

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Is there still a role for stem cell transplantation in multiple myeloma?

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1732781> since 2022-06-14T18:54:57Z

Published version:

DOI:10.1002/cncr.32060

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

This is the author's final version of the contribution published as:

Mina R, Lonial S. Is there still a role for stem cell transplantation in multiple myeloma? Cancer. 2019 Aug 1;125(15):2534-2543. doi: 10.1002/cncr.32060. Epub 2019 Apr 15. PMID: 30985927.

© 2019 American Cancer Society.

The publisher's version is available at:

<https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.32060>
| <https://doi.org/10.1002/cncr.32060>

When citing, please refer to the published version.

Link to this full text:

<http://hdl.handle.net/2318/1732781>

This full text was downloaded from iris-AperTO: <https://iris.unito.it/>

1
2
3 **Title:** Is there still a role for stem cell transplant in multiple myeloma?
4
5

6
7 **Running title:** Stem cell transplant for multiple myeloma
8
9

10 **Authors:** Roberto Mina¹ and Sagar Lonial¹
11
12

13 **Affiliations:** ¹ Hematology and Medical Oncology, Winship Cancer Institute, Emory University,
14
15 Atlanta, GA
16
17
18
19

20 **Correspondence to:** Roberto Mina, MD, Hematology and Medical Oncology, Winship Cancer
21
22 Institute, Emory University, Atlanta, GA
23
24 Email: roberto.mina.rm@gmail.com
25
26
27
28
29

30 Text pages: 25
31

32 References: 61
33

34 Tables: 3
35

36 Words: 6596
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ABSTRACT

High-dose chemotherapy and autologous stem cell transplant (ASCT) is a standard of care for newly diagnosed, transplant-eligible multiple myeloma (MM) patients.

The introduction of novel agents, from immunomodulatory drugs and proteasome inhibitors to monoclonal antibodies, now integrated in both induction and salvage regimens, has dramatically revolutionised the treatment landscape of MM, challenging the role of high-dose chemotherapy and ASCT to treat MM. These advances have led to a number of provocative questions: 1) what is the current role of SCT as compared to standard-dose therapy incorporating novel agents? 2) Should ASCT be performed upfront (“early”) or later (“delayed”) in the course of the disease? 3) Single or double ASCT? 4) Is allogeneic-SCT still an option for MM patients?

In this article, we provide an overview of available data, and evidence-based responses regarding the role of SCT in MM.

CONDENSED ABSTRACT

- High-dose melphalan and autologous stem cell transplant (ASCT) is the current standard approach for young, newly diagnosed myeloma patients as part of first line treatment.
- At relapse, salvage ASCT is a feasible and effective treatment option, whereas allogeneic-SCT have been considered an option for young, high-risk myeloma patients.

Introduction

Multiple myeloma (MM) is the second most common hematological malignancy and the most common indication for autologous stem cell transplantation (ASCT) in the US.^{1,2}

The natural history of MM was first changed by the introduction of high dose chemotherapy and ASCT,^{3,4} and then further improved upon by the use of novel agents, such as immunomodulatory drugs (IMiDs), thalidomide, lenalidomide and pomalidomide, proteasome inhibitors (PIs), bortezomib, carfilzomib and ixazomib, and most recently the monoclonal antibodies, elotuzumab and daratumumab.^{5,6} These therapeutics innovations have led to a significant survival improvement, with median overall survival (OS) of MM patients now ranging between 6 and 10 years, depending on the age of patients at diagnosis.^{2,7}

Given the wide availability of new targeted therapies for the treatment of MM, the role of SCT has been questioned in the last years, with several trials addressing the role and timing of transplant.

In this article we provide an overview of the available literature on the use of SCT to treat MM patients.

Stem cell transplant for newly diagnosed myeloma patients

Autologous stem cell transplant eligibility

High-dose melphalan followed by autologous stem cell rescue is currently a worldwide standard of care for newly-diagnosed (ND), transplant-eligible MM patients.^{8,9} In Europe, chronological age has been used to define ASCT eligibility, particularly in clinical trials, with

1
2
3 65 years as a cut-off to define ASCT-eligible and -ineligible patients. However, recent analysis
4
5 of both the European Blood and Marrow Transplantation (EBMT) and the Center for
6
7 International Blood and Marrow Research (CIBMTR) registries, clearly showed a constant
8
9 increase, from 1991/1995 to 2010, in the use of ASCT in older patients (over 65 years of age).
10
11 10,11

12
13
14 The feasibility of high dose melphalan and ASCT among older patients, has been evaluated in
15
16 several studies. ¹²⁻¹⁴ In a prospective study enrolling patients over 65 years of age, ASCT
17
18 conditioned with melphalan 100 mg/m², demonstrated to be feasible and effective (5-year OS:
19
20 63%), especially among patients aged 66-70 years, whose treatment-related mortality (TRM)
21
22 was lower than that of patients over 70 years of age (5% vs. 19%). ¹⁵ In the DSSM II trial, in
23
24 which patients received a tandem ASCT conditioned with melphalan 140 mg/m², no
25
26 difference in terms of TRM (1%) was reported between patients aged 60-65 and those over
27
28 66 years. ¹⁶ In another prospective trial comparing melphalan 140 mg/m² to melphalan 200
29
30 mg/m² in patients older than 65 years of age, the TRM at day +100 from transplant was 0% in
31
32 both arms, confirming the feasibility of delivering high-dose melphalan to older patients. ¹⁷
33
34
35 Many studies have confirmed that chronological age is not, itself, a limitation to ASCT.
36
37
38 Instead, organ function and comorbidities, as well as performance status, should be taken into
39
40 consideration to define ASCT eligibility ¹⁸ and currently, in the US, ASCT is considered and
41
42 may be appraised for patients up to the age of 80.
43
44
45

46 *Autologous stem cell transplant versus non transplant-based strategies*

47
48
49
50

51 The two first large trials to compare high-dose chemotherapy and ASCT with standard-dose
52
53 chemotherapy were conducted by the Intergroup Francophone du Myélome (IFM) and the
54
55 Medical Research Council (MRC) (Table 1). ^{3,4} In both trials, high-dose chemotherapy ad ASCT
56
57
58
59
60

1
2
3 significantly prolonged progression-free survival (PFS) and OS as compared to standard-dose
4 chemotherapy without transplantation. It should be noted that, at the time, limited salvage
5 options were available for these patients, accounting for the early improvement in OS for both
6 trials.
7
8
9

10
11 Several trials have been conducted thereafter to support the benefit of high-dose
12 chemotherapy and ASCT as compared to standard-dose chemotherapy, although only 1 trial
13 was able to detect a significant OS advantage among patients undergoing ASCT.¹⁹⁻²³ However,
14 all the studies comparing ASCT with standard-dose chemotherapy published before 2010 did
15 not include novel agents as part of the initial treatment of NDMM patients. With the
16 incorporation of IMiDs and PIs in the upfront treatment of MM patients, the need for ASCT as
17 part of first-line treatment has therefore been challenged.
18
19
20
21
22
23
24
25

26
27 To date, 4 phase III trials have compared high-dose chemotherapy and ASCT to novel-agents-
28 based regimens without ASCT. The first study, published by Palumbo et al. (RV-MM-209),
29 enrolled 402 NDMM patients who, after a lenalidomide-dexamethasone (Rd) induction, were
30 randomized to either 2 courses of high-dose melphalan (200 mg/m²) followed by ASCT, or 6
31 cycles of melphalan, prednisone and lenalidomide (MPR). Patients in the ASCT arm had
32 significantly longer PFS (median, 43 vs. 22 months; p<0.001) and 4-year OS (82% vs. 65%;
33 p=0.02).²⁴ Similar results were presented by Gay et al. in the EMN-441 phase III trial, in
34 which 389 NDMM patients, treated with Rd induction, were randomized to receive either
35 tandem ASCT or 6 cycles of cyclophosphamide, lenalidomide and dexamethasone (CRD).
36 Again, patients in the ASCT group displayed a prolonged median PFS (43 vs. 29 months;
37 p<0.001) and 4-year OS (86% vs. 73%; p=0.004) in comparison with patients in the no ASCT
38 arm.²⁵ In a pooled analysis of the two trials, the advantage of ASCT as compared to a
39 lenalidomide-based approach without ASCT, in terms of 5-year PFS (55% vs. 45%; p=0.01),
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 PFS2 (71% vs. 62%; $p=0.02$) and OS (87% vs. 71%; $p=0.03$) was confirmed also in patients in
4
5 CR.²⁶

6
7 The addition of bortezomib to lenalidomide and dexamethasone (RVD) significantly improved
8
9 median PFS (43 vs. 30 months; $p=0.002$) and OS (75 vs. 64 months; $p=0.025$) as compared to
10
11 Rd alone. Therefore, RVD has become a standard of care for NDMM patients.²⁷

12
13 A formal comparison between ASCT and RVD was performed in the IFM 2009 trial. Seven
14
15 hundred patients, after 3 RVD induction cycles, were randomized to 1 course of high-dose
16
17 melphalan (200 mg/m²) and ASCT followed by 2 further RVD cycles or 5 RVD cycles without
18
19 ASCT, and all patients received lenalidomide maintenance. A higher rate of CR (59% vs. 48%;
20
21 $p=0.03$) and minimal residual disease negativity (79% vs. 65%; $p<0.001$) among patients in
22
23 the ASCT arm was observed, translating into a 35% reduction in the risk of progression or
24
25 death (median PFS 50 vs. 36 months; HR 0.65, $p<0.001$) in favour of patients transplanted in
26
27 comparison with those who received RVD only. No difference in terms of OS was noted at 4
28
29 years; however, a longer follow-up might be needed to highlight an OS difference between the
30
31 two arms, especially in light of the wealth of salvage treatment options that may cloud the OS
32
33 benefit.²⁸ Moreover, in all trials PFS is improved with early ASCT, suggesting improved depth
34
35 of response and better disease control for most patients.

36
37
38 In the European EMN02/HO95 trial, comparing 1 or 2 courses of melphalan 200 mg/m² and
39
40 ASCT to bortezomib, melphalan and prednisone (VMP) consolidation after a bortezomib-
41
42 based induction, patients randomized in the ASCT group displayed a higher rate of at least
43
44 very good partial response (VGPR; 86% vs. 74%; $p<0.001$) and a longer 3-year PFS (66% vs.
45
46 58%; $p=0.037$) as compared to patients in the VMP arm.²⁹

47
48
49 All the trials comparing ASCT to novel agent-based treatments without transplant for NDMM
50
51 patients conducted so far, continue to favour ASCT over a non-transplant approach in terms of
52
53 high quality responses and PFS, with two trials also reporting a significant OS advantage for
54
55
56
57
58
59
60

1
2
3 patients undergoing ASCT. For these reasons, ASCT still remains the standard of care for ND,
4
5 transplant-eligible myeloma patients.
6
7

8
9 *Early versus delayed autologous stem cell transplant*
10

11
12
13 Before the introduction of novel agents, the role of early ASCT as compared to that of a
14
15 delayed ASCT was addressed in 3 trials. In the study published by Fermand et al., a trend
16
17 towards a better PFS ($p=0.07$) and a longer interval without treatment, symptoms and
18
19 treatment-related toxicities, was observed for early over delayed ASCT, but no OS advantage.
20

21
22 ²⁰ A North American cooperative study comparing high-dose therapy and ASCT to standard-
23
24 dose therapy, offered a delayed ASCT to patients in the standard-dose arm; of these,
25
26 approximately 50% of patients with a follow-up received ASCT at relapse. At 7 year, the
27
28 overall survival was equal between the patients in the two arms (38% vs 39%). ²² In the
29
30 randomized CIAM study, specifically designed to compare early versus delayed ASCT, a
31
32 preliminary analysis, reported in abstract form, showed no OS difference between the two
33
34 arms. ³⁰
35
36

37
38 Two retrospective analysis compared early (within 12 months from diagnosis) versus delayed
39
40 (beyond 12 months) ASCT. Kumar et al. analysed 290 patients treated with an IMiD-based
41
42 induction and subsequently receiving ASCT. They showed a similar median time to
43
44 progression (TTP, 20 vs. 16 months; p : NS) from ASCT, as well as no difference in terms of 4-
45
46 year OS (73% in both groups) between early and delayed ASCT. However, the reasons for the
47
48 delayed ASCT are not clear, and a higher percentage of patients in the delayed ASCT group
49
50 had deeper responses to induction therapy. ³¹ Furthermore, this analysis may have limited
51
52 value given the short TTP in both arms. Similar results were reported by Dunavin et al. in an
53
54 analysis of 167 patients undergoing early or delayed ASCT; despite a trend towards a longer
55
56
57
58
59
60

1
2
3 median TTP in the early ASCT group (28 vs. 23 months; $p=0.055$), no differences in terms of
4 OS were noted between the two groups at 3 (90% vs. 82%) and 5 years (63% vs. 63%); again,
5
6 the median TTP is shorter than those seen in trials with modern maintenance approaches ³²

7
8
9 These trials showed the feasibility of a delayed ASCT; however, given the lack of a
10
11 randomization and the absence of stratification for baseline characteristics, is not clear which
12
13 subgroup of patients can actually benefit the most from a delayed ASCT.
14

15
16 In a pooled analysis of the RV-MM-209 and EMN-441 studies, only 53% of patients who did
17
18 not receive ASCT as part of first line treatment were able to receive ASCT at relapse. Patients
19
20 who underwent ASCT upfront not only had a longer PFS, but also benefited from a longer 4-
21
22 year PFS2 (71% vs 54%; $p<0.001$) and OS (84% vs 70%; $p<0.001$) as compared to those who
23
24 received a delayed ASCT. ³³ It must be noted that the patients in the non-transplant arm
25
26 received a suboptimal induction and consolidation (Rd-MPR/CRD) approach as compared to
27
28 current 3-drug regimens including a PI and an IMiD.
29

30
31 Nonetheless, this pooled analysis shows that a fraction of patients who do not receive ASCT
32
33 upfront may not be able to receive it at relapse. A possible explanation for this phenomenon is
34
35 related to ageing of patients, deterioration of performance status and comorbid conditions,
36
37 and type of relapse. However, in the more recent IFM 2009 trial, a higher rate (79%) of
38
39 patients who did not undergo ASCT upfront were instead able to receive a salvage ASCT, and
40
41 this probably reflects in the lack of OS survival observed between the two arms. Longer
42
43 follow-up is needed to evaluate the impact of delayed ASCT on PFS2 and OS. ²⁸
44
45
46
47
48

49 *Single versus tandem autologous stem cell transplant*
50
51
52
53
54
55
56
57
58
59
60

1
2
3 The role of a tandem ASCT as upfront treatment in NDMM patients and its superiority over a
4 single ASCT has been investigated, with conflicting results, and still remains a matter of
5 discussion (Table 2).
6
7

8
9 A first evidence of the superiority of tandem ASCT over single ASCT, came by the IFM study
10 published in 2003, demonstrating a longer median EFS (36 vs. 25 months; $p=0.03$) and OS (58
11 vs. 48 months; $p=0.01$) in patients receiving tandem ASCT. In a subgroup analysis, authors
12 reported that patients who benefited the most from tandem ASCT were those who failed to
13 achieve a VGPR after the first ASCT, which may be expected as induction therapy did not
14 include novel agents.³⁴
15
16

17
18 In the Italian trial published by Cavo et al, patients receiving tandem ASCT had a higher rate of
19 CR (47% vs. 33%) and a significantly prolonged median EFS (35 vs. 23 months; $p=0.001$), but
20 similar OS (median, 71 vs. 65 months; $p=0.9$) as compared to patients who received a single
21 ASCT.³⁵ Similarly, in a randomized study by Fermand et al conducted in NDMM patients,
22 double over single ASCT has yet to show an OS advantage.³⁶ Sonneveld et al. compared a non-
23 myeloblastic approach (two cycles of melphalan 70 mg/m²) to the same regimen followed by
24 ASCT in a phase III study; despite a higher CR rate (32% vs. 13%; $p<0.001$) and prolonged
25 median PFS (27 vs. 24 months; $p=0.006$), no difference in OS (50 vs. 55 months) was observed
26 between the two arms.³⁷
27
28

29
30 More recently, in a pooled analysis of four European trials, median PFS (50 vs. 38 months;
31 $p<0.001$) and 5-year OS (75% vs. 63%; $p=0.002$) were longer in patients receiving a second
32 transplant as compared to patients in whom a single ASCT was planned.³⁸
33
34

35
36 Similar results have been reported by a preliminary analysis of the European EMN02/HO95
37 trial, in which patients who received a tandem ASCT had a significantly longer 3-year PFS
38 (74% vs. 62%; $p=0.005$) as compared to those who received a single ASCT.³⁹
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 To address the role of consolidation therapy after a first ASCT, the phase III STAMINA trial
4 randomized NDMM patients who previously underwent a first ASCT, to either a second ASCT
5 or RVD consolidation, followed by lenalidomide maintenance.⁴⁰ At 38 months, the
6
7 investigators found no differences in terms of PFS (57% vs. 57%) and OS (86% vs 82%)
8
9 between the two groups.
10
11

12
13 Taking into consideration the conflicting results published so far, a second ASCT appears a
14 feasible and reasonable option, especially for high-risk MM patients and those who fail to
15
16 achieve at least a VGPR after the first transplant. Ongoing and future randomized trials should
17
18 ultimately define the role of a tandem ASCT in the general population.
19
20
21
22

23 24 *Early allogeneic stem cell transplant*

25
26
27
28
29 Allogeneic SCT (allo-SCT) is regarded as a potentially curative approach for MM due to the
30
31 graft versus myeloma (GvM) effect mediated by the donor immune system.⁴¹ However,
32
33 despite its biological rationale, the role allo-SCT for the treatment of MM is limited.
34

35
36 Two meta-analysis including studies that compared allo-SCT to ASCT as initial treatment for
37
38 NDMM failed to demonstrate a superiority, in terms of PFS and OS, of allo-SCT over ASCT; this
39
40 is despite higher rates of CR among patients in the allo-SCT group, that also experienced a
41
42 higher TRM than the ASCT group, and early and late relapses continue to be a major cause for
43
44 treatment failure.^{42,43}
45

46
47 To combine a highly effective cytoreductive procedure yet taking advantage of the GvM effect,
48
49 a tandem auto/mini-allo-SCT approach, using a reduced intensity conditioning (RIC) regimen,
50
51 has been designed and compared to the standard tandem ASCT for the initial treatment of
52
53 myeloma patients (Table 3).
54
55
56
57
58
59
60

1
2
3 In two trials only, both of which not randomized and designed before the novel agents era,
4 patients who underwent a tandem auto/allo-SCT had a clear PFS and OS advantage in
5 comparison with patients receiving a tandem ASCT. These results were not confirmed by
6 other studies, in which neither PFS nor OS were prolonged with auto/allo-SCT as compared to
7 tandem ASCT. ⁴⁴⁻⁵¹ Of notice, the majority of those trials did not incorporate the use of novel
8 agents in the induction and consolidation/maintenance phase.

9
10
11 To date, allo-SCT is not routinely recommended as part of initial treatment of NDMM patients,
12 due to the increased toxicity and the lack of a clear benefit for most patients. However, for
13 young, selected and motivated patients with high-risk MM, allogeneic transplant may be
14 considered, preferentially in the context of a clinical trials. ^{8,9}

25 26 **Salvage stem cell transplant for relapsed and/or refractory myeloma patients**

27 28 *Salvage autologous stem cell transplant*

29
30
31 Several retrospective studies have evaluated the role of salvage ASCT (sASCT) in the relapse
32 setting, demonstrating that a second, even a third, ASCT is a feasible and effective treatment
33 option among patients who have previously received ASCT. ⁵²⁻⁵⁴

34
35
36 A retrospective analysis of the EMBT registry, showed that sASCT is safe (1-year non relapse
37 mortality[NRM]: 2%) and effective (3-year OS: 46%). This study also demonstrated that
38 patients with a long relapse-free interval from previous ASCT (>36 months), had longer PFS
39 (p=0.045) and OS (p=0.019) as compared to patients with a shorter relapse-free interval (<36
40 months). ⁵⁵

41
42
43 Similar results were confirmed in a retrospective analysis by Lemieux et al., in which 93% of
44 patients achieved at least an objective response after sASCT, 46% of them reaching a VGPR.

1
2
3 No treatment-related death were observed, and median PFS after sASCT was 18 months.

4 Again, the duration of response (DOR) from previous ASCT (>24 months) was associated with
5 longer PFS and OS.
6
7

8
9 In a matched-pair analysis comparing sASCT to conventional chemotherapy in patients
10 previously treated with ASCT, sASCT significantly extended median OS (56 vs. 25 months;
11 p=0.04) as compared to conventional chemotherapy. ⁵⁶
12
13

14
15 The only prospective evaluation of sASCT has been conducted in the context of the Myeloma X
16 trial; at relapse, after a bortezomib-based re-induction, patients were randomized to sASCT or
17 cyclophosphamide. sASCT significantly extended median PFS (19 vs. 11 months; p<0.001), but
18 no OS (65 vs. 56 months; p=0.19), as compared to cyclophosphamide. However, the use of
19 salvage cyclophosphamide alone is not considered a standard treatment approach given the
20 wide availability of novel agents at relapse.
21
22
23
24
25
26
27
28

29 A retrospective analysis showed that a sASCT is safe (TRM: 6%) and effective (CR rate: 44%;
30 median PFS 14 months) even in patients who received maintenance therapy after the upfront
31 ASCT. ⁵⁷
32
33
34

35 These studies demonstrate that sASCT is a safe and effective treatment option for RRMM
36 patients. Both the American and European guidelines regard sASCT as a feasible treatment
37 option among relapsed patients with a previous, adequate stem-cell collection. ^{8,9,58}
38
39

40 However, given the growing number of effective anti-myeloma drugs, it is important to
41 carefully select those patients who might benefit the most from a sASCT (e.g. prolonged
42 remission from first ASCT, adequate performance status).
43
44
45
46
47
48
49
50

51 *Salvage allogeneic stem cell transplant*
52
53
54
55
56
57
58
59
60

1
2
3 Data on allo-SCT in the relapse setting is scarce, mainly provided by retrospective analysis
4 and single-center institutions. A European analysis of the EBMT registry on the use of allo-SCT
5 among MM patients, showed a steady increase in the use of allo-SCT, particularly later in the
6 course of the disease, with a parallel increase in the use of RIC over myeloablative
7 conditioning. Among 3405 MM patients receiving allo-SCT after ASCT, 5-year PFS and OS were
8 15% and 32%, respectively, while NRM was 29%, confirming high toxicity and relapse rate,
9 with limited benefit.⁵⁹

10
11
12 In a retrospective study including 169 MM patients relapsed after a first ASCT, 68 patients
13 who had an available donor and underwent RIC allo-SCT, were compared to 94 patients
14 without a donor.⁶⁰ At two year, PFS was prolonged in the donor group (42%) as compared to
15 the no-donor group (18%; $p < 0.001$) but at a the cost of a significantly higher incidence of
16 NRM (22% vs. 1%; $p < 0.001$). This is likely to be reflected in the lack of OS difference between
17 the two groups (54% vs. 53%; $p = 0.33$).

18
19
20 Freytes et al. evaluated 289 patients receiving either a second ASCT or an allo-SCT after a first
21 ASCT. At 1 year, the NRM was significantly higher in the allo-SCT group as compared to the
22 second ASCT one (13% vs. 2%; $p < 0.001$), whereas 3-year PFS (6% vs. 12%) and OS (20% vs.
23 46%) was longer among patients receiving a second ASCT.

24
25
26 Kroger et al. showed allo-SCT to be effective as salvage treatment for patients relapsing after
27 ASCT, with a ORR at day +100 after transplant of 95%, including 46% of patients achieving a
28 CR. Of notice, NRM was significantly lower (10% vs. 53%, $P = 0.001$) in patients with a human
29 leucocyte antigen (HLA)-matched compared to -mismatched SCT. At 5 year, PFS was 20%,
30 though 41% of matched patients in CR were alive and free from progression.⁶¹ This study
31 demonstrated that a careful selection of patients and donors can optimize efficacy and safety
32 of allo-SCT, yet does not make a sufficiently convincing case for allo-SCT in the salvage setting.
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 To date, there is no clear advantage for a salvage allo-SCT over ASCT, particularly considering
4 the constantly improving treatment armamentarium and the availability of targeted drugs
5 and immunological approaches to treat MM. Thus, the role of allo-SCT at relapse remains
6 limited to clinical trials.
7
8
9
10

11 12 13 **Stem cell transplant for patients with high-risk multiple myeloma** 14 15

16
17
18 MM is characterized by a variety of recurrent cytogenetic and molecular abnormalities. Of
19 them, t(4;14), t(14;16), t(14;20) del17p and gain 1q and 1p deletion, have been associated
20 with a poor prognosis.⁶²
21
22

23
24 In a pooled analysis of 4 European phase III trials, high risk patients, defined as harbouring
25 either t(4;14) or del17p, or failing to achieve a CR after the induction phase, greatly benefit
26 from a tandem ASCT as compared to patients who received a single ASCT only, both in terms
27 of PFS (median, 42 vs. 21 months, HR:0.41; p=0.006) and 5-year OS (70% vs. 17%, HR 0.22;
28 p<0.001).³⁸
29
30
31
32
33

34
35 More recently, in a subset analysis of high-risk MM patients treated in the context of the
36 EMN02/HO95 trial, showed a positive impact on PFS of double as compared to single ASCT
37 (HR: 5.7; p=0.024). This, however, is in contrast with the STAMINA trial, that demonstrated
38 no benefit for tandem ASCT, even among high-risk patients. A possible explanation for this
39 discrepancy is the different induction regimen of the two studies, bortezomib-
40 cyclophosphamide-dexamethasone (VCD) in the EMN02/HO95 study, RVD (predominantly)
41 in the STAMINA trial. The different induction therapy may at least partially account for the
42 PFS benefit seen in the European trial in favour of tandem ASCT. At present, the benefit of
43 tandem ASCT for high-risk patients remains unclear, particularly if RVD induction is used.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 To evaluate the role of allo-SCT in high-risk FISH patients, Roos-Weil et al. conducted a
4
5 retrospective analysis on 143 MM patients who underwent allo-SCT, either as part of the
6
7 initial strategy or as salvage treatment, comparing their outcomes to those of standard risk
8
9 patients.⁶³ The authors found no difference in 3-year PFS (30% vs. 17%; p=0.9), relapse rate
10
11 (53% vs. 75%; p=0.9) and OS (45% vs. 39%; p=0.8) between high-risk and standard risk FISH
12
13 patients. TRM was 25% at 2 years, and 47% and 43% of patients developed any grade acute
14
15 and chronic graft versus host disease (GVHD), respectively. Interestingly, the occurrence of
16
17 chronic GVHD was associated to prolonged PFS. In the study conducted by the IFM and
18
19 including high-risk patients, no PFS/OS benefit was observed in patients undergoing tandem
20
21 ASCT or ASCT/allo-SCT.⁴⁶
22
23

24
25 Kroger et al. retrospectively analysed the outcomes of 73 high-risk myeloma patients treated
26
27 with either a tandem ASCT or tandem auto/allo-SCT; while no significant differences were
28
29 noted in terms of molecular remission rate (50% vs. 40%) and 5-year PFS (24% vs. 30%;
30
31 p=0.7) between the two groups, patients in the tandem auto/allo-SCT had a significantly
32
33 higher 1-year NRM (23% vs. 2%) as compared to those in the tandem ASCT group.
34

35
36 Based on these data, the International Myeloma Working Group (IMWG) recommended
37
38 consideration of a tandem ASCT for NDMM with high-risk cytogenetic features.⁶² Allo-SCT,
39
40 though not routinely recommended, may be considered for young patients with a high-risk
41
42 MM in the context of a clinical trials.
43

44 45 46 47 **Conclusion**

48
49 Even in the era on novel agents, ASCT remains a standard of care for ND, transplant-eligible
50
51 MM patients. ASCT improves the depth and the quality of responses, and prolongs survival as
52
53 compared to standard-dose therapy, and is therefore an essential component of a complex
54
55 treatment strategy that integrates the use of novel agents in the induction,
56
57
58
59
60

1
2
3 consolidation/maintenance, with high-dose chemotherapy and ASCT. Taking into
4
5 consideration the efficacy and safety of ASCT, as well as data from randomized studies
6
7 showing that a significant proportion of patients might not receive ASCT at relapse, we
8
9 recommend performing ASCT as part of the initial treatment, as the disease is never as
10
11 sensitive as it is at the time of presentation. However, a plan for a delayed ASCT at first
12
13 relapse, with early stem cell harvest, in young patients without high-risk myeloma, may be
14
15 considered based on patient's preferences. The limited benefit of tandem ASCT over a single
16
17 ASCT remains unclear. The most robust data suggest that high-risk patients and patients with
18
19 a sub-optimal response after the first ASCT might benefit from a second transplant, though
20
21 they are most likely to get greater benefit from newer consolidation and maintenance
22
23 approaches.⁶⁴ At relapse, sASCT represents an effective treatment option; however, given the
24
25 wide availability of new drugs, physicians should consider the type and the duration of
26
27 response obtained after prior ASCT, in order to select those patients who will benefit the most
28
29 from a sASCT. Currently, there is no data to support the use of upfront allo-SCT. At relapse,
30
31 allo-SCT may be considered as a treatment option for high-risk, young and motivated patients
32
33 in the context of a clinical trial. However, newer immune, antibody and cellular-based
34
35 approaches, will likely be used early in the course of the disease to eradicate clones of
36
37 resistant disease.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. Becker N. Epidemiology of multiple myeloma. *Recent Results Cancer Res.* 2011;183:25-35.
2. Vincent Rajkumar S. Multiple myeloma: 2014 Update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2014;89(10):999-1009.
3. 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.
4. 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.
5. Moreau P. How I treat myeloma with new agents. *Blood.* 2017;130(13):1507-1513.
6. Larocca A, Mina R, Gay F, Brinthen S, Boccadoro M. Emerging drugs and combinations to treat multiple myeloma. *Oncotarget.* 2017;8(36):60656-60672.
7. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia.* 2014;28(5):1122-1128.
8. Shah N, Callander N, Ganguly S, et al. Hematopoietic Stem Cell Transplantation for Multiple Myeloma: Guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* 2015;21(7):1155-1166.
9. Gay F, Engelhardt M, Terpos E, et al. From transplant to novel cellular therapies in multiple myeloma: European Myeloma Network guidelines and future perspectives. *Haematologica.* 2018;103(2):197-211.
10. Auner HW, Szydlo R, Hoek J, et al. Trends in autologous hematopoietic cell transplantation for multiple myeloma in Europe: increased use and improved outcomes in elderly patients in recent years. *Bone Marrow Transplant.* 2015;50(2):209-215.
11. Costa LJ, Zhang MJ, Zhong X, et al. Trends in utilization and outcomes of autologous transplantation as early therapy for multiple myeloma. *Biol Blood Marrow Transplant.* 2013;19(11):1615-1624.
12. Merz M, Neben K, Raab MS, et al. Autologous stem cell transplantation for elderly patients with newly diagnosed multiple myeloma in the era of novel agents. *Ann Oncol.* 2014;25(1):189-195.
13. Ozaki S, Harada T, Saitoh T, et al. Survival of multiple myeloma patients aged 65-70 years in the era of novel agents and autologous stem cell transplantation. A multicenter retrospective collaborative study of the Japanese Society of Myeloma and the European Myeloma Network. *Acta Haematol.* 2014;132(2):211-219.
14. Bashir Q, Shah N, Parmar S, et al. Feasibility of autologous hematopoietic stem cell transplant in patients aged ≥ 70 years with multiple myeloma. *Leuk Lymphoma.* 2012;53(1):118-122.
15. Gay F, Magarotto V, Crippa C, et al. Bortezomib induction, reduced-intensity transplantation, and lenalidomide consolidation-maintenance for myeloma: updated results. *Blood.* 2013;122(8):1376-1383.
16. Straka C, Liebisch P, Salwender H, et al. Autotransplant with and without induction chemotherapy in older multiple myeloma patients: long-term outcome of a randomized trial. *Haematologica.* 2016;101(11):1398-1406.
17. Garderet L, Beohou E, Caillot D, et al. Upfront autologous stem cell transplantation for newly diagnosed elderly multiple myeloma patients: a prospective multicenter study. *Haematologica.* 2016;101(11):1390-1397.

18. Saad A, Mahindra A, Zhang MJ, et al. Hematopoietic cell transplant comorbidity index is predictive of survival after autologous hematopoietic cell transplantation in multiple myeloma. *Biol Blood Marrow Transplant*. 2014;20(3):402-408 e401.
19. 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.
20. Femand 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.
21. Palumbo A, Bringhen S, Petrucci MT, et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. *Blood*. 2004;104(10):3052-3057.
22. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. *J Clin Oncol*. 2006;24(6):929-936.
23. Segeren CM, Sonneveld P, van der Holt B, et al. Overall and event-free survival are not improved by the use of myeloablative therapy following intensified chemotherapy in previously untreated patients with multiple myeloma: a prospective randomized phase 3 study. *Blood*. 2003;101(6):2144-2151.
24. 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.
25. 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.
26. Mina R PM, Corradini P, et al. Treatment intensification with autologous stem-cell transplantation and lenalidomide maintenance improves survival outcomes of newly diagnosed multiple myeloma patients in complete response. *Clinical Lymphoma Myeloma and Leukemia*. 2018;Accepted for publication.
27. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet*. 2017;389(10068):519-527.
28. 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.
29. Cavo M BM, Dimopoulos MA et al. Intensification Therapy with Bortezomib-Melphalan-Prednisone Versus Autologous Stem Cell Transplantation for Newly Diagnosed Multiple Myeloma: An Intergroup, Multicenter, Phase III Study of the European Myeloma Network (EMN02/HO95 MM Trial). *Blood*. 2016;128.
30. Facon T MJ, Harousseau JL, et al. Front-line or rescue autologous bone marrow transplantation (ABMT) following a first course of high dose melphalan (HDM) in multiple myeloma (MM)—preliminary results of a prospective randomized trial (CIAM protocol). *Blood*. 1996;;88(suppl 1):685a. Abstract 2729.

- 1
- 2
- 3 31. Kumar SK, Lacy MQ, Dispenzieri A, et al. Early versus delayed autologous
- 4 transplant after immunomodulatory agents-based induction therapy in patients
- 5 with newly diagnosed multiple myeloma. *Cancer*. 2012;118(6):1585-1592.
- 6 32. Dunavin NC, Wei L, Elder P, et al. Early versus delayed autologous stem cell transplant
- 7 in patients receiving novel therapies for multiple myeloma. *Leuk Lymphoma*.
- 8 2013;54(8):1658-1664.
- 9 33. Gay F, Oliva S, Petrucci MT, et al. Autologous transplant vs oral chemotherapy and
- 10 lenalidomide in newly diagnosed young myeloma patients: a pooled analysis.
- 11 *Leukemia*. 2017;31(8):1727-1734.
- 12 34. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell
- 13 transplantation for multiple myeloma. *N Engl J Med*. 2003;349(26):2495-2502.
- 14 35. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared
- 15 with double autologous stem-cell transplantation for multiple myeloma: Bologna 96
- 16 clinical study. *J Clin Oncol*. 2007;25(17):2434-2441.
- 17 36. Femand JP AC, Marolleau JP. Single versus tandem high dose therapy (HDT)
- 18 supported with autologous blood stem cell (ABSC) transplantation using unselected or
- 19 CD34-enriched ABSC: Results of a two by two designed randomized trial in 230 young
- 20 patients with multiple myeloma (MM). *Hematol J*. 2003;4(Suppl 1):S59.
- 21 37. Sonneveld P, van der Holt B, Segeren CM, et al. Intermediate-dose melphalan compared
- 22 with myeloablative treatment in multiple myeloma: long-term follow-up of the Dutch
- 23 Cooperative Group HOVON 24 trial. *Haematologica*. 2007;92(7):928-935.
- 24 38. Cavo M SH, Rosiñol L, et al. . Double Vs Single Autologous Stem Cell Transplantation
- 25 After Bortezomib-Based Induction Regimens For Multiple Myeloma: An Integrated
- 26 Analysis Of Patient-Level Data From Phase European III Studies. *Blood*. 2013;122(21).
- 27 39. Cavo M PM, Di Raimondo F, et al. . Upfront Single Versus Double Autologous Stem Cell
- 28 Transplantation for Newly Diagnosed Multiple Myeloma: An Intergroup, Multicenter,
- 29 Phase III Study of the European Myeloma Network (EMN02/HO95 MM Trial). . *Blood*.
- 30 2016;128(22).
- 31 40. Stadtmauer EA PM, Blackwell B, et al. . Comparison of Autologous Hematopoietic Cell
- 32 Transplant (autoHCT), Bortezomib, Lenalidomide (Len) and Dexamethasone (RVD)
- 33 Consolidation with Len Maintenance (ACM), Tandem Autohct with Len Maintenance
- 34 (TAM) and Autohct with Len Maintenance (AM) for up-Front. *Blood*. 2016;128(22).
- 35 41. Donato ML, Siegel DS, Vesole DH, et al. The graft-versus-myeloma effect: chronic graft-
- 36 versus-host disease but not acute graft-versus-host disease prolongs survival in
- 37 patients with multiple myeloma receiving allogeneic transplantation. *Biol Blood*
- 38 *Marrow Transplant*. 2014;20(8):1211-1216.
- 39 42. Armeson KE, Hill EG, Costa LJ. Tandem autologous vs autologous plus reduced
- 40 intensity allogeneic transplantation in the upfront management of multiple myeloma:
- 41 meta-analysis of trials with biological assignment. *Bone Marrow Transplant*.
- 42 2013;48(4):562-567.
- 43 43. Kharfan-Dabaja MA, Hamadani M, Reljic T, et al. Comparative efficacy of tandem
- 44 autologous versus autologous followed by allogeneic hematopoietic cell
- 45 transplantation in patients with newly diagnosed multiple myeloma: a systematic
- 46 review and meta-analysis of randomized controlled trials. *J Hematol Oncol*. 2013;6:2.
- 47 44. Bjorkstrand B, Iacobelli S, Hegenbart U, et al. Tandem autologous/reduced-intensity
- 48 conditioning allogeneic stem-cell transplantation versus autologous transplantation in
- 49 myeloma: long-term follow-up. *J Clin Oncol*. 2011;29(22):3016-3022.
- 50 45. Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell
- 51 transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

- 1
2
3 autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple
4 myeloma. *Blood*. 2006;107(9):3474-3480.
- 5 46. Moreau P, Garban F, Attal M, et al. Long-term follow-up results of IFM99-03 and
6 IFM99-04 trials comparing nonmyeloablative allotransplantation with autologous
7 transplantation in high-risk de novo multiple myeloma. *Blood*. 2008;112(9):3914-
8 3915.
- 9 47. Giaccone L, Storer B, Patriarca F, et al. Long-term follow-up of a comparison of
10 nonmyeloablative allografting with autografting for newly diagnosed myeloma. *Blood*.
11 2011;117(24):6721-6727.
- 12 48. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for
13 newly diagnosed myeloma. *N Engl J Med*. 2007;356(11):1110-1120.
- 14 49. Gahrton G, Iacobelli S, Bjorkstrand B, et al. Autologous/reduced-intensity allogeneic
15 stem cell transplantation vs autologous transplantation in multiple myeloma: long-
16 term results of the EBMT-NMAM2000 study. *Blood*. 2013;121(25):5055-5063.
- 17 50. Rosinol L, Perez-Simon JA, Sureda A, et al. A prospective PETHEMA study of tandem
18 autologous transplantation versus autograft followed by reduced-intensity
19 conditioning allogeneic transplantation in newly diagnosed multiple myeloma. *Blood*.
20 2008;112(9):3591-3593.
- 21 51. Krishnan A, Pasquini MC, Logan B, et al. Autologous haemopoietic stem-cell
22 transplantation followed by allogeneic or autologous haemopoietic stem-cell
23 transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3
24 biological assignment trial. *Lancet Oncol*. 2011;12(13):1195-1203.
- 25 52. Grovdal M, Nahi H, Gahrton G, et al. Autologous stem cell transplantation versus novel
26 drugs or conventional chemotherapy for patients with relapsed multiple myeloma
27 after previous ASCT. *Bone Marrow Transplant*. 2015;50(6):808-812.
- 28 53. Garderet L, Iacobelli S, Koster L, et al. Outcome of a Salvage Third Autologous Stem Cell
29 Transplantation in Multiple Myeloma. *Biol Blood Marrow Transplant*. 2018.
- 30 54. Gonsalves WI, Gertz MA, Lacy MQ, et al. Second auto-SCT for treatment of relapsed
31 multiple myeloma. *Bone Marrow Transplant*. 2013;48(4):568-573.
- 32 55. Michaelis LC, Saad A, Zhong X, et al. Salvage second hematopoietic cell transplantation
33 in myeloma. *Biol Blood Marrow Transplant*. 2013;19(5):760-766.
- 34 56. Yhim HY, Kim K, Kim JS, et al. Matched-pair analysis to compare the outcomes of a
35 second salvage auto-SCT to systemic chemotherapy alone in patients with multiple
36 myeloma who relapsed after front-line auto-SCT. *Bone Marrow Transplant*.
37 2013;48(3):425-432.
- 38 57. Manjappa S, Fiala MA, King J, Kohnen DA, Vij R. The efficacy of salvage autologous stem
39 cell transplant among patients with multiple myeloma who received maintenance
40 therapy post initial transplant. *Bone Marrow Transplant*. 2018.
- 41 58. Anderson KC, Alsina M, Bensinger W, et al. Multiple myeloma. *J Natl Compr Canc Netw*.
42 2011;9(10):1146-1183.
- 43 59. Sobh M, Michallet M, Gahrton G, et al. Allogeneic hematopoietic cell transplantation for
44 multiple myeloma in Europe: trends and outcomes over 25 years. A study by the EBMT
45 Chronic Malignancies Working Party. *Leukemia*. 2016;30(10):2047-2054.
- 46 60. Patriarca F, Einsele H, Spina F, et al. Allogeneic stem cell transplantation in multiple
47 myeloma relapsed after autograft: a multicenter retrospective study based on donor
48 availability. *Biol Blood Marrow Transplant*. 2012;18(4):617-626.
- 49 61. Kroger N, Shimoni A, Schilling G, et al. Unrelated stem cell transplantation after
50 reduced intensity conditioning for patients with multiple myeloma relapsing after
51 autologous transplantation. *Br J Haematol*. 2010;148(2):323-331.
- 52
53
54
55
56
57
58
59
60

- 1
2
3 62. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-
4 risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood*.
5 2016;127(24):2955-2962.
- 6 63. Roos-Weil D, Moreau P, Avet-Loiseau H, et al. Impact of genetic abnormalities after
7 allogeneic stem cell transplantation in multiple myeloma: a report of the Societe
8 Francaise de Greffe de Moelle et de Therapie Cellulaire. *Haematologica*.
9 2011;96(10):1504-1511.
- 10 64. Nooka AK, Kaufman JL, Muppidi S, et al. Consolidation and maintenance therapy with
11 lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients.
12 *Leukemia*. 2014;28(3):690-693.
- 13 65. Mai EK, Benner A, Bertsch U, et al. Single versus tandem high-dose melphalan followed
14 by autologous blood stem cell transplantation in multiple myeloma: long-term results
15 from the phase III GMMG-HD2 trial. *Br J Haematol*. 2016;173(5):731-741.
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

Table 1.

Phase III studies comparing autologous stem cell transplant to non-transplant approaches based on novel agents

Author	Study design	Response	PFS (median, months)	OS (median, months)	Ref.
Palumbo, 2014	MPR x 6 cycles vs. high-dose Melphalan + ASCT (x2)	-	43 vs. 22 P<0.001	4-year: 82% vs 65% P=0.004	24
Gay, 2015	CRD x 6 cycles vs. high-dose Melphalan + ASCT (x2)	-	43 vs. 29 P<0.001	4-year: 86% vs 73% P=0.004	25
Cavo, 2016	VMP x 4 cycles vs. high-dose Melphalan + ASCT (x1 vs. x2)	≥VGPR: 86% vs. 74% p<0.001	3-year PFS 66% vs. 58% p=0.037	-	29
Attal, 2017	RVD x 5 cycles vs. high-dose Melphalan + ASCT (x1) + RVD x 2 cycles	CR: 59% vs. 48% p<0.001	50 vs. 36 P<0.001	4-year: 81% vs 82% p: ns	28

CR, complete response; VGPR, very good partial response; MPR, melphalan, prednisone, lenalidomide; CRD, cyclophosphamide, lenalidomide, dexamethasone; RVD, lenalidomide, bortezomib, dexamethasone; VMP, bortezomib, melphalan, prednisone.

Table 2.**Selected studies comparing single versus double autologous stem cell transplant**

Author, study group / trial	Study design	PFS (median, months)	OS (median, months)	Ref.
Attal, 2003	Mel140 mg/m ² + TBI 8 Gy + ASCT vs. Mel140 mg/m ² + ASCT1 → Mel140 mg/m ² + TBI 8 Gy + ASCT2	25 vs. 36 p=0.03	48 vs. 58 p=0.1	34
Fermand, 2003	Mel140 + ASCT vs. Mel140 mg/m ² + ASCT1 → Mel140 mg/m ² + VP16 + TBI 12 Gy + ASCT2	31 vs. 33 -	-	36
Cavo, 2007	Mel200 mg/m ² + ASCT vs. Mel200 mg/m ² ASCT1 → Mel140 mg/m ² + Bu 1 mg/Kg + ASCT2	25 vs. 35 p=0.01	65 vs. 71 p=0.9	35
Mai, 2016	Mel200 mg/m ² + ASCT x 1 vs. Mel200 mg/m ² + ASCT x 2	25 vs. 29 p: ns	75 vs. 79 p: ns	65
Cavo, 2016	Mel200 mg/m ² + ASCT x 1 vs. Mel200 mg/m ² + ASCT1 x 2	45 vs. NR 3-year: 60% vs. 73% p=0.03	-	39
Staudtmaer, 2016	Mel200 mg/m ² + ASCT1 → lenalidomide maintenance Vs. Mel200 mg/m ² + ASCT x 2 → lenalidomide maintenance	38-months: 57% vs. 52% p=ns	38-months: 82% vs. 83% p=ns	40

Mel, melphalan; NA, not available.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

Table 3.

Selected studies comparing tandem autologous versus autologous/allogeneic-RIC stem cell transplant in NDMM patients

Author	Population	Conditioning regimens		Follow-up (median, months)	PFS (median, months)	OS (median, months)	TRM	Ref.
		ASCT	Allo-SCT					
Garban, 2006 Moreau, 2008	NDMM patients del13 + or B2M > 3 mg/dl	Mel200, Mel200	Bu-Flu	56	22 vs. 19 p=0.58	48 vs. 34 p=0.07	NA vs. 11%	45,46
Bjorkstrand, 2001 Gharton 2013	NDMM patients	Mel200	Flu-TBI 200 CGy	86	8-year 12% vs. 22% P=0.027	8-year: 39% vs 49% p=0.03	3-year, 3% vs. 13%	44,49
Bruno, 2007 Giaccone, 2011	NDMM patients	Mel200	TBI 200 cGy	96	35 vs. 29 p=0.02	80 vs. 54 p=0.01	2% vs. 10%	47,48
Rosinol, 2008	NDMM not in nCR/CR after 1st ASCT	Mel200 or CVB	Flu-Mel	62	31 vs. NR p: 0.08	58 vs. NR p=0.9	5% vs. 16%	50
Krishnan, 2011	NDMM after a prior ASCT	Mel200	TBI 200 cGy	40	3-year: 46% vs. 43% p=0.7	3-year: 80% vs. 71% p=0.2	NA	51

NDMM, newly diagnosed multiple myeloma; del13, deletion 13q; B2M, beta-2 microglobuline; Mel200, melphalan 200 mg/m², Flu, fludarabine; NA, not available; nCR, near complete response; CVB, cyclophosphamide, etoposide, BCNU.