MIDD Applied Post-Approval: Examples with Ibrutinib, a BTK Inhibitor

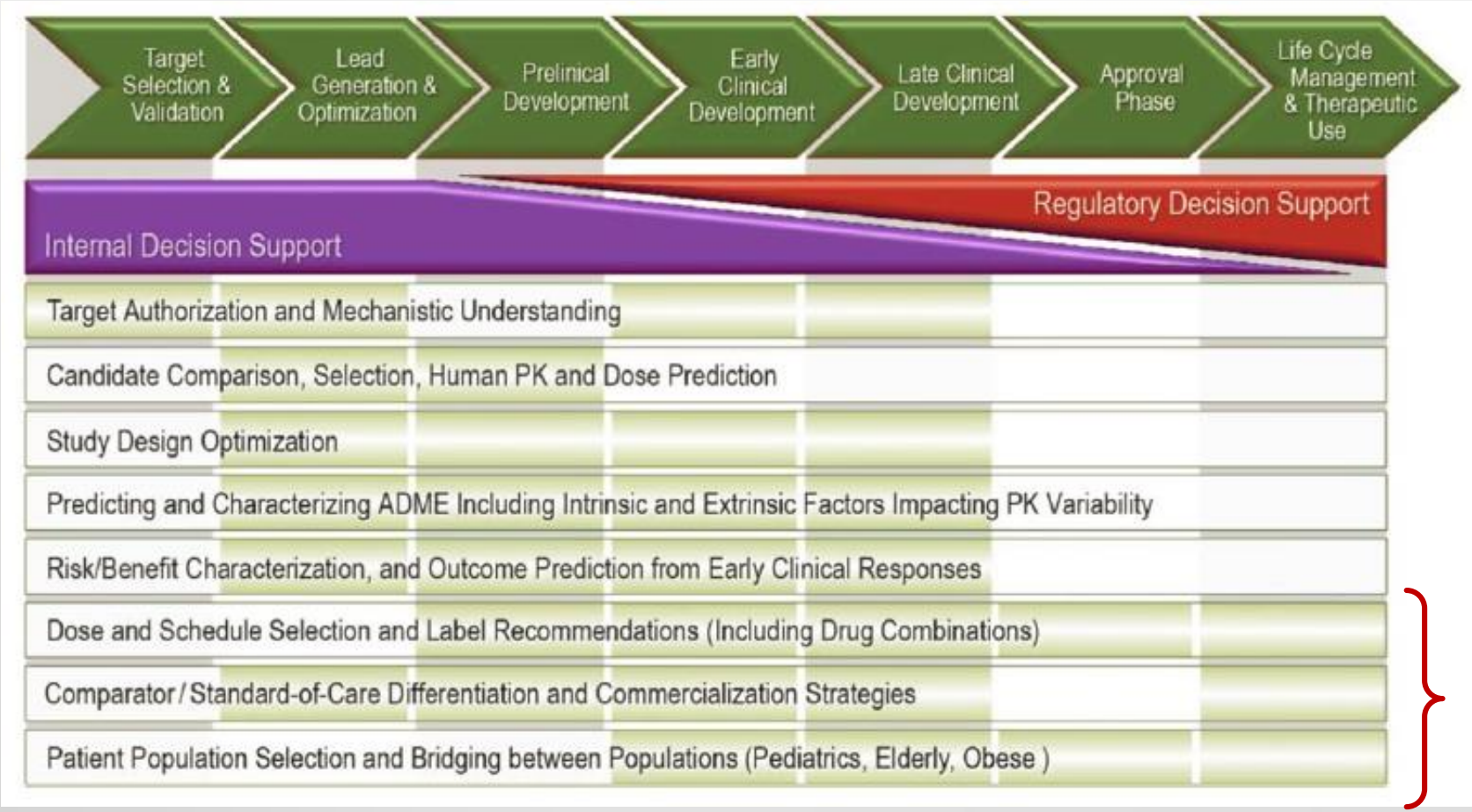
Daniele Ouellet, PhD

Sr Director & TA-Group Leader

Global Clinical Pharmacology, Janssen R&D

MIDD: Model Informed Drug Development

MIDD by Phase

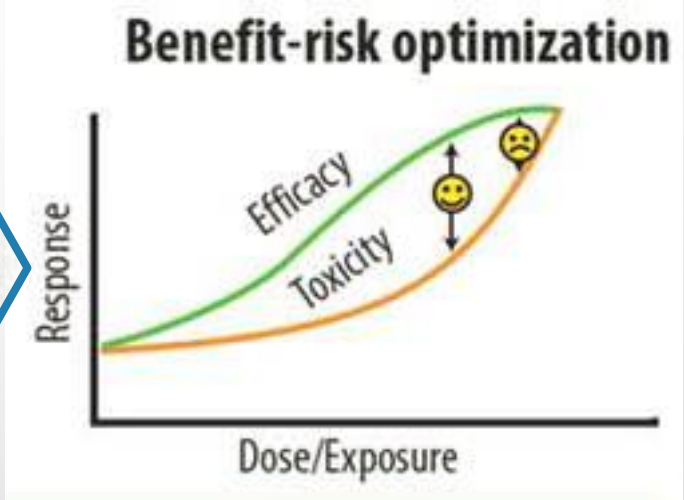


EFPIA MID3 Workgroup; CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122

Post Marketing Activities

- Bridging Populations
  - Ethnic / Regional Differences
  - Pediatric population
- Bridging Indications
  - Other disease(s)
- Labeling Support
  - Completion of Clin Pharm Package
    - DDI, organ impairment
  - Dosage Administration
    - New formulations

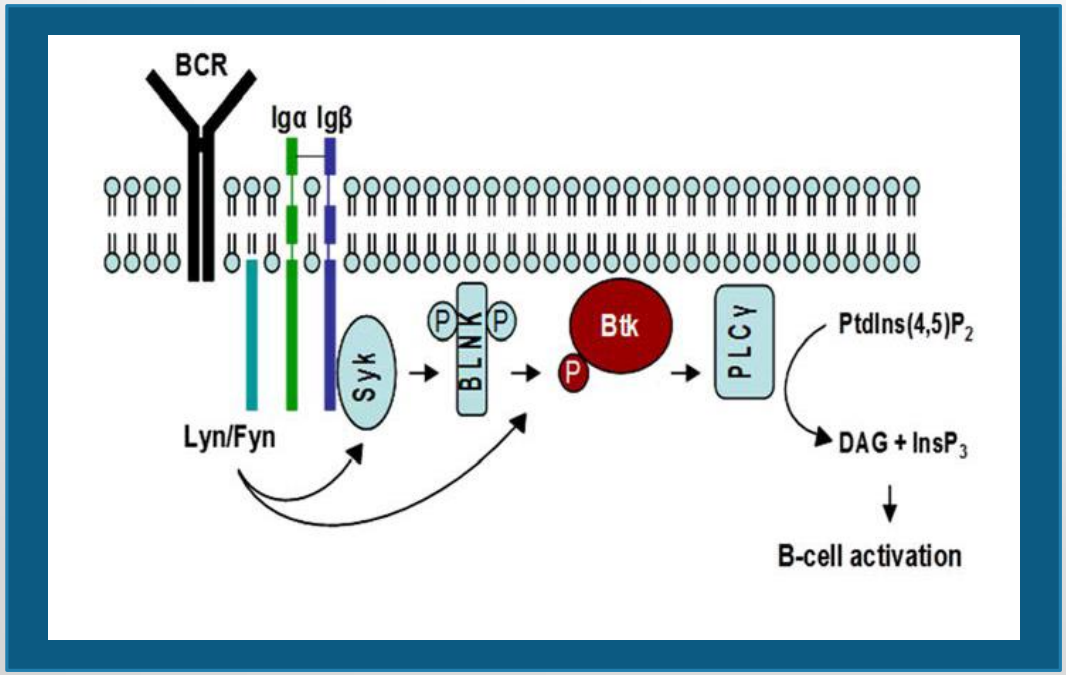
<u>Capitalize</u> on quantitative understanding of efficacy/toxicity exposure response



Venkatakrishnan K et al. CPT 2015; 97: 37-54.

Ibrutinib – Covalent BTK Inhibitor

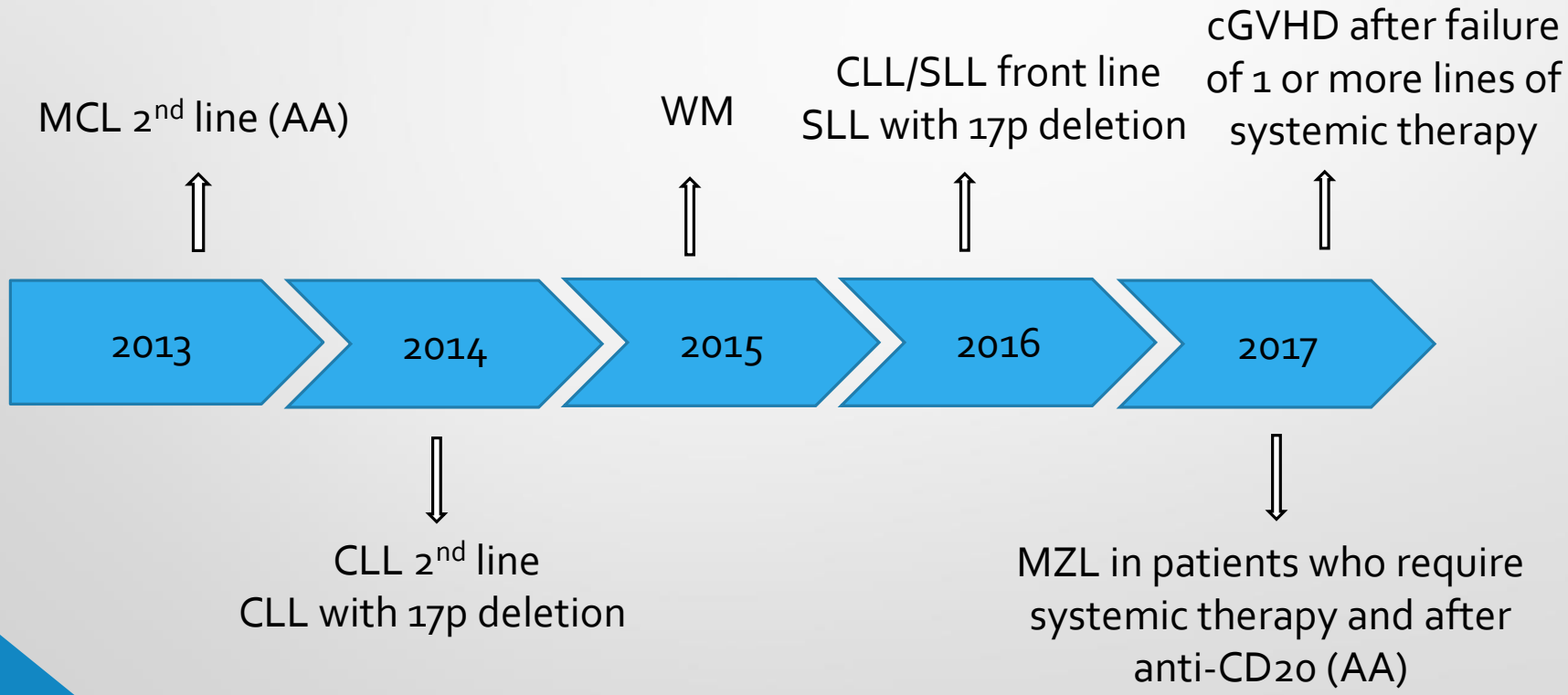
- Bruton's tyrosine kinase (Btk) is an enzyme in the B-cell receptor (BCR) signal transduction pathway involved in B cell proliferation.
- Ibrutinib (PCI-32765) is a covalent inhibitor of Bruton's tyrosine kinase with IC50 of 0.46 nM (bind to cysteine residue Cys 481 of BTK).
- BTK inhibition targeted for B-cell malignancies and other diseases that involves abnormal activation of B-cell pathway.



Summary of Clinical Pharmacology; Summary Basis of Approval 2013

Indications (FDA) Monotherapy or In Combination

- Approved for various B cell malignancies (monotherapy and/or combination) and cGVHD



MCL = Mantle Cell Lymphoma; CLL = Chronic Lymphocytic Leukemia;
SLL = Small Lymphocytic Lymphoma; WM = Waldenström's macroglobulinemia
cGVHD = Chronic Graft versus Host Disease; MZL = Marginal Zone Lymphoma

MIDD Activities to Support Ibrutinib

- Development of ibrutinib in various combinations, different indications & populations
- Continued assessment of drug-drug interactions
  - Use of PBPK model for predictions of the effects of different doses of inhibitors on ibrutinib, and other scenarios
  - Predictions of ibrutinib exposure with different dose adjustment based on understanding of target engagement & exposure response
  - Fulfillment of PMRs/PAMs including study with omeprazole (PAM)
- Support pediatric development
  - Predictions of starting dose
  - Bayesian evaluation of pediatric exposure and recommendations of clinical dose in different age cohorts
- Support development of different formulations

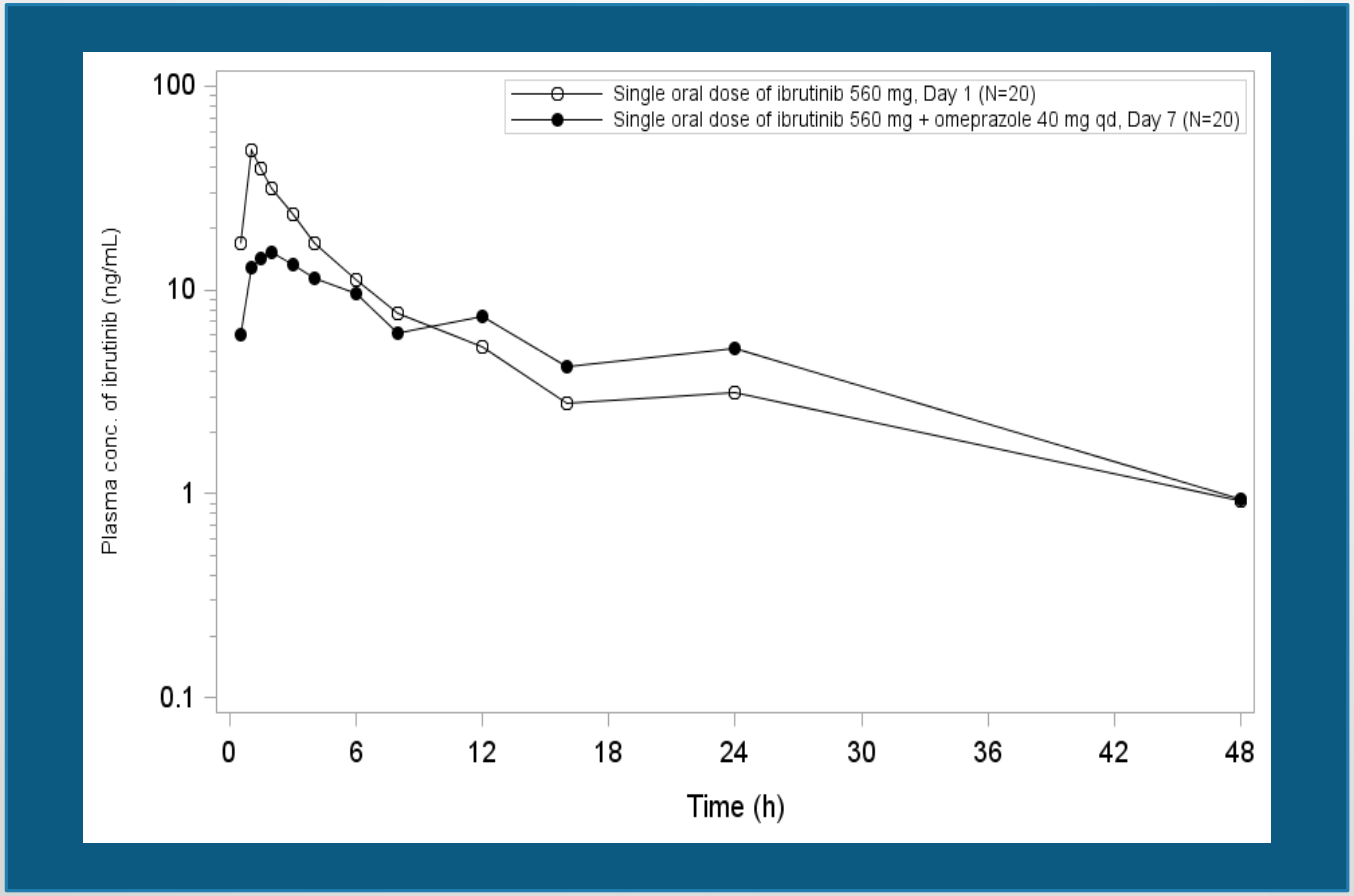
PBPK=Physiologically Based Pharmacokinetic Modelling;
PMR=Post-Marketing Requirements; PAM=Post Authorization Measure

PAM: DDI Study with PPI

- Rationale
  - Ibrutinib is a weak base with pH dependent solubility (practically insoluble at pH ≥ 3)
  - BCS Class 2 (high permeability/low solubility) with rapid absorption (Tmax 1-2 hrs)
  - Food increases Cmax (2- to 4-fold) and AUC (2-fold); ibrutinib can be taken with or without food
- Study Objective
  - Evaluate effect of repeat dose omeprazole, a proton pump inhibitor (PPI), on the single dose PK of ibrutinib
- Study Design
  - Single center, open-label, sequential design drug interaction study in 20 healthy subjects. Ibrutinib 560 mg administered alone on Day 1 and with omeprazole on Day 7. Omeprazole 40 mg administered on Days 3 to 7.

ClinicalTrials.gov Identifier: NCT02638116

Plasma Concentration Ibrutinib Alone and With Omeprazole



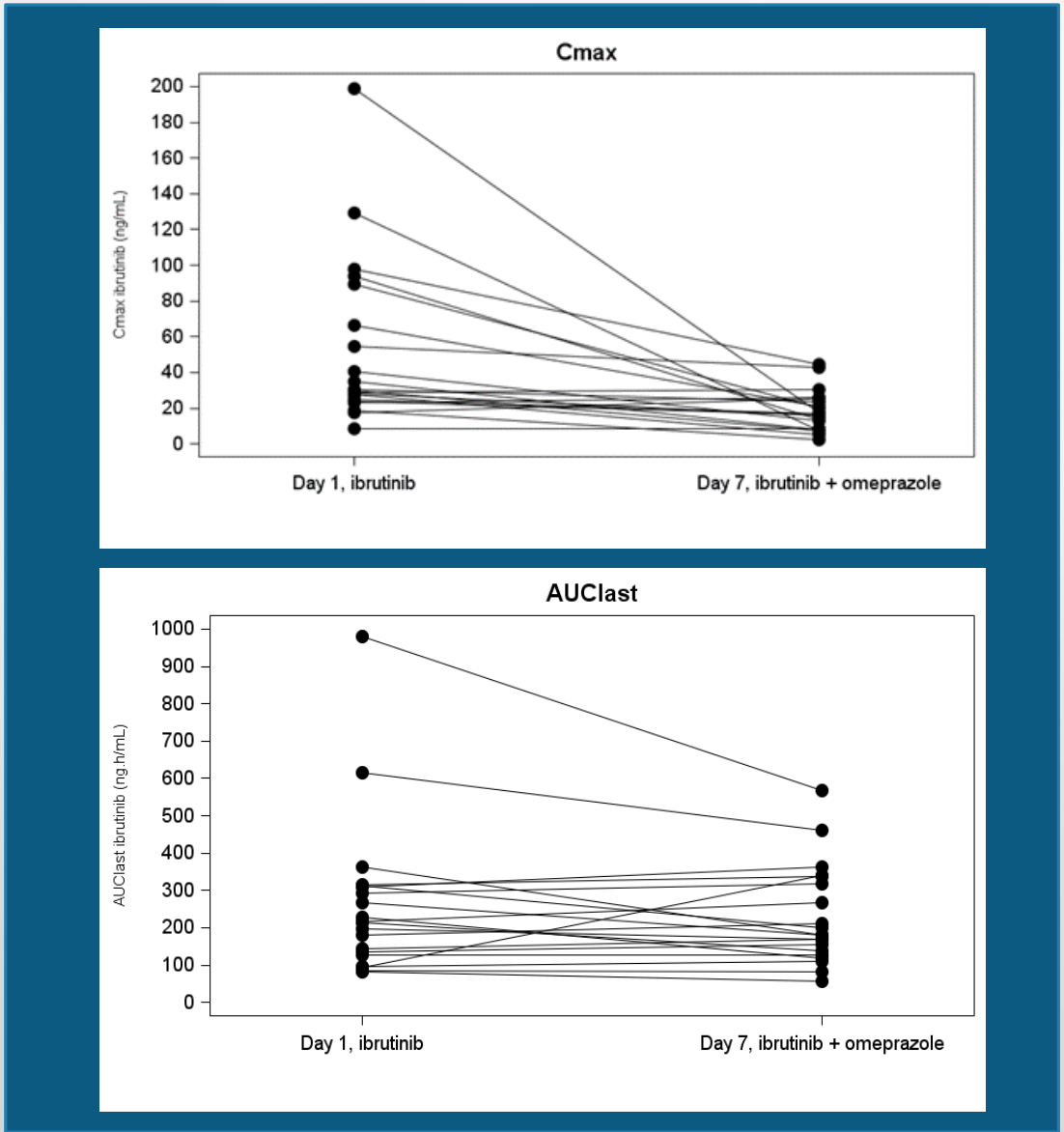
Blood 2016 128:1588

Comparison of PK parameters of ibrutinib alone and with omeprazole

	Geometric Mean		Geometric Mean Ratio (90% CI), %
	Ibrutinib Alone	Ibrutinib + omeprazole	
N	20	20	20
$C_{max,}$ ng/mL	39.5	14.8	37.5 (26.4–53.4)
$AUC_{24h,}$ ng.h/mL	176	147	83.4 (68.0–102.2)
$AUC_{48h,}$ ng.h/mL	217	213	98.3 (83.1–116.3)
$AUC_{last,}$ ng.h/mL	210	195	92.5 (77.8–109.9)
Tmax, hr	1.0 (0.5–4.0)	2.0 (0.5–24.2)	NA
Half-life, hr	11.4 ± 5.1	15.0 ± 10.6	NA

Results Study CLL1005

Effect of Omeprazole on Individual Cmax and AUC



Results Study CLL1005

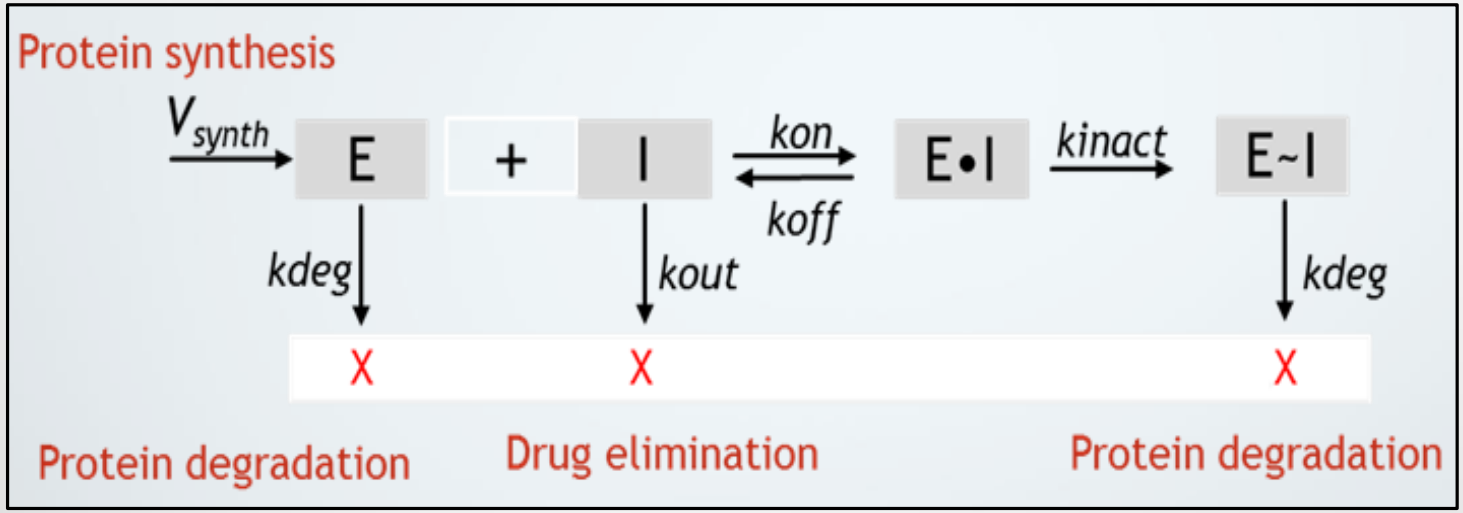
How to quantitatively evaluate impact of lower Cmax?

- Based on MoA with covalent binding, lower Cmax unlikely to affect inhibition of target
  - Evaluate in quantitative manner using mechanistic model
  - Predict BTK target inhibition of ibrutinib based on PK profiles with/without omeprazole and binding kinetics
  - Sensitivity analysis for different parameters
  - Compare outcome to clinical BTK occupancy data
- Exposure-response for clinical efficacy based on AUC and Cmax

Results to be presented at ASCPT March 2018
By Nahor Haddish-Berhane et al.

Mechanistic model of BTK inhibition by Ibrutinib

E = BTK I = Ibrutinib

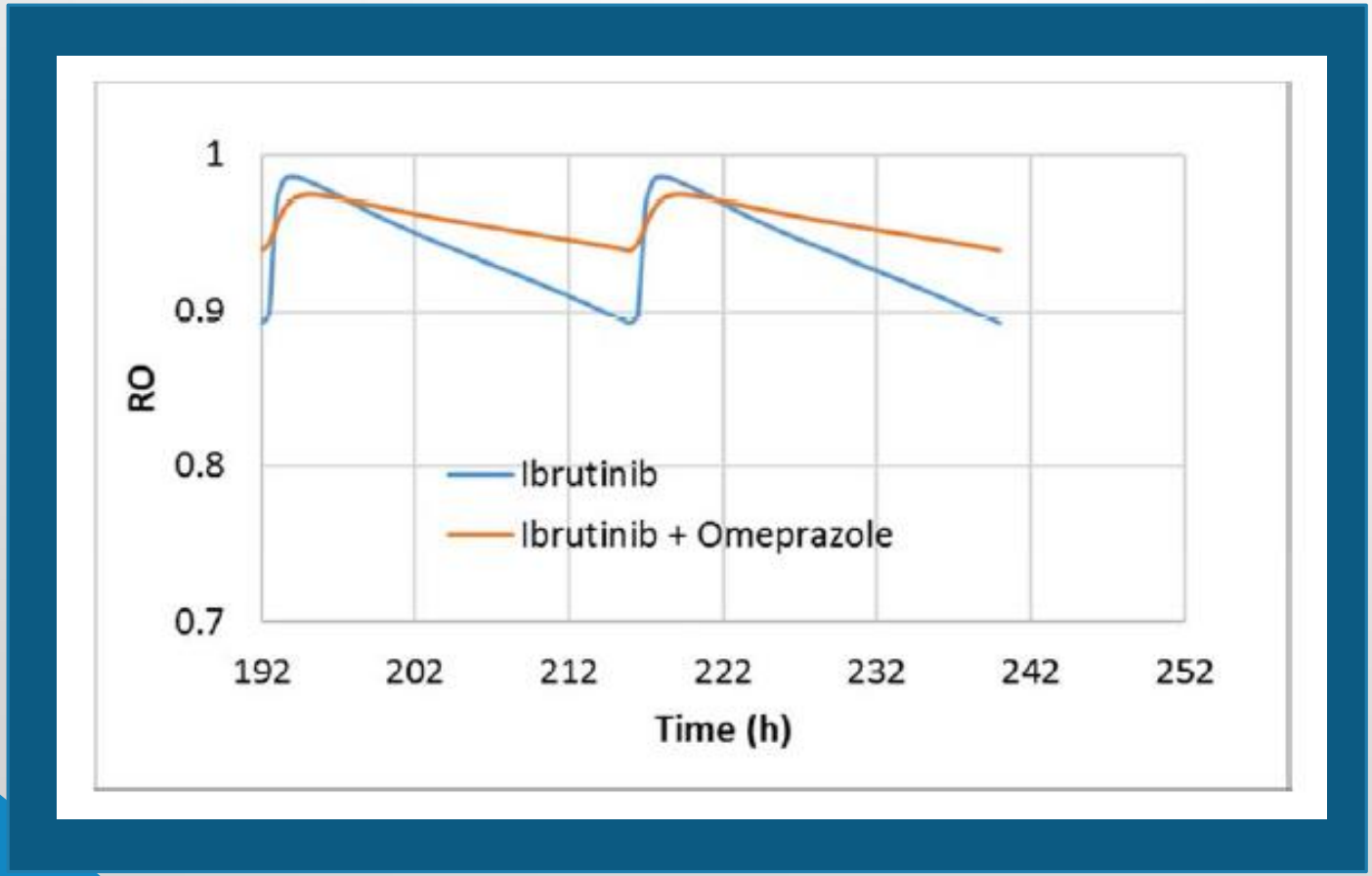


k_{on}	2.4×10^{5}	(1/M·s)	Association rate (ref 1)
k_{off}	5.7×10^{-5}	(1/s)	Dissociation rate (ref 1)
KD	0.24	nM	Affinity (k_{off}/k_{on}) (ref 1)
k_{inact}	0.0084	1/s	Covalent binding rate (exp data)
BTK half-life	24	h	BTK protein half-life (ref 2)

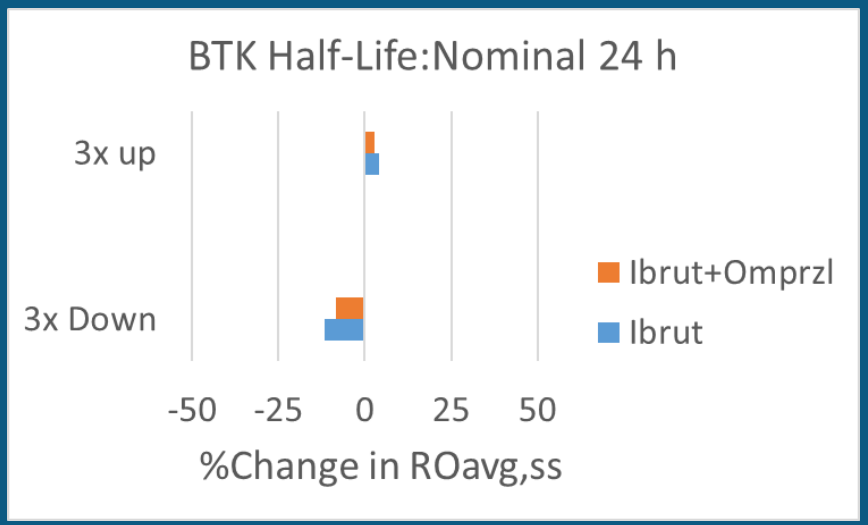
Ref 1: Woyach JA et al; N Engl J Med 2014;370(24): 2286–94;
Ref 2: Saffran DC et al; N Engl J Med 1994;330:1488-91; Evans et al; J Pharmacol Exp Ther 2013; Aug, 346:219-228; Hutchinson CV and Dyer MJS; Br J Haematol 2014; April,166:12-22

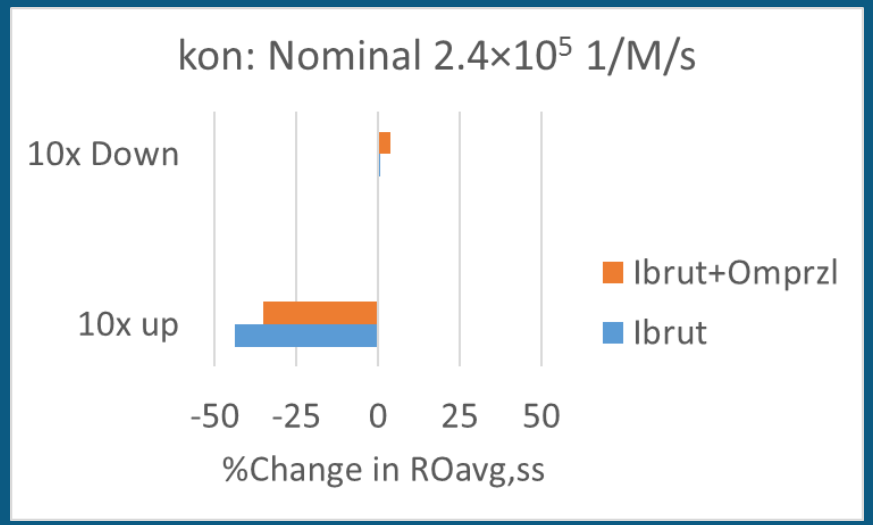
Predicted Receptor Occupancy (RO) for Steady-State Ibrutinib Alone and with Omeprazole

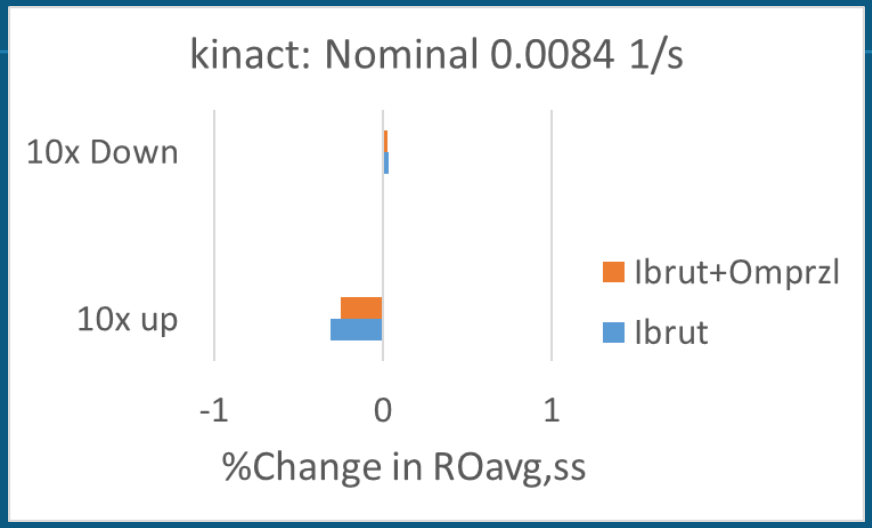
No relevant difference in average RO (94% and 96% for ibrutinib alone and with omeprazole, respectively)



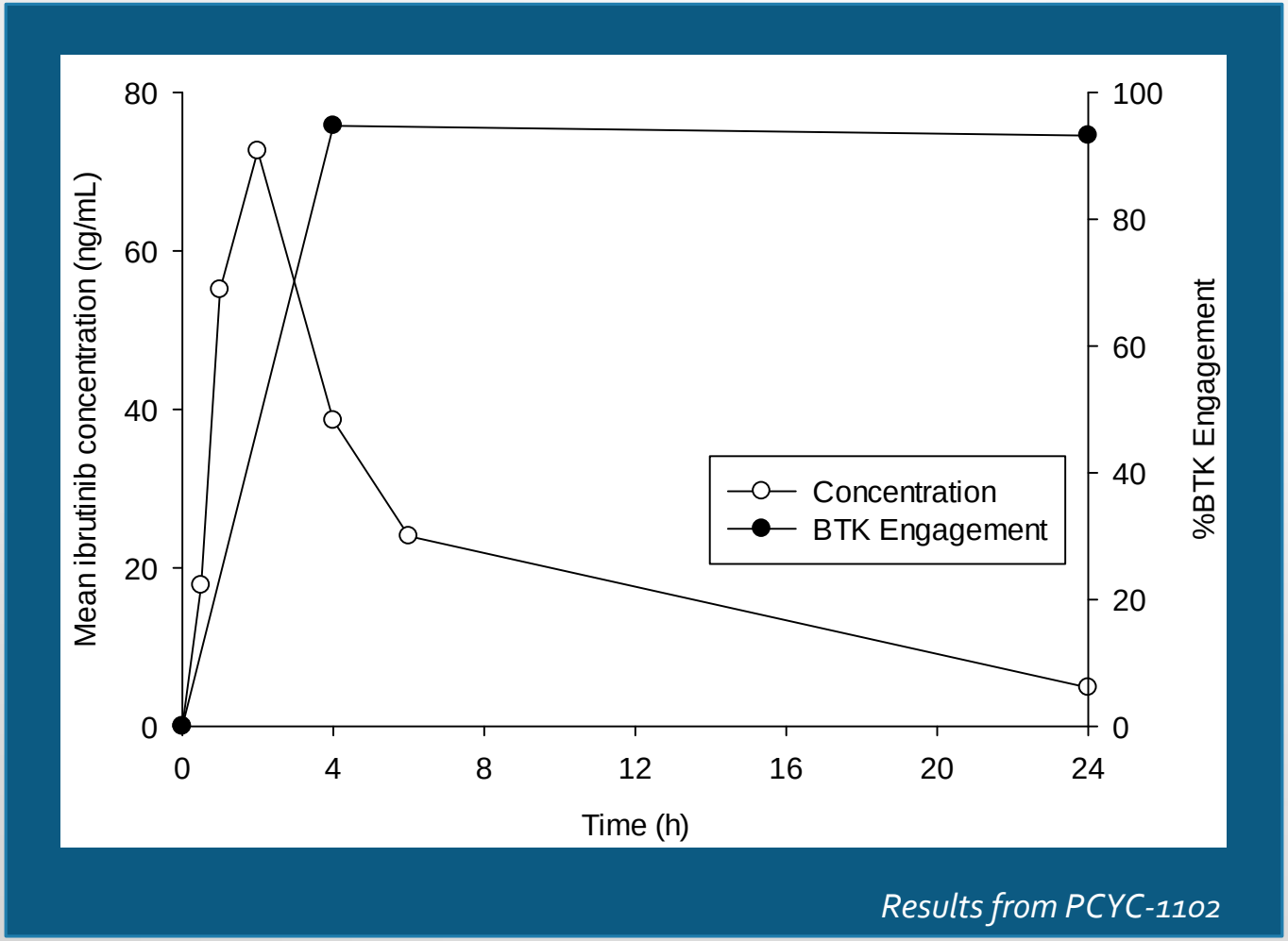
Sensitivity Analysis for Different Parameter Assumptions







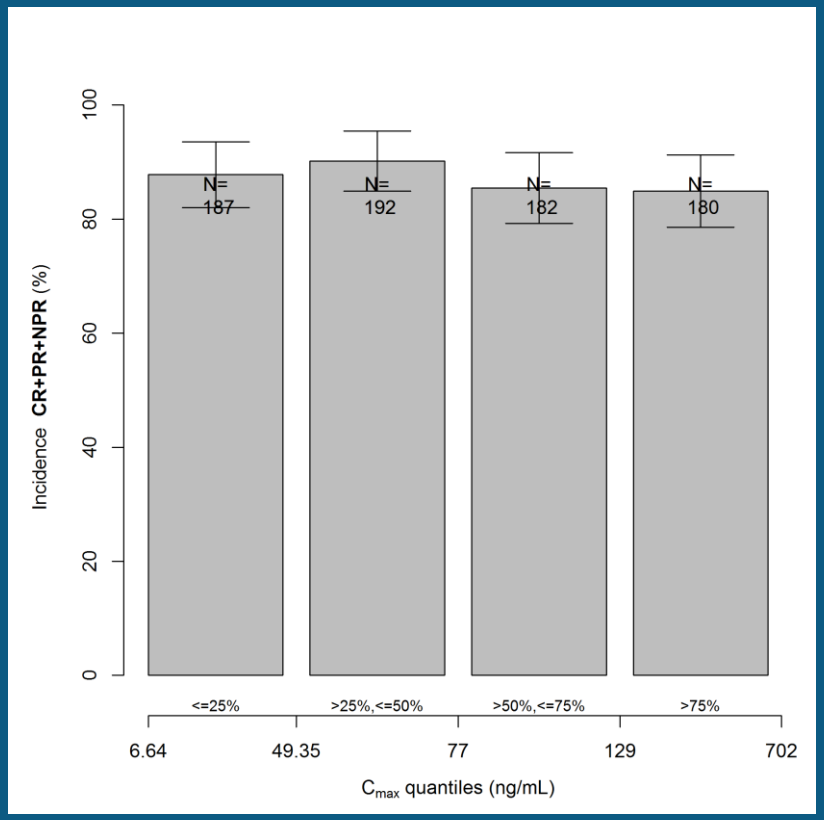
BTK Receptor Occupancy and Ibrutinib PK After SD Administration

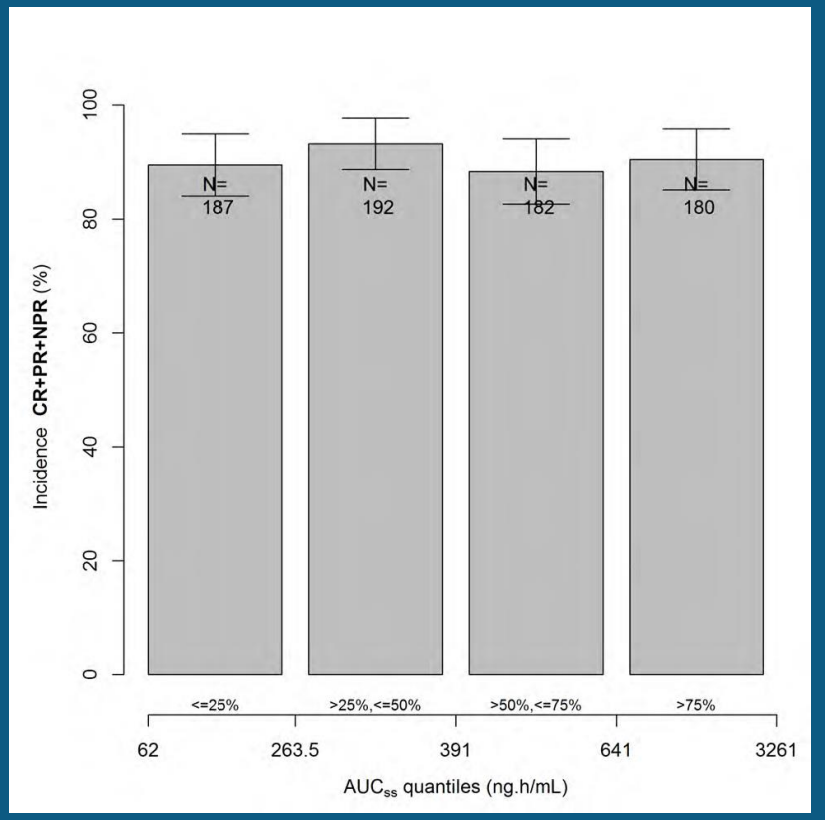


Results from PCYC-1102

SD=Single Dose

Relationship between Efficacy and Exposure (Cmax and AUC)





Efficacy is ORR and shown in Subjects with CLL; Similar profiles in Subjects with MCL

Conclusions

- Mechanistic model developed to support outcome of the drug interaction study with omeprazole and provide clinical recommendations with no dose adjustments and no restrictions
- Data support lack of clinical relevance for the difference in Cmax given that AUC was similar with and without omeprazole
- Small example to illustrate how MIDD is used to support post-marketing activities for ibrutinib

DDI=Drug Drug Interaction

Acknowledgments

- **<u>Thanks to colleagues who performed this work:</u>**
- **Jan de Jong**, Janssen La Jolla, GCP leader for ibrutinib
- **Nahor Haddish-Berhane**, Janssen Spring House, for modeling
- **Juthamas Sukbuntherng**, Pharmacyclics, GCP leader
- **Peter Hellemans** (Beerse) and **James Jiao** (Raritan), Janssen, for their contributions to the omeprazole clinical study