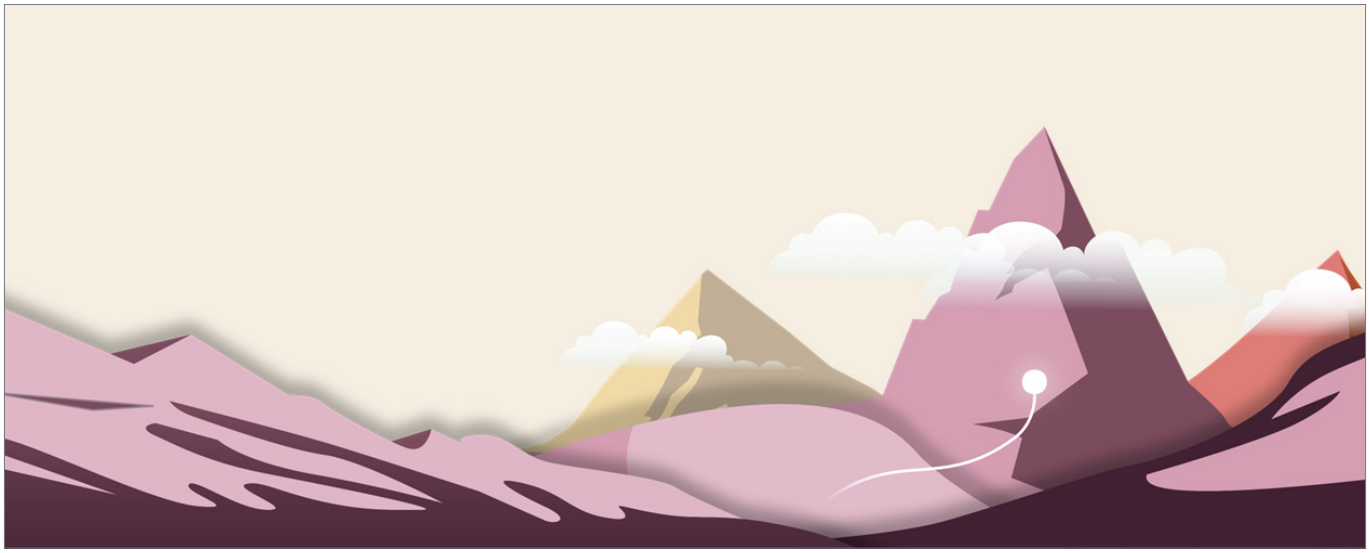
A VOYAGE OF DISCOVERY: EXPLORING THE LATEST FINDINGS ON 1Q21+

Highlights from a symposium sponsored by Sanofi presented during the 4th European Myeloma Network Meeting, where faculty explored data and controversies surrounding 1q21+ in multiple myeloma



Introduction

Aberrations in region 2, band 1 of the long arm of chromosome 1 (1q21+ or 1q+) are among the most common cytogenetic abnormalities (CAs) in multiple myeloma (MM).[1] Three copies of chromosome 1q is classified as gain(1q), while four or more is classified as amplification, or amp(1q).[1,2] The prevalence of 1q+ is ~40% in patients with newly diagnosed MM (NDMM) and up to 80% in relapsed/refractory MM (RRMM).[2,3] 1q+ is associated with poor prognosis,[2,4] and outcomes appear to worsen with increasing 1q copy number.[1]

However, some questions around 1q+ remain unresolved, including whether it is an independent indicator of high risk, and how it should impact clinical practice. Here we present a summary of presentations from a Sanofi-sponsored symposium held during the 4th European Myeloma Network Meeting, where the faculty addressed these issues.

Evidence that 1q+ is a high-risk feature in MM

1q+ confers poorer outcomes

Retrospective analysis of patients with NDMM (n=1376) showed that 1q+ has a similar impact on disease progression to other high-risk markers, including immunoglobulin heavy chain gene translocation, del(17p), higher International Staging System (ISS) stage and age ≥70 years.[5] A similar impact to known high-risk CAs (HRCAs) on overall survival (OS) and progression-free survival (PFS) was also demonstrated in a large meta-analysis of 7072 patients with NDMM.[6] Furthermore, the impact of 1q+ on survival has been reported across the MM continuum, regardless of induction regimen or transplant status.[3,7,8]

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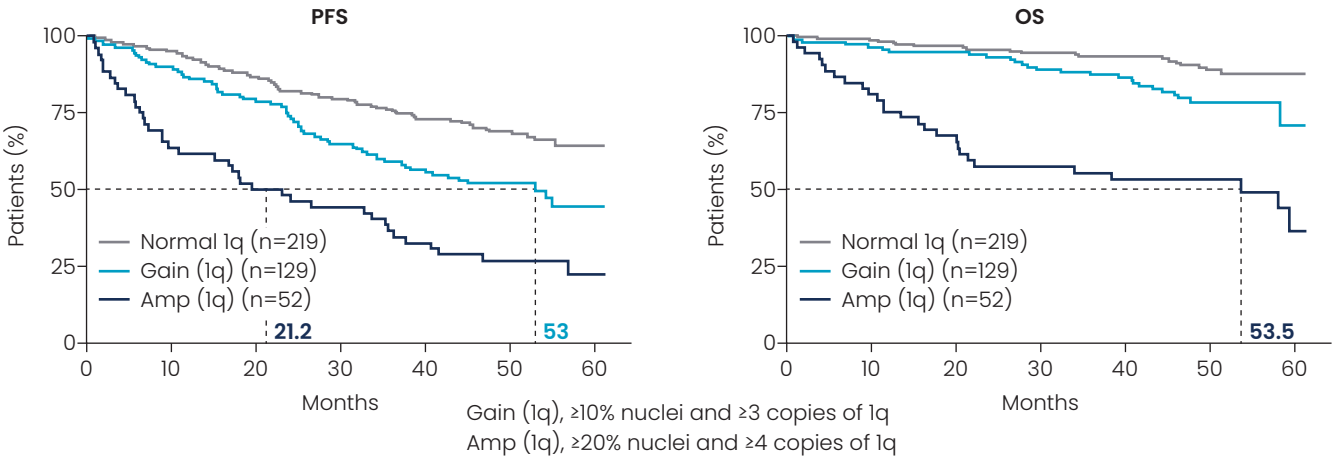
Figure 1: Survival analysis according to 1q+ status of transplant-eligible patients with NDMM treated with KCd or KRd in the FORTE trial (n=474)[9]



C, cyclophosphamide; d, dexamethasone; K, carfilzomib; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; R, lenalidomide

Additional copies of 1q indicate a worse prognosis

In the open-label, phase 2 FORTE trial evaluating transplant-eligible patients with NDMM (n=474) with the regimens of carfilzomib/cyclophosphamide/dexamethasone (KCd) vs carfilzomib/lenalidomide/dexamethasone (KRd), progressively poorer outcomes as 1q copy number increased were observed despite use of these new drug combinations.[9] PFS was shorter with gain(1q) compared with normal 1q (HR 1.65; P=0.005) and in those with amp(1q) vs gain(1q) (HR 1.90; P=0.002), while OS was significantly worse with amp(1q)[9] (**Figure 1**). Among patients who reached minimal residual disease (MRD) negativity (n=257), those with amp(1q) were more likely to lose negative status, with 4-year cumulative incidence of loss of 63%, 49% and 32% for amp(1q), gain(1q) and normal 1q, respectively.[10]

1q+ often co-occurs with other HRCAs

Gain(1q) often coexists with t(4;14), t(14;16), del(1p) and del(17p).[7] A retrospective study of 1376 patients with NDMM reported that t(4;14) and t(14;16) were significantly more frequent in patients with 1q+ (P<0.001).[5] A similar retrospective chart analysis of 201 patients with NDMM in the US receiving bortezomib (V) plus Rd induction therapy who had 1q+ co-occurring with any HRCA had median PFS of 25.1 months (95% CI, 12.0–32.6), which was significantly worse than high-risk patients without 1q+ (P=0.02).[11] This study further suggested that additional copies of 1q may indicate worse prognosis even in the absence of other HRCAs since patients with isolated 1q+ had poorer PFS than standard-risk patients and this was more pronounced in patients with amp(1q).[11]

Incorporating 1q+ into staging systems improves prognostic accuracy

The R-ISS risk stratification system incorporates HRCAs, but not 1q+.[4,12] However, including 1q+ in staging may more accurately predict clinical outcomes.[6,13] Gain(1q) and amp(1q) were independent prognostic factors in a meta-analysis of 2,596 patients with NDMM and could refine risk prediction.[14] Incorporating gain(1q) into 'R-ISS-1q' staging led to significant upstaging (stage I to II: 28%; stage II to III: 7.5%), with nearly identical outcome discrimination between groups compared with R-ISS staging.

Other novel staging systems incorporating 1q+ include The Mayo Additive Staging System (MASS)[13] and the second revision of the R-ISS (R2-ISS).[6] MASS identified three groups of patients with significantly different PFS and OS (P<0.001),[13] while R2-ISS was particularly useful for stratifying patients with intermediate-risk NDMM and revealed significantly different PFS and OS for each of four stages (P<0.0001).

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Remaining controversies around 1q+ as an independent risk predictor

The importance of 1q copy number is unclear

A retrospective chart analysis of patients with NDMM treated with VRd showed similar PFS for patients with isolated gain(1q) and those with standard risk without 1q+ (74.5 vs 65.0 months, respectively), while patients with isolated amp(1q) had significantly lower PFS at 34.7 months,[11] suggesting the increased risk associated with 1q+ is driven by amp(1q). Similarly, the FORTE trial OS analysis showed that while outcomes were significantly worse with amp(1q), OS may be similar for patients with and without gain(1q) (**Figure 1**).[9]

1q+ may require additional high-risk features to confer a poor prognosis

While some data suggest isolated 1q+ may impact outcomes,[11] a large, retrospective study in 565 patients with NDMM found no difference in PFS when comparing patients with isolated 1q+ and those with standard risk (52.0 vs 52.8 months; P=0.810).[15] However, 1q+ is significantly associated with high-risk disease characteristics, including anaemia, thrombocytopenia, hypercalcaemia, greater age, and ISS stage III,[5] suggesting that its prognostic impact may be attributable to these associated high-risk features. Among patients with symptomatic MM (n=912), amp(1q) had the greatest impact on R-ISS stage III patients (OS of only 16 months compared with 46 months for those without 1q+; P<0.001), with little impact on stage I patients.[16] Other high-risk features, including high levels of circulating tumour cells (CTC), may also be important when associated with 1q+. In the FORTE trial, the 4-year cumulative incidence of MRD negativity loss was 69% for patients with high CTC/1q+, 52% for high CTC/normal 1q, and 41% for low CTC/1q+.[10]

Translating evidence to the clinic

Uncertainties remain over the clinical utility of 1q+ status in MM. While testing for HRCAs is standard,[4] guidelines are inconsistent on including 1q+ in definitions of high risk and recommendations for testing. ESMO,[17] NCCN,[18] and Mayo Stratification for Myeloma and Risk-Adapted Therapy[19] guidelines suggest inclusion of 1q+ in testing, while the International Myeloma Working Group4 recommends this only in a clinical trial context.

Appropriate cut-offs for the proportion of clones harbouring unique HRCAs are needed to identify patients with poor prognoses.[20] A good threshold for 1q+ may be 20%,[20,21] however, guidelines currently do not recommend a specific value. Some clinical trials have used inconsistent cut-off points (3–60%),[22-24] while others did not report a value.[25] More commonly, trials focus only on standard HRCAs and do not consider 1q+. Alignment on 1q+ testing is needed to enable consistent reporting and interpretation of data.

Clinical support for treating 1q+ in RRMM

Few phase 3 trials have reported 1q+ data in the RRMM setting; two investigated novel combination therapies with isatuximab[26] and a third examined an ixazomib combination.[22]

ICARIA-MM, an open-label phase 3 study, compared isatuximab plus pomalidomide and dexamethasone (Pd) with Pd alone in patients with RRMM (n=307) demonstrated an impressive, statistically significant PFS benefit and clinically meaningful improvement in OS with Isa-Pd versus Pd.[27] Post-hoc analysis showed the addition of isatuximab to Pd (Isa-Pd) improved PFS and OS for patients with 1q+ compared with Pd alone[26] (**Figure 2**).[27] Additionally, the Isa-Pd arm showed a similar PFS efficacy regardless of the presence of 1q+ and of other HRCAs, suggesting that the addition of isatuximab to Pd could overcome the negative prognosis associated with 1q+ in patients with RRMM.[26] Safety was similar in patients with and without 1q+ and was consistent with the overall treatment population. The most frequent treatment-emergent adverse events (TEAEs) that were more common for Isa-Pd vs Pd were infusion reactions, upper respiratory tract infections, and diarrhoea.[27]

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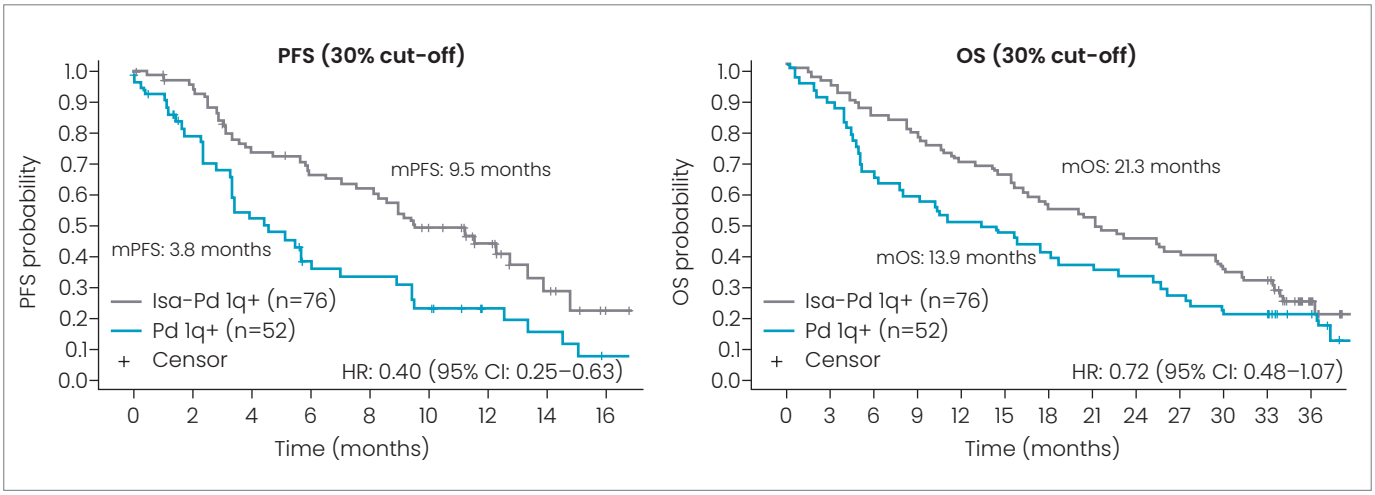
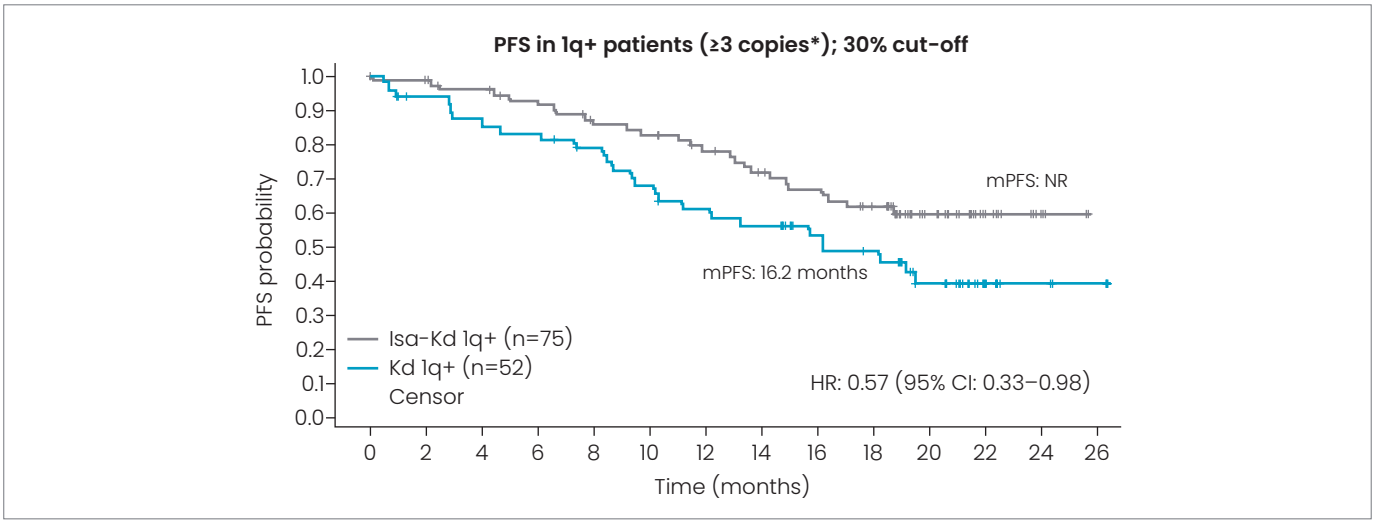
Figure 2: Survival analyses according to 1q+ status in patients with RRMM treated with isatuximab-Pd or Pd alone in the ICARIA-MM trial[26]



CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; m, median; P, pomalidomide; PFS, progression-free survival; OS, overall survival; RRMM, relapsed/refractory multiple myeloma

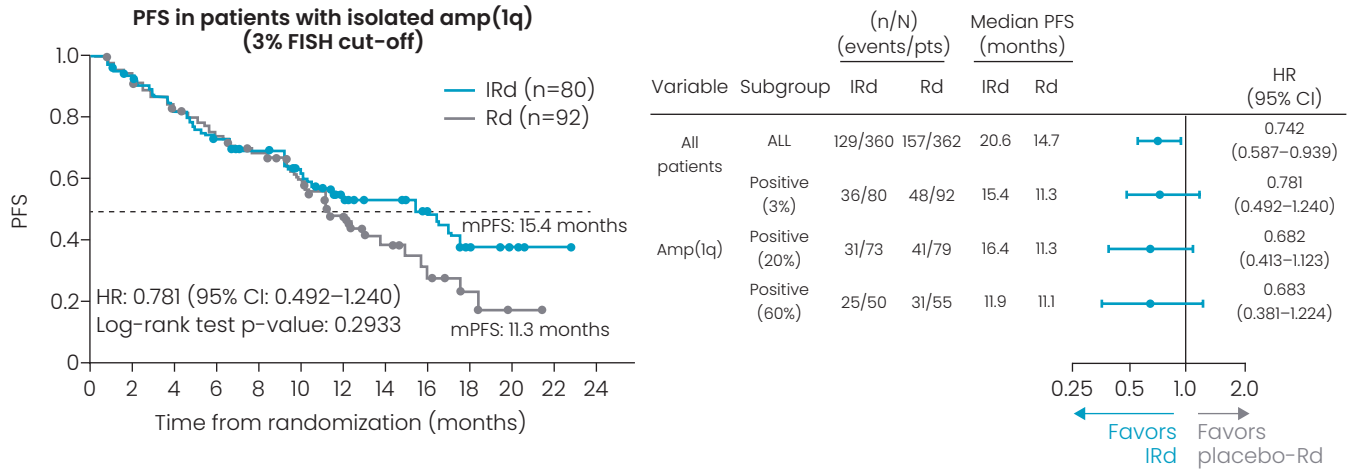
Figure 3: PFS according to 1q+ status in patients with RRMM treated with isatuximab-Kd or Kd alone in the IKEMA trial[28]



**With or without other high-risk cytogenetic abnormalities*
CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; K, carfilzomib; m, median; NR, not reached; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma

IKEMA, an open-label phase 3 trial, evaluated isatuximab plus Kd (Isa-Kd) compared with Kd alone in patients with RRMM (n=302) and revealed an unprecedented median PFS of 35.7 months with Isa-Kd, after 44 months of follow up.[28] Analysis of patients with 1q+ showed an improved PFS for patients receiving the isatuximab combination, regardless of the presence of other HRCAs (**Figure 3**).[26] Furthermore, Isa-Kd showed similar survival efficacy regardless of the presence of 1q+, with PFS benefit again seen across subgroups, suggesting that Isa-Kd may reduce the prognostic burden of 1q+. Similar safety findings to the overall population in both patient groups were observed. The most frequent TEAEs in the isatuximab group with higher incidence than the Kd group were infusion reactions, hypertension, diarrhoea and upper respiratory tract infection.[28]

Figure 4: PFS in patients with isolated amp(1q) with 3%, 20%, and 60% FISH cut-off[22]



CI, confidence interval; d, dexamethasone; FISH, fluorescence in situ hybridization; HR, hazard ratio; I, ixazomib; m, median; PFS, progression-free survival; pts, patients; R, lenalidomide

TOURMALINE-MM1, a double-blind phase 3 trial, compared ixazomib plus Rd with Rd alone in patients with RRMM (n=722), reporting significant survival benefit with the addition of ixazomib.[29] In a pre-specified analysis of patients with amp(1q) revealed a numerical improvement in PFS with ixazomib-Rd compared with Rd across 3%, 20% and 60% cut-off values, (**Figure 4**) suggesting the potential utility of ixazomib in this patient group.[22] Safety was similar in patients with and without amp(1q); common adverse events that were higher in the ixazomib group included thrombocytopaenia and rash.[22]

Conclusion

Evidence is accumulating on the importance of 1q+ as a marker of high risk disease and poorer outcomes in MM. Although some guidelines recognise 1q+ and some trials have reported outcomes based on 1q+ status, work is needed to eliminate remaining uncertainties and to standardise recommendations on testing and subsequent staging of patients with 1q+.

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