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## Anti-CD38 Monoclonal Antibodies in MM: Another Cook in the Kitchen?

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Monoclonal antibodies (mAbs) are a cornerstone in the treatment of multiple myeloma (MM). Among the available anti-CD38 mAbs, daratumumab has been approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), while isatuximab, MOR202 and TAK-079 are currently under investigation. Anti-CD38 mAbs have several mechanisms of action, including antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC), direct cellular apoptosis and extracellular ectoenzyme activity modulation.<sup>1</sup> Typical side effects of anti-CD38 mAbs are the infusion-related reactions (IRRs), which are thought to be related to the CDC activity of the compound. IRRs mainly occur during the first infusion and manifest primarily with a respiratory pattern.<sup>1</sup> In some patients, such as those with pre-existing chronic obstructive pulmonary disease or severe chronic asthma, IRRs may be a matter of concern, sometimes preventing patients to receive anti-CD38 mAbs.

The clinical activity of daratumumab highlights the importance of anti-CD38 mAbs, which, in the context of MM, play a role similar to that of anti-CD20 mAbs in CD20+ lymphoproliferative disease.

In this issue of *Lancet Haematology*, Raab and colleagues reported data on 91 relapsed and/or refractory (RR)MM patients treated with MOR202 alone or in combination with dexamethasone ± immunomodulatory drugs (IMiDs). In this study, no significant cytoreduction was observed with single-agent MOR202 (no response better than partial response [PR]). The absence of single-agent activity may be explained by its peculiar mechanisms of action: differently from other anti-CD38 mAbs, MOR202 induces ADCC and ADCP, but not CDC. Indeed, while isatuximab and daratumumab can be effectively used as single agents, this is less certain for MOR202. On the other hand, MOR202 showed a better tolerability due to the absence of CDC, given that IRRs are mainly related to this mechanism. This hypothesis is confirmed by the low rates of IRRs observed with MOR202 as single agent (40%) and by the even lower rates when added to dexamethasone-containing regimens (5-11%) (Table 1). These results compare favorably with those reported with daratumumab (48-50%) and isatuximab (38-56%).<sup>2-8</sup> Therefore, MOR202 could be an appealing anti-CD38 mAb in patients with severe pulmonary comorbidities, in order to reduce the risk of IRRs.

The long infusion time of daratumumab may be burdensome for both patients and healthcare facilities, while MOR202 was safely administered in as low as 30 minutes. This represents a possible advantage of this compound. However, in this setting, the subcutaneous formulation of daratumumab will soon change the current daily practice.<sup>9</sup>

Despite the absence of single-agent activity, a significant activity was observed when MOR202 was added to dexamethasone and IMiDs (median progression-free survival [PFS] not reached after a median follow-up of 16.6 months in the MOR202-lenalidomide-dexamethasone arm versus median PFS of 17.5 months after a median follow-up of 6.5 months in the MOR202-pomalidomide-dexamethasone arm), in line with the results observed with daratumumab and

isatuximab. Nevertheless, randomized trials are needed to prove the synergic effect of MOR202 with IMiDs. A phase III trial comparing MOR202-lenalidomide-dexamethasone versus lenalidomide-dexamethasone alone (NCT03952091) is ongoing.

In the current scenario, with the approval of daratumumab for the treatment of newly diagnosed and relapsed patients and with the investigation of isatuximab in phase III studies, a key element in the development of another anti-CD38 is its difference with currently available CD38 antibodies in terms of safety and efficacy. If MOR202 proved to induce a lower rate of IRRs, the absence of single-agent activity may limit its development, while conclusive data regarding its combinations with IMiDs are awaited. Another interesting area of investigation would be the feasibility of switching anti-CD38 in patients who have failed a previous treatment with an anti-CD38 mAb. However, the long-lasting downregulation of CD38 after anti-CD38 mAb exposure and the availability of other compounds targeting other specific plasma cell antigens (e.g. BCMA) may limit the applicability of sequential anti-CD38 retreatment.

While the achievement of a high efficacy is a priority in the oncological setting (compared to the decrease of the IRR rate), the good safety profile of MOR202 could be an appealing feature in non-neoplastic conditions. Many autoimmune conditions are caused by non-neoplastic plasma cells producing pathogenic antibodies, and therefore an anti-CD38 mAb could play a role in the treatment of these disorders.<sup>10</sup> A clinical trial testing MOR202 as a single agent in the treatment of anti-PLA2R antibody-positive membranous nephropathy is planned (NCT04145440). The ongoing trials will inform on the optimal setting of application of this molecule in neoplastic and non-neoplastic conditions and will affect its further development.

## Disclosures

MD declares no competing financial interests.

FG has received honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Takeda, and served on the advisory boards for Amgen, Bristol-Myers Squibb, Celgene, Janssen, Roche, Takeda, and AbbVie.

RM has received honoraria from Amgen, Celgene, Takeda and Janssen and served on the advisory boards for Janssen.

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**Table 1.** Selected clinical studies exploring an anti-CD38 monoclonal antibody alone or in combination with dexamethasone ± immunomodulatory drugs

Combination	Median of prior lines (range)	ORR	PFS	IRRs
Daratumumab single agent <sup>2</sup>	5 (2-14)	31%	4 months	48%
Isatuximab single agent <sup>3</sup>	4 (2-10)	26%	5 months	40%
MOR202 single agent <sup>4</sup>	3 (2-4)*	0%	1 month	40%
Isatuximab-dexamethasone <sup>3</sup>	4 (2-11)	44%	9 months	40%
MOR202-dexamethasone <sup>4</sup>	3 (2-4)**	28%	8 months	11%
Daratumumab-Rd <sup>5</sup>	1 (1-11)	93%	NR	48%
Isatuximab-Rd <sup>6</sup>	5 (1-12)	56%	8.5 months	56%
MOR202-Rd <sup>4</sup>	2 (1-2)**	65%	NR	6%
Daratumumab-Pd <sup>7</sup>	4 (1-13)	60%	9 months	50%
Isatuximab-Pd <sup>8</sup>	3 (2-4)	60%	11.5 months	38%
MOR202-Pd <sup>4</sup>	3 (2-3)**	48%	17.5 months	5%

\*Interquartile range of the biweekly cohort reported.

\*\*Interquartile range provided.

**Abbreviations.** ORR, overall response rate; PFS, progression-free survival; IRRs, infusion-related reactions; R, lenalidomide; d, dexamethasone; P, pomalidomide; NR, not reported.