Article:
Maybury, B, Cook, G, Pratt, G et al. (2 more authors) (2016) Augmenting Autologous Stem Cell Transplantation to Improve Outcomes in Myeloma. Biology of Blood and Marrow Transplantation, 22 (11). pp. 1926-1937. ISSN 1083-8791

https://doi.org/10.1016/j.bbmt.2016.06.004

Augmenting autologous stem cell transplantation to improve outcomes in myeloma

Authors

Bernard Maybury[1], Gordon Cook, Kwee Yong, Guy Pratt, Karthik Ramasamy

Affiliations: Department of General Medicine, John Radcliffe Hospital, Oxford

...

Author contributions

B.M. wrote the manuscript. K.R. conceived and wrote the manuscript. G.C, K.Y. and G.P. reviewed and revised the manuscript.

Correspondence address

Disclosure of conflict of interest

Summary

Consolidation with high dose chemotherapy and autologous stem cell transplantation (ASCT) is the standard of care for transplant eligible patients with multiple myeloma, based on randomised trials showing improved progression free survival with autologous transplantation following combination chemotherapy induction. These trials were performed before novel agents were introduced, and subsequently combinations of immunomodulatory drugs (IMiDs) and proteasome inhibitors as induction therapy have significantly improved rates and depth of response. Ongoing randomised trials are testing whether conventional autologous transplantation continues to improve responses following novel agent induction. While these results are awaited, it is important to review strategies for improving outcomes following ASCT. Conditioning prior to ASCT with higher doses of melphalan, and combinations of melphalan with other agents, including radiopharmaceuticals have been explored. Tandem ASCT, consolidation and maintenance therapy following ASCT have been investigated in phase III trials. Experimental cellular therapies using *ex vivo* primed dendritic cells , e*x vivo* expanded autologous lymphocytes, KIR-mismatched allogeneic NK cells, and genetically modified T cells are also in phase I trials to augment ASCT. This review summarises these strategies and highlights the importance of exploring strategies to augment ASCT even in the era of novel agent induction.

Keywords: multiple myeloma, autologous stem cell transplantation, conditioning, immunotherapy, minimal residual disease

Introduction

Myeloma represents just over 1% of all cancers, and despite a recent increase in available therapeutics, the disease remains incurable with estimated 5 year survival just over 50% (Pulte *et al,* 2015). Randomised controlled trial (RCT) evidence from France and the UK demonstrated improved disease response and overall survival following autologous haematopoietic stem cell transplantation (ASCT), compared with conventional chemotherapy (Attal *et al,* 1996; Child *et al,* 2003). However, subsequent trials from France, the USA and Spain did not show an overall survival benefit, although Fermand *et al*. did show an improvement in progression free survival (Bladé *et al,* 2005; Fermand *et al,* 2005a; Barlogie *et al,* 2006a). The differences in outcomes between groups may be accounted for, by prolonged use of conventional chemotherapy in the study by Fermand *et al*, and a high rate of ASCT salvage therapy at relapse in that by Barlogie *et al*. A Dutch trial demonstrated that after treatment with intermediate dose melphalan, further treatment with ASCT did not improve outcomes (Sonneveld *et al,* 2007). These trials support the use of high dose alkylating agents in myeloma treatment. For patients who are fit for high dose therapy (approximately one third of newly diagnosed patients), treatment with chemotherapy conditioning followed by ASCT has been the standard of care, and the standard conditioning regimen has been a single dose of intravenous melphalan at 200mg/m^2 (Moreau *et al,* 2002). There has been much interest in augmenting conditioning but no regimen has been shown to improve outcomes in a randomised trial. Adjunctive strategies have also been explored: second tandem ASCT; consolidation and maintenance chemotherapy; attempts to augment immune responses post transplant; and new drugs, particularly monoclonal antibodies. This review will evaluate the strategies employed and make recommendations for further research in this area.

Methods

We searched Pubmed using the terms myeloma, autograft, asct, autologous, transplant, graft, transplantation, conditioning, preparative regimen, treatment, RCT, randomised, trial, and induction in various permutations, yielding 1393 results, and abstracts from the American Society of Haematology (ASH) and American Society of Clinical Oncology (ASCO) Annual meetings. Reference lists from these search results were used to identify other relevant publications. In the tables, overall response rate (ORR) is the proportion of patients achieving a partial response (>50% reduction in paraprotein) or better.

Novel agent induction

Induction for transplant eligible patients with immunomodulatory drugs (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib) has improved response rates prior to ASCT. The HOVON50 trial demonstrated that substituting thalidomide for vincristine in the VAD regimen (vincristine, doxorubicin and dexamethasone) could increase pre-ASCT overall response rates (ORR)

from 54% to 72% (Lokhorst *et al,* 2008). The benefit conferred by thalidomide combinations in induction was confirmed by the Myeloma IX and Total Therapy 2 trials (Morgan *et al,* 2012; Barlogie *et al,* 2006b). The IFM 2005-01 trial demonstrated that bortezomib and dexamethasone was also superior to VAD, increasing the pre-ASCT response rate to 79% from 63%, (Harousseau *et al,* 2010), and a similar improvement with bortezomib-based induction was observed in the HOVON65/GMMGHD4 trial (Sonneveld *et al,* 2012). Cavo et al tested the addition of bortezomib to thalidomide plus dexamethasone, and this combination of both IMiD and proteasome inhibitor significantly improved both pre-ASCT ORR (93% vs. 79%) and progression-free survival (PFS) (Cavo *et al,* 2010). Combining lenalidomide with bortezomib plus dexamethasone produced an ORR of 94% in a phase II IFM study (Roussel *et al,* 2014). An ongoing phase II study of carfilzomib, lenalidomide and dexamethasone for both induction and maintenance obtained an ORR pre-ASCT of 98% and demonstrated no unexpected toxicity (Zimmerman *et al,* 2015).

The improvement in responses seen with newer induction programs has prompted further trials following induction comparing upfront ASCT with a non-transplant option of novel agent consolidation followed by maintenance. Recently published phase III trials comparing ASCT with lenalidomide-containing regimens found ASCT confers superior PFS, although at a median follow up of 52 months no differences in overall survival were observed (Palumbo *et al,* 2014a; Gay *et al,* 2015). An ongoing French/American RCT (the IFM/DFCI 2009 study) compares ASCT plus 2 cycles of VRD with 5 cycles of VRD alone, and results from the French cohort show superior complete response (CR) rate (58% vs 46%) and 3-year PFS (61% vs 48%) in the ASCT arm (Attal *et al,* 2015). EMN02/HO95 is a European 2x2 factorial RCT, currently recruiting patients to compare ASCT versus bortezomib, melphalan and prednisolone (VMP) intensification, and then consolidation with bortezomib, lenalidomide and dexamethasone (VRD) versus no consolidation (Sonneveld *et al,* 2014). The possible merits of a delayed transplant strategy are being evaluated in the PADIMAC phase II study for patients achieving very good partial response (VGPR) or CR after bortezomib, doxorubicin and dexamethasone (PAD): up to 20% of patients had negative minimal residual disease (MRD) post induction, and survival outcomes are awaited (Popat *et al,* 2014).

Conditioning for ASCT

High dose melphalan 200mg/m^2 (mel200) delivered as a single dose for conditioning has been shown in a randomised trial to be less toxic and at least as effective as melphalan 140mg/m^2 (mel140) plus 8Gy total body irradiation (TBI) (Moreau *et al,* 2002), and mel200 has since remained the gold standard for single ASCT in patients with normal renal function. Escalating the dose of melphalan above 200mg/m^2 is prohibitively toxic to the gastrointestinal tract. Minimising oral mucositis with protective agents amifostine (Spencer *et al,* 2005) and palifermin, a keratinocyte growth factor, may facilitate dose increases to 280mg/m^2 for a proportion of patients (Abidi *et al,* 2013). However wide

variability in melphalan exposure due to pharmacokinetic differences has been reported. In a pharmacokinetic study of high dose melphalan in 100 patients, higher mucositis rates and improved disease response were seen in patients with higher exposure to melphalan, as measured by increased area under the curve of both total and unbound melphalan (Nath *et al,* 2010).

Melphalan and chemotherapeutic agent combinations

A number of chemotherapeutic agents and combinations with Mel200 have been tested in clinical studies, but the majority of these studies enrolled fewer than 100 patients and were non randomised studies, so it is difficult to draw significant conclusions (Table I).

Regarding alkylating agents in combination with melphalan: oral busulfan is demonstrably too toxic, as 8% of patients in a Spanish study developed veno-occlusive disease, with a case fatality rate of 25% (Lahuerta *et al,* 2010). The intravenous busulfan formulation introduced in 2003 reduces hepatic exposure via the portal circulation, and a non-randomized study (n=153) comparing mel140 plus busulfan 9.6mg/kg i.v. with mel200 suggested a small benefit in terms of progression-free survival but increased treatment-related mortality, with neither difference reaching statistical significance (Blanes *et al,* 2013). Adding cyclophosphamide 120mg/kg to mel200 worsens outcomes (Desikan *et al,* 2000), and further addition of idarubicin progressively increases treatment-related mortality to 20% (Fenk *et al,* 2005). An RCT of cyclophosphamide, oral busulfan and total marrow irradiation versus two consecutive ASCT with mel200 found the chemoradiotherapy regimen to be more toxic with no significant improvement in efficacy (Knop *et al,* 2007). Reports from MD Anderson Cancer Centre using mel140 plus topotecan and cyclophosphamide in combination show outcomes comparable to mel200 but a controlled comparison is required (Donato *et al,* 2004; Kazmi *et al,* 2011). The addition of carmustine to mel200 in single arm studies was found to be safe, with comparable PFS and OS to previously published Mel200 studies (Comenzo *et al,* 2006; Chen *et al,* 2012). More recently bendamustine, which has shown single agent activity in relapsed myeloma, was combined with Mel200 at escalated doses reaching 225mg/m^2 with only one dose-limiting toxicity in the first 100 days post-transplant. (Mark *et al,* 2013)

Melflufen is a dipeptide pro-drug of melphalan, which by virtue of increased intracellular hydrolysis is concentrated in myeloma cells. Melflufen induces apoptosis in melphalan-resistant cells and is highly effective in mouse models (Chauhan *et al,* 2013). A phase I/II trial of melflufen and dexamethasone in relapsed-refractory myeloma is ongoing, but initial results are encouraging with an ORR of 60% (Magarotto *et al,* 2015). Based on these encouraging results, melflufen as a conditioning regimen prior to ASCT should be explored in future trials.

Topoisomerase inhibitors (doxorubicin, idarubicin, mitoxantrone, topotecan) have been tested in combination with melphalan as conditioning, although *in vitro* data on the combination is limited. The

addition of cyclophosphamide and idarubicin to mel200 was shown in an RCT to markedly increase treatment related mortality (Fenk *et al,* 2005), but adding cyclophosphamide and topotecan to mel140 produced promising outcomes in an uncontrolled series (Kazmi *et al,* 2011). Two small phase II studies of mitoxantrone combined with melphalan (combined n=55) suggest outcomes comparable to mel200 (Ballestrero *et al,* 2002; Beaven *et al,* 2011).

Arsenic trioxide with ascorbic acid has been explored in a randomised trial recruiting 48 patients, combined with mel200. There was no difference in response rate or survival, but no additional toxicity was noted (Qazilbash *et al,* 2008).

Melphalan with Proteasome Inhibitors and IMiDS

Synergistic myeloma cell kill *in vitro* has been noted with the combination of melphalan and bortezomib (Ma *et al,* 2003; Mitsiades *et al,* 2003). Bortezomib, by inhibiting the proteasome, interferes with DNA repair pathways and inhibitors of apoptosis, thus sensitising cells to DNA-damaging agents such as melphalan. There are currently no randomised data for the addition of bortezomib to ASCT conditioning. A French non-randomised phase II study found that adding bortezomib 1mg/m^2 to mel200 improved complete response (CR) rates from 11% to 35% (Roussel *et al,* 2010), but in contrast two other small studies (combined n=27) using non-randomized control patients observed no difference in response rate, though reassuringly no increase in toxicity was observed (Huang *et al,* 2012; Miyamoto *et al,* 2013). A phase I study suggests that bortezomib is more effective when given after melphalan dosing, rather than before, with an increase in CR rates from 11% to 30% (Lonial *et al,* 2010). In an uncontrolled series, 36% of patients with primary refractory myeloma obtained a CR after tandem ASCT with bortezomib given after melphalan (Nishihori *et al,* 2012). Lenalidomide at higher than licensed doses has been combined with mel200 in a phase I study of relapsed/refractory myeloma and no lenalidomide related dose-limiting toxicities were observed, with 8 of 21 patients (38%) achieving ≥CR (Forsberg *et al,* 2015). Carfilzomib is a recently licensed irreversible proteasome inhibitor, which has been studied in phase III trials in relapsed/refractory myeloma (Stewart *et al,* 2015); a phase I/II trial is currently underway in combination with melphalan as a conditioning regimen (CARAMEL trial, NCT01842308).

Augmentation with radiotherapy/radiopharmaceuticals

Total body irradiation displays excessive toxicity in trials, but targeted radiotherapy shows promising early results. Phase I/II trials of radiophosphonates (containing ^{153}Sm or ^{166}Ho, respectively) added to mel200 conditioning showed no change in outcomes with little toxicity, though renal failure due to thrombotic microangiopathy was seen with doses >30Gy of the ^{166}Holmium conjugate (Giralt *et al,* 2003; Dispenzieri *et al,* 2010). The combination of bortezomib with the ^{153}Samarium conjugate demonstrated promising synergy in mice and merits further clinical investigation (Goel *et al,* 2006).

CD66 is expressed on myeloma cells as well as the myeloid lineage: an anti-CD66 radioconjugate monoclonal antibody is selective for bone marrow, and appears to be safe in a phase I trial (Orchard *et al,* 2005), with results from the phase II trial awaited. Radio-conjugated CD20 antibodies show additional toxicity in phase I when added to mel200 for conditioning (^{90}Y-ibritumomab) (Dispenzieri *et al,* 2011), and limited efficacy when used as a single agent (^{131}I-tositumomab), which may relate to low CD20 expression on myeloma cells, with higher response rates correlating with expression of CD20 (Lebovic *et al,* 2012). Radioconjugate antibodies against CD38 and CD138 have been studied in animal models, but clinical trials are awaited (Green *et al,* 2013; Chérel *et al,* 2013). Tomotherapy (radiotherapy delivered from many emitters arranged radially to focus treatment, analogous to computed tomography scans) has hitherto only been studied in leukaemias and lymphomas (Pica *et al,* 2011), but studies in myeloma are underway. This would require a head-to-head comparison with molecularly targeted radiotherapy in future.

Tandem transplants

Two consecutive cycles of high dose chemotherapy, with each cycle followed by haematopoietic stem cell transplantation/rescue (tandem ASCT), has been extensively investigated by both European and US cooperative groups, in an attempt to improve responses (Table II). The Arkansas group have undertaken a series of Total Therapy Trials using intensive treatment including tandem ASCT, which have achieved impressive results, for instance 41% CR and median OS of 68 months in Total Therapy 1 (Barlogie *et al,* 2006c; Barlogie *et al,* 2007). However, these studies were uncontrolled, and patient selection was wholly at the discretion of the investigators. A fuller retrospective dataset from the same centre, that included patients treated off study protocols, demonstrated inferior results, but on multivariate analysis a second transplant was still associated with prolonged PFS and OS (Pineda-Roman *et al,* 2008).

Most randomised trials comparing single with tandem ASCT have shown no benefit in overall survival from tandem stem cell transplantation (Attal *et al,* 2003; Fermand *et al,* 2005b; Cavo *et al,* 2007; Mai *et al,* 2016; Sonneveld *et al,* 2007; reviewed by Kumar *et al*, 2009). Many of these trials utilised non-standard conditioning regimens (e.g. oral busulfan or TBI) which have since been shown to be inferior to standard mel200 (Attal *et al,* 2003; Fermand *et al,* 2005b; Cavo *et al,* 2007; Sonneveld *et al,* 2007). However the GMMG-HD2 trial, which used tandem standard mel200 ASCT, showed no difference in survival (Mai *et al,* 2016). The only trial to show a significant benefit for both PFS and OS was the IFM-94 study, but the outcomes (in both groups) were poor compared with more recent trials using newer agents as part of the treatment protocol (Attal *et al,* 2003). In a non-randomized comparison between the Dutch protocol (single transplant) and the German protocol (tandem ASCT), the latter was superior for overall survival, but regional variations in demographics and treatment could account for this difference (Sonneveld *et al,* 2013). Subgroup analyses suggest

there may be a survival advantage from a second ASCT in those patients who fail to achieve a deep response to the first ASCT (Attal *et al,* 2003; Cavo *et al,* 2007). In the majority of trials, treatment-related mortality is higher in the tandem ASCT arm, and in addition to this acute risk there may be an increased risk of long term complications such as second malignancies and myelodysplastic syndrome, although it is not clear that ASCT increases that risk over high dose conventional chemotherapy (Govindarajan *et al,* 1996). The deep responses achieved with proteasome inhibitors and immunomodulatory drug-based conditioning regimens, and wider use of consolidation and maintenance therapies, have both limited the use of tandem stem cell transplantation.

Consolidation

Relapse remains inevitable following ASCT, and consolidation therapy after transplant has been investigated as a way of prolonging progression-free survival, by deepening post transplant response. Several phase II and phase III studies of post-ASCT consolidation have been performed over the last 5 years (Table III), but there is not rigorous data to support its efficacy. Only one phase III trial is placebo controlled (Mellqvist *et al,* 2013), and uncontrolled studies are not able to be informative, because responses improve over months after ASCT regardless of further treatment. In a phase II comparison with historical controls, patients receiving cyclophosphamide, thalidomide and dexamethasone consolidation achieved better responses at 12 months (72% ≥VGPR versus 51%) (Rabin *et al,* 2012). In a phase III RCT bortezomib alone improved response and progression free survival but with no improvement in overall survival (Mellqvist *et al,* 2013). In a phase III trial of adding bortezomib to thalidomide and dexamethasone (i.e. VTD vs TD) for both induction and consolidation, there was no overall survival benefit, but 3-year progression free survival increased from 56% to 68% commensurate with deepening response (Cavo *et al,* 2010). The consistent finding of deeper responses with delayed progression but no effect on overall survival likely reflects more effective salvage treatment at relapse for the control group.

There are no randomised data on lenalidomide-based consolidation, but in an RCT of lenalidomide maintenance, all patients from both arms first received 2 months of lenalidomide consolidation and over this period the rate of ≥ VGPR increased from 58% to 69% (Attal *et al,* 2012). A phase II study of lenalidomide, bortezomib and dexamethasone in both induction and consolidation demonstrated good responses and impressive survival data with an estimated 77% 3 year progression-free survival (Roussel *et al,* 2014). Results from a phase II study of carfilzomib, lenalidomide and dexamethasone for induction, consolidation and maintenance (with lower doses of carfilzomib) showed that 88% of patients were MRD-negative after 4 cycles of consolidation, which will hopefully be reflected in future improved survival data (Zimmerman *et al,* 2015). Survival benefits from consolidation strategies following ASCT have yet to be confirmed in randomised studies.

Maintenance

Relapse after ASCT is primarily due to residual myeloma cells which continue to survive and proliferate, and maintenance therapy aims to control this process, by giving continuous low dose therapy until relapse (Table IV). However a concern is that although progression is delayed on maintenance, at relapse the disease could be refractory to further treatment and so benefits in overall survival would be limited. Such benefits must be balanced against toxicity, quality of life and cost effectiveness, given the long duration of maintenance approaches. Earlier maintenance studies did not include any consolidation, and the survival plots often diverge early, which suggests that most benefit is gained early after transplant. It is unclear if there are advantages to commencing maintenance after an effective course of consolidation treatment.

Interferon alpha had been used as a maintenance agent for many years, but it is uniformly poorly tolerated. Used as maintenance therapy after conventional chemotherapy, interferon alpha modestly prolonged PFS with no effect on OS (Drayson *et al,* 1998) but the US Intergroup S9321 trial found that it made no difference to progression or survival following ASCT (Barlogie *et al,* 2006a). A therapeutic dose of prednisolone conferred a survival benefit when used after VAD-based conventional chemotherapy (Berenson *et al,* 2002) but glucocorticoids as monotherapy in the post-ASCT population are redundant now given the improved clinical activity and tolerability observed with IMiDs and proteasome inhibitors. In a phase III comparison between dexamethasone and interferon maintenance, the dexamethasone group responded very badly to melphalan/dexamethasone at relapse, presumably due to selection of resistant clones (Alexanian *et al,* 2000).

Thalidomide maintenance has been subjected to a number of phase III trials, conferring a 10% increase in 4-year survival rate compared with no maintenance (Attal *et al,* 2006), and in an RCT comparing thalidomide plus prednisolone versus prednisolone alone, overall survival was increased by 10% at 3 years (Spencer *et al,* 2009). A smaller RCT of similar design found a non-significant trend towards increased survival in the thalidomide arm (Maiolino *et al,* 2012). However an RCT of thalidomide plus prednisolone versus no maintenance found no overall survival difference, and highlighted worse quality of life scores in the maintenance group (Stewart *et al,* 2013). In all of these trials, adverse events of grade 3 or 4 were much more common in the thalidomide arm, and this is reflected in a thalidomide discontinuation rate of 30% within a year in the study by Spencer *et al*.

In a joint German/Dutch trial comparing induction and maintenance with bortezomib versus vincristine-based induction and thalidomide maintenance, there were improved response rates and PFS, but overall survival difference barely reached statistical significance (p=0.049) on a multivariate analysis (Sonneveld *et al,* 2012). There was no difference in response during the maintenance phase,

between the two arms. In a post-hoc analysis, patients with renal impairment gained a significant benefit from the bortezomib arm (Scheid *et al,* 2014).

Two large RCTs of lenalidomide maintenance against placebo showed an early benefit in progression-free survival, which in the CALGB study prompted early termination (McCarthy *et al,* 2012). The CALGB trial (n=460) subsequently showed a small OS benefit, but no OS difference was seen in the IFM study (n=614). This study gave both arms 2 cycles of lenalidomide consolidation at a higher dose before randomisation (Attal *et al,* 2012) and the Kaplan-Meier overall survival plot of the CALBG study diverges early and is parallel thereafter, which suggested that any benefit in overall survival is derived from the first few months on lenalidomide. Both studies agreed that there are considerable toxicities from lenalidomide, with increased haematological adverse events and secondary cancers seen in the lenalidomide groups.

Combining bortezomib with lenalidomide in maintenance confers a high side effect burden, but in a phase II study demonstrated good results in patients with high risk myeloma or plasma cell leukaemia, with 93% overall survival at 3 years, and no patients stopped maintenance due to toxicity (Nooka *et al,* 2014). A non-randomised comparison between sequential cohorts receiving bortezomib and dexamethasone with either lenalidomide or thalidomide, as maintenance for low risk myeloma found no difference in survival or relapse rates (Nair *et al,* 2010). Maintenance with VRD is yet to be studied in a phase III randomised trial.

New agents

Histone deacetylase inhibitors (vorinostat and panobinostat) have been explored in phase III trials of relapsed/refractory myeloma in combination with bortezomib. Vorinostat demonstrated limited activity (Dimopoulos *et al,* 2013) but panobinostat in combination with bortezomib and dexamethasone increased progression free survival with overall survival data yet to show a significant difference (San-Miguel *et al,* 2014). Vorinostat has been combined with lenalidomide for maintenance after ASCT in a phase I study, with 14 of the 16 subjects having grade 3 or 4 adverse events during maintenance (Sborov *et al,* 2015), which compares unfavourably with lenalidomide monotherapy maintenance trials (McCarthy *et al,* 2012; Attal *et al,* 2012).

Several new monoclonal antibodies, antibody-drug conjugates and small molecules are in phase II and III trials for both newly diagnosed and relapsed/refractory myeloma. Adding elotuzumab (targeting SLAMF7) to lenalidomide and dexamethasone increased the response rate from 66% to 79% in relapsed or refractory patients, and progression-free survival from 14.9 months to 19.4 months in a phase III trial (Lonial *et al,* 2015). A phase I trial of elotuzumab in combination with bortezomib induced responses in 48% of patients with relapsed/refractory myeloma (Jakubowiak *et al,* 2012). The anti-CD38 daratumumab looks promising in phase I/II trials (Plesner *et al,* 2014; Moreau *et al,* 2014;

Lokhorst *et al,* 2015), and three phase III trials of daratumumab plus various chemotherapy regimens are currently recruiting in newly diagnosed and relapsed populations. The antibody-drug conjugates lorvotuzumab mertansine (with lenalidomide/dexamethasone, ORR 59%) (Berdeja *et al,* 2012) and indatuximab ravanstine (with lenalidomide/dexamethasone, ORR 78%) (Kelly *et al,* 2014); and the AKT inhibitor afuresertib (with bortezomib/dexamethasone, ORR 49%) (Voorhees *et al,* 2013) demonstrate activity in phase I trials in relapsed/refractory patients. Phase I trials of anti-PD1 monoclonal antibodies in combination with IMiDs (Badros *et al,* 2015; San Miguel *et al,* 2015), the anti-CD74 conjugate milatuzumab-doxorubicin and an anti-CD200 antibody are currently ongoing in relapsed myeloma.

None of these new agents is currently being investigated as part of an ASCT treatment protocol. Monoclonal antibodies are not particularly myelosuppressive: elotuzumab has lower neutropenia rates than the control group (Lonial *et al,* 2015), and although a minority of patients receiving daratumumab developed low cell counts this was not dose-dependent (Lokhorst *et al,* 2015). Given this low toxicity they are attractive targeted therapies for use in consolidation and maintenance phases, to inhibit residual myeloma clones.

Immunotherapy and cellular therapy

The reconstitution of the immune system following ASCT is an opportunity to augment the immune response against myeloma. Natural killer cells, components of the innate immune system with the potential to kill cancer cells, reconstitute quickly after ASCT, and the number of NK cells at day 30 correlates with PFS after ASCT (Rueff *et al,* 2014). Lymphocyte populations recover gradually over a year or more, and the early populations are abnormal, with an excess of CD8+ T cells and few CD4+ T cells, which have a narrow T-cell receptor repertoire. The lymphodepletion brought on by high dose therapy causes levels of cytokines IL-5 and IL-17 to rise, which in turn drive extrathymic proliferation of CD4+ T cells. This expansion of T cells in the absence of Treg expansion may facilitate an effective anti-myeloma adaptive immune response.

Maintenance therapy with interferon alpha was the earliest immunomodulatory therapy, augmenting the cellular anti-myeloma response and, although modestly effective as maintenance after ASCT, it was not adopted due to poor tolerability (Barlogie *et al,* 2006a). Another approach used ciclosporin in a small population of mixed haematological malignancies for one month after ASCT leading to a reaction akin to acute graft-versus-host disease, which was associated with improved disease-free survival but no overall survival difference (Marin *et al,* 2001).

Vaccine strategies include myeloma-Dendritic Cell (DC) fusion, autologous serum-loaded DCs, myeloma-peptide-stimulated T cells, and idiotypic DNA vaccination (fig. 1). A phase I trial of autologous DC-myeloma cell fusion cells injected into myeloma patients found these induced

expansion of myeloma-specific T cells *in vivo*, and stabilised disease progression in 11 of 16 patients (Rosenblatt *et al,* 2011). A small trial from the Mayo clinic of *ex vivo* stimulated DCs accompanying ASCT found improved survival compared to matched historical controls (Lacy *et al,* 2009), and a small Czech study looking at *ex vivo* stimulated DCs as monotherapy in pretreated patients found a modest improvement in outcomes (Zahradova *et al,* 2012). Two small trials of myeloma peptide vaccines followed by *ex vivo* T cell expansion and reinfusion showed these to be safe and effective at inducing lymphocyte responses (Rapoport *et al,* 2011; Rapoport *et al,* 2014) but no effect on clinical outcomes could be discerned from these small groups with only the former including a control arm. DNA vaccines (variable regions of paraprotein heavy and light chains, fused to tetanus toxin, in an expression vector) appear to be safe in phase I trials, though they only elicited an anti-idiotype immune response in 4 of 14 subjects (McCann *et al,* 2015). These vaccine strategies merit further investigation in clinical trials.

Engineered T cells with chimeric antigen receptors (CAR), which combine the antigen-binding fragment of antibodies with the signalling domains of the T cell receptor, have been used with some success against advanced leukaemias and lymphomas (Maude *et al,* 2014; Kochenderfer *et al,* 2013). CAR T cells targeting CD19 have been used as part of ASCT in 10 myeloma patients who were heavily pre-treated; 4 have responded to date, with one patient achieving a stringent CR which has lasted over 12 months (Garfall *et al,* 2015). CAR T cells against CD38 can effectively kill myeloma cells *in vitro* (Mihara *et al,* 2011), and phase I trials are ongoing for these (NCT01886976), and chimeric anti-kappa light chain T cells (NCT00881920). Toxicities from CAR T cell therapies include an infusional cytokine release syndrome and potential off target effects. In mouse studies, *ex vivo* expanded NK cells can inhibit growth of myeloma tumours (Garg *et al,* 2012). This concept is explored in phase I studies of autologous expanded NK cells (with chemotherapy, but without transplantation) in relapsed myeloma patients (NCT01313897; NCT01884688). Haploidentical but KIR-mismatched allogeneic NK cells are also being investigated as an adjunct to ASCT (Shi *et al,* 2008).

Trial endpoints

Overall survival remains the gold standard endpoint for trials in myeloma, but survival rates have improved with over a third of newly diagnosed patients living longer than 10 years in the UK (Cancer Research UK, 2014), so OS is a late endpoint for trials to report. Complete response rate has historically correlated poorly with overall survival (Baldini 1991; Riccardi *et al,* 2003; Durie *et al,* 2004), and clearly does not take account of quality of life aspects, which are affected by increasingly prolonged myeloma therapy regimens. In early trials, time to progression did correlate with overall survival, but with consolidation treatment this association is no longer seen (Alexanian *et al,* 2000; Attal *et al,* 2012; Maiolino *et al,* 2012; Sonneveld *et al,* 2012; Stewart *et al,* 2013). PFS2, the time

from first treatment to second relapse, takes account of tumour resistance induced by the first line of treatment, and to date studies have shown it is prolonged in association with PFS (Palumbo *et al,* 2014b; Tacchetti *et al,* 2014), but it has not yet been validated as a surrogate for OS, and still takes years of follow up to report mature data. By contrast, recent ASCT trials have shown an association between the depth of response and overall survival (Harousseau *et al,* 2009; Lahuerta *et al,* 2008) and this is particularly the case for prolonged (>3 years) complete response (Barlogie *et al,* 2008). However complete response rate still remains a relatively insensitive surrogate for overall survival, and as median survival continues to improve, particularly for transplant-eligible populations, we have to adopt earlier endpoints to study the gamut of new agents entering the field. Measuring MRD by multi-parameter flow cytometry accurately predicts overall survival in patients who have achieved a complete response (Paiva *et al,* 2012; Rawstron *et al,* 2015) and represents an opportunity to vastly shorten the time required for trials of aggressive treatment to report. ^{18}F-flurodeoxyglucose positron emission tomography (PET) CT scanning is also a predictor of PFS and OS, both after induction (Bartel *et al,* 2009) and after ASCT (Zamagni *et al,* 2015). Its predictive power is independent of CR status, but further studies are needed combining MRD measurement and PET CT to determine whether both independently provide prognostic information. These trials will still need long term follow up to identify late adverse events, the impact on quality of life and hopefully confirm the predictive power of these new endpoints.

Outstanding questions and future trial designs

We await with interest the final results of several studies testing ASCT against a block of novel agent consolidation therapy. Both PFS and OS remain crucial end points, as the latter depends on the ability to salvage patients following relapse. Future trials should be randomised and stratified by genetic risk to provide clear guidance for treatment decisions. Trials should consider using new end points such as MRD negativity (by high throughput flow cytometry or genetic sequencing) and sustained CR rates in addition to PFS and OS. A number of key questions should be addressed in the debate over ASCT as standard practice following induction therapy:

1. Is there a more effective conditioning regimen than mel200?
2. Does a block of consolidation therapy between ASCT and maintenance therapy improve clinical outcomes versus maintenance alone?
3. Does the addition of a proteasome inhibitor to IMiD-based maintenance improve outcomes?
4. What role should new monoclonal antibodies and kinase inhibitors play to improve post-ASCT response?
5. Are MRD, sustained CR and PET CT-negativity valid surrogate endpoints for overall survival?

Conclusion

ASCT remains the standard of care for eligible newly diagnosed myeloma patients, despite improvements in induction chemotherapy with IMiDs and proteasome inhibitors. Early trials of ASCT achieved complete remission lasting >10 years in a small minority of patients (Barlogie *et al,* 2006 (III)), and with advances in induction protocols it is likely that with ASCT consolidation this proportion will continue to increase. The most promising strategies for improving conditioning therapy, on the basis of phase II studies, are the addition of proteasome inhibitors or topoisomerase inhibitors, but these require confirmation in randomised trials. Melflufen and radioconjugate drugs have yet to be assessed as part of conditioning, but hold theoretical promise. Tandem ASCT upfront may improve responses in patients not achieving CR after their first transplant, but it does not offer an overall survival benefit over delayed second ASCT at relapse for most patients. We await with interest long-term OS data to see if there is a benefit from lenalidomide maintenance. Treatment following ASCT, with both an IMiD and a proteasome inhibitor in combination has achieved impressive results in phase II studies, but has not yet been systematically tested in a phase III study. Several monoclonal antibodies and kinase inhibitors are promising in early clinical trials and, although these targeted drugs are unlikely to replace ASCT, they may find a role in post-ASCT consolidation. Experimental therapies to augment cellular immune responses to myeloma have demonstrated biological activity in patients refractory to other lines of treatment, and despite high potential toxicity they merit investigation in the post-ASCT period, when patients are lymphocyte-deplete and the burden of disease is low. These new therapeutic strategies could substantially increase the proportion of patients achieving long-term disease control after ASCT. At the same time clinical trials need to report more rapidly and hopefully, if MRD continues to robustly translate into survival in reported studies, then the adoption in clinical trials of MRD detection as a key end point will greatly facilitate this.

Study	Treatment regimen	Number of patients	Treatment-related mortality (%)	Overall response rate (%)	Median progression-free survival (months)	Median overall survival (months)
Alkylating agents						
GEM2000 Lahuerta *et al*. (2010) 2 sequential single arms	Oral busulfan 12mg/kg plus melphalan 140mg/m^2	225	8.4	91	41	79
	Melphalan 200mg/m^2	542	3.5	91	31	71
Blanes *et al*. (2013) Matched control study	Busulfan 9.6mg/kg plus melphalan 140mg/m^2	51	4	90	33	65.5
	Melphalan 200mg/m^2	102	2	91	24	63
Desikan *et al*. (2000) Three-way matched control study (conditioning for the second of two tandem ASCTs)	Cylophosphamide 120mg/kg plus melphalan 200mg/m^2	19	0		27	39
	TBI 1125cGy plus melphalan 140mg/m^2	24	8		15	25
	Melphalan 200mg/m^2	43	0		61	76
Fenk *et al*. (2005)* RCT	Idarubicin 42mg/m^2, melphalan 200mg/m^2 and cyclophosphamide 120mg/kg	26	20	85	20	46
	Melphalan 200mg/m^2	30	0	83	16	66
Knop *et al*. (2007)* RCT	Total marrow irradiation 9Gy, oral busulfan 12mg/kg and cyclophosphamide 120mg/kg	100			38	
	Melphalan 200mg/m^2 (x2 ASCTs)	98			35	
Donato *et al*. (2004) Uncontrolled phase I; mixed patient population	Cyclophosphamide 3g/m^2, melphalan 140mg/m^2 and topotecan 17.5mg/m^2	18	0	89		
Kazmi *et al*. (2011) Uncontrolled phase II; mixed patient population	Cyclophosphamide 3g/m^2, melphalan 140mg/m^2 and topotecan 17.5mg/m^2	60	0	85	18.5	4YS 66%
Comenzo *et al*. (2006) Uncontrolled phase I/II	Carmustine 300mg/m^2 plus melphalan 200mg/m^2	49	2	88	28	56
Chen *et al*. (2012)	Carmustine 15mg/kg plus melphalan 200mg/m^2	118	0	96	34	61
Mark *et al*. (2013)	Melphalan 200mg/m^2 plus bendamustine escalating up to 225mg/m^2	25	0	100		

Proteasome inhibitors						
Roussel *et al*. (2010) Uncontrolled; matched comparison	Bortezomib 4mg/m^2 plus melphalan 200mg/m^2	54	0	94		
	Melphalan 200mg/m^2	115		97		
Huang *et al*. (2012) 2 arms stratified by tolerance of bortezomib	Bortezomib 4mg/m^2 plus melphalan 200mg/m^2	10	0	100	20	
	Melphalan 200mg/m^2	11	0	100	22	
Miyamoto *et al*. (2013) Uncontrolled; matched comparison	Bortezomib 1.3 or 2.6mg/m^2 plus melphalan 200mg/m^2	17	0	100		
	Melphalan 200mg/m^2	17	0	100		
Nishihori *et al*. (2012) Uncontrolled study in primary refractory population	Tandem ASCTs with melphalan 200mg/m^2 plus bortezomib 0.7-1.3mg/m^2	25	0	84	15	40
Topoisomerase inhibitors						
Kazmi *et al*. (2011) Uncontrolled study (upfront and refractory)	Topotecan 17.5mg/m^2, melphalan 140mg/m^2 and cyclophosphamide 3g/m^2	60	0	85	18.5	
Ballestrero *et al*. (2002) Uncontrolled study	Mitoxantrone 60mg/m^2 plus melphalan 180mg/m^2	20	0	90	26	45
Beaven *et al*. (2011) Uncontrolled study (upfront and refractory)	Mitoxantrone 60mg/m^2 plus melphalan 180mg/m^2	35	3		22	68
Other agents						
Qazilbash *et al*. (2008)* Phase II RCT	Melphalan 200mg/m^2, ascorbic acid 1g, plus arsenic trioxide 1.75mg/kg	15	0	86	25	
	Melphalan 200mg/m^2, ascorbic acid 1g plus arsenic trioxide 1.05mg/kg	17	0	70		
	Melphalan 200mg/m^2 plus ascorbic acid 1g	16	0	87		

* RCT, randomised controlled trial. TBI, total body irradiation. 4YS, 4 year survival

Table I. Trials of ASCT conditioning regimens since mel200 was established as the standard of care

Study	Treatment regimen	Number of patients	Treatment-related mortality (%)	Response	Median progression-free survival (months)	Median overall survival (months)
TT1 Barlogie *et al*. (2006c)	3x VAD, cyclophosphamide 6g/m^2, EDAP, 2x ASCT with mel200 (or mel140 + 8.5Gy TBI), interferon maintenance	231	5	40%≥VGPR	31	68
TT3 Barlogie *et al*. (2007)	2xVTD-PACE, 2x ASCT with mel200, 2xVTD-PACE, VTD for 1 year then TD for 2 years	303	5	56%≥VGPR	65% 5YPFS	74% 5YS
IFM-94* Attal *et al*. (2003) RCT	3-4xVAD, 1x ASCT with mel140, 1x ASCT with mel140+8GyTBI, interferon maintenance	200	6	50%≥VGPR	36	58
	3-4xVAD, 1x ASCT with mel140+8GyTBI, interferon maintenance	199	4	42%≥VGPR	29	48
MAG95* Fermand *et al*. (2005) RCT	High dose steroid and cyclophosphamide, 1x ASCT with Mel140, 1x ASCT with high dose chemotherapy + TBI 12Gy	114	7	38%≥VGPR	34	75
	High dose steroid and cyclophosphamide, 3-4x VAD, 1x ASCT with high dose chemotherapy + TBI 12Gy	113	12	37%≥VGPR	31	57
Bologna 96* Cavo *et al*. (2007) RCT	4x VAD, cyclophosphamide 7g/m^2, 1x ASCT with mel200, 1x ASCT mel120 + busulfan 12mg/kg, interferon maintenance	158	6	33%≥nCR	42	71
	4x VAD, cyclophosphamide 7g/m^2, 1x ASCT mel200, interferon maintenance	163	6	47%≥nCR	24	65
GMMG-HD2* Mai *et al*. (2016) RCT	Up to 6x VAD or VID, cyclophosphamide 4g/m^2, 2x ASCT with mel200, interferon maintenance	181	5	19% CR	29	75
	Up to 6x VAD or VID, cyclophosphamide 4g/m^2, 1x ASCT with mel200, interferon maintenance	177	2	16% CR	25	73
HOVON 24* Sonneveld *et al*. (2007) RCT	3-4x VAD, cyclophosphamide 4g/m^2, 2x mel70 (*without* ASCT), ASCT with cyclophosphamide 120mg/kg + TBI 9Gy, interferon maintenance	155	10	32% CR	27	50
	3-4x VAD, cyclophosphamide 4g/m^2, 2x mel70 (*without* ASCT), interferon maintenance	148	4	13% CR	24	55

VAD, vincristine/doxorubicin/dexamethasone. EDAP, etoposide/dexamethasone/cytarabine/cisplatin. VTD-PACE, bortezomib/thalidomide/dexamethasone with cisplatin/doxorubicin/cyclophosphamide/etoposide. TD, thalidomide/dexamethasone. VID, vincristine, idarubicin, dexamethasone. nCR, near-complete response (paraprotein only detectable with immunofixation)

Table II. Trials of tandem ASCT following induction

Study	Treatment regimen	Number of patients	Proportion with adverse events of grade 3/4 (%)	Proportion attaining ≥VGPR (%)	Median progression-free survival (months)	Median overall survival (months)
Rabin *et al*. (2012) Phase II after ASCT	3-6 cycles of CTD consolidation	45	40	72	26 (from consolidation)	NR
	No consolidation	40		51	21	71 months
Mellqvist *et al*. (2013)* RCT after ASCT	Bortezomib 1.3mg/m^2 (20 doses)	187	11	71	27 (from consolidation)	79% 3YS
	No consolidation	183	2	57	20	82% 3YS
Cavo *et al*. (2010)* RCT	3x VTD induction, tandem ASCT then 2x VTD consolidation	236	56	89	68% 3YS (from induction)	86% 3YS
	3x TD induction, tandem ASCT then 2x TD consolidation	238	33	74	56% 3YS	84% 3YS
Ladetto *et al*. (2010) Phase II Recruiting ≥VGPR after ASCT	4xVTD consolidation	39	54	100% (at recruitment)	60 (frominduction)	89% 3YS
Leleu *et al*. (2013) Retrospective cohort study	3x VTD, ASCT, then 2x VTD consolidation	121		83	62% 4YS	91% 4YS (estimated)
	3x VTD, ASCT, no consolidation	96		64	29% 4YS	84% 4YS (estimated)
Attal *et al*. (2012) (Pre-maintenance analysis)	After ASCT, 2x lenalidomide consolidation (thereafter randomised to maintenance or nil)	577		69% (after consolidation)	32% 4YS (from consolidation)	74% 4YS
Roussel *et al*. (2014) Phase II	3x RVD induction, ASCT with mel200, then 2x RVD consolidation, then 1 year lenalidomide maintenance	31	74	84	77% 3YS (from induction)	100% 3YS

CTD, cylophosphamide/thalidomide/dexamethasone. VTD, bortezomib/thalidomide/dexamethasone. TD, thalidomide/dexamethasone. RVD, lenalidomide/bortezomib/dexamethasone.

3YS/4YS, 3/4 year survival respectively.

Table III. Consolidation trials post ASCT in myeloma

Study	Treatment regimen	Number of patients	Adverse events of grade 3/4 (% of patients, or absolute number)	Proportion attaining ≥VGPR (%)	Median progression-free survival (months)	Median overall survival (months)
S9321* Barlogie *et al*.(2006) RCT	After ASCT or conventional therapy, interferon maintenance	121			23	69
	After ASCT or conventional therapy, no maintenance	121			18	62
Attal *et al*.(2006)* RCT	After ASCT, pamidronate 90mg plus thalidomide 400mg maintenance	201	177 events	67	51% 3YS	87% 4YS
	After ASCT, pamidronate maintenance	196	65 events	57	39% 3YS	74% 4YS
	After ASCT, no maintenance	200	40 events	55	38% 3YS	77% 4YS
Stewart *et al*.(2013)* RCT	After ASCT, thalidomide 200mg and prednisolone maintenance	165	140 events		28	68% 4YS
	After ASCT, no maintenance	163	39 events		17	60% 4YS
Spencer *et al*.(2009)* RCT following ASCT	Thalidomide 100-200mg for 1 year and indefinite prednisolone maintenance	114	51 events	65	31 (from maintenance)	86% 3YS (from maintenance)
	Indefinite prednisolone maintenance	129	32 events	44	18	75% 3YS
Maiolino *et al*.(2012)* RCT	After ASCT, dexamethasone plus thalidomide 200mg maintenance for 1 year	56	20 events	50	36	85% 2YS
	After ASCT, dexamethasone maintenance for 1 year	52	4 events	48	19	70% 2YS
Sonneveld *et al*.(2012)* RCT	PAD induction, ASCT, bortezomib 1.3mg/m^2 maintenance for 2 years	413	48%	76	35	61% 5YS
	VAD induction, ASCT, thalidomide 50mg maintenance for 2 years	414	46%	56	28	55% 5YS
Attal *et al*.(2012)* RCT	After ASCT, 2 cycles lenalidomide consolidation (25mg), then lenalidomide 10-15mg od until relapse	307	74%	84	41	73% 4YS
	After ASCT, 2 cycles lenalidomide consolidation (25mg), then no maintenance	307	43%	76	23	75% 4YS

McCarthy *et al*.(2012)* RCT	After ASCT, Lenalidomide 10-15mg maintenance	231	60%		46	88% 3YS
	After ASCT, Placebo	229	30%		27	80% 3YS
Palumbo *et al*.(2014)* 2x2 RCT	After ASCT or MPR, lenalidomide 10mg maintenance	126	53 events		42	88% 3YS
	After ASCT or MPR, no maintenance	125	7 events		22	80% 3YS
Gay *et al*. (2015)* 2x2 RCT	After ASCT or CRD, lenalidomide 10mg plus prednisolone maintenance	194	20%		38 (from maintenance)	83% 3YS
	After ASCT or CRD, lenalidomide 10mg maintenance	198	20%		29	88% 3YS
Nair *et al*.(2010) Comparison between TT3 and TT6 cohorts	After 2x ASCT, 3 years of VRD	177		61% CR	80% 2YS	85% 2YS
	After 2x ASCT, 1 year of bortezomib and 3 years of thalidomide plus dexamethasone	303		59% CR	83% 2YS	87% 2YS
Nooka *et al*.(2014) Phase II study in high risk disease	After ASCT, 3 years of RVD	45		96	32	93% 3YS

PAD, bortezomib, doxorubicin and dexamethasone; MPR, melphalan, prednisolone and lenalidomide; CRD, cyclophosphamide/lenalidomide/dexamethasone.

Table IV. Maintenance therapy trials after ASCT

REFERENCES

Abidi, M.H., Agarwal, R., Tageja, N., Ayash, L., Deol, A., Al-Kadhimi, Z., Abrams, J., Cronin, S., Ventimiglia, M., Lum, L., Ratanatharathorn, V., Zonder, J., Uberti, J. (2013) A Phase I Dose-Escalation Trial of High-Dose Melphalan with Palifermin for Cytoprotection Followed by Autologous Stem Cell Transplantation for Patients with Multiple Myeloma with Normal Renal Function. *Biology of Blood and Marrow Transplantation*, **19**, 56-61.

Alexanian, R., Weber, D., Dimopoulos, M., Delasalle, K. & Smith, T.L. (2000) Randomized trial of alpha-interferon or dexamethasone as maintenance treatment for multiple myeloma. *American Journal of Hematology,* **65**, 204-209.

Attal, M., Harousseau, J.-L., Stoppa, A.-M., Sotto, J.-J., Fuzibet, J.-G., Rossi, J.-F., Casassus, P., Maisonneuve, H., Facon, T., Ifrah, N., Payen, C., Bataille, R. (1996) A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *New England Journal of Medicine*, **335,** 91-97.

Attal, M., Harousseau, J.L., Facon, T., Guilhot, F., Doyen, C., Fuzibet, J.G., Monconduit, M., Hulin, C., Caillot, D., Bouabdallah, R., Voillat, L., Sotto, J.J., Grosbois, B., Bataille, R. & InterGroupe Francophone du Myelome. (2003) Single versus double autologous stem-cell transplantation for multiple myeloma. *The New England Journal of Medicine,* **349**, 2495-2502.

Attal, M., Harousseau, J.L., Leyvraz, S., Doyen, C., Hulin, C., Benboubker, L., Yakoub Agha, I., Bourhis, J.H., Garderet, L., Pegourie, B., Dumontet, C., Renaud, M., Voillat, L., Berthou, C., Marit, G., Monconduit, M., Caillot, D., Grobois, B., Avet-Loiseau, H., Moreau, P., Facon, T. & Inter-Groupe Francophone du Myelome (IFM). (2006) Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood,* **108**, 3289-3294.

Attal, M., Lauwers-Cances, V., Marit, G., Caillot, D., Moreau, P., Facon, T., Stoppa, A.M., Hulin, C., Benboubker, L., Garderet, L., Decaux, O., Leyvraz, S., Vekemans, M.C., Voillat, L., Michallet, M., Pegourie, B., Dumontet, C., Roussel, M., Leleu, X., Mathiot, C., Payen, C., Avet-Loiseau, H., Harousseau, J.L. & IFM Investigators. (2012) Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *The New England Journal of Medicine,* **366**, 1782-1791.

Attal, M., Lauwers-Cances, V., Hulin, C., Facon, T., Caillot, D., Escoffre, M., Arnulf, B., MACRO, M., Belhadj, K., Garderet, L., Roussel, M., Mathiot, C., Avet-Loiseau, H., Munshi, N.C., Richardson, P.G., Anderson, K.C., Harousseau, j.L. & Moreau, P. (2015) Autologous transplantation for multiple myeloma in the era of new drugs: A phase III study of the intergroupe francophone du myelome (IFM/DFCI 2009 trial). *Blood (ASH Annual Meeting Abstracts),* **126**, 391.

Badros, A.Z., Kocoglu, M.H., Ma, N., Rapoport, A.P., Lederer, E., Philip, S., Lesho, P., Dell, C., Hardy, N.M., Yared, J., Goloubeva, O. & Singh, Z. (2015) A phase II study of anti PD-1 antibody pembrolizumab, pomalidomide and dexamethasone in patients with Relapsed/Refractory multiple myeloma (RRMM). *Blood (ASH Annual Meeting Abstracts),* **126**, 506.

Baldini, L., Radaelli, F., Chiorboli, O., Fumagalli, S., Cro, L., Segala, M., Cesana, B.M., Polli, E.E. & Maiolo, A.T. (1991) No correlation between response and survival in patients with multiple myeloma treated with vincristine, melphalan, cyclophosphamide, and prednisone. *Cancer,* **68**, 62-67.

Ballestrero, A., Ferrando, F., Miglino, M., Clavio, M., Gonella, R., Garuti, A., Grasso, R., Ghio, R., Balleari, E., Gobbi, M. & Patrone, F. (2002) Three-step high-dose sequential chemotherapy in patients with newly diagnosed multiple myeloma. *European Journal of Haematology,* **68**, 101-106.

Barlogie, B., Kyle, R.A., Anderson, K.C., Greipp, P.R., Lazarus, H.M., Hurd, D.D., McCoy, J., Dakhil, S.R., Lanier, K.S., Chapman, R.A., Cromer, J.N., Salmon, S.E., Durie, B., Crowley, J.C. (2006a) Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: Final results of phase III US intergroup trial S9321. *Journal of Clinical Oncology*, **24,** 929-936.

Barlogie, B., Tricot, G., Anaissie, E., Shaughnessy, J., Rasmussen, E., Van Rhee, F., Fassas, A., Zangari, M., Hollmig, K., Pineda-Roman, M., Lee, C., Talamo, G., Thertulien, R., Kiwan, E., Krishna, S., Fox, M., Crowley, J. (2006b) Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *New England Journal of Medicine*, **354,** 1021-1030.

Barlogie, B., Tricot, G.J., van Rhee, F., Angtuaco, E., Walker, R., Epstein, J., Shaughnessy, J.D., Jagannath, S., Bolejack, V., Gurley, J., Hoering, A., Vesole, D., Desikan, R., Siegel, D., Mehta, J., Singhal, S., Munshi, N.C., Dhodapkar, M., Jenkins, B., Attal, M., Harousseau, J.L. & Crowley, J. (2006c) Long-term outcome results of the first tandem autotransplant trial for multiple myeloma. *British Journal of Haematology,* **135**, 158-164.

Barlogie, B., Anaissie, E., van Rhee, F., Haessler, J., Hollmig, K., Pineda-Roman, M., Cottler-Fox, M., Mohiuddin, A., Alsayed, Y., Tricot, G., Bolejack, V., Zangari, M., Epstein, J., Petty, N., Steward, D., Jenkins, B., Gurley, J., Sullivan, E., Crowley, J. & Shaughnessy, J.D.,Jr. (2007) Incorporating bortezomib into upfront treatment for multiple myeloma: Early results of total therapy 3. *British Journal of Haematology,* **138**, 176-185.

Barlogie, B., Anaissie, E., Haessler, J., van Rhee, F., Pineda-Roman, M., Hollmig, K., Alsayed, Y., Epstein, J., Shaughnessy, J.D.,Jr & Crowley, J. (2008) Complete remission sustained 3 years from treatment initiation is a powerful surrogate for extended survival in multiple myeloma. *Cancer,* **113**, 355-359.

Bartel, T.B., Haessler, J., Brown, T.L., Shaughnessy, J.D.,Jr, van Rhee, F., Anaissie, E., Alpe, T., Angtuaco, E., Walker, R., Epstein, J., Crowley, J. & Barlogie, B. (2009) F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. *Blood,* **114**, 2068-2076.

Beaven, A.W., Moore, D.T., Sharf, A., Serody, J.S., Shea, T.C. & Gabriel, D.A. (2011) Infusional mitoxantrone plus bolus melphalan as a stem cell transplant conditioning regimen for multiple myeloma. *Cancer Investigation,* **29**, 214-219.

Berdeja, J.G., Hernandez-Ilizaliturri, F., Chanan-Khan, A., Patel, M., Kelly, K.R., Running, K.L., Murphy, M., Guild, R., Carrigan, C., Ladd, S., Wolf, B.B., O'Leary, J.J. & Ailawadhi, S. (2012) Phase I study of lorvotuzumab mertansine (LM, IMGN901) in combination with lenalidomide (len) and dexamethasone (dex) in patients with CD56-positive relapsed or Relapsed/Refractory multiple myeloma (MM). *Blood (ASH Annual Meeting Abstracts),* **120**, 728.

Berenson, J.R., Crowley, J.J., Grogan, T.M., Zangmeister, J., Briggs, A.D., Mills, G.M., Barlogie, B. & Salmon, S.E. (2002) Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. *Blood,* **99**, 3163-3168.

Bladé, J., Rosiñol, L., Sureda, A., Ribera, J.M., Díaz-Mediavilla, J., García-Laraña, J., Mateos, M.V., Palomera, L., Fernández-Calvo, J., Martí, J.M., Giraldo, P., Carbonell, F., Callís, M., Trujillo, J., Gardella, S., Moro, M.J., Barez, A., Soler, A., Font, L., Fontanillas, M., San Miguel, J. (2005) High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: Long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. *Blood*, **106,** 3755-3759.

Blanes, M., Lahuerta, J.J., González, J.D., Ribas, P., Solano, C., Alegre, A., Bladé, J., San Miguel, J.F., Sanz, M.A., De La Rubia, J. (2013) Intravenous Busulfan and Melphalan as a Conditioning Regimen for Autologous Stem Cell Transplantation in Patients with Newly Diagnosed Multiple Myeloma: A Matched Comparison to a Melphalan-Only Approach. *Biology of Blood and Marrow Transplantation*, **19**, 69-74.

Cancer Research UK (2014) Myeloma survival statistics. WWW document. URL: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma [accessed 23.4.16].

Cavo, M., Tosi, P., Zamagni, E., Cellini, C., Tacchetti, P., Patriarca, F., Di Raimondo, F., Volpe, E., Ronconi, S., Cangini, D., Narni, F., Carubelli, A., Masini, L., Catalano, L., Fiacchini, M., de Vivo, A., Gozzetti, A., Lazzaro, A., Tura, S. & Baccarani, M. (2007) Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. *Journal of Clinical Oncology,* **25**, 2434-2441.

Cavo, M., Tacchetti, P., Patriarca, F., Petrucci, M.T., Pantani, L., Galli, M., Di Raimondo, F., Crippa, C., Zamagni, E., Palumbo, A., Offidani, M., Corradini, P., Narni, F., Spadano, A., Pescosta, N., Deliliers, G.L., Ledda, A., Cellini, C., Caravita, T., Tosi, P., Baccarani, M. (2010) Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: A randomised phase 3 study. *The Lancet*, **376**, 2075-2085.

Chauhan, D., Ray, A., Viktorsson, K., Spira, J., Paba-Prada, C., Munshi, N., Richardson, P., Lewensohn, R. & Anderson, K.C. (2013) In vitro and in vivo antitumor activity of a novel alkylating agent, melphalan-flufenamide, against multiple myeloma cells. *Clinical Cancer Research,* **19**, 3019-3031.

Chen, A.I., Negrin, R.S., McMillan, A., Shizuru, J.A., Johnston, L.J., Lowsky, R., Miklos, D.B., Arai, S., Weng, W.K., Laport, G.G. & Stockerl-Goldstein, K. (2012) Tandem chemo-mobilization followed by high-dose melphalan and carmustine with single autologous hematopoietic cell transplantation for multiple myeloma. *Bone Marrow Transplantation,* **47**, 516-521.

Chérel, M., Gouard, S., Gaschet, J., Sai-Maurel, C., Bruchertseifer, F., Morgenstern, A., Bourgeois, M., Gestin, J.F., Bodere, F.K., Barbet, J., Moreau, P. & Davodeau, F. (2013) ^{213}Bi radioimmunotherapy with an anti-mCD138 monoclonal antibody in a murine model of multiple myeloma. *Journal of Nuclear Medicine,* **54**, 1597-1604.

Child, J.A., Morgan, G.J., Davies, F.E., Owen, R.G., Bell, S.E., Hawkins, K., Brown, J., Drayson, M.T., Selby, P.J. (2003) High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *New England Journal of Medicine*, **348**, 1875-1883.

Comenzo, R.L., Hassoun, H., Kewalramani, T., Klimek, V., Dhodapkar, M., Reich, L., Teruya-Feldstein, J., Fleisher, M., Filippa, D., Nimer, S.D. (2006) Results of a phase I/II trial adding carmustine (300mg/m^2) to melphalan (200mg/m^2) in multiple myeloma patients undergoing autologous stem cell transplantation. *Leukemia*, **20**, 345-349.

Desikan, K.R., Tricot, G., Dhodapkar, M., Fassas, A., Siegel, D., Vesole, D.H., Jagannath, S., Singhal, S., Mehta, J., Spoon, D., Anaissie, E., Barlogie, B., Munshi, N. (2000) Melphalan plus total body irradiation (MEL-TBI) or cyclophosphamide (MEL-CY) as a conditioning regimen with second autotransplant in responding patients with myeloma is inferior compared to historical controls receiving tandem transplants with melphalan alone. *Bone Marrow Transplantation*, **25**, 483-487.

Dimopoulos, M., Siegel, D.S., Lonial, S., Qi, J., Hajek, R., Facon, T., Rosinol, L., Williams, C., Blacklock, H., Goldschmidt, H., Hungria, V., Spencer, A., Palumbo, A., Graef, T., Eid, J.E., Houp, J., Sun, L., Vuocolo, S. & Anderson, K.C. (2013) Vorinostat or placebo in combination with bortezomib in patients with multiple myeloma (VANTAGE 088): A multicentre, randomised, double-blind study. *The Lancet.Oncology,* **14**, 1129-1140.

Dispenzieri, A., Wiseman, G.A., Lacy, M.Q., Hayman, S.R., Kumar, S.K., Buadi, F., Dingli, D., Laumann, K.M., Allred, J., Geyer, S.M., Litzow, M.R., Gastineau, D.A., Inwards, D.J., Micallef, I.N., Ansell, S.M., Porrata, L., Elliott, M.A., Johnston, P.B., Hogan, W.J. & Gertz, M.A. (2010) A phase II study of ^{153}Sm-EDTMP and high-dose melphalan as a peripheral blood stem cell conditioning regimen in patients with multiple myeloma. *American Journal of Hematology,* **85**, 409-413.

Dispenzieri, A., Gertz, M.A., Lacy, M.Q., Laumann, K., LaPlant, B.R., Kumar, S., Buadi, F.K., Hayman, S.R., Dingli, D., Hogan, W.J., Ansell, S.M., Gastineau, D.A.,

Inwards, D.J., Micallef, I.N., Porrata, L.F., Johnston, P.B., Litzow, M.R. & Witzig, T.E. (2011) A phase I trial of zevalin radioimmunotherapy with high-dose melphalan (HDM) and autologous stem cell transplant (ASCT) for multiple myeloma (MM). *Blood (ASH Annual Meeting Abstracts),* **118**, 3095.

Donato, M.L., Aleman, A., Champlin, R.E., Weber, D., Alexanian, R., Ippoliti, C.M., de Lima, M., Anagnostopoulos, A., Giralt, S. (2004) High-dose topotecan, melphalan and cyclophosphamide (TMC) with stem cell support: A new regimen for the treatment of multiple myeloma. *Leukemia and Lymphoma*, **45**, 755-759.

Drayson, M.T., Chapman, C.E., Dunn, J.A., Olujohungbe, A.B. & Maclennan, I.C. (1998) MRC trial of alpha2b-interferon maintenance therapy in first plateau phase of multiple myeloma. MRC working party on leukaemia in adults. *British Journal of Haematology,* **101**, 195-202.

Durie, B.G., Jacobson, J., Barlogie, B. & Crowley, J. (2004) Magnitude of response with myeloma frontline therapy does not predict outcome: Importance of time to progression in southwest oncology group chemotherapy trials. *Journal of Clinical Oncology,* **22**, 1857-1863.

Fenk, R., Schneider, P., Kropff, M., Huenerlituerkoglu, A.N., Steidl, U., Aul, C., Hildebrandt, B., Haas, R., Heyll, A., Kobbe, G. (2005) High-dose idarubicin, cyclophosphamide and melphalan as conditioning for autologous stem cell transplantation increases treatment-related mortality in patients with multiple myeloma: Results of a randomised study. *British Journal of Haematology*, **130**, 588-594.

Fermand, J.-P., Katsahian, S., Divine, M., Leblond, V., Dreyfus, F., Macro, M., Arnulf, B., Royer, B., Mariette, X., Pertuiset, E., Belanger, C., Janvier, M., Chevret, S., Brouet, J.C., Ravaud, P. (2005a) High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: Long-term results of a randomized control trial from the group myelome-autogreffe. *Journal of Clinical Oncology*, **23,** 9227-9233.

Fermand, J.-P. on behalf of the Myélome Autogreffe Group (2005b) High does therapy supported with autologous blood stem cell transplantation in multiple myeloma: long term follow-up of the prospective studies of the MAG group [Xth International Myeloma Foundation Workshop, Sydney 2005]. WWW document. http://myeloma.org/pdfs/Sydney2005˙Fermand˙P8.pdf [accessed 20.6.2015].

Forsberg, P., Guarneri, D., Rossi, A., Pearse, R., Perry, A., Pekle, K., Greenberg, J., Shore, T., Gergis, U., Mayer, S., Van Besien, K., Jayabalan, D., Coleman, M., Ely, S., Niesvizky, R. & Mark, T.M. (2015) A phase I study of the addition of high-dose lenalidomide to melphalan conditioning for autologous stem-cell transplant in relapsed or refractory multiple myeloma. *Clinical Lymphoma Myeloma and Leukemia,* **15**, e291-e292.

Garfall, A.L., Maus, M.V., Hwang, W.T., Lacey, S.F., Mahnke, Y.D., Melenhorst, J.J., Zheng, Z., Vogl, D.T., Cohen, A.D., Weiss, B.M., Dengel, K., Kerr, N.D., Bagg, A., Levine, B.L., June, C.H. & Stadtmauer, E.A. (2015) Chimeric antigen receptor T cells against CD19 for multiple myeloma. *The New England Journal of Medicine,* **373**, 1040-1047.

Garg, T.K., Szmania, S.M., Khan, J.A., Hoering, A., Malbrough, P.A., Moreno-Bost, A., Greenway, A.D., Lingo, J.D., Li, X., Yaccoby, S., Suva, L.J., Storrie, B., Tricot, G., Campana, D., Shaughnessy, J.D.Jr, Nair, B.P., Bellamy, W.T., Epstein, J., Barlogie, B. & van Rhee, F. (2012) Highly activated and expanded natural killer cells for multiple myeloma immunotherapy. *Haematologica,* **97**, 1348-1356.

Gay, F., Magarotto, V., Petrucci, M.T., Di Raimondo,F., Pour, L., Caravita, T., Scudla, V., Cafro, A.M., Liberati, A.M., Spada, S., Vladimir, M., Pescosta, N., Ria, R., Offidani, M., Bringhen, S., Bernardini, A., Patriarca, F., Corradini, P., Foà, R., Cascavilla, N., Catalano, L., Spencer, A., Hajek, R., Boccadoro, M. & Palumbo, A. (2015) Autologous Transplantation Versus Cyclophosphamide-Lenalidomide-Prednisone Followed By Lenalidomide-Prednisone Versus Lenalidomide Maintenance in Multiple Myeloma: Long-Term Results of a Phase III Trial. *Blood (ASH Annual Meeting Abstracts)*, **126**, 392.

Giralt, S., Bensinger, W., Goodman, M., Podoloff, D., Eary, J., Wendt, R., Alexanian, R., Weber, D., Maloney, D., Holmberg, L., Rajandran, J., Breitz, H., Ghalie, R. & Champlin, R. (2003) ^{166}Ho-DOTMP plus melphalan followed by peripheral blood stem cell transplantation in patients with multiple myeloma: Results of two phase 1/2 trials. *Blood,* **102**, 2684-2691.

Goel, A., Dispenzieri, A., Geyer, S.M., Greiner, S., Peng, K.W. & Russell, S.J. (2006) Synergistic activity of the proteasome inhibitor PS-341 with non-myeloablative 153-Sm-EDTMP skeletally targeted radiotherapy in an orthotopic model of multiple myeloma. *Blood,* **107**, 4063-4070.

Govindarajan, R., Jagannath, S., Flick, J.T., Vesole, D.H., Sawyer, J., Barlogie, B. & Tricot, G. (1996) Preceding standard therapy is the likely cause of MDS after autotransplants for multiple myeloma. *British Journal of Haematology,* **95**, 349-353.

Green, D.J., Jones, J.C., Hylarides, M.D., Hamlin, D.K., Wilbur, D.S., Lin, Y., Kenoyer, A.L., Frayo, S.L., Bensinger, W.I., Gopal, A.K., Orozco, J.J., Gooley, T.A., Wood, B.L., Pagel, J.M. & Press, O.W. (2013) Anti-CD38 pretargeted radioimmunotherapy eradicates multiple myeloma xenografts in a murine model. *Blood (ASH Annual Meeting Abstracts),* **122**, 882.

Harousseau, J.L., Avet-Loiseau, H., Attal, M., Charbonnel, C., Garban, F., Hulin, C., Michallet, M., Facon, T., Garderet, L., Marit, G., Ketterer, N., Lamy, T., Voillat, L., Guilhot, F., Doyen, C., Mathiot, C. & Moreau, P. (2009) Achievement of at least very good partial response is a simple and robust prognostic factor in patients with multiple myeloma treated with high-dose therapy: Long-term analysis of the IFM 99-02 and 99-04 trials. *Journal of Clinical Oncology,* **27**, 5720-5726.

Harousseau, J.-L., Attal, M., Avet-Loiseau, H., Marit, G., Caillot, D., Mohty, M., Lenain, P., Hulin, C., Facon, T., Casassus, P., Michallet, M., Maisonneuve, H., Benboubker, L., Maloisel, F., Petillon, M.-O., Webb, I., Mathiot, C., Moreau, P. (2010) Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: Results of the IFM 2005-01 phase III trial. *Journal of Clinical Oncology*, **28,** 4621-4629.

Huang, W., Li, J., Li, H., Kang, W., Bo, J., Zhao, Y., Gao, C., Zhou, D. & Yu, L. (2012) High-dose melphalan with bortezomib as conditioning regimen for autologous stem cell transplant in patients with newly diagnosed multiple myeloma who exhibited at least very good partial response to bortezomib-based induction therapy. *Leukemia & Lymphoma*, **53**, 2507-2510.

Jakubowiak, A.J., Benson, D.M., Bensinger, W., Siegel, D.S., Zimmerman, T.M., Mohrbacher, A., Richardson, P.G., Afar, D.E., Singhal, A.K. & Anderson, K.C. (2012) Phase I trial of anti-CS1 monoclonal antibody elotuzumab in combination with bortezomib in the treatment of relapsed/refractory multiple myeloma. *Journal of Clinical Oncology,* **30**, 1960-1965.

Kazmi, S.M., Saliba, R.M., Donato, M., Wang, M., Hosing, C., Qureshi, S., Anderlini, P., Popat, U., Champlin, R.E., Giralt, S.A. & Qazilbash, M.H. (2011) Phase II trial of high-dose topotecan, melphalan and CY with autologous stem cell support for multiple myeloma. *Bone Marrow Transplantation,* **46**, 510-515.

Kelly, K.R., Chanan-Khan, A., Heffner, L.T., Somlo, G., Siegel, D.S., Zimmerman, T., Karnad, A., Munshi, N.C., Jagannath, S., Greenberg, A.L., Lonial, S., Roy, V., Ailawadhi, S., Barmaki-Rad, F., Chavan, S., Patel, P., Wartenberg-Demand, A., Haeder, T. & Anderson, K.C. (2014) Indatuximab ravtansine (BT062) in combination with lenalidomide and low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma: Clinical activity in patients already exposed to lenalidomide and bortezomib. *Blood (ASH Annual Meeting Abstracts),* **124**, 4736.

Knop, S., Bauer, K., Hebart, H., Wandt, H., Trumper, L., Liebisch, P., Maschmeyer, G., Peest, D., Wolf, H.H., Kroger, N., Straka, C., Pfreundschuh, M., Coser, P., Meisner, C., Kanz, L. & Einsele, H. (2007) A randomized comparison of total-marrow irradiation, busulfan and cyclophosphamide with tandem high-dose melphalan in patients with multiple myeloma. *Blood (ASH Annual Meeting Abstracts)*, **110**, 728.

Kochenderfer, J.M., Dudley, M.E., Kassim, S.H., Carpenter, R.O., Yang, J.C., Phan, G.Q., Hughes, M.S., Sherry, R.M., Feldman, S., Spaner, D., Nathan, D.N., Morton, K.E., Toomey, M.A. & Rosenberg, S.A. (2013) Effective treatment of chemotherapy-refractory diffuse large B-cell lymphoma with autologous T cells genetically-engineered to express an anti-CD19 chimeric antigen receptor. *Blood (ASH Annual Meeting Abstracts),* **122**, 168-168.

Kumar, A., Kharfan-Dabaja, M.A., Glasmacher, A. & Djulbegovic, B. (2009) Tandem versus single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis. *Journal of the National Cancer Institute*, **101**, 100-106.

Lacy, M.Q., Mandrekar, S., Dispenzieri, A., Hayman, S., Kumar, S., Buadi, F., Dingli, D., Litzow, M., Wettstein, P., Padley, D., Kabat, B., Gastineau, D., Rajkumar, S.V. & Gertz, M.A. (2009) Idiotype-pulsed antigen-presenting cells following autologous transplantation for multiple myeloma may be associated with prolonged survival. *American Journal of Hematology,* **84**, 799-802.

Ladetto, M., Pagliano, G., Ferrero, S., Cavallo, F., Drandi, D., Santo, L., Crippa, C., De Rosa, L., Pregno, P., Grasso, M., Liberati, A.M., Caravita, T., Pisani, F., Guglielmelli, T., Callea, V., Musto, P., Cangialosi, C., Passera, R., Boccadoro, M. & Palumbo, A. (2010) Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma. *Journal of Clinical Oncology,* **28**, 2077-2084.

Lahuerta, J.J., Mateos, M.V., Martinez-Lopez, J., Rosinol, L., Sureda, A., de la Rubia, J., Garcia-Larana, J., Martinez-Martinez, R., Hernandez-Garcia, M.T., Carrera, D., Besalduch, J., de Arriba, F., Ribera, J.M., Escoda, L., Hernandez-Ruiz, B., Garcia-Frade, J., Rivas-Gonzalez, C., Alegre, A., Bladé, J. & San Miguel, J.F. (2008) Influence of pre- and post-transplantation responses on outcome of patients with multiple myeloma: Sequential improvement of response and achievement of complete response are associated with longer survival. *Journal of Clinical Oncology,* **26**, 5775-5782.

Lahuerta, J.J., Mateos, M.V., Martínez-López, J., Grande, C., de la Rubia, J., Rosiñol, L., Sureda, A., García-Laraña, J., Díaz-Mediavilla, J., Hernández-García, M.T., Carrera, D., Besalduch, J., de Arriba, F., Oriol, A., Escoda, L., García-Frade, J., Concepción Rivas-González Adrían, A., Bladé, J., San Miguel, J.F. (2010) Busulfan 12 mg/kg plus melphalan 140 mg/m^2 versus melphalan 200 mg/m^2 as conditioning regimens for autologous transplantation in newly diagnosed multiple myeloma patients included in the PETHEMA/GEM2000 study. *Haematologica*, **95**, 1913-1920.

Lebovic, D., Kaminski, M.S., Anderson, T.B., Detweiler-Short, K., Griffith, K.A., Jobkar, T.L., Kandarpa, M. & Jakubowiak, A. (2012) A phase II study of consolidation treatment with iodione-131 tositumomab (bexxar™) in multiple myeloma (MM). *Blood (ASH Annual Meeting Abstracts),* **120**, 1854.

Leleu, X., Fouquet, G., Hebraud, B., Roussel, M., Caillot, D., Chretien, M.L., Arnulf, B., Szalat, R., Garderet, L., Benajiba, L., Pegourie, B., Regny, C., Royer, B., Caulier, A., Stoppa, A.M., Garciaz, S., Touzeau, C., Chaleteix, C., Fermand, J.P., Loiseau, H.A., Facon, T., Attal, M., Moreau, P. & Intergroupe Francophone du Myelome (IFM). (2013) Consolidation with VTd significantly improves the complete remission rate and time to progression following VTd induction and single autologous stem cell transplantation in multiple myeloma. *Leukemia,* **27**, 2242-2244.

Lokhorst, H.M., Schmidt-Wolf, I., Van Der Holt, P.S., Martin, H., Barge, R., Bertsch, U., Schlenzka, J., Bos, G.M.J., Croockewit, S., Zweegman, S., Breitkreuz, I., Joosten, P., Scheid, C., Van Marwijk-Kooy, M., Salwender, H.-J., Van Oers, M.H.J., Schaafsma, R., Naumann, R., Sinnige, H., Blau, I., Verhoef, G., De Weerdt, O., Wijermans, P., Wittebol, S., Duersen, U., Vellenga, E., Goldschmidt, H. (2008) Thalidomide in induction treatment increases the very good partial

response rate before and after high-dose therapy in previously untreated multiple myeloma. *Haematologica*, **93,** 124-127.

Lokhorst, H.M., Plesner, T., Laubach, J.P., Nahi, H., Gimsing, P., Hansson, M., Minnema, M.C., Lassen, U., Krejcik, J., Palumbo, A., van de Donk, N.W., Ahmadi, T., Khan, I., Uhlar, C.M., Wang, J., Sasser, A.K., Losic, N., Lisby, S., Basse, L., Brun, N. & Richardson, P.G. (2015) Targeting CD38 with daratumumab monotherapy in multiple myeloma. *The New England Journal of Medicine,* **373**, 1207-1219.

Lonial, S., Kaufman, J., Tighiouart, M., Nooka, A., Langston, A.A., Heffner, L.T., Torre, C., McMillan, S., Renfroe, H., Harvey, R.D., Lechowicz, M.J., Khoury, H.J., Flowers, C.R. & Waller, E.K. (2010) A phase I/II trial combining high-dose melphalan and autologous transplant with bortezomib for multiple myeloma: A dose- and schedule-finding study. *Clinical Cancer Research,* **16**, 5079-5086.

Lonial, S., Dimopoulos, M., Palumbo, A., White, D., Grosicki, S., Spicka, I., Walter-Croneck, A., Moreau, P., Mateos, M.V., Magen, H., Belch, A., Reece, D., Beksac, M., Spencer, A., Oakervee, H., Orlowski, R.Z., Taniwaki, M., Rollig, C., Einsele, H., Wu, K.L., Singhal, A., San-Miguel, J., Matsumoto, M., Katz, J., Bleickardt, E., Poulart, V., Anderson, K.C., Richardson, P. & ELOQUENT-2 Investigators. (2015) Elotuzumab therapy for relapsed or refractory multiple myeloma. *The New England Journal of Medicine,* **373**, 621-631.

Ma, M.H., Yang, H.H., Parker, K., Manyak, S., Friedman, J.M., Altamirano, C., Wu, Z.Q., Borad, M.J., Frantzen, M., Roussos, E., Neeser, J., Mikail, A., Adams, J., Sjak-Shie, N., Vescio, R.A. & Berenson, J.R. (2003) The proteasome inhibitor PS-341 markedly enhances sensitivity of multiple myeloma tumor cells to chemotherapeutic agents. *Clinical Cancer Research,* **9**, 1136-1144.

Magarotto, V., Sonneveld, P., Paba-Prada, C., Plesner, T., Mellqvist, U-H., Byrne, C., Harmenberg, J., Nordström, E., Palumbo, A. & Richardson, P.G. (2015) Encouraging preliminary data in ongoing open-label phase 1/2 study of safety and efficacy of melflufen and dexamethasone for patients with relapsed and relapsed-refractory multiple myeloma. *Haematologica (EHA Abstracts)*, **100**(s1):89

Mai, E.K., Benner, A., Bertsch, U., Brossart, P., Hänel, A., Kunzmann, V., Naumann, R., Neben, K., Egerer, G., Ho, A.D., Hillengass, J., Raab, M.S., Neubauer, A., Peyn, A., Ko, Y., Peter, N., Scheid, C. & Goldschmidt, H. (2016) Single versus tandem high-dose melphalan followed by autologous blood stem cell transplantation in multiple myeloma: Long-term results from the phase III GMMG-HD2 trial. *British Journal of Haematology,* published on-line ahead of print.

Maiolino, A., Hungria, V.T., Garnica, M., Oliveira-Duarte, G., Oliveira, L.C., Mercante, D.R., Miranda, E.C., Quero, A.A., Peres, A.L., Barros, J.C., Tanaka, P., Magalhaes, R.P., Rego, E.M., Lorand-Metze, I., Lima, C.S., Renault, I.Z., Braggio, E., Chiattone, C., Nucci, M., de Souza, C.A. & Brazilian Multiple Myeloma Study Group (BMMSG/GEMOH). (2012) Thalidomide plus dexamethasone as a maintenance therapy after autologous hematopoietic stem cell transplantation improves progression-free survival in multiple myeloma. *American Journal of Hematology,* **87**, 948-952.

Marin, G.H., Menna, M.E., Bergna, M.I., Malacalza, J., Martin, C., Mendez, M.C., Klein, G., Montero-Labat, L., Gil, M.A., Saba, S., Gardenal, L., Mansilla, E., Orlando, S., Canepa, C. & Piccinelli, G. (2001) Induction of anti-tumor activity following autologous stem cell transplantation: Immunotherapeutic implications. *Transplantation Proceedings,* **33**, 2004-2007.

Mark, T.M., Reid, W., Niesvizky, R., Gergis, U., Pearse, R., Mayer, S., Greenberg, J., Coleman, M., Van Besien, K. & Shore, T. (2013) A phase 1 study of bendamustine and melphalan conditioning for autologous stem cell transplantation in multiple myeloma. *Biology of Blood and Marrow Transplantation,* **19**, 831-837.

Maude, S.L., Frey, N., Shaw, P.A., Aplenc, R., Barrett, D.M., Bunin, N.J., Chew, A., Gonzalez, V.E., Zheng, Z., Lacey, S.F., Mahnke, Y.D., Melenhorst, J.J., Rheingold, S.R., Shen, A., Teachey, D.T., Levine, B.L., June, C.H., Porter, D.L. & Grupp, S.A. (2014) Chimeric antigen receptor T cells for sustained remissions in leukemia. *The New England Journal of Medicine,* **371**, 1507-1517.

McCann, K.J., Godeseth, R., Chudley, L., Mander, A., Di Genova, G., Lloyd-Evans, P., Kerr, J.P., Malykh, V.B., Jenner, M.W., Orchard, K.H., Stevenson, F.K. & Ottensmeier, C.H. (2015) Idiotypic DNA vaccination for the treatment of multiple myeloma: Safety and immunogenicity in a phase I clinical study. *Cancer Immunology, Immunotherapy,* **64**, 1021-1032.

McCarthy, P.L., Owzar, K., Hofmeister, C.C., Hurd, D.D., Hassoun, H., Richardson, P.G., Giralt, S., Stadtmauer, E.A., Weisdorf, D.J., Vij, R., Moreb, J.S., Callander, N.S., Van Besien, K., Gentile, T., Isola, L., Maziarz, R.T., Gabriel, D.A., Bashey, A., Landau, H., Martin, T., Qazilbash, M.H., Levitan, D., McClune, B., Schlossman, R., Hars, V., Postiglione, J., Jiang, C., Bennett, E., Barry, S., Bressler, L., Kelly, M., Seiler, M., Rosenbaum, C., Hari, P., Pasquini, M.C., Horowitz, M.M., Shea, T.C., Devine, S.M., Anderson, K.C. & Linker, C. (2012) Lenalidomide after stem-cell transplantation for multiple myeloma. *The New England Journal of Medicine,* **366**, 1770-1781.

Mellqvist, U.H., Gimsing, P., Hjertner, O., Lenhoff, S., Laane, E., Remes, K., Steingrimsdottir, H., Abildgaard, N., Ahlberg, L., Blimark, C., Dahl, I.M., Forsberg, K., Gedde-Dahl, T., Gregersen, H., Gruber, A., Guldbrandsen, N., Haukas, E., Carlson, K., Kvam, A.K., Nahi, H., Lindas, R., Andersen, N.F., Turesson, I., Waage, A., Westin, J. & Nordic Myeloma Study Group. (2013) Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: A nordic myeloma study group randomized phase 3 trial. Blood, 121, 4647-4654.

Mihara, K., Bhattacharyya, J., Kitanaka, A., Ihara, A., Sakai, A., Kuroda, Y., Asaoku, H., Takihara, Y. & Kimura, A. (2011) T-cell immunotherapy with a chimeric receptor against CD38 is effective in eliminating myeloma cells. *Blood (ASH Annual Meeting Abstracts),* **118**, 885.

Mitsiades, N., Mitsiades, C.S., Richardson, P.G., Poulaki, V., Tai, Y.T., Chauhan, D., Fanourakis, G., Gu, X., Bailey, C., Joseph, M., Libermann, T.A., Schlossman, R., Munshi, N.C., Hideshima, T. & Anderson, K.C. (2003) The proteasome inhibitor PS-341 potentiates sensitivity of multiple myeloma cells to conventional chemotherapeutic agents: Therapeutic applications. *Blood,* **101**, 2377-2380.

Miyamoto, T., Yoshimoto, G., Kamimura, T., Muta, T., Takashima, S., Ito, Y., Shiratsuchi, M., Choi, I., Kato, K., Takenaka, K., Iwasaki, H., Takamatsu, Y., Teshima, T. & Akashi, K. (2013) Combination of high-dose melphalan and bortezomib as conditioning regimen for autologous peripheral blood stem cell transplantation in multiple myeloma. *International Journal of Hematology,* **98**, 337-345.

Moreau, P., Facon, T., Attal, M., Hulin, C., Michallet, M., Maloisel, F., Sotto, J.-J., Guilhot, F., Marit, G., Doyen, C., Jaubert, J., Fuzibet, J.-G., François, S., Benboubker, L., Monconduit, M., Voillat, L., Macro, M., Berthou, C., Dorvaux, V., Pignon, B., Rio, B., Matthes, T., Casassus, P., Caillot, D., Najman, N., Grosbois, B., Bataille, R., Harousseau, J.-L. (2002) Comparison of 200 mg/m^2 melphalan and 8 Gy total body irradiation plus 140 mg/m^2 melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: Final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. *Blood*, **99**, 731-735.

Moreau, P., Mateos, M., Bladé, J., Benboubker, L., de la Rubia, J., Facon, T., Comenzo, R.L., Fay, J.W., Qin, X., Masterson, T., Schecter, J., Ahmadi, T. & San Miguel, J. (2014) An open-label, multicenter, phase 1b study of daratumumab in combination with backbone regimens in patients with multiple myeloma. *Blood (ASH Annual Meeting Abstracts),* **124**, 176.

Morgan, G.J., Davies, F.E., Gregory, W.M., Bell, S.E., Szubert, A.J., Coy, N.N., Cook, G., Feyler, S., Johnson, P.R.E., Rudin, C., Drayson, M.T., Owen, R.G., Ross, F.M., Russell, N.H., Jackson, G.H., Anthony Child, J. (2012) Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation: MRC Myeloma IX randomized trial results. *Haematologica*, **97,** 442-450.

Nair, B., van Rhee, F., Shaughnessy, J.D.,Jr, Anaissie, E., Szymonifka, J., Hoering, A., Alsayed, Y., Waheed, S., Crowley, J. & Barlogie, B. (2010) Superior results of total therapy 3 (2003-33) in gene expression profiling-defined low-risk multiple myeloma confirmed in subsequent trial 2006-66 with VRD maintenance. *Blood,* **115**, 4168-4173.

Nath, C.E., Shaw, P.J., Trotman, J., Zeng, L., Duffull, S.B., Hegarty, G., McLachlan, A.J., Gurney, H., Kerridge, I., Kwan, Y.L., Presgrave, P., Tiley, C., Joshua, D., Earl, J. (2010) Population pharmacokinetics of melphalan in patients with multiple myeloma undergoing high dose therapy. *British Journal of Clinical Pharmacology*, **69**, 484-497.

Nishihori, T., Alekshun, T.J., Shain, K., Sullivan, D.M., Baz, R., Perez, L., Pidala, J., Kharfan-Dabaja, M.A., Ochoa-Bayona, J.L., Fernandez, H.F., Yarde, D.N., Oliveira, V., Fulp, W., Han, G., Kim, J., Chen, D.T., Raychaudhuri, J., Dalton, W., Anasetti, C. & Alsina, M. (2012) Bortezomib salvage followed by a phase I/II study of bortezomib plus high-dose melphalan and tandem autologous transplantation for patients with primary resistant myeloma. *British Journal of Haematology,* **157**, 553-563.

Nooka, A.K., Kaufman, J.L., Muppidi, S., Langston, A., Heffner, L.T., Gleason, C., Casbourne, D., Saxe, D., Boise, L.H. & Lonial, S. (2014) Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients. *Leukemia,* **28**, 690-693.

Orchard, K., Cooper, M., Lewington, V., Tristram, M., Zivanovic, M., Thom, J., Quadri, S., Richardson, D., Causer, L. & Johnson, P. (2005) Targeted radiotherapy in the conditioning prior to haematopoietic stem cell transplantation: Results of a phase I radiation dose escalation study using yttrium-90-labelled anti-CD66 monoclonal antibody demonstrating high BM uptake of radiation. *Blood (ASH Annual Meeting Abstracts),* **106**, 2189.

Paiva, B., Gutierrez, N.C., Rosinol, L., Vidriales, M.B., Montalban, M.A., Martinez-Lopez, J., Mateos, M.V., Cibeira, M.T., Cordon, L., Oriol, A., Terol, M.J., Echeveste, M.A., de Paz, R., de Arriba, F., Palomera, L., de la Rubia, J., Diaz-Mediavilla, J., Sureda, A., Gorosquieta, A., Alegre, A., Martin, A., Hernandez, M.T., Lahuerta, J.J., Bladé, J., San Miguel, J.F. & PETHEMA/GEM (Programa para el Estudio de la Terapeutica en Hemopatias Malignas/Grupo Espanol de Mieloma) Cooperative Study Groups. (2012) High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. *Blood,* **119**, 687-691.

Palumbo, A., Cavallo, F., Gay, F., Di Raimondo, F., Yehuda, D.B., Petrucci, M.T., Pezzatti, S., Caravita, T., Cerrato, C., Ribakovsky, E., Genuardi, M., Cafro, A., Marcatti, M., Catalano, L., Offidani, M., Carella, A.M., Zamagni, E., Patriarca, F., Musto, P., Evangelista, A., Ciccone, G., Omedé, P., Crippa, C., Corradini, P., Nagler, A., Boccadoro, M., Cavo, M. (2014a) Autologous transplantation and maintenance therapy in multiple myeloma. *New England Journal of Medicine*, **371**, 895-905.

Palumbo, A., Gay, F., Musto, P., Caravita, T., Larocca, A., Rossi, D., Ben Yehuda, D., Offidani, M., Donato, F., Finsinger, P., Omede, P., Conticello, C., Nagler, A., Ria, R., Cavalli, M., Mina, R., Petrucci, M.T., Hardan, I., Cavallo, F. & Boccadoro, M. (2014b) Continuous treatment (CT) versus fixed duration of therapy (FDT) in newly diagnosed myeloma patients: PFS1, PFS2, OS endpoints. *Journal of Clinical Oncology (ASCO Meeting Abstracts),* **32**, 8515.

Pica, G., Vagge, S., Beltrami, G., Nati, S., Catania, G., Corvò, R. & Carella, A.M. (2011) A phase I study of hypofractionated tailored total marrow or total lymphoid irradiation with helical tomotherapy plus chemotherapy as a conditioning regimen for autologous stem cell transplantation. *Blood (ASH Annual Meeting Abstracts),* **118**, 4523.

Pineda-Roman, M., Barlogie, B., Anaissie, E., Zangari, M., Bolejack, V., van Rhee, F., Tricot, G. & Crowley, J. (2008) High-dose melphalan-based autotransplants

for multiple myeloma: The Arkansas experience since 1989 in 3077 patients. *Cancer,* **112**, 1754-1764.

Plesner, T., Arkenau, H., Lokhorst, H.M., Gimsing, P., Krejcik, J., Lemech, C., Minnema, M.C., Lassen, U., Laubach, J.P., Ahmadi, T., Yeh, H., Guckert, M.E., Feng, H., Brun, N.C., Lisby, S., Basse, L., Palumbo, A. & Richardson, P.G. (2014) Safety and efficacy of daratumumab with lenalidomide and dexamethasone in relapsed or relapsed, refractory multiple myeloma. *Blood (ASH Annual Meeting Abstracts),* **124**, 84.

Popat, R., Cavenagh, J.D., Owen, R.G., Streetly, M., Schey, S.A., Koh, M., Crowe, J., Quinn, M.F., D'Sa, S., Virchis, A., Cook, G., Crawley, C., Pratt, G., Cook, M., Oakervee, H.E., Counsell, N., Adedayo, T., Evans, A., Braganca, N., Smith, P., lyons-Lewis, J., Rabin, N. & Yong, K.L. (2014) Subcutaneous PAD as induction therapy for patients with newly diagnosed myeloma: A phase 2 trial assessing the impact of minimal residual disease (MRD) in patients with deferred autologous stem cell transplantation (PADIMAC). *Blood (ASH Annual Meeting Abstracts),* **124**, 4745.

Pulte, D., Jansen, L., Castro, F.A., Emrich, K., Katalinic, A., Holleczek, B., Brenner, H., Geiss, K., Meyer, M., Eberle, A., Luttmann, S., Stabenow, R., Hentschel, S., Nennecke, A., Kieschke, J., Sirri, E., Kajüter, H., Mattauch, V., Eisemann, N., Kraywinkel, K., Gondos, A., Krilaviciute, A. (2015) Trends in survival of multiple myeloma patients in Germany and the United States in the first decade of the 21st century. *British Journal of Haematology*, **171,** 189-196.

Qazilbash, M.H., Saliba, R.M., Nieto, Y., Parikh, G., Pelosini, M., Khan, F.B., Jones, R.B., Hosing, C., Mendoza, F., Weber, D.M., Wang, M., Popat, U., Alousi, A., Anderlini, P., Champlin, R.E. & Giralt, S. (2008) Arsenic trioxide with ascorbic acid and high-dose melphalan: Results of a phase II randomized trial. *Biology of Blood and Marrow Transplantation,* **14**, 1401-1407.

Rabin, N., Percy, L., Khan, I., Quinn, J., D'Sa, S. & Yong, K.L. (2012) Improved response with post-ASCT consolidation by low dose thalidomide, cyclophosphamide and dexamethasone as first line treatment for multiple myeloma. *British Journal of Haematology,* **158**, 499-505.

Rapoport, A.P., Aqui, N.A., Stadtmauer, E.A., Vogl, D.T., Fang, H.B., Cai, L., Janofsky, S., Chew, A., Storek, J., Akpek, G., Badros, A., Yanovich, S., Tan, M.T., Veloso, E., Pasetti, M.F., Cross, A., Philip, S., Murphy, H., Bhagat, R., Zheng, Z., Milliron, T., Cotte, J., Cannon, A., Levine, B.L., Vonderheide, R.H. & June, C.H. (2011) Combination immunotherapy using adoptive T-cell transfer and tumor antigen vaccination on the basis of hTERT and survivin after ASCT for myeloma. *Blood,* **117**, 788-797.

Rapoport, A.P., Aqui, N.A., Stadtmauer, E.A., Vogl, D.T., Xu, Y.Y., Kalos, M., Cai, L., Fang, H.B., Weiss, B.M., Badros, A., Yanovich, S., Akpek, G., Tsao, P., Cross, A., Mann, D., Philip, S., Kerr, N., Brennan, A., Zheng, Z., Ruehle, K., Milliron, T., Strome, S.E., Salazar, A.M., Levine, B.L. & June, C.H. (2014) Combination immunotherapy after ASCT for multiple myeloma using MAGE-A3/Poly-ICLC immunizations followed by adoptive transfer of vaccine-primed and costimulated autologous T cells. *Clinical Cancer Research,* **20**, 1355-1365.

Rawstron, A.C., Gregory, W.M., de Tute, R.M., Davies, F.E., Bell, S.E., Drayson, M.T., Cook, G., Jackson, G.H., Morgan, G.J., Child, J.A. & Owen, R.G. (2015) Minimal residual disease in myeloma by flow cytometry: Independent prediction of survival benefit per log reduction. *Blood,* **125**, 1932-1935.

Riccardi, A., Mora, O., Tinelli, C., Porta, C., Danova, M., Brugnatelli, S., Grasso, D., Tolca, B., Spanedda, R., De Paoli, A., Barbarano, L., Cavanna, L., Giordano, M., Delfini, C., Nicoletti, G., Bergonzi, C., Rinaldi, E., Piccinini, L. & Ascari, E. (2003) Response to first-line chemotherapy and long-term survival in patients with multiple myeloma: Results of the MM87 prospective randomised protocol. *European Journal of Cancer,* **39**, 31-37.

Rosenblatt, J., Vasir, B., Uhl, L., Blotta, S., Macnamara, C., Somaiya, P., Wu, Z., Joyce, R., Levine, J.D., Dombagoda, D., Yuan, Y.E., Francoeur, K., Fitzgerald, D., Richardson, P., Weller, E., Anderson, K., Kufe, D., Munshi, N. & Avigan, D. (2011) Vaccination with dendritic cell/tumor fusion cells results in cellular and humoral antitumor immune responses in patients with multiple myeloma. *Blood,* **117**, 393-402.

Roussel, M., Moreau, P., Huynh, A., Mary, J.Y., Danho, C., Caillot, D., Hulin, C., Fruchart, C., Marit, G., Pegourie, B., Lenain, P., Araujo, C., Kolb, B., Randriamalala, E., Royer, B., Stoppa, A.M., Dib, M., Dorvaux, V., Garderet, L., Mathiot, C., Avet-Loiseau, H., Harousseau, J.L., Attal, M. & Intergroupe Francophone du Myelome (IFM). (2010) Bortezomib and high-dose melphalan as conditioning regimen before autologous stem cell transplantation in patients with de novo multiple myeloma: A phase 2 study of the Intergroupe Francophone du Myelome (IFM). *Blood,* **115**, 32-37.

Rueff, J., Medinger, M., Heim, D., Passweg, J. & Stern, M. (2014) Lymphocyte subset recovery and outcome after autologous hematopoietic stem cell transplantation for plasma cell myeloma. *Biology of Blood and Marrow Transplantation,* **20**, 896-899.

San-Miguel, J.F., Hungria, V.T., Yoon, S.S., Beksac, M., Dimopoulos, M.A., Elghandour, A., Jedrzejczak, W.W., Gunther, A., Nakorn, T.N., Siritanaratkul, N., Corradini, P., Chuncharunee, S., Lee, J.J., Schlossman, R.L., Shelekhova, T., Yong, K., Tan, D., Numbenjapon, T., Cavenagh, J.D., Hou, J., LeBlanc, R., Nahi, H., Qiu, L., Salwender, H., Pulini, S., Moreau, P., Warzocha, K., White, D., Bladé, J., Chen, W., de la Rubia, J., Gimsing, P., Lonial, S., Kaufman, J.L., Ocio, E.M., Veskovski, L., Sohn, S.K., Wang, M.C., Lee, J.H., Einsele, H., Sopala, M., Corrado, C., Bengoudifa, B.R., Binlich, F. & Richardson, P.G. (2014) Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: A multicentre, randomised, double-blind phase 3 trial. *The Lancet.Oncology,* **15**, 1195-1206.

San Miguel, J., Mateos, M., Shah, J.J., Ocio, E.M., Rodriguez-Otero, P., Reece, D., Munshi, N.C., Avigan, D., Ge, Y., Balakumaran, A., Marinello, P., Orlowski, R.Z. & Siegel, D. (2015) Pembrolizumab in combination with lenalidomide and low-dose dexamethasone for Relapsed/Refractory multiple myeloma (RRMM). *Blood (ASH Annual Meeting Abstracts),* **126**, 505.

Sborov, D.W., Benson, D.M., Williams, N., Huang, Y., Bowers, M.A., Humphries, K., Efebera, Y., Devine, S. & Hofmeister, C.C. (2015) Lenalidomide and vorinostat maintenance after autologous transplant in multiple myeloma. *British Journal of Haematology,* **171**, 74-83.

Scheid, C., Sonneveld, P., Schmidt-Wolf, I.G., van der Holt, B., el Jarari, L., Bertsch, U., Salwender, H., Zweegman, S., Blau, I.W., Vellenga, E., Weisel, K., Pfreundschuh, M., Jie, K.S., Neben, K., van de Velde, H., Duehrsen, U., Schaafsma, M.R., Lindemann, W., Kersten, M.J., Peter, N., Hanel, M., Croockewit, S., Martin, H., Wittebol, S., Bos, G.M., van Marwijk-Kooy, M., Wijermans, P., Goldschmidt, H. & Lokhorst, H.M. (2014) Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: A subgroup analysis from the HOVON-65/GMMG-HD4 trial. *Haematologica,* **99**, 148-154.

Shi, J., Tricot, G., Szmania, S., Rosen, N., Garg, T.K., Malaviarachchi, P.A., Moreno, A., Dupont, B., Hsu, K.C., Baxter-Lowe, L.A., Cottler-Fox, M., Shaughnessy, J.D. Jr, Barlogie, B. & van Rhee, F. (2008) Infusion of haplo-identical killer immunoglobulin-like receptor ligand mismatched NK cells for relapsed myeloma in the setting of autologous stem cell transplantation. *British Journal of Haematology,* **143**, 641-653.

Sonneveld, P., Van Der Holt, B., Segeren, C.M., Vellenga, E., Croockewit, A.J., Verhoef, G.E.G., Cornelissen, J.J., Schaafsma, M.R., Van Oers, M.H.J., Wijermans, P.W., Westveer, P.H.M., Lokhorst, H.M. (2007) Intermediate-dose melphalan compared with myeloablative treatment in multiple myeloma: Long-term follow-up of the Dutch Cooperative Group HOVON 24 trial. *Haematologica,* **92,** 928-935.

Sonneveld, P., Schmidt-Wolf, I.G.H., Van Der Holt, B., El Jarari, L., Bertsch, U., Salwender, H., Zweegman, S., Vellenga, E., Broyl, A., Blau, I.W., Weisel, K.C., Wittebol, S., Bos, G.M.J., Stevens-Kroef, M., Scheid, C., Pfreundschuh, M., Hose, D., Jauch, A., Van Der Velde, H., Raymakers, R., Schaafsma, M.R., Kersten, M.-J., Van Marwijk-Kooy, M., Duehrsen, U., Lindemann, W., Wijermans, P.W., Lokhorst, H.M., Goldschmidt, H.M. (2012) Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: Results of the randomized phase III HOVON-65/ GMMG-HD4 trial.*Journal of Clinical Oncology*, **30**, 2946-2955.

Sonneveld, P., Scheid, C., van der Holt, B., Jarari, L.e., Bertsch, U., Salwender, H., Zweegman, S., Vellenga, E., Broyl, A., Wolfgang Blau, I., Weisel, K., Wittebol, S., Bos, G.M.J., Stevens, M., Schmidt-Wolf, I.G., Pfreundschuh, M., Hose, D., Jauch, A., van de Velde, H., Raymakers, R., Schaafsma, M.R., Kersten, M.J., van Marwijk Kooy, M., Duehrsen, U., Lindemann, H.W., Wijermans, P.W., Lokhorst, H. & Goldschmidt, H. (2013) Bortezomib induction and maintenance treatment improves survival in patients with newly diagnosed multiple myeloma:Extended follow-up of the HOVON-65/GMMG-HD4 trial. *Blood (ASH Annual Meeting Abstracts),* **122**, 404.

Sonneveld, P., Cavo, M., Einsele, H. & Mellqvist, U. (2014). A randomized phase III study to compare bortezomib, melphalan, prednisone (VMP) with high dose melphalan followed by bortezomib, lenalidomide, dexamethasone (VRD) consolidation and lenalidomide maintenance in patients with newly diagnosed multiple myeloma. Study Protocol version 6. WWW document. URL: http://hovon.nl/studies/studies-per-ziektebeeld/mm.html?getfile=1&studie=75&studieveld=26 [accessed 10.10.2015].

Spencer, A., Horvath, N., Gibson, J., Prince, H.M., Herrmann, R., Bashford, J., Joske, D., Grigg, A., McKendrick, J., Prosser, I., Lowenthal, R., Deveridge, S., Taylor, K. (2005) Prospective randomised trial of amifostine cytoprotection in myeloma patients undergoing high-dose melphalan conditioned autologous stem cell transplantation. *Bone Marrow Transplantation*, **35**, 971-977.

Spencer, A., Prince, H.M., Roberts, A.W., Prosser, I.W., Bradstock, K.F., Coyle, L., Gill, D.S., Horvath, N., Reynolds, J. & Kennedy, N. (2009) Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. *Journal of Clinical Oncology,* **27**, 1788-1793.

Stewart, A.K., Rajkumar, S.V., Dimopoulos, M.A., Masszi, T., Spicka, I., Oriol, A., Hajek, R., Rosinol, L., Siegel, D.S., Mihaylov, G.G., Goranova-Marinova, V., Rajnics, P., Suvorov, A., Niesvizky, R., Jakubowiak, A.J., San-Miguel, J.F., Ludwig, H., Wang, M., Maisnar, V., Minarik, J., Bensinger, W.I., Mateos, M.V., Ben-Yehuda, D., Kukreti, V., Zojwalla, N., Tonda, M.E., Yang, X., Xing, B., Moreau, P., Palumbo, A. & ASPIRE Investigators. (2015) Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *The New England Journal of Medicine,* **372**, 142-152.

Stewart, A.K., Trudel, S., Bahlis, N.J., White, D., Sabry, W., Belch, A., Reiman, T., Roy, J., Shustik, C., Kovacs, M.J., Rubinger, M., Cantin, G., Song, K., Tompkins, K.A., Marcellus, D.C., Lacy, M.Q., Sussman, J., Reece, D., Brundage, M., Harnett, E.L., Shepherd, L., Chapman, J.A. & Meyer, R.M. (2013) A randomized phase 3 trial of thalidomide and prednisone as maintenance therapy after ASCT in patients with MM with a quality-of-life assessment: The National Cancer Institute of Canada clinicals trials group myeloma 10 trial. *Blood,* **121**, 1517-1523.

Tacchetti, P., Pantani, L., De Stefano, V., Zamagni, E., Peccatori, J., Pezzi, A., Califano, C., Nozza, A., Tosi, P., Terragna, C., Ciambelli, F., Cangini, D., Galieni, P., Cangialosi, C., De Sabbata, G., Elice, F., Palumbo, A. & Cavo, M. (2014) Superior PFS2 with VTD vs TD for newly diagnosed, transplant eligible, multiple myeloma (MM) patients: Updated analysis of GIMEMA MMY-3006 study. *Blood (ASH Annual Meeting Abstracts),* **124**, 196.

Voorhees, P.M., Spencer, A., Sutherland, H.J., O'Dwyer, M.E., Huang, S., Stewart, K., CHB, , Chari, A., Rosenzwieg, M., Nooka, A.K., Rosenbaum, C.A.,

Hofmeister, C.C., Smith, D.A., Antal, J.M., Santiago-Walker, A., Gauvin, J., Opalinska, J.B. & Trudel, S. (2013) Novel AKT inhibitor afuresertib in combination with bortezomib and dexamethasone demonstrates favorable safety profile and significant clinical activity in patients with Relapsed/Refractory multiple myeloma. *Blood (ASH Annual Meeting Abstracts),* **122**, 283.

Zahradova, L., Mollova, K., Ocadlikova, D., Kovarova, L., Adam, Z., Krejci, M., Pour, L., Krivanova, A., Sandecka, V. & Hajek, R. (2012) Efficacy and safety of id-protein-loaded dendritic cell vaccine in patients with multiple myeloma--phase II study results. *Neoplasma,* **59**, 440-449.

Zamagni, E., Nanni, C., Mancuso, K., Tacchetti, P., Pezzi, A., Pantani, L., Zannetti, B., Rambaldi, I., Brioli, A., Rocchi, S., Terragna, C., Martello, M., Marzocchi, G., Borsi, E., Rizzello, I., Fanti, S. & Cavo, M. (2015) PET/CT Improves the Definition of Complete Response and Allows to Detect Otherwise Unidentifiable Skeletal Progression in Multiple Myeloma. *Clinical Cancer Research*, **21**, 4384-4390.

Zimmerman, T.M., Griffith, K.A., Jasielec, J., Rosenbaum, C.A., McDonnell, K., Waite-Marin, J., Berdeja, J.G., Raje, N.S., Reece, D.E., Vij, R., Alonge, M., Rosebeck, S., Gurbuxani, S., Faham, M., Kong, K.A., Levy, J. & Jakubowiak, A.J. (2015) Phase II MMRC trial of extended treatment with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX) plus autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (NDMM). *Journal of Clinical Oncology* (*ASCO Meeting Abstracts),* **33**, supplement 8510.