



Review

No needles needed: All-oral therapy options for relapsed and refractory multiple myeloma

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ABSTRACT

Immense progress has been made for the treatment of multiple myeloma over the past two decades, with patient outcomes improving dramatically as a result. Patient quality of life, however, is constantly challenged by complications of the disease, side effects of therapy and the overall burden receiving continuous treatment. Compared to parenteral agents, all-oral regimens can provide logistically favorable alternatives and are associated with improved quality of life. Here, we review the currently available and investigational oral therapies for relapsed and refractory multiple myeloma and provide a practical clinical reference tool. We explore the factors that dictate the selection of therapy, such as prior drug refractoriness, disease biology and patient-specific considerations. Regimens with their respective supporting clinical data are organized by the degree of prior treatment, from lenalidomide-sensitive to heavily pretreated patients. We explore common challenges such as renal insufficiency and cytopenias. Lastly, we review investigational oral agents.

1. Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy with an incidence of 35,000 cases in the US/year [1]. While it is still considered an incurable disease, treatment has evolved dramatically over the past two decades, with patient outcomes improving significantly as a result. The current day treatment armamentarium for relapsed & refractory multiple myeloma (RRMM) has expanded to include multiple generations of proteasome inhibitors (PIs) and immunomodulatory agents (IMiDs), monoclonal antibodies (MABs), and novel targeted agents. More recently, anti-B Cell Maturation Antigen (BCMA) therapies such as antibody-drug conjugates and autologous chimeric antigen receptor T-cells (CART) have entered the fray [2].

With this progress, however, is increasing recognition of the multifaceted treatment burden MM patients endure. In contrast to many other hematologic malignancies, MM patients are often treated with continuous (versus fixed-duration) therapy [3]. Given the improvement in global outcomes, patients may remain on active myeloma treatment for years, with standard-of-care parenteral therapies often necessitating weekly office visits. These requirements can significantly reduce patients' quality of life. For frail patients or those with geographic barriers to their care, it can be prohibitive. COVID-19 has imposed additional

complexity to the care of MM patients and expert opinions have highlighted the importance of reducing the frequency of in-person office and treatment visits [4]. All-oral regimens, by nature, can provide patients with logistically favorable options, expand treatment access, and have been associated with improved overall quality of life [5].

Recently, novel oral agents such as Selinexor have demonstrated important efficacy in heavily pretreated patients [6]. Venetoclax, a B-cell lymphoma 2 protein (Bcl-2) inhibitor, is a highly active, oral therapy in patients harboring the t(11;14) translocation and is accepted as the first personalized anti-myeloma therapy [7]. Most experts agree, however, that there remains a significant need for potent, well-tolerated, all-oral regimens that are highly active in patients who are relapsed and refractory to the current armamentarium of PIs, IMiDs and MABs.

Here, we review the current and investigational oral treatment regimens for RRMM, contextualize their clinical utility, and provide a framework for selecting an optimal therapy.

2. Approaching RRMM

A tenet of approaching RRMM is first determining prior drug refractoriness or failure. Over the past few years, there has been significant evolution in the treatment of patients with newly diagnosed

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multiple myeloma (NDMM) which results in an immensely more heterogeneous relapsed and refractory population than ever before. While considered the standard induction strategy for nearly a decade, triplet regimens consisting of a PI, ImiD and dexamethasone (Dex) are now challenged by daratumumab (Dara)-containing triplets and quadruplets [8,9,10]. For even longer, up-front autologous stem cell transplant (ASCT) consolidation has been the dogma for eligible patients, but the timing of transplant is under increased scrutiny in the modern era [8]. Further challenging treatment paradigms are the concepts of early intervention in smoldering multiple myeloma as well as fixed-duration, measurable residual disease (MRD)-directed therapy [11,12]. Thus, the increasing variability in the up-front and maintenance settings results in significant patient heterogeneity at relapse. As with all MM regimens, selection of an all-oral regimen for RRMM is a multifaceted decision, with refractoriness to prior therapies being paramount. Additional factors, such functional status, comorbidities, and patient preference, as well as disease-specific factors, such as biology (i.e. cytogenetics) and nature of progression (biochemical versus clinical progression with CRAB), are also important considerations [13]. Regarding the data to support each regimen, seemingly nuanced differences between clinical trial populations and design can have significant clinical impact and the applicability of trial data to an individual patient must be thoroughly assessed. Lastly, it is expert consensus that “triplet” (3 drug) regimens are preferred over two drug “doublet” regimens in each line of therapy in RRMM. Although a particular triplet may not be substantiated by a randomized trial, this recommendation is extrapolated from the demonstrated superiority of triplets over doublets in nearly every instance. A doublet may be reasonable in select scenarios such as patient frailty or limited access to certain therapies [8].

3. Oral regimens in the early relapsed setting (1–2 prior lines)

Given the frequency of lenalidomide (Len) use in frontline and maintenance settings, the treatment strategy at first or second relapse is heavily influenced by Len sensitivity or refractoriness, particularly if an

all-oral regimen is desired. While refractory myeloma is defined as disease progression while on or within 60 days of therapy, the question of Len refractoriness becomes more granular as continuous and maintenance therapy is usually dose-attenuated (5, 10, or 15 mg) [8]. While there is no defined dose that constitutes Len refractoriness, there is limited evidence to support Len-based therapy after progression on a “low” dose and most experts agree that such instances should be considered Len-refractory [14]. Thalidomide (Thal) failure, in the frontline and maintenance setting however, may not portend inferior responses to Len based on multiple subgroup analyses and retrospective data [15].

3.1. Len-sensitive

Select regimens for Len-sensitive RRMM are listed in Table 1. It should be noted that the trials that support these regimens generally included patients with 1–2 prior lines of therapy. Large proportions of patients had relapsed disease, but refractoriness to standard-of-care agents such as bortezomib (BTZ) was low [16,17,18,19,20,21]. The efficacy of Len in patients with IMiD-sensitive or naïve disease has been well-established for many years. Similarly, the toxicity of Len and the necessary precautions and dose modifications have been characterized in dozens of trials with long term follow up. The efficacy of a Len-Dex doublet was reported in two concurrent phase III, placebo-controlled randomized trials in 2007. In both instances, Len-Dex resulted in superior PFS and OS compared to placebo-Dex [16,17]. In patients who are Len-sensitive or naïve, and prefer or require an all-oral regimen, a Len-based regimen should be considered.

Ixazomib (Ixa) is a second-generation, oral PI with a unique toxicity profile compared to BTZ and Carfilzomib (CFZ). Ixa received FDA approval in 2015 in combination with Len-Dex (IRd) in patients refractory to at least one line of therapy based on the early results of the phase III TOURMALINE MM-1 trial which compared IRd vs Rd. Dosing was previously established at 4 mg weekly on days 1, 8 & 15 of a 28-day schedule. At a median follow up of 14.8mo, the addition of Ixa resulted in statistically significant

Table 1
Oral regimens for Len-sensitive RRMM.

Regimen	Dose	Schedule	Evidence & citation	Population / prior therapy	Efficacy	Clinical considerations & AE profiles
Len-Dex (Rd)	Len 25mg Dex 40/20mg	28 day schedule Days 1-21 Days 1, 8, 15, 22	Phase III MM-009 (2007) ¹⁷ Control arm: Dex	Median age: 63 Median prior lines: ≥2 11% prior BTZ 62% prior ASCT	ORR: 61% mPFS: 11.1mo mOS: 29.6mo OS advantage? yes	VTE ppx required Anticipated toxicity: neutropenia, anemia, diarrhea, fatigue, rash
Ixa-Len-Dex (IRd)	Ixa 4mg Len 25mg Dex 40mg	28 day schedule Days 1, 8, 15 Days 1-21 Days 1, 8, 15, 22	Phase III TOURMALINE MM1 (2016, 2020) ^{18,19} Control arm: Rd	Median age: 66 Median prior lines: 1 21% IMiD refractory 1% PI refractory	ORR: 78% mPFS: 20.6mo mOS: 53.6mo OS advantage? No	VTE & VZV ppx required PFS but not OS benefit over RD Anticipated toxicity: myelosuppression, GI toxicity, fatigue, rash, peripheral neuropathy
Ixa-Cy-Dex (ICyD)	Ixa 4mg Cy 300mg/m ² Dex 40mg	28 day schedule Days 1, 8, 15 Days 1, 8, 15 Days 1, 8, 15, 22	Phase I/II Kumar S, et al 2019 ²⁰	Median age: 63 Median prior lines: 2-3 58% prior BTZ 85% prior IMiD 19% refractory to any line	ORR: 48% mPFS: 14.3mo	VZV ppx required Limit to PI-sensitive patients based on MUK8 Anticipated toxicity: myelosuppression, GI toxicity, rash, fatigue, peripheral neuropathy

Median Progression Free Survival (mPFS), Median Overall survival (mOS). Prophylaxis (Ppx) Varicella Zoster Virus (VZV) Venous Thromboembolism (VTE).

superior PFS (20.6 vs 14.7mo, HR 0.74). This benefit was more pronounced in the subgroup of patients with high-risk cytogenetics (21.4 vs 9.7mo) [18]. Longer term follow-up at a median of 85mo showed no difference in OS between the two groups (53.6 vs 51.6mo, HR 0.939; $p = 0.495$). The authors noted imbalances in subsequent therapies, such as Dara, that may have influenced the results [19]. While no OS benefit was observed, in instances where therapy is limited to all-oral regimens and more potent subsequent therapies (e.g. CFZ or CART) are not applicable, any PFS benefit becomes increasingly important.

Ixazomib-Cyclophosphamide-Dex (IxaCyDex) was studied in a phase II trial in which only 19% of patients had refractory disease, but the majority of patients had received prior ASCT and were exposed to both a PI and IMiD. In the whole study population, IxaCyDex showed an overall response rate (ORR) of 45% and a median PFS (mPFS) of 14.2 months. Notably, the subgroup of older patients (≥ 65 yo) who were generally less pretreated (51% having received 1 prior line versus 27% for patients < 65 , and 43% having received prior ASCT, 43% vs 83%) had an ORR of 64% and mPFS of 18.7mo. In all patients, this regimen was well-tolerated with a median relative dose intensity (defined as the proportion of received compared to planned dose) of 90% [20]. More recently, the MUK Eight trial evaluated IxaCyDex vs CyDex in a frail population who received a median of 4 prior lines of treatment, nearly all of whom were at least exposed to Len and BTZ. The addition of Ixa did not result in improved PFS or OS and was associated with higher rates of toxicity [21]. The exact proportion of BTZ-refractory patients was not reported but it is possible that many patients were PI-refractory and did not derive therapeutic benefit from Ixa. Thus, this regimen should likely be reserved for less refractory and PI-sensitive patients.

In an attempt to optimize efficacy, alternative doses and schedules of Ixa have been studied. IxaDex with Ixa at 4 mg weekly was compared to 5.5 mg weekly in a randomized phase II study. The higher dose appeared to produce higher response rates (ORR 54 vs 31%), but at the expense of increased toxicity, mainly, more grade 3 fatigue, thrombocytopenia and GI toxicity [22]. Twice weekly Ixa dosing, akin to a 21-day BTZ

schedule, has also been evaluated in a phase I trial of IxaDex and in a triplet with LenDex (IRd) in patients with NDMM. While the demonstrated toxicity was deemed acceptable, higher rates of grade 3 AEs were seen compared to historical data at the maximum tolerated dose (MTD) of Ixa 3 mg twice weekly on days 1, 4, 8, 11 of a 28-day schedule [23]. While we recognize these alternative dosing options, which may be beneficial in certain patients, we include only the FDA-approved dose and schedule in each Ixa-based regimen in this review.

3.2. Len-refractory

Len refractoriness generally portends worse response to most classes of subsequent therapy [24]. Select oral regimens for Len-refractory disease in the “early” relapsed setting are listed in Table 2. Pomalidomide (Pom) is a second-generation Thal analogue that has activity in Len-resistant RRMM and there is now a plethora of clinical experience with Pom in doublet and triplet combinations. Pom-Dex has been studied in single-arm phase II studies and has more recently served as the control therapy in large phase III studies. Recognizing variations between trial populations, Pom-Dex has been associated with ORR of 33–46% and PFS of 4–7mo in Len-refractory patients [25,26,27]. (See Table 3.)

To help determine the optimal class of therapy (PI vs IMiD) in Len-refractory patients, Pom-Dex was recently compared to Ixa-Dex, another all-oral regimen, in a randomized phase II study. All patients were Len-refractory, exposed or intolerant of BTZ (but not refractory), and the majority received ≥ 3 prior lines of therapy. ORR in the Ixa-Dex group was 38% and 41% in the Pom-Dex group. PFS was higher for Ixa-Dex at 7.1 vs 4.8mo (HR 0.847), but this did not meet statistical significance [28]. Notably, both regimens were well-tolerated and median duration of responses (DOR) were 14.8 and 14.3mo, respectively. While Ixa-Dex did not demonstrate superiority over Pom-Dex, these results suggest Ixa-Dex is a reasonable doublet regimen in Len-refractory, PI-exposed patients and may be useful in Pom-intolerant patients.

Table 2
Oral regimens for Len-refractory RRMM.

Regimen	Dose	Schedule	Evidence & citation	Population / prior therapy	Efficacy	Clinical considerations & AE profiles
Pom-Dex (Pd)	Pom 4mg Dex 40mg	28 day schedule Days 1-21 Days 1, 8, 15, 22	Randomized Phase II Dimopoulos M, et al 2021 ²⁸ Comparator arm: Ixa-Dex	Median age: 68 Median prior lines: 3 100% Len refractory 100% PI-exposed	ORR: 41% mPFS: 4.8mo mOS: immature PFS advantage? no	VTE ppx required Anticipated toxicity: neutropenia, anemia, diarrhea, fatigue, rash
Ixa-Dex (Id)	Ixa 4mg Dex 20mg	28 day schedule Days 1, 8, 15 Days 1,2, 8, 9, 15, 16, 22, 23	Randomized Phase II Dimopoulos M, et al 2021 ²⁸ Comparator arm: Pom-Dex	Median age: 72 Median prior lines: 3 100% Len refractory 100% PI-exposed	ORR: 38% mPFS: 7.3mo mOS: immature PFS advantage? no	VZV ppx required Limited to PI-sensitive patients Anticipated toxicity: thrombocytopenia, GI toxicity, fatigue, peripheral neuropathy
Ixa-Pom-Dex (IPd)	Ixa 4mg Pom 4mg Dex 40mg	28 day schedule Days 1, 8, 15 Days 1-21 Days 1, 8, 15, 22	Phase II Krishnan A, et al 2018 ²⁹	Median age: 62 Median prior lines: 2 100% Len refractory 59% PI refractory	ORR: 48% mPFS: 8.6mo mOS immature	VTE & VZV ppx required Anticipated toxicity: myelosuppression, GI toxicity, fatigue, rash, peripheral neuropathy
Pom-Cy-Dex (PCyD)	Pom 4mg Cy 50mg BID Dex 40mg	28 day schedule Days 1-21 Days 1-21 Days 1, 8, 15, 22	Phase II Van Oekelen, O et al 2020 ³²	Median age: 65 Median prior lines: 3 100% Len refractory 42% PI refractory	ORR 73% mPFS: 13.3mo mOS: 57.2mo	VTE ppx required Anticipated toxicity: myelosuppression, infections, GI toxicity, fatigue, rash

Table 3

Oral regimens in later lines of therapy (3+).

Regimen	Dose	Schedule	Evidence & citation	Population / prior therapy	Efficacy	Clinical considerations & AE profiles
Sel-Dex (Sd)	Seli 80mg Dex 20mg	28 day schedule Both on Days 1, 3, 8, 10, 15, 17, 22, 24	Phase II STORM 2019 ³⁵	Median age: 65 Median prior lines: 7 100% triple-class refractory	ORR 26% ≥ MR 39% mPFS: 3.7mo mOS: 8.6mo mOS of patients achieving MR or better: 15.6mo	Frequent dose interruptions & reductions Anticipated toxicity: myelosuppression, fatigue, GI toxicity, anorexia
Sel-Pom-Dex (SPd)	Seli 60mg Pom 4mg Dex 40mg	28 day schedule Days 1, 8, 15, 22 Days 1-21 Days 1, 8, 15, 22	Phase I/II White, D et al 2021 ³⁹	Median age: 66 Median prior lines: 3 85% Len refractory 49% PI-exposed 26% Dara-Refractory	ORR at RP2D: 57% ORR in Pom-refractory: 44% mPFS: NR at 3.9mo	VTE ppx required Anticipated toxicity: myelosuppression, fatigue, GI toxicity, anorexia

Creatinine (Cr), Not reached (NR).

The combination of Pom, Ixa and Dex has also been studied as an all-oral triplet regimen in two, single-arm phase II studies. In both trials, all patients were Len-refractory and PI-refractoriness was allowed (in contrast to the prior Ixa vs Pom trial which excluded PI-refractory patients). Krishnan, et al. reported an ORR of 48% and PFS of 8.6mo for the 25 patients treated at the RP2D, nearly 60% of whom were double-refractory to Len and a PI [29]. Vorhees, et al. studied PomIxaDex in a 100% double-refractory population. Of 29 patients evaluable for response, the ORR was 51.7%. Median PFS was significantly lower than other Pom and Ixa studies at 4.4mo. The median DOR, however, was 16.8mo, which highlights the heterogeneity of RRMM biology and suggests there is a subset of patients who may derive significant benefit from a PI-IMiD-Dex combination despite being double-class refractory [30]. While there are no randomized comparisons of Pom & Ixa-containing *triplets* versus *doublets* in this setting (i.e. PomIxaDex vs PomDex), expert opinion endorses triplet regimens in nearly all instances, if not precluded by side effects or other factors [8].

Cyclophosphamide (Cy) has been a staple therapy for newly diagnosed and RRMM for many decades and is commonly administered in both PI and IMiD combination therapy. In addition to direct myeloma cytotoxicity, Cy, particularly at lower, metronomic dosing, has been shown to alter the myeloma tumor microenvironment to a more favorable, immunostimulatory phenotype. In combination with IMiDs, a more pronounced downregulation of T-regulatory cells and activation of T-effector and natural killer (NK) cells has been observed [31,32]. The REPEAT study evaluated the addition of continuous low-dose oral Cy (50 mg daily) and continuous prednisone (20 mg daily) to standard dose Len in a Len-refractory cohort of patients who had received a median of 3 prior lines. Of the 67 patients treated at the RP2D, the ORR was 66.7% and mPFS was 12.1mo, a remarkable finding considering all patients were Len-refractory [33].

Cy has also been evaluated in combination with Pom-Dex (PomCy-Dex) in numerous phase trials at variable doses ranging from 50 mg every other day to 400 mg/m² weekly. A more recent trial assessed standard dose Pom-Dex with metronomic Cy dosing of 50 mg BID. 33 patients were treated, all of whom were Len refractory and over half of whom were PI & Len refractory. The ORR was 73% and PFS was 13.3mo. Notably, 48% of patients in this cohort harbored at least one high risk cytogenetic abnormality [32]. These data demonstrate that low dose metronomic Cy, which is widely available and well-tolerated, can strongly synergize with IMiDs and induce long remissions in IMiD-refractory patients.

A notable limitation to these Pom, Ixa, & Cy-based regimens in the current day is the lack of data supporting their efficacy in Dara-

refractory patients. The aforementioned RRMM trials were conducted before the widespread use of Dara and certainly before the frontline use of Dara in regimens such as D-Rd and D-VRd.

4. Oral regimens in later lines of therapy (3+)

Refractoriness to multiple drug classes represents a change in disease biology and has historically been associated with a very poor prognosis, particularly those who are triple-class refractory (PI, IMiD and Dara) and beyond [34]. Selinexor (Sel) is a novel selective and potent inhibitor of the nuclear export protein, exportin 1 (XPO1), that has demonstrated activity in multiple malignancies. In the phase II STORM trial, 122 patients, all of whom were triple-class refractory and 53% of whom had high risk cytogenetic abnormalities, the ORR of weekly Sel with twice weekly Dex was 26%. In the ITT population, mPFS and mOS were 3.7 and 8.6mo, respectively. For patients achieving a response (≥MR), mOS was 15.6mo. High rates of hematologic toxicity were observed with 58% of patients experiencing ≥ Grade 3 thrombocytopenia. Fatigue, nausea and reduced appetite were also common and 18% of patients discontinued therapy due to treatment-related adverse events [35]. In a multi-center retrospective analysis, a subset of penta-refractory patients from the STORM trial were compared to a matched cohort with similar disease and treatment characteristics who were treated with standard agents. Patients treated with Sel in the STORM trial had improved OS: median of 10.4 compared to 6.9mo [36].

Sel was subsequently evaluated in the phase III BOSTON trial in combination with BTZ and Dex (SVd vs Vd). SVd resulted in improved PFS, 13.9 vs 9.5mo compared to Vd. Notably, the sustained benefit of Sel in patients with high-risk cytogenetics and prior Len refractoriness was observed, suggesting that the novel mechanism of action may overcome these traditionally poor-risk features [37]. Sel is being investigated in several other combinations in the phase II basket-design STOMP trial. Of the 11 investigational arms in STOMP, three are all-oral combinations: LenDex (SRd), PomDex (SPd) and IxaDex (SId). To date, there is little available on SRd in Len-refractory patients. While SId remains under investigation in the STOMP trial, a previous single-center phase I/II trial of SId observed preclusive rates of grade 3 nausea, vomiting, fatigue and cytopenias. ORR for evaluable patients was 22% and the investigators decided not to enroll an expansion cohort [38]. Sel in combination with PomDex, however, demonstrated significant activity in heavily pre-treated patients, 85% of whom were Len refractory, 29% Pom refractory and 26% who had prior Dara. ORR at the RP2D was 65% and mPFS was 12.2mo. Notably, of the 16 Pom-refractory patients and the 15 patients

with prior Dara, the ORR were 44 and 60%, respectively. Hematologic TRAEs were expectedly common with grade ≥ 3 neutropenia, anemia and thrombocytopenia rates of 55%, 32%, and 31%, respectively [38]. While dose-reductions are common, SelDex and SelPomDex are oral regimens with demonstrated efficacy in triple-class refractory patients who have otherwise limited treatment options [39].

5. Common scenarios

5.1. Alkylator Naïve

Since their initial investigation in the 1960s, alkylating agents such as melphalan (Mel) and cyclophosphamide (Cy) remain cornerstones of MM treatment. Single-agent intravenous Mel is the most frequently used ASCT conditioning regimen, while oral Mel remains a part of several standard-of-care regimens such as BTZ, Mel, prednisone (VMP) and Mel, Thal, prednisone (MPT) across the world [40,41]. Cy, similarly, is frequently utilized in every phase of the disease. Like each class of targeted agents, alkylating agents offer a unique cytotoxic mechanism that may be preserved despite refractoriness to other drug classes, particularly if patients have limited or no prior exposure during induction and ASCT. While most Mel-based oral regimens were studied in NDMM, regimens such as MPT or IMP have anecdotally provided efficacious options for patients with refractory disease, especially when sensitive to the partner agent [41,42]. In addition to cytotoxicity, as previously discussed, Cy at low-dose, metronomic dosing can induce favorable immunomodulation in refractory patients and augment the efficacy of IMiDs such as Pomalidomide. Various oral regimens containing Mel and Cy are listed in Table 4. (See Table 5.)

5.2. Renal insufficiency

Paraprotein-induced renal injury is a hallmark of MM and acute & chronic renal impairment, as well as end stage renal disease (ESRD), remain common challenges when treating the disease. Staple therapies such as Len and alkylating agents are renally excreted and can require significant dose attenuations. These therapies can also cause significant myelotoxicity and dose-limiting cytopenias. There are alternative oral agents and combinations that can be very useful in these settings. While inferior in head-to-head efficacy comparisons to Len, Thal, the original immunomodulatory agent, exhibits a unique toxicity profile compared to its derivatives with cytopenias being very infrequently observed [43,44]. The safety and pharmacokinetics of Thal in patients with renal impairment and ESRD were demonstrated shortly after its introduction to the field. Plasma concentrations of Thal were not significantly different in patients with severe renal impairment, whereas plasma concentrations (AUC) of Len increase 2–3 fold in the setting of severe renal dysfunction [45]. In addition to Thal, Pom has been evaluated in patients with renal insufficiency and ESRD in combination with Dex. In a multi-cohort phase II study, patients with varying degrees of renal insufficiency (eGFR 30–40 ml/min/1.73m², eGFR <30 ml/min/1.73m², or <30 and dialysis-dependent) were given standard Pom doses (4 mg on days 1–28 of a day 28 day cycle) with either Dex 40 or 20 mg weekly. Plasma concentrations were similar in each cohort, though it was noted that Pom concentrations were lower after dialysis. The authors concluded Pom can be administered without dose-reductions in patients with all degrees of renal insufficiency and that it should be dosed after (rather than before) dialysis due to increased clearance [46].

Ixazomib has demonstrated acceptable safety in patients with severe renal insufficiency and ESRD with the recommended dose reduction to from 4 mg to 3 mg weekly (days 1, 8, & 15 of a 28-day cycle). This is supported by a phase Ib trial studying pharmacokinetics and safety of Ixazomib in cohorts of patients with normal renal function, severe renal impairment and ESRD. While AEs were similar among all the groups, the most common of which were nausea, vomiting, diarrhea and fatigue, the severe renal impairment group and ESRD group experienced higher rates of anemia: 43 & 29% versus 5% in the normal renal function cohort, respectively [47]. The triplet IxaThalDex was evaluated in a single-arm phase II study in patients who received 1–3 prior lines of therapy which included patients with moderate renal impairment (>GFR 15 ml/min). The cohort was minimally refractory with only 10% of patients being refractory to an IMiD and a PI. The ORR was 56.4% and mPFS was 13.8mo [48].

In contrast to Mel, Cy is readily excreted in the urine and while dose reductions are required, it is an effective and safe agent in patients with severe renal impairment and ESRD [45]. Cy-Thal-Dex (CTD) has been indirectly compared with the analogous Mel-based regimen, MPT, in elderly patients with NDMM and renal impairment. CTD was associated with longer event-free survival (EFS) and OS with lower rates of neutropenia and infections [49]. While close monitoring and dose attenuations are necessary, ITD & CTD triplets and ThalDex & IxaDex doublets can be useful all-oral regimens for patients with renal insufficiency and ESRD. A PomDex doublet has also been evaluated in both settings and can be safely administered (after dialysis in the setting of ESRD). As previously discussed, IxaCyDex may also be a useful regimen in this setting, if patients are not PI-refractory. Recommended renal dose adjustments are outlined in Table 4.

5.3. Cytopenias

Dose-limiting cytopenias are another common challenge when approaching MM, which are usually multifactorial; stemming from the disease itself as well as the acute and chronic effects of therapy. Decades of clinical experience with Len and Pom have well elucidated the known hematologic toxicity, with Grade 3 neutropenia rates reported in the ranges of 25 and 50%, respectively, in addition to lower but significant rates of anemia and thrombocytopenia [16,50]. Thalidomide, while inferior in head-to-head efficacy comparisons, is associated with significantly lower rates of hematologic toxicity. In the foundational ECOG trial of ThalDex vs Dex in NDMM, rates of grade ≥ 3 neutropenia were seen in 9 vs 6% in the ThalDex and Dex arms, respectively [51]. Large retrospective comparisons of ThalDex vs LenDex noted 0, 0, 0.6% rates of Grade ≥ 3 anemia, thrombocytopenia and neutropenia, respectively, in patients who received ThalDex, compared to 4.4%, 4.8% and 14% of patients who received LenDex [52].

Ixazomib similarly is associated with low rates of hematologic toxicity. In the recent TOURMALINE MM4 study of Ixazomib vs placebo maintenance after induction in newly diagnosed, transplant-ineligible patients, very low rates of neutropenia were observed: 1.9 and 2.1% grade 3 neutropenia and thrombocytopenia, respectively, compared to 1.4 and 0% in the placebo group [53]. When combined in a triplet regimen, IxaThalDex has shown to have low rates of Grade ≥ 3 neutropenia and thrombocytopenia of 2.2 and 7.8% in a large phase II trial of IxaThalDex in patients with RRMM. There was a higher rate of Grade ≥ 3 anemia at 17% [54].

Table 4

Useful oral regimens in specific scenarios [55].

Regimen	Dose			Schedule	Evidence & citation	Population / prior therapy	Efficacy	Clinical considerations & AE profiles
Akylator Naive								
Mel-Pred-Thal (MPT)	Mel 0.25mg/kg Pred 2mg/kg Thal 100mg			6 week schedule Days 1-4 Days 1-4 Continuous	Phase III IFM 99-06 2007 ⁴¹ Control arms: MP, Mel100 ASCT	Ages 65-75 Newly diagnosed, transplant-ineligible	ORR: 76% mPFS: 14.3mo mOS: 33.4mo	VTE ppx required Anticipated toxicity: myelosuppression, infections, fatigue, peripheral neuropathy
Ixa-Mel-Pred (IMP)	Induction: Ixa 4mg Mel 9.0 mg/m ² Pred 60 mg/m ² Maintenance: Ixa 4mg			Induction: 42 day cycles x9 Days 1, 8, 22, 29 Days 1-4 Days 1-4 Maintenance: 28-day cycles Days 1, 8, 15	Phase II San-Miguel, J et al 2018 ⁴²	Median age: 74 Newly diagnosed, transplant-ineligible	ORR 65% mPFS 18.4mo Estimated 3 year OS: 68%	VZV ppx required Anticipated toxicity: myelosuppression, infections, fatigue, GI toxicity, peripheral neuropathy
Renal dysfunction								
Cy-Thal-Dex	CrCl >30: Cy 500mg Thal 100mg Dex 40mg	CrCl 10-29 Cy 375mg Thal 100mg Dex 40mg	CrCl <10 Cy 250 Thal 100mg Dex 40mg	21 day schedule Days 1, 8, 15 Days 1-21 Days 1-4, 12-15	Phase III MRC Myeloma IX 2012 ⁵⁵	Median age: 59 Newly diagnosed, transplant-eligible MM	ORR 82.5% mPFS 27mo	VTE & VZV ppx required Anticipated toxicity: Neutropenia, infection, GI toxicity, fatigue, peripheral neuropathy
Ixa-Cy-Dex	CrCl >30: Ixa 4mg Cy 300mg/m ² Dex 40mg	CrCl 10-29 Ixa 3mg Cy 225mg/m ² Dex 40mg	CrCl <10 Ixa 3mg Cy150mg/m ² Dex 40mg	28 day schedule Days 1, 8, 15 Days 1, 8, 15 Days 1, 8, 15, 22	Phase I/II Kumar S, et al 2019 ²⁰	Median age: 63 Median prior lines: 2-3 58% prior BTZ 85% prior IMiD 19% refractory to any line	ORR: 48% mPFS: 14.3mo	VZV ppx required Anticipated toxicity: myelosuppression, infections, fatigue, GI toxicity, peripheral neuropathy
Ixa-Thal-Dex	CrCl >30: Ixa 4mg Thal 100mg Dex 40mg	CrCl <30 Ixa 3mg Thal 100mg Dex 40mg	ESRD Ixa 3mg Thal 100mg Dex 40mg	28 day schedule Days 1, 8, 15 Days 1-28 Days 1, 8, 15, 22	Phase II Bergin, K et al 2021 ⁴⁸	Median age: 64 10% IMiD refractory 10% PI refractory	ORR 56.4% mPFS 13.8 mOS NR at 32mo	VTE & VZV ppx required Anticipated toxicity: GI toxicity, peripheral neuropathy, Grade II cytopenias (Grade 3 ≤10%)
Pom-Dex	Pom 4mg Dex 40mg			28 day schedule Days 1-12 Days 1, 8, 15, 22	Phase II MM-013 2017 ⁴⁶	Median age: 72 Median prior lines: 4 100% Prior Len 97% prior BTZ	Multi-cohort ORR: 14-39.4% PFS 2.4-6.5mo	VTE ppx required Anticipated toxicity: neutropenia, anemia, diarrhea, fatigue, rash
Cytopenias								
Ixa-Thal-Dex	CrCl >30: Ixa 4mg Thal 100mg Dex 40mg	CrCl <30 Ixa 3mg Thal 100mg Dex 40mg	ESRD Ixa 3mg Thal 100mg Dex 40mg	28 day schedule Days 1, 8, 15 Days 1-28 Days 1, 8, 15, 22	Phase II Bergin, K et al 2021 ⁴⁸	Median age: 64 10% IMiD refractory 10% PI refractory	ORR 56.4% mPFS 13.8 mOS NR at 32mo	VTE & VZV ppx required Anticipated toxicity: GI toxicity, peripheral neuropathy, Grade II cytopenias (Grade 3 <10%)

Creatinine clearance (CrCl).

6. Off-label alternative regimens

6.1. Histone de-acetylase inhibitors (HDACi)

HDAC inhibitors such as Panobinostat (Pan) and Vorinostat (Vor) have shown meaningful activity in RRMM [56,57,58]. While studied most commonly with BTZ and CFZ, both agents have been evaluated in all-oral combinations. In a phase I trial of IxaPanDex, 3 of 11 patients Len-refractory patients experienced a minimal response and the study was not expanded to a phase II cohort [59]. PanLenDex, alternatively, demonstrated a 36% ORR in 22 Len-refractory patients which resulted in a mPFS of 6.5 months [60]. Pan received accelerated FDA approval in 2015 in combination with BTZ and Dex for the treatment of MM in patients who had received at least 2 prior lines of therapy including BTZ and an IMiD. However, as of December 2021, this indication was withdrawn by the FDA due to insufficient post-accelerated approval data

confirming Pan's clinical benefit [61]. It remains approved outside of the United States. Vor was evaluated in phase IIB study in combination with Len in a Len-refractory population. The ORR was 25% and median PFS was 5.3mo [57]. Vor is FDA approved for the treatment of cutaneous T-cell lymphoma (CTCL) but remains an off-label alternative for myeloma patients with limited treatment options.

6.2. Clarithromycin

Clarithromycin (CAM) is an additional agent recognized to have activity in RRMM that has been studied in numerous treatment combinations for over a decade. CAM in combination with LenDex (BiRD) and PomDex (Cla-PD) has shown activity in RRMM [62,63]. There are several proposed mechanisms of CAM's anti-myeloma activity. As a CYP3A4 inhibitor, CAM reduces the clearance of corticosteroids, increasing the total dose delivered to the MM tumor [64]. CAM has also

Table 5
Off-Label alternative oral regimens.

Regimen	Dose	Schedule	Evidence & citation	Population / prior therapy	Efficacy	Clinical considerations & AE profiles
Pan-Len-Dex	Pan 20mg Len 25mg Dex 40mg	28 day schedule Days 1, 3, 5, 8, 10, 12, 15, 17, 19 Days 1-21 Days 1, 8, 15	Phase II Chari A, et al 2017 ⁶⁰	Median age: 64 Median prior lines: 3 88% Len refractory 52% PI refractory	ORR in Len-refractory: 36% mPFS 6.5mo mOS NR at 33mo	Pan not FDA approved in USA VTE ppx required Anticipated toxicity: neutropenia, thrombocytopenia, fatigue, QT prolongation
Vor-Len-Dex	Vor 400mg Len 25mg Dex 40mg	28 day schedule Days 1-7, 15-21 Days 1-21 Days 1, 8, 15, 22	Phase II Sanchez L, et al 2017 ⁵⁷	Median age: 64 Median prior lines: 5 100% Len refractory 80% BTZ-exposed	ORR 24% mPFS 5.3mo	VTE ppx required Anticipated toxicity: Myelosuppression, GI toxicity
Clarithromycin-Pom-Dex (ClaPD)	Cla 500mg (BiD) Pom 4mg Dex 40mg	28 day schedule Days 1-28 Days 1-21 Days 1, 8, 15, 22	Phase II Mark, T et al 2019 ⁶³	Median age: 58 Median prior lines: 5 84% Len refractory 78% PI refractory	ORR in Len-refractory: 58% mPFS 7.7mo mOS 19.2mo	Caution in Elderly patients VTE ppx required Anticipated toxicity: myelosuppression, GI toxicity, fatigue, transaminitis, elevated Cr, electrolyte derangements

been shown to alter the autophagy pathway and ultimately increase the cellular toxicity of IMiDs [65]. Additionally, CAM appears to have immunomodulatory activity by altering the inflammatory microenvironment via suppression of interleukin-(IL)-1 and IL-6 and tumor necrosis factor alpha (TNF α), all of which are also implicated in MM cell adhesion to bone marrow stromal cells [66,67]. Importantly, a recent phase III trial compared the addition of clarithromycin to Rd (BiRD) to Rd alone in an elderly, transplant-ineligible NDMM population. While CR rates were higher in the clarithromycin group (22.6 vs 14.6%), there was no difference in PFS and there were unexpectedly higher rates of steroid-related & infectious AEs and more deaths in the experimental group [62]. In heavily pretreated patients with limited options, clarithromycin-containing combinations remain an option, but caution should be exercised based on this data.

7. Investigational agents (non-FDA approved agents)

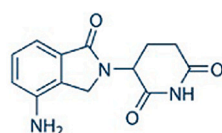
7.1. CELMoDs

Cereblon E3 Ligase Modulators (CELMoDs) are a novel class of small molecules developed based on the structure and functionality of their IMiD precursors. CELMoDs' structures were optimized to induce maximal cereblon-mediated ubiquitination of key cellular transcription factors (Ikaros and Aiolos), which ultimately results in multiple myeloma cell death and other immunomodulatory activity [68]. There are currently two investigational CELMoDs in clinical trials, Iberdomide and Mezigdomide (CC-92480). The chemical structures of Len and Mezigdomide (CC-92480) are pictured below [69,70].

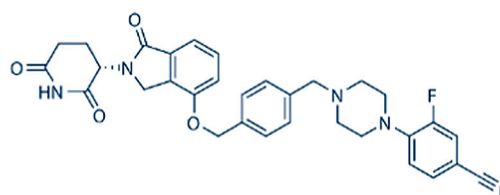
In preclinical models, Iberdomide, demonstrated activity in Len and Pom-resistant cell lines, which confirmed that Cereblon can remain targetable after IMiD failure [68]. Iberdomide (Iber) has since been evaluated in a phase I/II trial in combination with Dex. In 107 patients with RRMM who received a median of 6 prior lines of therapy and 97% of whom were triple-class refractory, the ORR was 26.2% and median OS was 11.2mo. A smaller cohort of 24 patients who received prior anti-BCMA therapies demonstrated similar responses and no new toxicity signals were identified [71]. Iber is currently being evaluated in numerous combination therapies including BTZ, CFZ, Dara and as single-agent maintenance after ASCT and as monotherapy for high risk smoldering myeloma. More recently, trials investigating the all-oral combinations of Iber, Ixazomib, and Dex as well as Iber, metronomic low-dose Cy, and Dex have opened to enrollment.

Mezigdomide is a second-generation CELMoD that has demonstrated exciting efficacy in heavily pretreated patients. The combination of Mezigdomide and Dex was first evaluated in a multi-cohort phase I study in patients who received a median of 6 prior lines of therapy, roughly 50% of whom were triple-class refractory. At the RP2D of 1 mg on a 21/28 day schedule, the ORR was 54.5%, a historically high estimate, particularly for an oral therapy [72]. Mezigdomide is currently being investigated in a phase I/II basket design trial in combination with BTZ, CFZ, Elotuzumab and Dara. It will likely be studied as part of all-oral combinations in the future.

Lenalidomide



Mezigdomide
(CC-92480)



7.2. Bcl-2 inhibitors

The t(11;14) is a hallmark genetic event of mantle cell lymphoma and has been identified in ~20% of patients with multiple myeloma. This gene fusion juxtaposes the CCND1 gene (Cyclin D1) with the immunoglobulin heavy chain locus and has been identified as a predictive biomarker for susceptibility to bcl-2 inhibition. Venetoclax (Ven) is a selective Bcl-2 inhibitor with potent activity in multiple hematologic malignancies and two trials to date support the utility of Ven in RRMM [73]. The phase III BELLINI trial compared Ven, BTZ and Dex versus BTZ and Dex with predefined patient subgroups harboring t(11;14) and those with high bcl-2 expression. The trial was halted early and the protocol amended after more deaths were recorded in the Ven group. After subgroup analyses, the investigators recognized an increased risk of death, mostly due to infections, in patients without t(11;14). In contrast, patients harboring the translocation experienced a dramatic benefit in PFS with a HR of 0.10. Patients without t(11;14) but with high expression of bcl-2 by quantitative PCR also benefited significantly from the addition of Ven [7].

The combination of Ven & Dex, an all-oral regimen without BTZ, was also recently evaluated in t(11;14) patients. The ORR for the 20 patients in the phase I portion was 68%. In the more heavily pretreated phase II group who received a median of 5 prior lines of therapy, and nearly all of whom were refractory to Dara, the ORR was 48%. For all patients, 61% patients were estimated to have ongoing responses at 12 months. In exploratory analyses, the authors noted that response to therapy was independent of concurrent high-risk cytogenetics (del17p, gain1q) [74]. Taken together, these data suggest that Ven may be a personalized anti-MM therapy as it appears highly active in patients with t(11;14).

Currently, Ven use should be restricted to patients with confirmed t(11;14) given the increased risk of death in the overall population in the BELLINI trial. While efficacy is encouraging, estimates suggest 40–50% of patients with t(11;14) do not respond to Ven and there is an active effort to further elucidate Ven sensitivity. Emerging pre-clinical data suggests myeloma exhibiting a B-cell-like immunophenotype may be predictive of response [75]. Additional Ven-based oral regimens are under investigation, such as Ven, Ixazomib and Dex, in phase I trials in both RRMM and AL-amyloidosis.

Lisafotoclax (APG-2575) is a second generation, selective bcl-2 inhibitor in early phase clinical trials in multiple hematologic malignancies. In a phase I study, primarily comprised of patients with chronic lymphocytic leukemia (CLL), doses were escalated to 1200 mg daily. Interestingly, there were no DLTs and no patients experienced tumors lysis syndrome (TLS), a phenomena previously observed with Ven. Rates of grade 3–4 neutropenia in this study were low at 13%. While the cohort of multiple myeloma patients was small (6) and presumably spread across multiple dose levels, no responses were observed. Two early phase trials are ongoing studying lisafotoclax in combination with Len and Pom in patients with RRMM. Based on the previous efficacy of Ven, lisafotoclax may offer an additional targeted agent, perhaps with a unique AE profile [76].

7.3. BRAF & MEK inhibitors

With the advent of next generation sequencing (NGS), there is increasing recognition of the genomic heterogeneity of multiple myeloma at diagnosis and clonal evolution at relapse [77]. Activating mutations in the mitogen-activated protein kinase (MAPK) pathway, or the RAS/RAF/MEK/ERK signaling cascade, have been implicated in the oncogenesis of approximately 20% of all cancers and the advent of targeted BRAF, MEK and KRAS inhibitors have revolutionized the treatment of diseases such as BRAF^{V600} mutant melanoma [78,79]. In multiple myeloma, KRAS and NRAS mutations are estimated to be present in 21% and 19% of patients, respectively. BRAF^{V600} has been identified in roughly 4% of newly diagnosed and nearly 10% of patients with relapsed disease [80].

While the prognostic significance of these genetic aberrancies has not been thoroughly elucidated to date, multiple prospective studies have shown meaningful efficacy of BRAF and MEK inhibitors in heavily pretreated patients [81,82]. Recently, a phase II study of patients harboring BRAF V600E and K mutations evaluated the combination of encorafenib 450 mg PO daily and binimetinib 45 mg PO daily in patients with a median of 5 prior lines of therapy. Of 11 patients evaluable for efficacy, the ORR was 82% with 27% of patients achieving a CR or near-CR, respectively. PFS and DOR were immature at the time of report and longer term follow up is awaited [80]. In addition to encorafenib and binimetinib, the MEK inhibitor cobimetinib is being studied in the Myeloma Developing Regimens Using Genomics (MyDRUG) trial. This is multicohort, non-randomized, mutation-driven trial assessing the efficacy of various therapies for their respective target: cobimetinib (KRAS/NRAS/BRAF), FGFR3 (enasidenib), IDH (erdafinib), CDKN2c (abemaciclib), t(11;14) (venetoclax). Preliminary data for the cohort of patients with KRAS, NRAS and BRAF mutations who received cobimetinib was recently reported. Seven patients were enrolled who had received a median of 1 prior line of therapy (range 1–3). 4, 2 and 1 patients had NRAS, KRAS and BRAF mutations, respectively. Of the six patients evaluable for response, 4 achieved a PR and 2 achieved a VGPR. Median duration of treatment was 1 year and no DLTs were observed [83].

Taken together, the available data suggests that patients harboring activating RAS and BRAF mutations can be identified using commercially available NGS assays and may derive significant therapeutic benefit from targeted inhibitors. Additional accrual and longer follow up are needed to estimate PFS and DOR. Based on the availability to date, toxicity appears consistent with known AE profiles of these compounds.

8. Conclusions and future directions

The treatment of MM has evolved dramatically since the advent of IMiD and PIs roughly two decades ago. As patient outcomes continue to improve, there is growing recognition of the impact of prolonged treatment on patient quality of life. Weekly and twice weekly treatments can inflict significant treatment fatigue, in addition to financial hardship associated with the logistics of traveling to receive care. In instances where patients are limited by frailty or geographic restrictions, the frequency of office visits and treatment may be preclusive to many IV and subcutaneous agents. Compared to parenteral therapies, all-oral regimens often require significantly fewer in-office visits which can reduce barriers and improve patient access to treatment. Additionally, in the COVID-19 era, reducing the frequency of potential exposure is recognized by experts as a priority given the immunologic compromise of MM patients.

There currently exist a variety of all-oral regimens for patients at virtually every stage of their MM journey. As with all MM treatments, selection of therapy is an individualized process and should be based on a variety of patient and disease factors, with refractoriness to prior therapy being of utmost importance. Additional details, such as existing comorbidities and toxicity to prior therapy, as well as disease-specific factors, such as cytogenetics, are also necessary considerations. IMiD-sensitivity (Len) versus refractoriness is a critical distinction on which therapy should be based. In both the early Len-sensitive and refractory settings, IMiD-based regimens in combination with Cy or Ixa are supported by numerous phase II and III trials. In more heavily pretreated patients, Selinexor is an oral option that may retain its efficacy in patients with biologically high-risk disease. Oral agents such as Ixa, Thal and Cy may also be of significant utility in patients with renal dysfunction. In patients who are naïve/sensitive to classical alkylating chemotherapy and ASCT, Mel and Cy containing regimens remain efficacious.

There are multiple classes of novel agents under clinical investigation that have demonstrated promising efficacy to date. CELMoDs (iberdomide and mezigdomide) are a novel class of cereblon modulators

and while mechanistically similar to their IMiD precursors, they are structurally unique and have demonstrated meaningful activity in Len and Pom-resistant patients. Bcl-2 inhibition with Ven is an emerging treatment strategy in RRMM and represents a new era of personalized MM therapy. Lysaftoclax (APG-2575) is a second generation bcl-2 inhibitor in early phase trials and there are preclinical efforts to help elucidate both which t(11;14) and non-t(11;14) patients derive benefit from bcl-2 inhibition. In addition to predictive cytogenetic markers, detection of oncodriver mutations via NGS is being employed in MM and inhibitors of BRAF, RAS and MEK have also demonstrated significant efficacy in patients with relapsed disease with otherwise limited treatment options.

Practice points

- All-oral regimens can offer logistically favorable treatment options and are associated with improved quality of life, compared to parenteral therapies
- Selection of therapy is dictated by numerous disease and patient-specific factors. Prior drug refractoriness is a critical distinction as RRMM is an increasingly heterogeneous population due to the ever-evolving frontline treatment landscape
- Lenalidomide-based regimens are preferred in IMiD-sensitive patients while multiple regimens utilizing a Pomalidomide backbone have efficacy in Len-refractory patients. Selinexor may offer an oral option to highly pretreated patients. Thalidomide, ixazomib and cyclophosphamide can be useful in patients with renal dysfunction while melphalan and cyclophosphamide-containing regimens may be useful in patients naïve to alkylator chemotherapy
- Novel agents such as CELMoDs, bcl-2 inhibitors and BRAF & MEK inhibitors are under clinical investigation with promising activity. The latter of which may offer personalized treatments for patients harboring t(11;14) and MAPK pathway mutations, respectively

Research agenda

- Development of novel, oral therapeutics
- Clinical trials investigating the efficacy of existing oral agents in Daratumumab-refractory agents, given the frequency of upfront and second-line use
- Clinical trials investigating the efficacy of existing oral agents in patients who are refractory to next-generation T-cell redirecting therapies
- Elucidation of bcl-2 inhibitor sensitivity in both t(11;14) and non-t(11;14) patients

Conflicts of interest

Joseph Franz and Elizabeth Myrus have no conflicts to disclose. Larysa Sanchez reports the following: Consultancy: Takeda. Josh Richter reports the following: Speakers Bureau: Janssen, BMS, Sanofi. Advisory Board: Celgene, Janssen, BMS, Karyopharm, Sanofi, X4 pharmaceuticals, Oncopeptides, Adaptive Biotechnologies, Secura Bio, AstraZeneca, Takeda. Consultancy: BMS, Secura Bio, Oncopeptides, GSK.

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