

Efficacy and safety of oral ixazomib, intravenous (IV) daratumumab, and IV/oral dexamethasone (IDd) in relapsed/refractory multiple myeloma (RRMM) patients with 1–3 prior therapies: Results of the second interim analysis (IA2) of a phase 2 study

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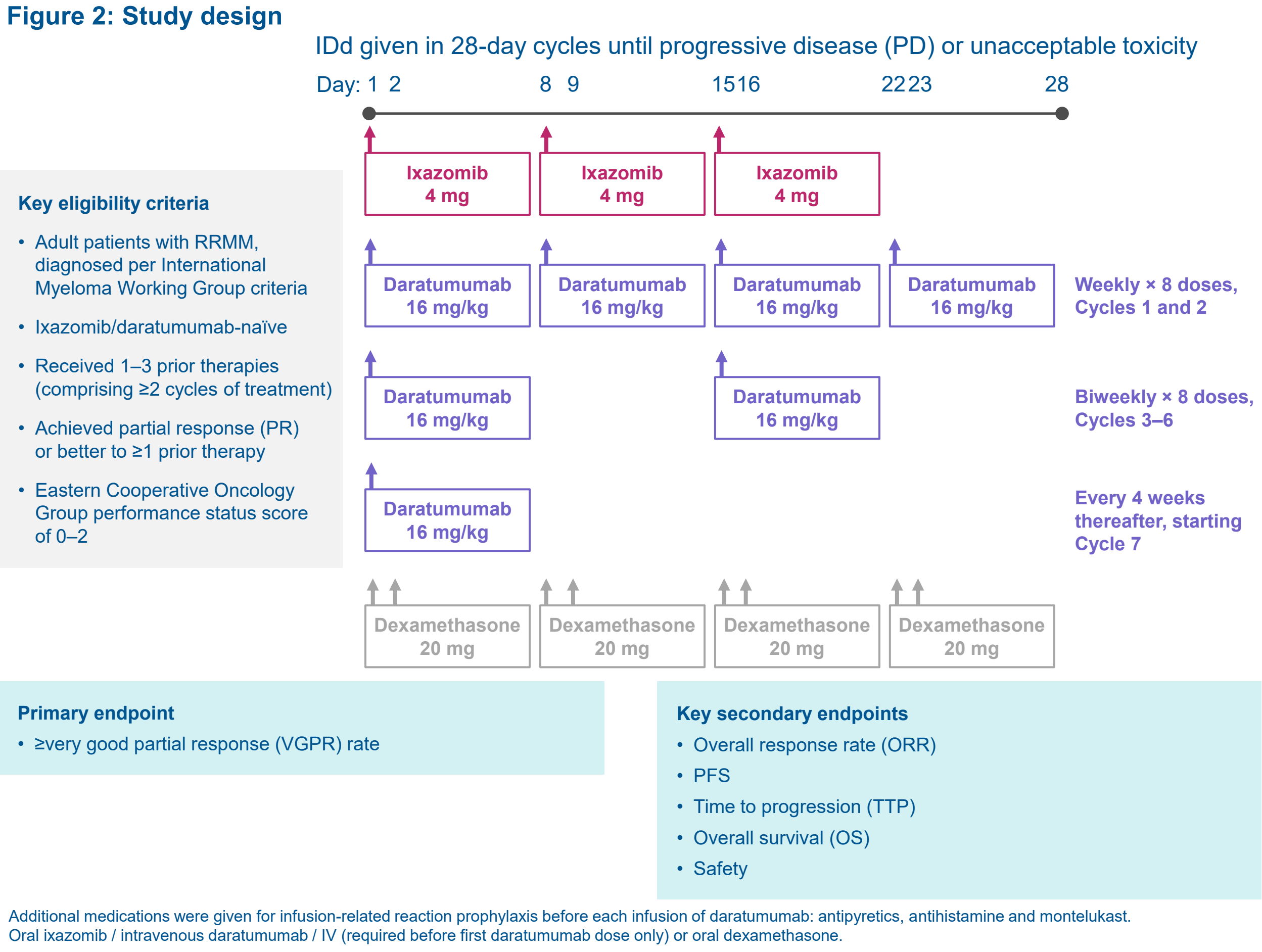
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Treatment of RRMM

- Although the introduction of new, more effective therapies has improved the prognosis for patients with multiple myeloma (MM) in recent years, most patients will ultimately relapse¹
 - Treatment of RRMM is complex and continues to present a therapeutic challenge
 - Proteasome inhibitors (PI), immunomodulatory drugs (IMiD) and monoclonal antibodies remain key components of therapy
- The oral PI ixazomib is approved in combination with lenalidomide-dexamethasone (Rd) for patients with ≥1 prior therapy,^{2,3} and daratumumab is approved in various regimens, including with bortezomib (Vd)^{4,5}
- Prolonged PI-based therapy is associated with improved outcomes compared with shorter, fixed-duration therapy^{6,7}
 - In CASTOR (daratumumab-bortezomib-dexamethasone [DVd] vs Vd), bortezomib (V) was limited to 8 cycles⁸
- The IDd regimen with oral ixazomib may enable longer-term PI therapy than DVd
- In this prospective, open-label, multicenter, phase 2 study (NCT03439293), we use a treat-to-progression approach to evaluate IDd in RRMM

Methods

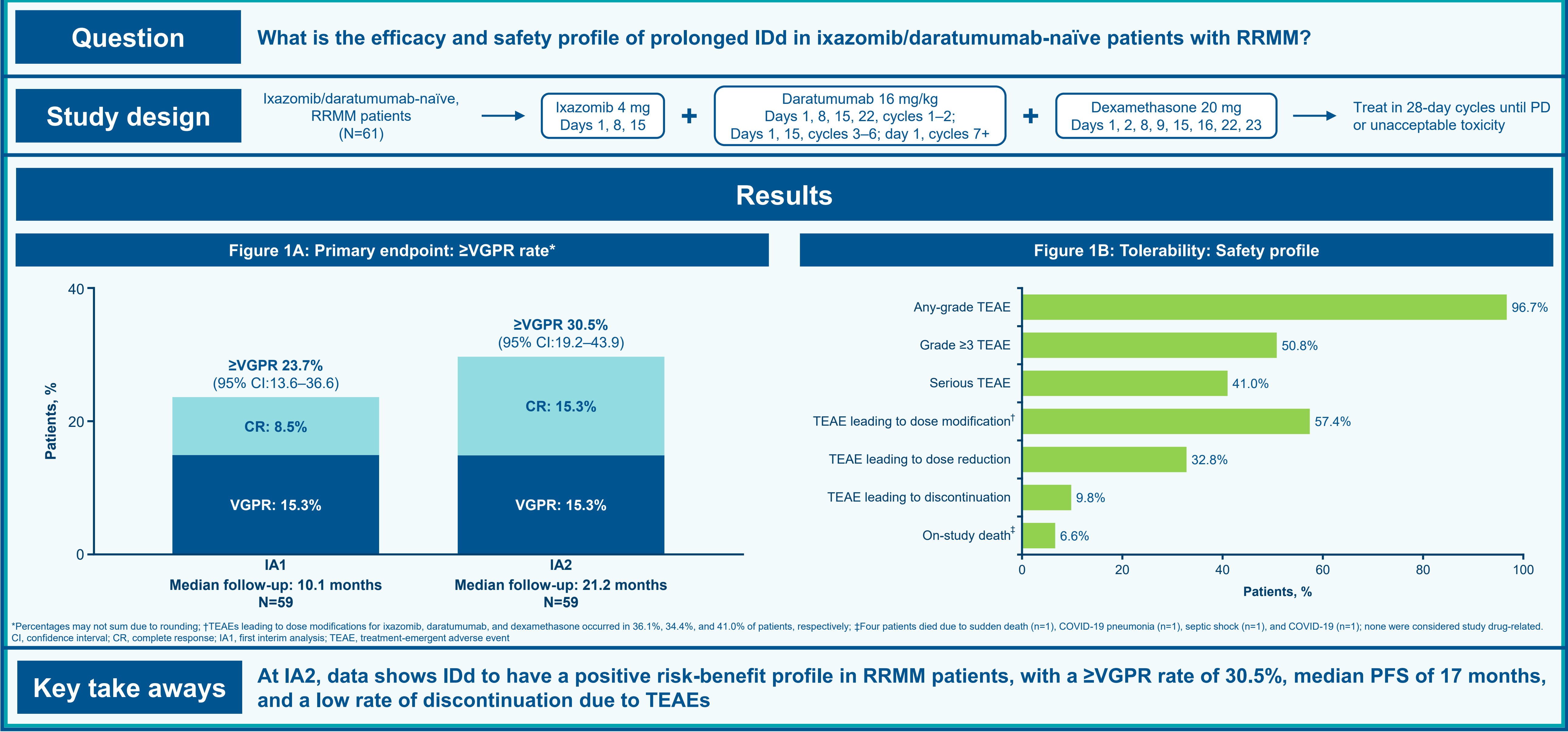
- The study design and key eligibility criteria for this phase 2 trial are presented in **Figure 2**
- Here, we report data from IA2, conducted after ~50% of progression-free survival (PFS) events had occurred (data cut-off: Jan 1, 2021)



Results

- Patient demographics and disease characteristics are shown in **Table 1**

Table 1: Patient demographics and disease characteristics	
	Enrolled patients (N=61)
Median age, years (range)	69 (51–84)
Aged ≥75 years, n (%)	12 (19.7)
Male, n (%)	32 (52.5)
International Staging System disease stage, n (%)	
I	29 (47.5)
II	19 (31.1)
III	12 (19.7)
Missing	1 (1.6)
Cytogenetics, n (%)	
High-risk [del(17p), t(4;14), t(14;16)]	16 (26.2)
Corresponding standard risk	40 (65.6)
Unclassifiable	5 (8.2)
Expanded high-risk [del(17p), t(4;14), t(14;16), amp1q21]	26 (42.6)
Corresponding standard risk	22 (36.1)
Unclassifiable	13 (21.3)
Prior lines of therapy, n (%)	
1	36 (59.0)
2	16 (26.2)
3	9 (14.8)
Lenalidomide-refractory, n (%)	21 (34.4)



- Treatment exposure**
- Relative dose intensity (RDI) for ixazomib, daratumumab, and dexamethasone at IA1 and IA2 are shown in **Table 2**
 - At data cut-off for IA2, patients had received a median of 16 cycles of IDd (**Table 3**)
 - A total of 37.7% of patients were ongoing at the time of analysis
- Treatment response**
- Among 59 response-evaluable patients, the confirmed ≥VGPR rate was 30.5% at IA2 compared with 23.7% at IA1 (**Figure 1A, Summary Panel**)
 - The ORR at IA2 was 69.5%; responses by IA are shown in **Table 4**
 - The rates of ORR and CR increased from IA1 to IA2

Table 2: Relative dose intensity in the safety population at IA1 and IA2

	Enrolled patients (N=61)	
	IA1	IA2
Median RDI	%	%
Ixazomib	100.0	100.0
Daratumumab	96.1	96.8
Dexamethasone	93.7	90.8
<100% RDI	n (%)	n (%)
Ixazomib	26 (42.6)	30 (49.2)
Daratumumab	43 (70.5)	45 (73.8)
Dexamethasone	36 (59.0)	40 (65.6)
≥95% RDI	n (%)	n (%)
Ixazomib	20 (32.8)	21 (34.4)
Daratumumab	27 (44.3)	20 (32.8)
Dexamethasone	32 (52.5)	36 (59.0)

Table 3: Duration of therapy in the safety population at IA1 and IA2

	Enrolled patients (N=61)	
	IA1	IA2
Median number of treatment cycles received, n (range)		
IDd	8 (1–20)	16 (1–32)
Ixazomib	8 (1–20)	16 (1–32)
Daratumumab	9 (1–20)	16 (1–32)
Dexamethasone	9 (1–20)	16 (1–32)

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Disclosures

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PFS, TTP, and OS

- After a median follow-up of 21.2 months at IA2, median PFS in the overall study population was 17.0 months (95% CI: 10.2–not estimable [NE]) (**Figure 3**)
 - In the high-risk [del(17p), t(4;14), t(14;16)] cytogenetics subgroup, median PFS was 12.0 months (95% CI: 2.9–22.1) (**Figure 3**)
 - In the expanded high-risk (high-risk and/or amp1q21) cytogenetics subgroup, median PFS was 10.1 months (95% CI: 3.7–22.1) (**Figure 3**)
- Median TTP in the overall study population was 21.1 months (95% CI: 10.3–NE) (**Figure 4A**)
- With 11 patients having died, the 1-year OS rate was 91.4% (95% CI: 80.6%–96.3%) (**Figure 4B**)
- Median time to ≥VGPR was NE (range, 1.0–28.9 months)
- Median time to overall response was 1.9 months (range, 0.9–20.9 months)

Figure 3: Kaplan-Meier analyses of PFS in the overall study population; the high-risk cytogenetics subgroup; and the expanded high-risk cytogenetics subgroup

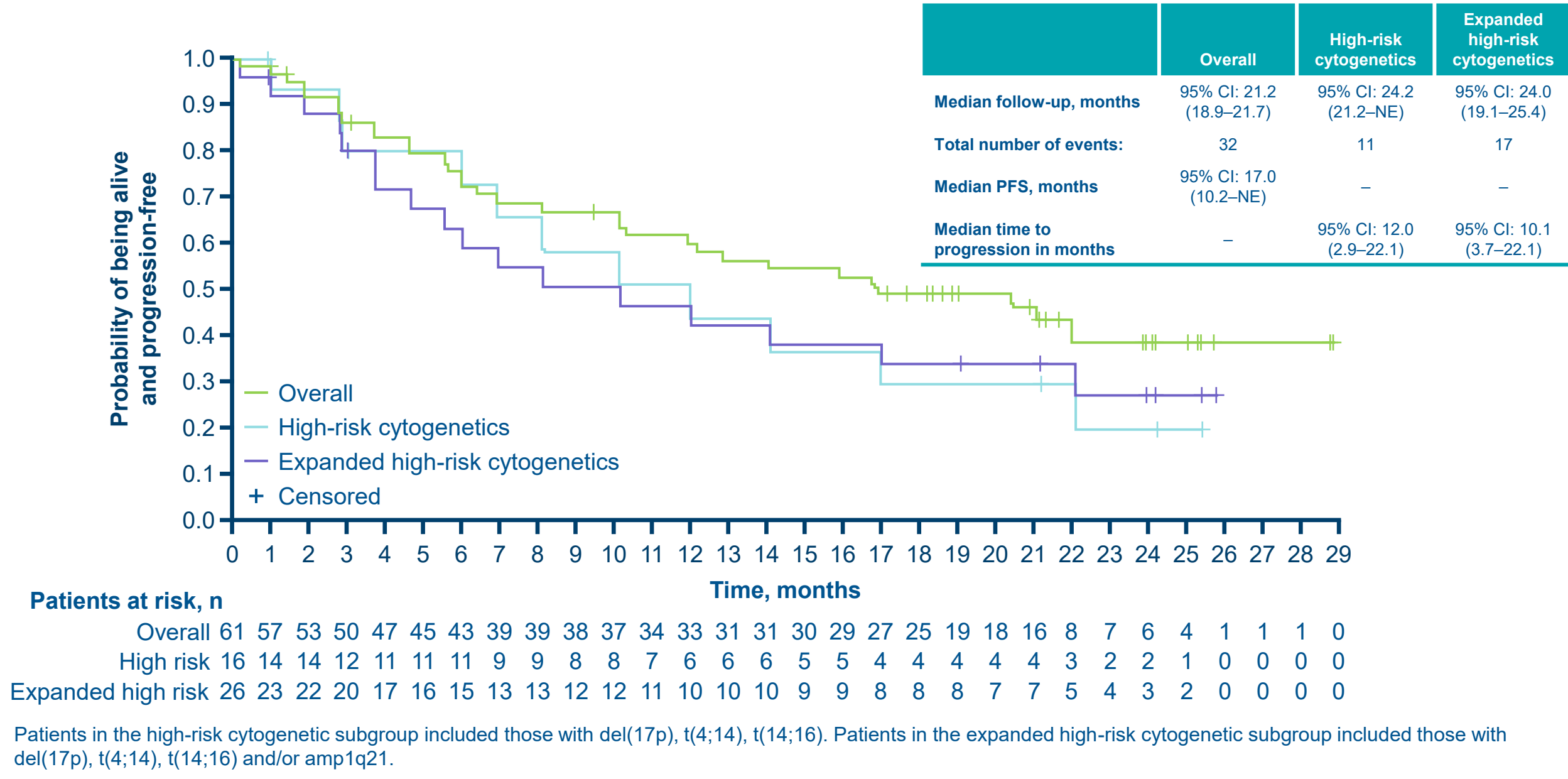
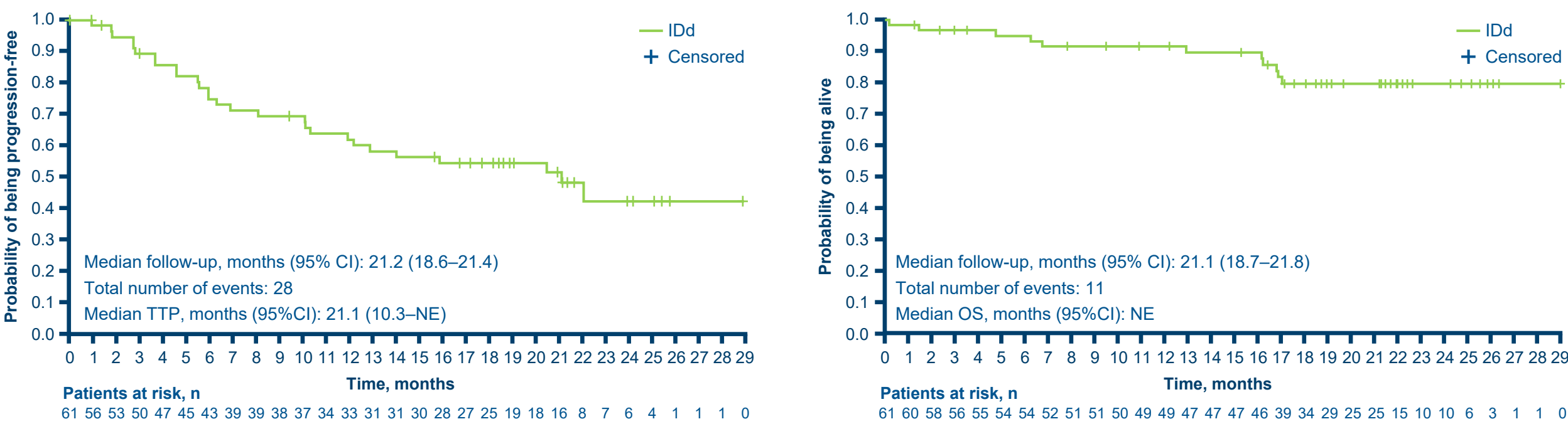


Figure 4: Kaplan-Meier analyses of A) TTP and B) OS, in the overall study population



MRD

- Minimal residual disease (MRD) was evaluated at time of CR in 8 patients: 2 of the 8 patients were MRD-negative (detection level: 10⁻⁵)
- Two patients were MRD-negative at 6 cycles post-CR, and 1 patient was MRD-negative at 12 cycles post-CR (**Figure 3**)

*MRD status was confirmed by next-generation sequencing.

†At CR there were 2 additional patients for whom the MRD status was indeterminate at the 10⁻⁵ level of sensitivity.

Safety

- An overview of the safety profile of the IDd regimen is shown in **Figure 1B, Summary Panel**
- The most common TEAEs (occurring in >20% of patients at any grade or >5% at grade ≥3) were diarrhea (39.3% [grade ≥3, 1.6%]), anemia (27.9% [8.2%]), thrombocytopenia (26.2% [11.5%]), fatigue (21.3% [3.3%]), and pneumonia (13.1% [11.5%])
- Infections and infestations TEAEs were seen in 57.4% of patients (grade ≥3, 24.6%)
 - These events were serious in 26.2% of patients and included pneumonia (9.8%) and COVID-19 or COVID-19 pneumonia (4.9%)
- The rate of any-grade peripheral neuropathy (PN; high-level term) was 18.0% (grade ≥3, 1.6%)
 - PN occurred in 28.6% and 12.5% of patients with and without a history of PN, respectively.
- Four patients died on study due to sudden death, COVID-19 pneumonia, septic shock, and COVID-19 (n=1 each); none were considered study drug-related (**Figure 1B, Summary Panel**)

Conclusions

- These IA2 results in RRMM patients, including just over a quarter with high-risk cytogenetics, show a positive risk-benefit profile for IDd
 - ≥VGPR rate: 30.5% (increased from IA1)
 - ORR: 69.5% (increased from IA1)
 - Median PFS: 17.0 months (comparable to that seen with DVd in CASTOR [16.7 months]⁹)
 - Overall and individual rates of grade 3/4 adverse events generally numerically lower than with DVd in CASTOR⁹
 - Discontinuation rate due to TEAEs was low with no new safety signals identified
- IDd was also active in lenalidomide-refractory patients and those with (expanded) high-risk cytogenetics
- More than a third of patients remain on therapy
 - The final analysis is expected in 2022



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