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Progression-free survival according to the presence of adverse cytogenetic abnormalities in patients with multiple myeloma receiving ixazomib-based vs placebo-based therapy: A pooled analysis of the TOURMALINE-MM1, MM2, MM3, and MM4 phase 3 studies

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Background

A number of cytogenetic abnormalities (deletion, translocation or amplification of chromosomal loci) are associated with poorer prognosis in multiple myeloma (MM), including del(17p), t(4;14), t(14;16), and amp1q21,^{1,2} and are included in the 2016 International Myeloma Working Group definition of high-risk cytogenetics¹

Proteasome inhibitors (PIs), including oral ixazomib, are a cornerstone of MM therapy,³ and there is a general consensus that treatment with PIs benefits patients carrying these cytogenetic abnormalities.¹ This has been demonstrated for ixazomib- vs placebo-based therapy in a number of phase 3 studies:

- In **TOURMALINE-MM1**, relapsed, refractory, or relapsed and refractory multiple myeloma (RRMM) patients with high-risk cytogenetic abnormalities treated with the oral PI ixazomib plus lenalidomide-dexamethasone (Rd) had similar progression-free survival (PFS) to those with standard-risk cytogenetics,⁴ suggesting that addition of ixazomib to Rd may have abrogated the increased risk conferred by cytogenetic abnormalities⁴

- Additionally, patients with high-risk and expanded high-risk cytogenetics treated with ixazomib-lenalidomide-dexamethasone (IRd) demonstrated a treatment benefit (overall survival [OS] hazard ratio [HR] <1) in the final OS analysis of **TOURMALINE-MM1**⁵

- Similarly, **TOURMALINE-MM2** showed that newly diagnosed multiple myeloma (NDMM) patients with expanded high-risk cytogenetics treated with IRd had improved PFS compared with placebo-Rd⁶

- In the maintenance setting, **TOURMALINE-MM3** patients with high-risk cytogenetics who received ixazomib maintenance following autologous stem cell transplant (ASCT) had improved PFS vs placebo⁷ and in **TOURMALINE-MM4** transplant-ineligible patients with expanded high-risk cytogenetics who received ixazomib given as post-induction maintenance demonstrated PFS benefit vs placebo⁸

Aim of the current analysis

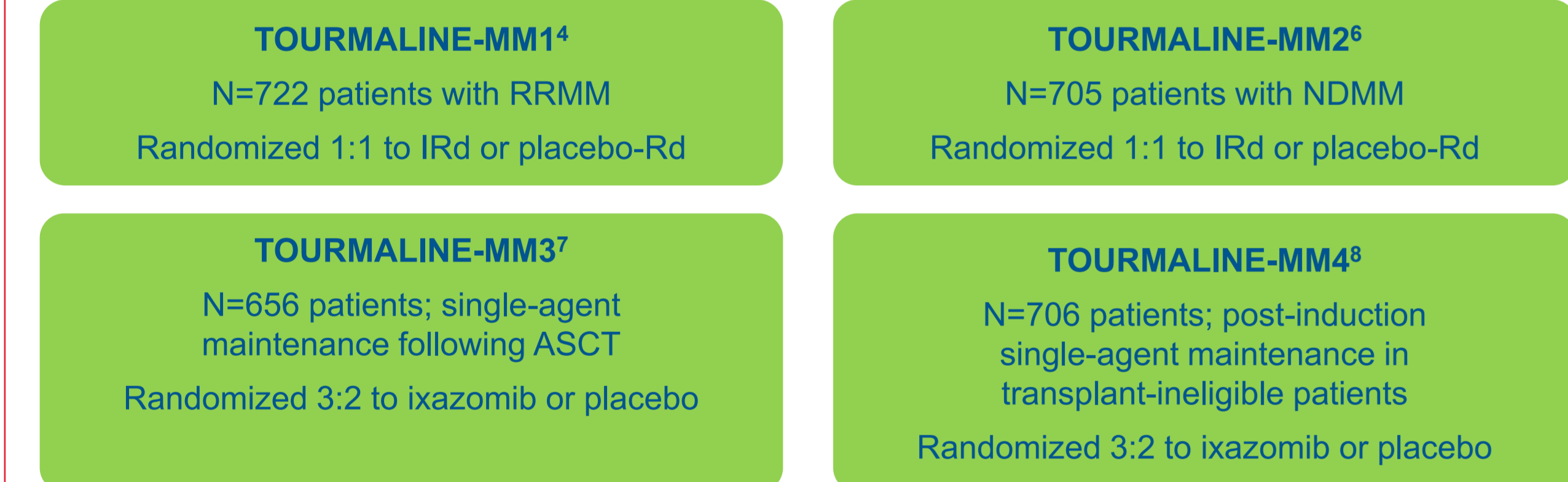
To assess PFS benefit in patients receiving ixazomib- vs placebo-based therapy according to specific adverse cytogenetic abnormalities via a pooled analysis of four TOURMALINE studies (MM1, MM2, MM3, and MM4)

Methods

Studies included in the pooled analysis

- Full methods for TOURMALINE-MM1, MM2, MM3 and MM4 have been published previously^{4,6-8}
- All four studies were randomized, placebo-controlled phase 3 trials (Figure 2)

Figure 2: The four phase 3 TOURMALINE studies included in the pooled analysis



Cytogenetic subgroups

- Patients with MM characterized by specific cytogenetic abnormalities were categorized into subgroups, defined by the presence of one or more of the following:
 - High-risk subgroup:** del(17p), t(4;14), and t(14;16)
 - Expanded high-risk subgroup:** high-risk abnormalities plus amp1q21

- Complementary standard-risk cytogenetic subgroups: defined based on the absence of these (expanded) high-risk abnormalities in samples available for testing (excluding patients whose samples were missing or unevaluable)

Cytogenetic evaluations

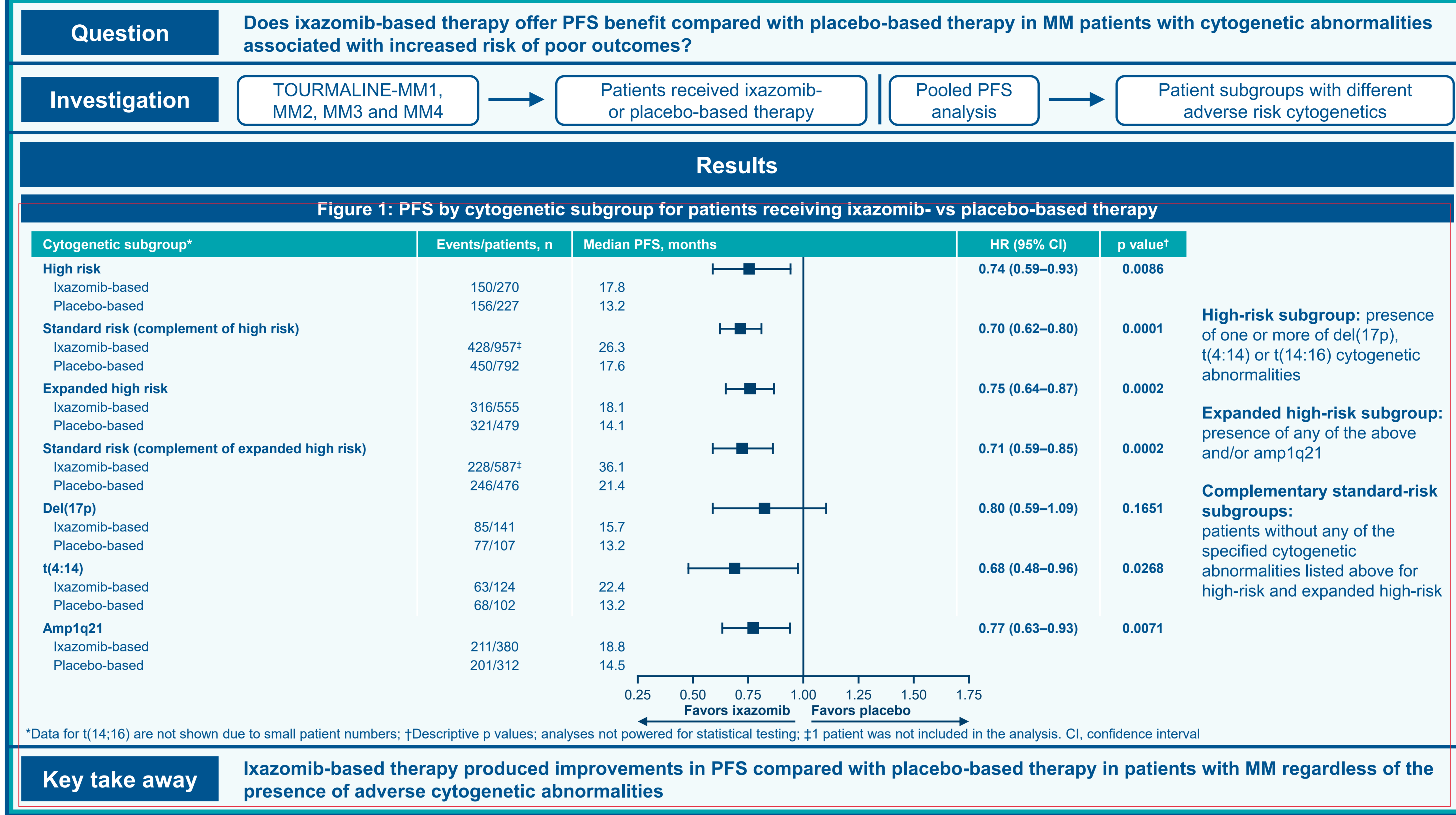
- In **TOURMALINE-MM1/MM2**, cytogenetic abnormalities were assessed by a central laboratory at screening using fluorescence in situ hybridization (FISH) in enriched CD138+ plasma cells from bone marrow aspirates
 - The presence of del(17p), t(4;14), and t(14;16) were defined based on cut-offs of 5%, 3%, and 3% positive cells, respectively, based on the false-positive rates (technical cut-offs) of the FISH probes used; cut-off values of 3% (MM1) and 20% (MM2) were used for amp1q21

- In **TOURMALINE-MM3/MM4**, cytogenetic assessment was performed locally using FISH or conventional karyotyping with locally defined thresholds for positivity; result reports were interpreted centrally by a hematopathologist

Statistical analysis

- Pooled data on progression events and deaths were used to generate Kaplan-Meier estimates for PFS with ixazomib vs placebo in the defined cytogenetic patient subgroups and for patients with ≥1 of the 4 individual cytogenetic abnormalities (and/or any of the other 3 cytogenetic abnormalities)

- Statistical comparisons of PFS in ixazomib vs placebo pooled treatment groups were based on unstratified HRs and descriptive log-rank p values



- A sensitivity analysis stratified by study was also conducted by aggregating stratified HR from individual studies (weighted method to calculate overall HR)
 - The pooled adjusted HR was derived from adjusting the determination of the overall HR applying the studies as covariate
 - The pooled weighted HR utilizes the derived weights for each study, aggregated over the studies to obtain the pooled HR

Results

Patients

- A total of 2247 patients in the pooled analysis population were evaluable for the presence/absence of del(17p), t(4;14), and t(14;16) cytogenetic abnormalities, of whom 497 (22%) were classified as high risk and 1750 (78%) were standard risk (Table 1)

- Expanded cytogenetic risk (high-risk cytogenetic abnormalities plus amp1q21) was evaluable in a total of 2098 patients, 49% (ixazomib) and 50% (placebo) of whom had at least one cytogenetic abnormality and were classified as expanded high risk (Table 1)

Table 1: Cytogenetic risk subgroups by study and treatment group

Patients, n (%)	Evaluable for del(17p), t(4;14) and t(14;16) cytogenetic abnormalities (N=2247)		Evaluable for del(17p), t(4;14), t(14;16), and amp1q21 cytogenetic abnormalities (N=2098)	
	Ixazomib-based (n=1228)	Placebo-based (n=1019)	Ixazomib-based (n=1143)	Placebo-based (n=955)
MM1	High risk 75, Standard risk* 200	High risk 62, Standard risk* 216	Expanded high risk 155, Standard risk* 122	Expanded high risk 154, Standard risk* 126
MM2	High risk 60, Standard risk* 231	High risk 63, Standard risk* 234	Expanded high risk 134, Standard risk* 164	Expanded high risk 146, Standard risk* 153
MM3	High risk 61, Standard risk* 252	High risk 54, Standard risk* 152	Expanded high risk 116, Standard risk* 154	Expanded high risk 88, Standard risk* 89
MM4	High risk 74, Standard risk* 275	High risk 48, Standard risk* 190	Expanded high risk 150, Standard risk* 148	Expanded high risk 91, Standard risk* 108
Total	High risk 270 (22%), Standard risk* 958 (78%)	High risk 227 (22%), Standard risk* 792 (78%)	Expanded high risk 555 (49%), Standard risk* 588 (51%)	Expanded high risk 479 (50%), Standard risk* 476 (50%)

*Standard risk complement of (expanded) high risk (i.e. patients without any of the specified abnormalities).

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Disclosures

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Figure 5: PFS for patients with t(4;14) cytogenetic abnormality receiving ixazomib- vs placebo-based therapy

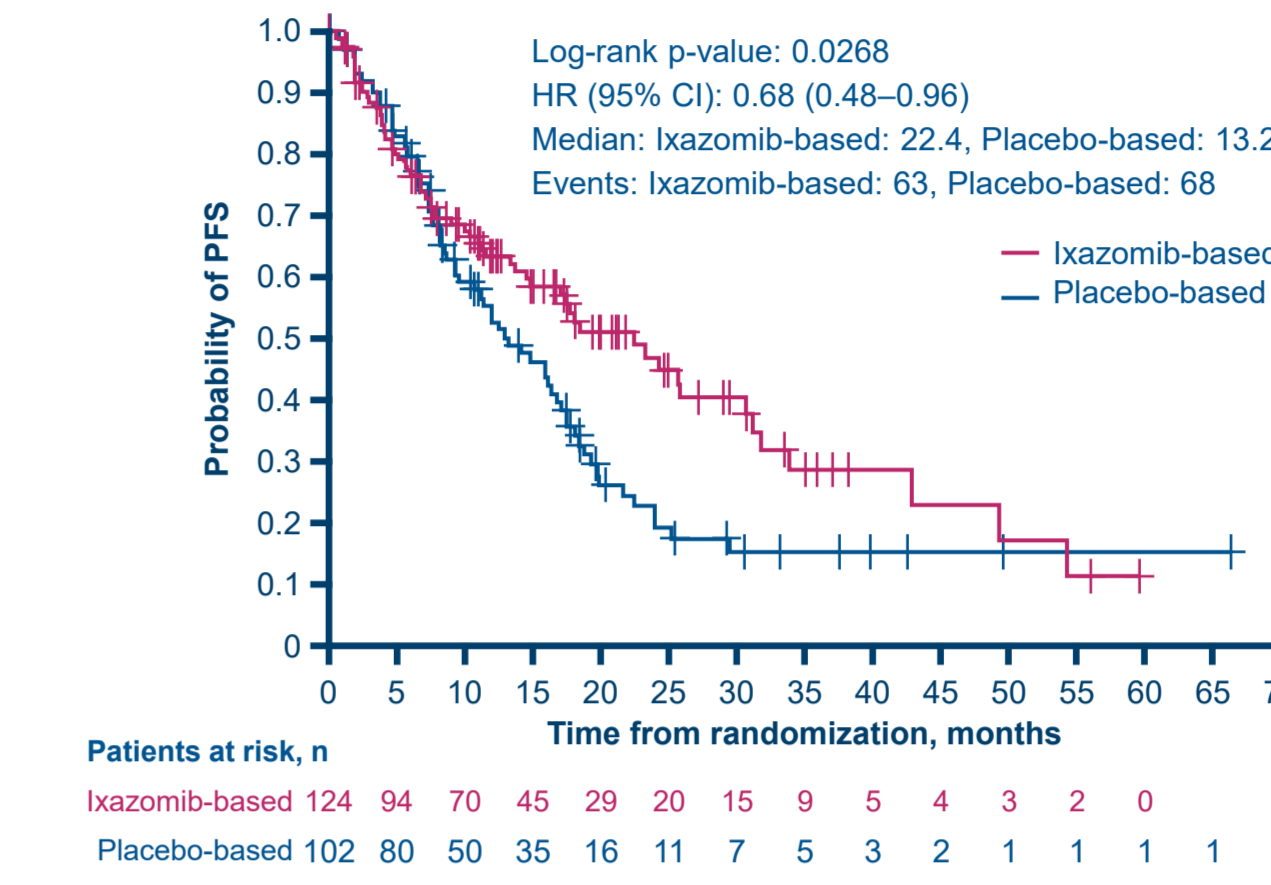
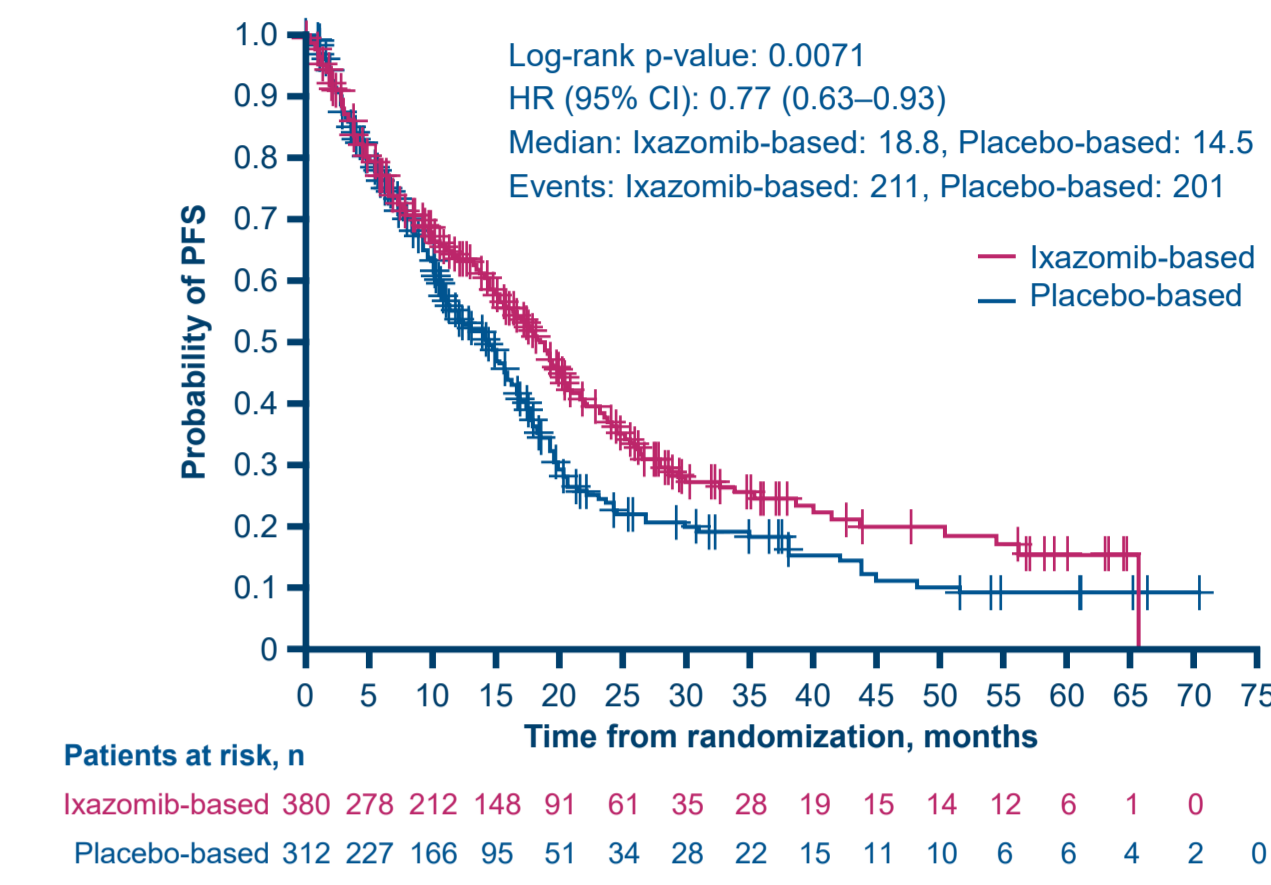


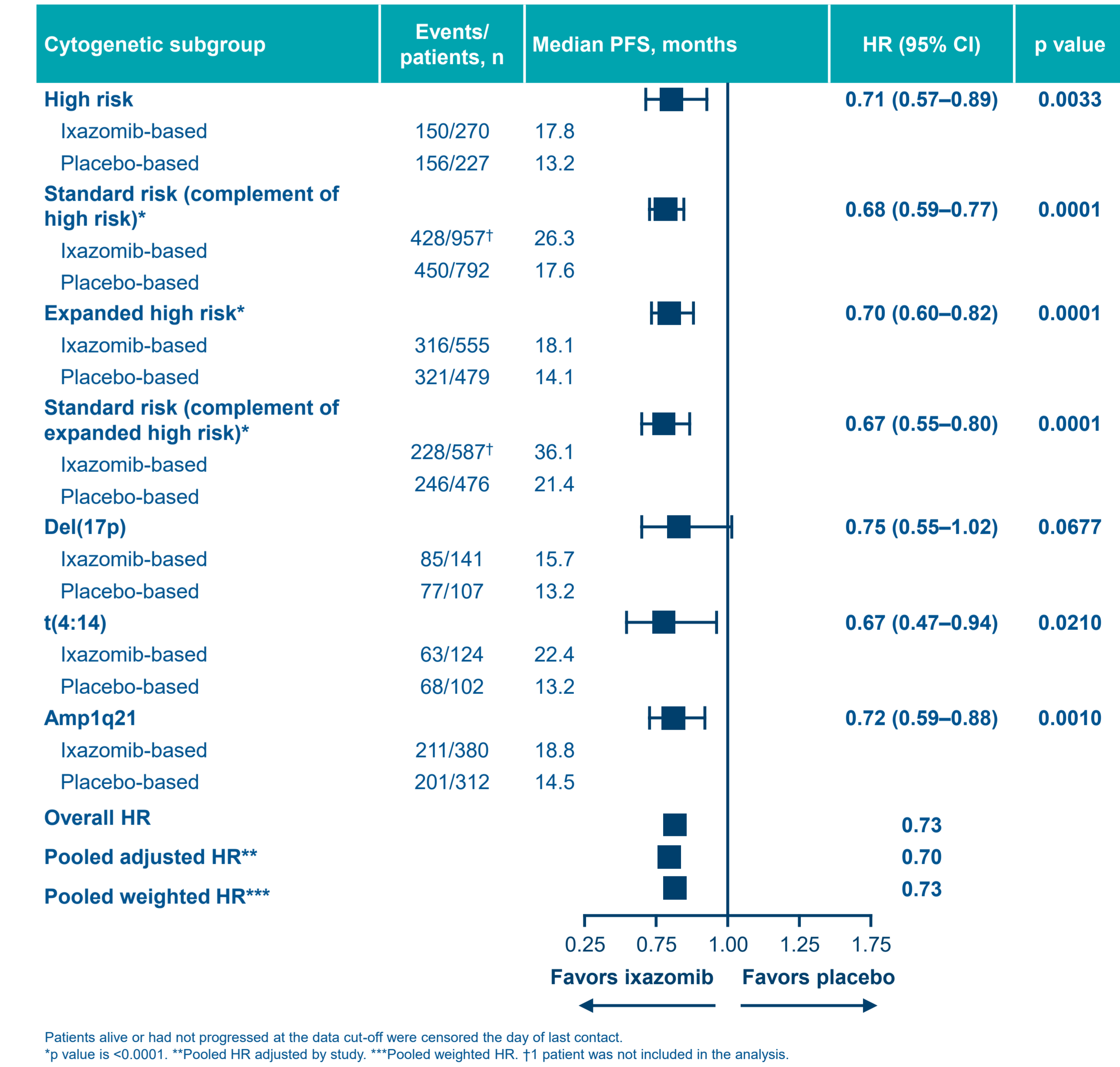
Figure 6: PFS for patients with amp1q21 cytogenetic abnormality receiving ixazomib- vs placebo-based therapy



PFS sensitivity analysis

- The sensitivity analysis of PFS stratified by study shown in Figure 7 supports the PFS benefit with ixazomib- vs placebo-based therapy demonstrated in the main analysis

Figure 7: PFS with ixazomib- vs placebo-based therapy regardless of cytogenetic risk stratified by study



Conclusions

- This pooled analysis demonstrated a PFS benefit with ixazomib- vs placebo-based therapy regardless of the presence of specific adverse cytogenetic abnormalities
 - The magnitude of benefit in patients with (expanded) high-risk cytogenetic abnormalities was similar to the respective complementary standard-risk subgroups
- The greatest magnitudes of benefit (lowest HRs) with ixazomib- vs placebo-based therapy were in patients with t(4;14) (HR 0.68) and amp1q21 (HR 0.77)
- Ixazomib combined with Rd or as single-agent maintenance therapy did not abrogate the negative impact of high-risk cytogenetic abnormalities
 - The differences in eligibility criteria and patient populations among the studies may have contributed to difficulties in interpreting the data
- Ixazomib-based therapy may be a viable treatment option for patients with MM who have expanded high-risk cytogenetic abnormalities

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