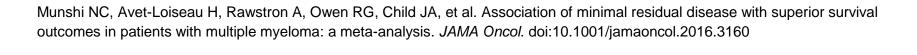
Supplementary Online Content



eTable. Treatment information and patient population data of included studies

eFigure. Overall survival in patients achieving CR according to cytogenetic risk category (FISH) and MRD status. CR, complete response; FISH, fluorescent in situ hybridization; MRD, minimal residual disease; OS, overall survival

This supplementary material has been provided by the authors to give readers additional information about their work.

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Supplementary Table 1. Treatment information and patient population data of included studies

| Reference | Study design | Follow -up, (mo) | N | Study objective | Age range, (years) | MRD detection method | Time of MRD assessment | ISS | Statistics | Regimen | Mainte nance | Depth of response |
|-----------------------|--|-------------------------|----|---|--------------------------|----------------------------|---|--|--|--|-----------------|---|
| Rawstron 2002 | Prospective | up to 39 | 45 | Whether MFC results (levels of malignant vs normal plasma cells) predict outcomes after HDT and SCT | 41–65 | MFC | 3 months after Tx; 3–6 month intervals thereafter | NS | Univariate (log-rank test) and multivariate (Cox- regression) analysis | C-VAMP followed by MEL + HD ASCT | None | Following induction: 22% CR, 78% PR Following HD: 73% CR: 42% MRD ⁺ |
| San Miguel 2002 | Prospective, randomized, multicenter PETHEMA trial | 65 (PFS), 53 (OS) | 87 | Determine whether changes in the plasma cell compartment (MRD using MFC) could predict disease outcome | 31–70 | PCR | 3 months after ASCT, 1 month after 12 cycles chemotherapy | 58–61% stage II 39–42% stage III | Mann- Whitney U, Wilcoxon for between- group differences. Kaplan-Meier for survival curves | VBMCP/VBAD followed by ASCT or 8 cycles chemotherapy | IFNα + DEX | MRD ⁻ : 36% of ASCT patients vs 15% CT patients (p=0.04) |
| Ferrero 2014 | GIMEMA trial | 93 | 39 | Impact of MRD kinetics on survival when using VTD consolidation | 42–69 | PCR | After 2 VTD courses, end of treatment, every 6 months until relapse | NS | Univariate Cox proportional hazards model | VTD, MEL, ASCT | None | Full MRD: 18% Major MRD: 67% |
| Bakkus 2004 | NS | NS | 67 | Whether post- SCT tumor load predicts duration of response | 30–65 | PCR | 3–6 months post-HDT | stage IIA, 47% stage IIIA, 8% stage IIIB | Log-rank test | VAD, MEL± TBI with single or tandem autologous PBSCT | None | 28% CR |

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| Dal Bo 2013 | Prospective | 18 | 44 | Whether presence of MRD 3 months post- SCT predicts relapse or death | 52.2 – 64 | MFC | 3 months | NS | Log-rank test | MEL, ASCT | None | 32.6% CR, 40% MRD ⁻ |
|------------------|---|----|--------------------------------------|--|---------------------|-----|---|---|---|---|----------------------------|--|
| Paiva 2011 | Prospective | 32 | 102 | Prognostic value of MFC vs IF vs SFLC | 65–84 | MFC | After 6 cycles of induction | 29% stage I, 38% stage II, 33% stage III | Two-sided log-rank test | VMP vs VTP for 6 cycles | VT vs VP for max 3 y | CR 43%, MRD 30% |
| Paiva 2008 | Prospective | 57 | 295 | Prognostic value of post-SCT MFC remission | 29–70 | MFC | 100 days | 39% stage I, 41% stage II, 20% stage III | Log-rank test | VBMCP/VBAD, MEL, ASCT | None | 50% CR, 42% MRD ⁻ |
| Korthals 2012 | NS | 61 | 53 | Whether pre- and post-SCT MRD status predicts EFS/OS | 31–75 | PCR | 3–6 months after SCT | 11% stage I+II, 89% stage III | Kaplan-Meier plots and the log-rank test | Idarubicin/dex amethasone induction, MEL, ASCT | IFN or THAL | 25% nCR, 21% MRD ⁻ |
| Korthals 2013 | Retrospective | 45 | 42 | Whether MRD status in PB predicts remission status | 31–66 | PCR | 3 mo | 12% Stage I+II, 88% Stage III | Kaplan-Meier plots and the log rank test. | Idarubicin/dex amethasone induction, MEL, ASCT | IFN or THAL | 28% CR |
| Swedin 1998 | NS | 29 | 36 | Utility and clinical value of ASO-PCR to evaluate MRD | 31–60 | PCR | 3 + 6 months after ASCT, 6 months thereafter | NS | Log rank test | VAD, MEL, ASCT | IFN | 50% CR |
| Rawstron 2013 | Prospective | 71 | 397 (INT) and 245 (nINT) | Prognostic value of MRD, measured using MFC, on outcomes | NS | MFC | 100 days after ASCT (intensive pathway only) | NS | Fisher's exact test | CTD vs CVAD (INT) or CTDa vs MP (nINT), MEL and ASCT | THAL vs no THAL | MRD ⁻ 62% (INT) and 15% (nINT) |
| Roussel 2014 | Prospective, multicenter, single-arm, | 39 | 31 | Response with RVD induction/ consolidation | 33–65 | MFC | Baseline, post- induction/pre- ASCT, post- | 48% stage I, 36% | Kaplan-Meier | RVD, MEL, ASCT | LEN for 1 year | 58% CR, 68% MDR ⁻ |

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| | open-label, phase II study | | | | | | ASCT, post- consolidation, end of treatment | stage II, 16% stage III | | | | |
|---------------------|--|------|----|---|---------------------|-----|--|--|--|---|--------------|---|
| Fukomoto 2016 | Retrospective | 40.9 | 78 | Impact of immunophenoty pic CR (MFC) on survival outcomes | 44-87 | MFC | Bone marrow samples taken at presentation, and at VGPR/CR | 53% stage III | Univariate analysis and multivariate analysis using a Cox proportional hazards model | 87% IMiD- based regimens and 94% BORT- based therapies | BORT+ DEX | 44% iCR |
| Sarasquet e 2005 | Prospective (GEMM2000) | NS | 32 | Compare ASO real-time qPCR vs MFC for MRD monitoring | 59 ± (SD) 9.7 | PCR | 3 months after transplant | NS | Mann- Whitney U and Kruskal- Wallis tests | VBCMP/VBAD, MEL, ASCT | None | 58% IF ⁻ CR |
| Ludwig 2015 | Randomized, open-label, multicenter, phase II | 33 | 98 | Response rates after VTD vs VTDC induction | 33–68 | MFC | 40–269 days after SCT | 18–24% stage I, 45–47% stage II, 31–35% stage III | NS | VTD vs VTDC, single or double ASCT | None | MRD ⁻ : 53% (VTD) 33% (VTDC) |

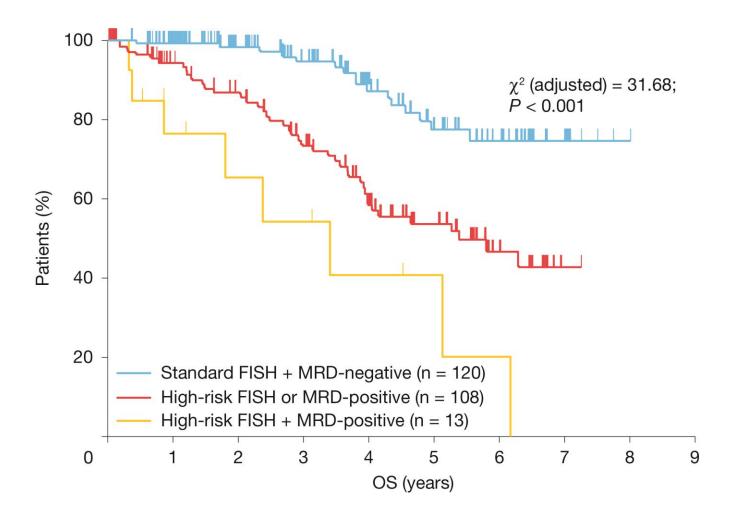
Abbreviations: ASCT = autologous stem cell transplantation; BORT = bortezomib; C-VAMP = cyclophosphamide, vincristine, adriamycin plus methylprednisolone; CR = complete response; CT = chemotherapy; CTD = cyclophosphamide-thalidomide-dexamethasone; CTDa= attenuated CTD; CVAD = cyclophosphamide-vincristine-doxorubicin-dexamethasone; DEX = dexamethasone; HD = high-dose; IF = immunofixation; IFN α = interferon alfa; INT = intensive pathway; MEL = melphalan; MFC = multiparameter flow cytometry; mo = months; MP = melphalan-prednisolone; MRD = minimal residual disease; nINT = non-intensive pathway; NS = not specified; PFS = progression-free survival; OS = overall survival; PBSCT = peripheral blood stem cells transplant; PR = partial response; (q)ASO-PCR = (quantitative) allele-specific oligonucleotide polymerase chain reaction; SCT = stem cell transplantation; sFLC = serum free light chain; TBI = total body irradiation; THAL = thalidomide; Tx = transplantation; VBAD = vincristine-bis-chloroethylnitrosourea-doxorubicin-dexamethasone; VBMCP = vincristine-bis-chloroethylnitrosourea-melphalan-cyclophosphamide-prednisolone; VMP = bortezomib-melphalan-prednisolone; VP = bortezomib-prednisolone; VTP = bortezomib-thalidomide-dexamethasone; VTDC = bortezomib-thalidomide-dexamethasone-cyclophosphamide; VTP = bortezomib-thalidomide-prednisolone

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