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Supplementary appendix

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Supplement to: Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet* 2019; published online Nov 14. http://dx.doi.org/10.1016/S0140-6736(19)32556-5.

Supplementary Appendix

This appendix provides additional information about the isatuximab ICARIA-MM phase 3 study.

Supplement to: Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low dose dexamethasone versus pomalidomide and low dose dexamethasone in relapsed and refractory multiple myeloma: a randomized, multicenter, open-label, Phase 3 study

Contents

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Additional Methods

Please see published ICARIA protocol manuscript for further details on methodology: Richardson PG, Attal M, Campana F, et al. Isatuximab plus pomalidomide (Pom)/dexamethasone (Dex) vs Pom/Dex in relapsed/refractory multiple myeloma: ICARIA Phase III study design. *Future Oncology* 2017; 14(11): 1035–1047.[1]

Minimal Residual Disease assessment

For patients who remained MRD positive, one additional sample could be collected. No more than 3 post treatment samples were to be obtained. MRD negativity rate was defined as the proportion of patients with negative MRD by bone marrow aspirate at any time point after first dose.

The clonoSEQ Assay is a next-generation sequencing (NGS) based assay that identifies rearranged IgH (VDJ), IgH (DJ), IgK, and IgL receptor gene sequences, as well as translocated BCL1/IgH (J) and BCL2/IgH (J) sequences. The assay also includes primers that amplify specific genomic regions present as diploid copies in normal genomic DNA (gDNA) to allow determination of total nucleated cell content.

Testing began with gDNA extracted from bone marrow aspirate. Extracted gDNA quality was assessed and rearranged immune receptors amplified using a multiplex PCR. Reaction-specific index barcode sequences for sample identification were added to the amplified receptor sequences by PCR. Sequencing libraries were prepared from barcoded amplified DNA, which were then sequenced by synthesis using NGS. Raw sequence data were uploaded from the sequencing instrument to the Adaptive analysis pipeline. These sequence data were analyzed in a multi-step process: first, a sample's sequence data were identified using the sample index sequences. Next, data were processed using a proprietary algorithm with in-line controls to remove amplification bias.

When the clonoSEQ Clonality (ID) assessment was conducted, the immune repertoire of the sample was checked for the presence of DNA sequences specific to "dominant" clone(s) consistent with the presence of a lymphoid malignancy. Clonal sequences were assessed for their suitability as ID sequences (to be used for subsequent tracking) by first aggregating highly similar sequences and requiring that the frequency of the sequence was at least 3% as a percentage of all sequences in the locus. The clone had to have a frequency of at least 0.2% of all nucleated cells in the sample with sufficient abundance and differentiation from a polyclonal background. Each sequence being considered for MRD tracking was compared against a B cell repertoire database and assigned a uniqueness value that, together with its abundance relative to other sequences, is used to assign the sequence to a sensitivity bin which was used in the estimation of the reported limit of detection and limit of quantitation on the patient report. During clonoSEQ Tracking (MRD) assessment, the complete immunoglobulin receptor repertoire was again assessed, and the previously identified dominant clonotype sequence(s) were detected and quantified to determine the sample MRD level.

MRD negativity (ITT population) was observed in the isatuximab arm in 8 (5.2%) patients at 10^{-5}, but none in the control arm (at any sensitivity level). Of these 8 patients, 6 patients were in CR, 1 patient was in biochemical CR (all criteria for CR fulfilled but bone marrow plasma cell count missing) and 1 patient was considered as non-PD (non-evaluable for response as baseline central lab M protein was below the criterion for measurable disease). Of the 2 patients in the control arm who were MRD positive, 1 patient was in CR and 1 patient was in biochemical CR (all criteria for CR were fulfilled but bone marrow plasma cell count was missing). There were 10 (6.5%) patients at 10^{-4}, and 2 (1.3%) at 10^{-6} in the isatuximab arm.

Definitions

Overall Response Rate: defined as the proportion of patients with stringent complete response, complete response, very good partial response, and partial response, as assessed by the IRC using IMWG response criteria.[2]

Overall Survival: defined as the time from date of randomization to date of death from any cause.

Prior treatment failure defined as meeting one of the following:

1. Progression while on or within 60 days from end of treatment with lenalidomide and/or a proteasome inhibitor
2. If previous response is ≥ partial response (PR) to lenalidomide and/or a proteasome inhibitor the patient must have progressed within 6 months after discontinuation of treatment.
3. Patients who develop intolerable toxicity after a minimum of 2 consecutive cycles of a regimen containing lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, ixazomib) alone or in combination. Intolerance was defined as:
    a. Proteasome inhibitor-containing regimens: any toxicity leading to discontinuation of a proteasome inhibitor. E.g. ≥grade 2 peripheral neuropathy or neuropathic pain. Peripheral neuropathy must be ≤ grade 1 before study entry (NCI-CTCAE v4.03)
    b. Lenalidomide-containing regimens: any toxicity leading to discontinuation of lenalidomide. E.g. grade 3 rash. Rash and any other non-hematologic adverse events must not have been grade 4 at any time. All non-hematologic adverse events must be ≤ grade 1 before study entry

Stable disease: defined as not meeting criteria for CR, VGPR, PR, MR or PD. Two consecutive assessments were required.

Nonprogressive disease: defined as M-protein below level of eligibility at baseline, not meeting criteria for progressive disease or complete response.

Poor prognosis: Patients with poor prognosis includes all the following groups: Age ≥75, patients receiving >3 prior lines of therapy, renal function <60 mL/min/1.73m2, ISS stage III and R-ISS stage III at study entry, and patients with high risk cytogenetics.

Statistical Analyses

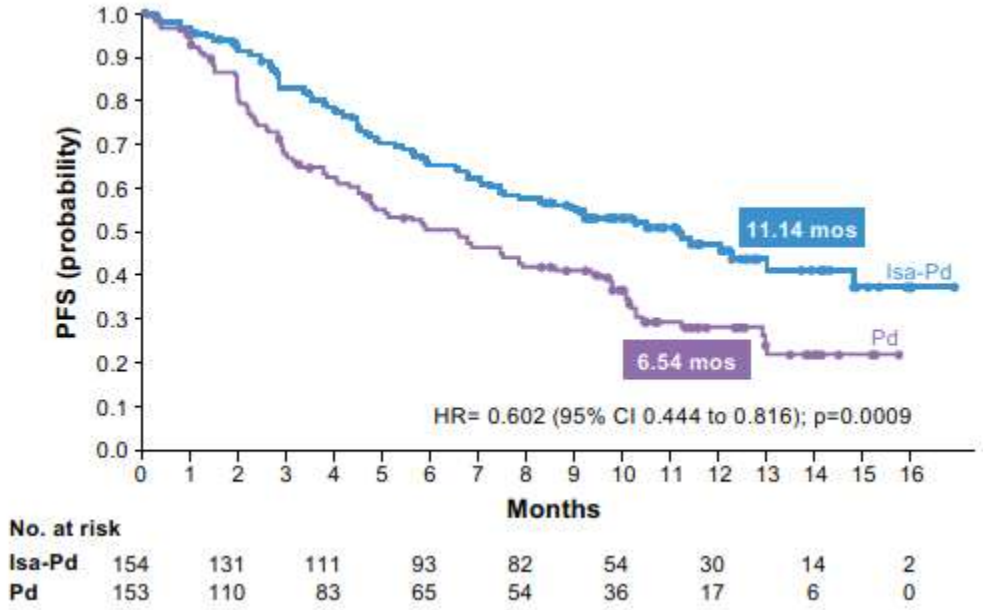
The HR of progression-free survival adjusted in multivariate analyses for demographic and baseline characteristics defined in the statistical analysis plan was 0.484 (95% CI 0.334 to 0.702). This lower adjusted HR compared with the HR from the primary analysis of progression-free survival provides further evidence of the robustness of the results of the primary progression-free survival analysis and even suggests that there could have been some confounding factors among the analyzed covariates that may have influenced the treatment effect in the primary analysis in favor of the control arm.

An interim analysis of overall survival was performed at the time of the progression-free analysis. The 1-sided nominal significance levels for the interim and final analyses of survival obtained using an O'Brien and Fleming α-spending function were 0.0008 and 0.0244 respectively.

Inverse Probability of Censoring Weights (IPCW) analysis

In order to estimate the treatment effect in the absence of a switch to subsequent anti-cancer therapy with daratumumab, a sensitivity analysis using the IPCW method was performed. Overall, in the IPCW analysis, patients were weighted according to the probability of switching to daratumumab based on the values of prognostic covariates at baseline and over time and patients switching to daratumumab were censored at the time of -initiation of daratumumab. Patients who did not receive daratumumab with characteristics similar to patients who received daratumumab were given higher weights. Region of the world and disease response over time were identified as the main factors contributing to a shift to daratumumab. The stratified HR from the IPCW analysis was 0.708 (0.451 to 1.111) which is consistent with the ITT-estimate of 0.687 (0.461 to 1.023). These results should be interpreted with caution as all factors contributing to the initiation of daratumumab may have not been captured in the model.

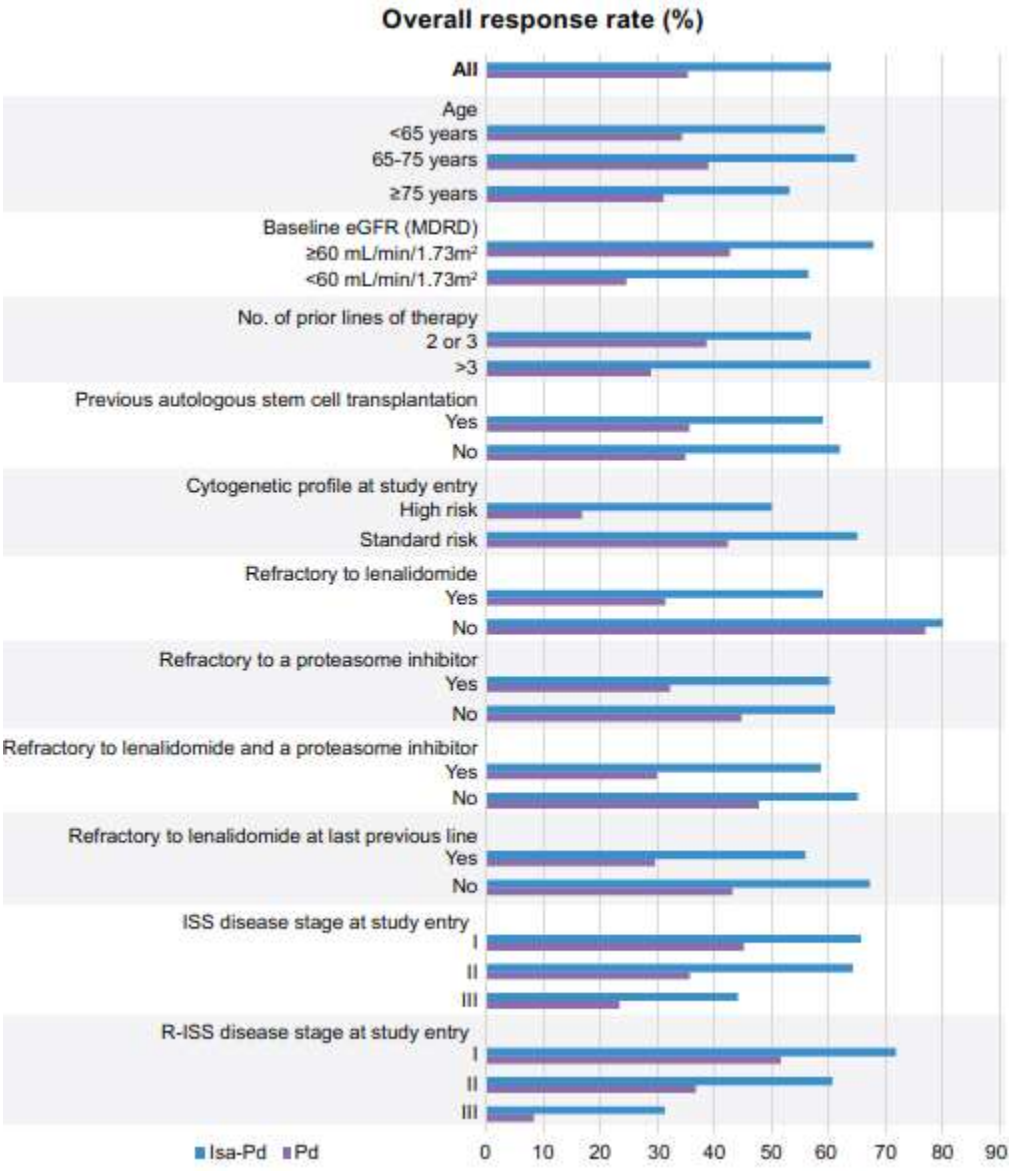
Figure S1: Investigator Assessed Progression-free Survival (local laboratory and radiology data, intent-to-treat population)



Data cut-off: 11 October 2018; median follow up 11.6 months
CI, confidence interval; Dex, dexamethasone; HR, Hazard ratio; Isa, isatuximab; PFS, progression-free survival; Pom, pomalidomide

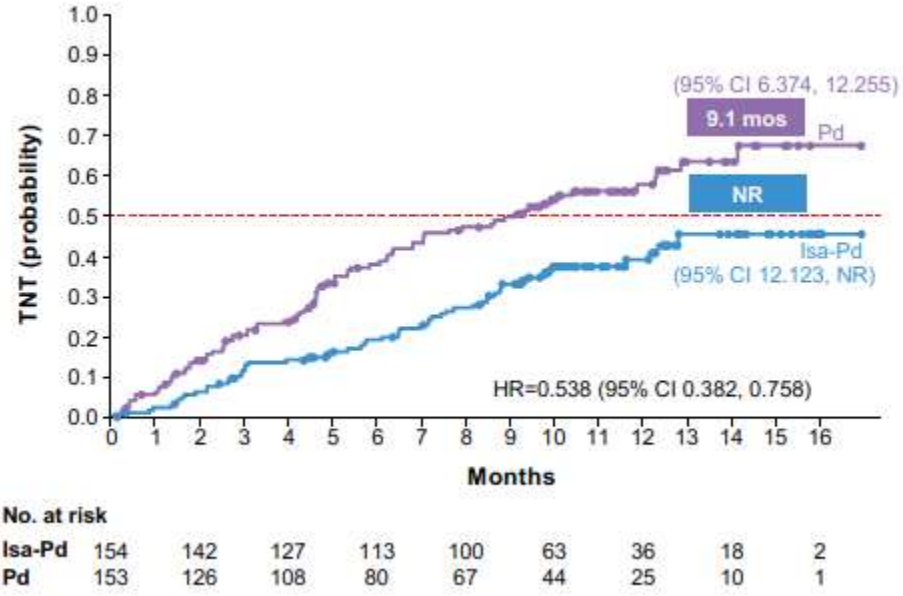
Kaplan–Meier analysis of progression-free survival in the intent-to-treat population, i.e. all patients who were randomized (regardless of treatment received), as assessed by investigators. HR and corresponding 95% confidence intervals are from a Cox proportional hazard model stratified by age and number of previous lines of therapy. One sided p-value is derived from a log-rank test.

Figure S2: Overall Response Rate Subgroup Analysis



eGFR, estimated glomerular filtration rate; ISS, International Staging System;
MDRD, Modification of Diet in Renal Disease Study equation
High-risk was defined as del(17p), t(4;14), or t(14;16) by FISH.
Cytogenetics was performed by a central laboratory with cut-off 50% for del(17p), 30% for t(4;14) and t(14;16).

Figure S3: Time to Next Treatment



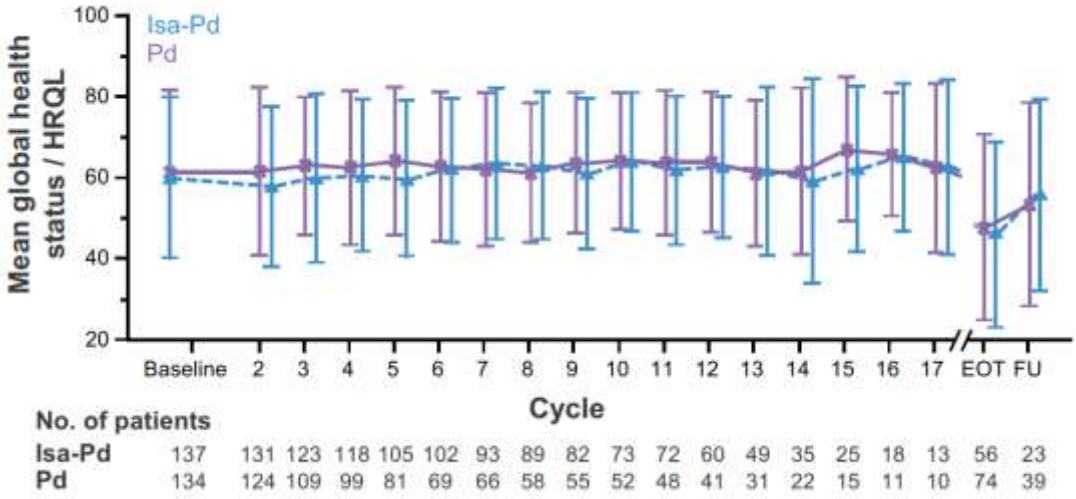
Data cut-off: 11 October 2018
Median follow-up time: 11.6 months (IQR 10.2, 14.1) isatuximab; 11.7 months (IQR 10.0, 13.9) control

CI, confidence interval; d, dexamethasone; HR, Hazard ratio; Isa, isatuximab; m, median; mo, months; NR, not reached; P, pomalidomide; TNT, time to next treatment, IQR, Interquartile range

Patients with further anti-myeloma treatment, n (%)	**Isa-Pd (n=60/154; 39.0%)**	**Pd (n=83/153; 54.2%)**
Alkylating agents	40 (66.7)	33 (39.8)
PIs	34 (56.7)	39 (47.0)
Bortezomib	18 (30.0)	21 (25.3)
Carfilzomib	21 (35.0)	19 (22.9)
Ixazomib	0	3 (3.6)
IMiDs	14 (23.3)	19 (22.9)
Lenalidomide	7 (11.7)	6 (7.2)
Pomalidomide	5 (8.3)	11 (13.3)
Thalidomide	3 (5.0)	3 (3.6)
mAbs (Daratumumab)	6 (10.0)	45 (54.2)
Other (Atezolizumab)	0	2 (2.4)

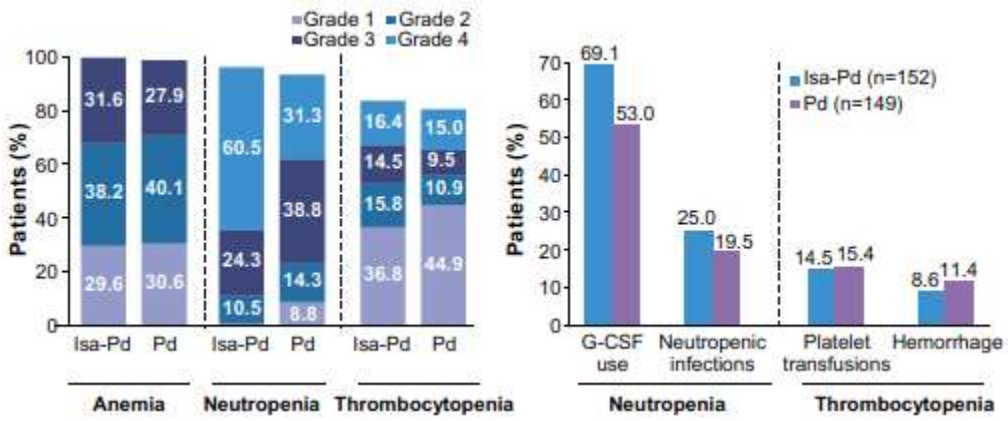
d, dexamethasone; IMiD: immunomodulatory drug; Isa, isatuximab; mAb, monoclonal antibody; PI, proteasome inhibitor; P, pomalidomide

Figure S4: Global Health Scale Change from Baseline



BL, baseline; d, dexamethasone; EOT, end of therapy; FU, follow-up; HRQL, health-related quality of life; Isa, isatuximab; P, pomalidomide

Figure S5: Incidence and Management of Hematologic Adverse events and Hematologic Laboratory Abnormalities



AE, adverse event; d, dexamethasone; G-CSF, granulocyte-colony stimulating factor; Isa, isatuximab; P, pomalidomide

Table S1. Investigator Assessed Response (intent-to-treat population)

	Isatuximab + pomalidomide + dexamethasone (N=154)	**Pomalidomide + dexamethasone (N=153)**
Best Overall Response [n (%)]		
Complete response (CR)	8 (5.2)	1 (0.7)
Stringent complete response (sCR)	1 (0.6)	1 (0.7)
Very good partial response (VGPR)	43 (27.9)	9 (5.9)
Partial response (PR)	45 (29.2)	38 (24.8)
Minimal response	9 (5.8)	21 (13.7)
Stable disease	33 (21.4)	51 (33.3)
Progressive disease	7 (4.5)	15 (9.8)
Unconfirmed progressive disease	2 (1.3)	4 (2.6)
Not evaluable/Not assessed	6 (3.9)	13 (8.5)
Overall Response		
Responders (sCR, CR, VGPR or PR)	97 (63.0)	49 (32.0)
95% CI*	0.5484, 0.7062	0.2472, 0.4004
Odds ratio (95% CI)	3.612 (2.195, 5.953)	
VGPR or better	52 (33.8)	11 (7.2)
95% CI*	0.2635, 0.4182	0.0364, 0.1250
Odds ratio (95% CI)	6.581 (3.179, 14.611)	

*estimated using Clopper-Pearson method

Table S2. Safety Summary

Treatment Emergent Adverse Event (TEAE)	Isa-Pd (N=152)	Pd (N=149)
	All grades, n (%)	All grades, n (%)
Any TEAE	151 (99.3)	146 (98.0)
Any drug-related grade ≥3 TEAE	109 (71.7)	71 (47.7)
Any serious TEAE	94 (61.8)	80 (53.7)
Any serious drug-related TEAE	54 (35.5)	24 (16.1)
Any TEAE leading to definitive discontinuation	11 (7.2)	19 (12.8)
TEAE leading to death during treatment period	12 (7.9)	14 (9.4)

References

1. Richardson PG, Attal M, Campana F, et al. Isatuximab plus pomalidomide/dexamethasone versus pomalidomide/dexamethasone in relapsed/refractory multiple myeloma: ICARIA Phase III study design. *Future Oncol* 2018; **14**(11): 1035-47.
2. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol* 2016; **17**(8): e328-e46.