In August, myeloma experts convened in Queenstown for the HSANZ (Haematology Society of Australia and New Zealand) 2018 Multiple Myeloma Summit. This year’s meeting included presentations from a range of local and international experts in myeloma, the second most common haematological cancer, including Donna Reece (Canada), Hang Quach (Melbourne), and Ola Landgren (New York). Nine of the many excellent presentations from the meeting have been summarised for your convenience in this review. Please feel free to send us any comments or feedback. Convenor, Ken Romeril.

**REAL-WORLD OUTCOMES FOR MM IN AUSTRALIA AND NZ IMPROVING OUTCOMES BASED ON WHAT WE HAVE LEARNT**

Presented by A/Prof Hang Quach

PFS outcomes from real-world patients treated with carfilzomib-, bortezomib- and lenalidomide-based regimens are reportedly lower than clinical trial outcomes, with treatment-related toxicity and early treatment cessation the main reasons. Data from the MRDR (Myeloma & Related Diseases Registry; n>2000; –20% from NZ) show significantly shorter OS durations for older patients or those with higher revised ISS stage or renal impairment.

**Treatment aims in MM**

Good disease control is best obtained with minimising the toxicity and the impact of treatment on quality of life. Both depth and duration of response are key correlates of survival, as is MRD negativity. It is becoming increasingly apparent that responses dictate outcomes. Patients who achieve then lose a deep response quickly may have biologically more aggressive disease than those who achieve and maintain a lesser response. Survival curves for patients with a sustained response plateau over time (operational cure); thus, durability of response is as important as depth of response for achieving OS. The overall goal of treatment is therefore to induce and maintain a deep response using available resources.

**Principles guiding MM treatment**

**Upfront therapy in MRDR**

Among MRDR registrants (who include patients aged >65 years), autologous autologous SCT (n=469) versus no SCT improved outcomes (see Figure 1). Furthermore, those aged 65–70 years had survival rates comparable with younger patients and better than same-age non-SCT counterparts. Room for improvement in uptake of autologous SCT among older patients was advocated, as it was performed in only 56% of patients aged 65–70 years. In Australia, renal impairment, although not a contraindication, appears to impact on the decision to proceed to SCT. Patients with renal impairment who underwent autologous SCT had survival rates comparable with those without renal impairment, and better than those who did not undergo SCT. Renal impairment is also a poor prognostic indicator, so achieving deep, durable responses in these patients is important.

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**Abbreviations used in this review**

- **BCMA**: B-cell maturation antigen
- **CAR**: chimeric antigen receptor
- **CR**: complete response
- **CRES**: CAR T-cell encephalopathy syndrome
- **CRS**: cytokine-release syndrome
- **FISH**: fluorescence in situ hybridisation
- **ISS/R-ISS**: (Revised) International Staging System
- **MM**: multiple myeloma
- **MRD**: minimal residual disease
- **ORR**: overall response rate
- **OS**: overall survival
- **PFS**: progression-free survival
- **PI**: proteasome inhibitor
- **SCT**: stem-cell transplantation
- **(VG)PR**: (very good) partial response

**Drug regimens**

- **CyBorD**: cyclophosphamide, bortezomib, dexamethasone
- **RVD**: lenalidomide, bortezomib, dexamethasone
- **VCD**: bortezomib, cyclophosphamide, dexamethasone
- **VMP**: bortezomib, melphalan, prednisone
- **VTD**: bortezomib,thalidomide, dexamethasone

Figure 1. Best clinical response to first-line therapy among MRDR patients

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Consolidation & maintenance therapy

Consolidation bortezomib is less commonly used in Australia, due to regulations limiting its use to four cycles. However, it can be considered for patients who fail to achieve a deep response; e.g. high-genetic-risk patients. Relevant findings regarding the use of consolidation therapy were discussed, including limitations of the STAMINA trial, which concluded lack of benefit.6-10 Patients with deep responses following SCT do gain further benefit from maintenance therapy, as demonstrated in a trial of post-SCT lenalidomide versus placebo.11

Transplant-ineligible patients

MRDR data show that 77% of transplant-ineligible patients received VCD, with non-bortezomib regimens reserved for elderly/frail patients.2 However, early bortezomib discontinuation is a significant issue; 34% received <9 cycles, for which the VGPR rate is >60%. While most discontinuations were due to toxicity, some were ‘planned’ cessations, even after 1–3 cycles, which is a concern as drug discontinuation independently predicts worse outcome.12 Approaches to minimise toxicity, including changing to once-weekly, subcutaneous bortezomib, were outlined.

Optimising treatment

It has been shown that there is significant patient dropout with each line of therapy.13 The greatest gains are therefore seen with first-line and possibly second-line treatment. VCD was used as first-line therapy for 75% of MRDR patients, resulting in greater depth or response compared with non-bortezomib (thalidomide) regimens, which translated to longer survival initially.12

How to improve

The costs associated with novel regimens being investigated in clinical trials are often prohibitive, so the focus should be on achieving an optimal response with minimal treatment, bearing in mind that not all myelomatous disease will respond to, and not all patients will tolerate, the same treatment intensity. As such, regionally relevant, prospective clinical trials that focus on response-adapted and/or tolerance-tailored approaches are needed.

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PFS of high-risk transplant-eligible patients has increased with the introduction of novel agents. Bortezomib is an important component of induction therapy. Post-transplant maintenance is key. Modifications of conditioning regimen may be beneficial. Transplantation is a safe and relatively inexpensive option. Maintenance may also be an option, but as yet there has been no head-to-head comparison with lenalidomide. A 2012 trial reported that bortezomib-based therapy had mostly received only immunomodulatory drug-based induction. Bortezomib maintenance may also be an option. In the past, patients received fixed-duration bortezomib-based regimens (CyBorD) with lenalidomide and dexamethasone (RVD) consolidation with len maintenance (ADM), tandem autologous SCT with len maintenance (TAM) and autologous SCT with len maintenance (AM) for up-front treatment of patients with multiple myeloma (MM); primary results from the randomized phase III trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0702 – STAMINA Trial) (ASH 2016). Blood 2016; 128:LB1-1 [Abstract].

Other strategies are required to improve results. Personalised approaches, targeted agents and immunotherapies may be agnostic for subgroups.

There is little evidence for allogeneic SCT in high-risk patients, but a number of trials have looked at autologous SCT. The EMM02/H095 study included a comparison between tandem and single autologous SCT, and found that tandem autologous SCT resulted in better survival, driven largely by high-risk participants. In contrast, data from the randomised STAMINA trial, which included comparisons of tandem autologous SCTs with single autologous SCTs with or without consolidation (in which all trial patients received maintenance lenalidomide) did not show a benefit with tandem SCT. Differences in study protocols and within the populations/subgroups, and with real-world autologous SCT, were discussed, leading to the conclusion that questions still remain. Dr Reece’s institution’s 10-year experience, which she acknowledged was biased towards healthier individuals, suggests that tandem autologous SCT recipients had longer PFS and OS compared with single and no SCT recipients, but the question of whether they all needed their second SCT was raised.

Despite improvements in myeloma survival, cure remains elusive, and effective sequential regimens are still required to control the disease with good quality of life. When improved tolerability is needed, tweaking an existing working regimen may be preferable to switching to another. Challenges to managing myeloma include the heterogeneous nature of both disease and patients, the rapidly changing options, and limitations due to funding.

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**MM: MANAGEMENT OF FIRST RELAPSE PROGRESS AND CHALLENGES**

Presented by Dr Donna Reece

Despite improvements in myeloma survival, cure remains elusive, and effective sequential regimens are still required to control the disease with good quality of life. When improved tolerability is needed, tweaking an existing working regimen may be preferable to switching to another. Challenges to managing myeloma include the heterogeneous nature of both disease and patients, the rapidly changing options, and limitations due to funding.

**The changing landscape**

In the past, patients received fixed-duration bortezomib-based regimens (CyBoRd with or without autologous SCT or VMP), but lenalidomide maintenance now also features in Canadian regimens. Hence, there are three recognised groups of relapsed myeloma patients.

1. No prior lenalidomide (or stopped prior to relapse).
2. Progression on lenalidomide as part of first-line therapy.
   - Maintenance after autologous SCT, or lenalidomide plus dexamethasone if transplant-ineligible.
3. Candidates for second ‘salvage’ autologous SCT.
   - Generally offered to patients in first relapse with >2-year benefit from first transplant.

**Conditioning**

Melphalan 200 mg/m² has been standard for pre-SCT conditioning for 20 years, providing PFS durations of 2 years without effective maintenance. Data from three retrospective reports of busalfun 12–16 mg/kg and melphalan 140 mg/m² and one SCT have suggested a PFS of 3 years in the absence of maintenance therapy, although post-SCT CR rates are not higher with higher melphalan 200 mg/m². Follow-up of a phase 3 trial that had been previously terminated when no difference in response rates was seen initially suggested a PFS benefit with a regimen of AUC-based dosing of busulfan plus melphalan 70 mg/m² compared with melphalan 200 mg/m² alone. The trial was reopened with a primary endpoint change to PFS, and while CR did not differ between the groups, PFS continued to be better in the busulfan/melphalan arm, and this was driven by high-risk patients.

**Salvage autologous SCT**

Dr Reece believes that treatment choices should be based on patient-, disease- and treatment-related factors. She noted that regimens for relapsed myeloma over the last decade have typically included lenalidomide plus dexamethasone, CyBoRd/RF, RVD and cyclophosphamide, lenalidomide plus dexamethasone, and some of these are still reasonable to use in the current era of novel therapy. A second salvage autologous SCT in the era of novel agents remains an option for selected patients in first relapse at Dr Reece’s centre; the data for its use in subsequent relapse are limited and likely suboptimal. Data for patients who have undergone salvage SCT progressing on lenalidomide maintenance are being gathered in a national MCRN Database project.

**Triple regimens**

At Dr Reece’s centre, triplet regimens are generally preferred, although elderly/frail patients may tolerate doublets better. Also, while some patients will do very well simply with the lenalidomide plus dexamethasone doublet, they are currently difficult to identify. Another strategy studied in several centres includes adding a third ‘on demand’ agent at time of next progression to lenalidomide plus dexamethasone in relapsed patients.
Phase 3 trials
Phase 3 trials investigating adding a PI or a monoclonal antibody to the lenalidomide plus dexamethasone ‘backbone’ in relapse or refractory MM include ASPIRE (+ carfilzomib), TOURMALINE-MM1 (+ ixazomib), ELOQUENT-2 (+ elotuzumab) and POLLUX (+ daratumumab). Try trials comparing bortezomib plus dexamethasone include a comparison with carfilzomib plus dexamethasone (ENDEAVOR), and the addition of panobinostat (PANORAMA-1), daratumumab (CASTOR) or elotuzumab. In all these trials, the investigative regimens (all triplets, except one) were associated with significant improvements in PFS when compared with the control doublet regimens. Subgroup analyses have been performed for first versus subsequent relapse, high-risk cytogenetics and prior drug therapy, but there are no outcome data for patients with >1 of these parameters present.

Toxicities
Haematological toxicities with the new combinations are reasonable and manageable. Specific toxicities to be aware of include peripheral neuropathy with bortezomib-based regimens, vascular toxicity (hypertension, cardiac failure and renal failure) with carfilzomib-containing regimens, infections/pneumonia with immunotherapies and diarrhoea with immunomodulatory drugs.

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Mortality/survival
While the age-standardised rate increased during 2004 to 2016, the age-standardised mortality rate remained stable, suggesting improvements in treatment. However, age-standardised mortality rates were highest among Māori/Pasifika. The presented data showed evidence of improved OS in recent years for patients aged ≤70 years and also for those >70 years. While OS curves suggest that Māori/Pasifika do worse than other ethnicities, these ethnicities already have shorter life expectancy, and the difference is not reflected in cause-specific survival curves. When analysed by broad regions, survival, including myeloma-specific survival, tends to be better for the northern DHBs.

Impact of bortezomib and SCT
The presented survival data showed that OS has improved since PHARMAC started funding bortezomib in May 2011, although other changes in myeloma management, such as recent use of lenalidomide, could contribute. This improvement in OS has been evident for patients aged >70 years as well as those ≤70 years. The data also confirm that most current patients are being prescribed bortezomib (see Table 1). Autologous SCT is performed for very few patients aged >70 years and less than half of those ≤70 years. The uptake of autologous SCT by patients was highest in the Midland region and slightly delayed for patients in the Northern region.

This was a presentation of analyses conducted on data from four merged datasets, with patient level linkage by unique NHI (nonresidents excluded) [Milne R et al. Multiple Myeloma Summit: its humanistic and economic burden in New Zealand. In preparation for publication at the time of reporting]. Only registrations since 2004 were included, mortality was calculated using the number of deaths from the mortality register. Only registrations were included, mortality was calculated using the number of deaths from the mortality register. Only registrations were included, mortality was calculated using the number of deaths from the mortality register. Only registrations were included, mortality was calculated using the number of deaths from the mortality register. Only registrations were included, mortality was calculated using the number of deaths from the mortality register.
While nontransplanted patients have an OS benefit with bortezomib treatment, further benefit is attained by autologous SCT. A multivariate analysis showed that OS was improved by autologous SCT and bortezomib treatment, and confirmed it was worse for advanced age, higher degree of social deprivation and regions south of Auckland, while ethnicity and sex had no independent significant impact.

### CyBorD – 5-YEAR SURVIVAL DATA

**Presented by Dr Ken Romeril**

In 2010, there was limited access to bortezomib (Velcade®) in NZ for selected patients, and in May 2011 it was approved by Pharmac for ≤9 induction cycles (36 doses). Around that time, a common treatment approach for new autologous SCT-eligible patients with MM was agreed on in Wellington, based on trial data showing that bortezomib induction improved PFS (IMSG 15/05 trial) and CR rates after autologous SCT (Ladetto), as well as the original CyBorD schedule for CyBorD (Mayo Clinic). The current approach used in Wellington includes four induction cycles of CyBorD for transplant-eligible patients with the option of 4-5 cycles of consolidation, while transplant-ineligible and bortezomib-naïve relapsed patients receive ≤9 cycles of CyBorD or VMP.

### Wellington study

Dr Romeril presented unpublished data from a study of the standard approach with four CyBorD cycles for 70 autologous-SCT-eligible patients, median age 62 years, with new MM (21 high-risk), MRD analyses were performed at day 100, and all participants were offered five cycles of VTD consolidation. The CR/year CR rate (IMWG criteria) was 46% and the VGFR or better rate was 23%. OS and PFS were both significantly better in participants who underwent autologous SCT, and the respective estimated 3-year and 5-year OS rates for the whole cohort were 81% and 64% (compared with 52% from Australasian registry data).

### Genetic risk

Another single-centre study by Dr Romeril’s group of 140 patients with MM confirmed that multiple-hit patients had very poor OS, which reflects findings from the IMWG. Dr Romeril’s group included five patients with t(14;16) who had shorter survival and were resistant to bortezomib. Recent data have identified associations with MAF, BRAF, DIS3 and ATM mutations for these patients.

While there were insufficient data on MRD in the Wellington study to plot, participants who were MRD-negative at day 100 had tended to do well. When compared with the Mayo study, the study from Dr Romeril’s group had more stage II and III participants, which likely explained their worse OS outcomes despite a similar CR rate.

### Future

The future will depend on what drugs are available. Carfilzomib, lenalidomide plus dexamethasone induction provides high CR rates at a cost. The increased use of lenalidomide following the autologous SCT for low-dose maintenance would be desirable, pending Pharmac approval. We can also expect that more oral agents will become available.

### TAKE-HOME MESSAGES

- CyBorD induction yields very good CR rates and OS rates
- Patients who had an autologous SCT had improved survival
- Extra post-SCT therapy with either VTD consolidation or five more cycles of CyBorD will confer excellent OS outcomes
- Once-weekly bortezomib can overcome some high-risk genetics, but not double- or triple-hits or t(14;16) cases

### REFERENCES


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Overview of CAR T-cell therapy

CAR (chimeric antigen receptor) T-cell recipients undergo leukapheresis to extract T-cells, which are expanded in the laboratory and genetically modified to express a CAR. First-generation CARs consist of a single-chain variable fragment of a monoclonal antibody directed against a specific antigen on the extracellular surface of the T-cell, linked to a transmembrane domain and the intracellular portion of a T-cell receptor (CD3). Second-generation CARs contain an intracellular costimulatory domain attached to CD3ζ and third-generation CARs contain two intracellular costimulatory domains. In order to receive autologous CAR T-cells, the patient first receives lymphodepleting chemotherapy in order to deplete endogenous T-cells and allow the CAR T-cells to expand in the recipient after infusion.

CAR T-cell therapy trials

The most success with CAR T-cell therapy to date has come with anti-CD19 CAR T-cells used in the treatment of relapsed or refractory B-cell malignancies. There are now second-generation anti-CD19 CAR T-cell products approved in the US by the FDA to treat relapsed/refractory B-cell nodal lymphoma and B-cell acute lymphoblastic leukemia (disaguncleucel and axicabtagene ciloleucel). The vast majority of CAR T-cell trials are being undertaken in the US and China, with only three in Australia and none in NZ at the time of reporting. While many CAR T-cell therapies have provided sizeable improvements over standard care, there is still room for improvement with approximately 40% long-term PFS rates reported in phase 2 anti-CD19 CAR T-cell trials in relapsed/refractory B-cell non-Hodgkin’s lymphoma. Specific toxicities associated with CAR T-cell therapy include: i) CRS (cytokine-release syndrome), which usually occurs within 7 days of starting treatment; and ii) CRES (cytokine-releasing syndrome), which usually occurs within 14 days; severe CRS and CRES can result in ICU admission, but both are reversible.

The NZ ENABLE-2 phase 1 trial plans to enrol 12 patients with relapsed/refractory aggressive B-cell lymphoma to receive third-generation anti-CD19 CAR T-cell therapy. Responses will be assessed at 3 months, and the participants will be followed for 24 months, with long-term follow-up undertaken via Cellular Therapies Registry.

BCMA as a target of CAR T-cell therapy in myeloma

Several factors support the rationale for CAR T-cell therapy in myeloma, including: i) the impressive response rates in other B-cell malignancies; ii) the large number of candidate plasma cell-restricted target antigens; and iii) it is possible to live without plasma cells if CAR T-cells persist for a long time (replacement with intravenous immunoglobulins). BCMA, member 17 of the tumour necrosis factor receptor superfamily, is a target antigen that is often strongly expressed in plasma cells of patients with myeloma. Preclinical data show in vitro anti-BCMA CAR T-cells were cytotoxic, and in vivo murine models showed anti-BCMA CAR T-cell caused xenografted plasmacytomas to shrink and improved survival.

Results from early phase CAR T-cell trials in myeloma

The first in-human anti-BCMA CAR T-cell trial for relapsed/refractory myeloma initially treated ten patients in a phase 1 dose-escalation trial with second-generation CAR T-cells (CD28 costimulation at NCI) at starting doses of 3×10^6 cells/kg, but only two participants achieved a PR or better. A higher dose of 9×10^6 cells/kg was then trialled in 16 heavily pretreated patients (nine with high-risk cytogenetics). The ORR for this group was 81%, with a VGPR/CR rate of 63%. Eleven of 14 participants treated were MRD-negative, and serum BCMA levels decreased significantly in those who achieved significant antmyeloma responses. The first two patients had 80% and 90% plasma cell burden and developed severe CRS, which led to subsequent participants being selected to have <30% plasma cells in their bone marrow, and severe CRS rates were significantly improved. Extensive neurological toxicity was not seen. Of note, one patient with relapse at 1 year had a population of BCMA-negative plasma cells, suggesting an antigen-escape mechanism.

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Pros and cons of CAR T-cell therapy in myeloma

- Early phase trials show excellent response rates in heavily pretreated patients
- Infrequent therapy allows treatment-free intervals
- Accounts for ~20% of myeloma
- Combinations (e.g. with carfilzomib and dexamethasone) are likely to have more BCL-2 versus MCL-1
- Active only in cyclin D-expressing cells, with responses more likely when there was reduction in cyclin D1, which almost exclusively occur in patients with t(11;14) translocations.

MAP kinase pathway

The MAP kinase pathway, which is involved in transcription and is triggered by Ras proteins, is a second hit in myeloma, and 17% and 6% of patients have mutations in NRas and KRas, respectively. The next step in this pathway involves Raf proteins, and B-Raf is mutated in about 3% of patients with myeloma. Most patients acquire these mutations as the disease progresses, increasing from about ~7% in monoclonal gammopathy of undetermined significance to ~45% in relapsed/refractory MM. Ras mutations also occur at higher rates in t(11;14) myeloma than in t(4;14) and the trisomies. In addition, around 10% of t(11;14) patients acquire mutations in cyclin D1, which almost exclusively occur in patients with t(11;14) translocations.

Morphology

In addition to the distinct biology in t(11;14) myeloma, a distinct phenotype is seen. Plasmablastic morphology is rare, and the cells often have a lymphoplasmatocytic maturation of the nucleus without prominent nucleioli. Immunohistochemistry or cell markers may be necessary to distinguish these cells from lymphoma.

Clinical characteristics

An analysis that included 365 patients with t(11;14) myeloma has shown lower rates of intact immunoglobulins and higher rates of light-chain only IgG myeloma. The same analysis revealed that compared with patients without t(11;14) myeloma, those with this translocation have a higher CR rate, but also a higher stable disease rate due to increased refractoriness to induction therapy. In terms of survival, PFS was similar to patients with no translocation (but better than those with other translocations), while OS was intermediate between the no and other translocation groups. Another analysis has suggested that survival in t(11;14) myeloma treated with bortezomib or thalidomide is better in patients whose myeloma is CD20-positive.

Venetoclax

Preclinical data on venetoclax showed that among myeloma cell lines, venetoclax was active only in cyclin D-expressing cells, with responses more likely when there was more BCL-2 versus MCL-1; this was supported by a higher ORR among participants with versus without high BCL2 when venetoclax was combined with bortezomib and dexamethasone. A trial of venetoclax monotherapy in patients with relapsed/refractory MM showed that the ORR was higher in the 30 participants with t(11;14) than the 36 without this translocation (40% vs. 6%). An ASCO 2018 presentation reported an ORR of 100% and a VGPR or better rate of 86% in a small dose-escalation trial of venetoclax combined with carfilzomib and dexamethasone in patients with relapsed/refractory t(11;14) MM.

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MRD testing is relevant in MM as negativity is achievable for both newly diagnosed and relapsed/refractory patients, and it is able to be used to predict clinical outcomes.\(^1\) The main focus of Prof Landgren’s talk was to address the question of whether MRD should be used to guide myeloma treatment. To address this in the absence of data, three clinical scenarios were developed and are discussed below.

**Scenario 1:**
Can MRD guide therapy in newly diagnosed patients?

The current treatment paradigm for newly diagnosed MM consists of induction therapy and maintenance therapy, with consolidation therapy in between for transplantation candidates. In this scenario, MRD-positive transplantation candidates go straight to autologous SCT, whereas MRD-negative transplantation candidates undergo stem cell collection and storage for future (delayed) transplantation.\(^1\)

Support for this scenario comes from the IFM 2009 trial, which compared three cycles of VRD followed melphalan plus SCT and two more cycles of VRD versus eight cycles of VRD.\(^5\) In the final MRD analysis of this trial, high-sensitivity detection (10\(^{-6}\)) revealed that more participants in the transplant arm became MRD-negative, and that participants who were MRD-negative had PFS duration that was similar regardless of treatment arm and that was superior to MRD-positive participants.\(^2\) Also, participants with high-risk cytogenetics who became MRD-negative had significantly better PFS than standard-risk MRD-positive participants, and MRD negativity was associated with longer PFS in both high- and standard-risk cytogenetic groups. Prof Landgren noted that this all makes sense considering the complexity of the genomic landscape in MM, and that every patient at diagnosis has several parallel myeloma subclones that respond differently to given drugs.\(^7\)

**Scenario 2:**
Can maintenance be used in relapsed myeloma?

Modern therapies for relapsed/refractory myeloma are effective, but their long-term feasibility is less clear. The ASPIRE and POLLUX trials were important in showing the survival improvement with the addition of carfilzomib and daratumumab, respectively, to lenalidomide and dexamethasone,\(^8,9\) the daratumumab arm of the POLLUX had a MRD negativity rate of \(-25\%^{\circ}\).\(^7\) Prof Landgren has proposed the notion of using MRD to guide maintenance therapy in patients receiving combination therapy for relapsed/refractory MM.\(^1\) He discussed his experience with this protocol, providing good results in patients who were switched to maintenance therapy after achieving MRD negativity three times.

**Scenario 3:**
Should relapse treatment be started at MRD positivity?

Prof Landgren noted that while updated response criteria focus on MRD, the definition of relapse has not been updated for some time; the current definition of progressive disease includes an increase of 25% from lowest confirmed response value in ≥1 of several criteria.\(^10\) He also noted that there has been no recent update to the treatment paradigm for progressive disease. Specifically, there is no defined laboratory cut-off for restarting treatment, worsening of laboratory results and/or onset of symptoms is usually the trigger for treatment, and the duration of relapse therapy is shorter than the treatment duration for newly diagnosed patients. Prof Landgren noted that in his experience, when MRD is used to guide treatment of relapsed MM (see Figure 2), the range of times between MRD positivity and the development of symptoms or worsening of overall laboratory results ranges from around 3 to 18 months. However, he emphasized that starting therapy at conversion from MRD negativity to MRD positivity is not an established strategy, and no current guideline exists to recommend this; while it may be an appealing strategy, there are no current molecular/clinical data for myeloma, and studies will be needed to investigate this important question. A phase 2 trial is currently recruiting to evaluate a short course of daratumumab and lenalidomide for reverting MRD positivity back to MRD negativity (NCT03490344).

**Where is treatment heading?**

An increasing number of CAR T-cell and 4-drug combination therapies are under investigation, along with earlier start to therapy and the development of new better drugs, all of which should lead to achieving deeper responses. Advances in MRD testing in development include real-time VDJ (gene variable, diversity and joining) tracking and 10-colour flow cytometry, as well as the use of immuno-PET \(^{82}z-CD38,\) [MALDI](https://www.medsafe.govt.nz) (matrix-assisted laser desorption/ionisation) mass spectrometry and analyses of circulating tumour cells/circulating free DNA.

**TAKE-HOME MESSAGES**

- Evolution of therapy and MRD testing in MM is progressing fast
- Beyond 2020, we are likely to see:
  - three- and four-drug combinations (with or without SCT)
  - higher MRD rates
  - MRD used for clinical decision making
- Clinical needs include:
  - more studies to test hypotheses focusing on MRD-guided treatment
  - easy access to sensitive, reliable MRD assays that are usable in standard care settings

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