ABOUT THE AUTHOR

Richard LeBlanc, MD

Dr Richard LeBlanc is a hematologist and medical oncologist at Maisonneuve-Rosemont hospital. He obtained his MD degree at Laval University in 1995. He was certified in internal medicine in 1998 and in hematology in 2000 at Laval University. Thereafter, he spent two years as a research fellow at the Dana Farber Cancer Institute, Harvard Medical School in Boston, from 2000 to 2002, to develop an expertise in multiple myeloma. In 2004, he completed his training in medical oncology at Montreal University. He is an associate professor of medicine at the department of medicine, Université de Montréal. Since 2012, he is the Myeloma Canada Chair at the Université de Montréal. His practice and interests focus on improvements in care, teaching and research in multiple myeloma.

TO TRANSPLANT OR NOT TO TRANSPLANT IN MULTIPLE MYELOMA

Introduction and benefits of autologous stem cell transplantation

Multiple myeloma (MM) is the second most common hematologic cancer resulting from proliferation and accumulation of abnormal plasma cells (myeloma cells) with a preferential homing in the bone marrow. It causes significant morbidity including lytic bone lesions, renal insufficiency, anemia and infections to name just a few.[1] Although MM remains largely incurable, it is a chemo-sensitive disease. The use of high-dose intravenous melphalan (100-140 mg/m2) in the treatment of MM was first studied almost 4 decades ago.[2] Subsequently, the dose of melphalan was increased and was followed by autologous hematopoietic stem cell to decrease the aplasia-associated toxicity.[3,4] Results from phase 3 studies comparing chemotherapy alone to chemotherapy followed by high-dose melphalan and autologous stem cell transplantation appeared in the mid-90s with the publication of the IFM-90 study[5] demonstrating significant clinical benefits on response rate, event-free survival and even overall survival in a cohort of two hundred previously untreated patients under the age of 65 years. This landmark study was followed by confirmatory studies in the early 2000's.[6-8] Within the last 2 decades, although improvement in the treatment of transplant-eligible patients is mostly the result of better induction regimens[9,10] and due to the addition of maintenance therapies,[11-13] autologous stem cell transplantation remains a cornerstone treatment for MM patients. Indeed, despite novel and more effective treatments for MM, autologous stem cell transplantation continues to demonstrate clinical benefits (**Table 1**).[9,10,14-17] Moreover, tandem autologous transplantation has demonstrated progression-free survival and overall survival benefits for some patients with poor risk cytogenetics.[17]

In 2022, with better knowledge of MM, awareness of potential consequences of high-dose melphalan and with novel and more effective treatment modalities, the role of autologous stem cell transplantation is certainly becoming a question for debate. The purpose of this article is to present the pros and cons of autologous stem cell transplantation in our Canadian reality (**Figure 1**). This article aims to better assess its role as a therapeutic option considering our health system's limited resources in which many novel drugs will not be available/accessible in Canada for several more years to come.

Risk of high-dose melphalan

High-dose melphalan is well known for significant risk of adverse effects such as severe bone marrow suppression which can result in infection or bleeding, severe gastrointestinal toxicity such as nausea, vomiting, diarrhea and mucositis with ulceration that further increase the risk of infection via bacterial translocation, among other risks.[18] The risk of early mortality within the first few months after autologous stem cell transplantation is approximately 1-2%[5] and predominantly the result of infectious complications.

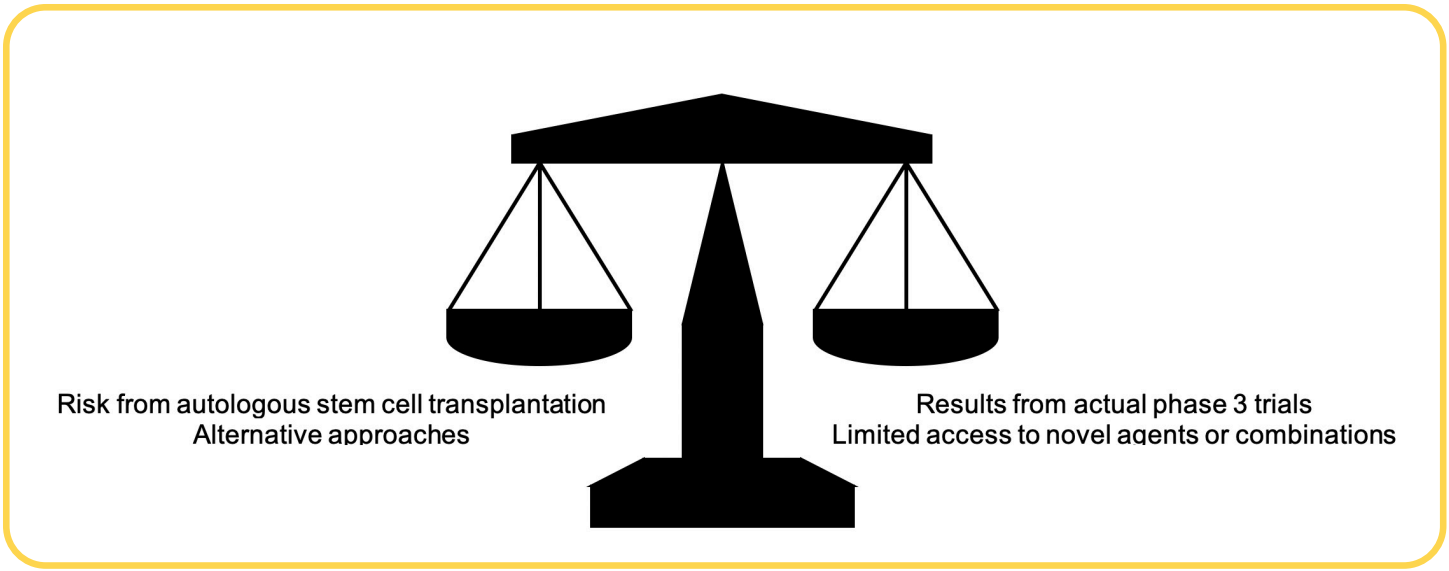

Figure 1. *Weighing the pros and cons of autologous stem cell transplantation; courtesy of Richard LeBlanc, MD*

Beyond the risk of complications and mortality associated with high-dose melphalan is the risk of second primary malignancy. In a retrospective cohort study looking at 841 consecutive MM patients who underwent autologous stem cell transplantation between 1989 and 2009, the overall cumulative incidence of second primary malignancies was found to be 5.3% at 5 years and 11.2% at 10 years when nonmelanoma skin cancers were excluded from the final analysis.[19] In addition, this risk is further increased with the use of lenalidomide in maintenance therapy.[19,20] Melphalan as an alkylating agent that induces DNA damage and high-dose melphalan exposure increases mutational burden detected between diagnosis and relapse by 10-20%.[21] Clinically, melphalan has been shown to increase the relative risk of acute myeloid leukemia by 10-50 fold and the risk of myelodysplastic syndrome by 100 fold in a database analysis of over 9,000 recipients of hematopoietic cell autotransplants between 1995 and 2010 for Hodgkin lymphoma (n = 916), non-Hodgkin lymphoma (n = 3546) and MM (n = 4566), reported to the Center for International Blood and Marrow Transplant Research.[22] This is particularly important since overall survival of myeloma patients is improving. In a recent analysis of 14,532 myeloma patients, the 10-year survival rate favored patients who did not receive transplant.[23] In addition, for long term survivors after autologous stem cell transplantation, the 10-year cumulative incidence of severe and/or life-threatening chronic health conditions is approaching 60%, representing a significant morbidity burden for these patients.[24] As non-transplant regimens become more effective, autologous stem cell transplantation might eventually be regarded as unnecessary and may require a re-examination of its risk-benefit profile.

Alternative approaches

The combination of immunomodulatory drugs and proteasome inhibitors in addition to dexamethasone have been shown to have substantial activity against MM.[25,26] These observed benefits from the combination raise questions about the role of autologous stem cell transplantation. The IFM 2009 study compared the bortezomib-lenalidomide-dexamethasone (VRD) combination in induction and consolidation with or without autologous stem cell transplantation, followed by lenalidomide maintenance as a first line treatment for transplant-eligible patients. Although median progression-free survival was significantly longer in the transplant group (50 months vs 36 months; HR 0.65; p<0.001),[9] a long-term follow-up analysis at 95 months, demonstrated median PFS2 to be similar (HR 0.96; p=0.751) between the two groups as well as the rate of overall survival at 60.2% in the VRD arm compared with 62.2% in the transplant arm (HR 1.03; p=0.815).[27] However, 77% of patients randomized in the non-transplant group in first line treatment received autologous stem cell transplantation at time of relapse.[27] Similarly, the FORTE trial compared the carfilzomib-lenalidomide-dexamethasone (KRd) combination in induction and consolidation with or without autologous stem cell transplantation followed by maintenance therapy in first line treatment for transplant-eligible patients with newly-diagnosed MM and who were aged 65 years or younger. Although the overall response rate was similar in both groups, sustained minimal residual disease negativity rate and progression-free survival were in favor of the transplantation group.[10] These trials still suggest a potential role for autologous stem cell transplantation, although, perhaps, not as first-line treatment (**Table 1**).

Studies References	n	Induction	Intensification	Consolidation	Maintenance	≥PR	≥VGPR	≥CR	MRD	PFS (months)	OS (%)
RV-MM-PI-209[14]	273	Rd x 4	**ASCT x 2 vs MPR x 6**	None	**Len vs none**	- -	- -	36% 34%	NE NE	m: 43.0 m: 22.4	@4y: 81.6% @4y: 65.3%
EMN-441[15]	389	Rd x 4	**ASCT x 2 vs RCd x 6**	None	**Len+pred vs Len alone**	- -	- -	33-37% 23-27%	NE NE	m: 43.3 m: 28.6	@4y: 86% @4y: 73%
EMN02[17]	1197	VCD x 3-4	**ASCT x 1-2 vs VMP x 4**	**VRD x 2 vs none**	Len	95% 95%	84% 77%	44% 40%	NA NA	m: 56.7 m: 41.9	@5y: 75.1% @5y: 71.6%
IFM2009[9]	700	VRD x 3	**ASCT x 1 vs VRD x 3**	VRD x 2	Len x 1y	99% 97%	88% 77%	59% 48%	79%* 65%*	m: 50 m: 36	@4y: 81% @4y: 82%
FORTE[10]	474	**KRd x 4 vs KRd x 4 vs KCd x 4**	**ASCT x 1 KRd x 4 ASCT x 1**	**KRd x 4 KRd x 4 KCd x 4**	**K-Len vs Len alone**	97% 94% 91%	89% 87% 76%	54% 57% 42%	80%# 69%# 73%#	m: NR m: 55.3 m: 53	@4y: 86% @4y: 85% @4y: 76%
MANHATTAN[40]	41	DKRd x 8	As per SoC	-	As per SoC	100%	95%	95%	71%∞	@1y:98%	@1y: 100%

Table 1. *Studies influencing the decision for autologous stem cell transplantation; courtesy of Richard LeBlanc, MD*

** Performed for patients achieving ≥VGPR after consolidation and maintenance (sensitivity level of 10^{-4})*
 # Performed for patients achieving ≥VGPR before maintenance and every 6 months during maintenance (sensitivity level of 10^{-5})
∞ Performed after DKRd for 8 28-day cycles (sensitivity level of 10^{-5})
Abbreviation*: ASCT, autologous stem cell transplantation; CR, complete response; DKRd, daratumumab-carfilzomib-lenalidomide-dexamethasone; K, carfilzomib; KCd, carfilzomib-cyclophosphamide-dexamethasone; KRd, carfilzomib-lenalidomide-dexamethasone; Len, lenalidomide; m, median; MPR, melphalan-prednisone-lenalidomide; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; PR, partial response; pred, prednisone; RCd, lenalidomide-cyclophosphamide-dexamethasone; Rd, lenalidomide-dexamethasone; SoC, standard of care; VCD, bortezomib-cyclophosphamide-dexamethasone; VGPR, very good partial response; VMP, bortezomib-melphalan-prednisone; VRD, bortezomib-lenalidomide-dexamethasone; y, year; @, at.*
*Characters **in bold** represent part of randomization for these studies*

Aside from immunomodulatory drugs and proteasome inhibitors, monoclonal antibodies against CD38 have emerged as very effective therapeutic options available to clinicians. In randomized phase 3 trials, daratumumab has been shown to significantly improve progression-free survival and overall survival, both in first-line treatment[28-31] and in a relapsed setting.[32-38] Specifically in transplant-eligible patients, the randomized phase 2 GRIFFIN trial comparing lenalidomide, bortezomib, and dexamethasone (RVd) with or without daratumumab (quadruplet) in induction and consolidation treatment in addition to autologous stem cell transplantation and maintenance therapy, demonstrated an impressive 99% overall response rate of daratumumab-based treatment. The daratumumab arm (D-RVd) also achieved a ≥CR of 51.5% compared to the RVd arm at 42.3% , a ≥VGPR of 90.9% compared with 73.2% for the RVd arm and a significantly higher minimal residual disease negativity rate of 51% compared to 20.4% in the RVd arm (P<0.0001).[39] After a median follow-up of 22.1 months, the estimated 24-month progression-free survival was 95.8% (95% CI, 89.2-98.4) in the D-RVd group and 89.8% (95% CI, 77.1-95.7) in the RVd group. Based on these promising results, the phase 2 MANHATTAN nonrandomized clinical trial evaluated the efficacy of the quadruplet treatment daratumumab-KRd in newly-diagnosed transplant-eligible myeloma patients in the absence of high-dose melphalan and autologous stem cell transplantation. Treatment was administered for eight 28-day cycles and resulted in a minimal residual disease negativity rate of 71%, (29 of 41 patients) with a 1-year progression-free survival rate and overall survival rate of 98% and 100%, respectively (**Table 1**).[40]

Discussion

Over the last few decades, myeloma patients have achieved longer survival rates as a result of the discovery and approval of novel therapies and combinations.[41] However, in Canada, accessibility to many of these treatments are limited and varies from one province to another. For example, most centers still use cyclophosphamide-bortezomib-dexamethasone (CyBorD) as an induction treatment for transplant-eligible myeloma patients instead of the more effective RVd or KRd combinations.[42] Also, daratumumab-based therapies as first line treatment options, such as those used in the CASSIOPEIA[31], GRIFFIN[39] and MANHATTAN[40] trials, are not available in Canada, nor are the use of quadruplet treatments. In the context of these access limitations and considering the literature showing randomized trials with currently-available agents in Canada still demonstrating clinical benefit with the use of autologous stem cell transplantation, it is prudent to continue the use of transplantation for transplant-eligible myeloma patients as part of the therapeutic armamentarium.

However, impressive results from the MANHATTAN trial with the absence of high-dose melphalan followed by autologous stem cell transplantation are certainly noteworthy. Based on these results, a large randomized, multicenter, 3-arm, phase 2 (ADVANCE) study (NCT04268498) comparing initial treatment with VRd vs KRd vs daratumumab-KRd is presently recruiting. After 8 cycles, patients achieving minimal residual disease negativity will receive maintenance therapy with lenalidomide for up to 2 years. Those with minimal residual disease positivity will have the option to receive an autologous stem cell transplant if available, before initiating the same maintenance therapy. To better evaluate the role of autologous stem cell transplantation, a similar minimal residual disease adapted strategy will be used in the phase 3 MIDAS IFM 2020-02 trial (NCT04934475). After induction treatment with isatuximab-KRd for 6 cycles, patients who achieve minimal residual disease negativity will be randomized to the same treatment as a consolidation for 6 cycles vs high-dose melphalan and autologous stem cell transplantation followed by isatuximab-KRd consolidation for 2 cycles. All patients will receive 3 years of maintenance therapy with lenalidomide. The results of this study may eventually elucidate a sub-population for whom autologous stem cell transplantation can be avoided.

Numerous novel therapies are also emerging with certain immunotherapeutic modalities demonstrating particularly promising results, such as chimeric antigen receptor (CAR)-T and bispecific antibodies. Although still early in their development lifecycle, these therapeutic modalities have shown impressive results in heavily pre-treated relapsed/refractory MM patients.[43-52] Their benefits in earlier use have yet to be demonstrated in clinical trials which will take several more years, but certainly the clinical efficacy of these new agents will have to be compared with that achieved using autologous stem cell transplantation before they are widely adopted.

Conclusion

Without doubt, the role of autologous stem cell transplantation will be open for discussion based on the rapid improvement of myeloma therapies. The day may soon arrive when the risks of autologous stem cell transplantation will outweigh its clinical benefits in light of the availability of novel, more effective and safer therapeutic options. Until such time as clinical trials clearly demonstrate that autologous stem cell transplantation can be avoided and alternative therapeutic modalities are fully available for Canadian patients, autologous stem cell transplantation

will remain the standard of care in Canada despite the associated morbidity, mortality and second primary malignancy risks. The eligibility criteria for patients who may be candidates for transplantation are more stringent than those criteria for patients undergoing chemo-immunotherapy alone and, as such, autologous stem cell transplantation as first line treatment should be considered in eligible patients to avoid subsequent ineligibility.

References:

1. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011;364(11):1046-1060.

2. McElwain TJ, Powles RL. High-dose intravenous melphalan for plasma-cell leukaemia and myeloma. Lancet. 1983;2(8354):822-824.

3. Barlogie B, Hall R, Zander A, Dicke K, Alexanian R. High-dose melphalan with autologous bone marrow transplantation for multiple myeloma. Blood. 1986;67(5):1298-1301.

4. Barlogie B, Alexanian R, Dicke KA, et al. High-dose chemoradiotherapy and autologous bone marrow transplantation for resistant multiple myeloma. Blood. 1987;70(3):869-872.

5. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med. 1996;335(2):91-97.

6. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003;348(19):1875-1883.

7. Fermand JP, Katsahian S, Divine M, et al. 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. J Clin Oncol. 2005;23(36):9227-9233.

8. Blade J, Rosinol L, Sureda A, et al. 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. 2005;106(12):3755-3759.

9. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. N Engl J Med. 2017;376(14):1311-1320.

10. Gay F, Musto P, Rota-Scalabrini D, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. Lancet Oncol. 2021;22(12):1705-1720.

11. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1770-1781.

12. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. J Clin Oncol. 2017;35(29):3279-3289.

13. Gay F, Jackson G, Rosinol L, et al. Maintenance Treatment and Survival in Patients With Myeloma: A Systematic Review and Network Meta-analysis. JAMA Oncol. 2018;4(10):1389-1397.

14. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med. 2014;371(10):895-905.

15. Gay F, Oliva S, Petrucci MT, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. Lancet Oncol. 2015;16(16):1617-1629.

16. Gay F, Oliva S, Petrucci MT, et al. Autologous transplant vs oral chemotherapy and lenalidomide in newly diagnosed young myeloma patients: a pooled analysis. Leukemia. 2017;31(8):1727-1734.

17. Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. Lancet Haematol. 2020;7(6):e456-e468.

18. Melphalan for Injection Product Monograph. Apotex Inc. https://pdf.hres.ca/dpd_pm/00041663.PDF. 2017.

19. Krishnan AY, Mei M, Sun CL, et al. Second primary malignancies after autologous hematopoietic cell transplantation for multiple myeloma. Biol Blood Marrow Transplant. 2013;19(2):260-265.

20. Palumbo A, Bringhen S, Kumar SK, et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. Lancet Oncol. 2014;15(3):333-342.

21. Maura F, Weinhold N, Diamond B, et al. The mutagenic impact of melphalan in multiple myeloma. Leukemia. 2021;35(8):2145-2150.

22. Radivoyevitch T, Dean RM, Shaw BE, et al. Risk of acute myeloid leukemia and myelodysplastic syndrome after autotransplants for lymphomas and plasma cell myeloma. Leuk Res. 2018;74:130-136.

23. Miles B, Mackey JD. Increased Risk of Second Primary Malignancy and Mortality at ten Years After Stem Cell Transplant for Multiple Myeloma: An Analysis of 14,532 Patients. Cureus. 2021;13(7):e16372.

24. Arora M, Chen Y, Hageman L, et al. Morbidity burden in survivors of multiple myeloma who underwent autologous transplantation: A Bone Marrow Transplantation Survivor Study. Cancer. 2020;126(14):3322-3329.

25. Roussel M, Lauwers-Cances V, Robillard N, et al. Front-line transplantation program with lenalidomide, bortezomib, and dexamethasone combination as induction and consolidation followed by lenalidomide maintenance in patients with multiple myeloma: a phase II study by the Intergroupe Francophone du Myelome. J Clin Oncol. 2014;32(25):2712-2717.

26. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood. 2010;116(5):679-686.

27. Perrot AL-C, V.; Cazaubiel, T.; Facon, T.; Caillot, D.; Clement-Filliatre, L. Early Versus Late Autologous Stem Cell Transplant in Newly Diagnosed Multiple Myeloma: Long-Term Follow-up Analysis of the IFM 2009 Trial. ASH 2020, abstract 143.

28. Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med. 2018;378(6):518-528.

29. Mateos MV, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. Lancet. 2020;395(10218):132-141.

30. Facon T, Kumar S, Plesner T, et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med. 2019;380(22):2104-2115.

31. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019;394(10192):29-38.

32. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;375(8):754-766.

33. Spencer A, Lentzsch S, Weisel K, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica. 2018;103(12):2079-2087.

34. Mateos MV, Sonneveld P, Hungria V, et al. Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Patients With Previously Treated Multiple Myeloma: Three-year Follow-up of CASTOR. Clin Lymphoma Myeloma Leuk. 2020;20(8):509-518.

35. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;375(14):1319-1331.

36. Bahlis NJ, Dimopoulos MA, White DJ, et al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. Leukemia. 2020;34(7):1875-1884.

37. Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. Lancet. 2020;396(10245):186-197.

38. Dimopoulos MA, Terpos E, Boccadoro M, et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(6):801-812.

39. Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood. 2020;136(8):936-945.

40. Landgren O, Hultcrantz M, Diamond B, et al. Safety and Effectiveness of Weekly Carfilzomib, Lenalidomide, Dexamethasone, and Daratumumab Combination Therapy for Patients With Newly Diagnosed Multiple Myeloma: The MANHATTAN Nonrandomized Clinical Trial. JAMA Oncol. 2021;7(6):862-868.

41. Corre J, Perrot A, Hulin C, et al. Improved survival in multiple myeloma during the 2005-2009 and 2010-2014 periods. Leukemia. 2021.

42. Cherniawsky HM, Kukreti V, Reece D, et al. The impact of lenalidomide maintenance on second-line chemotherapy in transplant eligible patients with multiple myeloma. Eur J Haematol. 2021;106(5):673-681.

43. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021;398(10297):314-324.

44. Munshi NC, Anderson LD, Jr., Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med. 2021;384(8):705-716.

45. Usmani SZ, Garfall AL, van de Donk N, et al. Teclistamab, a B-cell maturation antigen x CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. Lancet. 2021;398(10301):665-674.

46. Trudel SC, AD; Krishnan, AY; Fonseca, R; Spencer, A; Berdeja, et al. Cevostamab Monotherapy Continues to Show Clinically Meaningful Activity and Manageable Safety in Patients with Heavily Pre-Treated Relapsed/ Refractory Multiple Myeloma (RRMM): Updated Results from an Ongoing Phase I Study. ASH 2021, abstract 157.

47. Krishnan AM, MC; Berdeja, JG; Oriol, A; van de Donk, NWCJ; Rodriguez-Otero, P; et al. Updated Phase 1 Results from MonumenTAL-1: First-in-Human Study of Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D x CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma. ASH 2021, abstract 158.

48. Zonder JR, J; Bumma, N; Brayer, J; Hoffman, JE; Bensinger, WI; et al. Early, Deep, and Durable Responses, and Low Rates of Cytokine Release Syndrome with REGN5458, a BCMAxCD3 Bispecific Monoclonal Antibody, in a Phase 1/2 First-in-Human Study in Patients with Relapsed/Refractory Multiple Myeloma (RRMM). ASH 2021, abstract 160.

49. Li CW, D; Song, Y; Li J; Huang, H; Chen, B; et al. A Phase 1/2 Study of a Novel Fully Human B-Cell Maturation Antigen-Specific CAR T Cells (CT103A) in Patients with Relapsed and/or Refractory Multiple Myeloma. ASH 2021, abstract 547.

50. Raje NS, N; Jagannath, S; Kaufman, JL; Siegel, DS; Munshi, NC; et al. Updated Clinical and Correlative Results from the Phase I CRB-402 Study of the BCMA-Targeted CAR T Cell Therapy bb21217 in Patients with Relapsed and Refractory Multiple Myeloma. ASH 2021, abstract 548.

51. Sebag MR, NS; Bahlis, NJ; Costello, C; Dholaria, B; Solh, M; et al. Elranatamab (PF-06863135), a B-Cell Maturation Antigen (BCMA) Targeted CD3-Engaging Bispecific Molecule, for Patients with Relapsed or Refractory Multiple Myeloma: Results from Magnetismm-1. ASH 2021, abstract 895.

52. Kumar SDS, A; Shah, N; Rodriguez, C; Voorhees, PM; Bueno, OF; et al. A Phase 1 First-in-Human Study of Tnb-383B, a BCMA x CD3 Bispecific T-Cell Redirecting Antibody, in Patients with Relapsed/ Refractory Multiple Myeloma. ASH 2021, abstract 900.