Translational Clinical Oncology

Dose Selection in Early Oncology Trials

Yan Ji, Ph.D.
Novartis Institutes for Biomedical Research
ASCPT, Washington DC
March 16, 2017

NOVARTIS

Oncology drug development has made substantial progress

More efficacious and safer treatment for longer-term use is necessary

Combination therapy

Chemotherapy

Targeted therapy

Immuno therapy

Image from https://www.ehuub.com/Service/FileResult?path=~%2Fhub%2Fupload%2FFee&fileName=13-10-2014-1413232616_Chemotherapy.jpg&contentType=image%2Fjpeg

NOVARTIS

Oncology dose finding paradigm has been changing

From identifying maximum tolerated dose (MTD) to optimizing dose regimen

- MTD may not be the optimal dose
- Maximum efficacy may be achieved below the MTD
- Optimal biologic dose to saturate target and block pathway
- Cancer may become chronic disease
- Long-term cumulative toxicity is important to address

NOVARTIS

Post marketing trials were required to optimize dose in recent oncology submissions

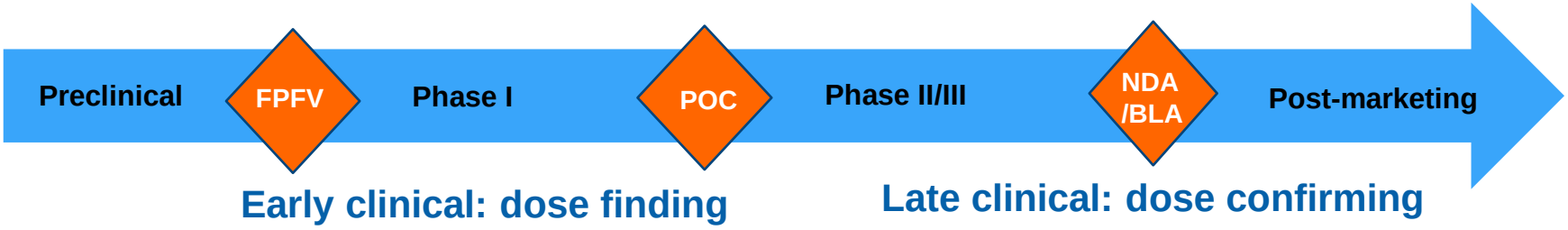
Compound	M&S summary	Post Marketing Requirements
Axitinib	PK and E-R modeling enabled dose escalation schemes	Dose escalation schemes approved
Trametinib	E-R relationship with biomarkers	No evident impact
Vismodegib	Exposure/Responder analysis	No evident impact
Trastuzamab emtansine	Narrow therapeutic window	Impact on dose uncertain, pending additional analyses
Cabozantinib	~80% dose reductions	Possibly new dose trial
Pazopanib	Dose modifications not supported	Develop 100mg formulation
Ipilimumab	ER suggests higher dose	Explore higher dose
Vandetanib	No exposure-efficacy, yes with toxicity	Explore other regimens

NOVARTIS

Dose optimization in oncology is challenging

- Narrow therapeutic index
- High variability of drug response
  - Heterogeneity of the disease and patients
  - Phase I patients not representing intended population
  - Heavily pre-treated and concomitant medications
- Development of drug resistance
- Complexity of the biology
- Linkage of biomarkers to clinical outcome can be difficult
- Limitation in study design due to severity of disease
- Urgency to deliver effective treatments to patients

M&S in early oncology trials can inform dose optimization

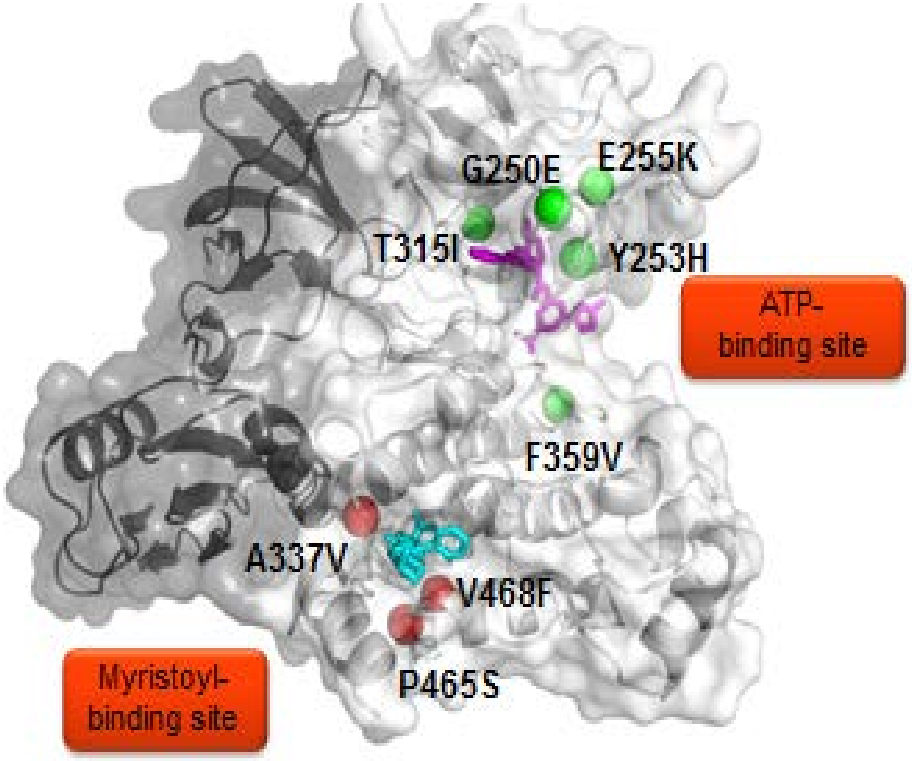


- Characterize exposure-response and therapeutic window
- Characterize time course of response
- Identify the biomarkers that correlate to pathway inhibition
- Leverage preclinical data
- Characterize inter-patient variability
- Inform both dose and schedule

NOVARTIS

Case Study 1: ABL001

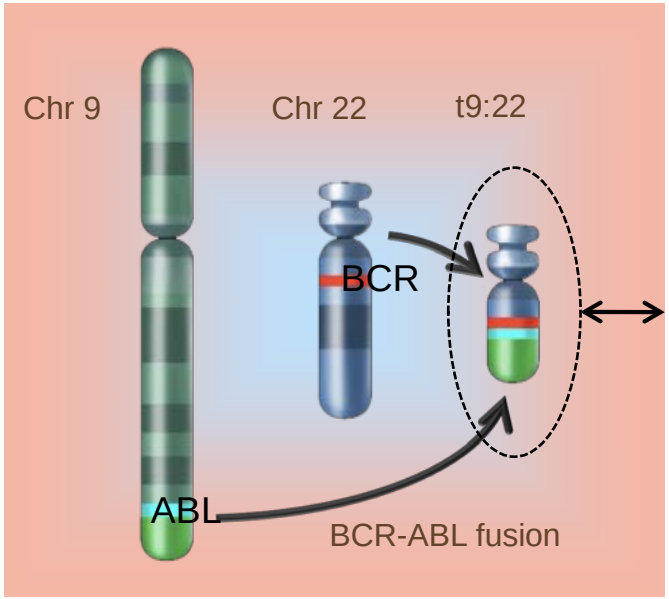
Allosteric Bcr-Abl inhibitor for Chronic Myeloid Leukemia



ABL001
First in class allosteric inhibitor

Gleevec® (Imatinib)
Tasigna ® (Nilotinib)
Sprycel ® (Dasatinib)
Bosulif ® (Bosutinib)
Inclusig ® (Ponatinib)

Chromosomal Translocation



Biomarker of response
Molecular Response

NOVARTIS

Molecular response: primary efficacy endpoint

Measurement of Bcr-Abl transcript

- Assessed in peripheral blood by RT-PCR
- International scale: log reduction of transcript levels

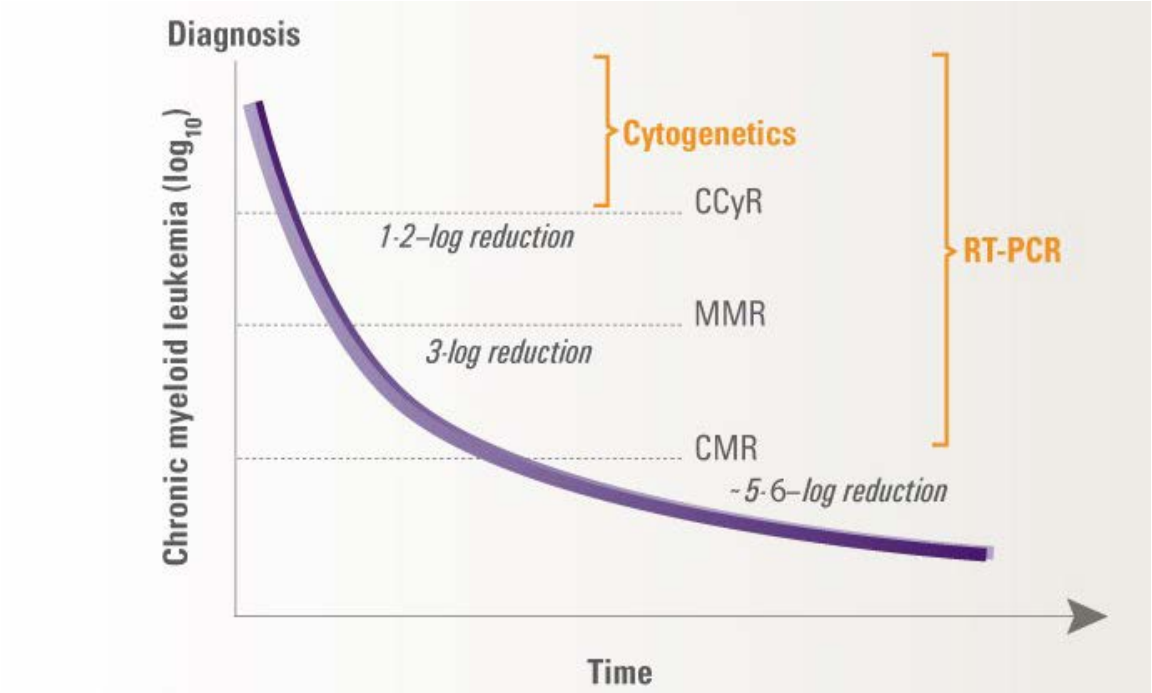
  >10%: failed MR

  ≤10%: MR1

  ≤0.1%: MR3 (MMR)

  ≤0.01%: MR4 (CMR)

  ≤0.0032%: MR4.5

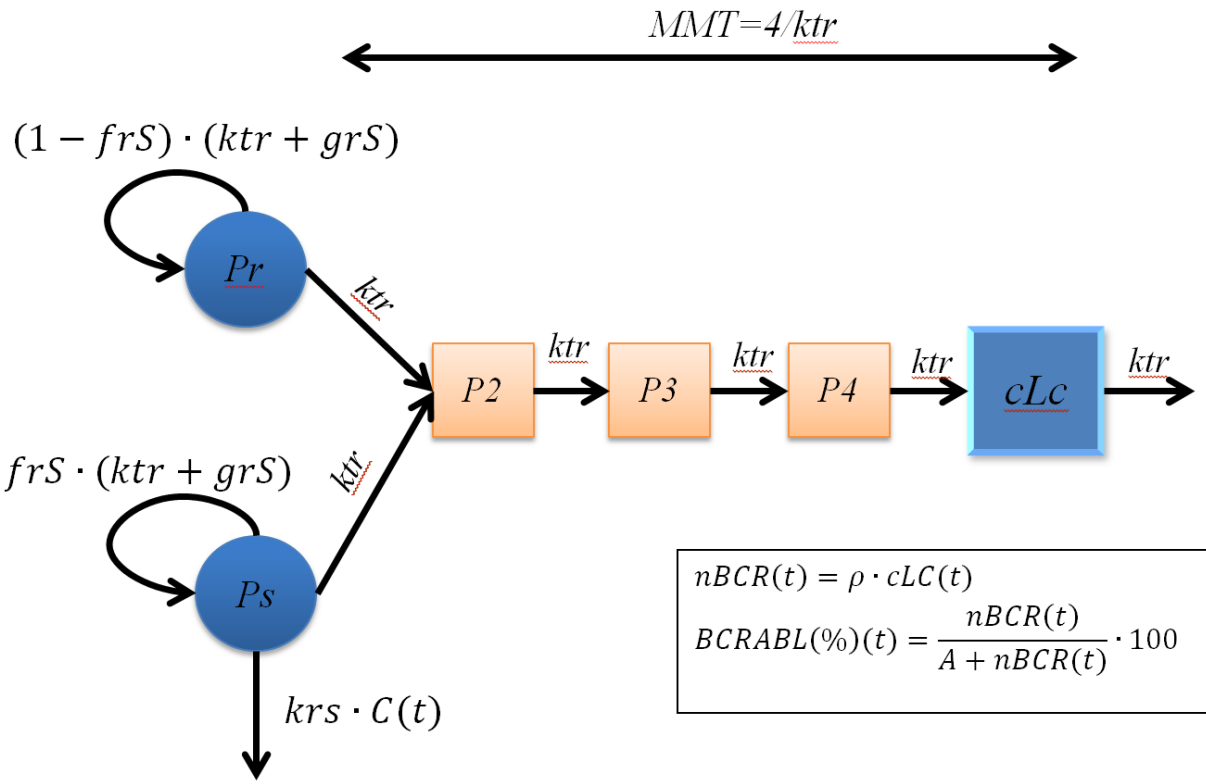


MMR=major molecular response.
CMR=complete molecular response.
RT-PCR=reverse transcription polymerase chain reaction.

NOVARTIS

PKPD semi-physiological model

- Mimics leukemic cell maturation: Maturation time
- Reproduces disease progression: Immature cells turnover rate
- Accounts for existing resistance: Fraction of sensitive cells



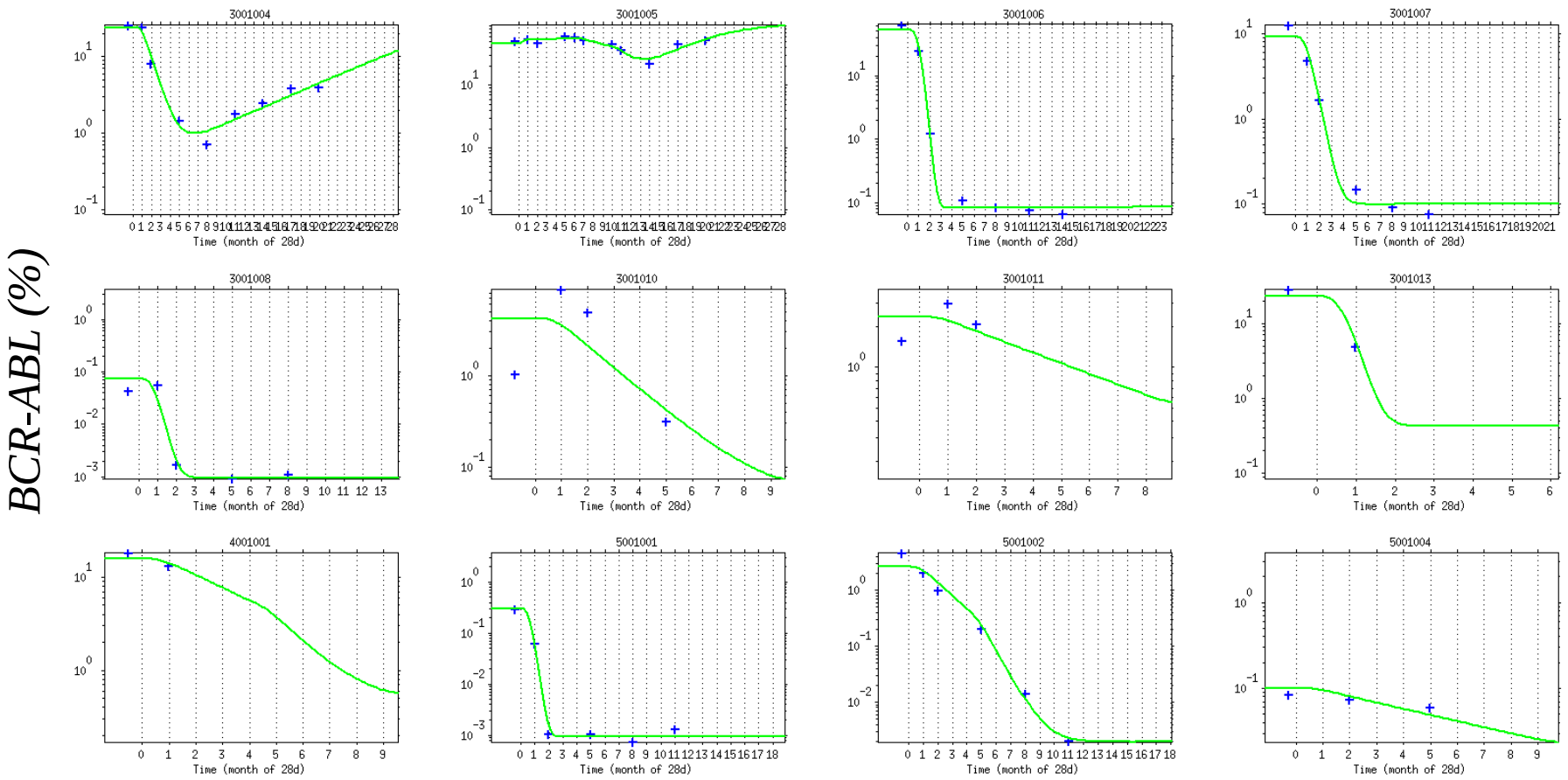
$$nBCR(t) = \rho \cdot cLC(t)$$

$$BCRABL(\%)(t) = \frac{nBCR(t)}{A + nBCR(t)} \cdot 100$$

- Describe BCR-ABL(%) kinetics
- Estimate concentration for stable disease
- Provide exposure target for dose and schedule optimization

NOVARTIS

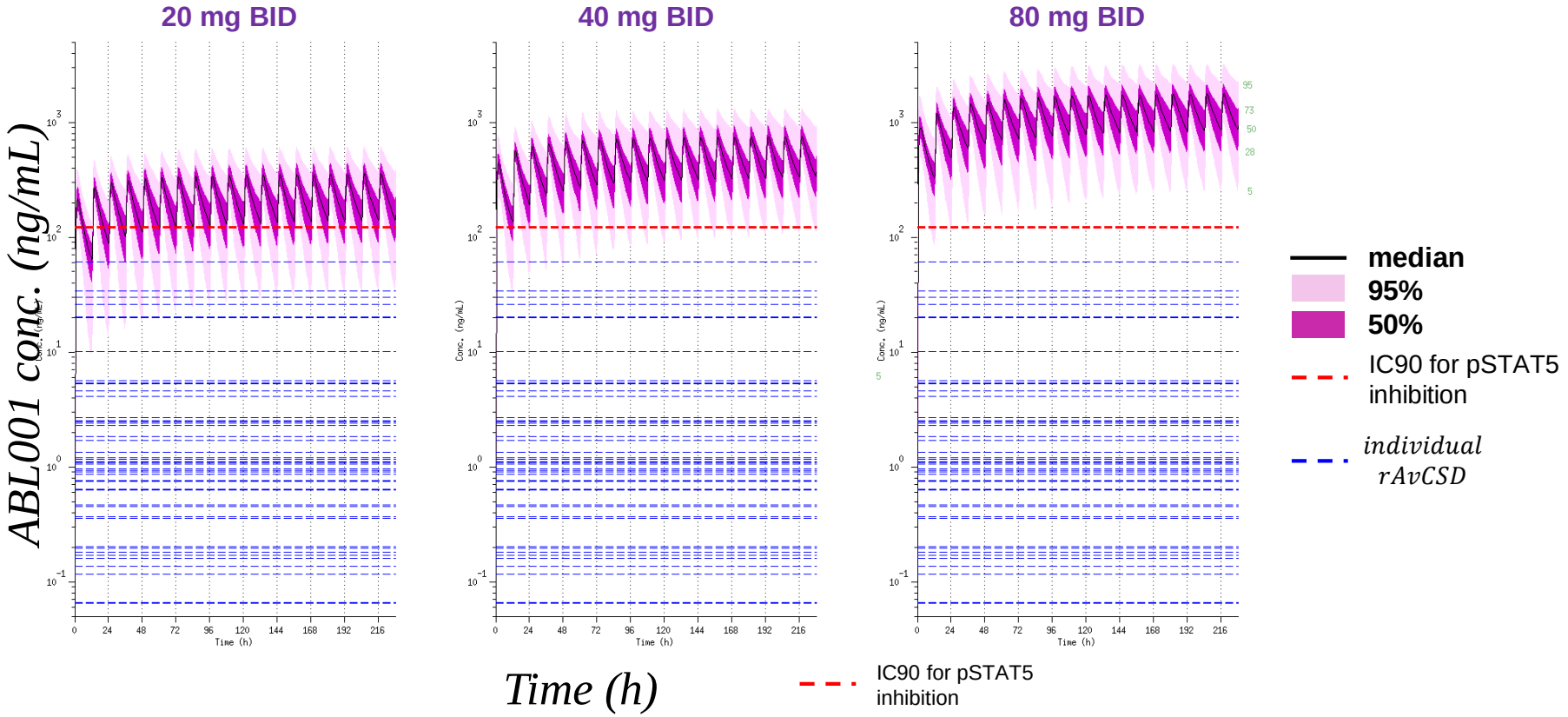
Individual PD profiles



NOVARTIS

Individual average concentration for stable disease vs. PK

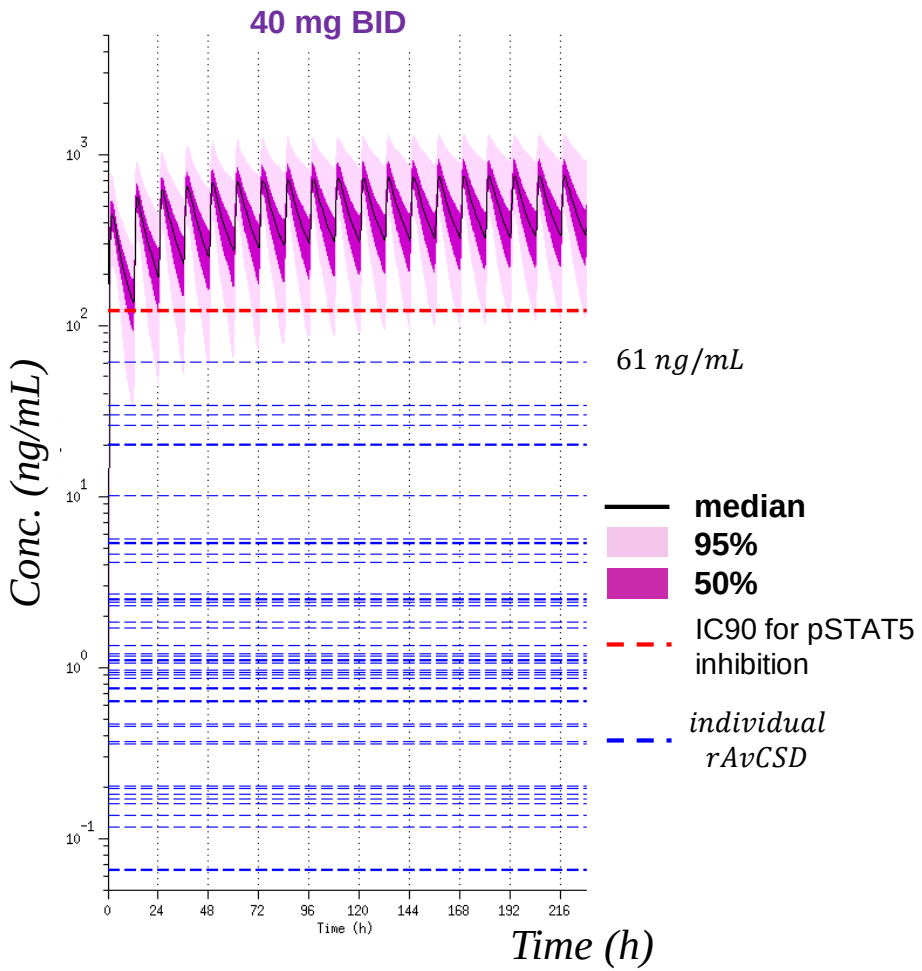
- Population average concentration for stable disease **= 1 ng/ml**
- Individual values ranging from **0.07 to 61 ng/ml** due to large variability on estimated individual disease progression



NOVARTIS

Clinical PKPD analysis results are consistent with preclinical data

- Required average concentration for stable disease **= 1 ng/ml**
- Individual values ranging from **0.07 to 61 ng/ml** (0.014 to 122 nM)
- IC90 for pSTAT5 inhibition KCL-22 xenograft mice after PPB correction: **121 ng/mL (free: 11 nM)**
- In vitro gIC50 KCL-22 cell line expressing WT BCR-ABL: **1 ng/mL (2.1 nM)**



NOVARTIS

PK/PD analysis supported dose selection for Phase I expansion

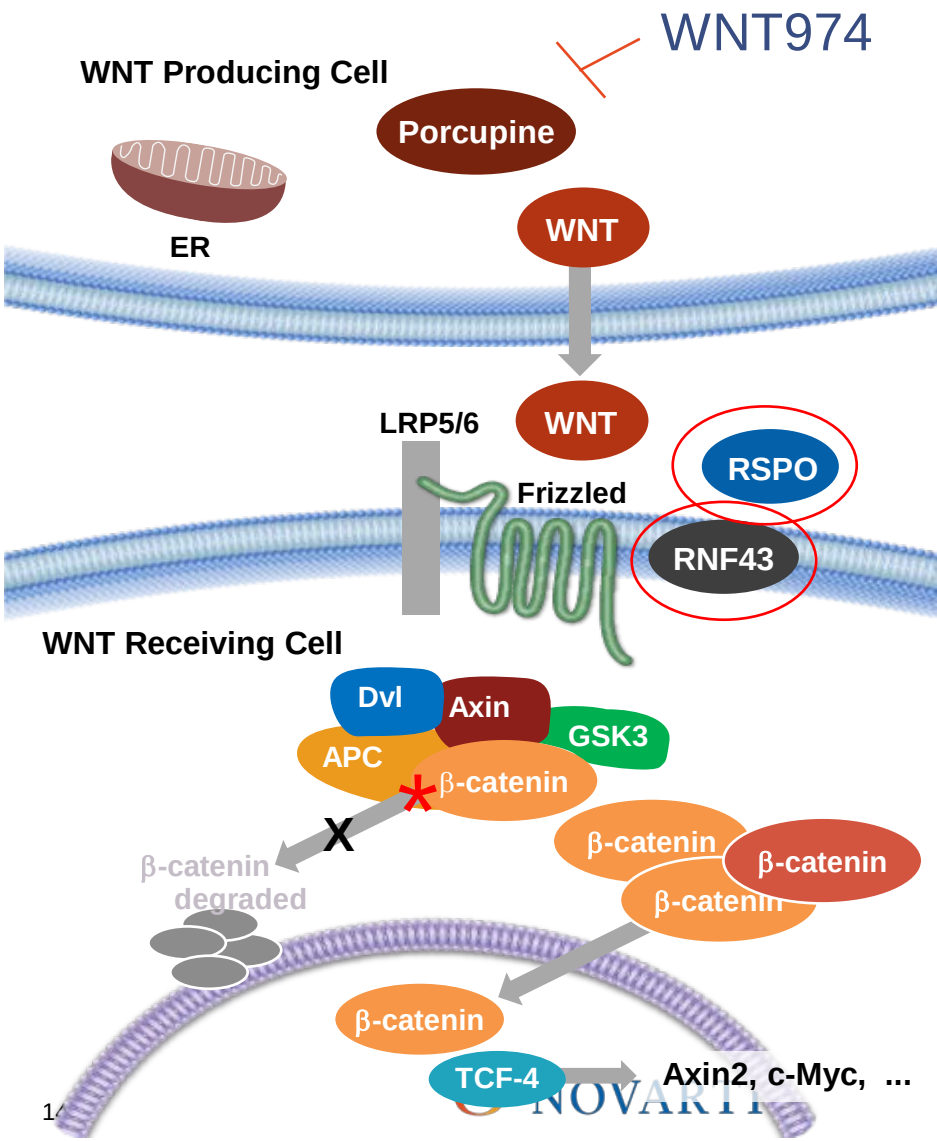
- Clear advantage of 40 mg vs. 20 mg BID

BID Dosing	Percent (95% CI) patients with at least 1 log 10 reduction			
Tx Duration	20 mg	40 mg	80 mg	All doses
6 months	33% (24-42)	41% (31-51)	48% (38-58)	40.6%
12 months	42% (32-52)	53% (43-63)	56% (46-66)	50.3%

NOVARTIS

Case Study 2: WNT974

- WNT ligands activate the pathway
- Porcupine is required for WNT ligand formation
- WNT974 blocks Porcupine activity
- RNF43 and RSPO regulate Wnt pathway signaling



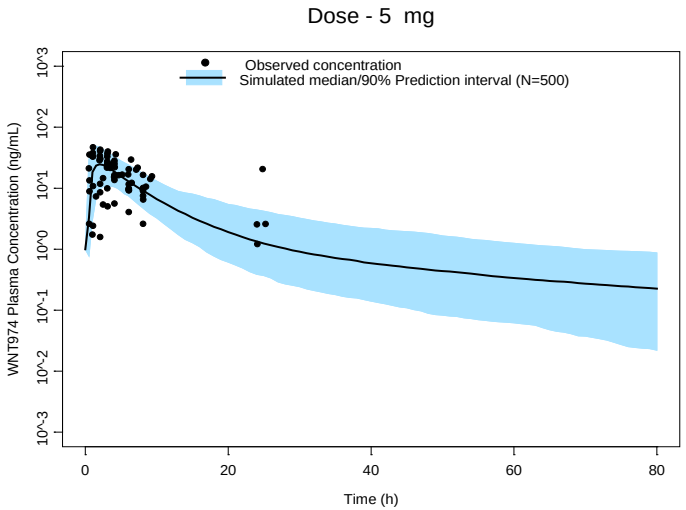
PK modeling and ER analysis to support dose finding

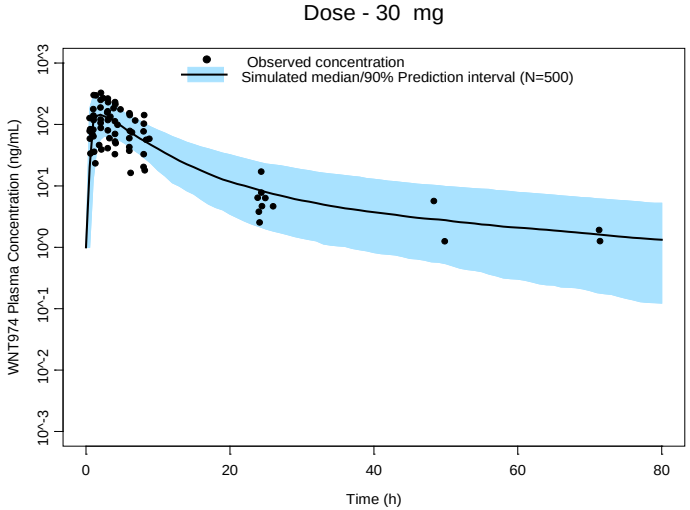
- Exposure-response analysis identified a therapeutic window
- PK simulations found a dose yielding exposures within that window
- That dose has been selected as the recommended dose for expansion

Analysis	**Objective**
Population PK modeling	To characterize PK
ER analysis for biomarker	To explore and characterize the relationship of exposure vs. PD biomarker
Logistic regression for safety	To explore and characterize the relationship of exposure vs. AE

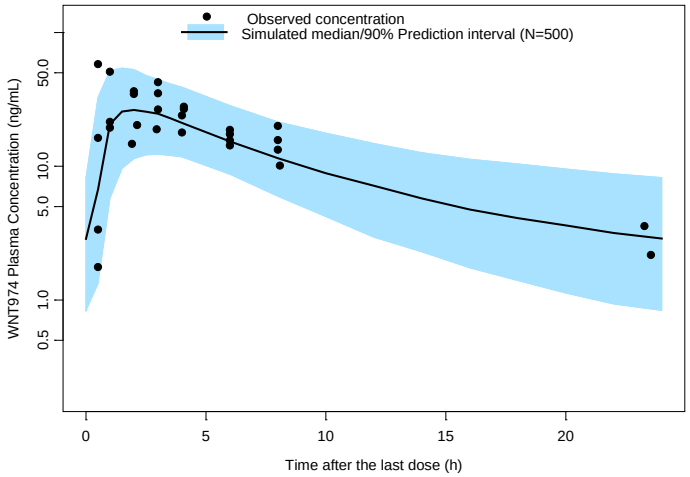
Population PK modeling

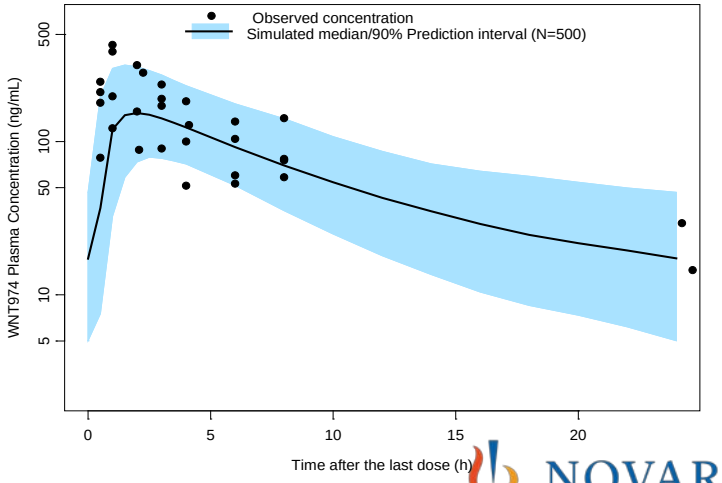
Single-dose





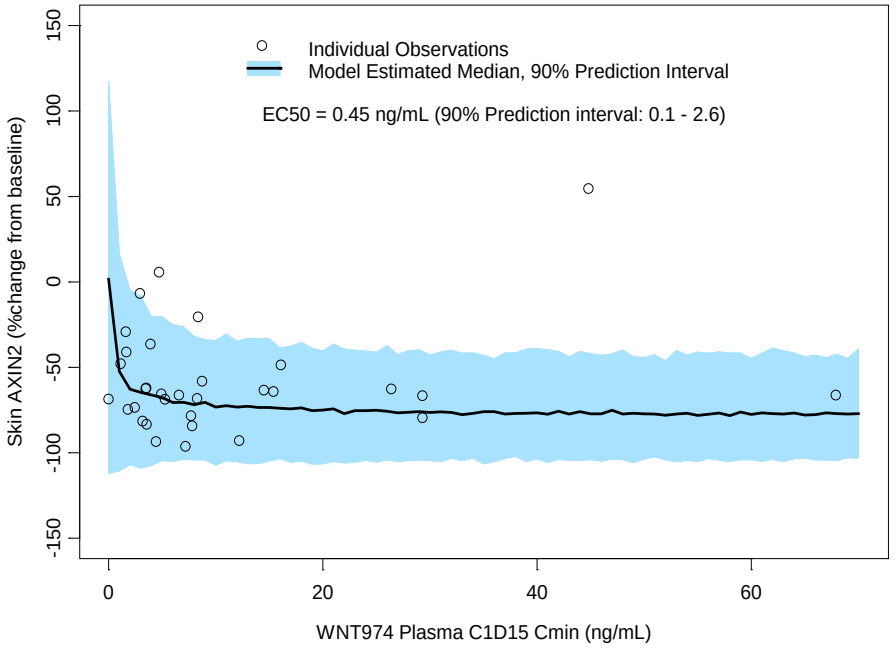
Repeat-dose

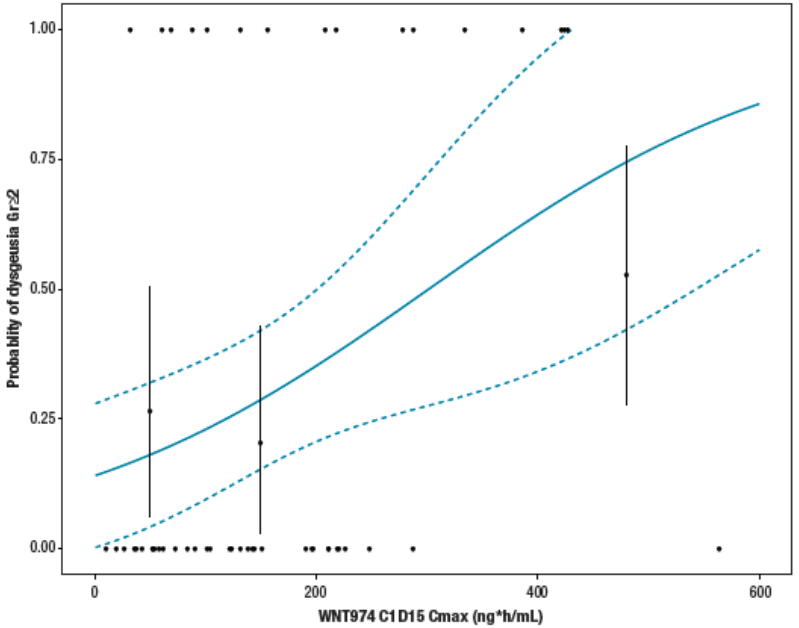




NOVARTIS

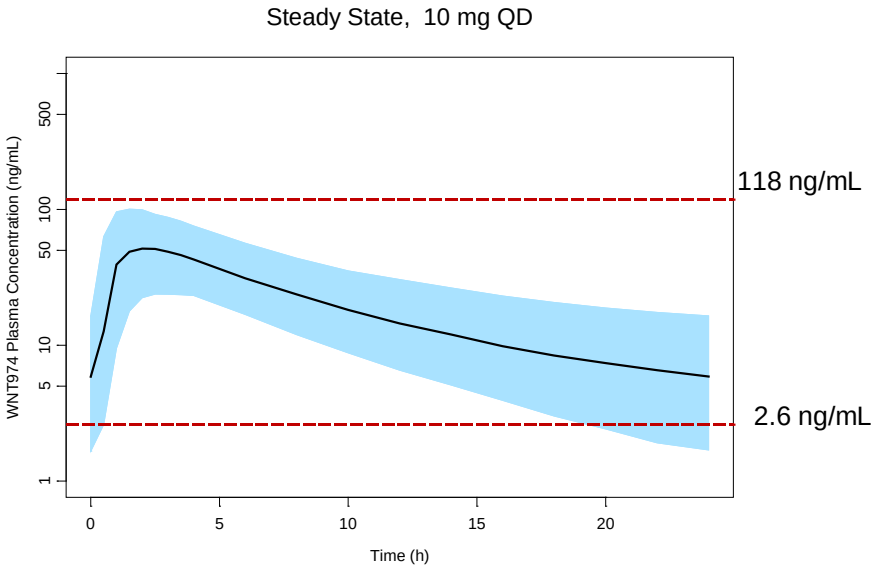
Exposure-response analysis for PD biomarker and safety





NOVARTIS

Integrative analysis of PK, PD and safety data supported dose selection for Phase I expansion

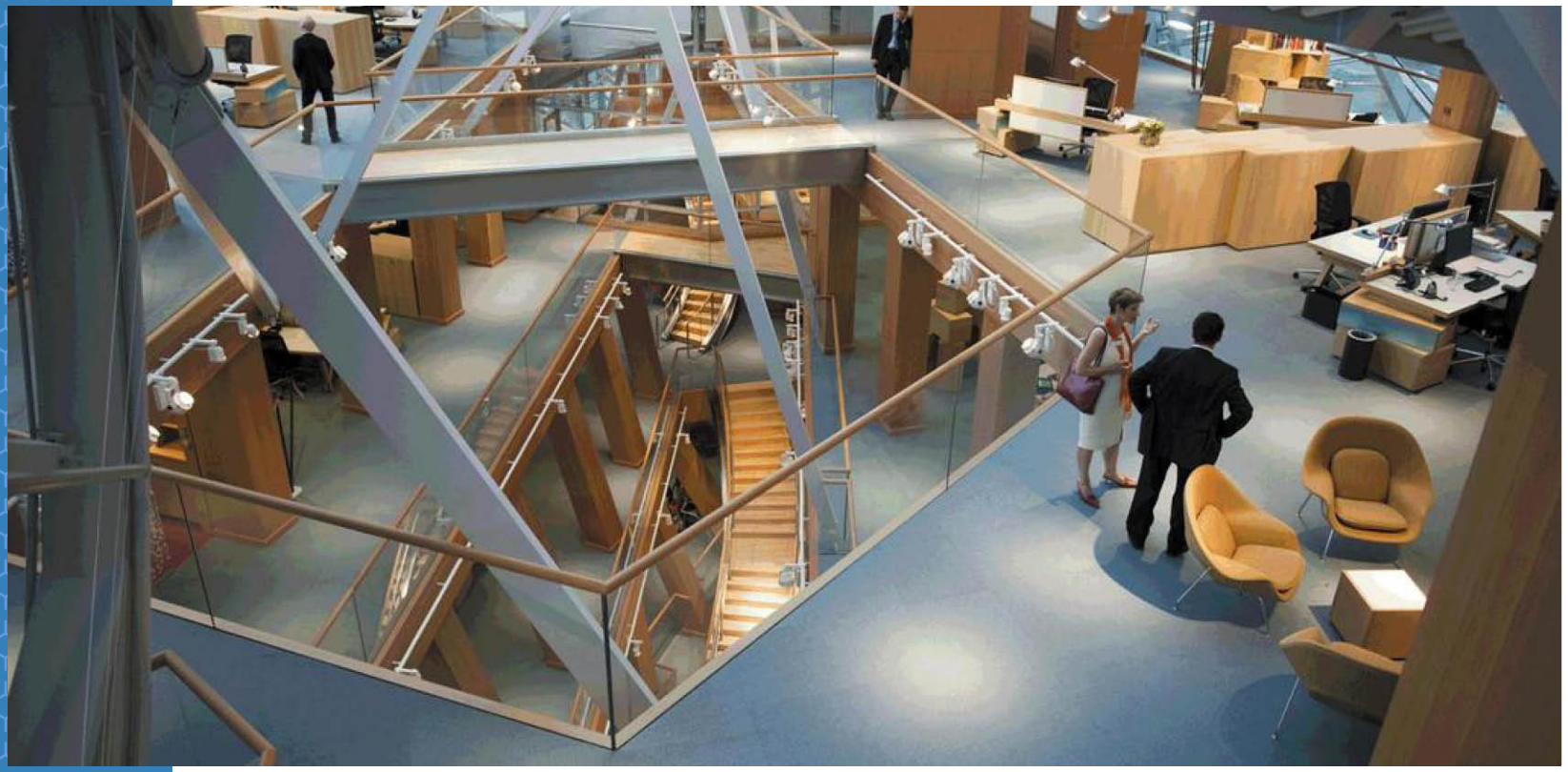


Endpoint	Criteria	Exposure threshold
Biomarker	>50% maximal inhibition with 95% probability	Ctrough,ss > 2.6 ng/mL
AE	50% probability that <25% patients have Gr>=2	Cmax,ss < 118 ng/mL

NOVARTIS

Summary

- Prospective M&S in early oncology trials informs dose optimization
- M&S integrates data including PK, biomarker, efficacy and safety
- Models are continuously refined based on emerging data
- Greater need to apply quantitative methods to understand drug response



Thank you

- Varsha Iyer, Christophe Meille (ABL001)
- The individuals who worked to discover and develop these medicines
- The patients who participated in our clinical trials

NOVARTIS