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A look backward and forward in the regulatory and treatment history of multiple myeloma: Approval of novel-novel agents, new drug development, and longer patient survival

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Introduction

The past decade has seen significant advances in our understanding and treatment of multiple myeloma (MM) and its precursor diseases. These advances include gains in knowledge of the underlying pathobiology including molecular and cellular prognostic factors for disease progression. In parallel we have witnessed the availability of novel therapeutics. Together these advances have translated into improvements in long-term clinical benefit and survival in MM. Indeed, it has been shown that patients diagnosed in the last decade have experienced almost doubling of median survival time.¹ This manuscript aims to review and give further insight into drug development and novel drug approvals that have revolutionized the treatment of MM.

After half a century of treatments that conferred only modest benefit at the expense of toxicity the last decade has brought the rapid development of novel therapies and the development of laboratory techniques that have uncovered a deeper understanding of myeloma biology. An important development has been the ability to detect minimal residual disease (MRD) with greater sensitivity using both multi-color flow cytometry and next

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generation sequencing. This has been important because newer therapies have achieved higher response rates that in many instances have been “deeper” in nature.² With the importance of MRD as a marker of long-term clinical benefit established by two independent groups^{3,4} the International Myeloma Working Group (IMWG) recently revised the MM response criteria by adding “MRD negativity” as a deeper and more stringent response than stringent complete response.⁵ These advances have contributed to the longer overall survival (OS) of patients diagnosed with MM in the past decade and an expectation of further improvement in the coming decade with rapid approval of drugs by the US Food and Drug administration (FDA) and the European Medicines Agency (EMA).

Advent of Novel Therapies and Approvals by Regulatory Bodies

As already alluded to, improvements in survival for patients with MM in the past decade has largely been attributed to the introduction of more efficacious treatment regimens, beginning with autologous stem cell transplant (ASCT), followed by the introduction of novel therapies, namely immunomodulators (IMiDs) and proteasome inhibitors (PIs). Expectations are that in the coming decade improvements in survival will continue to accrue as novel agents are added to the IMiDs and PIs. With four new agents approved by the US FDA in the last year, there is great enthusiasm for the coming decade. More important than the number of approvals, is the unique characteristics of each drug approved and the forward thrust drug development in MM has received. US FDA approvals in the past year have included the first histone deacetylase (HDAC) inhibitor for MM (panobinostat), the first anti-CD38 antibody (daratumumab), the first orally administered PI (ixazomib) making an oral PI/IMiD triple regimen possible, and the first agent thought to activate anti-MM natural killer (NK) cells (elotuzumab). Below we will describe some of the evidence leading to novel drug approvals in MM this past decade by both the FDA and EMA below [Table 1].

Immunomodulatory drugs [IMiD]

Thalidomide was the first IMiD shown to have activity in MM and its efficacy led to the development of lenalidomide.^{6,7} Thalidomide and lenalidomide are currently indicated in combination with dexamethasone for the treatment of newly diagnosed MM (NDMM) and MM, respectfully. Lenalidomide was initially approved in the US based on two randomized studies that showed a benefit in time to progression (TTP) compared to control. The EMA approved thalidomide in combination with melphalan and prednisone as first line treatment of patients with NDMM 65 years or ineligible for high dose chemotherapy and lenalidomide and approved lenalidomide for transplant ineligible patients with NDMM and in combination with dexamethasone for relapsed refractory MM (RRMM).^{8,9} The most recent IMiD to receive an approval is pomalidomide which in combination with dexamethasone is currently indicated in the US and EMA for patients who have received at least two prior therapies including lenalidomide and a PI.^{10,11} Pomalidomide was initially approved in the US under the accelerated approval program based on objective response rate (ORR) from a study comparing pomalidomide to pomalidomide with dexamethasone in patients with RRMM who had previously received bortezomib and lenalidomide. The ORR in the combination arm was 33% compared to 8% in the pomalidomide only arm.¹¹ Subsequently, it received regular approval based on a phase 2 randomized study comparing

pomalidomide plus low dose dexamethasone to high dose dexamethasone. The median progression-free survival (PFS) for the pomalidomide arm was 4.2 months compared to 2.7 months with a HR of 0.68 ($p = .003$).¹²

Proteasome inhibitors [PIs]

Bortezomib was the first PI approved for MM and currently has received broad indications by both the FDA and EMA.^{13,14} Approvals in the US were based on monotherapy and combination randomized trials in the RRMM and NDMM setting, respectively showing efficacy in terms of TTP, PFS, and OS. Bortezomib was followed by carfilzomib which initially received accelerated approval in the RRMM setting for patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent.¹⁵ The approval was based on a single arm monotherapy study demonstrating an ORR of 61% and a median duration of response (DoR) of 7.8 months. Subsequently, the indication was broadened to include treatment in combination with dexamethasone or with dexamethasone and lenalidomide for patients with RRMM who have received 1-3 lines of prior therapy. This additional indication was based on the ASPIRE and APEX trials.^{16,17} In ASPIRE, PFS in the carfilzomib, lenalidomide, and dexamethasone arm was significantly improved (median, 26.3 months) compared to lenalidomide dexamethasone alone (median, 17.6 months) with a HR of 0.69 ($p = 0.0001$). The EMA has approved carfilzomib in combination with either lenalidomide and dexamethasone or dexamethasone alone for the treatment of patients who have received at least one prior therapy.¹⁸

Recently the FDA approved ixazomib, the first orally administered PI, which is indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received at least one prior therapy. The approval was based on the TOURMALINE-MM1 study, a double-blind randomized study that compared ixazomib, lenalidomide, and dexamethasone to lenalidomide and dexamethasone in patients who had previously received one treatment regimen.¹⁹ The median PFS was 20.6 months in the ixazomib arm compared to 14.7 months in the placebo arm with a HR of 0.74 ($p = 0.01$). In Europe, based on the negative opinion of the Committee for Medicinal Products for Human Use (CHMP) the EMA initially denied ixazomib an approval on 5/26/2016 stating it “was of the opinion that, based on the currently available data, the benefits of ixazomib did not outweigh its risks and recommended that it be refused marketing authorization.”²⁰ However the sponsor asked the EMA for a re-examination of its decision and this led to the conditional approval of ixazomib on 9/15/2016 in Europe. The CHMP reverted its initial decision after consulting with a group of disease experts and considering the safety profile and its route of administration. Given there was some uncertainty regarding the magnitude of PFS benefit, the marketing authorization was conditional and contingent on the sponsor providing further confirmatory data.²⁰

HDAC inhibitors [HDIs]

Panobinostat is the first HDAC inhibitor approved in MM. In the US it was approved under the accelerated approval program, and is indicated for use in combination with bortezomib and dexamethasone, for the treatment of patients who have received at least 2 prior

regimens, including bortezomib and an IMiD.²¹ It was studied in a double-blind randomized study that compared panobinostat, bortezomib, and dexamethasone to bortezomib and dexamethasone in RRMM (1-3 prior lines of therapy).²² The median PFS in the panobinostat arm was 12 months compared to 8 months in the placebo arm with a HR of 0.63 ($p<0.0001$). However, given the toxicity profile, the rate of on-treatment deaths, and the amount of missing data, the FDA consulted with the Oncology Drug Advisory Committee (ODAC) during the review process to attain advice on the benefit-risk analysis. Specifically, the combination arm appeared more toxic with serious adverse events reported in 60% of patients in the panobinostat arm compared to 42% in the placebo arm. Common grade 3-4 adverse events occurring more frequently in the panobinostat arm included thrombocytopenia (67% vs. 31%), lymphopenia (53% vs. 40%), diarrhea (26% vs. 8%), asthenia or fatigue (24% vs. 12%), and peripheral neuropathy (18% vs. 15%).²² Concerning adverse events included severe diarrhea and severe and fatal cardiac events, arrhythmias and electrocardiogram changes; on treatment deaths not related to disease was 7%.²²

The ODAC voted 5-2 against approval of panobinostat and the FDA meeting minutes state that “Those committee members who voted in the negative described unease regarding the lack of additional data, such as improvement in overall survival or quality of life endpoints, to support the observed improvement in PFS. While these committee members generally agreed that Trial 2308 demonstrated that panobinostat shows activity in patients with myeloma, concerns with the toxicity and uncertain magnitude of PFS improvement were cited as contributing to a negative benefit:risk profile overall.”²³ Based on the FDA review and the ODAC recommendations, FDA requested the drug sponsor submit additional data on the pre-specified subgroup of patients who had received at least two prior standard therapies, including bortezomib and an IMiD and based on these results granted accelerated approval.²⁴ The efficacy results in terms of PFS reported in this sub-group was a median of 10.6 months in the panobinostat arm compared to 5.8 months in the placebo arm with a HR of 0.52.²⁵ The granting of accelerated approval was contingent on the requirement the sponsor conduct confirmatory trials demonstrating a benefit in OS or disease-related symptoms and the creation of a risk evaluation and mitigation strategy (REMS) to educate prescribers on gastrointestinal and cardiac toxicities. The EMA similarly approved panobinostat in combination with bortezomib and dexamethasone for patients who have received at least two prior regimens including bortezomib and an IMiD.²⁶

Monoclonal antibodies

Daratumumab, the first anti-CD38 monoclonal antibody approved by the regulatory agencies, received accelerated approval by the FDA based on a single arm study demonstrating promising efficacy based on ORR in a highly pre-treated patient population. The current US indication is for the treatment of patients who have received at least three prior lines of therapy including a PI and an IMiD or who are double-refractory to a PI and an IMiD.²⁷ The single arm study demonstrated an ORR of 29% with a median DoR of 7.4 months. The most significant adverse event observed was infusion reaction (48%) but were mostly grade 1-2 in severity. Similarly, the EMA granted conditional approval with an indication for the treatment of patients whose prior therapy included a PI and an IMiD and who had experienced disease progression on the last therapy.²⁸

More recently, important data was presented and published on the utility of daratumumab in combinations. CASTOR, a randomized study compared daratumumab, bortezomib, and dexamethasone to bortezomib and dexamethasone in patients who had received at least one previous therapy and had experienced a partial response. The median PFS was not reached in the daratumumab arm and was 7.2 months in the control arm with a HR of 0.39 ($p<0.001$).²⁹ POLLUX, a second randomized study, compared daratumumab, lenalidomide, and dexamethasone to lenalidomide and dexamethasone in patients who had received at least one previous therapy. The median PFS was not reached in the daratumumab arm and was 18.4 months in the control arm with a HR of 0.37 ($p<0.001$).³⁰ The results of these studies are likely to lead to the use of daratumumab in triplet combinations earlier in the course of disease treatment.

Elotuzumab is an antibody that targets SLAMF7 a surface protein expressed on both MM and NK cells. Its activity is likely mediated through both antibody-dependent cell-mediated cytotoxicity (ADCC) of MM cells and direct activation of NK cells. The initial results of elotuzumab monotherapy were disappointing with no responses observed.³¹ However, subsequent early phase combination trials suggest possible synergism. This led to the randomized trial, ELOQUENT-2, that assigned patients who had 1-3 prior lines of therapy to either elotuzumab, lenalidomide, dexamethasone or lenalidomide and dexamethasone.³² The median PFS in the elotuzumab arm was 19.4 months compared to 14.9 months in the control arm with a HR of 0.70 ($p<0.001$). These results led to the granting of regular approval by the FDA with an indication in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.³³ Similarly, the EMA approved elotuzumab for patients at least one prior therapy.³⁴

MM – Extending the regulatory envelope

Possibly more so than many other cancers, MM exemplifies the increasing versatility and adaptability of regulatory agency approvals. Although, the “gold standard” efficacy endpoint is overall survival, in MM, most approvals have been based on durable ORR (accelerated) and TTP/PFS (regular). With the availability of modern and potent therapies, median survival of patients has approached to more than 10 years. This poses major challenges in duration of trials when using endpoints such as OS. Furthermore, with the number of available therapies ever expanding, most patients are likely to receive the common drug classes at some point of their disease which leads to cross-over confounding issues when using OS as a primary endpoint. Given these intricacies, FDA in general has used its “regulatory flexibility” in drug approvals to make available the appropriate drugs to the appropriate patient population. As previously mentioned, panobinostat received accelerated approval not based on the intention-to-treat population but the subgroup of patients who received the most benefit compared to risk (IMiD and PI refractory). Of the 4 most recent 2015 approvals, three (panobinostat, ixazomib, elotuzumab) were based on randomized studies utilizing PFS as the primary endpoint and daratumumab received accelerated approval based on a single arm study using ORR and DoR. In fact, most FDA accelerated approvals have been based on ORR from single arm studies but with the contingency that sponsors conduct randomized trial(s) to confirm clinical benefit. Furthermore, in very rare

disease populations outside of MM, FDA has used its flexibility and has granted regular approval based on small single arm studies when conducting a randomized trial would not be practical or ethical.³⁵ Novel therapies have demonstrated large magnitudes in complete response rates and therefore moving forward, the role of MRD negativity is likely to play an important role as a regulatory endpoint “likely to predict clinical benefit.” In fact, two recent meta-analyses have shown the association between MRD negativity and OS.^{3,4}

Ongoing clinical trials and new drugs in development

The MM treatment drug “space” is continuing to expand, with completely new drug classes, MM targets, and immunotherapies currently undergoing evaluation alongside phase 3 trials evaluating new combinations and lines of therapy for approved drugs. Immunotherapies, in particular, pose a very exciting time in drug development. Checkpoint inhibitors, for example, have altered treatment paradigms in various solid tumors including melanoma, non-small cell lung and head and neck cancer, and renal, transitional, and Merkel Cell carcinomas. These same checkpoint inhibitors have also entered the hematologic malignancy space with the approval of nivolumab for refractory Hodgkin's disease. In addition to PD-1/PD-L1 checkpoint inhibitors, cellular-based immune therapies appear very promising especially in MM. For example, chimeric antigen receptor (CAR) T cell therapies have shown promising signs of activity in early phase MM trials. CAR-T cell therapies under development target BCMA, an antigen expressed primarily on plasma cells and some B cells but not hematopoietic stem cells. In a dose escalation study of 12 patients, one patient achieved a stringent complete response, two achieved very good partial responses, and one patient a partial response with the remainder of patients with stable disease.³⁶

The number of trials listed on clinicaltrials.gov are testament to the accelerated tempo of MM drug development. As of 10/14/2016, when searching for “interventional, recruiting trials,” 336 MM clinical trials are found. These include 270 phase 1 or 2 trials, thirty-four phase 3 trials, and five phase 4 trials. Of the 34 phase 3 trials, thirty are specifically designed for MM, including four trials evaluating novel-novel agents not previously approved in any indication for MM (nivolumab, pembrolizumab, and venetoclax). Excitingly, of the 88 ongoing phase 1/2 or phase 2 trials, thirty are utilizing novel treatments including vaccines, CAR-T, and PD-1/PD-L1 therapies. Table 2 lists select phase 1-3 trials that are actively recruiting and utilize novel therapies in MM.

The introduction of more efficacious drugs with improved safety profiles compared to more traditional chemotherapies has allowed investigators to potentially move these drugs to the precursor SMM setting. When searching clinicaltrials.gov for “smoldering multiple myeloma” trials, 19 active and/or enrolling trials are found. Of these, four are industry-sponsored trials, two are phase 3 trials and twelve are phase 1/2 or phase 2, including eight trials that utilize agents not approved in MM including four utilizing various PD-1/PD-L1 inhibitors. Table 3 lists select trials utilizing novel-novel therapies in MM. Table 4 describes select promising drug targets be utilized and respective preclinical/early clinical evidence.

Future directions

Taken together, the availability of a potent armamentarium of novel drugs has ushered in a new era in the treatment of not only MM but potentially smoldering MM in the future. As more drugs are approved for MM, outstanding questions regarding patient management remain. In particular, the timing and line of therapy to use each of these novel therapies largely remain unanswered. It has been established that in both the NDMM and RRMM setting triple drug regimens are superior to doublets. However, thus far, all of the randomized trials leading to approvals have used doublet control arms and therefore which triple drug regimen should be used in different settings remains unclear. As drug development continues and randomized trials are designed, it will be important to utilize relevant combination regimens in control arms to not only attain important scientific data but also to maintain equipoise for patients enrolled on clinical trials. In addition, given the availability of fairly well tolerated monoclonal antibodies (elotuzumab and daratumumab), the utility of their addition to triple drug regimens will have to be understood. In the future, questions regarding the sequencing of regimens will also have to be addressed. Furthermore, with the incremental improvements being achieved using novel regimens, the benefit of up-front ASCT will have to be continuously addressed along with the duration of and drug(s) used for maintenance therapy. Practical treatment considerations also exist for the community oncologist and patient that not only revolves around using the “best” combination but evermore important the cost of novel regimens to patients and payers.

In conclusion, excitement continues to grow in the MM community as gains continue to be achieved in treatment regimens and monitoring (ex. MRD assessment). However moving forward, newer clinical trial designs maybe needed such as “master protocols” to help answer remaining uncertainties.

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Table 1
Drugs approved in the US and Europe between 2003-2016 for the treatment of patients with multiple myeloma

Drug	Drug class	Route/dose/schedule	FDA: approved indication	FDA: prior therapy	FDA: approval date [§]	FDA: approval type	FDA approval endpoint	EMA approval date [§]
Bortezomib	PI	IV/1.5 mg/m ² *	NDMM and RRRM	0	05/13/2003	Regular	ORR/DoR [#] , TTP, PFS, OS	04/26/2004
Carfilzomib		IV/20-56 mg/m ² *	Mono-therapy or in combo with d or Rd for RRRM	>1	7/20/2012	Regular	ORR/DoR [#] , PFS	11/19/2015
Ixazomib		PO/4 mg/q3wks with 1wk off	In combo with Rd for RRRM	>1	11/20/2015	Regular	PFS [#]	9/15/2016
Thalidomide	IMiD	PO/200 mg/qd	In combo with d for NDMM	0	5/26/2006	Regular	ORR/DoR [#] , TTP	4/16/2008
Lenalidomide		PO/25 mg/dl-21 of 28d cycles	In combo with d for NDMM, RRRM, maintenance	0	6/29/2006	Regular	TTP [#] , PFS	6/14/2007
Pomalidomide		PO/4 mg/dl-21 of 28 day cycles	In combo with d for RRRM	>2 (PI, IMiD)	2/8/2013	Regular	ORR/DoR [#] , PFS	8/5/2013
Liposomal doxorubicin	DNA inter-calator	IV/30 mg/m ² /d4 q21d cycle × 8	In combo with V for RRRM	>1 (no prior V)	5/17/2007	Regular	TTP [#]	1/22/2008
Panobinostat	HDACi	PO/20 mg/qod × 3 doses/wk for wks 1 and 2 q21d cycle × 8 cycles	In combo with Vd for RRRM	>2 (PI, IMiD)	2/23/2015	Accelerated	PFS [#]	8/28/2015
Daratumumab	Anti-CD38 MAb	IV/16 mg/kg/qwk × 8 wks, then every other wk; wk 9-24 then q4 wks	Monotherapy for RRRM	>3 (PI, IMiD)	11/16/2015	Accelerated	ORR/DoR [#]	5/20/2016
Elotuzumab	Anti-SLAMF7 MAb	IV/10 mg/kg/qwk × 8 wks, then every other wk	In combo with Rd for RRRM	1-3	11/30/2015	Regular	PFS [#]	5/11/2016

[§] Dates specified are for the 1st approved multiple myeloma indication for each drug;

* See carfilzomib and bortezomib label;

[#] Indicates endpoint used for initial approval

Abbreviations: PI: proteasome inhibitor; IMiD: immunomodulatory drug; HDACi: histone deacetylase inhibitor; Mab: monoclonal antibody; wk: week; d: day; q: every; NDMM: newly diagnosed multiple myeloma; RRRM: relapsed refractory multiple myeloma; ORR: objective response rate; DoR: duration of response; TTP: time to progression; PFS: progression-free survival; OS: overall survival; combo: combination; d: dexamethasone; R: lenalidomide; V: bortezomib.

Table 2
Select recruiting trials utilizing novel-novel agents in phase 1-3 multiple myeloma specific clinical trials

Phase	Class	Drug	Study Title	Sponsor
3	BCL-2 inhibitor	Venetoclax	A Study Evaluating Venetoclax in MM Subjects Who Are Receiving Bortezomib and Dexamethasone as Standard Therapy (NCT02755597)	AbbVie
	PD-1 inhibitor MAb	Nivolumab	Study of Combinations of Nivolumab, Elotuzumab, Pomalidomide and Dexamethasone in MM (NCT02726581)	Bristol-Myers Squibb
		Pembrolizumab	Study of Lenalidomide and Dexamethasone With or Without Pembrolizumab in Participants With ND Treatment Naive MM (NCT02579863)	Merck
			Study of Pomalidomide and Low Dose Dexamethasone With or Without Pembrolizumab in Refractory or RRMM (NCT02579863)	
2	Alkylating agent	Bendamustine	Multicenter Clinical Trial to Investigate the Efficacy and Safety of Bendamustine, Dexamethasone and Thalidomide in RR MM Patients After Treatment With Lenalidomide and Bortezomib or Which Are Ineligible to One of These Drugs (NCT01526694)	Azienda Ospedaliera di Bolzano
			Study of MLN9708 Plus Oral Dexamethasone or Plus Oral Cyclophosphamide and Dexamethasone or Plus Bendamustine and Dexamethasone or Plus Oral Thalidomide and Dexamethasone Followed by Maintenance With MLN9708 in ND Elderly MM (NCT02586038)	Silvio Aime
	BRAF/MEK inhibitors	Encorafenib Binimetinib	BRAF/MEK Inhibition in RRMM (NCT02834364)	University of Heidelberg Medical Center
	BTK inhibitor	Ibrutinib	Study of Ibrutinib in Combination With Bortezomib and Dexamethasone in Subjects With RRMM	Pharmacyclics
	CAR-T	CART-19	CART-19 Post-ASCT for MM (NCT02794246)	University of Pennsylvania
	XPO1 inhibitor (SINE)	Selinixor	Selinixor Treatment of Refractory Myeloma (NCT02336815)	Karyopharm Therapeutics
	MIL	MIL	Tadalafil and Lenalidomide Maintenance With or Without Activated Marrow Infiltrating	Sidney Kimmel Cancer Center

Phase	Class	Drug	Study Title	Sponsor
			Lymphocytes in High Risk Myeloma (NCT01858558)	
	PD-1 inhibitor MAb	Pembrolizumab	Phase 2 Multi-center Study of Anti-PD-1 During Lymphopenic State After HDT/ASCT for MM (NCT02331368)	University of Michigan Cancer Center
			Pembrolizumab in MM Patients With Residual Disease	PETHEMA Foundation
	Vaccine	Dendritic cell vaccine	Dendritic Cell/Myeloma Fusion Vaccine for Multiple Myeloma (NCT02728102)	NHLBI
	Viral	Edmonston viral strain	A Phase II Trial of Oncolytic Virotherapy by Systemic Administration of Edmonston Strain of Measles Virus (NCT02192775)	University of Arkansas
1 or 1/2	Alkylating agent	Bendamustine	Carfilzomib With Bendamustine and Dexamethasone in MM (NCT02002598)	Columbia University
			Study of Bendamustine and IXAZOMIB Plus Dexamethasone in RRMM (NCT02477215)	Medical College of Wisconsin
			Carfilzomib In Combination With Bendamustine And Dexamethasone In Refractory Or Relapsed Multiple Myeloma (NCT02056756)	Stichting Hemato-Oncologie voor Volwassenen Nederland
	Antibody-drug conjugate	SL-401 (IL3/diphtheria toxin)	SL-401 in Combination With Pomalidomide and Dexamethasone in Relapsed or Relapsed and Refractory Multiple Myeloma (NCT02661022)	Stemline Therapeutics
		GSK2857916 (BCMA/MMAF)	Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, Immunogenicity and Clinical Activity of GSK2857916 (NCT02064387)	Glaxo Smith Kline
	BiTE MAb	BI 836909 (BCMA/CD3)	Phase I Dose Escalation of i.v. and s.c. BI 836909 Monotherapy in Last Line Multiple Myeloma Patients (NCT02514239)	Boehringer Ingelheim
	BTK inhibitor	Ibrutinib	Study of Ibrutinib in Combination With Pomalidomide and Dexamethasone in Subjects With RRMM (NCT02548962)	Pharmacyclics
			Study of the Bruton's Tyrosine Kinase Inhibitor in Combination With Carfilzomib in Subjects With RRMM	

Phase	Class	Drug	Study Title	Sponsor
	CAR-T	CART-138	Treatment of Chemotherapy Refractory MM by CART-138 (NCT01886976)	Chinese PLA General Hospital
		CART-19	CART-19 Post-ASCT for Multiple Myeloma (NCT02794246)	University of Pennsylvania
		CART-BCMA	CART-BCMA Cells for Multiple Myeloma (NCT02546167)	
			Study of T Cells Targeting B-Cell Maturation Antigen for Previously Treated Multiple Myeloma (NCT02215967)	National Cancer Institute Clinical Center
			Study of bb2121 in Multiple Myeloma (NCT02658929)	bluebird bio
	CD38 MAb	Isatuximab	Isatuximab Single Agent Study in Japanese RRMM Patients (NCT02812706)	Sanofi
		MOR03087	A Phase I/IIa Study of Human Anti-CD38 Antibody MOR03087 in RRMM (NCT01421186)	MorphoSys AG
	HDAC inhibitor	Romidepsin	Study of Pomalidomide, Dexamethasone, and Romidepsin for RRMM (NCT01979276)	Cornell/Weill Medical College
		Vorinostat	A Study of Carfilzomib, Lenalidomide, Vorinostat, and Dexamethasone in RRMM (NCT01297764)	Hackensack Medical Center
	ICAM-1 Mab	BI-505	A Phase I/II Study of BI-505 in Conjunction With Autologous Stem Cell Transplant in MM (NCT02756728)	BioInvent
	IL-15 agonist	ALT-803	A Study of ALT-803 in Patients With RRMM (NCT02099539)	Altor Bioscience
	KSP inhibitor	Filanesib	Filanesib in Combination With Pomalidomide and Dexamethasone for RRMM Patients (NCT02384083)	PETHEMA Foundation
	Natural killer cells	Haploidentical NK cells	Expanded Natural Killer Cells for MM Study (NCT01040026)	University Hospital, Switzerland
PD-1 inhibitor MAb	Pembrolizumab	Anti-PD-1 (MK-3475) and IMiD (Pomalidomide) Combination Immunotherapy in RRMM (NCT02289222)	University of Maryland	
	Pidilizumab	Lenalidomide and Pidilizumab in Treating Patients With RRMM (NCT02077959)	Ohio State University	
PD-L1 inhibitor MAb	Durvalumab	A Study to Determine the Safety and Efficacy for the Combination of Durvalumab and Daratumumab in RRMM (NCT02807454)	Celgene	

Phase	Class	Drug	Study Title	Sponsor
	Proteasome Inhibitor	VLX1570	A Study of VLX1570 and Dexamethasone in Myeloma Patients (NCT02372240)	Vivolux AB
	XPO1 inhibitor (SINE)	KPT-8602	Study of the Safety, Tolerability and Efficacy of KPT-8602 in Patients With RRMM (NCT02649790)	Karyopharm Therapeutics
		Selinexor	Selinexor and Backbone Treatments of Multiple Myeloma Patients (NCT02343042)	
			Selinexor and Pegylated Liposomal Doxorubicin For RRMM (NCT02186834)	Lee Moffitt Cancer Center

Abbreviations: MM: multiple myeloma; MAb: monoclonal antibody; ND: newly diagnosed; RR: relapsed refractory; BiTE: Bispecific T cell engager; CAR-T: chimeric antigen receptor T cells; SINE: selective inhibition of nuclear export; MIL: marrow infiltrating lymphocytes; NHLBI: National Heart, Lung, and Blood Institute; HDAC: histone deacetylase; NK: natural killer

Table 3
Select on-going and not yet recruiting trials utilizing novel and novel-novel agents in smoldering myeloma

Drug	Class	Phase	Study Title	Sponsor	Recruitment
Carfilzomib	Proteasome Inhibitor	2	Carfilzomib in Treatment Patients Under 65 Years With High Risk SMM (NCT02415413)	PETHEMA Foundation	Recruiting
			Carfilzomib, Lenalidomide, and Dexamethasone for SMM (NCT01572480)	National Cancer Institute Clinical Center	Active, not recruiting
Daratumumab	CD38 MAb		A Study to Evaluate 3 Dose Schedules of Daratumumab in Participants With SMM (NCT02316106)	Janssen	Recruiting
Elotuzumab	SLAMF7 MAb	2	Trial of Combination of Elotuzumab Lenalidomide and Dexamethasone in High-Risk SMM (NCT02279394)	Dana-Farber Cancer Institute	Recruiting
			Biomarker Study of Elotuzumab in High Risk SMM (NCT01441973)	Bristol-Myers Squibb	Active, not recruiting
Ixazomib	Proteasome Inhibitor	2	Ixazomib and Dexamethasone in High Risk SMM: A Clinical and Correlative Pilot Study (NCT02697383)	Memorial Sloan Kettering Cancer Center	Recruiting
			Trial of Combination of Ixazomib and Lenalidomide and Dexamethasone in SMM (NCT02916771)	Dana-Farber Cancer Institute	Not yet recruiting
Pembrolizumab	PD-1 Inhibitor MAb	2	Pembrolizumab for SMM (NCT02603887)	M.D. Anderson Cancer Center	Recruiting
Atezolizumab	PD-L1 Inhibitor MAb	1	Pilot Study Of Anti-PD-L1, Atezolizumab In Asymptomatic Myeloma (NCT02784483)	Yale University	Recruiting
Nivolumab	PD-1 Inhibitor MAb	2	Nivolumab + Lenalidomide + Dexamethasone In SMM (NCT02903381)	Dana-Farber Cancer Institute	Not yet recruiting
Durvalumab/PVX-410	PD-1 Inhibitor MAb/Vaccine	1b	A Phase 1b Study of PVX-410, a Multi-Peptide Cancer Vaccine, and Durvalumab With and Without Lenalidomide for Patients With SMM (NCT02886065)	Massachusetts General Hospital	Not yet recruiting
Siltuximab	IL 6 MAb	2	A Study of Siltuximab in Patients With High-risk SMM (NCT01484275)	Janssen	Not yet recruiting
Anakinra	IL-1 receptor antagonist	1	Lenalidomide and Dexamethasone With or Without Anakinra in Treating Patients With Early Stage Multiple Myeloma (NCT02492750)	Mayo Clinic	Recruiting

Abbreviations: SMM: smoldering multiple myeloma; MAb: monoclonal antibody

Table 4
Select novel drug/biological targets in multiple myeloma drug development

Drug target	Rationale and evidence in MM
BCL-2	Early pre-clinical data suggest over-expression of BCL-2 in MM cells preventing apoptosis. ASCO 2016 phase 1 clinical trial abstracts showed activity as monotherapy and in combination with bortezomib ^{37,38}
BCMA	Pre-clinically, it has been shown that overexpression or activation of BCMA (selectively expressed on myeloma cells) by its ligand, APRIL, promotes human MM progression in vivo. ³⁹ This has led to CAR-T, BiTE, and ADC drug modalities (see text).
BRAF/MEK	A subset of tumors harbor V600 mutations. Early evidence of clinical activity in inhibiting the pathway ⁴⁰
BTk	ibrutinib is cytotoxic to malignant plasma cells from patients with MM ⁴¹ Inhibition of ITK may contribute to activity ⁴² Early data suggest clinical activity ⁴³
PD-1/PD-L1	Pre-clinical data show high expression of PD-L1 on myeloma cells and increased expression of PD-1 on NK and T cells ^{44,45} High response rates observed in single arm combination studies ⁴⁶
ICAM-1	Pre-clinically, an antibody against an epitope of ICAM-1, strongly expressed on the surface of MM cells from MM patients, showed macrophage-dependent anti-myeloma activity. ⁴⁷
KSP	Pre-clinically, KSP inhibitors have shown to arrest cells in mitosis and induces apoptosis due to degradation of the BCL2 family survival protein MCL-1 early phase clinical trials have suggested activity. ⁴⁸
XPO1	Pre-clinically, XPO1 was found to be a vulnerable target in MM. ⁴⁹ In cell lines, preliminary evidence suggest that inhibitors may restore sensitivity of multidrug-resistant myeloma cells. ⁵⁰

Abbreviations: MM: multiple myeloma; ASCO: American Society of Clinical Oncology; CAR-T: chimeric antigen receptor T cells; BiTE: bispecific T cell engager; ADC: antibody-drug conjugate; KSP: kinesin spindle protein