Model-Informed Drug Development (MIDD) for Ixazomib, an Oral Proteasome Inhibitor

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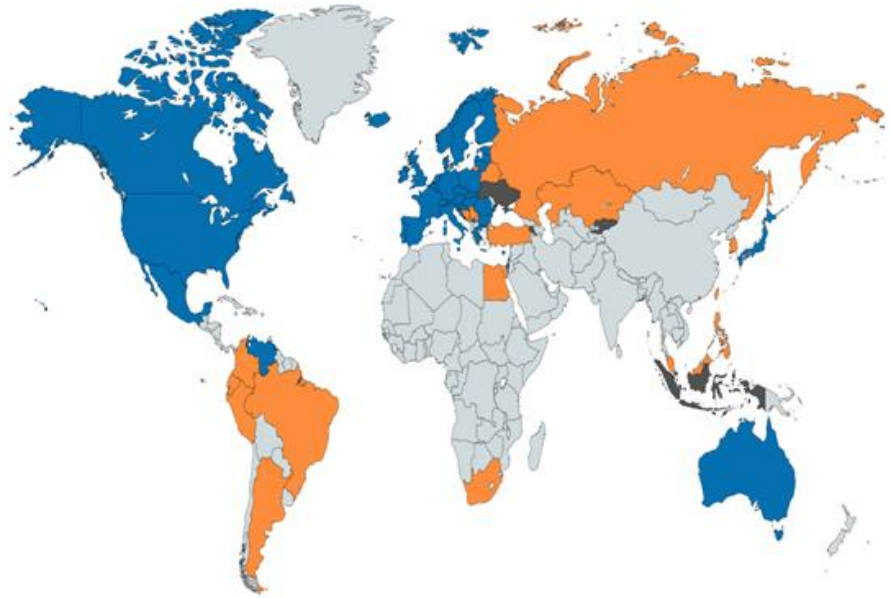
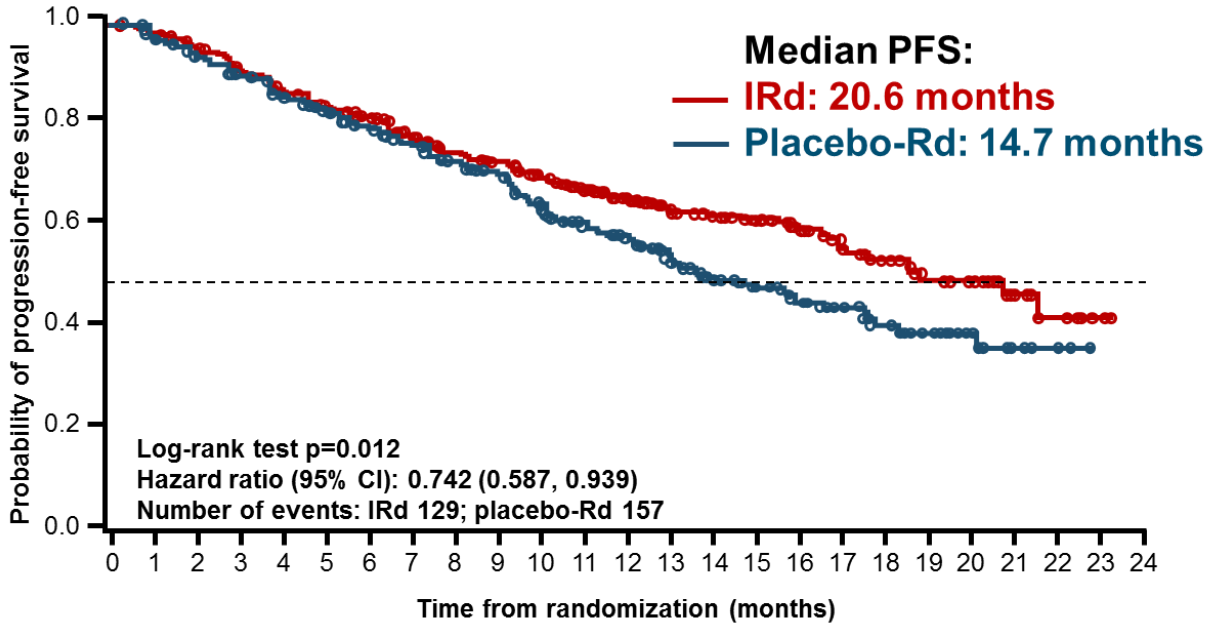
Ixazomib, an oral proteasome inhibitor

- Ixazomib in combination with lenalidomide and dexamethasone (Rd) is approved for the treatment of previously treated multiple myeloma (MM) in 40 countries

NINLARO® (ixazomib) capsules



- Approval was based on the results of the global, randomized, double-blind, placebo-controlled, phase 3 TOURMALINE-MM1 study in relapsed/refractory MM (RRMM)[1]



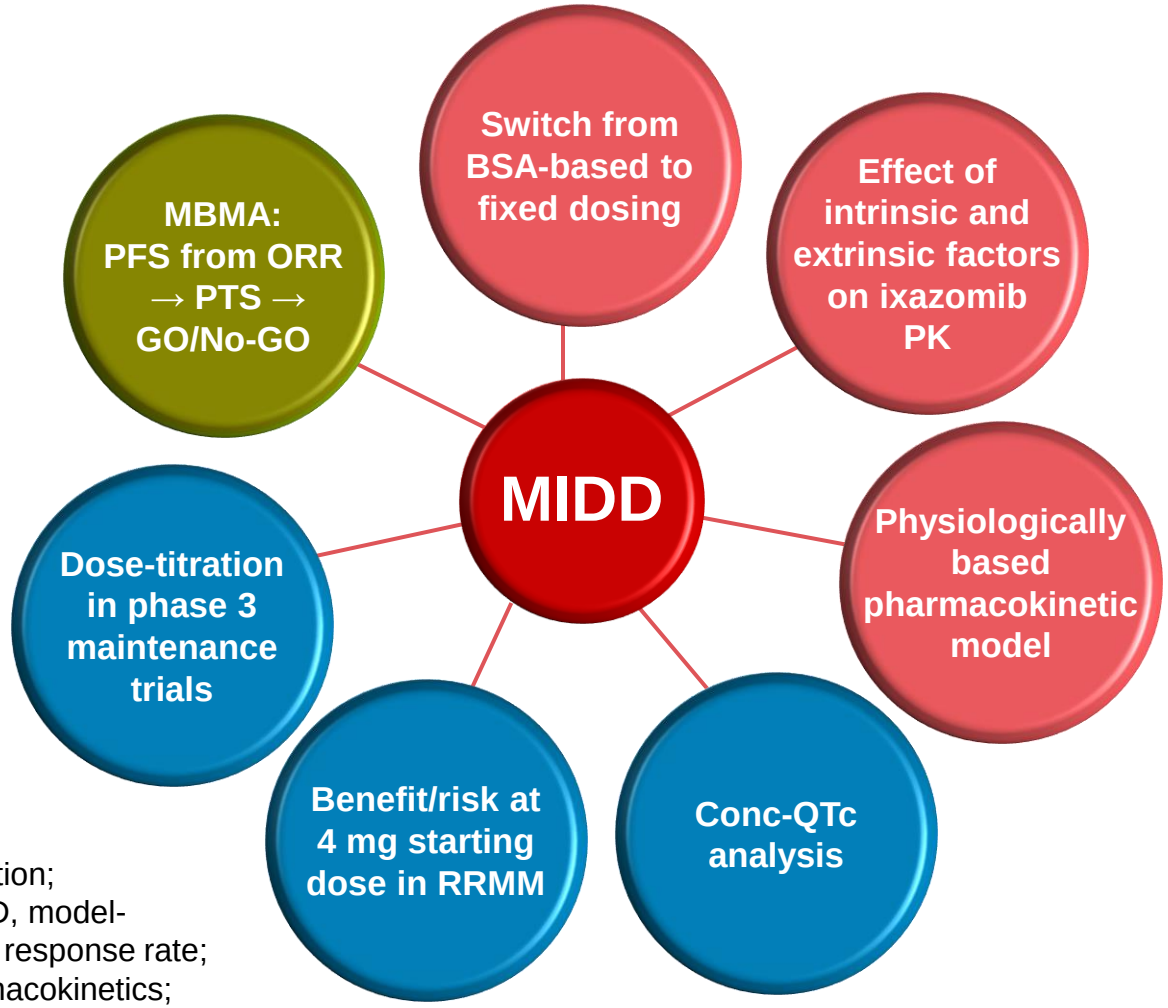
1. Moreau P, et al. N Engl J Med 2016;374(17):1621–34.

MIDD across the development continuum for ixazomib

Model-based meta-analysis

Exposure-response analysis

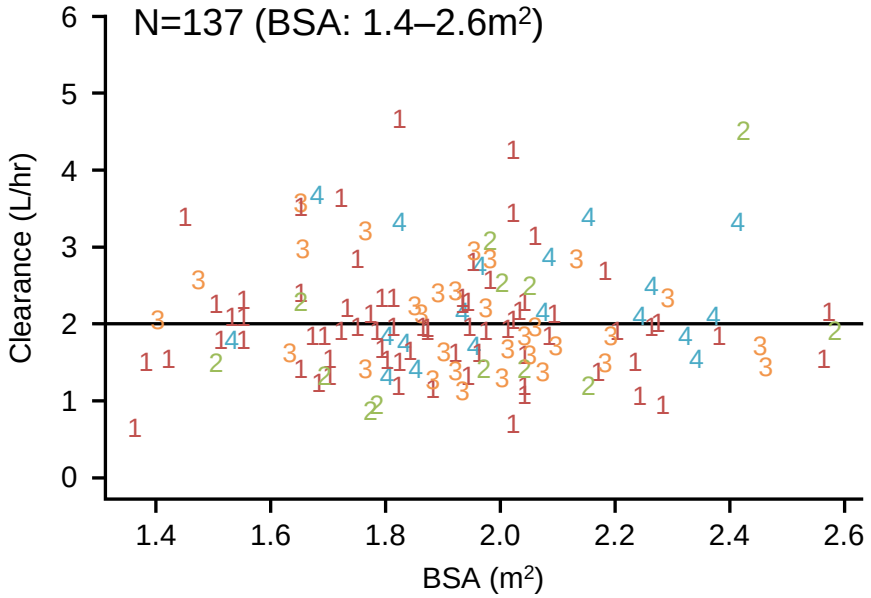
Understanding sources of PK variability

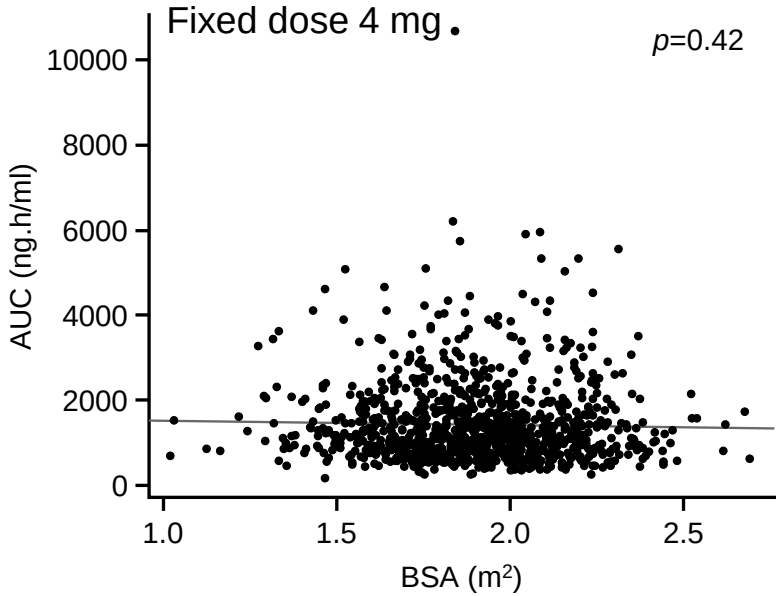


BSA, body surface area; Conc, concentration; MBMA, model-based meta-analysis; MIDD, model-informed drug development; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetics; PTS, probability of technical success; RRMM, relapsed/refractory multiple myeloma

Switch from BSA-based to fixed dosing (N=137 patients)

- No effect of BSA on clearance based on population PK analysis using data from four phase 1 studies





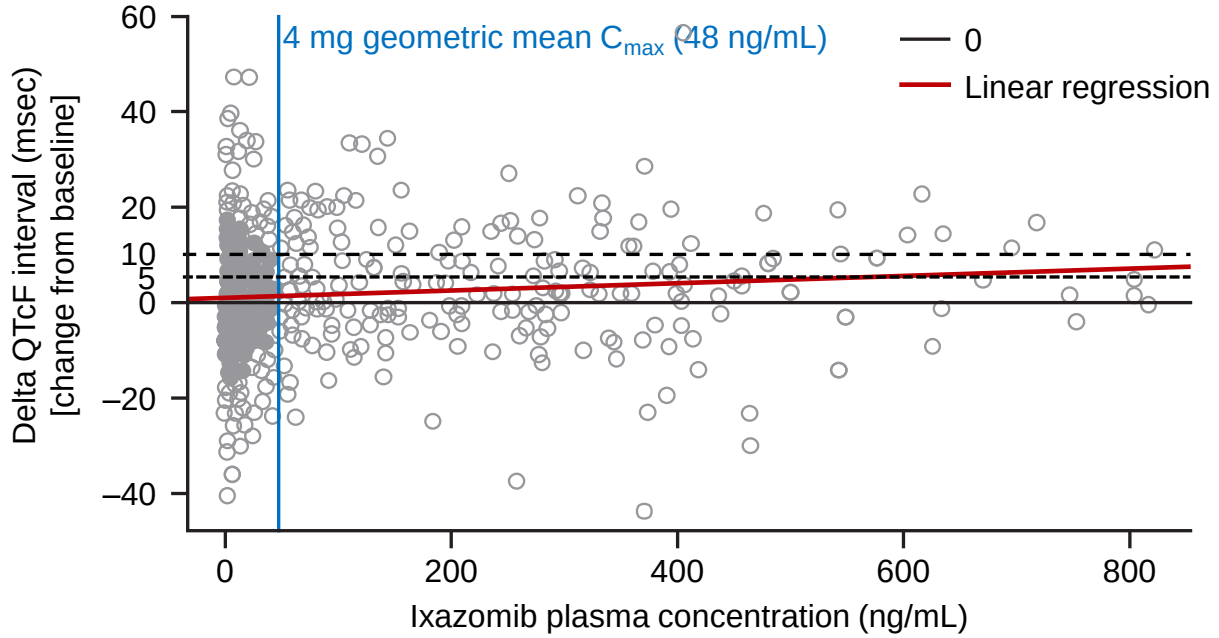
- Clinical development switched posology from BSA-based to fixed dosing, simplifying capsule strength manufacture and dosing in global clinical studies

BSA, body surface area; PK, pharmacokinetics

1. Gupta N, et al. Br J Clin Pharmacol 2015;79(5):789–800.

Concentration-QTc analysis in lieu of a dedicated QTc study (N=245 patients)

- Ixazomib did not prolong the QTc interval at clinically relevant exposures
  - At the 4 mg dose, mean change from baseline in QTcF was estimated to be 0.07 msec (90% CI: –0.22, 0.36) from the model-based analysis



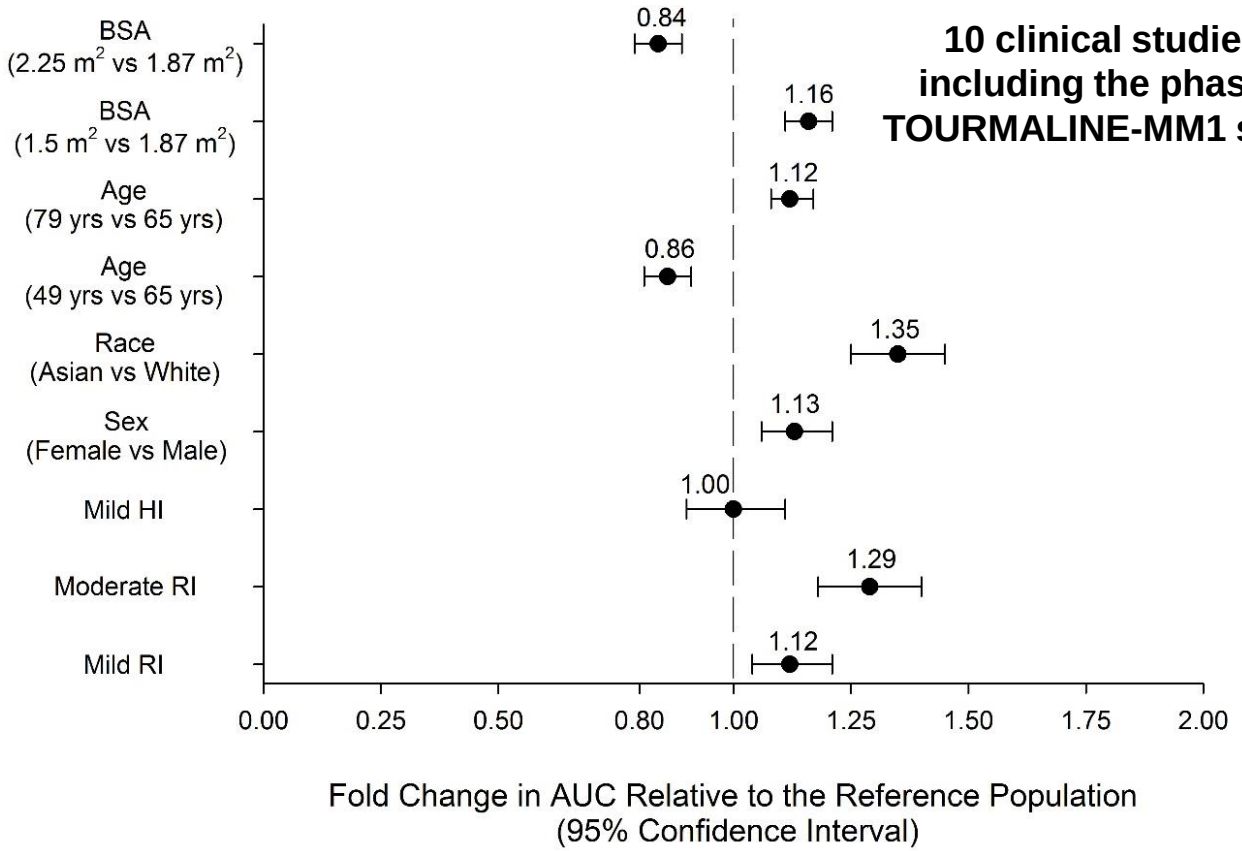
- From USPI: NINLARO did not prolong the QTc interval at clinically relevant exposures based on pharmacokinetic–pharmacodynamic analysis of data from 245 patients

USPI, United States Prescribing Information

Gupta N, et al. Cancer Chemother Pharmacol 2015;76(3):507–16.

Population PK analysis to examine effect of intrinsic and extrinsic factors on ixazomib PK (N=755 patients)

- No dose adjustment of ixazomib is required based on
  - BSA
  - Sex
  - Age
  - Race
  - Mild/moderate renal impairment,
  - Mild hepatic impairment



10 clinical studies, including the phase 3 TOURMALINE-MM1 study

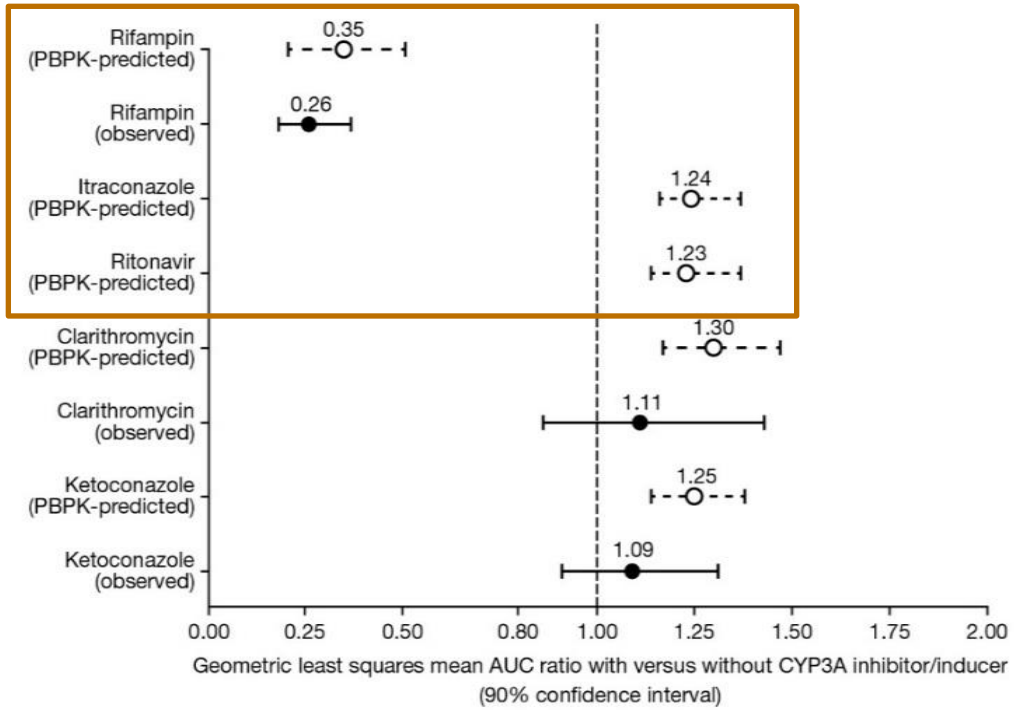
For BSA and Age, median values are compared 5th and 95th percentile

AUC, area under the curve; BSA, body surface area; HI, hepatic impairment; PK, pharmacokinetics; RI, renal impairment

Gupta N, et al. Clin Pharmacokinet 2017;e-pub ahead of print, doi: 10.1007/s40262-017-0526-4.

Application of a PBPK model to facilitate regulatory review

- Ixazomib AUC not meaningfully altered with strong CYP3A inhibitors, indicating minor role for CYP3A in ixazomib clearance
  - However, strong CYP3A inducer rifampin decreased AUC by 74%
- Clinical DDI study results reconciled well by PBPK model incorporating minor contribution of CYP3A to overall ixazomib clearance
  - Model quantitatively considered the strength of induction of CYP3A and intestinal P-glycoprotein by rifampin



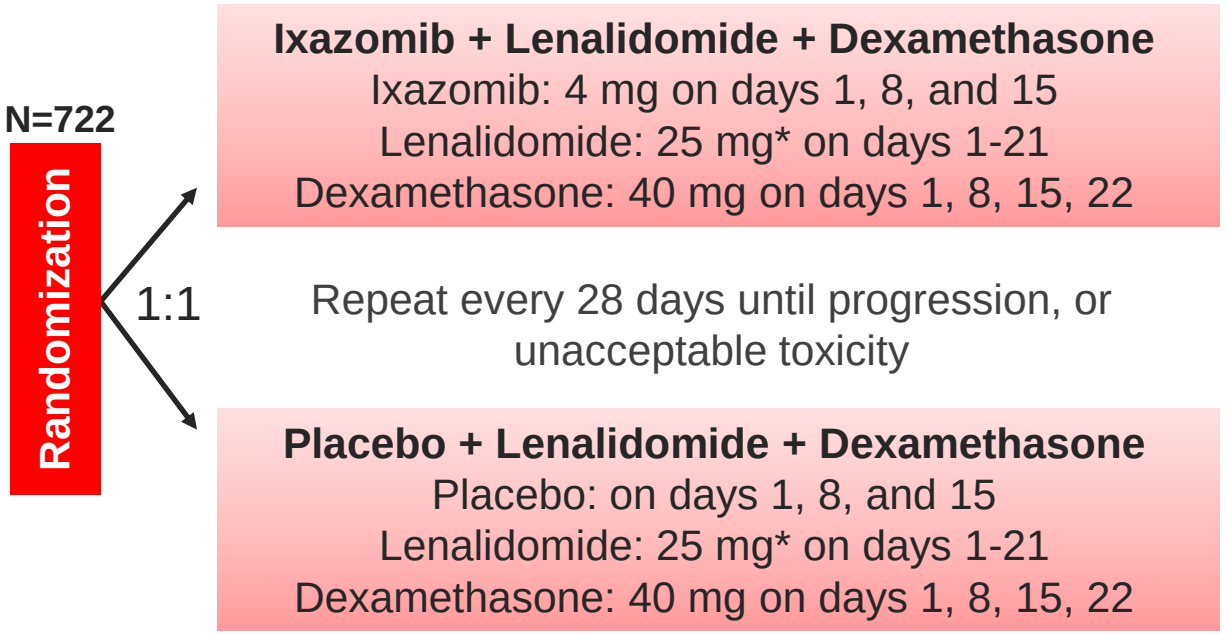
Results used during regulatory review to explain clinically significant effect of rifampin despite lack of strong CYP3A inhibitor effect

AUC, area under the curve; CYP, cytochrome P450; DDI, drug-drug interaction; PBPK, physiologically-based pharmacokinetic

Gupta N, et al. Manuscript in preparation.

TOURMALINE-MM1: A randomized, double-blind phase III study of ixazomib + lenalidomide-dexamethasone (IRd) vs placebo-Rd in RRMM

Global, double-blind, randomized, placebo-controlled study design



Stratification:
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

Primary endpoint:
- PFS

Key secondary endpoints:
- OS
- OS in patients with del(17p)

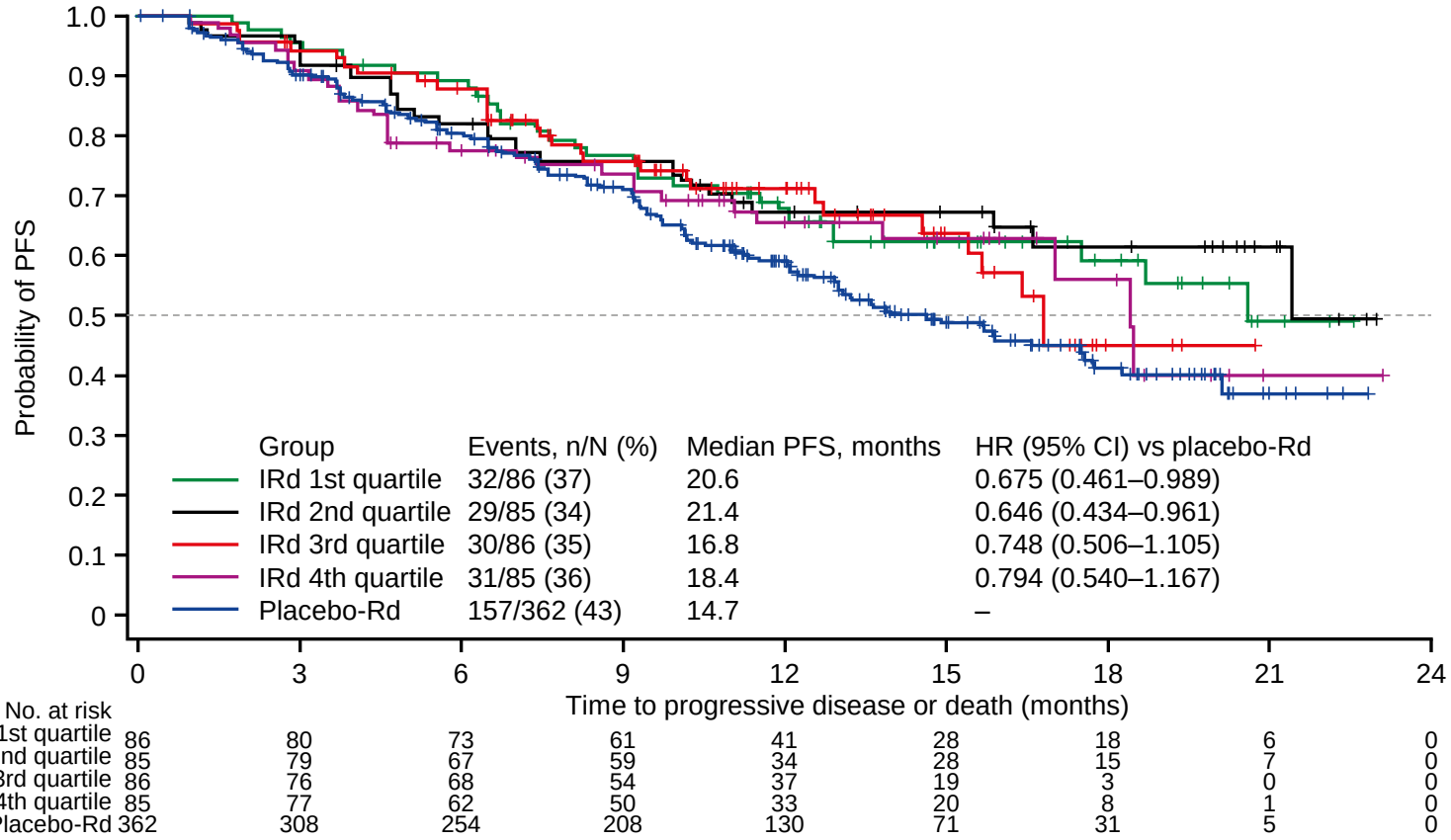
*10 mg for patients with creatinine clearance ≤60 or ≤50 mL/min, depending on local label/practice

ISS, International Staging System; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor

Moreau P, et al. New Engl J Med 2016; 374(17): 1621-34.

Exposure–efficacy analyses from TOURMALINE-MM1 to support benefit–risk profile of ixazomib-Rd (N=345 patients)

- Ixazomib exposure was not a significant predictor of PFS (p=0.25)
  - Median PFS was longer in all ixazomib exposure quartiles in the ixazomib-Rd arm compared to the placebo-Rd arm of the study

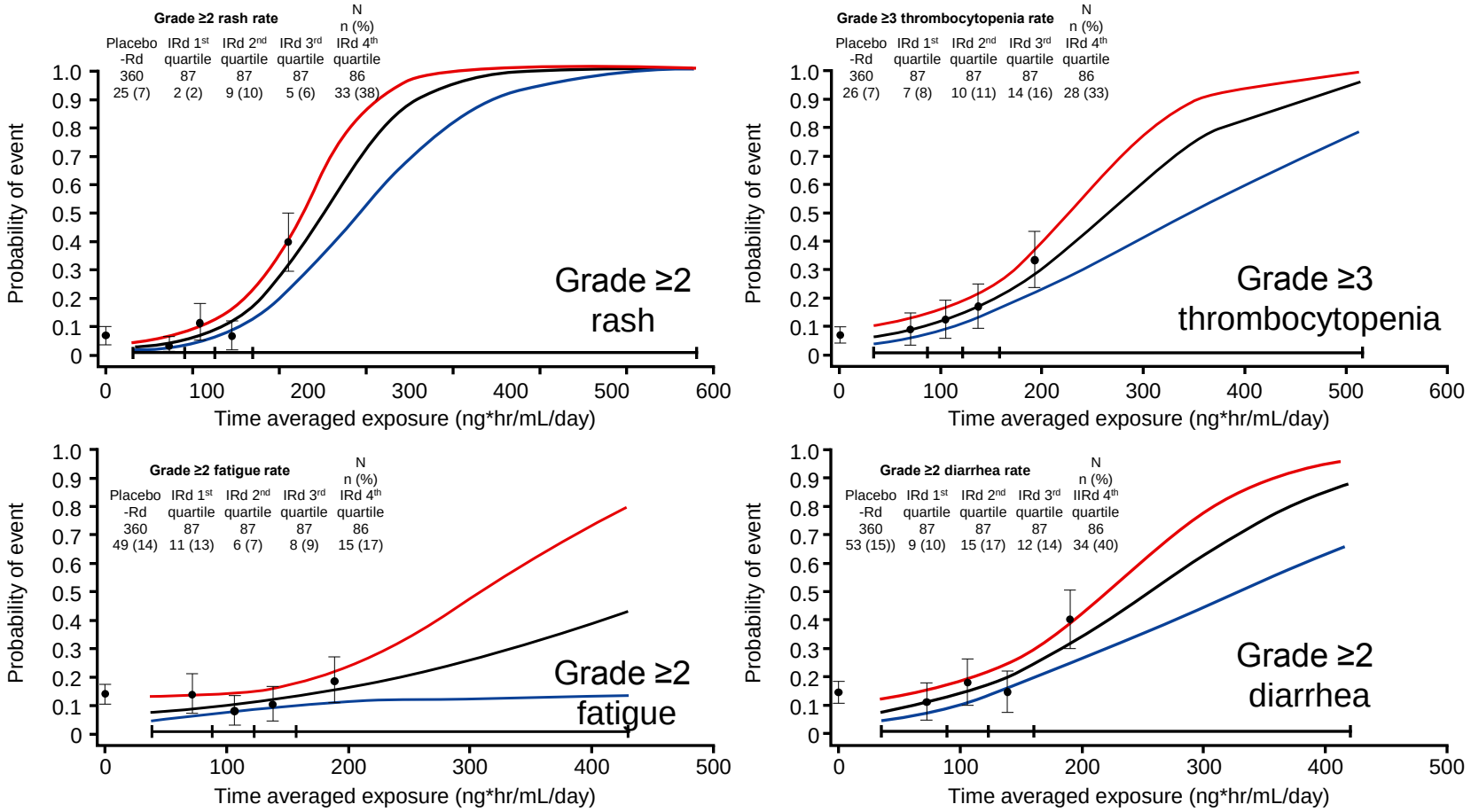


PFS, progression-free survival

Gupta N, et al. Manuscript in preparation.

Exposure–safety analyses from TOURMALINE-MM1: relationship between ixazomib exposure and TEAEs

- Statistically significant relationships were identified between ixazomib exposure and the probability of TEAEs of clinical interest, supporting dose reduction guidelines



TEAE, treatment-emergent adverse event

Gupta N, et al. Manuscript in preparation.

Exposure–response analyses to support the dose-titration approach in phase 3 ixazomib maintenance studies

- At a 3 mg dose of ixazomib, the analysis predicted that the probabilities of TEAEs would be reduced compared to the 4 mg dose

- Accordingly, to appropriately balance benefit vs risk, a starting dose of 3 mg with escalation to 4 mg, if tolerated, is being used in the phase 3 maintenance trials:

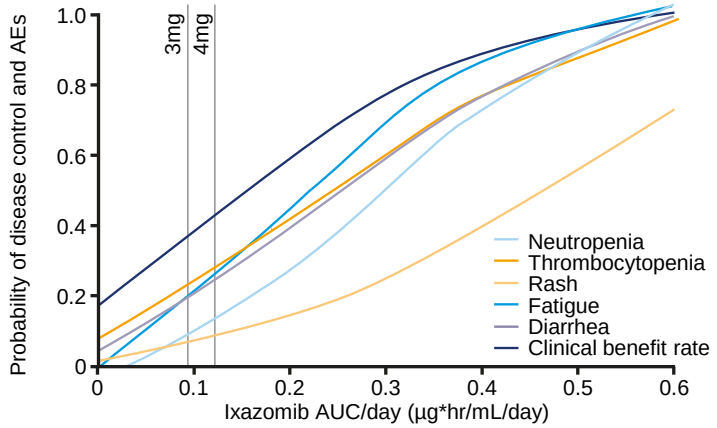
TOURMALINE-MM3 (NCT02181413):

Phase 3 study of ixazomib vs placebo as maintenance therapy post-ASCT in multiple myeloma patients with post-transplant response (≥PR)

TOURMALINE-MM4 (NCT02312258):

Phase 3 study of ixazomib vs placebo as maintenance therapy in multiple myeloma patients not eligible for ASCT achieving ≥PR after 6–12 months of initial therapy

Relationship between exposure and TEAEs or clinical benefit rate, and ixazomib exposure associated with 3 mg and 4 mg doses



Outcome measure	Estimated probability of event, %	
	Ixazomib 4 mg weekly	Ixazomib 3 mg weekly
Neutropenia, grade ≥ 3	16	10
Thrombocytopenia, grade ≥ 3	28	23
Rash, grade ≥ 2	10	8
Fatigue, grade ≥ 2	26	19
Diarrhea, grade ≥ 2	24	19
Clinical benefit rate (≥SD)	44	37

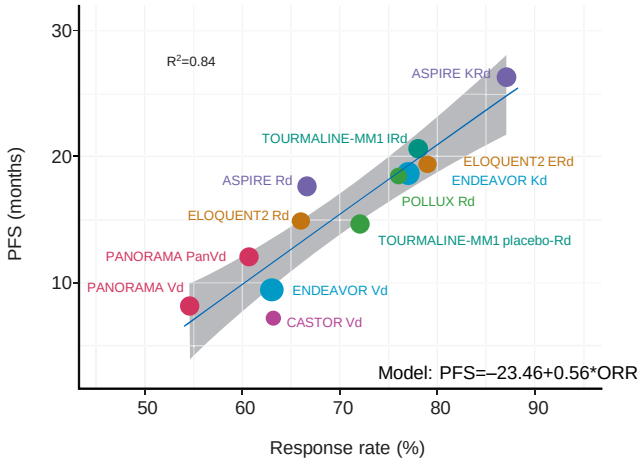
SD stable disease

ASCT, autologous stem cell transplantation; NDMM, newly diagnosed multiple myeloma; TEAE, treatment-emergent adverse event

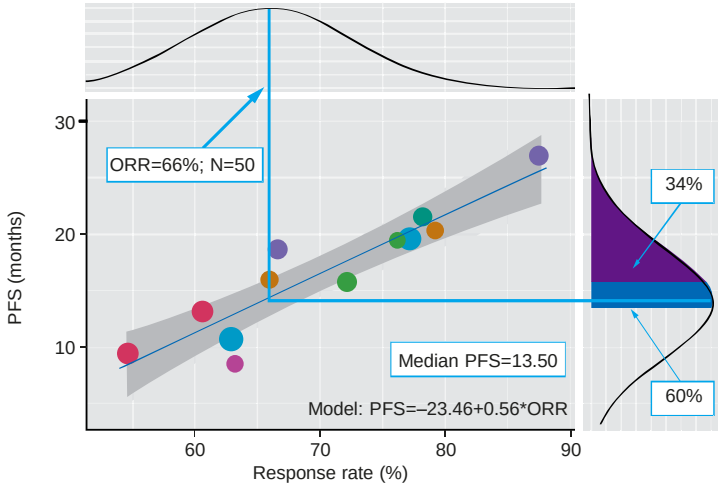
Gupta N, et al. Invest New Drugs 2016;34(3):338–46.

Model-based meta-analysis (MBMA) for Go/No-Go decision making

- MBMA predicted a PFS of 20 months based on an ORR of 78% for ixazomib-Rd,[1] consistent with the reported results of TOURMALINE-MM1[2]



Relationship between ORR and median PFS using data from 7 phase 3 studies. The blue line represents the linear regression line and the gray band represents the 95% CI.



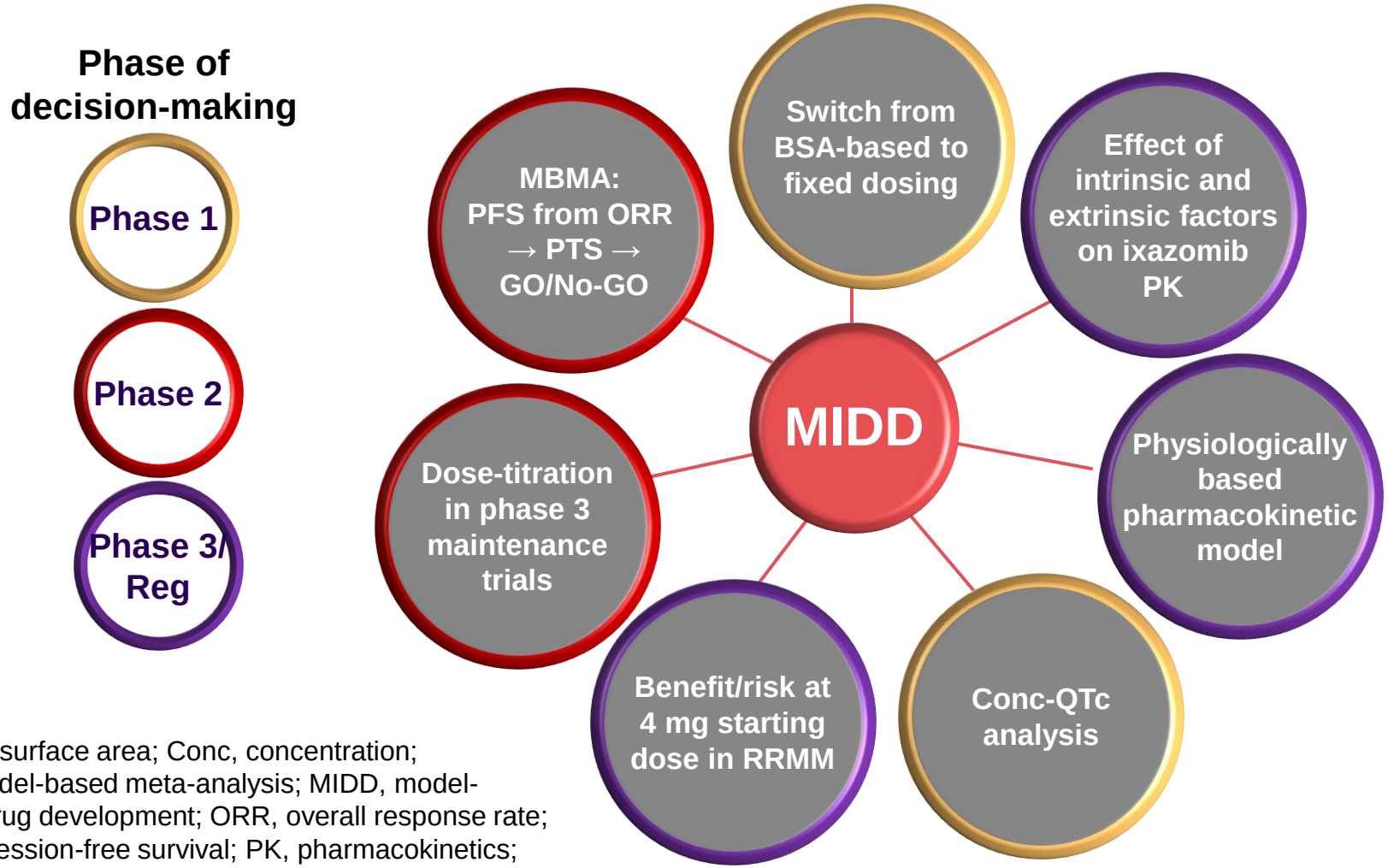
An illustrative example of predicting PFS using ORR. The probability of achieving the TPP (PFS 15 months) is 34% (purple area) and the probability of achieving the minimum detectable PFS is 60% (blue area).

- This can help estimate the PTS to achieve gold-standard efficacy targets in the target product profile, informing 'GO/No-GO' decisions at the molecule, as well as cross-molecule/portfolio level when comparing assets being developed for a common indication

CI, confidence interval; ICd, ixazomib, cyclophosphamide, dexamethasone; ORR, overall response rate; PFS, progression-free survival; PTS, probability of technical success; TPP, target product profile

1. Gupta N, et al. J Pharmacokinet Pharmacodyn 2016;43(suppl):S110.
2. Moreau P, et al. N Engl J Med 2016;374(17):1621–34.

MIDD across the development continuum for ixazomib



BSA, body surface area; Conc, concentration; MBMA, model-based meta-analysis; MIDD, model-informed drug development; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetics; PTS, probability of technical success; RRMM, relapsed/refractory multiple myeloma

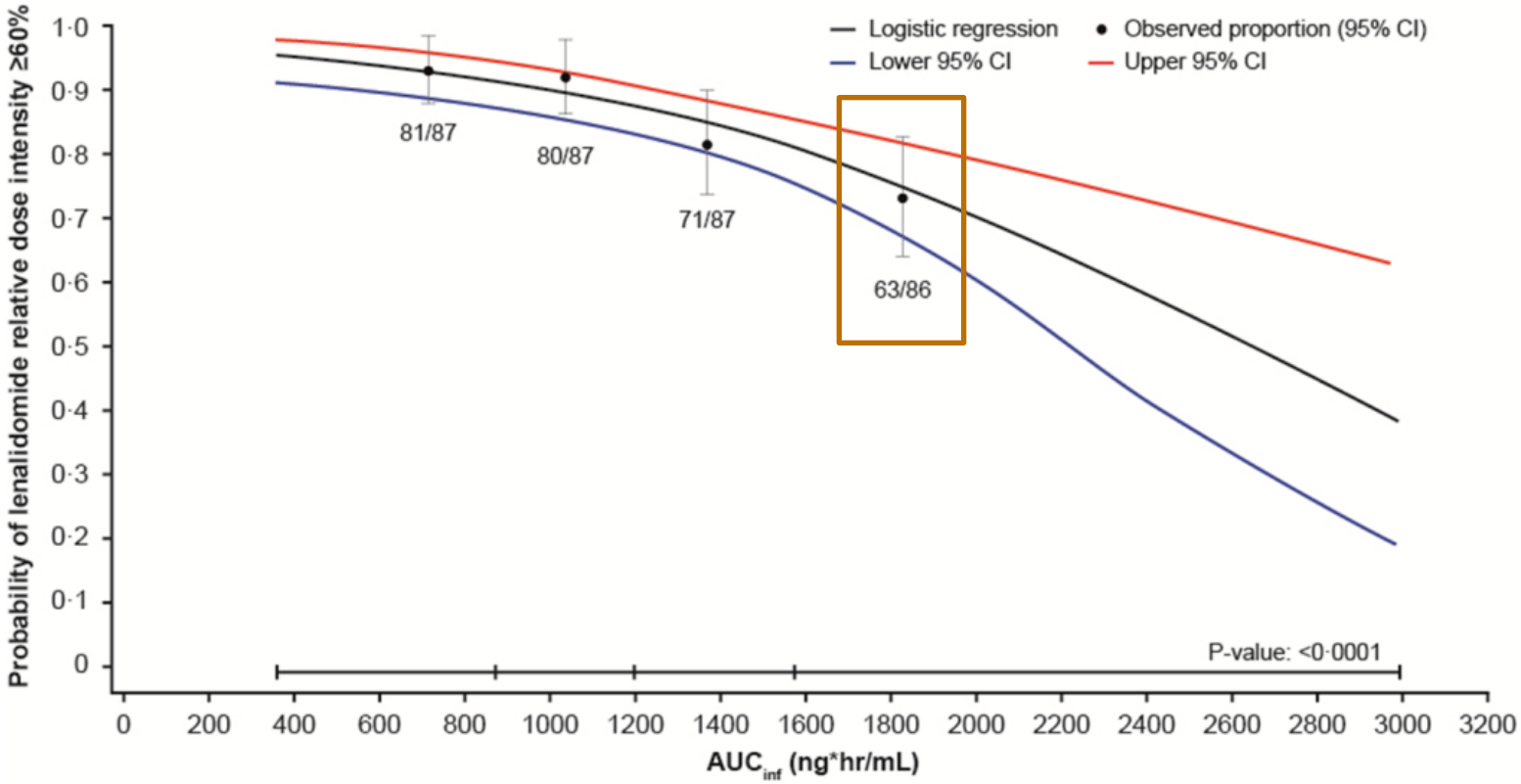
Acknowledgments

- Patients and their families
- Investigators
- Ixazomib team members

- Editing support during the development of this presentation was provided by Steve Hill of FireKite, an Ashfield company, part of UDG Healthcare plc, which was funded by Millennium Pharmaceuticals, Inc., and complied with Good Publication Practice 3 ethical guidelines (Battisti WP, et al. Ann.Intern.Med. 2015;163:461-464)

Exposure–response analyses from TOURMALINE-MM1: relationship between ixazomib exposure and lenalidomide RDI

- Consistent with the findings of a phase 1/2 study of ixazomib-Rd, higher ixazomib exposures were associated with a lower probability of lenalidomide RDI ≥60% in TOURMALINE-MM1



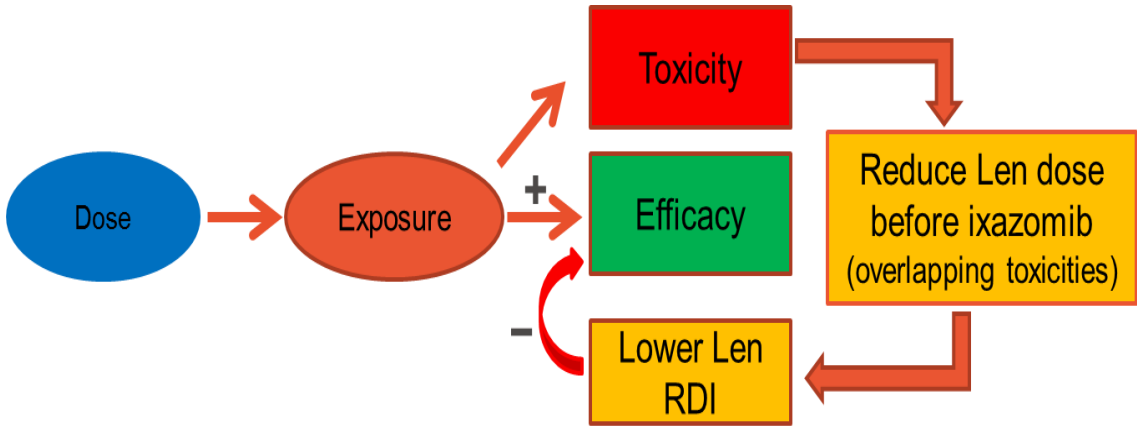
CI, confidence interval; RDI, relative dose intensity

Gupta N, et al. Manuscript in preparation.

Exposure–response analyses from TOURMALINE-MM1: relationship between ixazomib exposure and lenalidomide RDI

- Exposure–response analysis results suggest that ixazomib doses higher than 4 mg, in combination with Rd, may lead to higher rates of TEAEs, and may negatively impact lenalidomide RDI
  - This may counteract the potential positive effects of a higher ixazomib dose on the overall efficacy of ixazomib-Rd
- This analysis supported the dose-reduction guidelines in the Japan phase 2 bridging study to maximize the benefit–risk profile for this population

Schematic illustrating the relationship between ixazomib dose, systemic exposure, and lenalidomide RDI



RDI, relative dose intensity; TEAE, treatment-emergent adverse event

Gupta N, et al. Manuscript in preparation.