

# Melflufen—A Novel Agent in the Treatment of Relapsed/Refractory Multiple Myeloma

An Expert Interview with Paul G Richardson

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## Paul G Richardson

Dr. Paul Richardson joined the Jerome Lipper Multiple Myeloma Center in 1999 after a visiting fellowship, and has served as faculty in cancer pharmacology at Dana-Farber Cancer Institute (DFCI) since 1994. He was appointed Clinical Director in 2001. His major clinical research has been focused on the development of novel agents for the treatment of multiple myeloma and combination strategies designed to improve efficacy, with one example being the landmark Intergroup Francophone Myeloma (IFM)/DFCI clinical trial in newly diagnosed patients eligible for stem cell transplant treated with the combination of lenalidomide, bortezomib, and dexamethasone (RVD). He has authored or co-authored over 720 articles in peer-reviewed journals. In addition to holding positions on the editorial boards of leading journals, he has been Chairman of the Multiple Myeloma Research Consortium and the Clinical Trials Core, a member of the American Society of Clinical Oncology (ASCO) Hematologic Malignancies Subcommittee and ASCO Internet Cancer Information Committee, and has currently been Chair of the Alliance Myeloma Committee since 2011. He has achieved many honors and awards throughout his distinguished career, to name a few: the prestigious Warren Alpert Foundation Prize in recognition of the successful therapeutic targeting of the ubiquitin-proteasome pathway in 2012, one of Thomson Reuters Science Watch top 19 investigators at DFCI for the most highly cited research in 2016, the International Myeloma Foundation's Robert A Kyle Lifetime Achievement Award in 2017, and the Morse Research Award at DFCI in 2019 for outstanding clinical research.

## Keywords

Multiple myeloma, melflufen, dexamethasone, relapsed/refractory

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Multiple myeloma (MM) is the second most common hematological malignancy after non-Hodgkin's lymphoma.<sup>1</sup> Although recent decades have seen considerable advances and improvements in clinical outcomes for patients with MM,<sup>2</sup> MM remains incurable, with a high disease burden.<sup>3</sup> Clonal evolution and genomic instability within myeloma clones inevitably lead to disease progression and treatment resistance.<sup>4</sup> An increasing number of patients are becoming refractory to multiple treatments; therefore, there is a need for new drugs with novel mechanisms of action.

Melflufen (melphalan flufenamide) is a novel peptide–drug conjugate that has shown efficacy in relapsed/refractory MM. In an expert interview, Dr Richardson discusses the recently published O-12-M1 phase I/II study, which investigated the efficacy and safety of melflufen in the setting of triple-class refractory patients, i.e., those who have progressed after proteasome inhibitors, immune modulators, and antibodies.<sup>5</sup>

## Q. What are the most important unmet needs in the treatment of multiple myeloma?

There has been tremendous progress in the past 20 years with the advent of novel therapies, which initially focused on proteasome inhibition and immune modulation, and then the introduction of monoclonal antibodies. However, despite the success of these platforms, the disease remains incurable, and resistance and relapses are frequent, with the disease ultimately becoming refractory in each individual patient over time. Therefore, we are continuously looking for novel mechanisms of action that target fundamentally different aspects of tumor biology. In addition to B-cell maturation antigen (BCMA)-targeting strategies, including antibodies, but also excitingly chimeric antigen receptor T-cell (CAR-T) therapy,<sup>6</sup> we have several small molecule targets including the selective inhibition of nuclear export proteins (SINE), the best example of which is selinexor, and the inhibition of histone deacetylase, including panobinostat, which show promise.<sup>7,8</sup> Beyond these, there remains a challenge.

Most importantly, we face the dilemma in myeloma of 'stemness,' a complicated entity reflecting the fact that, while CD38 targeting has been very successful, and BCMA has been very encouraging, these targets are relatively downstream of the molecular ontogeny of myeloma development, and the stemness that precedes it remains a challenge. In that setting, true immune adjuvants, such as elotuzumab, which activate natural killer cells on the myeloma cell surface have shown promise.<sup>9</sup> However, these

do not address the fundamental complexity of the disease and the essence of stemness. The ability to deliver an agent that is highly targeted and deliver efficacy into core disease is a major frontier. After CD38-targeted treatment has failed, extramedullary disease has become an important new area of unmet medical need.<sup>10</sup> In the relapsed/refractory setting, after monoclonal antibodies and other platform approaches have run out of steam, what do we have to offer the patient? In that regard, new strategies are urgently needed.

### **Q. Could you tell us a little about melflufen and its mechanism of action?**

Melflufen is an important new agent in my view. It is a novel peptide conjugate, ultimately a melphalan-derived warhead (melflufen flufenamide) that rapidly delivers its payload directly into the tumor cell. The drug conjugate is highly lipophilic and therefore safe, and readily enters the bone marrow. In contrast, melphalan is lipophobic and requires dose escalation.<sup>11</sup> The conjugate is also highly dependent on the action of aminopeptidases, which are enriched in myeloma cells.<sup>12</sup> This means that when the conjugate enters the cell, it is cleaved and the active drug is enriched in the cell, where it shows striking and targeted cytotoxicity against the tumor. This confers several advantages, including an absence of dose-limiting toxicities such as mucositis, (which is dose-limiting for melphalan), and alopecia. In addition, its cytotoxicity is over 50 times higher than that of melphalan, allowing it to overcome resistance to prior chemotherapy exposure.<sup>13</sup> We are also beginning to understand other properties of melflufen, including its strong antiangiogenic action, which is important since plasma cells are enriched with new vessel formation, and disrupting that process is crucial. This is also important in extramedullary disease, making it an additionally very attractive drug in the setting of relapsed/refractory MM.

### **Q. What was the rationale for and design of the O-12-M1 study?**

The first-in-human trial of melflufen in solid tumors demonstrated that the conjugate could be safely administered at active doses; the primary toxicity was hematological.<sup>14</sup> These findings informed the O-12-M1 study, which was an international, multicenter study that had both dose escalation and dose expansion components, as a phase I/II study (ClinicalTrials.gov Identifier: NCT01897714). The study explored intravenous melflufen combined with dexamethasone for the majority of patients.<sup>5</sup> In addition, a small cohort of patients received single-agent melflufen to demonstrate what the drug could achieve without the benefit of added steroids. It is important to bear in mind that, in patients with relapsed/refractory MM, everyone is steroid resistant. Despite this, the majority of novel agents benefit from the addition of steroids, and melflufen is no exception. In the phase II portion, we treated with the maximum tolerated dose that was defined from the phase I portion, and included the combination and single-agent cohorts. The study enrolled 75 patients over 7 sites: 23 in the phase I portion of the study and 58 in the phase II portion, of whom 13 were treated with single agent.

### **Q. What were the major efficacy and safety findings of this study?**

The dose escalation study started at 15 mg, then 25 mg, and ultimately 40 mg, infused every 3 to 4 weeks, with the highest dose tested being 55 mg. Traditionally, we think of alkylating agents as being dosed per meter squared, but there is clear evidence that fixed dosing with alkylators can be effective. We therefore used fixed doses. At 15 mg, 25 mg and 40 mg,

the drug was well tolerated. At 55 mg, neutropenia and thrombocytopenia occurred in three patients. We therefore did not test the highest planned dose of 70 mg. The maximum tolerated dose was defined at 40 mg. We also investigated the dosing schedule. Initially, we used a 3-weekly schedule, which was intensive and active, but we found that prolonging the interval to 4 weeks allowed more time for hematologic recovery, and so the 4-weekly schedule was adopted going forward. The dexamethasone dosage was 40 mg once a week, serving as a convenient low dosage.<sup>5</sup>

When we looked at single-agent melflufen in the 11 patients who were available for evaluation of efficacy and the 13 who were evaluable for safety, 40 mg was generally well tolerated and manageable in terms of side effects, but the response signal was modest. It was very clear that the dexamethasone was adding to the efficacy of the drug. The clinical benefit rate in the single-agent melflufen group was 23%, whereas in the combination group it was 49%. In addition, the partial response rate was 10% for the single-agent group and 31% in the combination group, suggesting that the combination should be used. In the 45 patients who received the combination, the clinical benefit rate was 50%, which is encouraging in the setting of relapsed/refractory disease with an overall response rate of 31%. Stable disease was achieved in a further 30%. Overall, only 16% progressed; a favorable finding in this setting. In the time-to-event analyses, these responses were found to be quite durable, which is important as this study has considerable maturity in follow-up at a median of 28 months. Median progression-free survival (PFS) in all patients was 6 months and overall survival (OS) was 21 months. This provides evidence for activity in this population, with meaningful benefits in PFS and OS.<sup>5</sup>

The median number of prior therapies in the study population was 5 (range 4.0–6.5), reflecting a heavily pretreated population. A relatively small, but not trivial, number of patients had been exposed to antibodies (15 daratumumab and 2 elotuzumab), as opposed to the current treatment paradigm. Patients with high-risk cytogenetics were also well represented.<sup>5</sup>

In terms of safety, tolerability was favorable, and overall toxicities were mild to moderate and proved reversible. Cytopenia and neutropenia were the dominant toxicities, and proved manageable with dose reduction, dose delay and blood product support or growth factors. There were limited non-hematological toxicities; we did not see significant mucositis or alopecia. Gastrointestinal side effects were modest. The rate of serious adverse events was around 27%, including pneumonia in four patients, and two septic events. The number of upper respiratory tract infections was quite low compared with other studies in this setting; however, there were infections in a minority of patients that contributed to mortality. There were four fatal events study-wide, but all in patients with rapidly progressing disease and within 30 days of the last dose of melflufen, with two of these infectious. The two septic events occurred immediately in patients who had been enrolled on the trial and had received one dose of melflufen;<sup>5</sup> significant bleeding did not occur.

### **Q. What will be the next steps in the clinical development of melflufen?**

This study has defined that 40 mg of melflufen and 40 mg dexamethasone will be the platform going forward. It has also shown that this drug is effective in the setting of triple-class refractory patients. In terms of ongoing and future studies, the HORIZON study (ClinicalTrials.gov identifier: NCT02963493) is a large multicenter, international, phase II trial that

has enrolled over 150 patients;<sup>15</sup> final results are promising and will be presented shortly. These findings confirm the efficacy that was seen in the O-12-M1 study, and have also shown activity in extramedullary disease, a very important consideration as mentioned earlier. The OCEAN trial (ClinicalTrials.gov identifier: NCT03151811) is an international, randomized, phase III study comparing melflufen and dexamethasone with pomalidomide and dexamethasone in a less heavily pretreated group of patients (two or more prior lines of therapy), and is almost fully enrolled.<sup>16</sup>

Combination studies are also ongoing. The ANCHOR trial (ClinicalTrials.gov identifier: NCT03481556) is investigating the combination of melflufen and bortezomib in one cohort, and melflufen and daratumumab in another cohort. Early results have shown that combinations appear to be effective and generally well tolerated so far, suggesting that melflufen has the potential to be a partner drug with a number of existing drugs that are mainstays of MM therapy, and further enhance efficacy with the potential to meaningfully improve outcomes in patients with relapsed/refractory multiple myeloma. □

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