Supplementary Online Content

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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.

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	Maintenance	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	12% stage IIA, 47% stage IIIA, 8% stage IIIB	Log-rank test	VAD, MEL± TBI with single or tandem autologous PBSCT	None	28% CR

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/dexamethasone 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/dexamethasone 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^-

	open-label, phase II study						ASCT, post-consolidation, end of treatment	stage II, 16% stage III				
Fukomoto 2016	Retrospective	40.9	78	Impact of immunophenotypic 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
Sarasquete 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; IFNα = 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-prednisone; VMP = bortezomib-melphalan-prednisolone; VP = bortezomib-prednisolone; VT = bortezomib-thalidomide; VTD = bortezomib-thalidomide-dexamethasone; VTDC = bortezomib-thalidomide-dexamethasone-cyclophosphamide; VTP = bortezomib-thalidomide-prednisolone

Supplementary Figure. 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.