An overview of treatment options for patients with relapsed/refractory multiple myeloma and renal impairment

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Abstract: Renal impairment (RI) is a relatively common complication of multiple myeloma, which increases in frequency as disease becomes more advanced and recovery of renal function becomes less likely as patients progress through lines of therapy. Clinical trials in the relapsed/refractory multiple myeloma (RRMM) setting have not uniformly included patients with RI or robustly reported their outcomes. Here, we review existing data among patients with RI and RRMM across drug classes (including immunomodulatory agents, proteasome inhibitors, monoclonal antibodies, antibody-drug conjugates, chimeric antigen receptor T-cell therapies, and exportin-1 inhibitor) to provide an improved understanding of available treatment options for this important population. We highlight data from pivotal clinical trials, including data relating to renal response (as defined by the International Myeloma Working Group) and discuss real-world experiences in patients with RI, where applicable. Despite substantial advances in RRMM treatment, the presence of RI remains associated with reduced overall survival. Consistent inclusion of patients with RI, and uniform reporting of their outcomes, should be encouraged in future prospective trials of treatments for RRMM.

Keywords: multiple myeloma, refractory, relapsed, renal impairment, renal response

Introduction
Renal impairment (RI) is present in up to 50% of patients with multiple myeloma (MM) at diagnosis,1-3 and 2%-4% of patients with MM who present with RI require dialysis.4 As patients progress through lines of therapy for MM, existing RI often worsens.5 Of patients without RI at diagnosis, roughly 25% will develop RI during later stages of disease.6 Recovery of renal function is less likely in patients with relapsed/refractory MM (RRMM) compared to those with newly diagnosed MM (NDMM).7

Renal damage in MM is primarily caused by the toxic effects of monoclonal free light chains (FLCs), which lead to a host of renal pathologies including monoclonal cast nephropathy (MCN).1,3,4,6 The International Myeloma Working Group (IMWG) defines RI in MM as serum creatinine greater than 2mg/dL or reduced creatinine clearance (CrCl < 40 mL/min), either (or both) of which is found to be the result of myeloma.1 For evaluation of CrCl, estimated glomerular filtration rate (eGFR) can be assessed via either the Modification of Early Renal Disease (MDRD)7 or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)8,9 equation.

Studies have shown that RI is associated with reduced overall survival (OS) and increased risk of early mortality in MM,5,10,11 with some suggesting a correlation between outcomes and degree of estimated glomerular filtration rate (eGFR) decline.4,10 A recent meta-analysis12 of six randomized controlled trials conducted through 2019 found that RI conferred a higher
relative risk of disease progression or death among participants. Improvements in both OS and renal function have been reported with novel treatments for RRMM, particularly when compared to conventional chemotherapy.10 Though improvement in renal function is associated with improved survival, OS remains inferior among patients with baseline RI compared to those with no RI at MM diagnosis.10,11

Several issues confound the evaluation of outcomes in patients with RI and MM: (1) lack of a standardized definition of RI and renal recovery across clinical trials, (2) exclusion of patients with RI from trials or lack of clear reporting of enrollment criteria pertaining to renal dysfunction, (3) the inherent shortfall of measuring renal function in patients with acute kidney injury (AKI) using equations developed for renal function estimation in chronic kidney disease (CKD), and (4) establishing the correct cause of RI since the age group of patients with MM commonly present with vascular and metabolic disorders.3,12

The aim of this review is to provide available efficacy and safety data for RRMM treatments among patients with RI, with a focus on pivotal clinical trials and real-world experience. Recent advances seen with approved novel therapies such as immunomodulatory drugs, proteasome inhibitors (PIs), monoclonal antibodies, small molecule inhibitors and antibody-drug conjugates (ADCs) will be highlighted, as well as emerging data with cellular therapies. Special attention will be given to analyses that detail renal response to therapy, particularly as defined by the IMWG1 (Table 1).

### Mechanisms of renal damage in MM

When present in normal amounts, monoclonal FLCs are freely filtered at the glomerulus, endocytosed by proximal tubule cells, and catabolized. In plasma cell dyscrasias such as MM, monoclonal FLCs can reach concentrations that exceed the absorptive and catabolic capacities of the proximal tubule cells.4,6 Monoclonal FLCs that remain in the proximal tubules can activate apoptotic pathways and cause intense inflammation that leads to fibrosis, whereas those that reach the distal nephron can interact with Tamm-Horsfall protein (urothelin) to form aggregates that precipitate and lead to cast formation and nephronal occlusion (Figure 1).4 Roughly 90% of patients with MM who present with AKI have the hallmark pathologic feature of MCN.13 Other monoclonal FLC-mediated pathologies can co-exist with proximal tubule fibrosis and MCN, including light-chain amyloidosis, monoclonal immunoglobulin deposition disease, acquired Fanconi syndrome, and acute tubular necrosis.3,4 Additional factors that contribute to RI include dehydration, hypercalcemia, and the use of nephrotoxic drugs (e.g. non-steroidal anti-inflammatory drugs, contrast media, particular antibiotics, and certain anticancer treatments).4,14 The median age at diagnosis of MM is approximately 70 years;15 as such, normal age-related decline in renal function and the presence of comorbidities that often increase with age (e.g. Type II diabetes, heart failure, and atherosclerotic

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**Table 1. IMWG criteria for the definition of renal response to antimyeloma therapy.**  

<table>
<thead>
<tr>
<th>Baseline eGFR, mL/min/1.73 m²</th>
<th>Best CrCl responseb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>&lt;50</td>
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<tr>
<td>Partial response</td>
<td>&lt;15</td>
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<tr>
<td>Minor response</td>
<td>&lt;15</td>
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<td>15–29</td>
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</tbody>
</table>

CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; IMWG, International Myeloma Working Group.  
*eGFR is based on the Modification of Diet in Renal Disease formula or the Chronic Kidney Disease Epidemiology Collaboration equation.  
bRenal overall response defined as a best response of minor response or better.
vascular disease) could exacerbate RI among patients with MM.

**Early advances in the treatment of patients with MM and RI**

In the era of conventional chemotherapy for MM, RI was present in roughly twice as many early-death patients compared with those who survived longer than 60 days. A single-institution study of 423 patients with MM treated with conventional chemotherapy showed that baseline RI was associated with a significantly lower response to chemotherapy. Both response to chemotherapy and severity of RI were independent factors associated with survival.

Major improvements in survival of patients with MM and RI resulted from the introduction of novel agents such as early immunomodulatory drugs (thalidomide, lenalidomide), the first PI (bortezomib), and monoclonal antibodies (e.g. isatuximab, daratumumab). A retrospective analysis of over 1700 patients with symptomatic MM (roughly 50% of which had an eGFR <60 mL/min/1.73 m²) treated between 1990 and 2011 found that upfront use of novel agents (mostly thalidomide and bortezomib) was independently associated with a reduced risk of early death (hazard ratio (HR) 0.446; 95% confidence interval (CI): 0.24–0.83; p =0.009). Another retrospective analysis of 1538 patients with MM treated between 2000 and 2011, including 680 with RI at diagnosis, found that the use of novel agents (i.e. thalidomide, lenalidomide, and bortezomib) as first-line therapy significantly improved median OS compared with conventional chemotherapy (60 versus 21 months, respectively; log-rank p <0.001).

**Novel RRMM treatments for patients with RI**

Although the aforementioned investigations were conducted in the setting of front-line therapy for
NDMM, the profound impact of novel agents on patients with RI extends to the RRMM setting. Adjunctive treatment with high cut-off hemodialysis (HCO-HD), which utilizes membranes with larger pore size than conventional HD membranes and facilitates the removal of monoclonal FLCs,21 has been suggested as a means to induce renal recovery and independence from dialysis in patients with RI and MM.13 Independent phase II22 and phase III23 randomized controlled trials confirmed greater reduction of monoclonal FLCs with HCO-HD compared with standard high-flux HD, though neither showed a significant difference in the primary outcome of HD independence at 90 days. A recent meta-analysis, which included data from these two randomized trials as well as from three observational studies, noted heterogeneity between study populations but found no difference in survival or renal benefits with HCO-HD versus conventional HD, though a trend toward higher dialysis independence was seen in the HCO-HD group.24 Hemodiafiltration with ultrafiltrate regeneration offers an alternative approach to removing monoclonal FLCs and has been associated with less albumin loss than HCO-HD.25 A small observational study26 suggested that hemodiafiltration with ultrafiltrate regeneration may result in sustained FLC reduction with potential for renal recovery in patients with RI and MM. Large-scale, randomized studies will be needed to better characterize the adjunctive impact of HCO-HD and hemodiafiltration with ultrafiltrate regeneration on clinical outcomes in patients with RI and MM.

The remainder of this section will review existing and emerging evidence for the efficacy and safety of novel systemic agents in patients with RRMM and RI, with a focus on subgroup analyses from pivotal phase III randomized clinical trials (Table 2). Renal response data, particularly those in conformity with IMWG criteria1 for renal response, are summarized in Table 3. Real-world experience in patients with RRMM and RI will be discussed throughout.

**Immunomodulatory drug-based regimens**

Thalidomide and later-generation immunomodulatory drugs (i.e. lenalidomide and pomalidomide) have anti-angiogenic, immunomodulatory, and direct cytotoxic effects on myeloma cells.27 Lenalidomide is largely excreted unchanged in the urine and requires dose adjustment for different levels of renal function.28,29 The approval of lenalidomide + dexamethasone (Rd) for patients with RRMM was based on two pivotal phase III trials, MM-00930 and MM-010.31 A retrospective analysis32 of the 353 patients randomized to Rd during these two trials was conducted to investigate the efficacy and safety of the combination in patients with RRMM and various degrees of RI. Of the 353 patients, 82 (24%) had moderate RI (CrCl ≥ 30 to < 60 mL/min) and 16 (5%) had severe RI (CrCl < 30 mL/min). After a median follow-up of 31.3 months, OS for patients with moderate or severe RI was significantly shorter than for patients with mild or no RI (29.0 and 18.4 months, respectively, compared with 38.9 months; p = 0.006 for both comparisons). The majority (72%) of patients with moderate-to-severe RI experienced at least one level of improvement in CrCl (i.e. from severe to moderate or from moderate to mild or no RI). Higher levels of RI were associated with greater risk of grade 3 or 4 adverse events (AEs) including thrombocytopenia, neutropenia, anemia, and pneumonia.

Phase II trials33,34 and several small real-world studies35–37 of patients with RRMM and RI have reported similar efficacy and safety data for Rd. One real-world study36 examined the efficacy of Rd in patients with RI and its impact on RI reversal (according to IMWG criteria,1 Table 1). Twelve of 50 patients studied had RI (defined as CrCl < 50 mL/min). Partial response (PR) or better was documented in 58% of patients with RI (similar to the 60% ≥ PR rate in patients without RI); median progression-free survival (PFS) and median OS were also similar between patients with and without RI (9 versus 8 months and 14 versus 16 months, respectively). Five of the 12 patients (42%) with RI achieved a renal response to Rd (three achieved a complete renal response (CRR) and two achieved a minor renal response).

Unlike lenalidomide, pomalidomide is extensively metabolized by the liver, with limited renal clearance of active drug.38 Pomalidomide + low-dose dexamethasone (Pd) was approved for RRMM based on results from the pivotal, phase III MM-003 trial,39 which compared the combination to high-dose dexamethasone alone. A post hoc analysis40 of 447 patients from MM-003 examined the impact of baseline renal function (CrCl ≥ 30 to < 60 mL/min versus CrCl ≥ 60 mL/min) on efficacy and safety. Median PFS was similar between study arms regardless of baseline renal
Table 2. Subgroup analyses of patients with RRMM and RI from select pivotal phase III trials (darker shading: data for subgroup analysis; no shading: data for the overall population).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment (number of patients in RI subgroup)</th>
<th>Cut-off for RI</th>
<th>Median (range) prior lines</th>
<th>Median PFS</th>
<th>Median OS</th>
<th>ORR, %</th>
<th>MRD– rate (10^5 sensitivity), %</th>
<th>Safety</th>
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<tr>
<td></td>
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<td></td>
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<td>Months</td>
<td>Months</td>
<td>ORR, %</td>
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<td>n</td>
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<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
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<td></td>
<td>Grade ≥ 3 AEs, %</td>
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<tr>
<td>MM-003&lt;sup&gt;29,40&lt;/sup&gt;</td>
<td>Pd&lt;sup&gt;a&lt;/sup&gt; [n = 93] 60&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CrCl ≥ 30 to &lt; 60 mL/min</td>
<td>5 (2–12)</td>
<td>4.0 (0.48 [0.33; 0.70])</td>
<td>10.4 (0.65 [0.44; 0.98])</td>
<td>28</td>
<td>NA</td>
<td>300</td>
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<tr>
<td>OPTIMIS MM&lt;sup&gt;41,42&lt;/sup&gt;</td>
<td>Pd [n = 56]</td>
<td>CrCl ≥ 30 to &lt; 60 mL/min</td>
<td>2 (1–2)</td>
<td>1.9</td>
<td>4.9</td>
<td>11</td>
<td>NA</td>
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<tr>
<td>OPTIMIS MM&lt;sup&gt;41,42&lt;/sup&gt;</td>
<td>Pd [n = 56]</td>
<td>CrCl ≥ 30 to &lt; 60 mL/min</td>
<td>2 (1–2)</td>
<td>9.5</td>
<td>NA</td>
<td>NA</td>
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<td>ASPIRE&lt;sup&gt;43,44&lt;/sup&gt;</td>
<td>KRd [n = 79]</td>
<td>CrCl ≥ 30 to &lt; 60 mL/min</td>
<td>2 (1–3)</td>
<td>26.3 (0.69 [0.57; 0.83])</td>
<td>NA (0.72 [0.51; 1.02])</td>
<td>87.1</td>
<td>NA</td>
<td>392</td>
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<td>OPTIMIS MM&lt;sup&gt;41,42&lt;/sup&gt;</td>
<td>Pd [n = 56]</td>
<td>CrCl ≥ 30 to &lt; 60 mL/min</td>
<td>2 (1–2)</td>
<td>9.5</td>
<td>NA</td>
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<td>CASTOR&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Dara-Vd [n = 57]</td>
<td>CrCl ≥ 20 to ≤ 60 mL/min</td>
<td>2 (1–9)</td>
<td>14.9 (0.49 [0.32; 0.76])</td>
<td>42.1 (0.66 [0.44; 0.99])</td>
<td>74.1</td>
<td>NA</td>
<td>85</td>
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<tr>
<td>POLLUX&lt;sup&gt;46,47,48&lt;/sup&gt;</td>
<td>Dara-Rd [n = 80]</td>
<td>CrCl ≥ 30 to &lt; 60 mL/min</td>
<td>1 (1–11)</td>
<td>33.6 (0.41 [0.26; 0.65])</td>
<td>NA 0.74 (0.51; 1.02)</td>
<td>283</td>
<td>90.1 NA</td>
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<tr>
<td>APOLLO&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Dara-Pd [n = 40]</td>
<td>CrCl ≥ 30 to ≤ 60 mL/min</td>
<td>2 (1–5)</td>
<td>12.1 (0.59 [0.35; 0.99])</td>
<td>NA 0.74 (0.51; 1.02)</td>
<td>283</td>
<td>90.1 NA</td>
<td>283</td>
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<td>CANDOR&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Dara-Kd [n = 38]</td>
<td>CrCl ≥ 15 to &lt; 50 mL/min</td>
<td>2 (1–10)</td>
<td>6.5</td>
<td>23.7</td>
<td>49.5</td>
<td>NA</td>
<td>97</td>
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<tr>
<td>ICARIA-MM&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Isa-Pd [n = 55]</td>
<td>eGFR ≥ 30 to &lt; 60 mL/min/1.73 m²</td>
<td>3 (2–11)</td>
<td>9.5 (0.50 [0.30; 0.85])</td>
<td>NA (0.53 [0.30; 0.85])</td>
<td>56.4</td>
<td>5.5</td>
<td>54</td>
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<tr>
<td>IKEMA&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Isa-Kd [n = 43]</td>
<td>eGFR ≥ 15 to &lt; 60 mL/min/1.73 m²</td>
<td>2 (1–4)</td>
<td>9.5 (0.27 [0.11; 0.66])</td>
<td>NA 0.72 (0.51; 1.02)</td>
<td>92.1</td>
<td>7.6</td>
<td>70</td>
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<tr>
<td>ENDEAVOR&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Kd [n = 85]</td>
<td>CrCl ≥ 15 to &lt; 50 mL/min</td>
<td>2 (1–3)</td>
<td>17.6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>389</td>
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</table>
| AE, adverse event; CI, confidence interval; CrCl, creatinine clearance; d, dexamethasone; Dara, daratumumab; HR, hazard ratio; Isa, isatuximab; K, carfilzomib; MRD–, minimal residual disease-negative; NA, not available; NE, not estimable; NR, not reached; ORR, overall response rate; OS, overall survival; P, pomalidomide; PFS, progression-free survival; R, lenalidomide; RI, renal impairment.  

<sup>a</sup>MM-003 compared pomalidomide + low-dose dexamethasone with high-dose dexamethasone monotherapy.  

<sup>b</sup>Data from extended follow-up analysis of POLLUX<sup>46</sup> similar to data from the first interim analysis<sup>48</sup> (median PFS NR versus 11.4 months; HR 0.36; 95% CI: 0.22–0.60).
function, and OS benefit versus high-dose dexamethasone was sustained in patients with baseline CrCl ≥ 30 to < 60 mL/min (Table 2). Renal response, based on IMWG criteria, was similar between groups (Table 3). Rates of grade 3/4 AEs were similar across renal function subgroups.

Similar results were seen in a pooled analysis of patients with RRMM and moderate RI (CrCl ≥ 30 mL/min to < 60 mL/min) from MM-003 and two other trials of Pd (MM-002 (phase II) and MM-010 (phase III)). In this analysis, median OS was shorter for patients with moderate RI versus those without RI (10.5 versus 14.0 months; \( p = 0.004 \)). Though not designed to be comparative in nature, the phase II MM-013 trial is unique in that it prospectively investigated Pd in 81 patients with RRMM and moderate RI (eGFR ≥ 30 mL/min/1.73 m²), severe RI (eGFR < 30 mL/min/1.73 m²), or severe RI requiring hemodialysis. Median OS was 16.4 months, 11.8 months, and 5.2 months in the three groups, respectively, and renal response (as defined by IMWG) was achieved by 18.2%, 35.3%, and 7.1% of patients. A small real-world study examined efficacy and safety of Pd in 70 patients, of which 12 (17.1%) had an eGFR < 45 mL/min/1.73 m². Median PFS and OS for the eGFR < 45 versus ≥ 45 mL/min/1.73 m² groups were 5.2 months and 7.4 versus 14.1 months, respectively; neither difference reached statistical significance and AE rates were similar between the groups.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Definition of RI</th>
<th>n(^a)</th>
<th>Treatment arms experimental vs comparator</th>
<th>Complete renal response (%; reversal of renal impairment)b</th>
<th>Median time to complete renal response (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM-003(^40)</td>
<td>CrCl &lt; 60 mL/min (RI) vs CrCl ≥ 60 mL/min (normal renal function)</td>
<td>298</td>
<td>Pd vs d(^c)</td>
<td>32 vs 43</td>
<td>NA</td>
</tr>
<tr>
<td>OPTIMISMM(^42)</td>
<td>CrCl &lt; 60 mL/min (RI) vs CrCl ≥ 60 mL/min (normal renal function)</td>
<td>163</td>
<td>PVd vs Vd</td>
<td>NA</td>
<td>1.1 vs 4.9(^d)</td>
</tr>
<tr>
<td>ENDEAVOR(^45)</td>
<td>CrCl &lt; 50 mL/min(^e)</td>
<td>NA(^e)</td>
<td>Kd vs Vd</td>
<td>15.3 vs 14.1</td>
<td>8.1 vs 6.4</td>
</tr>
<tr>
<td>ICARIA-MM(^52)</td>
<td>eGFR &lt; 60 mL/min/1.73 m² (RI) vs eGFR ≥ 60 mL/min/1.73 m² (normal renal function)</td>
<td>183</td>
<td>Isa-Pd vs Pd</td>
<td>71.9 vs 38.1</td>
<td>–</td>
</tr>
<tr>
<td>IKEMA(^53)</td>
<td>eGFR &lt; 60 mL/min/1.73 m² (RI) vs eGFR ≥ 60 mL/min/1.73 m² (normal renal function)</td>
<td>215</td>
<td>Isa-Kd vs Kd</td>
<td>52.0 vs 30.8</td>
<td>7.8 vs NC</td>
</tr>
</tbody>
</table>

CrCl, creatinine clearance; d, dexamethasone; eGFR, estimated glomerular filtration rate; IMWG, International Myeloma Working Group; Isa, isatuximab; K, carfilzomib; NA, not available; NC, not calculable; P, pomalidomide; RI, renal impairment; V, bortezomib.

\(^a\)Number of patients with known CrCl levels.

\(^b\)Complete renal response defined as improvement in eGFR from < 50 mL/min/1.73 m² at baseline to ≥ 60 mL/min/1.73 m² (no renal impairment) in at least one post-baseline assessment, per IMWG recommendations.

\(^c\)MM-003 compared pomalidomide + low-dose dexamethasone with high-dose dexamethasone monotherapy.

\(^d\)Time to first improvement in renal function.

\(^e\)Patients were divided into renal subgroups by CrCl ≥ 15 to < 50, ≥ 50 to < 80, and ≥ 80 mL/min, but a formal definition of RI was not made; 184 patients had CrCl ≥ 15 to < 50 mL/min.
In total, available data show that patients with RI and RRMM achieve survival benefit from the addition of lenalidomide or pomalidomide to dexamethasone, though generally to a lesser extent than patients without RI. Prospective, late-phase renal response data for the immunomodulatory drugs are limited, but retrospective and real-world data for Rd and phase II data for Pd show that improvement in renal function is possible when these agents are added to dexamethasone.

Proteasome inhibitor-based regimens

Proteasome inhibitors (i.e. bortezomib, carfilzomib, and ixazomib) exert their effects on myeloma cells through a variety of mechanisms including activation of apoptotic pathways, inhibition of angiogenesis, and alteration of cell adhesion. Regimens containing bortezomib, the first-in-class proteasome inhibitor, have long been considered the standard of care for patients with MM and RI, owing largely to its nonrenal metabolism and the breadth of evidence supporting its efficacy in this patient population. Following its initial FDA approval for MM in 2003, multiple studies have demonstrated the ability of bortezomib-based regimens to induce rapid and significant response, with potential RI reversal, in patients with RRMM.

The randomized phase III ENDEAVOR trial compared carfilzomib + dexamethasone (Kd) with bortezomib + dexamethasone (Vd) for patients with RRMM, revealing improvement in the primary outcome of PFS with Kd. A post hoc exploratory subgroup analysis evaluated the efficacy and safety of both treatment regimens in patients with various degrees of RI at baseline (grouped by CrCl ≥ 15 to <50 (n = 184), CrCl ≥ 50 to <80 (n = 363), and CrCl ≥ 80 mL/min (n = 382)). Improvements in PFS, OS, and ORR were observed in the Kd arm across renal subgroups; results for patients with CrCl < 50 mL/min are highlighted in Table 2. In patients with CrCl ≥ 15 to <50 mL/min, roughly 15% achieved CRR and time to complete renal response was similar across treatment arms (Table 3).

A large real-world study utilized electronic medical record data from US oncology clinics to compare renal response rates (as defined by IMWG; Table 1) among patients with RRMM and RI (defined as baseline eGFR < 50 mL/min/1.73 m²) who were treated with Kd (n = 543) or Vd (n = 1005) in the second through fourth line of treatment. For patients receiving second-line treatment, those who received Kd versus Vd demonstrated significantly better renal overall response rates (51.4% versus 39.6%; log-rank p < 0.0001) and renal complete response rates (26.6% versus 22.2%; log-rank p = 0.0229). Consistent results were observed among patients in the third- and fourth-line settings and among patients in the second-line setting with eGFR < 15 mL/min/1.73 m². A combined analysis of patients from both treatment groups (and across second through fourth lines of treatment) found that patients who achieved renal response had longer OS and time to next treatment (TTNT) than renal nonresponders.
Ixazomib, an oral proteasome inhibitor approved for use in RRMM, was approved in combination with Rd based on results of the phase III TOURMALINE-MM1 trial.68 Patients with mild-to-moderate RI (CrCl \( \geq 30 \) to \( 60 \) mL/min) comprised 25% of the 722 patients in the trial. Though no prespecified or post hoc subgroup analyses have been performed for patients with RI, the relatively large contribution of these patients to overall trial results suggests that ixazomib benefits can be safely extended to patients with CrCl \( \geq 30 \) mL/min.

Overall, substantial evidence for the benefit of bortezomib and carfilzomib exists for patients with RI and RRMM, though analyses of renal subgroups within phase III trials were largely post hoc in nature. The phase III ENDEAVOR trial revealed superior efficacy with Kd versus Vd in patients with RI and RRMM, with similar renal response rates and time to renal response between arms. A large real-world study showed improved overall and complete renal response rates with Kd versus Vd, and renal response was associated with improved OS. Phase III data specific to patients with RI has not been reported for ixazomib.

**Real-world benefit of combining immunomodulatory drugs and proteasome inhibitors.** Building on experiences from the OPTIMISMM trial, researchers utilized the Flatiron Health database to assess outcomes and renal response by first- and second-line drug class (i.e. PIs, immunomodulatory drugs, and monoclonal antibodies) among patients with MM and RI (defined as eGFR \( < 50 \) mL/min/1.73 m\(^2\)). Though patients who received monoclonal antibodies were included in the analysis, low treatment rates with these therapeutics during the study period (2011–2019) precluded robust analyses of outcomes with this drug class. After adjustment for multiple factors, patients with RI at the start of second-line treatment had worse OS compared with non-RI patients (median 2.67 versus 4.44 years, respectively; adjusted HR 1.49; 95% CI: 1.33–1.68). Among 920 patients with RI at the start of second-line therapy who received at least one eGFR measurement during treatment, 19% achieved a CRR. Patients who received a PI + immunomodulatory drug combination were significantly more likely to have a CRR than those without use of either treatment class (adjusted OR: 3.89; 95% CI: 1.71–8.86), and those who achieved a CRR with the combination had significantly improved OS compared to those not receiving either treatment who did not achieve CRR (adjusted HR: 0.53; 95% CI: 0.32–0.88). Results from this study confirmed the association of RI with inferior OS in patients with RRMM and highlighted both the benefit of combining PIs with immunomodulatory drugs in early lines of therapy and the significance of achieving CRR.

**Monoclonal antibody-based regimens**

Monoclonal antibodies (i.e. daratumumab, isatuximab, and elotuzumab) exert their antitumor activity via immune-mediated mechanisms that selectively target myeloma cells with minimal impact on normal tissue. Daratumumab is a CD38 monoclonal antibody approved as monotherapy and in multiple combinations for the treatment of patients with relapsed/refractory disease. A pooled analysis of the two noncomparative studies (phase I/II GEN501 and phase II SIRIUS) that led to the approval of daratumumab monotherapy in patients with RRMM revealed that 37% of patients had a baseline CrCl of \( \geq 30 \) to \( < 60 \) mL/min. The ORR (27.8%) in that subgroup was consistent with that observed in the overall combined population (31.1%).

In the pivotal phase III POLLUX trial, which compared daratumumab + lenalidomide + dexamethasone (Dara-Rd) to Rd in patients with RRMM, the primary end point of PFS was significantly lengthened with the addition of daratumumab. Patients with CrCl \( \geq 30 \) mL/min were allowed to enroll in POLLUX, and a post hoc subgroup analysis at the time of the first interim analysis found that the PFS benefit seen in the overall study population was maintained in patients with moderately impaired renal function (defined as CrCl \( \geq 30 \) to \( < 60 \) mL/min). The PFS benefit was maintained after an extended follow-up period and the ORR was also higher in patients with RI who received daratumumab (Table 2). The phase IIb trial of daratumumab + pomalidomide + dexamethasone (Dara-Pd) versus Pd (EQUULEUS, \( n = 103 \)) included 31 patients with a baseline CrCl of \( < 60 \) mL/min (those with CrCl of \( \geq 45 \) mL/min were eligible for enrollment). The ORR in this prespecified subgroup of patients was 58.1%, similar to that for the overall study population (60.2%). The phase III trial of Dara-Pd versus Pd (APOLLO, \( N = 304 \)) allowed patients with CrCl \( \geq 30 \) mL/min to enroll. Patients in the
prespecified subgroup of CrCl $\leq 60\,\text{mL/min}$ comprised 26% (40 of 151) and 31% (47 of 153) of patients in the Dara-Pd and Pd groups, respectively. Median PFS benefit in these patients (Table 2) was similar to that for the overall study population.

The pivotal phase III CASTOR trial\textsuperscript{50} provided the basis for the approval of daratumumab + bortezomib + dexamethasone (Dara-Vd) for the treatment of RRMM. CASTOR, which compared Dara-Vd to Vd alone, allowed patients with CrCl $>20\,\text{mL/min}$ at screening to enroll. Patients in the prespecified subgroup of CrCl $\leq 60\,\text{mL/min}$ comprised 23% (57 of 243) and 30% (70 of 233) of patients in the Dara-Vd and Vd groups, respectively. Median PFS benefit in these patients (Table 2) was similar to that for the overall study population.

CANDOR\textsuperscript{51} the phase III trial of daratumumab + carfilzomib + dexamethasone (Dara-Kd) \textit{versus} Kd, allowed enrollment of patients with CrCl $\geq 20\,\text{mL/min}$ at screening. A prespecified subgroup analysis of PFS by level of baseline renal function ($\geq 15$ to $<50$, $\geq 50$ to $<80$, and $\geq 80$ mL/min) was performed. Patients with CrCl $\geq 15$ to $<50\,\text{mL/min}$ comprised 12% of patients (38 of 311) in the Dara-Kd group and 18% of patients (27 of 154) in the Kd group with evaluable CrCl at baseline. The PFS benefit seen with Dara-Kd in the overall population was extended to patients with CrCl $\geq 15$ to $<50\,\text{mL/min}$ (Table 2).

The phase II DARE study\textsuperscript{73} of daratumumab + dexamethasone enrolled 38 patients with RRMM and severe RI (defined as either eGFR $<30\,\text{mL/min/1.73m}^2$ or requiring hemodialysis). At study initiation, 17 patients (48.6%) were on dialysis. A preliminary analysis of efficacy and safety was conducted for 35 patients who were at least 5 months into treatment. The 6-month PFS rate for the overall population was 50%, with an ORR of 45.7%. In patients requiring dialysis, the ORR was 35.3%. The renal response rate (as defined by IMWG\textsuperscript{1} Table 1) was 17.1% (Table 4).

Real-world experience of daratumumab in patients with RI is also available. Case reports\textsuperscript{74–77} and a small case series\textsuperscript{78} of dialysis-dependent patients with RRMM who received daratumumab-based therapy have consistently reported benefit, in some instances with reduction of dialysis frequency\textsuperscript{75,76} or full dialysis independence.\textsuperscript{74,77}
A retrospective, single-center study analyzed 91 patients with RRMM who received daratumumab as monotherapy or in combination with novel agents. Patients were grouped by renal function (eGFR $< 30$ (n = 11), $\geq 30$ to 60 (n = 27), and $\geq 60$ mL/min/1.73 m$^2$ (n = 53)). Median PFS was similar across groups (17.5, 22.4, and 17.3 months, respectively), and 11 patients in the eGFR $\geq 30$ to $< 60$ mL/min/1.73 m$^2$ group achieved a renal response (defined as eGFR $> 60$ mL/min/1.73 m$^2$ in two consecutive visits for patients with baseline RI).

Isatuximab is a monoclonal antibody that binds to a specific epitope of the CD38 receptor and possesses the unique ability to induce direct apoptosis of myeloma cells. The first approval of isatuximab resulted from the pivotal phase III IKEMA trial, which compared isatuximab + pomalidomide + dexamethasone (Isa-Pd) to Pd in patients (N = 307) with RRMM. ICARIA-MM enrolled patients with eGFR $\geq 30$ mL/min/1.73 m$^2$, and efficacy and safety outcomes were examined in a prespecified subgroup analysis of patients with RI (defined as eGFR $< 60$ mL/min/1.73 m$^2$). Of 287 patients with evaluable eGFR at start of therapy, 55 (38.7%) in the Isa-Pd group and 49 (33.8%) in the Pd group had RI; each arm included one patient with eGFR $< 30$ mL/min/1.73 m$^2$. The PFS benefit of Isa-Pd versus Pd was consistent with that seen for the full study population; overall response and MRD negativity rates among patients with RI were higher in the Isa-Kd arm (Table 2). Complete renal response rates improved with Isa-Kd (52.0%) versus Kd (30.8%), as did time to first renal response (Table 3). Patients with eGFR $< 30$ mL/min/1.73 m$^2$ at baseline were more likely to achieve minor renal response with the addition of isatuximab. Isa-Kd was associated with a manageable safety profile in patients with and without RI. Notably, the presence of RI was not associated with higher rates of grade 3 or higher cardiac failure, which is a known toxicity of carfilzomib.

Real-world experience of isatuximab in patients with RI is also available. A case report of a dialysis-dependent patient with RRMM who received therapy with Isa-Pd was recently published. Following seven prior lines of therapy, the patient’s free light chain $\lambda$ level dropped from 2,070 mg/L to 412 mg/L 12 days after starting Isa-Pd. The patient experienced no infusion reactions or clinically meaningful drops in white blood cell count during treatment with Isa-Pd, and his disease remained well controlled after seven cycles of treatment.

Elotuzumab is a humanized monoclonal antibody targeted against signaling lymphocyte activation molecule-7 (SLAMF7). Two phase III randomized trials, ELOQUENT-2 and ELOQUENT-3, led to the approval of elotuzumab with Rd and Pd, respectively. Enrollment was allowed for patients with CrCl $\geq 30$ mL/min (ELOQUENT-2) and $\geq 45$ mL/min (ELOQUENT-3), but neither trial reported on safety or efficacy outcomes stratified by renal function. A small phase Ib study found elotuzumab to be both tolerable and effective for treatment of patients with MM and RI, including...
those with end-stage renal disease. Enrollment was allowed for patients with three levels of renal function: normal (CrCl $\geq 90$ mL/min ($n = 8$)), severely impaired (CrCl $< 30$ mL/min, not requiring dialysis ($n = 9$)), and end-stage (requiring dialysis ($n = 9$)). Overall responses occurred in 75%, 67%, and 56% of patients in the three renal function groups, respectively, and two patients in the severe RI group (including one with RRMM) achieved a minor renal response (as defined by the IMWG; Table 1). No difference in grade 3/4 AEs was observed between renal function groups. The efficacy and safety observed in patients with RI during this small phase Ib trial has not been confirmed in late-phase clinical trials.

In total, the dramatic efficacy benefits seen in phase III trials of daratumumab and isatuximab in RRM extend to subgroups of patients with RI. Phase II data and numerous real-world experiences have indicated that improvement of renal function is possible with daratumumab; however, phase III trials of daratumumab-based regimens have not reported on renal response rates. Phase III trials of isatuximab-based regimens have provided robust analyses of efficacy, safety, and renal response data for patients with RI. Late-phase data for elotuzumab have not been reported separately for the population of patients with RI.

Antibody-drug conjugates

Belantamab mafodotin is a first-in-class ADC that delivers a microtubule-disrupting agent, monomethyl auristatin F, to B-cell maturation antigen (BCMA)-expressing myeloma cells. Belantamab mafodotin received FDA approval in patients with RRMM based on the phase II DREAMM-2 study. Patients with eGFR $\geq 30$ mL/min/1.73 m$^2$ at screening were allowed to enroll in DREAMM-2. A post hoc analysis was conducted to explore efficacy and outcomes across patients with varying levels of renal function at enrollment: normal (eGFR $\geq 90$ mL/min/1.73 m$^2$), mildly impaired ($\geq 60$ to $< 90$ mL/min/1.73 m$^2$), and moderately impaired ($\geq 30$ to $< 60$ mL/min/1.73 m$^2$). Patients with moderate RI comprised roughly 25% of patients in each dosing cohort. Overall response rates were similar across renal function groups and consistent with results for the overall DREAMM-2 study population. Median PFS was similar among patients with and without any degree of RI, as were rates of keratopathy and grade 3/4 AEs. Results for the moderate RI group are detailed in Table 4.

CAR T-cell therapies

Based on results from the phase II KarMMA trial, idecabtagene vicieuxel became the first FDA-approved, BCMA-directed chimeric antigen receptor (CAR) T-cell therapy. Though patients with inadequate renal function (defined as CrCl $\leq 45$ mL/min) were excluded from the KarMMA trial, two small studies offer some insight into outcomes and safety of CAR T-cell therapies among patients with RI. A post hoc analysis of combined data from two phase I trials of different anti-BCMA CAR T-cell therapies stratified patients (combined $n = 59$) according to impaired renal function (IRF; defined as eGFR $< 90$ mL/min/1.73 m$^2$) and normal renal function (NRF, eGFR $\geq 90$ mL/min/1.73 m$^2$). Patients with eGFR $< 30$ mL/min/1.73 m$^2$ were excluded from the analysis. Patients with IRF and NRF had median PFS of 181 days versus 266 days and median OS of 238 days versus 877 days (log-rank $p < 0.05$ for each comparison), and eGFR significantly improved in the IRF group over the first 6 months of therapy. A small study of 7 patients with RRMM and RI (median stage 4 CKD; eGFR 15 to 29 mL/min/1.73 m$^2$; patients requiring dialysis excluded) explored outcomes with CAR T-cell therapies directed at either BCMA alone or the combination of BCMA and CD19. All patients achieved response to treatment, with 4 (57%) achieving stringent complete response. All patients also achieved renal response, with 5 (71%) achieving renal complete response. The median time to first renal response was 9 days and median time to best renal response was 32 days.

Selinexor

Selinexor is a first-in-class, oral selective inhibitor of exportin-1 (XP01), a protein involved in the exportation of tumor suppressor proteins from the nucleus. Based on the phase IIb STORM trial, selinexor (in combination with low-dose dexamethasone) is FDA-approved for the treatment of adult patients with RRMM who have received at least four prior therapies (including PIs, immunomodulatory drugs, and an anti-CD38 monoclonal antibody). STORM enrolled 122 patients with CrCl $\geq 20$ mL/min; CrCl was $< 60$ mL/min in 39 patients (32%) and $< 40$ mL/min in 14 patients
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Dose modifications for RI among novel agents for the treatment of RRMM

Per the FDA’s 2020 Guidance Document,98 therapeutic proteins require a dedicated renal impairment study, with exception of proteins with a molecular weight greater than 69 kDa. In the case of treatments for RRMM, this exclusion applies to monoclonal antibodies, ADCs, and CAR T-cell therapies. Of the novel small molecules currently used for the treatment of RRMM, ixazomib and lenalidomide require dose adjustment for RI. Though renal clearance of ixazomib is minimal,99 a reduced starting dose (3 mg versus 4 mg) is recommended for patients with CrCl < 30 mL/min.100

Chen et al.28 reported that lenalidomide is predominantly excreted unchanged via the kidneys and recommended dose adjustments based on renal function. According to prescribing information99 for lenalidomide, on days 1–21 of 28-day cycles, a daily dose of 25 mg is recommended for patients with normal renal function (CrCl > 60 mL/min). In patients with IRF, 10 mg daily is recommended for patients with CrCl ≥ 30 to < 60 mL/min, 15 mg every-other-day for patients with CrCl < 30 mL/min not requiring dialysis, and 5 mg daily for patients with CrCl < 30 mL/min requiring dialysis (dose should be administered after dialysis). To better understand appropriate dosing of lenalidomide, and to prevent under- or over-dosing among patients with RI, the phase I/II PrECOG study101 analyzed the maximum tolerated dose of lenalidomide in patients with relapsed MM and RI, as well as the efficacy and safety of lenalidomide + dexamethasone in these patients. Based on the absence of dose-limiting toxicities during phase I, and on the lack of difference in AEs and response rates between daily and less frequent dosing in phase II, the authors concluded that lenalidomide can be given at full dose (25 mg daily) in patients with a CrCl ≥ 30 mL/min or at doses of at least 15 mg daily to those with CrCl < 30 mL/min, even when on dialysis, without the need to decrease the dose frequency.

Conclusion

Renal impairment is a frequent complication of MM that negatively impacts survival. Historically, many trials have either excluded patients with RI or failed to report outcomes in this important subset of patients. Phase III trials reporting efficacy and safety data in patients with RRMM and RI are summarized in Table 2. Though a key therapeutic goal in patients with MM and RI, improvement in renal function has not been uniformly evaluated in late-phase clinical trials of novel therapies for RRMM (Table 3). Furthermore, the majority of these studies are not powered to detect differences between the treatment arms for patients with RI. Real-world experiences supporting safety and efficacy, including renal response and reversal of dialysis, have surfaced for various novel RRMM regimens, adding to the evidence base for selected treatments.

Treatment options for patients with RRMM are rapidly expanding and improving outcomes, yet the ideal treatment for patients with RI remains unknown. Optimizing treatment of the underlying myeloma is critical in patients with RI, and better MM therapies will be required to correct the prognostic imbalance between patients with RI and the general RRMM population. Despite growing awareness of the negative impact of RI on survival in patients with MM, the consistency with which randomized controlled trials reported enrollment criteria related to renal dysfunction, prevalence of RI in enrolled patients, and outcomes among patients with RI did not significantly improve between 2005 and 2019.12 Available data for patients with RI and RRMM stem largely from subgroup analyses of phase III studies, comparisons among which are inherently
limited by differences in eligibility criteria between trials (e.g. different CrCl cutoffs and exclusion of patients with severe RI in some trials). These data support the combination of monoclonal antibodies in combination with PIs or immunomodulatory drugs to be efficacious and safe in patients with RI and RRMM. Reliable and consistent reporting of efficacy and safety data for subgroups of patients with RI, including data on renal response and preferentially as part of prespecified analyses, should be encouraged in future trials. In addition, trials designed to prospectively evaluate outcomes in large populations of patients with RI (including those on dialysis) are essential to provide optimal myeloma therapy to this population. Real-world data collected from robust databases may supplement information provided from clinical trials and further support the translation of study findings to real-world practice.102

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References

2. Eleutherakis-Papaiakou V, Bamias A, Gika D, et al. Renal failure in multiple myeloma:


