Dear Editor

The aim of the ICARIA-MM Phase 3 study (ClinicalTrials.gov, number NCT02990338) was to determine the progression-free survival benefit of isatuximab plus pomalidomide and dexamethasone compared with pomalidomide and dexamethasone alone in patients with relapsed and refractory multiple myeloma [1]. Results from this study demonstrated that the addition of isatuximab to pomalidomide and dexamethasone provides a significant benefit for progression-free survival over pomalidomide and dexamethasone alone. Additionally, results showed a positive treatment effect in all subgroups, including revised international staging system (R-ISS) stage at study entry [1].

The R-ISS, as defined by the international myeloma working group (IMWG), combines the original ISS (beta-2 microglobulin and albumin) with chromosomal abnormalities (del[17p] and/or t[4;14] and/or t[14;16]; determined by fluorescence in situ hybridization) and lactate dehydrogenase (LDH) results [2]. Like the ISS, the R-ISS is based on three stages; patients with beta-2 microglobulin <3.5 mg/L and albumin ≥3.5 g/dL, standard-risk for cytogenetics abnormalities and normal LDH (≤upper limit of normal) are allocated as stage I; patients with beta-2 microglobulin ≥5.5 mg/L and either high-risk for cytogenetics abnormalities or high LDH (> upper limit of normal) are allocated to stage III; and patients who do not meet criteria for stage I or stage III are allocated to stage II.

In the original analysis of the ICARIA-MM study results, the interpretation of the IMWG criteria for R-ISS allocated patients with unknown cytogenetic abnormalities or missing beta-2 microglobulin at baseline as R-ISS stage I or stage II (Table 1) [1]. R-ISS was allocated based on several parameters measured at baseline, including beta-2 microglobulin, albumin, LDH and cytogenetic abnormalities (characterized by central laboratory fluorescence in situ hybridization testing of purified CD138+ plasma cells from baseline bone marrow aspirate). Among patients for whom the cytogenetic abnormalities status was unknown, but other variables were available and allowed the R-ISS status to be determined, 19 patients were allocated as R-ISS stage I and nine patients as R-ISS stage II. In addition, six patients with missing beta-2 microglobulin were allocated as R-ISS stage II, following the R-ISS definition that suggests this stage when a patient does not meet criteria to be allocated as stage I or stage III (Table 1).

A more conservative way of allocating the R-ISS status would be to separate the patients with unknown cytogenetic abnormalities and missing beta-2 microglobulin at baseline into a fourth category named ‘unclassified’. In the ICARIA-MM study, a total of 34 patients (19 R-ISS stage I and 15 R-ISS stage II according to the original allocation) would have been allocated to ‘unclassified’ (Table 2).

To further investigate if this alternative R-ISS allocation approach would lead to different conclusions about the ICARIA-MM study, the authors conducted a post hoc analysis to assess the progression-free survival benefit using the alternative R-ISS staging allocation in which the 34 patients with unknown cytogenetics and missing beta-2 microglobulin at baseline were allocated to an ‘unclassified’ R-ISS stage at study entry. A comparison of the results from this post hoc analysis is shown in Table 3. The hazard ratios for progression-free survival remain in favour of isatuximab plus pomalidomide and dexamethasone compared with pomalidomide and dexamethasone alone.
### Table 1
R-ISS stage at study entry according to beta-2 microglobulin, albumin, LDH and cytogenetic abnormalities results measured at baseline (original allocation used in ICARIA-MM), intent-to-treat population

| Beta-2 microglobulin (mg/L) | Albumin (g/dL) | LDH  | Cytogenetic abnormalities (FISH) | R-ISS       | Number of patients |
|-----------------------------|----------------|------|---------------------------------|-------------|--------------------|
| <3.5                        | ≥3.5           | ≤ULN | High-risk                       | Stage II    | 11                 |
|                             |                |      | Standard-risk                   | Stage I     | 51                 |
|                             |                |      | Unknown                         |             | 19                 |
| ≥3.5–<5.5                   |                |      | High-risk                       | Stage II    | 15                 |
|                             |                |      | Standard-risk                   | Stage I     | 32                 |
|                             |                |      | Unknown                         |             | 28                 |
| ≥5.5                        |                |      | High-risk                       | Stage III   | 20                 |
|                             | >ULN           |      | Standard-risk                   | Stage I     | 15                 |
|                             |                |      | Unknown                         |             | 5                  |
| Missing                     |                |      | Standard-risk                   | Stage II    | 28                 |
|                             |                |      | Unknown                         |             | 9                  |
|                             |                |      | High-risk                       | Stage II    | 14                 |
|                             |                |      | Standard-risk                   | Stage I     | 51                 |
|                             |                |      | Unknown                         |             | 17                 |

Abbreviations: FISH, fluorescence in situ Hybridization; LDH, lactate dehydrogenase; R-ISS, revised international staging system; ULN, upper limit of normal.

### Table 2
R-ISS stage at study entry according to the original allocation used in ICARIA-MM and to the alternative allocation method, intent-to-treat population

|                    | Isa-Pd (n = 154) | Pd (n = 153) | All (N = 307) |
|--------------------|------------------|--------------|--------------|
| R-ISS stage at study entry, original allocation, n (%) |                |              |              |
| Stage I            | 39 (25.3)        | 31 (20.3)    | 70 (22.8)    |
| Stage II           | 99 (64.3)        | 98 (64.1)    | 197 (64.2)   |
| Stage III          | 16 (10.4)        | 24 (15.7)    | 40 (13.0)    |
| Unknown            | 0                | 0            | 0            |
| R-ISS stage at study entry, alternative allocation, n (%) |                |              |              |
| Stage I            | 31 (20.1)        | 20 (13.1)    | 51 (16.6)    |
| Stage II           | 91 (69.1)        | 91 (69.5)    | 182 (69.3)   |
| Stage III          | 16 (10.4)        | 24 (15.7)    | 40 (13.0)    |
| Unclassified       | 16 (10.4)        | 18 (11.8)    | 34 (11.1)    |

Abbreviations: d, dexamethasone; Isa, isatuximab; P, pomalidomide; R-ISS, revised international staging system.

dexamethasone in all R-ISS stage subgroups, independently of the R-ISS allocation method used.

Phase 3 trials studying patients with relapsed/refractory multiple myeloma since the R-ISS was developed [2] started reporting survival by R-ISS stages I–III subgroups if high-risk cytogenetics data were available. However, these results are not calculated for the R-ISS unclassified subgroup. For example, in APOLO, the Phase 3 study of daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone, the median progression-free survival for R-ISS stage I was not estimable in the daratumumab arm versus 10.4 months in the control arm, with a hazard ratio (95% confidence interval) of 0.51 (0.24–1.10). The median progression-free survival for R-ISS stages II and III were 12.3 months and 2.8 months in the daratumumab arm versus 6.5 and 3.4 months in the control arm, with hazard ratios (95% confidence intervals) of 0.58 (0.39–0.85) and 1.38 (0.62–3.11), respectively [3].

It is important to note that with the original R-ISS allocation method used in the ICARIA-MM study, patients with R-ISS stage III were not inappropriately allocated to either stage II or stage I. Additionally, the number of patients in each unclassifiable cohort in the alternative R-ISS allocation approach, that is, n = 16 for isatuximab plus pomalidomide and dexamethasone and n = 18 for the pomalidomide and dexamethasone, is low. Assuming that a truly random population of patients is part of these cohorts, it is also likely that only a significant randomization error could produce a real difference in outcome, such as having all patients in stage I in one cohort and stage III in another. Since this is an unlikely event, the alternative R-ISS allocation approach then reflects the whole population regardless of R-ISS stage. Because the conclusion of the trial is that all stages improve outcomes, then the whole population should equally do so. Although the original R-ISS allocation method used in ICARIA-MM did not ultimately change the interpretation of the results, in studies where the missing data are larger than it was in ICARIA-MM, it might be important to avoid using the original R-ISS allocation approach described in this letter. Finally, the conclusions of ICARIA-MM results did not change, supporting the
use of these different methodologies and the data derived as part of the broader conclusions from this Phase 3, approval-finding study [4].

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CONFLICT OF INTEREST
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AUTHOR CONTRIBUTIONS
Paul G. Richardson and Aurore Perrot were coprimary investigators of the ICARIA-MM study. Hiroyuki Takamatsu contributed to the analysis plan, and dataset specifications. Patient-level data will be anonymised, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi’s data-sharing criteria, eligible studies, and process for requesting access are at: https://www.clinicalstudydatarequest.com.

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