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35 years of academic trials focusing on high-dose therapy and autologous stem cell transplantation: the Intergroupe Francophone du Myélome (IFM) experience

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Frontline high-dose therapy (HDT) is, in 2025, the standard of care for patients with multiple myeloma (MM) who are eligible for autologous stem cell transplantation (ASCT). Prior to high-dose melphalan, induction therapy with quadruplet combinations is also proposed systematically when possible. Lenalidomide maintenance until progression is also recommended per international guidelines. This strategy has been developed over recent decades, based on results of phase 3 trials designed and conducted by different academic groups. With these therapeutic advances, the median overall survival (OS) for patients with MM has increased from 5 years in the 1990s, to over 15 years at present. Here, we present the contribution of the French myeloma cooperative group Intergroupe Francophone du Myélome (IFM) to these advances in the newly diagnosed transplant-eligible (NDTE) setting.

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CONVENTIONAL CHEMOTHERAPY VS ASCT: THE IFM 90 TRIAL

The seminal paper of the French cooperative group was the report on the IFM 90 study, aimed at comparing conventional chemotherapy (CC) with ASCT as part of frontline therapy [1]. In the late 1980s, oral melphalan plus prednisone (MP) was the standard of care (SoC), and the addition of anthracyclines and/or vincristine to MP did not significantly increase efficacy [2]. In 1984, the concept of high-dose melphalan (HDM) was introduced by McElwain and Powles, first in the relapse setting, but subsequently as frontline therapy [3]. The severe myelosuppression with HDM alone was counterbalanced by concurrent use of stem cell support, which was evaluated in different phase 2 trials in Europe and the United States (US) [4]. The efficacy of frontline HDM and ASCT was highly promising, but prospective phase 3 trials were needed to assess whether ASCT had superior efficacy over CC. At the time of initiation of the IFM90 trial, the median OS with CC was 3 years, and there was a true skepticism regarding the superiority of ASCT regarding OS.

Between 1990 and 1993, 200 patients under the age of 65 years (median age, 57) with newly diagnosed MM (NDMM) were prospectively randomized into the IFM 90 study to receive either conventional therapy (CC) or HDT [1]. The CC arm consisted of the combination of vincristine, melphalan, cyclophosphamide and prednisone (VMCP), alternating with vincristine, carmustine, doxorubicin and prednisone (VBAP). Patients in the CC arms received 18 3-week cycles (12 months of treatment). In the HDT arm, patients were treated with 4–6 alternating cycles of VMCP and VBAP before receiving HDM (140 mg/m^2) and 8 Gy total body irradiation (TBI), followed by ASCT. The response rate among the patients who received HDT was 81% (including complete responses [CRs] in 22% and very good partial responses [VGPRs] in 16%), compared with 57% (CRs in 5% and VGPRs in 9%) in the group treated with CC ($p < 0.001$). The probability of event-free survival (EFS) for five years was 28% in the HDT group and 10% in the CC group ($p = 0.01$); the estimated 5-year overall survival (OS) rate was 52% in the HDT group and 12% in the CC group ($p = 0.03$). Treatment-related mortality was similar in the two groups. This study was the first to show the superiority of ASCT compared to CC in terms of response rate, EFS, and OS. These results were confirmed seven years later by the British Medical Research Council [5]. Consequently, ASCT became the SoC for frontline therapy, at least in younger patients (≤65 years) with normal renal function, and remains in 2025 the SoC recommended by international guidelines [6].

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SINGLE VS TANDEM TRANSPLANT: THE IFM 94-01 TRIAL

Strategies based on further intensification were subsequently explored with the aim of improving on the results obtained with a single ASCT. The IFM was the first to conduct a prospective trial, IFM 94-01, comparing single versus tandem HDT [7]. Between October 1994 and March 1997, 399 patients aged ≤60 years were randomly assigned at the time of diagnosis to receive one or two ASCTs. In each group, patients were initially treated with a continuous intravenous infusion of vincristine and doxorubicin over a 24-h period for four days, with 40 mg of oral dexamethasone per day on days 1 through 4 (the VAD regimen). Three or four cycles of VAD were administered at three-week intervals. In the group that received a single transplant, the preparative regimen was melphalan 140 mg/m^2 and 8 Gy TBI. In the group that received a double transplant, patients received the first transplant after preparation with melphalan alone (140 mg/m^2). Before the second ASCT, patients received the same melphalan and TBI regimen as the single-transplant group. A CR or VGPR was achieved by 42% and 50% of patients in the single-and double-transplant groups, respectively ($p = 0.10$). The probability of surviving event-free for seven years after the diagnosis was 10% and 20% in the single- and double-transplant groups, respectively ($p = 0.03$). The estimated 7-year OS was 21% and 42% in the single- and double-transplant groups, respectively ($p = 0.01$). Among patients who did not achieve a VGPR within three months after one transplantation, the probability of surviving seven years was 11% and 43% in the single- and double-transplant groups, respectively ($p < 0.001$). Four factors were significantly related to survival: baseline serum levels of beta2-microglobulin (β2M; $p < 0.01$) and lactate dehydrogenase ($p < 0.01$), age ($p < 0.05$), and treatment group ($p < 0.01$). Based on these data, tandem ASCT became an important option for patients with high tumor burden at diagnosis and suboptimal response to the first HDT.

THE OPTIMAL CONDITIONING REGIMEN: THE IFM 95-02 TRIAL

The initial clinical results of HDT were obtained with two types of conditioning regimens prior to ASCT, using either HDM alone or HDM in combination with TBI. The IFM group prospectively compared melphalan 140 mg/m^2 plus 8 Gy TBI (arm A) and melphalan 200 mg/m^2 (Mel200, arm B) in the IFM 95-02 trial [8]. A total of 282 evaluable patients were enrolled, 140 in arm A and 142 in arm B. Baseline characteristics and disease response to 4 cycles of the VAD regimen performed before randomization and ASCT were identical in the two treatment arms. In arm B, hematologic recovery was significantly faster for both the duration of neutropenia and thrombocytopenia, transfusion requirements were also significantly lower, and the median duration of hospitalization was significantly shorter. In arm A, the incidence of severe mucositis was significantly increased. The median duration of EFS was similar in both arms (21 months vs 20.5 months, $p = 0.6$), but the 45-month survival was 65.8% in arm B, compared with 45.5% in arm A ($p = 0.05$). This difference might be attributed in part to better salvage regimens after relapse in arm B, compared with arm A. These data showed that Mel200 was a less toxic, and at least as effective, conditioning regimen compared with the melphalan-TBI. As a result, Mel200 became the preferred preparative regimen, and to date, no other conditioning regimen has demonstrated superiority over Mel200 in randomized trials [6, 9].

THE FIRST RISK-ADAPTED STRATEGY: THE IFM 99 TRIALS

The IFM examined prognostic factors for progression-free survival (PFS) and OS in transplant-eligible patients with NDMM treated with HDT. Thierry Facon reported one of the first prognostic indices for OS based on two simple baseline parameters: β2M levels and chromosome 13 deletion (del13) identified by fluorescence in situ hybridization (FISH) [10]. Patients with high β2M and presence of del13 had a shorter OS, compared to those with neither or only one of these adverse prognostic features at diagnosis.

Based on these findings, the IFM designed three prospective trials using this simple classification. Patients with either 0 or 1 adverse factor were included in the IFM 99-02 trial, evaluating the impact of thalidomide maintenance after ASCT; patients with 2 adverse factors, considered to be high-risk, were included either in the IFM 99-03 study evaluating the sequence of ASCT followed by reduced intensity conditioning (RIC) allogeneic SCT (alloSCT) in case of sibling donor, or in the IFM 99-04 trial, evaluating tandem ASCT, with or without an anti-interleukin 6 (IL6) antibody, when a human leukocyte antigen (HLA)-matched sibling was not identified.

In the IFM 99-02 trial, 597 patients with standard-risk MM (β2M ≤ 3 mg/L and/or no del13 by FISH) were randomly assigned to receive no further treatment (arm A), pamidronate alone (arm B), or thalidomide plus pamidronate (arm C) 2 months after tandem ASCT [11]. A CR or VGPR was achieved by 55% of patients in arm A, 57% in arm B, and 67% in arm C ($p = 0.03$). The 3-year post-randomization probability of EFS was 36% in arm A, 37% in arm B, and 52% in arm C ($p < 0.009$). The effect of thalidomide on EFS differed according to the response achieved after double ASCT. Patients who had ≥VGPR did not benefit from thalidomide, while those who failed to achieve ≥VGPR had a significantly longer EFS on the thalidomide arm, indicating that thalidomide may mostly act by further reducing the tumor mass after HDT, consistent with a consolidation rather than a pure maintenance effect. The 4-year post-diagnosis probability of survival was 77% in arm A, 74% in arm B, and 87% in arm C ($p < 0.04$); however, updated results did not confirm the survival advantage of the thalidomide-containing arm. Moreover, maintenance treatment with pamidronate did not decrease the incidence of bone events. This study was one of four randomized trials testing thalidomide maintenance, an approach that is currently not used due to its significant cumulative neurotoxicity, and the availability of lenalidomide, which is used instead for maintenance.

For high-risk patients (high β2M and del13 positivity), we evaluated the impact of a murine anti-IL-6 monoclonal antibody, BE-8, as part of the second conditioning regimen in the multicentre prospective randomised IFM 99-04 trial of tandem ASCT [12]. Conditioning for the first ASCT was accomplished with Mel200, and for the second one with melphalan 220 mg/m^2 plus dexamethasone, with or without BE-8 infusion. This trial included 219 patients, of whom 166 were randomized, 85 without BE-8 (arm A) and 81 with BE-8 (arm B). The median OS and EFS for patients in arms A and B were 41 and 30 months, respectively. Response rates, OS, and EFS were not different between the two study arms. The OS at 54 months was 46% in arm A and 51% in arm B ($p = 0.90$); median EFS was 35 months in arm A and 31 in arm B ($p = 0.39$). In high-risk patients who received the dose intensity of melphalan at 220 mg/m^2, the results were encouraging, but the addition of the anti-IL-6 monoclonal antibody to the second conditioning regimen did not improve OS or EFS [10].

The IFM 99-03 trial evaluated the sequence of ASCT followed by RIC alloSCT in patients with high-risk NDMM [13]. On an intent-to-treat (ITT) basis, OS and EFS did not differ significantly between treatment arms in the IFM 99-03 and IFM 99-04 studies [14]. Our conclusion was that in patients with high-risk de novo MM, the combination of ASCT followed by dose-reduced alloSCT was not superior to tandem dose-intensified, melphalan-based ASCT [14].

LENALIDOMIDE MAINTENANCE AS SOC: THE IFM 2005-02 TRIAL

The IFM 2005-02 trial assessed the efficacy of lenalidomide as maintenance therapy following ASCT in patients with NDMM, based on the findings of the IFM 99-02 trial. As mentioned previously, IFM 99-02 demonstrated that although thalidomide maintenance improved PFS and OS, thalidomide had poor tolerability, necessitating investigation of alternative options, such as lenalidomide, with a more favorable safety profile [11].

From July 2006 to August 2008, the IFM 2005-02 trial enrolled 460 patients with a median age of 55 years [15]. Median follow-up was

45 months at the time of the first report. After induction and ASCT, participants were randomly assigned to receive either lenalidomide or a placebo for two cycles of consolidation (25 mg per day, on days 1–21 of 28-day cycles), followed by maintenance therapy (10 mg per day, increased to 15 mg per day, if tolerated after three months) until disease progression, death, or unacceptable toxicity. Lenalidomide was associated with prolonged PFS across all subgroups, with a median PFS of 41 months, compared to 23 months in the placebo group. PFS at the three-year follow-up was 66% in the lenalidomide group, compared with 39% in the placebo group [15]. Interestingly, consolidation with lenalidomide prior to maintenance therapy significantly increased response rates, with 78.5% of patients achieving VGPR or better, compared to 58.9% in the placebo group. OS was similar between the two groups at the time of data cutoff. However, patients receiving lenalidomide experienced a higher incidence of secondary malignancies (leading to the decision in january 2011 of using a fixed duration of lenalidomide maintenance as opposed to the same study run by the CALGB group 100104 which did continue indefinite lenalidomide [16]), highlighting the need for stringent long-term monitoring and comprehensive risk assessment. Nevertheless, the pivotal findings from the IFM 2005-02 study were essential for obtaining regulatory approval for lenalidomide as a maintenance therapy. This approval was further supported by the meta-analysis conducted by McCarthy et al., which compiled data from 1208 patients across three randomized controlled trials [17].

NOVEL AGENTS TO IMPROVE RESPONSE RATES DURING INDUCTION PRIOR TO ASCT: THE IFM 2005-01 TRIAL

Until 2005, VAD was the induction regimen most widely used prior to ASCT and considered the SoC. Bortezomib was approved by the US Food and Drug Administration (FDA) in 2003 for relapsed/refractory MM and was immediately evaluated in the upfront setting by the IFM. The primary objective of incorporating this novel agent as induction was to increase the response rate and improve long-term outcomes, but also to reduce the proportion of patients requiring a second ASCT because of a suboptimal response (<VGPR) to the first ASCT. Therefore, the IFM designed a prospective study to compare bortezomib in combination with dexamethasone (VD) for both efficacy and safety in previously untreated MM patients. In IFM 2005-01, 482 patients were randomized to VAD ($n = 121$), VAD plus dexamethasone, cyclophosphamide, etoposide, and cis-platinum (DCEP) consolidation ($n = 121$), VD ($n = 121$), or VD plus DCEP ($n = 119$), followed by ASCT [18]. Patients who did not achieve VGPR underwent a second transplant. The primary endpoints were the post-induction CR and near CR (nCR) rates. Post-induction CR/nCR, ≥VGPR, and overall response rates were significantly higher with VD than with VAD. The CR/nCR and ≥VGPR rates were higher regardless of disease stage or adverse cytogenetic abnormalities, and response rates were similar in patients who did or did not receive DCEP consolidation. These superior response rates in the VD induction arms of the trial translated into better response rates after HDT. Indeed, after the first ASCT preceded by Mel200, CR/nCR and ≥VGPR rates remained significantly higher with VD than with VAD. This improvement also translated into improved PFS (median PFS, 36 months with VD vs 30 months with VAD) [18]. The OS was not superior in the bortezomib-dexamethasone arms of the study, due to effective salvage regimens at the time of relapse. Regarding safety, the incidence of severe adverse events (AEs) appeared similar between groups, although hematologic toxicity and AE-related deaths were more frequent with VAD. Rates of grade 2 (20.5% vs 10.5%) and 3–4 (9.2% vs 2.5%) peripheral neuropathy during induction through first transplant were, as expected, significantly higher with the VD combination. Multivariate analysis showed that International Staging System (ISS) stages II and III and achievement of response <VGPR both after induction therapy and after ASCT were adverse prognostic factors for PFS. The level of response achieved with VD in the IFM 2005-01 trial was therefore considered as of the benchmark for induction therapies, and, as a result, bortezomib-dexamethasone became the backbone of per-ASCT induction therapy against which other more complex regimens should be compared [18].

TRIPLE COMBINATIONS PRIOR TO ASCT: IFM 2007-02 AND 2013-04 TRIALS

Bortezomib and dexamethasone prior to ASCT became the SoC following the results of the IFM 2005-01 study [18]. Many cooperative groups tested the impact of adding a third agent to this combination, either thalidomide (VTD), cyclophosphamide (VCD), or lenalidomide (VRD), to further increase the response rate before HDM [19]. The IFM 2007-02 study was designed to compare VD as induction before HDT and ASCT to a combination of VD plus thalidomide (VTD) in patients with de novo MM [20]. Overall, a total of 199 patients were randomized to receive VD or VTD. After 4 cycles, the CR plus VGPR rate was significantly higher in the VTD arm (49% vs 36%, $p = 0.05$). After ASCT, the CR plus VGPR rate was significantly higher in the VTD arm (74% vs 58%, $p = 0.02$) [20]. Our findings, confirmed by other cooperative groups in Italy and Spain [18, 19], indicated that VTD could be considered a new effective triplet combination before HDT/ASCT.

Indeed, ten years ago, 3-drug combinations including bortezomib and dexamethasone plus either an immunomodulatory drug (IMiD; thalidomide or lenalidomide), cyclophosphamide, or doxorubicin (PAD) were the SoC prior to ASCT and recommended in the international guidelines, but very few comparative trials were available to define the optimal triplet combination [20–26]. Therefore, the IFM conducted the IFM 2013-04 randomized study to compare VTD with VCD as induction before HDT and ASCT in patients with NDMM [27]. Overall, a total of 340 patients were randomized to receive VTD or VCD. After 4 cycles, on an ITT basis, 66.3% of the patients in the VTD arm achieved ≥VGPR (primary end point), compared with 56.2% in the VCD arm ($p = 0.05$). In addition, the ORR was significantly higher in the VTD arm (92.3% vs 83.4% in the VCD arm; $p = 0.01$). Hematologic toxicity was higher in the VCD arm, with significantly increased rates of grade 3 and 4 anaemia, thrombocytopenia, and neutropenia. On the other hand, the rate of peripheral neuropathy (PN) was significantly higher in the VTD arm. Except for hematologic adverse events and PN, other grade 3 or 4 toxicities were rare, with no significant differences between the VTD and VCD arms. Our data supported the preferential use of VTD, rather than VCD, in preparation for ASCT [27].

VRD WITH OR WITHOUT ASCT: THE IFM 2009 TRIAL

In 2010, Richardson and colleagues reported the results of a phase 1/2 trial evaluating VRD followed either by ASCT or by maintenance alone [28]. In a post-hoc landmark analysis from 1 year after treatment initiation among 53 patients who had not progressed within 1 year, there was no difference in PFS by receipt/lack of ASCT. This phase 1/2 study raised the issue of the benefit of ASCT over VRD alone [28].

In the IFM 2009 study, 700 patients with de novo MM were randomly assigned to receive induction therapy with three cycles of VRD and then consolidation therapy with either five additional cycles of VRD ($n = 350$) or HDM plus ASCT followed by two additional cycles of VRD ($n = 350$) [29]. Patients in both groups received maintenance therapy with lenalidomide for 1 year. The primary end point was PFS. Median PFS was significantly longer in the group that underwent transplantation than in the group that received VRD alone (50 months vs 36 months; adjusted hazard ratio [HR] for disease progression or death, 0.65; $p < 0.001$). This benefit was observed across all patient subgroups, including those stratified by ISS stage and cytogenetic risk. The transplantation group had a higher CR rate (59% vs 48%) and a greater proportion of patients with undetectable minimal residual disease (MRD; 79% vs 65%). However, the OS rate at four years was similar between the two groups (81% for the transplantation group vs 82% for the VRD-alone group) [29]. These findings suggested that

while early transplantation could significantly increase PFS, it did not necessarily extend OS, indicating that delayed transplantation could be an option for some patients. Nevertheless, the significant PFS benefit did establish VRD followed by ASCT and lenalidomide maintenance as a robust SoC. For the first time, the association of MRD negativity with favorable outcome was demonstrated in a randomized phase 3 trial [29].

TRIPLET OR QUADRUPLET INDUCTION THERAPY: THE IFM CASSIOPEIA STUDY

Daratumumab was approved in 2015 in advanced myeloma patients. This allowed its development at earlier lines of therapy, especially in the frontline setting, in combination with SoC regimens. In the two-part, randomized, open-label, phase 3 CASSIOPEIA trial, the IFM evaluated whether the addition of daratumumab (Dara) to VTD before and after ASCT would improve the stringent CR (sCR) rate in patients with NDMM [30]. Between Sept 22, 2015, and Aug 1, 2017, 1085 patients were enrolled at 111 European sites and were randomly assigned (1:1) to receive four pre-transplant induction and two post-transplant consolidation cycles of VTD alone (VTD group, $n = 543$) or in combination with daratumumab (Dara-VTD group, $n = 542$). Patients who completed consolidation and had a partial response (PR) or better were re-randomized (1:1) to intravenous Dara maintenance (16 mg/kg every 8 weeks) or observation for ≤2 years. The primary endpoint of part 1 was sCR rates, assessed 100 days after transplantation. The primary endpoint for the maintenance phase was PFS from second randomization. At day 100 after transplantation, 157 (29%) of 543 patients in the Dara-VTD group and 110 (20%) of 542 patients in the VTD group in the intention-to-treat population had achieved sCR (odds ratio, 1.60; 95% confidence interval, 1.21–2.12; $p = 0.0010$). Two hundred and eleven (39%) patients in the Dara-VTD group achieved ≥CR, compared with 141 (26%) in the VTD group, and 346 (64%) of 543 versus 236 (44%) of 542 achieved MRD-negativity (10^{-5} sensitivity threshold, assessed by multiparametric flow cytometry; both $p < 0.0001$) [30]. Between May 30, 2016, and June 18, 2018, 886 patients were re-randomized to Dara maintenance ($n = 442$) or observation ($n = 444$). At the clinical cutoff date (September 1, 2023), the median follow-up was 80.1 months from first randomisation and 70.6 months from second randomisation. Median PFS from first randomization, regardless of second randomization, was significantly longer for the Dara-VTD group (83.7 months) than for the VTD group (52.8 months; HR 0.61; $p < 0.0001$) [31]. OS from first randomization, regardless of second randomization, was significantly longer in the Dara-VTD group than the VTD group (HR, 0.55; $p < 0.0001$). Median OS from first randomization, regardless of second randomization, was not reached (NR) in the Dara-VTD group or VTD group; estimated 72-month OS rates were 86.7% for the Dara-VTD group and 77.7% for the VTD group. PFS from second randomization was significantly longer in the Dara maintenance group than the observation-alone group (median PFS, NR vs. 45.8 months; HR, 0.49; $p < 0.0001$); benefit was observed with Dara-VTD with Dara maintenance, over Dara-VTD with observation, as well with VTD plus Dara maintenance over VTD with observation [31]. Based on these results, Dara-VTD was approved in 2019. Of note, daratumumab maintenance was not approved because of the control arm proposing no maintenance after the second randomization. Moreover, the study confirmed the prognostic value of MRD negativity in predicting favorable PFS, not only before maintenance but also after induction and prior to ASCT [32].

MRD-DRIVEN THERAPY: THE PHASE 3 IFM 2020-02 MIDAS STUDY

Following CASSIOPEIA, induction therapy with a quadruplet regimen became SoC in 2020, an approach further supported by findings from the GRIFFIN [33], PERSEUS [34], and GMMG-HD7 trials [35]. CASSIOPEIA showed the prognostic value of MRD negativity after induction, consistent with data from the GMMG HD7 prospective randomized study [35]. The phase 3 IFM2020-02 MIDAS trial assessed an MRD-driven consolidation and maintenance strategy following induction with 6 cycles of isatuximab, carfilzomib, lenalidomide, and dexamethasone (IsaKRD) [36, 37]. Patients achieving post-induction MRD-negativity at a threshold of 10^{-5} by next-generation sequencing (NGS) were randomized to either 6 additional cycles of IsaKRD (Arm A) or ASCT followed by 2 cycles of IsaKRD (Arm B), followed by lenalidomide maintenance. Patients who were MRD-positive after induction (MRD ≥ 10^{-5}) were randomized to either single ASCT plus 2 cycles of IsaKRD (Arm C) or tandem ASCT (Arm D), followed by isatuximab plus iberdomide maintenance. Between December 2021 and July 2023, 791 patients were enrolled across 72 IFM centers. Overall, 96% ($n = 757$) of patients completed induction. The best ORR was 95%. In the ITT population, 91% achieved ≥VGPR after induction, with MRD-negativity rates of 63% at 10^{-5} and 47% at 10^{-6} [36]. MRD-negativity rates differed across ISS stages and cytogenetic risk subgroups. IsaKRD induction yielded deep responses and high MRD-negativity rates. An MRD-negative status at 10^{-6} sensitivity before maintenance occurred in 86% of the patients in the ASCT group compared with 84% of those in the Isa-KRD group ($P = 0.64$), and in 32% of the patients in the tandem ASCT group compared with 40% of those in the single ASCT group ($P = 0.31$) [37]. This study is ongoing, and data regarding MRD durability and PFS were immature. Nevertheless, the first conclusions were the following: the percentage of patients with an MRD-negative status at 10^{-6} sensitivity before maintenance was not significantly higher with ASCT than with Isa-KRD among patients with a post-induction MRD-negative status at 10^{-5} sensitivity, nor was it significantly higher with tandem ASCT than with single ASCT among patients with a post-induction MRD-positive status at 10^{-5} [37]. Nevertheless, it is currently impossible to drive definite conclusions on the need to keep ASCT as a standard or not, due to the lack of long-term results, but also to the impossibility to have IsaKRD in the real life as induction regimen.

FUTURE DIRECTIONS

The Intergroupe Francophone du Myélome (IFM) was able to conduct randomized clinical trials rapidly, thanks to the commitment of all French centers. IFM is the only cooperative group in France, created in 1990 by the merger of 3 regional networks working on MM. IFM is administered by a board of directors, elected every 3 years by all members of the group. The board of directors appoints from among its members the executive committee and its president selected for 3 years, in charge of proposing to the board the strategy of the group. The president cannot be selected twice consecutively. All of the 80 centers that take care of patients with MM are included in IFM, allowing quick patient enrollment across the country. Some French speaking centres in Belgium are also part of the group. Throughout its history, IFM has always appointed two or three leaders, charged with proposing academic clinical studies aimed at answering important issues in the management of patients with transplant-eligible NDMM, including the value of ASCT vs conventional chemotherapies, the utility of single vs tandem ASCT, and the role of maintenance, etc. The results of each new study informed the design of subsequent clinical trials. IFM also developed strong translational research with a centralized approach for sampling, to streamline MRD assessment, cytogenetic testing, and imaging, to complement the clinical results. After completion of the MIDAS study, IFM is now running a prospective trial opened for enrolment in June 2025 aimed at comparing ASCT with bispecific antibody-based therapy as consolidation following induction in patients with NDMM (ElLen study, NCT06918002).

CONCLUSIONS

The Intergroupe Francophone du Myélome has developed in the last 35 years in NDMM patients eligible for ASCT 13 academic clinical trials (Table 1) to establish new SoCs over time. Starting

Table 1. randomized trials from the Intergroupe Francophone du Myélome in transplant-eligible NDMM.

Trial		Pts	Best response/MRD negativity	PFS/EFS	OS
IFM90 [1]	CC vs ASCT	100 100	CR + VGPR : 14% CR + VGPR : 38%, $p < 0.001$	7-year EFS : 8% 7-year EFS : 16%, $p < 0.01$	7-year 25% 7-year 43%, $p < 0.05$
IFM94 [6]	Single vs Tandem ASCT	199 200	CR + VGPR : 42% CR + VGPR : 50%, $p = 0.1$	7-year EFS : 10% 7-year EFS : 20%, $p = 0.03$	7-year 21% 7-year 42%, $p = 0.01$
IFM95-02 [7]	HDM140 + TBI vs HDM200	140 142	CR + VGPR : 43% CR + VGPR : 55%, $p = 0.06$	Median EFS : 21 mos Median EFS : 20.5 mos, $p = 0.6$	45-mo : 45.5% 45-mo : 65.8%, $p = 0.05$
IFM99-02 [9]	No maintenance vs Pamidronate maintenance vs Pamidronate + thalidomide main.	200 196 201	CR + VGPR : 55% CR + VGPR : 57% CR + VGPR : 67%, $p = 0.03$	3-year post-random EFS : 36% 3-year post-random EFS : 37% 3-year post-random EFS : 52%, $p < 0.009$	4-year OS : 77% 4-year OS : 74% 4-year OS : 87%, $p < 0.04$
IFM99-03 [11]	Single ASCT + RIC allo vs	65	CR + VGPR : 62.2%	Median EFS : 19 mos	Median OS : 48 mos
IFM99-04 [10]	Tandem ASCT +/− anti-IL6 MoAb	219	CR + VGPR : 55%	Median EFS : 22 mos, $p = 0.58$	Median OS : 34 mos, $p = 0.07$
IFM2005-02 [13]	Lenalidomide maintenance vs Placebo	307 307	CR + VGPR : 84% CR + VGPR : 76%, $p = 0.009$	4-year post-random PFS : 43% 4-year post-random PFS : 22%, $p < 0.001$	4-year OS post-random : 73% 4-year OS post-random : 75%
IFM2005-01 [15]	VAD vs VD	218 223	CR + VGPR : 15.1%[a] CR + VGPR : 37.7%[a], $p < 0.001$	Median PFS : 29.7 mos Median PFS : 36 mos, $p = 0.057$	3-year OS : 77.4% 3-year OS : 81.4%, NS
IFM2007-02 [17]	VD vs VTD	99 100	CR + VGPR : 36%[a] CR + VGPR : 49%[a], $p = 0.05$	Median PFS : 30 mos Median PFS : 26 mos, $p = 0.22$	NR NR
IFM2013-04 [24]	VTD vs VCD	169 169	CR + VGPR : 66.3%[a] CR + VGPR : 56.2%[a], $p = 0.05$	NR NR	NR NR
IFM2009[26]	VRD vs VRD + ASCT	350 350	CR : 48% MRD neg. : 65% CR : 59%, $p = 0.03$ MRD neg. : 79%, $p < 0.001$	Median PFS : 36 mos Median PFS, 50 mos, $p < 0.001$	4-year OS : 81% 4-year OS : 82%, NS
IFM2015-01 [27, 28] Cassiopeia	VTD vs VTD-daratumumab	542 543	CR or better : 61% MRD neg. and CR: 47% CR or better : 73%, $p < 0.001$ MRD neg. and CR : 59%, $p = 0.0001$	Median PFS : 52.8 mos Median PFS : 83.7 mos, $p < 0.0001$	72-mo OS : 86.7% 72-mo OS : 77.7%, $p < 0.0001$
IFM 2020-02 [34] Midas	Isa-KRD/Isa-KRD/lenalidomide vs Isa-KRD/ASCT/lenalidomide Isa-KRD/ASCT/isatux-len vs Isa-KRD/tandem ASCT/isatux-len	243 242 109 124	MRD neg.[b] : 84% MRD neg.[b] : 86%, $p = 0.64$ MRD neg.[b] : 40% MRD neg.[b] : 32%, $p = 0.31$	NR	NR

Pts patients, *MRD* minimal residual disease, *MRD neg* MRD negativity, *PFS* progression-free survival, *EFS* event-free survival, *OS* overall survival, *CC* conventional chemotherapy, *ASCT* autologous stem cell transplantation, *CR* complete response, *VGPR* very good partial response, *mos* months, *RIC* reduced-intensity conditioning, *MoAb* monoclonal antibody, *random* randomization, *VAD* vincristine-doxorubicin-dexamethasone, *VD* bortezomib-dexamethasone, *NS* not significant, *NR* not reported, *VTD* bortezomib, thalidomide, dexamethasone, *VCD* bortezomib, cyclophosphamide, dexamethasone, *Isa-KRD* isatuximab-carfilzomib-lenalidomide-dexamethasone, *Isatux-len* isatuximab-lenalidomide.

[a]Post-induction, prior to ASCT.

[b]10^{-6} premaintenance.

with the IFM90 study establishing ASCT as a pillar of frontline therapy, followed by the incorporation of novel agents during induction and maintenance, and developing now MRD driven strategies, the contribution of the French group to the myeloma therapeutic landscape is significant.

DATA AVAILABILITY

Available from the corresponding author upon reasonable request.

REFERENCES

1. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. N Engl J Med. 1996;335:91–7.
2. Myeloma Trialists'Collaborative group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6633 patients from 27 randomized trials. J Clin Oncol. 1998;16:3832–42.
3. Mc Elwain TJ, Powles RL. High-dose intravenous melphalan for plasma-cell leukaemia and myeloma. Lancet. 1983;2:822–4.
4. Harousseau JL, Moreau P. Autologous hematopoietic stem-cell transplantation for multiple myeloma. New Engl J Med. 2009;360:2645–54.
5. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003;348:1875–83.
6. Dimopoulos MA, Terpos E, Boccadoro M, Moreau P, Mateos MV, Zweegman S, et al. EHA-EMN Evidence-Based Guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma. Nat Rev Clin Oncol. 2025. https://doi.org/10.1038/s41571-025-01041-x.
7. Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med. 2003;349:2495–2502.
8. Moreau P, Facon T, Attal M, Hulin C, Michallet M, Maloisel F, et al. Comparison of 200 mg/m^2 melphalan and 8Gy total body irradiation plus 140 mg/m^2 melphalan as conditioning regimen for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma :final analysis of the Intergroupe Francophone du Myelome 9502 trial. Blood. 2022;99:731–5.
9. Lahuerta JJ, San-Miguel JF, Jiménez-Ubieto A, Alonso Fernández R, Paiva B, Puig N, et al. High-dose busulfan-melphalan vs melphalan and reinforced VRD for newly diagnosed multiple myeloma: a phase 3 GEM trial. Blood. 2025:blood.2025028313. https://doi.org/10.1182/blood.2025028313.
10. Facon T, Avet-Loiseau H, Guillerm G, Moreau P, Geneviève F, Zandecki M, et al. Chromosome 13 abnormalities identified by FISH analysis and serum beta2-microglobulin produce a powerful myeloma staging system for patients receiving high-dose therapy. Blood. 2001;97:1566–71.
11. Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood. 2006;108:3289–94.
12. Moreau P, Hulin C, Garban F, Yacoub-Agha I, Benboubker L, Attal M, et al. Tandem autologous stem cell transplantation in high-risk de novo multiple myeloma: final results of the prospective and randomised IFM99-04 protocol. Blood. 2006;107:397–403.
13. Garban F, Attal M, Michallet M, Hulin C, Bourhis JH, Yacoub-Agha I, et al. Prospective comparison of autologous stem cell transplantation followed by a dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. Blood. 2006;107:3474–80.
14. Moreau P, Garban F, Attal M, Michallet M, Marit G, Hulin C, et al. Long-term follow-up results of IFM99-03 and IFM99-04 trials comparing non myeloablative allotransplantation in high-risk de novo multiple myeloma. Blood. 2008;112:3914–15.
15. Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366:1782–91.
16. McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366:1770–81.
17. McCarthy PL, Holstein SA, Petrucci MT, Richardson PG, Hulin C, Tozi P, et al. Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-Analysis. J Clin Oncol. 2017;35:3279–89.
18. Harousseau JL, Attal M, Avet-Loiseau H, Marit G, Caillot D, Mohty M, et al. Bortezomib-dexamethasone is superior to vincristine-doxorubicin-dexamethasone as induction treatment prior to autologous stem cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase 3 trial. J Clin Oncol. 2010;28:4621–9.
19. Moreau P, Avet-Loiseau H, Harousseau JL, Attal M. Current trends in autologous stem cell transplantation for myeloma in the era of novel therapies. J Clin Oncol. 2011;29:1898–1906.
20. Moreau P, Avet-Loiseau H, Facon T, Attal M, Tiab M, Hulin C, et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide and dexamethasone as induction treatment prior to autologous stem cell transplantation in newly diagnosed multiple myeloma. Blood. 2011;118:5752–8.
21. Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, et al. GIMEMA Italian Myeloma Network. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet. 2010;376:2075–85.
22. Rosiñol L, Oriol A, Teruel AI, Hernandez D, Lopez-Jimenez J, de la Rubia J, et al. Programa para el Estudio y la Terapéutica de las Hemopatías Malignas/Grupo Español de Mieloma (PETHEMA/GEM) group. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood. 2012;120:1589–96.
23. Mai EK, Bertsch U, Dürig J, Kunz C, Haenel M, blau IW, et al. Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCD) versus bortezomib, doxorubicin and dexamethasone (PAd) in newly diagnosed myeloma. Leukemia. 2015;29:1721–9.
24. Reeder CB, Reece DE, Kukreti V, Mikhael JR, Chen C, Trudel S, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leukemia. 2009;23:1337–41.
25. Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood. 2012;119:4375–82.
26. Moreau P, san Miguel J, Ludwig H, Schouten H, Mohty M, Dimopoulos M, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;6:vi133–7.
27. Moreau P, Hulin C, Macro M, Caillot D, Chaleteix C, Roussel M, et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. Blood. 2016;127:2569–74.
28. Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood. 2010;116:679–86.
29. Attal M, Lauwers-Cances V, Hulin C, Leleu X, Caillot D, Escoffre M, et al. IFM 2009 Study. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. N Engl J Med. 2017;376:1311–20.
30. Moreau P, Attal M, Hulin C, Arnulf B, Belhadj K, Benboubker L, 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;394:29–38.
31. Moreau P, Hulin C, Perrot A, Arnulf B, Belhadj K, Benboubker L, et al. Intergroupe Francophone du Myélome, the Dutch-Belgian Cooperative Trial Group for Hematology Oncology and the CASSIOPEIA Investigators. Bortezomib, thalidomide, and dexamethasone with or without daratumumab and followed by daratumumab maintenance or observation in transplant-eligible newly diagnosed multiple myeloma: long-term follow-up of the CASSIOPEIA randomised controlled phase 3 trial. Lancet Oncol. 2024;25:1003–14.
32. Corre J, Vincent L, Moreau P, Hebraud B, Hulin C, Béné MC, et al. Daratumumab-bortezomib-thalidomide-dexamethasone for newly diagnosed myeloma: CASSIOPEIA minimal residual disease results. Blood. 2025:blood.2024027620. https://doi.org/10.1182/blood.2024027620.
33. Voorhees PM, Sborov DW, Laubach J, Kaufman JL, Reeves B, Rodriguez C, et al. Addition of daratumumab to lenalidomide, bortezomib, and dexamethasone for transplantation-eligible patients with newly diagnosed multiple myeloma (GRIFFIN): final analysis of an open-label, randomised, phase 2 trial. Lancet Haematol. 2023;10:e825–37.
34. Sonneveld P, Dimopoulos MA, Boccadoro M, Quach H, Ho PJ, Beksac M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2024;390:301–13.
35. Mai EK, Bertsch U, Pozek E, Fenk R, Besemer B, Hanoun C, et al. Isatuximab, lenalidomide, bortezomib, and dexamethasone induction therapy for transplant-eligible newly diagnosed multiple myeloma: final part 1 analysis of the GMMG-HD7 trial. J Clin Oncol. 2025;43:1279–88.
36. Perrot A, Touzeau C, Lambert J, Hulin C, Caillot D, Karlin L, et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone induction in newly diagnosed myeloma: analysis of the MIDAS trial. Blood. 2025;146:52–61.

37. Perrot A, Lambert J, Hulin C, Pieragostini A, Karlin L, Arnulf B, et al. Measurable residual disease-guided therapy in newly diagnosed myeloma. N Engl J Med. 2025;393:425–37.

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AUTHOR CONTRIBUTIONS

PM, AT, HD, LC, TC, AB, CT, and AP wrote the first draft of the manuscript. All authors contributed patients to this manuscript, provided critical feed-back, edited and wrote the manuscript, and approved the final manuscript (PM, CH, AT, HD, LC, TC, AB, SM, XL, LK, DC, CS, PF, MR, RG, MMa, MMo, LG, MT, FOP, LV, NM, JF, LM, MCV, MEB, JRE, JMSdC, JL, JYM, JPF, BA, JC, HAL, TF, JLH, CT, AP).

COMPETING INTERESTS

PM reports honoraria and advisory boards: Janssen, BMS, Amgen, Takeda, GSK, Sanofi, Pfizer, Abbvie. CH reports honoraria and advisory boards: Janssen, Sanofi, Amgen, Abbvie, BMS, Stemline Menarini. AT reports consulting: Amgen, GSK, Janssen, Pfizer, Sanofi, Stemline Menarini. HD reports consulting: Janssen, Pfizer, Sanofi, Stemline Menarini, BMS, Abbvie. TC reports consulting: Janssen, GSK, Pfizer, BMS, Stemline Menarini, Grifols, Sanofi. SM reports consulting: AbbVie, Adaptive Biotechnology, Amgen, BMS, GSK, Janssen, Kite, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda. XL reports honoraria and advisory boards: Janssen, Amgen, Abbvie, Regeneron, BMS, GSK, Roche, Takeda, Novartis, Sanofi, Pfizer, Oncopeptide, Ichnos. LK reports honoraria and advisory boards: Amgen, Celgene-BMS, Janssen, Takeda, Sanofi, Pfizer, Abbvie. DC reports advisory boards: BMS. CS reports honoraria and advisory boards: Janssen, Pfizer, Amgen, Sanofi, Takeda, GSK. PG reports consulting: AstraZeneca, Roche, Gilead, Janssen, BeiGene, Lilly. MR reports honoraria and advisory boards: Janssen, Amgen, GSK, Pfizer. MMa reports honoraria and advisory boards: Amgen, BMS, GSK, Janssen, Sanofi, Takeda. MMo reports honoraria and advisory boards: Abbvie, Adaptive Biotechnologies, Amgen, Astellas, BMS, GSK, Janssen, Jazz, Novartis, Pfizer, Sanofi, Stemline Menarini, Takeda. LG reports honoraria and advisory boards: Sanofi, Pfizer, BMS, Janssen. FOP reports honoraria: Sanofi. LV reports honorarias and advisory boards: Janssen, BMS, Takeda, Sanofi, Pfizer. NM reports honoraria and advisory boards from Janssen. MCV reports honoraria and advisory boards: Amgen, GSK, BMS, Stemline Menarini, Pfizer, Janssen, Sanofi, Takeda. JMSC reports honoraria and advisory boards: Janssen, Sanofi, GSK, Abbvie, Pfizer, Amgen. BA reports honoraria and advisory boards: Janssen, BMS, Amgen, Sanofi. JC reports honoraria and advisory boards: Janssen, Sanofi, Bristol Myers Squibb, Pfizer and Adaptive. CT reports honoraria and advisory boards: Janssen, Pfizer, Amgen, Sanofi, Takeda, GSK, Abbvie, Menarini, BMS. A.P. reports honoraria and advisory boards: AbbVie, Amgen, BMS, GSK, Janssen, Pfizer, Sanofi, Takeda. The rest of the authors have no conflicts of interest.

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