IMW 2019 | ICARIA-MM: Cytogenetic subgroup analysis

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At the XVII International Myeloma Workshop (IMW), Boston, US, Simon J. Harrison, Peter MacCallum Cancer Center and Royal Melbourne Hospital, Melbourne, AU, presented a subgroup analysis from the ICARIA-MM trial (NCT02990338) of patients with high-risk cytogenetics.[1]

The phase III ICARIA-MM trial compared isatuximab (Isa) + pomalidomide (P) + dexamethasone (d, Isa-Pd) to Pd alone in patients with relapsed/refractory multiple myeloma (RRMM). Patients (n= 307) were randomized (1:1) to Isa-Pd or Pd and received treatment until disease progression (PD) or unacceptable toxicity. The study had a primary endpoint of progression-free survival (PFS), with secondary endpoints of overall response rate (ORR) and overall survival (OS).[2]

The original report from the ICARIA-MM trial was presented by Prof. Paul Richardson at the American Society of Clinical Oncology (ASCO) meeting earlier this year. At ASCO Prof. Richardson and colleagues showed, at a median follow-up of 11.6 months, that Isa-Pd provided a statistically significant improvement in PFS (Isa-Pd *vs* Pd: 11.53 *vs* 6.47 months, hazard ratio [HR]: 0.596, 95% CI, 0.436–0.814). Median OS was not reached in either arm. ORR was higher in the Isa-Pd arm at 60.4% compared to 35.3% in the Pd arm. The main reason for discontinuation was PD or an adverse event (AE). Read the full results on the Multiple Myeloma Hub now.[2]

Subgroup analysis: patients with high-risk cytogenetics[1]

At the IMW meeting, a subgroup analysis from ICARIA-MM was presented, comparing safety and efficacy of Isa-Pd to Pd in patients with high- and standard-risk cytogenetics.

- High-risk cytogenetics pre-specified as ≥ one of the following:
  - del(17p) – 50% cut-off
  - t(4;14) – 30% cut-off
  - t(14;16) – 30% cut-off
- Baseline cytogenetic profiles of the intention-to-treat (ITT) population are shown in **Table 1**

Table 1. Cytogenetics in the ITT population at baseline[1]

Cytogenetic Risk	**Isa-Pd (n= 154), %**	**Pd (n= 153), %**
Standard	66.9	51
High	15.6	23.5
del(17p)	9.1	15
t(4;14)	7.8	9.2

Isa-Pd, isatuximab-pomalidomide and dexamethasone

t(14;16)	0.6	2.6
del(17p) and t(4;14)	1.9	2.6
del(17p) and (14;16)	0	0.7
Unknown or missing	17.5	25.5
Isa-Pd, isatuximab-pomalidomide and dexamethasone		

- Safety analysis by cytogenetic risk is shown in **Table 2**
    - High-risk patients experienced more grade III or higher treatment-emergent AE (TEAEs) though the addition of Isa to the Pd regimen did not increase events leading to discontinuation
    - Treatment-related mortality did not increase in either subgroup
        - Two treatment-related grade V TEAEs occurred; both in the Pd arm, one in a patient with high-risk cytogenetics, and one in a patient with standard risk cytogenetics
    - Median duration of treatment exposure:
        - High-risk (Isa-Pd *vs* Pd): 32 *vs* 18 weeks
        - Standard-risk (Isa-Pd *vs* Pd): 42 *vs* 31.1 weeks
- Isa-Pd had a manageable safety profile in both standard- and high-risk patients

Table 2. Safety by cytogenetic subgroup

	High-risk		Standard-risk	
%	**Isa-Pd (n= 23), %**	**Pd (n= 34), %**	**Isa-Pd (n= 103), %**	**Pd (n= 76), %**
Grade ≥ III TEAE	95.7	67.6	85.4	76.3
Serious TEAE	73.9	50	58.3	61.8
TEAE leading to definitive discontinuation	8.7	23.5	6.8	7.9
Grade V TEAE (fatal)	26.1	4 (11.8)	3.9	5.3
Grade ≥ III events occurring in > 10% of patients in either subgroup				
Laboratory abnormalities				
Neutropenia	82.6	25*	85.4	69.7

* n= 33. Isa-Pd, isatuximab, pomalidomide dexamehasone; TEAEs, treatment-emergent adverse events

Thrombocytopenia	47.8	27.3*	26.2	25
TEAEs				
Febrile neutropenia	13	0	11.7	2.6
Pneumonia	21.7	17.6	15.5	18.4

* n= 33. Isa-Pd, isatuximab, pomalidomide dexamehasone; TEAEs, treatment-emergent adverse events

- Efficacy results by cytogenetics are displayed in **Table 3**
  - Odds ratio for Isa-Pd *vs* Pd (95% CI):
    - ORR, high-risk: 5 (1.33–19.79)
    - ORR, standard-risk: 2.54 (1.33–4.86)
    - ≥ Very good partial response (VGPR), high-risk: 14.41 (1.57–667.48)
    - ≥ VGPR, standard-risk: 4.78 (1.9–13.57)
  - The ORR and PFS (**Table 4**) benefit of Isa-Pd *versus* Pd was maintained in patients with high-risk cytogenetics
    - Benefit in ORR and PFS was also maintained regardless of the high-risk cytogenetic cut-off used

Table 3. Response rates by cytogenetics

	High-risk		Standard-risk	
%	**Isa-Pd (n= 24), %**	**Pd (n= 36), %**	**Isa-Pd (n= 103), %**	**Pd (n= 78), %**
ORR	50	16.7	65	42.3
CR/sCR	0	0	3.9	1.3
VGPR	29.2	2.8	28.2	7.7
PR	20.8	13.9	33	33.3

CR, complete response; Isa-Pd, isatuximab- pomalidomide and dexamethasone; ORR, overall response rate; PR, partial response; s, stringent; VGPR, very good partial response;

Table 4. PFS by cytogenetics

	Median PFS, months			
Isa-Pd *vs* Pd (n)	**Isa-Pd**	**Pd**	**HR**	**95% CI**
All patients (154 *vs* 153)	11.5	6.5	0.6	0.44–0.81

Isa-Pd, isatuximab-pomalidomide and dexamethasone; PFS, progression free survival

Cytogenetic risk				
High (24 *vs* 36)	7.5	3.7	0.66	0.33–1.28
Standard (103 *vs* 78)	11.6	7.4	0.62	0.42–0.93
del(17p)				
Yes (14 *vs* 23)	9.1	7.4	0.76	0.3–1.92
No (118 *vs* 95)	11.5	5.6	0.57	0.4–0.82
t(4;14)				
Yes (12 *vs* 14)	7.5	2.8	0.49	0.19–1.31
No (119 *vs* 101)	11.6	7	0.58	0.4–0.83
Isa-Pd, isatuximab-pomalidomide and dexamethasone; PFS, progression free survival				

Conclusion

Isa-Pd provided an ORR and PFS benefit over Pd, which was maintained in patients with high-risk cytogenetics, independent of the cytogenetic cut-off definition. Additionally, the safety profile was manageable in this patient population.

Isa-Pd could provide a new treatment option for patients with RRMM with high-risk cytogenetics who typically have few options available.

References:

1. Harrison S.J. *et al.*, Efficacy of isatuximab/pomalidomide/dexamethasone in relapsed/refractory multiple myeloma: ICARIA-MM high-risk cytogenetics subgroup analysis. 2019 Sep 14. Abstract #AB530 XVII International Myeloma Workshop, Boston, US.

2. Richardson P.G. *et al.* A phase III randomized, open label, multicenter study comparing isatuximab, pomalidomide, and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM). 2019 Jun 02. Abstract #8004. American Society of Clinical Oncology meeting, Chicago, US.

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