# Expert Forum

## HSANZ Myeloma Summit

Making Education Easy | 19-21 August 2016, St Moritz Hotel, Queenstown

## In this review:



**Abbreviations used in this review**
**ASCT** = autologous stem cell transplantation
**CR** = complete response
**CyBorD** = cyclophosphamide/bortezomib/dexamethasone
**HR** = hazard ratio
**IMiDs** = immunomodulatory imide drugs
**MM** = multiple myeloma
**MRD** = minimal residual disease
**OS** = overall survival
**PFS** = progression-free survival
**PR** = partial response
**RCT** = randomised controlled trial
**SNP** = single nucleotide polymorphism
**TNF** = tumor necrosis factor
**VGPR** = very good partial response
**VTD** = bortezomib/thalidomide/dexamethasone

myeloma new zealand


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This publication is a summary of selected presentations delivered at the Haematology Society of Australia and New Zealand (HSANZ) Inaugural International Myeloma Summit Meeting held in Queenstown in August 2016. The exciting program featured two international speakers, Professor Paul Richardson from the Dana-Farber Cancer Institute, Boston and Professor Ola Landgren from the Memorial Sloan-Kettering Cancer Center, New York. New insights into the diagnosis and treatment of myeloma were presented at the meeting, with sessions chaired by Dr David Simpson, Dr Peter Ganly, Dr Ken Romeril and Dr Hugh Goodman. This review covers presentations in which scientific content was determined by Professor Ola Landgren, Dr Ken Romeril, Professor Paul Richardson and Dr David Simpson.


## SMOULDERING MYELOMA – BIOLOGICAL INSIGHTS TO EARLY TREATMENT STRATEGIES


*– Professor Ola Landgren, Memorial Sloan-Kettering Cancer Center, New York*


### Early treatment: Spanish experience

A randomised, open-label, phase III trial of lenalidomide/dexamethasone for high-risk smouldering multiple myeloma (MM) undertaken in Spain compared time to progression of MM and secondary endpoints including response rates and duration of response in patients (n = 119) receiving either induction with lenalidomide 25 mg/day (days 1-21) plus dexamethasone 20 mg/day (days 1-4 and 12-15) at 4-week intervals for nine cycles, followed by a maintenance regimen of lenalidomide 10 mg/day (days 1-21 of each 28-day cycle) for 2 years, or observation only.[1] The trial revealed a complete response (CR) rate during the induction phase of 14%, with an increase to 26% during the maintenance phase. Despite the fairly low CR rate, treatment delivered a significant difference in time to progression, with a progression rate of 23% versus 76% in the observation arm (HR 0.18; 95% CI 0.09-0.32, $p < 0.001$). At 60 months, overall survival (OS) rates were 94% for the treatment arm versus 80% for the observation arm (HR for death 0.31; $p = 0.03$). Follow-up at a median of 75 months revealed a continued benefit on time to progression with lenolidomide/dexamethasone compared with observation only; median time to progression not reached (95% CI 47 months–not reached) versus 23 months (95% CI 16-31 months), HR 0.24 (95% CI 0.14-0.41), $p < 0.0001$.[2] Progression to MM occurred in 39% of patients in the treatment group compared with 86% of patients in the observation group. Importantly, survival in patients who had received subsequent treatments at the time of progression to active disease did not differ between groups (HR 1·34; 95% CI 0·54-3·30, $p = 0·50$), suggesting that treated patients who converted to myeloma responded as well to subsequent treatment as those who had not previously been treated. The OS benefit continued at 75-months follow-up (HR 0.43; 95% CI 0.21-0.92, $p = 0.024$). Professor Landgren pointed out that there were several methodological issues with this study.

### Biologic insights in early disease

In a study published in JAMA Oncology, Professor Landgren and colleagues investigated carfilzomib/ lenalidomide/dexamethasone therapy in adult patients with newly-diagnosed MM (n = 45) or high-risk smouldering MM (n = 12).[3] All patients received eight cycles of combination therapy followed by 2 years of lenalidomide maintenance. Among the 12 patients with smouldering MM, all had received at least a partial response (PR) after two cycles and among 11 patients completing eight cycles, 100% exhibited at least a very good partial response (VGPR; 55% exhibited a stringent CR, 18% a CR and 27% a near CR). The depth of this response was assessed by measuring minimal residual disease (MRD) status by multiparametric flow cytometry and next-generation sequencing at the completion of 8 cycles and MRD negativity was found in 10 of the 12 patients.

Large studies show that MM is genetically very heterogeneous with several recurrent mutations including KRAS, NRAS, BRAF and TP53.[4] Professor Landgren and colleagues are currently aiming to define the mutational landscape at baseline in high-risk smouldering MM patients to assess mutational profiles in relation to treatment response in MM patients. Preliminary findings in 17 patients with smouldering MM and 39 with newly diagnosed MM treated with carfilzomib/lenalidomide/dexamethasone have exhibited CR rates of 94% and 56%, respectively.[5] DNA was isolated from CD138+ cells and whole exome sequencing and tumour only

analysis using TGen JetStream analysis pipeline were undertaken for all patients with somatic mutations identified using variant callers Mutect, Seurat and Strelka. A similar mean number of mutations were detected per patient for the two groups (53 in newly diagnosed MM and 52 in smouldering MM). Prior studies have demonstrated significantly recurrent mutations in individual genes as well as signalling pathways in MM.

Due to the molecular heterogeneity seen in MM, Professor Landgren does not believe that targeted therapy will be effective in the newly diagnosed MM setting. Among the many mutated genes identified in this disease, a total of 15 significantly recurrent mutations of individual genes have been identified in this patient group.[4,6] Consistent with other studies, Professor Landgren's study found that 44% of newly diagnosed MM patients had a mutation in at least one of the 15 identified genes, however, strikingly only one (6%) of the 17 smouldering MM patients had a mutation in any of the 15 identified genes (this patient had mutations in FAM46C and TRAF3).[5] Investigating the mutational landscape by treatment response, Prof Landgren and colleagues found that compared with newly diagnosed MM patients achieving a CR, those not achieving a CR had a higher frequency of mutations in the 15 identified genes, with rates of 32% and 59%, respectively.[5] Prior studies have also demonstrated significantly recurrent mutations in signalling pathways in MM.[4,7] Such pathways include the NF-κB pathway (classical and alternative), the histone modifying enzyme pathway and the coagulation cascade.[4,7]

## Ongoing/upcoming studies

The immediate goal for Professor Landgren and colleagues is to sequence approximately 100 patients with smouldering MM, with an aim to understand the different subclones. He pointed out that there are two approaches to the treatment of myeloma, `hit harder' or `figure out the biology'. The ongoing Spanish CESAR trial has taken the former approach and will investigate carfilzomib/lenalidomide/dexamethasone plus high-dose melphalan and autologous stem cell transplantation (ASCT) followed by maintenance with lenalidomide and dexamethasone in patients <65 years of age with high-risk smouldering MM (Clinical Trials NCT02415413). Another proposed investigation is the Mayo ASCENT (Aggressive Smoldering Cure Evaluating Novel Rx Transplant) trial looking at combination therapy with carfilzomib/lenalidomide/dexamethasone/daratumumab plus high-dose melphalan and ASCT followed by a lighter carfilzomib/lenalidomide/dexamethasone/daratumumab therapy then maintenance with lenalidomide.

Professor Landgren pointed out that responses are already good, with MRD negativity shown in 10 of 12 patients in his study and he worries that by adding more therapies we may just be over treating patients; however, on the other hand, he acknowledges that myeloma is a nasty disease.[3] His group have opted to focus on figuring out the biology of the disease. Updated unpublished results from their recent study show stringent CR/CR rates of 89% and sustained 3-year MRD $10^{-6}$ negativity of 69%. He raises the question as to whether in order to achieve 100% response rates we should just elevate treatment for all patients or figure out who may require more aggressive therapy. The aim is to dissect mechanisms of MRD positivity and develop specific treatment targets. To this end, the group is collecting samples from patients with smouldering MM and undertaking molecular profiling at diagnosis and longitudinally. They are also developing trials treating early for MRD conversion. Ongoing projects include the re-opening of their carfilzomib/lenalidomide/dexamethasone plus lenalidomide maintenance study, a randomised study of carfilzomib/lenalidomide/dexamethasone plus lenalidomide maintenance versus lenalidomide/dexamethasone plus lenalidomide maintenance and the development of monoclonal antibody studies (e.g. targeting CD38). Ideal treatments will have a low toxicity profile, be convenient, have high efficacy and engender high quality of life.

### TAKE-HOME MESSAGES:

- The median number of somatic mutations is similar in newly diagnosed MM and high-risk smouldering MM patients
- Mutational profile is associated with depth of treatment response in newly diagnosed MM patients
- Importantly, high-risk smouldering MM patients lack significantly recurrent MM mutations, suggestive of treatment responsive disease biology in high-risk smouldering MM
- Professor Landgren and colleagues results support clinical studies focusing on early treatment initiation in high-risk smouldering MM patients.

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# INDUCTION THERAPY FOR MYELOMA AND APPROACH TO HIGH-RISK CYTOGENETICS

*– Dr Ken Romeril, Wellington Blood and Cancer Centre*

## Historical perspective

The first reported case of MM dates back to 1844. In the 1970s treatment for myeloma comprised melphalan and prednisone with an average survival of approximately 2 years. Individuals with concomitant renal failure were generally not treated. In 1983, a new approach using high-dose melphalan (100-140 mg/m$^2$) was pioneered by McElwain and Powles.[1] In 1987, Dr Romeril treated six patients at Wellington hospital with high-dose melphalan; however, this treatment was given without stem cell rescue and some patients did not recover their marrows – the approach was abandoned. In 1994, autologous stem cell transplantation (ASCT) for myeloma commenced at Wellington Hospital. At that time, melphalan and cyclophosphamide plus prednisone were being used, and subsequently vincristine/doxorubicin/dexamethasone induction to preserve stem cells. By 2004, novel agents such as thalidomide were available and there was a change away from vincristine/doxorubicin/dexamethasone to cyclophosphamide/dexamethasone. This was the beginning of a new era in myeloma therapy. Richardson et al. in 2010 introduced lenalidomide/bortezomib/dexamethasone therapy for newly diagnosed MM.[2] Dr Romeril estimates that there are approximately 400 new myeloma patients diagnosed each year in New Zealand, of which approximately 40 are treated in Wellington.

## Cytogenetic testing

The International Myeloma Working Group consensus has recently updated the definition for high-risk MM based on cytogenetics. Cytogenetic abnormalities conferring poor prognosis include: t(4;14), del(17/17p), t(14;16), t(14;20), nonhyperdiploidy and gain (1q).[3] In an audit of 200 transplant-eligible cytogenetic patients in Wellington, Dr Romeril and colleagues found only 6% with t(4;14), 10% with P53 deletion, 3% with t(14;16), 10% with 1q gains and 4% with MYC. Cytogenetic risk features are summarised in **Figure 1**.

| | High risk | Standard risk |
|---|---|---|
| Cytogenetic abnormality | FISH t(4:14), t(14:16) t(14;20) del17p, gain (1q) | All others including FISH T(11;14) and t(6;14) |
| | Nonhyperdiploid karyotype | |
| | Karyotype del 13 | |
| | GEP: high risk signature | |

FISH = fluorescence in situ hybridisation; GEP = gene expression profiling

**Figure 1. Summary of cytogenetic risk features in MM.**

In order to obtain a comprehensive genomic profile in MM, Walker et al. investigated copy number abnormalities with high-resolution single nucleotide polymorphism (SNP) mapping arrays.[4] They found that the most frequent deletions were at 1p (30%), 6q (33%), 8p (25%), 12p (15%)/13q (59%), 17p (7%), 20 (12%) and 22 (18%), while fluorescence in situ hybridisation and expression quartile analysis revealed genes of prognostic importance located at 1p (FAF1, CDKN2C), 1q (ANP32E) and 17p (TP53).

With regard to t(4;14), Dr Romeril explained that patients with this abnormality tend to respond to therapy early on, but tend to relapse quite quickly. A study by Avet-Loiseau and colleagues in 2010 found that short-term bortezomib plus dexamethasone induction improves outcomes in patients with t(4;14) myeloma, but has no effect on the outcome of those with del(17p).[5] At that time, Pharmac agreed to provide bortezomib for t(4;14) myeloma patients.

## Ultra high risk or triple hit

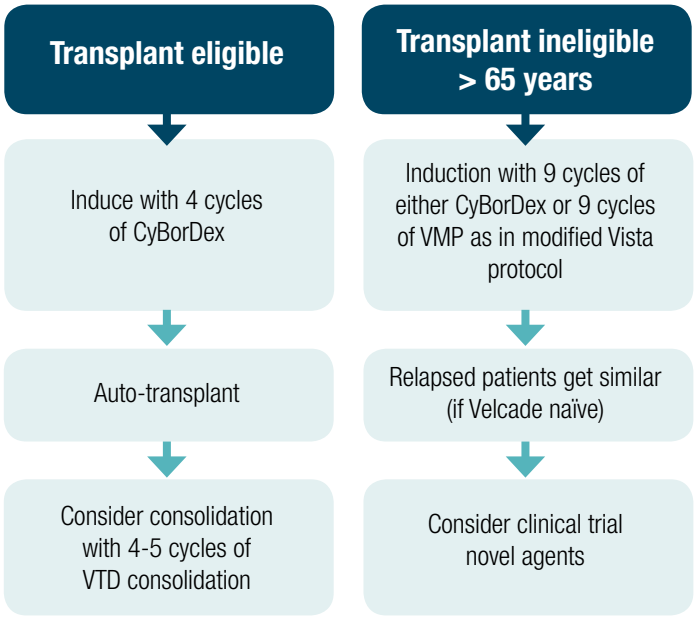
Dr Romeril explained that transplant-eligible patients with a standard risk profile exhibit a progression-free survival (PFS) approaching 4 years and an OS approaching 10 years, while patients with high-risk cytogenetics have an OS of <3 years, reduced to 9-12 months in those with ultra high risk (>3 cytogenetic abnormalities). Dr Romeril refers to the ultra high-risk category as triple hit, analogous to the double hit in some of the lymphomas. These are co-segregated adverse FISH lesions and include an IgH such as t(4;14) or t(14;16), a P53 deletion, a 1q gain and a 1P deletion. In their cohort of 200 auto-transplant patients, there were three cases with >3 cytogenetic abnormalities. New drugs are needed for treating such patients.

## Treating MM with bortezomib

In 2013, data published from a phase 3 trial by the Nordic Myeloma Study Group investigating bortezomib monotherapy as consolidation after stem cell transplantation in MM showed a significant benefit for PFS (27 months vs 20 months in controls; p = 0.037).[6] An Italian study looking at bortezomib/thalidomide/dexamethasone (VTD) consolidation after ASCT for MM revealed VGPR and CR rates of 85% and 15% after ASCT with an increase to 49% and 49% after VTD.[7] Investigating the use of cyclophosphamide/bortezomib/dexamethasone (CyBorD) for induction therapy in newly-diagnosed MM, Reeder et al. concluded that the regimen in highly effective, producing VGPR and CR rates exceeding those observed with other induction regimens and mimicking that seen with high-dose therapy and stem cell transplantation.[8]

In May 2011, Pharmac approved Bortezomib [Velcade®] for MM in NZ and funding for up to nine induction cycles (36 doses). Based on the literature, the Wellington group agreed on a common treatment approach for new auto-eligible MM cases (**Figure 2**), using CyBorD induction in transplant-eligible patients or CyBorD or bortezomib/melphalan/prednisone in those ineligible for transplant.

An audit by Dr Romeril and colleagues of 70 MM patients (median age 62 years) with symptomatic disease (predominantly stage III; 18 considered high risk due to t[4;14]) receiving induction with CyBorD revealed a CR/near CR rate after




CyBorDex = cyclophosphamide/bortezomib/dexamethasone; VMP = bortezomib/melphalan/prednisone; VTD = bortezomib/thalidomide/dexamethasone

**Figure 2. Current Wellington approach to treating MM.**

4 cycles of 46%, a VGPR rate of 23%, a PR rate of 23% and a rate of progression of 6%. On day 100, MRD analysis was undertaken and all patients offered five cycles of VTD. Patients receiving ASCT did better than those not receiving such transplant and a significant (p = 0.01) association was seen with PFS and high versus standard genetic risk. Among the whole cohort, the estimated OS at 3 years was 81%; 4-year data show an OS of 74%.

## TAKE-HOME MESSAGES:

- CyBorD induction yields very good CR rates
- Allows adequate stem cell harvests
- Extra post-auto therapy with either VTD consolidation or five more cycles of CyBorD will confer excellent OS figures
- Once-weekly bortezomib schedule has low neuropathy rates and low thrombosis risk
- Bortezomib induction can overcome some high-risk genetics, but not double and triple hits and some t(14;16) cases
- In the treatment of high-risk genetics, use the most potent drugs available, consider a tandem auto approach and suggest that patients get their affairs in order if they have an ultra high-risk profile, as survival is only 8 months.

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# NEW DIRECTIONS IN TREATING MM IN THE ERA OF NOVEL AGENTS: RELAPSED AND REFRACTORY DISEASE – A US PERSPECTIVE

*– Professor Paul Richardson, Dana-Farber Cancer Institute, Boston*

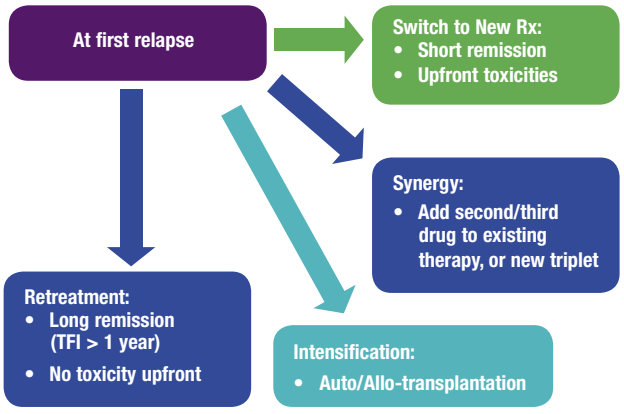
Professor Richardson explained the importance of effective induction therapy and maintaining remission for as long as possible in MM. He stressed that 3-4 drug platforms are essential in treating relapsing/refractory MM and should be consider the standard of care. Once relapse occurs, MM becomes more challenging to treat; however, patients are now living longer, even in the relapsed/refractory setting. Extramedullary relapsed/refractory MM, if it develops, is very difficult to treat.

There have been 18 FDA approvals in the past 13 years for the treatment of MM and during this time median survival has increased from 3-5 years to 7-10 years, with additional prolongation from maintenance. However, all patients eventually relapse and there is a need for effective agents to improve outcomes and to treat high-risk patients. The recognition of the microenvironment in MM is key to overcoming conventional drug resistance, as is an understanding of angiogenesis and the interaction between plasma cells and bone marrow. The multiple genetically distinct subclones that are present at MM diagnosis evolve over time and can result in disease progression and treatment resistance.[1-5] Tumour heterogeneity and clonal tiding are becoming increasingly understood in MM and there is a good argument for putting a big net around the disease in terms of treatment. However, Professor Richardson points out the issue of genotoxic therapy, which is a consideration given that patients are living longer. There is also evidence that genotoxic treatment can influence subsequent disease course. He suggests that one such agent, melphalan, should not be used early in the disease.

## Treatment strategies for first relapse

Professor Richardson presented results from a whole genome sequencing study from a single patient involved in a clinical trial. At diagnosis, the patient had 5286 substitutions, 51 deletions and insertions, and 49 rearrangements. At the time of first relapse this patient's number of substitutions had doubled to 12581, and they had 606 deletions and insertions, and 113 rearrangements.

For first relapse, the US National Comprehensive Cancer Network (NCCN) suggest a number of options: retreatment with prior agent; switching to a new agent; adding a second/third drug to the existing regimen or a new triplet combination; or intensification to autologous/allogenic transplantation (**Figure 3**).[6]




Auto/Allo = autologous/allogenic; Rx = treatment; TFI = treatment-free interval

**Figure 3. Treatment strategies for MM at first relapse.** (Adapted from Ludwig et al. 2012[7])

## Key targets in MM

Approaches to treatment in MM target three key areas; excess protein production, genomic abnormalities and immune suppression.

### *Targeting protein degradation*

The inhibition of proteasome, which is responsible for the degradation of ubiquitinated proteins has emerged as a powerful strategy in MM and the first-in-class agent bortezomib has proven useful. The newer second-generation proteasome inhibitors carfilzomib, ixazomib and marizomib also show promise. Professor Richardson says that rechallenging with bortezomib in the relapsing refractory state is appropriate, but that the real game-changer has been carfilzomib. At his institution the preferred first-line regimen is lenalidomide/bortezomib/dexamethasone with carfilzomib/pomalidomide/dexamethasone as the first choice salvage regimen for relapse. This platform is generally well tolerated. Ixazomib has shown reasonable efficacy in phase III studies and is also well tolerated, providing a good option as a gentle agent (Professor Richardson uses this agent for his older patients). Marizomib (still in development) is the most potent proteasome inhibitor and it crosses the blood brain barrier with benefits in CNS myeloma.

The rationale behind combination therapy is strong, and such therapy is now standard of care in MM. The ASPIRE Phase III trial, published in 2015 demonstrated the efficacy of carfilzomib/lenalidomide/dexamethasone for relapsed disease, with a dramatic and unprecedented longer median PFS with the three drug regimen compared with lenalidomide/dexamethasone (26.3 vs 17.6 months; $p = 0.0001$).[8] The TOURMALINE-MM1 Study Group, in a phase III trial investigating the combination of ixazomib/lenalidomide/dexamethasone in relapsed, refractory, or relapsed and refractory multiple myeloma showed efficacy over lenalidomide plus dexamethasone (median PFS 20.6 vs 14.7 months; $p = 0.012$).[9] Furthermore, the median PFS in high-risk patients was similar to that in patients with standard-risk cytogenetics.

### *Targeting genomic mutations*

The goal is to target and overcome mutations and combination therapy plays a critical role. Next generation novel targeted therapies include panobinostat (a pan-deacetylase inhibitor [pan-DACi]), pomalidomide (an immunomodulator), ibrutinib (a Bruton's tyrosine kinase inhibitor) and melflufen (a novel cytotoxic agent). Pan-DACi inhibit growth and promote death of myeloma cells through inhibition of histone DAC [HDAC] enzymes. Panobinostat also upregulates CD38.

A number of studies demonstrate the efficacy of panobinostat/bortezomib/dexamethasone combination therapy in relapsed or relapsed and refractory MM, with a PFS of up to 7.4 months.[10-12] Professor Richardson and colleagues frequently use panobinostat on protocol and see merit in this class of drug.

### *Targeting immune suppression*

The goal is to restore anti-MM immunity with the use of immunomodulatory imide drugs (IMiDs), monoclonal antibodies, vaccines, checkpoint inhibition and cellular therapy. IMiDs such as thalidomide and lenalidomide were the first immuno-oncologics used in MM and were very successful. Lenalidomide is the classic IMiD used in MM and upregulates NK, T and NKT cells, and targets regulatory T cell abnormalities in myeloma. In addition to their antiangiogenic effect, IMiDs enhance the production of the cytokine interleukin-2 (IL-2), which spurs T cell production and inhibits TNF, IRF4 and MYC.[13]

A newer IMiD, pomalidomide has demonstrated promising activity and manageable toxicity in advanced relapsed and refractory MM, with overall response rates of up to 94% in combination with bortezomib and dexamethasone.[14-23] As mentioned above, pomalidomide has become Professor Richardson and colleagues first choice IMiD at first relapse and beyond.

Monoclonal antibodies targeting myeloma include lucatumumab, dacetuzumab, elotuzumab, daratumumab, isatuximab, XmAb®5592, huN901-DM1, nBT062-maytansinoid, siltuximab, BHQ880 and RAP-011.[24] These agents target the antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and apoptosis/growth arrest pathways (**Figure 4**).

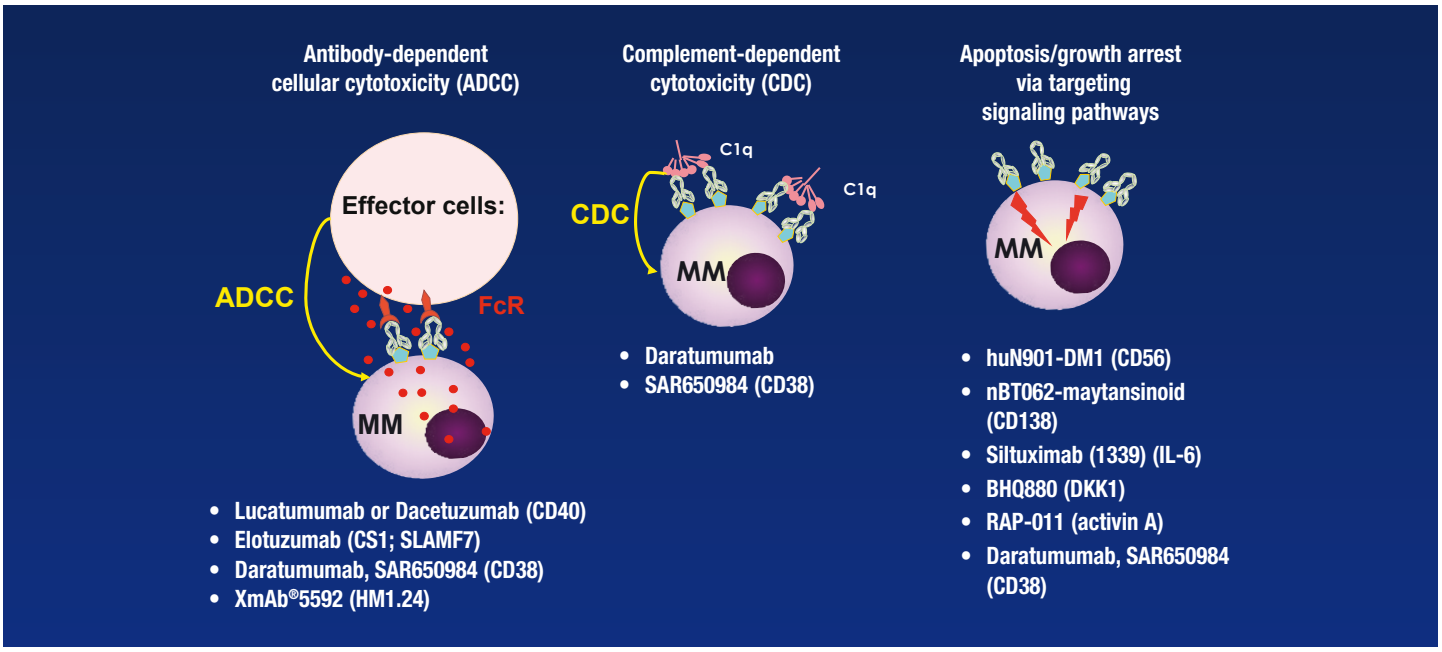



**Figure 4. Monoclonal antibody-based therapeutic targeting of myeloma.** (Adapted from Tai and Anderson 2011[24])

Monotherapy studies of daratumumab, which targets CD38 (a cell surface protein that is overexpressed on MM cells), have shown encouraging efficacy and a good safety profile in heavily pretreated and refractory MM.[25,26] Professor Richardson has been treating patients with this agent and reports that it is a fantastic rescue agent. The CASTOR phase III study of daratumumab/bortezomib/dexamethasone versus bortezomib/dexamethasone for relapsed or refractory MM showed a 61% reduction in the risk of disease progression or death with the daratumumab-containing regimen, with 1-year PFS rates of 60.7% and 26.9%, respectively.[27] The POLLUX open-label, randomised, phase III study conducted in 18 countries investigating daratumumab/lenalidomide/dexamethasone versus lenalidomide/dexamethasone in relapsed or refractory MM showed remarkable benefit, with a 63% reduction in the risk of progression or death; this benefit was consistent across subgroups.[28] The combination of daratumumab/lenalidomide/dexamethasone doubled CR/stringent CR rates and quadrupled MRD-negative rates.

Elotuzumab, an immunostimulatory monoclonal antibody that recognises SLAMF7 and causes myeloma cell death via a dual mechanism of action, also has proven efficacy in the setting of relapsed or refractory MM. The phase III ELOQUENT-2 study revealed clinical benefits of elotuzumab/lenalidomide/dexamethasone versus lenalidomide/dexamethasone alone, with 1-year PFS rates of 68% and 57%, respectively, and a 30% relative reduction in the risk of disease progression or death in the elotuzumab group (HR 0.70; 95% CI 0.57-0.85; $p < 0.001$).[29] This study had a high proportion of patients (30%) with a high-risk cytogenetic profile.

In summary, Professor Richardson presented a timeline of the evolution of treatments for MM, with selected new classes and targets in 2016 and beyond (**Figure 5**).

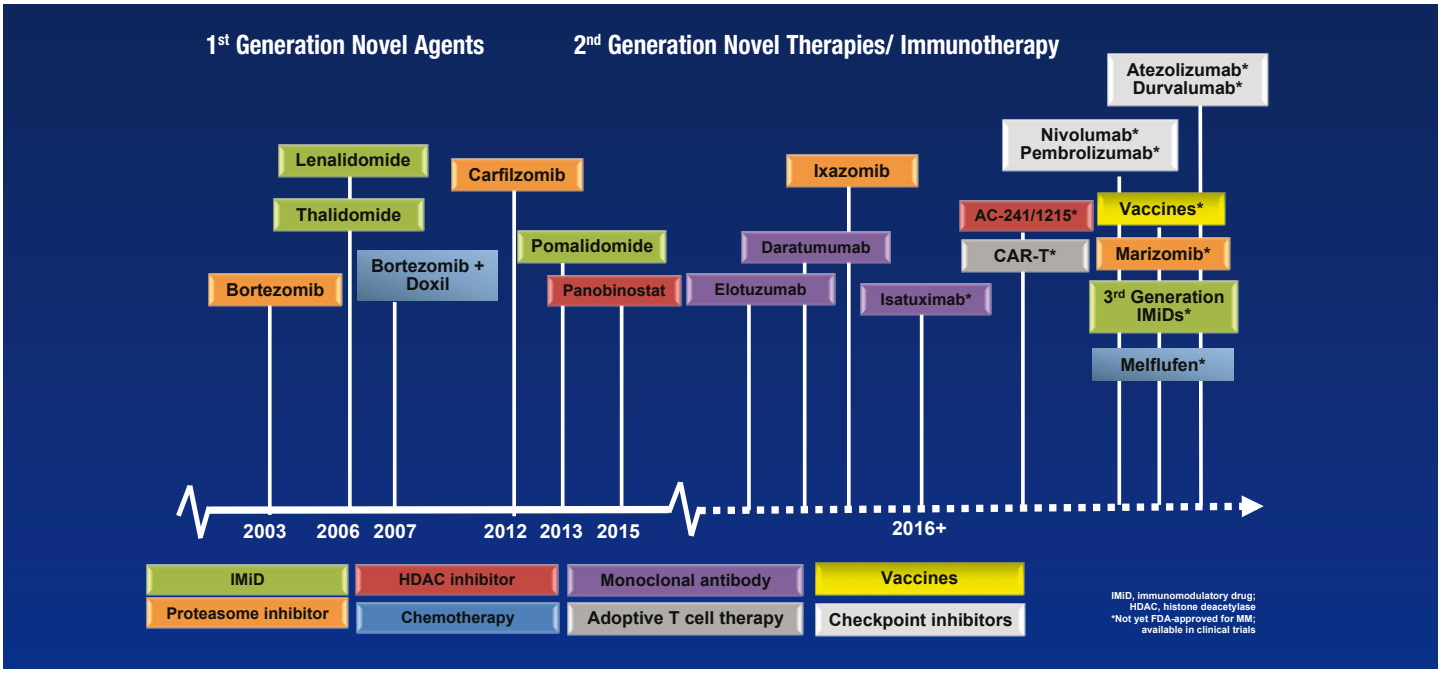



**Figure 5. Continuing evolution of MM treatment.**

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## AN AUDIT OF MYELOMA OUTCOMES FROM THE CANCER REGISTRY

*– Dr David Simpson, North Shore Hospital*

The Cancer Registry Act in 1994 mandated reporting of new cases to the Ministry and shifted the identification of cases from being primarily hospital based to mostly laboratory based. This increased the number of myeloma registrations by around 30% a year. The other impact of the Act was that the quality of information the Ministry received was significantly better, which allowed for more accurate coding of the cancer.

The Registry data show an increase in the number of new myeloma cases per year in NZ from just over 200 in 1995 to 350 in 2013. Over the past few years there has been a slight increase in the incidence of myeloma in NZ. An analysis of the 4761 registry cases revealed a median age at diagnosis of 70 years, which is consistent with the rest of the world. Analysis by age band revealed 1643 cases <65 years of age, 1407 in the 65-75 year age range, 1330 in the 75-85 year range and 381 over 85 years of age. Analysis of myeloma registry data by era of treatment revealed the following: before the year 2000 = 1311 cases; 2000-05 = 1156 cases; 2006-10 = 1321 cases and 2011-13 = 973 cases. With regard to OS, the data are reassuring, with an improvement seen in each successive era (**Figure 6**). Analysis by age band showed the most significant survival benefit for those aged <65 years (transplant eligible group), with a 4-year OS of approximately 70% in the most recent era. The least improvement is seen in the over 85 age group, with a 4-year OS of less than 15%, a rate similar to that during the previous 15 years.

When analysed by treating DHB, OS was similar between the DHBs during the first three era bands, however, during the 2011-13 era, patients treated at the Waitemata DHB exhibited a significant survival benefit when compared to the national average (this was not seen at the other DBHs). Further analysis of the Waitemata data for the 2011-13 era revealed a dramatic difference in the OS for the over 65 age group but not for the under 65 age group when compared with the national average; the difference was not significant for the over 85 age group. Dr Simpson and colleagues theorise that the following may be reasons for this difference in OS in the 2011-13 era in those aged 65-85 years at their DHB (Waitemata): 1. They are more likely to give bortezomib to the elderly; 2. They tend to give more cycles of bortezomib to the elderly; 3. They are more likely to change to IMiDs; 4. They possibly have better access to research drugs; 5. They have better salvage strategies (e.g. teniposide).

With an increase in the median survival from 3 to 10 years over the last 15 years or so, it is not surprising that point prevalence data suggest an increase of 300% in those alive with myeloma in NZ since the year 2000. The point prevalence of myeloma in the Waitemata region is higher than that for the Auckland and Counties Manukau DHBs, with a 400% increase (it is the fastest growing DHB).

The average age of survivors in 2013 was 68.4 years and surprisingly this had not significantly changed since 2005, at which time the median age was 70 years. Dr Simpson explained that with patients living longer with MM one would expect to see an increase in their age and is unsure of the reason for this result. He believes it may be that the full impact of the new treatments may have not shown at the time of the 2013 data collection.

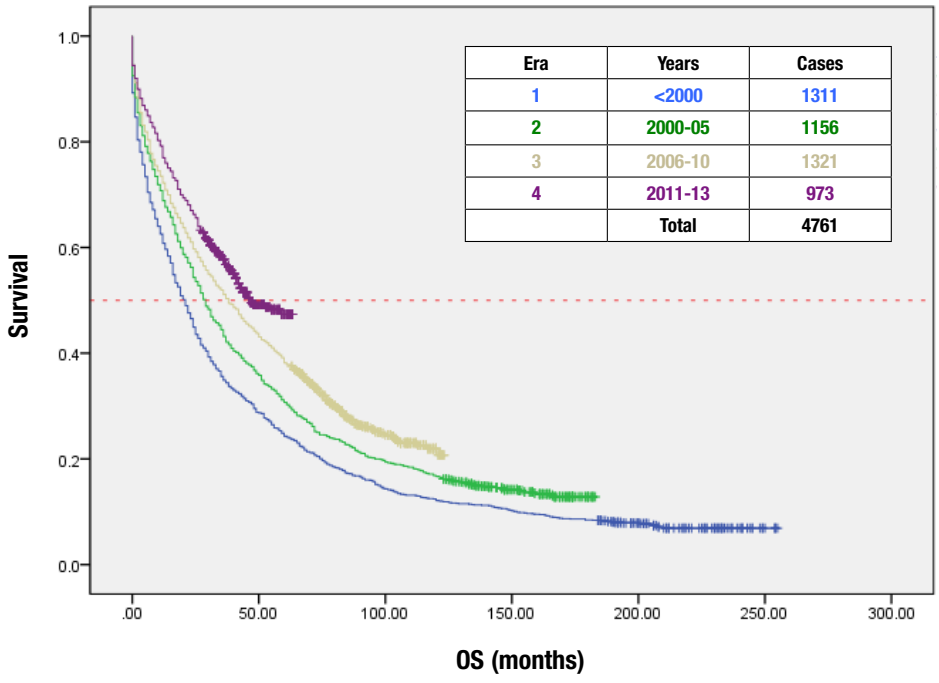


**Figure 6. Survival in MM by treatment era in NZ.**

# THE EMERGING ROLE OF MONOCLONAL ANTIBODY THERAPY AND IMMUNOTHERAPY IN MULTIPLE MYELOMA

*– Professor Paul Richardson, Dana-Farber Cancer Institute, Boston*

Approaches to treatment in MM target three key areas; excess protein production, genomic abnormalities and immune suppression. Agents involved in restoring immune function in MM include immunomodulatory drugs, monoclonal antibodies, checkpoint inhibitors, vaccines and cellular therapies. Professor Richardson explained that we are on the cusp of new discoveries in immuno-oncology for myeloma.

## Immune modulation with lenalidomide maintenance therapy

Lenalidomide maintenance post stem-cell transplantation for MM has clear benefits on time to progression and OS, with a recent meta-analysis of three RCTs demonstrating an OS benefit with lenalidomide maintenance post ASCT compared to placebo or no maintenance (controls).[1-3] Median OS for lenalidomide recipients versus controls was not reached versus 86 months (HR 0.74; 95% CI 0.62-0.89; log-rank p = 0.001), and 5-, 6-, and 7-yr OS rates were greater in the lenalidomide versus the control group (71% vs 66%, 65% vs 58%, and 62% vs 50%, respectively). The median survival gain with this agent was 2.5 years.[3]

The DETERMINATION parallel US and French trials will investigate delayed versus early transplant with lenalidomide maintenance and antimyeloma triple therapy (lenalidomide/bortezomib/dexamethasone) in MM. Those in the transplant arm received ASCT prior to lenalidomide maintenance. Preliminary data show that transplantation improved MRD negativity with rates of 80% in the transplant arm versus 65% in the lenalidomide arm (p = 0.001); the rates of CR, VGPR and PR were 59%, 29% and 11% versus 49%, 29% and 20%, respectively.[4] The PFS difference between the groups at 4 years was 8.8 months in favour of transplantation. However, median OS at 4 years did not significantly differ between the two groups (80% with transplantation versus 83% without). In the transplant group, the rate of toxicity leading to death was double that in the non-transplant group (16% versus 8%) and more cases of fatal acute myeloid leukaemia (AML)/myelodysplastic syndrome (MDS) were seen in the transplant group (11% vs 2%).

## Monoclonal antibody-based therapeutic targeting of myeloma

Daratumumab, a human IgG1 monoclonal antibody that binds CD38-expressing cells, is a very promising agent that induces cell death through direct and indirect mechanisms (**Figure 7**).[6-9] CD38 is highly and ubiquitously expressed in myeloma cells.[6,7] Daratumumab monotherapy studies have shown encouraging efficacy and safety in heavily pretreated and refractory MM patients.[10,11] A pooled analysis of data from 148 heavily pretreated and refractory MM patients treated with 16 mg/kg daratumumab revealed an OR rate of 31%.[12] This data formed the basis of the FDA approval for the use of this agent in MM.

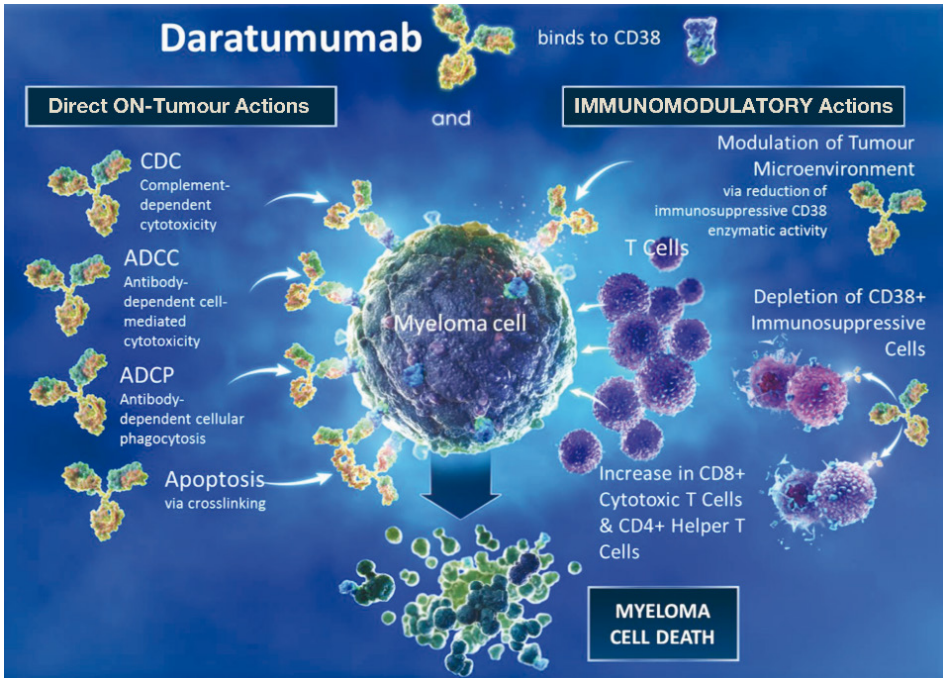


**Figure 7. Daratumumab mechanisms of action**

Daratumumab/lenalidomide/dexamethasone combination therapy for refractory and relapsed/refractory MM was investigated in a phase I/II study and showed an OR rate of 81% at a median of 15.6 months' follow-up.[13] An OR rate of 71% has been demonstrated with daratumumab/pomalidomide/dexamethasone combination therapy.[14] The CASTOR phase III study of daratumumab/bortezomib/dexamethasone versus bortezomib/dexamethasone for relapsed or refractory MM showed a 61% reduction in the risk of disease progression or death with the daratumumab-containing regimen.[15]

The POLLUX open-label, randomised, phase III study investigating daratumumab/lenalidomide/dexamethasone versus lenalidomide/dexamethasone in relapsed or refractory MM patients showed remarkable benefit with an OR rate of 93% and a 63% reduction in the risk of progression or death; this benefit was consistent across age groups and was unaffected by treatment history including prior lenalidomide exposure.[16] Furthermore, significantly higher MRD-negative rates were seen in the daratumumab-treated group. The compelling results of daratumumab combined with lenalidomide/dexamethasone suggest the agent has potential as a new standard of care for myeloma patients after ≥1 prior treatment.

Isatuximab is another promising anti-CD38 monoclonal antibody. A dose finding phase II trial of single agent isatuximab in relapsed/refractory MM showed the agent to be generally well tolerated with an OR rate of 20-29% at a dose ≥10 mg/kg, with a median duration of response of 8.75-12.9 months.[17] The OR rate was similar across subgroups, including high-risk cytogenetics. Professor Richardson is currently leading a trial of isatuximab combined with pomalidomide and is seeing excellent results with very good tolerability.

The phase III ELOQUENT-2 study revealed clinical benefits of elotuzumab/lenalidomide/dexamethasone versus lenalidomide/dexamethasone alone, with 1-year PFS rates of 68% and 57%, respectively, and a 30% relative reduction in the risk of disease progression or death in the elotuzumab group (HR 0.70; 95% CI 0.57-0.85; p < 0.001).[18] This study had a high proportion of patients (30%) with a high-risk cytogenetic profile.

## Targeting the checkpoint pathway

Targeting the PD-1 pathway, one of the most critical checkpoint pathways responsible for mediating tumour-induced immune suppression, pembrolizumab shows promising therapeutic activity.[19] Preliminary findings of the KEYNOTE-023 phase I trial of pembrolizumab/lenalidomide/dexamethasone in relapsing/refractory MM found

this combination to be well tolerated with promising antimyeloma activity, with an OR rate of 76% (VGPR 24%; PR 53%) over a median follow-up of 287 days.[20]

KEYNOTE-183, a phase III study investing pomalidomide/low dose dexamethasone with or without pembrolizumab in refractory or relapsed MM is currently recruiting patients, as is KEYNOTE-185, a phase III study of lenalidomide/low dose dexamethasone with or without pembrolizumab in newly diagnosed and treatment-naïve MM.

## Vaccination trials

Several MM vaccines have been developed and clinical trials are ongoing. A phase II trial of vaccination with dendritic cell/tumour fusions following ASCT has demonstrated immunologic and clinical responses in MM.[21] Consistent with a vaccine-mediated effect on residual disease, 24% of patients who achieved a partial response following transplant were converted to CR/near CR after vaccination and at >3 months post-transplant.

An evaluation by Bae et al. of a cocktail of HLA-A2-specific peptides XBP1 US184-192, heteroclitic XBP1 SP367-375, native CD138260-268 and native CS1239-247, for their ability to elicit multipeptide-specific cytotoxic T lymphocytes (MP-CTLs) using T cells from smouldering MM patients suggests that this treatment has the potential to induce effective and durable memory MP-CTL in such patients.[22] Patients could potentially benefit from a therapeutic vaccine to prevent or delay progression of smouldering MM to active disease.

## Cellular therapies (CAR-T)

Chimeric antigen receptor (CAR)-modified T cell therapy shows promise in MM and there are a number of potential targets including CD19, CD138, CD38, CD56, kappa, Lewis Y, CD44v6, CSa (SLAMF7) and BCMA. In a single patient with advanced, refractory MM, Garfall et al. administered an infusion of CTL19 cells (a cellular therapy consisting of autologous T cells transduced with an anti-CD19 chimeric antigen receptor) after high-dose melphalan and ASCT.[23] The result was a CR with no evidence of progression 12 months after treatment. Clinical trials of CAR-T are underway and many questions remain about the optimal CAR treatment protocol.

## TAKE-HOME MESSAGES:

- Innovations (proteasome inhibitors, IMiDs) to date have produced significant improvements in PFS and OS: recent approvals (e.g. carfilzomib, Ixazomib) will augment this
- Next wave of therapies are crucially agnostic to mutational thrust?
- Baseline immune function appears to also be a key barrier to success but may be targetable (e.g. use of PD-1/PD-L1 blockade)
- Monoclonal antibodies (elotuzumab, daratumumab, isatuximab) have activity in high-risk disease and represent true new novel mechanisms, as well as other immuno-therapeutics (e.g. checkpoint inhibitors, vaccines)
- New insights to mechanisms of drug action (e.g. AC 241) are further expanding therapeutic opportunities with combinations
- Numerous other small molecule inhibitors show promise (e.g. HDAC inhibitors, CXCR4, BCL, AKT, CDK, HSP 90, Nuclear Transport, KSP, BET bromodomain proteins/MYC, DUBs, MEK)
- Further refinement of prognostics and MRD will guide therapy.

## CONCLUDING REMARKS FROM THE CONVENORS:

I was thrilled with the whole meeting which was enhanced by a variety of outstanding presentations. I wish to thank all the contributors for their hard work and also wish to thank our two US-based guest speakers namely Professors Paul Richardson and Ola Landgren for giving up their time to travel to New Zealand. It was decided at the conclusion of the meeting to look at making this a biennial event and I look forward to seeing you all in Queenstown in 2018.

**Ken Romeril**
Co-convenor

As co-convenor I want to acknowledge the hard work and vision of Ken Romeril in setting up what is hopefully the first of many myeloma summits. The need for a dedicated myeloma summit has been building, with more agents available increasing the complexity of decision-making, and improved outcomes increasing patient numbers seen in clinics. The first meeting has set a high standard for future meetings to aspire to.

**David Simpson**
Co-convenor

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