

# The numerous facets of 1q21<sup>+</sup> in multiple myeloma: Pathogenesis, clinicopathological features, prognosis and clinical progress (Review)

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**Abstract.** Multiple myeloma (MM) is a malignant neoplasm characterized by the clonal proliferation of abnormal plasma cells (PCs) in the bone marrow and recurrent cytogenetic abnormalities. The incidence of MM worldwide is on the rise. 1q21<sup>+</sup> has been found in ~30-40% of newly diagnosed MM (NDMM) patients. 1q21<sup>+</sup> is associated with the pathophysiological mechanisms of disease progression and drug resistance in MM. In the present review, the pathogenesis and clinicopathological features of MM patients with 1q21<sup>+</sup> were studied, the key data of 1q21<sup>+</sup> on the prognosis of MM patients were summarized, and the clinical treatment significance of MM patients with 1q21<sup>+</sup> was clarified, in order to provide reference for clinicians to develop treatment strategies targeting 1q21<sup>+</sup>.

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## 1. Introduction

Multiple myeloma (MM) is a neoplasm malignant characterized by the clonal proliferation of abnormal plasma cells (PCs) in the bone marrow and recurrent cytogenetic abnormalities that

can lead to bone marrow failure, bone destruction, hypercalcemia, anaemia, infection, kidney dysfunction and neurologic symptoms (1,2). The incidence of MM worldwide is on the rise. In 2020, the age-standardized incidence rate of MM was 1.78 per 100,000 people globally, and the age-standardized mortality rate was 1.14 per 100,000 people globally (3-5). The occurrence, progression, treatment, resistance and prognosis of MM are all associated with cytogenetic abnormalities (6-8). Previous studies revealed that cytogenetic abnormalities, such as t(4;14), t(14;16), t(14;20), 1q21<sup>+</sup>, del(1p), and del(17p), can be used as predictors of poor prognosis (9-12). Among them, 1q21<sup>+</sup> is one of the most common chromosomal abnormalities in MM, including 1q21 gain (three copies) and 1q21 amplification ( $\geq 4$  copies) (13). 1q21<sup>+</sup> has been found in ~30-40% of patients with newly diagnosed MM (NDMM) (14,15).

1q21<sup>+</sup> is associated with the pathophysiological mechanisms of disease progression and drug resistance in MM (16,17). Besides, co-existence of certain high-risk cytogenetic abnormalities is common in some patients with MM, and further worsens the prognosis for 1q21<sup>+</sup> patients (18,19). Therefore, both the International Myeloma Working Group (IMWG) and Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) 3.0 have taken 1q21<sup>+</sup> as an important reference factor for risk stratification (20-22). In recent years, the introduction of autologous hematopoietic stem cell transplantation (ASCT), immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and an anti-CD38 monoclonal antibody have greatly improved the outcomes of patients with MM (23-26). However, the overall survival (OS) of patients with MM and 1q21<sup>+</sup> remains to be improved (27,28). In the present review, the pathogenesis and clinicopathological features of MM patients with 1q21<sup>+</sup> were reviewed, the key data of 1q21<sup>+</sup> on the prognosis of patients with MM were summarized and the clinical treatment significance of MM patients with 1q21<sup>+</sup> were clarified, for the purpose of providing reference for clinicians to develop treatment strategies targeting 1q21<sup>+</sup>.

## 2. Pathogenesis and clinicopathological features of 1q21<sup>+</sup> in patients with MM

The evolution of MM is a complex and progressive process in which initial carcinogenic events, namely primary

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immunoglobulin heavy chain (IGH) translocations and hyper-diploid karyotypes, have occurred in the early stages of monoclonal gammopathy of uncertain significance and smoldering MM, followed by disease progression to symptomatic MM (29,30) (Fig. 1). Chromosome arm 1q21<sup>+</sup> is a secondary genomic event occurring in patients with MM (16). 1q21<sup>+</sup> occurs in subclones of cells with primary translocations, manifesting as chromosome 1q duplications, unbalanced whole-arm translocations of chromosome 1q, or jumping translocations detected by G-banding (30-33). Among them, jumping translocations involve unbalanced translocations between non-homologous chromosomes, caused by the exchange of the pericentromeric region of 1q with other chromosomal sites, which involves the de-condensation of pericentromeric chromatin of 1q and the intranuclear replication of 1q, and the subsequent fusion of the acquired region with the centromere or telomere end of another chromosome (34,35). The jumping translocation can increase the copy number of 1q, which may be the potential mechanism of 1q21<sup>+</sup> (30-36).

The genetic instability of 1q pericentromeric region of 1q12 and its neighbor 1q21, as well as the overexpression of certain genes that may be present during 1q21 amplification, are closely associated with disease progression in MM (14,36). Previous studies have found proliferation and dysregulation of G1/S cell cycle checkpoints in most MM cells with 1q21<sup>+</sup> (30). 1q21<sup>+</sup> can upregulate the activity of cyclin D by driving the oncogene CDC28 protein kinase regulatory subunit 1B (CKS1B), to further drive the proliferation of downstream cells and promote the circulation of PCs (37-39). 1q21<sup>+</sup> is a copy number alteration that is most relevant to transcriptome, and corresponds to genome-wide transcriptional regulation, rather than being restricted to this genomic region. It is associated with the upregulation of cyclin D2 (CCND2) and other oncogene-driven proliferation programs, such as PDL1 downregulation and Slam family member 7 (SLAMF7), G protein-coupled receptor class c group 5-member D (GPC5D), and apoptosis regulator BCL2 family member (MCL1) upregulation predicted by 1q21 gain or amplification (40). Interleukin-6 receptor (IL6R) and ADAR1 (an RNA editing enzyme in 1q21 region near IL6R) are critical genes located within the minimally amplified 1q21 region. The 1q21 state is closely related to the levels of IL6R and ADAR1 (41,42). IL6R and ADAR1 collaborate to induce a hyper-activation of the STAT3 pathway, and high levels of IL6 in MM cells result in sustained activation of the STAT3 pathway (43-45). The amplification of 1q21 leads to elevated expression of IL6R and ADAR1. High IL6R confers hypersensitivity to IL6 stimulation, leading to constitutive activation of the STAT3 pathway. However, high expression of ADAR1-P150 results in a hyper-activation of the STAT3 pathway, and ultimately increases the survival rate of MM cells (42). In addition, the expression of some genes (EANP32E, ARNT, BCL9, 2ILF2, MUC1, MCL1, NEK2, PSMD4, PDZK1 and SETDB1) is associated with 1q21<sup>+</sup>, promoting cell proliferation (31,46-55).

In terms of epigenetic regulation, copy number gains of 1q21 originate in part by the hypomethylation of 1q12 pericentromeric heterochromatin (56). A total of 25% of the genes associated with MM-specific methylated regions lie within the 1q21.1 region. The demethylation of Family with sequence similarity 72 (FAM72) gene in the 1q21 region increases the

expression of FAM72, while FAM72 promotes MM cell proliferation through the forkhead box M1 (FOXO1) transcription factor signaling pathway (57). Moreover, the transcription factor PBX homeobox (PBX)1 is ectopically expressed by genetic amplification and epigenetic activation of its own preserved regulatory domain. By binding to reprogrammed super-enhancers, PBX3 directly regulates critical oncogenic pathways and FOXO1-dependent transcription programs to activate MM cell proliferation (58).

In addition to gene drive, changes in the bone marrow microenvironment further contribute to the formation of a high-risk disease state with 1q21<sup>+</sup> (30). Complement factor C1q, as an activator protein in the classical activation pathway, participates in the recognition stage of classical activation pathway and has the ability to regulate various immune cell responses (59). C1q has two classical cell surface receptors (C1qRs): cC1qR binds to the collagen 'stalks' tail, whereas gC1qR binds to the globular 'heads' (60). GC1qR promotes MM cell line survival by suppressing the MM-inhibiting role of C1q and contributing to the stabilization of the CKS1BmRNA through insulin-like growth factor 2 mRNA binding protein 3 (IGF2BP3) (61).

In patients with NDMM, the presence of 1q21<sup>+</sup> is likely to be associated with other cytogenetic abnormalities (Table I). Previous studies revealed that the presence of 1q21<sup>+</sup> was highly related to the co-existence of other high-risk cytogenetic abnormalities, such as t(4;14), t(14;16) and del(17p) (62,63). In addition, 1q21<sup>+</sup> is also associated with some markers of disease burdens. Previous studies have shown that 1q21<sup>+</sup> was significantly associated with the presence of  $\beta$ 2-microglobulin >5.5 mg/l, haemoglobin <10 g/dl, platelet count <100 K/ $\mu$ l, glomerular filtration rate <30 ml/min/1.73 m<sup>2</sup>, lactate dehydrogenase (LDH) level >300 U/l, and plasma creatinine level (18,19,64-68). A retrospective study suggested that patients with 1q21<sup>+</sup> were more prone to experience anaemia, hypoalbuminemia, renal insufficiency, high LDH and a high proportion of R-ISS-III (69). Furthermore, they were more likely to be accompanied by del(13q14), t(4;14), and del(1p) (69).

Patients with 1q21<sup>+</sup> present with a more aggressive clinical course. Osteopathy is one of the characteristic clinical manifestations of MM. Osteopathy, such as myeloma, is present in >80% of patients with MM at diagnosis, which ranges from osteoporosis to typical lytic lesions, and then to advanced lesions such as structural bone defects or pathological fractures (70). In a retrospective study of 308 patients with MM, the presence of 1q21 gain was associated with a higher level of thymidine kinase (TK) (P=0.026) and a lower level of amino-terminal propeptide of type I procollagen (PINP) (P=0.030) (71). Among them, TK is a cell proliferation marker. Elevated TK1 serum levels may correlate with high activity and high aggressiveness of MM cells, while PINP is closely related to various bone metabolism disorders, tumor bone metastasis and MM progression (72). Similarly, in a prospective study of 64 patients with MM, PINP levels differed dependent on the disease stage, with median concentrations decreasing in advanced stages of patients with MM (73). The standard deviation scores values of PINP were significantly lower in MM patients with advanced bone disease. A significantly lower concentration of PINP was found to be typical for patients with numerous (>3) bone lytic lesions (73). In addition,

Table I. Clinicopathological features of patients with 1q21+ multiple myeloma (18,19,62-69).

Category	Classification	Content
Cytogenetic abnormalities coexisting with 1q21+	IgH rearrangement	t(4;14), t(14;16)
Markers associated with 1q21+	Variation of chromosome arm	del(13q), del(1p), del(17p)
	Markers of disease burden	$\beta 2$ -microglobulin >5.5 mg/l, hemoglobin <10 g/dl, platelet count <100 K/ $\mu$ l, glomerular filtration rate <30 ml/min/1.73 m <sup>2</sup> , lactate dehydrogenase >300 U/l, plasma creatinine
	Markers of cell proliferation	TK1 (positively correlated)
	Markers of bone formation	PINP (negative correlation)

TK1, thymidine kinase 1; PINP, amino-terminal propeptide of type I procollagen.

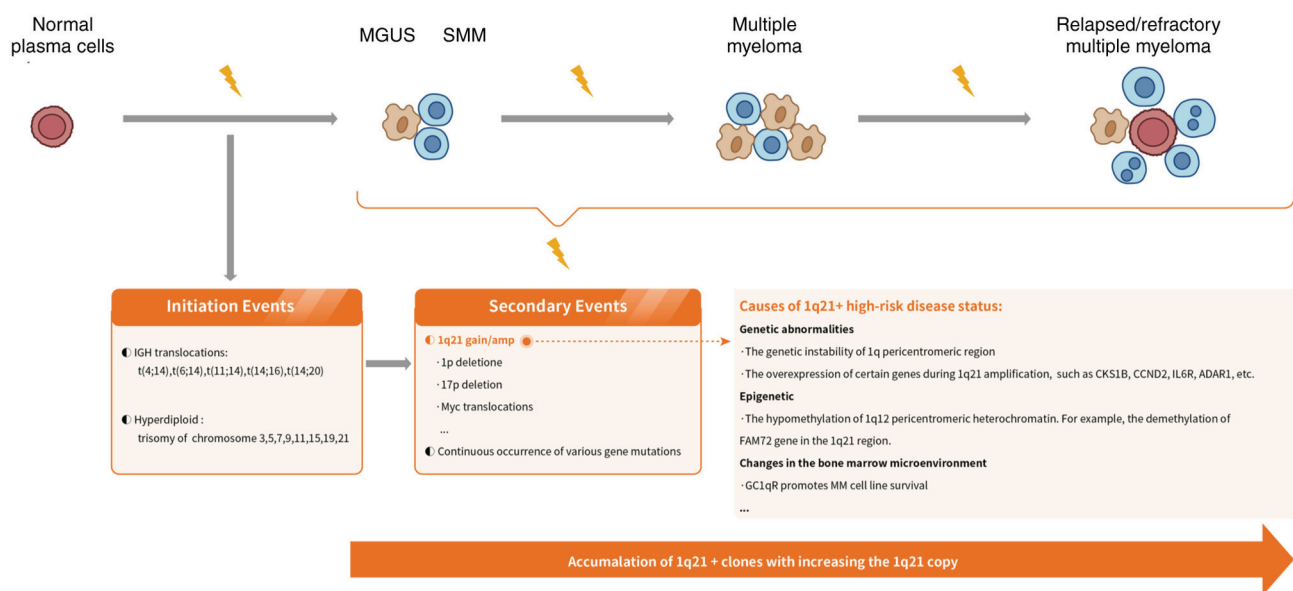


Figure 1. The role of 1q21+ and other cytogenetic abnormalities in multiple myeloma initiation and progression and the causes of 1q21+ high-risk disease status (modified from 154,155). Amp, amplification; IGH, immunoglobulin heavy chain; MGUS, monoclonal gammopathy of undetermined significance; SMM, smouldering myeloma; CKS1B, CDC28 protein kinase regulatory subunit 1B; CCND2, cyclin D2; IL6R, interleukin-6 receptor; ADAR1, an RNA editing enzyme in 1q21 region near IL6R; FAM72, Family with sequence similarity 72; C1qR, a receptor for globular heads of C1q.

PINP inversely correlated with LDH. These studies suggested a possible impact of gain 1q21 on advanced bone disease, thus with possible impact on adverse prognosis of the patients with MM.

### 3. Impact of 1q21+ on prognosis

With the deepening understanding of MM, the influence or weight of various baseline risk factors in predicting the outcomes of patients with MM may change. Recently, two major prognostic scoring systems have been successively released; namely, the second revision of the International Staging System (R2-ISS) issued by the European Myeloma Network (EMN) and the Mayo Additive Staging System (MASS) developed by the Mayo Clinic based on single-center data (21,22). The R2-ISS stratifies patients with NDMM into the following risk groups: i) low (0), ii) low/intermediate (0.5-1), iii) intermediate/high (1.5-2.5) and iv) high (3-5) by assigning

different weight scores to the six included variables: ISS II, ISS III, del(17p), high LDH, t(4;14) and 1q<sup>+</sup> (22). The MASS includes IgH translocation, 1q<sup>+</sup>, chromosome 17 abnormality, ISS stage III, and elevated LDH as high risk (HR) factors. Patients with 0, 1, or  $\geq 2$  HR abnormalities are considered as stage I, II, or III, respectively (21). Both staging systems take 1q<sup>+</sup> as a HR factor and use it as a basis for stratification, which has been supported by several recent studies (68,74). A meta-analysis involving 2,596 patients with MM found that 1q gain was associated with inferior survival in NDMM, irrespective of current standard therapies, and should be considered as an independent risk factor (68). Similarly, in a post-hoc analysis of another clinical study, 1q gain at relapse was associated with shorter OS, independent of other risk markers or time of relapse (74). This means that 1q gain can be an independent poor prognostic factor for both NDMM and relapsed MM. A retrospective study of 248 Chinese patients with NDMM detected that 1q21+ was an independent poor

Table II. Prognostic effects of 1q21\*.

Feature	Prognosis	Number of patients	Proportion of patients with 1q21*, %	Detection threshold for 1q21+ by FISH, %	PFS	(Refs.)
1q21+ copy number $\geq 3$	No significant effect	912	• 3 copies, 16.4 • $\geq 4$ copies, 10.9	20	3 vs. $\geq 4$ copies: P>0.05	(63)
		290	Thalidomide group, 48.1 • 3 copies, 33.6 • $\geq 4$ copies, 15.2	20	3 vs. 4 vs. $\geq 4$ copies 14.0 (95%CI, 8.07-19.93) vs. 14.0 (95%CI, 5.47-22.53) vs. 10.0 (95%CI, 4.12-15.88) months P>0.05	(86)
		667	Bortezomib group, 47.5 • 3 copies, 27.4 • $\geq 4$ copies, 22.3	20	3 vs. $\geq 4$ copies 23.2 (18.7-27.7) vs. 22.0 (17.1-26.9) months P>0.05	(87)
			• 3 copies, 28.2 • $\geq 4$ copies, 15.9			
	Worse prognosis	1,068	• 3 copies, 19.5 • $\geq 4$ copies, 12.1	5	3 vs. $\geq 4$ copies: P>0.05	(88)
		248	• 3 copies, 38.7 • $\geq 4$ copies, 13.3	-	3 vs. $\geq 4$ copies: not reached vs. 24 months, P=0.0403	(28)
		201	3 copies, 25.9 $\geq 4$ copies, 12.9	20	3 vs. $\geq 4$ copies: 74.5 (55.9-78.8) vs. 34.7 (15.6-61.1) months	(82)
		161	3 copies, 36 $\geq 4$ copies, 23.6	5	3 vs. $\geq 4$ copies: 26.0 vs. 15.1 months	(89)
1q21+ co-existence of other high-risk cytogenetic abnormalities		194	-	20	3 vs. $\geq 4$ copies: 50 vs. 26.0 months	(90)
		934	53.1	5.5	t(4;14) + 1q21 vs. 1q21: P>0.05	(63)
	No significant effect	667	100	20	t(4;14) + 1q21 vs. 1q21: P=0.214	(87)
		201	46.7	20	t(4;14) + 1q21 vs. 1q21: HR 4.18, P=0.008	(82)
	Worse prognosis	213	100	7.9	t(4;14) + 1q21 vs. 1q21: HR, 3.00; P=0.047,	(92)

Table II. Continued.

Feature	Prognosis	Number of patients	Proportion of patients with 1q21 <sup>+</sup> , %	Detection threshold for 1q21 <sup>+</sup> by FISH, %	PFS	(Refs.)
	t(14;16)	934	53.1	5.5	t(14;16) + 1q21 vs. 1q21 P<0.0001	(63)
		5,141	-	-	t(14;16) + 1q21 vs. 1q21 20.5 vs. 31.8 months, P=0.003	(91)
		201	46.7	20	t(14;16) + 1q21 vs. 1q21: HR, 2.80; P=0.036	(82)
	del(17p)	934	53.1	5.5	del(17p) + 1q21 vs. 1q21: P=0.0221	(63)
		213	100	7.9	del(17p) + 1q21 vs. 1q21: HR, 2.33, P=0.023	(92)
		201	46.7	20	del(17p) + 1q21 vs. 1q21: HR, 2.5; P=0.01	(82)

FISH, fluorescence *in situ* hybridization; CI, confidence interval; HR, hazard ratio.

prognostic factor in patients with NDMM. According to the mSMART 3.0 stages, double-hit and triple-hit groups had the worst prognosis, with a median progression-free survival (PFS) of 22 months and a median OS of 32 months, respectively (69). Another retrospective study of 505 Chinese NDMM patients (47% with 1q21<sup>+</sup>) confirmed the prognostic stratification value of R2-ISS staging system in Chinese patients with NDMM and evaluated the impact of 1q21<sup>+</sup> on survival. The median PFS and OS of patients carrying the 1q21<sup>+</sup> mutation were 33.3 and 62.6 months, respectively, significantly shorter than those without 1q21 abnormality [PFS, 50.8 months; OS, not reached (NR); P<0.001] (75).

1q21 gain has long been considered as an early driver event, and 1q21 amplification a progression-related late event, both of which have negative prognostic implications, although the prognostic implications of increased copy number of 1q21<sup>+</sup> are still controversial (Table II) (76-85). In a cohort study of 912 symptomatic patients with MM, patients with 1q21<sup>+</sup> showed inferior PFS (34 vs. 20 months, P<0.001) and OS (75 vs. 44 months, P<0.001) compared with those without 1q21<sup>+</sup>, but increased copies of 1q21<sup>+</sup> had no effect on prognosis (18). Increasing evidence has identified that patients with MM and three copies of 1q21 had comparable survival with patients with more than three copies. A cohort study demonstrated that in 290 cases of patients with NDMM treated with bortezomib-based therapy and 1q21 copy number ≥3 significantly worse outcomes were observed; and there was no statistically significant difference between median PFS and OS in patients who had three, four, or at least five copies of 1q21 (86). This conclusion was confirmed in another study with an enlarged sample (667 patients) and extended follow-up (87). A real-world study which included 1,068 diagnosed MM Chinese patients reported that the variation in copy number of 1q<sup>+</sup> (copy number <3) had no significant impact on the survival of MM patients with 1q abnormalities (88). Similarly, in a meta-analysis, there was no significant difference in the prognosis between 1q21 gain and 1q21 amplification for patients with thalidomide and those with bortezomib, both being associated with adverse outcome (68). There are also differences with the aforementioned views. Several studies have revealed that the prognosis of patients with MM is worse when 1q21 copy number ≥4; for instance, You *et al* (28) revealed that 1q21 amplification had worse PFS than 1q21 gain (24 months vs. not reached, P=0.0403). Neben *et al* (77) discovered that a 1q21 copy number of three has a marginal negative effect, and having more than three copies significantly reduces PFS and OS. Similarly, Schmidt *et al* (82) and Gao *et al* (89) both revealed that copy number of 1q21 ≥4 led to a poor prognosis. In a recent retrospective study of 794 patients with MM, the median PFS times of normal copy number of 1q, 1q gain and 1q amplification were 49, 50 and 26 months, respectively (P=0.268), and the median OS times were NR, NR and 41 months, respectively (P=0.001), suggesting that 1q21 amplification had a greater negative impact on prognosis than 1q21 gain (90). This might be related to the dose response of genes in the chromosome 1q region.

The coexistence of 1q21<sup>+</sup> with other high-risk cytogenetic abnormalities often affects the prognosis of patients (Table II). A retrospective analysis included 201 patients with NDMM (including 107 patients with 1q21<sup>+</sup>) who received induction



with lenalidomide, bortezomib and dexamethasone (RVD). In subgroup analyses, patients with co-occurring 1q<sup>+</sup> and t(4;14), t(14;16) or del(17p) had a median PFS of 25.1 months (95% CI, 12.0-32.6 months), significantly lower than patients with only t(4;14), t(14;16) and/or del(17p) ( $P=0.02$ ) (82). Another retrospective study of 934 patients with NDMM (53.1% of patients with 1q<sup>+</sup>), who received IMiDs or PIs, indicated that in 496 cases of patients with 1q<sup>+</sup>, 24.4% of the patients were accompanied by other high-risk cytogenetic abnormalities, such as del(17p), t(4;14) and t(14;16), and their PFS ( $P=0.0294$ ) and OS ( $P=0.0381$ ) were significantly worse than those of patients with 1q<sup>+</sup> only (63). Among them, patients with co-occurring 1q<sup>+</sup> and t(14;16) had the worst outcome, with significantly shorter PFS ( $P<0.0001$ ) and OS ( $P=0.0004$ ) (63). This is consistent with previous studies (82,91). Similar findings were also observed in patients with co-occurring 1q<sup>+</sup> and del(17p), with significantly shorter PFS ( $P=0.0221$ ) and OS ( $P=0.0046$ ) (63). However, co-occurrence of 1q21<sup>+</sup> and t(4;14) remains controversial. Schmidt *et al* (82) and Pasvolsky *et al* (92) found that co-occurrence of 1q21<sup>+</sup> and t(4;14) was associated with worse PFS. Yang *et al* (63) identified that t(4;14) had no significant impact on PFS and OS in patients with 1q<sup>+</sup>. A retrospective study of 667 patients with NDMM revealed that patients with 1q21 gain and t(4; 14) had a worse prognosis, but the incidence and prognostic impact of 1q21 gain does not rely on the highly concurrent t(4;14) (87). 1q21 gain was strongly associated with a shorter median PFS and OS in both t(4;14) negative and positive patients with MM. By contrast, t(4;14) did not retain prognostic value in the 1q21 gain subgroup (87). Furthermore, the detrimental prognostic effect of 1q21<sup>+</sup> was more profound in R-ISS-II and R-ISS-III patients. As testified by a cohort study, in R-ISS II patients, OS was significantly lower in those with 1q21<sup>+</sup> than in those without 1q21<sup>+</sup> (40.1 vs. 70.9 months,  $P=0.002$ ), while in R-ISS III patients, OS was worse in those with 1q21<sup>+</sup> than in those without 1q21<sup>+</sup> (16.6 months vs. 43 months,  $P=0.028$ ) (18).

#### 4. Treatment of MM patients with 1q21<sup>+</sup>

**ASCT.** Currently, different graded treatment strategies are adopted for MM in clinical practice. The treatment strategies for NDMM are determined by ASCT and risk stratification (93). ASCT uses a very large dose of chemoradiotherapy to clear MM cells, destroy the autoimmune system, and transfuse autologous hematopoietic stem cells to rebuild hematopoietic and immune function, so as to achieve the purpose of further eliminating MM cells (94-96). ASCT is the upfront choice for newly diagnosed patients with MM. If the patient is younger than 70 years old with favourable performance status, or older than 70 years old with favourable general performance status, ASCT should be the upfront choice after effective therapy (13,97). Previously, a real-world study of 1,068 Chinese patients with NDMM revealed that upfront ASCT could eliminate the adverse prognostic effect of 1q21 gain but not 1q21 amplification (98). Therefore, in clinical practice, ASCT is often combined with other medications as part of a normative overall treatment for NDMM patients (88,98-100). A recent retrospective study included patients with NDMM who received ASCT combined with VRD (V, bortezomib; R, lenalidomide; D, dexamethasone)

or VRD only for 8 cycles (69). The aforementioned study identified that the proportion of patients with 1q21<sup>+</sup> was 54.4% and they showed a poor prognosis with the VRD regimen. However, ASCT could overcome the adverse effects significantly, and it played an important role in the prognosis of patients with 1q21<sup>+</sup> ( $P<0.05$ ) (69). Similarly, in a retrospective study of 1,491 patients with NDMM (100 patients in the 1q+/1p group) who received induction with IMiD combined with PI or bortezomib-cyclophosphamide-dexamethasone, with a pretreatment regimen of Busulfan in combination with melphalan or melphalan only, and who received ASCT, a median OS was not reached in the 1q+/1p-group compared with 81.1 months in the control group (HR, 1.25; CI, 0.3-4.6;  $P=0.73$ ); the objective response rate (ORR) was 94% in both groups, and ASCT had a positive effect on ORR and OS compared with the historical control (98).

**Immunomodulatory agents/proteasome inhibitors.** NCCN guidelines state that VRD is recommended as a standard first-line therapy for patients with NDMM, regardless of suitability for transplantation (93,101,102). Thalidomide, lenalidomide and pomalidomide are all IMiDs. IMiDs exert their anti-myeloma activity mainly by binding cereblon (CRBN), the substrate receptor protein of the CRL4 E3 ubiquitin ligase (CRL4CRBN) complex, leading to rapid ubiquitination and degradation of two specific B-cell transcription factors, the Ikaros family of zinc-finger proteins Ikaros (IKZF1) and Aiolos (IKZF3) (103-105). Thus, the direct target of IMiDs is CRBN (106,107). IMiDs can directly eliminate MM cells, promote the apoptosis of neovascular cells and enhance the immune reaction of natural killer cells (108-110). PIs can covalently bind to the hydroxyl group of the N-terminal threonine of the proteasome and inhibit the normal degradation of intracellular proteins by the proteasome, resulting in myeloma cell cycle arrest and promoting MM cell apoptosis (111,112). The target of PI was the proteasome  $\beta 5$  subunit (113,114). Among them, bortezomib could reversibly inhibit the chymoprotease-like activity of proteasome  $\beta 5$  subunit (115). Carfilzomib inhibits chymotrypsin-like activity by irreversibly binding to the proteasome  $\beta 5$  subunit (116). Ixazomib preferentially binds to the 20S proteasome  $\beta 5$  subunit to inhibit chymotrypsin-like activity (114). A summary of studies on IMiDs and PIs in NDMM patients with 1q21<sup>+</sup> over the past 3 years is presented in Table III (81,117-121). In a previous study, patients with 1q21 gain receiving bortezomib-based treatment had significantly improved the OS and PFS when compared with non-bortezomib treatment (3-year PFS, 62.8 vs. 8.75%;  $P=0.0385$ ; 3-year OS, 82.3 vs. 18.8%;  $P=0.0154$ ) (81). In a cohort study, the combination of PIs and IMiDs produced improved outcomes in patients with 1q21<sup>+</sup>, but only partially alleviated the effects of 1q21<sup>+</sup> (18). However, An *et al* (86) discovered that 1q21 gain had no significant impact on the prognosis of thalidomide-treated patients and that 1q21 gain had a median PFS (22.4 months vs. 20.0 months;  $P=0.625$ ) and OS (30.0 vs. 22.0 months,  $P=0.355$ ) compared with patients without 1q21<sup>+</sup>. The prognosis was significantly worse in patients treated with bortezomib, compared with patients without 1q21, patients with 1q21 had significant shorter PFS (13.5 months vs. 43.0 months;  $P<0.001$ ) and OS (24.0 vs. 54.0 months,  $P<0.001$ ) (86). Similarly, in the

Table III. Summary of studies on immunomodulatory drugs and proteasome inhibitors in patients with newly diagnosed multiple myeloma and 1q21<sup>+</sup> over the past 3 years.

Drug	Treatment regimen	Number of patients	Proportion of patients with 1q21 <sup>+</sup> , %	Detection threshold for 1q21 <sup>+</sup> by FISH, %	CR	PFS	OS	(Refs.)
Bortezomib (VRD)	The bortezomib group is defined as patients receiving 4 cycles of BTD chemotherapy. The non-bortezomib group is defined as patients receiving a regimen free of bortezomib, including TCD, TD and VADT	63	46.0	-	Bortezomib group vs. non-bortezomib group: 57.14 vs. 21.43% (P=0.01)	Bortezomib group vs. non-bortezomib group in 3-year PFS: 62.8 vs. 8.75%; P=0.0385	Bortezomib group vs. non-bortezomib group in 3-year OS: 82.3 vs. 18.8%; P=0.0154	(81)
Carfilzomib triple combination therapy	KRD + ASCT: KRD X4 + ASCT + KRD X4, KRD12, KCD + ASCT: KCD X4+ ASCT+ KRD X4 <sup>a</sup>	474	45.0	-	Normal 1q group vs. 1q gain group vs. 1q amplification group: 52 vs. 50 vs. 38%	1q gain vs. normal 1q: HR 1.65, CI 1.14-2.37, P=0.007; 1q amplification vs. normal 1q: HR, 3.04 (CI, 1.99-4.65); P<0.001; 1q gain vs. normal 1q: HR, 1.84 (CI, 1.21-2.81); P=0.004	1q gain vs. normal 1q: HR 1.88 (CI, 0.98-3.58); P=0.056; 1q amplification vs. normal 1q: HR=5.88 (CI, 3.10-11.17); P<0.001. 1q gain vs. normal 1q: HR, 3.13 (CI, 1.73-5.68), P<0.001	(121)
Bortezomib and dexamethasone	After 3-4 cycles of induction therapy with bortezomib and dexamethasone, patients were divided into the ASCT and non-ASCT groups based on their age, physical condition and willingness for ASCT	258	49.2	20	NA	In patients with +1q, the PFS time was 22.2 (95% CI, 15.8-28.5) months and the 3- and 5-year PFS rate was 35.1 and 15.3%, respectively. In patients without +1q, the PFS was 41.1 (95% CI 28.6-53.6)	The median OS was 47.4 (95% CI, 34.7-59.5) months in patients with +1q, whereas OS was not reached in patients without +1q (P=0.048)	(117)

Table III. Continued.

Drug	Treatment regimen	Number of patients	Proportion of patients with 1q21+, %	Detection threshold for 1q21+ by FISH, %	CR	PFS	OS	(Refs.)
VRD or KRD	Patients were randomized to receive either bortezomib or carfilzomib, combined with lenalidomide and dexamethasone, followed by indefinite or 2-year maintenance therapy with lenalidomide	1,087	30.5	-	NA	months and the 3-and 5-year PFS rate was 51.3 and 26.7%, respectively Patients with +1q the median PFS was 29 months, while the patients without +1q was 42 months (VRD, HR= 1.51; P=0.011; KRD, HR=1.63; P=0.002)	VRD, 3-year OS, 74 vs. 86% (HR, 1.47; P=0.069) KRD, 3-year OS, 82 vs. 88% (HR= 1.34; P=0.185)	(118)
Bortezomib	Retrospective study: Triple induction therapy with bortezomib, including VTD or VCD	250	66.8	20	Patients with +1q vs. patients without +1q: 40.4 vs. 59.6% (P=0.587)	Patients with +1q vs. patients without +1q in PFS (median, 35 vs. 55 months, P=0.05)	Patients with +1q vs. patients without +1q in OS (median, 74 vs. 168 months, P=0.00025)	(119)
Lenalidomide	Patients were randomized to receive lenalidomide or lenalidomide + vorinostat 100 days after induction with CTD, CRD, or KCRD and ASCT	556	33	-	NA	PFS of 1q gain patients in the lenalidomide maintenance group (HR, 1.5; P=0.2) compared with the observation group	OS of 1q gain patients in the lenalidomide maintenance group (HR=1.1; P=0.9) compared with the observation group	(120)

<sup>a</sup>In carfilzomib triple combination therapy, the cut-off level of 1q gain was 10% of nuclei with  $\geq 3$  copies of 1q, while 1q amplification was defined as 20% of nuclei with  $\geq 4$  copies of 1q. FISH, fluorescence *in situ* hybridization; CR, complete response; PFS, progression free survival; OS, overall survival; BTD, bortezomib, thalidomide and dexamethasone; TCD, thalidomide, cyclophosphamide and dexamethasone; TD, thalidomide and dexamethasone; VADT, vincristine, doxorubicin, dexamethasone and thalidomide; VCD, bortezomib, cyclophosphamide and dexamethasone; VRD, bortezomib, lenalidomide and dexamethasone; VTD, bortezomib, thalidomide and dexamethasone; ASCT, autologous hematopoietic stem cell transplantation; HR, high risk; CI, confidence interval; CTD, cyclophosphamide, dexamethasone and thalidomide; CRD, cyclophosphamide, lenalidomide, and dexamethasone; KCRD, carfilzomib, lenalidomide and dexamethasone combined with CRD.



ENDURANCE ECOG-ACRIN E1A11 trial, 1q21<sup>+</sup> was associated with poorer outcome either with VRD or carfilzomib + lenalidomide + dexamethasone (KRD) (118). This may be due to the high expression of 26S proteasome non-ATPase regulatory subunit 4 (PSMD4) in patients with 1q21<sup>+</sup> as PSMD4 may mediate resistance to bortezomib by enhancing proteasome activity, resulting in enhanced protein degradation, decreased protein load and reduced apoptosis (51,122).

Subclonal cereblon mutations in patients treated with IMiDs are associated with MM recurrence and prognosis. The NCRI Myeloma XI study enrolled 178 patients with NDMM (19% of patients with 1q<sup>+</sup>) who received induction therapy with thalidomide, lenalidomide, or carfilzomib and lenalidomide combined with dexamethasone and cyclophosphamide. The aforementioned study found that progressive clonal expansion was a feature of 17.5% 1q gain cases, whereby 1q gain at diagnosis evolved into 1q amplification at relapse. Compared with normal 1q<sup>+</sup>, 1q<sup>+</sup> from presentation and evolution of new gain (1q<sup>+</sup>) at relapse were both associated with significantly shorter OS (HR, 2.11; P=0.0040; and HR, 2.00; P=0.021, respectively) (71).

Ixazomib combined with lenalidomide-dexamethasone therapy has been shown to be beneficial in patients with relapsed/refractory MM. In a double-blind, randomized and placebo-controlled phase III clinical (TOURMALINE-MM1) study, 722 patients with relapsed/refractory MM were randomized 1:1 to IRD group (ixazomib + lenalidomide + dexamethasone) and RD group (lenalidomide + dexamethasone). The results revealed a 40% prolongation of PFS in the IRD group compared with the RD group (HR, 0.74; 95% CI, 0.59-0.94; P=0.01) (123). Post hoc analysis revealed a significant PFS benefit for the IRD group in the 'expanded high-risk' cohort including partial 1q21 amplification patients (HR, 0.66; 95% CI: 0.47-0.93). However, no significant difference was observed between the two groups in patients with 1q21 amplification only (HR, 0.78; 95% CI, 0.49-1.24 for a detection threshold of 3% for 1q21<sup>+</sup> by fluorescence *in situ* hybridization (FISH); HR 0.682; 95% CI, 0.413-1.123 for a detection threshold of 20% for 1q21<sup>+</sup> by FISH; HR, 0.683; 95% CI, 0.381-1.224 for a detection threshold of 60% for 1q21<sup>+</sup> by FISH (124). This suggests that ixazomib has limited efficacy in patients with 1q21 amplification.

In addition, the copy number of 1q21<sup>+</sup> affects the efficacy of IMiDs and PIs. In the FORTE study of induction and consolidation with carfilzomib, 474 transplantation-eligible patients with NDMM were randomized to receive either induction with KRD followed by ASCT and KRD (KRD\_ASCT group), 12 KRD cycles (KRD12), or induction with K-cyclophosphamide (C)-d followed by ASCT and KCD (KCD\_ASCT group). The proportion of patients with 1q<sup>+</sup> in the aforementioned study was 55% (32% with 1q gain and 13% with 1q amplification). As indicated by the results, KRD-ASCT, compared with induction and consolidation with both KRD12 and KCD-ASCT, demonstrated significantly prolonged PFS with an HR of 0.64 (P=0.023) and 0.53 (P<0.001), respectively. 1q amplification presaged lower OS compared with normal 1q (HR, 5.88; 95% CI, 3.10-11.17; P<0.001) and 1q gain (HR, 3.13; 95% CI, 1.73-5.68; P<0.001). However, subgroup analyses based on early treatment suggested that KRD\_ASCT completely abrogated the PFS disadvantage conferred by 1q gain (HR, 1.25

vs. normal 1q; 95% CI, 0.58-2.7; P=0.565), but patients with 1q amplification still exhibited a very poor outcome (121,125).

#### *Monoclonal antibodies*

**CD38.** CD38 antibodies have become a critical part of relapsed MM and its first-line therapy. CD38 is highly expressed by MM cells and is a cell surface receptor target for antibody therapy in patients with MM (126). The eliminating effect of CD38 antibody on tumor cells is mainly achieved through the Fc-mediated immune-effector mechanisms, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis and secondary crosslinking-induced apoptosis (127). Daratumumab and Isatuximab, both CD38-targeting antibodies, have been approved by FDA. Daratumumab, an IgG1κ humanized monoclonal antibody that binds to CD38, reduces levels of myeloid-derived suppressor cells (CD38<sup>+</sup>MDSCs), regulatory T cells (CD38<sup>+</sup>Tregs), and B cells (CD38<sup>+</sup>Bregs) (128,129). Isatuximab is a chimeric humanized IgG1 monoclonal antibody that binds to a specific epitope on the human cell surface antigen CD38 (130). Isatuximab can induce MM cell death by caspase-dependent apoptosis and lysosome-mediated non-apoptotic cell elimination (131). A summary of studies on CD38 antibodies in patients with 1q21<sup>+</sup> over the past 3 years is presented in Table IV.

Several studies have revealed that Daratumumab may improve the rate of MRD negativity and PFS in patients with newly diagnosed 1q21<sup>+</sup>, but has limited effect on patients with relapsed 1q21<sup>+</sup>. The GRIFFIN study included 207 transplantation-eligible patients with NDMM who were randomized to the D-RVD group (n=104) and the RVD group (n=103), and revealed that for patients with 1q21<sup>+</sup>, the rates of MRD negativity (10<sup>-5</sup>) in the D-RVD group and the RVD group were 61.8 and 28.6% (OR, 4.04; 95% CI, 1.38-11.81), respectively, and that the median PFS in the D-RVD group was higher (NR vs. 47.9 months) (OR, 0.42; 95% CI, 0.14-1.27) (132). This result suggests that the combination of D-RVD induction/consolidation with ASCT and R + DARA maintenance therapy increased the rate of MRD negativity and PFS in the 1q21<sup>+</sup> subgroup. However, the poor prognosis of 1q21<sup>+</sup> may be difficult to be overcome with Daratumumab in patients with MM and relapsed 1q21<sup>+</sup>. A study that investigated the outcomes of all patients with refractory MM receiving Daratumumab found that before initiating the treatment with Daratumumab, patients who were 1q21<sup>+</sup> positive and classified as high-risk for GEP70 had the worst outcomes (0.3 and 0.8 years, respectively for PFS and OS), while patients without 1q21<sup>+</sup> and low-risk for GEP70 did not reach the median PFS and OS (133). This observation indicates that a poor prognosis associated with 1q21<sup>+</sup> may not be overcome by Daratumumab. Another multicenter retrospective study enrolled 232 RRMM patients who received a DARA-based regimen and underwent FISH following 1st-3rd line therapies (134). At a median follow-up of 35.7 months in the study, the median PFS for patients with 1q21<sup>+</sup> using the DARA-based regimen was 24.6 months, and the ORR was 57.9%. There were no significant differences in PFS and ORR between patients with 1q21<sup>+</sup> using the DARA regimen and patients without 1q21<sup>+</sup>. Similarly, there were also no significant differences in PFS or ORR among patients with 1q21<sup>+</sup> using different treatment regimens. The prognosis and response

Table IV. Summary of studies on CD38 antibodies in patients with multiple myeloma and 1q21<sup>+</sup> over the past 3 years.

Drug	Treatment regimen	Number of patients	Proportion of patients with 1q21 <sup>+</sup> , %	Detection threshold for 1q21 <sup>+</sup> by FISH, %	CR	PFS	OS	(Refs.)
Daratumumab	4 cycles of D-RVD or RVD induction, ASCT, 2 cycles of D-RVD or RVD consolidation, and 24 cycles of R ± D maintenance therapy	207	30.0	-	RVD 1q <sup>+</sup> vs. RVD 1q <sup>+</sup> : 57.6 vs. 57.1% (OR, 1.02; 95% CI, 0.37-2.82)	D-RVD 1q <sup>+</sup> vs. RVD 1q <sup>+</sup> : NR vs. 47.9 months (OR, 0.42; 95% CI, 0.14-1.27)	NA	(132)
Daratumumab	Daratumumab monotherapy, DRd, DPd or DBd	232	24.5	-	CR of patients with 1q21 <sup>+</sup> treated with the Daratumumab-based regimen: 3 (5.26%); There was no significant difference in ORR between patients with 1q21 <sup>+</sup> and patients without 1q21 <sup>+</sup> (P=0.09)	1q21 <sup>+</sup> vs. non-1q21 <sup>+</sup> : 24.5 (95% CI, 18.6-29.4) vs. 23.5 (95% CI, 21.1-28.1) months, P=0.392	NA	(134)
Isatuximab	Isa-Pd vs. Pd	307	41.7	30	NA	1q21 <sup>+</sup> : 9.5 vs. 3.8 months HR, 0.40 (95% CI, 0.25-0.63) Non-1q21 <sup>+</sup> : 11.6 vs. 9.5 months, HR, 1.19 (95% CI, 0.68-2.10)	1q21 <sup>+</sup> : 21.3 vs. 13.9 months HR: 0.72 (95% CI, 0.48-1.07) Non-1q21 <sup>+</sup> : 21.3 vs. 21.2 months, HR, 1.30 (95% CI, 0.80-2.14)	(138)
Isatuximab	Isa-KD vs. KD	302	41	30	NA	1q21 <sup>+</sup> Isa-KD vs. 1q21 <sup>+</sup> KD: NR vs. 16.2 months HR, 0.57 (95% CI, 0.33-0.98)	NA	(138)

FISH, fluorescence *in situ* hybridization; CR, complete response; PFS, progression-free survival; OS, overall survival; ASCT, autologous hematopoietic stem cell transplantation; R ± D, lenalidomide ± daratumumab; RVD, lenalidomide, bortezomib and dexamethasone; D-RVD, daratumumab combined with RVD; ORR, objective response rate; CI, confidence interval; HR, hazard ratio; OR, odds ratio; NR, not reached; DRd, daratumumab, lenalidomide and dexamethasone; DPd, daratumumab, pomalidomide and dexamethasone; DBd, daratumumab, bortezomib and dexamethasone; Isa-Pd, isatuximab, pomalidomide and dexamethasone; Pd, pomalidomide and dexamethasone; Isa-KD, isatuximab, carfilzomib and dexamethasone; KD, carfilzomib and dexamethasone.

profiles in patients with  $1q21^+$  using the DARA regimen were similar to those with standard-risk cytogenetics (SRCyto) or other high-risk cytogenetics (HRCyto) (134). Although the prognosis in patients with  $1q21^+$  using the DARA regimen in this study was similar to that in patients without  $1q21^+$ , given that median PFS and ORR were lower in patients with  $1q21^+$  compared with historical controls (80,119,125) further studies are required to validate the role of Daratumumab in patients with relapsed  $1q21^+$ .

In patients with newly diagnosed high-risk  $1q21^+$ , Isatuximab may improve the rate of MRD negativity. Recently, an interim analysis of the GMMG-CONCEPT study was released. The aforementioned study included 153 high-risk patients with NDMM and aimed to evaluate the efficacy and safety of the Isa + KRD quadruplet (Isatuximab + carfilzomib + lenalidomide + dexamethasone) regimen in this population. The study considered patients with  $del(17p)$  or  $t(4;14)$  or  $t(14;16)$  or  $>3$  copies of  $1q21$  with ISS II or III as high risk and enrolled 127 transplantation-eligible patients and 26 transplantation-ineligible patients, with 36.0% of patients with  $1q21^+$ . In the study, by the end of consolidation therapy, 63 (67.7%) cases in the transplantation-eligible (TE-ITT) group reached MRD negativity, 3 (3.2%) cases had MRD positivity, and 23 (24.7%) cases had not completed the consolidation therapy. In the transplantation-ineligible (TNE-ITT) group, 13 cases (54.2%) reached MRD negativity, no one had MRD positivity, and 11 (45.8%) cases had not completed the consolidation therapy. The ORR was 94.9% in the TE-ITT group, complete response (CR) was achieved in 57.7% of patients in the TNE-ITT group, and very good partial response (VGPR) was achieved in 30.8% of patients. Although no separate analysis was performed for patients with  $1q21^+$ , it still could be observed that the combination of Isatuximab based on KRD was effective in high-risk NDMM patients with  $1q21^+$  and increased the rate of MRD negativity (135).

Unlike Daratumumab, the efficacy of Isatuximab in the treatment of relapsed/refractory MM with  $1q21^+$  has been demonstrated in several studies. In the phase III studies ICARIA-MM and IKEMA, the addition of Isatuximab (Isa) to the backbone of pomalidomide-dexamethasone (PD) or carfilzomib-dexamethasone (KD), respectively, improved PFS among patients with relapsed/refractory MM, and subgroup analyses suggested benefit among patients with  $1q21^+$  (136,137). Recently, four  $1q21$ -related subgroups from ICARIA-MM and IKEMA were analyzed and showed improvement in median PFS and OS in patients with  $1q21^+$  in the Isa-PD group when compared with the PD group. The median PFS was 9.5 and 3.8 months (HR, 0.40; 95% CI, 0.25-0.63) in patients with  $1q21^+$ , and the median OS was 21.3 and 13.9 months (HR, 0.72; 95% CI, 0.48-1.07). The median PFS and OS of patients with  $1q21^+$  and patients without  $1q21^+$  were similar in the Isa-PD group, with a median PFS of 9.5 and 11.6 months, respectively in both groups (HR=1.19; 95% CI, 0.68-2.10) and a median OS of 21.3 and 21.2 months, respectively (HR, 1.30; 95% CI, 0.80-2.14). In patients with  $1q21^+$ , the median PFS was improved in the Isa + KD group compared with the KD group (NR vs. 16.2 months, HR, 0.57; 95% CI, 0.33-0.98) (138). The aforementioned study has shown that Isatuximab combined with PD or KD can all improve the poor prognosis of  $1q21^+$  in patients with relapsed/refractory MM.

**Elotuzumab.** Elotuzumab is a monoclonal antibody targeting signaling lymphocytic activation molecule family member 7 (SLAMF7), which is highly expressed by MM cells (139). Elotuzumab can not only directly act on SLAMF7 that is highly expressed on the surface of PCs to inhibit inter-cellular adhesion, thereby reducing the growth stimulation effect of stromal cells on myeloma cells, but also target, bind to and label SLAMF7 on the surface of myeloma cells, and enhance antibody-dependent cellular cytotoxicity in myeloma cells mediated by NK cells (140,141).

The SWOG-1211 study is a randomized, multicenter phase II clinical study that included 100 ASCT-ineligible patients with high-risk NDMM, where high-risk MM is defined as: High risk based on gene expression profiling analysis,  $t(14;16)$ ,  $t(14;20)$ ,  $del(17p)$  or  $1q21^+$ , primary plasma cell leukaemia and elevated serum LDH ( $\geq 2$  times the upper limit of normal). The proportion of patients with  $1q21^+$  was 47%. In the aforementioned study, there was no significant difference in prognosis between the RVD + elotuzumab group and the RVD group, with a PFS of 31 and 34 months, respectively (HR=0.968; 80% CI, 0.697-1.344;  $P=0.45$ ). Similarly, in patients with  $1q21^+$ , the addition of elotuzumab did not improve the prognosis, with a median PFS of 41 months (95% CI, 22-NR) in the RVD group and 32 months (95% CI, 18-NR) in the RVD + elotuzumab group, with no statistical difference between the two groups (142).

Recently, a multicenter, single-arm phase II clinical study analyzed the efficacy and safety of elotuzumab combined with KRD (Elo-KRD) regimen in NDMM patients without an intent for ASCT. The study included 46 patients with NDMM, including 35% of patients with  $1q21^+$ . After 8 courses of Elo-KRD, a total of 26 (58%) patients achieved stringent complete response (sCR) and/or MRD negativity. Finally, 17 (38%) patients achieved sCR, 21 (47%) patients achieved CR or better, 38 (84%) patients achieved VGPR or better, and 39 (87%) patients achieved PR or better. In the evaluation of MRD, 26 (63%) patients achieved MRD negativity following 8 courses of Elo-KRD, among whom 19 (44%) patients remained MRD negativity during the 8th to 12th courses and 15 (50%) patients sustained MRD negativity lasting for  $>1$  year. This study demonstrated a significant increase in sCR in NDMM patients treated with elotuzumab + KRD but did not specifically evaluate the actual efficacy of elotuzumab in patients with  $1q21^+$  (143).

**Selective inhibitors of nuclear export.** Selinexor is an oral selective inhibitor of nuclear export that has been approved by FDA for the treatment of relapsed/refractory MM. The target of Selinexor was exportin 1 (XPO1)/chromosome region maintenance 1, and selinexor reversibly inhibits tumor suppressor proteins (TSPs), growth regulators and oncogenic protein RNAs from the nucleus by blocking XPO1, which leads to nuclear accumulation of TSPs, reduction of oncoproteins such as c-myc and cyclinD1, cell cycle arrest and tumor cell apoptosis (144-147).

The MARCH study is a multicenter, single-arm phase II clinical study that included 82 RRMM patients who had disease refractory to PI and IMiD, including 64.6% of patients with  $1q21^+$  (148). In the aforementioned study, selinexor 80 mg combined with dexamethasone 20 mg was administered orally

in patients on day 1 and day 3 of each week in 4-week cycle for multiple cycles. The results demonstrated an ORR of 29.3% (95% CI, 19.7-40.4), a median duration of response of 4.7 months, and median PFS and OS of 3.7 and 13.2 months, respectively (148). The aforementioned study did not analyze patients with 1q21<sup>+</sup> separately but had a high proportion of patients with 1q21<sup>+</sup>. Similarly, the STOMP-XKd study, which involved 32 patients with RRMM, evaluated the safety and efficacy of selinexor (80 or 100 mg) + carfilzomib (56 or 70 mg/m<sup>2</sup>) + dexamethasone (40 mg) (XKD). The results showed that 53% of patients had high-risk cytogenetics del(17p), t(4;14), t(14;16) and/or gain 1q. The ORR was 78% after treatment with XKD, and median PFS was 15 months. In addition, XKD was well tolerated (149). Therefore, selinexor combined with dexamethasone could be used as a clinical option for the treatment of patients with RRMM, including 1q21<sup>+</sup>.

## 5. Conclusions

The interaction of MM cells with the bone marrow micro-environment generates a high-risk ecosystem that facilitates MM cell survival and immune response failure. 1q21<sup>+</sup> is a secondary genomic event that occurs following primary IGH translocations. Therefore, the occurrence of 1q21<sup>+</sup> is crucial for the evolution of myeloma cells to a high-risk state. In addition to the internal reasons such as genetic instability and gene driving in the pericentromeric region of chromosome 1, the genetic mechanism of 1q21<sup>+</sup> also includes the protective effect of bone marrow microenvironment on MM cells. Therefore, the presence of 1q21<sup>+</sup> predisposes to the risk of drug resistance and disease progression. The precise molecular mechanisms of acquiring 1q21<sup>+</sup> and its effect on MM pathophysiology are yet to be fully elucidated. Further studies are required to assess the impact of the ecosystem formed by the bone marrow microenvironment and MM cells on 1q21<sup>+</sup>-induced resistance and aggressiveness.

As one of the most common cytogenetic abnormalities in MM, 1q21<sup>+</sup> plays a role in the risk stratification of MM. In the past, both R-ISS and IMWG risk staging systems included 1q21<sup>+</sup> in the intermediate-risk group (150,151). However, the 2016 IMWG consensus paper considered that patients with 1q21<sup>+</sup> had a worse treatment outcome and 1q21<sup>+</sup> was included in the high-risk group in the updated mSMART (152,153). Recently, both R2-ISS and MASS staging systems identified 1q21<sup>+</sup> as a high-risk stratification factor (21,22). This indicates that the prognostic role of 1q21<sup>+</sup> in MM has been widely recognized. In addition, although 1q21<sup>+</sup> has been identified as a potentially poor prognostic factor, the effect of 1q21<sup>+</sup> copy number on prognosis remains to be explored in more depth.

The application of CD138 immunomagnetic bead sorting combined with FISH technology is the most reliable method for the detection of 1q21<sup>+</sup>, but the threshold for 1q21<sup>+</sup> in FISH testing varies significantly from <5-30% in various studies at present (89,154). EMN recommended 20% as the threshold for FISH testing (15), while most clinical trials generally do not report the threshold for 1q21<sup>+</sup> by FISH testing or use a laboratory-defined threshold for evaluation. Inconsistencies in the thresholds for 1q21<sup>+</sup> by FISH testing may result in differences in prognostic indicators such as PFS. If using 20% as

the threshold for positive 1q21<sup>+</sup>, it might miss some patients with minor clones of 1q21<sup>+</sup>. For example, the retrospective study used 20 healthy donors' bone marrow specimens to set the thresholds for 1q21<sup>+</sup> by MACS-FISH and direct-FISH and establish by a 'mean + 3x standard deviation' calculation, the cut-off values for each abnormality were 5% for 1q21<sup>+</sup>. The result indicated that 1q21<sup>+</sup> clone sizes of 5-20% had clear adverse prognostic significance, and 5% was a reliable cut-off value for 1q21<sup>+</sup> (89). If the EMN threshold had been applied to that study, then 25% of patients who tested positive for 1q21<sup>+</sup> would have been considered negative. Therefore, there is currently a lack of reasonable threshold criteria for 1q21<sup>+</sup> by FISH testing to improve evaluation of the prognostic status of patients with 1q21<sup>+</sup>.

The therapeutic limitation of MM is determined by clonal heterogeneity. 1q21<sup>+</sup> is highly heterogeneous due to its association with the expression of multiple driver genes, posing numerous challenges to its treatment. IMiD/PI induction regimens alleviated the PFS disadvantage of 1q gain in some studies but did not improve the prognosis of 1q amplification. IMiD/PI induction, upfront high-dose therapy, and ASCT had a positive, but limited effect on the ORR and OS in patients with 1q21<sup>+</sup>. Daratumumab may improve the rate of MRD negativity and PFS in patients with newly diagnosed 1q21<sup>+</sup>, but there is a lack of clinical evidence that would be beneficial for patients with relapsed 1q21<sup>+</sup>. The actual efficacy in patients with 1q21<sup>+</sup> was not specifically evaluated in studies of elotuzumab and selinexor. Isatuximab may improve the rate of MRD negativity in patients with newly diagnosed high-risk 1q21<sup>+</sup>, and in patients with RRMM, Isatuximab combined with PD or KD can all enhance the poor prognosis of 1q21<sup>+</sup>. Based on the existing results in the field of 1q21<sup>+</sup>, Isatuximab combined with IMiD and PI may be the therapy of the highest potential to improve the prognosis of patients with 1q21<sup>+</sup>.

In summary, as one of the most common cytogenetic abnormalities in MM, 1q21<sup>+</sup> is closely related to the occurrence, progression, treatment, drug resistance and prognosis of MM. Patients with MM and 1q21<sup>+</sup> tend to exhibit higher disease burden, more aggressive clinical manifestations, and more co-occurring high-risk cytogenetic abnormalities. Therefore, both R2-ISS and MASS staging systems identified 1q21<sup>+</sup> as a high-risk stratification factor. The present review summarized the efficacy of ASCT, PI, IMiD, monoclonal antibodies and selective nuclear export inhibitors in the treatment of MM patients, especially in 1q21<sup>+</sup> patients. Among them, isatuximab combined with IMiD or PI maybe the most potential therapy to improve the prognosis of patients with 1q21<sup>+</sup> MM. However, for patients with 1q21<sup>+</sup> who have no response to existing drug therapies, further studies on risk stratification are still needed to overcome the poor prognosis caused by clonal heterogeneity and provide personalized treatment options for them.

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## Authors' contributions

LW was responsible for designing the theme of the review and ensuring that the descriptions are accurate and agreed by all authors. NL and ZX were responsible for ideas, collecting relevant studies from databases and writing of the manuscript. HL made critical modifications to important knowledge content within the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

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## Competing interests

ZX is a Sanofi employee and may hold shares and/or stock options in the company. The other authors declare that they have no competing interests.

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