Industry Perspectives on Dose Optimization

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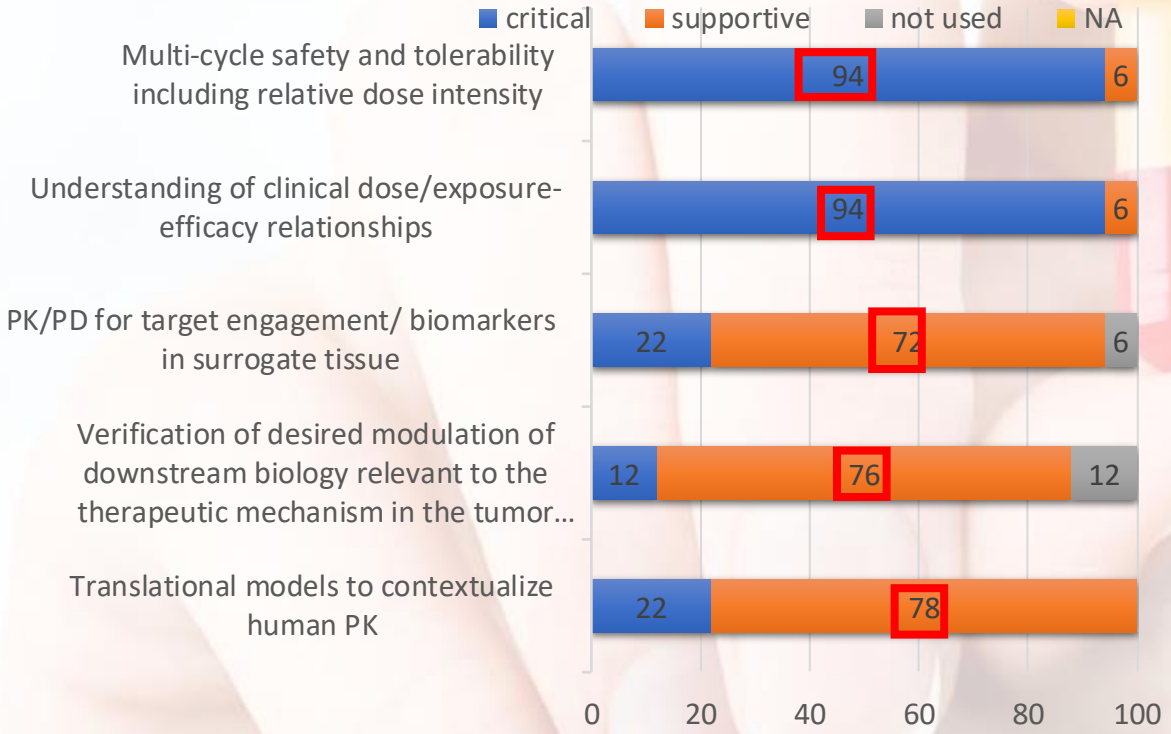
On Behalf of IQ CPLG Oncology Dose Optimization WG

IQ CPLG Dose Optimization Working Group

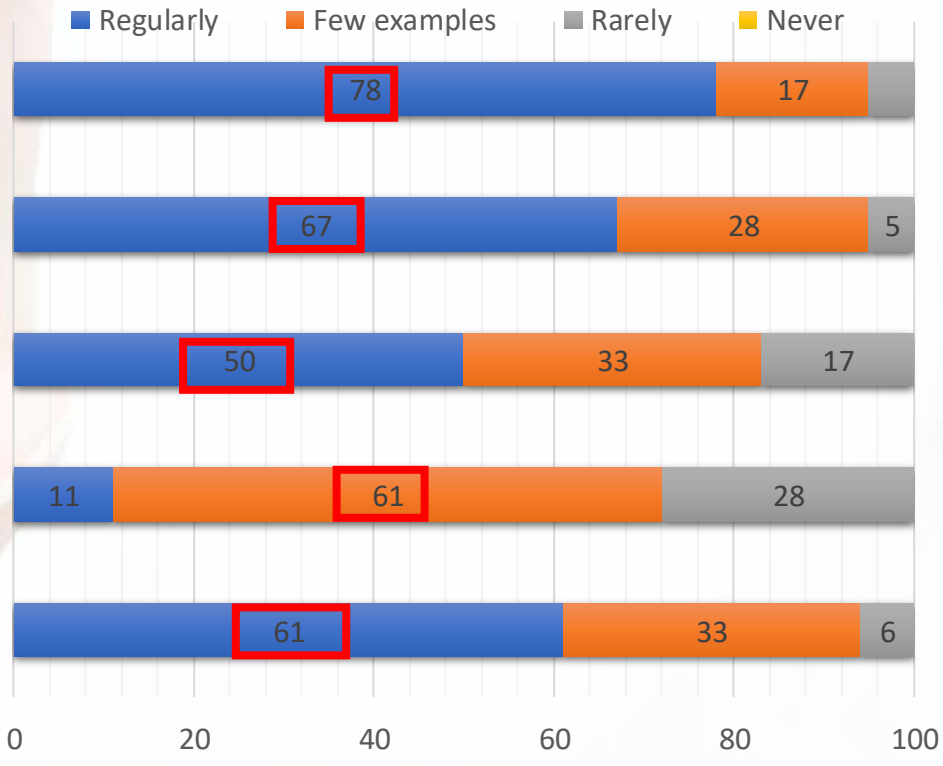
- To provide IQ recommendations for the dose optimization strategies for Oncology programs
- Conducted a survey to gain insights on the current industry practice for oncology dose finding
  - Dose optimization related PMC/PMR that were successfully completed
  - Importance of various factors in dose selection
  - Study design preference to support dose optimization
  - Impact of Project Optimus on dose optimization strategies including study designs
  - Challenges/barriers towards dose optimization
  - Impact of recent advances in technologies, analytics to help with dose selection
- 18 member companies responded to survey
  - One response per company and respondents were encouraged to provide consolidated clinical pharmacology feedback from their company

Importance of various factors in optimal dose/schedule selection

1. How important is this?



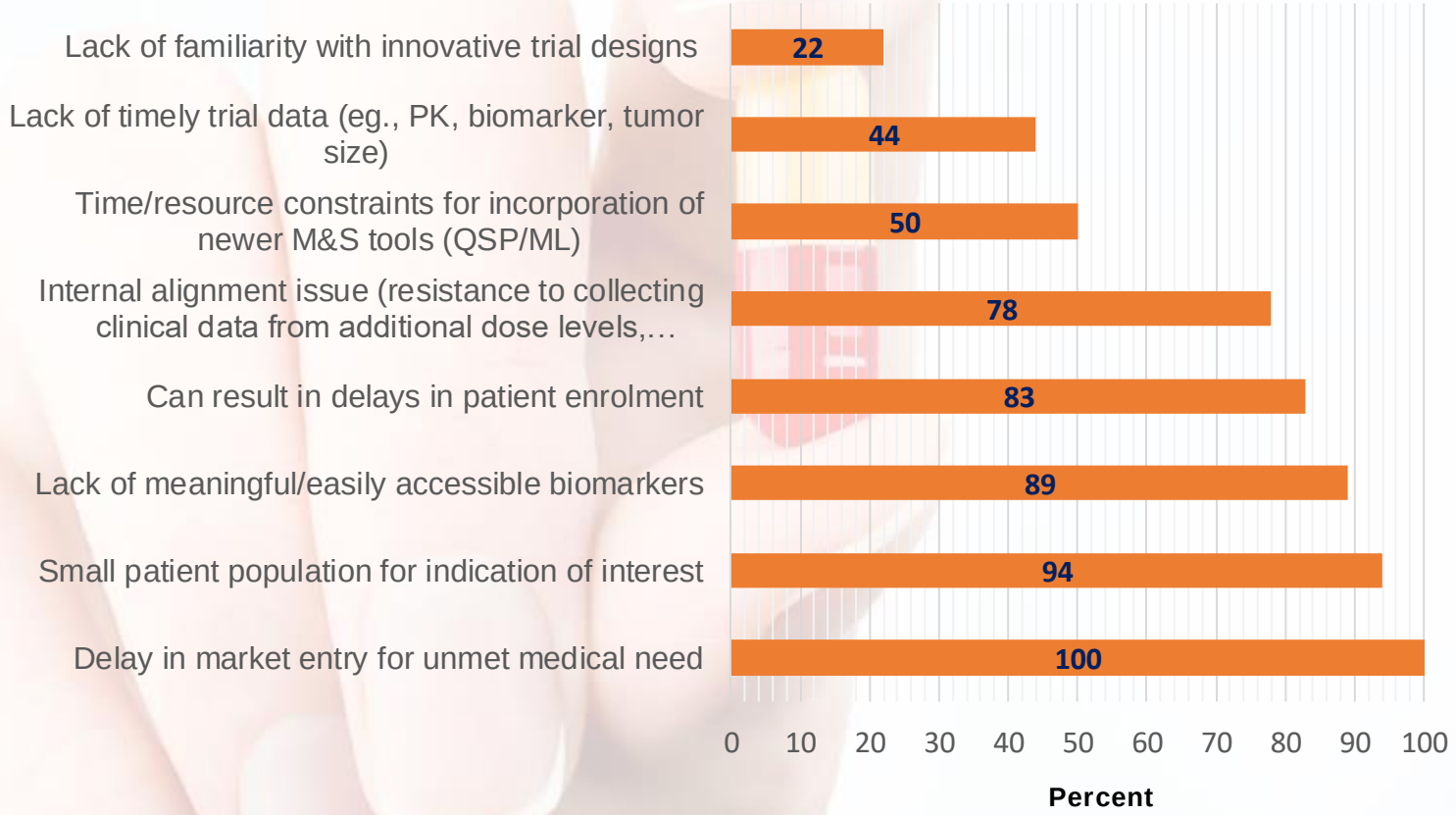
2. How often in practice you have available information?



- ✓ Sponsors agree that a clear understanding of the clinical dose/exposure-efficacy relationship including multi-cycle safety/tolerability is critical and this information is often available.
- ✓ Sponsors consider evidence of PD effect in tumor/TME & surrogate tissues as supportive. Importantly, PD information in tumor is not usually available to help with dose selection – likely don't have proactive PD biomarker strategy coupled with operational challenges

IQ CPLG Oncology Dose Optimization WG Survey Results 2022

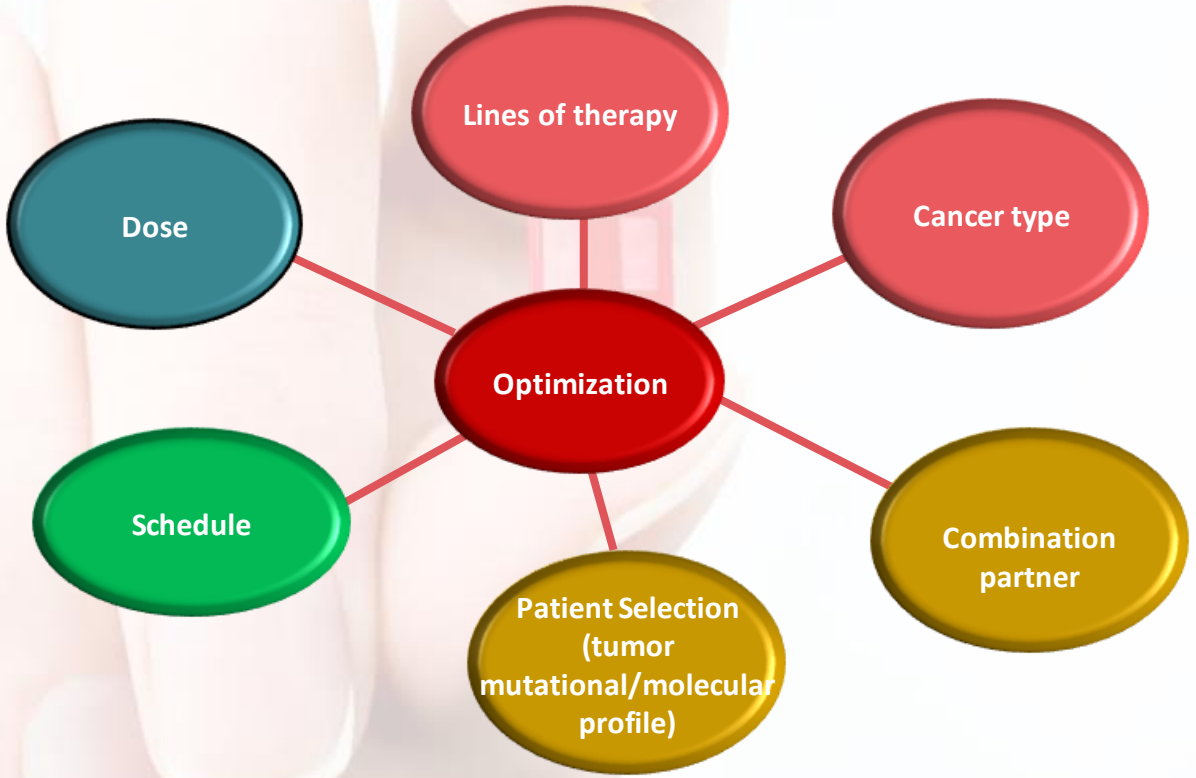
Feasibility challenges that sponsors are facing for dose optimization



- All sponsors highlighted issues with delay in market entry, patient enrollment etc
- Sponsors also highlighted issues with internal alignment within their company
  - Project Optimus will lead to better cross functional alignment
- Some sponsors noted lack of time and resources to leverage newer methodologies and PK/biomarker/tumor size data in dosing decisions

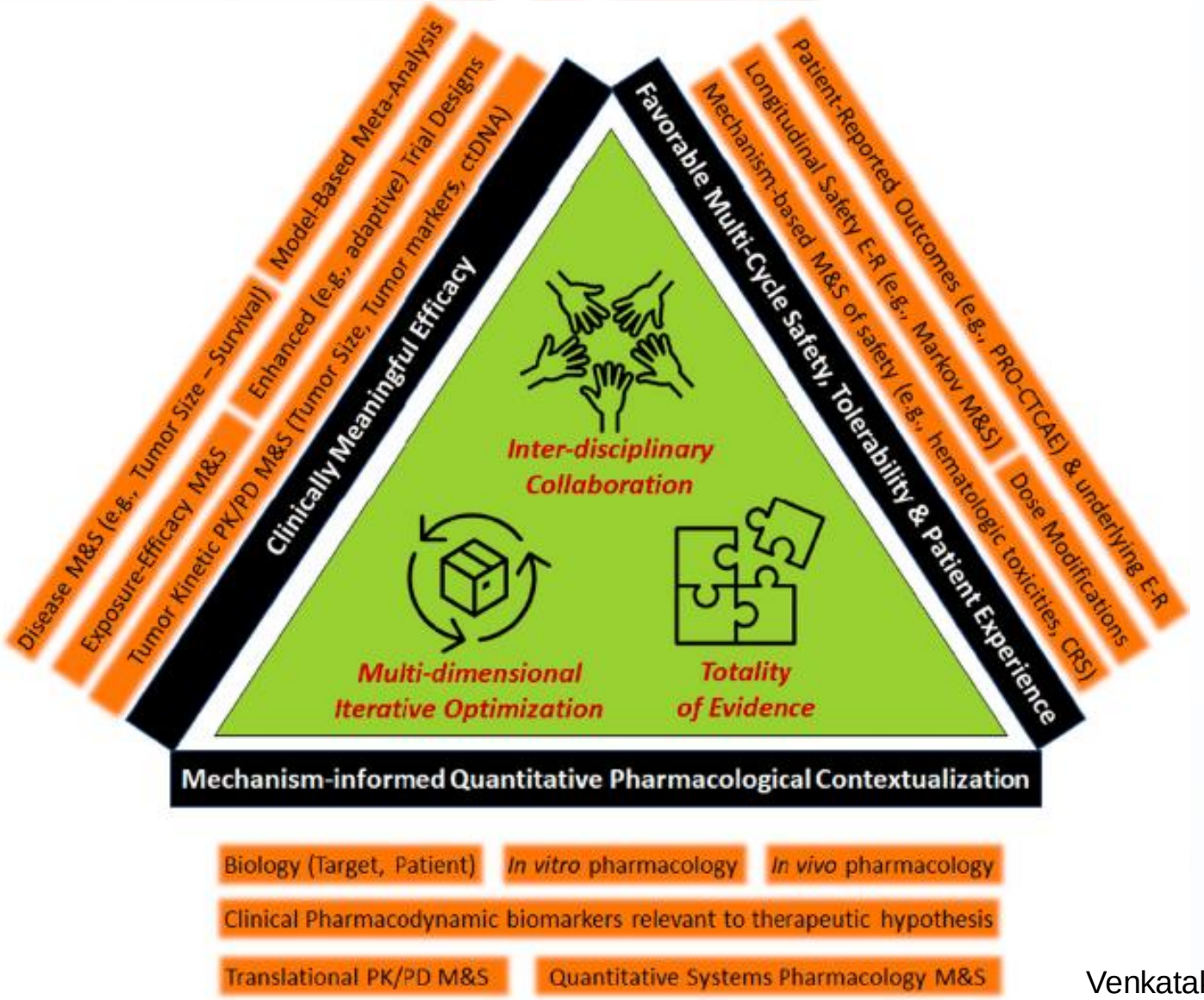
IQ CPLG Oncology Dose Optimization WG Survey Results 2022

Oncology drug development is a multidimensional optimization problem



While there is a need to optimize dose there is also a need to identify patient population (e.g., line of treatment, cancer types, tumor mutational/molecular profile) that can benefit from therapy, combination partner selection and dose/schedule of the selected combination partner

Towards an Evidentiary Framework for Informing Adequacy of Dose Optimization

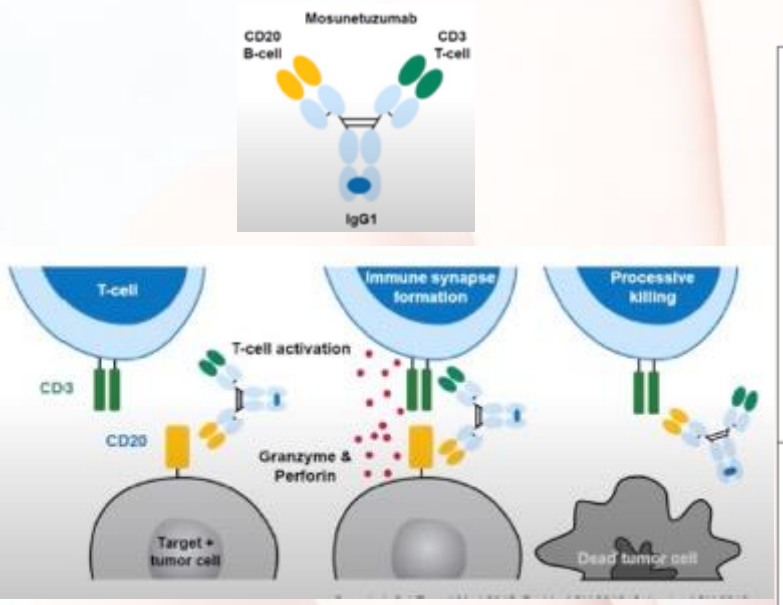


Venkatakrishnan *et al.* Clin Pharmacol Ther. 2022

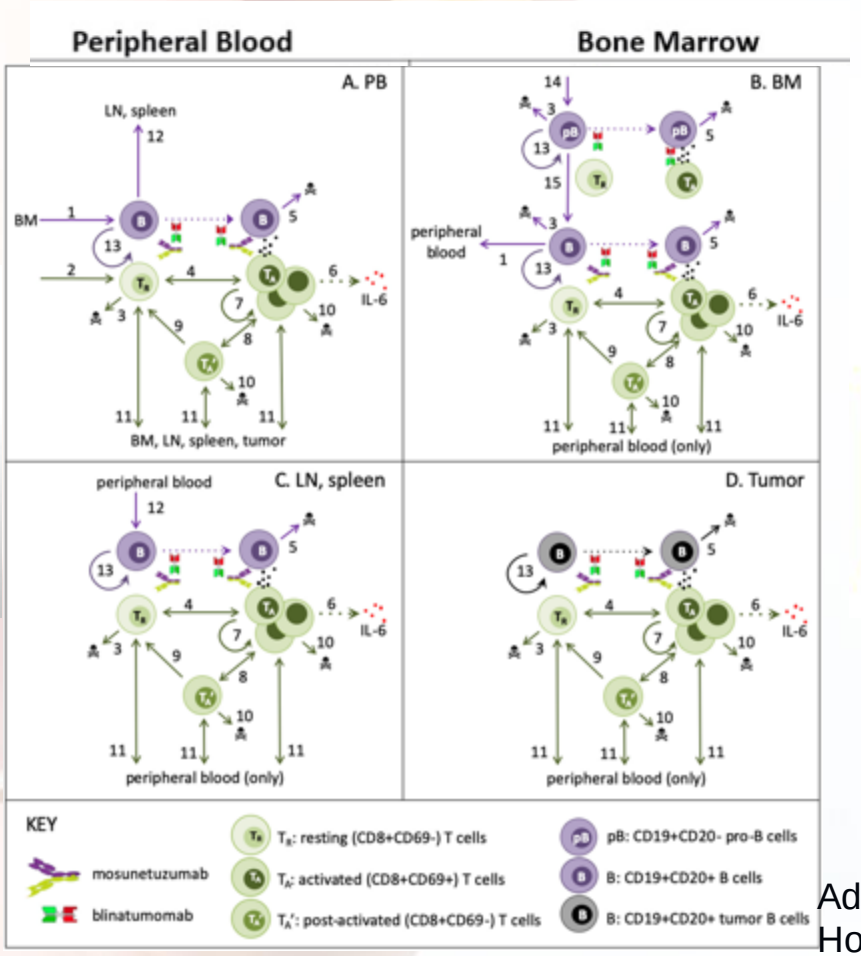
Mosunetuzumab: Step-Up Dosing Hypothesis Supported by QSP

Leveraged translational systems modeling (QSP) to mitigate the risk of cytokine release syndrome (CRS) in a Phase I trial of mosunetuzumab (CD20/CD3 bispecific antibody) in NHL

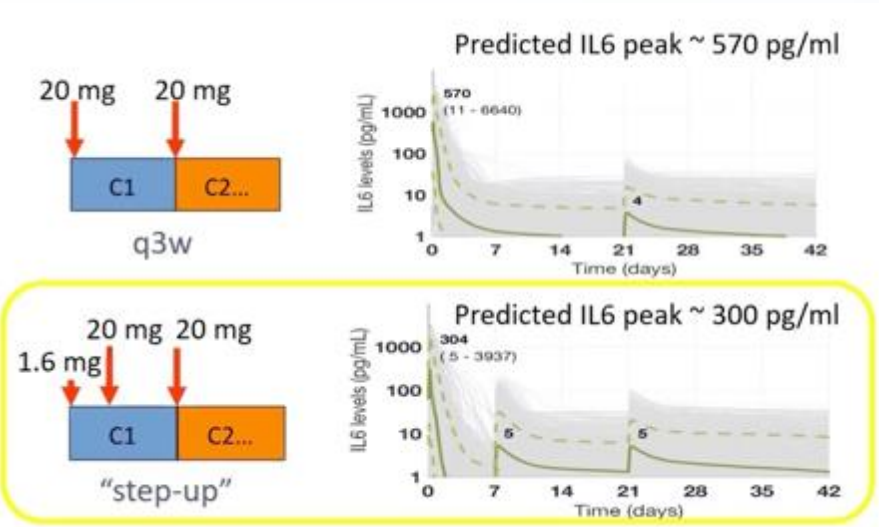
Mechanism of Action



Systems Modeling of IL6 Kinetics



Model Predicted IL6 Following Fixed Dosing vs Step Up Dosing Regimens

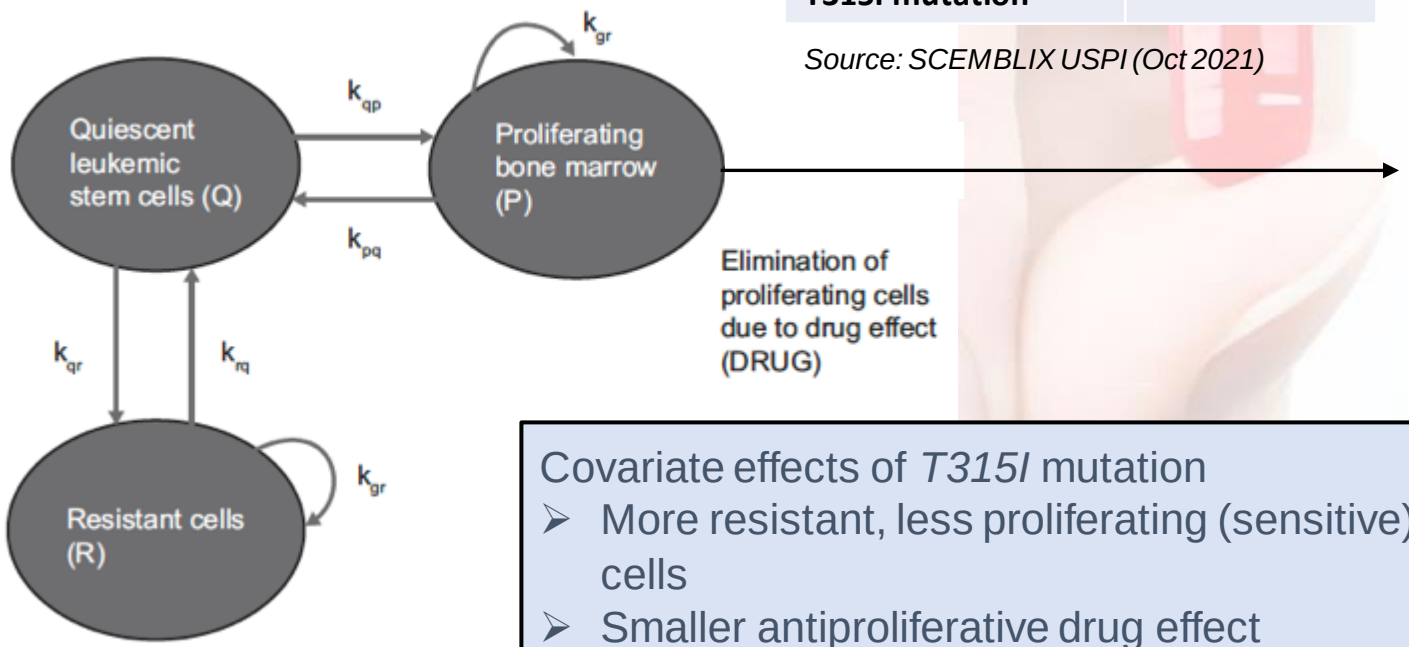


Adapted from Chi-Chung Li & Iraj Hosseini. AAADV, 2019
Hosseini *et al*. NPJ Syst Biol Appl. 2020

Asciminib: Tumor Kinetic M&S to Inform Dose Selection

Indication	Dosage
Ph+ CML-CP, previously treated with 2 or more TKIs	**80 mg/day** (80 mg QD or 40 mg BID)
Ph+ CML-CP with T315I mutation	**200 mg BID**

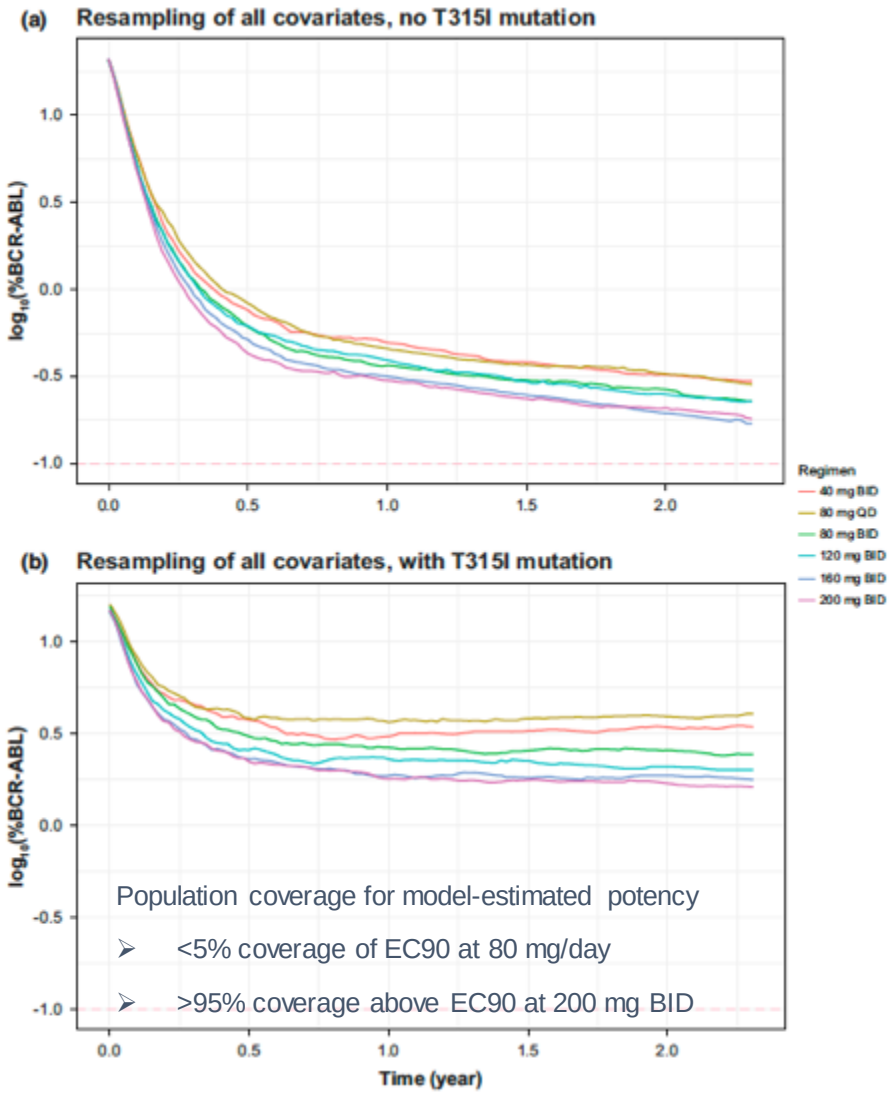
Source: SCEMBLIX USPI (Oct 2021)



Covariate effects of *T315I* mutation

- More resistant, less proliferating (sensitive) cells
- Smaller antiproliferative drug effect

Median simulated time-course of *BCR::ABL1*



Adapted from Venkatakrishnan K, ACoP 13, 2022
Combes FP *et al*. Clin Pharmacol Ther. 2022

Key Takeaways

- A case-by-case approach to multidimensional dose optimization is warranted in oncology drug development by leveraging Totality of Evidence approach (translational pharmacology, PK/PD biomarkers, safety & long-term tolerability, efficacy endpoints and modeling & simulation approaches) to progressively decrease uncertainty over the development lifecycle
  - Mindset change: Dose finding study design to characterize the dose response curve, but not MTD
  - Multidisciplinary collaboration: Identification of clinical relevant biomarkers to support dose selection
  - Long term tolerability, PRO-CTCAEs
  - Quantitative pharmacology tools

- Enhance communication & close partnership with HAs; tools such as dose snapshot template (*Friends of Cancer Research White Paper*) can facilitate Internal alignment as well as enable communication with HAs

- Oncology dose findings operate with uncertainty. Alignment of level of uncertainty on dose selection with HAs is critical.

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