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Treatment options for relapse after autograft in multiple myeloma – report from an EBMT educational meeting

Laurent Garderet, Gordon Cook, Holger W. Auner, Benedetto Bruno, Henk Lokhorst, Jose Antonio Perez-Simon, Firoozeh Sahebi, Christof Scheid, Curly Morris, Anja van Biezen, Mohamad Sobh, Mauricette Michallet, Gösta Gahrton, Stefan Schönland & Nicolaus Kröger show less

Abstract

Major improvements have been made in the treatment of myeloma. However, all patients, perhaps with some exceptions, eventually relapse, even after autologous stem cell transplantation (ASCT). In that setting, the combinations of new drugs, namely the IMiDs and the proteasome inhibitors along with steroids, give encouraging results in relapsed patients. The median progression-free survival (PFS) is 20 months with lenalidomide plus dexamethasone plus ixazomib and 26 months with lenalidomide plus dexamethasone plus carfilzomib. Monoclonal antibodies have emerged as an additional new treatment option. The antibody anti-SLAMF7, elotuzumab, in combination with lenalidomide plus dexamethasone gives a median PFS of 20 months. The antibody daratumumab, targeting CD38, alone has an outstanding activity in previously heavily treated patients. Its use in combination is ongoing. Transplantation remains a major treatment option. For patients who relapse at least 18 months from the initial ASCT, a second ASCT can be performed with an expected time to progression of 19 months from the time of transplantation. For patients relapsing earlier and/or with high-risk characteristics and who are still chemosensitive, with a suitable donor, an allogeneic transplantation can be considered. The optimal treatment combination and sequence remain to be determined.

Keywords: Myeloma, relapse, proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, autologous stem cell transplantation, allogeneic stem cell transplantation

Introduction

Autologous stem cell transplantation (ASCT) is the standard treatment for younger newly diagnosed patients with multiple myeloma (MM). However, ultimately all patients will experience relapse following ASCT. The number of treatment options after relapse to an autograft is increasing.[1 Oscio EM, Richardson PG, Rajkumar SV, et al. New drugs and novel mechanisms of action in multiple myeloma in 2013: a report from the International Myeloma Working Group (IMWG). *Leukemia*. 2014;28:525–542.[CrossRef], [PubMed], [Web of Science ®],2 Laubach J, Garderet L, Mahindra A, et al. Management of relapsed multiple myeloma: recommendations of the international myeloma working group. *Leukemia*. 2016;30:1005–1017.[CrossRef], [PubMed], [Web of Science ®]] One must first consider what type of relapse is occurring as this will affect future treatment strategies. Three parameters have a major role in the treatment decision: (1) The disease characteristics: is it high or standard risk? In this regard, the cytogenetic analysis has a prognostic impact as well as whether there is an extramedullary relapse. (2) The past treatment efficacy and toxicity and the duration of response after the autograft. (3) The patient characteristics:

does he/she have comorbidities? and what is the patient's choice? With the need for treatment established, the patient can be treated with a nontransplant approach or a transplant approach with either another autologous or/and an allogeneic transplantation.[3–5 Holstein SA, Richardson PG, Laubach JP, et al. Management of relapsed multiple myeloma after autologous stem cell transplant. *Biol Blood Marrow Transplant.* 2015;21:793–798. Giralt S, Garderet L, Durie B, et al. American Society of Blood and Marrow Transplant, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network and International Myeloma Working Group Consensus conference on salvage hematopoietic cell transplantation in patients with relapsed multiple myeloma. *Biol Blood Marrow Transplant.* 2015;21:2039–2051. Bruno B, Auner HW, Gahrton G, et al. Stem cell transplantation in multiple myeloma and other plasma cell disorders (report from an EBMT preceptorship meeting). *Leuk Lymphoma.* 2016;6:1–13.]

The Chronic Malignancies Working Party of the European Society of Blood and Marrow Transplantation organized an Educational meeting in January 2016 in Hamburg/Germany addressing the issue of myeloma treatment relapse options following a previous autologous transplantation. This report summarized the options presented by the members of the faculty.

Immunomodulatory drugs

Immunomodulatory drugs (IMiDs) were the first new drugs to join standard chemotherapy to improve the treatment of myeloma. They have a dual mechanism of action, involving both a direct tumoricidal activity and a immunomodulation. The tumoricidal effect occurs through several mechanisms, including disruption of stromal support, induction of tumor suppressor genes and activation of caspases. The immunomodulatory effects includes T-cell and natural killer (NK)-cell activation, and increased expression of death effector molecules, which lead to enhanced immune cell function. There are currently three major IMiDs, namely thalidomide, lenalidomide (Revlimid®) and pomalidomide (Imnovid® in Europe and Pomalyst® in the United States).

In 1999, the Arkansas group reported the efficacy of single agent thalidomide in the relapse setting.[6 Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med.* 1999;341:1565–1571.[CrossRef], [PubMed], [Web of Science ®]] The overall response rate (ORR) was 32% with a two-year PFS of 20% and overall survival (OS) of 48%. At that time, the thalidomide dose range was high from 200 mg to 800 mg per day with a high toxicity, especially peripheral neuropathy. Currently, thalidomide is rarely given above 200 mg per day which is usually well tolerated. If combined to steroid, namely dexamethasone, the ORR increases to 46%.[7 von Lilienfeld-Toal M, Hahn-Ast C, Furkert K, et al. A systematic review of phase II trials of thalidomide/dexamethasone combination therapy in patients with relapsed or refractory multiple myeloma. *Eur J Haematol.* 2008;81:247–252.[CrossRef], [PubMed], [Web of Science ®]] The second-generation IMiD, lenalidomide, was reported in two pivotal studies published in 2007 with similar results.[8 Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med.* 2007;357:2123–2132.[CrossRef], [PubMed], [Web of Science ®],9 Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med.* 2007;357:2133–2142.[CrossRef], [PubMed], [Web of Science ®]] Lenalidomide plus dexamethasone induces a partial response or better of 60% with a time to progression of 11 months. In a phase-I study, pomalidomide was first tested in patients refractory to both proteasome inhibitors and immunomodulatory drugs. In combination with dexamethasone, the ORR was 34%.[10 Richardson PG, Siegel D, Baz R, et al. Phase 1 study of pomalidomide MTD, safety, and efficacy in patients with refractory multiple myeloma who have received lenalidomide and

bortezomib. *Blood*. 2013;121:1961–1967.[CrossRef], [PubMed], [Web of Science ®] The optimal dose was established of 4 mg per day, for 21 days followed by 7 days off therapy.[11 Leleu X, Attal M, Arnulf B, et al. Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: intergroupe francophone du myélome 2009-02. *Blood*. 2013;121:1968–1975.[CrossRef], [PubMed], [Web of Science ®] Pomalidomide plus weekly low-dose dexamethasone was then shown to be superior to dexamethasone alone. In this trial, patients had received a median of 5 (2–14) lines of treatment, including 70% with a prior ASCT. The PFS was 4 months versus 1.9 months and the OS was 12 months versus 8 months in favor of pomalidomide plus dexamethasone.[12 San Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomized, open-label, phase 3 trial. *Lancet Oncol*. 2013;14:1055–1066.[CrossRef], [PubMed], [Web of Science ®] In 2015, the IFM reported a potential efficacy of pomalidomide for patients harboring the 17 p deletion.[13 Leleu X, Karlin L, Macro M, et al. Pomalidomide plus low-dose dexamethasone in multiple myeloma with deletion 17p and/or translocation (4;14): IFM 2010-02 trial results. *Blood*. 2015;125:1411–1417.[CrossRef], [PubMed], [Web of Science ®]]

These three drugs are all approved by the health authorities in the relapse setting in Europe except pomalidomide which is not currently funded in the United Kingdom. Pomalidomide is restricted to patients who relapse/progress after having received at least two prior therapies (including lenalidomide and bortezomib) and have disease progression on/or within 60 days of completion of the last therapy.[14 Dimopoulos MA, Leleu X, Palumbo A, et al. Expert panel consensus statement on the optimal use of pomalidomide in relapsed and refractory multiple myeloma. *Leukemia*. 2014;28:1573–1585.[CrossRef], [PubMed], [Web of Science ®]]

Proteasome inhibitors

Proteasome inhibitors block the degradation of intracellular proteins in the ubiquitin–proteasome system and trigger proteotoxic stress preferentially in multiple myeloma cells.[15 Auner HW, Cenci S. Recent advances and future directions in targeting the secretory apparatus in multiple myeloma. *Br J Haematol*. 2015;168:14–25.[CrossRef], [PubMed], [Web of Science ®],16 Moreau P, Richardson PG, Cavo M, et al. Proteasome inhibitors in multiple myeloma: 10 years later. *Blood*. 2012;120:947–959.[CrossRef], [PubMed], [Web of Science ®] The first in this class was bortezomib (Velcade[®], a boronic acid-based proteasome inhibitor) followed by carfilzomib (Kyprolis[®], an epoxyketone) and more recently the orally bioavailable boronic acid-based ixazomib (Ninlaro[®]).

In a pivotal phase-II study, bortezomib monotherapy (plus dexamethasone in patients with a suboptimal response) administered to 202 patients with relapsed or refractory (RR) MM was associated with an ORR of 35%. The median duration of response (DOR) was 12 months, and median OS was 16 months.[17 Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med*. 2003;348:2609–2617.[CrossRef], [PubMed], [Web of Science ®] The phase-III APEX study confirmed the efficacy of single-agent bortezomib in RR MM.[18 Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2005;352:2487–2498.[CrossRef], [PubMed], [Web of Science ®] The study included 669 RR MM patients with a median of two prior therapies who were randomized to intravenous (IV) bortezomib or intensive high-dose dexamethasone. Bortezomib was superior in terms of ORR (38% vs. 18%, $p < .001$), median TTP (6.2 vs. 3.5 months, $p < .001$) and one-year OS rate (80% vs. 66%, $p = .003$). Bortezomib activity was independent of chromosomal abnormalities such as del(13) and t(4;14).[19 Sagaster V, Ludwig H, Kaufmann H, et al. Bortezomib in relapsed multiple myeloma: response

rates and duration of response are independent of a chromosome 13q-deletion. *Leukemia*. 2007;21:164–168.[CrossRef], [PubMed], [Web of Science ®]] Major bortezomib-related toxicities included peripheral neuropathy, gastrointestinal symptoms, fatigue, thrombocytopenia, neutropenia, and herpes zoster reactivation. The addition of dexamethasone to IV bortezomib improved rates of response without prohibitive toxicity.[20 Jagannath S, Richardson PG, Barlogie B, et al. Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone. *Haematologica*. 2006;91:929–934.[PubMed], [Web of Science ®]]

In contrast to bortezomib, carfilzomib is an irreversible proteasome inhibitor.[21 Demo SD, Kirk CJ, Aujay MA, et al. Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome. *Cancer Res*. 2007;67:6383–6391.[CrossRef], [PubMed], [Web of Science ®]] Two parallel phase-II studies, PX-171-003-A1 and PX-171-004, evaluated carfilzomib in patients with RR MM. In the open-label, single-arm phase-II PX-171-003-A1 study, patients received carfilzomib 20 mg/m² IV twice weekly for 3 out of 4 weeks in cycle 1, then 27 mg/m² in a similar schedule for up to 12 cycles. Patients had a median of 5 prior lines of therapy including 75% with a prior ASCT and 80% were refractory to or intolerant of both bortezomib and lenalidomide. ORR was 24% with median DOR of 7.8 months and a median OS of 15.6 months. Common adverse events included fatigue, anemia, nausea, and thrombocytopenia. Twelve percent experienced peripheral neuropathy, primarily grades 1 to 2. Some significant cardiopulmonary toxicity as well as renal dysfunction was also encountered.[22 Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood*. 2012;120:2817–2825.[CrossRef], [PubMed], [Web of Science ®]]

In the PX-171-004 study, carfilzomib with low-dose dexamethasone premedication was given to two cohorts of bortezomib-naïve RR MM patients. Patients in cohort 1 received IV carfilzomib 20 mg/m² for all treatment cycles, while those in cohort 2 received 20 mg/m² in cycle 1 and 27 mg/m² in subsequent cycles. The ORR was 59% and 64% in cohorts 1 and 2, respectively. Median DOR was 13 months and not reached, and median TTP was 8 months and not reached, respectively.[23 Vij R, Wang M, Kaufman JL, et al. An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naïve patients with relapsed and/or refractory multiple myeloma. *Blood*. 2012;119:5661–5670.[CrossRef], [PubMed], [Web of Science ®]]

The ENDEAVOR study [24 Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomized, phase 3, open-label, multicentre study. *Lancet Oncol*. 2016;17:27–38.[CrossRef], [PubMed], [Web of Science ®]] compared bortezomib–dexamethasone with carfilzomib–dexamethasone in 922 patients with relapsed/refractory myeloma, of whom 58% had previously undergone an ASCT. Patients received treatment with carfilzomib (20 mg/m² on days 1 and 2 of cycle 1; 56 mg/m² thereafter) or bortezomib (1.3 mg/m²; intravenous bolus or subcutaneous injection). Median progression-free survival was superior in the carfilzomib group compared to the bortezomib group (18.7 months vs. 9.4 months). Serious adverse events were reported in 48% of the patients in the carfilzomib group and in 36% of the patients in the bortezomib group. Importantly, the toxicity profiles differed between the two proteasome inhibitor groups, with cardiopulmonary events occurring more frequently in the patients treated with carfilzomib, but with higher neuropathy rates in the bortezomib group. Discontinuation rates were comparable in the two groups.

Recent phase-I and phase-II trials of the orally bioavailable proteasome inhibitor ixazomib showed that the drug has promising single-agent activity in relapsed myeloma along with a favorable toxicity profile and that addition of dexamethasone enhances the response rates.[25–27 Kumar SK,

LaPlant B, Roy V, et al. Phase 2 trial of ixazomib in patients with relapsed multiple myeloma not refractory to bortezomib. *Blood Cancer J.* 2015;5:e338.
 Richardson PG, Baz R, Wang M, et al. Phase 1 study of twice-weekly ixazomib, an oral proteasome inhibitor, in relapsed/refractory multiple myeloma patients. *Blood.* 2014;124:1038–1046.
 Kumar SK, Bensinger WI, Zimmerman TM, et al. Phase 1 study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma. *Blood.* 2014;124:1047–1055.] The findings suggest an important role for this two-drug combination and have informed further clinical development (also refer to the following section).

Triplet combinations incorporating an IMiDs and a proteasome inhibitor

IMiDs are now combined with other very active drugs and especially with the proteasome inhibitors and the monoclonal antibodies (Table 1). The most active three drug combinations are currently bortezomib plus thalidomide and dexamethasone (VTD), lenalidomide (Revlimid®) plus dexamethasone with either bortezomib (RVD or VRD), carfilzomib (CRD) or ixazomib or with the monoclonal antibodies elotuzumab or daratumumab. HDAC inhibitors in different combinations are also under investigation.

Table 1. Pivotal randomized phase-III clinical trials with triple combinations in the relapse setting.

Regimen [Ref]	Phase	n	ORR %	≥PR%	≥VGPR%	CR/nCR%	TTP mo	PFS mo	OS mo
VTD	III	135	93	86	61	45	19.5	18.3	2 years 71%
TD [29]		134	83	74	38	21	13.8	13.6	2 years 65%
Btz + Dex + Pano	III	387	60	33		27	12	11	NA
Btz + Dex [28]		381	54	39		15	8	8	NA
Len dex + Carfil	III	396	87	87	69	31	NA	26	2 years 73%
Len dex [31]		396	66	66	40	9		17	2 years 65%
Len dex + Elo	III	321	79	46	33	4	NA	19	NA
Len dex [38]		325	66	38	28	7	NA	14	NA
Len dex + Ixazomib	III	360	78	66	48	11	21	20	NA
Len dex [32]		362	71	64	39	6	15	14	NA

Btz: bortezomib; Carfil: suppress the z; CR/nCR: complete response/near complete response; Dex: dexamethasone; Elo: elotuzumab; Len: lenalidomide; mo: median months; NA: not available; ORR: overall response rate; OS: overall survival; Pano: panobinostat; PFS: progression-free survival; PR: partial remission; TD: thalidomide dexamethasone; TTP: time to progression; VGPR: very good partial remission; VTD: velcade thalidomide dexamethasone.

The superiority of a triplet combination over a doublet in the relapse setting post ASCT was first demonstrated in 2012. In a phase-III study that was limited to patients with a first relapse or progression after at least one prior ASCT,[29 Garderet L, Iacobelli S, Moreau P, et al. Superiority of the triple combination of bortezomib-thalidomide-dexamethasone over the dual combination of thalidomide-dexamethasone in patients with multiple myeloma progressing or relapsing after autologous transplantation: the MMVAR/IFM 2005-04 Randomized Phase III Trial from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol.* 2012;30:2475–2482.[CrossRef], [PubMed], [Web of Science ®]] the IFM and EBMT compared the efficacy and safety of a PI-containing triple combination (bortezomib–thalidomide–dexamethasone [VTD]) with that of thalidomide–dexamethasone (TD). VTD resulted in a significantly longer median time to progression (19.5 vs. 13.8 months), a higher complete response plus near-complete response rate (45% vs. 21%), and a longer median duration of response (17.9 vs. 13.4 months) compared to TD. However, peripheral neuropathy, infection, and thrombocytopenia were significantly more frequent with VTD.

In a phase-II study of bortezomib and dexamethasone in combination with lenalidomide in patients with RR MM, of whom 36% had received a prior ASCT, median progression-free and overall survival were 9.5 and 30 months, respectively.[30 Richardson PG, Xie W, Jagannath S, et al. A phase 2 trial of lenalidomide, bortezomib, and dexamethasone in patients with relapsed and relapsed/refractory myeloma. *Blood*. 2014;123:1461–1469.[CrossRef], [PubMed], [Web of Science ®]] In this study, the triple combination was considered tolerable with a very low rate of grade 3/4 neuropathies (3%).

The ASPIRE investigators compared carfilzomib–lenalidomide–dexamethasone to lenalidomide–dexamethasone in relapsed/refractory myeloma patients, of whom 56% had previously undergone an ASCT.[31 Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2015;372:142–152.[CrossRef], [PubMed], [Web of Science ®]] Median progression-free survival was significantly improved with carfilzomib compared with the control group (26.3 months vs. 17.6 months). A complete response or better was observed in 31.8% and 9.3% of patients in the respective groups. Adverse events of grade 3 or higher were reported in 83.7% and 80.7% of patients in the carfilzomib and control groups, respectively; 15.3% and 17.7% of patients discontinued treatment owing to adverse events. Importantly, patients treated with the three-drug regimen reported superior health-related quality of life and there was a trend toward improved overall survival in the carfilzomib group.

The phase-III TOURMALINE-MM1 study (NCT01564537) results reported at the 2015 Annual Meeting of the American Society of Hematology showed that addition of the oral proteasome inhibitor ixazomib to lenalidomide–dexamethasone improved median progression-free survival from 14.7 to 20.6 months and VGPR + CR rates from 39% to 48.1%, at comparable adverse event rates in RR MM patients that were not refractory to lenalidomide or proteasome inhibitor-based therapy.[32 Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2016;374:1621–1634.[CrossRef], [PubMed], [Web of Science ®]]

While other drug combinations including proteasome inhibitors (such as those including cyclophosphamide or adriamycin, both with dexamethasone) have been reported or are still being investigated, and with the limitations of cross-trial comparisons, the triple combination of carfilzomib–lenalidomide–dexamethasone as investigated in the ASPIRE trial should probably be considered as the current most effective proteasome inhibitor-based regimens in RR MM.

For pomalidomide, the most promising combinations are those with cyclophosphamide or bortezomib. In a phase-II trial involving patients with RR MM who were lenalidomide refractory and received at least two prior therapies, patients received pomalidomide 4 mg days 1–21 plus weekly dexamethasone 40 mg in a 28-day cycle, with or without oral cyclophosphamide 400 mg days 1, 8, and 15. The triple combination pomalidomide–cyclophosphamide–dex was superior with a rate of PR or better of 65%, a PFS of 9.2 months and an OS of 16.4 months.[33 Baz R, Martin TG, Lin HY, et al. Randomized multicenter phase II study of pomalidomide, cyclophosphamide, and dexamethasone in relapsed refractory myeloma. *Blood*. 2016;127:2561–2568.[CrossRef], [PubMed], [Web of Science ®]] A phase-III study is ongoing comparing pomalidomide dexamethasone with or without bortezomib.[34 Richardson PG, Craig Hofmeister C, Raje NS, et al. A phase 1, multicenter study of pomalidomide, bortezomib, and low-dose dexamethasone in patients with proteasome inhibitor exposed and lenalidomide-refractory myeloma (Trial MM-005). *ASH annual meeting*, 2015. Abst 3036.]

Monoclonal antibodies

The use of monoclonal antibodies (mAbs) are emerging as new successful therapeutic strategies in multiple myeloma. Of these, CD38 (daratumumab, isatuximab, MOR202) and SLAMF7 (Elotuzumab) targeting mAbs are most advanced in clinical development.[35–38 Lokhorst HM, Plesner T, Laubach, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med.* 2015;373:1207–1219. Martin K, Strickland S, Glenn M, et al. A phase I trial of SAR650984, a CD38 monoclonal antibody, in relapsed or refractory multiple myeloma. *J Clin Oncol.* 2014;32:8532. Raab S, Goldschmidt H, Agis, et al. A phase 1/2a study of the human anti-CD38 antibody MOR202 (MOR03087) in relapsed or refractory multiple myeloma. *Haematologica.* 2015;100:S789. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med.* 2015;373:621–631.] Daratumumab and isatuximab have marked single-agent activity in extensively pretreated MM and show enhanced efficacy combined with other agents, especially with IMiDs (Table 2). Elotuzumab has no single-agent activity in advanced MM; however, significantly improved progression-free survival was shown when elotuzumab was combined with lenalidomide–dexamethasone or bortezomib–dexamethasone (Table 1).

Table 2. Anti-CD38 Monoclonal antibodies phase-I and phase-II studies.

Regimen (ref)	Phase	n	≥PR%	≥VGPR%	CR/nCR%	PFS/OS mo	Main toxicity
Daratumumab [35]	I-II	42	36	10	5	PFS:5.6/NA	IRR: 71% Fatigue, allergic rhinitis Grade 3/4: Pneumonia, thrombocytopenia
Daratumumab [46]	II	106	29	13	2.8 sCR	NA/OS:17.5	IRR:42% Fatigue, anemia
Isatuximab [36]	I	18	33	NA	11	NA	IRR: 50%
Len dex + Daratumumab [51]	I-II	32	34	53	25	NA	IRR: 56%
Len dex + Isatuximab [36]	I-II	12	58	33	NA	NA	Nausea, cough, fatigue Grade ^{3/4} : neutropenia, thrombocytopenia
Pom dex + Daratumumab [52]	Ib	77	58	30	7	NA	IRR: 61%

CR/nCR: complete response/near complete response; Dara: daratumumab; Dex: dexamethasone; IRR: infusion-related reaction; Len: lenalidomide; mo: median months; NA: not available; OS: overall survival; PFS: progression-free survival; Pom: pomalidomide; PR: partial remission; VGPR: very good partial remission.

Various mechanisms explain the workings of these antibodies, which include direct induction of apoptosis, complement dependent cytotoxicity (CDC), antibody dependent cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP).[39–41 van de Donk NW, Kamps S, Mutis T, et al. Monoclonal antibody-based therapy as a new treatment strategy in multiple myeloma. *Leukemia.* 2012;26:199–213.

Balasa B, Yun R, Belmar NA, et al. Elotuzumab enhances natural killer cell activation and myeloma cell killing through interleukin-2 and TNF-alpha pathways. *Cancer Immunol Immunother.* 2015;64:61–73.

Overdijk MB, Verploegen S, Bogels M, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. *MAbs.* 2015;7:311–321.]

CD38

CD38 is a 46 kDa type-II transmembrane glycoprotein.[42 Malavasi F, Funaro A, Roggero S, et al. Human CD38: a glycoprotein in search of a function. *Immunol Today* 1994;15:95–96.[CrossRef],

[PubMed],⁴³ de Weers M, Tai YT, van der Veer, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol.* 2011;186:1840–1848.[CrossRef], [PubMed], [Web of Science ®]] Lymphoid as well as myeloid but also nonhematopoietic tissues express CD38 on their surface.[⁴⁴ Deaglio S, Mehta K, Malavasi F. Human CD38: a (r)evolutionary story of enzymes and receptors. *Leukemia Res.* 2001;25:1–12.[CrossRef], [PubMed], [Web of Science ®]] Virtually all MM cells express high levels of CD38, similar to normal plasma cells.[⁴³ de Weers M, Tai YT, van der Veer, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol.* 2011;186:1840–1848.[CrossRef], [PubMed], [Web of Science ®],⁴⁴ Deaglio S, Mehta K, Malavasi F. Human CD38: a (r)evolutionary story of enzymes and receptors. *Leukemia Res.* 2001;25:1–12.[CrossRef], [PubMed], [Web of Science ®]] CD 38 is also expressed on 80% of resting NK cells and monocytes (at lower levels) and interestingly also on activated T cells and subsets of various immune effector cells including dendritic cells, regulatory T cells and myeloid-derived suppressor cells.[⁴⁵ Krejcik J, Casneuf T, Nijhof I, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood.* 2016;128:384–394.[CrossRef], [PubMed]] Of note, CD38 is also expressed in lungs leading to common infusion reactions, and red blood cells leading to inability to cross match blood in patients in need of transfusions.

Daratumumab

Daratumumab is a human IgG1 (κ subclass) antibody blocking the CD38 molecule. It binds specifically to amino acids 233–246 and 267–280 of CD38 that enables an optimal interaction between the Fc portion of the antibody and complement or antibody dependent cytotoxic cells.[⁴³ de Weers M, Tai YT, van der Veer, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol.* 2011;186:1840–1848.[CrossRef], [PubMed], [Web of Science ®]]

In a phase-I–II clinical trial (GEN501 study), daratumumab as a single agent was evaluated in relapsed MM or MM refractory to two or more previous lines of therapy, including Auto-SCT in the majority of patients.[³⁵ Lokhorst HM, Plesner T, Laubach, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med.* 2015;373:1207–1219.[CrossRef], [PubMed], [Web of Science ®]] Part 1 of the study had a dose escalation design and in part 2 different dosing schedules were devised. In part 1, the maximum tolerated dose was not reached. In 16 mg/kg cohort of part 2, the overall response rate (ORR) was 36% with 15 patients showing at least PR, including two patients with VGPR and two with CR. ORR were lower in the 8 mg/kg cohort (10%). Median PFS in the 16 mg/kg groups was 5.6 months, while 65% of responding patients had not progressed until 12 months of follow-up. Daratumumab infusion appeared to be safe. In part 2 of the GEN501 study, 48% of patients experienced infusion-related reactions which were mild (all grades, 71%; grade 3, 1%), mainly restricted to the first infusion.

The encouraging results of the GEN501 were corroborated by Lonial et al. in the SIRIUS (MMY 2002) trial which enrolled 106 patients – the majority refractory to bortezomib or lenalidomide and had received a median of 5 prior lines of treatment, including 80% with a prior ASCT. Patients treated with 16 mg/kg daratumumab, featured a PR in 29% with sCR in 3% of the patients. Median PFS was 3.7 months with a one year OS of 65%. 21% of those patients that were refractory to bortezomib, carfilzomib, pomalidomide, or lenalidomide showed PRs or better.[⁴⁶ Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomized, phase 2 trial. *Lancet.* 2016;387:1551–1560.[CrossRef], [PubMed], [Web of Science ®]]

Usmani et al. presented at ASH 2015 the combined analysis of 146 patients treated with 16 mg/kg daratumumab of the GEN501 and SIRIUS trial.[47 Usmani A, Weiss B, Bahlis NJ, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. *Blood*. 2015;126:29.] The ORR was 31%, duration of response was 7.6 months and 46% of responders remained progression free at 1 year after a median follow-up of 9.3 month. In this combined analysis after a median follow-up of 14.8 months, estimated OS was 19.9 months. Importantly, ORR was similar irrespective of ISS, number of prior therapies and refractory status.

Isatuximab and MOR 202

Isatuximab has been evaluated in relapsed/refractory MM patients in a dose escalation study. With dosing up to 20 mg/kg the MTD was not reached and in 18 heavily pretreated patients a dose of 10 mg isatuximab induced at least PR in 33% including CR in 11%.[36 Martin K, Strickland S, Glenn M, et al. A phase I trial of SAR650984, a CD38 monoclonal antibody, in relapsed or refractory multiple myeloma. *J Clin Oncol*. 2014;32:8532.[CrossRef]] In an ongoing phase-I dose-escalation study, MOR202 is well tolerated and the MTD has not been reached. Some long-lasting tumor control has been observed.[37 Raab S, Goldschmidt H, Agis, et al. A phase 1/2a study of the human anti-CD38 antibody MOR202 (MOR03087) in relapsed or refractory multiple myeloma. *Haematologica*. 2015;100:S789.]

Combination therapies including monoclonal antibodies

IMiDs

The rationale for combining IMiDs with elotuzumab and CD38 targeting mAbs comes from preclinical studies showing the activation of the effector cells of ADCC by lenalidomide.[48–50 Collins SM, Bakan CE, Swartzel GD, et al. Elotuzumab directly enhances NK cell cytotoxicity against myeloma via CS1 ligation: evidence for augmented NK cell function complementing ADCC. *Cancer Immunol Immunother*. 2013;62:1841–1849. van der Veer MS, de Weers M, van Kessel B, et al. Towards effective immunotherapy of myeloma: enhanced elimination of myeloma cells by combination of lenalidomide with the human CD38 monoclonal antibody daratumumab. *Haematologica*. 2011;96:284–290. Endell J, Boxhammer R, Wurzenberger C, et al. The activity of MOR202, a fully human anti-CD38 antibody, is complemented by ADCP and is synergistically enhanced by lenalidomide in vitro and in vivo. *Blood*. 2012;120:4018.]

In the randomized phase-III trial (ELOQUENT-2) in RR MM (1–3 prior therapies), elotuzumab (10 mg/kg) combined with lenalidomide–dexamethasone improved median PFS by 4.5 months (14.9 to 19.4 months), as compared to lenalidomide–dexamethasone. This PFS benefit was independent of age (patients 65 years of age or older), presence of del(17p), or creatinine clearance of less than 60 ml/min. Also the overall response rate was higher in the elotuzumab group compared to the control group (79% vs. 66%).[38 Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med*. 2015;373:621–631.[CrossRef], [PubMed], [Web of Science ®]]

Phase-I–II trials of daratumumab and isatuximab with lenalidomide–dexamethasone in RR MM showed impressively high response rates that improved over time. Interestingly, response (\geq PR: 48%) was also achieved in lenalidomide-refractory patients.[36 Martin K, Strickland S, Glenn M, et al. A phase I trial of SAR650984, a CD38 monoclonal antibody, in relapsed or refractory multiple myeloma. *J Clin Oncol*. 2014;32:8532.[CrossRef],51 Plesner T, Arkenau H, Gimsing P, et al. Daratumumab in combination with lenalidomide and dexamethasone in patients with relapsed

or relapsed and refractory multiple myeloma: updated results of a phase 1/2 study (GEN503). *Blood*. 2015;126:507.] Pomalidomide combined with daratumumab induced a high overall response rate in RR MM patients including a \geq PR: 67% in double refractory patients.[52 Chari A, Lonial S, Suvannasankha A, et al. Open-label, multicenter, phase 1b study of daratumumab in combination with pomalidomide and dexamethasone in patients with at least 2 lines of prior therapy and relapsed or relapsed and refractory multiple myeloma. *Blood*. 2015;126:508.[CrossRef], [PubMed], [Web of Science ®]]

Immune-modulating effects by daratumumab: contributing to efficacy?

Immune monitoring of patients included in GEN501 and SIRIUS trials showed robust immune effects (T cell increases, increased CD8+/CD4 + ratios, increased antiviral responses, and increased T cell clonality) which were surprising to observe in heavily pretreated, relapsed and refractory patients. Improved clinical responses were associated with changes in these parameters. Additionally, a subpopulation of regulatory T cells expressing high CD38 levels and known to be extremely immune suppressive were completely eliminated by daratumumab treatment. These data suggest a previously unknown immune modulatory role of daratumumab that may contribute to its efficacy, and a potential role for CD38 immune-targeted therapies.[45 Krejcik J, Casneuf T, Nijhof I, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood*. 2016;128:384–394.[CrossRef], [PubMed]]

Autologous stem cell transplantation

To date, multiple reports of salvage autologous stem cell transplantation (sASCT) have been published, though they are primarily retrospective single center or registry-based studies [53–55 Lemieux E, Hulin C, Caillot D, et al. Autologous stem cell transplantation: an effective salvage therapy in multiple myeloma. *Biol Blood Marrow Transplant*. 2013;19:445–449. Jimenez-Zepeda VH, Mikhael J, Winter A, et al. Second autologous stem cell transplantation as salvage therapy for multiple myeloma: impact on progression-free and overall survival. *Biol Blood Marrow Transplant*. 2012;18:773–779. Grovdal M, Nahi H, Gahrton G, et al. Autologous stem cell transplantation versus novel drugs or conventional chemotherapy for patients with relapsed multiple myeloma after previous ASCT. *Bone Marrow Transplant*. 2015;50:808–812.] (Table 3). Nonetheless, these studies highlighted the clinical utility and feasibility of sASCT, primarily where there is clear evidence of chemo-sensitive disease at relapse and under-pinned the prognostic impact of remission duration after first ASCT.[56 Kobayashi T, Kuroda J, Fuchida S, et al. The response to second-line induction with bortezomib and dexamethasone is predictive of long-term outcomes prior to high-dose chemotherapy with autologous stem cell transplantation for multiple myeloma. *Intern Med*. 2013;52:961–968.[CrossRef], [PubMed], [Web of Science ®]] Most reports identified that the number of prior lines of prior therapy had a significant impact on outcomes suggestive of the most appropriate timing of sASCT.[57 Fenk R, Liese V, Neubauer F, et al. Predictive factors for successful salvage high-dose therapy in patients with multiple myeloma relapsing after autologous blood stem cell transplantation. *Leuk Lymphoma*. 2011;52:1455–1462.[Taylor & Francis Online], [Web of Science ®]] There has been however no data to direct clinicians in the timing of sASCT, that is, whether at biochemical or symptomatic relapse. In the EBMT database, since 1995, 38,741 MM patients were reported to be in first relapse post-ASCT; however, most patients (83%) did not undergo a sASCT. When examined in a temporal setting, though sASCT was performed in 4443 patients, there has been a constant increase in the sASCT year on year to more than 500 patients per year since 2012 (Figure 1).

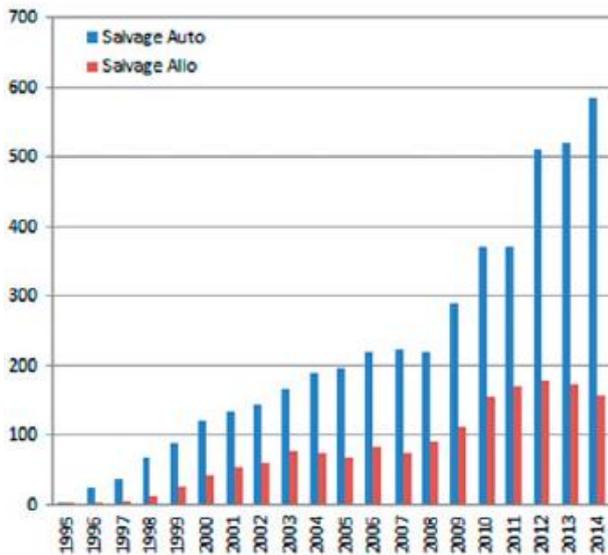


Figure 1. Since 1995, evolution of autologous and allogeneic stem cell transplantation performed to treat relapse occurring after an initial autologous transplantation in Europe (EBMT registry).

Table 3. Autologous and allogeneic stem cell transplantation studies in the relapse setting postautograft.

Study [Ref]	Phase	n	≥PR%	≥VGPR%	CR/nCR%	NRM %	RR %	PFS mo	OS mo
Auto Myeloma X [58]	Pro	297	79%	59%	39.3%	1	79%	19	67
Auto [62]	Retro	137	NA	NA	NA	4	91	5 years 4%	5 years 29%
Auto [61]	Retro	94	NA	NA	NA	1	81	2 years 18%	2 years 54%
Auto [64]	Retro	42	71%	NA	33%	10	72	NA	3 years 54%
Auto [65]	Retro	14	64%	NA	21%	7	NA	6.8	29
Auto [66]	Retro	27	NA	56%	NA	3.7	NA	19	23
Allo [62]	Retro	152	NA	NA	NA	15	83	5 years 2%	5 years 9%
Allo [61]	Retro	75	12%	28%	17.6%	22	48	2 years 42%	2 years 53%
Allo [63]	Retro	19	NA	NA	NA	33	22	3 years 46%	3 years 93%
Allo [64]	Retro	42	41%	NA	21%	43	33	NA	3 years 29%
Allo [65]	Retro	26	69%	NA	31%	11	NA	7.3	13
Allo [66]	Retro	19	NA	37%	NA	5.3	NA	6	19

Auto: autologous stem cell transplantation; Allo: allogeneic stem cell transplantation; CR/nCR: complete response/near complete response; mo: median months; NA: not available; NRM: nonrelapse mortality; OS: overall survival; PFS: progression-free survival; Pro: prospective; PR: partial remission; Retro: retrospective; RR: relapse rate; VGPR: very good partial remission.

The first prospective randomized trial studying sASCT versus nontransplant consolidation (NTC) after first relapse and reinduction with a bortezomib-containing regimen has been reported by Cook et al.[58 Cook G, Williams C, Brown JM, et al. High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomized, open-label, phase 3 trial. *Lancet Oncol.* 2014;15:874–885.[CrossRef], [PubMed], [Web of Science ®]] This multicenter, randomized, open-label, phase-III study recruited patients with relapsed myeloma after a previous ASCT, reinducing disease control using a bortezomib-based regimen. Chemosensitive patients were randomly assigned (1:1), to sASCT or NTC consisting of oral cyclophosphamide (400 mg/m² per week for 12 weeks). This trial showed a clear advantage in

terms of time to progression, (19 vs. 11 months; $p < .0001$) for sASCT compared to NTC. Now, with extended follow-up and poststudy relapse management details, there is evidence of a clear advantage in the PFS2 postdisease progression in the sASCT versus NTC cohort, despite the use of sASCT at on-protocol progression in a cohort of the NTC patients, as presented at ASH 2015. Furthermore, with a median follow-up which is 52 months, the median survival was superior in the sASCT compared with NTC cohorts (67 vs. 52 months; Log Rank $p = .022$). A reduced hazard of death in the sASCT group compared to NTC (HR = 0.56, 95%CI: [0.35, 0.90], $p = .0169$) was evident with CR/sCR to re-induction therapy (HR 0.14, $p = .032$), β_2 M level < 3.5 mg/L (HR 0.35, $p = .039$) and the absence of high-risk *iFISH* (HR 0.36, $p = .007$) associated with improved OS in favor of sASCT (manuscript in preparation). To date, this advantage in postprogression management and survivorship is not at the expense of an increased risk of second primary malignancies. It should however be mentioned that, nowadays, single-agent cyclophosphamide control arm is not a standard consolidation method for RRMM.

This study, incorporated into the international relapsed myeloma guidelines, highlights several issues that need to be addressed prospectively. Though offering a dataset on which to base clinical decision making, the role of sASCT in the setting of IMiD or combined IMiD and PI usage remains to be clarified. Furthermore, the role of post-sASCT consolidation and maintenance has not been addressed. Both these issues will be addressed in the up and coming UKMRA Myeloma XII study (http://medhealth.leeds.ac.uk/info/410/haematological_oncology/1760/haematological_oncology) due to commence recruitment in Q2 of 2016. UKMRA Myeloma XII study aims, firstly, to determine what the impact on depth of response will be when sASCT conditioning is augmented by the addition of a proteasome inhibitor and, secondly, what will the influence on durability of response be with post-sASCT consolidation and maintenance therapy. In this study, induction treatment will use an Ixazomib-containing induction regimen (ixazomib/thalidomide/dexamethasone; ITD), which will build on the proven efficacy of PI/IMiD combinations. Furthermore, following the sASCT randomization comparing a conventional and an augmented transplant schema, an ixazomib-containing consolidation and maintenance strategy will be tested. Incorporated into this study is a comprehensive assessment to define the MRD^{negative} rate postreinduction, post-sASCT and conversion after ITD consolidation.

The last issue that needs addressing is that of availability of sufficient PBSC for a sASCT. For many patients, it was not possible to collect enough hematopoietic stem cells or, for logistical reason enough stem cells were not collected and stored, that would support two transplants. Until recently there has been no data to indicate if re-mobilization after a prior ASCT is feasible. The myeloma X study has shown that PBSC can be remobilized successful in 55–60% of patients.[59 Parrish C, Morris CT, Williams CD, et al. Stem cell harvesting after bortezomib-based re-induction for myeloma relapsing after autologous transplant: results from the BSBMT/UKMF myeloma X (Intensive) trial. *Biol Blood Marrow Transplant*. 2016;22:1009–1016.[CrossRef], [PubMed], [Web of Science ®]] There is an outstanding question, though, about whether such remobilized cells have any evidence of the replicative stresses induced by a previous transplant, either functionally or genomically. Myeloma X has not provided any evidence on this subject and no such data exists in the human system but, ongoing research will hopefully answer this issue in time.

Thus, with long-term follow-up analysis, a sASCT offers both a disease control durability and a survival advantage when compared to a NTC, after bortezomib-based reinduction therapy in patients with MM relapsing after a prior ASCT. These data are key for patient-centered clinical decision making.[4 Giralt S, Garderet L, Durie B, et al. American Society of Blood and Marrow Transplant, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network and International Myeloma Working Group Consensus conference on

salvage hematopoietic cell transplantation in patients with relapsed multiple myeloma. *Biol Blood Marrow Transplant.* 2015;21:2039–2051.[CrossRef], [PubMed], [Web of Science ®]

Allogeneic stem cell transplantation

In myeloma, allogeneic stem cell transplantation is mostly performed in the relapse setting. The EBMT data registry shows that the numbers are still increasing over the years (Figure 1). Most reports on allografting as rescue strategy after a previous autograft have been single-center or retrospective registry analyses.[4 Giral S, Garderet L, Durie B, et al. American Society of Blood and Marrow Transplant, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network and International Myeloma Working Group Consensus conference on salvage hematopoietic cell transplantation in patients with relapsed multiple myeloma. *Biol Blood Marrow Transplant.* 2015;21:2039–2051.[CrossRef], [PubMed], [Web of Science ®],60 Lokhorst H, Einsele H, Vesole D, et al. International Myeloma Working Group consensus statement regarding the current status of allogeneic stem-cell transplantation for multiple myeloma. *J Clin Oncol.* 2010;28:4521–4530.[CrossRef], [PubMed], [Web of Science ®],61 Festuccia M, Martino M, Ferrando F, et al. Allogeneic stem cell transplantation in multiple myeloma: immunotherapy and new drugs. *Expert Opin Biol Ther.* 2015;15:857–872.[Taylor & Francis Online], [Web of Science ®]] Some retrospective studies have compared allogeneic to autologous stem cell transplantation.[62–66 Freytes CO, Vesole DH, LeRademacher L, et al. Second transplants for multiple myeloma relapsing after a previous autotransplant—reduced-intensity allogeneic vs autologous transplantation. *Bone Marrow Transplant.* 2014;49:416–421. De Lavallade H, El-Cheikh J, Faucher C, et al. Reduced-intensity conditioning allogeneic SCT as salvage treatment for relapsed multiple myeloma. *Bone Marrow Transplant.* 2008;41:953–960. Mehta J, Tricot G, Jagannath S, et al. Salvage autologous or allogeneic transplantation for multiple myeloma refractory to or relapsing after a first-line autograft. *Bone Marrow Transplant.* 1998;21:887–892.

Qazilbash MH, Saliba R, De Lima M, et al. Second autologous or allogeneic transplantation after the failure of first autograft in patients with multiple myeloma. *Cancer.* 2006;106:1084–1089. Wirk B, Byrne M, Dai Y, et al. Outcomes of salvage autologous versus allogeneic hematopoietic cell transplantation for relapsed multiple myeloma after initial autologous hematopoietic cell transplantation. *J Clin Med Res.* 2013;5:174–184.] Overall, these studies showed the feasibility of allografting in relapsed multiple myeloma even though they included heterogeneous patient groups, differences in conditioning regimens and supportive care. Of note, Patriarca et al. reported an interesting study based on the availability of a suitable donor either related or unrelated in patients who relapsed after a first-line autograft.[67 Patriarca F, Einsele H, Spina F, et al. Allogeneic stem cell transplantation in multiple myeloma relapsed after autograft: a multicenter retrospective study based on donor availability. *Biol Blood Marrow Transplant.* 2012;18:617–626.[CrossRef], [PubMed], [Web of Science ®],68 Patriarca F, Einsele H, Spina B, et al. Long term follow-up of a multicenter retrospective study based on donor availability in multiple myeloma patients relapsed after autotransplant. *Hematologica.* 2015;100:B 011.] One-hundred sixty-nine consecutive patients underwent HLA typing at disease recurrence. The study was designed on the intent to treat principle and included only those patients who underwent HLA typing immediately after the relapse. Of the 169 consecutive patients evaluated, 75 had found a donor and 72 (96%) underwent an allograft after reduced-intensity conditionings. Twenty-four transplants were from a HLA-identical sibling (32%) and 48 from an unrelated donor (68%). The two-year nonrelapse mortality was 22% in patients with a HLA-compatible donor (donor group) versus 1% for those without (no donor group). In the first report, the two-year progression-free survival and 2-year overall survival were 42% and 54%; and 18% and 53% in the donor group and the no-donor group, respectively.[67 Patriarca F, Einsele H, Spina F, et al. Allogeneic stem cell transplantation in multiple myeloma relapsed after autograft: a multicenter retrospective study based on donor availability. *Biol Blood Marrow Transplant.*

2012;18:617–626.[CrossRef], [PubMed], [Web of Science ®]] Significantly better response ($p < .0001$) did not translate into better short-term overall survival given a higher treatment-related mortality in the donor group. However, in a recent update at a median follow-up of 87 months, presented at the meeting of the Italian Society of Hematology (Florence, 2015),[68 Patriarca F, Einsele H, Spina B, et al. Long term follow-up of a multicenter retrospective study based on donor availability in multiple myeloma patients relapsed after autotransplant. *Hematologica*. 2015;100:B 011.] the 5-year progression-free survival was 21% in the donor group and 3% in the no-donor group ($p < .001$) whereas, importantly, 5-year overall survival was 40% in the donor group and 19% in the no-donor group ($p = .007$), the difference to the advantage of the donor group being significantly higher in this updated report. By multivariate analysis, availability of a donor, chemosensitive disease at the time of the allograft and longer duration of salvage treatment were significant predictors for favorable progression free survival. Moreover, high-risk karyotype at diagnosis was significantly associated with shorter overall survival. Of note, the time interval from the autograft to relapse had no significant impact on clinical outcomes after the allograft. This study further confirms that significant differences in clinical outcomes between ‘donor groups’ and ‘no donor groups’ may be seen only after a number of years of follow-up.

The current paradigm for the treatment of multiple myeloma include novel agents with potent antimyeloma activity, their potentially curative combination with the *graft-vs-myeloma* effect, however, has unfortunately never been explored in well-designed large prospective studies though their efficacy in relapsed patients after an allograft has been reported in many studies.[61 Festuccia M, Martino M, Ferrando F, et al. Allogeneic stem cell transplantation in multiple myeloma: immunotherapy and new drugs. *Expert Opin Biol Ther*. 2015;15:857–872.[Taylor & Francis Online], [Web of Science ®]] Recent reports rather convincingly further support a strong synergy between donor T cells and novel agents. Interestingly, Giaccone et al., in a comparative study, showed higher response rates to salvage therapies with bortezomib-, thalidomide-, or lenalidomide-containing regimens in patients relapsed after an allograft, and significantly longer overall survival from relapse after the allograft than after a second autograft,[69 Giaccone L, Storer B, Patriarca F, et al. Long-term follow-up of a comparison of nonmyeloablative allografting with autografting for newly diagnosed myeloma. *Blood*. 2011;117:6721–6727.[CrossRef], [PubMed], [Web of Science ®]] corroborating with results of the EBMT-NMAM2000 study.[70 Gahrton G, Iacobelli S, Bjorkstrand B, et al. Autologous/reduced-intensity allogeneic stem cell transplantation vs autologous transplantation in multiple myeloma: long-term results of the EBMT-NMAM2000 study. *Blood*. 2013;121:5055–5063.[CrossRef], [PubMed], [Web of Science ®]] Recently, Montefusco et al. reported on a retrospective matched-pair analysis on the use of lenalidomide as salvage therapy after autologous or allogeneic transplantation (personal communication). Lenalidomide was significantly more effective in long-term disease control in the ‘allograft group’ rather than in ‘autograft group’ and this translated into a significantly longer overall survival.

Patient risk stratification should soon help optimize individual therapies. The recently Revised International Staging System by the International Myeloma Working Group showed that there is a group of newly diagnosed patients with high-risk features, including chromosomal abnormalities, where overall and progression-free survivals are very poor even in the era of new drugs.[71 Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol*. 2015;33:2863–2869.[CrossRef], [PubMed], [Web of Science ®]] In this patient group, new effective treatments should be sought especially if relapse occurs early after upfront therapy. In the EBMT NMAM2000 study, a poor prognostic impact – although weak – of del13 chromosomal abnormality seen after ASCT, was abrogated after tandem auto/RIC allogeneic transplantation [72 Bjorkstrand B, Iacobelli S, Hegenbart U, et al. Tandem autologous/reduced-intensity conditioning allogeneic stem-cell transplantation versus autologous transplantation in myeloma: long-term follow-up. *J Clin Oncol*]

2011;29:3016–3022.[CrossRef], [PubMed], [Web of Science ®]] and the negative prognostic impact of high-risk cytogenetics, appeared to be partly neutralized by graft versus myeloma in a recent study.[73 Kröger N, Badbaran A, Zabelina T, et al. Impact of high-risk cytogenetics and achievement of molecular remission on long-term freedom from disease after autologous-allogeneic tandem transplantation in patients with multiple myeloma. Biol Blood Marrow Transplant. 2013;19:398–404.[CrossRef], [PubMed], [Web of Science ®]]

All together, given that myeloma patients invariably relapse despite the recent improvement in overall survival, the case may be made that relapsed patients after an autograft may most benefit from the potentially curative effect of graft versus myeloma and its combination with potent antimyeloma agents especially if high-risk features are present at diagnosis.[74 Kröger N, Shimoni A, Schilling G, et al. Unrelated stem cell transplantation after reduced intensity conditioning for patients with multiple myeloma relapsing after autologous transplantation. Br J Haematol. 2010;148:323–331.[CrossRef], [PubMed], [Web of Science ®]] Consolidation/maintenance postallogeneic transplantation using the novel agents could also improve the outcome.

Conclusions

Even though major therapeutic improvements have emerged to treat myeloma, all patients eventually relapse, perhaps with some exceptions following allogeneic transplantation and some new drug combinations. The treatment algorithm in the relapse setting has become confusing in contrast to the first line treatment where the sequence of induction followed, if eligible, by autologous stem cell transplantation and consolidation is well accepted. We suggest in Figure 2, a treatment pathway starting with different reinduction options according to initial treatment and followed by a transplant or no transplant approach. The role of immunotherapy with the monoclonal antibodies in this treatment algorithm is currently under investigation but it will definitely be an important part of the treatment in the near future.

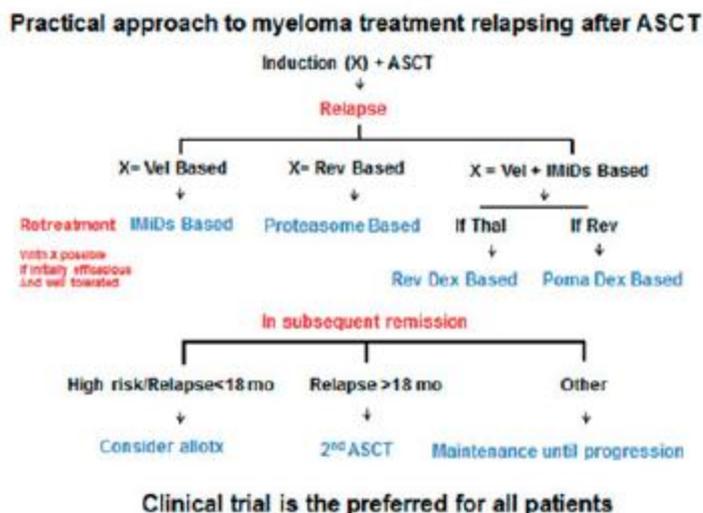


Figure 2. Treatment algorithm for relapse post autologous stem cell transplantation.

Many questions remain

At relapse, should we start treatment at biochemical or at clinical relapse? Should we incorporate in the clinical relapse the new criteria that are used in the first-line treatment namely a bone marrow plasmacytosis above 60% and/or more than one bone lesion on MRI and/or a ratio of involved over uninvolved free light chain above 100?

Do we need to perform an ASCT? There are strong arguments supporting the use of a second ASCT if the relapse occurs at least 18 months after the first ASCT. There is also the scenario of patients treated initially with a tandem ASCT and who relapse sometimes many years later. Can we perform a third transplant and if so what is the outcome? The EBMT is currently conducting a retrospective registry based analysis to answer this question.

Allogeneic transplantation is very much criticized mostly because of its NRM and morbidity. Toxicity has decreased substantially with the use of less myeloablative regimens but at the cost of an increased relapse rate. However, it remains the only potentially curable treatment of myeloma. Much effort will be made in the coming years to improve immunomodulation post allogeneic transplantation incorporating the new drugs. The checkpoint inhibitors may be an opportunity to increase the very potent antimyeloma allogeneic effect. For the time being, one should consider allogeneic transplantation in first relapse in a 'chemosensitive' disease. It is now very clear that it should not be proposed, as it was done in the past, as a 'last ditch' effort to control the disease.

How to obtain a new remission at relapse? It very much depends on the efficacy and toxicity of the previous treatments. Retreatment with the initial combination can be done as long as there is at least a treatment-free interval of 6 months and the treatment was efficacious with an acceptable toxicity. More often, if the first line treatment was bortezomib based, the relapse treatment will be lenalidomide based and vice versa. If a combination of bortezomib plus lenalidomide was given and patients are refractory to these two drugs, we now have access to pomalidomide and carfilzomib. The challenge is now how to treat the quadruple refractory patients.

Should we use a doublet or a triplet? Triplet combinations have shown to be superior both in the first line and the relapse setting with an increased response rate and improved PFS but less convincing results for OS. Triplet gives the opportunity to target more malignant clones at once and leaves less chance for an aggressive clone to emerge. However, at subsequent relapse, one will have access to less treatment option with the initial triplet use compared to the doublet and in the end OS may be similar. Which triplet to use? We will soon have access to at least four triplet options, three lenalidomide–dexamethasone based, namely plus carfilzomib, plus elotuzumab, or plus ixazomib. Except for the combination of lenalidomide dexamethasone plus carfilzomib which has a median PFS of 26 months, the two other combinations have a shorter PFS of around 20 months. The combination of bortezomib plus dexamethasone and panobinostat has a PFS of 11 months. For all four combinations, the toxicity is different as well as their potential efficacy for subpopulations such as high-risk cytogenetic patients.

How long should the treatment be? If the goal is to proceed to transplantation, either autologous or allogeneic, at least a partial remission should be obtained. As in the first-line setting, four cycles are usually given but if the patient has a continuous decrease in its monoclonal peak with an acceptable toxicity, six cycles can be done: the better the response before transplant the better the outcome. Outside of the transplant setting, continuous treatment (maintenance) until the next relapse is more frequently undertaken but side effects may be limiting, while for some patients who experience a very good persistent response a treatment free period can be considered. One remaining question is the dose of steroids and the length of its use. Usually, the dose of steroids is progressively tapered

and stopped after one or two years, but this is very much related to the physician's choice. There is little evidence to assist this decision.

New treatment options are emerging, mostly immune interventions such as bispecific monoclonal antibodies, immune checkpoint inhibitors and CAR T cells. New treatment combinations will emerge with a shift in the treatment paradigm with less, if any, chemotherapy and more targeted drugs and immunotherapy. The first goal is to prolong survival but the ultimate one is cure.

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