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Abstract

Introduction: Multiple myeloma (MM) is a hematologic malignancy characterized by proliferation of malignant plasma cells. Patient outcome has improved markedly over the last decades due to the introduction of novel therapeutic agents such as bortezomib, thalidomide and lenalidomide. However, MM still remains largely incurable and patients eventually become refractory to available treatments. To address this unmet medical need, a variety of new molecules are currently being developed in preclinical models and/or are being investigated in clinical studies.

Areas covered: We summarized available data on new investigational drugs showing anti-myeloma single-agent activity and that might have a role in the future therapeutic armamentarium against MM. Besides their single-agent activity, the synergic potential of these new agents with the currently approved drugs will be pivotal in their integration into consolidated MM backbone therapies. The drugs discussed include alkylators, new proteasome inhibitors, novel anti-CD38 monoclonal antibodies, Bcl-2 inhibitors, Cyclin-Dependent-Kinase inhibitor, Kinesin-spindle protein inhibitors,, MEK1/2 inhibitors, AKT inhibitors and PIM-Kinase inhibitors.

Expert Opinion: Isatuximab, oprozomib, melflufen, venetoclax and filanesib seem to be the most promising agents with single agent activity. Nevertheless, lack of clinical activity as single agent does not imply clinical inefficacy in combination treatments.

Keywords: multiple myeloma, single-agent, alkylator, proteasome inhibitor, monoclonal antibody, BCL-2 inhibitor, CDK inhibitor, kinesin-spindle protein inhibitor, MEK inhibitor, AKT inhibitor, PIM-Kinase inhibitor.

1. Introduction

Multiple myeloma (MM) is the second most frequent hematologic malignancy representing 10%[1] of all hematologic cancers and causing about 60000 annual deaths worldwide[2].

Approximately, the probability to be diagnosed with myeloma during a lifetime is 0.8 percent[3]. MM is more frequent in the elderly, with a median age at diagnosis of about 70 years[4].

MM onset[5] is due to neoplastic transformation of premalignant monoclonal plasma cells derived from post-germinal-center B cells. Primary and secondary genetic mutations, epigenetic alterations, genomic instability and cancer microenvironment play a fundamental role in the ontogenesis, clonal evolution and heterogeneity of MM cells[6].

Diagnostic criteria were recently updated by Rajkumar and collegues including biomarkers associated with a nearly inevitable progression to symptomatic myeloma. Besides evidence of ≥10% bone marrow clonal plasma cells or a biopsy-proven plasmacytoma and the presence of one or more CRAB features (hypercalcemia, renal failure, anemia, or lytic bone lesions), nowadays also clonal bone marrow plasma cells ≥60%, involved/uninvolved serum free light chain (FLC) ratio ≥100, and >1 focal lesion on magnetic resonance imaging (MRI) are considered myeloma-defining events[7].

MM is a heterogeneous biological entity[8], and its prognosis is related not only to host factors, but also to the disease characteristics, such as stage, cytogenetics and genomic features. Indeed, the International Myeloma Working Group (IMWG) has recently introduced the Revised International Staging System (RISS) to better dissect different disease categories within MM associated with different outcomes[9]. The RISS combines elements of tumor burden (serum albumin, β_2-microglobulin, and lactate dehydrogenase level) and disease biology [high risk cytogenetics such as t(4;14), t(14;16), or del(17p)].

As for the treatment of MM, patients may be eligible or not for autologous stem cell transplantation (ASCT). In addition, elderly patients or patients not eligible for ASCT may be categorized as fit or

frail[10] according to chronological age, performance status, and geriatric assessment[11], and their fitness status is another relevant aspect to select therapy.

MM prognosis, in terms of both progression-free survival (PFS) and overall survival (OS), is improving especially thanks to introduction of novel agents, such as immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs). The introduction of monoclonal antibodies (MoAb) is the most recent therapeutic advance in the field, and these agents are quickly changing the treatment landscape of MM. Median OS doubled in the last decade, reaching a median of 7-10 years[12]. ASCT-eligible patients are treated with novel agent-based induction therapy prior to stem cell harvest. Multi-drug combinations are particularly useful in patients with aggressive disease, such as plasma cell leukemia or multiple extramedullary plasmacytomas.

Melphalan-, bortezomib-, or lenalidomide-containing regimens are valid options in ASCT-ineligible patients, and treatment can be administered until progression, or for a fixed duration of time (12–18 months). Of note, available studies clearly suggest that maintenance therapy improves PFS[13].

Despite the indisputable progresses in quantity and quality of life, MM treatment still remains challenging: patients eventually relapse and may develop drug resistance. In case of relapse, the choice of regimen depends on many factors, such as patient fitness, duration of remission, type and number of prior regimens, response and toxicities from prior regimens, and disease aggressiveness. Patients who become refractory to IMiDs and PIs have a poor prognosis; therefore, there is an urgent need in biomedical research to develop newer agents with anti-myeloma activity.

Of note, monotherapy has still a role not only in maintenance setting but also in multi-refractory or frail elderly MM patients.

In this article, we will provide an overview of the most recent drugs used as single-agent that can have a role in MM. In particular, we will describe their mechanisms of action (Table 1) and summarize pre-clinical and clinical safety and efficacy results.

2. NEW INVESTIGATIONAL DRUGS

2.1 Alkylators

2.1.1 Meflufen

Melphalan-flufenamide (melflufen; l-melphalanyl-p-l-fluoro phenylalanine ethyl ester)[14] is a novel melphalan-containing prodrug, highly lipophilic, with a more potent antitumor activity[15] than its parent drug melphalan despite identical alkylating capacity. Melflufen, thanks to its high lipophilicity, is rapidly incorporated into the tumor cells, then hydrolysed by aminopeptidase N, which is highly expressed[16] in MM cells, leading to liberation and accumulation of melphalan inside malignant cells. Melphalan hydrophilicity is responsible for its slow rate of transportation out of cells, leading to 10-fold[17] higher concentration of melphalan, and it is associated with high tumor cell cytotoxicity. Preclinical in vitro and in vivo studies[16] demonstrate that melflufen is a more potent anti-MM agent than melphalan, it overcomes melphalan-resistance, induces synergistic anti-MM activity in combination with bortezomib, lenalidomide or dexamethasone, and has anti-angiogenic effects[18].

Melflufen is under evaluation[19] in combination with dexamethasone 40 mg weekly in an ongoing Phase 1-2a study. Relapsed and/or refractory MM (RRMM) patients with measurable disease and at least 2 prior lines of therapy are eligible (NCT01897714). The phase 1 portion established the maximum tolerated dose (MTD) of melflufen to be 40 mg every 3 weeks in combination with low-dose dexamethasone.

In the phase 2 portion, 31 patients received the MTD, 58% of them were double refractory (IMiDs and PIs) and 42% were triple refractory (IMiDs, PIs and alkylators). Treatment-related Grade 3 (G3) or G4 adverse events (AEs) were reported in 27 patients (87%). Those occurring in >5% of patients were: thrombocytopenia (68%), neutropenia (55%), anemia (42%), leukopenia (32%); febrile neutropenia, fatigue, pyrexia, asthenia and

hyperglycemia, each occurring in 6% of patients. Serious AEs (SAEs) occurred in 9 patients (29%), but were related to study drug in only 5 patients (16%) including 3 febrile neutropenia, 1 fever and 1 pneumonia. Fifteen (48%) patients discontinued treatment due to AEs. Twenty-three patients were evaluable for response: one achieved a very good partial response (VGPR) and 10 a partial response (PR), for an overall response rate (ORR) of 48%. Similar ORRs (≥PR) were seen in PI-refractory (43%), IMiD-refractory (40%), alkylator-refractory (62%), double-refractory (38%) and triple-refractory (50%) patients. The median PFS was 7.6 months (Table 2).

A phase 2, single arm study (NCT02963493)[20] will evaluate melflufen in combination with dexamethasone in MM patients refractory to pomalidomide and/or daratumumab. All patients in the study will be treated with melflufen on day 1 and dexamethasone on days 1, 8, 15 and 22 of each 28-day cycle. Estimated enrolment is 78 patients. Primary outcome measure will be the ORR at completion of treatment for all patients (approximately 2 years). Secondary outcome measures will be: progression free survival, overall survival and duration of response (Table 2).

2.2 New Proteasome Inhibitors

Proteasome catalytic activity was discovered in 1988[21] and led to the synthesis of bortezomib (PS-341)[22], the first-in-class PI that nowadays represents a cornerstone in MM treatment. Proteasome inhibition leads to the accumulation of cyclin- or CDK-inhibitors and tumor suppressor proteins; it interferes with the clearance of misfolded[23] proteins[24] and inhibits the NF-κB transcription factor pathway through the prevention of IκB (Inhibitor of NF-κB) degradation after its polyubiquitination by IKK (IκB kinase)[25]. Recently, ubiquitin-proteasome system has been identified as a regulator of DNA damage-repair proteins[26]. Indeed, proteasome inhibition augments chromosomal instability of neoplastic plasma cells impairing homologous recombination. This aspect

could have clinical implications in the design of combination treatments.

After bortezomib, several other PIs have been synthesized and are at different stages of clinical development. The boronic acid derivative ixazomib reversibly binds the chymotrypsin-like β_5-subunit and showed a good efficacy and safety profile in RRMM patients[27]. The oral administration route of the drug improves patients' quality of life and compliance. The intravenous epoxyketone carfilzomib[28] is an irreversible inhibitor of β_5-subunit chymotripsin-like active site that showed improved efficacy in RRMM[29], and promising results in the frontline setting[30]. More recently, other irreversible PIs have been introduced, such as the oral available epoxyketone oprozomib and the salinosporamide marizomib.

2.2.1 Oprozomib

Oprozomib (ONX-0912; previously PR-047) selectively inhibits the chymotrypsin-like activity of 20S proteasome subunit. In vivo studies, using 2 distinct human MM xenograft mouse models, showed that ONX-0912 was well tolerated, inhibits tumor growth, and prolonged survival in mice[31].

A multicenter, open-label, phase 1b/2 study (NCT01416428)[32] assessed single-agent oprozomib in patients with relapsed hematologic malignancies, including MM. In the phase 1b portion of the study, the MTD[33] of oprozomib was 300 mg/day on days 1, 2, 8, and 9 of a 14-day cycle (2/7 schedule) or 240 mg/day on days 1-5 of a 14-day cycle (5/14 schedule). During the phase 2 portion, 2 MM patients in the 5/14 schedule died due to treatment-related gastrointestinal (GI) hemorrhage. The study protocol was then amended and patients were subsequently enrolled on the step-up dosing schedules 2/7 (240 mg/day in cycle 1, stepped-up to a target dose of 300 mg/day thereafter) and 5/14 (150 mg/day in cycle 1, stepped-up to 180 mg/day thereafter). Therefore three cohorts of patients with three different

schedules were analysed: cohort A consisted of patients following the 2/7, 240/300 mg/day step-up schedule, and the original 2/7, 300 mg/day schedule; cohort B included patients treated with the 5/14, 150/180 mg/day step-up schedule; cohort C consisted of patients treated with the original 5/14, 240 mg/day schedule. Among patients with MM, the proportions of patients who discontinued treatment due to AEs were 44%, 12%, and 48% in the A, B, and C cohorts, respectively. The most common G≥3 AEs in the A, B, C schedules included diarrhea (27%, 12%, 33%), anemia (19%, 9%, 30%), thrombocytopenia (12%, 3%, 33%), and fatigue (19%, 9%, 15%), while G≥3 nausea and vomiting were reported mostly in cohort C (37%). Among response-eligible patients with MM, ORRs were 34%, 22%, and 25% in the A, B, and C cohorts, respectively. Among bortezomib-refractory MM patients, ORRs were 28% (n=29) in cohort A (biweekly schedule) and 17% (n=24) in cohorts B+C (5/14 schedules), respectively; among carfilzomib-refractory patients, ORRs were 8% (n=13) and 10% (n=21) in the cohorts A, and B+C, respectively (Table 2).

2.2.2 Marizomib

Marizomib (NPI-0052, Salinosporamide A), derived from the marine actinobacterium Salinispora tropica[34], potently inhibits all three 20S proteasome subunits[35] with a higher specificity compared to other PIs. Marizomib is able to overcome the phenomenon of compensatory hyper activation of the caspase-like (C-L) and trypsin-like (T-L) proteasome subunits during the process of effective inhibition of the chymotrypsin-like (CT-L) activity.

In a phase 1 study (NCT00629473)[36], the MTD was established as 0.5 mg/m^2 over 120-min infusion on days 1, 4, 8, 11, in 3-week cycles. The most common treatment related

AEs were fatigue (37%) and nausea (23%). Dose-limiting-toxicities (DLTs) were mainly neurologic and included cognitive impairment, hallucinations, aphasia, and gait disturbance. No G4 AEs were observed, and the ORR was 14% (Table 2).

Another phase 1 study (NCT00461045)[37] compared once weekly vs. twice weekly administration of marizomib in 68 RRMM patients. MTD was reached at 0.7 mg/m^2 over 10-min infusion once a week, and at 0.5 mg/m^2 over 120-min infusion twice weekly. DLTs were similar to those found in NCT00629473 trial, with the addition G3 acute renal failure, G3 nausea and vomiting, and G3 fatigue. ORR in the once weekly schedule was 3%, while it increased to 11% in the twice-weekly administration arm (Table 2).

2.3 MoAb targeting CD38

Human CD38 is a type II single chain transmembrane molecule of 45 kD, encoded by the CD38 gene on chromosome 4, ubiquitously expressed in virtually all tissues, not only on cell surfaces, but also in intracellular organelles[38]. As a receptor, it regulates the activation and proliferation of T lymphocytes by NF-KB recruitment; as an ectoenzyme, it catalyses the synthesis of nucleotides involved in Calcium fluxes regulation and activation of signalling pathways critical for different biological processes. In MM cells, CD38 is highly over-expressed and plays an important role in cell growth and survival, therefore it represents an attractive target for new drugs[39,40] (Figure 1). Daratumumab is the first of this class of novel agents, and showed impressive results in RRMM patients[41–43]. Based on these positive results daratumumab has been approved by the FDA as monotherapy in patients who received ≥3 prior lines of therapy, and in combination with lenalidomide-dexamethasone or bortezomib-dexamethasone in patients who have received at least one prior therapy. Evaluation of Daratumumab in the frontline setting is currently ongoing[44]. Another promising anti-CD38 MoAb currently under clinical evaluation as single agent is SAR650984 (isatuximab).

2.3.1 Isatuximab

SAR650984 (Isatuximab)[45] is a humanized IgG1 MoAb, generated by hybridoma technology, with strong proapoptotic activity and potent effector functions, such as complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). Isatuximab[46] also elicits a direct pro-apoptotic effect, capable of inducing crosslinking-independent apoptosis in addition to the crosslinking-dependent apoptosis. Preclinical investigations revealed that SAR650984 inhibited CD38 ectoenzyme activity.

In a phase 1 trial (NCT01084252)[47], 35 patients with RRMM were enrolled - 34/35 previously treated with PI and an IMiD (57% had carfilzomib and/or pomalidomide). SAR650984 was given IV weekly (QW) or every 2 weeks (Q2W). Dose levels were: 0.3, 1, 3, 5, 10 and 20 mg/kg Q2W and 10 mg/kg QW. MTD was not reached. Isatuximab-related G≥3 AEs included pneumonia (n = 3), and hyperglycemia, hypophosphatemia, pyrexia, apnea, fatigue, thrombocytopenia and lymphopenia in 1 patient each.

In the phase 2 of the study[48], 97 patients with RRMM (≥3 lines of anti-MM therapy or refractory to IMiDs and PIs) were randomized to isatuximab 3 mg/kg Q2W; 10 mg/kg Q2W x 2 cycles then monthly (Q4W); 10 mg/kg Q2W; and 20 mg/kg QW x 4 doses then Q2W of 28-day cycles. At doses ≥10 mg/kg, the ORR was 24% (18/74) and it was similar in all subgroups (defined by age, renal function, prior lines of therapy). Of note, the ORR raised to 44% (8/18) in patients with abnormal cytogenetics.

Most common AEs were nausea (33%), fatigue (30%), dyspnea (26%), and cough (24%), which were typically G≤2. Infusion-associated reactions (IARs) occurred in 49% of cases, mostly G≤2, 94% during the first infusion. Six patients discontinued therapy due to AEs, 2 due to IARs (Table 2).

Efficacy and safety of isatuximab are under evaluation also for intermediate- and high-risk smoldering MM (SMM) in the NCT02960555 phase 2, single arm study[49], in which an estimated group of 63 SMM patients will receive isatuximab 20 mg/kg IV on days 1, 8, 15, and 22 during cycle 1; isatuximab 20 mg/kg IV on days 1 and 15 during cycles 2-6; isatuximab 20 mg/kg IV monthly on day 1 during cycles 7-30. ORR and PFS will be calculated as primary and secondary outcome measures, respectively (Table 2).

2.4 Small molecules

2.4.1 Venetoclax

Venetoclax is an oral drug that selectively inhibits the antiapoptotic protein Bcl-2 (B-cell lymphoma 2) (Figure 1). This drug has shown significant activity in many hematological malignancies such as chronic lymphocytic leukemia (CLL)[50] and acute myeloid leukemia (AML)[51], in which tumor cells rely on Bcl-2 activity to maintain a prosurvival status. In vitro, venetoclax showed to induce death of MM cell lines and primary cells from patients. MCL1 is another antiapoptotic protein that is not targeted by venetoclax and acts as a resistance factor in cells exposed to the drug. Indeed, a high expression ratio of BCL2 to MCL1 predicts a peculiar sensitivity to venetoclax-induced killing[52]. Interestingly, MM cells harboring t(11;14) express a high BCL2/MCL1 ratio, laying the biological basis to look closely at the efficacy of this drug in this subgroup of patients in clinical trials. A phase 1, open-label study evaluated venetoclax monotherapy in RRMM patients[53]. Following a 2-week lead-in period, a 21-day cycle with oral daily venetoclax ranging from 300 to 1200 mg was given according to established dosing cohorts (3+3 design). At the last interim analysis (July 2016) 66 heavily pre-treated patients (median 5 prior lines, range 1-15) were enrolled in the study, 30 in the dose escalation cohorts and 36 in the safety expansion portion. More than 90% of patients were previously exposed

to Bortezomib and/or Lenalidomide and 61% were double-refractory. Given the strong biologic rationale, a large number of patients showing FISH positivity for t(11;14) were enrolled in the trial (30/66, 46%). All patients experienced at least an AE (67% grade 3-4), but only 8 patients had to discontinue the drug due to AEs. The MTD was not reached, thus the safety expansion cohort proceeded with a dose of 1200 mg. Common severe AEs were nausea, abdominal pain and infections. The ORR was 21% in the total cohort, but the vast majority of responses were reported in patients with t(11;14). In this population an impressive 40% of ORR and 27% of at least VGPR were reported with a median duration of response of 10 months (Table 2).

Given the interesting activity as a single agent, trials exploring the addition of venetoclax to consolidated MM backbone therapy are currently ongoing. Dexamethasone proved to increase the expression of Bcl-2 along with the pro-apoptotic protein Bim, sensitizing MM cells to venetoclax-induced cell death[54]. On the other hand, Bortezomib induces the degradation of the venetoclax resistance factor MCL-1[55,56] increasing venetoclax-induced cell death in MM xenograft models[57]. Based on these biologic data, a phase 1b study of venetoclax in combination with Bortezomib-Dexamethasone in RRMM is currently ongoing with intriguing initial results (ORR 58%, 84% in Bortezomib non-refractory patients)[58]. A phase 3, randomized, double-blind trial evaluating Bortezomib-Dexamethasone with either Venetoclax or placebo has been planned in RRMM patients (NCT02755597).

2.4.2 Dinaciclib

Dinaciclib is an injective small molecule that selectively inhibits many types of Cyclin-dependent kinases (CDKs), namely CDK1-2-5 and 9[59]. By binding regulatory ligands called cyclins, these proteins favour cell cycle progression, a mechanism frequently dysregulated in cancer. In first-in-human studies, Dinaciclib showed an acceptable

tolerability and activity in solid tumors[60] and CLL patients[61]. In MM, many recurrent cytogenetic abnormalities, in particular Immunoglobulin Heavy chain locus translocations, directly or indirectly cause the dysregulation of Cyclin D1, D2 and D3 genes. Single-agent Dinaciclib was tested in a phase 1/2 open label study in 27 patients with RRMM treated with less than 5 prior therapeutic lines[62]. Dinaciclib was given intravenously on day 1 of 21-day cycles until disease progression or unacceptable toxicity for a maximum of 12 cycles. In the dose escalation phase, 3 planned cohorts were established at 30, 40, and 50 mg/m^2. In the phase 2 part of the study, Dinaciclib was given at 50 mg/m^2, which was determined to be the MTD. Overall, patients received a median of 2 cycles (range 1-12), 15% of patients discontinued the drug due to AEs, the main reason for discontinuation was disease progression (67% of patients). The main observed AEs were leukopenia, thrombocytopenia and gastrointestinal toxicity, in particular diarrhea (87% of patients) and nausea (53% of patients), however grade 3-4 AEs were rare. ORR was 11%, whereas 19% of patients had a confirmed minor response or better. Median PFS was 3.5 months with a duration of response of 7.7 months (Table 2).

Dinaciclib is the first CDK inhibitor demonstrating single-agent activity in MM with a manageable safety profile. Interestingly, Dinaciclib-induced inhibition of CDK-5 interferes with unfolded protein response. In vitro studies showed that neoplastic cells in high-protein turnover disorders - like MM - could not be able to repair the damage caused by other antineoplastic agents[63]. This observation provided the rationale to using combination regimens with Dinaciclib. In particular, proteasome inhibitors exploit unfolded protein response[64] to induce myeloma cell death and the inhibition of CDK-5 in vitro sensitizes myeloma cells to bortezomib- or carfilzomib-induced apoptosis[65]. Currently a phase 1 trial evaluating the combination of Dinaciclib-Bortezomib-Dexamethasone in RRMM is ongoing (NCT01711528).

2.4.3 Filanesib

Filanesib is an injective small molecule acting as an inhibitor of Kinesin spindle protein (KSP) (Figure 1). During mitosis, KSP is essential to permit bipolar spindle assembly and centrosome separation. The inhibition of this protein led to a prolonged mitosis arrest and eventually cell death[66]. In MM cells arrested in mitosis by KSP inhibition, a rapid depletion of MCL-1[67] and the induction of apoptosis through the activation of the proapoptotic protein BAX (Bcl-2-associated X protein)[68] are the most active mechanisms inducing cell death. The first-in-human study in advanced solid tumors[69] showed no objective responses. A phase 2 trial of filanesib in RRMM[70] was started based on the particular sensitivity of the hematopoietic lineage in general and of MM cell in particular to KSP inhibition[69]. The trial included 2 cohorts evaluating both Filanesib as a single agent (cohort 1, 32 patients), and Filanesib combined with low-dose Dexamethasone (cohort 2, 55 patients). In both cohorts, Filanesib was given at a dose of 1.5 mg/m^2 intravenously on days 1-2 every 2 weeks. Patients with more than 2 prior treatment regimens were enrolled, notably 31% of patients enrolled in cohort 1 were refractory to Bortezomib, Lenalidomide and Dexamethasone. Only 8% of patients discontinued the trial due to AEs. DLTs were hematologic, with 30-40% of patients experiencing grade 3-4 neutropenia, thrombocytopenia and anemia. These AEs could be easily managed with optimized supportive care, for example the use of prophylactic G-CSF. Filanesib showed single-agent activity with an ORR of 16% and a duration of response of 8.6 months in cohort 1. In the Filanesib-Dexamethasone cohort, a similar ORR was observed (15%). Lonial and colleagues[70] identified a potential marker at baseline which was associated with Filanesib resistance. High plasma levels of an acute phase protein, namely α1-acid glycoprotein (AAG), reduced the active free portion of Filanesib, thus impairing its efficacy (ORR 0% in the high-AAG group versus 21% in the

low-AAG group) (Table 2).

Given the good tolerability and activity as single-agent even in heavily pre-treated patients, Filanesib combination therapies are currently being evaluated within clinical trials. Preliminary data from a phase 1 study showed that Filanesib-Carfilzomib combination induced an ORR of 42% in Bortezomib-refractory patients[71]. Other phase 1-2 trials are testing new combinations such as Filanesib-Bortezomib-Dexamethasone[72] (ORR 29% in 14 patients with proteasome inhibitors-refractory disease receiving filanesib at a dose of $\geq$1.25 mg/m^2) and Filanesib-Pomalidomide-Dexamethasone[73] (currently ongoing). Moreover, a large multicentre trial of single agent Filanesib in RRMM patients refractory to Carfilzomib and/or Pomalidomide is ongoing (NCT02092922).

2.4.4 Trametinib

Trametinib is an oral inhibitor of MEK1/2 (Figure 1), a protein kinase involved in the RAS/mitogen-activated protein kinase (MAPK) pathway[74]. The drug prevents phosphorylation of MEK1/2 inhibiting tumoral cell growth in vitro and in xenografts models, in particular when activating mutations in the MAPK pathway (KRAS, NRAS, BRAF) are present[74]. In advanced melanoma harbouring BRAF V600E/V600K activating mutation, Trametinib has demonstrated a good clinical activity leading to its approval by the Food and Drug Administration (FDA) as single-agent or in combination with a BRAF-inhibitor[75]. Recently, the mutational spectrum of MM cells has been defined by several groups[76–79], identifying the MAPK pathway as the most frequently affected by activating mutations. Mutations in KRAS, NRAS and/or BRAF, proteins acting upstream of MEK1/2, occur in up to 50% of MM cases. Based on these data, Hueck and colleagues retrospectively analysed a cohort of 58 patients with mutation in MAPK pathway, who were treated with off-label Trametinib as a single-agent or in combination

with other drugs[80] (Table 2). Patients had received a median of 5 prior therapies (range 1-20). The majority of them (51 patients) showed a confirmed mutation in KRAS, NRAS and/or BRAF, and only in 7 cases the mutation had been inferred by gene expression data. Only 22/58 patients received single-agent Trametinib and the ORR was 14%. The most common AEs related to the drug were rash (53%), diarrhea (31%) and cardiac toxicity (9%) leading to discontinuation respectively in 20%, 8% and 5% of cases. Data of this retrospective study need to be confirmed in a prospective clinical trial. Currently, a phase 2 biomarker-driven trial in RRMM patients is ongoing[81]: patients are independently recruited into KRAS/NRAS/BRAF mutated or non-mutated groups and receive oral Trametinib 2 mg daily on a 28-day cycle. In case of progression or suboptimal response, GSK2141795 (a PI3K/AKT pathway inhibitor) is added to the treatment based on the rationale that alternative activation of pro-proliferative pathways can overcome MAPK pathway inhibition[82]. There is initial evidence that the concomitant inhibition of PI3K/AKT pathway may augment efficacy, suggesting a potential synergy between these drug classes. However, safety could be an issue due to the poor tolerability of Trametinib in combination with another PI3K/AKT inhibitor (Afuresertib) in a phase 1 trial in patients with advanced solid tumors[83].

Another strategy to avoid the activation of alternative pathways guiding MM cell proliferation is to inhibit upstream regulators in the KRAS/NRAS/BRAF pathway. As an example, the overexpression of BRAF and of other RAF isoforms (such as ARAF and CRAF) activates both MEK-dependent and MEK-independent downstream mechanisms and the concomitant inhibition of all RAF isoforms may induce strong antimyeloma effects[84].

2.4.5 Afuresertib

Afuresertib is a reversible oral inhibitor of all the 3 isoforms of AKT (also known as protein kinase B) (Figure 1). AKT is a serine/threonine kinase involved in the phosphatidylinositide 3-kinase (PI3K)- AKT-mammalian target of rapamycin (mTOR) signalling and it acts as a hub for many cellular functions dysregulated in cancer, such as proliferation promotion, prevention of apoptosis and angiogenesis[85–87]. AKT is highly expressed in MM cell lines and primary cells from patients[88] and its expression augments along with disease progression. Differently from other cancer types, in MM, aberrant AKT expression is not driven by mutations in PI3K/AKT/mTOR pathway but largely by bone marrow microenvironment cytokine production[89]. Selective pharmacological inhibition of AKT led to MM cell death in preclinical studies[90]: these results led physicians to explore this drug in clinical trials. Spencer and colleagues[91] have evaluated the AKT-inhibitor Afuresertib in a first-in-human study in 73 patients with advanced relapsed or refractory hematologic malignancies. In this phase 1/2 trial, RRMM patients accounted for the 47% of total patient population (median prior lines 5.5; prior PIs (88%), IMiDs (97%). Afuresertib was given as a single-agent and in dose-escalation from 25 to 150 mg orally once daily. Two DLTs (grade 3 abnormal liver function tests) were reported at 150 mg, therefore the dose chosen for the second part of the study was 125 mg. The most frequent treatment-related AEs were gastrointestinal intolerance with nausea (23.3%), diarrhea (20.5%), dyspepsia (19.2%) and reflux disease (15.1%). Grade 3 AEs were rare (< 10%), and no grade 4-5 AEs were observed. The ORR in MM patients was 8.8% (3/34) with a median duration of response of 319 days (range 210-569). Efficacy was dose-dependent with no objective responses observed with doses lower than 125 mg. Three additional patients showed a minimal response (median duration of response 357 days, range 158-485).

Afuresertib showed single-agent activity with a good safety profile (Table 2). Moreover, preclinical studies found a synergistic activity of this drug in combination with bortezomib, inducing cell death in MM cell lines[92]. Afuresertib-bortezomib-dexamethasone demonstrated promising clinical activity in a phase 1b study, with 33% ORR in Bortezomib-refractory patients[93].

2.4.6 LGH447

LGH447 is an oral, potent and selective pan-PIM kinase inhibitor (Figure 1). PIM proteins are serine/threonine kinases that were first identified as a preferred Proviral Integrarion sited of Moloney (PIM) murine leukemia virus in mice models of virus-induced lymphomas[94]. There are 3 homologues proteins belonging to this family (PIM1-PIM2-PIM3). Each of these proteins is capable to induce a tumoral behaviour in the cells through the promotion of cell-cycle progression and survival[95]. Interestingly, PIM proteins are constitutively expressed in hematologic tumors and in particular PIM-2 is expressed at higher levels in MM in comparison with other malignancies[96], playing a role also in MM-associated bone reabsorption[97]. Pharmacologic inhibition of PIM-2 impairs MM cell proliferation in vitro and in xenograft models, mainly through downregulation of mammalian target of rapamycin C1 (mTOR-C1) activity[96]. Overall these data prompted the clinical development of PIM inhibitors.

The activity and safety of LGH447 in MM patients has been evaluated in a first-in-human open-label phase 1 dose-escalation study[98]. Overall, 54 heavily pre-treated RRMM patients were enrolled (median of 4 prior lines of therapy), and 69% of them were already exposed to both PIs and IMiDs. Treatment consisted of single-agent oral LGH447 once daily given until progression or unacceptable toxicity. Doses ranged from 70 mg to 700 mg, and the identified MTD was 500 mg. AEs were mild, in particular grade 3-4 toxicities

were mainly hematologic (thrombocytopenia 19%, anemia 19%, and neutropenia 13%). Only 7% of patients discontinued due to AEs. ORR was 10% (4 PR and 1 VGPR in 48 evaluable patients), with an additional 10% of patients achieving a minimal response (Table 2). Notably clinical responses were not seen below the dose of 150 mg daily.

The association of this drug with dexamethasone, bortezomib, lenalidomide, pomalidomide[99] and afuresertib[100] showed synergy in vitro, supporting the evaluation of combination therapies including PIM inhibitors in MM patients.

3 EXPERT OPINION

In MM several drugs with a strong biologic rationale and interesting pre-clinical results have been tested as single-agents. However very few of them have achieved high clinical results to be further investigated and possibly be approved as standard treatments.

Of note, Kortuem et al analyzed many phase 1 and 2 clinical studies to better understand the future role of new drugs as single agents and they concluded that an ORR cut-off of 20% was highly predictive of future regulatory approval[101]. Nevertheless, heavily pretreated patients who are often refractory to all available drugs might fail to achieve at least 20% ORR with a single-agent approach, and this could prevent them from receiving potentially useful molecules. In a complex disease as MM, the lack of single-agent activity does not imply the ineffectiveness of such agent. Indeed, as an example, although elotuzumab did not show clinical activity as single agent[102], it led to remarkable results in terms of PFS and ORR in the relapsed/refractory setting when used in combination with lenalidomide and dexamethasone[103]. The drugs reviewed in this paper could be divided into two main groups. The first group is composed by drugs belonging to PIs, anti-CD38 MoAbs, and alkylators classes, whose efficacy in MM treatment has been

already established. The second group includes drugs referred to as “small molecules”, and they represent new, protein inhibitors acting on recently identified targets in MM.

In the first group, isatuximab seems to be the most promising single agent in terms of safety and efficacy, confirming CD-38 directed therapy as a valid strategy in MM field. Its efficacy in patients previously treated with daratumumab will be evaluated in a phase 1b trial[104].

In the setting of SMM the current standard of care is observation. However, there is evidence of delayed progression to active disease and increased OS in patients treated with lenalidomide and dexamethasone[105], and the appropriate strategy in this setting is a matter of debate. In particular, the NCT02960555 phase 2 trial will assess the role of isatuximab in SMM patients.

Oprozomib, an oral PI with characteristics very similar to carfilzomib, showed an ORR >20%. Notably these results were observed also in bortezomib-refractory patients. GI toxicities were the major concern, especially for 2 fatal cases of treatment-related GI haemorrhages that lead to protocol amendment and added a step-up dosing approach.

Although Marizomib is an inhibitor of all 20S proteasome subunits, it did not show exciting results in terms of ORR (≈10%) as a single agent. Nevertheless, safety profile of marizomib seems acceptable. These results encourage the evaluation of marizomib in combination with other drugs with a compatible safety profile.

In the future, the AEs spectrum and the efficacy of new PIs in patients refractory to first and second-generation PIs (as an example Bortezomib and Carfilzomib) will help us to choose the right PI in the right patient at the right time. Moreover, a deeper knowledge of PIs resistance mechanisms is needed to make more appropriate clinical choices. For instance, PI-resistant MM cells with a more immature phenotype could be less dependent

on unfolded protein response for their survival, theoretically leading to cross-resistance to all the drugs belonging to this class[106].

Although melflufen was not evaluated as single-agent stricto sensu because it was used in association with low-dose dexamethasone, the ORR of 47% reported in the phase 2 trial seemed to confirm the therapeutic role of alkylators in MM. Further studies are needed to define safety profile, especially in terms of secondary neoplasm. Notably, the NCT02963493 trial will evaluate melflufen in pomalidomide- and/or daratumumab-refractory patients. This could be a strategy to overcome the biologic heterogeneity of MM cells[107], given the generalized cytotoxic effect mediated by this melphalan-analogue agent.

Small molecules specifically target biologically relevant proteins in MM cell biology. Unfortunately, efficacy results of targeted therapy – as well as results with small molecules - are limited by the biologic heterogeneity of malignant cells[77]. So far, small molecules have in fact been used in heavily pretreated patients where clonal heterogeneity of MM cells reaches its maximum levels[79]. The clinical activity of these drugs in earlier MM stages needs to be further evaluated. Moreover, because of the inproved life expectancy of MM patients, nowadays it is not infrequent to find patients refractory to all approved therapeutic options after years of treatments. In these clinical situations, having drugs with new mechanisms of actions without any type of cross-resistance to previous treatments is crucial.

Venetoclax is the only small molecule showing excellent single-agent clinical results in terms of ORRs (21%), increasing to 40% in the subgroup of patients with t(11;14). In the near future this drug could represent the first example of successful tailored treatment based on MM cell characteristics. Furthermore, patients with primary Plasma Cell Leukemia are frequently positive for t(11;14)[108] and show a very poor outcome with

currently used treatments. Therefore, in the future venetoclax might also be investigated and might play a central role in this setting. The safety profile is another advantage of Venetoclax, since only 12% of patients had to stop treatment for toxicity.

Dinaciclib, filanesib, trametinib, afuresertib and LGH447 showed ORRs ≈10-15% in heavily pretreated RRMM patients, encouraging their integration into MM backbone treatments according to biologic rationale and safety profile. For example, filanesib achieved a 16% in ORR as single agent, while when combined with carfilzomib it reached a 42% ORR[71], even among bortezomib-refractory patients. All small molecules are quite well-tolerated. Moreover, apart from dinaciclib and filanesib, these agents are orally available, thus easy to be administered and with a good impact on patients' quality of life. Further studies are needed to better define their safety and efficacy profile when used in combination with other drugs and also to identify the best combination in PI or IMIDs-based backbone treatments.

The identification of biomarkers to predict MM cells sensitivity to each of these drug classes will be pivotal to select the most suitable patients' population to treat.

In conclusion, isatuximab, oprozomib, melflufen, venetoclax, and filanesib appear to be the most promising drugs with single-agent activity. A better definition of their safety and efficacy profile is currently ongoing, and these agents could improve the treatment armamentarium for patients with relapsed/refractory MM or intolerant to standard regimens.

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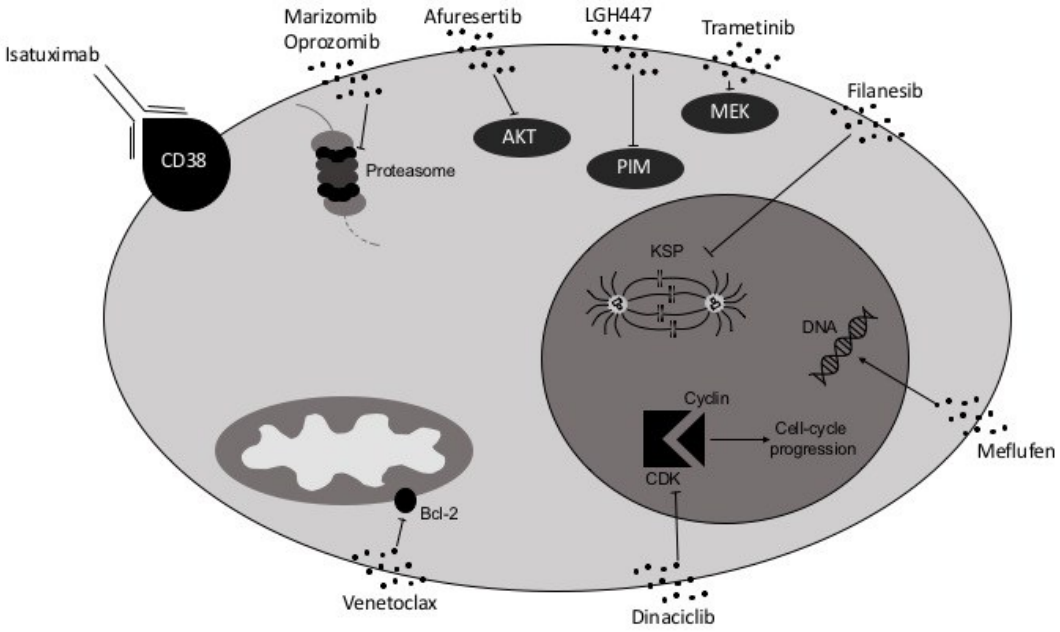
Figure 1. Investigational drugs with single-agent activity in multiple myeloma.



Bcl-2: B-cell lymphoma 2; CDK: Cyclin-dependent kinase; KSP: Kinesin Spindle Protein; MEK: MAPK/ERK kinase; PIM: Pim Proto-oncogene serine/threonine-protein kinase; AKT: V-Akt Murine Thymoma Viral Oncogene-Like Protein 1.

Table 1: summary of new investigational drugs evaluated for single agent activity and their mechanisms of action.

CLASS	DRUG	MECHANISM OF ACTION	STUDY PHASE
Alkylator	Melflufen	Irreversible DNA damage Angiogenesis inhibition[18,109]	I/II, II
Proteasome inhibitor	Marizomib	Irreversible inhibition of C-L, T-L, and CT-L subunits of the 20S proteasome[110,111]	I
	Oprozomib	Irreversible inhibition of CT-L subunit of the 20S proteasome[31]	I/II
Monoclonal antibody	Isatuximab	Binding to the CD38 receptor and killing tumor cells principally via ADCC[112]	I/II, II
Bcl-2 inhibitor	Venetoclax	BH3-mimetic acting as a Bcl-2 inhibitor, leading to programmed cell death[50]	I/Ib
CDK inhibitor	Dinaciclib	CDK1-2-5-9 inhibition impairing cell cycle progression[59]	I/II
KSP inhibitor	Filanesib	Prolonged mitosis arrest leading to cell death[66]	I, II
MEK1/2 inhibitor	Trametinib	Inhibition of tumoral cell growth[74]	Retrospective data, II
AKT inhibitor	Afuresertib	Inhibition of tumoral cell growth, apoptosis promotion[85–87]	I/II
PIM-Kinase inhibitor	LGH447	Inhibition of tumoral cell growth and impairment of neoplastic cell survival[95]	I

Legend: C-L: caspase-like; T-L: trypsin-like; CT-L: chymotrypsin-like; BH3: Bcl-2 homology domain 3; CDK: cyclin-dependent kinase; KSP: kinesin spindle protein; MEK: MAPK/ERK kinase; PIM: Pim Proto-oncogene serine/threonine-protein kinase; AKT: V-Akt Murine Thymoma Viral Oncogene-Like Protein 1.

Table 2: features of clinical trials evaluating novel investigational drugs with single agent activity for the treatment of MM, and summary of their safety and efficacy results.

DRUG	STUDY (PHASE)	SCHEDULE	N° PATIENTS	MEDIAN N° OF PRIOR THERAPIES (RANGE)	RESPONSE	TIME TO EVENT	KEY TOXICITIES
Melflufen	NCT01897714 (I)[113,114]	Melflufen in escalation dose of 15, 25, 40, 55 mg IV every 21 days plus oral dexamethasone 40 mg weekly MTD at 40 mg	15	Not reported	Not reported	Not reported	4 DLTs in 6 patients enrolled in the 55 mg cohort (neutropenia and thrombocytopenia)
	NCT01897714 (II)[19]	Melflufen 40 mg IV every 21 days plus oral dexamethasone 40 mg weekly	31	4 (2-9)	11/23 (47%) ≥PR (1 VGPR)	Median PFS 7.6 months	G≥3 AEs in 27 patients (87%): thrombocytopenia (68%), neutropenia (55%), anemia (42%), leukopenia (32%). Febrile neutropenia, fatigue, pyrexia, asthenia and hyperglycemia in 6% of patients each. SAE related to study drug in 5 patients (16%) including 3 febrile neutropenia, 1 fever and 1 pneumonia
	NCT02963493 (II)[20]	Melflufen 40 mg IV every 28 days plus oral dexamethasone 40 mg weekly	Estimated 78	Not yet published	Not yet published	Not yet published	Not yet published

Marizomib	NCT00629473 (I)[36,115]	Marizomib in escalation dose of 0.075-0.15-0.3-0.4-0.5-0.6 mg/m^2 IV on days 1, 4, 8, and 11 every 3 weeks plus dexamethasone 20 mg orally the day of infusion, the day before and the day after MTD at 0.5 mg/m^2 over 120-min infusion	35 RRMM patients / 44 total	≥2	4/27 (14%) ≥PR (1 VGPR)	Median PFS: 5 months for 10 patients in 0.5 mg/m^2 cohort	6 DLT (all CNS toxicities) G≥3 AEs: hallucination (5%), delirium/confusional state/feeling drunk/disorientation (5%), cognitive disorder (5%), fatigue (5%), thrombocytopenia (5%)
	NCT00461045 (I)[37]	Schedule A: marizomib 0.025-0.7 mg/m^2 IV once weekly on days 1, 8, and 15 of 4-week cycles MTD at 0.7 mg/m^2 over 10-min infusion Schedule B: 0.15-0.6 mg/m^2 twice weekly on days 1, 4, 8, and 11 of 3-week cycles with or without dexamethasone 20 mg orally the day of infusion and the day after MTD at 0.5 mg/m^2 over 120-min infusion	68 (32 in A, 36 in B)	4 (1-11) in A 6 (2-19) in B	Schedule A: 3% PR Schedule B: 11% PR	Not reported	Schedule A: 6 DLTs (G3 acute renal failure, G3 nausea and vomiting, G3 fatigue, G2 hallucinations, G3 mental status changes, G3 balance disorders, G3 confusional state) Schedule B: 4 DLTs (G3 nausea, G4 confusional state, G2 gait disturbance, G2 paranoia) Other G≥3 AEs: thrombocytopenia (8% in B)
Oprozomib	NCT01416428 (Ib)[33,116]	Schedule A: oprozomib orally once daily on days 1, 2, 8, and 9 of a 14-day cycle MTD at 300 mg/d	41 (21 in A, 20 in B)	3 (1-6) in A 2 (1-8) in B	Schedule A: 5/15 (33%) ≥PR (3 VGPR)	Not reported	Schedule A: 3 DLTs (hypotension, G3 diarrhea and G4 thrombocytopenia)

		Schedule B: oprozomib orally on days 1–5 of a 14-day cycle. The starting dose was 150 mg/day (mg/d); doses were escalated in 30-mg increments up to 330 mg/d MTD at 240 mg/d			Schedule B: 6/19 (31%) ≥PR (2 VGPR)		Schedule B: 2 DLTs (G3 renal failure and G3 tumor lysis syndrome) G≥3 AEs in schedule A: thrombocytopenia; anemia; neutropenia (10%); diarrhea (38%); vomiting (19%); nausea; pyrexia; hyperglycemia (10%) G≥3 AEs in schedule B: thrombocytopenia (20%); anemia (15%); diarrhea (35%); nausea (20%); hypophosphatemia (15%); vomiting, fatigue, decrease appetite (10%)
	NCT01416428 (II)[32]	2/7 step-up dosing schedule (A): oprozomib 240/300 mg orally once daily on days 1, 2, 8, and 9 of a 14-day cycle 5/7 step-up dosing schedule post-amend (B): 150/180 mg/day 5/14 schedule (C): oprozomib 240 mg orally on days 1–5 of a 14-day cycle	102 (41 in A; 34 in B; 27 in C)	4 in A; 3.5 in B; 5 in C	Schedule A: 13/38 (34%) ≥PR (4 VGPR) Schedule B: 7/32 (21%) ≥PR (3 VGPR) Schedule C:	Median PFS: 6 months in A; 3.7 months in B; 3.8 months in C.	G≥3 AEs in the cohort A: anemia (19%); thrombocytopenia (12%); neutropenia (5%); diarrhea (27%); fatigue (20%); nausea (7%); G≥3 AEs in the cohort B: thrombocytopenia and anemia (9%); diahrrea (12%); fatigue (9%)

					6/24 (25%) ≥PR (3 VGPR)		G≥3 AEs in the cohort C: 3 death for GI bleeding, 2 oprozomib-related; thrombocytopenia (33%); anemia (30%); neutropenia (15%); nausea and vomiting (37%); diarrhea (33%); fatigue (15%); acute kidney injury, hypophosphatemia, abdominal pain (11%)
Isatuximab	NCT01084252 (I)[47,117]	Isatuximab 0.3, 1, 3, 5, 10 and 20 mg/kg IV every 2 weeks and 10 mg/kg every week	35	6 (2-14)	8/34 (23%) ≥PR (2 CR)	Not reported	G≥3 AEs: pneumonia (9%)
	NCT01084252 (II)[48]	Isatuximab 3 mg/kg IV every 2 weeks (A) 10 mg/kg IV every 2 weeks for 2 cycles then every 4 weeks (B), or 10 mg/kg IV every 2 weeks (C), or 20 mg/kg IV every week for 1 28-day cycle, then every 2 weeks (D)	97 RRMM	5 (2-14)	ORR A: 9% (2/23), B: 20% (5/25), C: 29% (7/24), & D: 24% (6/25)	Median duration of response: 6.6 months	Most AEs: nausea (33%), fatigue (30%), dyspnea (26%), and cough (24%), typically G ≤2 IARs in 49% of patients, mostly G ≤2, 94% during the 1st infusion 6% patients discontinued therapy due to AEs, 2% due to IARs
	NCT02960555 (II)[49]	Isatuximab 20 mg/kg IV every week on days 1, 8, 15 and 22 during cycle 1, then on days 1 and 15 between cycle 2-6, then once monthly until cycle 30	Estimated 63 intermediate and high risk SMM patients	Not yet published	Not yet published	Not yet published	Not yet published

Venetoclax	NCT01794520 (I)[53]	Venetoclax 300, 600, 900, or 1200 daily	66 RRMM	5 (1-15)	ORR: 21% (15% ≥VGPR) ORR in t(11;14) patients 40% (27% ≥VGPR)	TTP 2.6 months TTP n t(11;14) patients: 6.6 months	AEs (all grade): nausea (48%), diarrhea (36%), neutropenia (32%), thrombocytopenia (32%), fatigue (27%), anemia (23%), back pain (21%), and vomiting (21%) G≥3 AEs: thrombocytopenia (26%), neutropenia (20%) lymphopenia (15%), anemia (14%) and decreased white blood cells (12%) 2 DLTs at 600mg: abdominal pain and nausea
Dinaciclib	NCT01096342 (I/II)[62]	Dinaciclib 30,40, 50mg/m^2 on day 1 of a 21-day cycle	27 RRMM	4 (1-5)	ORR: 11%	Median PFS: 3.5 months	G≥3 AEs at 50 mg/m^2: diarrhea (13%), neutropenia (13%), blurred vision (13%) 1 DLT at 40mg/m^2: G3 constipation
Filanesib	NCT00821249 (II)[70]	Cohort 1: Filanesib 1.5mg/m^2 IV on days 1-2 every 2 weeks Cohort 2: Filanesib as cohort 1 plus Dexamethasone 40mg weekly	Cohort 1: 32 RRMM Cohort 2: 55 RRMM	Cohort 1: 6 (range not reported) Cohort 2: 8 (range not reported)	Cohort 1: ORR 16% Cohort 2: ORR 15%	Not reported	G≥3 AEs: thrombocytopenia (44% cohort 1, 42% cohort 2), anemia (38% and 50%), neutropenia (38% and 38%), fatigue (16% and 8%), leukopenia (13 and 4%) and pneumonia (3% and 12%)

Trametinib	Retrospective data[80]	Not reported (single agent off-label trametinib or combination-therapy with other drugs)	22 RRMM receiving single agent Trametinib	5 (1-20)	ORR 14%	Not reported	AEs in single-agent Trametinib population not reported. Overall AEs: rash (53%), diarrhea (31%) and cardiac toxicity (9%)
Afuresertib	NCT00881946 (I/II)[91]	Dose escalation from 25 to 150 mg orally once daily MTD at 125 mg	34 RRMM	5.5 (2-10)	ORR 9%	Not reported	No DLTs in MM patients. AEs in MM patients: nausea (21%), diarrhea (26%), dyspepsia (21%), fatigue (21%), anorexia (15%), gastrointestinal reflux (9%)
LGH447	NCT01456689 (I)[98]	Dose escalation from 70 to 700 mg orally once daily MTD at 500 mg	54 RRMM	4 (1-16)	ORR 10%	Not reported	8 DLTs: G≥3 thrombocytopenia (1 each at 200, 250, 350, 500 mg), G3 fatigue (1 each at 500 and 700 mg), G3 hypophosphatemia (1 at 300 mg), vaso-vagal syncope (1 at 700 mg) G≥3 AEs: thrombocytopenia (18%), anemia (18%), neutropenia (13%), and fatigue (11%)
Legend: MTD: maximum tolerated dose; PR: partial response; VGPR: very good partial response; PFS: progression free survival; AE: adverse event; G: grade; SAE: serious adverse event; RRMM: relapsed/refractory multiple myeloma; ORR: overall response rate; TTP: time to progression; DLT: dose limiting toxicity.							

ARTICLE HIGHLIGHTS BOX

- MM is the second most frequent hematologic malignancy representing 10% of all hematologic cancers and causing about 60000 annual deaths worldwide.
- Median OS doubled in the last decade, reaching a median of 7-10 years especially thanks to introduction of combination therapies incorporating PIs, IMiDs, and recently MoAbs.
- Despite the progresses, MM still remains an incurable disease. PIs and IMiDs refractory patients have poor outcomes, therefore there is an urgent clinical need for new drugs in MM field.
- In this paper we described the mechanism of action of promising experimental drugs used as single agents in MM therapy, summarizing safety and efficacy results.
- Anti-CD38 MoAb isatuximab, oral PI oprozomib, alkylating agent melflufen, oral Bcl-2 inhibitor venetoclax, and KSP inhibitor filanesib appear to be the most promising drugs with single-agent activity. Indeed, they showed at least 20% of ORR among heavily pretreated MM patients with an acceptable toxicity profile. Their role within combination treatment is currently being evaluated.
- Molecules with lower single-agent activity deserve further evaluation in synergic combination regimens, especially in the presence of a strong biological rationale.

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Declaration of interest

F. Gay has acted in an advisory capacity for Takeda, Seattle Genetics, Roche, MundiPharma and Johnson & Johnson. F. Gay also declares honoraria from Takeda, Amgen, Celgene, Johnson & Johnson and Bristol Myers Squibb. A. Palumbo is an employee of Takeda. A. Larocca declares honoraria from Amgen, Bristol Myers Squibb, Celgene and Jansen-Cilag. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.