Modeling and Simulation with Evolving Cancer Therapies: Combinations, Cancer Immunotherapy, and More

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Outline

Modeling and Simulation with Evolving Cancer Therapies

- Overview
  - Today’s Anti-cancer Agents
  - Dose Optimization Strategy in Oncology

- Case Examples
  - 2NME Combo Phase 1b Design – translational PK/PD
  - NME+SOC Combo Dosing Optimization – clinical PK/PD
  - aPDL1 Dose Justification – exposure-response and PK/tumor/survival

- Final Remarks
**Overview**

**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
  - CD28/CD80
  - CD137/CD73/LMx203/40L
  - CD27/CD75
  - HMGB1
  - HSP
  - IL-2
  - IL-12
  - CTLA-4
  - PD-L1/2
  - PD-L1/2
  - CD40

- Trafficking of T cells to tumors
  - LFA-1/ICAM1
  - Selectins
  - VEGF
  - Endothelin B receptor
  - Initiation of T cells into tumors
  - Recognition of cancer cells by T cells
  - T cell receptor

- Killing of cancer cells
  - T cell granule content
  - PD-L1/2
  - PD-L1/2
  - IDO
  - TGF-beta
  - CTLA-4
  - VISTA

**Drug Targets**

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NME: new molecular entity; SOC: standard of care
Overview

Dose Optimization Strategy in Oncology

Preclinical-to-clinical translation
- Homogeneous xenograft vs. heterogeneous patients
- Species difference (e.g. resistance development, ATA)
- Safety: challenging

Early-to-late clinical translation
- Predictive biomarkers (target and indication specific)
- Translation of early response to long-term efficacy
- Chronic safety: challenging

Opportunity for M&S Based Dose Optimization:
- **PK:**
  - Dose adjustment based on intrinsic/extrinsic factors (high PK variability in oncology patients)
  - ATA effect for biologics
  - Poly-pharmacy for co-mobility (PK DDI)
- **Biomarker:**
  - Demonstration of pathway inhibition
  - Dosing justification based on target-specific or indication-specific biomarkers
- **Clinical efficacy/safety:**
  - Optimize therapeutic window

Complexity double/triple with combination therapy!
Overview

Modeling and Simulation in Drug Development

Project Modeling (Molecule-specific)

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

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

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

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Chen & Mellman; Immunity 2013
Translational PK/PD M&S Approach

**STAGE 1 – Fitting (Mouse)**
- Mouse PK

**STAGE 2 – Simulation (Human)**
- Human PK

**Mouse Efficacy**
- Drug Conc. vs. Effect
- Tumor Volume vs. Time

**%TGI at Clinical Exposures**
- Concentrations vs. Time

**Rationale of the PK/PD Approach**

- Mouse PKPD model to correlate drug concentration and anti-tumor response
- Use of human PK to correct for inter-species difference in drug exposure
- Correction for inter-species difference in protein binding or target binding
- Assume same PD parameters in mouse and human
- Retrospective analysis of 8 anti-cancer agents suggested good correlation between simulated xenograft TGI driven by human PK and clinical response
- This analysis suggests >60% TGI in preclinical models, at clinically relevant exposures, are more likely to lead to clinical response

**TGI: tumor growth inhibition**

**Clinical Question:** At what doses do we combine NMEs?

**Impact:** Ph1b design with stepwise combo dose escalation with different degrees of tumor inhibition

**2NME Case Example: Translational PK/PD**

**2NME Phase 1b Combo Dose Selection**

TGI ≥ 80% (Optimal Target)
TGI ≥ 60% (Minimal Target)
TGI < 60% (Below Target)

Translational PK/PD suggested good probability of anti-tumor activity during 2NME Ph1b dose escalation.
NME+SOC Case Example: Clinical PK/PD

Optimization of Dosing Schedule for NME+SOC

Clinical Question: Is there potential loss of efficacy for alternative dose/schedule?

Impact: Use tumor response M&S to optimize dosing schedule

Clinical PK/PD of longitudinal tumor response suggested low risk of losing efficacy with intermittent PI3K dosing, which can be investigated as alternative dosing option to potentially mitigate safety risk.

Rene Bruno, Laurent Claret, Tong Lu, Joe Ware, PI3K team, et al.
Case Examples

Modeling and Simulation in Drug Development

- Project Modeling (Molecule-specific)
  - aPDL1
  - IND
  - EOP2
  - BLA/ND
  - Pre-IND
  - Pre IND
    - Human dose projection: translational PK/PD
    - Exposure and target engagement at site of action: tissue PK/PD, PBPK/PD
  - Phase I/II/III
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Chen & Mellman; Immunity 2013
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.


Chen & Mellman; *Immunity* 2013
**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?

**Impact:** Overall exposure-response analyses based on IMvigor210 study suggested no significant exposure-efficacy and exposure-safety relationship, supporting the Atezolizumab dosing of 1200 mg q3w in 2L+ mUC patients.

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Rene Bruno, Pascal Chanu, Laurent Claret, Steve Eppler, Sandhya Girish, Smita Kshirsagar, Alyse Lin, Mark Stroh, Helen Winter, Atezo team et al.
Longitudinal tumor size models are used to estimate tumor growth inhibition (TGI) metrics based on sum of longest diameters (SLD) of target lesions per RECIST 1.1.

For the case of cancer immunotherapy (CIT), response to treatment may not necessarily be “chemotherapy-like”:

- Response patterns with CIT are potentially diverse, and might include delayed responses with an initial increase in tumor burden before regression (pseudoprogression) or appearance of new lesions.
- TGI modeling provides another avenue (in addition to the Immune-Related Response Criteria) to capture the diverse responses to CIT.
aPDL1 Case Example: PK/tumor/survival

Tumor Response Data from Atezolizumab Phase 2 Study in NSCLC (POPLAR)

Atezolizumab (1200 mg IV q3w)

Docetaxel (75 mg/m^2 IV q3w)

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Rene Bruno, Pascal Chanu, Laurent Claret, Steve Eppler, Sandhya Girish, Smita Kshirsagar, Alyse Lin, Mark Stroh, Helen Winter, Atezo team et al.
**aPDL1 Case Example: PK/tumor/survival**

**TGI Model for Atezolizumab Phase 2 Study in NSCLC (POPLAR)**

The bi-exponential Stein model:

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

\[ f(t) = \exp(-KS \times t) + \exp(KG \times t) - 1 \]

- \( f(t) \) = tumor size (mm) at time \( t \) (week)
- \( KS \) = shrinkage-rate constant (1/week)
- \( KG \) = growth-rate constant (1/week)

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**Slower KG in Atezo Arm**

**logKG Correlated with Atezo Exposure**

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Rene Bruno, Pascal Chanu, Laurent Claret, Steve Eppler, Sandhya Girish, Smita Kshirsagar, Alyse Lin, Mark Stroh, Helen Winter, Atezo team et al.
OS Model for Atezolizumab Phase 2 Study in NSCLC (POPLAR)

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

The Atezolizumab POPLAR project suggested validity of TGI~OS modeling in CIT. This approach is being further evaluated and leveraged for broader CIT development.

Rene Bruno, Pascal Chanu, Laurent Claret, Steve Eppler, Sandhya Girish, Smita Kshirsagar, Alyse Lin, Mark Stroh, Helen Winter, Atezo team et al.
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 evolving 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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**NME+SOC Example:**
Rene Bruno
Laurent Claret
Tong Lu
Joseph Ware
PI3K team

**aPDL1 Example:**
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