American Association for Cancer Research

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Oncology Dose Finding Workshop

June 13, 2016

Walter E. Washington Convention Center

Washington, DC

American Association for Cancer Research

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Welcome and Workshop Objectives

Workshop Co-Chairs:

Geoffrey Kim, MD

Amy McKee, MD

Pasi Jänne, MD, PhD

Eric Rubin, MD

Highlights from 2015 Dose Finding Workshop

Dose Finding of Small-Molecule Oncology Drugs: Optimization throughout the Development Life Cycle
Jänne, et al., Clin Cancer Res 22:2613-2617

Nonclinical Evaluations of Small-Molecule Oncology Drugs: Integration into Clinical Dose Optimization and Toxicity Management
Dambach, et al.,Clin Cancer Res 22:2618-2622

Rendering the 3 + 3 Design to Rest: More Efficient Approaches to Oncology Dose-Finding Trials in the Era of Targeted Therapy
Nie, et al., Clin Cancer Res 22:2623-2629

Lessons Learned: Dose Selection of Small Molecule–Targeted Oncology Drugs
Bullock, et al., Clin Cancer Res 22:2630-2638

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Session I

Exposure-Response Relationships and Modeling/Simulation for Dose Finding

Chair: Geoffrey Kim, MD

Speakers:

Dinesh De Alwis, PhD
Shruti Agrawal, PhD
Chyi-Hung Hsu, PhD
Diane Wang, PhD
Gabriel Helmlinger, MD, PhD

Panelists:

Kelvin Dickenson
Jin Jin, PhD
Sumithra Mandrekar, PhD
Lillian Siu, MD
Yaning Wang, PhD

Optimal Dosing for Targeted Therapies in Oncology: A focus on the development of Pembrolizumab.

Dinesh de Alwis, PhD
Quantitative Pharmacology and Pharmacometrics. Merck

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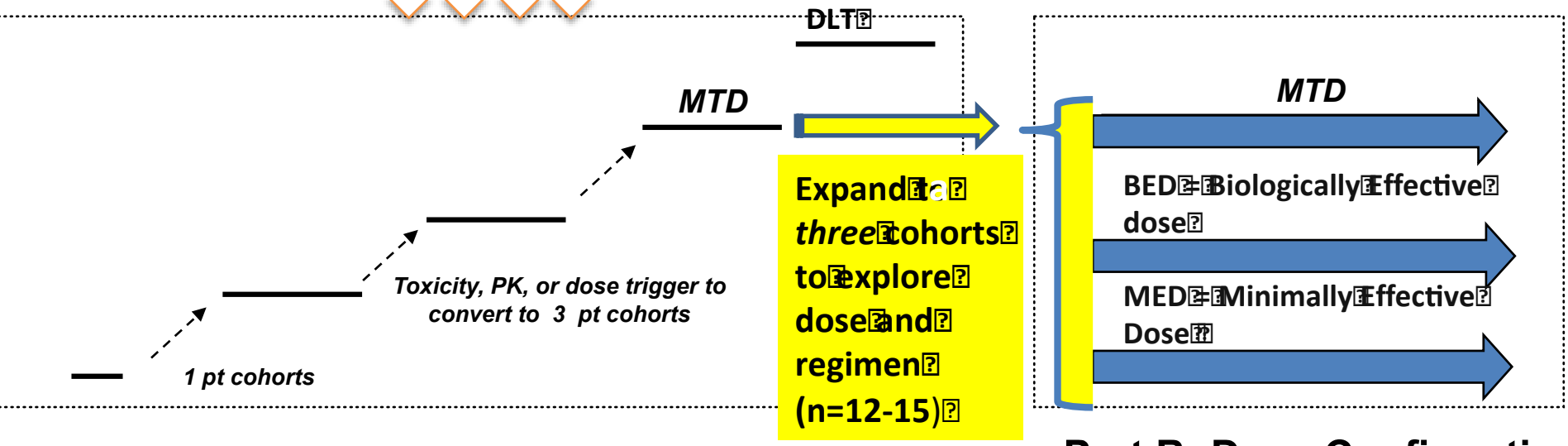
Impact Phase 1 Design and aid in Go/No GO, Use of Pharmacological Model Based Phase 1 Design

What about efficacious dose? Deserves more attention



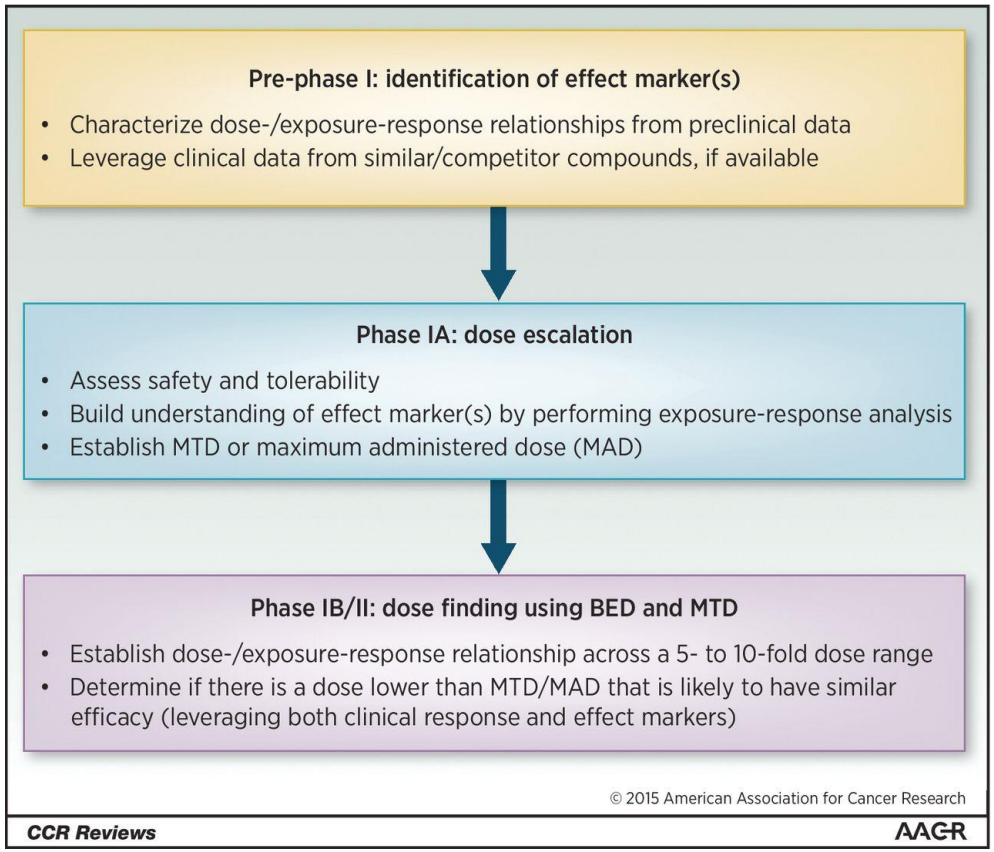
Part A: Dose Escalation

1 pt cohorts → 3 pt cohorts (with 3 pt expansion if DLT)
Dose escalation to MTD

Part B: Dose Confirmation (2-3 arm study exploring MED, BED and MTD dose range / regimen

Dose Finding for Targeted Agents

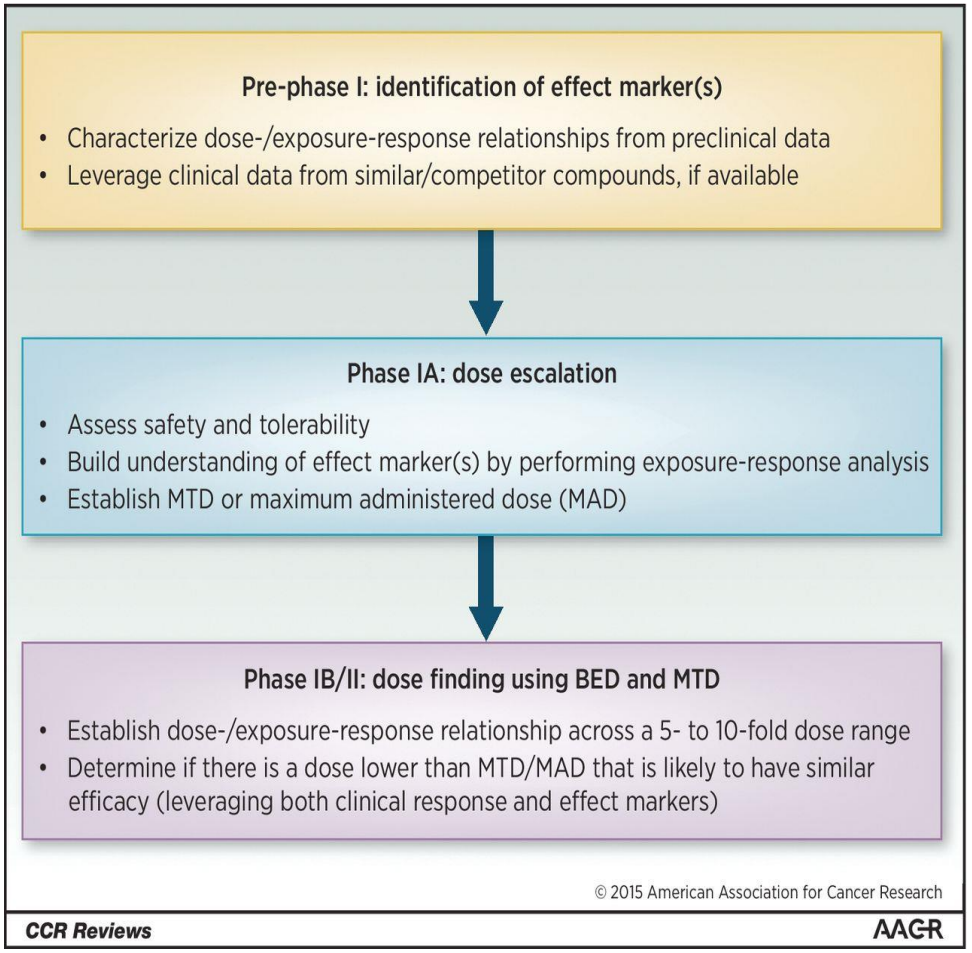
- **Pre-clinical**
- **We need to use all available PK, Biomarker, Efficacy, Safety data to develop translational *in silico* models that can predict the optimal biologically effective dose and MTD to increase p(TS) in the clinic**
  - **Doing the right PD and efficacy experiment to understand dose and regimen**
- **Phase I (informed by pre-clinical)**
  - **Focus on collecting information for informing dose-finding study**
  - **Targeted therapies (mABs)**
    - **Collect the appropriate PD biomarker data (e.g direct or indirect target engagement)**
    - **Tumor Size based modeling in Phase IB (particular indication)**
      - » **Dose selection**
      - » **Go/No Go**



Clin Cancer Res 2016;22:1318-1324

Oncology Drug Development: Phase 1b/2

- **Design of Ph 1b/2**
  - Randomized Studies
  - Evaluate more than one dose
  - Look at surrogate end points to make early go / no go decisions based on safety, efficacy (e.g tumor size)
  - Look for factors contributing to individualized response: exposure, demographics or tumor genetics, etc ...
  - Establish POC
    - Has drug reached the site of action?
    - Has POM been established?
    - Has efficacy been established in the targeted patient population (e.g is it better than SOC)?
    - Has an adequate therapeutic range been established?



Clin Cancer Res 2016;22:1318-1324

KEYTRUDA®
(MK-3475, pembrolizumab)
Case Study

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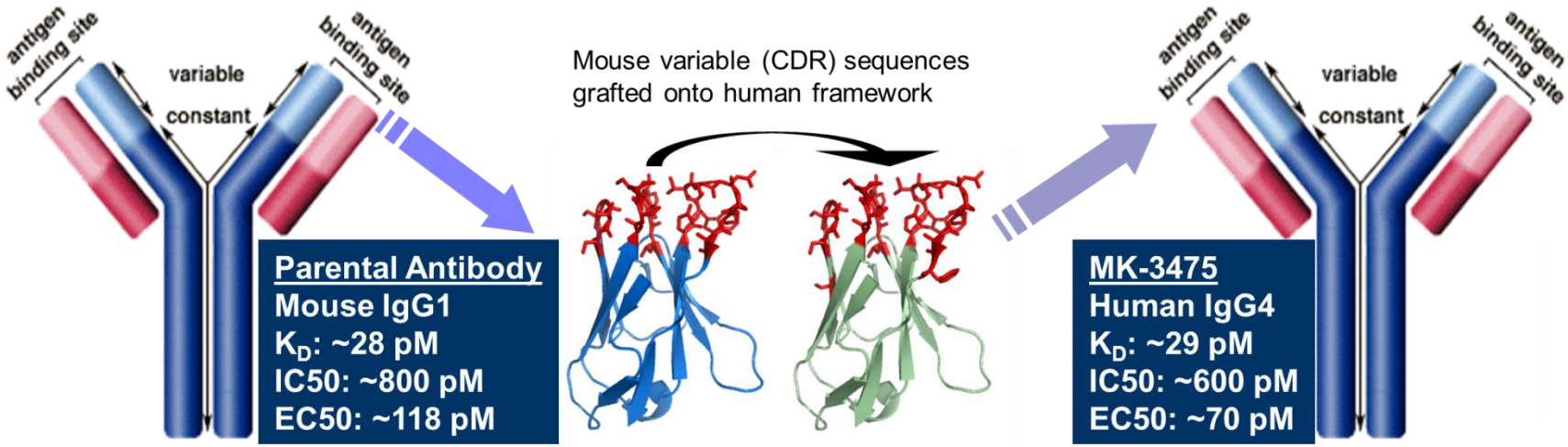
KEYTRUDA® product characteristics

- Potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype



- Blocks interaction between programmed death (PD) -1 and its ligands, PD-L1 and PD-L2 => enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection
  - Keytruda blocks interaction of PD-1 on peripheral Tcells –enhancing T cells response against tumors

Initiation of KEYTRUDA® Clinical Program

- Preclinical data suggested that KEYTRUDA® would have anti-tumor activity in multiple cancers

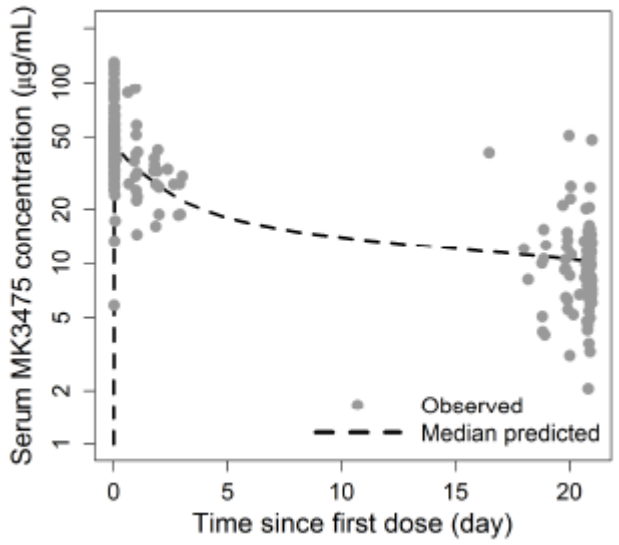
- US IND was opened on **Jan 7, 2011**
  - *A Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinomas and Melanoma (Protocol 001)*
    - *Initial intent was to define DLT, characterize PK, and establish POC*

Part A: FIH Dose Escalation and PK/PD Evaluation

- Part A-1 dose escalation study
  - Objectives:
    - To define DLT, MTD (Maximum Administered Dose), and characterize PK
  - Design:
    - Open label, non randomized traditional 3+3 dose escalation followed by a small expansion cohort n~32
      - 1mg/kg Q2W →3 mg/kg Q2W →10 mg/kg Q2W
  - Results
    - No DLT at tested doses
    - Objective response in 2 out of 3 first melanoma patients
      - First response at 3 mg/kg Q2W in melanoma
    - Based on a strong activity signal, amendment was issued to expand melanoma cohort
      - 10 mg/kg Q2W (MAD) selected as the first dose

PK profile support for Q3W dosing

- *Pharmacokinetic profile is typical for a therapeutic mAb with low clearance (0.22 L/h), limited volume of distribution (3.7 L) and low variability (28 % CV on CL)*
- *26 day half life (95% CI 24-28 days)*



A Strong Data, from Cohort B1, Accelerated the Development Program

Objective Response Rates and Duration of Response based on Independent Radiology Review using RECIST 1.1 Criteria

	Objective Response (N, 95% CI)	Complete Response (N, 95% CI)	Duration of Response (days) Median (Range)
All MEL N=85	40% (34‡; 29% - 51%)	3.5% (3; 0.7% - 10%)	**Not reached (28-240+)**
IPI Naïve N=58	43.1% (25; 30% - 57%)	3.4% (2; 0.4% - 11.9%)	**Not reached (30-240+)**
IPI Treated N=27	33.3% (9‡; 16% - 54%)	3.7% (1; 0.1% - 19%)	**Not reached (28-169+)**

All patients dose at 10 mg/kg.

Includes all patients who received the first dose as of April 25, 2012. Centrally available response information as of Dec. 3, 2012.

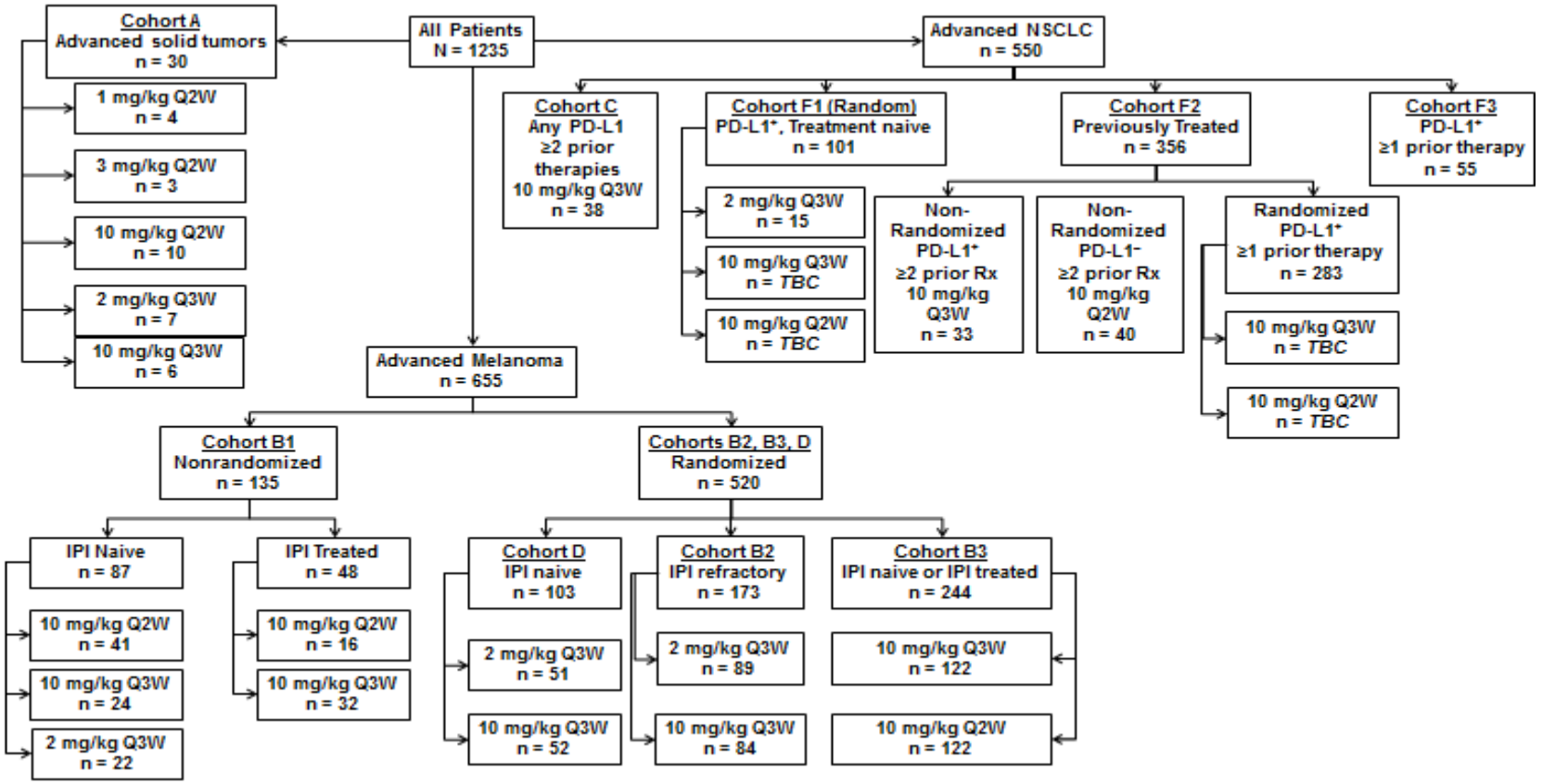
† **Confirmed objective response is defined as a complete response or partial response that is evident on two consecutive CT scans obtained at least 4 weeks apart.**

Protocol 001 (PN001) First in Human (FIH) to Registration

Cohort Expansion

From a small Phase 1-the study expanded to a 655-melanoma patient multi-part study

- 5 amendments, between Dec-2011 to Sep-2013, to answer emerging questions
- **4 "phase 2 study-like"** parts including 3 randomized dose comparison sub-studies

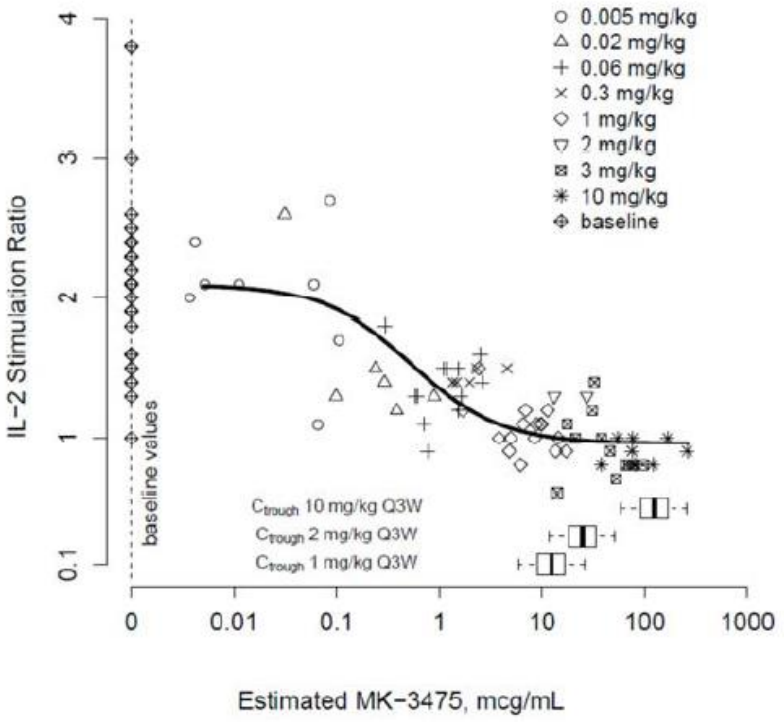


Defining a dose range for the pivotal B2 cohort

- Part A-2 dose expansion study
  - Objectives:
    - To evaluate PK/PD of Q3W dosing schedule
    - Intra-patient dose escalation to explore PK PD of KEYTRUDA® in 0.005 to 10 mg/kg Q3W
      - Basis for translational PK/PD to define the efficacious dose of 2 mg/kg Q3W
      - Patients were escalated in 3 steps (at days 1, 8 and 22) from low (0.005 to 0.06 mg/kg) to high doses (2 and 10mg/kg)
      - Ex vivo IL-2 assay developed
        - » No IL-2 release from lymphocytes with activated PD-1 pathway
        - » SEB causes release, further enhanced by pembrolizumab effect on PD-1

Ex-vivo IL2 assay: Peripheral PK-PD in the Clinic to inform efficacious dose

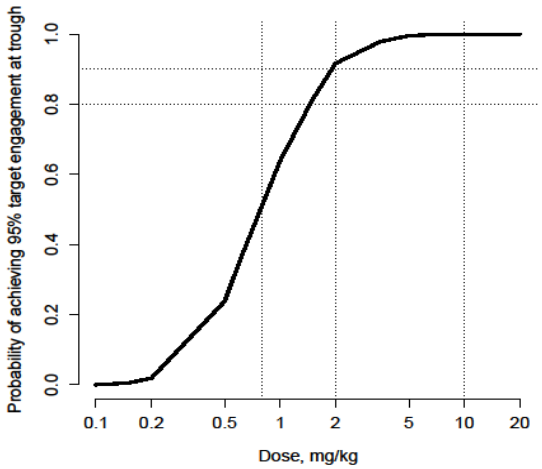
- 95-% saturation level reached at ~1 mg/kg Q3W
- Simulations show, > 95% of the effect of Keytruda on the *ex vivo* IL-2 release is achieved at C_{trough} reached with a dose regimen of ~1 mg/kg Q3W
- Therefore, 1 mg/kg Q3W is lower boundary for clinical efficacy

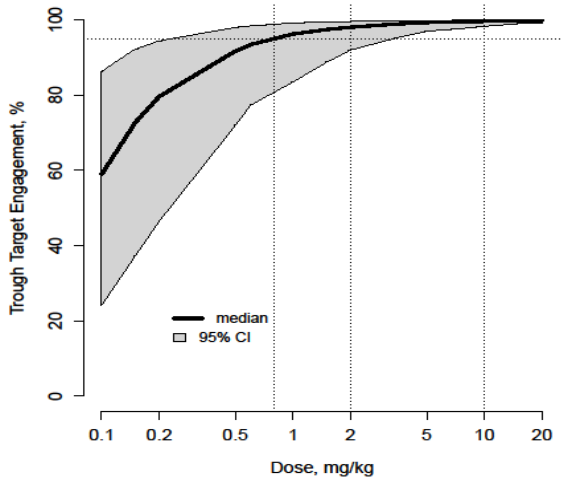


Keytruda Exposure is Associated with Complete Functional Blockade of PD-1 in the *ex vivo* IL-2 Release Assay at Doses of 1 mg/kg Q3W or Higher

Selection of optimally efficacious dose

- At 1 mg/kg Q3W, the probability of achieving full target engagement is 64%
- ≥ 2 mg/kg the probability is 90% or higher (including 10 mg/kg).
- Dose of 2 mg/kg falls likely near the plateau of the underlying exposure-response achieving near-maximal clinical efficacy
- Proposed efficacious dose: 2 mg/kg Q3W





Can Translational PK-PD further inform our choice ?

Semi-mechanistic tPKPD model

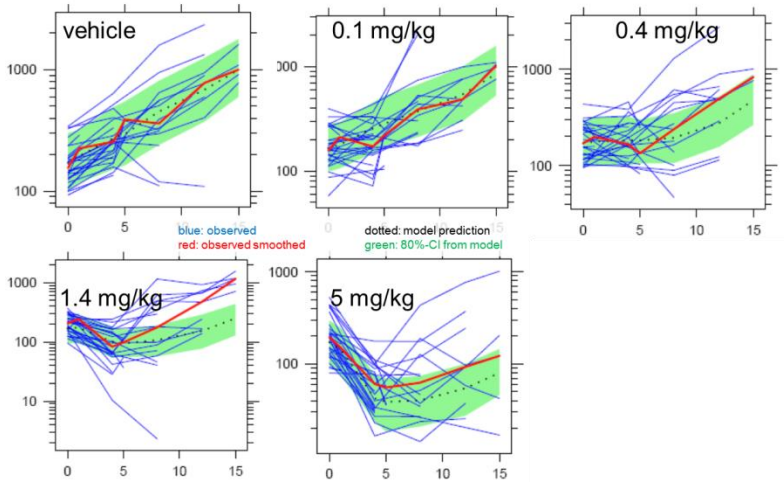
Step 1: Develop mouse model relating

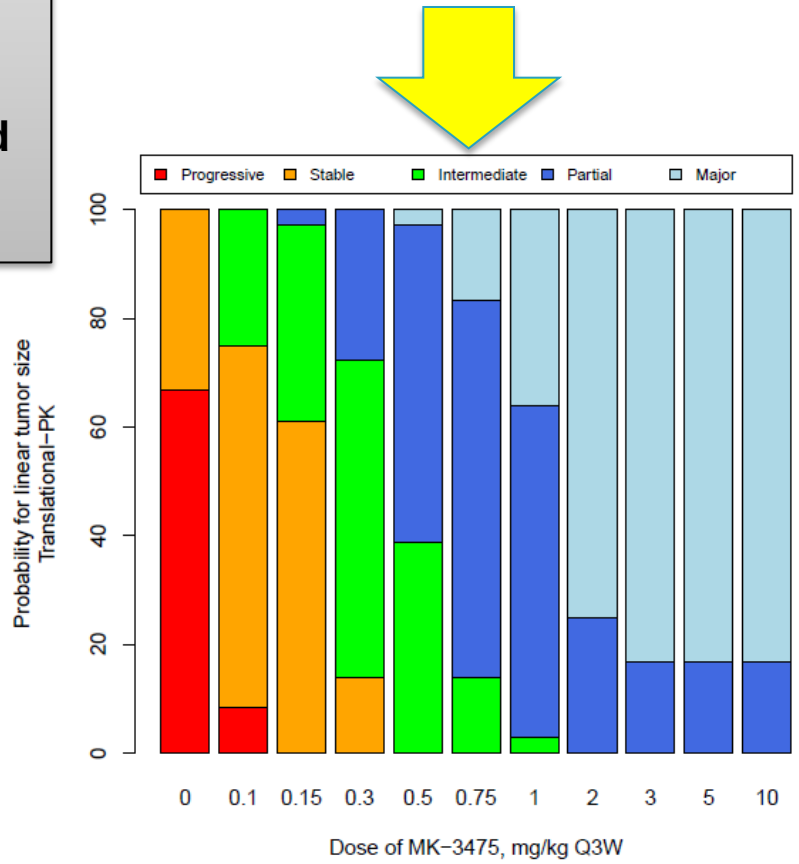
PK → Target binding → tumor growth inhibition

Step 2: Translation to human by adjusting PK and tumor growth parameters

Dose of 2 mg/kg every *3 weeks* or more shows maximal response. Dose range of 2 - 10 Q3W determined for clinical trials

Model fit tumor data from mouse





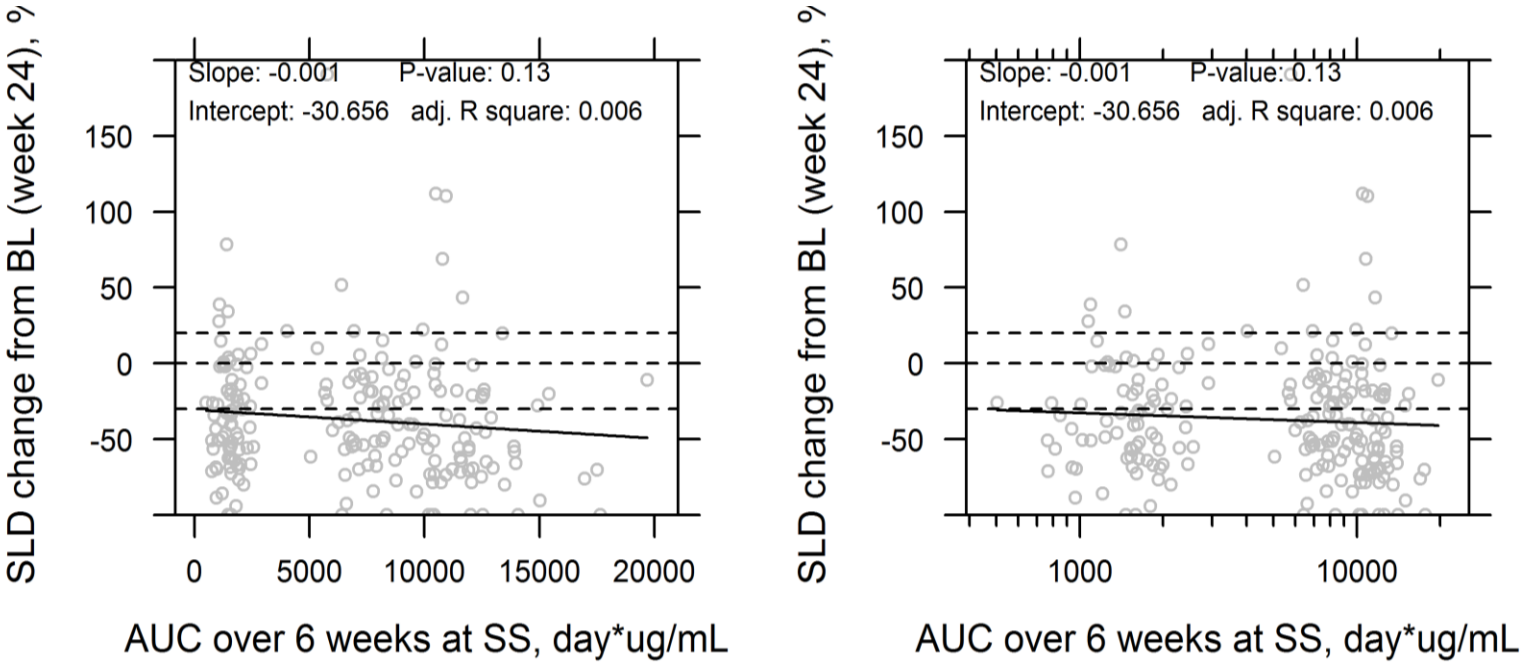
PK-PD modeling guides a critical decision on KEYTRUDA®

- Team discussion on what doses to take forward based on results **from non-randomized studies** (B1)
  - ORR ipi treated 10Q2: 56% > 10Q3: 27%
  - ORR ipi naïve 2Q3 : 45%, 10Q3: 37%, 10Q2 :46%

Based on the Translational modeling, ex-Vivo IL-2 data and observed clinical data, what dose or doses would you take forward into B2 pivotal cohort?

PK-PD modeling guides a critical decision on KEYTRUDA® dose

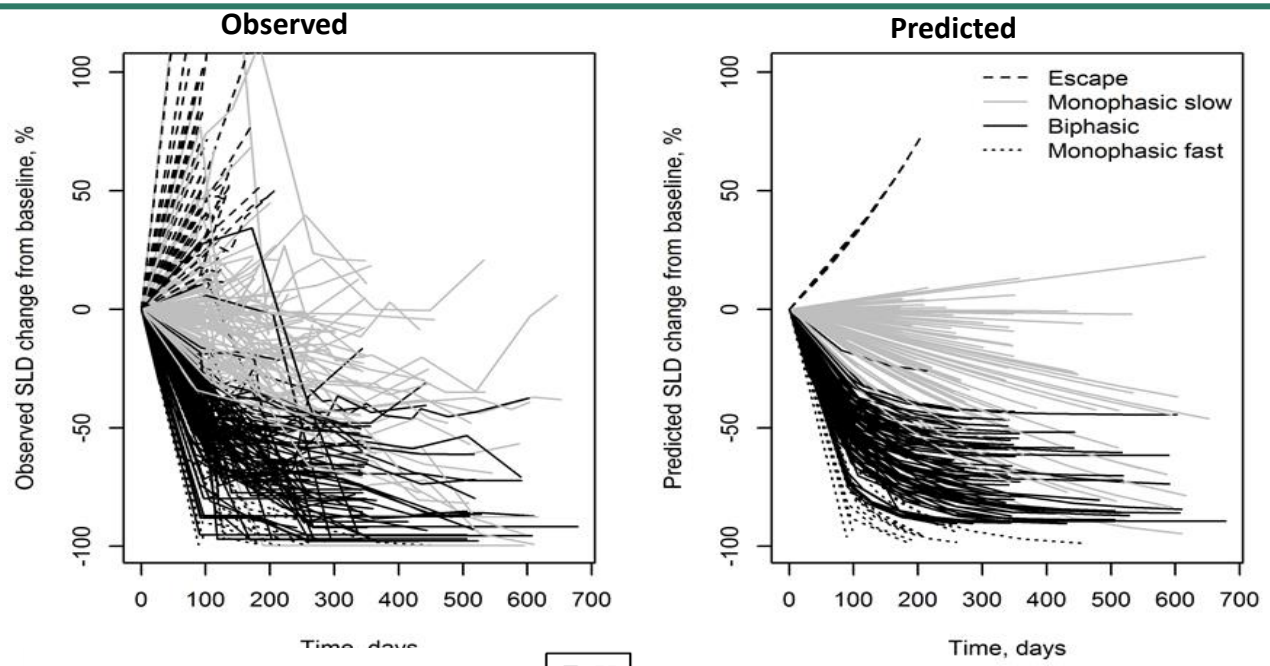
- Exposure-**response** analysis: flat exposure-response between 2Q3, 10Q3, 10Q2
  - Key point: Tumor size change was used for modeling as response instead of conventional RECIST criterion
  - Change in Tumor size vs Exposure: no difference between 2Q3, 10Q3, 10Q2

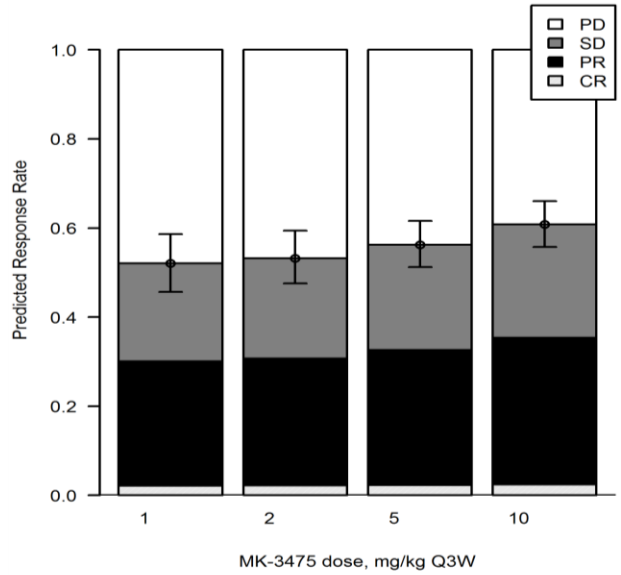


The black line shows the (log)linear regression of change from baseline vs. AUC.

Dashed reference lines indicate +20%, 0 and -30% change.

Tumor Response model Characterizes Growth Patterns and Overall Predictions with Dose



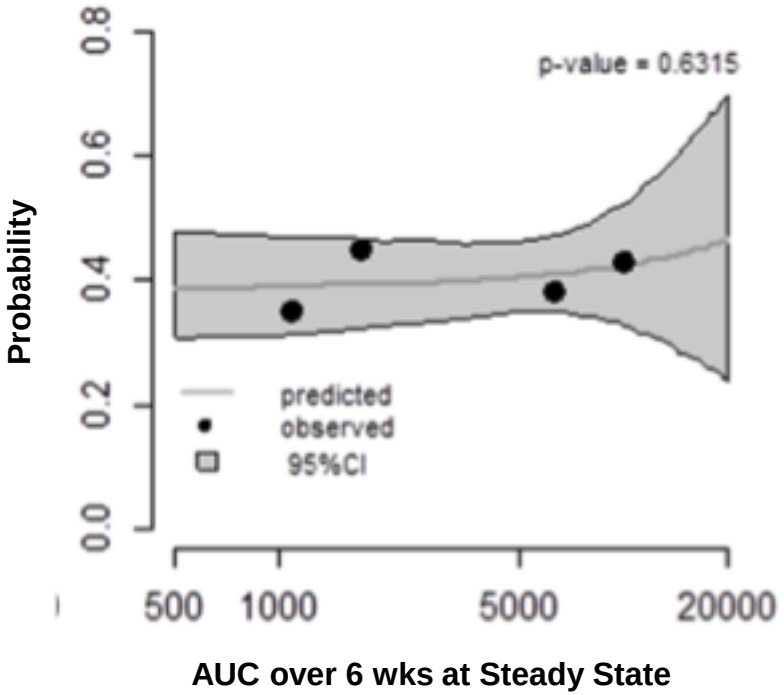


Relatively flat exposure-response relationships in efficacy [tumor size reduction] resulting in optimally efficacious dose of 2 mg/kg Q3W

22

Flat exposure-AE relationship resulting in supporting optimally efficacious dose of 2 mg/kg Q3W

AEs (AEOSI; AEs of special interest)



Solid lines represent model estimated probability and shaded areas represent the 95% confidence intervals. P-values represent significance level of the exposure-response term when forced into the model.

Later, response and survival in P001 confirmed predictions

IPI-naïve population

	P001 Part D	
	2 mg/kg Q3W	10 mg/kg Q3W
ORR (%)	33	35
OS (median)	not reached	not reached
12-month OS rate (%)	72	64

IPI-refractory population

	P001 Part B2			
	2 mg/kg Q3W	10 mg/kg Q3W		
ORR (%)	25	25		
OS (median, mo)	not reached	18.3		
6-month OS rate (%)	79	77		

Ongoing ORR in KEYNOTE 001*

- **B2**
  - **2Q3 86%**
  - **10Q3 90%**
- **D**
  - **2Q3 94%**
  - **10Q3 89%**
- **B1**
  - **All doses 87%**

***An ongoing response is defined as a patient who did not have a progressive disease event based on independent central review in the response duration analysis, is alive, and did not start a new anti-cancer treatment**

All Part D and B2 patients had min. of 9-months follow up. All B1 patients with min. 1 year follow up.

PK/PD Findings supported Development and Approval

- Exposure-Response analysis was key to identifying optimal dose.
- A wide therapeutic range was established, based on Exposure-Response, Exposure-Safety analyses

- **Approval of KEYTRUDA® based upon positive risk/benefit**
  - Efficacy based on cohort B2 173 IPI-refractory patients, with 80 patients at the 2 mg/kg recommended dose
- **Received Accelerated Approval on Sept 4, 2014**
  - Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit.
  - Two confirmatory trials (P002 (IPI-treated) and P006 (IPI-naïve)) were conducted to confirm the safety and efficacy of KEYTRUDA

Acknowledgements

- Rik de Greef
- Scott Ebbinghaus
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- Jeff Sachs
- V Sriram
- Melissa Tice
- Chandni Valiathan

Nivolumab Dose Selection: Challenges, Opportunities and Lessons Learned for Cancer Immunotherapy

Shruti Agrawal, PhD

Shruti.Agrawal@BMS.com

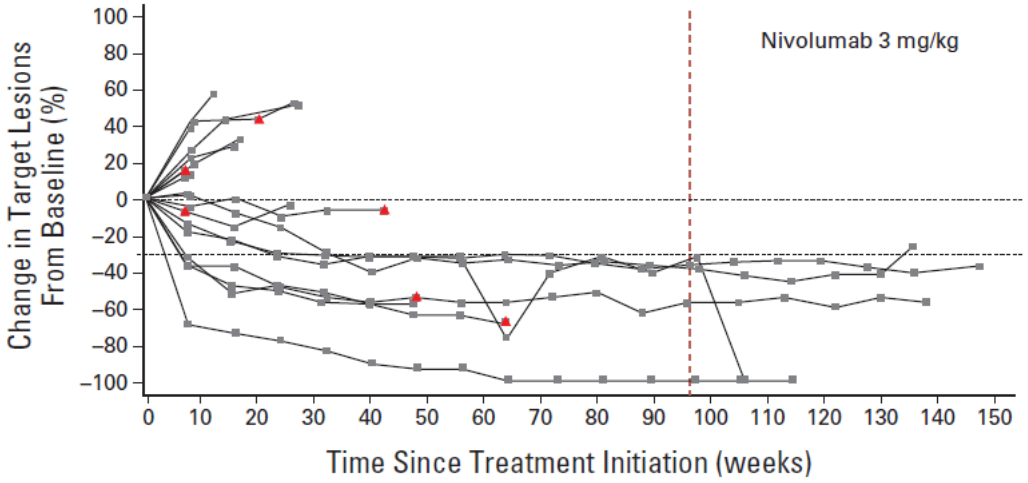
Bristol-Myers Squibb

Outline

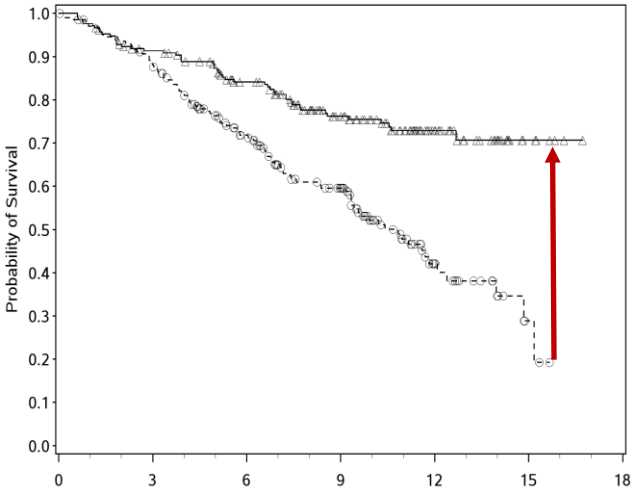
- What is cancer immunotherapy?
- Nivolumab monotherapy dose selection
- Effect of disease state on the PK of monoclonal antibodies
- Translational approaches to accelerate immunotherapy development
- Future directions

What is cancer immunotherapy?

Immunotherapy is a type of **cancer** treatment designed to boost the body's natural defenses to fight the **cancer**



Red triangles: New lesions



Nivolumab (events: 50/210), median and 95% CI : NA

Dacarbazine (events 96/208), median and 95% CI : 10.84 (9.33, 12.09)

Characteristics of tumor-response to I-O Agents

- **Patients who do not progress tend to have durable disease control**
- **Unconventional responses: reduction in target tumor burden despite appearance of new lesions**

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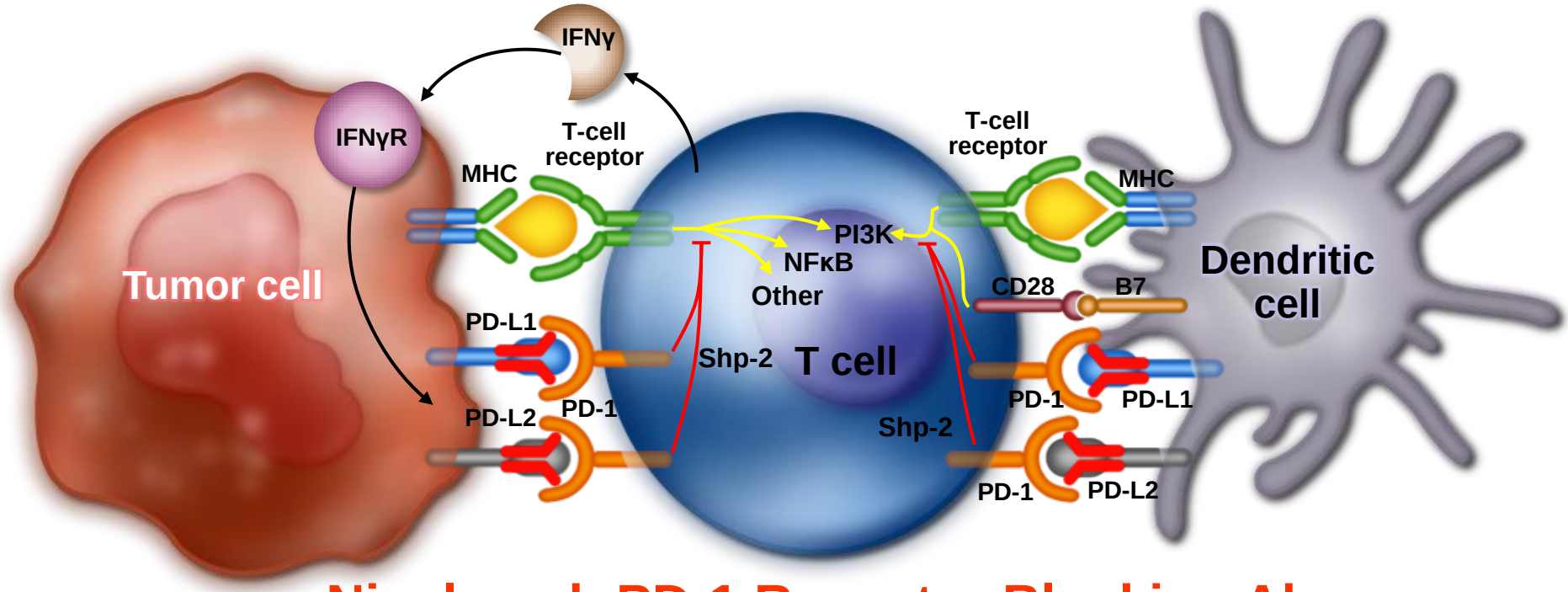
Topalian et al. J Clinical Oncology 2013; 32-1020-30, Robert et al. N Engl J Med 2015;372:320-30

Role of PD-1 Pathway in Suppressing Anti-tumor Immunity and MOA of Nivolumab (anti-PD-1 inhibitor)

Recognition of tumor by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 up-regulation on tumor

Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells



Nivolumab PD-1 Receptor Blocking Ab

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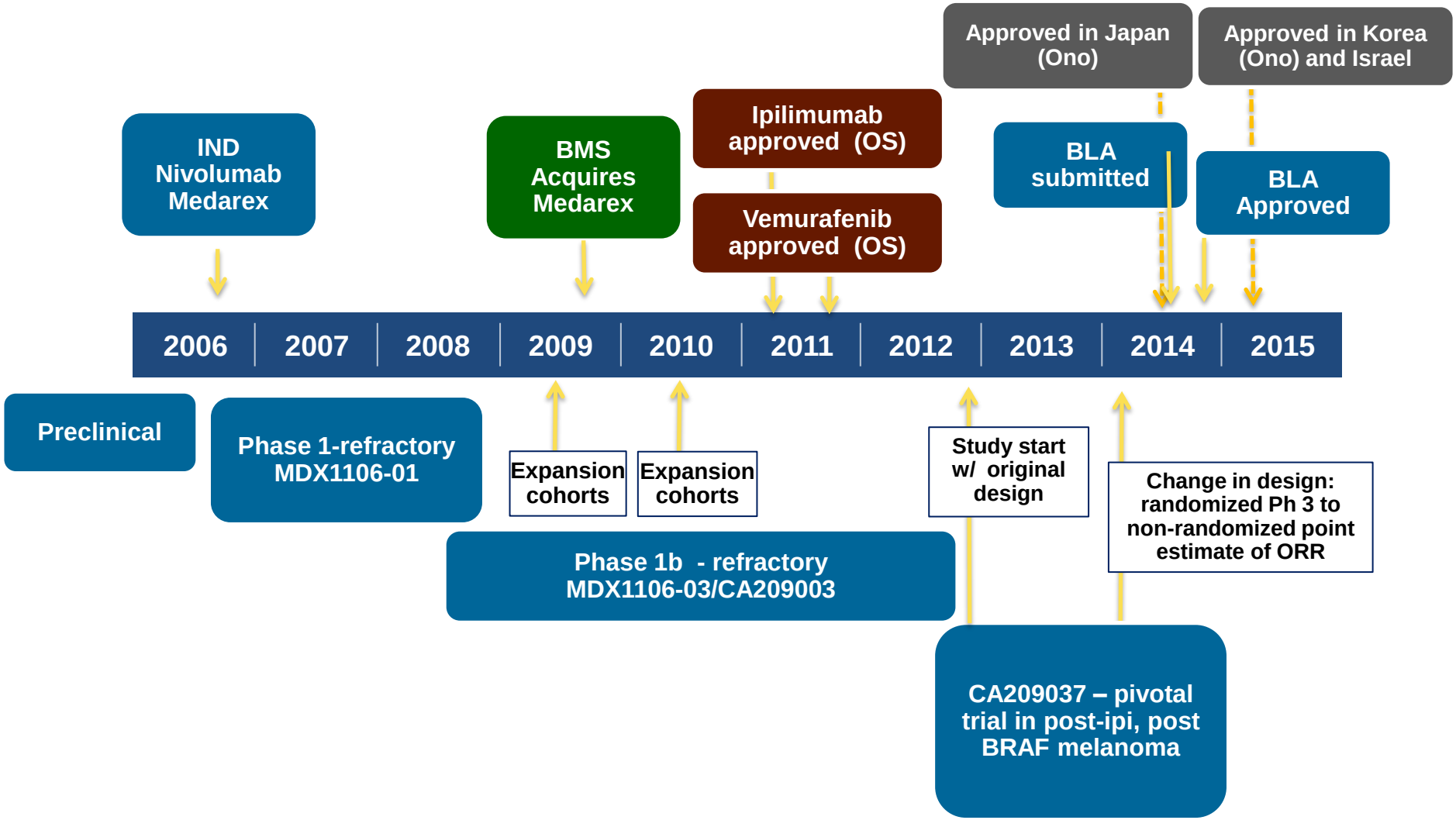
Non-Clinical Activity of Nivolumab

Fully human monoclonal IgG4 antibody:

- **Binds to Programmed Death Receptor-1 (PD-1) on T cells, macrophages and monocytes**
- **Binds with high affinity (low nM) to PD-1 in humans and cynomolgus macaques**
- **Does not elicit antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity**
- **Promotes cytokine production/proliferation in *in vitro* allo-MLR assay**
- **Mediates antitumor activity in both PD-L1+ and PD-L1- preclinical models**

Overview of Nivolumab Development and Melanoma Landscape



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First-in-Human (MDX1106-01) SAD Study

Study Design: Single-ascending dose study, with allowance for subsequent dosing 12 weeks later

Dose selection

- Nonclinical data indicated an efficacious dose in the range of 1-10 mg/kg in humans (allometric scaling)
- Starting dose of 0.3 mg/kg was supported by nonclinical pharmacology and toxicology data
- Dose escalation to 10 mg/kg

Tumor Type Selection

- MEL, RCC, CRC, NSCLC, CRPC
- Relapsed/Refractory

Results (N= 39): supported continued clinical investigation

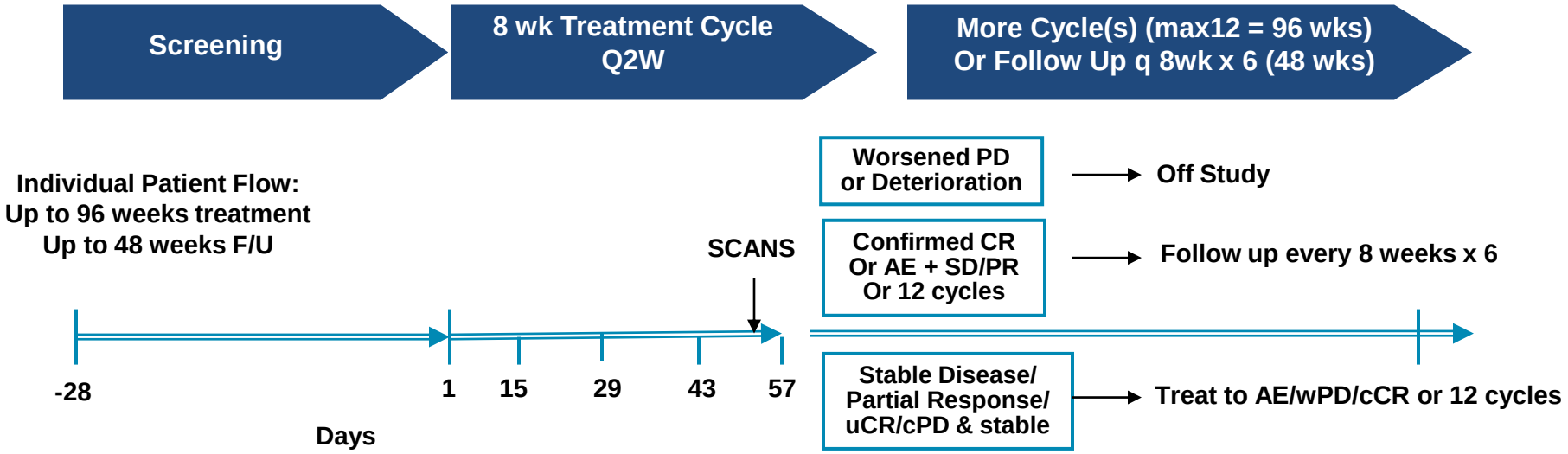
Anti-tumor activity

- PR with RCC subject @ 10 mg/kg, 3 doses, 15+ mos duration
- CR with CRC subject @ 3 mg/kg, 5 doses, 23+ mos duration
- SD with MEL subject @ 10 mg/kg (retreated), 11 doses, 22+ mos duration

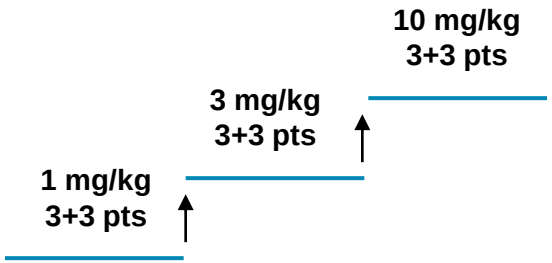
Safety acceptable

- SAE of Gr 3 colitis/diarrhea after 5 doses @ 1 mg/kg over 9 mos. Resolved with steroids

Ph 1b CA209003 (MDX1106-03) MAD
Original Study Design



Dose Escalation and Enrollment Sequence



6 pts at MTD/highest tested dose (HTD)

Expansion Cohorts

MEL + RCC (N = 16 in tumor type)
NSCLC (N=16)
mCRPC (N=16)

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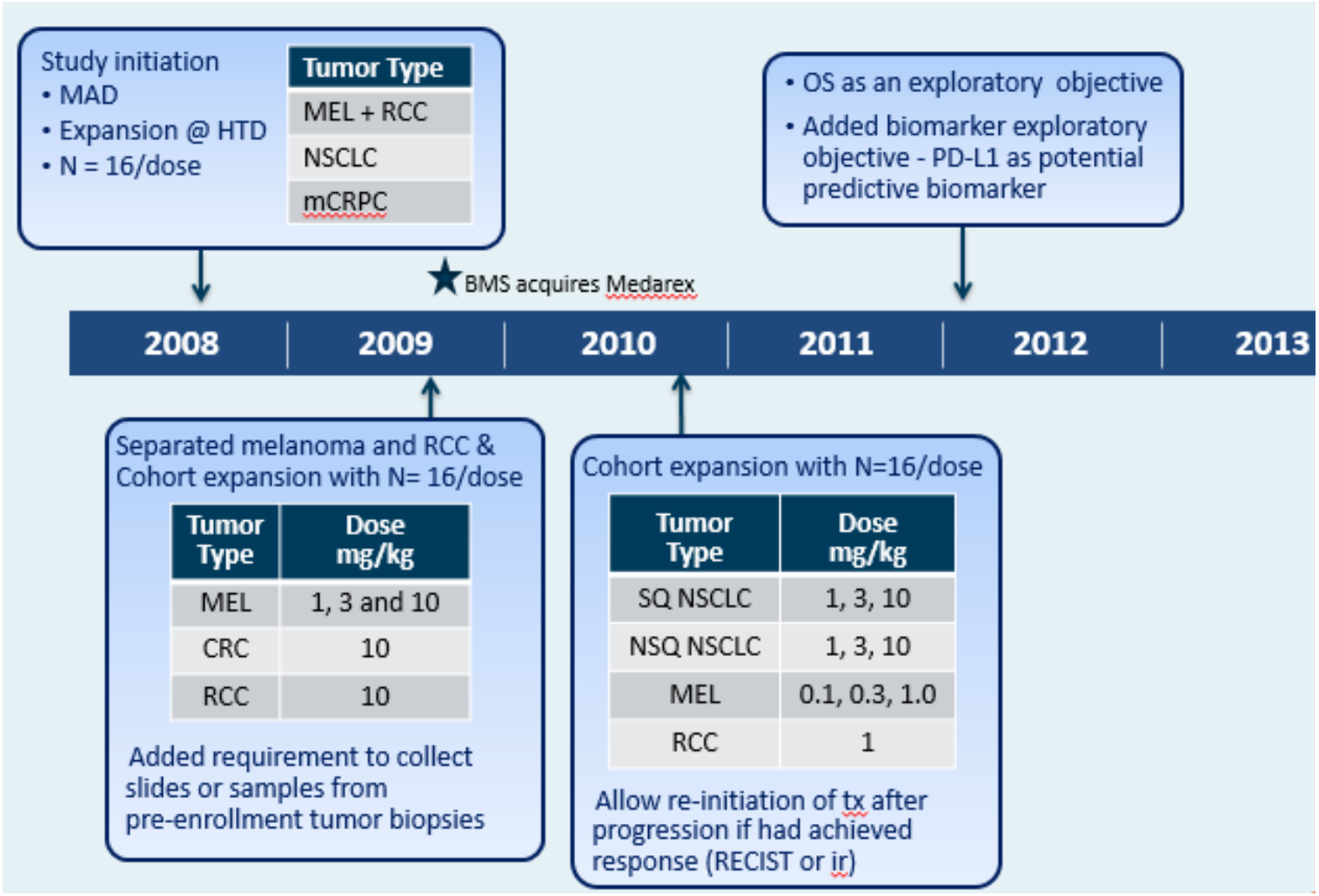
Dose-Ranging Expansion Cohorts to Assess Safety, Response Rate, and Durability of Response: Moving away from MTD approach



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Approach for Ph 2/3 Dose Selection

One dosing regimen across multiple solid tumors was considered possible based on mechanism of action

Review of CA209003 safety/efficacy

- **N = 306 for safety and efficacy across all tumor types**
- **Minimum follow-up for efficacy population was 8 months**
- **Median duration of therapy in the safety population was 16.0 weeks (range = 2.0-121.7 weeks)**
- **Focus on AE profile, grade 3-4 AE/SAE and AEs of Special Interest (AESI)**
- **Dose-response of ORR, PFS by tumor type**

Integrated Quantitative Analyses to estimate Dose/Exposure-Response and relationships to biomarkers, safety and efficacy

- **Exposure-receptor occupancy analysis**
- **Population Pharmacokinetics**
- **Exposure-Response by OR, PFS at 24 wks, tumor growth dynamics**
- **Dose-Safety by cumulative probability of high-grade drug related SAE**

Dose information across tested tumor types

Median (range)	Dose (mg/kg Q2W)					
	0.1 (N = 17)	0.3 (N = 18)	1 (N = 86)	3 (N = 54)	10 (N = 131)	Total (N = 306)
Duration of therapy (weeks)	24.0 (8–87)	17.5 (4–90)	20.0 (2–100)	22.6 (2–101)	15.9 (2–122)	16.1 (2–122)
Number of infusions	11.0 (4–43)	8.5 (2–43)	10.0 (1–49)	9.5 (1–48)	8.0 (1–51)	8.0 (1–51)
Cumulative dose per pt	2.3 (0–36)	5.4 (1–29)	10.1 (1–48)	28.6 (3–138)	77.8 (2–508)	30.9 (0–508)
Dose intensity per pt (mg/kg/2 weeks)	0.1 (0–1)	0.4 (0–1)	1.0 (1–1)	2.9 (2–3)	9.8 (2–11)	2.9 (0–11)

- The median duration of treatment was 16 weeks
- Dose intensity was > 90% across all dose levels

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Similar Safety Profile Across Doses

Treatment-related AEs, % (n)	Dose (mg/kg Q2W)					
	0.1 (N = 17)	0.3 (N = 18)	1 (N = 86)	3 (N = 54)	10 (N = 131)	Total (N = 306)
Any grade	77 (13)	78 (14)	81 (70)	74 (40)	71 (93)	75 (230)
Grade 3–4	29 (5)	17 (3)	14 (12)	20 (11)	16 (21)	17 (52)
Serious grade 3–4	6 (1)	0	5 (4)	9 (5)	11 (14)	8 (24)
Leading to DC	18 (3)	0	11 (9)	7 (4)	12 (16)	11 (32)
Deaths	-	-	2 (2)	4 (2)	1 (1)	2 (5)

DC = discontinuation

- MTD was >= 10 mg/kg Q2W
- AEs were generally manageable and reversible with use of immuno-suppressants
- Frequency of DR-AE, Gr 3-4 DR-AE and AE leading to DC similar across dose groups
- Pneumonitis was a rare but potentially significant AE

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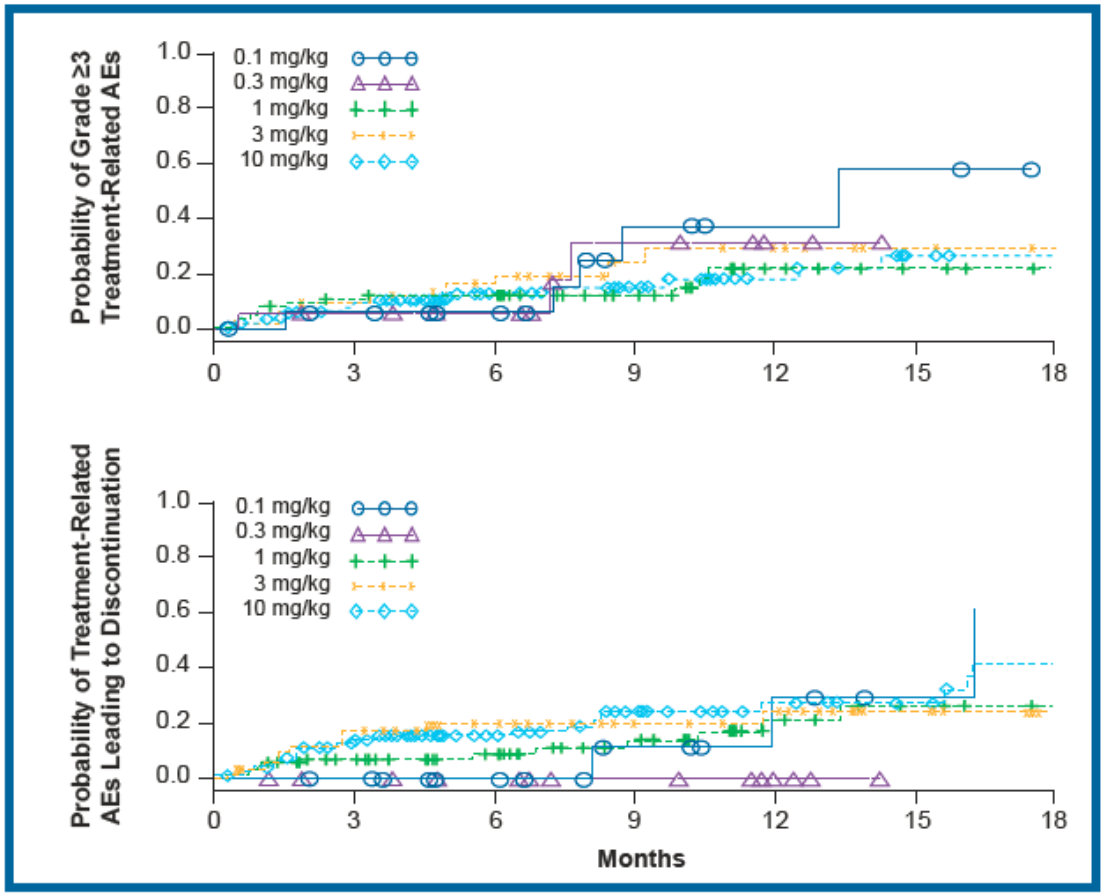
Integrated dose-response for safety



The probability of AEs-DC appeared to be lower in the ≤1 mg/kg compared with 3 and 10 mg/kg dose levels

The probabilities of both grade ≥3 treatment-related AEs and AE-DC were similar between 3 and 10 mg/kg dose levels

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Activity/Durability Across Tumor Types

Dose (mg/kg)	MEL (N = 107)		NSCLC (N = 129)		RCC (N = 34)	
	ORR, % (n/N)	PFS rate at 24 weeks, %	ORR, % (n/N)	PFS rate at 24 weeks, %	ORR, % (n/N)	PFS rate at 24 weeks, %
0.1	35 (6/17)	41	-	-	-	-
0.3	28 (5/18)	35	-	-	-	-
1	31 (11/35)	51	3 (1/33)	26	28 (5/18)	50
3	41 (7/17)	55	24 (9/37)	40	-	-
10	20 (4/20)	35	20 (12/59)	33	31 (5/16)	67
Dash indicates that data were not collected						

- **High ORR and longer PFS achieved at lower dose levels for highly-immunogenic tumor types of melanoma and RCC**
- **Higher ORRs were observed for NSCLC at 3 and 10 mg/kg but not at 1 mg/kg**

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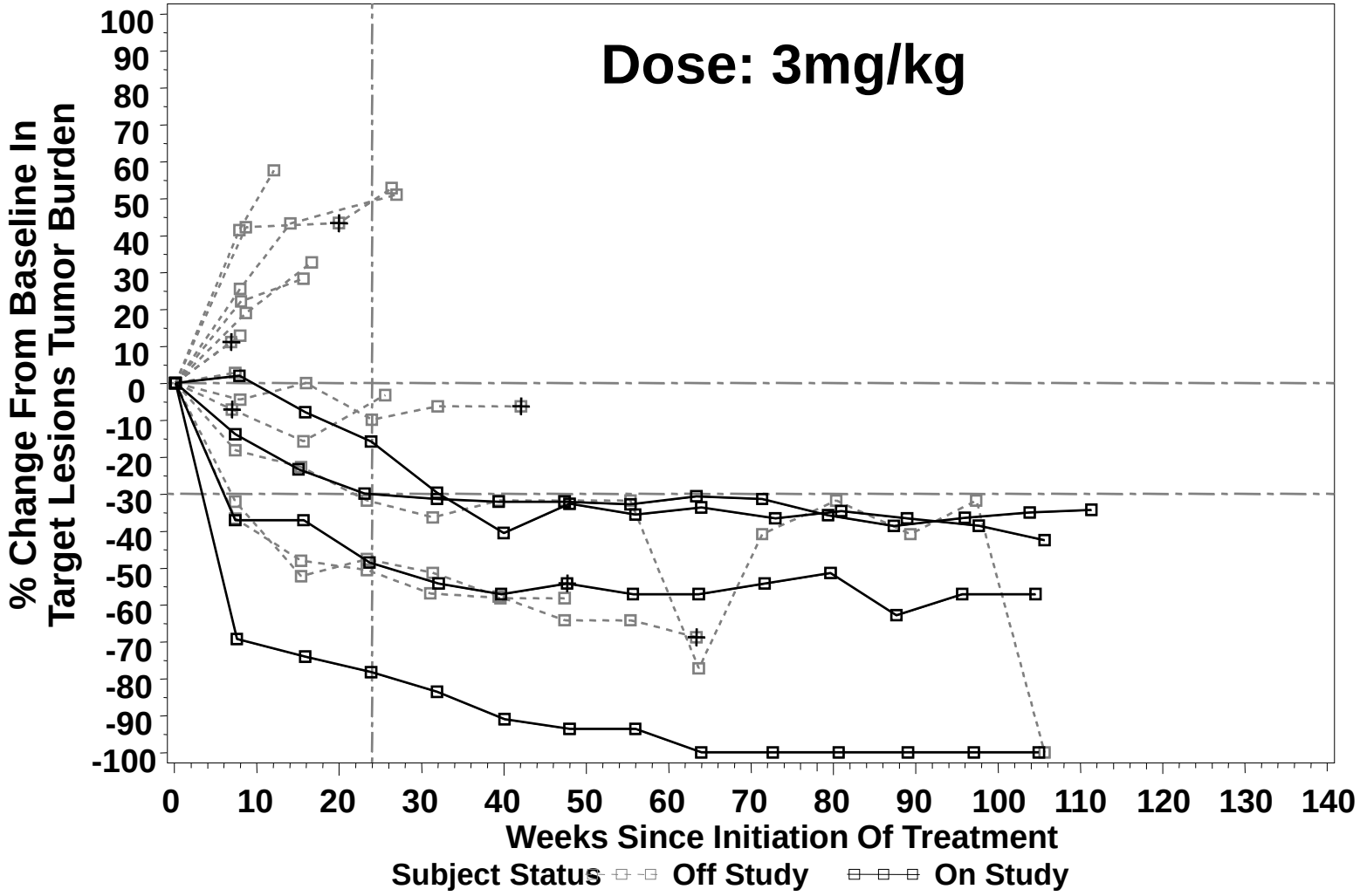
Durability and Depth of Response in Melanoma

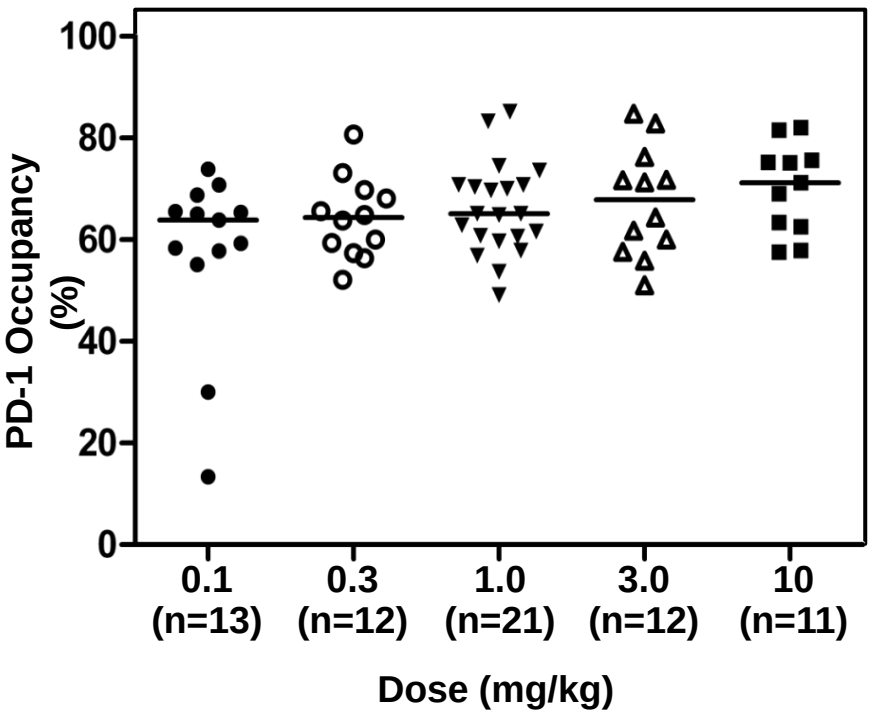


+: 1st Occurence of New Lesion

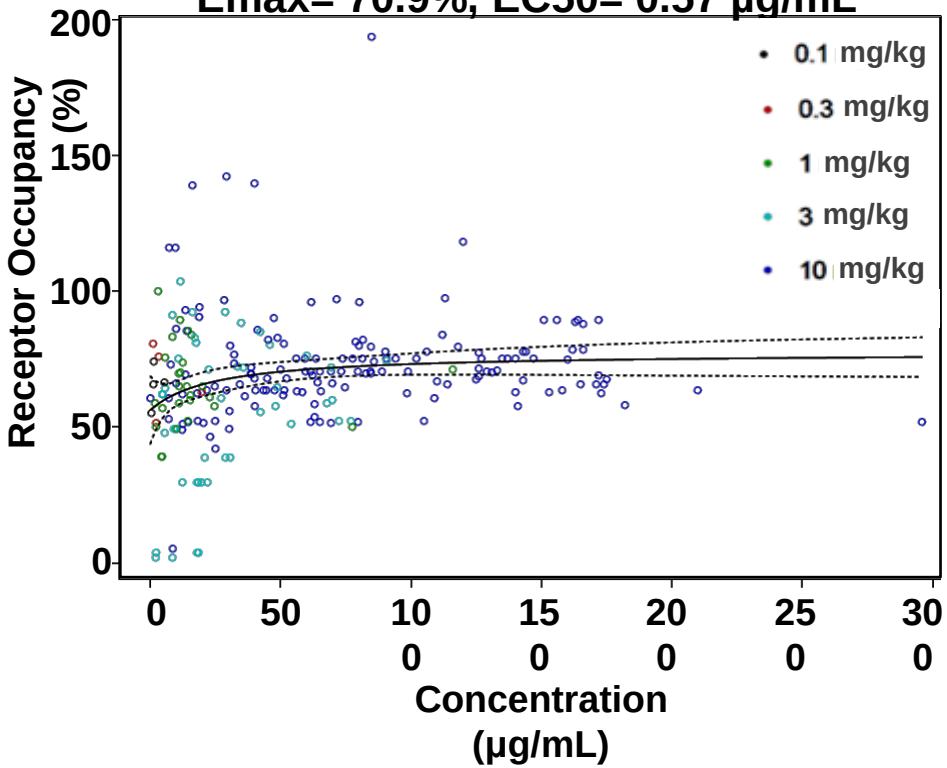
Feb 24, 2012 Snapshot. Response Evaluable Subjects Dosed by July 1, 2011

Peripheral PD-1 Receptor Occupancy

8 weeks post-dose RO from 69 MEL subjects



Emax model (CA209001 and -003 data)
Emax= 70.9%, EC50= 0.57 µg/mL



Peripheral receptor occupancy saturated at ≥ 0.3 mg/kg dose

The peripheral pharmacodynamic data did not differentiate activity by dose level and may have limited value in understanding dose-response relationships.

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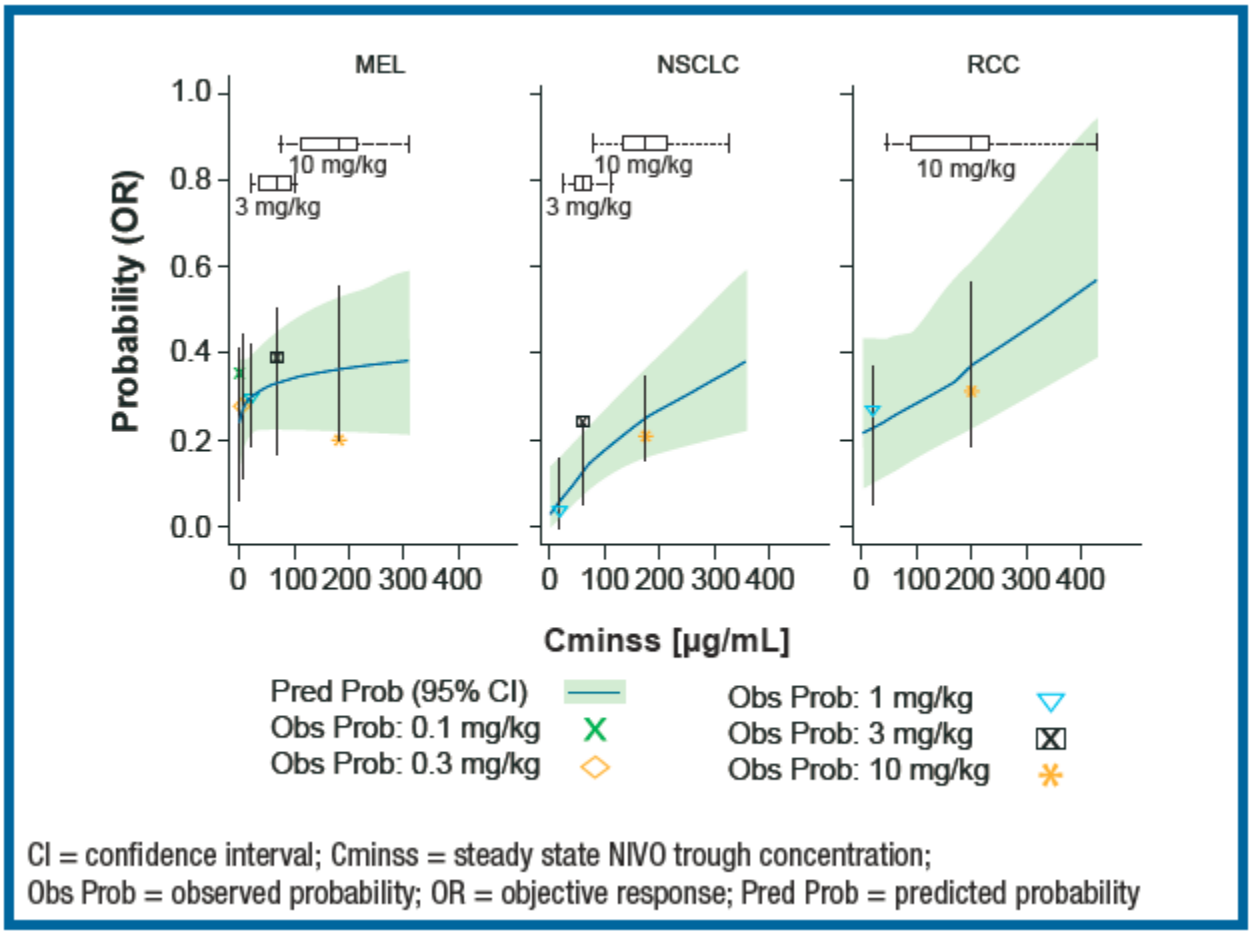
Exposure-Response of Efficacy, by Tumor Type



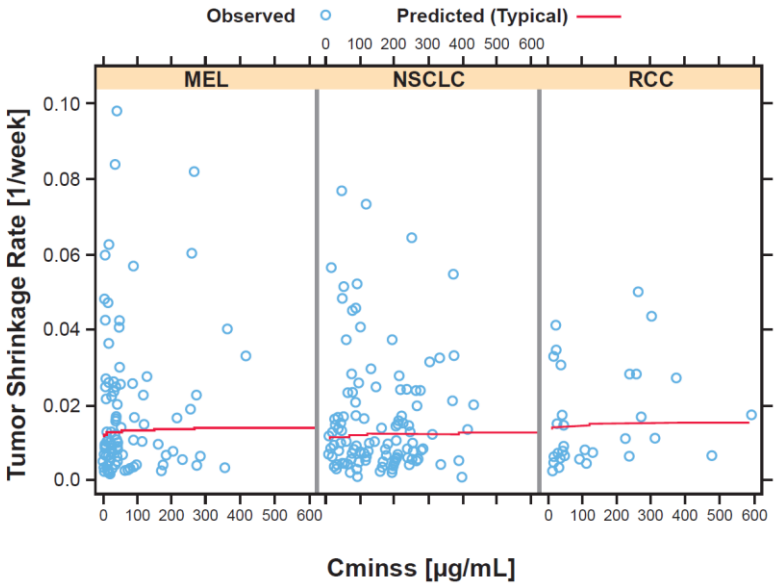
CI = confidence interval; Cminss = steady state NIVO trough concentration;
Obs Prob = observed probability; OR = objective response; Pred Prob = predicted probability

Exposure-response is relatively flat for MEL at doses ≥1 mg/kg and NSCLC at doses ≥ 3 mg/kg

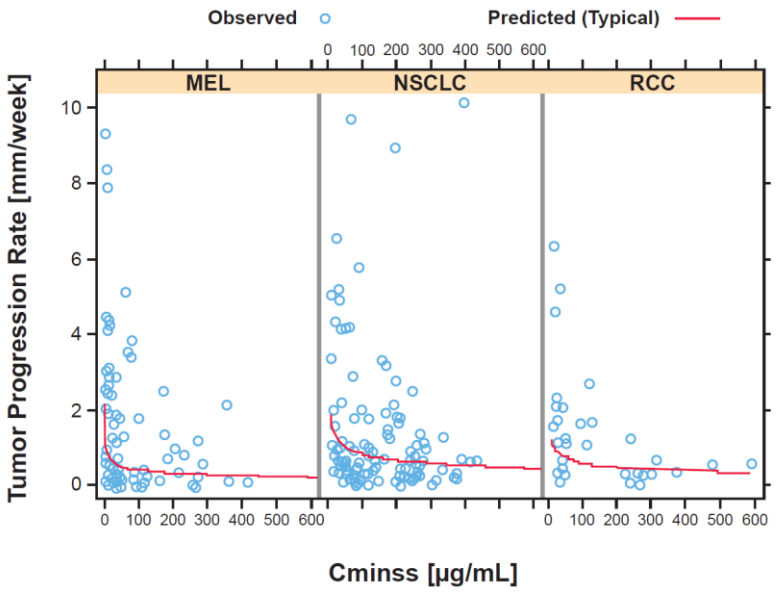
A consistent pattern observed with PFS at 24 Wk, which is independent of follow-up period

Exposure vs. Shrinkage Rate and Progression Rate by Tumor Type

Shrinkage Rate



Progression Rate



Exposure-response for tumor shrinkage rate was relatively flat

Tumor progression rate tended to decrease with increasing exposure for NSCLC compared to Melanoma

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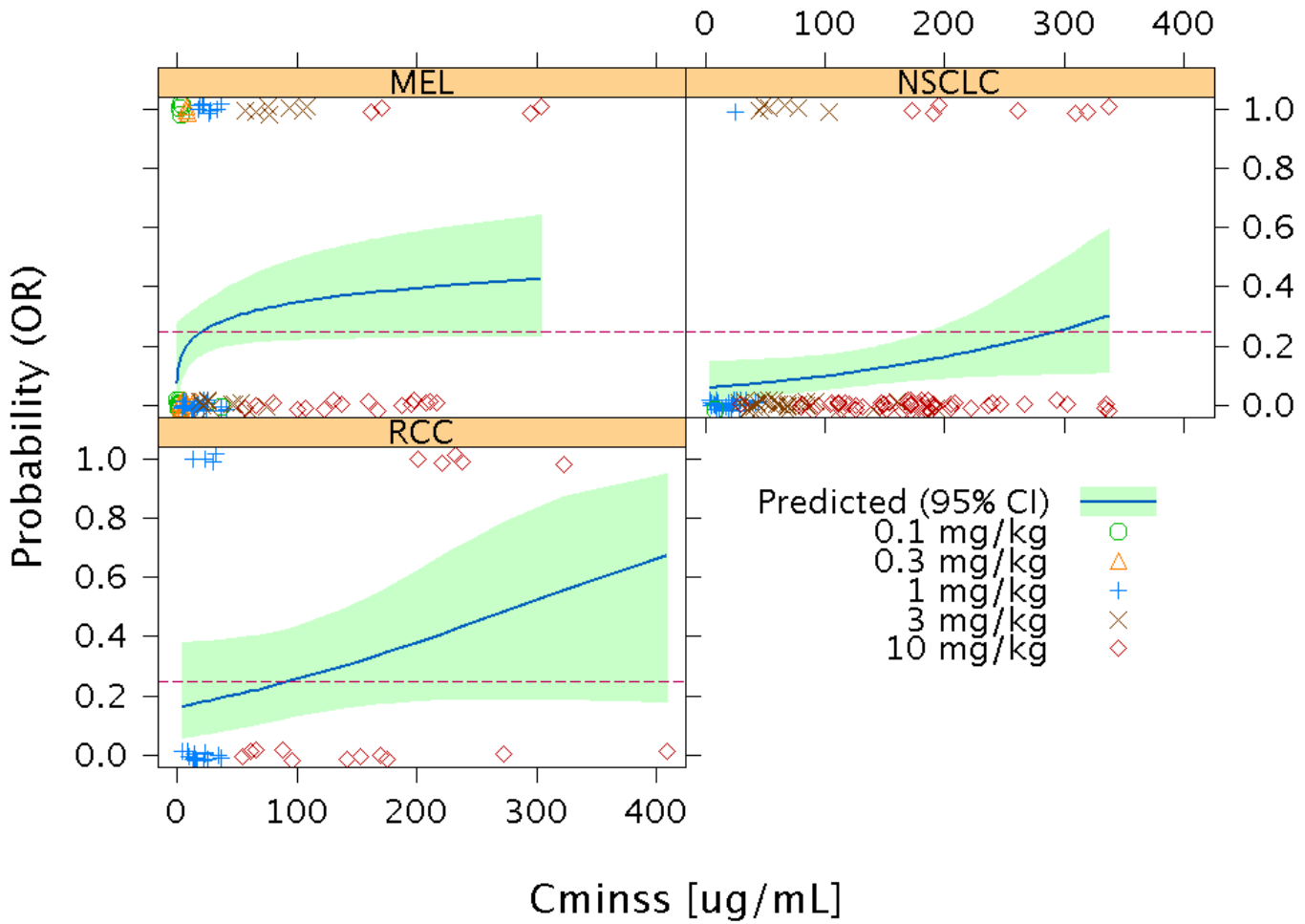
Summary of Data for Dose Selection for Phase 2/3 in Solid Tumors

- Peripheral receptor occupancy saturated at low dose levels; did not provide meaningful differentiation of observed activity
- Nivolumab 10 mg/kg Q2W was safe and tolerable
- Observed activity and exposure-response analyses for various efficacy response measures (early measure, durability of response and mechanistic tumor growth dynamic modeling) indicated that higher nivolumab doses/exposures are required for low immunogenic tumor types
- Based on the totality of the data, nivolumab 3 mg/kg Q2W was selected as the monotherapy dose for further evaluation across all tumor types
- This dose was shown to provide long term survival benefit across multiple tumor types irrespective of PD-L1 expression

Lessons learned: Disease status affects PK of monoclonal antibodies



Visual observation of early data showed that responders had higher exposure compared to non-responders within the dose level

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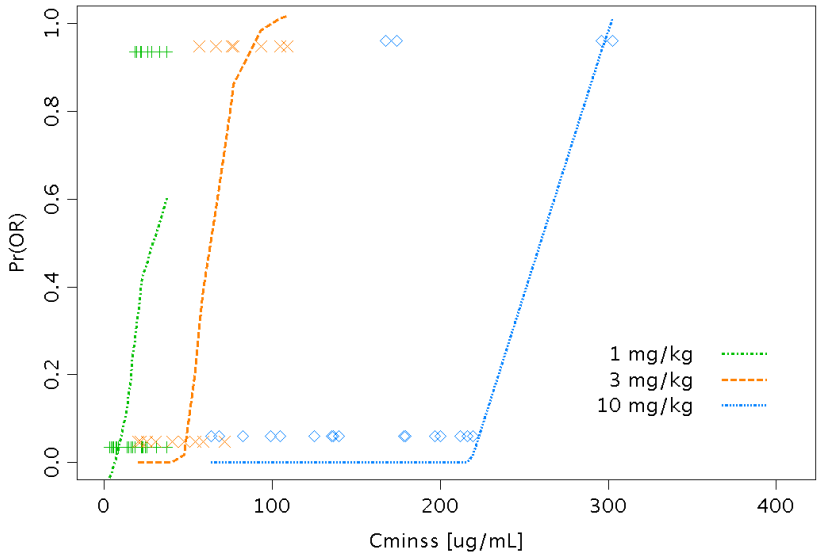
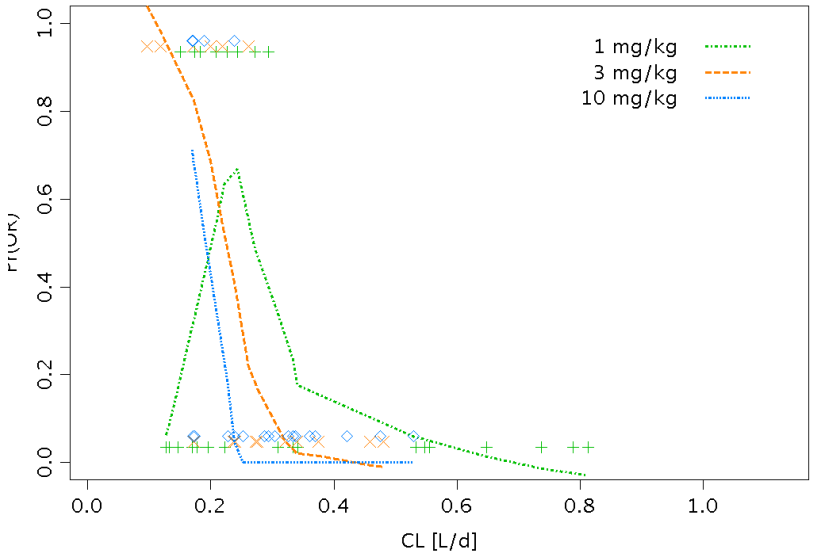
Exploration of Exposure/Dose-Response: Melanoma

Pr(OR) vs Cminss, by Dose



Pr(OR) vs CL, by Dose



- **Exposure (Cminss) alone does not explain the Pr(OR)**
- **Pr(OR) appears to be more closely associated with CL**

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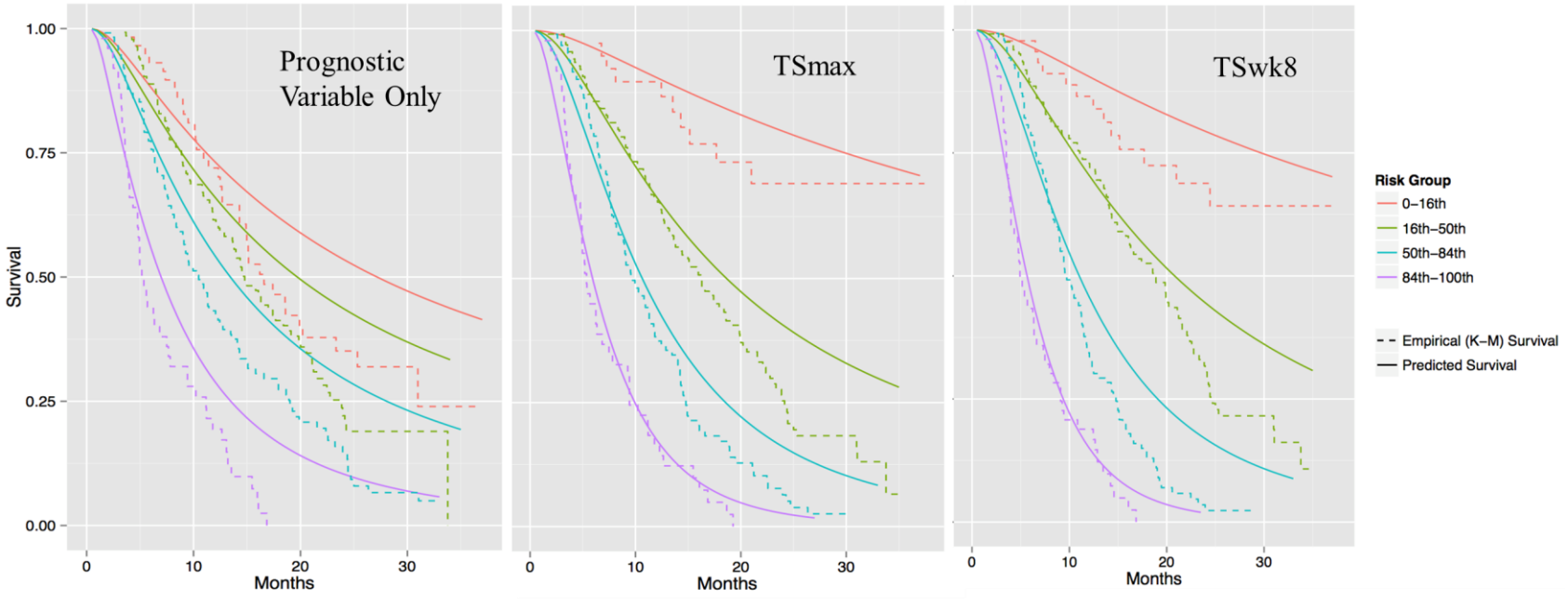
Translational approaches to accelerate immunotherapy development

Leveraging totality of IO data to accelerate dose selection for IO combinations

Early tumor shrinkage is predictive of survival



Suryawanshi et al. ACoP 2015. S-11

Model predicted tumor shrinkage is based on nonlinear mixed-effects mixture-model of TGD

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IO systems pharmacology to predict immunotherapy combination efficacy

Melanoma immuno-oncology pilot PhysioMap: cells, cytokines, and biomarkers

Blood/Plasma

Pilot: circulating immune cells, cytokines, chemokines, RO, therapy A and B

Stage 2: expand immune cells, 3 more therapies (checkpoint inhibitors, agonists)

Transport

Tumor & lymph node

Pilot cell types: CD4: Naïve, Th, Th1, Th2, Th17, Treg, TEM; CD8: Naïve, CTL, TEM; NK, B, DC, M1/M2 Macrophages, MDSC, Cancer

Stage 2 cell types: CD4: TFH , TCM; CD8: TCM; B: Naïve, Plasma (short & long lived), Memory; VEC, LEC, CAF, pDC, N1/N2 Neutrophils, TIE2-Expressing Monocytes, Lymph node fibroblasts

Pilot mediators and markers (21): IL1, IL2, IL4, IL6, IL7, IL10, IL12, IL15, IL17, IL21, IL23, IFNg, TGFb, GMCSF, IDO, ~~Chemokines~~, LDH, tumor associated antigens, antibodies, nivo, ipi

Stage 2 mediators and markers (39): IL18, IFN1, TNFalpha, CXCL8, CXCL9, CXCL12, CCL4, CCL2, CCL5, CCL20, CCL21, CCL22, MCSF, PGE2, ICAM1, VEGFA, VEGFC, Ang2, ECM, MMP

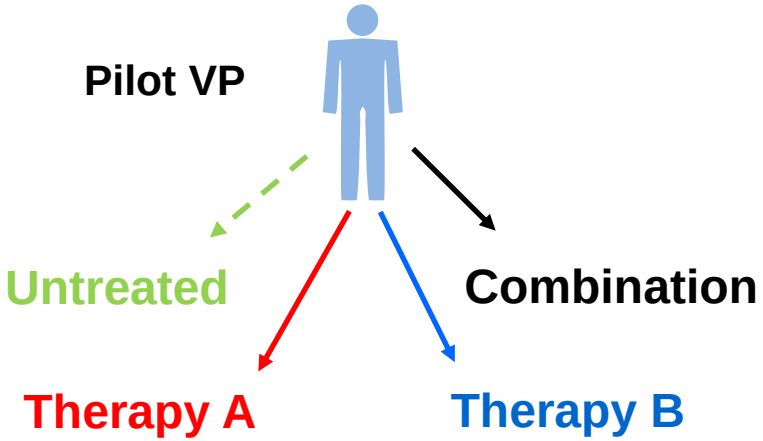
Pilot cell associated markers: MHC, CTLA4, B7, CD28, PD-1, PD-L1, PD-L2 FoxP3, Granzymes

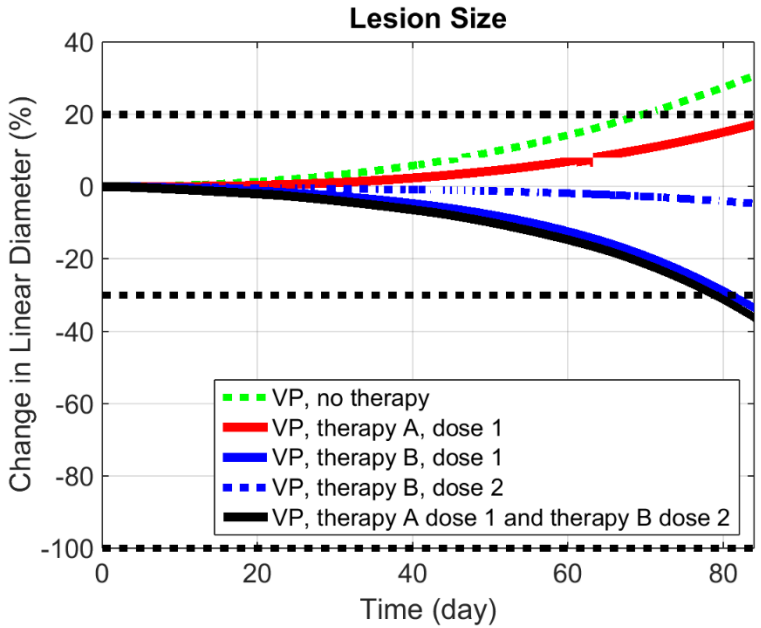
Stage 2 cell associated markers: LAG3, sLAG3, CD137, CD137L, GITR, GITRL

Some of the new processes in Stage 2: hypoxia, vessel and ECM density (metastatic potential), cancer and immune migration to the lymph node, adaptive immune response in the lymph node

Schmidt B. ASCPT 2016

Pilot virtual patient: Lesion response to combination therapies





- Different IO therapies tested in same VP
- Note the simulated increased response for the combination relative to monotherapies at the same concentrations
- Alternate VPs will facilitate exploring phenotypes that may have greater benefit from the combination

Schmidt B. ASCPT 2016

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Future directions in optimizing cancer immunotherapy development

- Establishing optimal regimen: sequenced or concurrent administration of combinations
- Dosing frequency
- Duration of treatment/number of combination doses
- Triple combinations
- Combinations with multiple treatment modalities

Acknowledgements

- Patients enrolled in clinical trials
- Clinical Pharmacology and Pharmacometrics group at Bristol-Myers Squibb
- Nivolumab and ipilimumab clinical development teams

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Evaluating and Quantifying Benefit of Exposure-Response Modeling for Dose Finding

Chyi-Hung Hsu and José Pinheiro
Janssen R&D

FDA-AACR: Oncology Dose-finding Workshop
June 13, 2016

Outline

- Motivation
- Dose-exposure-response modeling framework
- Simulation study comparing DR- and ER-based estimation in dose selection
- Conclusions

Motivation

- Poor understanding of (efficacy and safety) dose response is one of the root causes of late phase attrition and post-approval problems
- Difficulties in dose finding
  - ➢ Limitations of current practice:
    - ✓ Few doses
    - ✓ Sample size based on power to detect DR signal (dose vs. placebo)
- Exposure-response modelling could be very helpful and useful for improving dose selection
  - ➢ How to quantify the potential benefit of ER modelling?

Dose-Exposure-Response Framework Utilized in Simulations

- Underlying ER model
- Sources of Variability
- Relating ER model to DR model

Exposure-response model

- Exposure-response model

$$\mu_i = E_0 + \frac{E_{max}\ AUCi^{h}}{EC_{50}{}^{h} + AUCi^{h}}$$

μ_i : average PD response

E_0: placebo response,

E_{max}: max effect,

EC_{50} (not subject-specific): AUC giving 50% of E_{max},

h: Hill coefficient

- $AUC_i = d / CL_i$, CL_i is the "***true***" clearance of patient i receiving dose d

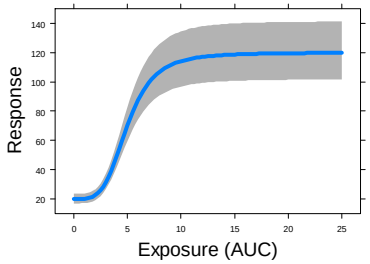
Note: $f = 1$ for simplicity

Exposure-response model: variability and uncertainty

- PD variability (σ_y)

  conditional on μ_i, PD response y_i assumed log-normally distributed

$$log(y_i)|\mu_i \sim N(log(\mu_i), \sigma_y^2)$$

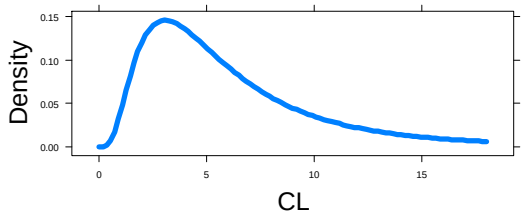


  $\sigma_y \approx$ coeff. of variation (CV) of PD

- PK intrinsic variability (σ_{CL})

  clearance assumed log-normally distributed

$$log(CL_i) \sim N\left(log(TVCL), \sigma_{CL}^2\right)$$

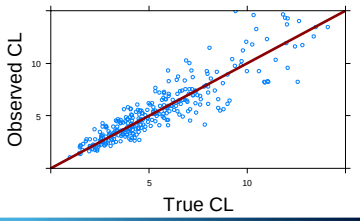


- PK measurement error/variability (σ_U)

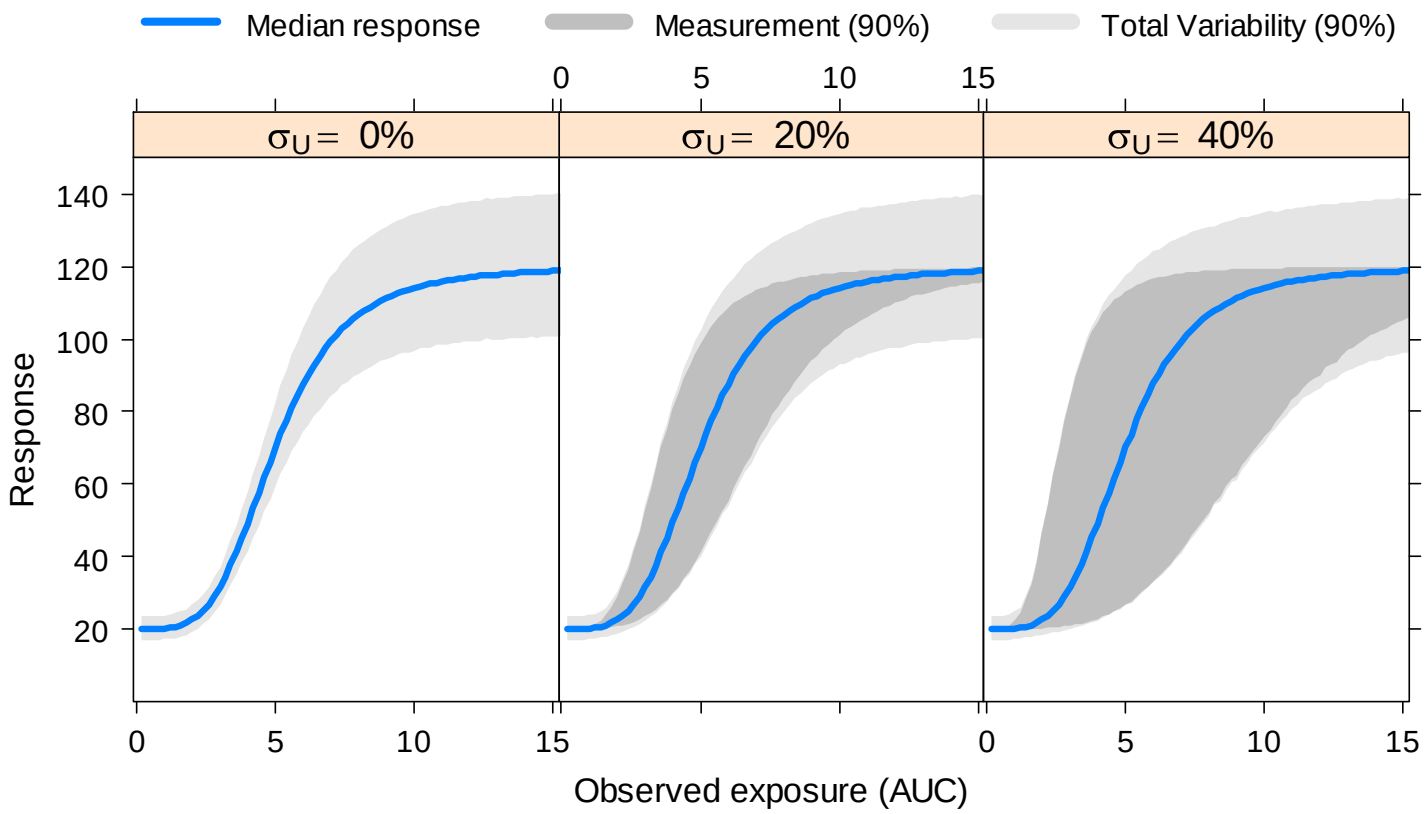
  In practice, CL_i might be measured with errors.

  Observed value

$$log\left(CL_i^*\right)|CL_i \sim N\left(log(CL_i), \sigma_U^2\right)$$



Impact of measurement variability on response



Mixture of responses from different true AUCs

- increase overall variability
- could compromise parameter estimations

Translating ER into DR model

- Sigmoid-Emax ER model can be re-expressed as a DR model

$$\mu_i = E_0 + \frac{E_{\max} AUCi^h}{EC50^h + AUCi^h} = E_0 + \frac{E_{\max} \left(d/CLi\right)^h}{EC50^h + \left(d/CLi\right)^h} = E_0 + \frac{E_{\max} d^h}{ED50_i^h + d^h}$$

- $ED_{50\,i} = CL_i\, EC_{50}$ is the (subject-specific) dose at which 50% of the max effect is attained
- E_0, E_{max}, and h defined as in ER model
- From distributional assumptions of ER model

$$log(ED_{50_i}) \sim N\left(log(TVCL) + log(EC_{50}),\ \sigma^2_{CL}\right)$$

Dose-Response model (cont.)

- DR model accommodates intrinsic inter-subject PK variation (σ_{CL}) by allowing ED_{50} to vary with patient, and two models, without measurement variability, are equivalent
- In practice, subject-level ED_{50} is often not estimable, so a population ED_{50}, not varying with subject, is used.

$$\mu_i = E_0 + \frac{E_{\max} d^h}{ED_{50}^h + d^h}$$

Simulation Study

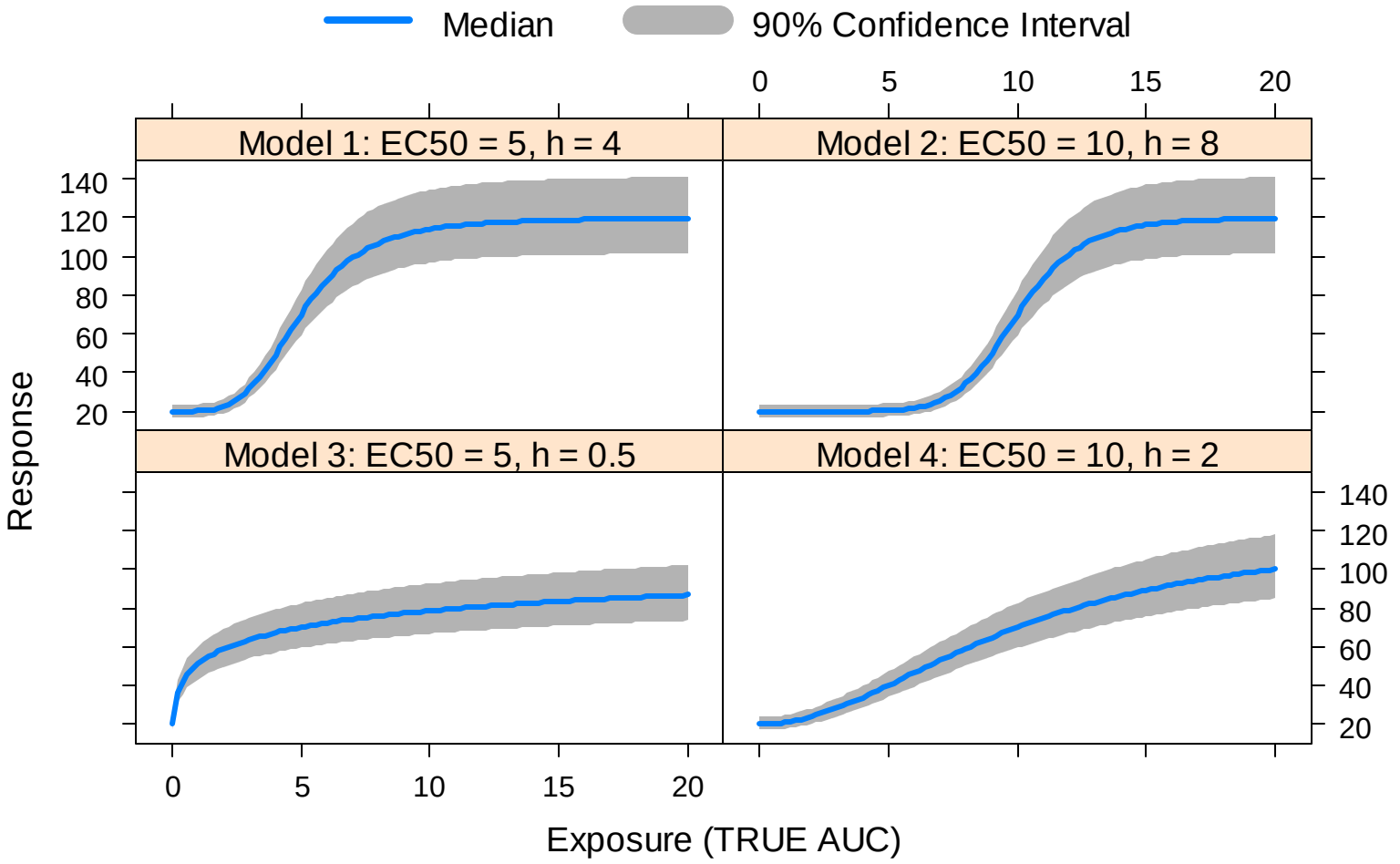
Simulation study

- Goal: quantify relative performance of ER vs. DR modeling for dose selection under various scenarios – identify key drivers
- Simulation study design
  - Design: 5-arm, parallel groups: 0, 25, 50, 75, and 100 mg: 30 subjects per arm
  - Combinations of 120 scenarios considered – 4 key drivers of interest
    1) Sig-Emax ER models (4), all with E_0=20 and E_{max}=100 and TVCL = 5

Model	***1***	***2***	***3***	***4***
EC50	5	10	5	10
h	4	8	0.5	2

    1) PD variability (2): σ_y = 10% and 20%
    2) intrinsic PK variability (3): σ_{CL} = 30%, 50%, and 70%
    3) PK measurement variability (5): σ_U = 0%, 20%, 40%, 60%, and 80%

Exposure-Response Models Considered

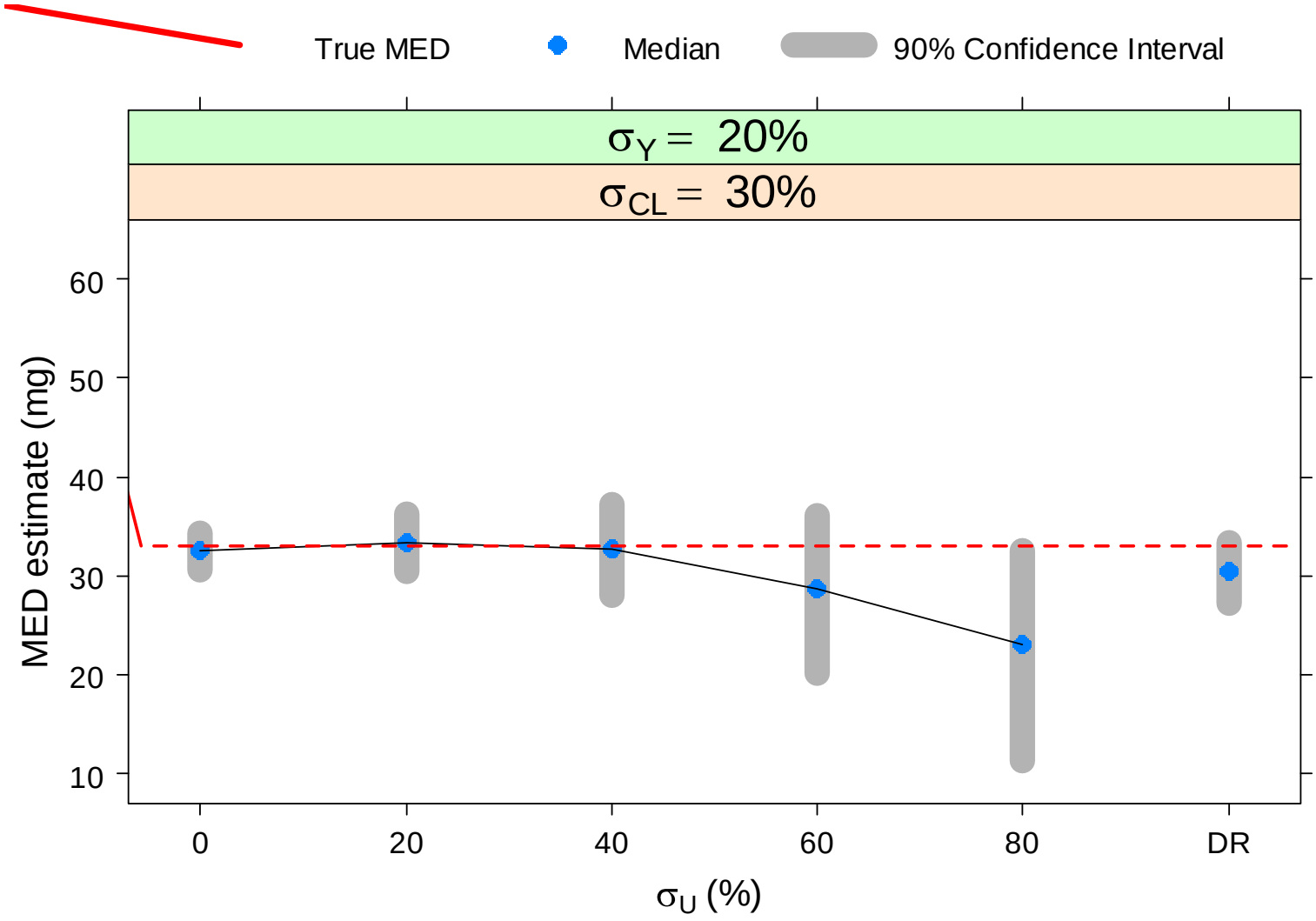


Simulation study (cont.)

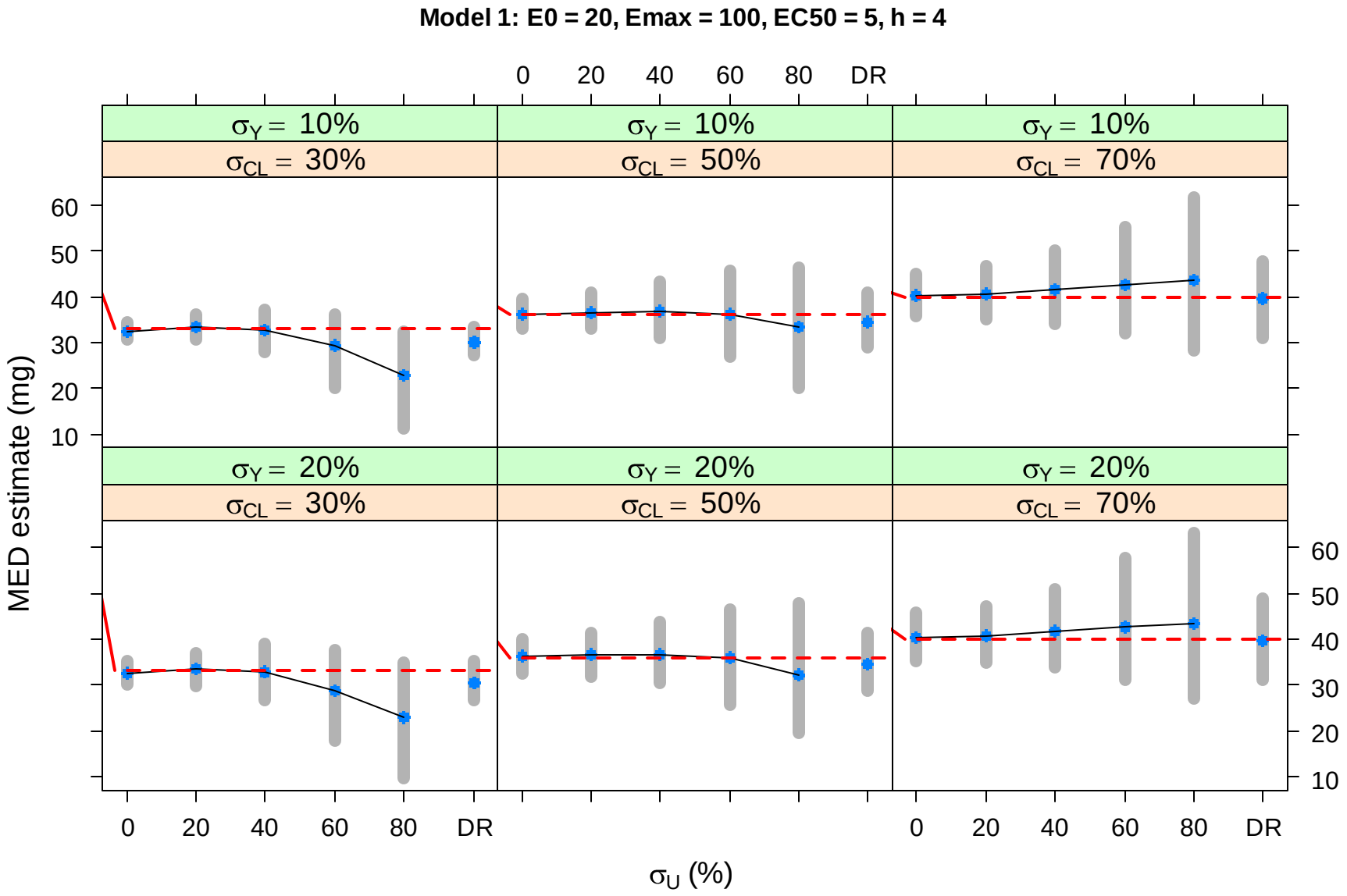
- Simulating PD response under assumed scenario
  1. Simulate "true" individual clearance
  2. Simulate "observed" clearance
  3. Simulate PD response according to "true" clearance
- Model fitting
  - Bayesian methods with non-informative priors
  - ER estimation: sigmoid-Emax exposure-response model using "observed" clearance
  - DR estimation: sigmoid-Emax dose-response model with population ED50
- Target dose selection
  - Use a Bayesian definition for the minimum effective dose (MED) – smallest dose producing a clinically relevant improvement Δ (60) over placebo, with (posterior) probability of at least p% (70%)

Results

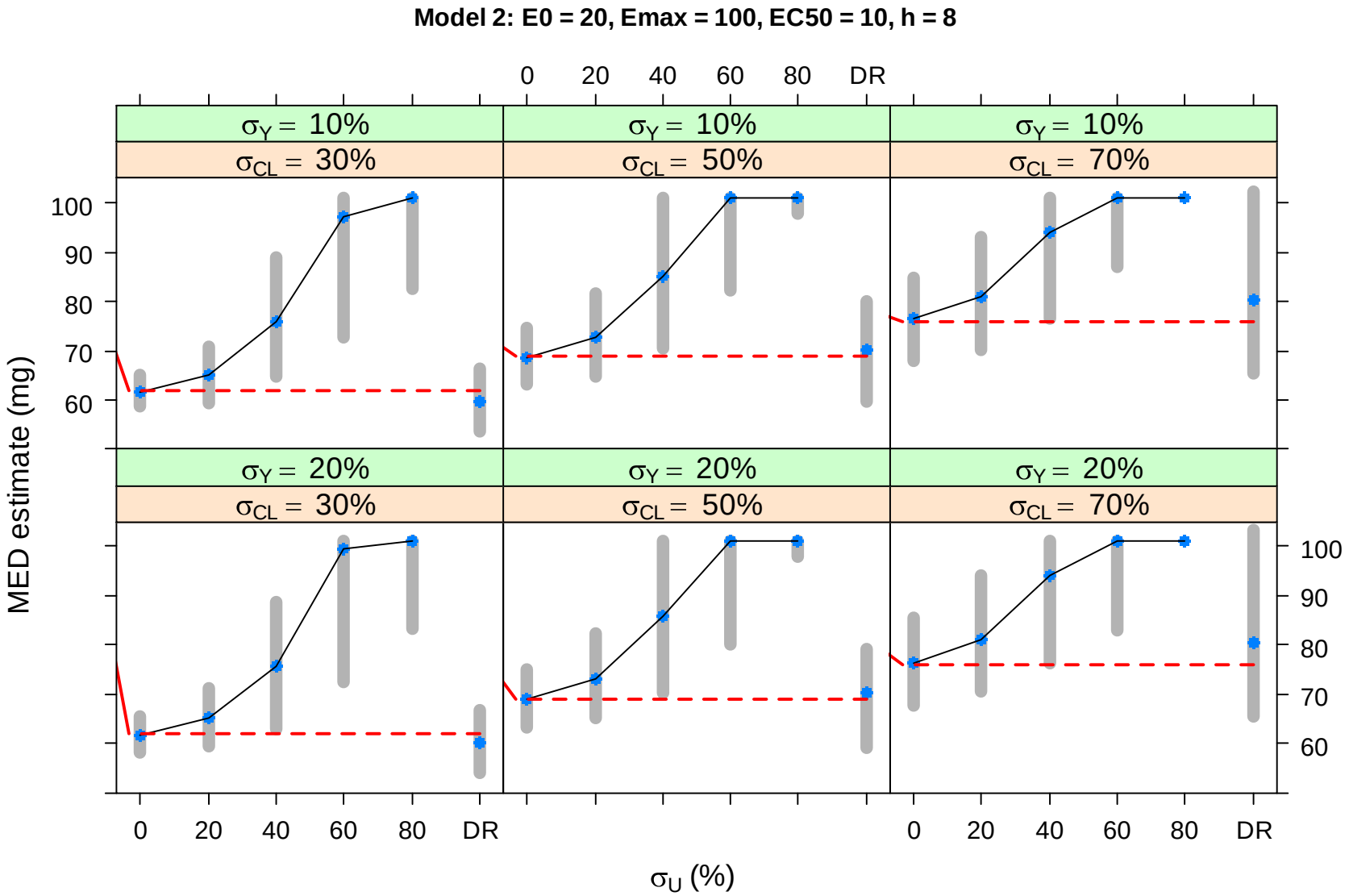
MED estimation – Model 1



MED estimation – Model 1



MED estimation – Model 2



Note: estimates truncated at 101 mg (if > 100 mg)

MED Performance of ER vs. DR – models 1 & II

- Under 0% PK measurement error, ER provides substantial gains over DR - smaller bias (≈ 0 for ER) and variability.
- MED estimation performance of ER deteriorates as σ_U increases: up to 20%, still superior to DR, but same, or worse for $\sigma_U = 40\%$; DR better than ER for $\sigma_U > 40\%$.
- Performance of DR worsens with increase in σ_{CL} - dose decreases its predictive power for the response.
- Bias of ER MED estimate decreases with σ_{CL} from 30% to 50%, but increases (and changes sign) from 50% to 70%. Its variation is not much affected.
- ER and DR MED estimates variability ↑ with σ_Y, but not by much
- Model 2: estimation features magnified: ER performance worsens more dramatically with σ_U, DR deterioration with σ_{CL} also more severe. ER only competitive with DR $\sigma_U \leq 20\%$

Conclusions

Conclusions

- Relative performance of two approaches highly depends on:
  - intrinsic PK variability (σ_{CL})
  - accuracy of the exposure measurements (i.e., the measurement error, σ_U)
- ER modeling for dose selection and DR estimation can produce substantial gains in performance compared to DR modeling
- Advantage of ER over DR increases with intrinsic PK variability, if observed exposure is reasonably accurate
- As PK measurement error increases, DR becomes preferable to ER, especially for dose selection.
- Performance driver of ER modeling σ_U can be improved via better technology (e.g., PK models, bioassays), while σ_{CL}, which dominates DR performance, is dictated by nature
- Impact of model uncertainty also to be investigated to extend results presented here. Extensions of MCP-Mod (DR-based) to ER modeling could be considered.

- Acknowledgements
  - William Gillespie
  - Amit Roy
  - Ashish Sanil

- Reference

- Bretz F, Pinheiro J, Branson M. (2005). Combining multiple comparisons and modeling techniques in dose-response studies. *Biometrics*. 61, 738-748
- Hsu, Chyi-Hung.(2009) "Evaluating Potential Benefits of Dose–exposure–response Modeling for Dose Finding." *Pharmaceutical Statistics* 8, no. 3: 203–15

Thank you

Simulation study

- MED estimation:
  - clinically relevant difference: $\Delta = 60$
  - posterior probability threshold: $p = 0.7$
  - Estimates truncated at 101 mg (if > 100 mg)
- True MED values: depend on model and σ_{CL}

	σ_{CL}		
Model	30%	50%	70%
1	33	36	40
2	62	69	76
3	66	74	82
4	72	80	89

- Non-informative priors for all parameters in Bayesian modeling
- 1,000 simulations used for each of 120 scenarios
- Bayesian estimation using MCMC algorithm OpenBUGS 3.0.2 (linux cluster)

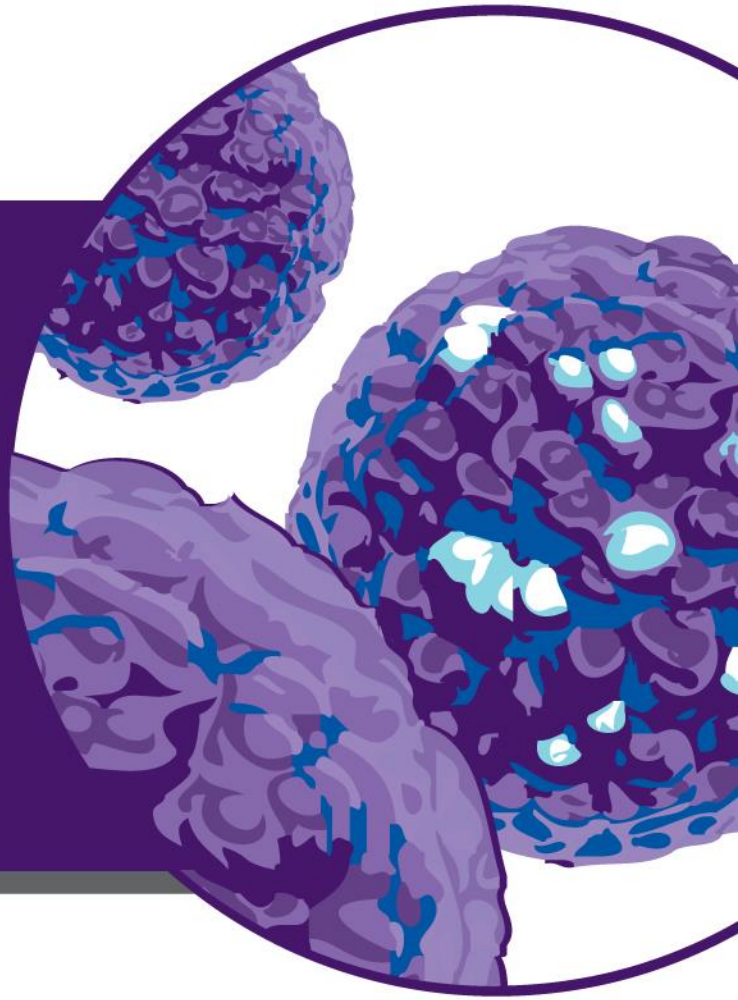
American Association for Cancer Research

FINDING CURES TOGETHER℠

Break

9:35 – 9:50 am

Model Based Decision Making in Oncology Dose Selection and Study Design



Diane Wang, Ph.D
Pfizer, Inc

Oncology
A Pfizer Research Unit

Oncology Dosing Paradigm

- MTD determined in Ph 1 and used as the RP2D
- It is rare for Ph 2 studies of oncology drugs to evaluate more than one dose, although this approach is common in other therapeutic areas
  - Exposure-responses are rarely well defined – No dose optimization
  - Inter-patient variability in efficacy/safety is not adequately evaluated
  - Long term cumulative toxicity is not adequately addressed due to short life expectancy of patients compared to Ph3 or intended patient population
  - Higher failure rate of Ph 3 trials
- Many recently approved oncology drugs are labeled for use at doses that may not be optimal (Sachs et al. Clin Cancer Res. 22(6): 1316-24, 2016).

Optimizing Dosing of Oncology Drugs/Conference on Clinical Cancer Research: Schilsky et al, Clinical Cancer Research, Nov 2013

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Challenges in Optimizing Dosing of Oncology Drugs

- Lack of PD markers to guide dose selection for solid tumors
  - Accessibility to tumor tissues
  - Availability of measurable PD markers
  - Assay with adequate accuracy and precision
  - PD marker stability – require fresh tissues
  - Correlation between PD marker and efficacy endpoint
    - Target modulation vs. PFS, OS

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Challenges in Optimizing Dosing of Oncology Drugs

- Need for development of new drugs quickly often takes precedence over the need to find the “right” dose
  - Unmet medical need and competitive landscape
  - Longer time to efficacy endpoint readout and slow patient enrollment
- Cost
- MTD approach was designed for cytotoxic chemotherapy while for new targeted agents, the “optimal biologic dose” might be more relevant
- A comprehensive strategy is needed for drug development that includes dose optimization but does not unnecessarily delay market entry for potentially important new drugs

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Strategy to Guide Optimal Dosing Selection for Targeted Therapies

- No ideal one-size-fits-all approach to dose selection
- One alternative approach recommended has been to define a biologically effective dose using an “effect” marker
- Effect markers could be pharmacodynamic, target engagement or disease progression marker (e.g. tumor size change)
- Recent examples of these approaches include small and large molecules such as cetuximab, idelasib, pembrolizumab and vismodegib

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Sachs et al. Clin Cancer Res. 22(6): 1316-24, 2016

Model Based Dose Selection and Study Design

- Case 1 - Dose selection for a small molecular inhibitor
  - Biomarker modulation
  - Dose/Exposure (PK) and potential DDI
  - Safety
  - Efficacy
- Case 2 – Modified MTD/RP2D determination for a combination therapy (target therapy + chemo)
  - Evaluation of overlapping toxicity by simulation
  - Modified MTD/RP2D determination by introducing Granulocyte-colony stimulating factor (G-CSF) use during MTD determination and exploring alternative dosing schedules

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Case 1 - PF-X Evaluation in Phase 1

- PF-X is a small molecule inhibitor currently in Phase 2 development
- Evaluated in hematologic and solid tumor patientss in Phase 1 studies
- First-In-Patient (FIP) study in advanced hematologic malignancies (AML, MDS, MF, CML) over a dose range of 5-600 mg QD
- Exhibited linear pharmacokinetics over the dose range tested. Primarily metabolized by CYP3A4/5
- Signs of clinical activity were observed in 23/47 subjects across different indications and a wide dose range (10-600 mg QD)
- Protocol defined DLT criteria were not met; 400 mg QD was considered to be the MTD due to a safety finding noted at 600 mg QD

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PF-X Evaluation in Phase 1 (continued)

- Skin punch biopsies were collected from 26 patients in three clinical trials (hematologic and solid tumor studies; dose range: 25-640 mg)
  - at baseline and at steady state to measure biomarker expression
- Quantitative real-time polymerase chain reaction used to measure expression of a transcription factor, which is a marker for pathway activation/signaling
- Inhibition of signaling results in biomarker remaining inactive and prevents expression of genes that mediate tumor growth
- Modulation of biomarker gene expression (PD) vs. dose/exposure (PK) of PF-X evaluated
- Integrated assessment of PK, PD, safety and efficacy used to hone in on the clinical dose for further evaluation

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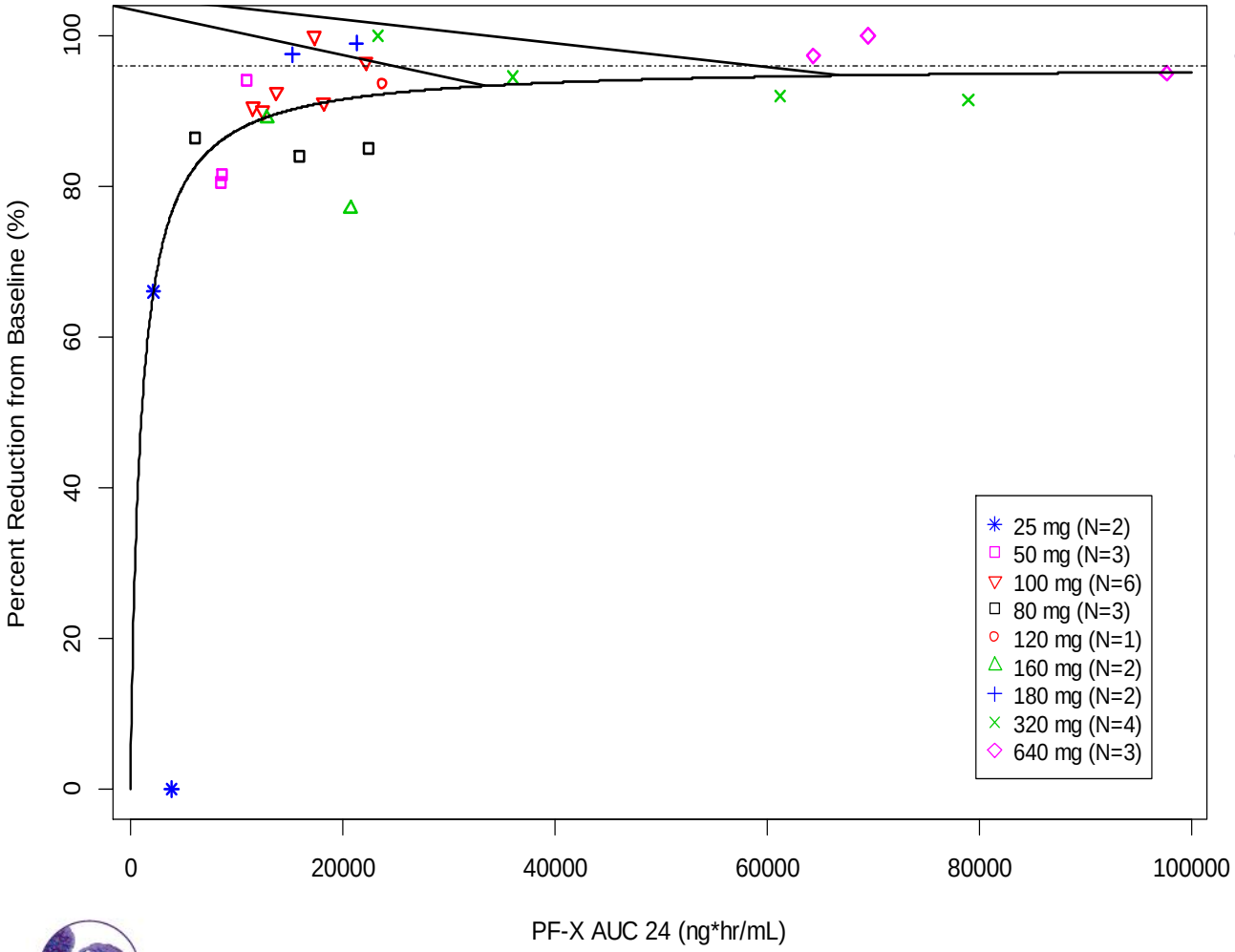
Dose Selection : Change from Baseline of Biomarker vs. Steady State Exposure



- Similar level of pathway modulation at doses ≥ 100 mg QD
- No advantage from pathway modulation perspective to going higher in dose
- Correlation between pathway modulation and efficacy endpoint not established but used for dose selection of other compounds in the same class

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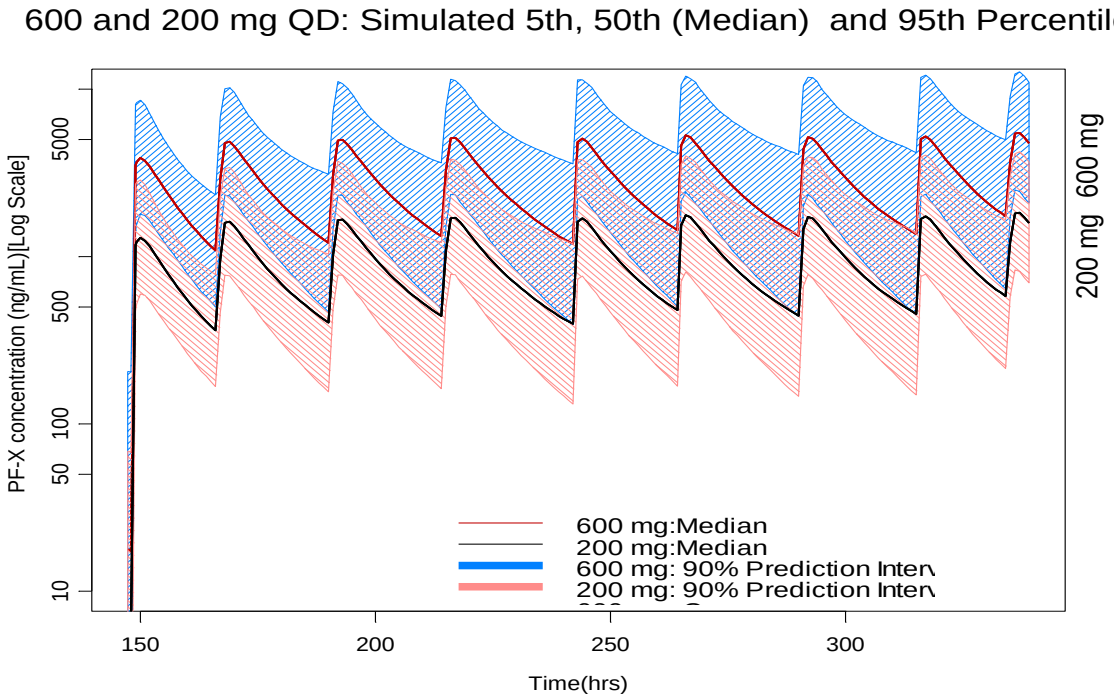
Simulated Steady State Exposures – 200 mg



- Significant overlapping in exposure at the 200 mg dose vs. 600 mg.
- A strong CYP3A4 inhibitor (ketoconazole) increased PF-X mean AUC by 2.4-fold and mean C_{max} by 1.4-fold
- Use of anti-fungal azoles is clinically necessary to manage patients with hematological malignancies. Therefore, not possible to prohibit.

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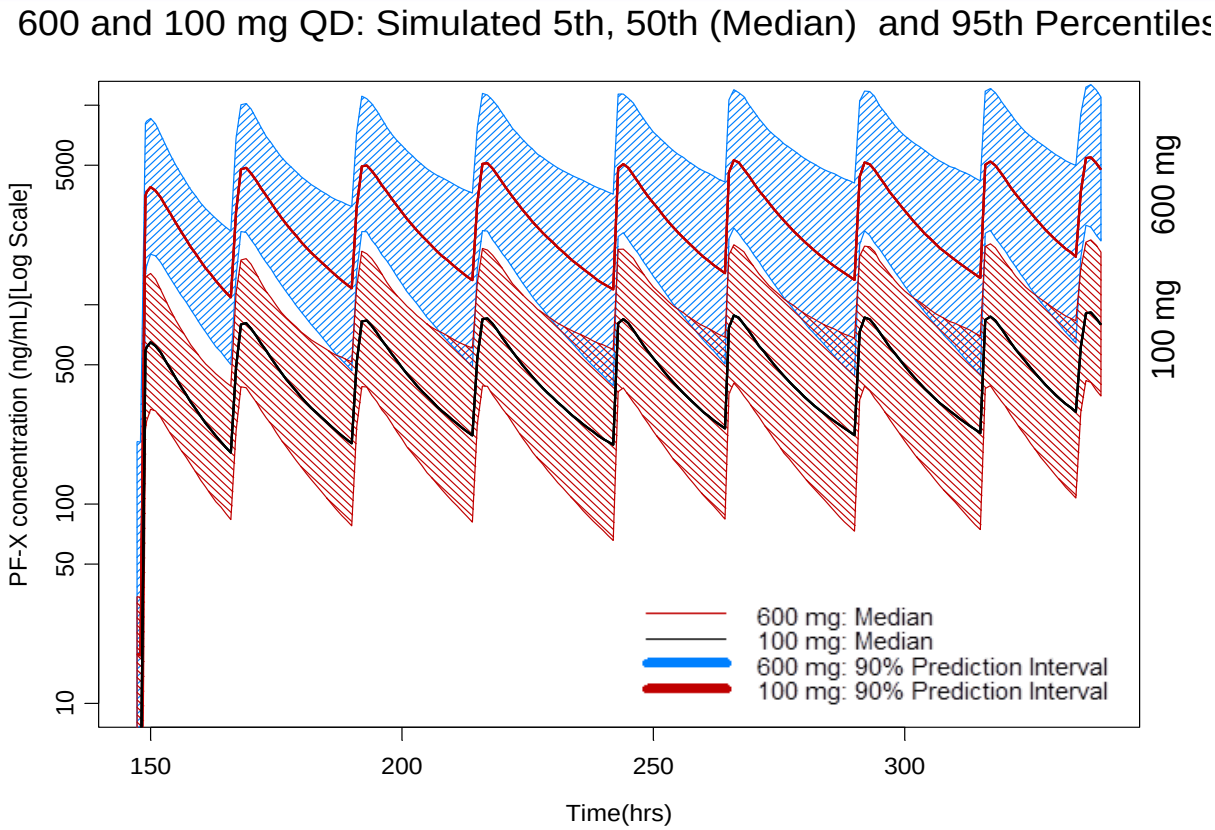
Simulated Steady State Exposures – 100 mg



- No overlapping in Cmax which is the driver for the safety signal between 100 mg and 600 mg
- Minimal overlapping in Cmax expected between 100 mg and 600 mg considering potential DDI with azoles

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PF-X Phase 2 Dose Selection

- 100 mg dose was selected for further evaluations in Ph 2 clinical trials based on
  - Similar down-regulation of pathway activation marker at ≥ 100 mg
  - Observation of clinical activity across a wide range of doses in the FIP study
  - Exposure level and DDI potential on co-administration with a CYP3A4 inhibitor (such as clinically necessary azoles in AML/MDS) in relation to the exposure range that had safety signals
  - Better safety/tolerability profile of PF-X at lower doses

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Case 2 - Model aided Study Design for MTD/RP2D Determination

- Drug A (300 mg) was approved for the treatment of solid tumor X
- Drug B was in phase 1 clinical trial as monotherapy and 50 mg was identified as the MTD
- Pre-clinical model showed synergistic effect in solid tumor X when Drug B is given in combination with Drug A
- A Phase 1B clinical trial is designed to evaluate the safety, PK, and early sign of efficacy in patients with solid tumor X
- No available markers of target modulation for dose selection
- MTD approach will be used for RP2D

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Challenge for the combined therapy of Drug A and B

- Neutropenia toxicity was shown to be one of the major side effects for both Drug A and Drug B in their respective clinical trials

- A combined therapy of Drug A and Drug B may manifest enhanced neutropenia toxicity, and limit the MTD doses for the two agents, and thus lead to sub-optimal efficacy for the combined therapy

- Prediction of the potential neutropenia toxicity of the combined therapy may help a better study design and neutropenia management

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PK/PD Model for Predicting Neutrophil Profile for the Combined Therapy of Drug A and Drug B in Solid Tumor X

- Drug A neutrophil effect follows the established PK-neutrophil relationship when dosed alone (literature data)
- Drug B neutrophil effect follows the established PK-neutrophil relationship when dosed alone in phase 1 clinical trial
- Assume additive effect of Drug A and Drug B on neutrophil reduction (synergistic effect could have more profound combined effect):

$$EFFECT = 1 - E_{max,A} \cdot C_A/(C_A + EC_{50,A}) - E_{max,B} \cdot C_B/(C_p + EC_{50,B})$$

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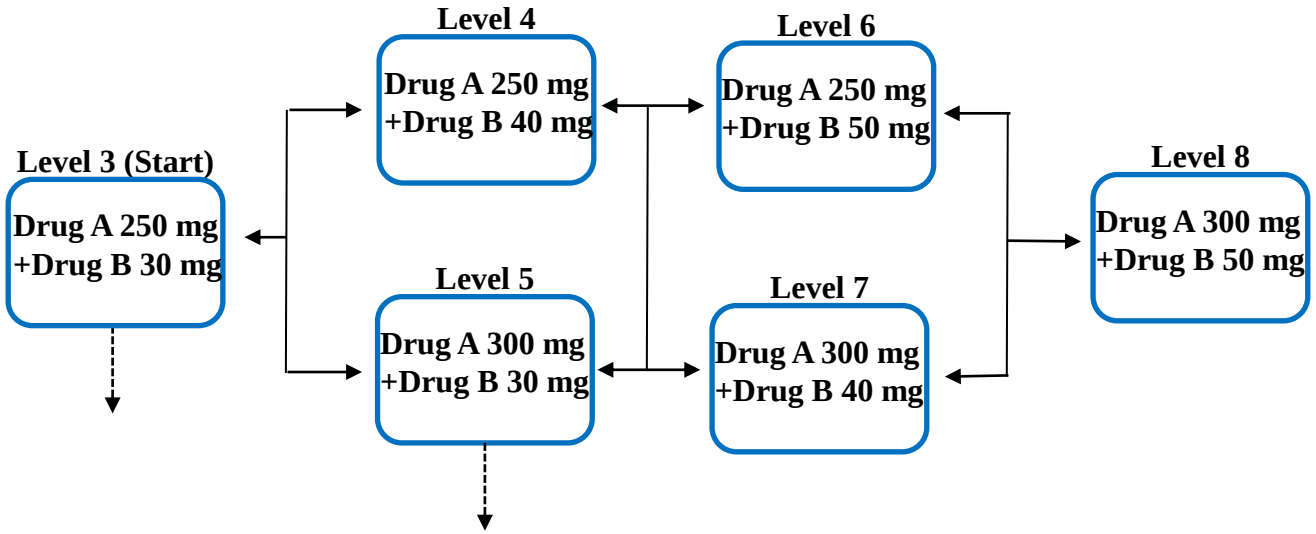
Drug A and B Combination Therapy Dose Escalation Scheme



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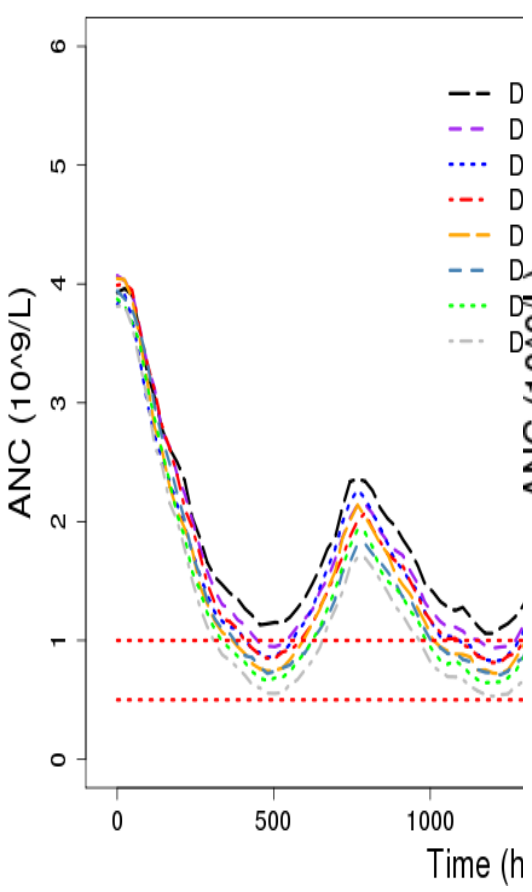
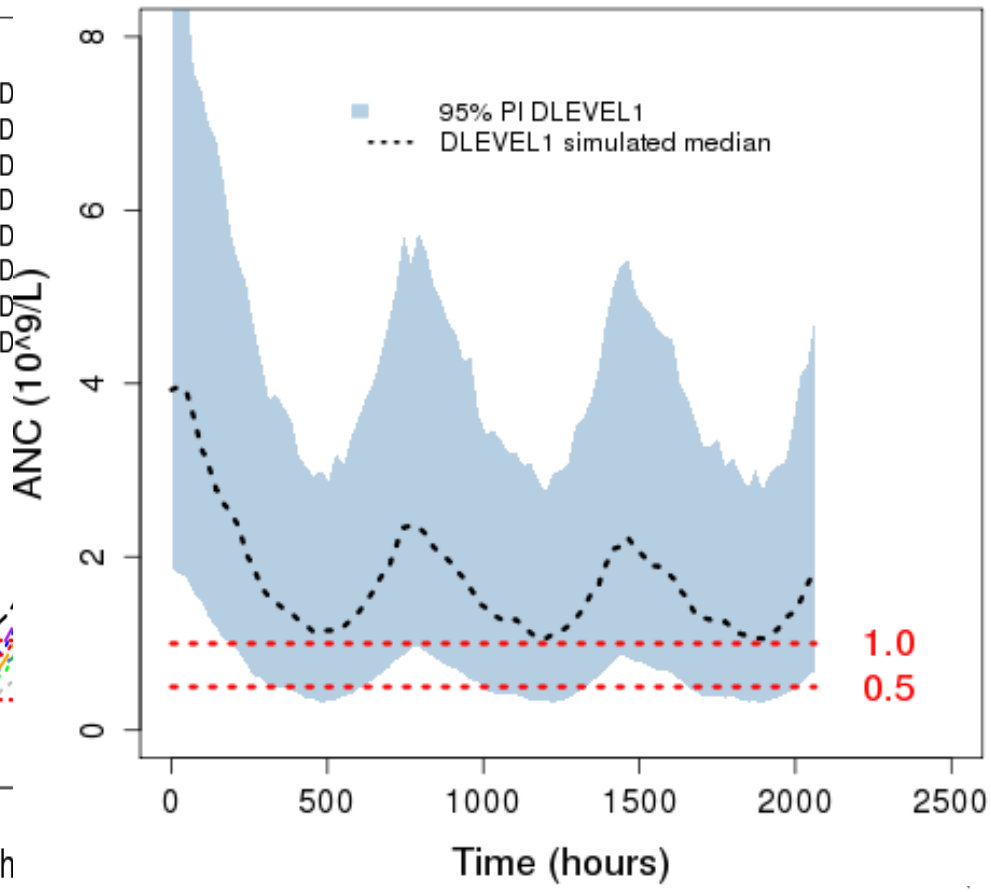
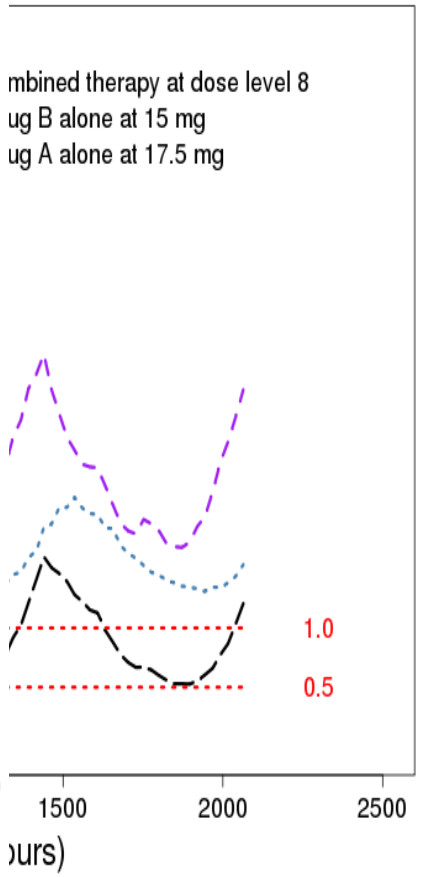
Predicted Neutrophil Profiles of the Combination Therapy at Each Dose Level







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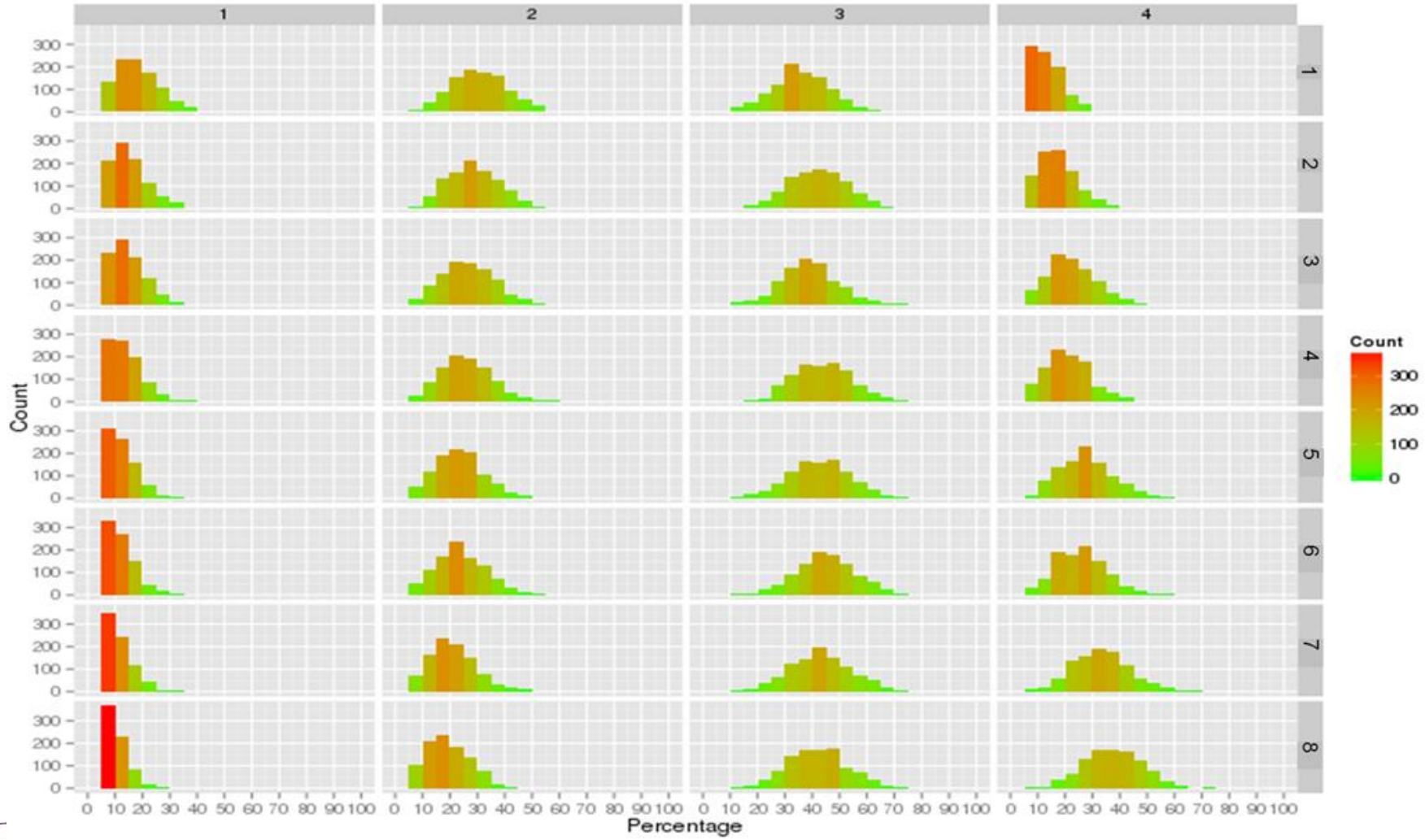
ANC=Absolute neutrophil count.
DLEVEL=dose level.

Predicted Probability of Neutropenia Incidence at Each Grade across Dose Levels



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Predicted Median Percentage (90% CI) of Patients in Each Neutropenia Grade across Dose Levels

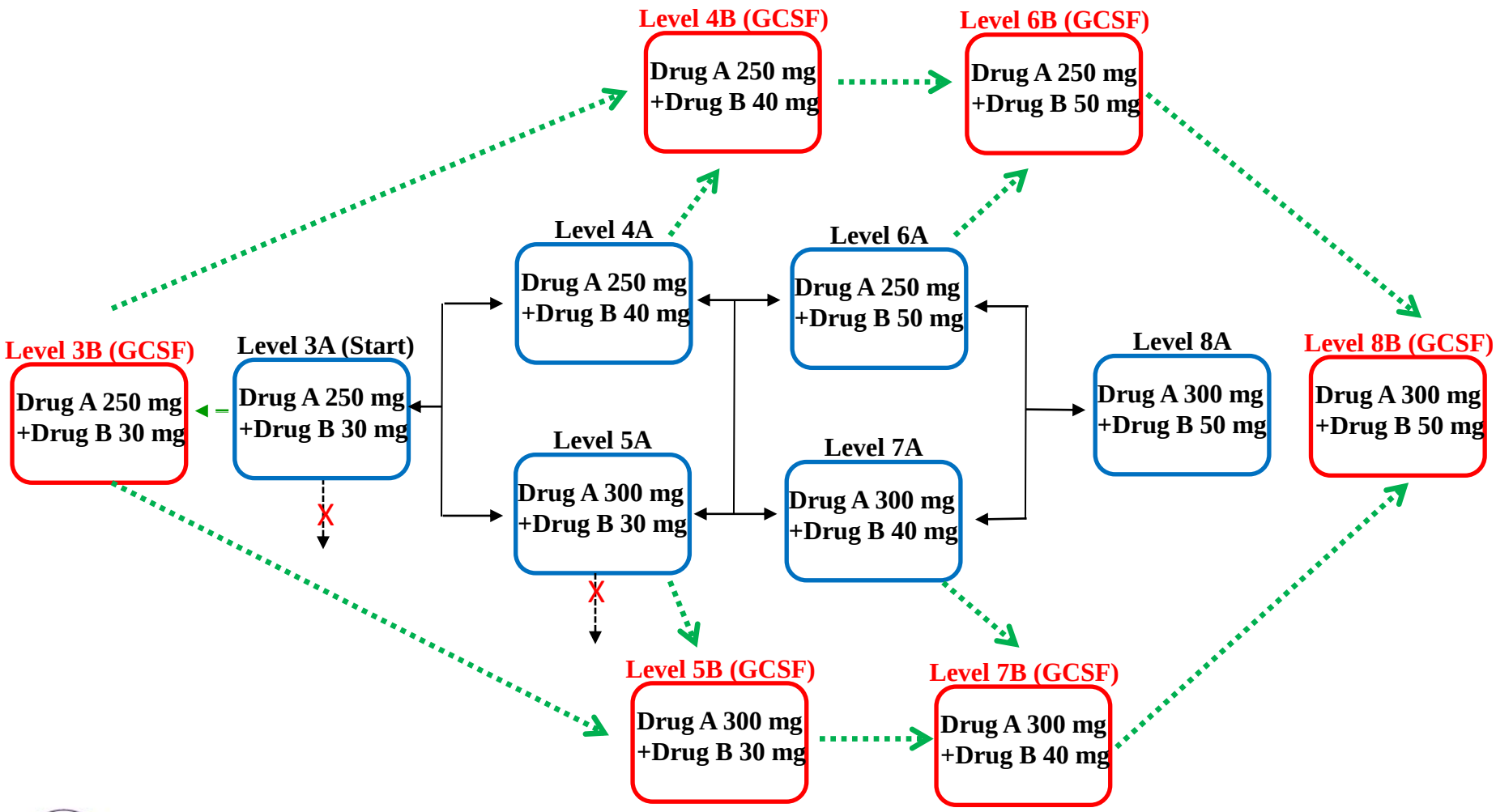
Dose level	Drug A (PO, mg)	Drug B (PO, mg)	Grade 1	Grade 2	Grade 3	Grade 4	≥ Grade 3
1 (-2)	200	30	15 (5, 30)	30 (15, 45)	35 (15, 50)	10 (5, 20)	45 (25, 60)
2 (-1)	250	20	10 (5, 25)	25 (10, 45)	40 (20, 55)	15 (5, 30)	55 (30, 65)
3 (1)	250	30	10 (5, 25)	25 (10, 40)	35 (20, 55)	20 (5, 35)	55 (30, 65)
4 (2A)	250	40	10 (5, 25)	25 (10, 40)	40 (25, 60)	20 (5, 35)	60 (35, 70)
5 (2B)	300	30	10 (5, 20)	20 (5, 35)	40 (20, 60)	25 (10, 40)	65 (35, 75)
6 (3A)	250	50	10 (5, 20)	20 (5, 35)	40 (25, 60)	25 (10, 40)	65 (35, 75)
7 (3B)	300	40	10 (5, 20)	20 (5, 35)	40 (20, 60)	30 (15, 50)	70 (40, 85)
8 (4)	300	50	5 (5, 15)	15 (5, 30)	40 (20, 60)	35 (20, 55)	75 (45, 95)

Grade 1 ANC < 2•10^9/L; Grade 2 ANC < 1.5•10^9/L; Grade 3 ANC < 1.0•10^9/L; Grade 4 ANC < 0.5•10^9/L. The same subject can be counted in the different grade per dose level.

Data presented as median values (5th percentile, 95th percentile) of percentage of patients in each grade across 1000 simulations.

300 mg is the approved drug A clinical dose against NSCLC; 50 mg is the MTD of drug B in phase 1 clinical trail.

Drug A and B Combination Therapy Dose Escalation Strategy



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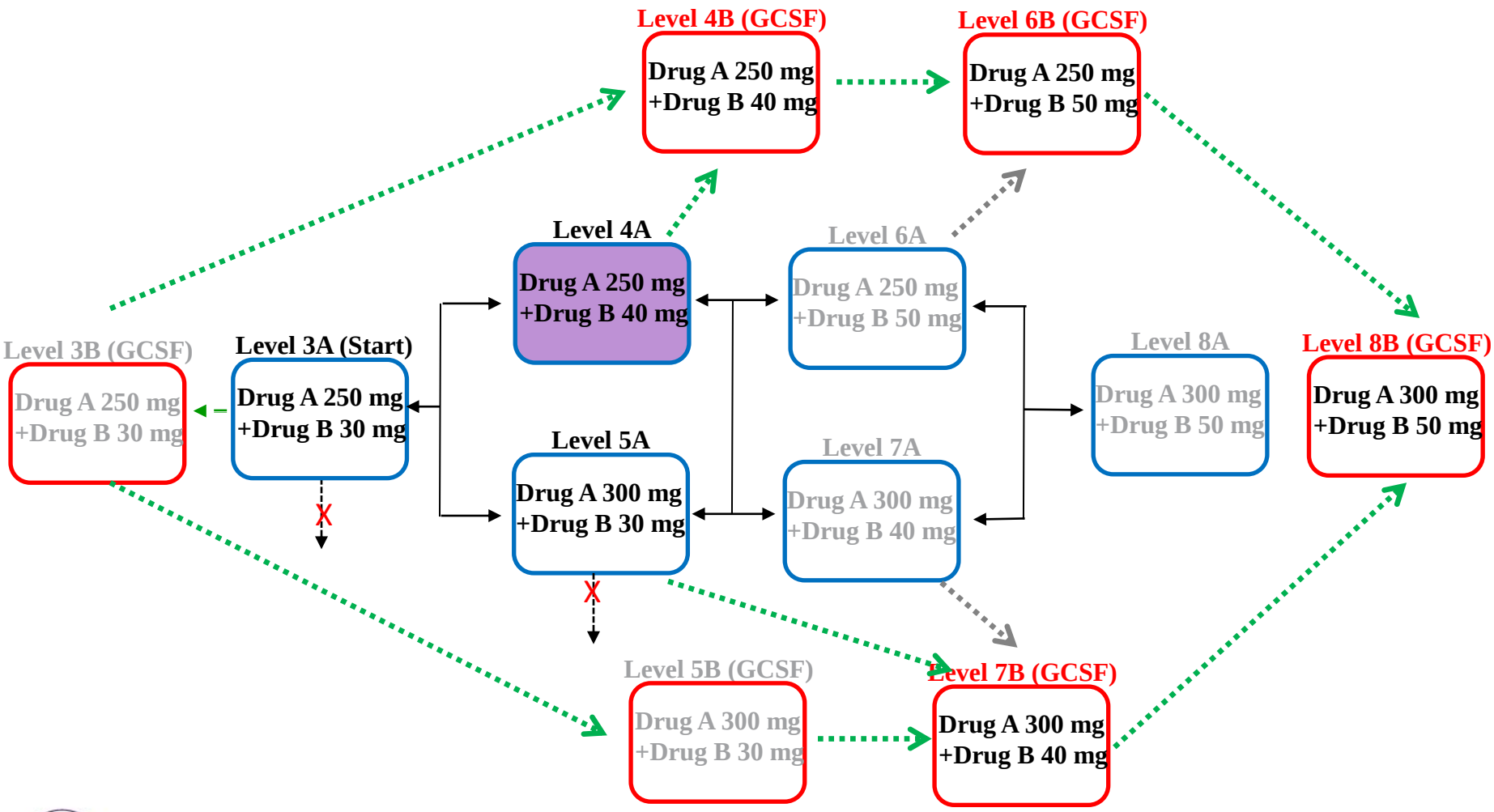
Green dotted arrows happen if more than 66% subjects had > Grade 3 neutropenia in the dose level

Drug A and B Combination Therapy Dose Escalation Strategy (Example)



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Green dotted arrows happen if more than 66% subjects had > Grade 3 neutropenia in the dose level

Summary

- Prediction of the probability of neutropenia grade percentage at each dose level was conducted assuming additive effect of Drug A and Drug B on neutropenia
- At the starting dose level, the predicted median percentage of patients who may have grade 3 and 4 neutropenia is projected to be around 55%.
- The predicted median percentage of patients who may have grade 3 and 4 neutropenia is 45%, 55%, 55%, 60%, 65%, 65%, 70% and 75%, respectively, for the increasing dose levels from Dose Level 1 to 8.
- There's high possibility that dose reduction will occur in majority of patients at lower dose levels before reaching the MTD of the combined Drug A and Drug B therapy

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Summary (continued)

- Introducing secondary prophylaxis G-CSF use before dose reduction in DLT evaluation period as a mitigation strategy for neutropenia management to maximize the potential efficacy of the Drug A and Drug B combination therapy, the DLT evaluation period will be extended to 2 cycles for G-CSF dose escalation cohorts
- Other alternative dosing schedules are also being explored to mitigate neutropenia without G-CSF use

Overall, modeling and simulation is a useful tool in dose selection and more informed study design

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Acknowledgement

- Naveed Shaik
- Yanke Yu
- Kourosh Parivar

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American Association for Cancer Research

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Gabriel Helmlinger's slides have been withheld from this presentation.

Session I

Panel Discussion

Exposure-Response Relationships and Modeling/Simulation for Dose Finding

Chair: Geoffrey Kim, MD

Speakers:

Dinesh De Alwis, PhD
Shruti Agrawal, PhD
Chyi-Hung Hsu, PhD
Diane Wang, PhD
Gabriel Helmlinger, MD, PhD

Panelists:

Kelvin Dickenson
Jin Jin, PhD
Sumithra Mandrekar, PhD
Lillian Siu, MD
Yaning Wang, PhD

American Association for Cancer Research

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Lunch Break
11:50 am – 12:50 pm

American Association for Cancer Research

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Session II

Non-Clinical Models Used for Go/No-Go Decisions

Chair: Todd Palmby, PhD

Speakers:

Darren Cross, PhD

Chandni Valiathan, PhD

Alan Korman, PhD

Juliet Williams, PhD

Panelists:

Hans Loland

Thomas Jaki, PhD

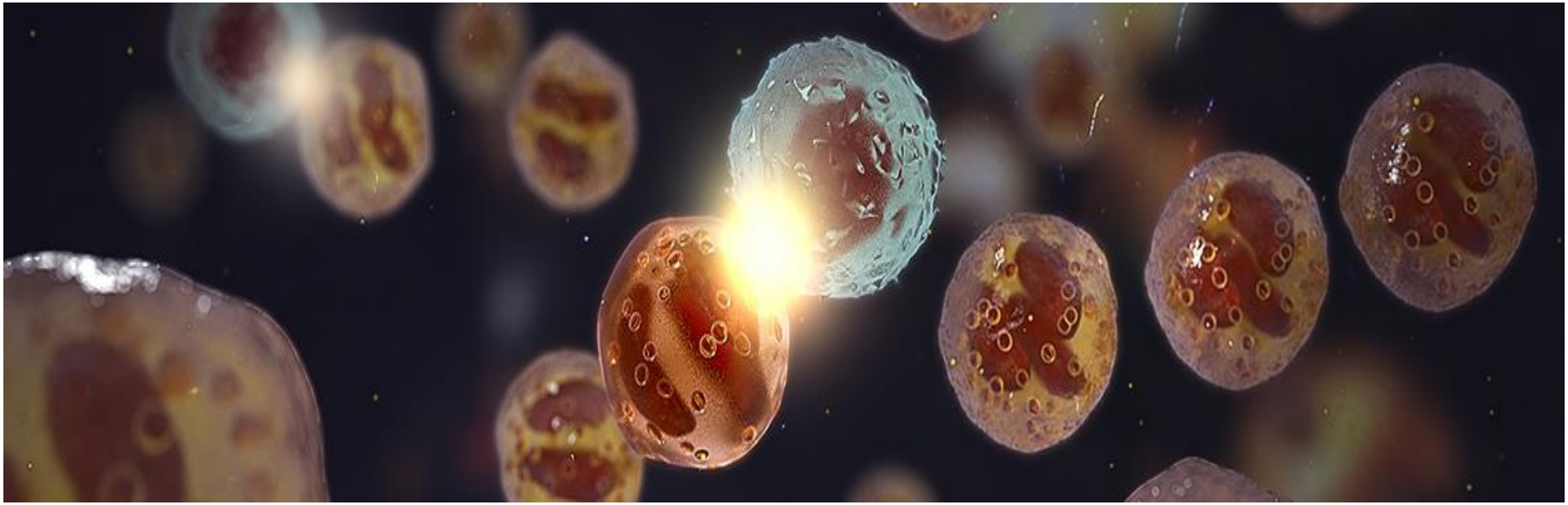
Mark Ratain, MD

Amit Roy, PhD

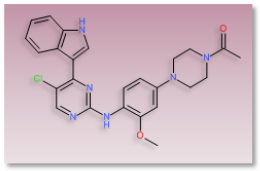
Karthick Vishwanathan, PhD

The journey of osimertinib discovery: from the lab to the clinic

Darren Cross, Principal Scientist, AstraZeneca

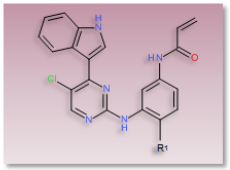


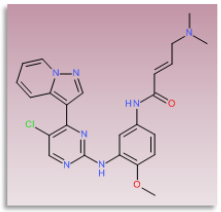
Non-clinical Development of Osimertinib



May 2009 ← Set of 40 compounds evaluated using a biochemical assay from a CRO (WT & DM)

Oct 2009 ← Cys-797 covalently targeted from novel template using the acrylamide functionality

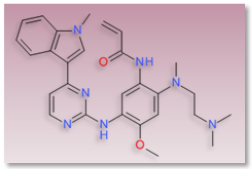




Lead optimisation transition → **January 2011**

AZD9291 first synthesised 9th June 2011

March 2012 ← AZD9291 selected as clinical candidate



March 2013 ← AZD9291 achieves FTIM

April 2014 ← AZD9291 granted Breakthrough Therapy designation by the U.S. FDA

AZD9291 (Tagrisso™) receives U.S. FDA approval → **Nov 2015**

Osimertinib (Tagrisso/AZD9291) discovery program progressed from initiation (2009) to first clinical dose (2013) in only 4 years

FTIM to US FDA approval ~2.5 years

Start to Approval in 6.5 years

- Speed of discovery phase was underpinned by key principles;
  - Specific chemistry design goals that were defined early (target & mechanism)
  - Exploitation of institution kinase expertise & innovative structure-based drug design for rapid identification and development of novel chemical equity
  - Robust non-clinical assay platform enabling rapid efficacy & mechanistic pharmacodynamic supportive data generation
  - Strong predictive modelling capability
- Purpose of today is to share some of these key aspects

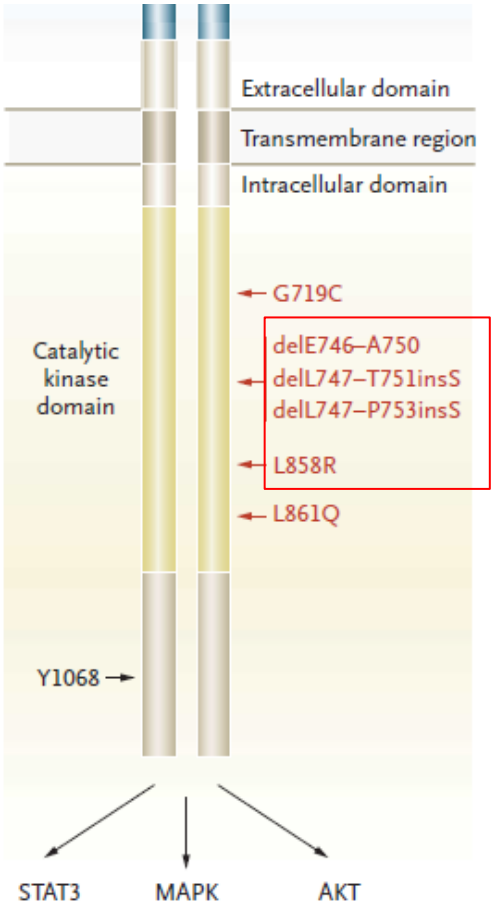
Background to EGFRmutant NSCLC

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

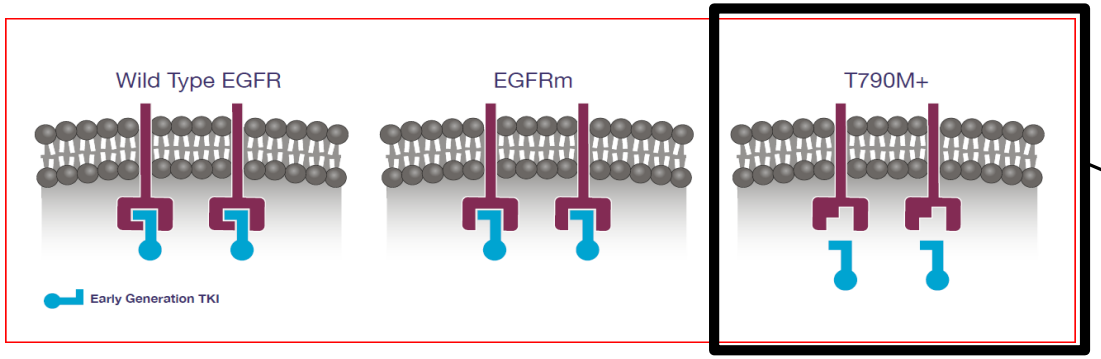


Common activating mutations

- Activating mutations in EGFR (EGFRm) were identified in subset of NSCLC
- EGFRm also sensitises tumours to inhibition by TKIs e.g. erlotinib, gefitinib, afatinib
- This lead to the approval of EGFR TKIs in EGFRm NSCLC
- However, despite high response rates and durable benefit, tumours ultimately relapse due to acquired resistance
- Gain of a second EGFR mutation, T790M, was identified as a prevalent escape mechanism in ~60% of cases

T790M was an area of high unmet need

Gefitinib, erlotinib, afatinib



Resistance mechanism

1st generation EGFR TKI's such as gefitinib are not potent against T790M

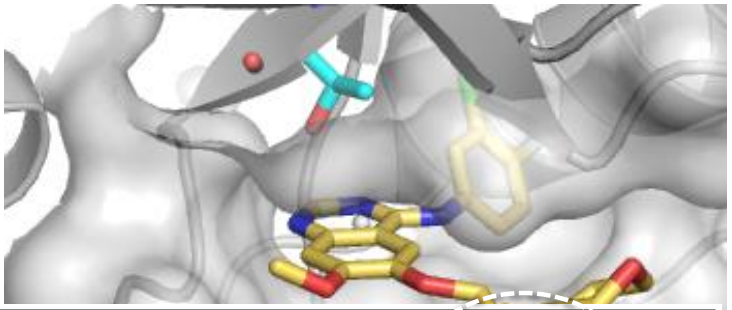
2nd generation irreversible EGFR inhibitors e.g. afatinib and dacomitinib were subsequently developed

- These compounds potently inhibit EGFRm
- They have increased activity towards T790M, but potent WT EGFR activity likely prevents reaching sufficient clinical exposures

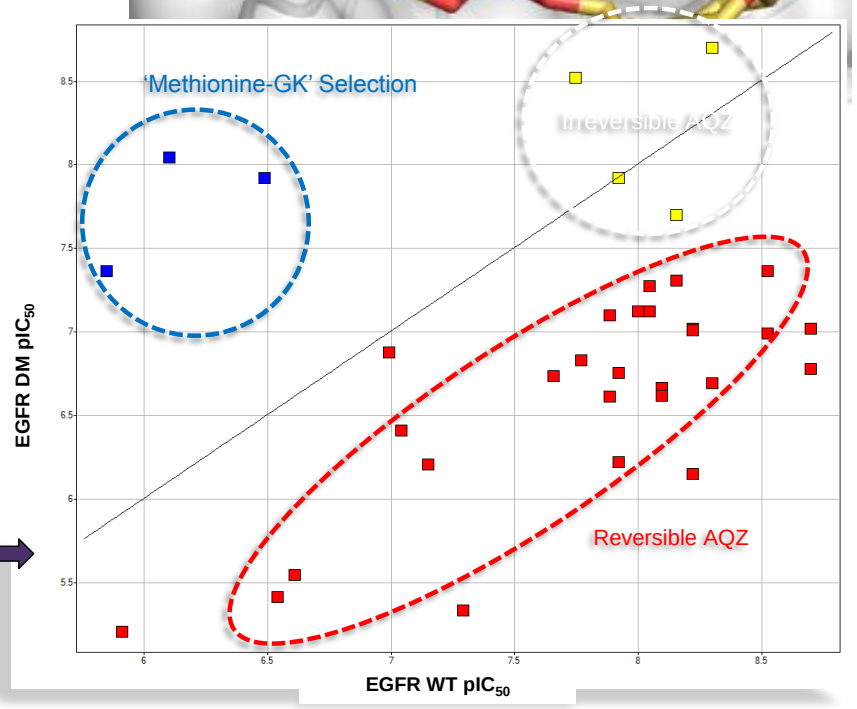
No approved therapies had existed to specifically address T790M acquired EGFR-TKI resistance

Mutant-Selective EGFR Inhibitor Hypothesis

- Specific design goal from outset (profile with activity against mutants and selectivity over WT)
- Specific mechanistic hypothesis (selection of compounds from AZ Projects targeting methionine gatekeepers[1])
- Rapid concept testing using commercial biochemical assays against focussed set of 40 compounds
- Enabled faster chemistry lead generation start vs higher throughput screening approaches



Generation	Activating Mutants (AM)	Double Mutant (DM)	Wild-Type (WT)
1st	Active	Inactive	Active
2nd	Highly Active	Active	Highly Active
3rd	Active	Active	Margin



1. Ward, R. A et al, J. Med. Chem. 2013, 56, 7025.

EGFRmutant Non-clinical Disease Cell Line Models

Clinical EGFR mutation	Cell line model
Exon 19 del	PC-9, H1650, HCC827, (HCC4006)*
L858R	H3255, (11-18)*
Ex19del/ T790M	PC-9VanR
L858R/ T790M	H1975
Wild-type EGFR	A431, H2073, LoVo

* Collaborator assays

Advantage

- EGFR cell line models importantly mimic relevant disease context (target/ pathway biology)
- Multiple models that can represent disease diversity (albeit limited for EGFRm)
- Models enable target validation (target/pathway inhibition, phenotype) and chemistry development/ SAR support
- Availability of well characterised assays with known compound sensitivity benchmarks was highly impactful to moving quickly

Disadvantage

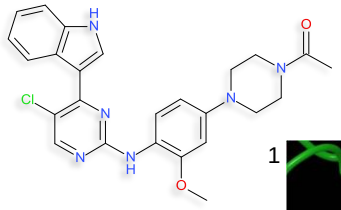
- Cell line models do not represent heterogeneity of tumours
- Models do not recapitulate more complex tumour biology e.g. stroma, immune-microenvironment

Developing mutant selective chemistry leads

- Mutant-selective examples identified based on a pyrimidine scaffold
- Molecular modelling deployed to optimally target Cys-797 by covalent mechanism
- Paired concept molecules with in vitro cell assay data quickly defined irreversible binding mechanism as key to design strategy

Compound	DM (μM, enzyme)	WT (μM, enzyme)	DM/WT Selectivity	DM (μM, cell)
1	0.009	0.79	88	0.77

Compound	DM (μM, enzyme)	AM (μM, cell)	DM (μM, cell)	WT (μM, cell)	DM/WT Selectivity	Log $D_{7.4}$
2	0.0063	0.029	0.022	0.55	25	>4.3



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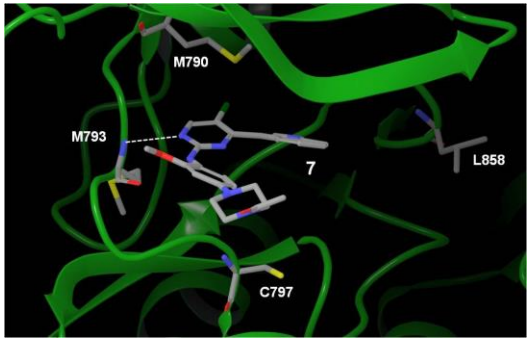
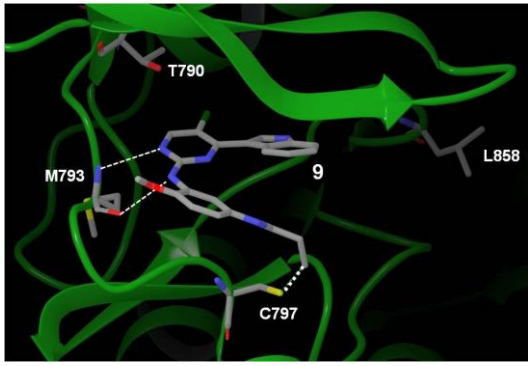
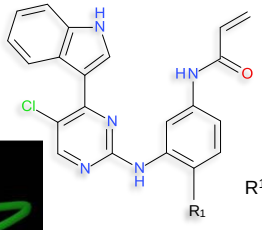
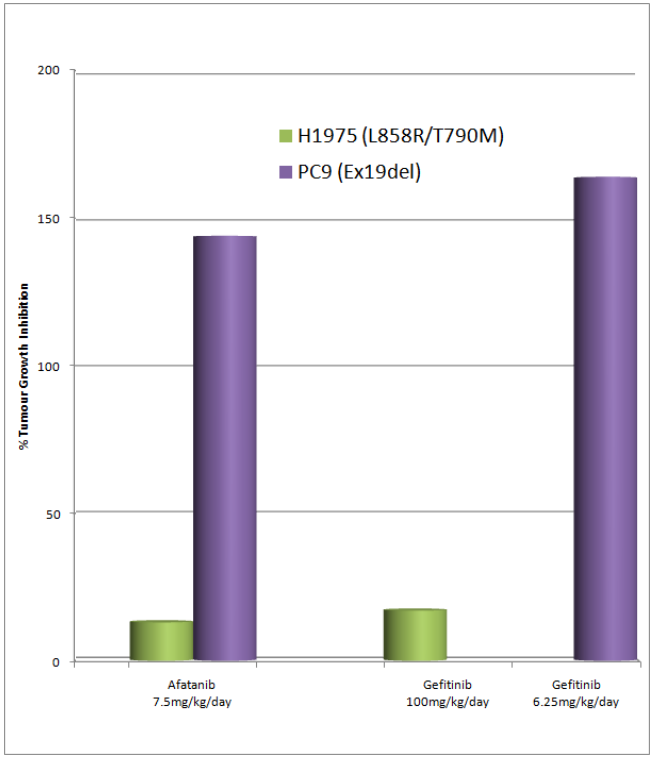






1. Ward, R. A et al, J. Med. Chem. 2013, 56, 7025.

Exploiting EGFRmutant Non-clinical Xenograft Disease Models In Vivo

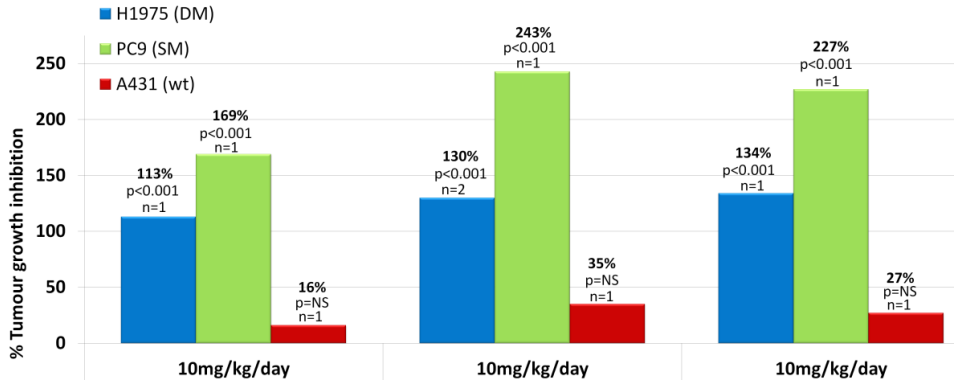


Advantage

- Xenograft enable rapid and amenable efficacy testing
- Provide platform for developing pharmacodynamic data and for building PK:PD:efficacy relationship
- Availability of well characterised and robust models was key factor in project acceleration

Disadvantage

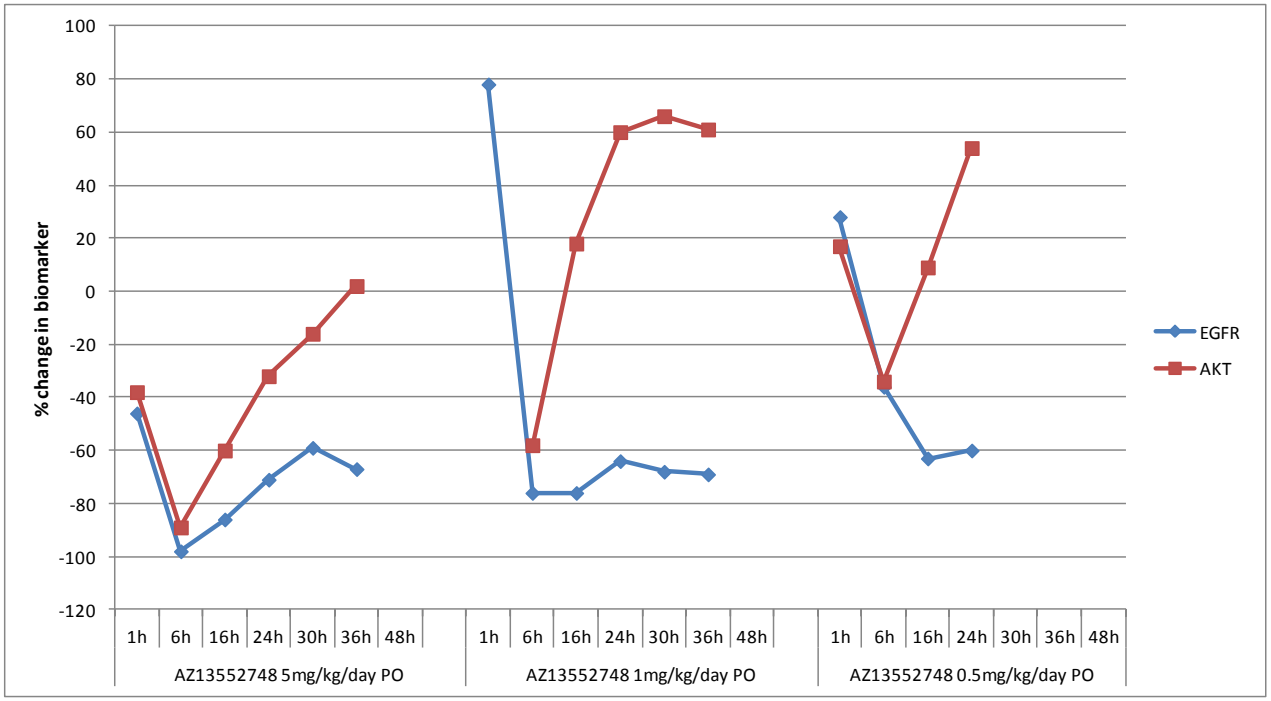
- Cannot be used to mimic more complex tumour biology
- More limited to investigation of cancer cell intrinsic mechanisms



profiling of lead candidates in vivo

Optimised testing to enable robust higher throughput compound testing (shortened to 7-day efficacy, decreased cohort size, streamlined cascade) across H1975, PC-9 and A431 (wt) models to rapidly drive lead optimisation and lead selection/ prioritisation, together with in vitro cell potency data for compound prioritisation

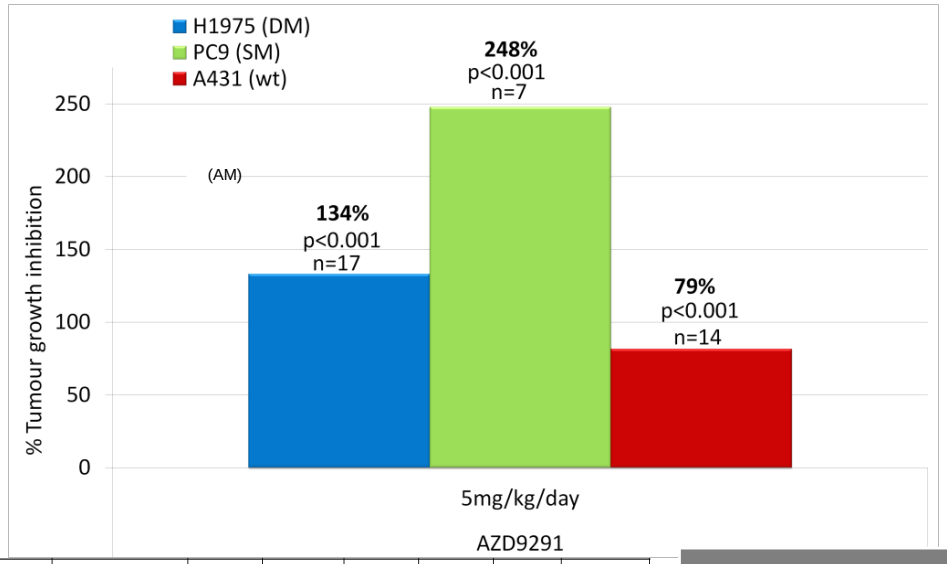
Pharmacodynamic Data to Support Mechanistic Validation and Defining Target Inhibition/ Efficacy Relationship

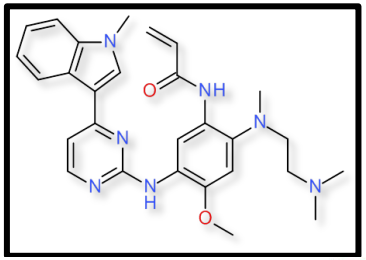


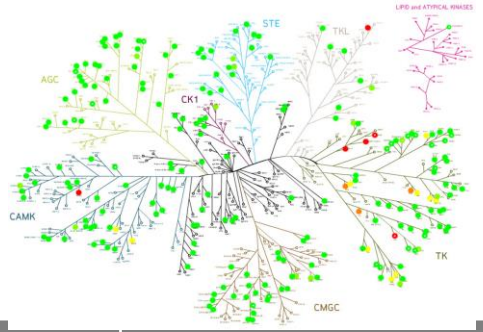
% change in phospho/total ratios for EGFR and Akt in response to osimertinib (AZ13552748) in H1975 xenograft model

- Xenografts enabled dose and time-course impact on pharmacodynamic endpoints to be established in vivo
- Phospho-EGFR and phospho-Akt measured (ELISA) to determine target and signalling impact
- Data used to build understanding of PK:PD requirements to aid lead selection
- Data also essential for dose to human modelling

Selection of osimertinib as drug candidate







	H1975 (L858R/T790M)	PC-9 VanR (ex19del/T790M)	PC-9 (ex19del)	H3255 (L858R)	H1650 (ex19del)	LoVo (WT)	A431 (WT)	NCI-H2073 (WT)
AZD9291	15	6	17	54	13	480	1684	1865
Dacomitinib	40	6	0.7	1.3	0.05	12	34	26
Afatinib	22	3	0.6	1	1.2	14	33	25
Gefitinib	3102	741	7	12	18	59	73	61
Erlotinib	6073	1262	6	10	6	84	252	108

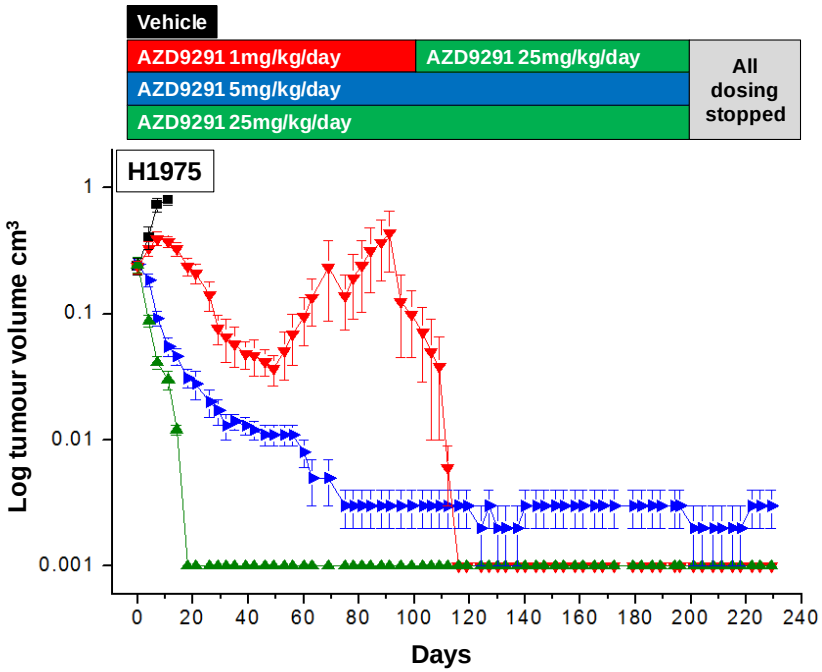
IC50 vs phospho-EGFR; nM

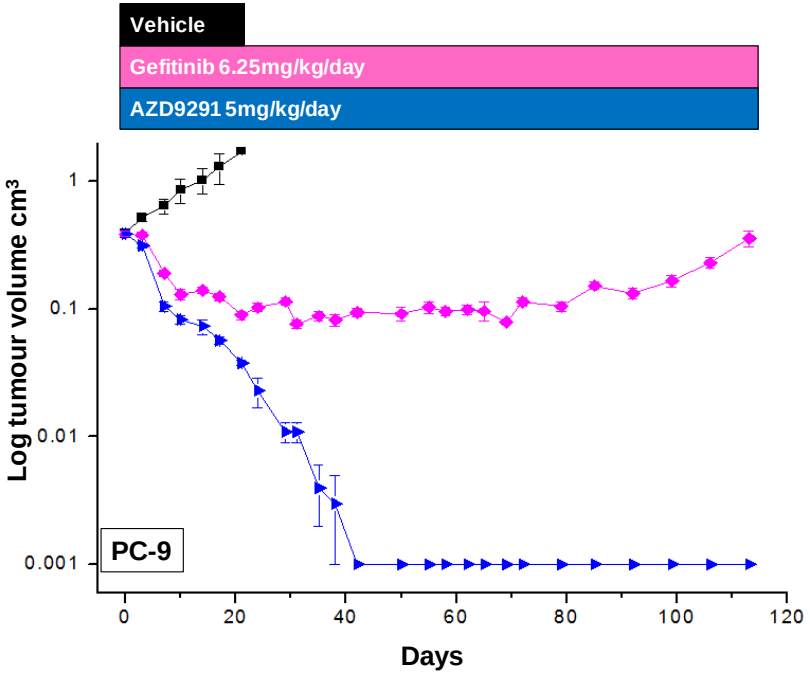
	AZD9291
Cellular Activity (H1975 / PC9 / A431) *(DM vs WT Selectivity)*	0.015 / 0.017 / 0.48 μM *(32-fold)*
IGF1R (biochemical)	2.9 μM
hERG IC_{50} (Ionworks)	16 μM
Aq. Solubility (mesylate salt, pH=6.8, μg/mL)	>490
Predicted dose to Man	17-90mg (PC9) 7-38mg (H1975)
Predicted maximum absorbable dose	207 mg

Cross et al. (2014) Cancer Discovery, 4, 1046-1061

Finlay et al.J. Med. Chem. 57, 8249 - 8267 (2014)

Osimertinib Demonstrates Profound Efficacy in Xenograft Models

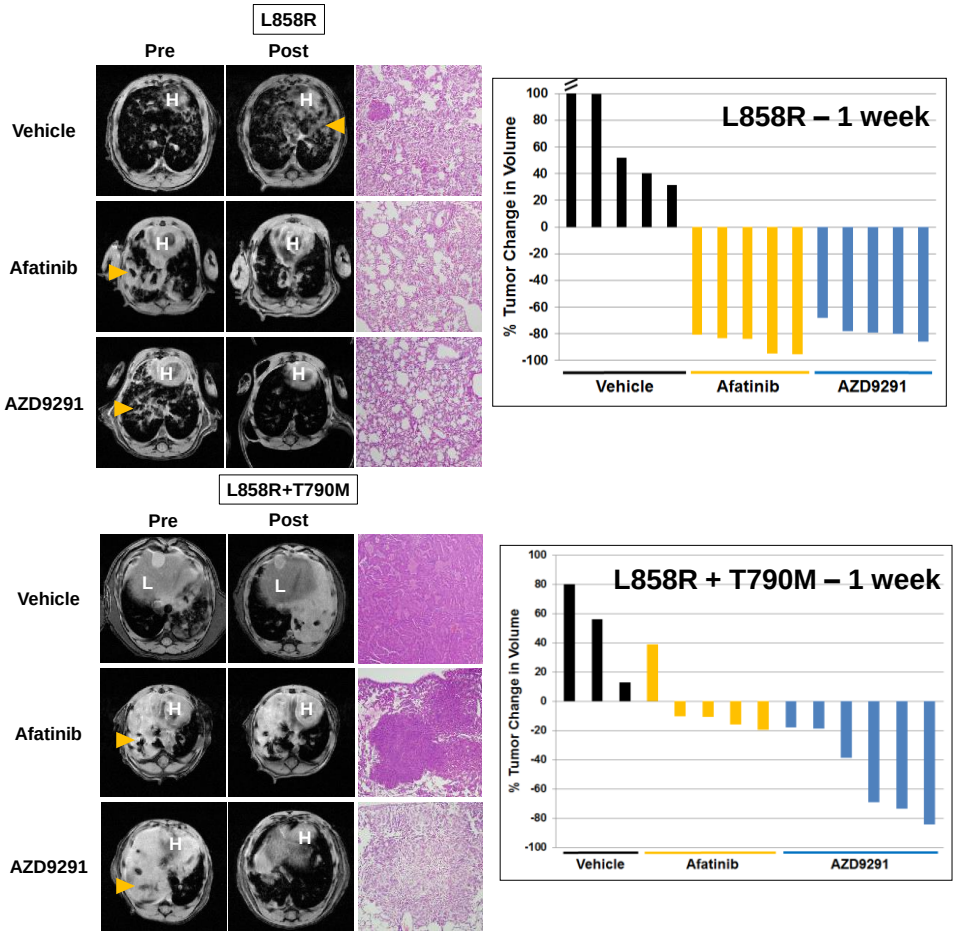




- AZD9291 causes complete and sustained tumour response at low doses
- Compound is chronically tolerated in murine studies
- Long term dosing experiments increased confidence in target hypothesis and drug

Cross et al. (2014) Cancer Discovery, 4, 1046-1061

Transgenic Genetic Engineered Mouse (GEM) Models Provide Valuable Model Platform



(William Pao collaboration, Vanderbilt)

Advantage

- Reproduce human tumor development in the genetic character and the originating tissue
- Can mimic tissue stroma and immune-microenvironment
- May therefore provide disease model that can more closely mimic human disease
- Opportunity for more complex biological investigation e.g. immuno combinations

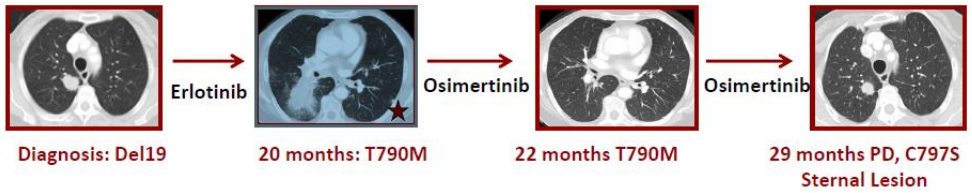
Disadvantage

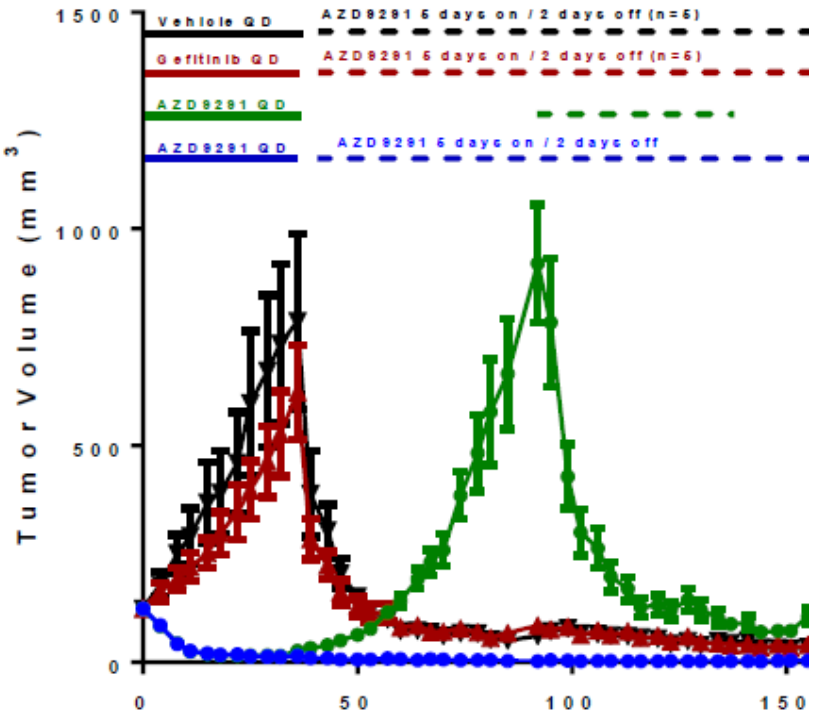
- Still may not fully mimic human tumour e.g. heterogeneity, mutational burden
- Difficult to maintain mouse models
- Challenges for using drug efficacy evaluation (tumor latency, time for tumor formation etc.)

GEM models provided additional validation to build confidence in taking osimertinib forward into clinical

Cross et al. (2014) Cancer Discovery, 4, 1046-1061

Patient Derived Explant (PDX) Models Offer Significant Potential as an In Vivo Experimental Platform





(Pasi Janne collaboration, Belfer/DFCI)

Osimertinib efficacy in co-clinical PDX study

Advantage

- Derived from relevant human clinical tumours
- PDX generally resemble human tumour of origin and therefore closer recapitulate heterogeneity.
- Panel of PDX models enable co-clinical studies
- PDX models may provide platform that most closely aligns to clinic

Disadvantage

- May not fully represent human tumour of origin e.g. clonal selection
- Human tumour micro-environment is replaced by mouse stroma and in different tissue context
- Growing in immuno-deficient mice precludes investigation of more complex immuno biology
- Attrition in establishing models
- Not suitable for routine drug discovery activities

Application of pre-clinical modelling & simulation

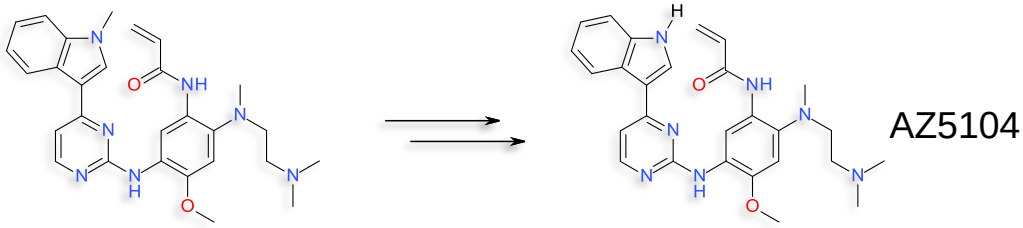
Building a pre-clinical dose / schedule model anchored to the biology

- Integrating existing clinical knowledge, pre-clinical *in vitro* & *in vivo* data to provide a quantitative PK:PD understanding of the target/pathway modulation requirements to achieve efficacy
- Use mathematical model to bridge between clinical and pre-clinical data to predict human dose and schedules

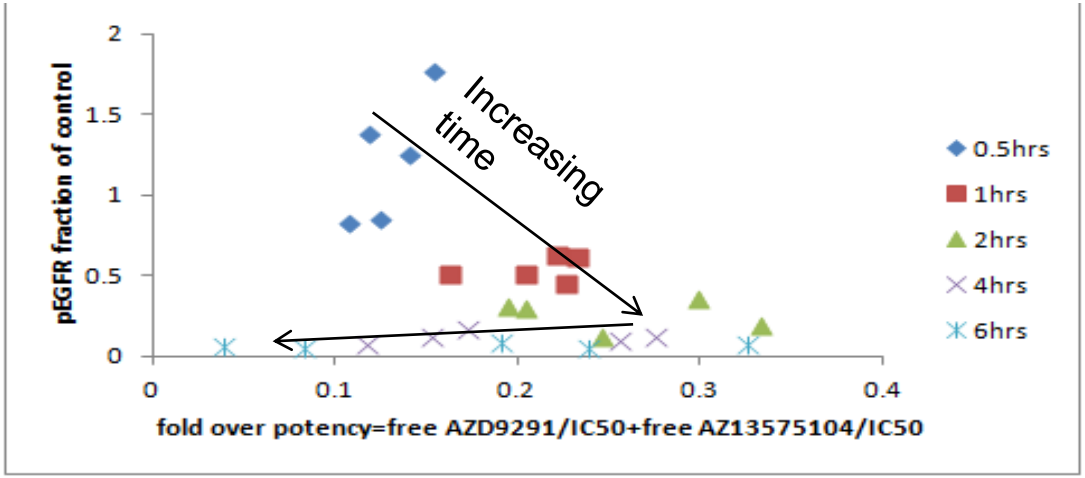
Modelling is now embedded very early in thinking of AZ Oncology projects

Challenges of Predicting Human Dose For Osimertinib

Evidence of metabolic loss of indole N-methyl group *in vivo*



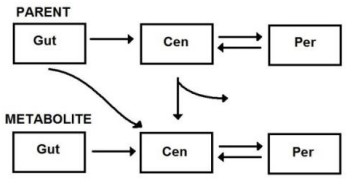
- Osimertinib was found to have a circulating active metabolite in rodent studies
- AZ5104 is potent irreversible inhibitor against mutant & wt EGFR
- Therefore needed to incorporate metabolite into human modelling



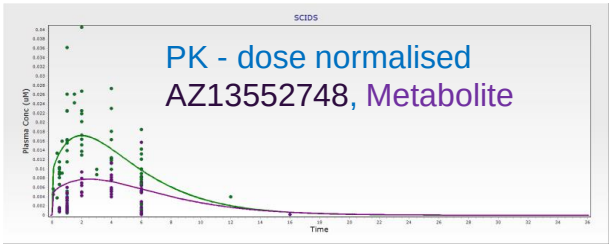
- PKPD relationship shows time delay
- This is to be expected for irreversible binders where time delay is due to protein turnover
- Therefore requires more complex modelling

Understanding relationship between PK, biomarker and anti-tumour activity critical to aiding dose prediction

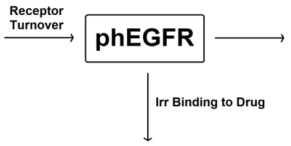
PK model parent, metabolite



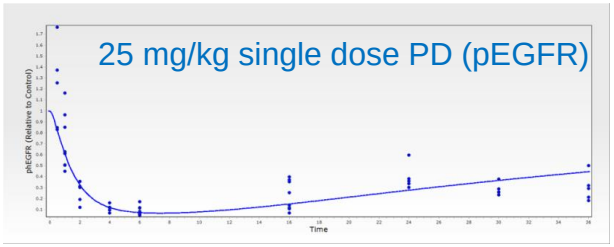
PK



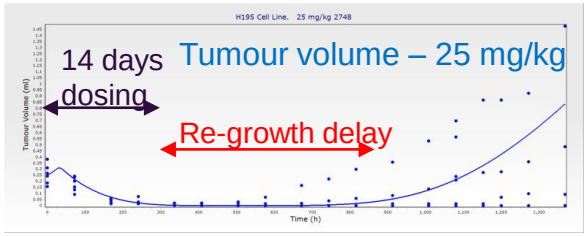
PD



PK-PD-TGI model describes data for doses used in efficacy/PD studies



TGI

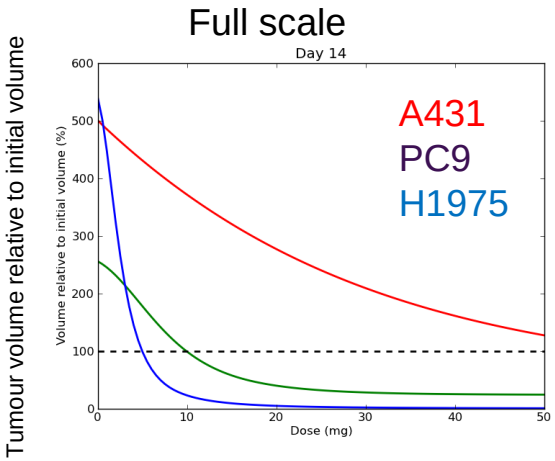


Mouse PK-PD-Efficacy model was more complex to incorporate metabolite and PK issues

- Use non-clinical data to inform how PK/exposure relates to target inhibition and efficacy in disease relevant context
- Anchor dose/schedule to target+pathway modulation
- Modelling was underpinned by robust data in meaningful disease models

Using Modelling for Forward Translation: Predicted Low Clinical Doses to Achieve Xenograft Activity Levels

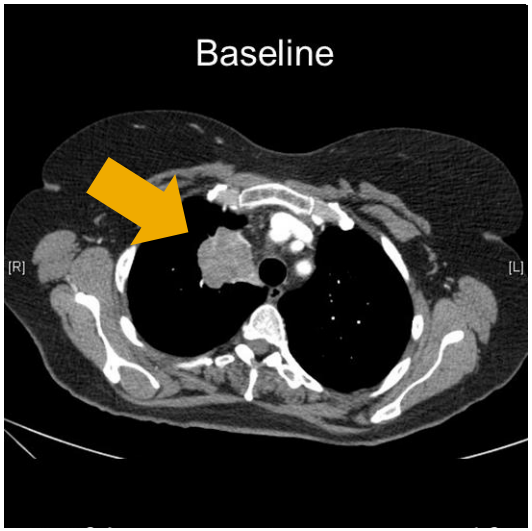
- Using predicted human PK (including metabolite) linked to PK:PD:efficacy model
- 50% comparison across models suggested dose of 7, 17, 130 mg/day in H1975, PC9 and A431

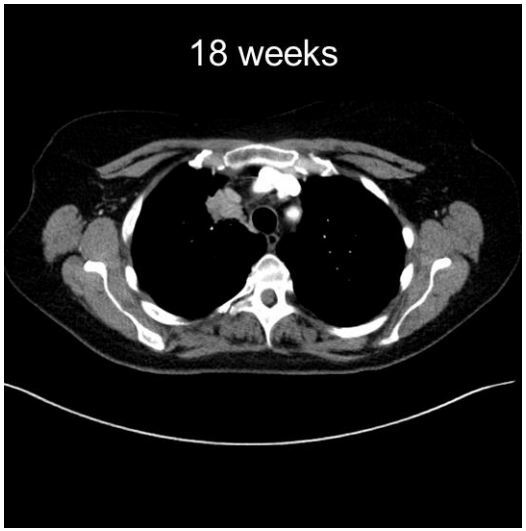


Tumour Regression	H1975	PC9	A413
10%	5.2	11	67
50%	7	17	130
75%	10	35	#N/A

- Model gave confidence in first dose level of 20mg was in zone predicted to see efficacy
- Modelling helped understand potential contribution of metabolite
- Modelling was important to support taking drug into clinic

Osimertinib – early clinical activity at 20 mg dose





- Patient with Ex19Del and T790M+ pre-gefitinib
- Progressed on gefitinib immediately before osimertinib
- Dose escalation Cohort 1 **(20 mg/day)**
- Modelling was accurate in predicting efficacy at first dose level

** Presented by Prof M Ranson at The European Cancer Congress 2013; European Journal of Cancer Vol 49, supplement 3: LBA 33*

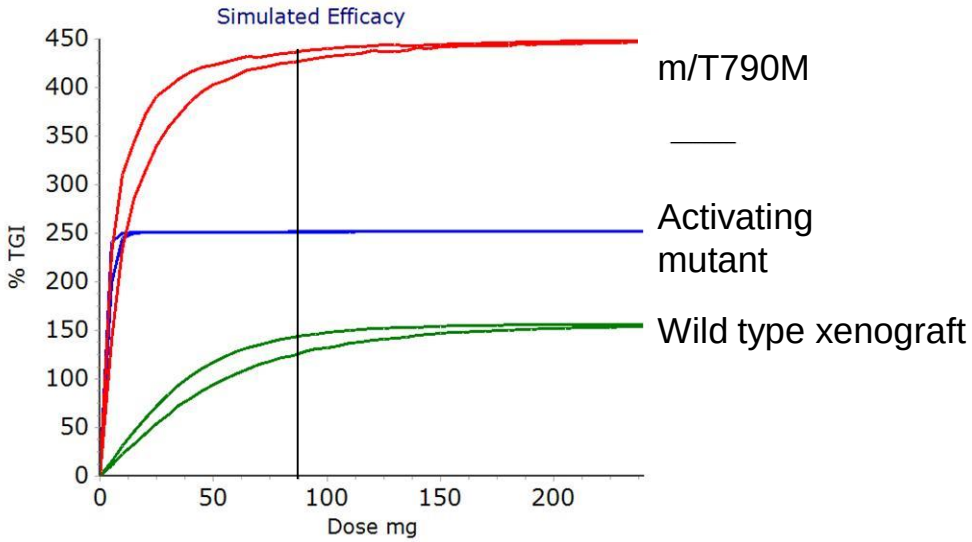
Using Modelling for Reverse Translation: Helping Inform Ph II Dose

Response rate in T790M positive cohorts

	20 mg	40 mg	80 mg	160 mg	240 mg	Total
N (157)	10	32	61	41	13	157
ORR (95% CI)	50% (19, 81)	59% (41, 76)	66% (52, 77)	51% (35, 67)	54% (25, 81)	59% (51, 66)

Presented by Pasi A Jänne at the 2015 European Lung Cancer Conference. Ann Oncol 2015; 26(Suppl 1): i60, LBA3.

- Doses 20-240mg investigated
- Responses observed at all doses
- MTD not identified
- What is optimal dose to take forward?



- Use PK:PD:efficacy model to put differences between mouse and human PK and variability into context and simulate clinical dose response
- Modelling suggested dose response vs mutant EGFR saturates by 80mg
- Although not decision-making, analysis helped build confidence in selecting 80mg as PhII dose

Summary of Presentation: Key Points

- A range of robust non-clinical models that mimic relevant disease context are key for all aspects of drug discovery

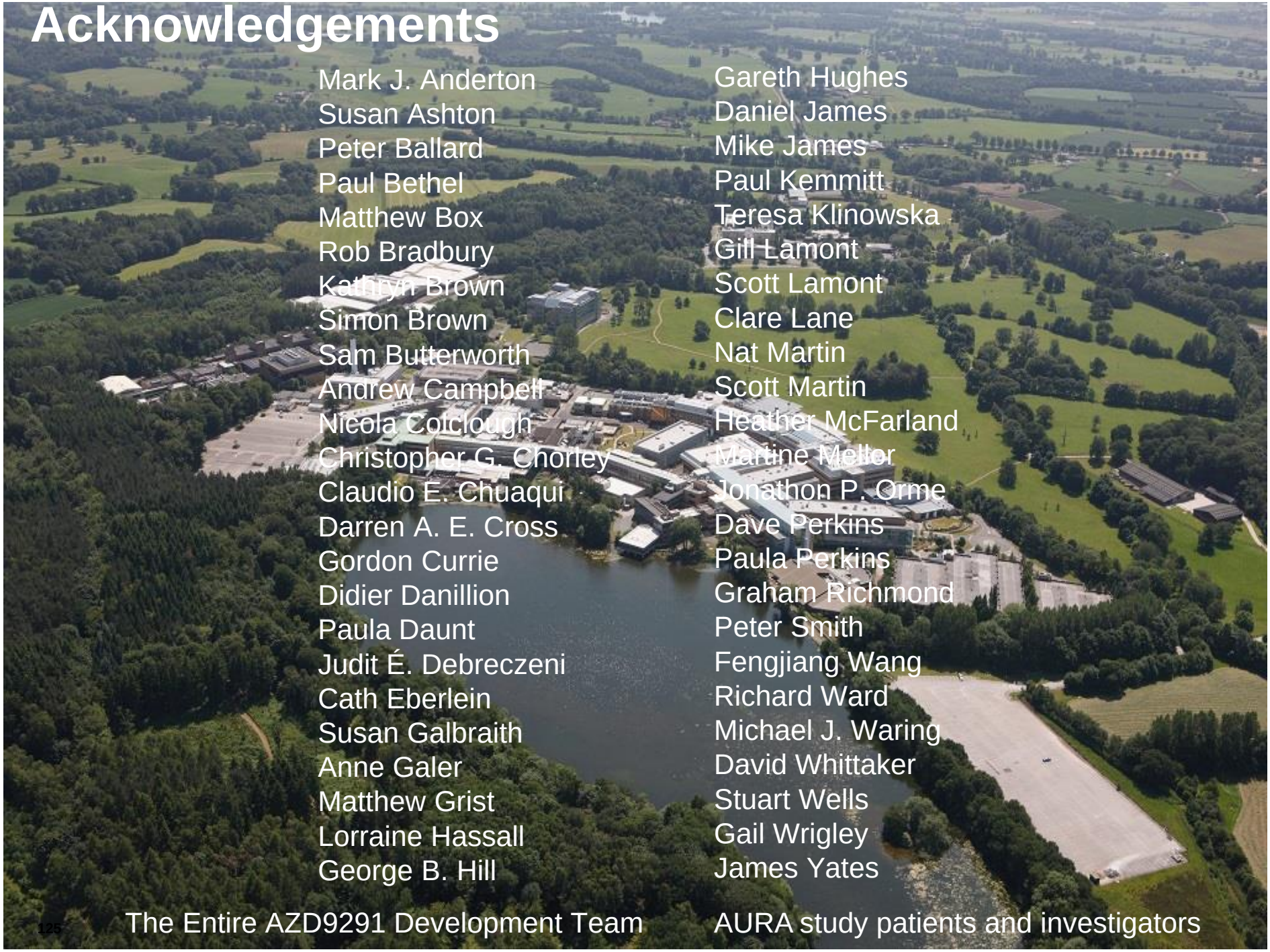
- Models only need to be as complex as necessary to support specific objective.
    - Each model platform has pro's and con's.
    - Key is to use range of models in a complementary manner e.g. xenografts for drug optimisation, PDX/ GEMM for drug positioning & complex studies.

- Simulated PK:PD:efficacy modelling is increasingly impactful to support human dose/ scheduling predictions.
    - Important to anchor models to appropriate biology
    - Drug exposure is not a sufficient surrogate

- Modelling tools and capabilities are now highly advanced.
    - Key challenges remain for applying to combinations (e.g. non-clinical data, biological understanding & model limitations)
    - Validating approaches using clinical data (e.g. difficulty of generating rich clinical PK:PD data sets)

- Predictive modelling is important to embed early and can influence multiple areas e.g.
    - Clinical dose prediction
    - Maximising therapeutic index
    - Delaying/ preventing resistance strategies
    - Informing optimal combination strategies

Acknowledgements



Mark J. Anderton
Susan Ashton
Peter Ballard
Paul Bethel
Matthew Box
Rob Bradbury
Kathryn Brown
Simon Brown
Sam Butterworth
Andrew Campbell
Nicola Colclough
Christopher G. Chorley
Claudio E. Chuaqui
Darren A. E. Cross
Gordon Currie
Didier Danillion
Paula Daunt
Judit É. Debreczeni
Cath Eberlein
Susan Galbraith
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Matthew Grist
Lorraine Hassall
George B. Hill
Gareth Hughes
Daniel James
Mike James
Paul Kemmitt
Teresa Klinowska
Gill Lamont
Scott Lamont
Clare Lane
Nat Martin
Scott Martin
Heather McFarland
Martine Mellor
Jonathon P. Orme
Dave Perkins
Paula Perkins
Graham Richmond
Peter Smith
Fengjiang Wang
Richard Ward
Michael J. Waring
David Whittaker
Stuart Wells
Gail Wrigley
James Yates

The Entire AZD9291 Development Team

AURA study patients and investigators

Translational model to Establish Dose Range Selection for Pembrolizumab

June 13th, 2016
FDA-AACR: Oncology Dose Finding Workshop

Chandni Valiathan

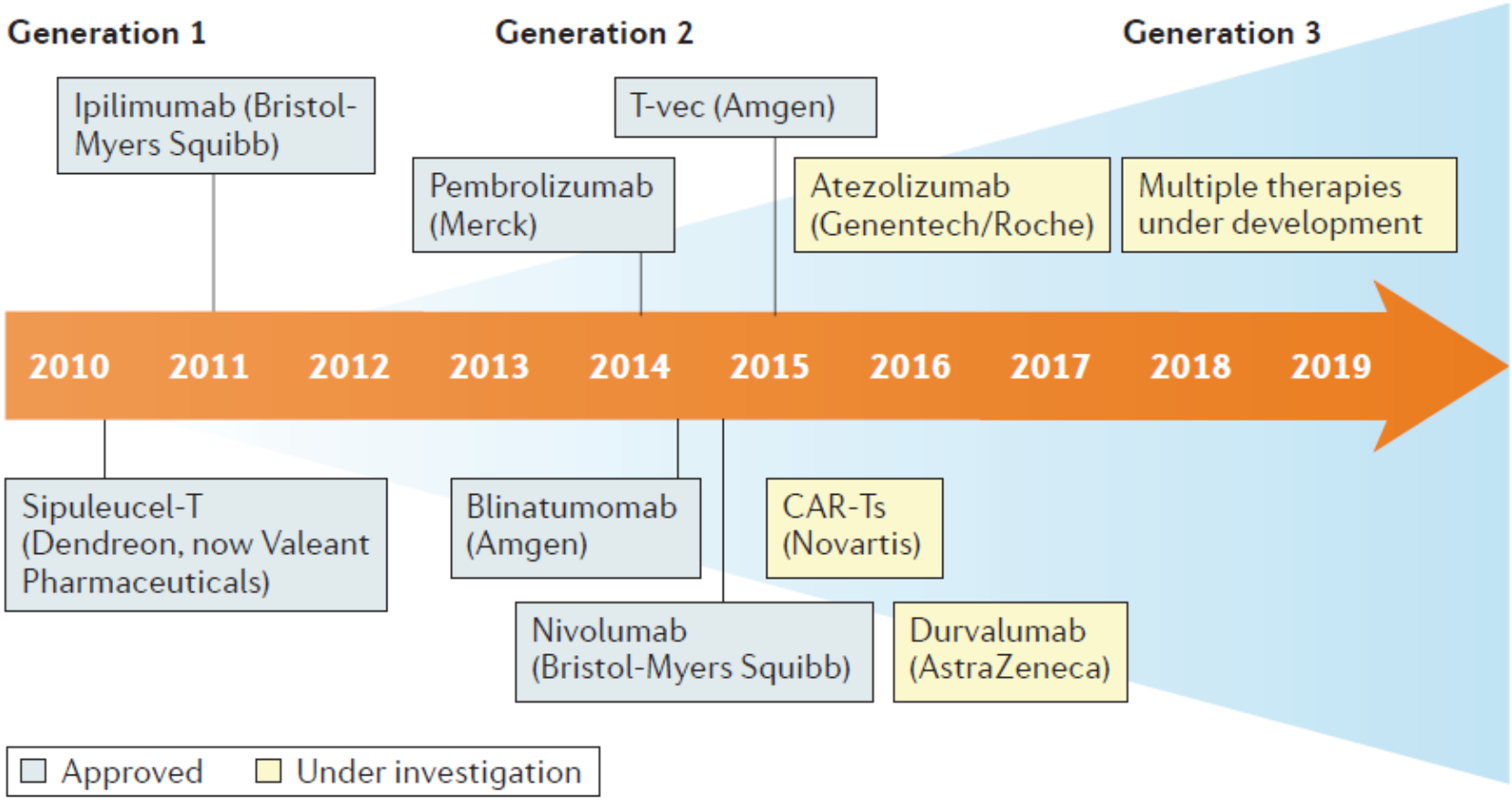
Andreas Lindauer, Khamir Mehta, V Sriram, Jeroen Elassaiss-Schaap, Rik de Greef, Dinesh de Alwis

Additional thanks to: Anna Georgieva Kondic and the Pembrolizumab team

Outline of talk

- Background:
  - Immuno-oncology: a novel class of cancer therapy
  - Pembrolizumab: mechanism of action
- Criteria and challenges in clinical dose selection and translational model development
- Translational Physiology Based PK-PD model development
- Model simulations for dose selection
- Summary and key points

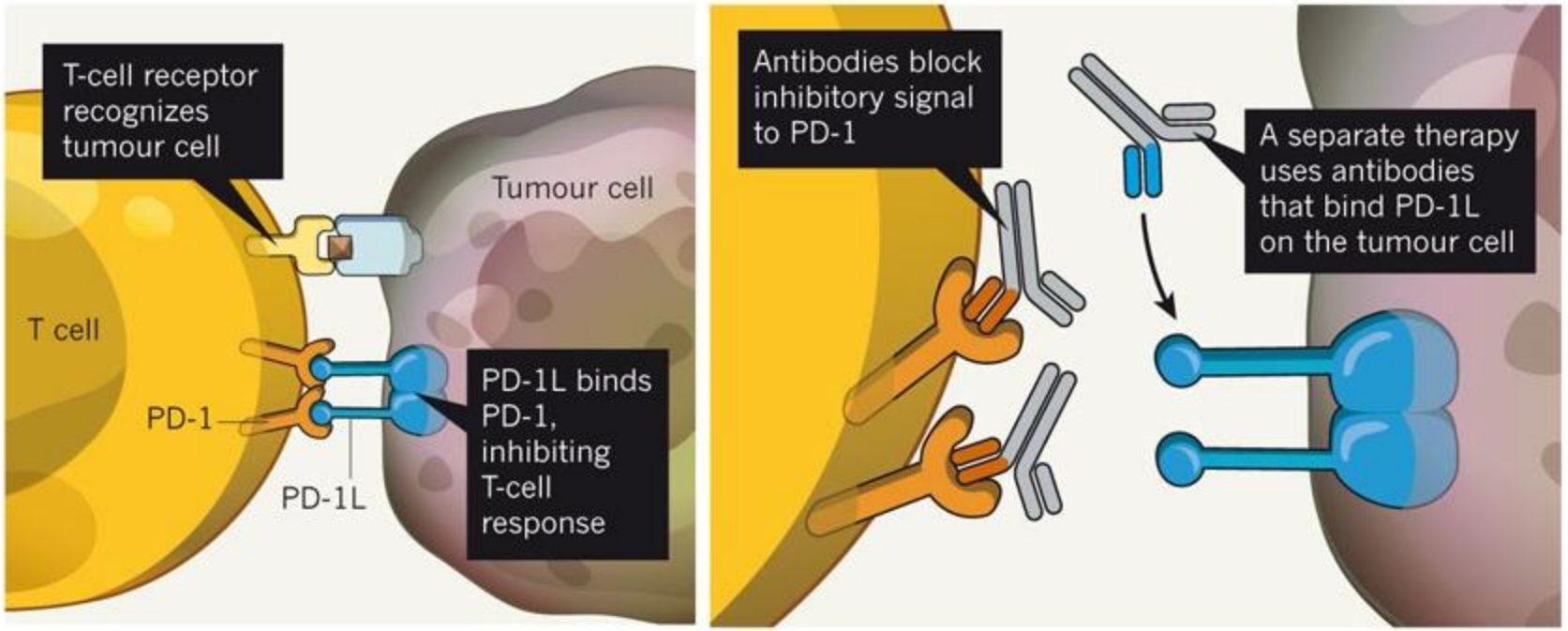
Progress in immuno-oncology has accelerated since 2010



Axel Hoos, Nature Reviews Drug Discovery 15, 235–247 (2016)

Pembrolizumab mechanism of action

- Pembrolizumab is a humanized IgG4 and a high-affinity Anti-PD-1 blocking antibody
- Pembrolizumab blocks the inhibitory receptor on T-cells thus re-activating them to recognize and kill tumor cells



Source: http://blogs.nature.com/spoonful/2013/04/melanoma-drug-joins-breakthrough-club.html

Challenges in dose selection strategy using translational methods

PK-PD-Efficacy relationship

Population Variability

(not usually known apriori)

Target PK/PD/Efficacy in target population

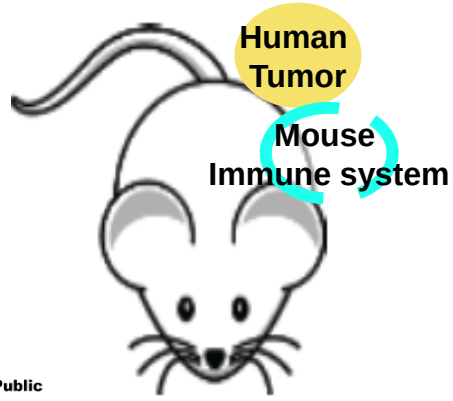
- *Preclinical model for immuno-oncology?*
- *Translation of efficacy from pre-clinical to clinical?*
- *PD biomarker?*
- *PK parameter that correlates with efficacy?*

Dose level + Frequency

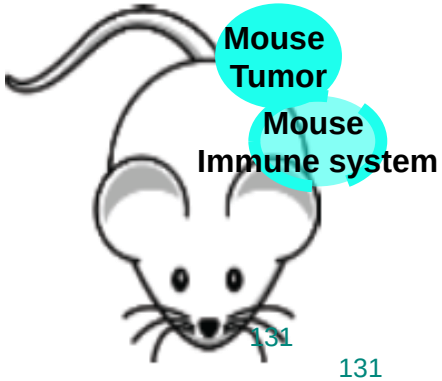
Challenges in pre-clinical species selection for translational methods in immuno-oncology

- Human antibodies are not generally cross-reactive across species
- The immune system is an important component of immuno-oncology therapies
- Need appropriate pre-clinical tools to evaluate immuno-oncology therapies
  - Syngeneic mouse models with active immune system
  - Humanized mouse models with “human” immune systems and human tumors

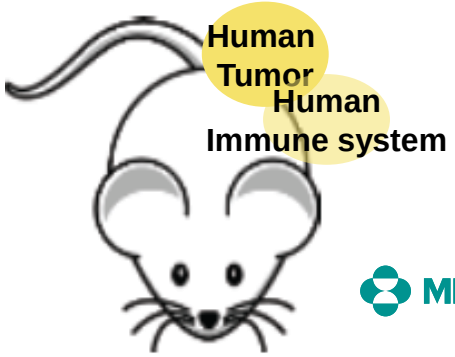
XENOGRAFT



SYNGENEIC



HUMANIZED



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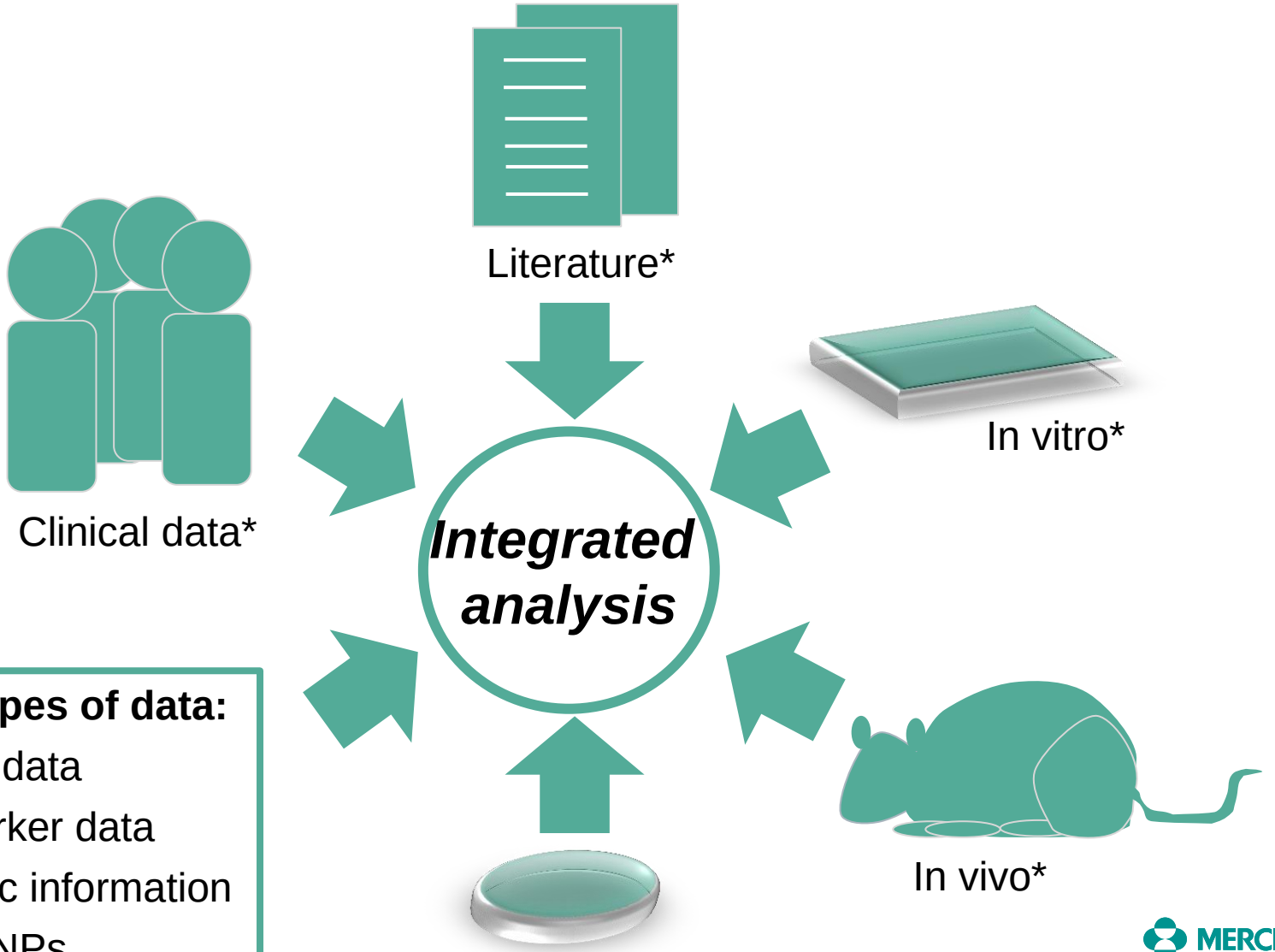
Integration of data from various sources can help



Other types of data:

- Image data
- Biomarker data
- Genetic information
  e.g SNPs

* *Integrated in translational model*

Challenges in dose selection strategy using translational methods

PK-PD-Efficacy relationship

Population Variability

(not usually known apriori)

Target PK/PD/Efficacy in target population

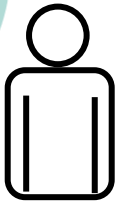
- *Preclinical model for immuno-oncology?*
- *Translation of efficacy from pre-clinical to clinical?*
- *PD biomarker?*
- *PK parameter that correlates with efficacy?*

Dose level + Frequency

Dose Selection for Pembrolizumab using a translational PK/PD model

Manuscript submitted:
Lindauer A. et al., *Translational Pharmacokinetic/Pharmacodynamic Modeling of Tumor Growth Inhibition Supports Dose-Range Selection of the Anti–PD-1 Antibody Pembrolizumab*

Phase 1 trials showed promising results and suggested less frequent dosing

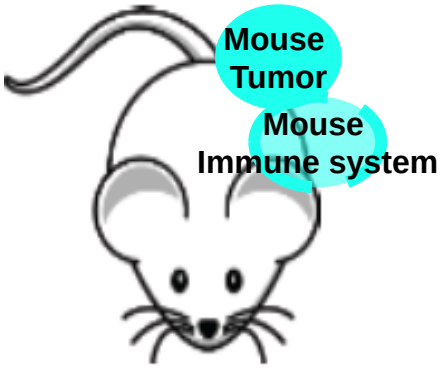


- Dose escalation performed with 1, 3 and 10mg/kg doses on a once every two weeks (Q2W) schedule
- Traditional method of selecting the maximum tolerated dose would have suggested 10mg/kg Q2W as the recommended dose
- Pharmacokinetics was typical of other therapeutic mAb with low clearance, limited volume of distribution and low variability
- 26 day half life led to the proposal of once every 3 week dosing
- Additional IL-2 data suggested that saturation might occur around 1mg/kg Q3W

Pre-clinical experiments were performed to better understand the dose-response relationship

- Preclinical mouse experiments were designed after the phase 1 study – a deviation from the norm
- Syngeneic tumor-bearing mice treated with a range of doses

0.1 – 5 mg/kg
(various dosing intervals)



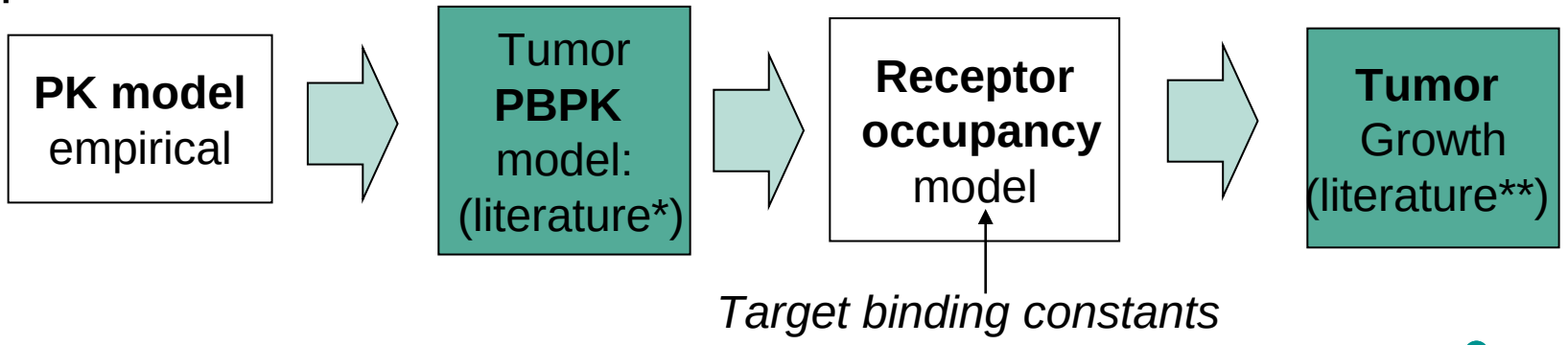
Plasma PK

Blood and Tumor Receptor Occupancy

Tumor growth inhibition

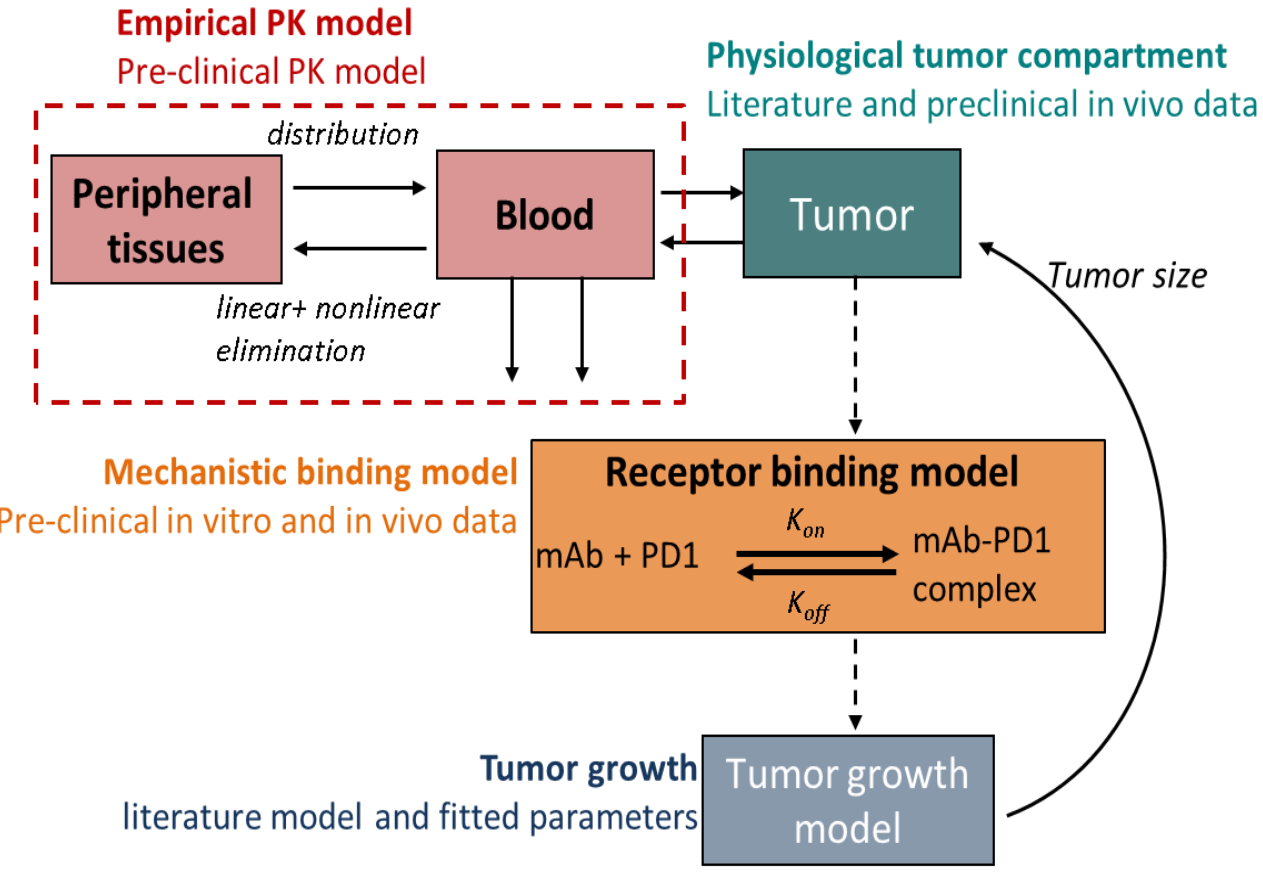
A physiology based PK-PD model was developed from mouse data and models from literature

- A plasma PK model was developed from *in vivo* mouse data
- A physiology based tumor PK model from literature was fine-tuned
- A receptor occupancy component was added to link tumor PK to tumor growth inhibition
- The tumor growth inhibition model was also taken from literature and fine-tuned to available mouse data
- The model was validated on external data and showed good performance



*Shah, D.K. & Betts, A.M.. J Pharmacokinet. Pharmacodyn. 39, 67–86 (2012).
**Simeoni, M. et al.. Cancer Res. 64, 1094–1101 (2004).

Final PB-PK-PD model structure and data sources



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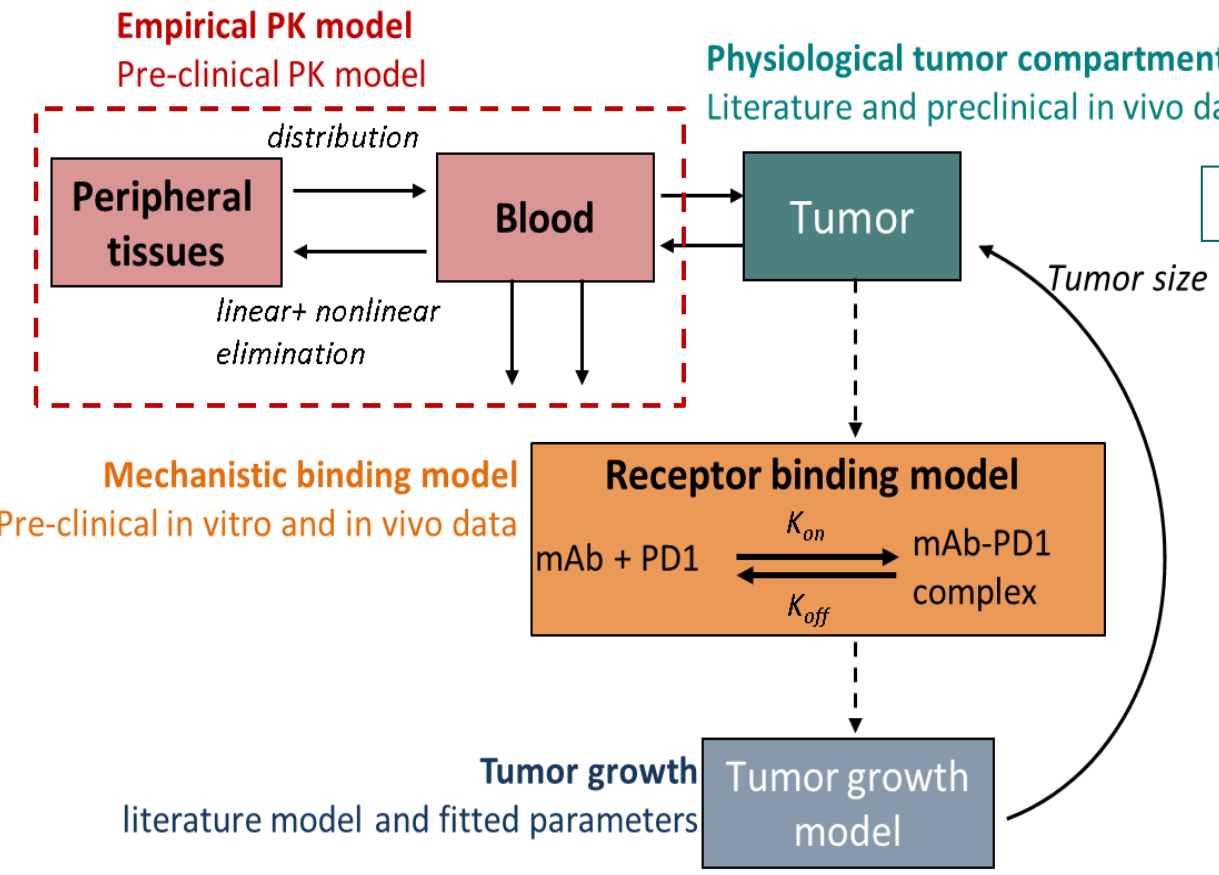
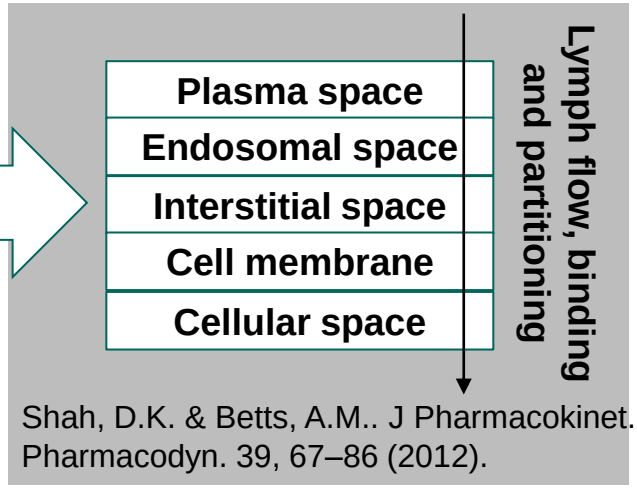


Simeoni, M. et al.. Cancer Res. 64, 1094–1101 (2004).



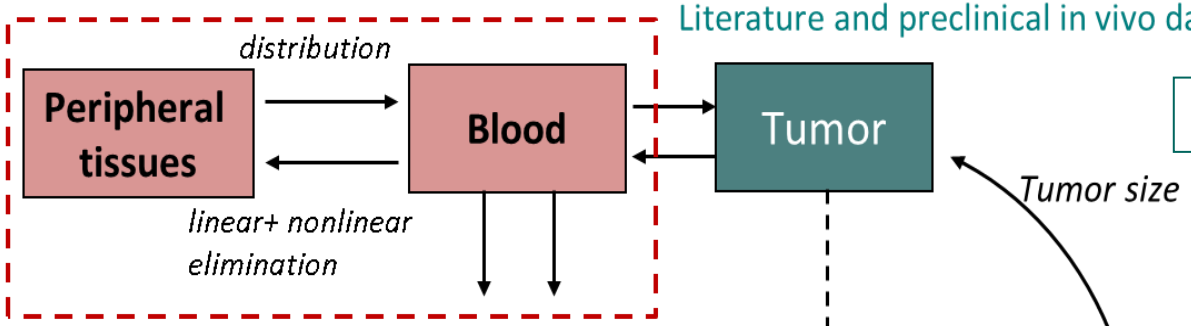
Shah, D.K. & Betts, A.M.. J Pharmacokinet. Pharmacodyn. 39, 67–86 (2012).

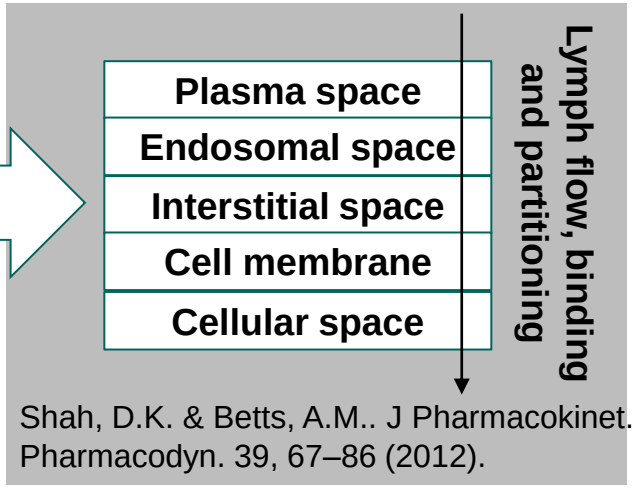
Manuscript submitted:
Lindauer A. et al., *Translational Pharmacokinetic/Pharmacodynamic Modeling of Tumor Growth Inhibition Supports Dose-Range Selection of the Anti–PD-1 Antibody Pembrolizumab*

Final PB-PK-PD model structure and data sources

Empirical PK model
Pre-clinical PK model

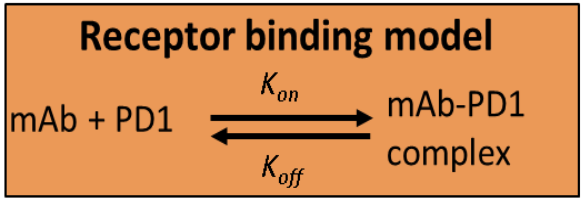
Physiological tumor compartment
Literature and preclinical in vivo data



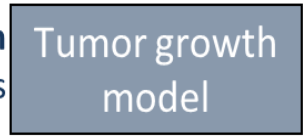


Shah, D.K. & Betts, A.M.. J Pharmacokinet. Pharmacodyn. 39, 67–86 (2012).

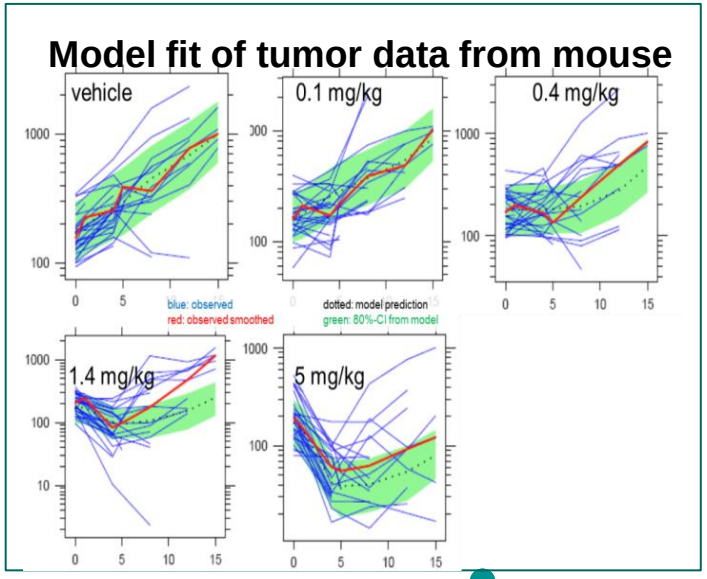
Mechanistic binding model
Pre-clinical in vitro and in vivo data



Tumor growth
literature model and fitted parameters



Simeoni, M. et al.. Cancer Res. 64, 1094–1101 (2004).



Manuscript submitted:
Lindauer A. et al., *Translational Pharmacokinetic/Pharmacodynamic Modeling of Tumor Growth Inhibition Supports Dose-Range Selection of the Anti–PD-1 Antibody Pembrolizumab*

A translational model for human simulations was developed by integrating various data sources

PK model empirical

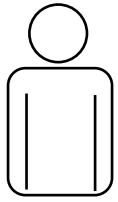
Receptor occupancy model

Tumor **PBPK** model: (literature)

Tumor Growth (literature)

Simulated Human Tumor Responses

hybrid components



PK model empirical MK-3475

Target binding constants

- *Melanoma typical size*
- *Melanoma typical growth*

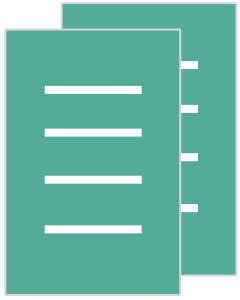
(literature,1D to 3D and back, allometric scaling)

Various techniques were used to bridge between mouse and man

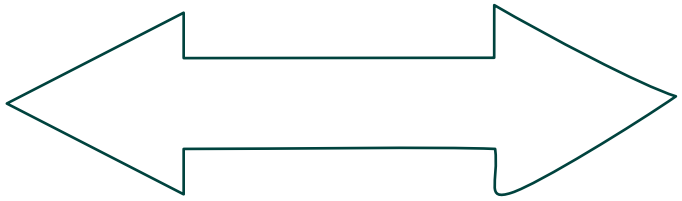
- The physiology based tumor PK model had a parameter structure that was species independent
- Where available, clinical data and models were used directly
- Allometric scaling and assumptions were made where applicable in order to bridge to the clinical setting
- Literature sources were used to augment and understand the range of responses that might be seen
- Converted one-dimensional tumor measurements in literature to volume measurements for model simulations

Method used to translate linear tumor size to volume for model development and simulation

- A range of tumor growth rates (slow, medium, fast) were identified in literature
- Linear growth rate from literature was converted to volumetric growth rate

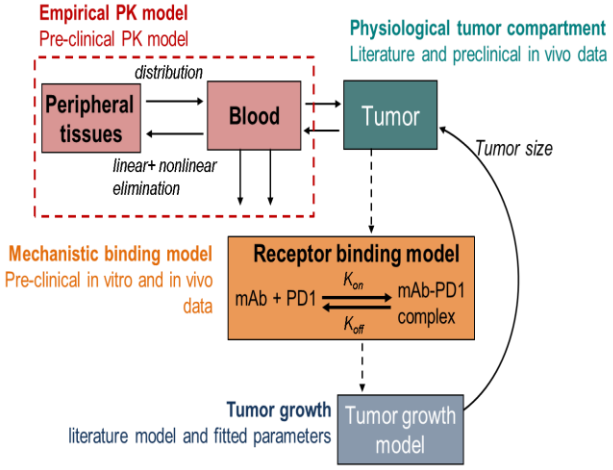


Linear tumor size and growth rate



Shape factor conversion for tumor growth rate:

- assume
  - spherical tumor
  - 1-5 tumors
  - similar sized tumors
- Simple algebra to identify a shape factor
- Shape factor used to convert between linear and volumetric size

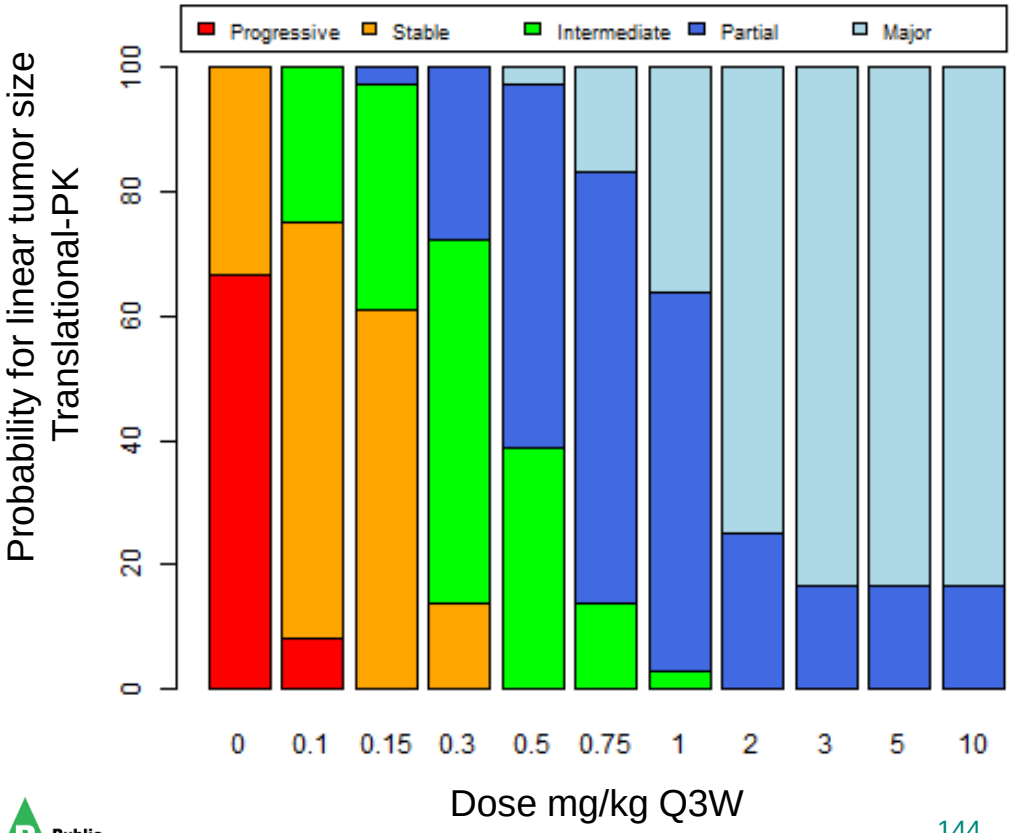


Model based on volume-based growth rate

Simulations provided guidance for the effect of increasing dose on tumor growth inhibition

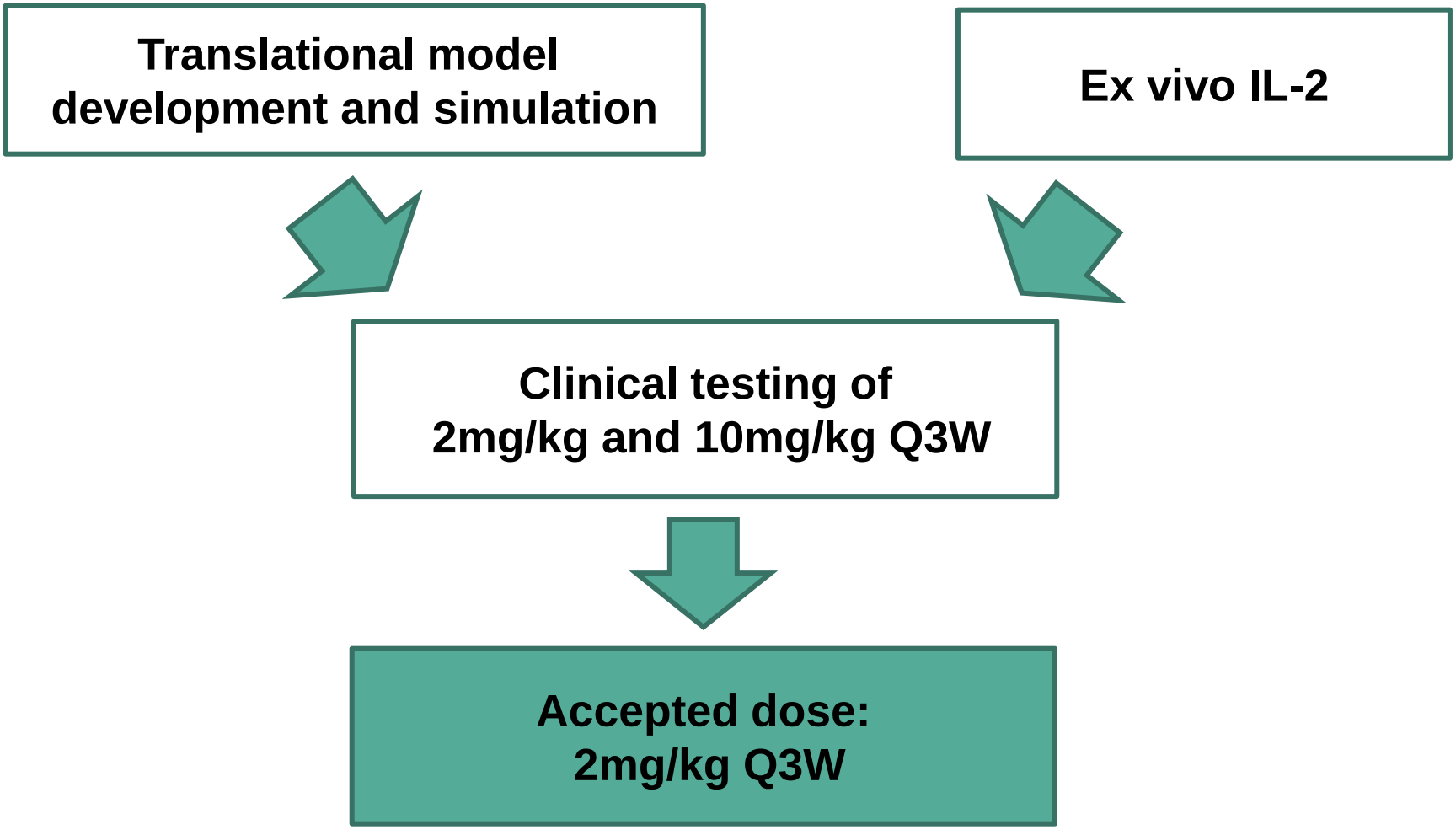
Change from baseline (CFB) for each simulation replicate categorized into clinical response categories in analogy to the RECIST criteria

Conclusion: probability to achieve partial response reaches a plateau for doses equal or greater than 2 mg/kg Q3W with reduced probability for lower doses.



Progressive disease: CFB < -20%
Stable disease: -20% < CFB < 10%
Intermediate response: 10% < CFB < 30%
Partial response: 30% < CFB < 50%
'Major' response: CFB > 50%

Clinical implications of model simulations



Novel paradigm for dose selection in Oncology

Summary and key steps

- Developed a translational model that integrated data from various sources to provide recommendations
- Key steps:
  - Designing and performing pre-clinical experiments to understand and develop a translational model after clinical efficacy was observed
  - Innovative ways to integrate literature information
- Still learning – some techniques might be applicable to other programs and new techniques will also be needed

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Alan Korman's slides have been withheld from this presentation.

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Juliet Williams's slides have been withheld from this presentation.

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Session II Panel Discussion

Non-Clinical Models Used for Go/No-Go Decisions

Chair: Todd Palmby, PhD

Speakers:

Darren Cross, PhD

Chandni Valiathan, PhD

Alan Korman, PhD

Juliet Williams, PhD

Panelists:

Hans Loland

Thomas Jaki, PhD

Mark Ratain, MD

Amit Roy, PhD

Karthick Vishwanathan, PhD

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Break

2:35– 2:50 pm

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Session III

Designs for Dose Optimization Studies: Pre-Market and Post-Market

Chair: Eric Rubin, MD

Speakers:

Haleh Saber, PhD
Pasi Jänne, MD, PhD
Ying Lu, PhD
Chao Liu, PhD
Matthew Guo, PhD

Panelists:

Kelvin Dickenson
Serban Ghiorghiu, MD
Hans Loland
Sumithra Mandrekar, PhD
Lie Nie, PhD
Nam Atiqur Rahman, PhD
Lillian Siu, MD

Dose selection: MABEL for immune oncology products

Haleh Saber
Deputy Director
CDER/OHOP/DHOT

Questions to answer

- What have we learned thus far?
- How FIH doses compare to doses given safely to patients: too low or too high?
- What has been the basis of FIH dose selection?
- Is there a FIH dose approach that is safe for all products examined?
- Is there a need to optimize the Phase 1 clinical trial design?

Abbreviations

- AE: adverse event
- CRS: cytokine release syndrome
- DHOT: Division of Hematology Oncology Toxicology
- DLT: dose-limiting toxicity
- FIH: first-in-human
- IND: Investigational New Drug application
- IRR: infusion-related reaction
- K_D: dissociation constant
- MABEL: minimally anticipated biological effect level
- MOA: mechanism of action
- MTD: maximum tolerated dose
- NOAEL: no-observed adverse effect level
- PA: pharmacologic activity
- RO: receptor occupancy

What is MABEL?

- Minimally anticipated biological effect level
- An approach to setting the FIH dose
- Various approaches may be used:
  - Xenograft studies
  - In vitro binding data
  - In vitro activity studies
  - Other data, e.g.: estimation of antigen expression in patients, PK modeling, etc.
- May be used when:
  - When animal species are expected to produce results that are not relevant (immune oncology products)
  - There is no relevant species to conduct a toxicology study

What led to MABEL?

- In 2006, administration of TGN1412, a CD28 mAb to healthy volunteers resulted in life-threatening conditions in 6 subjects
- AEs due to cytokine storm and multi-organ failure.
- Manifestation of AEs within 90 min of a single dose
- The FIH dose (0.1 mg/kg) was 500 fold lower than the animal dose at NOAEL (50 mg/kg)
- The FIH dose was at 90% RO (K_D= 1.88 nM)

❖ *Prompted: FIH dose at 10% RO for immune oncology products*

The current paradigm

- Current preference: 20% receptor occupancy (RO) or 20% pharmacologic activity (PA) at the FIH dose
- Various methods used for RO and PA
- We used the following in our analysis:

$$RO = C_{max} / (K_D + C_{max})$$

$$PA = C_{max} / (EC_{50} + C_{max})$$

$\alpha = 1$

$$v = \frac{V_{max}[S]}{K_m + [S]}$$

$$E = \frac{E_{max} C^{\alpha}}{EC_{50}^{\alpha} + C^{\alpha}}$$

Goutelle et al. The Hill equation: a review of its capabilities in pharmacological modelling: Fundamental & Clinical Pharmacology 22 (2008) 633–648

DHOT analysis

- Collected INDs that used MABEL: >100 INDs
- Oncology indications only
- Included only antibodies and CD3-XX bispecifics
- Products
  - With risk of T-cell activation, e.g.: checkpoint inhibitors, stimulators, CD3-XX bispecifics, poorly understood MOA but may be involved in activation of immune system
  - With sufficient human data, e.g. : availability of MTD or human recommended dose, or multiple cohorts tested
- N= 31 INDs (5 bispecifics and 26 antibodies)

Target of antibodies

- CD40, OX40, OX40L, GITR, CTLA-4, PD-1, PD-L1, B7 family, CD19, CD33, CD38, CSF-R, etc

Collected the following data

- Pharmacology: binding and activity data
- Toxicology: conducted in animals? If so, was the data used to set the FIH dose?
- Phase 1 trial design
  - FIH dose and rationale
  - Dose escalation scheme
  - Single patient vs 3+3
  - Intra-patient dose escalation
  - Treatment for IRRs/CRS
    - Prophylactically vs post-occurrence

Independently obtained the FIH dose based on nonclinical data

- Used 2 approaches to identify FIH doses:
  - binding data (20%- 80% RO)
  - activity data (20%- 80% PA)

  - WHY only these 2 approaches?
    - Data available for most INDs and therefore able to cross examine INDs
    - Binding data available for TGN1412, hence can compare to the super-agonist
    - Difficulties associated with other approaches: e.g. clinical candidate not fully active in mouse xenograft studies

Preliminary Conclusions (bispecifics)

- Not enough bispecifics to make firm conclusions

Preliminary Conclusions (antibodies)

- For half the INDs, the start dose was very low, e.g. 100 or 1000 fold lower than doses administered to patients with acceptable/manageable toxicities.
- Approaches used by the sponsors to set the FIH dose:
  - % occupancy or % activity (most INDs with new target): multiple approaches for each
  - Mouse xenograft data
  - Other approaches:
    - expression level of target in patients and PK modeling;
    - unclear approach
  - Based on doses of approved drugs or drugs in the development

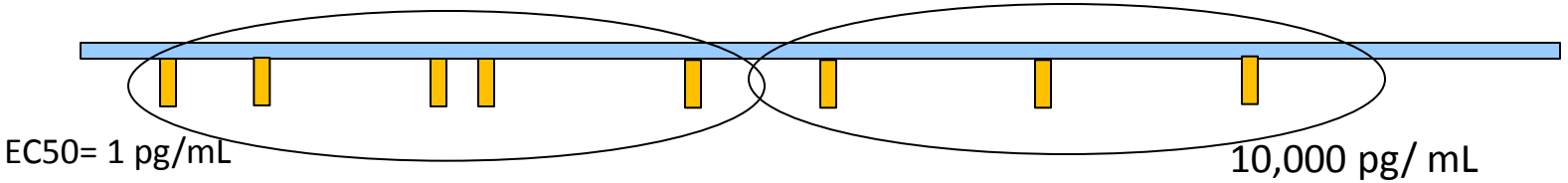
Preliminary Conclusions

We independently defined the FIH dose (using 20%-80% RO or 20%-80% PA; Slide 6) and compared them to doses given to patients with acceptable toxicities

- A FIH dose based on 20% RO may be too low

Preliminary Conclusions

- Activity data assists in hazard identification: T-cell proliferation, T-cell activation, cytokine release, cell lysis
- High variability in activity data/ cell-based assays
  - Up to 10,000 fold differences in mean EC50s
- Selecting a FIH dose based on in vitro activity data could
  - result in a high FIH dose; when assays are not optimized (selection of cells, incubation time, target: effector ratios, etc)
  - result in too low of a FIH dose; when assays are well optimized



Example: checkpoint stimulator

In vitro activity assays to assess immune system activation	**EC50 (activity)**	**KD (binding)**
• Cytokine release assay: negative in soluble; positive plate-bound • T-cell proliferation: positive • T-cell activation: positive Most sensitive: T-cell proliferation Least sensitive: cytokine release	Range for Mean EC50s= 20 pM-190 pM (**9 fold difference**) Range of all EC50s= 0.5-600 pM (**1200 fold difference**) <u>EC50s from cytokine release</u> Cytokine 1: 130 pM (12- 390 pM) Cytokine 2: 110 pM (18-300 pM) Cytokine 3: 150 pM (22-550 pM) Cytokine 4: 155 pM (27-600 pM) Cytokine 5: 190 pM (30-570 pM) <u>EC50 from T-cell proliferation:</u> 20 pM (0.5-30 pM) <u>EC50 from T-cell activation:</u> 30 pM (6-130 pM)	KD= 1.7 pM- 5 pM (**3 fold**)

Preliminary Conclusions

- Side-by-side comparative data to similar products (marketed or in development) can aid in dose selection
  - Resulted in FIH doses higher than 20% RO or PA
  - Non-MABEL approaches used

FIH dose	Highest human dose	FIH dose rationale
60 mg/ saturated	180 mg/ saturated	Based on other products inhibiting the same target
30 mg/ saturated	600 mg/ saturated	Based on other products inhibiting the same target

Preliminary Conclusions
Frequency of administration in patients: antibodies

- Majority (77%): Q2W or less frequent administration
- 6 out of 26 (23%): weekly

Frequency of administration in Phase 1			
Total # of antibodies: 26			
Q2W or less frequent:	Q2W or Q3W:	Single dose:	Q4W:
20/ 26 (77%)	17/26 (65%)	1/26 (4%)	2/26 (8%)

Preliminary Conclusions

- None of the antibodies examined resulted in cytokine storm in patients despite high doses given… cytokine storm was seen with a single dose of TGN1412 at 90% RO
  - IRRs/ CRS: common. They were manageable. All protocols had measures incorporated for treatment and stopping rules in place
  - Addressed by reducing the rate of infusion in addition to medications.
  - IRRs/CRS may be more prominent when Fc domain is modified for increased ADCC activity

Preliminary Conclusions

- Strategies to address CRS/ IRRs did not seem to affect trial design
- Common features of trial design:
  - Staggered dosing
  - Readiness to treat CRS/ IRRs
- Variability in FIH clinical trial design
  - Single patient, 3+3 design, intra-patient escalation, inter-patient escalation.
  - Dose escalation: e.g. 3- 10 fold in between cohorts at low doses

Examples of FIH trial designs

Week	Patient 1	Patient 2	Patient 3
1	0.01 mg/kg (10% RO)		
2	0.03 mg/kg		
3	0.1 mg/kg	0.03 mg/kg	
4	0.15 mg/kg (70% RO)	0.1 mg/kg	
5	⇩	0.15 mg/kg	0.1 mg/kg
6	⇩	0.15 mg/kg (70% RO)	0.15 mg/kg
7	Follow for 4 weeks	⇩	0.15 mg/kg
8			0.15 mg/kg (70% RO)
9		Follow for 4 weeks	⇩
10			Follow for 4 weeks

- Weekly
- Intra-patient escalation up to 0.15 mg/kg (~9 mg; 70% RO), then 3+3
- completion of the intra-patient escalation portion: ~ 1 yr
- From IND submission to the maximum-administered-dose of 15 mg/kg: 3 years
- 15 mg/kg (900 mg; saturated)

Dose in mg/kg (flat dose equivalent)	RO	# Patients
0.0001 (6 mcg)	6%	1
0.001 (60 mcg)	55%	1
0.01 (600 mcg)	Saturated	3
0.03	Saturated	3
0.1	Saturated	3
0.3	Saturated	3
1	Saturated	3
3	Saturated	3

- Q3W
- In ~ one year escalated from FIH dose to 1 mg/kg
- Do patients at low doses (e.g. 0.0001 mg/kg) benefit?

Examples of FIH trial designs

Dose in mg/kg (flat dose equivalent)	RO	# Patients
0.0001 (6 mcg)	2%	2
0.0005 (30 mcg)	10%	2
0.005 (300 mcg)	50%	4
0.05	90%	4
0.5	Saturated	4
1	Saturated	6
2	Saturated	6
4 (240 mg)	Saturated	6

- Single dose
- From IND submission to the dose of 4 mg/kg: 5 yr
- Do patients at low doses (e.g. 0.0001 mg/kg) benefit?

Dose in mg	RO	# Patients
0.2 (200 mcg)	50%	3 + 3
0.8	80%	⇩
3.2	Saturated	
12	Saturated	
40	Saturated	
130	Saturated	
400	Saturated	
1200	Saturated	

- Q3W
- From IND submission to the dose of 1200 mg: ~2yr

Recommendations for immune oncology antibodies

- *No recommendations for CD3-XX bispecifics at this time: 3 with daily administration and 2 weekly; one with insufficient human data; one with no K_D*
- When using a FIH dose based on activity data, be sure assays are optimized
- More work needed to address FIH dose selection
  - Until then:
  - Whichever method is used to set the FIH dose: Compare the FIH dose selected to the estimated RO (Slide 6) as a point of reference?

How to minimize exposure to sub-therapeutic doses? *open for discussion*

- Consider the following design for Phase 1 trials of mAbs?
  - Intra-patient dose escalation in a subset of 2-3 patients, when the FIH dose is at <50% RO?
    - Switch to 3+3 at ≥ 80% RO?
  - Single patient cohorts when the FIH dose is 50%-75% RO?
    - Switch to 3+3 at ≥ 80% RO?
- Allow higher than a MABEL dose if a side-by-side comparison is done using an approved drug or a drug in development?

Examples of immune oncology mAbs in our database: FIH doses compared to highest human doses

Target or class	*FIH dose (MABEL approaches)	HHD (time from IND submission to this dose)	HHD : FIH dose
OX40	200 mcg/ 50% RO	1200 mg (2 yr) / saturated	6000
CD40 (increased ADCC); Q3W administration	36 mcg/ <10% RO	3.6 mg (1.5 y)/ 90% RO Phase 1 ongoing	100
CD40; Q3W administration	6 mcg / 10% RO	60 mg (1 yr)/ saturated	10,000
GITR	6 mcg/ <10% RO	240 mg (5 yr)/ saturated	40,000
GITR	1.5 mcg/ 30% RO	30 mg/ saturated	20,000
CD38	6 mcg/ <10% RO	1.2 g (5 yr)/ saturated	200,000
CD38	300 mcg/ 15% RO	RHD= 960 mg/ saturated	3200
B7-H3	600 mcg/ 10% RO	900 mg (3 yr)/ saturated	1500
	***FIH dose (MABEL or other approaches**	**HHD**	**FIH dose rationale**
General knowledge of target	30 mg/ saturated	1.2 g/ saturated	MABEL based on xenograft studies.
Checkpoint inhibitor	30 mg/ saturated	600 mg/ saturated	Based on other products inhibiting the same target
Checkpoint inhibitor	60 mg/ saturated	180 mg/ saturated	Based on other products inhibiting the same target

*Converted to flat dose using 60 kg as the BW
** Cut-off date: May 1, 2016
RO is based on in vitro binding data
HHD: highest human dose; RHD: recommended human dose; RO: receptor occupancy

Working group

- Ramadevi Gudi
- John Leighton
- Michael Manning
- Haleh Saber
- Emily Wearne

Development of Osimertinib in EGFR Mutant Lung Cancer

Pasi A. Jänne, M.D.,Ph.D.
Lowe Center for Thoracic Oncology
Dana Farber Cancer Institute

Disclosure Information

Pasi A. Jänne, MD, PhD

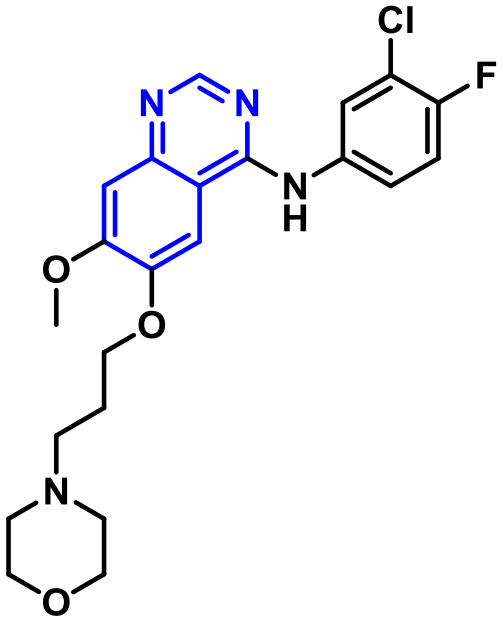
Consultant for: Astra Zeneca, Boehringer Ingelheim, Pfizer, Genentech, Roche, Sanofi-Aventis, Clovis Oncology, Chugai Pharmaceuticals, Merrimack Pharmaceuticals

Research Support: Astellas, AstraZeneca

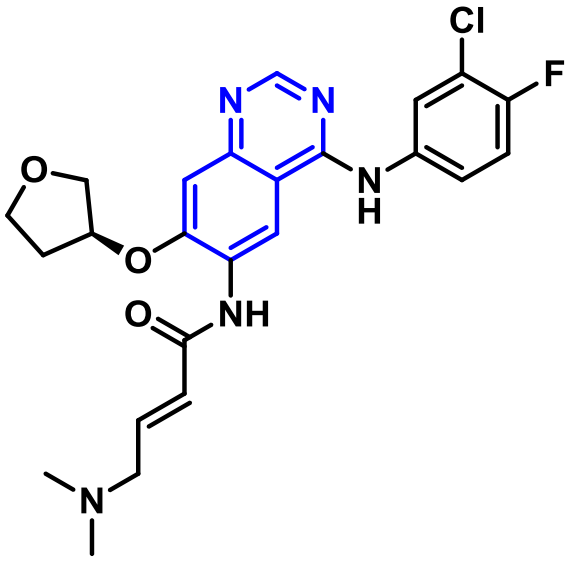
Stockholder in: Gatekeeper Pharmaceuticals

Other: LabCorp – post-marketing royalties from DFCI owned intellectual property on EGFR mutations

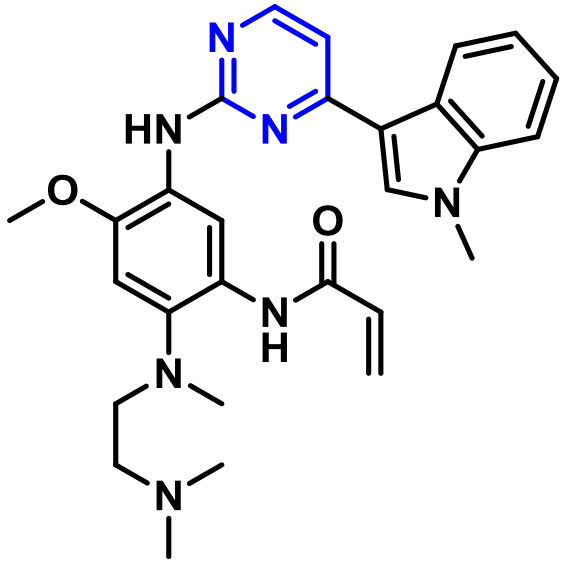
Activity Profiles of EGFR Inhibitors



Gefitinib



Afatinib

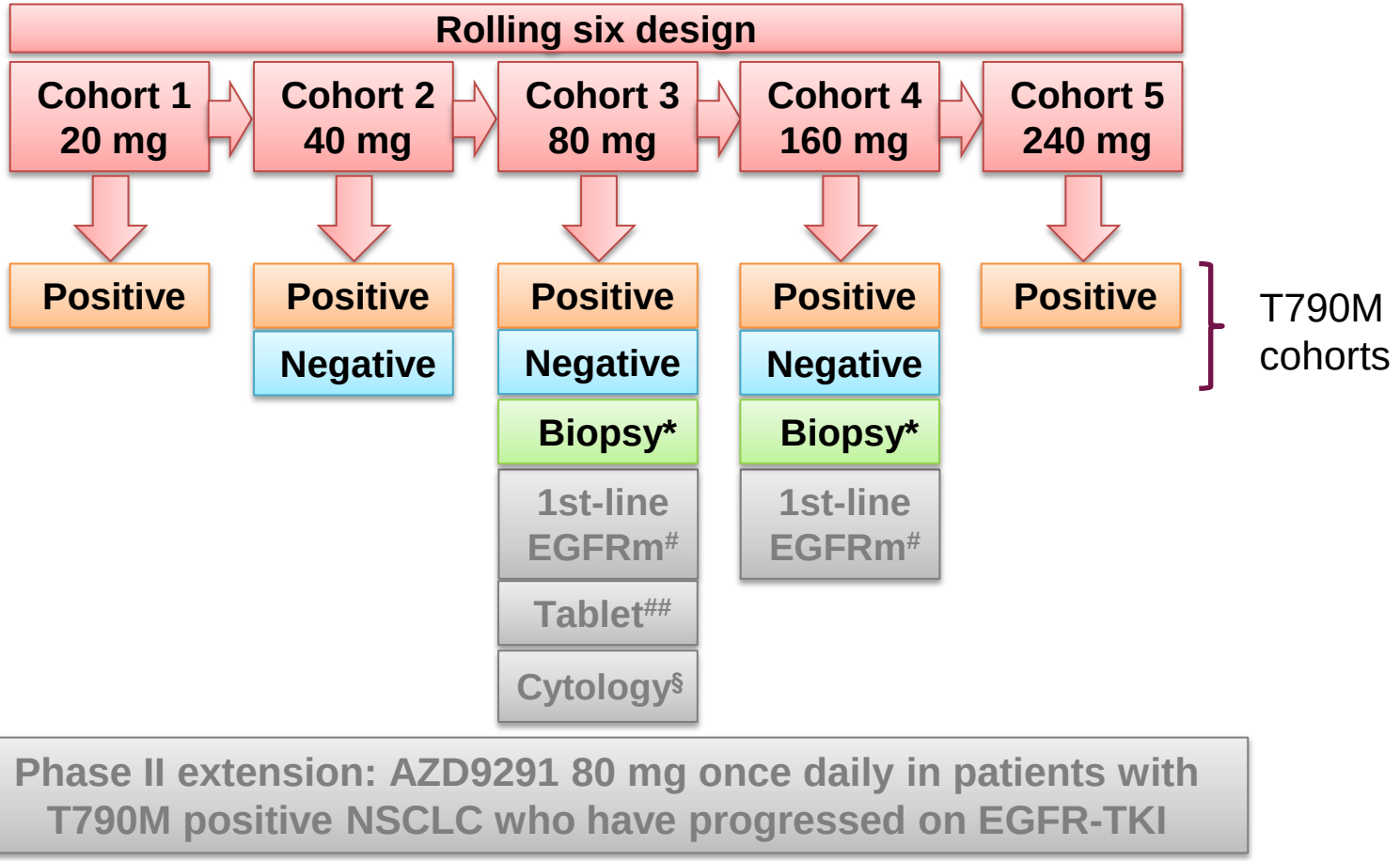


Osimertinib

	Gefitinib	Afatinib	Osimertinib
Wild Type EGFR	+++	++++	+
EGFR exon 19/L858R	+++	++++	++++
EGFR T790M	-	+	++++

Phase I / II dose escalation / expansion and extension study design

Primary objective – assessment of the safety, tolerability and efficacy (ORR) of AZD9291 in patients with acquired resistance to EGFR-TKIs



*Paired biopsy cohort patients with T790M positive tumours; safety and efficacy data only reported here
#Prior therapy not permissible in this cohort
##Not selected by mutation status, US only
§T790M positive from cytology specimen, Japan only
ORR, objective response rate

Jänne et al. ELCC 2015

Baseline demographics and disease characteristics

Characteristic	Escalation N=31	Expansion N=252
Gender, % Male / Female	35 / 65	38 / 62
Age, median (range); years	61 (39–81)	60 (28–88)
Race, % Caucasian / Asian / Other / Not reported	16 / 68 / 3 / 13	33 / 60 / 2 / 4
Histology, % Adeno / Squamous / Other / Missing	94 / 3 / 3 / 0	96 / 1 / 3 / 0.4
Prior lines of systemic therapy, median (range)	3 (1–12)	3 (1–12)
Prior EGFR-TKIs, median (range)	1 (1–4)	2 (1–5)
Regimen, %		
Gefitinib	22 (71)	146 (58)
Erlotinib	15 (48)	150 (60)
Afatinib	0	59 (23)
Other	3 (10)	8 (3)
EGFR mutation type by central test, % Exon 19 / L858R / Other / None / Unknown	Central testing not performed for escalation	54 / 29 / 4 / 5 / 8
Central T790M status, % Positive / Negative / Unknown	Central testing not performed for escalation	65 / 27 / 8

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Summary of adverse events, all grades

Patients with an AE, n (%)	20 mg (N=21)	40 mg (N=58)	80 mg (N=103)	160 mg (N=80)	240 mg (N=21)	Total (N=283)
Any AE	21 (100)	56 (97)	102 (99)	78 (98)	21 (100)	278 (98)
Any AE, drug-related*	15 (71)	40 (69)	88 (85)	72 (90)	21 (100)	236 (83)
Any AE ≥ Grade 3	6 (29)	25 (43)	40 (39)	33 (41)	9 (43)	113 (40)
Any AE ≥ Grade 3, drug-related*	3 (14)	3 (5)	14 (14)	23 (29)	4 (19)	47 (17)
Any AE leading to death	2 (10)	2 (3)	5 (5)	0	1 (5)	10 (4)
Any AE leading to death, drug-related*	1 (5)	0	0	0	0	1 (0.4)
Any AE leading to dose interruption	4 (19)	7 (12)	24 (23)	23 (29)	6 (29)	64 (23)
Any AE leading to dose reduction	0	2 (3)	1 (1)	18 (23)	10 (48)	31 (11)
Any AE leading to discontinuation	3 (14)	4 (7)	7 (7)	8 (10)	2 (10)	24 (8)
Any AE leading to discontinuation, drug-related*	2 (10)	0	1 (1)	7 (9)	1 (5)	11 (4)
Any serious AE	5 (24)	13 (22)	26 (25)	20 (25)	5 (24)	69 (24)
Any serious AE, drug-related*	4 (19)	1 (2)	5 (5)	6 (8)	1 (5)	17 (6)

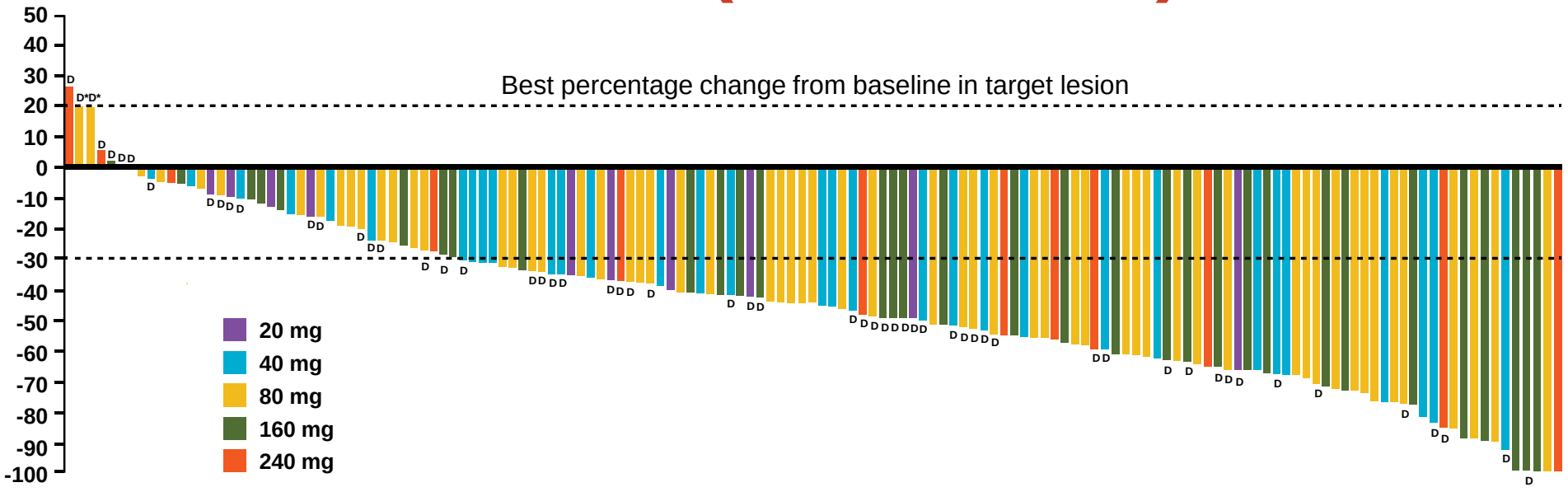
Jänne et al. ELCC 2015

All-causality adverse events

Patients with an AE, %	20 mg (N=21)		40 mg (N=58)		80 mg (N=103)		160 mg (N=80)		240 mg (N=21)		Total (N=283)	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3
AE by preferred term, occurring in >15% of patients overall												
Diarrhoea	29	0	47	2	36	1	68	3	76	5	50	2
Rash, grouped terms	24	0	33	0	38	0	63	3	76	5	46	1
Decreased appetite	38	10	19	0	26	3	24	0	33	0	25	2
Nausea	14	5	17	0	18	1	34	1	43	0	24	1
Dry skin	14	0	16	0	15	0	36	0	24	0	22	0
Paronychia	14	0	9	0	21	2	29	4	38	5	22	2
Pruritus	14	0	21	0	19	0	20	0	38	0	21	0
Fatigue	24	5	26	0	16	0	19	0	19	5	19	1
Constipation	5	0	26	0	21	0	18	0	14	0	19	0
Cough	19	0	17	0	13	0	21	0	0	0	16	0
Select AEs of interest												
Hyperglycaemia (n=8)	0	0	3	0	4	0	3	0	0	0	3	0
QT prolongation (n=10)	0	0	2	0	4	1	5	0	5	0	4	0.4
ILD-like events* (n=8)	0	0	0	0	3	2	6	4	0	0	3	2

Jänne et al. ELCC 2015

Response rate in T790M positive cohorts (central test)

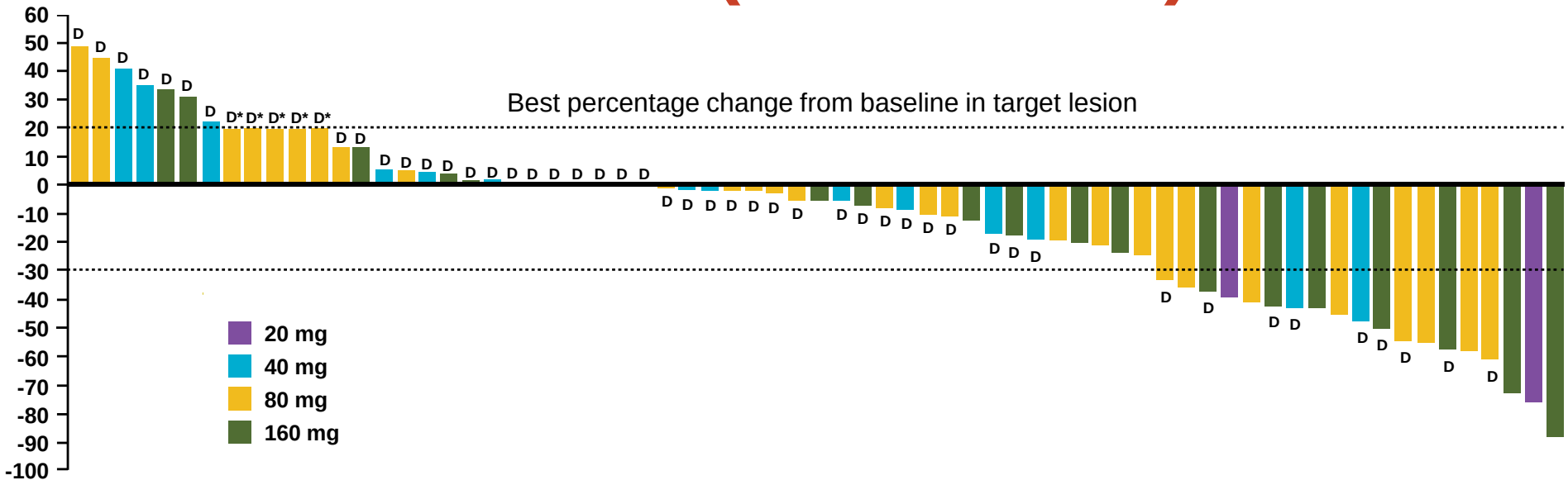


DCR (CR+PR+SD) in patients with centrally tested T790M positive tumours was 90% (141 / 157; 95% CI 84, 94)

	20 mg	40 mg	80 mg	160 mg	240 mg	Total
N (157)	10	32	61	41	13	157
ORR (95% CI)	50% (19, 81)	59% (41, 76)	66% (52, 77)	51% (35, 67)	54% (25, 81)	59% (51, 66)

Jänne et al. ELCC 2015

Response rate in T790M negative cohorts (central test)

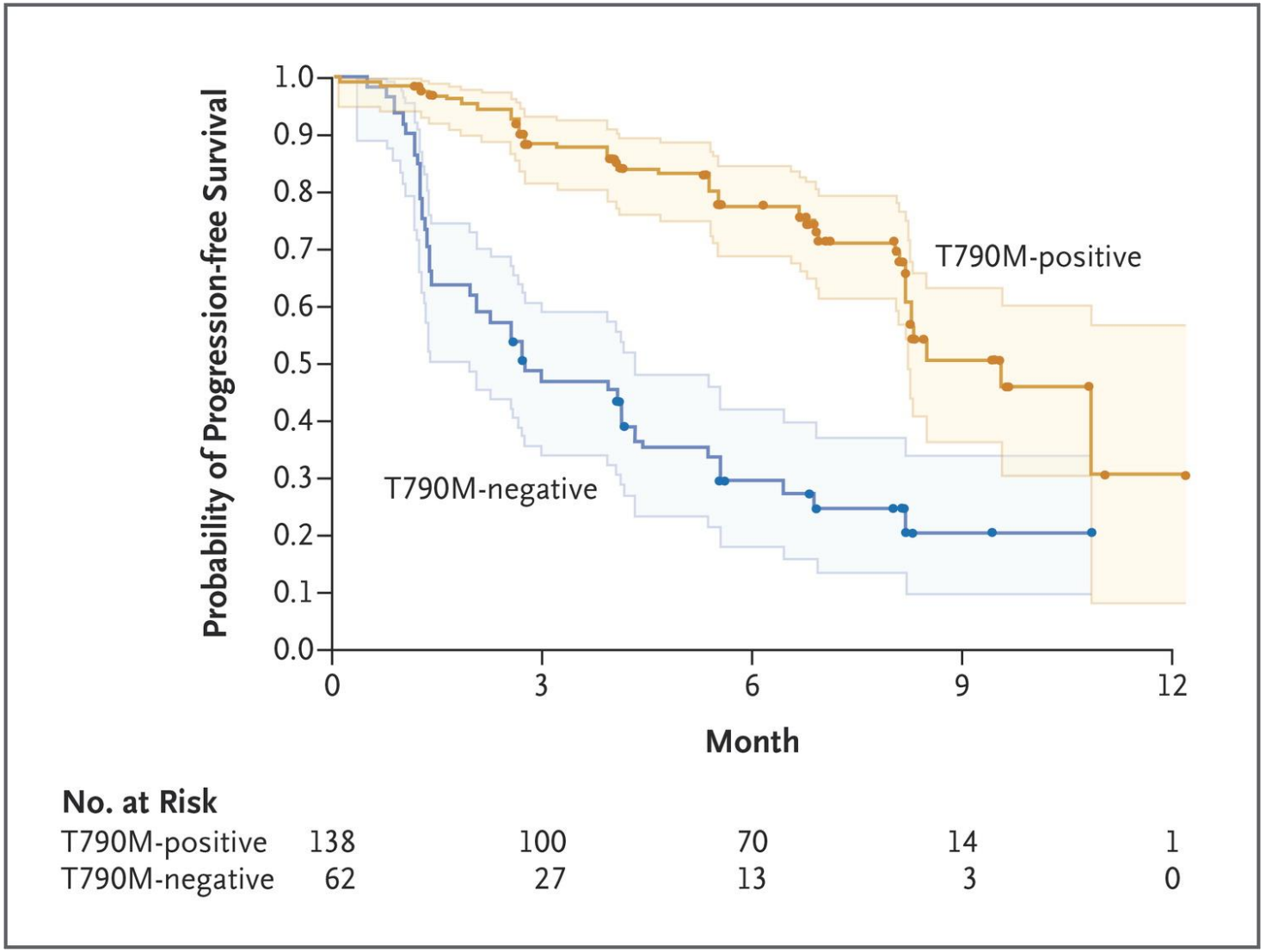


DCR (CR+PR+SD) in patients with centrally tested T790M positive tumours was 64% (44 / 69; 95% CI 51, 75)

	20 mg	40 mg	80 mg	160 mg	Total
N (69)	3	17	29	20	69
ORR (95% CI)	67% (9, 99)	12% (2, 36)	21% (8, 40)	30% (12, 54)	23% (14, 35)

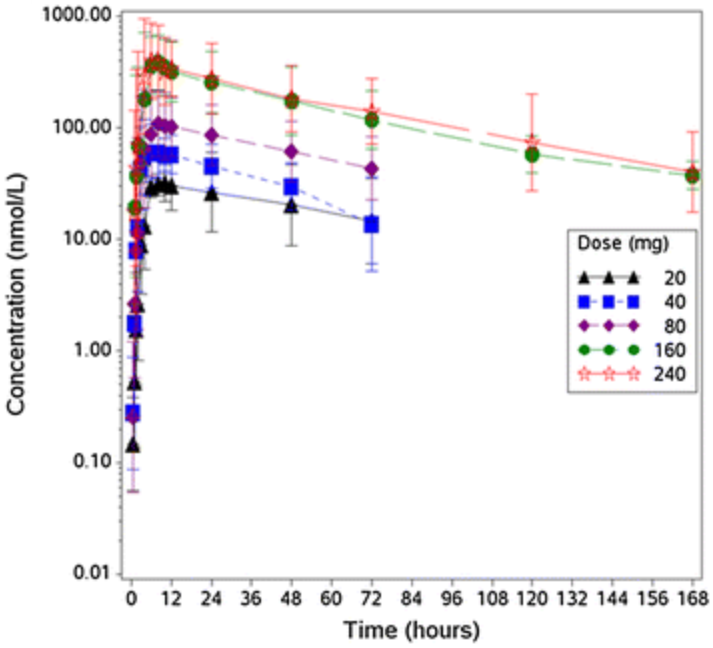
Jänne et al. ELCC 2015

Efficacy of Osimertinib is greater in T790M positive patients

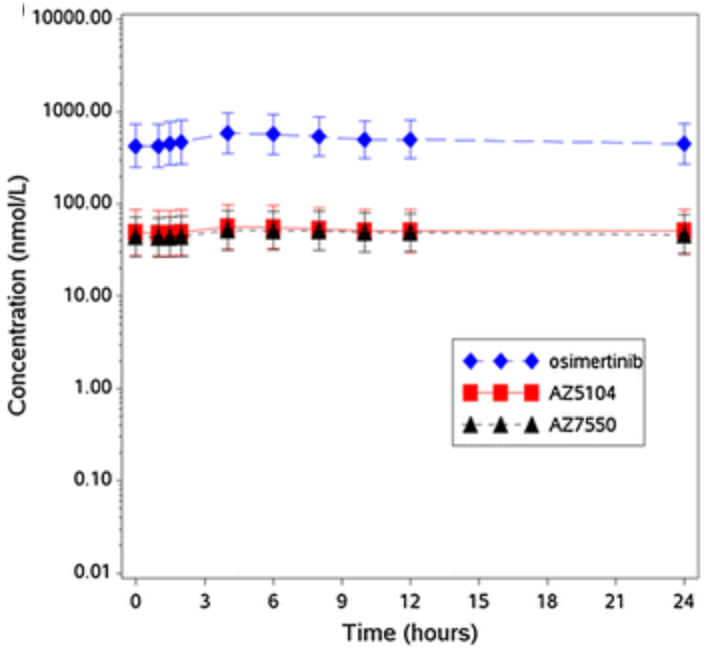


Jänne et al, NEJM, 2015

Single and multiple dose PK of osimertinib



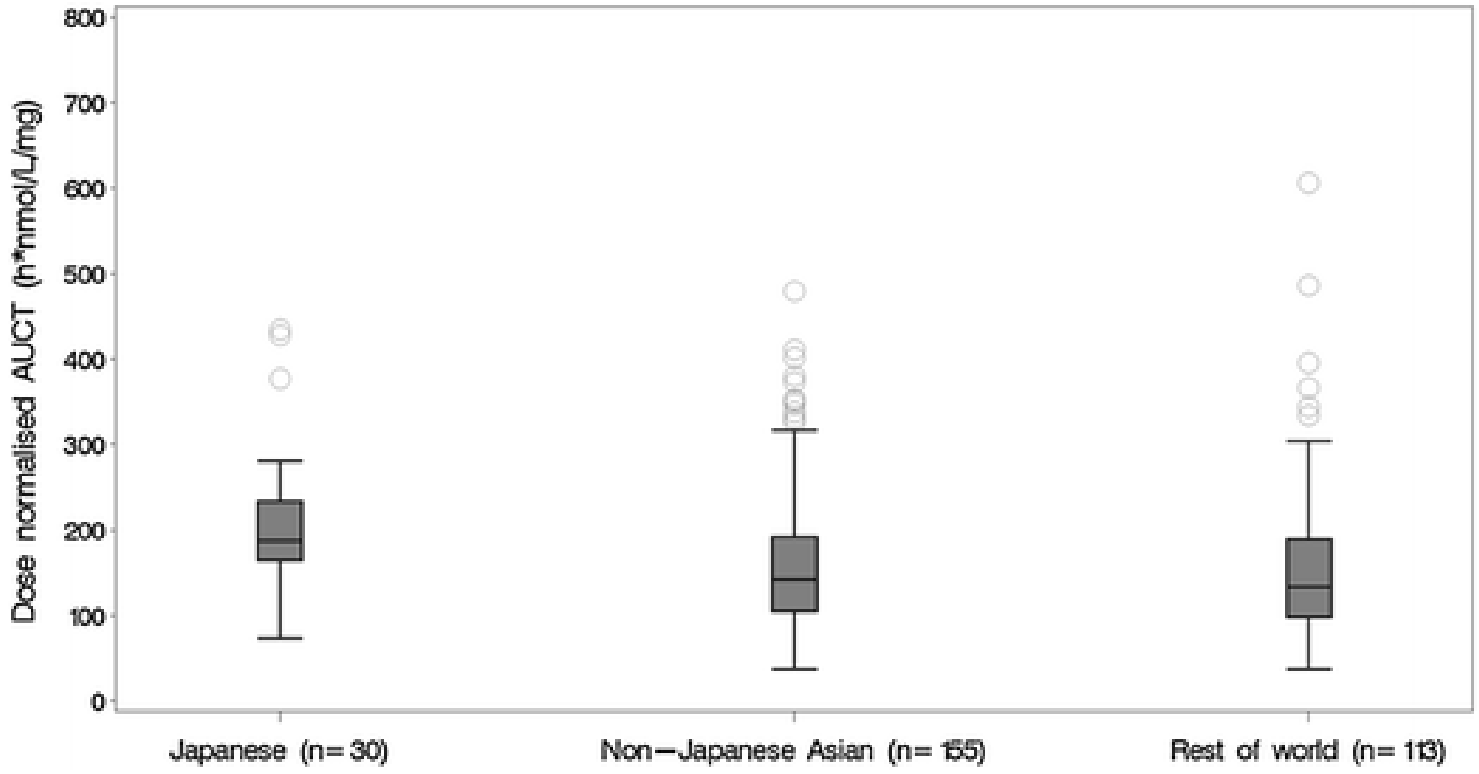
Single dose



Multiple dosing

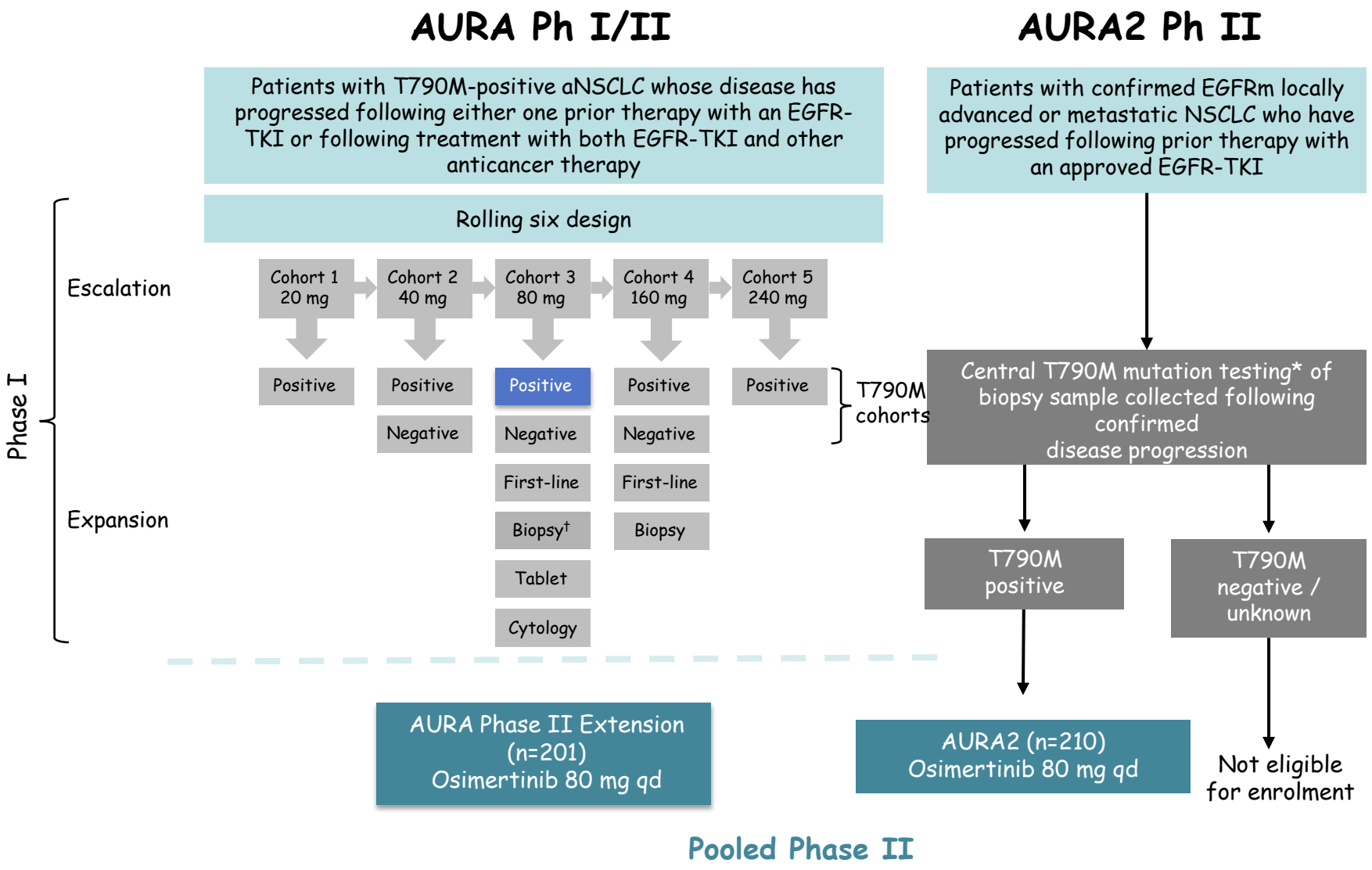
Planchard et al. Cancer Chemother Pharmacol 2016

Osimertinib exposure in different ethnic populations

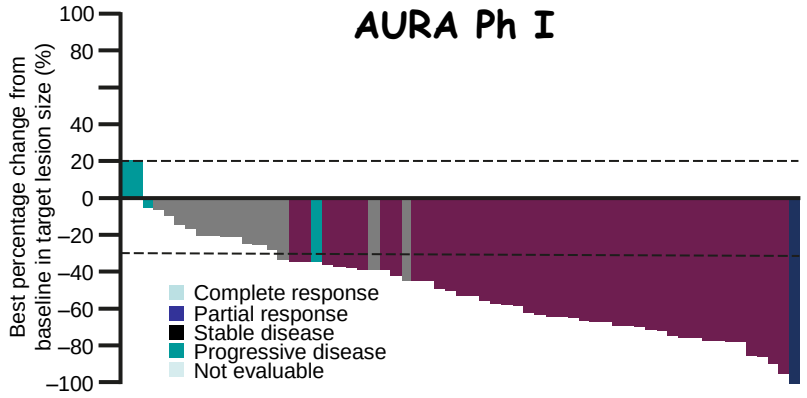


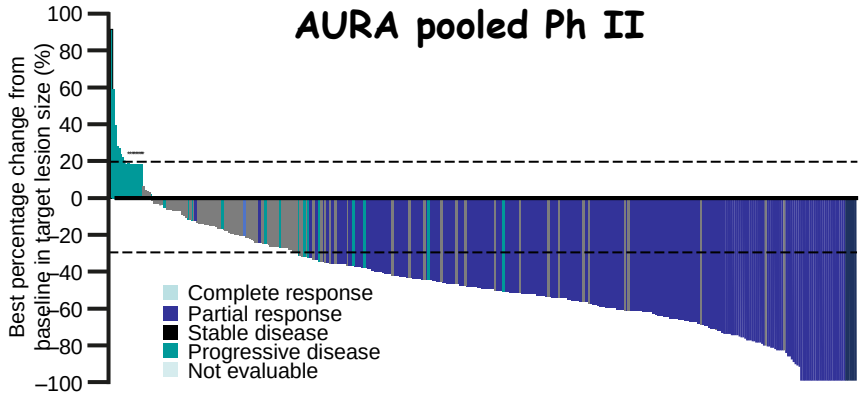
Planchard et al. Cancer Chemother Pharmacol 2016

Osimertinib Phase I & II studies



Osimertinib – phase I and phase II studies

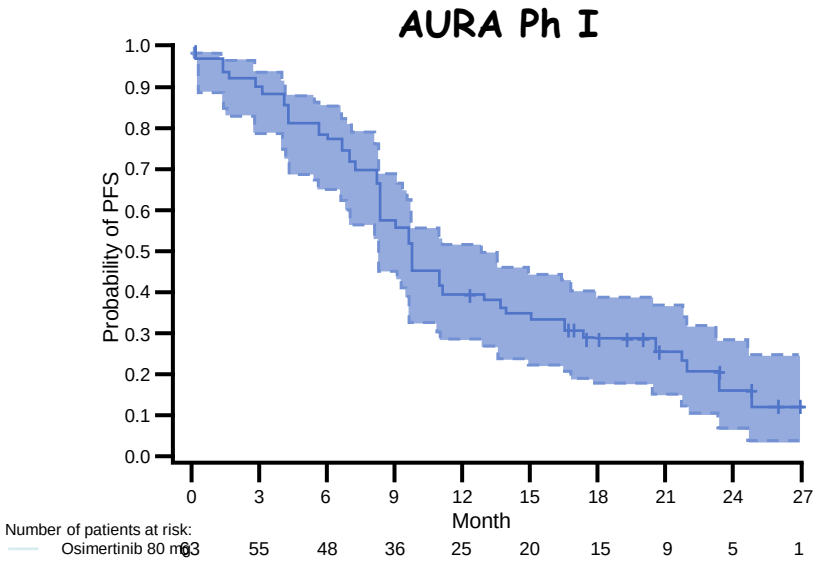


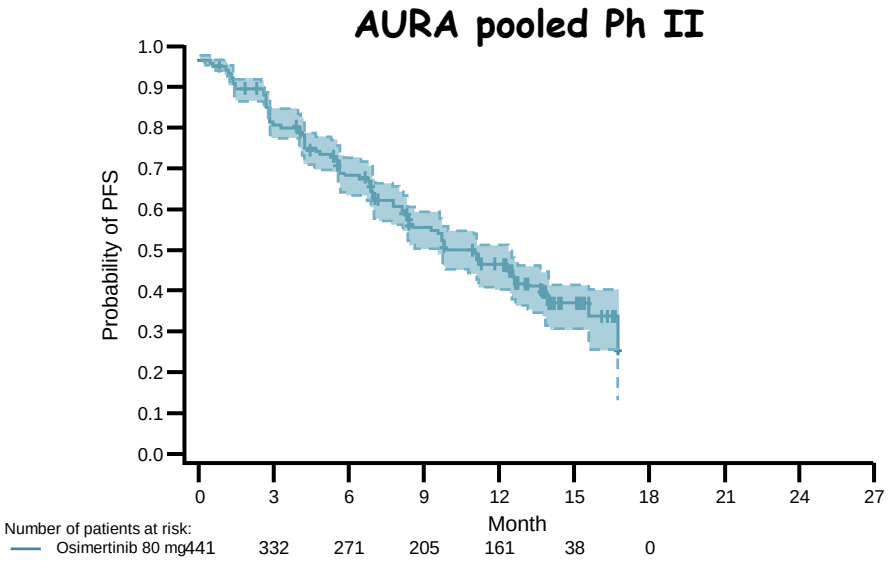


	AURA Ph I (80 mg) N=61	AURA pooled Ph II (80 mg) N=397
Confirmed ORR	71% (95% CI 57, 82)	66% (95% CI 61, 71)
Disease control rate†	93% (95% CI 84, 98)	91% (95% CI 88, 94)
Best objective response		
Complete response	1	6
Partial response	42	256
Stable disease ≥6 weeks	14	99
Progressive disease	2	25

Yang et al. ELCC 2016

Progression-free survival with osimertinib





	AURA Ph I (80 mg) N=63	AURA pooled Ph II (80 mg) N=411
Median PFS,* months (95% CI)	9.7 (8.3, 13.6)	11.0 (9.6, 12.4)
Remaining alive and progression-free,† % (95% CI)		
12 months	41 (29, 53)	48 (42, 53)
18 months	29 (18, 41)	NC
24 months	17 (8, 30)	NC

Yang et al. ELCC 2016

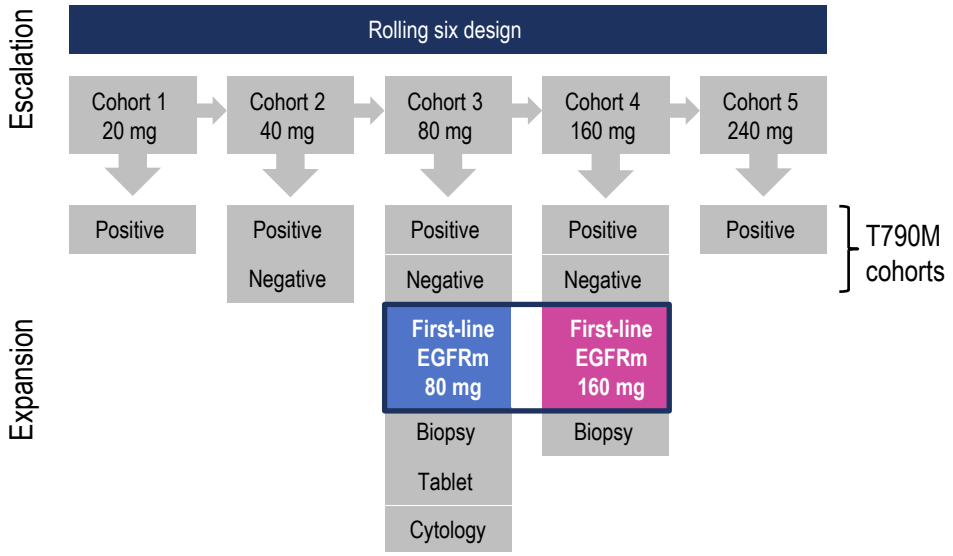
Osimertinib – Summary of Clinical Development

- Regulatory approval for EGFR T790M positive patients in the US, EU and Japan
  - Fastest oncology drug approval
    - First patient treated 3/13; first approval 11/15
- Phase III trial vs. chemotherapy in T790M positive patients
  - Completed enrollment
- Phase III trial vs. gefitinib/erlotinib in EGFR TKI naïve patients
  - Completed enrollment

First line cohorts from osimertinib Phase I study

First-line cohort objective

- Safety and tolerability of osimertinib (80 mg or 160 mg qd orally) as first-line therapy for patients with EGFRm advanced NSCLC



Key inclusion criteria:

- Aged ≥18 (≥20 in Japan)
- Locally advanced or metastatic NSCLC
- No prior therapy for advanced disease
- Measurable disease at baseline
- Patients must have EGFR mutation positive NSCLC (local test)

Key exclusion criteria:

- Prior history of ILD
- Symptomatic brain metastases

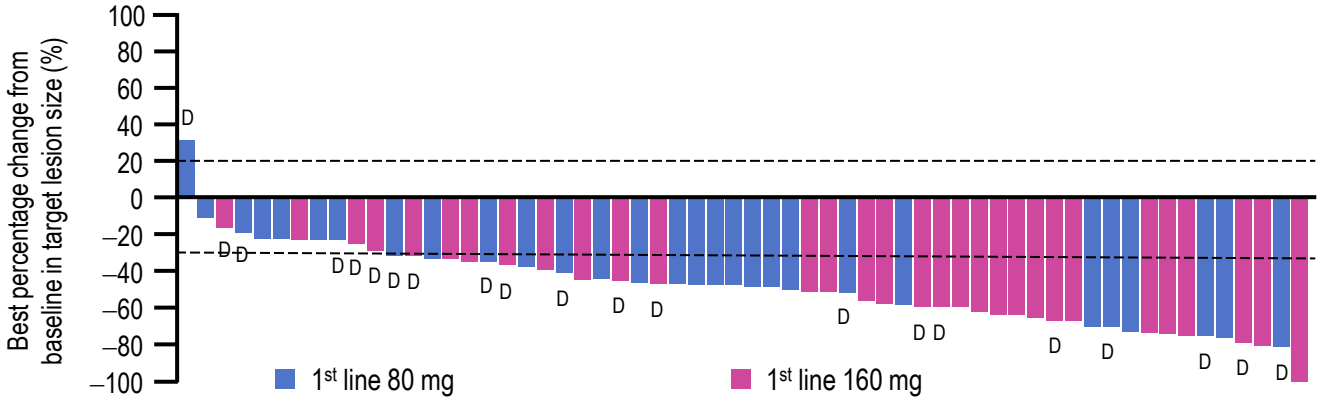
Ramalingam et al. ELCC 2016

Summary of adverse events in osimertinib EGFRm first-line cohorts

AE category, all causality, n (%)	Safety analysis set*		
	80 mg n=30	160 mg n=30	Total N=60
Any AE	30 (100)	30 (100)	60 (100)
Any AE ≥Grade 3	13 (43)	15 (50)	28 (47)
Any AE leading to death	0	0	0
Any AE leading to dose interruption	8 (27)	9 (30)	17 (28)
Any AE leading to dose reduction†	3 (10)	14 (47)	17 (28)
Any AE leading to discontinuation	4 (13)	2 (7)	6 (10)
Any serious AE	11 (37)	7 (23)	18 (30)
AE category, drug-related‡			
Any AE	29 (97)	30 (100)	59 (98)
Any AE ≥Grade 3	4 (13)	6 (20)	10 (17)
Any AE leading to discontinuation	2 (7)	1 (3)	3 (5)
Any serious AE	4 (13)	1 (3)	5 (8)

Ramalingam et al. ELCC 2016

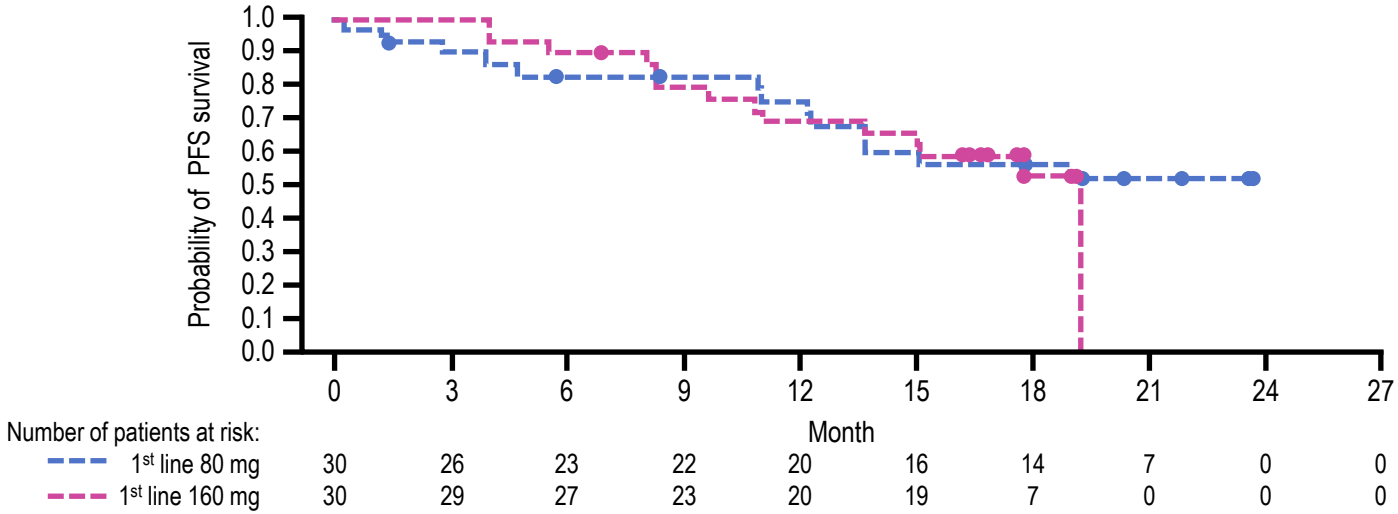
Tumour response to osimertinib in EGFRm first-line cohorts (investigator assessed)



	80 mg n=30	160 mg n=30	Total N=60
Confirmed ORR	67% (95% CI 47, 83)	87% (95% CI 69, 96)	77% (95% CI 64, 87)
Disease control rate*	93% (95% CI 78, 99)	100% (95% CI 88, 100)	98% (95% CI 89, 100)
Best objective response			
Complete response	0	2	2
Partial response	20	24	44
Stable disease ≥6 weeks	8	4	12
Progressive disease	2	0	2

Ramalingam et al. ELCC 2016

PFS in osimertinib EGFRm first-line cohorts (investigator assessed)

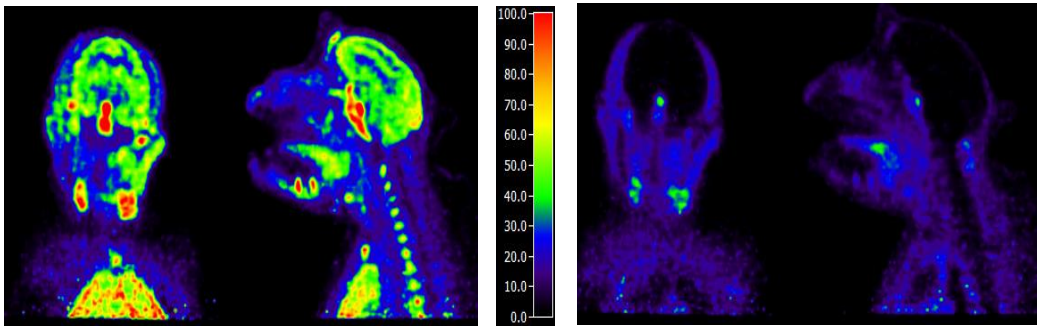


	80 mg n=30	160 mg n=30	Total N=60
Median PFS,* months (95% CI)	NC (12.3, NC)	19.3 (11.1, 19.3)	19.3 (13.7, NC)
Remaining alive and progression-free,† % (95% CI)			
12 months	75 (55, 88)	69 (49, 83)	72 (59, 82)
18 months	57 (36, 73)	53 (32, 70)	55 (41, 67)

Ramalingam et al. ELCC 2016

Osimertinib (AZD9291) effectively penetrates the brain

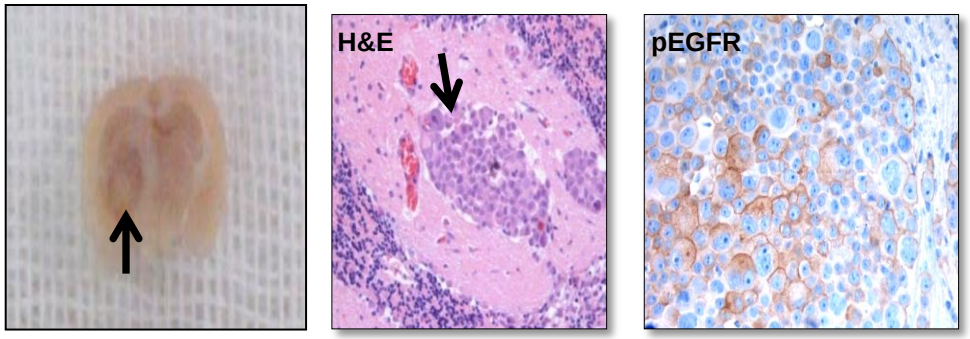
[^{11}C]AZD9291 Radioactivity (kBq / cc) [^{11}C]CO-1686

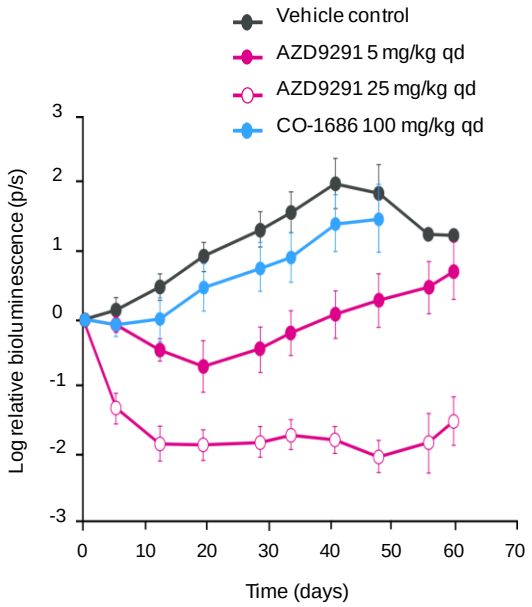


Summation images acquired 5 min up to 2 h after intravenous microdose (<3 μg) injection

	Brain to blood ratio $AUC_{0-90\ min}$ (corrected for radioactivity in cerebral blood)
[^{11}C]AZD9291 (n=3)[1]	2.6 ± 1.4
[^{11}C]CO-1686 (n=2)[1]	0.025
[^{11}C]gefitinib (n=2)[2]	0.28

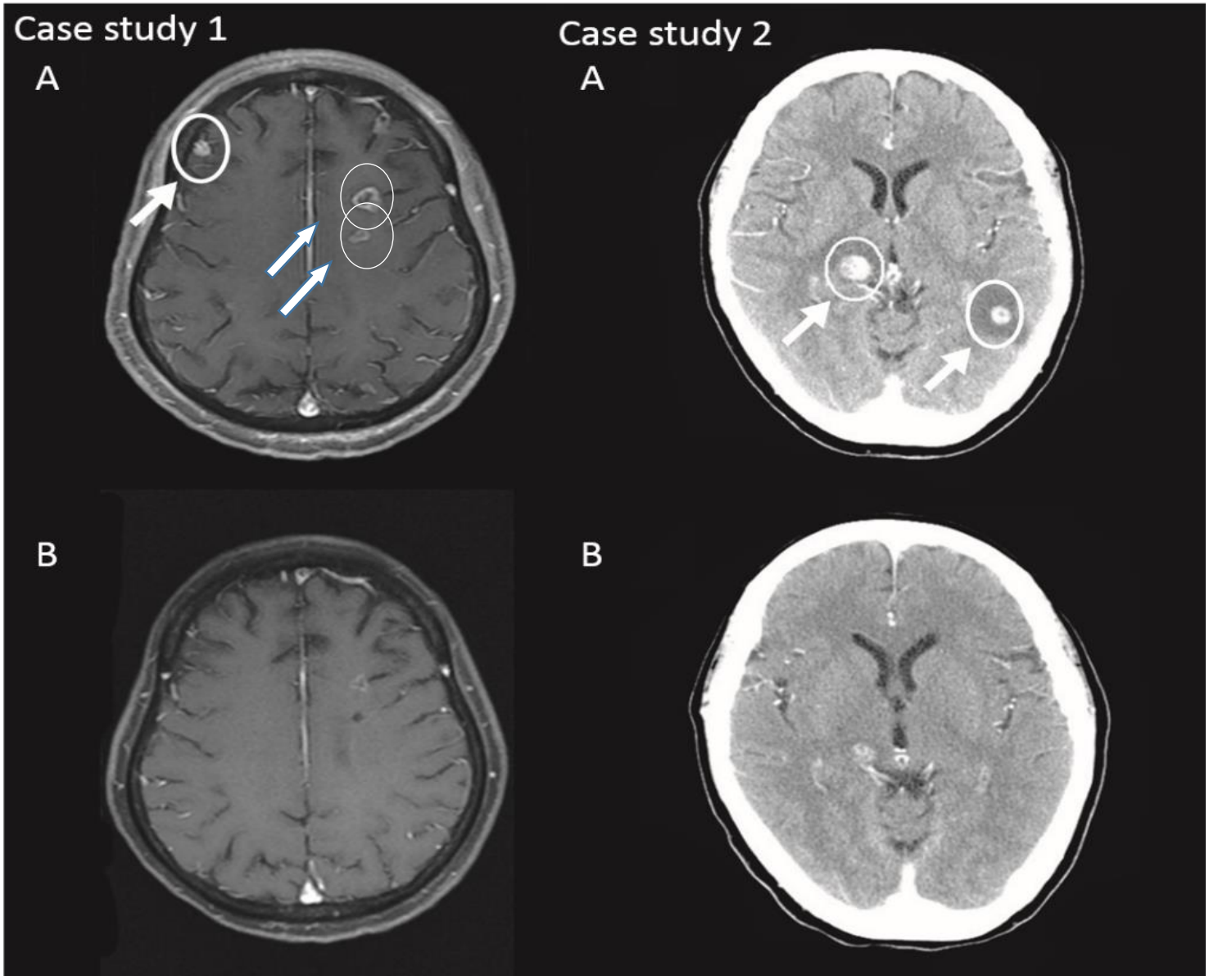
Intra carotid injection model of brain metastases using PC9 cells





Ballard et al. CCR 2016 *in press*

Efficacy of Osimertinib in brain metastases



40 mg **80 mg**

BLOOM Study – evaluation of osimertinib in patients with leptomeningeal carcinomatosis

Osimertinib LM cohort 1

Advanced or metastatic EGFRm NSCLC and confirmed diagnosis of LM by positive CSF cytology

Key inclusion criteria:

- Primary tumor with EGFR L858R or exon 19 deletion
- Prior EGFR-TKI treatment
- ECOG PS 0–2
- Stable extracranial disease
- At least one LM lesion by MRI scan

Osimertinib 160 mg QD

Assessments

- Adverse events*
- Efficacy assessment:
  - OS
  - Brain MRI and extracranial MRI or CT scan*†
  - CSF cytology
  - Neurological exam*
  - CNS symptoms*
- PK in CSF
- Quantification of EGFRm DNA in CSF

Yang et al ASCO 2016

BLOOM Study – patient characteristics

Characteristic, n	N=21
Gender: male / female	6 / 15
Age: median (range), years	59.0 (44–75)
Smoking status: current / former / never	1 / 5 / 15
ECOG PS: 0 / 1 / 2	1 / 11 / 9
Neurological assessment at baseline: normal / abnormal	11 / 10
Prior lines of systemic therapy: median (range)	3.0 (1–8)
Prior whole brain radiotherapy	11
Prior EGFR-TKIs†: gefitinib / erlotinib / dacomitinib / HM61713 (BI 1482694)	16 / 3 / 1 / 1
Prior systemic response to EGFR-TKI: partial response / stable disease / progressive disease	14 / 6 / 1
Tumor tissue EGFRm mutation status (local test)‡: Ex19Del / L858R	9 / 13

- Two patients had T790M detected in CSF at study entry; 6 patients had T790M detected in plasma
- Duration of treatment: 1–49 weeks ongoing

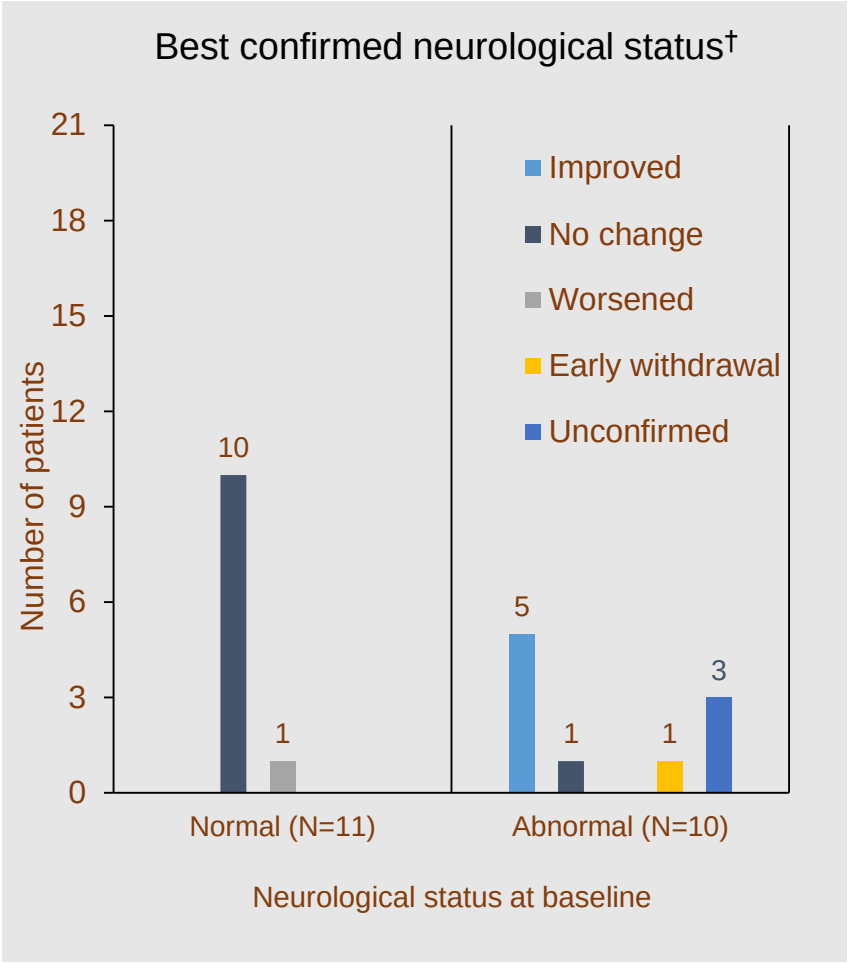
Yang et al ASCO 2016

Efficacy and Neurological Improvement in LM Patients Treated with Osimertinib

Efficacy assessments were conducted on 21 patients

- Seven patients had confirmed* radiological improvement
- Two patients had confirmed* CSF cytology clearance; no tumor cells were detected in two consecutive CSF samples
- Five patients had confirmed* improved neurological function

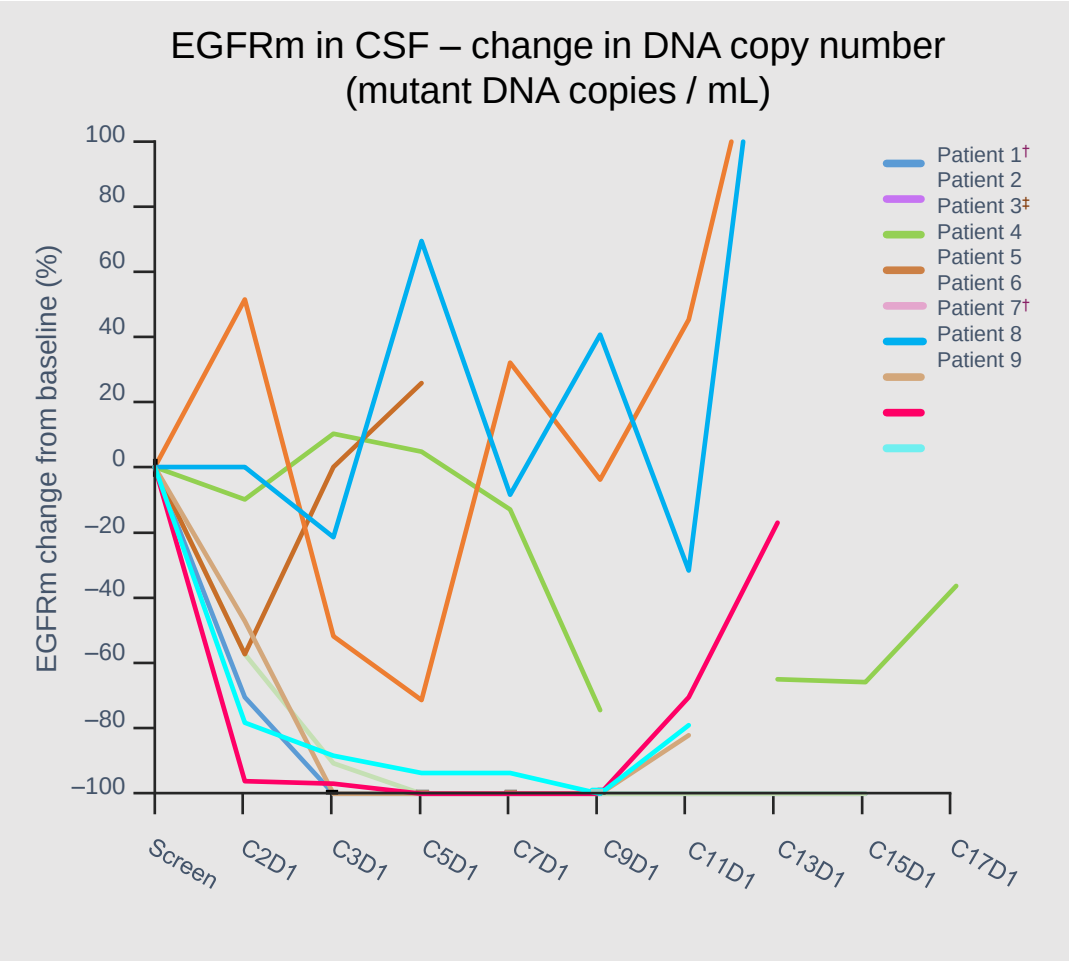
Best MRI imaging intracranial response, n (%)	N=21	
	Confirmed*	Unconfirmed
Responding	7 (33)	1 (5)
Stable disease	9 (43)	2 (10)
Early withdrawal	2 (10)	



Yang et al ASCO 2016

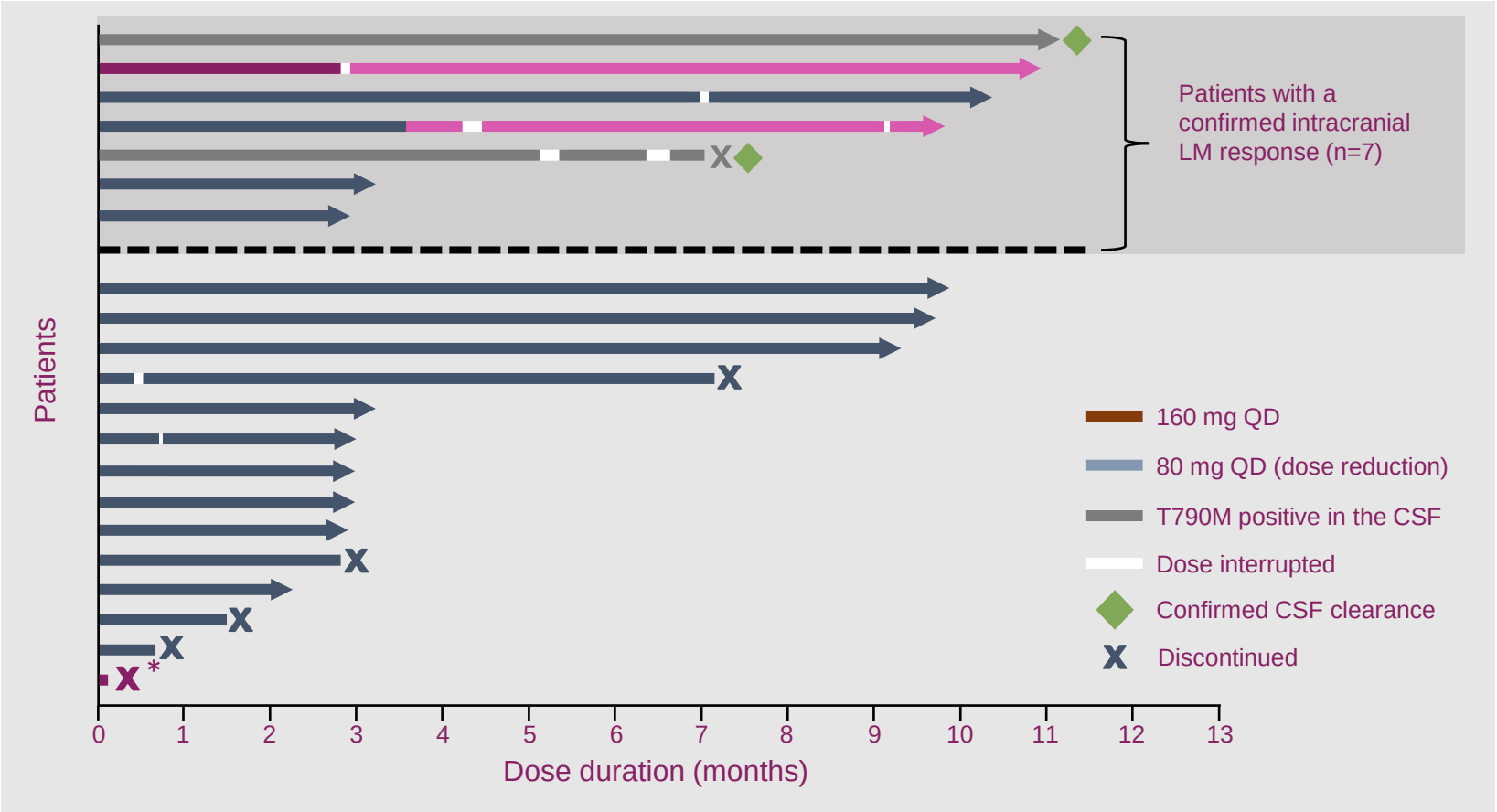
Evidence of PD in CSF in LM Patients Treated with Osimertinib

- Droplet digital PCR was used to detect EGFRm DNA copy number; data were available for 9 patients*
- All patients had EGFR-TKI sensitizing mutations detected in screening CSF; 2 patients had T790M
- Among them, 6 patients had a >50% decrease in EGFRm DNA copies up to C9D1; 5 had sustained decrease
  - 4/6 improved neurological function
  - 4/6 LM-MRI responded;
    2/6 LM-MRI stable disease
  - 2/6 CSF clearance



Yang et al ASCO 2016

Treatment duration of LM Patients Treated with Osimertinib



Fifteen patients are ongoing treatment at time of data cut-off (March 10, 2016)
7 of whom have been on treatment for >9 months

Yang et al ASCO 2016

Development of Osimertinib in EGFR Mutant Lung Cancer

- Effective in patients with EGFR T790M
  - Multiple effective doses (20 to 240 mg) evaluated across ethnic populations
    - 80 mg dose developed further
    - No MTD or DLTs
    - Wide therapeutic window; effective in brain metastases
- Ongoing development
  - Phase III in second line (EGFR T790M) and first line (EGFR L858R/Del 19)
  - Patients with LM disease (160 mg)

Finding Safe and Efficacious Dose Using Sequential Generalized Likelihood Ratio Statistics

Ying Lu, Ph.D.
VA Cooperative Studies Program Palo Alto Coordinating Center
Stanford Cancer Institute and Center for Innovative Study Design
Department of Biomedical Data Science, Stanford University

Joint work with T.L Lai, B. Narasimhan@Stanford, J. Bartoff@USC
and A. Gewitz@UCSF, Y. Song@SJTU

Changing Clinical Trial Landscape

- Traditional approach for early development of oncology drugs
  - Phase I evaluates safety and dose relationship: find an estimate $\hat{\eta}_0$ of the MTD η as a RP2D
  - Phase II evaluates efficacy signals: e.g. Simon's two-stage design to test $H_0: p(\eta) \leq p_0$ vs $H_1: p(\eta) \geq p_1$
  - Phase II is separated from phase I and doesn't account for the uncertainty of RP2Ds: test $K_0: p(\hat{\eta}_0) \leq p_0$ vs $K_1: p(\hat{\eta}_1) \geq p_1$
- The changing landscape of phase I trials in oncology (Wong 2016)
  - MTD is less appropriate RP2D for molecular targeted agents
  - Early evidence of efficacy becomes an integrate component
  - Several Bayesian statistical methods have been developed to identify and select safe and efficacious doses as RP2Ds
  - It is less known for frequentist approaches, such as the sequential GLR tests

Outlines

Goal: introduce a general approach based on sequential generalized likelihood ratio test (GLRT) to combine phase I and II trials for testing efficacy under safety constraints (Bartroff, et al. 2014).

1. Brief history of sequential testing in clinical trials

2. Combination of Phase I + II design for safety and efficacy

3. Take-home messages

History of Sequential Testing for Clinical Trials

- Utility recognized as early as 1950s
  - Likelihood: $f_\theta(x)$, x observations and θ model parameter
  - Likelihood ratio: $f_{\theta_1}(x)/f_{\theta_2}(x)$ (Neyman-Pearson lemma)
  - Difference between LRT and GSLRT
  - Wald's optimality theorem
- Group sequential methods: $\leq$ M groups, error spending
  - Armitage, McPherson, Rowe (69) : Repeated significance tests
  - Haybittle (71); Peto (76)
  - Pocock (77); O'Brien and Fleming (79); Lan & DeMets (83)
  - Wang and Tsiatis (87);
  - Emerson and Fleming (89) : Power family
- Bartroff, Lai, and Shih. *Sequential Experimentation in Clinical Trials*. Springer Series in Statistics 298, 2013

A New Phase I-II Approach

Current:

- Phase I: find estimate $\hat{\eta}_0$ of the optimal dose η (e.g. MTD, BOD)
- Phase II: Test $K_0: p(\hat{\eta}_0) \leq p_0$ (e.g. Simon's two-stage design)

Proposed Phase I-II Design:

1. Choose a joint efficacy-toxicity model
2. Combined phase I +II approach:
   - Stage 0: find an estimate $\hat{\eta}_0$ of the optimal dose η (e.g. MTD, BOD) based on phase I toxicity data and enroll additional patients to dose $\hat{\eta}_0$.
   - Stage I: test efficacy hypothesis: $H_0: P(\text{efficacy}|x = \hat{\eta}_l) \leq p_0$.
     - if rejected, $\hat{\eta}_l$ is the recommended dose for phase IIb or III.
     - If not, use all toxicity data to updated the optimal dose to $\hat{\eta}_{l+1}$; enroll more patients to dose $\hat{\eta}_{l+1}$; repeat stage I

Use Group Sequential GLR Test

Test $H_0: P(\text{efficacy}|x=\eta) \le p_0$ vs. $H_1: P(\text{efficacy}|x=\eta) \ge p_1$

- GLR statistic $\Lambda_{\ell,i}$ comparing $\hat{\theta}_l$ versus θ_i at ℓ^{th} stage

Modified Haybittle-Peto Boundaries (Lai and Shih 04)

Stop and	H_0 at stage	if		
reject	$1 \le \ell < L$	$p(\hat{\eta}_\ell; \hat{\beta}_\ell) > p_0$	and	$\Lambda_{\ell,0} \ge b$
accept	$1 \le \ell < L$	$p(\hat{\eta}_\ell; \hat{\beta}_\ell) < p_1$	and	$\Lambda_{\ell,1} \ge \tilde{b}$
reject	L	$p(\hat{\eta}_L; \hat{\beta}_L) > p_0$	and	$\Lambda_{L,0} \ge c$

- Boundaries $b, \tilde{b},$ and c are chosen so that

$$\max_{\beta \in S_{0.0}} P(H_0 \text{ is rejected } |\hat{\eta}, \beta\ ) = \text{type I error}$$

$$\min_{\beta \in S_{0.1}} P(H_0 \text{ is rejected}|\hat{\eta}, \beta) \approx \text{power}$$

- Small loss in power compared to most-powerful fixed sample test
- Strong asymptotic optimality properties

Simulation Study 1:Current Practice

Phase I: EWOC (Babb et al 98)

- Colon Cancer Trial setting, *n=24* patients
- $\rho = P(toxicity|x = x_{min})$
- Priors: $\eta \sim Uniform[x_{min}, x_{max}]$, $\rho \sim Uniform[0,1/3]$
- $[x_{min}, x_{max}]$=$[140,425]$

Phase II: Simon's 2-stage

- $p_0 = 0.1; p_1 = 0.25; \alpha = .01, .02, .03, .04, .05$; power=.80

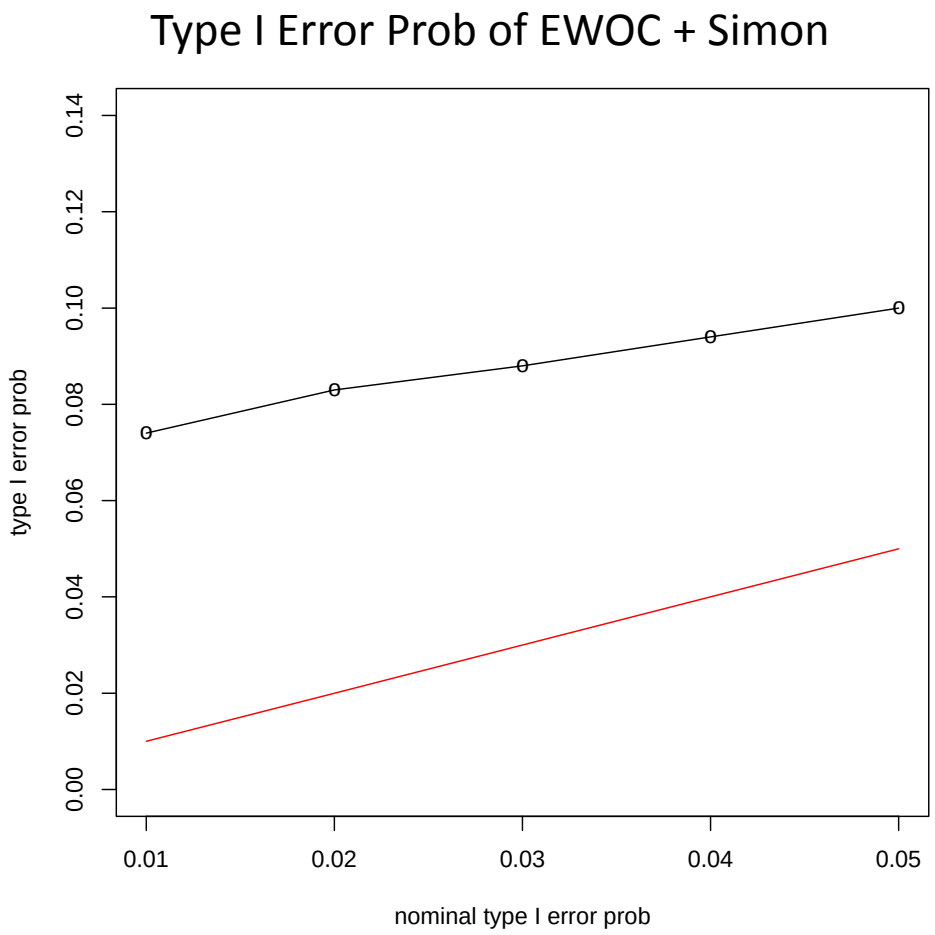
Truth: (η, ρ)=$(250,0.1)$, $p(\eta)$=$p_0 = 0.1$, $p(x_{max})$=0.9

- Logistic regression toxicity/efficacy model
- 100,000 simulations

Simulation Study 1:Current Practice

$\hat{\eta}$	min	med	max	mean	RMSE
EWOC	141.0	246.9	362.7	239.8	29
α	.01	.02	.03	.04	.05
Simon	18/25/2/7	18/30/2/8	18/35/29	22/44/3/11	22/58/3/14
$P(\text{Rej } H_0)$	.074 (.0008)	.083 (.0009)	.088 (.0009)	.094 (.0009)	.100 (.0009)

Simulation Study 1:Current Practice



Simulation Study 2: Phase I-II Design

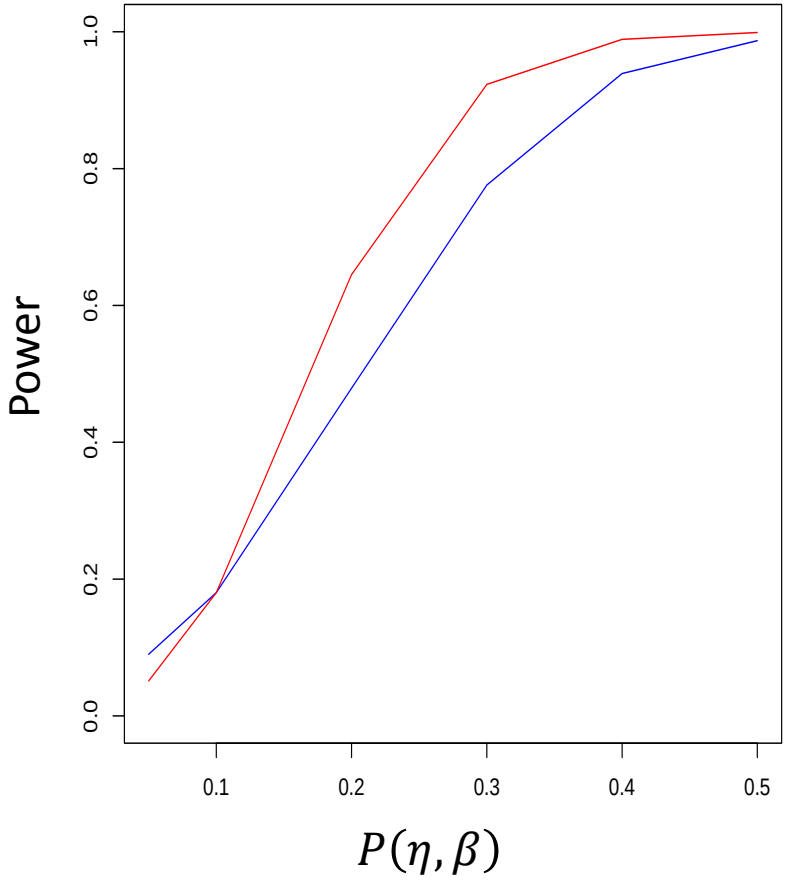
Phase I: EWOC (Babb et al 98): same, m=24

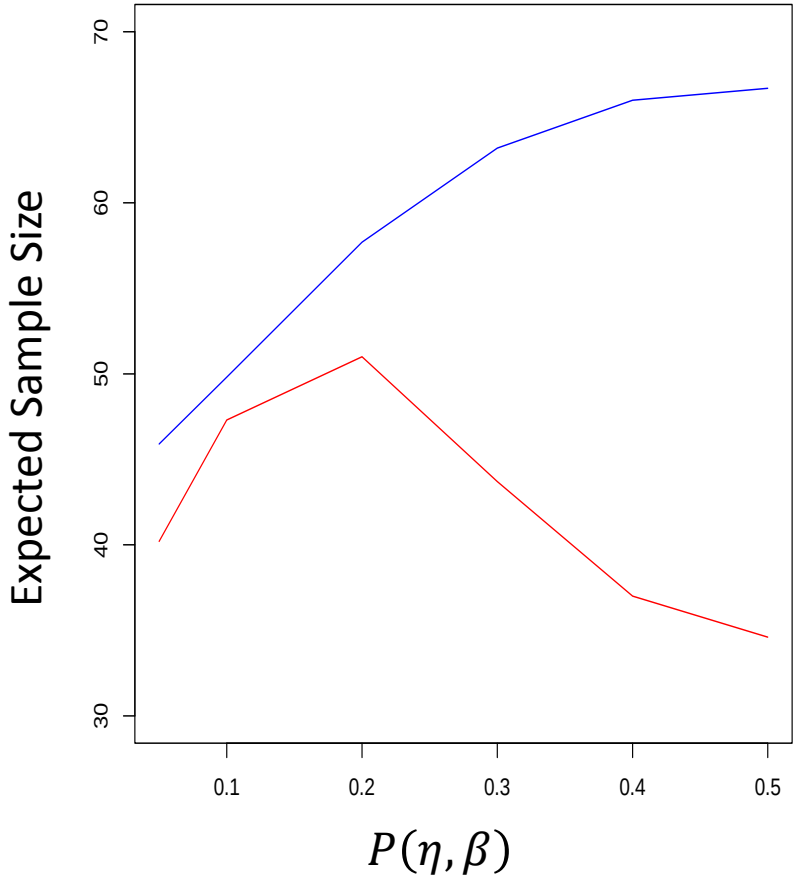
Phase II: 5-Stage GLR test

$n_1 = n_2 = n_3 = n_4$ =10, n_5 =3, $\alpha = .18, power = .8$;
group 1 included all patients in phase I

Simulation Study 2: Comparison w/ Phase I-II Design

Comparisons between the Current Practice (Trad) and the New Design





Simulation Study 2: Comparison w/ Phase I-II Design

Comparison	Method	$P(\eta;\beta)$					
		5%	10%	20%	30%	40%	50%
$P(\hat{\eta}_{rec},\beta)$	Trad	.101	.150	.233	.319	.409	.499
	New	.054	.102	.202	.296	.392	.486
Overall Resp Rate	Trad	.096	.140	.219	.310	.405	.498
	New	.061	.104	.200	.293	.381	.474
OD	Trad	.303	.314	.326	.327	.336	.331
	New	.291	.312	.289	.256	.252	.249
RMSE$(\hat{\eta}_{rec})$	Trad	51.0	52.2	52.4	52.3	71.7	52.1
	New	28.4	29.0	29.3	28.6	29.0	29.8

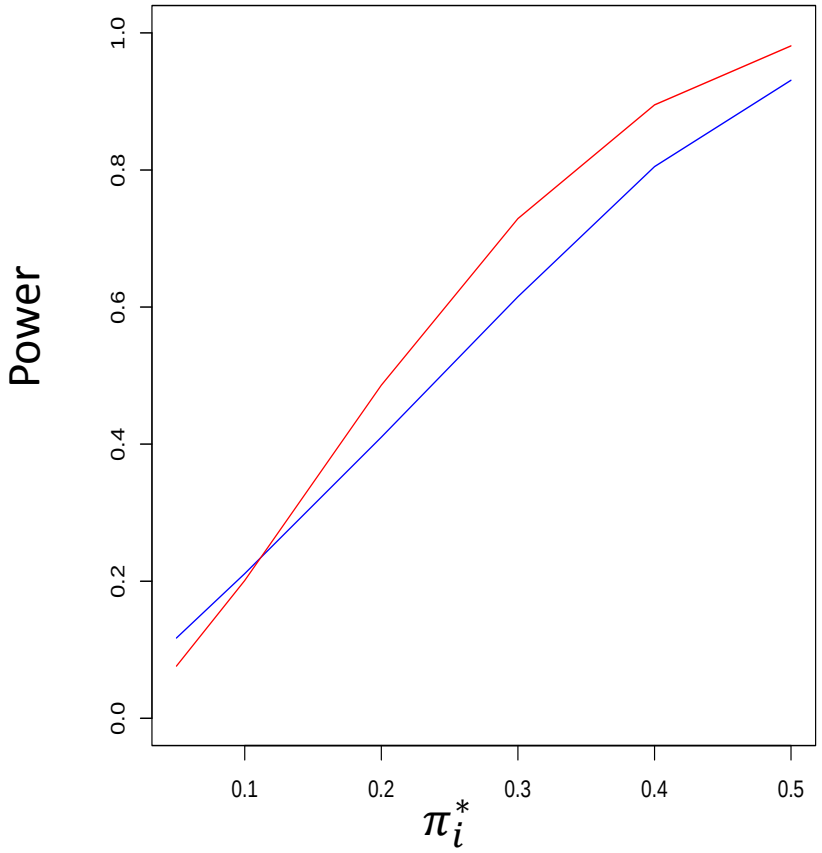
Simulation Study 3: Discrete Dose Space

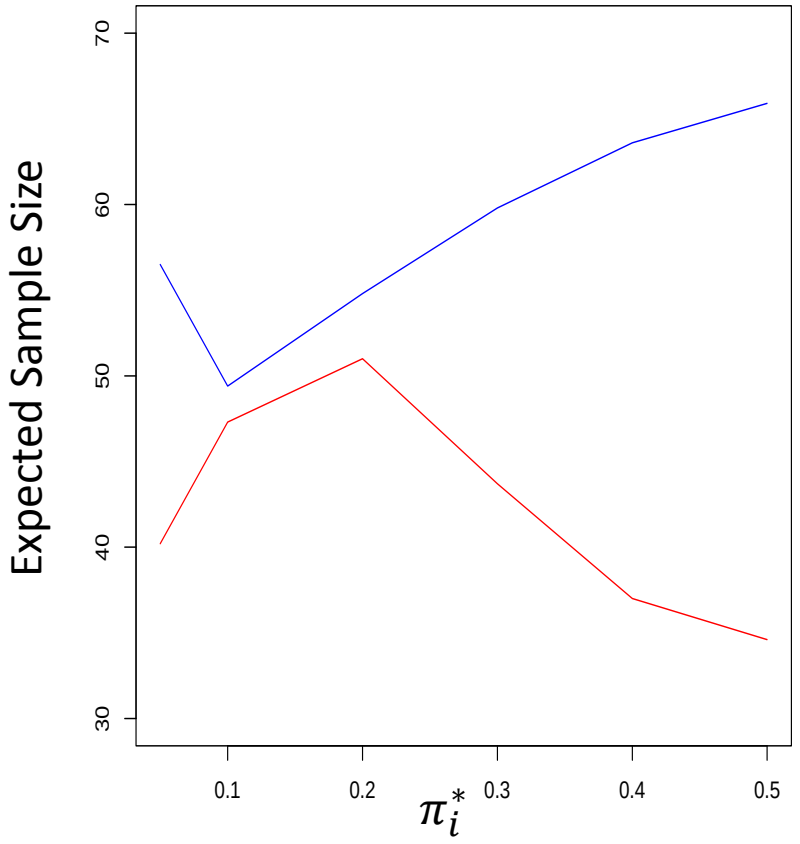
Example of discrete dose space and monotonic toxicity and efficacy

- Dosing space: {140,200,250,300,350,425}
- Isotonic MLEs for both toxicity and efficacy
- Traditional, Phase I: m=24; Phase II: Simon's 2 stage: n=43
- GLR test: matched the type I error for Trad.
- 10,000 simulations

Simulation Study 3: Discrete Dose Space

Comparisons between the Current Practice (Trad) and the New Design





Simulation Study 3: Discrete Dose Space

Comparison	Method	π_i^*					
		5%	10%	20%	30%	40%	50%
$\hat{\pi}_i^*$	Trad	.072	.116	.194	.274	.357	.449
	New	.030	.061	.131	.206	.295	.395
Overall Resp Rate	Trad	.185	.225	.286	.350	.416	.492
	New	.196	.388	.296	.364	.441	.524
OD	Trad	.390	.388	.366	.347	.328	.320
	New	.376	.363	.361	.370	.390	.406
RMSE$(\hat{\lambda}_i^*)$	Trad	56.5	57.4	56.7	56.9	56.5	57.2
	New	60.1	60.9	59.1	52.9	58.3	57.9

Other Examples and Implementation Details

- Other examples:
  - Toxicity and response dependent model
- Critical value determinations
- Adaptive extensions

See Bartroff, et al. (SIM 2014 and Springer 2013)

Extension of Zhang, Sargent and Mandrekar (2006)

Joint Safety and Efficacy Model for Optimal Biological Dose (OBD)	
Variable: $y_{0,i}+y_{1,i}+y_{2,i} = 1$	Probability $y_{k,i}=1$, $k = 0,1,2$
toxicity: $y_{2,i}$	$\psi_2(x;\theta)=exp(\alpha_2+\beta_2 x)/[1+exp(\alpha_2+\beta_2 x)]$
response w/o toxicity: $y_{1,i}$	$\psi_1(x;\theta)=exp(\alpha_1+\beta_1 x)/\{[1+exp(\alpha_1+\beta_1 x)][1+exp(\alpha_2+\beta_2 x)]\}$
no response & toxicity: $y_{0,i}$	$\psi_0(x;\theta)=1/\{[1+exp(\alpha_1+\beta_1 x)][1+exp(\alpha_2+\beta_2 x)]\}$

Uniform prior for components of θ.

OBD η: $\psi_1(\eta;\theta) = \max_{\{x:\psi_2(x;\theta)<\pi_0\}} \psi_1(x;\theta)$

$H_0: \psi_1(\eta;\theta) \le p_0$ vs. $H_1: \psi_1(\eta;\theta) \ge p_1$

- A similar GLRT can be constructed

Extension of Chiang and Conforti (1989)

Basic assumptions (Chiang & Conforti, Math. Bios. 89)

- the remaining drug at time t after x units of drug administered at time s

  $$x\vartheta ds e^{-\tau(t-s)}$$

  ϑ is absorbing parameter and τ is discharge parameter

- the remaining drug at time t after for x units drug administered in $[s_1, s_2\ ]$

  $$D(t; s_1, s_2) = \frac{x\vartheta}{\tau} e^{-\tau t}\left(e^{\tau(s_2 \wedge t)} - e^{\tau(s_1 \wedge t)}\right)$$

- the cumulative dose AUC

  $$AUC(t; s_1, s_2) = \int_0^t D(u;\ s_1, s_2)\, du$$

  $$= \frac{x\vartheta}{\tau^2}\left\{\tau(t \wedge s_2 - s_1) + e^{-\tau(t \wedge s_2 - s_1)} - 1 + (e^{\tau s_2} - e^{\tau s_1})\left(e^{-\tau s_2} - e^{-\tau t \wedge s_2}\right)\right\}$$

Extension of Chiang and Conforti (1989)

Models for toxicity and efficacy endpoints:

- modeling hazard rate for the first toxicity event at time t as a function of dose concentration
- model probability of response: a logistic function of cumulative exposure (AUC) by the end of treatment T
- likelihood function based on joint observation
- application of GLR test for inference and dose selection

Extension of Chiang and Conforti (1989)

Advantages:

- flexible to address delayed toxicity
- easy to evaluate different dosage
- easy extension to drug combinations

Disadvantages:

lack of data to verify the model

Take-Home Messages

- Standard practice can have incorrect type I error probability in Phase II
- Artificial barrier between Phase I, II removed: both efficacy and toxicity data are utilized
- Group sequential GLRT methods can improve both average sample size and power for Phase I-II
- Publicly available R package

Thanks for Dr. Lei Nie's helpful suggestions

Thank you for your attention

Dose Adjustment Integrated Exposure-Response Analysis (DAIER) For Dose Optimization

Lenvatinib in Renal Call Carcinoma

Chao Liu, Ph.D., M.Stat.
Division of Pharmacometrics
Office of Clinical Pharmacology
OTS/CDER/FDA

June 13th, 2016

Outline

- **Background**
  - Post-marketing Dose Optimization Trial
  - Exposure-Response (E-R) Analysis
- **Case Study**
  - Lenvatinib in Renal Cell Carcinoma
- **Summary**

Background

- **Post-marketing dose optimization trial**
  - Maximize effectiveness and minimize toxicity
  - Dose adjustment is common
  - Selection of alternative dosing regimen is challenging

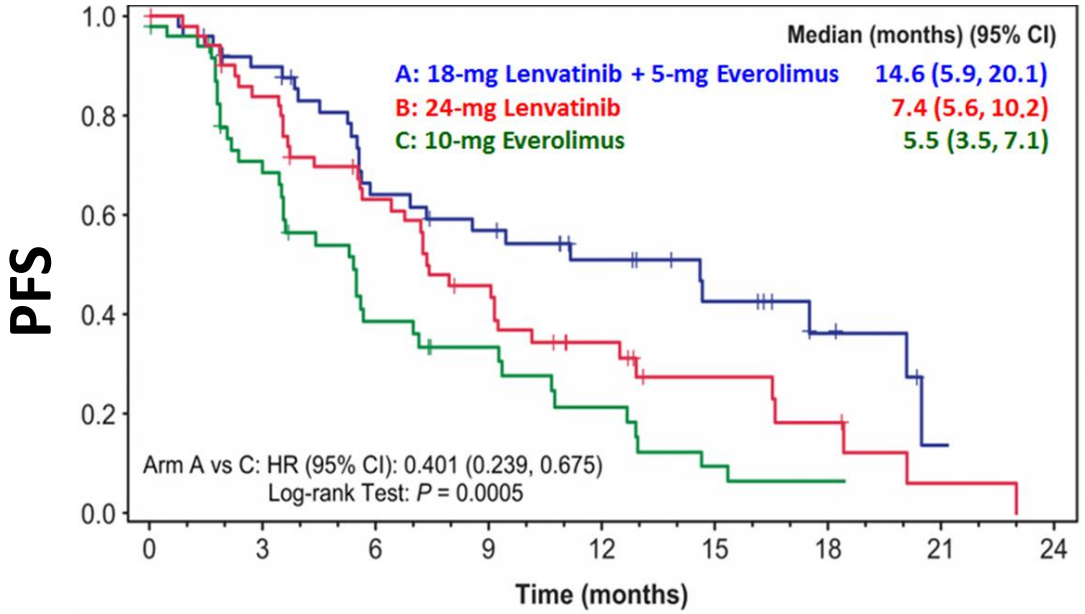
- **Modeling and simulation for dose-finding**
  - Understand the exposure-response (E-R) relationship
  - Design optimal future studies through trial simulations

Select the promising dosing regimen(s) to study based on the available data

Case Study: Lenvatinib for RCC

Tyrosine kinase inhibitor (TKI) for

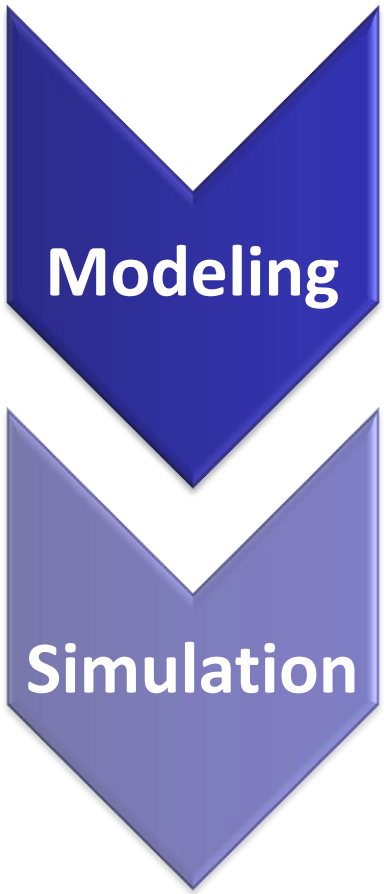
- Differentiated Thyroid Cancer (DTC)
- Advanced Renal Cell Carcinoma (RCC)
  - Approved Dose: 18-mg Lenvatinib + 5-mg Everolimus QD
  - **89%** patients required **dose reduction/interruption**



PMR To Conduct a Dose Optimization Study

Which Dosing Regimen to Study?

General Workflow



Quantify the exposure-response for

- **Efficacy**
- **Safety**

Evaluate different dosing regimens

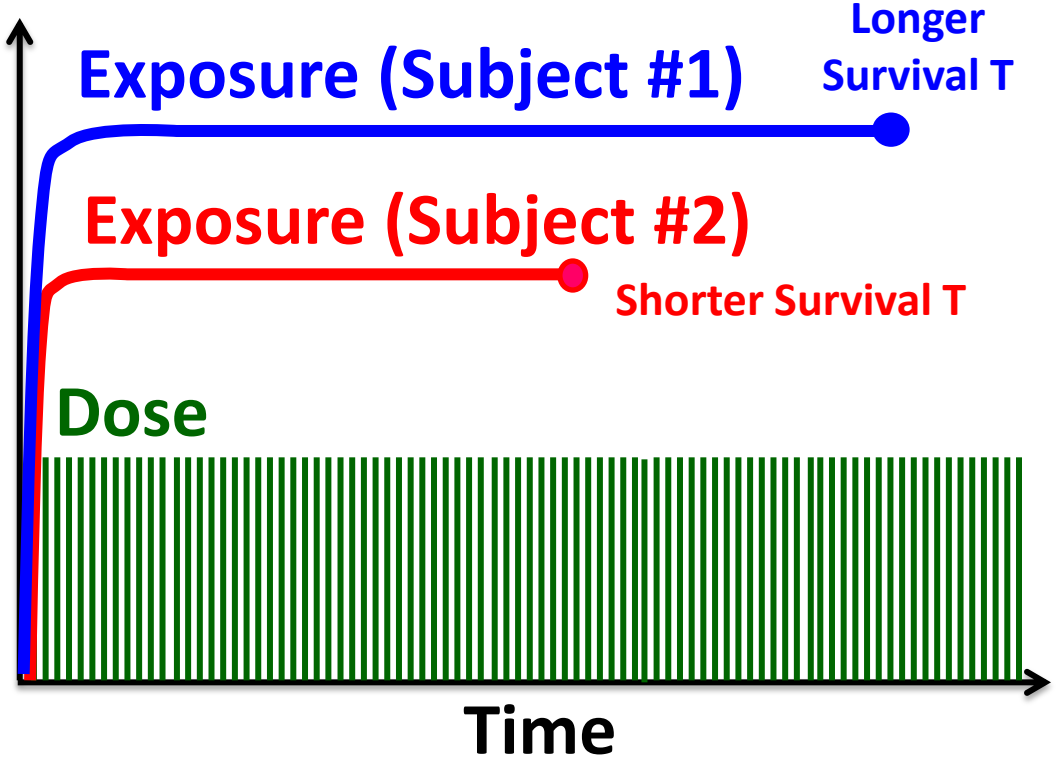
Option 1: Lower Dose Levels	Option 2: Dose Holidays	Option 3: Lower Dose Levels + Up-titrations

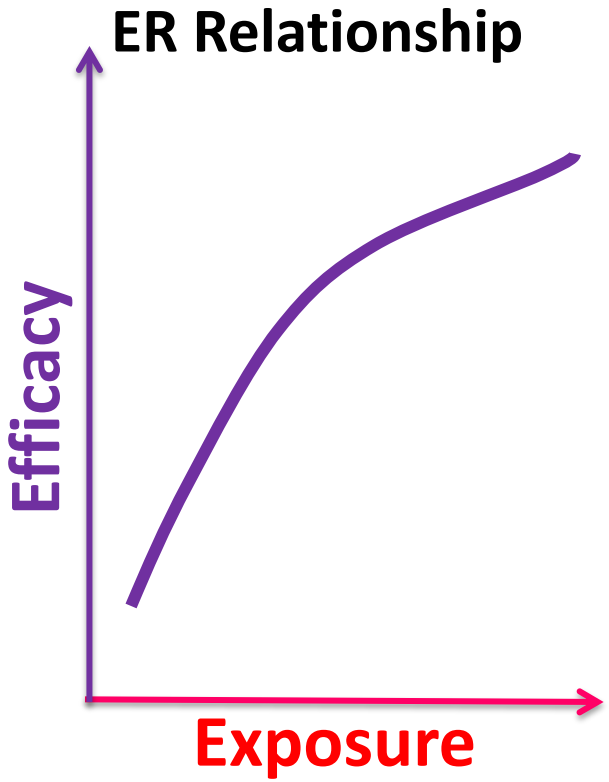
Predict Dose/Exposure → • Efficacy • Safety

CHALLENGE : How to handle dose adjustment driven by AE

AE: Adverse Event

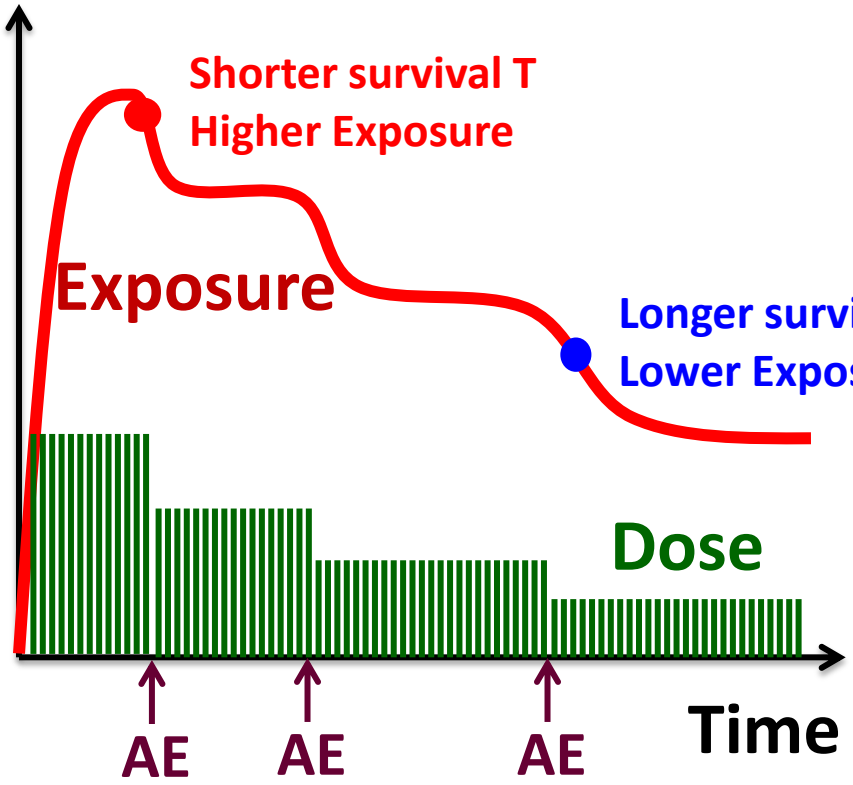
Traditional E-R Analysis in Oncology

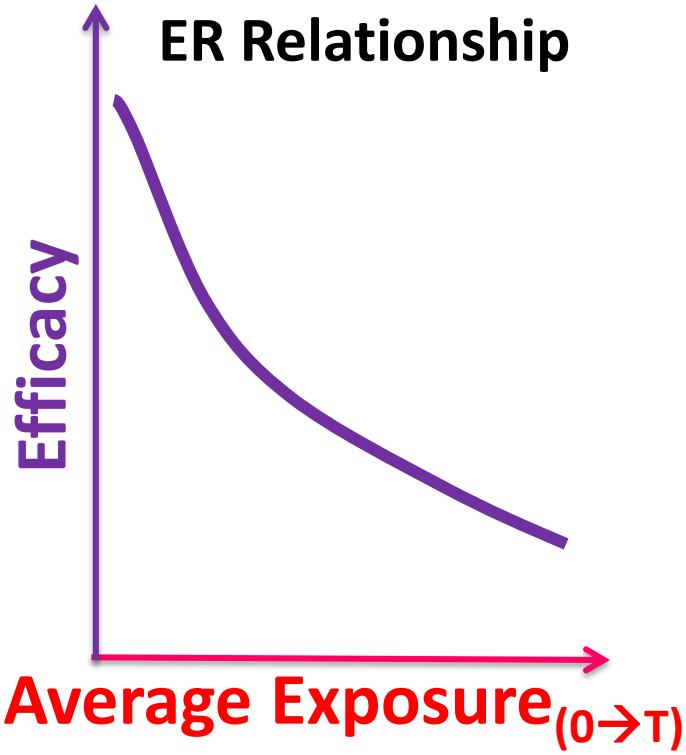




- Constant exposure metrics over time
- Predict the exposure profile based on the pre-defined dose

Dose Adjustment Raises Challenges for Traditional E-R Analysis



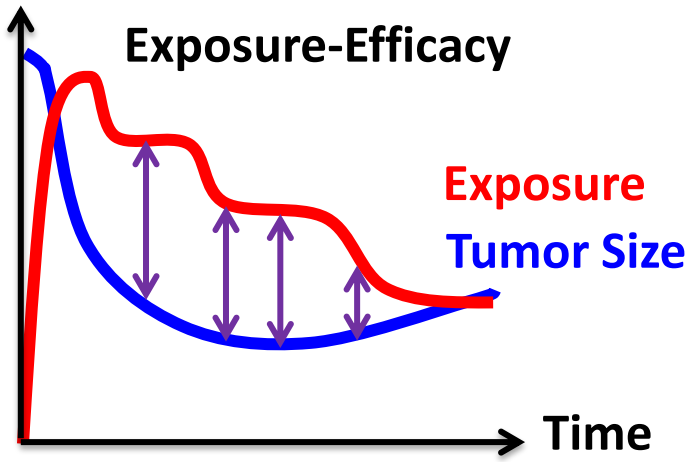


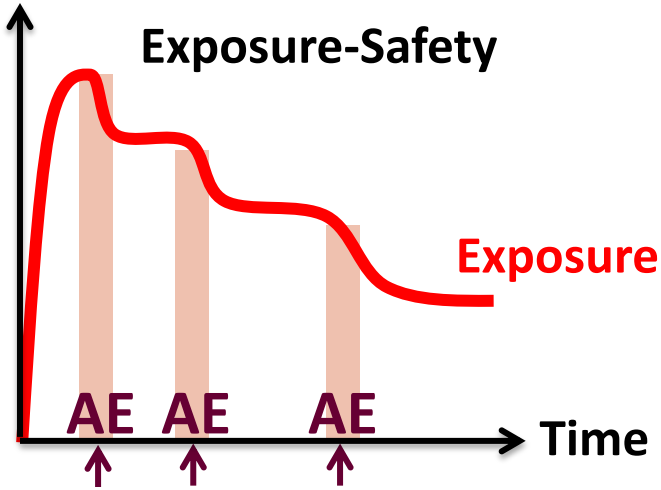
- Exposure not constant over time
- Biased ER relationship
- Cannot predict exposure profile (dose/exposure-AE interaction)

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

Solution:
Dose Adjustment Integrated E-R (DAIER) Analysis

- Time – vary exposure
  - Exposure at each time interval
- Longitudinal tumor size used
  - Capture the varying drug effect over time
- Adverse event was associated with the concurrent exposure





- Dynamically generate dose/exposure profile

AE: Adverse Event

DAIER Analysis: Lenvatinib

Modeling

Estimate E-R relationship for
- Efficacy: time course of tumor sizes
- Safety: dose-altering adverse events

Simulation

Evaluate different dosing regimens

Step 1: Generate dynamic dosing history
- E-R model for safety utilized

Step 2: Evaluate efficacy
- Predict the time course of the tumor sizes

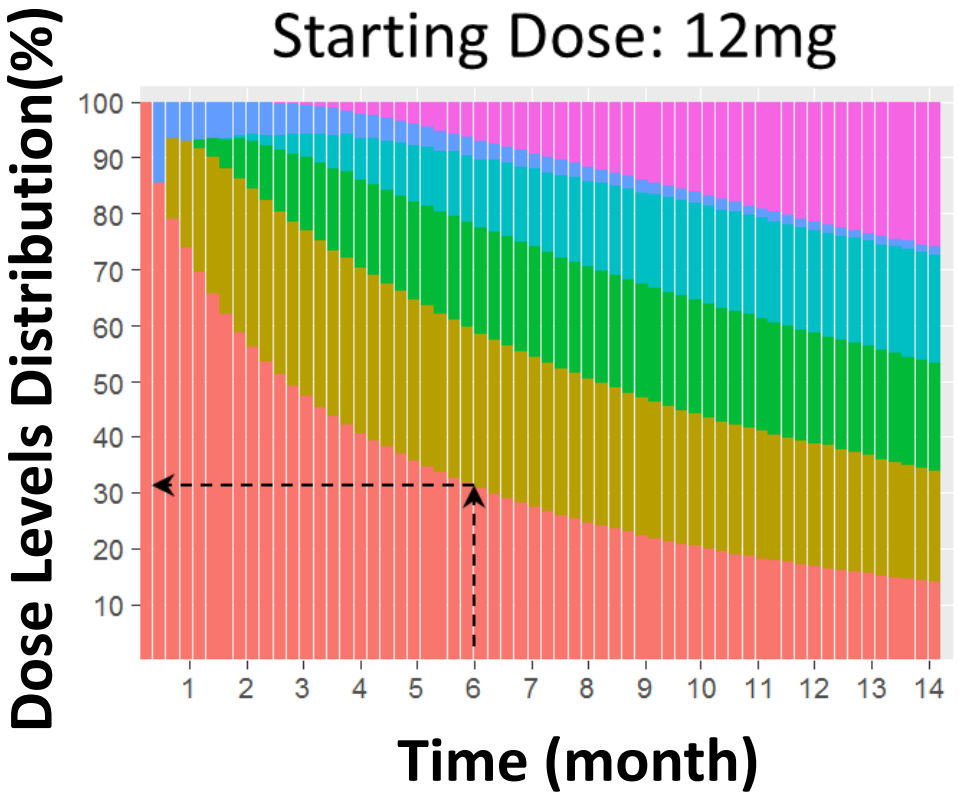
E-R Relationship Estimation

- **E-R for Efficacy:**
  - **An exposure - tumor dynamics model:**

Tumor Growth Rate = **Natural Growth Rate** - (**Suppression by lenvatinib** + **Suppression by everolimus**)

- **E-R for Safety:**
  - **An exposure – dosing altering AE model:**
    - **AE leading to dose adjustment was treated as one repeated event**
    - **A longitudinal logit mixed effect model for dose-altering AE was developed by sponsor**
    - **Basis for dosing history generation in the simulation step**

Dosing History Example



Lenvatinib Dose Level:

Withdrawn

Interruption

4 mg

8 mg

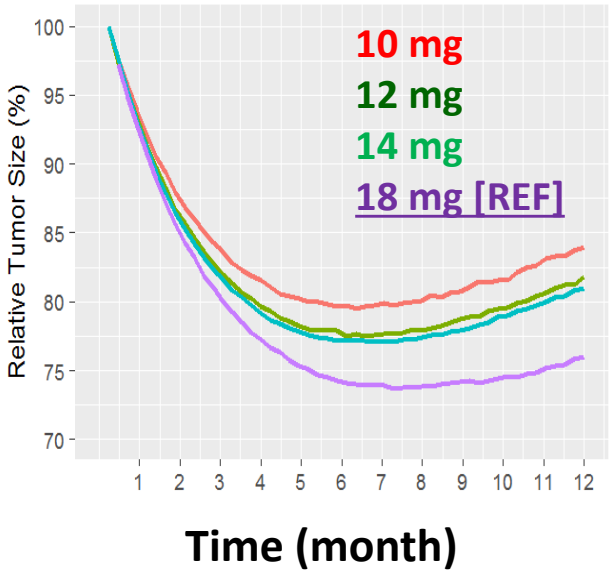
10 mg

12 mg

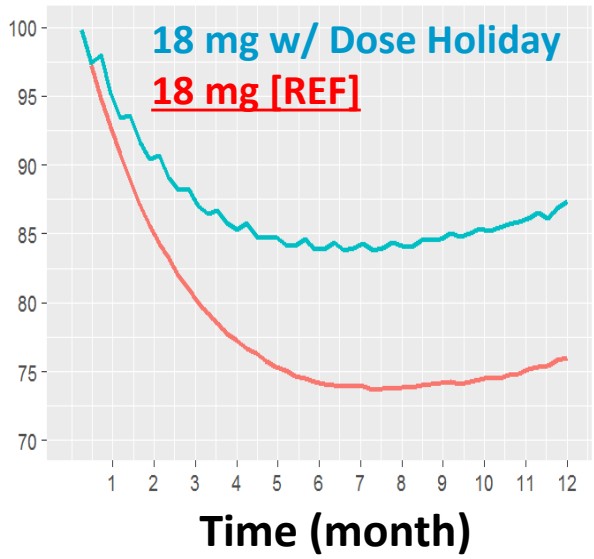
Titration Regimen	Starting Dose	1st Reduction	2nd Reduction	3rd Reduction	Withdrawn
	12 mg	10 mg	8 mg	4 mg	0 mg

Efficacy Profile Prediction

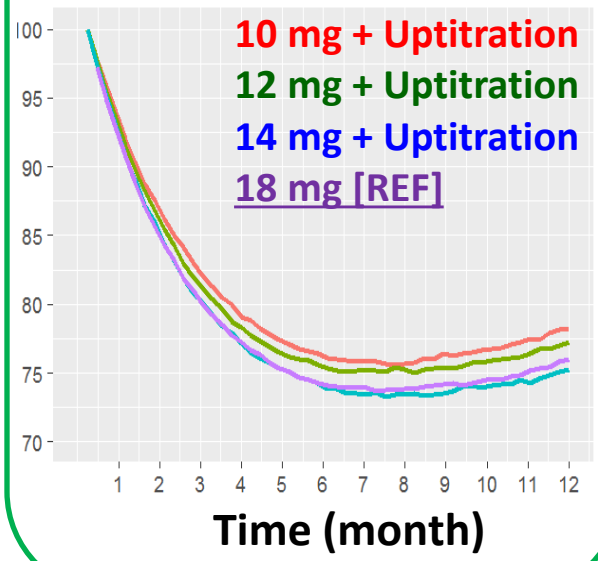
Lower Dose Levels



Dose Holidays



Lower Dose Levels + Up-titrations



- Tumor dynamics was simulated based on the simulated dosing record
- Lower Starting Doses + Uptitration could provide comparable efficacy

Regulatory Decisions on Lenvatinib

- **Post-marketing requirement (PMR) issued for dose optimization**
  - **Lower starting doses with the option of dose escalation**
    - ***14 mg Lenvatinib with up-titration + 5 mg everolimus***

Summary

- Dynamics dose adjustment was integrated in DAIER
- DAIER can be used to optimize the dosing regimen

- Assumptions
  - Selection of model structure
  - Same ER relationship for all dose-altering AEs
  - Toxicity accumulation not considered
  - Titration algorithm followed

- Limitations
  - Only target lesion included

Acknowledgements

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  - James Xu
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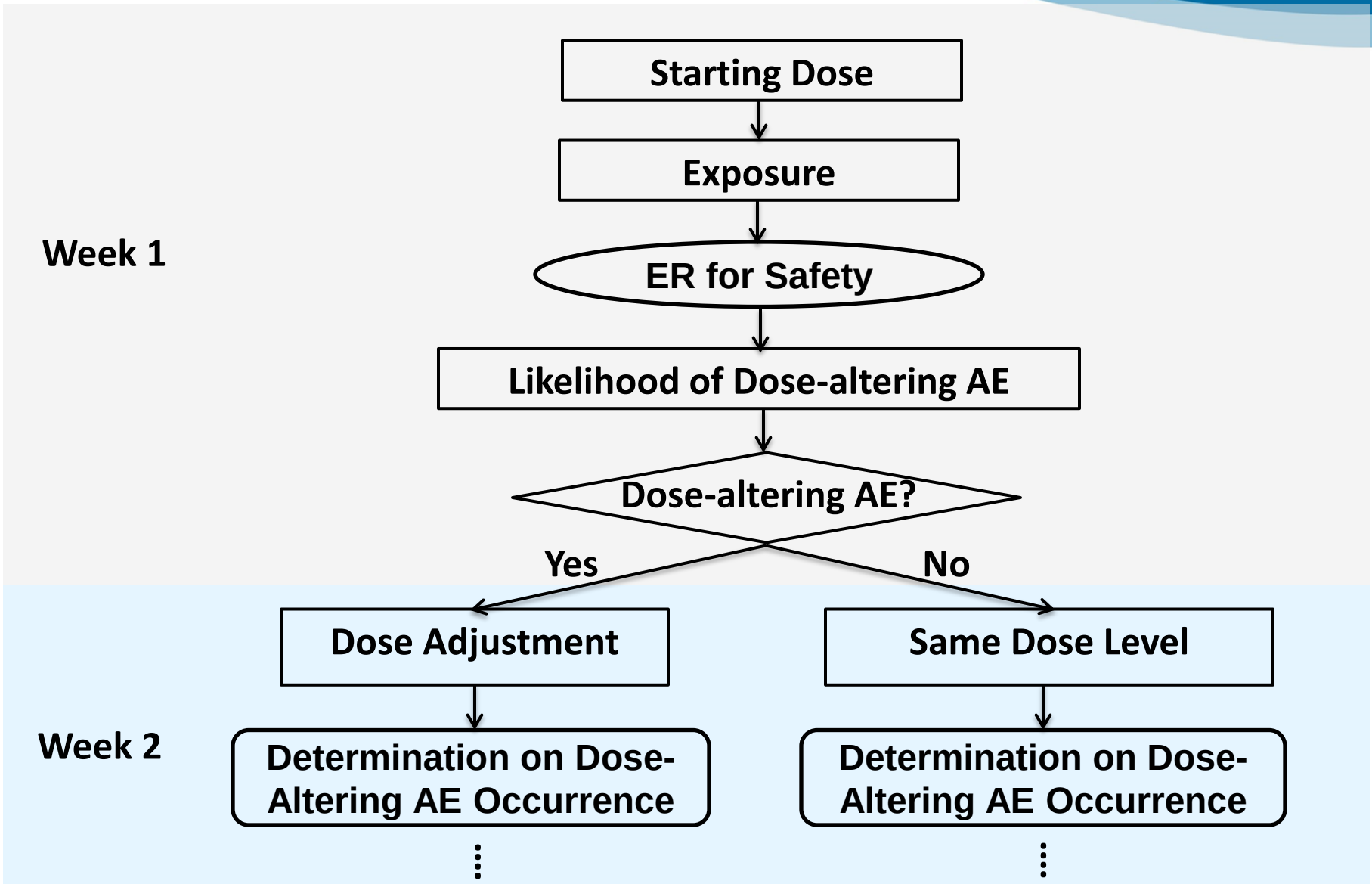
THANK YOU

Back-up

Dosing History Generation



AE: Adverse Event

ER Relationship for Tumor Dynamics

Tumor suppression by lenvatinib

$$\frac{dY(t)}{dt} = \text{Natural Growth} - \frac{Emax_{lenv} \times Expos_{lenv}}{Expos_{lenv} + EC50_{lenv} \times Resist\,(t)} \times Y(t) \times \text{Drug interaction}$$

$$- \frac{Emax_{ever} \times Dose_{lenv}}{Dose_{lenv} + EC50_{ever}} \times Y(t)$$

Tumor suppression by everolimus

- Y(t): sum of longest diameters of all target lesions at time t
- $Expos_{lenv:}$ lenvatinib AUC based on average dose between 2 tumor assessments
- $Dose_{ever}$: everolimus average dose between 2 tumor assessments

Dose Optimization Study

E7080-G000-218

FDA-AACR Dose Finding Workshop
June 13, 2016

Presented by Matthew Guo
Eisai Inc.

hhc
human health care

Agenda

- **Background**
  - Pivotal study (HOPE 205) design and key outcomes
  - Regulatory timeline
- **Dose Optimization Study Design**
  - Interactions with FDA modeling/simulation and Biostatistics groups, and External Bayesian experts
  - Study design

BACKGROUND

Pivotal study (HOPE 205)

- **An Open-Label, Multicenter Phase 1b/2 Study of E7080 Alone, and in Combination with Everolimus, in Subjects with Unresectable Advanced or Metastatic Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment**
  - **Phase 1b**: 3+3 design for sequential dose escalation to determine MTD; cohort expansion to confirm the MTD and determine the recommended Phase 2 (RP2) doses for E7080 in combination with everolimus
  - **Phase 2**: To compare the progression free survival (PFS) of 1) E7080 in combination with everolimus at the RP2 dose once daily and 2) single agent E7080 24 mg once daily to single agent everolimus 10 mg once daily in subjects with unresectable advanced or metastatic RCC and disease progression following one prior vascular endothelial growth factor (VEGF)-targeted treatment

Study 205 (RCC): Phase 1b
Determination of Recommended Phase 2 Dose

Cohort 1: Everolimus 5 mg daily + Lenvatinib 12 mg daily (n = 7)

- 1 DLT (Grade 3 abdominal pain)

Cohort 2: Everolimus 5 mg daily + Lenvatinib 18 mg daily (n = 11)

- 1 DLT (Failure to administer >75% of planned dose, due to intolerable Grade 2 fatigue associated with Grade 1 GI reflux and Grade 1 anorexia)

RP2D

Cohort 3: Everolimus 5 mg daily + Lenvatinib 24 mg daily (n = 2)

- 2 DLTs
  - Grade 3 nausea and vomiting
  - Failure to administer >75 % of the planned dose of study medication, due to intolerable Grade 2 stomatitis

Study 205: Phase 2, Study Design

An open-label, randomized, multicenter study (56 sites)

153 patients

- Unresectable advanced or metastatic RCC
- Progression on or within 9 mo of stopping prior tx
- 1 prior progression on or after prior VEGF or VEGFR-targeted therapy
- Measurable disease
- ECOG PS ≤1

RANDOMIZE

- **Lenvatinib 18 mg orally qd + Everolimus 5 mg orally qd**
- **Lenvatinib 24 mg orally qd**
- **Everolimus 10 mg orally qd**

Primary endpoint

- PFS (by Inv)

Secondary endpoints

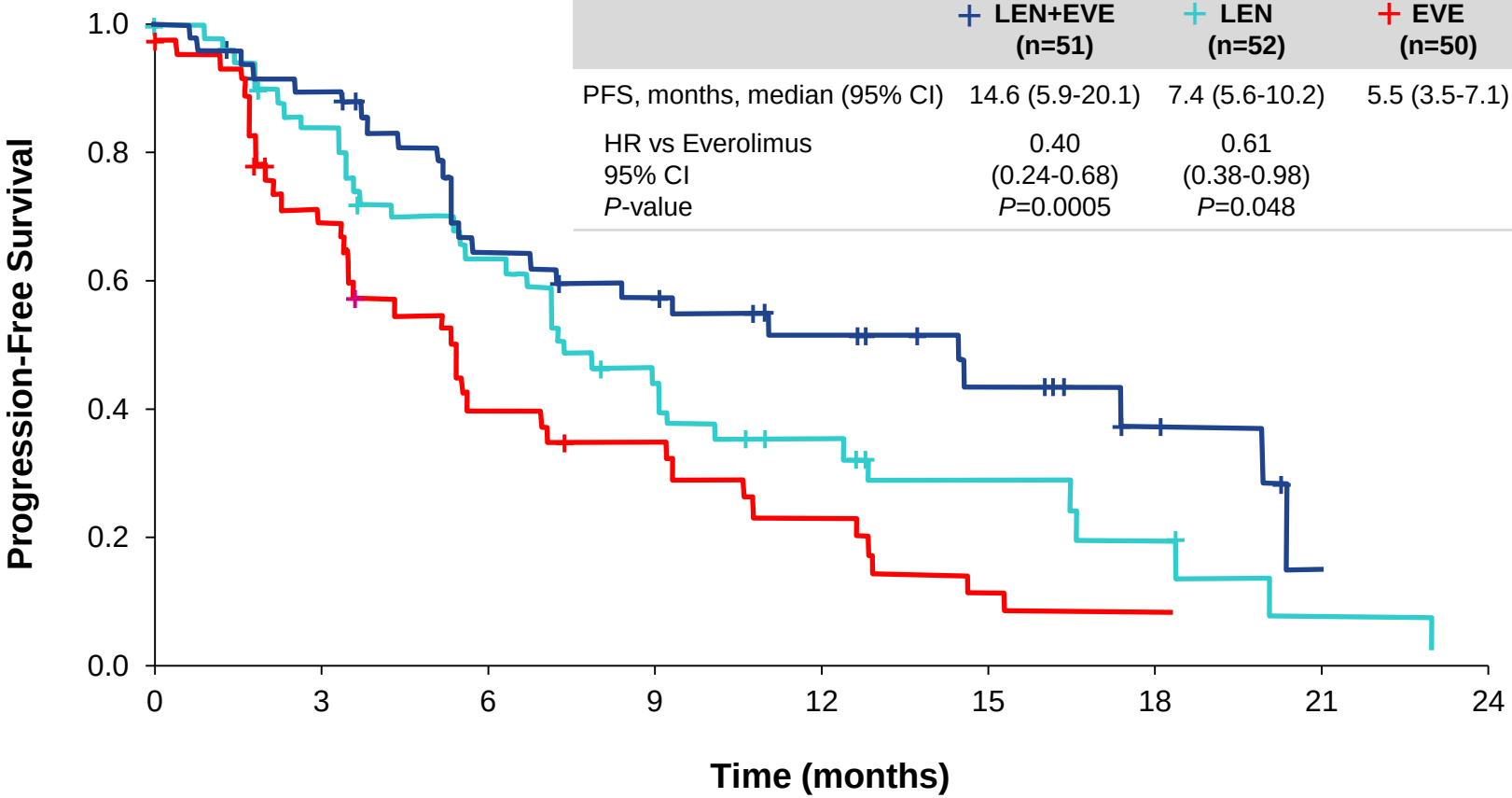
- OS
- ORR
- Disease control rate
- Clinical benefit rate
- PK/PD

- Enrollment period: March 2012 - July 2013
- Data Cut-off for primary analysis: 13 June 2014 (when the 90th PFS event occurred)
- Post-hoc blinding independent imaging review (IIR) conducted per FDA request

Progression-Free Survival by Investigator

Study 205 (according to SAP)

	LEN+EVE (n=51)	LEN (n=52)	EVE (n=50)
PFS, months, median (95% CI)	14.6 (5.9-20.1)	7.4 (5.6-10.2)	5.5 (3.5-7.1)
HR vs Everolimus	0.40	0.61	
95% CI	(0.24-0.68)	(0.38-0.98)	
P-value	*P*=0.0005	*P*=0.048	



Number at risk:

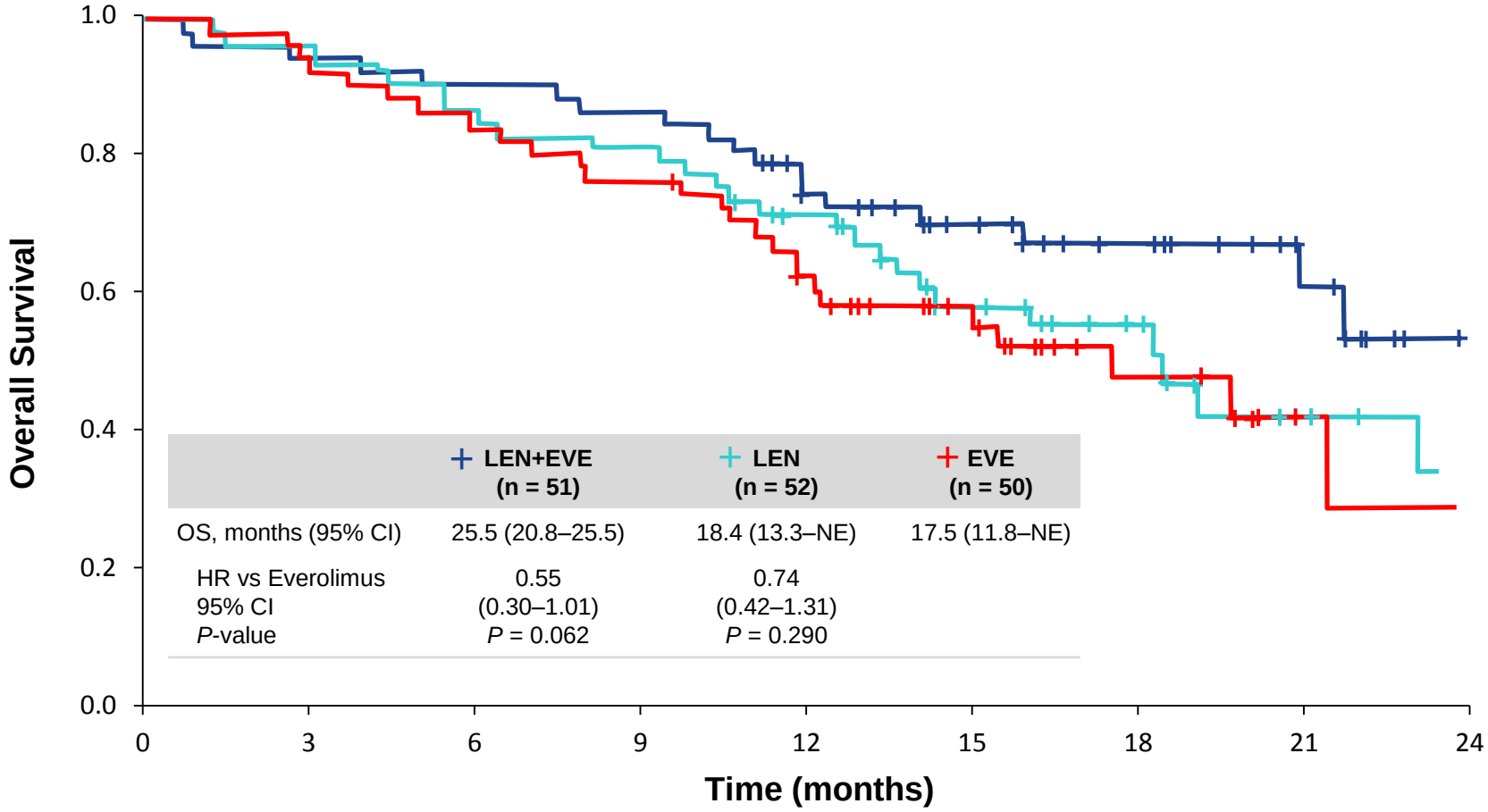
Lenvatinib/Everolimus	51	41	27	23	16	10	5	1	0
Lenvatinib	52	41	29	20	11	6	4	1	0
Everolimus	50	29	15	11	7	3	1	0	0

CI, confidence interval; HR, hazard ratio; LEN+EVE, lenvatinib + everolimus; PFS, progression-free survival.

Source: Module 5.3.5.1, Study 205 CSR, Figure 1

Overall Survival

Study 205 (Data cut-off date: 13 Jun 2014, Primary Analysis according to SAP)



Number at risk:

Lenvatinib/Everolimus	51	48	46	44	34	26	18	9	1
Lenvatinib	52	50	45	42	34	22	14	7	3
Everolimus	50	46	42	38	29	20	10	3	1

CI, confidence interval; HR, hazard ratio; LEN+EVE, lenvatinib + everolimus; NE, not evaluable; OS, overall survival.

Study Treatment Extent of Exposure

Study 205

	Lenvatinib 18mg + Everolimus 5mg (n = 51) n (%)	Lenvatinib 24mg (n = 52) n (%)	Everolimus 10mg (n = 50) n (%)
Duration of Treatment (days)			
Median (Min, Max)	231.0 (20, 688)	224.5 (4, 700)	123.5 (8, 611)
No. of Cycles Received			
Mean (SD)	10.7 (7.24)	9.2 (5.95)	7.1 (5.62)
Median (Min, Max)	9.0 (1, 25)	8.5 (1, 25)	5.0 (1, 22)

Overview of Treatment-Emergent AEs

Study 205

	Lenvatinib 18mg + Everolimus 5mg (n = 51) n (%)	Lenvatinib 24mg (n = 52) n (%)	Everolimus 10mg (n = 50) n (%)
TEAEs	51(100.0)	52(100.0)	50(100.0)
Treatment-Related TEAEs	51(100.0)	51(98.1)	49(98.0)
TEAEs with CTCAE ≥ 3	37(72.5)	44(84.6)	27(54.0)
Treatment-Related TEAEs with CTCAE ≥ 3	31 (60.8)	34 (65.4)	21 (42.0)
Serious TEAEs	28(54.9)	27(51.9)	21(42.0)
Deaths	1(2.0)	3(5.8)	2(4.0)
Non-Fatal SAEs	27(52.9)	26(50.0)	21(42.0)
TEAEs leading to study drug dose adjustment	45(88.2)	47(90.4)	30(60.0)
TEAEs leading to study drug withdrawal	12(23.5)	13(25.0)	6(12.0)
TEAEs leading to study drug dose reduction	34(66.7)	31(59.6)	8(16.0)
TEAEs leading to study drug interruption	35(68.6)	36(69.2)	25(50.0)

Regulatory Timeline

- On July 27, 2015, FDA granted **Breakthrough Therapy** designation to lenvatinib for advanced and/or metastatic renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy
- On Nov. 16, 2015, Eisai filed sNDA. It was classified as priority review
- On May 13, 2016, FDA approved indication:

  LENVIMA® (lenvatinib), in combination with everolimus, is approved for the treatment of patients with advanced RCC following one prior anti-angiogenic therapy

FDA Post Marketing Requirement

PMR 3080-1 Conduct a clinical trial to evaluate the incidence of intolerable grade 2 and grade 3-5 adverse reactions of an oral starting dose of lenvatinib 14 mg daily with everolimus 5 mg daily compared to the starting dose of lenvatinib 18 mg daily with everolimus 5 mg daily, with a comparable objective response rate. Safety assessments will include the collection of adverse reactions, dose interruptions or modifications, the results of laboratory evaluations, and ECGs. Submit the final study report, datasets, and revised labeling.

The timetable you submitted on April 13, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	November 2016
Study Completion:	November 2020
Final Report Submission:	July 2021

DOSE OPTIMIZATION STUDY DESIGN

Collaboration with FDA and Bayesian expert

- **Several teleconferences were conducted between FDA modeling/simulation group, biostatistics group and Eisai**
- **Multiple scenarios regarding dosing schema were simulated**
- **External expert were consulted to explore Bayesian design.**

FDA simulation results

U.S. Food and Drug Administration
Protecting and Promoting Public Health
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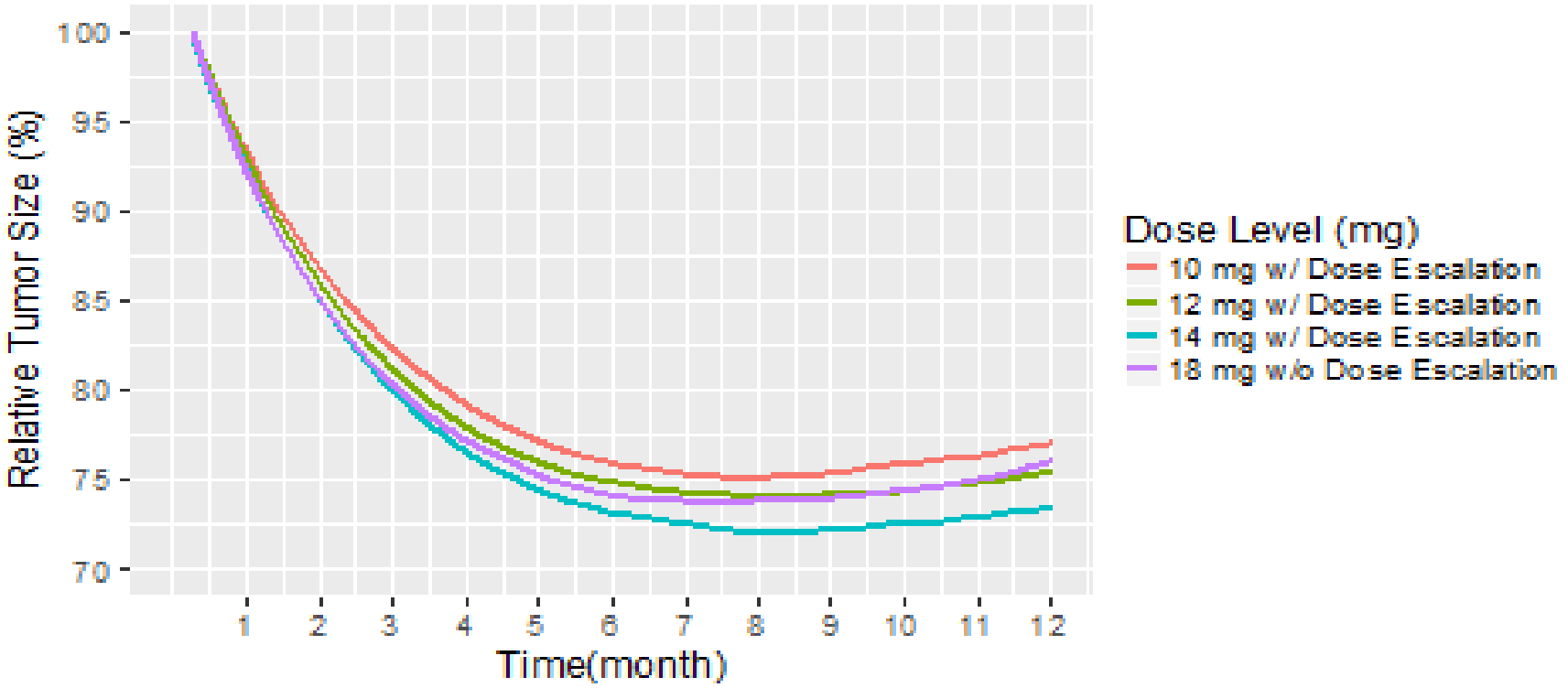
Simulated average tumor reductions with dose escalations



PRELIMINARY

DOSE ESCALATION: ONCE EVERY FOUR WEEKS

Proposed Study HOPE 218: Dose Optimization Study Design

Continuous daily dosing with dose reductions as performed in Study 205 until last enrolled reaches 6 months (Wk 24) or discontinued early

Patients (N=306)

- Predominant clear cell RCC
- One prior disease progression by VEGF-targeted treatment
- Prior PD-1/PD-L1 treatment is allowed
- Measureable disease at baseline
- KPS ≥ 70

1:1

Lenvatinib 18 mg QD
Everolimus 5 mg QD

Lenvatinib 14 mg QD
Everolimus 5 mg QD

→Lenvatinib can be escalated to 18 mg QD if no Gr. 2 (intolerable) or any ≥ Grr. 3 TEAEs that require dose reduction are observed in the first cycle (4 weeks) of treatment

Study Period: Approx. 48 months

Stratification by:
- **MSKCC prognostic groups (low, intermediate and high risk)**
- **Prior PD-1/PD-L1 treatment (yes, no)**

Proposed Study HOPE 218: Dose Optimization Study Design

- **Study Protocol Title**

  A Randomized, Double-blind, Phase 2 Trial to Assess Safety and Efficacy of Lenvatinib at Two Different Starting Doses (18 mg vs. 14 mg QD) in Combination with Everolimus (5 mg QD) in Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment

- **Primary endpoints:**
  - **ORR_{24w} (by independent review)**
  - **Treatment emergent adverse events (TEAE) with Gr.2 (intolerable) or >= Gr.3 by week 24**
- **Key secondary endpoints:**
  - **ORR, PFS**
  - **Overall safety profile**
  - **Plasma PK lenvatinib and everolimus exposure parameters**

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Statistical Designs (Non-inferiority and Superiority)
Study 218

- Sample size is based on detecting both the non-inferiority of ORR_{24W} and superiority of the primary safety endpoint of proportion of subjects with Gr. 2 (intolerable), Gr. 3, 4, and 5 TEAEs within 24 weeks after randomization in comparison of 14 mg arm to 18 mg arm

- Assuming 37% ORR_{24W} in the lenvatinib 18 mg arm and 45% ORR_{24W} in the lenvatinib 14 mg arm, non-inferiority margin of 0.76 on odds ratio and adjusting for the interim analyses, a total of 306 subjects (153 per arm) is required to achieve 80% statistical power at one-sided $\alpha = 0.05$

- In addition, a superiority test at two-sided $\alpha = 0.05$ will give 80% statistical power to detect a 15% drop in proportion of subjects with Gr. 2 (intolerable) or Gr. 3 above TEAEs within 24 weeks after randomization in the 14 mg arm

- 2 interim analyses will take place when 150 and 200 total subjects have completed 24 weeks follow-up or discontinued earlier

Non-inferiority Margin
Study 218

Non-inferiority margin on scale of treatment difference corresponding to odds ratio non-inferiority margin = 0.76 based on different ORR_{24wk} in control arm

ORR_{24wk} in 18 mg Arm	Non-inferiority margin on difference scale (lenvatinib 14 mg arm - lenvatinib 18 mg arm)
10%	-0.02
20%	-0.04
30%	-0.05
40%	-0.06
50%	-0.07
60%	-0.07

Interim analyses and stopping boundaries
Study 218

- **Two interim analyses will take place when 150 and 200 total subjects have completed 24 weeks follow-up or discontinue earlier**
- **Interim analysis will test both non-inferiority and futility of ORR_{24W}**
- **O'Brien-Fleming stopping boundary used for non-inferiority**
- **Interpolated non-binding stopping boundary used for futility**
- **Stopping Boundary**

Analysis #	Cumulative α Spent	Non-inferiority Boundary (p-value)	Cumulative β Spent	Futility Boundary (p-value)
Interim Analysis # 1	0.005	0.005	0.005	0.776
Interim Analysis #2	0.015	0.014	0.10	0.207
Final Analysis	0.050	0.045	0.2	0.045

THANK YOU!

backup

- **Bases for non-inferiority margin**
- **Based on the assumption from Study E7080-G000-205 that the confirmed ORR for lenvatinib 18 mg + 5 mg everolimus arm is 37% (19 responders out of N=51) vs. 6% for the everolimus arm (3 responders out of N=50), the 95% confidence interval of the odds ratio of lenvatinib 18 mg + everolimus arm vs. everolimus arm is (2.54, 34.06). Assuming a 70% retention of the effect of lenvatinib 18 mg + everolimus vs. everolimus, the non-inferiority margin on the odds ratio scale is estimated to be M=0.76 (ie Ha: OR (14 mg/18 mg)> M).**

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Session III Panel Discussion

Designs for Dose Optimization Studies: Pre-Market and Post-Market

Chair: Eric Rubin, MD

Speakers:

Haleh Saber, PhD
Pasi Jänne, MD, PhD
Ying Lu, PhD
Chao Liu, PhD
Matthew Guo, PhD

Panelists:

Kelvin Dickenson
Serban Ghiorghiu, MD
Hans Loland
Sumithra Mandrekar, PhD
Lie Nie, PhD
Nam Atiqur Rahman, PhD
Lillian Siu, MD

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Wrap Up

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Adjourn

Thank You for Participating!