ASCPT – Washington, DC – March 16, 2017
SYMPOSIUM – Finding the Right Dose in the Right Patients for Oncology and Immuno-oncology

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

Genentech
A Member of the Roche Group

Jin Y. Jin, Ph.D.
Associate Director and Principal Scientist
Global Head of Modeling and Simulation
Clinical Pharmacology
Genentech Inc.
South San Francisco, CA

Modeling and Simulation in Oncology Development

❑ Overview

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

❑ Case Examples

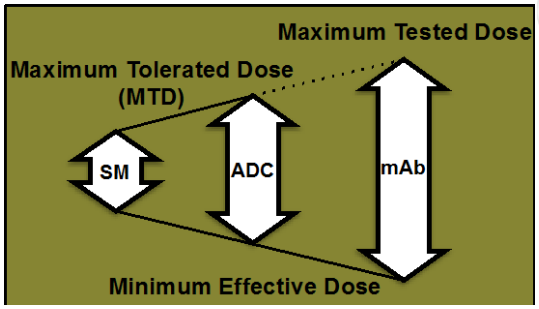
- **NME+SOC Combo Dose Selection** – *Benefit-risk analysis*
- **Cancer Immunotherapy Dose Justification** – *PK-tumor-survival*

❑ Final Remarks

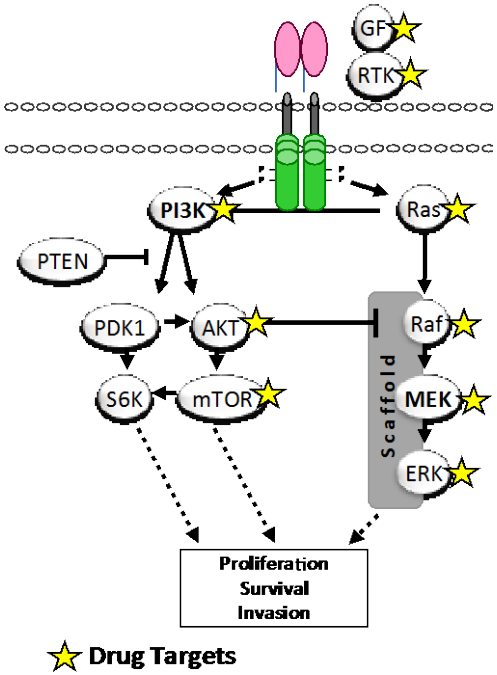
Today's Anti-Cancer Agents

Vision: Simultaneous inhibition of multiple targets to enhance activity in broader population with less resistance

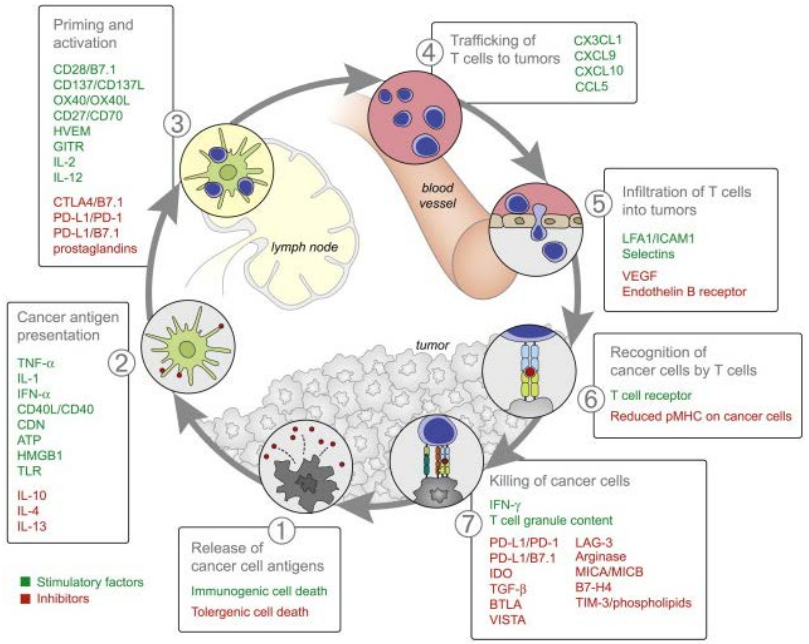
- ❑ Multiple mechanism of action
- ❑ Multiple molecule types
- ❑ Combination therapy (NME+SOC, NME+NME)



Kinase Pathways



Cancer Immunotherapy

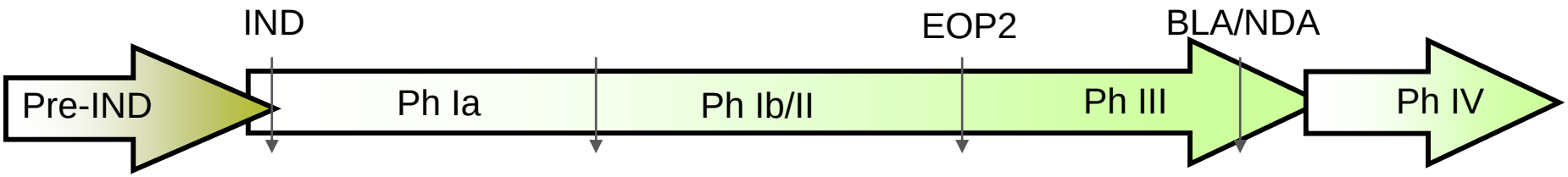


Chen & Mellman; Immunity 2013

NME: new molecular entity; SOC: standard of care

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

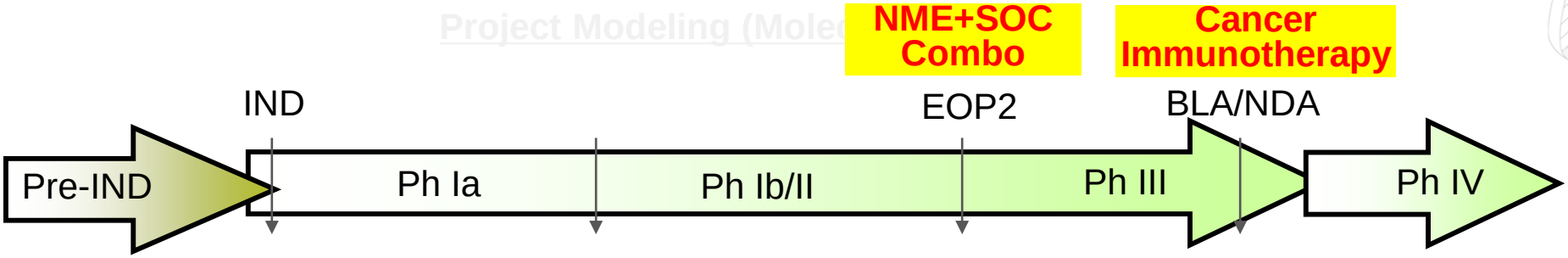
- Dose optimization: *translational & clinical PK/PD*
- Regimen and dosing schedule optimization: *longitudinal M&S*
- Effect of intrinsic factors: *PopPK, PBPK*
- Effect of extrinsic factors: *PopPK, PBPK*
- QT prolongation: *concentration-QT*
- Exposure and response at site of action: *biomarker PK/PD,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

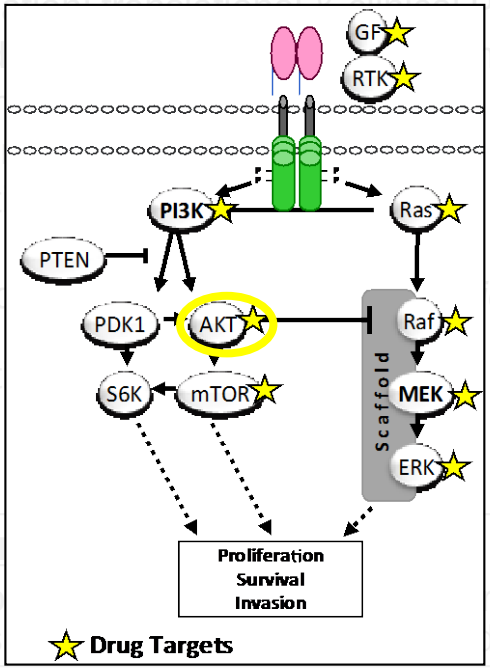
- Dose justification
- Clinical pharmacology characterization
- Decision making
- Label

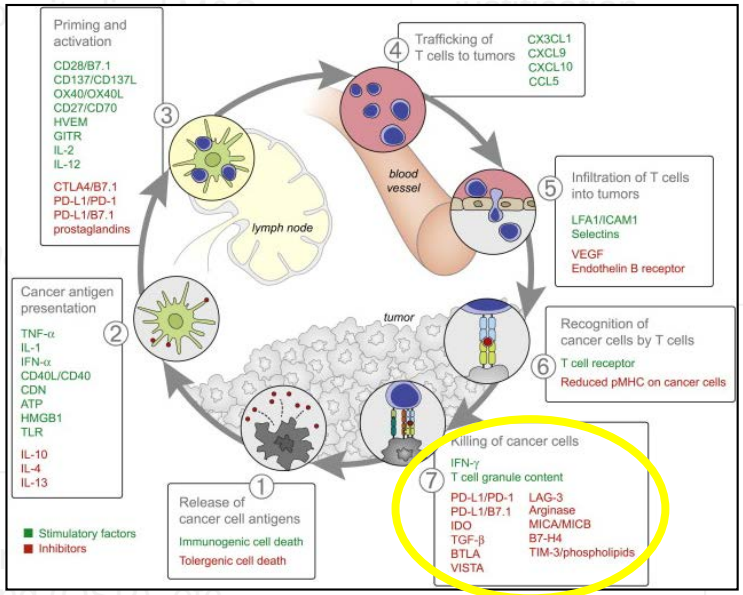
Platform Modeling (Cross-molecules)

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.

Modeling and Simulation in Drug Development





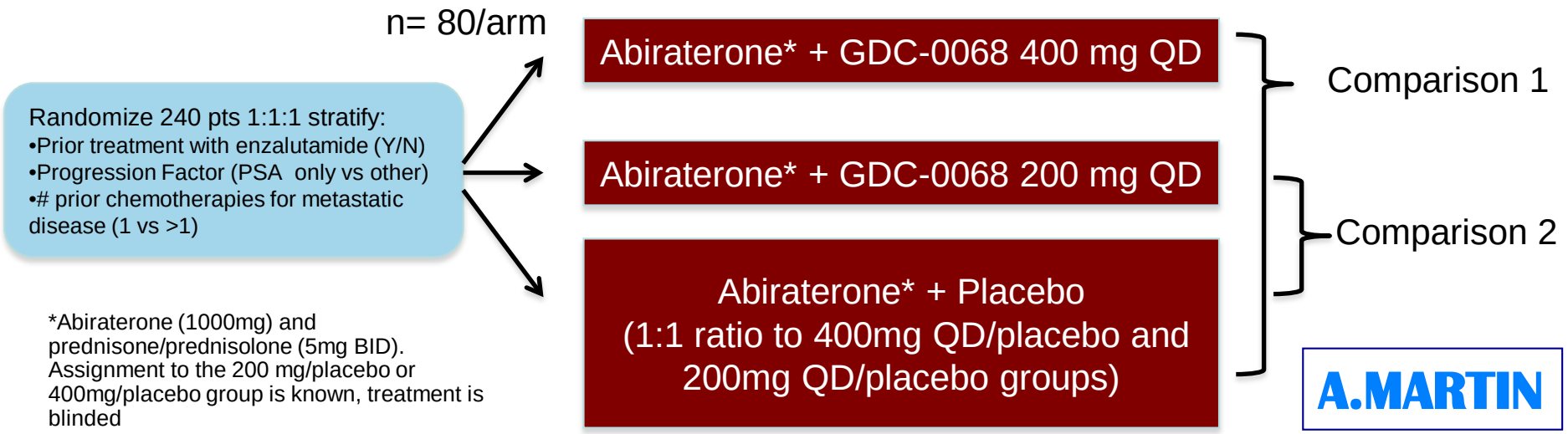


Chen & Mellman; Immunity 2013

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



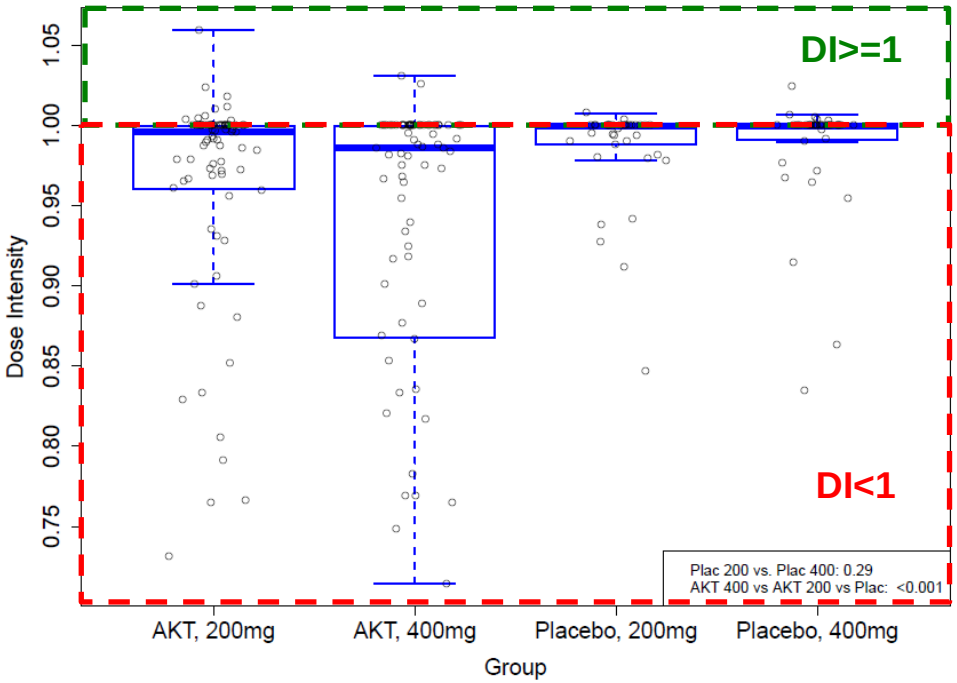
Clinical Question: What is the recommended Ipatasertib dose for further development in mCRPC?

Zhu R, et al, Abstract PI-133, ASCPT, 2017 (Thur Mar 16, 4:30-6:30)

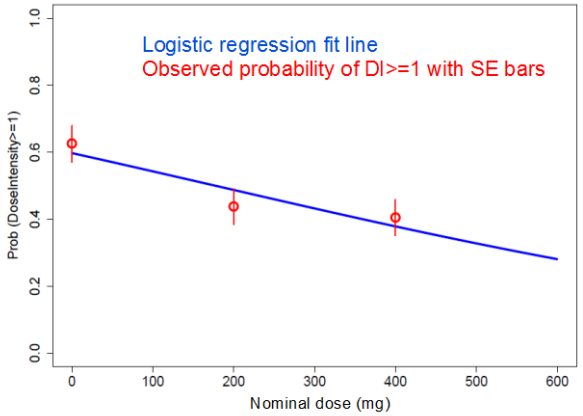
De Bono JS, et al. Abstract #5017, ASCO, 2016

Dose Selection: Account for Dose Reduction

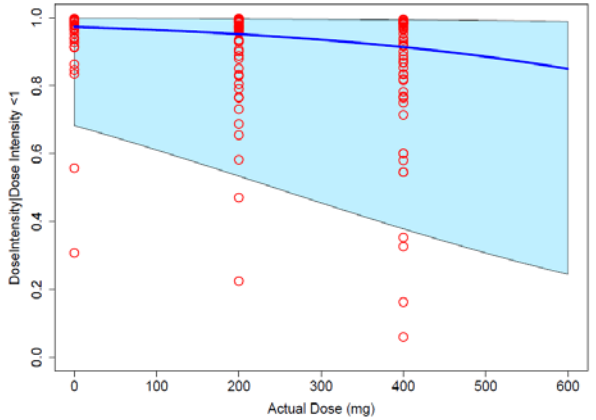
Clinical Question: How to account for the confounding effect of dose reduction in Phase 2?



DI Model 1: Prob(DI>=1) vs. Dose



DI Model 2: DI distribution in DI<1 population



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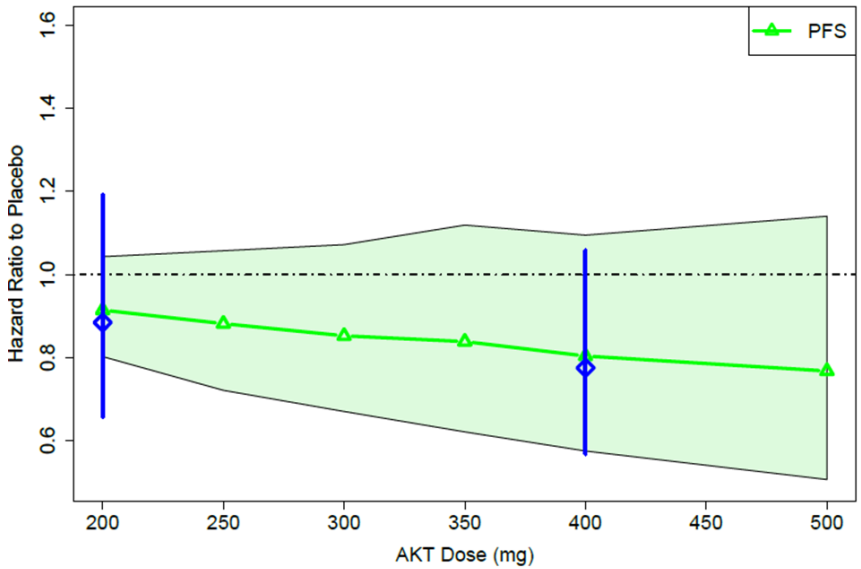
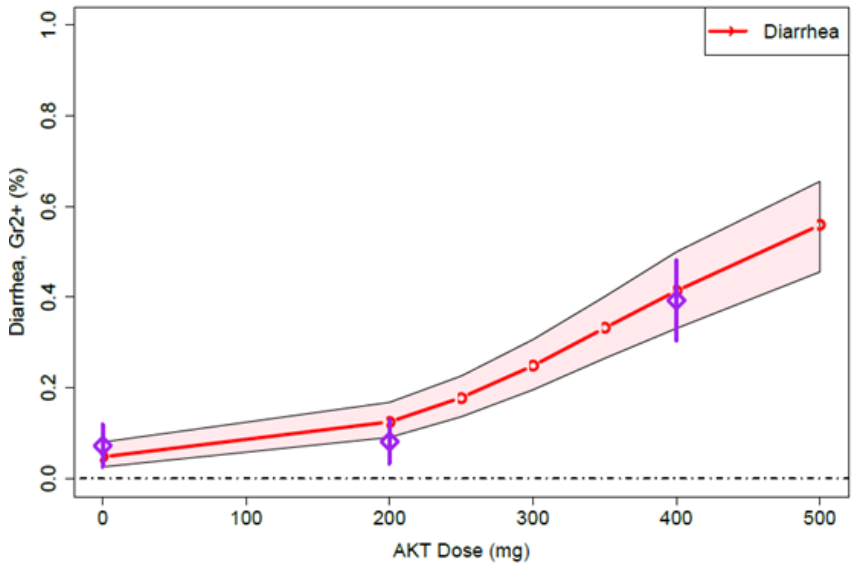
Dose Selection: Exposure-Response

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

Zhu R, et al, Abstract PI-133, ASCPT, 2017 (Thur Mar 16, 4:30-6:30)

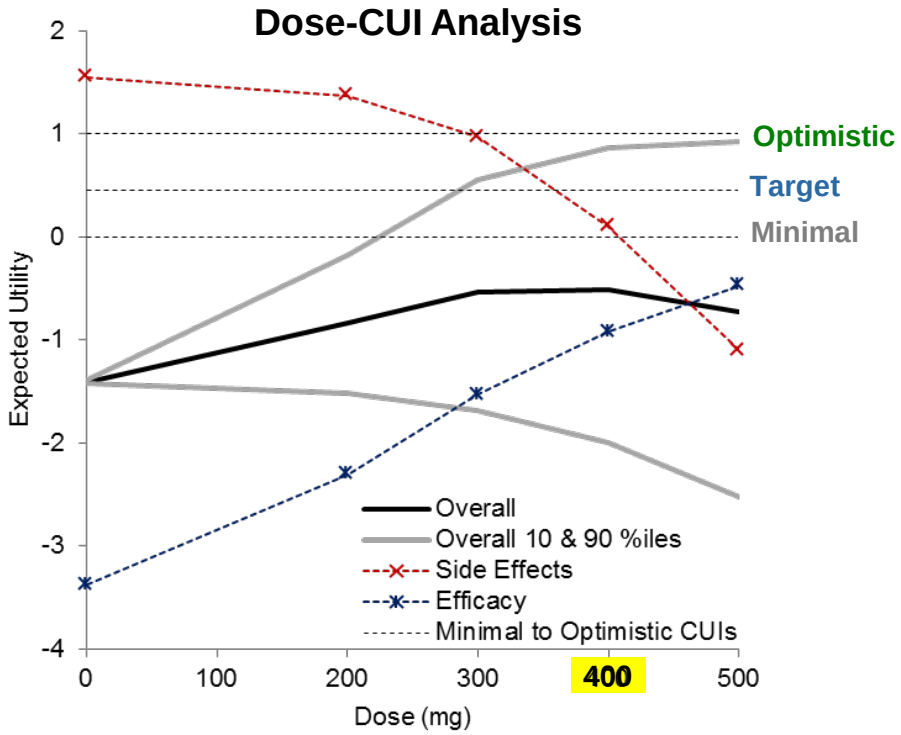
Dose Selection: Clinical Utility Index

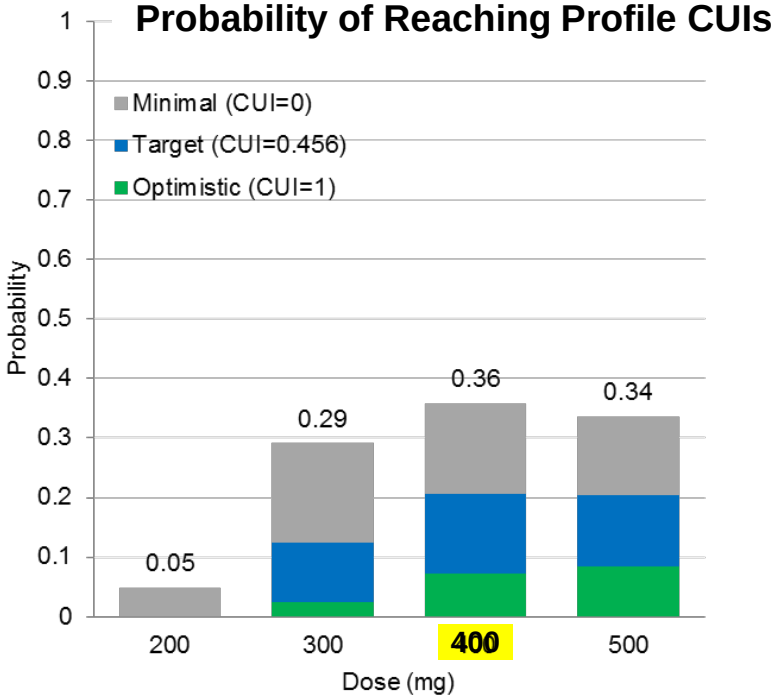
Optimistic, Target, and Minimal Product Profile (PP)
(Scenario #4)

- **rPFS HR (weight: 0.6)**
  0.65 0.7 0.73
- **G2+ Diarrhea (weight: 0.3)**
  25% 35% 45%
- **G2+ Rash (weight: 0.1)**
  6% 12% 18%

4 scenario tested varying E & S criteria & weight

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.





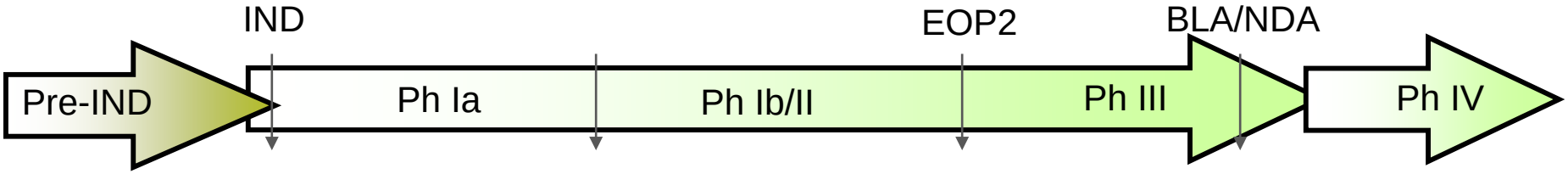
Impact: Overall, Ipatasertib 400mg QD dose was supported by M&S for further development in mCRPC.

Zhu R, et al, Abstract PI-133, ASCPT, 2017 (Thur Mar 16, 4:30-6:30)

Modeling and Simulation in Drug Development

Project Modeling (Molecule-specific)

Cancer Immunotherapy



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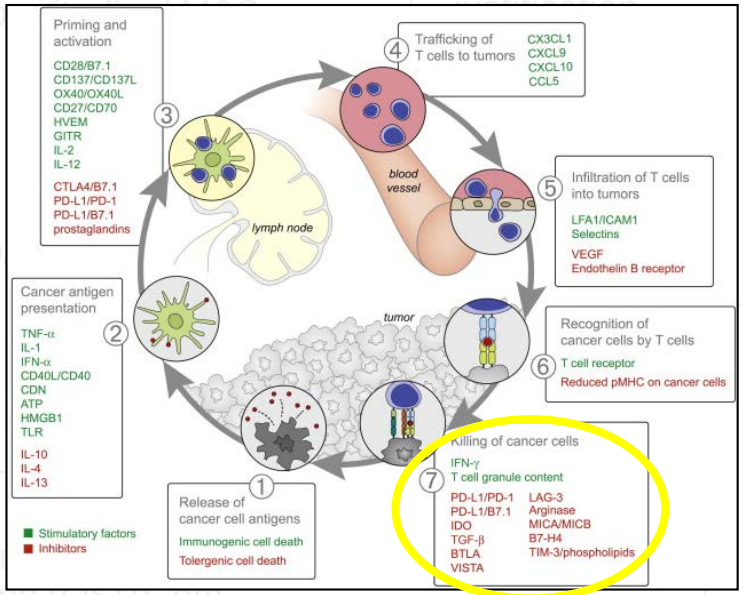
- Dose



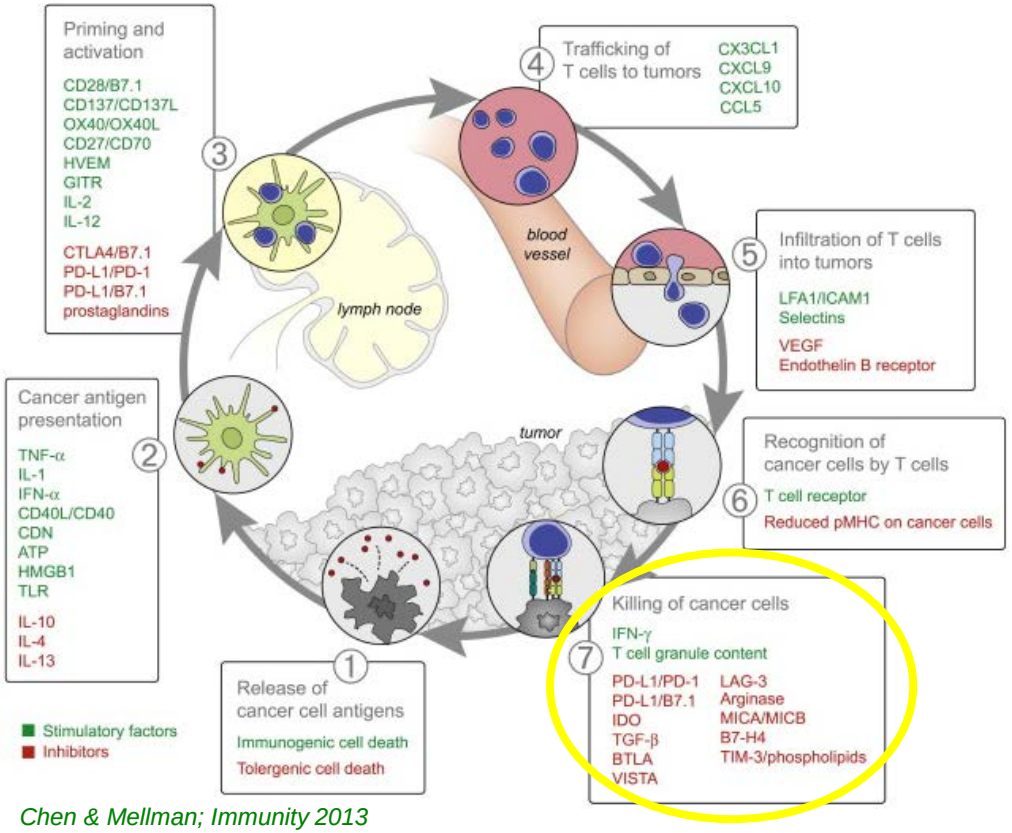
Platform Modeling (Cross-molecules)

M&S for molecule platform and/or disease platform: disease prog
endpoints, literature meta-analysis, system pharmacology modeling (QSP), etc.

Chen & Mellman; Immunity 2013

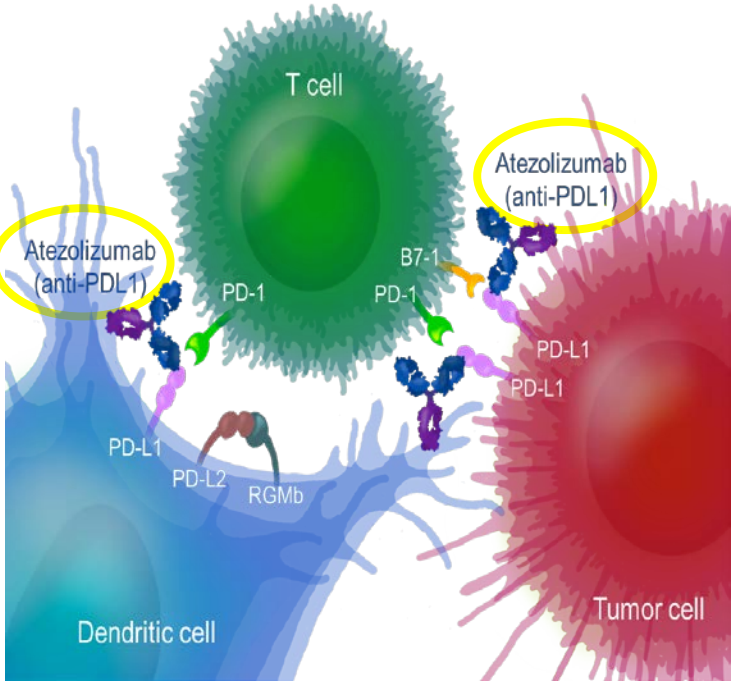
Cancer Immunotherapy and Atezolizumab

Cancer-immunity Cycle & Therapeutic Intervention



Chen & Mellman; Immunity 2013

PD-L1 and Atezolizumab



PD-L1, programmed death-ligand 1

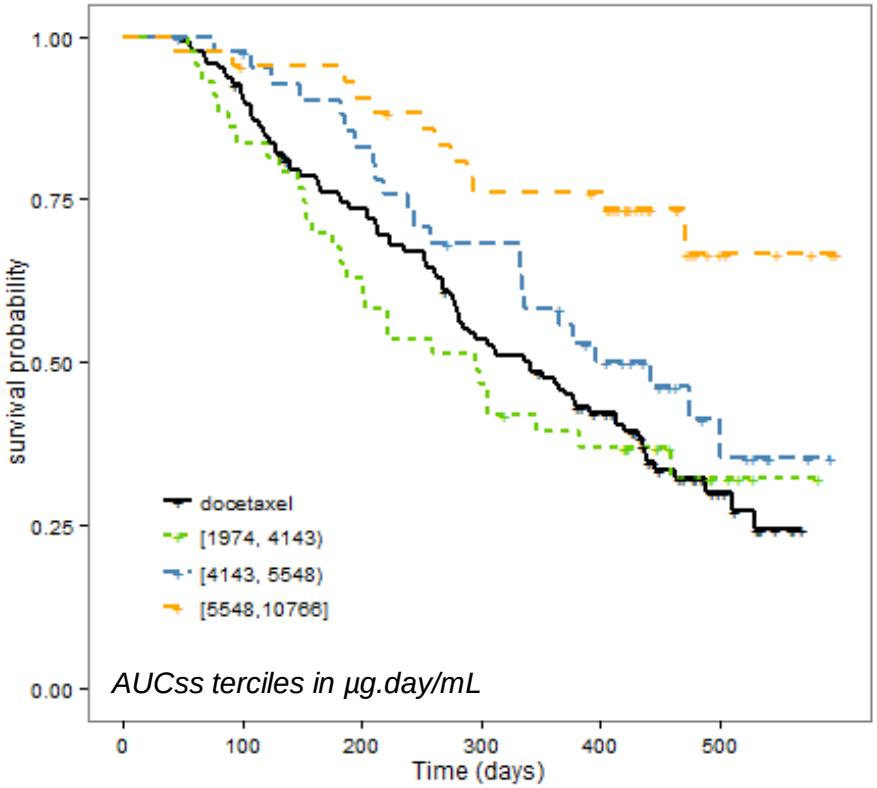
- Atezolizumab is a humanized engineered mAb that selectively targets PD-L1
  - By inhibiting interactions with receptors PD-1 and B7.1, anti-cancer immunity can be reinvigorated and enhanced[1,2]
- Atezolizumab has demonstrated efficacy and safety in a broad range of cancer types, including mUC, NSCLC and RCC[1,3-5]

[1] Herbst Nature 2014. [2] Chen Immunity 2013. [3] Powles Nature 2014.
[4] Rosenberg Lancet 2016. [5] Fehrenbacher Lancet 2016.

Atezolizumab in NSCLC: POPLAR Study

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 chemotherapy[1]

- 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)



Exposure-response:

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

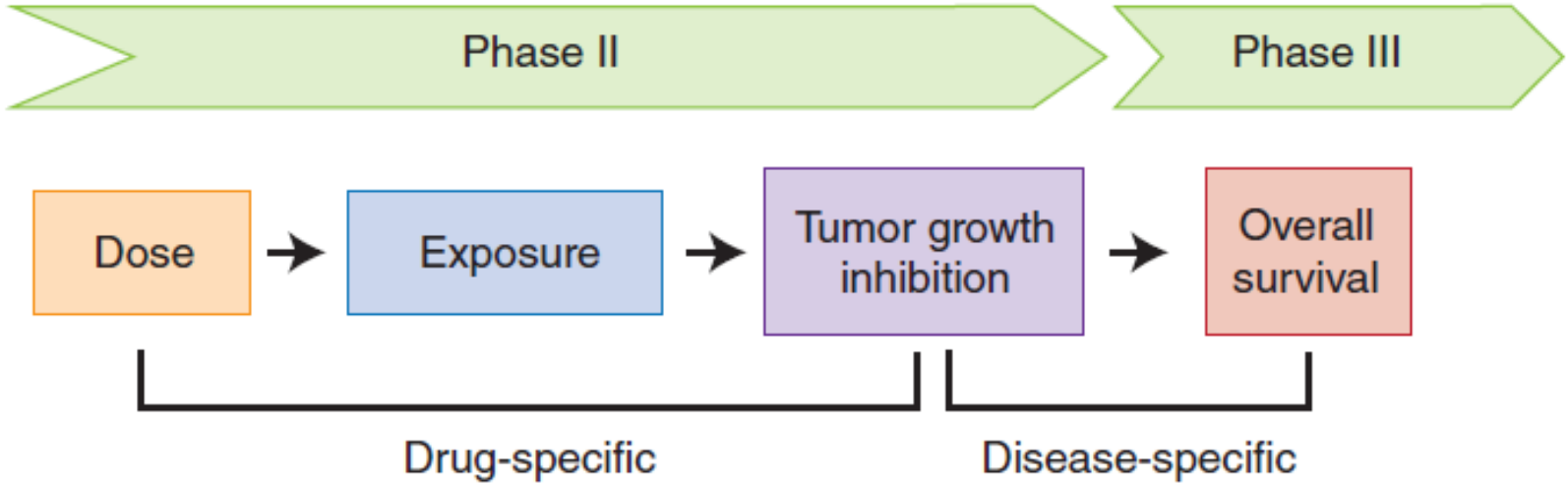
Clinical Question: Is there any dose adjustment need for Atezolizumab due to loss of efficacy in patients with lower exposure, or increased safety risk in patients with higher exposure?

[1] *Fehrenbacher et al, Lancet 387, 1837-1846, 2016*

Bruno et al. ACoP 2016

Oncology Modeling Framework

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

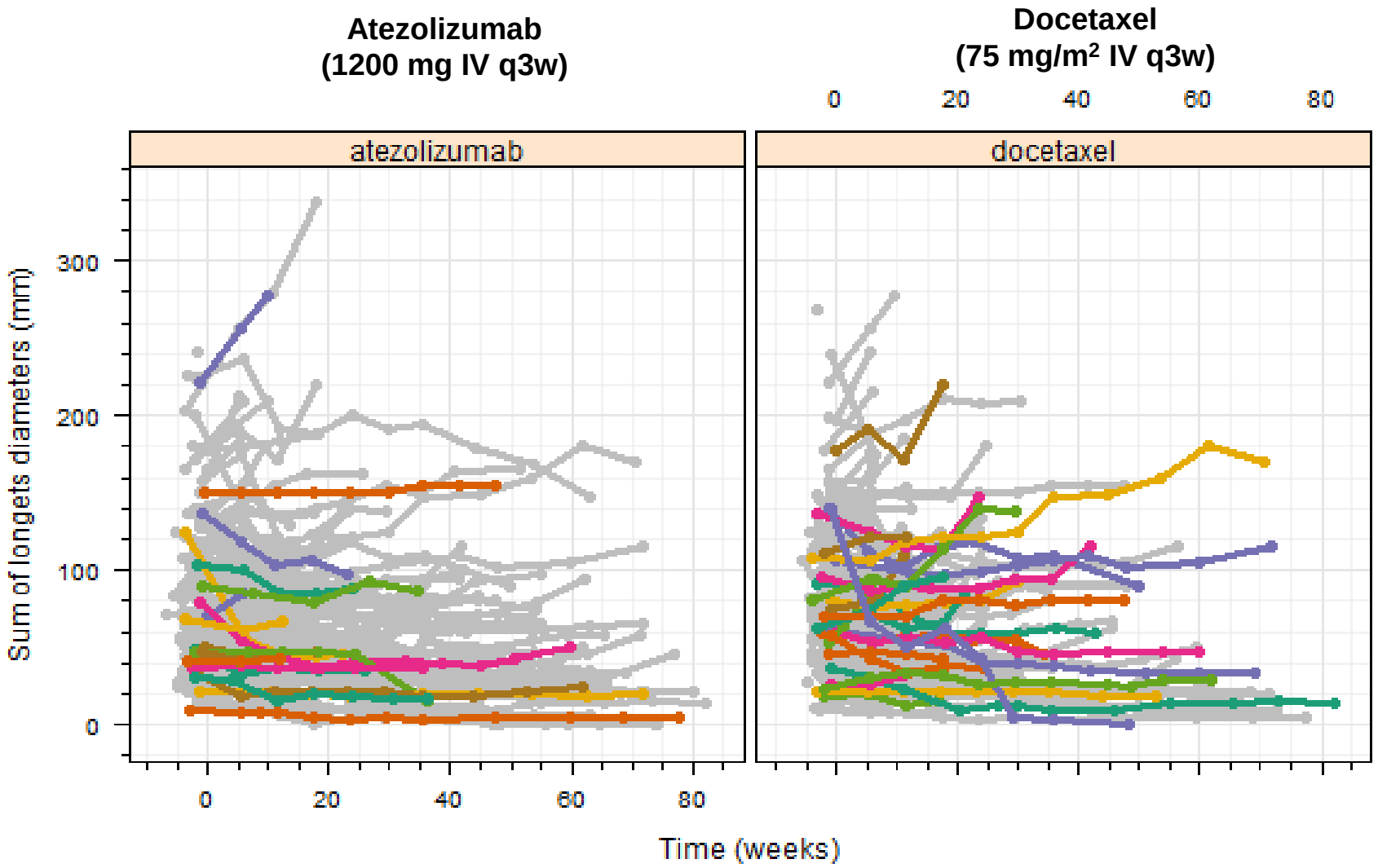


Q1: Can causality for exposure-response (via tumor growth inhibition) as a way to mitigate confounding by baseline prognostic factors?

Bruno et al. Clin Pharmacol Ther, 93:303-5, 2013

Courtesy of Rene Bruno

Tumor Response Data from POPLAR



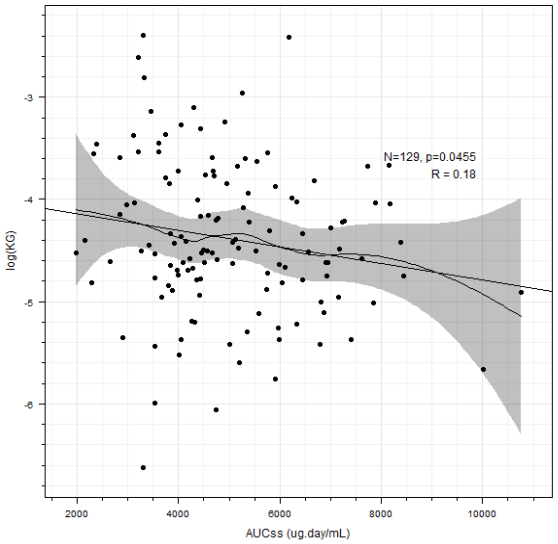
All profiles in grey, 50 patients taken at random are colored

Bruno et al. ACoP 2016

Dose Justification for Atezolizumab in NSCLC

The bi-exponential Stein model: $TS(t) = TS_0 * [\exp(-KS * t) + \exp(KG * t) - 1]$

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



AUCss terciles	Covariates	HR	CI	HR Plot
3393 [1974, 4143)	Original	0.98	(0.92,1.03)	
4750 [4143, 5548)	Original	0.72	(0.68,0.77)	
6903 [5548,10766]	Original	0.51	(0.46,0.56)	
3393 [1974, 4143)	Balanced	0.85	(0.81,0.89)	
4750 [4143, 5548)	Balanced	0.77	(0.73,0.82)	
6903 [5548,10766]	Balanced	0.62	(0.56,0.68)	

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

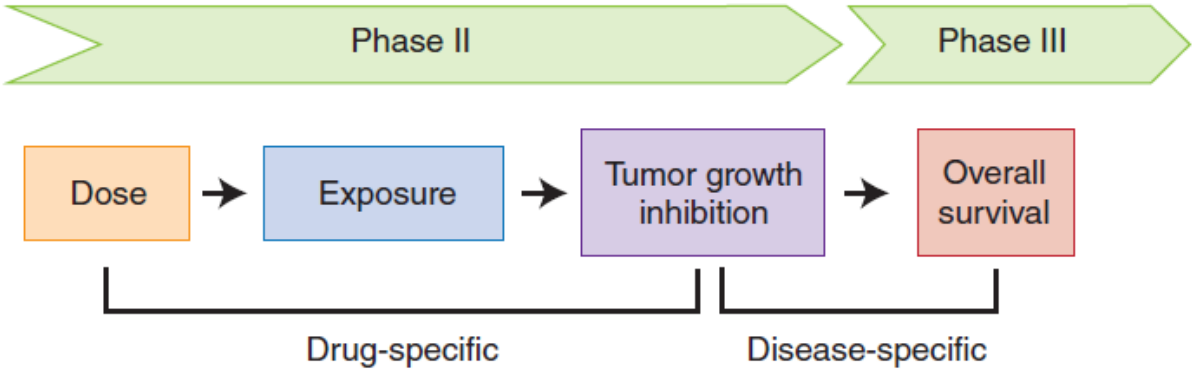
- Slower tumor growth (KG) in atezolizumab arm
- KG correlated with atezolizumab exposure
- In the multivariate OS model, with baseline prognostic factors and KG capturing treatment effect, atezolizumab exposure is no longer significant
- The multivariate OS model was used to simulate exposure-response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

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.

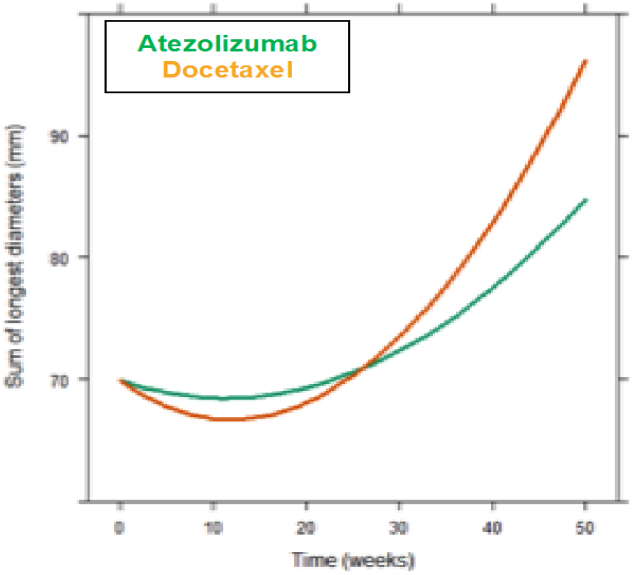
Bruno et al. ACoP 2016

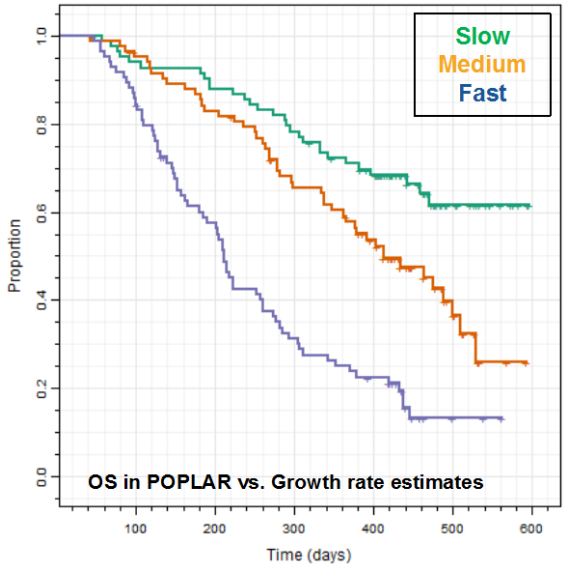
Oncology Modeling Framework

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?



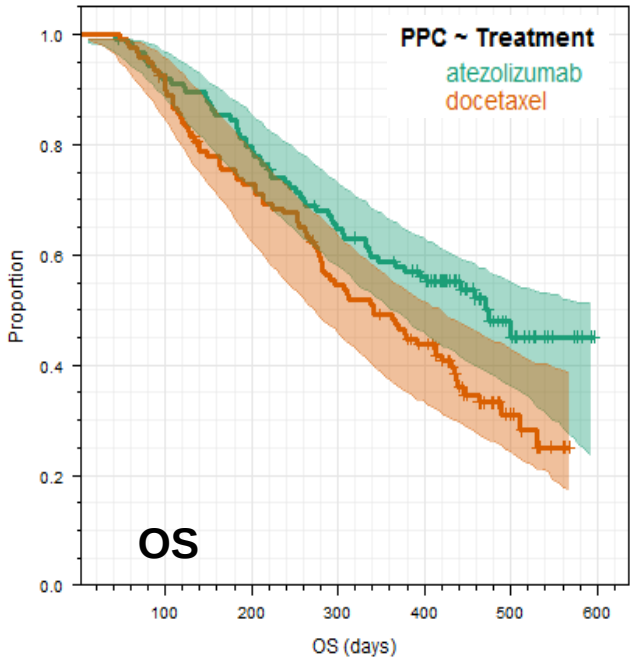


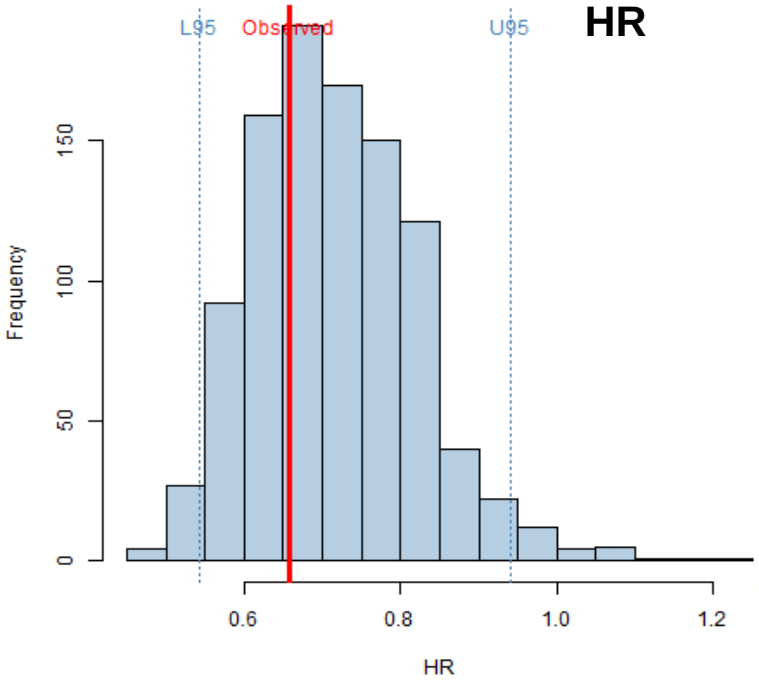
Bruno et al. Clin Pharmacol Ther, 93:303-5, 2013

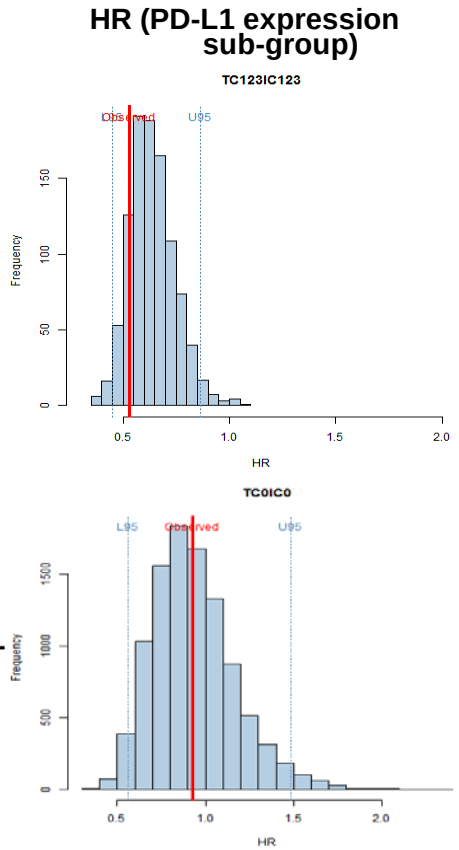
Bruno et al. ACoP 2016

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.

Bruno et al. ACoP 2016

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
    - …...

Acknowledgments

Ipatasertib Example:

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Rui Zhu
Ipatasertib team

Atezolizumab Example:

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Smita Kshirsagar
Alyse Lin
Mathilde Marchand (Certara)
Mark Stroh
Helen Winter
Atezolizumab team

Amita Joshi
Clin Pharm M&S group
Clinical Pharmacology Department

Investigators
Patients

Genentech
A Member of the Roche Group