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Review Article

Current status of drug development for patients with multiple myeloma: a review of comparison in China and the rest of world

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ABSTRACT

Multiple myeloma (MM) is a highly heterogeneous malignancy. The treatment of MM has been significantly advanced in recent years. B cell maturation antigen (BCMA)-targeted immunotherapy and chimeric antigen receptor T (CAR-T) cell therapy have been approved for the treatment of relapsed and refractory MM (RRMM), which will be launched in China shortly. The CD38 (cluster of differentiation 38) antibody, daratumumab, improves the clinical outcomes both RRMM and newly diagnosed MM patients. The combination of daratumumab, bortezomib and dexamethasone achieved favorable outcomes as the first-line therapy in China. However, high-risk patients have limited benefits from these advanced therapeutics, and usually relapse early, progressing into aggressive end-stage MM. Therefore, novel therapies are sought to improve the cancer prognosis in these patients. This review furnishes an overview of the recent clinical developments of these novel drugs and compares the drug candidates under development in China to the rest of the world.

Statement of Significance: The article provides new insights into the general MM treatment. The article overviews MM drug candidates in diverse modalities and compares clinical status and the data of representative drugs. The article summarizes current the treatment paradigm for newly diagnosed MM and relapsed MM in China

KEYWORDS: multiple myeloma; drug development; therapeutic modality; immunotherapy; clinical progress

INTRODUCTION

Multiple myeloma (MM) is a B-cell-involved hematological malignancy caused by the excessive clonal proliferation of terminally differentiated plasma cells in the bone marrow [1, 2]. Unlike normal plasma cells, these differentiated plasma cells are cancerous myeloma cells, which produce protective immunoglobulins, for example, an abnormal immunoglobulin protein called the M-protein (monoclonal protein) that accumulates in blood vessels and tissues. The diagnostic characteristics of myeloma are a surplus number of plasma cells in the bone marrow and extramedullary sites, elevated levels of monoclonal M-protein in serum and urine, osteolytic bone lesions, renal insufficiency, anemia and immunodeficiency. The MM is developed after a series of genetic changes [3, 4] and the transition of the bone marrow microenvironment with an "angiogenic switch," triggering the progression of monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM) to lead overt MM. The risk of progression from SMM to MM is as high as 10% per year of the disease course for the first 5 years (50% in 5 years), and MM frequently relapses after the treatment with one or two therapeutic agents [5–7].

MM has different types and subtypes, and the differential diagnosis is critical to initiate a treatment plan. A physical examination, complete medical history and blood and urine evaluations, including complete blood count (CBC) and

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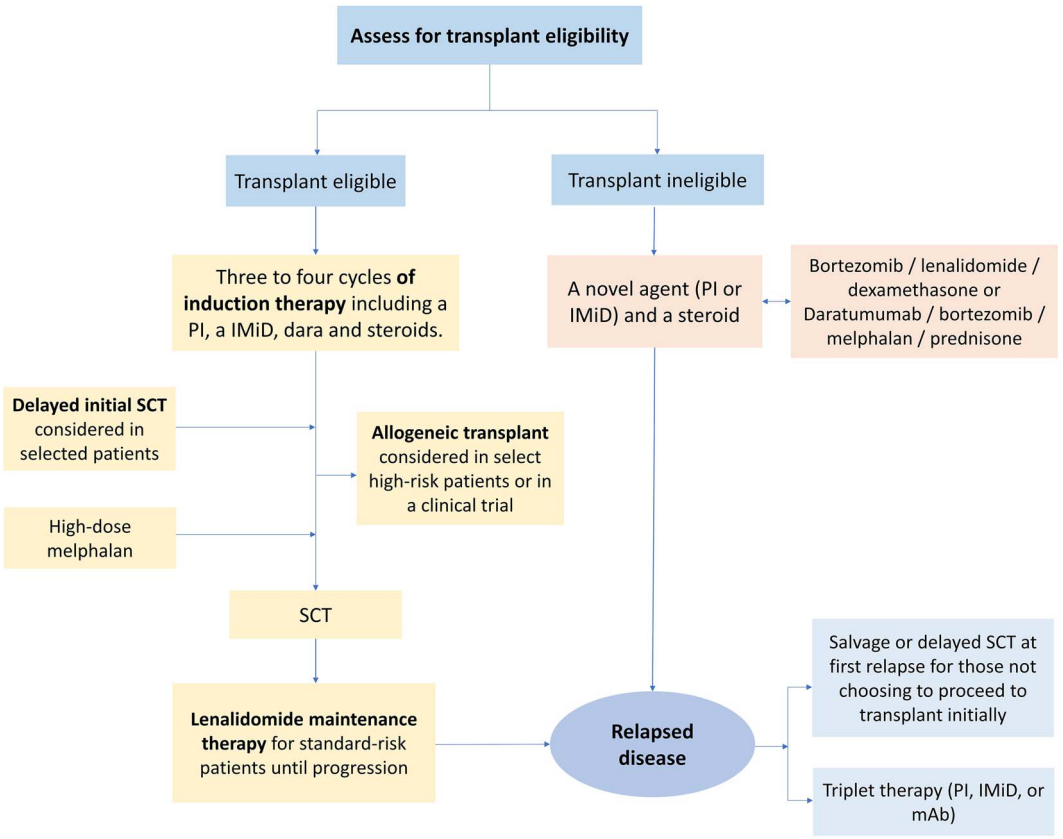

Figure 1. Flow diagram for general multiple myeloma treatment.

biochemical analyses, such as serum calcium and creatinine levels, amount of monoclonal M-protein in serum and urine and serum-free light chains measurements, are essential in diagnosing myeloma [8]. SMM heterogeneously comprises different patient groups and the risk of progression to MM decreases over time, thereby needing to be better risk stratified [9]. The progression of symptoms should be monitored frequently in patients with SMM, and more accurate genomic markers would be helpful to evaluate individual risk more precisely [9, 10].

MM is the second most common hematological malignancy in adults, accounting for 10%–13% of all hematologic malignancies [10, 11]. There were a total of one million cases, including 114 000 newly diagnosed cases of MM worldwide in 2017 [11, 12].

The incidence of MM varies widely across countries, ranging from 0.9 per 100 000 in Asian countries to 2.9 per 100 000 in the Americas and European countries. According to the Global Cancer Statistics 2020, the estimated new cases in 2022 in China and in the USA reach at 22 450 and 33 463, respectively, while the number of estimated death cases is higher in China than in the USA (17 360 vs. 14 150) [13]. African Americans, men and older adults are at increased risk of developing MM.

Since age is one of the risk factors, the incidence and prevalence of MM are expected to increase in the coming decades as the aging global population grows. Nevertheless, the survival rates of MM patients of all ages are now steadily improved due to the advancement in therapeutics [14, 15].

GENERAL TREATMENT STRATEGIES

MM is a treatable, albeit not fully curable, neoplastic disorder. Therefore, the treatment goal is to prolong survival, as measured by the achievement of a complete response (CR) and/or the prolongation of the overall survival (OS) [16].

The general treatment strategies in China are consistent with those in the rest of the world. In younger, otherwise healthy patients, the treatment of MM generally consists of a combination of therapies, including high-dose induction chemotherapy with two or three drugs, autologous stem cell transplantation (ASCT) and maintenance chemotherapy [17] (Fig. 1). Patients' age and renal function determine the eligibility for adopting ASCT. Patients who are not eligible for ASCT are treated with a more protracted chemotherapeutic regimen.

DRUGS FOR MULTIPLE MYELOMA

The standard chemotherapeutics induction regimens for MM in China and other countries included various proteasome inhibitors (PIs) and immunomodulators (IMiDs) in the past decade. In stem cell transplantation, drug therapies, including induction and maintenance therapies, constitute the treatment backbone [18, 19].

PIs, IMiDs and monoclonal antibodies (mAbs) have been incorporated into several treatment regimens. The three classes of anticancer drugs represented by bortezomib, lenalidomide and daratumumab have been the mainstay of myeloma treatment. Various drug candidates

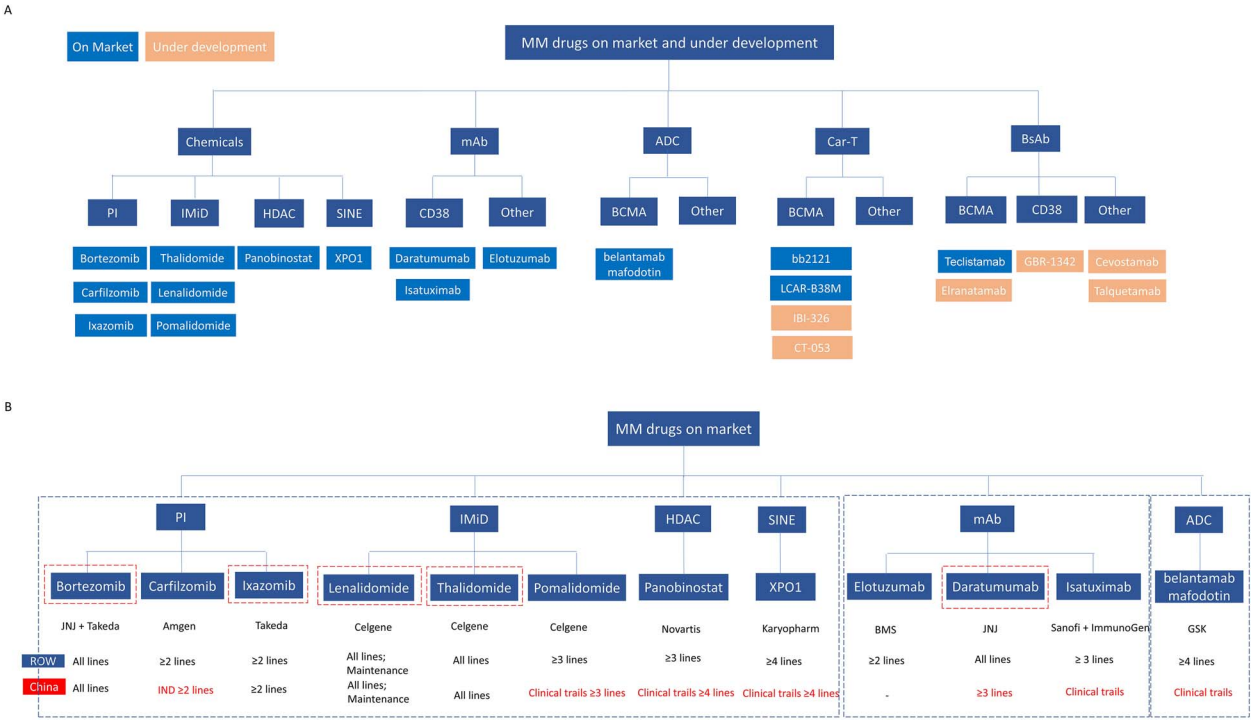

Figure 2. Overview of MM drug candidates on the market and under development.

targeting MM-specific antigens, such as B cell maturation antigen (BCMA), CD38 and Fc receptor homolog 5 (FcRH5), are currently in clinical development. Breakthrough drugs for MM on the market or under development are listed in Figure 2A. MM drugs can be categorized into chemicals [PI, IMiD, histone deacetylase (HDAC) and selective inhibitor of nuclear export (SINE)], mAbs, antibody–drug conjugates (ADC), bispecific antibodies (BsAbs) and chimeric antigen receptor T cell (CAR-T) therapeutics.

The approved drugs for MM and their market availabilities differ between China and other countries (Fig. 2B). Currently, there are more than 370 drug candidates worldwide and about 70 drugs in China under study for MM, showing a certain gap between China and other countries.

A) Various types of MM drugs on the market and under development.

B) Comparison of availability of representative MM drugs in China and the rest of the world (ROW).

mAbs: monoclonal antibodies; ADC: antibody drug conjugate; CAR-T: chimeric antigen receptor T cells; BsAb: bispecific antibody; PI: proteasome inhibitor; IMiD: immunomodulator; HDAC: histone deacetylase; SINE: selective inhibitor of nuclear export; BCMA: B cell maturation antigen.

CHEMICALS

The recent development and use of chemicals as MM drugs in China are similar to those in the rest of the world (Figure 3). The first-generation PIs have been the therapeutic backbone of multiple myeloma in the past few decades. A first-generation PI, bortezomib was approved by the US FDA in 2003 and eventually in China by 2009. Carfilzomib is a next-generation PI that selectively and irreversibly inhibits the proteasome enzymatic activities in a dose-dependent manner [20, 21]. Carfilzomib was approved by the US FDA in 2012 [22]. Ixazomib was approved by the FDA in 2015 and in China by 2018 and was the first oral PI with robust efficacy and a favorable safety profile in patients with MM.

The IMiD thalidomide has been used in combination with dexamethasone or melphalan/prednisone in the treatment of newly diagnosed MM and RRMM from 2003 [23, 24], despite its toxicity and high mortality in older adult patients [25]. One of the IMiDs, lenalidomide, exhibited more potent tumor necrosis factor (TNF)-α-inhibitory, antiangiogenic and immunomodulatory effects than thalidomide but with a more favorable neurologic safety profile. Lenalidomide was successfully launched in the US in 2005 for the treatment of MM and was approved in China by 2013 [24, 26]. A next-generation IMiD, pomalidomide was approved in 2013 in the US and 2020 in China (generics) for the treatment of MM patients who received at least two prior therapeutics, including lenalidomide and bortezomib, and had disease progression within 60 days of completion of the last therapy [27].

In addition to PIs and IMiDs, HDAC inhibitors have been used for the treatment of MM and reported to alter chromatin structure and affect transcriptional regulation, resulting in decreased transcription of tumor suppressor genes [28]. In 2015, panobinostat lactate became the first-approved HDAC inhibitor for MM in the US [29]. Panobinostat was also approved in Japan and the European Union in late 2015, and clinical trials investigating the use of panobinostat in MM patients who received at least four prior therapies were conducted in China.

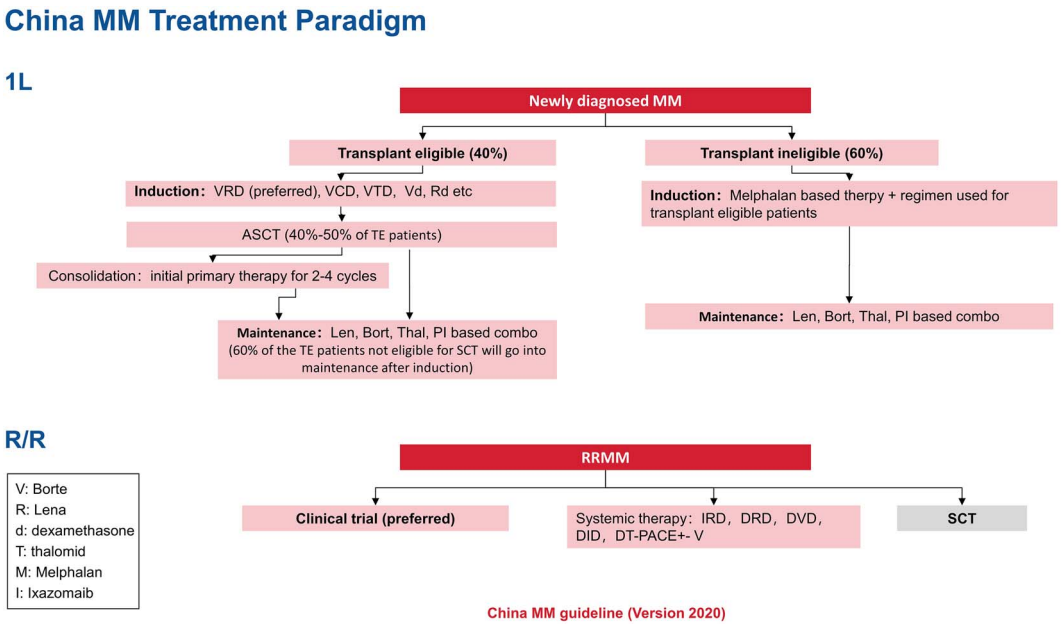

Figure 3. Current MM treatment paradigm in China.

Exportin-1, also known asXPO1 or CRM1, is a nuclear transport receptor that mediates exporting other proteins out of the nucleus and overexpressed in cancer cells, avoiding apoptosis and cell death [30]. Selinexor is an orally active SINE used against various hematological malignancies, including MM with less toxicity. In 2019, the US FDA granted accelerated approval to oral selinexor to be used in combination with dexamethasone for MM in adult patients who received at least four prior therapeutics (at least two PIs, one IMiD and an anti-CD38 mAb).

MONOCLONAL ANTIBODIES

The mAbs targeting MM cells pave the way for new approaches to treating MM. Antibodies display complex mechanisms of action, enhancing the immune system through antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) or hindering ligand-receptor binding. The number of available mAbs for various lines of treatment of MM differs between China and other countries (Table 1).

The most recent promising target, CD38, is a transmembrane glycoprotein highly expressed in hematological malignancies, including MM. The anti-CD38 mAb, daratumumab, has been reported to effectively kill isolated tumor cells obtained from MM patients, exerting ADCC and CDC, and inducing apoptosis through cross-linking of CD38 receptors [31, 32]. Daratumumab was approved by the US FDA in November 2015 as a single agent for treating patients with MM who received at least three prior lines of therapies, including a PI and an IMiD, or had dual resistance to PIs and IMiDs. The following year, the US FDA expanded this approval to use daratumumab in combination with lenalidomide/dexamethasone or bortezomib/dexamethasone in patients who received at least one prior therapy [31, 33]. In 2019, the US FDA further approved the use of daratumumab in combination with lenalidomide and dexamethasone (D-VTd) in patients with newly diagnosed MM who are ineligible for autologous stem cell transplantation, based on the better responses from D-VTd in 1085 patients [stringent complete response (Scr): 28.9% vs. 20.3%, P = 0.001). Subsequently, the US FDA approved a new subcutaneous form of daratumumab co-formulated with recombinant human hyaluronidase PH20 (rHuPH20) in 2020, reducing the drug administration time from hours to just minutes. Daratumumab was launched in China in 2019 and is currently used as a standard third-line treatment (Figure 3).

A second anti-CD38 MAb, isatuximab was approved to use in combination with pomalidomide and dexamethasone for the treatment of relapsed MM after at least two prior therapies (including lenalidomide and a proteasome inhibitor) in several countries, including the US, Canada and the European Union (EU) in 2020.

Elotuzumab is a humanized mAb against signaling lymphocytic activation molecule F7 (SLAMF7). Elotuzumab exerts ADCC, binding to CS1, stimulating host NK cells via the Fc receptor (CD16/FCGR3), triggering the release of perforin granules and leading to the lysis of the targeted myeloma cells. Previous clinical trials reported a higher overall response rate (ORR) and MRD-negative rate (50.1% vs. 35.6%) when elotuzumab was combined with lenalidomide, showing its potential in patients with RRMM [27, 33, 34]. In addition, Elotuzumab plus lenalidomide and dexamethasone (ERd) significantly improved progression-free survival (PFS) versus lenalidomide and dexamethasone (Rd) in patients with RRMM and 1–3 prior lines of therapy (LoTs) [35]. However, in patients with newly diagnosed multiple myeloma who are ineligible for hematopoietic stem-cell transplantation (HSCT), ERd did not significantly improve PFS versus Rd [36]. Elotuzumab remains an important treatment option for MM, but

Table 1. Monoclonal antibodies in clinical development for multiple myeloma

Monoclonal antibodies for the treatment of MM						
Target	**Drug name**	**Highest status**	**Treatment line**	**China (Y/N)**	**Status in China**	**Company**
CD38	Daratumumab	Launched	≥1	Y	Launched	Johnson & Johnson
	Isatuximab	Launched	≥1	Y	Phase III	Sanofi
	Felzartamab	Phase III	≥2	Y	Phase III	MorphoSys/ I-MAB
	Mezagitamab	Phase I/II	≥3	N	n. a	Takeda
	SAR442085	Phase I	≥3	N	n. a	Sanofi
SLAMF7(CS1)	Elotuzumab	Launched	≥2	N	n. a	BMS
Clinical Data Analysis						
Drug name	**Indication**	**Treatment combo**	**Enrollment**	**Clinical data**		**Reference**
Daratumumab	NDMM (Transplantation-ineligible)	D-Rd vs. Rd	737	30-month PFS: 70.6% 55.6% ($P < 0.001$)		NCT02252172
	NDMM (Transplantation-ineligible)	D-VMP vs. VMP	706	18-month PFS: 71.6% vs. 50.2%		NCT02195479
	Asian NDMM	D-VMP vs. VMP	220	mPFS: not reached vs. 18.2 months		NCT03217812
	NDMM (Transplantation-eligible)	D-VTd vs. VTd	1085	sCR: 28.9% vs. 20.3% ($P = 0.001$)		NCT02541383
Isatuximab	NDMM, TIMM	RVd + Isatuximab vs RVd	662	MRD-negative rate: 50.1% vs. 35.6%		NCT03617731
Felzartamab	RRMM	Rd + Felzartamab vs. Rd	291	n. a		NCT03952091; CTR20192600

*NDMM, newly diagnosed multiple myeloma; TIMM, transplantation-ineligible multiple myeloma; RRMM, relapsed or refractory multiple myeloma.

further research needs to focus on which patient population it may benefit the most. In late 2015, elotuzumab was approved and launched in the US to use in combination with lenalidomide and dexamethasone to treat MM after one to three prior lines of therapies. Clinical trials with elotuzumab have not yet been conducted in China.

ANTIBODY-DRUG CONJUGATES

ADCs are a promising new class of targeted therapeutic drugs for MM. ADCs improve the efficacy of naked antibodies, performing targeted delivery of highly cytotoxic chemotherapy to malignant cells. Compared with other antibody-involved approaches, ADC is independent of immune function, which is relatively compromised in MM patients [37].

Considering this potential benefit, novel ADCs have been explored for the treatment of MM. BCMA and CD138 were found as the most promising and active targets in treating MM through preclinical studies (Table 2). The BCMA-targeting ADC, belantamab mafodotin was recently approved in the US as a fifth-line treatment of RRMM based on the outcome from a single-arm trial reporting an ORR of 34%. The only ongoing MM ADC trial in China is a phase III clinical trial with belantamab mafodotin. The safety and antitumor activity of single-agent anti-CD138 ADC, indatuximab ravtansine in MM have been preliminarily investigated in phase I/IIa study and further studies are ongoing regarding the use of indatuximab ravtansine in combination steroids/IMiD.

Thus far, the development of ADC for the treatment of MM has remained at the stage of single-agent, dose-escalation trials. ADCs are yet to be explored whether ADCs could emerge as a tolerable monotherapy or a combination therapy in improving the treatment response. Belantamab mafodotin and indatuximab ravtansine have been elucidated in phase I/II trials when combined with proteasome inhibitors and lenalidomide, anticipating the first-line approval.

BISPECIFIC ANTIBODIES

BsAbs are engineered to recognize two different antigens simultaneously. The prototype of this class is the IgG-like bispecific T-cell engager (BiTE). The antibody's single-chain variable fragments bind to an antigen expressed

Table 2. ADCs in the clinical development for multiple myeloma

ADCs for the treatment of MM						
Target	**Drug name**	**Highest status**	**Treatment line**	**China (Y/N)**	**Status in China**	**Company**
BCMA	Belantamab mafodotin	Launched	≥4	Y	Phase III	GSK/Seagen
	HDP-101	Phase I/II	≥4	N	n. a	Heidelberg Pharma/Huadong
	CC-99712	Phase I	≥4	N	n. a	BMS(Celgene)/ Sutro
CD138	Indatuximab ravtansine	Phase II	≥4	N	n. a	Biotest
Clinical Data Analysis						
Drug name	**Indication**	**Treatment combo**	**Enrollment**	**Clinical data**		**Reference**
Belantamab mafodotin	RRMM, 4 L	Belantamab	221	ORR, 34%		NCT03525678
	RRMM, 3 L	Belantamab mafodotin + Pd	60	ORR, 88.9%		NCT03715478
	RRMM, 2 L	Belantamab mafodotin + Vd	52	ORR, 78%		NCT03544281
	NDMM (transplant-ineligible), 1 L	Belantamab + RVd	12	n. a		NCT04091126
	NDMM (transplant-ineligible), 1 L	Belantamab + Rd	18	n. a		n. a

*NDMM, newly diagnosed multiple myeloma; RRMM, relapsed or refractory multiple myeloma.

on a malignant cell and are linked to second single-chain variable fragments recognizing the T-cell antigen CD3. Subsequently, the malignant cells are effectively bridged to the T cells, which evoke cytotoxicity due to the proximity.

IgG-like BiTE formats of BCMA, CD38, GPRC5D and FcRH5-targeted BsAbs have been developed for the treatment of MM and used in clinical trials (Table 3). The high potency of anti-MM BsAbs at picomolar quantities in in vitro studies prompted the targeted applicability with high specificity but for relatively low expressing antigens, such as BCMA. Teclistamab targeting BCMA and CD3 receptors achieved an ORR of 65% in 157 patients as a late-stage treatment.

GBR 1342, a bispecific cell engager targeting CD38, is under investigation in phase I clinical trial (NCT03309111). Another phase I trial (NCT03399799) of JNJ-6440754, a bispecific T-cell engager targeting GPRC5D is ongoing following the demonstration of tumor growth suppression through preclinical models. The bispecific cell engager, cevostamab targeting FcRH5, is also evaluated in phase I, multicenter, open-label, dose-escalation study (NCT03275103). Besides, AMG-701 has entered the investigational new drug (IND) application stage in China, as well as Y150, a BsAbs targeting CD38 and CD3 manufactured by a Chinese company. In conclusion, BsAbs for the treatment of MM are still in a very early stage, and only a few trials in China are in progress.

CAR-T CELL THERAPIES

The key question regarding CAR-T cell therapy in the treatment of MM is whether the effectiveness and safety could be as promising as that in the treatment of B-cell acute lymphoblastic leukemia (B-ALL). In 2021 and 2022, two BCMA CAR-T cell therapies were approved in the US for treating RRMM, with ORRs of more than 70% and 90%, respectively (Table 4). The CAR-T cells incorporate the variable region into chimeric receptors, including costimulatory domains of T-cell receptors, to reprogram the engineered immune effector T cells to eliminate malignant cells. In the treatment of MM, CAR-T cells can target through differentiation antigens present only on plasma cells, the best example being BCMA. The durability of the BCMA CAR-T cell responses has not yet been determined, and multiple versions of this approach are under the investigational stage in the US and China. Increased numbers of RRMM patients participated in phase I trials, especially in China because the Chinese clinical guidelines stipulates

Table 3. BsAbs in the clinical development for multiple myeloma

BsAbs for the treatment of MM						
Target	**Drug name**	**Highest status**	**Treatment line**	**China (Y/N)**	**Status in China**	**Company**
BCMAxCD3	Teclistamab	NDA	RRMM, ≥4	Y	Phase I/II	J&J/Genmab
	Elranatamab	Phase III	RRMM, ≥4	Y	Phase I/II	Pfizer
	CM336	Phase I/II	RRMM, ≥4	Y	Phase I/II	Conmedbio
	EMB-06	Phase I/II	RRMM, ≥4	Y	Phase I/II	EpimAb
	REGN5458	Phase I/II	RRMM, ≥4	N	n. a	Regeneron
	Pavurutamab/Amgen701	Phase I	RRMM, ≥4	Y	IND	BeiGene/Amgen
	TNB-383B	Phase I	RRMM, ≥4	N	n. a	AbbVie
	Alnuctamab	Phase I	RRMM, ≥4	N	n. a	BMS
CD38xCD3	GBR1342	Phase I	RRMM, ≥4	N	n. a	Glenmark
	Y150	Phase I	RRMM, ≥4	Y	Phase I	YZY Biopharma
FcRH5xCD3	Cevostamab	Phase I	RRMM, ≥4	N	n. a	Roche
GPRC5DxCD3	Talquetamab	Phase II	RRMM, ≥4	Y	Phase I/II	J&J/Genmab
Clinical Data Analysis						
Drug name	**Indication**	**Treatment phase**	**Enrollment**	**Clinical data**		**Reference**
Teclistamab	RRMM, 4 L+	Teclistamab, Phase II	192	n. a		NCT04557098
	RRMM, 4 L+	Teclistamab, Phase I	157	Single-arm, ORR: 65%		NCT03145181
Elranatamab	RRMM, 4 L+	Elranatamab, Phase I	90	Single-arm, ORR: 70%		NCT03269136

*RRMM, relapsed or refractory multiple myeloma.

high number of recruitments for Phase I studies. In addition, BCMA has been coexpressed with other targets, such as CD19, TACI, CD38 and CS1 in designing dual CAR-T cell therapies, and several clinical trials on BCMA-targeting CAR-T cell therapies have been conducted in the US.

TREATMENT APPROACHES FOR NEWLY DIAGNOSED MM AND RELAPSED MM

Chemical drugs can be administered as monotherapy but are often used in combination or sequence to circumvent the clonal evolution making cells resistant and resulting in treatment failure. The most effective approach is combining at least three classes of drugs targeting different pathways simultaneously [38].

The selection of appropriate therapy for initial induction in patients with newly diagnosed MM and subsequent treatment of RRMM is based on the disease stage, risk stratification, patient age, the presence of comorbidities such as renal impairment [39], prior drug exposures, previous treatment response and drug toxicities [40, 41].

Long-term follow-up of the front-line treatments is required for the relapsed patients, based on the robust survival data. The unmet needs in clinical practice, such as the optimal induction therapy and the proper sequence of therapies, could be fulfilled based on the long-term therapy data.

DISCUSSION

Regarding advances in drug development for the treatment of MM, differences in drug availability and accessibility in China and the rest of the world exist due to varying drug developmental stages and therapy types. The most widely used drug combinations are almost similar in China and other countries. For example, PIs, IMiDs and dexamethasone combinations are commonly used. ASCT therapies in other countries offer more options with standard-of-care combinations and more approved drugs are available for first-line treatment, such as daratumumab-based combination therapies.

Breakthrough clinical studies using mAbs, such as daratumumab, elotuzumab and isatuximab, have revolutionized the treatment of MM. BsAbs platforms are rapidly evolving. More recently, new approaches in protein engineering have transformed cancer therapeutics again. Novel antimyeloma drugs, such as ADCs and BsAbs, showed encouraging preclinical results through multiple studies and are currently being investigated in clinical settings. Single-agent ADC was investigated in clinical trials, and the advanced one was launched in 2020. Combining these novel drugs with traditional chemical drugs seems more effective and might result in better clinical outcomes. On the other hand, the majority of trials investigating the feasibility of immune checkpoint inhibitors in MM have been suspended by the US FDA due to adverse side effects, and the recent

Table 4. CAR-Ts in the clinical development for multiple myeloma

CAR-Ts for the treatment of MM						
Target	**Drug name**	**Highest status**	**Treatment line**	**China (Y/N)**	**Status in China**	**Company**
BCMA	Ide-cel/BB2121	Launched	RRMM, ≥4	N	n. a	Celgene/Bluebird
	LCAR-B38M/JNJ4528	Launched	RRMM, ≥4	Y	Phase II	J&J/Legend Bio
	IBI326/CT103	Phase II	RRMM, ≥4	Y	Phase I/II	Innovent/IASO
	CT053	Phase II	RRMM, ≥4	Y	Phase I/II	CARsgen
	BCMA-CAR-T	Phase I/II	RRMM, ≥4	Y	Phase I	Simcere/Pregene
Clinical Data Analysis						
Drug name	**Indication**	**Treatment phase**	**Enrollment**	**Clinical data**		**Reference**
Ide-cel/BB2121	RRMM, 4 L+	Ide-cel, Phase II	140	sCR/CR, 33%; ORR, 73.4%		NCT03361748
LCAR-B38M/JNJ4528	RRMM, 4 L+	LCAR-B38M, Phase I/II	97	sCR, 67%; ORR, 97%		NCT03548207
IBI326/CT103	RRMM, 4 L+	IBI326, Phase I/II	79	sCR/CR, 58.2%; ORR, 94.9%		NCT05066646
CT053	RRMM, 4 L+	CT053, Phase I/II	14	ORR, 100%		NCT03975907
BCMA-CAR-T	RRMM, 4 L+	BCMA-CAR-T	34	ORR, 88.2%		NCT03661554

*RRMM, relapsed or refractory multiple myeloma.

failure of ERd vs Rd for NDMM has cast some doubt on the combined efficacy of Elotuzumab [42, 43].

Elsewhere in the world, two BCMA CAR-T cell therapies were approved in 2021 and 2022 for treating RRMM, with high overall responses and long progression-free survival, which will be soon approved in China. With the scaling up, the potential rescue effect of CAR-T cell therapies might result in broad application in the future. The development of effective treatments for advanced, high-risk (e.g., deletion of chromosome 17p) and refractory disease stages is highly needed. Of note, the first T cell engager, teclistamab was approved by the FDA in 2022 [44, 45].

While therapeutic advancements are made, MM patients continue to experience progressively shorter periods of remission followed by relapse, and their disease eventually becomes resistant to all available regimens, including PIs, IMiDs and mAbs [46]. Incorporating mAbs and new immunotherapeutics in the treatment regimen while simultaneously exploring new therapeutic modalities is critical to addressing the remaining clinical need. Identifying why there are differences in the available drugs or those under development between China and the rest of the world is imperative. For example, elucidating the differences in the disease characteristics, patient behavior, cost of drugs, types of health care and health delivery systems might provide insight into expanding the treatment landscapes. However, determining these differences is beyond the scope of this review and needs more real-world studies, which are in our plans for future studies.

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DATA AVAILABILITY

The authors confirm that the data supporting the findings of this study are available within the article.

CONFLICT OF INTEREST STATEMENT

Wenjin Li, Jingyu Zhang and Zhenyu Xiao are employees of Roche (China) Holding Ltd and hold stocks or other ownership interests in F. Hoffmann–La Roche.

Lei Huang was an intern of Roche (China) Holding Ltd.

Elizabeth Punnoose is an employee of Genentech, Ltd and holds stocks or other ownership interests in F. Hoffmann–La Roche.

AUTHOR CONTRIBUTIONS

Lei Huang (Data curation-Equal, Formal analysis-Equal, Project administration-Equal, Resources-Equal, Software-Equal, Visualization-Equal, Writing – original draft-Lead, Writing – review & editing-Equal), Jingyu Zhang (Project administration-Equal, Resources-Equal, Supervision-Equal, Writing – Review & editing-Equal), Elizabeth Punnoose (Investigation-Equal, Resources-Equal, Supervision-Equal, Validation-Equal, Writing – review & editing-Equal), Zhenyu Xiao (Methodology-Equal, Resources-Equal, Validation-Equal, Writing – review & editing-Equal), Wenjin Li (Conceptualization-Lead, Data curation-Lead, Formal analysis-Lead, Funding acquisition-Lead, Investigation-Equal, Methodology-Lead, Project administration-Lead, Resources-Lead, Supervision-Lead, Validation-Equal, Visualization-Supporting, Writing – original draft-Equal, Writing – review & editing-Lead).

ETHICS AND CONSENT STATEMENT

Not required.

ANIMAL RESEARCH STATEMENT

Not applicable.

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