Positron Emission Tomography With Computed Tomography (PET/CT) and Minimal Residual Disease (MRD) for Efficacy Assessment in Transplant-Ineligible Newly Diagnosed Multiple Myeloma (Ti NDMM) Patients: IMROZ Analysis

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INTRODUCTION

- Minimal residual disease (MRD) negativity is a measure of response in the bone marrow that is now widely used in clinical trials. However, MRD is limited by patchy infiltration of bone marrow plasma cells and by absence of potential plasmacytoma assessment[1]
- Imaging-based response assessment that is noninvasive, such as positron emission tomography (PET)/computed tomography (CT) scans, may overcome these limitations while also being able to distinguish between metabolically active multiple myeloma from nonactive multiple myeloma[1]
- Isatuximab (Isa) is a CD38 monoclonal antibody that is approved in combination with pomalidomide and dexamethasone or carfilzomib and dexamethasone for relapsed/refractory multiple myeloma in numerous geographies[2,3]
- Isa is also approved for use with bortezomib, lenalidomide, and dexamethasone (VRd) in transplant-ineligible newly diagnosed multiple myeloma (Ti NDMM) patients, based on the Phase 3 IMROZ study (NCT03319667), which showed Isa-VRd is more effective than VRd as induction in patients with Ti NDMM[3,4]
- Here, we present an analysis of IMROZ (NCT03319667), investigating PET/CT negativity (−) with MRD− in frontline efficacy assessment

METHODS

- In IMROZ, 484 patients were randomly assigned 3:2 to Isa-VRd (n=291) or VRd (n=193) across the global and Chinese extension populations
- Eligible patients were aged 18-80 years with untreated NDMM ineligible for transplant owing to age or comorbidities
- After 24 weeks of induction with Isa-VRd or VRd, patients had continuous treatment with Isa-Rd or Rd until disease progression (PD) or withdrawal
- Baseline MRD was assessed by next-generation sequencing (NGS) at 10^{-5} sensitivity at baseline, and then in case of complete response (CR) or very good partial response (VGPR) at end of initiation, and every 6 months for 2 years then once a year until PD
- PET/CT scans were assessed by central review and performed at baseline then yearly until PD
  - If positive for soft-tissue plasmacytoma, PET/CT scans were repeated at time of CR and/or end of induction, then following the timepoints for MRD assessment
- According to the 5-point Deauville scoring system, PET/CT positivity was defined as fluorodeoxyglucose (FDG) uptake corresponding to a Deauville score (DS) ≥4, while negativity was defined as a DS ≤3

RESULTS

- Among the IMROZ global and China populations, 244 (83.8%) Isa-VRd and 162 (83.9) VRd patients had PET/CT at baseline, of which 153 (62.7%) and 101 (62.3%) were PET/CT positive, respectively (**Table 1**)
  - Of these, 123 (42.3%) and 84 (43.5%) were PET positive at baseline with a post-baseline PET/CT assessment (**Table 2**)
- 155 patients presented with plasmacytoma at baseline (95 Isa-VRd, 60 VRd)

Table 1. Summary of PET/CT results at study entry

	Isa-VRd (N=291)	VRd (N=193)
PET at baseline, n (%)		
Number	244 (83.8)	162 (83.9)
PET positive	153 (62.7)	101 (62.3)
PET negative	91 (37.3)	61 (37.7)
Patients with extramedullary/paramedullary disease at study entry, n (%)		
Number	291	193
Yes and PET positive	78 (26.8)	54 (28.0)
Yes and PET negative	8 (2.7)	4 (2.1)
Yes and PET results not available	9 (3.1)	2 (1.0)
No and PET positive	75 (25.8)	47 (24.4)
No and PET negative	83 (28.5)	57 (29.5)
No and PET results not available	38 (13.1)	29 (15.0)

CT, computed tomography; Isa, isatuximab; PET, positron emission tomography; VRd, bortezomib, lenalidomide, and dexamethasone.

Table 2. Summary of best post-baseline FDG PET 5-point DS as per IRC

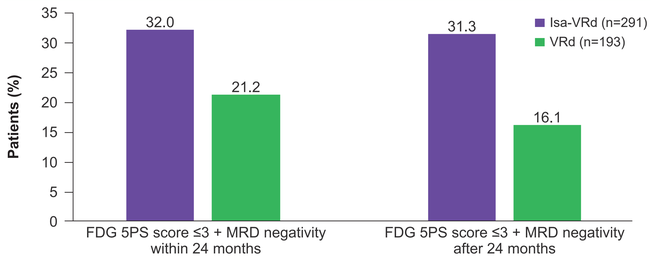
	Isa-VRd (N=291)	VRd (N=193)
Best post-baseline FDG PET DS, n (%)		
Patients with PET positive at baseline and a post-baseline PET assessment	123	84
DS 1	37 (30.1)	17 (20.2)
DS 2	31 (25.2)	14 (16.7)
DS 3	45 (36.6)	40 (47.6)
DS 4	10 (8.1)	9 (10.7)
DS 5	0	4 (4.8)
PET negative at post-baseline (DS ≤3)	113 (91.9)	71 (84.5)
PET positive at post-baseline (DS ≥4)	10 (8.1)	13 (15.5)

DS, Deauville score; FDG, fluorodeoxyglucose; IRC, Independent Review Committee; Isa, isatuximab; PET, positron emission tomography; VRd, bortezomib, lenalidomide, and dexamethasone.

Double Negativity

- In the intent-to-treat population, the double negativity rate (PET/CT FDG DS ≤3 + NGS MRD−) within 24 months of treatment was significantly higher in those receiving Isa-VRd than VRd (**Figure 1**; odds ratio [OR], 1.741; 95% CI, 1.140–2.661; *P*=0.0050)
- In patients who achieved double negativity after 24 months of treatment, similar results were observed (**Figure 1**; OR , 2.378; 95% CI, 1.505–3.756; *P*<0.0001)
- Similar results were observed in patients with plasmacytoma, although not significant (double negativity rate in Isa-VRd: 42.1%, VRd: 35.0%; OR, 1.410; 95% CI, 0.699–2.842; *P*=0.1687)

Figure 1. Double negativity rates within 24 months and after 24 months of treatment, among PET-positive patients at baseline



FDG, fluorodeoxyglucose; 5PS, five-point scale; Isa, isatuximab; MRD, minimal residual disease; PET, positron emission tomography; VRd, bortezomib, lenalidomide, and dexamethasone.

Concordance Between NGS MRD and PET/CT

- As seen in **Table 3**, accuracy between MRD negativity and PET/CT negativity was observed

Table 3. Concordance between MRD and PET/CT in overall post-baseline assessments in the global and China cohort (both arms combined)

	Post-baseline PET/CT		
	Positive (n=26)	Negative (n=276)	Accuracy[a]
NGS MRD, n (%)			
Positive	8 (30.8)	83 (30.1)	0.6513
Negative	8 (30.8)	162 (58.7)	

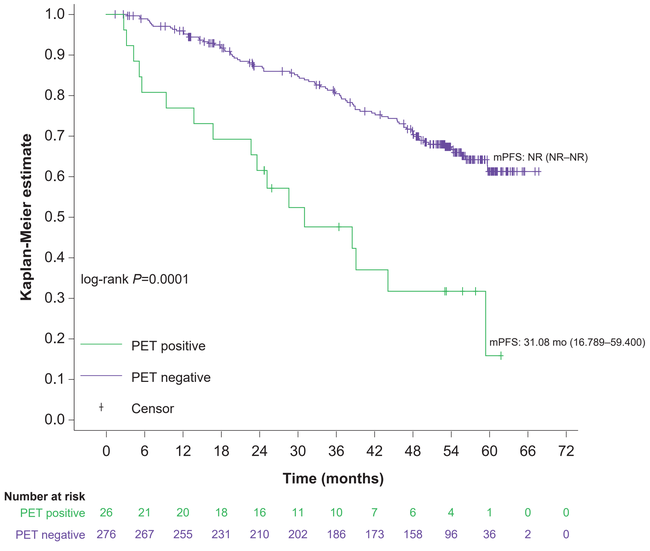
[a]Accuracy was calculated as the number of patients with concordant MRD/PET results divided by the total number of patients with available MRD/PET results.

CT, computed tomography; MRD, minimal residual disease; NGS, next-generation sequencing; PET, positron emission tomography.

Progression-Free Survival

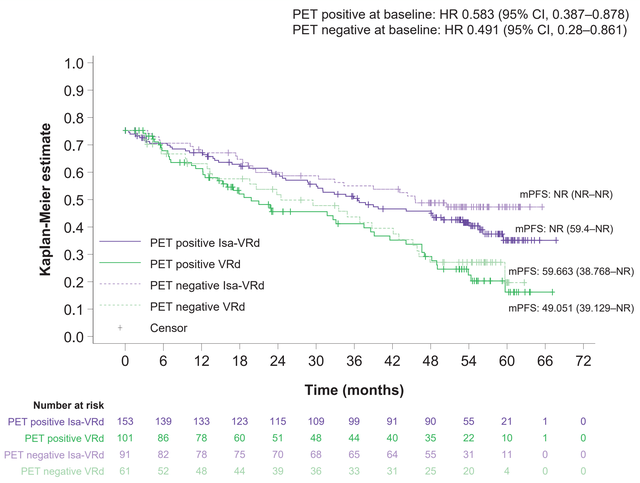
- Patients who were PET negative post-baseline had a longer median progression-free survival (PFS) than those who were PET positive (**Figure 2**; hazard ratio [HR], 0.298; 95% CI, 0.176–0.503; P<0.0001)
- Patients receiving Isa-VRd had a longer median PFS compared with those receiving VRd, regardless of their PET status at baseline (**Figure 3**)
- Subgroup analysis of PFS in patients who were double negative within 24 months favored the Isa-VRd arm (**Figure 4**; hazard ratio [HR], 0.298; 95% CI, 0.176–0.503; P<0.0001)

Figure 2. PFS by PET/CT status at post-baseline overall



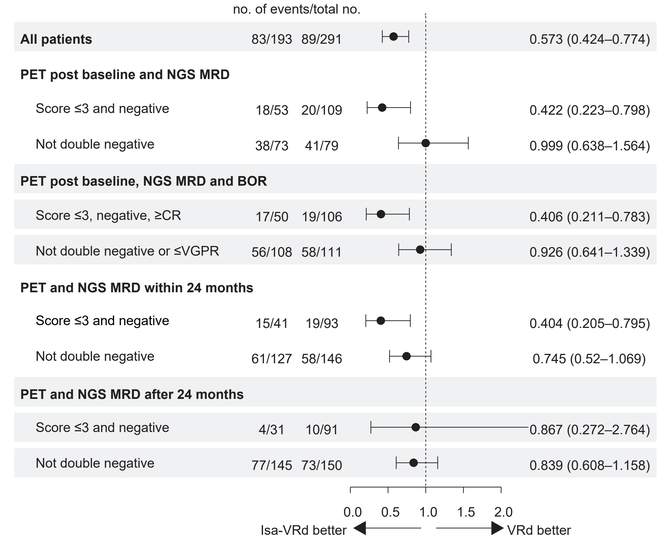
CI, confidence interval; CT, computed tomography; HR, hazard ratio; mPFS, median PFS NR, not reached; PET, positron emission tomography; PFS, progression-free survival.

Figure 3. PFS by PET/CT status at baseline and by treatment group



CI, class interval; CT, computed tomography; HR, hazard ratio; Isa, isatuximab; mPFS, modified progression-free survival; NR, not reached; PET, positron emission tomography; PFS, progression-free survival; VRd, bortezomib, lenalidomide, and dexamethasone.

Figure 4. Subgroup analysis by PET/CT post-baseline and NGS MRD status



BOR, best overall response; CI, confidence interval; CR, complete response; CT, computed tomography; Isa, isatuximab; MRD, minimal residual disease; NGS, next-generation sequencing; PET, positron emission tomography; VGPR, very good partial response; VRd, bortezomib, lenalidomide, and dexamethasone.

CONCLUSIONS

- This post hoc analysis of IMROZ shows the prognostic value of baseline PET/CT findings
- Accuracy was observed between PET/CT negativity and NGS MRD negativity
- Patients who were PET negative post-baseline had improved PFS compared with those who were PET positive
- Significantly more Isa-VRd patients than VRd patients reached double negativity or double negativity plus CR, which translated to an improved PFS in patients treated with Isa-VRd

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QUESTIONS:
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