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# **BCMA loss in the epoch of novel immunotherapy for multiple myeloma: from biology to clinical practice**

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## **Abstract**

The treatment of multiple myeloma (MM) is evolving rapidly. In the past few years, chimeric antigen receptor (CAR) modified T-cell and bispecific antibody (BsAb) are bringing new treatment options to relapsed/refractory (RR) MM patients. Currently, B-cell maturation antigen (BCMA) has emerged as the most commonly used target of T-cell based immunotherapies for RRMM. Clinical data have demonstrated promising efficacy and manageable safety profile of both CAR T-cell and BsAb therapies in heavily pretreated RRMM. However, most patients suffer from relapses at later time points, and the resistance mechanism remains largely unknown. Theoretically, loss of antigen is a potential tumor intrinsic resistance mechanism against BCMA-targeted immunotherapies. Therefore, strategies to overcome this kind of drug resistance are needed for these patients. In this review, we will discuss the loss of BCMA in the new epoch of immunotherapy for MM.

## **Keywords**

BCMA, multiple myeloma, antigen escape, immunotherapy, T-cell

## Introduction

Multiple myeloma (MM), the second most common hematological malignancy, is characterized by uncontrolled plasma cell proliferation, which typically causes destructive osseous bone lesions, acute kidney injury, anemia, and hypercalcemia (1, 2). In the past twenty years, integration of proteasome inhibitors (PI) and immunomodulatory drugs (IMiD) into the MM treatment has significantly improved the survival outcome of patients (3). To date, although MM is considered a largely incurable disease, the evolution of MM therapy is ongoing (4). In the mid-2010s, monoclonal antibodies (mAb) targeting CD38 and signaling lymphocytic activation molecule F7 (SLAMF7), i.e. daratumumab and elotuzumab, have been incorporated into the standard of care, bringing the MM treatment into the new immunotherapy era (5). Unlike the conventional chemotherapies, these novel agents should recognize specific surface antigens in order to locate MM cells and, in turn, kill them selectively. In principle, the presents of target antigen is an essential prerequisite for a successful treatment.

More recently, the next revolution of the immunotherapy for MM has been started with B-cell maturation antigen (BCMA) directed treatments including antibody drug conjugate (ADC), bispecific antibodies (BsAb), and chimeric antigen receptor (CAR) modified T-cell therapies (6). Although these novel immunotherapies are highly effective even in heavily pretreated relapsed/refractory (RR) MM patients, most patients suffer from relapses at later time points. A recent meta-analysis showed a median progression free survival (PFS) of merely 12.2 months in RRMM patients who were treated with BCMA-targeted CAR T-cells (7). However, the underlying mechanism of resistance is currently not fully understood.

To date, novel immunotherapies such as ADC, BsAb, and CAR T-cells targeting other antigens have also been used in diverse hematological malignancies including leukemia and lymphoma (8-10). So far, antigen loss has already been described as a tumor intrinsic resistance mechanism against BsAb and CAR T-cell therapies for leukemia and lymphoma. For instance, CD19 loss was detected in approximately 40% of patients with B-cell acute lymphoblastic leukemia treated with anti-CD19 CAR T-cells, and point mutations in CD19 gene was reported as a mechanism for CD19 loss in these patients (11). Likewise, in B-cell non-Hodgkin lymphoma (B-NHL), CD20 negative relapses were observed in patients who received REGN1979, a CD20/CD3-targeted BsAb (12, 13). On the other hand, antigen loss following ADC treatments was less frequently reported. Theoretically, antigen loss may also be a potential mechanism of resistance in anti-BCMA immunotherapies for MM. Indeed, in MM patients, biallelic BCMA loss has been reported in three cases relapsing from BCMA targeted CAR T-cell therapies (14-16). In this review, we will summarize the nature of BCMA

loss based on the currently available data. Furthermore, strategies to overcome drug resistance caused by BCMA loss will be discussed.

## **Biology of BCMA and anti-BCMA immunotherapies for MM**

Biology of BCMA as well as clinical data on BCMA-directed novel immunotherapies for MM have been summarized in previous review articles (17-20). Since the current review does not focus on these issues, at this point, we will just provide a brief overview for the completeness of this review.

### ***Biology of BCMA***

BCMA, also referred to as tumor necrosis factor receptor superfamily 17 (TNFRSF17) or CD269, is a transmembrane glycoprotein highly expressed in plasma cells and almost absent in other human tissues. BCMA can be cleaved from the cell membrane by  $\gamma$ -secretase, releasing soluble BCMA (sBCMA) into the blood stream (21). The BCMA encoding gene is located on the human chromosome band 16p13.1 (22). In normal plasma cells, BCMA binds to B-cell activating factor (BAFF) and a proliferation inducing ligand (APRIL), regulating the maturation and differentiation of B-cells into plasma cells and supporting survival of long-lived plasma cells (23-26). In MM, several survival and anti-apoptotic pathways could be activated by binding of BAFF or APRIL to BCMA, e.g. nuclear factor  $\kappa$  light chain enhancer of activated B-cells (NF- $\kappa$ B), mitogen activated protein kinase (MAPK), and protein kinase B (AKT), resulting in MM cell proliferation and immunosuppression in the bone marrow microenvironment (27). Importantly, the expression level of BCMA is significantly increased on malignant versus healthy plasma cells (26, 28). Based on these biological features of BCMA, it is considered a therapy target for MM. To date, three classes of BCMA-directed immunotherapies have been investigated in human, including ADC, BsAb, and CAR T-cell (**Figure 1A**). As BCMA acts as an important factor contributing to survival of malignant plasma cells, loss of BCMA could be expected to place plasma cells at a selective growth disadvantage.

### ***Recent advances in anti-BCMA immunotherapies for MM***

In August 2020, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the first BCMA-targeted ADC, belantamab mafodotin, for the patients with RRMM (29). A few months later, the first anti-BCMA CAR T-cell therapy idecabtagene vicleucel (also referred to as ide-cel or bb2121) was approved for RRMM

patients who have received four or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody (30). Most recently, the second anti-BCMA CAR T-cell therapy ciltacabtagene autoleucel (cilta-cel) has been granted FDA approval for the same indication as ide-cel (31). Besides, multiple BCMA-directed T-cell engaging BsAbs are under clinical investigation, and the early results have shown encouraging anti-MM efficacy (32, 33). Based on the outstanding anti-tumor effect and acceptable toxicity, these novel anti-BCMA immunotherapies may become a part of the standard MM treatment in near future.

### ***BCMA-targeted ADC***

ADC is composed of a mAb and a cytotoxic payload combined by a linker molecule. Belantamab mafodotin is the first in class ADC for MM patients. The pivotal randomized phase 2 DREAMM-2 trial demonstrated an overall response rate (ORR) of 31% and 34% in heavily pretreated RRMM patients receiving 2.5 mg/kg and 3.4 mg/kg Q3W, respectively (34). Keratopathy is the most common toxicity of belantamab mafodotin with an incidence of up to 100%, which may lead to treatment discontinuation (35). Currently, belantamab mafodotin in combination with VRd (bortezomib, lenalidomide, and dexamethasone) is being evaluated in transplant ineligible newly diagnosed (ND) MM (36). Other anti-BCMA ADCs e.g. AMG224 and MEDI2228 are under clinical investigation (37, 38).

### ***BCMA-targeted BsAb***

BsAb binds to MM and T-cells via CD3 and a tumor specific antigen e.g. BCMA to build an immune synapse, which subsequently leads to T-cell activation and cytotoxic effects. The first in class BCMA-directed BsAb AMG420 showed an ORR of 70% at 400 µg/day (33). However, further development of AMG420 has been stopped because of the short half-life time and the need of continuous infusion (17). For this reason, some other BsAbs with extended half-life have been developed, e.g. AMG701, teclistamab, REGN5458, TNB-383B, elranatamab, and CC-93269 etc. Preliminary efficacy data of these novel agents demonstrated an ORR of up to 90%, while some of the results were still immature (39-44). Cytokine release syndrome (CRS) is the most common adverse event of BsAb with an incidence of up to 90% (45). Clinical trials evaluating BsAbs in MM are ongoing (46).

### ***BCMA-targeted CAR T-cell***

CAR T-cell is another strategy to concur tumor utilizing T-cells. Genetically modified T-cells with a CAR recognizes tumor specific antigen, e.g. BCMA, and activates T-cell via the CD3ζ signaling domain. Additionally, some co-stimulatory domains such as CD28 and 4-1BB are incorporated to enhance T-cell activation and proliferation. So far, there are >20 different

BCMA-directed CAR T-cell products investigated within clinical trials, mainly in the United States and in China, showing an ORR of up to 100% in some studies (7, 47-50). In the phase 2 KarMMa trial, the first in class BCMA-targeted CAR T-cell therapy ide-cel had an ORR of 73%, and the median PFS was only 8.8 months (51). Noteworthy, in the updated results of the phase 1b/2 CARTITUDE-1 study, cilta-cel has not only shown a high ORR of 98% but also an encouraging long-term efficacy with a median duration of response of 21.8 months. Similar to BsAb, BCMA-directed CAR T-cell therapy presented a very high CRS rate of > 80%, which on the other hand correlated with a good treatment response (20). At present, various clinical trials evaluating BCMA-targeted CAR T-cell products, including allogeneic CAR T-cells, are enrolling (47).

### **BCMA loss: biology and clinical implication**

The novel anti-BCMA immunotherapies, especially BsAb and CAR T-cell, are highly effective in RRMM. In contrast, the currently available data have demonstrated that the majority of the patients relapse at later time points. As these novel agents are being integrated into the standard of care, elucidating the resistance mechanisms would be the next step in the drug development to improve the anti-MM efficacy and to plan a precise treatment strategy for each given patient. Currently, as these novel anti-BCMA agents are still in their “infancy”, evidence on the resistance mechanism is still very limited. However, BCMA loss represents a potential tumor intrinsic factor contributing to resistance against anti-BCMA immunotherapies. Here, we will discuss the biology of BCMA loss and its clinical implication.

#### ***BCMA loss is not a common event***

In general, the currently available data on anti-BCMA immunotherapies, mainly BsAb and CAR T-cells, have demonstrated that BCMA loss after treatment is not a common event, while the BCMA status remain positive in the majority of the patients (22). Mostly, BCMA loss was detected as the patients suffered from an unexpected relapse after immunotherapies. In **Table 1**, we provide an overview of clinical cases with BCMA loss after immunotherapies in RRMM.

The first case of BCMA loss was observed in a patient treated with BCMA-targeted CAR T-cells. Ali *et al.* reported a patient who relapsed two months after CAR-BCMA treatment, and the flow cytometry of the patient’s bone marrow showed a population of BCMA negative malignant plasma cells, whereas some other MM cells remained positive for BCMA (52). Similarly, Brudno *et al.* found a small number of MM cells that lacked of BCMA expression in

a patient 56 weeks after CAR-BCMA treatment by flow cytometry. However, in the resampling eight weeks later, the MM cells of this patient presented mixed BCMA expression, suggesting a reversible BCMA loss (53). In addition, Green *et al.* described a patient with presence of BCMA negative MM cells 60 days after anti-BCMA CAR T-cell therapy. Although some BCMA positive MM cells still existed in this patient, the BCMA expression level and the BCMA antigen binding capacity were strongly reduced (54). Decreased BCMA expression level was also observed by Cohen *et al.* in 12 out of 18 patients who received CART-BCMA, including 8 of 9 responders and 4 of 9 non-responders, while the BCMA expression “recovered” in later follow up of these patients (55). Furthermore, BCMA loss was found in 3 out of 71 patients (4%) at progression in the KarMMa study investigating ide-cel (51). In BsAb, Truger *et al.* reported a case of homozygous BCMA gene deletion after AMG420 treatment, and this is the only patient with BCMA loss following BsAb therapies (56). So far, BCMA loss after ADC has not yet been reported. Altogether, findings based on flow cytometry of bone marrow demonstrated that complete or partial BCMA loss could occur in a small proportion of RRMM patients following anti-BCMA CAR T-cell therapy. However, at present, there is still limited experience with antigen loss following BCMA-targeted immunotherapies in MM patients, and BCMA expression level does not belong to the routine tests at relapse. Therefore, the *de facto* incidence of BCMA loss is largely unknown. Theoretically, BCMA loss could appear at any time in the course of the disease.

### **Potential mechanisms of BCMA loss**

Although BCMA loss has been reported in several studies, to date, the underlying mechanisms of this event are not fully understood. In this section, we will summarize the potential mechanisms contributing to BCMA loss based on the currently available data.

With the rapid evolution of genomic diagnostics like whole genome sequencing and single cell RNA sequencing, the underlying biological mechanisms of BCMA loss after anti-BCMA immunotherapies were elucidated in the past few years. Da Vià *et al.* reported for the first time that homozygous BCMA gene deletion led to a complete and irreversible loss of BCMA expression in a RRMM patient relapsed from ide-cel. Furthermore, heterozygous BCMA gene deletion was present in 22% (37 out of 168) of MM patients that were anti-BCMA therapy naïve (including a set of hyperhaploid MM cases), indicating a higher risk of homozygous BCMA gene alteration after anti-BCMA immunotherapies (15). Likewise, Samur *et al.* and Leblay *et al.* found a similar biallelic BCMA loss (mutation + deletion or deletion + deletion) as a resistance mechanism in other RRMM patients treated with anti-BCMA CAR T-cells (14, 16). In addition, homozygous BCMA gene deletion had also been confirmed in a RRMM patient who received AMG420 BsAb therapy (56). Findings of these studies



hypothesized that the strong selection pressure by these highly effective T-cell based anti-BCMA immunotherapies might lead to selective expansion of a pre-existing minor population of BCMA negative MM cells that could also appear in focal lesions and/or extramedullary manifestations due to the spatial tumor heterogeneity. As a result of this, we observed a permanent genetic and/or genomic changes after BCMA-targeted T-cell immunotherapies in these patients (**Table 1**). On the other hand, as anti-BCMA ADC is less effective than CAR T-cell or BsAb therapies in MM (17), the selection pressure of ADC should also be lower. Thus, the incidence of BCMA loss in patients treated with ADC might be lower than that in CAR T-cells or BsAb. Interestingly, most of the patients with BCMA gene deletion did also show TP53 gene deletion, and TP53 mutations were also more frequent in patients with both del16p and del17p than those who had only del16p or del17p. However, it is still unknown if the co-occurrence of BCMA and TP53 loss is only an accidental event or has some correlation with each other. This observation has likewise raised the question whether the patients with BCMA gene deletion present generally more genomic changes than those without BCMA gene alterations do. Moreover, due to the so-called branching evolution and spatial genomic heterogeneity, BCMA expression might be heterogeneous in various focal lesions and/or at different time points in the disease course (57-60). These issues have yet to be addressed in future studies.

As previously mentioned,  $\gamma$ -secretase can shed BCMA from the MM cell surface and release sBCMA into blood (21). This might explain the reversible partial loss of BCMA expression reported in previous studies (53, 55). Indeed, a preclinical study using cell lines and mouse models demonstrated that inhibited  $\gamma$ -secretase activity could up-regulate the BCMA density on plasma cells and therefore increase the efficacy of anti-BCMA CAR T-cell therapy *in vivo* (61). Together, targeting  $\gamma$ -secretase might be a strategy to improve the anti-MM activity of BCMA-directed immunotherapies in patients without permanent BCMA loss.

Another potential mechanism related to BCMA loss is the interference by sBCMA. In a recent study of Chen *et al.*, the authors showed that high level of sBCMA in serum might lead to consistent decrease in the binding of anti-BCMA antibody to tumor cells in patients with RRMM (62). Since the majority of RRMM patients display elevated sBCMA, the functionally available BCMA on MM cell surface may be significantly reduced by sBCMA, meaning a functional BCMA downregulation in these patients.

Theoretically BCMA loss could also be caused by the so-called antigen masking. In B-cell acute lymphoid leukemia relapsing from anti-CD19 CAR T-cell therapy, it has been reported that an unintentional introduction of CAR gene into a CD19 positive blast cell could lead to expression of CAR on leukemic cells. Subsequently, these CARs on the leukemic blasts

bound in cis to CD19 epitope on the cell surface, masking the tumor cells from recognition by the “true” CAR T-cells, meaning a functional loss of antigen (63). However, this phenomenon has not yet been reported in CAR T-cell therapies for RRMM.

Further potential mechanisms that could be associated with BCMA loss include trogocytosis, and some epigenetic mechanisms, which have been described in other malignant hematological diseases. Trogocytosis is a process in which the target antigen on tumor cell is transferred to CAR T-cells. In mouse models of B-cell leukemia, trogocytosis could reduce the antigen (CD19) density on tumor cells, leading to fratricide killing, T-cell exhaustion, and decreased anti-tumor effect by CAR T-cells (64). Moreover, after rituximab containing therapy, downregulation of CD20 was observed in patients with diffuse large cell B-cell lymphoma. When the CD20 negative lymphoma cells were treated with 5-aza-2'-deoxycytidine *in vitro*, the expression of CD20 mRNA recovered within three days, suggesting that some epigenetic mechanisms might be involved in CD20 downregulation after rituximab (65). Theoretically, these mechanisms may also be related with BCMA loss in RRMM patients. However, the role of these mechanisms in BCMA has not yet been extensively evaluated.

### ***Strategies to overcome BCMA loss***

Even if the BCMA-directed immunotherapies are not effective any more due to the loss of target, several other treatment options could still recapture response in these patients. In principle, the strategies to overcome BCMA loss are dependent on the underlying mechanisms. The reversibility of BCMA loss is the most crucial determinant for planning further treatments. Here, we will discuss some alternatives that could be considered in RRMM patients with BCMA loss.

Homozygous BCMA gene deletion may lead to irreversible and complete loss of BCMA expression on MM cell surface (14, 15). In these patients, BCMA-targeted therapies is irreversibly ineffective. One of the strategies to overcome this kind of BCMA loss is targeting other antigens such as CD38, G protein coupled receptor class C group 5 member D (GPCR5D), Fc receptor-homolog 5 (FcRH5), CD19, and SLAMF7, etc. (66) (**Figure 1B**). CAR T-cell and BsAb therapies targeting antigens other than BCMA have already been summarized in other review articles, which we would recommend for readers interested in this topic (18, 20, 46, 67, 68). For instance, in a recent phase 1 study, the GPCR5D-directed BsAb talquetamab showed an encouraging ORR of 70% in RRMM patients, 30% of whom were previously treated with anti-BCMA agents (69). Moreover, cevostamab, an FcRH5-targeted BsAb, achieved an ORR of 36.4% (8 out of 22) in RRMM with prior exposure to anti-

BCMA therapies (70). These findings suggested that targeting antigens other than BCMA might be feasible in RRMM with prior anti-BCMA therapies, and the BCMA expression status was irrelevant for these agents. However, in a recent study, heterozygous deletions in GPRC5D and CD38 gene were found in 15% and 10% of MM patients who were T-cell immunotherapy-naïve, respectively, suggesting an increased risk of antigen loss following highly effective immunotherapies. On the contrary, gains of FcRH5 and SLAMF7 gene were significantly more frequent in RRMM compared to newly diagnosed (ND) MM, indicating a low risk of antigen loss in the disease course. Importantly, heterozygous BCMA gene deletion was present in 4 out of 50 RRMM patients who were heavily pretreated with other drugs but anti-BCMA immunotherapy naïve (56). Altogether, the expression of immunotherapy targets should be evaluated in the treatment decision making.

Another option for patients with irreversible BCMA loss is the so-called “multi-targeted” immunotherapy. For instance, a BCMA/CD200/CD16A trispecific antibody was developed to link NK-cells and MM cells *in vitro*, and BCMA and CD200 double-positive MM were more effectively killed when compared to single-positive cells (71). For CAR T-cells, this could be realized by co-administration of different mono-targeted CAR T-cells or by constructing a CAR T-cell that could simultaneously recognize more than one antigens (72). In preclinical settings with cell lines and mouse models, bispecific CAR T-cells targeting BCMA and GPRC5D could enhance the interactions between MM and CAR T-cells and could prevent relapse due to BCMA loss (73). Likewise, Feng *et al.* reported on a BCMA/CD38-targeted bispecific CAR T-cell, which could trigger robust cytotoxicity against MM cells expressing either BCMA or CD38 *in vitro* and could achieve complete tumor clearance in mice (74). More recently, another bispecific CAR T-cell targeting BCMA and CD24 has been developed by an US group, with strong cytotoxic effect in xenograft mouse models. In a recently published phase 1 first-in-human trial, a bispecific CAR T-cell targeting BCMA and CD38 (BM38) showed an ORR of 87% and a median PFS of 17.2 months. Interestingly, as demonstrated by flow cytometry, two patients presented BCMA or CD38 negative RRMM at baseline, and both patients responded to BM38 treatment. Unfortunately, the underlying mechanisms of CD38 and BCMA loss at baseline were not described in their study (75). These results suggested the feasibility of bispecific CAR T-cells even in RRMM patients with expression of only one target antigen. Combination of two different mono-targeted CAR T-cells is an alternative strategy to bispecific CAR T-cells. Some clinical trials investigating the combinations of anti-BCMA CAR T-cells with CD19- or CD38-directed CAR T-cells have shown similar anti-tumor efficacy in RRMM when compared with published data on monospecific anti-BCMA CAR T-cell therapies (76, 77). Loss of one of the both antigens has already been reported after co-administration of two different mono-specific CAR T-cells in

RRMM (76). Theoretically, because of the high immune selection pressure, loss of both antigens may be possible after multi-specific immunotherapies. However, studies addressing this issue are still lacking.

When compared with homozygous BCMA gene deletion, the more common type of BCMA loss is the reversible downregulation of BCMA expression following anti-BCMA therapies (53, 55). If the BCMA status maintains positive at relapse, an anti-BCMA retreatment could be considered in RRMM with previous exposure to BCMA-targeted therapies (**Figure 1C**). Indeed, effective belantamab mafodotin treatment after relapse from anti-BCMA CAR T-cell therapy has been described in case reports (78, 79). The differences in the mechanisms of action between ADCs and CAR T-cells also support the rationale of anti-BCMA retreatment with belantamab mafodotin in these cases, as ADCs react with MM cells primarily via T-cell independent mechanisms (79). Another druggable target is the  $\gamma$ -secretase, which can cleave BCMA from the MM cell membrane and lead to partial BCMA loss on the cell surface (21). In a phase 1 first-in-human trial of anti-BCMA CAR T-cells in combination with JSMD194, a  $\gamma$ -secretase inhibitor, for RRMM patients, JSMD194 increased BCMA expression level and might augment the anti-MM activity of CAR T-cells, with comparable toxicity profile like other CAR T-cell trials. Moreover, teclistamab or belantamab mafodotin in combination with  $\gamma$ -secretase inhibitor, e.g. LY-411575 and nirogacestat, is currently under clinical investigation in phase 1 trials (80, 81).

## Conclusions

BCMA-targeted treatments such as CAR T-cells, BsAbs, and ADCs have brought new hope for the patients with RRMM, and will be administered in earlier lines of therapy. They help to improve tumor control and may be cure of MM. For these novel targeted immunotherapies, the persistence of target antigen on the MM cells is an essential requirement. Generally, irreversible complete BCMA loss, which is caused by homozygous BCMA gene deletion, seems to be relatively rare after BCMA-directed treatments, based on data from clinical trials investigating CAR T-cells or BsAbs. In contrast, reversible partial loss or downregulation of BCMA presents a more common event following these targeted immunotherapies. As BCMA-directed treatments are becoming a part of the standard of care for RRMM, the BCMA expression status should be considered in the selection of therapeutic agents for each patient. Monitoring of several biomarkers such as sBCMA and tumor BCMA expression level might be helpful for therapeutic decisions. Analyses of BCMA status on different levels, i.e. whole genome sequencing, single cell RNA sequencing, flow cytometry and

immunohistochemistry etc., will provide useful information to elucidate the underlying biological mechanisms of BCMA loss in each patient. These strategies are also in alignment with the concepts of precision medicine. To date, data on BCMA loss are still very limited, as BCMA-directed immunotherapy is a young research field. In addition, the resistance mechanisms are not fully understood, and BCMA loss is not the only cause of relapse after these novel immunotherapies. Therefore, further studies are needed at this point.

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## Tables

**Table 1: Selected published cases on BCMA loss following targeted immunotherapies for relapsed/refractory multiple myeloma**

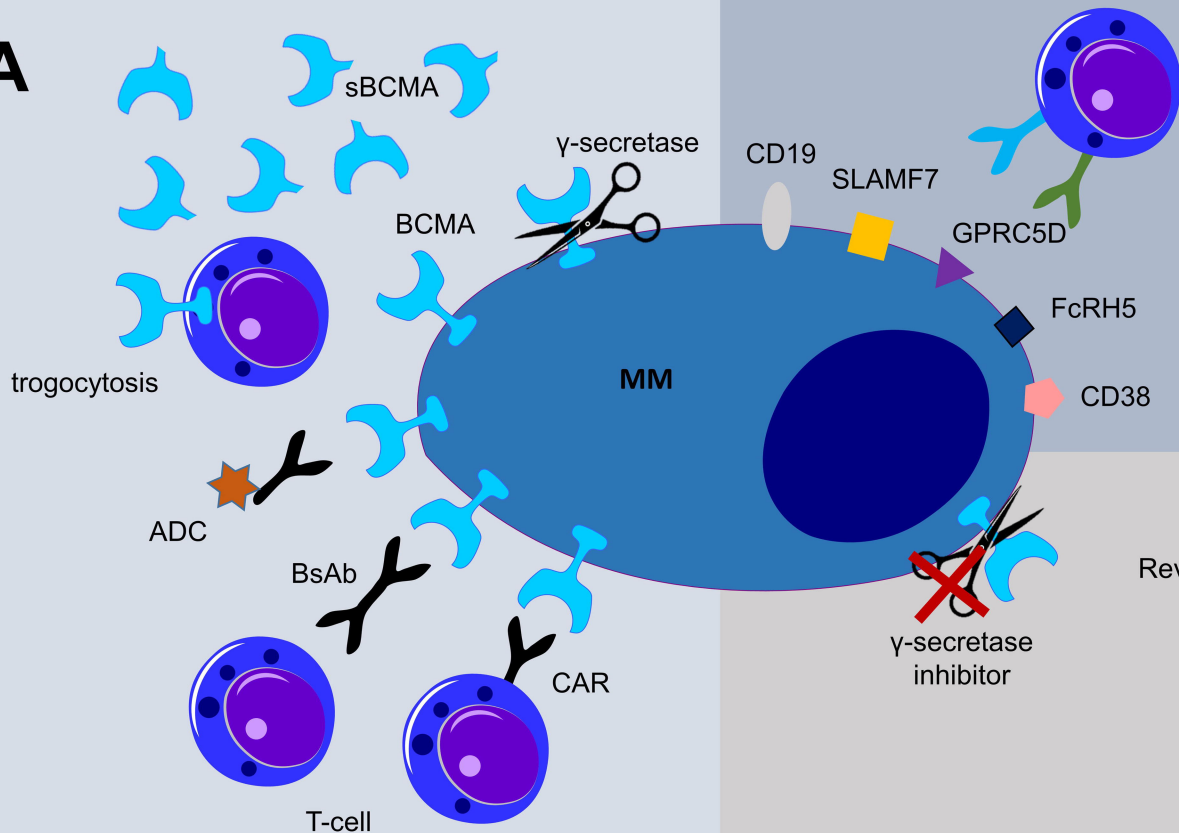
Authors	Year of publication	Type of immunotherapy	Product	Clinical trial identifier	Time point of BCMA loss	Methods	Frequency of BCMA loss in the study <sup>#</sup>	Biological mechanism of BCMA loss	Major findings	Reference
Ali <i>et al.</i>	2016	CAR T-cell	CAR-BCMA	NCT02215967	2 months after treatment	Flow cytometry	1/12	NR	Partial loss of BCMA expression in MM cells at progression in one patient	(52)
Brudno <i>et al.</i>	2018	CAR T-cell	CAR-BCMA	NCT02215967	56 weeks after treatment	Flow cytometry	1/16	NR	Mixed BCMA expression in one patient, with some MM cells negative for BCMA	(53)
Green <i>et al.</i>	2018	CAR T-cell	NR	NR	60 days after treatment	Flow cytometry	1/7	NR	Presence of BCMA negative MM cells in one patient. On MM cells retaining BCMA expression: 70% reduction of BCMA expression and fivefold reduction in BCMA antigen binding capacity in this patient	(54)
Cohen <i>et al.</i>	2019	CAR T-cell	CART-BCMA	NCT02546167	1 month after treatment	Flow cytometry	12/18	NR	Reduction of BCMA expression intensity in 67% (n=12) of the patients, including 8 of 9 responders and 4	(55)

									of 9 non-responders	
Truger <i>et al.</i>	2021	BsAb	AMG420	NCT02514239	6 months after treatment	IHC, WGS and RNA-seq	case report	Homozygous BCMA gene deletion	Complete BCMA loss caused by homozygous BCMA gene deletion in one patient	(56)
Da Vià <i>et al.</i>	2021	CAR T-cell	Idecabtagene-vicleucel	NCT03361748	5 months after treatment	IHC, WGS and RNA-seq	case report	Homozygous BCMA gene deletion	Complete BCMA loss caused by homozygous BCMA gene deletion in one patient	(15)
Samur <i>et al.</i>	2021	CAR T-cell	Idecabtagene-vicleucel	NCT02658929	8 months after treatment	IHC, WGS and RNA-seq	case report	BCMA gene deletion + mutation	Biallelic BCMA loss (mutation + deletion) in one patient	(14)
Leblay <i>et al.</i>	2020	CAR T-cell	NR	NR	NR	Cellular indexing of transcriptomes and epitopes by sequencing	case report	Homozygous BCMA gene deletion	Complete BCMA loss caused by homozygous BCMA gene deletion in one patient	(16)
Munshi <i>et al.</i>	2021	CAR T-cell	Idecabtagene-vicleucel	NCT03361748	NR	NR	3/71	NR	Loss of tumor BCMA expression was suspected in 3 of 71 patients (4%) at progression	(51)
Wang <i>et al.</i>	2022	CAR T-cell	China	ChiCTR-OIC-17011272	NR	Flow cytometry	1/21	NR	One (5%) patient relapsed with BCMA negative MM cells	(76)

BCMA - B-cell maturation antigen; BsAb - bispecific antibody; CAR T-cell - chimeric antigen receptor modified T-cell; IHC - immunohistochemistry; MM - multiple myeloma; NR - not reported; RNA-seq - single cell RNA sequencing; WGS - whole genome sequencing; # among the patients with evaluable BCMA expression at baseline and relapse

## Figure legend

**Figure 1: BCMA loss following targeted immunotherapies: (A) BCMA-directed immunotherapies:** At present, anti-BCMA CAR T-cell, BsAb, and ADC are available for the treatment of RRMM.  $\gamma$ -secretase can shed BCMA from cell membrane of MM cells and can subsequently release sBCMA into blood stream. Increase of sBCMA level can lead to decline of BCMA binding capacity on MM cells. BCMA could be transferred to CAR T-cells via trogocytosis, resulting in reversible partial BCMA loss. **(B) Irreversible complete BCMA loss:** In patients with irreversible complete BCMA loss, which is caused by homozygous BCMA gene deletion, other immunotargets could be considered for further treatments, e.g. CD38, FcRH5, GPRC5D, CD19, and SLAMF7. Multi-specific immunotherapies targeting more than one antigens seems to be a promising strategy to prevent drug resistance due to the loss of one single antigen. **(C) Reversible partial BCMA loss:**  $\gamma$ -secretase inhibitor is one option to increase BCMA density on MM cells. When the BCMA expression level recovers at later time points, an anti-BCMA retreatment could be considered. ADC – antibody drug conjugate; BCMA - B-cell maturation antigen; BsAb – bispecific antibody; CAR T-cell - chimeric antigen receptor modified T cell; FcRH5 - Fc receptor-homolog 5; GPRC5D - G protein coupled receptor class C group 5 member D; MM – multiple myeloma; RR – relapsed/refractory; sBCMA – soluble BCMA; SLAMF7 - signaling lymphocytic activation molecule F7

**A****B**

Irreversible and complete  
BCMA loss

↓

Targeting other antigens  
Multi-specific immunotherapy

**C**

Reversible and partial  
BCMA loss

↓

Anti-BCMA  
retreatment  
feasible