

- Continuously learn and confirm paradigm using novel quantitative and experimental approaches is key for success in drug development
  - **Modeling and simulation** throughout the life cycle of a drug to effectively interrogate:
    - Dose, exposure, efficacy, and safety
    - Preclinical and clinical
    - Historical and emerging data
    - Disease biology
    - Mechanism of action
    - Concentration and response at site of action
    - ……

- **Clinical trial designs** that enable the study of dose-exposure-response
  - Optimized and adaptive design
  - Multiple dose and schedules
  - Effective measurements of drug activity – imaging, biomarkers, efficacy/safety endpoints
  - Assessment of exposure and response at site of action
  - ……
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Atezolizumab Example:
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Patients

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