Allocation and Validation of the Second Revision of the International Staging System in the ICARIA-MM and IKEMA Studies

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INTRODUCTION

- In 2015, the International Staging System[1] (ISS) underwent a revision[2] (R-ISS) to include certain high-risk chromosomal abnormalities as prognostic factors
- Recently, the R-ISS was further revised[3] (second revision of the ISS [R2-ISS]), to include 1q21+ and account for the additive prognostic significance of having multiple risk factors present
  - R2-ISS improved the ability to discriminate between the large group of patients deemed "intermediate-risk" by the R-ISS by splitting this group into low-intermediate (Stage II) and intermediate-high (Stage III)
- R2-ISS was validated using data from clinical trials of patients with newly diagnosed multiple myeloma (MM),[3] but has yet to be validated in patients with relapsed/refractory MM (RRMM) or in patients treated with monoclonal antibodies (mAb)
- Isatuximab (Isa) is an anti-CD38 mAb approved for use in multiple countries[4-6] to treat adults with RRMM when given in combination with either pomalidomide-dexamethasone (Pd) or carfilzomib-dexamethasone (Kd)
- We sought to validate the prognostic value of the R2-ISS among patients with RRMM who were treated in the Phase 3 ICARIA-MM (Isa-Pd vs Pd) and IKEMA (Isa-Kd vs Kd) studies, results of which have been previously reported[7-10]
  - The impact of early relapse on R2-ISS staging was also evaluated
- We also aimed to examine the benefit of Isa-based triplet therapy (Isa-Pd, Isa-Kd) vs doublet therapy (Pd, Kd), by R2-ISS stage

METHODS

- Pooled patients from the treatment (Isa-based triplet) and control (doublet) arms of ICARIA-MM (N=307) or IKEMA (N=302) were re-allocated into R2-ISS stage using the scoring strategy outlined by D'Agostino et al[3]
  - Values were assigned to individual risk factors: ISS Stage II (1.0); ISS Stage III (1.5); lactate dehydrogenase greater than the upper limit of normal (1.0); del(17p) present (1.0); t(4;14) present (1.0); and 1q21+ present (0.5)
  - The sum of risk factor values was used to determine R2-ISS stage (**Table 1**)
- To minimize the number of patients deemed not classifiable, an allowance was made for missing data when the sum of available risk factors reached a certain threshold

Table 1. Risk factor scoring strategy to determine R2-ISS stage

Total risk factor score	R2-ISS stage
0	I
0.5–1.0	II
1.5–2.5	III*
3.0–5.0	IV†

*If patients had 1 missing risk factor, and the missing risk factor was not ISS stage, and the total score of existing non-missing risk factors was 1.5, then R2-ISS was classified as Stage III irrespective of the score value assigned to the missing risk factor
†If the total score of non-missing risk factors was at least 3.0, patients were designated as R2-ISS Stage IV, irrespective of the number of missing risk factors
ISS, International Staging System; R2-ISS; second revision of the ISS

- Early relapse (includes RRMM; excludes primary refractory) was defined as follows:
  - Relapsed <12 months from initiation of the most recent line of therapy for patients with ≥2 prior lines of therapy
  - Relapsed <18 months for patients with 1 prior line of therapy
  - Relapsed <12 months from autologous stem cell transplantation
- Progression-free survival (PFS), according to disease assessment by an independent review committee, was the primary endpoint (ICARIA-MM data cutoff Oct 11, 2018; IKEMA data cutoff Jan 14, 2022)
- Overall survival (OS) was included as an exploratory endpoint (ICARIA-MM data cutoff Jan 27, 2022; IKEMA data cutoff Jan 14, 2022 [immature IKEMA OS data])
- The Kaplan-Meier method was used to construct validation curves by R2-ISS stage and to examine outcomes by Isa-based triplet vs doublet
- Hazard ratios (HRs) and corresponding confidence intervals (CIs) were estimated using the Cox proportional hazards model

RESULTS

- Classification of study participants by risk factors considered for R2-ISS staging, and by re-allocation into R2-ISS stage, is shown in **Table 2**
  - More ICARIA-MM participants (30.9%) than IKEMA participants (11.9%) were missing 1q21+ data. This was due to the retrospective nature of 1q21+ assessment in ICARIA-MM (due to lack of leftover material and patient consent withdrawal) compared with the prospective analysis in IKEMA

Table 2. Baseline risk factors considered for R2-ISS scoring and summary of R2-ISS Stage

	ICARIA-MM			IKEMA		
Patient characteristic, n (%)	**Isa-Pd (n=154)**	**Pd (n=153)**	**All (N=307)**	**Isa-Kd (n=179)**	**Kd (n=123)**	**All (N=302)**
ISS stage at study entry						
Stage I	62 (40.3)	51 (33.3)	113 (36.8)	89 (49.7)	71 (57.7)	160 (53.0)
Stage II	55 (35.7)	56 (36.6)	111 (36.2)	63 (35.2)	31 (25.2)	94 (31.1)
Stage III	34 (22.1)	43 (28.1)	77 (25.1)	26 (14.5)	20 (16.3)	46 (15.2)
Unknown	3 (1.9)	3 (2.0)	6 (2.0)	1 (0.6)	1 (0.8)	2 (0.7)
del(17p)*						
Present	14 (9.1)	23 (15.0)	37 (12.1)	18 (10.1)	16 (13.0)	34 (11.3)
Absent	118 (76.6)	95 (62.1)	213 (69.4)	143 (79.9)	96 (78.0)	239 (79.1)
Unknown or missing	22 (14.3)	35 (22.9)	57 (18.6)	18 (10.1)	11 (8.9)	29 (9.6)
LDH‡						
≤ ULN	106 (68.8)	102 (66.7)	208 (67.8)	137 (76.5)	97 (79.5)	234 (77.7)
> ULN	48 (31.2)	51 (33.3)	99 (32.2)	42 (23.5)	25 (20.5)	67 (22.3)
Missing	0	0	0	0	1 (<0.1)	1 (<0.1)
t(4;14)*						
Present	12 (7.8)	14 (9.2)	26 (8.5)	22 (12.3)	20 (16.3)	42 (13.9)
Absent	119 (77.3)	101 (66.0)	220 (71.7)	137 (76.5)	89 (72.4)	226 (74.8)
Unknown or missing	23 (14.9)	38 (24.8)	61 (19.9)	20 (11.2)	14 (11.4)	34 (11.3)
1q21+†						
Present	76 (49.4)	52 (34.0)	128 (41.7)	75 (41.9)	52 (42.3)	127 (42.1)
Absent	38 (24.7)	46 (30.1)	84 (27.4)	84 (46.9)	55 (44.7)	139 (46.0)
Unknown or missing	40 (26.0)	55 (35.9)	95 (30.9)	20 (11.2)	16 (13.0)	36 (11.9)
R2-ISS stage						
Stage I	11 (7.1)	9 (5.9)	20 (6.5)	31 (17.3)	17 (13.8)	48 (15.9)
Stage II	27 (17.5)	24 (15.7)	51 (16.6)	47 (26.3)	38 (30.9)	85 (28.1)
Stage III	52 (33.8)	47 (30.7)	99 (32.2)	68 (38.0)	37 (30.1)	105 (34.8)
Stage IV	16 (10.4)	18 (11.8)	34 (11.1)	11 (6.1)	10 (8.1)	21 (7.0)
Not classified	48 (31.2)	55 (35.9)	103 (33.6)	22 (12.3)	21 (17.1)	43 (14.2)
R2-ISS stage for patients with early relapse						
Stage I	6 (6.5)	5 (5.3)	11 (5.9)	5 (8.2)	5 (10.9)	10 (9.3)
Stage II	12 (12.9)	12 (12.8)	24 (12.8)	15 (24.6)	12 (26.1)	27 (25.2)
Stage III	36 (38.7)	30 (31.9)	66 (35.3)	27 (44.3)	21 (45.7)	48 (44.9)
Stage IV	10 (10.8)	14 (14.9)	24 (12.8)	7 (11.5)	4 (8.7)	11 (10.3)
Not classified	29 (31.2)	33 (35.1)	62 (33.2)	7 (11.5)	4 (8.7)	11 (10.3)

*del(17p) and t(4;14) were assessed during screening for ICARIA-MM and IKEMA by a central laboratory with a cut-off of 50% and 30%, respectively †1q21+ (cut-off of 30%) was assessed by a central laboratory prospectively during screening for IKEMA and retrospectively for ICARIA-MM ‡LDH assessment at baseline for IKEMA: Isa-Kd (n=149); Kd (n=122); All (n=301)
d, dexamethasone; Isa, isatuximab; ISS, International Staging System; K, carfilzomib; LDH, lactate dehydrogenase; P, pomalidomide; R2-ISS, second revision of the ISS; ULN, upper limit of normal

- Of the 294 patients with early relapse, 21 were reclassified as R2-ISS Stage I, 51 as R2-ISS Stage II, 114 as R2-ISS Stage III, 35 as Stage IV, and 73 were not classified (**Table 2**)
- Compared with the whole population, more patients with early relapse were classified as R2-ISS Stages III and IV (51% vs 42%) than R2-ISS Stages I and II (24% vs 33%) (**Table 2**)
- Of the 609 enrollees, 68 were reclassified as R2-ISS Stage I, 136 as R2-ISS Stage II, 204 as R2-ISS Stage III, 55 as Stage IV, and 146 were not classified
  - The distribution of single risk factors present among patients within each R2-ISS stage is shown in **Table 3**

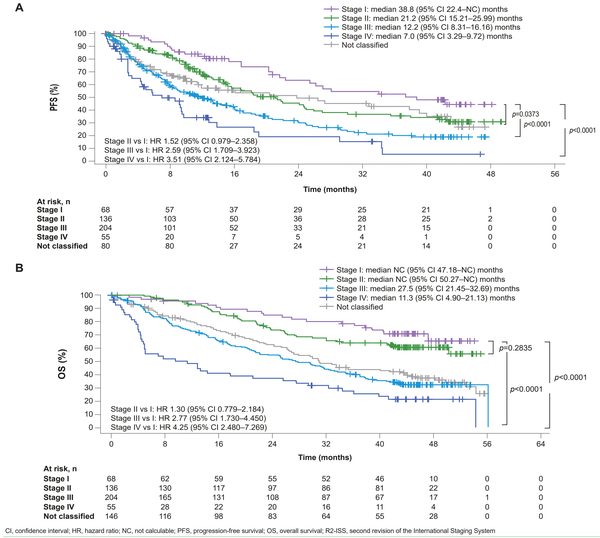
Table 3. Distribution of risk factors across R2-ISS stages

	R2-ISS stage					
Risk factor, n (%)	**Stage I (n=68)**	**Stage II (n=136)**	**Stage III (n=204)**	**Stage IV (n=55)**	**Not classified (n=146)**	**All (N=609)**
No risk factors present	68 (100)	0	0	0	0	68 (11.2)
ISS Stage II	0	48 (35.3)	89 (43.6)	15 (27.3)	53 (36.3)	205 (33.7)
ISS Stage III	0	0	62 (30.4)	39 (70.9)	22 (15.1)	123 (20.2)
LDH >ULN	0	19 (14.0)	58 (28.4)	47 (85.5)	42 (28.8)	166 (27.3)
del(17p)* present	0	10 (7.4)	25 (12.3)	27 (49.1)	9 (6.2)	71 (11.7)
t(4;14)* present	0	6 (4.4)	42 (20.6)	18 (32.7)	2 (1.4)	68 (11.2)
1q21+† present	0	53 (39.0)	142 (69.6)	47 (85.5)	13 (8.9)	255 (41.9)

*del(17p) and t(4;14) were assessed during screening for ICARIA-MM and IKEMA by a central laboratory with a cut-off of 50% and 30%, respectively
†1q21+ (cut-off of 30%) was assessed by a central laboratory during screening for IKEMA and retrospectively for ICARIA-MM
ISS, International Staging System; LDH, lactate dehydrogenase; R2-ISS, second revision of the ISS; ULN, upper limit of normal

- After a median follow-up duration of 11.6 months (ICARIA-MM) and 44 months (IKEMA), PFS was shorter among patients reclassified as R2-ISS Stage II (HR 1.52; 95% CI 0.979–2.358), Stage III (HR 2.59; 95% CI 1.709–3.923), and Stage IV (HR 3.51; 95% CI 2.124–5.784) compared with Stage I (**Figure 1A**)
  - Consistent with the R2-ISS, this validation showed that the median PFS decreased with increasing stage: Stage I, 38.8 months; Stage II, 21.2 months; Stage III, 12.2 months; Stage IV, 7.0 months
- After a median follow up of 52.4 months (ICARIA-MM) and 44 months (IKEMA), OS was also shorter among patients reclassified as R2-ISS Stage II (HR 1.30; 95% CI 0.779–2.184), Stage III (HR 2.77; 95% CI 1.730–4.450), and Stage IV (HR 4.25; 95% CI 2.480–7.269) compared with Stage I (**Figure 1B**)
  - Median OS was not reached for both Stage I and Stage II, and was 27.5 months and 11.3 months for Stages III and IV, respectively; there was a clear separation of the curves observed despite Stage I and II medians not being reached
- The presence of individual R2-ISS risk factors (compared with their absence) was similarly associated with shorter PFS (**Figure 2A**) and OS (**Figure 2B**)

Figure 1. Validation curves showing (A) PFS and (B) OS by R2-ISS stage (pooled data from ICARIA-MM and IKEMA). One-sided *p*-values are presented.



CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival; OS, overall survival; R2-ISS, second revision of the International Staging System

Figure 2. Hazard ratios of (A) PFS and (B) OS, by subgroups with individual risk factors (pooled data from ICARIA-MM and IKEMA)

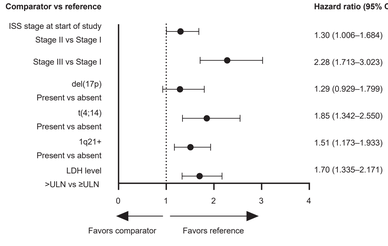
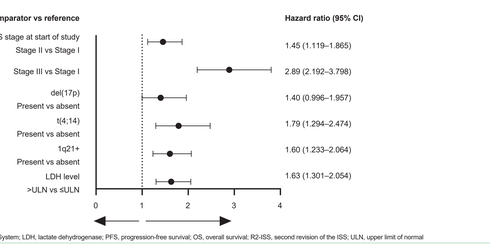


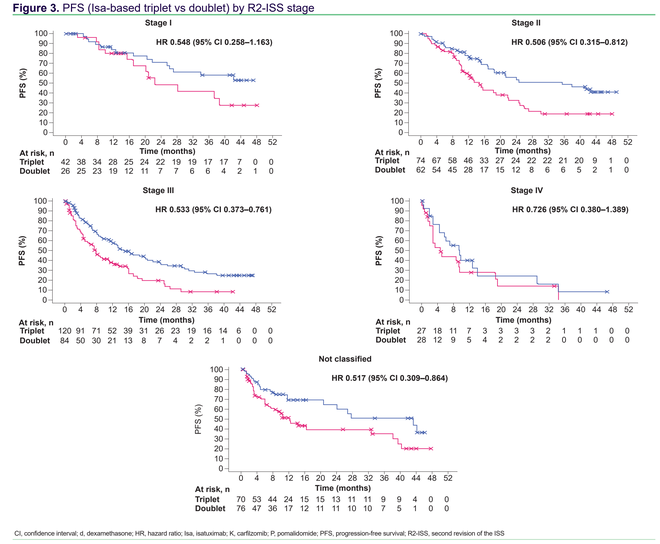
Figure 2. Hazard ratios of (A) PFS and (B) OS, by subgroups with individual risk factors (pooled data from ICARIA-MM and IKEMA)



CI, confidence interval; ISS, International Staging System; LDH, lactate dehydrogenase; PFS, progression-free survival; OS, overall survival; R2-ISS, second revision of the ISS; ULN, upper limit of normal

- Adding Isa to Pd or Kd led to longer PFS compared with receiving doublet therapy for all patients (median 23.9 vs 11.8 months, respectively; HR 0.544 (95% CI 0.436–0.680)
  - A consistent treatment effect was observed across all R2-ISS stages (**Figure 3**)

Figure 3. PFS (Isa-based triplet vs doublet) by R2-ISS stage



CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; K, carfilzomib; P, pomalidomide; PFS, progression-free survival; R2-ISS, second revision of the ISS

CONCLUSIONS

- To our knowledge, this is the first study to validate the R2-ISS in patients with RRMM and in patients treated with an anti-CD38 mAb, using pooled data from two Phase 3 studies (ICARIA-MM and IKEMA)
  - Consistent with the R2-ISS, this validation showed decreasing PFS by stage. A progressive decline in OS and separation of the curves was seen as R2-ISS stage progressed from Stage I to Stage IV; further maturation of IKEMA OS data may yield better discrimination between R2-ISS Stage II vs Stage I
  - More patients with early relapse are classified as R2-ISS Stage III and IV
  - In this analysis, the IKEMA OS data were not mature
- Isa-based triplet therapy led to improved PFS, regardless of R2-ISS stage, when compared with doublet therapy
- Overall, our data show that R2-ISS, as a prognostic scoring system, can be applied to patients with RRMM in the era of novel agents, including monoclonal antibodies

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