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2017 ASH Annual Meeting

ANZMAP Multiple Myeloma Highlights

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Australia / New Zealand Myeloma Ambassador Program

Australian & New Zealand – Myeloma Ambassador Program (ANZMAP)

ANZMAP is a non-promotional educational program, supported by Celgene, established to support the development of a multiple myeloma (MM) educational presentation based on data presented at key international conferences. These data are shared with Australian & New Zealand physicians by program Ambassadors. The content of the slide resource represents the opinions of the Ambassadors.

Program Objectives

- Share insight into new pivotal data in the management and diagnosis of MM
- Discuss clinical perspectives of how the data applies to Australian and New Zealand practice
- Develop an educational presentation of key data to share with colleagues

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ANZMAP MULTIPLE MYELOMA HIGHLIGHTS FROM ASH 2017

This publication provides summaries of key clinically relevant multiple myeloma data presented at the 59th ASH Annual Meeting and Exposition, 9–12 December 2017 in Atlanta, Georgia, USA. The Chair (Associate Professor Peter Mollee) and clinicians involved in the Australian and New Zealand Myeloma Ambassador Program (ANZMAP) selected the presentations and when germane provided a brief commentary. The members of the ANZMAP ASH 2017 team were: Dr Emad Abro, Dr Alejandro Arbeláez, Dr Henry Chan, Dr Pasquale Fedele, Dr Anupkumar George, Dr Naadir Gutta, Dr Amit Khot, Associate Professor Muhajir Mohamed, Dr Nalini Pati, Dr Dejan Radeski and Dr Ruth Spearing. ANZMAP is a non-promotional educational program established to support the development of multiple myeloma educational presentations based on data delivered at key international conferences.

NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM)

Autologous stem cell transplantation versus bortezomib-melphalan-prednisone for newly diagnosed multiple myeloma: second interim analysis of the Phase 3 EMN02/HO95 study

Authors: Cavo M et al

The randomised EMN02/HO95 MM trial is currently the largest phase III study to compare autologous stem cell transplant (ASCT) with a bortezomib (Velcade)-based regimen in patients ≤ 65 years old. The study prospectively compared ASCT vs proteasome inhibitor-based intensification therapy, single vs double ASCT and consolidation therapy vs no consolidation (followed by lenalidomide maintenance). Data from the second interim analysis of the study were presented at ASH 2017.

Following bortezomib-cyclophosphamide-dexamethasone induction therapy, eligible patients were randomised (R1) to receive standard-dose intensification treatment with bortezomib-melphalan-prednisone (VMP) for four 42-day cycles or high-dose intensification treatment with melphalan 200 mg/m^2 (HDM) plus ASCT. A second randomisation (R2) to receive or not receive consolidation therapy was planned after the intensification phase, followed by lenalidomide maintenance in both arms. In centres committed to a double ASCT policy, patients were randomised (1:1:1) to receive VMP or single ASCT (ASCT-1) or two sequential courses of HDM (administered 2 to 3 months apart) plus double ASCT (ASCT-2). The primary study endpoint was progression free survival (PFS) from R1.

Of the 1503 patients registered, 1192 were eligible for R1; 695 patients were randomly assigned to ASCT and 497 patients to VMP. The groups were well matched for age, gender and ISS stage and high-risk (HiR) cytogenetic profile defined by t(4;14) ± t(14;16) ± del(17p) positivity. Median follow-up from R1 was 38 months.

Upfront ASCT was associated with a 24% reduction in risk of progression or death compared with VMP treatment (Figure 1). The median PFS was not reached in the ASCT group compared with 44 months in the VMP group. The 3-year estimates of PFS were 64% vs 57%, respectively (HR=0.76; p=0.002). The benefit with ASCT was maintained across predefined high- and standard-risk subgroup, although the high-risk groups had more markedly improved PFS with ASCT vs VMP. In a multivariate Cox regression analysis, randomisation to ASCT was an independent predictor of prolonged PFS.

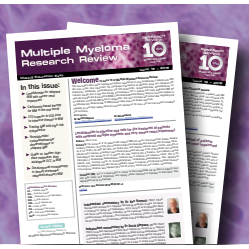
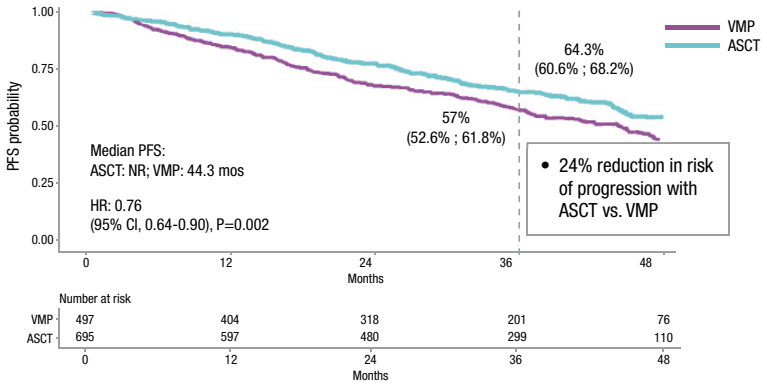


Figure 1. Progression free survival: upfront ASCT vs VMP regimen



ASCT: autologous stem cell transplantation, VMP: bortezomib, melphalan, and prednisone

Adapted from Cavo M et al. ASH 2017, oral presentation 397.

Possibly due to the immaturity of the data, there was no difference in overall survival (OS); 85% in both treatment arms. However, in analyses of high-risk subgroups, patients had significantly improved OS following ASCT compared with VMP: e.g. patients with R-ISS stage III (69% vs 47%; HR=0.43; p=0.009) and HiR cytogenetics (74 % vs 61%; HR=0.60; p=0.027)

The authors concluded that HDM plus ASCT significantly increased the rate of high quality responses, ultimately leading to improved PFS compared with VMP. Randomisation to ASCT was an independent predictor for improved PFS and significantly prolonged OS in patients with poor prognosis. The results support the use of upfront ASCT in NDMM patients.

Oral presentation: 397

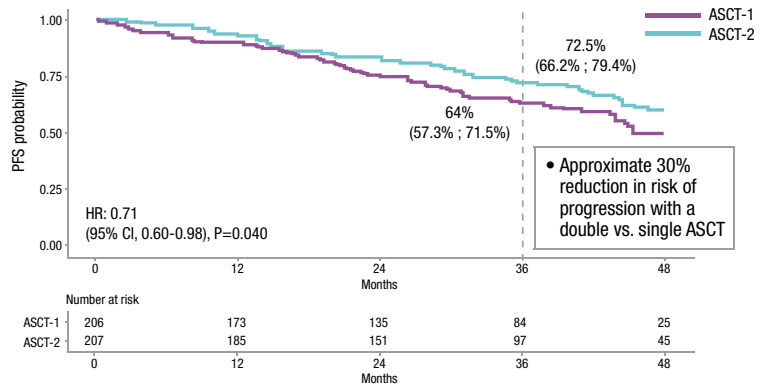
Double autologous stem cell transplantation significantly prolongs progression-free survival and overall survival in comparison with single autotransplantation in newly diagnosed multiple myeloma: an analysis of Phase 3 EMN02/HO95

Authors: Cavo M et al

In the EMN02/HO95 trial centres with a double ASCT policy, 618 patients were randomly assigned to VMP (n=203) or ASCT-1 (n=208) or ASCT-2 (n=207). 415 patients who were randomised to receive ASCT-1 or ASCT-2 were included in this pre-specified analysis; the median follow-up from R1 was 36 and 39 months respectively.

A second transplant improved the depth of response with about 25% of patients achieving an improved response; more than 50% of patients achieved at least a complete response. Although the median PFS had not been reached in either group, patients who had upfront double ASCT had significant improvement in PFS (Figure 2). The 3-year estimate of PFS was 73% after double ASCT compared with 64% after a single ASCT (HR=0.71; p=0.040), which represented a 30% reduced risk of progression or death. The PFS benefit associated with double vs single transplant was also seen in the high-risk subgroups; e.g. for patients with high-risk cytogenetics (median NR vs 27 months, HR=0.42; p=0.014). In a multivariate Cox regression analysis, randomisation to ASCT-2 was a leading independent predictor of PFS. (HR=0.66; p=0.029).

Figure 2. Progression free survival following upfront double vs single ASCT



ASCT1: single ASCT; ASCT-2: double ASCT

Adapted from Cavo M et al. ASH 2017, oral presentation 401

Overall survival was also significantly prolonged with double compared with single ASCT (3-year rate: 89% vs 82%; HR=0.51; p=0.011) in the overall population and in the subgroups of patients with adverse prognosis. In standard-risk patients (R-ISS I or standard-risk cytogenetics) a second ASCT did not significantly improve OS.

The authors concluded that upfront double ASCT significantly improved PFS and OS compared with single ASCT in the overall patient population and for poor prognosis patient subgroups. Patients with high-risk cytogenetics and other poor-prognostic features were the most likely to benefit from double ASCT in terms of reduced risk of progression and death.

Oral presentation: 401

COMMENTS

- *A strong point for this study is the large number of patients enrolled; the study accrued 1499 evaluable patients. At the cut-off date 1 July 2017, 1192 were included in the analysis. Median follow up 37.8 months.*
- *Standard-risk [NDMM] patients may not achieve a benefit with a second ASCT.*

Lenalidomide maintenance significantly improves outcomes compared to observation irrespective of cytogenetic risk: results of the Myeloma XI trial

Authors: Jackson G et al.

An updated analysis of the Myeloma XI trial was presented at ASH 2017. Myeloma XI, which is the largest maintenance study to date, compares lenalidomide 10 mg, days 1–21/28 until disease progression with observation alone. There are pathways for transplant eligible (TE) and transplant non-eligible patients (TNE) and the study was powered for both PFS and OS, with these being co-primary endpoints. 1971 patients, (1248 TE and 723 TNE), were randomised between lenalidomide (n=1137) and observation (n=834), and cytogenetic data was available for 774 patients. The arms were well balanced for clinical and risk features.

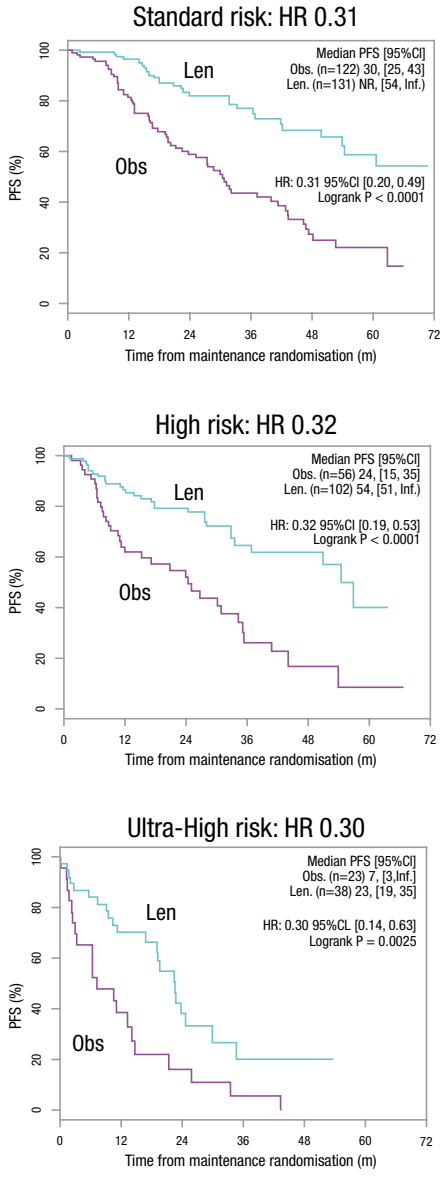
The significant reduction in risk of progression with maintenance lenalidomide persisted at the longer follow up (30.6 months). In TE patients, lenalidomide maintenance improved PFS from 30 to 57 months (Table 1). The PFS benefit was seen irrespective of induction therapy received or cytogenetic risk status (Figure 3)

Table 1. Lenalidomide maintenance improved progression free survival (PFS)

Patient population	Median PFS in months		Hazard ratio	Log rank p-value
	Observation	Lenalidomide		
All	20 (n=834)	39 (n=1137)	0.46	<0.0001
Transplant eligible	30 (n=518)	57 (n=730)	0.48	<0.0001
Transplant non-eligible	11 (n=316)	26 (n=407)	0.44	<0.0001

n=number of patients in arm

Figure 3. Lenalidomide maintenance improved progression free survival irrespective of cytogenetic risk (transplant-eligible data)
http://www.post-ash.co.uk/myeloma/



- **High risk - presence of any one of t(4:14), t(14;16), t(14;20), del(17p), or gain(1q).**
- **Ultra-high risk - presence of more than one lesion**
- **Standard risk - absence of any of the above lesions.**

Adapted from Jackson et al. ASH 2017, oral presentation 436

The PFS2 data (PFS from randomisation to second progression) indicated that the initial benefit of maintenance therapy was maintained (lenalidomide 64 months vs observation 45 months; HR: 0.67, p<0.0001). There was no evidence of an increase in mutational instability or significant toxicity with lenalidomide maintenance and secondary primary malignancies did not impact patient outcomes.

In TE patients, lenalidomide improved the 3-year OS from 80.2% to 87.5% (HR: 0.69, p=0.0130) however in TNE patients, subsequent treatment regimens attenuated the benefit.

The authors concluded that lenalidomide maintenance improves outcomes of NDMM irrespective of cytogenetic risk status.

Oral presentation: 436

COMMENTS

- *This in conjunction with three other large studies provides strong evidence. There are data from more than 2000 TE patients (1248 in Myeloma XI) showing a consistent doubling of PFS out to 60 months with lenalidomide maintenance.*
- *There was also a significant doubling of PFS in the TNE patients.*
- *No significant toxicity was noted. The dose in Myeloma XI (10 mg lenalidomide days 1-21/28) was lower than in some other lenalidomide maintenance studies.*
- *The benefit irrespective of cytogenetic risk is of importance.*

Phase 3 randomized study of daratumumab plus bortezomib, melphalan, and prednisone (D-VMP) versus bortezomib, melphalan, and prednisone (VMP) in newly diagnosed multiple myeloma (NDMM) patients (Pts) ineligible for transplant (ALCYONE)

Authors: Mateos M-V et al.

The ALCYONE study is a phase 3 randomised, open-label, multicentre study which included 706 NDMM patients who were aged ≥65 years or otherwise ineligible for ASCT. Patients were randomised to receive 9 cycles of either bortezomib (Velcade), melphalan and prednisone alone (VMP, n=356) or VMP combined with daratumumab (D-VMP, n=350) as front-line therapy. In the daratumumab treatment arm, patients received 16 mg/kg of daratumumab once weekly for 6 weeks (cycle 1), followed by once every 3 weeks (cycles 2–9). Following the 9 cycles, patients in the daratumumab treatment arm continued to receive daratumumab 16 mg/kg every 4 weeks until disease progression. PFS was the primary study endpoint. The median follow-up was 16.5 months.

Adding daratumumab reduced the risk of disease progression or death by 50%, compared with VMP alone (Figure 4). The median PFS with D-VMP was not reached and was 18.1 months for VMP. The PFS treatment benefit of D-VMP vs VMP was consistent across all pre-specified subgroups, including patients aged ≥75 years, ISS stage III, and high-risk cytogenetics.

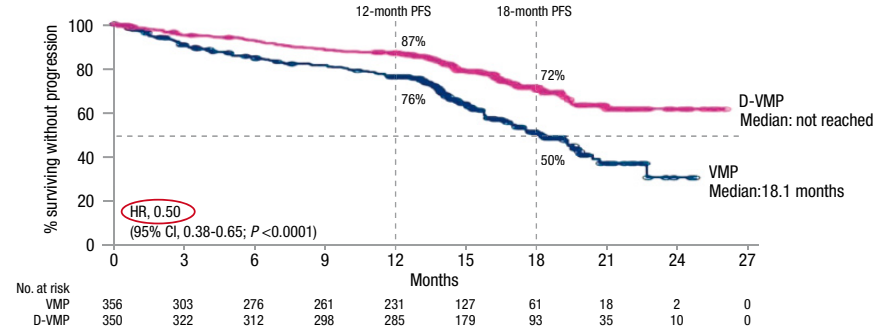
Patients treated with D-VMP had significantly higher rates of overall response (91% vs 74%), and MRD-negativity (22% vs 6%); both p<0.0001. OS data were immature after 93 deaths (45 vs 48 deaths for D-VMP vs VMP).

Overall, the safety profile of daratumumab plus VMP was consistent with the known safety profile of the VMP and daratumumab alone. The most common (≥10%) grade 3/4 TEAEs (D-VMP/VMP) were neutropenia (40%/39%), thrombocytopenia (34%/38%), anaemia (16%/20%), and pneumonia (11%/4.0%). 28% of patients experienced daratumumab-associated IRRs which were mostly grade 1 or 2 and typically occurred during the first infusion.

In summary, combining daratumumab and VMP in transplant ineligible NDMM patients doubled PFS (compared with VMP alone) driven by more patients achieving deep responses, including a more than three-fold higher rate of MRD-negativity.

Oral presentation: LBA-4

Figure 4. Patients who received D-VMP had a 50% reduction in the risk of progression or death compared with VMP alone



Separation between PFS curves started early – i.e. during the 9 cycles of D-VMP

Patients were randomised to receive 9 cycles of either bortezomib (Velcade), melphalan and prednisone alone (VMP, n= 356) or VMP combined with daratumumab (D-VMP, n=350) as front-line therapy. Following the 9 cycles, patients in the daratumumab treatment arm continued daratumumab every 4 weeks until disease progression

D-VMP: daratumumab, bortezomib, melphalan, and prednisone; VMP: bortezomib, melphalan, and prednisone

Adapted from Mateos et al. ASH 2017, #LB4

COMMENT

- *Results from this study were simultaneously published in the New England Journal of Medicine - Mateos M-V, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med. 2017. doi: 10.1056/NEJMoa1714678 http://www.nejm.org/doi/pdf/10.1056/NEJMoa1714678*

RELAPSED OR REFRACTORY MULTIPLE MYELOMA

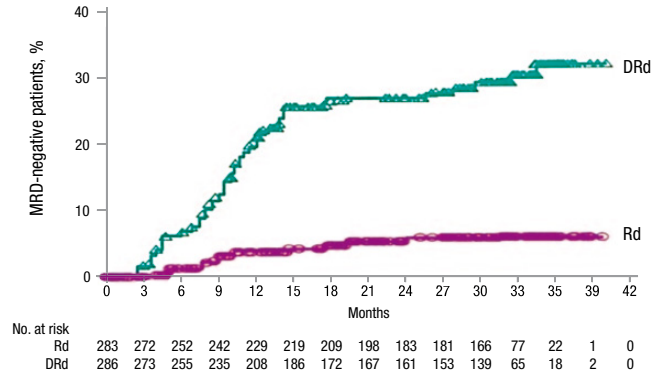
Daratumumab, lenalidomide, and dexamethasone (DRd) versus lenalidomide and dexamethasone (Rd) in relapsed or refractory multiple myeloma (RRMM): updated efficacy and safety analysis of POLLUX

Authors: Dimopoulos MA et al.

The POLLUX study is a randomised international phase III trial comparing daratumumab plus lenalidomide and dexamethasone (DRd) with lenalidomide and dexamethasone alone (Rd). The analysis reported at ASH 2017 provided updated efficacy and safety data from POLLUX after a median follow-up of 32.9 months.

The improvement in PFS with DRd compared with Rd persisted (median not reached vs 17.5 months; HR:0.44; p<0.0001) and a continued deepening in the ORR was observed with DRd compared with Rd (93% vs 76%; p<0.0001). MRD-negative rates were more than 3-fold higher with DRd compare with Rd at all sensitivity thresholds evaluated. At a sensitivity threshold of 10^{-5}, MRD-negativity rates were 27% for DRd vs 5% for Rd (p<0.0001) and patients with MRD-negative status accumulated more rapidly with DRd vs Rd (Figure 5).

Figure 5. MRD negativity occurs more rapidly with DRd compared with Rd and increases over time



DRd: daratumumab, lenalidomide, dexamethasone; Rd: lenalidomide and dexamethasone; MRD: minimum residual disease
Patients who received ≥1 prior line of therapy were randomized (1:1) to Rd (lenalidomide: 25 mg PO on Days 1-21 of each 28-day cycle; dexamethasone: 40 mg PO per week) with or without daratumumab (16 mg/kg IV weekly for Cycles 1 and 2, q2w for Cycles 3-6, then q4w until disease progression

Adapted from Dimopoulos MA et al. ASH 2017, oral presentation 739.

The safety profile remained unchanged and no new safety signals arose during the longer follow up. There was no difference in the rate of secondary primary malignancies between treatment groups (7% of patients in each group).

In conclusion, the updated analysis shows that DRd continues to have significant PFS benefit compared with Rd alone. Response to DRd deepened with longer-term follow up. Importantly, the favourable safety profile was maintained.

Oral presentation: 739

Durable clinical responses in heavily pretreated patients with relapsed/refractory multiple myeloma: updated results from a multicentre study of bb2121 anti-BCMA CAR T cell therapy

Author: Berdeja JG et al.

CAR T cell therapies have demonstrated robust and sustained clinical responses in several hematologic malignancies. To test the safety and efficacy of CAR T cells in RRMM, a BCMA-directed CAR T-cell therapy, bb2121 was designed. bb2121 consists of autologous T cells transduced with a lentiviral vector encoding a novel CAR incorporating an anti-BCMA scFv, a 4-1BB costimulatory motif and a CD3-zeta T cell activation domain.

This study (NCT02658929) was a multicentre, phase I, dose escalation trial of bb2121 in patients with RRMM who had received ≥ 3 prior regimens, including a proteasome inhibitor and an immunomodulatory agent, or were double-refractory, and had ≥ 50% BCMA expression on malignant cells. The study tested various doses (50, 150, 450, 800, and 1200 x 10^6 CAR+ T cells) with an active dose range of 150–800 x 10^6 CAR+ T cells emerging.

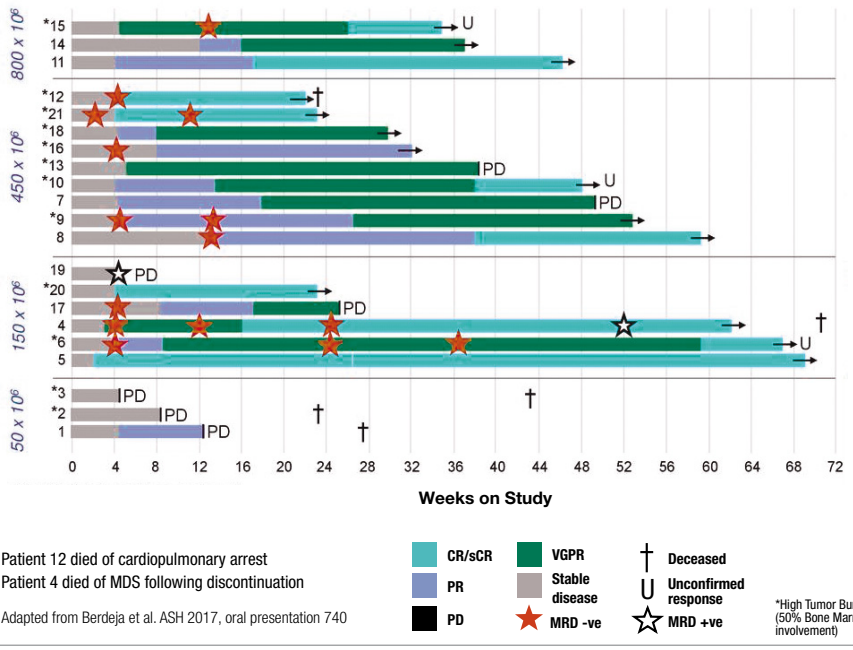
Patients received conditioning with fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2) before a single infusion of the CAR T cell therapy. The incidence of adverse events including dose-limiting toxicities (DLTs) was the primary outcome measure.

21 heavily pre-treated patients were infused with bb2121. The patients had received a median of 7 prior lines of therapy, with 29% of patients being refractory to bortezomib, lenalidomide, carfilzomib, pomalidomide, and daratumumab. All patients had received prior ASCT. The median time since diagnosis was 4 years, and 43% of patients had high-risk cytogenetics.

The median follow-up after bb2121 infusion was 40 weeks (range 6.6 to 69 weeks). As of data cut-off, no DLTs and no treatment-emergent Grade 3 or higher neurotoxicity had been observed. Cytokine release syndrome (CRS), primarily Grade 1 or 2, was reported in 15 of 21 (71%) patients: 2 patients had Grade 3 CRS that resolved in 24 hours. CRS was more common in the higher dose groups but did not appear related to tumour burden. There were five deaths, three from disease progression, one cardiac arrest and one myelodysplastic syndrome following discontinuation.

The overall response rate was 94% (17/18) and 9 of 10 evaluable patients achieved MRD negativity. The time to first response was 1 month and there were durable ongoing responses over 1 year (Figure 6). The responses continued to improve as late as month 15. The median PFS had not been reached in the active-treatment cohort.

Figure 6. Deep and durable tumour response following single infusion of bb2121 in active treatment cohorts (150–800 x 10^6 CAR+T cells)



Adapted from Berdeja et al. ASH 2017, oral presentation 740

In summary, bb2121 shows promising efficacy at active doses 150–800 x 10^6 CAR+ T cells, with manageable CRS and no DLTs to date. bb2121 induced durable and deepening responses in a heavily pre-treated population with RRMM. A global trial, KarMMa (NCT03361748) is open for enrolment.

Oral presentation: 740

A multicenter open label phase II study of pomalidomide, cyclophosphamide and dexamethasone in relapsing multiple myeloma patients initially treated with lenalidomide, bortezomib and dexamethasone

Authors: Garderet L et al. on behalf of the Intergroupe Francophone du Myelome (IFM)

This phase II trial investigated the efficacy and safety of adding weekly oral cyclophosphamide to pomalidomide and dexamethasone (PCD) in patients experiencing their first relapse following initial treatment in the IFM 2009/DFCI trial. The aim was also to find an effective salvage regimen to induce new remission in patients relapsing after exposure to lenalidomide and bortezomib (NCT02244125).

The study enrolled eligible patients who had relapsed myeloma after receiving initial treatment according to the IFM 2009/DFCI protocol (lenalidomide, bortezomib and dexamethasone (RVD) as induction and consolidation plus lenalidomide maintenance for 1 year; Arm A received ASCT at first relapse. Arm B received ASCT upfront). 100 patients (50 each from Arms A and B) were included. All patients received 4 cycles of oral pomalidomide 4 mg on day 1–21, oral cyclophosphamide 300 mg on days 1, 8, 15 and 22, and oral dexamethasone 40 mg days 1–4 and day 15–18 of a 28-day cycle. Responders who had not received ASCT initially (IFM 2009/DFCI Arm A) underwent ASCT and received two additional cycles of PCD, while those who had already been transplanted (IFM 2009/DFCI Arm B) received 5 cycles of PCD. All patients subsequently received pomalidomide plus dexamethasone maintenance until disease progression. The rate of partial response (PR) or better after the initial 4 cycles of PCD was the primary endpoint.

After 4 cycles of PCD, objective responses were achieved in 82 of 97 patients (91%): 1 CR: 32 VGPR and 49 PR. Stable disease was observed in 3 patients and progressive disease in 6. 94% (45/48) of patients in IFM 2009/DFCI Arm A could proceed to a first ASCT after the 4 cycles.

Toxicity was mostly haematological and manageable. There was no grade 3 or 4 peripheral neuropathy. Drug discontinuation rates were: pomalidomide, 6%, cyclophosphamide 8% and dexamethasone 9%. Dose reduction rates were pomalidomide 35%, cyclophosphamide 30% and dexamethasone 39%.

In conclusion, an all oral combination, PCD, was effective at first relapse following initial treatment with lenalidomide, bortezomib and dexamethasone.

Oral presentation: 837

COMMENTS

- *A significant number of patients required pomalidomide dose reductions due to cytopenia. The authors indicated that in future studies they would start with a lower dose of pomalidomide and then dose escalate if tolerated.*
- *Dexamethasone was given as a pulse dose in this study, which can be difficult to tolerate.*
- *Although most transplant naïve patients who relapsed after first-line treatment received a second-line ASCT, about 6% of patients didn't receive a salvage transplant, suggesting consideration of ASCT as a first-line rather than second-line option.*

Subcutaneous delivery of daratumumab in patients (pts) with relapsed or refractory multiple myeloma (RRMM): PAVO, an open-label, multicenter, dose escalation phase 1b study

Authors: Chari A et al.

Internationally, daratumumab has been approved as monotherapy and in combination with proteasome inhibitors or immunomodulatory drugs in patients with RRMM. Currently, daratumumab is administered intravenously (IV) and is associated with infusion related reactions (IRRs) in approximately 50% of patients.

Updated data from the open-label, multicentre Phase 1b PAVO (NCT02519452) study was presented at ASH 2017. Daratumumab co-formulated with recombinant human hyaluronidase enzyme (rHuPH20) and administered subcutaneously has low rates of IRRs. rHuPH20 temporarily breaks down the hyaluronan barrier, allowing rapid administration of larger volumes of injected drugs.

In the Part 1 dose-finding study, RRMM patients were subcutaneously administered mixed formulations of daratumumab and rHuPH20 (DARA-MD) using a syringe pump; DARA 1200 mg + rHuPH20 30000 U (in 60 mL) or DARA 1800 mg + rHuPH20 45000 U (in 90 mL). In Part 2, a concentrated co-formulation of DARA SC (1800 mg in 15 mL) and rHuPH20 (30000 U) in a single, premixed vial was administered over 3 to 5 minutes by manual SC injection. In both parts, the primary endpoints were safety and daratumumab trough plasma concentration (C_{trough}) up to Cycle 3 Day 1. At June 30, 2017, 53 patients were enrolled in Part 1 (DARA-MD 1200 mg, n=8; DARA-MD 1800 mg, n=45) and 25 patients in Part 2 (DARA SC 1800 mg). Note that the DARA SC patients in Part 2 tended to be less heavily pretreated than those in Part 1.

The SC administration resulted in a slower systemic absorption compared with IV daratumumab; however, the maximum C_{trough} was similar or higher following

1800 mg SC compared with 16 mg/kg IV. After 4 weeks of dosing, the maximum daratumumab plasma concentration following DARA SC 1800 mg or 16 mg/kg IV were similar (Figure 7).

Overall,1800 mg-DARA-MD (20%≥VGPR) and 1800 mg-DARA SC (28%≥VGPR) achieved similar response rates. 12%(3/25) of patients receiving DARA SC experienced IRRs; all after the first injection and within 6 hours; no grade 4 IRRs or discontinuations were reported. SC administration was well tolerated with few injection site reactions.

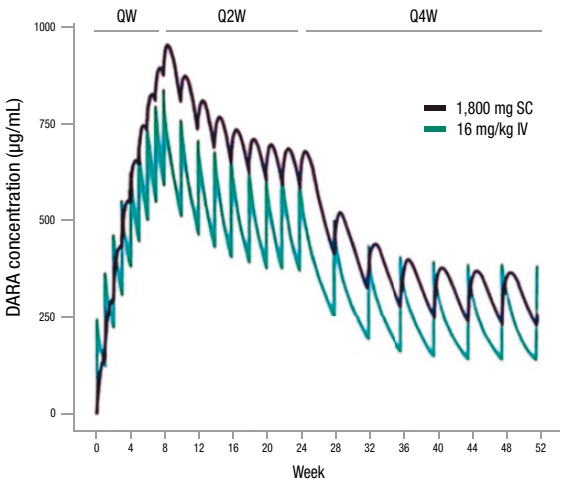
The authors concluded that SC administration of daratumumab + rHuPH20 was well tolerated, with lower than expected rates of IRRs in all groups, but particularly in those treated with DARA SC 1800 mg administered over only 3 to 5 minutes. Phase 3 studies are planned.

Oral presentation: 838

COMMENT

- *This is an encouraging new potential method of administration for daratumumab which will save time.*

Figure 7. Mean concentration-time profile simulation for SC and IV daratumumab



Dosing schedule is once weekly in cycles 1 to 2, every 2 weeks (Q2W) in cycles 3 to 6 and every 4 weeks (Q4W) thereafter.

Adapted from Chari et al. ASH 2017, oral presentation 838

LIGHT CHAIN (AL) AMYLOIDOSIS

Two studies presented at ASH 2017 investigated the role of daratumumab, a human IgG1k monoclonal antibody targeting the CD38 surface antigen on plasma cells, in AL amyloidosis. Although the biology of the clonal plasma cell in AL amyloidosis is distinct from that of myeloma, the cells do express surface CD38, providing a rationale for the use of daratumumab in AL amyloidosis.

Safety and tolerability of daratumumab in patients with relapsed light chain (AL) amyloidosis: preliminary results of a Phase II study.

Authors: Sanchorawala V et al.

Sanchorawala et al. studied the tolerability of daratumumab in a small number of patients with relapsed AL amyloidosis (NCT02841033). The particular concern was infusion-related reactions (IRR), which are frequently reported in RRMM.

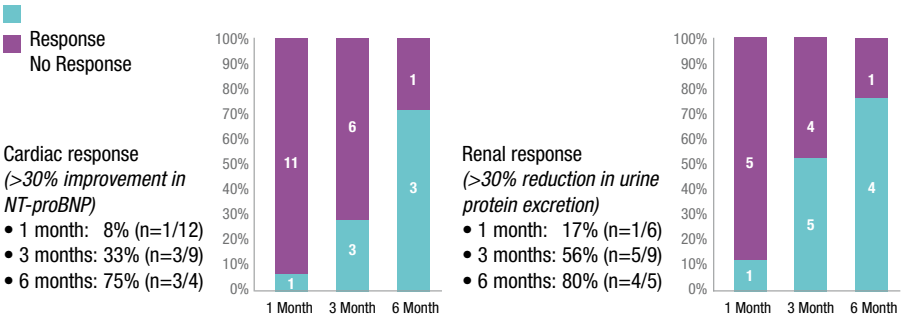
Patients with relapsed AL amyloidosis after ≥1 prior therapy, and involvement of at least one major vital organ, received daratumumab 16 mg/kg IV infusion weekly for weeks 1–8, followed by every 2 weeks for weeks 9–24 and every 4 weeks thereafter until progression or unacceptable toxicities, for up to 24 months. The first infusion of daratumumab was administered in 1000 mL, the second infusion in 500 mL if no grade 1 or greater reactions occurred throughout the first 3 hours of the first infusion, and subsequent doses were administered in 500 mL of saline.

Prior to infusion, all patients received paracetamol, diphenhydramine, loratidine, famotidine, monteleukast, ondansetron and methyprednisolone. Diphenhydramine, famotidine and methyprednisolone 40 mg were also administered 2 hours after the start of infusion during the first 2 infusions even if there was no reaction. Methylprednisolone 20 mg and monteleukast were administered 24 and 48 hours after start of infusion for the first 2 infusions and then monteleukast was optional. All patients received prophylaxis with acyclovir.

Eight patients were enrolled. The median age was 69 years (range, 60–83), and the median number of prior therapies was 3 (range,1–6); 3 patients were refractory to prior therapy. The median number of organ systems involved was 2 (range, 1–4). All patients had cardiac biomarker stage II or III disease. At the time of report, 7 patients remained in the study and 65 infusions had been completed. No patient experienced a grade 3 or 4 IRR and only 2 patients experienced grade 1 nausea and vomiting during first infusion, which resolved after an antiemetic. There were no interrupted or delayed infusions.

Preliminary data suggest a rapid haematologic response after 1 dose of daratumumab in patients with AL amyloidosis. Organ responses became evident after a month (Figure 8).

Figure 8. Organ response following daratumumab IV treatment in patients with relapsed AL amyloidosis



Adapted from Sanchorawala et al. ASH 2017, oral presentation 507

The authors concluded that daratumumab infusion is well tolerated in patients with relapsed AL amyloidosis, with minimal IRRs when administered with appropriate pre- and post-medications. Preliminary data suggested a rapid haematologic response after 1 dose of daratumumab in patients with AL amyloidosis.

Oral presentation: 507

A prospective phase II of daratumumab in previously-treated systemic light-chain (AL) amyloidosis.

Authors: Roussel M et al.

Roussel et al. presented the preliminary results of a prospective multicentre, phase II study of daratumumab in AL amyloidosis (NCT02816476). The trial planned to recruit 40 patients with evaluable AL amyloidosis, who have received ≥1 prior therapy and have at least one major vital organ involvement. Daratumumab is given in the standard dose (16 mg/kg) and schedule for a total of six 28-day cycles. The objectives are to assess haematologic responses, organ responses and safety.

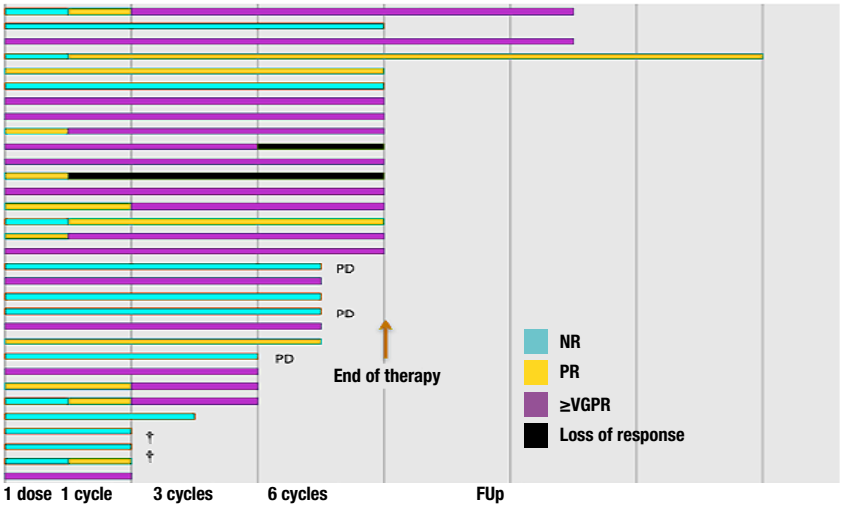
The 36 patients enrolled had a median age of 69 years (range, 45–83) and had a median number of prior therapies of 3 (1–5). 64% and 58% of patients had heart and kidney involvement, respectively. Five patients discontinued study treatment before 6 cycles due to disease progression (n=3) or death (1 cardiac progression and 1 lung cancer).

The overall hematologic response rate in 32 evaluable patients at 6 months (or at last evaluation) was approximately 60%: 44% ≥VGPR (7 with normal FLC levels and 2 with CR) and 16% PR. The responses were usually very rapid (Figure 9).

In conclusion, daratumumab was well tolerated and demonstrated encouraging efficacy with deep and rapid responses in previously-treated patients with AL amyloidosis; the response rate was twice that seen in RRMM.

Oral presentation: 508

Figure 9. Haematological response over time with daratumumab treatment in patients with relapsed AL amyloidosis



Adapted from Roussel et al. ASH 2017, oral presentation 508

COMMENTS

- *Daratumumab is a very active agent in AL amyloidosis and shows great promise as monotherapy.*
- *Rapid response, occurring as early as after only one dose.*
- *Daratumumab appears to be well tolerated in AL amyloidosis with no significant infusion reactions, however, adequate premedication may be important in preventing 1st dose reactions.*
- *Organ responses have been demonstrated in kidney and heart – up to 75%–80% within 6 months.*
- *Future studies will examine the use of daratumumab in stage III cardiac AL amyloidosis and in combination with chemotherapy in the upfront setting.*

SUPPORTIVE CARE

Two dose series of high-dose influenza vaccine is associated with longer duration of serologic immunity in patients with plasma cell disorders

Authors: Branagan A et al.

Patients with plasma cell disorders (PCDs) are highly susceptible to infections, including influenza. Despite routinely vaccinating PCD patients against seasonal influenza, infections remain common. A double-blind, randomised clinical trial was conducted during the 2015–16 flu season, comparing two doses of Fluzone® High-Dose influenza vaccine (initial and booster after 30 days) with standard of care (SOC) influenza vaccination (single age-based vaccination; standard dose <65 years and high-dose ≥ 65 years plus placebo booster after 30 days). Patients were randomised 2:1 ratio. HAI titres were analysed at baseline, 30 days after the first injection (Day 30), 30 days after the second injection (Day 60), and at the end of the flu season (April 30).

81 patients received two doses of Fluzone High-Dose vaccine and 41 patients received a single SOC influenza vaccination. At Day 60, seroprotection against all influenza vaccine strains (HAI > 40) was significantly higher with double high-dose vaccination (88%) compared with SOC vaccination (64%) ($p<0.05$); and at the end of flu season was 59% and 33%, respectively ($p=0.07$).

Protective HAI antibody titres fell rapidly in these PCD patients. Typically, HAI titres slowly decrease following a peak protective response, but do not drop below protective levels until 6 months post vaccination. However, PCD patients in this study began to lose HAI seroprotection within 4 months and even after 30 days. Subgroup analysis identified patients who were likely to have an inadequate response to influenza vaccination; including older patients, patients with active disease.

The authors concluded that a two-dose series of high-dose vaccine may mitigate loss of vaccine-induced HAI titres and allow more durable serologic protection throughout the flu season. More studies are needed to determine the optimal dose and timing of influenza vaccination in PCD patients.

Oral presentation: 438

COMMENTS

- *This was only a serological study; clinical endpoints would be useful.*
- *There are Australian centres already using a two-dose influenza vaccine strategy.*
- *This strategy is important given the loss of response over time; which was less marked with two doses.*
- *Importantly, the study identified patient subgroups which are likely to have an inadequate response to influenza vaccination (e.g. disease status worse than partial response and increased lines of prior therapy).*

Tackling Early Morbidity and Mortality in Myeloma (TEAMM): assessing the benefit of antibiotic prophylaxis and its effect on healthcare associated infections in 977 patients.

Authors: Drayson MT et al.

The TEAAMM study was a randomised, double-blind, placebo-controlled multicentre phase III clinical trial assessing the benefits of levofloxacin prophylaxis in patients with symptomatic NDMM. Many MM patients die before they have time to respond to antimyeloma therapy, with infection in the first 12 weeks being the main cause of the high early death rate.

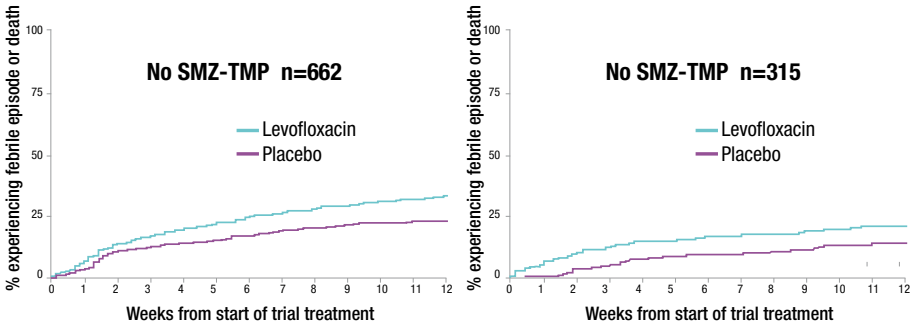
977 patients were randomised 1:1 to receive 500 mg levofloxacin or placebo tablets once daily for 12 weeks (dose adjusted for renal function). Patients could continue routine non-bacterial antimicrobial prophylaxis, including thrice weekly sulfamethoxazole-trimethoprim (SMZ-TMP) for pneumocystis. Faecal and throat samples were taken every 4 weeks to detect for carriage of resistant organisims. The primary endpoint was the number of febrile episodes (defined as an oral temperature of ≥38°C treated with anti-infectives) and/or death by any cause in the first 12 weeks.

Levofloxacin prophylaxis was found to significantly reduce febrile episodes or death in the first 12 weeks, with 19% (95/489) of patients experiencing events in the levofloxacin arm (87 febrile episodes; 4 deaths; 4 febrile episodes and death) compared with 27% (134/488) in placebo arm (112 febrile episodes; 15 deaths; 7 febrile episodes and death); HR:0.66 p=0.002. After 52 weeks there was no survival benefit (p=0.94).

Of 586 infections, there were 329 infections from 214 patients in the placebo arm and 257 infections from 189 patients in the levofloxacin arm (chi-square=7.55, p=0.006) with differences emerging after 4 weeks. Levofloxacin significantly reduced the number of reported invasive gram-negative infections, but not the number of reported gram-positive infections. There was no significant difference between the two arms for carriage or infection with *Clostridium difficile*, MRSA and ESBLGnB.

SMZ-TMP also significantly reduced the number of febrile episodes and deaths and the effect of SMZ-TMP and levofloxacin were additive (Figure 10). Cox regression adjusting for baseline factors showed levofloxacin and SMZ-TMP prophylaxis were significant predictors for reduction of febrile episodes or death during the 12 weeks from the start of trial treatment.

Figure 10. Prophylactic levofloxacin and sulfamethoxazole-trimethoprim (SMZ-TMP) reduced febrile episodes or death



Adapted from Drayson et al. ASH 2017, oral presentation 903

In conclusion, prophylactic use of 12 weeks levofloxacin for patients undergoing treatment for active myeloma significantly reduces febrile episodes and deaths without increasing healthcare associated infections or carriage of key nosocomial pathogens.

Oral presentation: 903

COMMENT

- *This was a very practical study which is likely to change practice.*

RESOURCES

ANZMAP ASH 2017 Slide Set (available by request through the ANZMAP Ambassadors or Myeloma Australia's Medical and Scientific Advisory Group (MSAG) - support@myeloma.org.au)

ASH 2017 Conference Review - Multiple Myeloma Focus (AU)

ASH 2017 Conference Review - Multiple Myeloma Focus (NZ)

ABBREVIATIONS USED IN THIS REVIEW

ASCT: autologous stem cell transplantation
BCMA: B cell maturation antigen
D-VMP: daratumumab, bortezomib, melphalan, and prednisone
CAR: Chimeric antigen receptor
CR: complete response
CRS: cytokine release syndrome
DARA-MD: daratumumab with recombinant human hyaluronidase enzyme (rHuPH20) by SC infusion of a mix and deliver formulation
DARA-SC: daratumumab co-formulated with rHuPH20 delivered by manual SC injection.
DLT: dose limiting toxicity
DRd: daratumumab, lenalidomide, dexamethasone
EOS/T: end of study/therapy
ESBLGnB: extended-spectrum beta-lactamase producing Gram-negative bacteria
FLC: free light chain
HAI: hemagglutination inhibition assay
HDM: high-dose melphalan
HDT-ASCT: high-dose therapy/autologous stem cell transplantation
HiR: high risk
HiR-cyto-3: high risk cytogenetic profile defined by t(4;14) ± t(14;16) ± del(17p)
HR: hazard ratio
ISS: International Staging System
IV: intravenous
MM: multiple myeloma
MR: minimal response
MRD: minimal residual disease
MRSA: methicillin resistance *Staphylococcus aureus*
NDMM: newly diagnosed multiple myeloma
NR: no response
NR: not reached
ORR: overall response rate
OS: overall survival
PCD: pomalidomide, cyclophosphamide, dexamethasone
PCD: plasma cell disorders
PD: progressive disease
PFS: progression free survival
PFS2: PFS from randomisation to second progression
PR: partial response
Rd: lenalidomide and dexamethasone
R-ISS: Revised International Staging System
RRMM: relapsed or refractory multiple myeloma
RVD: lenalidomide, bortezomib, dexamethasone
SAEs: serious adverse events
SC: subcutaneous
sCR: stringent complete response
SD: stable disease
SOC: standard of care
SMZ-TMP: sulfamethoxazole-trimethoprim SMZ-TMP
SPM: secondary primary malignancy
TEAE: treatment emergent adverse event
TE: Transplant eligible
TNE: Transplant non-eligible
VGPR: very good partial response
VMP: bortezomib, melphalan, and prednisone

This publication has been created with funding from Celgene Pty Ltd. This review may contain unapproved products or unapproved uses of approved products. Please consult the full Data Sheets for any medications mentioned in this article at www.medsafe.govt.nz before prescribing.

Treatment decisions based on these data are the full responsibility of the prescribing physician.