SUPPLEMENTARY APPENDIX

Supplementary methods

Literature search and study selection

Medical subject heading (MeSH) terms for MM were “multiple myeloma” and “neoplasm, residual.” Non-MeSH search terms were “Kahler disease” (or “Kahler’s disease” or “myelomatosis” or “plasma cell myeloma”) and “minimal residual disease” (or “MRD”). Selected congress abstracts published between 2016 and 2019, including additional literature, were manually reviewed. Bibliographies of SLR articles on MM published between 2014 and 2019 were reviewed manually to identify additional potentially relevant publications. Additional sources were used for validation, including studies identified in public assessment reports published by the European Medicines Agency and the US Food and Drug Administration.

Population, interventions, comparisons, outcomes, and study design (PICOS) criteria were used to define eligibility. Patients could have received any type of therapy except allogeneic stem cell transplantation. Studies with PFS or OS data that could not be extracted or reconstructed were excluded. Studies with patients who did not have a primary diagnosis of MM were also excluded, as were those with MRD measured only in peripheral blood or assessed only by positron emission tomography–computed tomography scanning.

Data extraction and preparation

Other baseline characteristics such as patient age, disease setting, and cytogenetic profile were also extracted. Information on the number and types of previous lines of therapy, MRD parameters including the definition, type (prespecified, secondary, or exploratory endpoint), method of evaluation (MFC, NGF, NGS, or PCR), and level of sensitivity of the MRD technique were extracted.

HRs and p-values were collected for PFS and OS comparing MRD-negative patients with MRD-positive patients. HRs for PFS and OS, stratified by MRD status, were estimated for subgroups by 1) disease settings (NDMM patients who were transplant eligible or transplant ineligible, and patients with RRMM); 2) MRD sensitivity threshold at 10^{-4} , 10^{-5}, and 10^{-6} defined as one MM cell per 10,000, 100,000, and 1,000,000 nucleated cells, respectively; 3) cytogenetic risk (high risk and standard risk) wherein high risk was predominantly defined as the presence of t(4;14) and t(14;16), and/or del(17p) abnormalities, and standard risk was defined as the absence of high risk genetic abnormalities; 4) method of MRD assessment (MFC, NGF, NGS, and PCR); 5) depth of

clinical response at the time of MRD measurement; MRD was only measured in patients achieving CR or better, or those achieving VGPR or better; and 6) measurement of MRD status pre-maintenance and at 12 months after start of maintenance therapy.

Supplementary Table 1. Main characteristics of the studies included in the meta-analysis

ASCT, autologous stem cell transplantation; BiCTd, clarithromycin, cyclophosphamide, thalidomide, and dexamethasone; C-VAMP, vincristine, amethopterine, methotrexate, and prednisone + cyclophosphamide; CRd, lenalidomide, cyclophosphamide, and dexamethasone; CTd, cyclophosphamide, thalidomide, and dexamethasone. CVAd=cyclophosphamide, vincristine, doxorubicin, and dexamethasone; D-Rd, daratumumab, lenalidomide, and dexamethasone; D-Vd, daratumumab, bortezomib, and dexamethasone; D-VMP, daratumumab, bortezomib, melphalan, and prednisone; HDT, high-dose chemotherapy; ImiD, immunomodulatory drugs; KCd, carfilzomib, cyclophosphamide and dexamethasone; KMP, carfilzomib, melphalan and prednisone; LEN, lenalidomide; PACE, cisplatin, doxorubicin, cyclophosphamide, etoposide; Pad, bortezomib, doxorubicin and dexamethasone; PI, protease inhibitors; Rd, lenalidomide plus dexamethasone; RCd, lenalidomide cyclophosphamide and dexamethasone; RVd, lenalidomide, bortezomib, and dexamethasone; SCT, stem cell transplantation; VAd, vincristine, doxorubicin, and dexamethasone; VBAD, vincristine, carmustine, adriamicine, and dexamethasone; VBMCP, vincristine, carmustine, melphalan, cyclophosphamide, and prednisone; Vd, bortezomib and dexamethasone; VCd, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan and prednisone; VRd, bortezomib, lenalidomide, and dexamethasone; VTd, bortezomib, thalidomide, and dexamethasone; VTdC, bortezomib, thalidomide, and dexamethasone + cyclophosphamide; VTP, bortezomib, thalidomide, and prednisone.

Supplementary Figure 1. Forest plots of (A) PFS and (B) OS by disease setting

CI, confidence interval; HR, hazard ratio; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; No., number; OS, overall survival; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; TE, treatment eligible; TIE, treatment ineligible.

Supplementary Figure 2. Forest plots of (A) PFS and (B) OS by MRD sensitivity thresholds of 10^{-4}, 10^{-5}, and 10^{-6}

[a]MRD assessed at sensitivity threshold of 2×10^{-6}. CI, confidence interval; HR, hazard ratio; MRD, minimal residual disease; No., number; OS, overall survival; PFS, progression-free survival.

Supplementary Figure 3. Forest plots of (A) PFS and (B) OS by cytogenetic risk

CI, confidence interval; HR, hazard ratio; MRD, minimal residual disease; No., number; OS, overall survival; PFS, progression-free survival.

Supplementary Figure 4. Forest plots of (A) PFS and (B) OS by method of MRD assessment.

The MFC subgroup only includes studies with MRD assessment at the 10^{-5} and 10^{-6} sensitivity thresholds. CI, confidence interval; HR, hazard ratio; MFC, multiparameter flow cytometry; MRD, minimal residual disease; NGS, next-generation sequencing; No., number; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival.

Supplementary Figure 5. Forest plots of (A) PFS and (B) OS by depth of clinical response at the time of MRD measurement. Complete response or better subgroup includes studies that reported immunophenotypic complete response, stringent complete response, or near-complete response. Very good partial response or better subgroup does not overlap with complete response. CI, confidence interval; HR, hazard ratio; MRD, minimal residual disease; No., number; OS, overall survival; PFS, progression-free survival.

Supplementary Figure 6. Forest plots of PFS by assessment of MRD status pre-maintenance and at 12 months after start of maintenance therapy.

Includes only those studies that measured MRD pre-maintenance and at 12 months after start of maintenance therapy. CI, confidence interval; HR, hazard ratio; MRD, minimal residual disease; No., number; PFS, progression-free survival.

Supplementary Table.

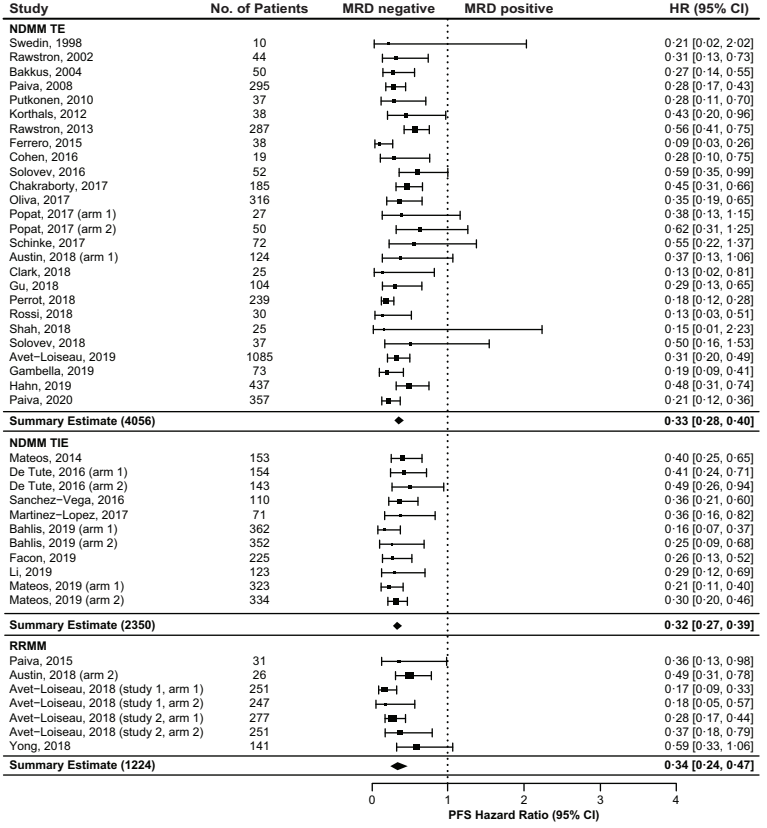
Study	Study type	Study population	Study treatment	Total participants assessed for MRD, n	Participants who achieved MRD negativity, %
Swedin, 1998	Non-randomised clinical trial	NDMM-TE	VAd and HDT induction + ASCT	10	50%
Rawstron, 2002	Non-randomised clinical trial	NDMM-TE	C-VAMP and HDT induction + ASCT	45	59%
Bakkus, 2004	Non-randomised clinical trial	NDMM-TE	Conventional chemo + ASCT	60	30%
Paiva, 2008	Non-randomised clinical trial	NDMM-TE	VBMCP/VBAd induction + ASCT + melphalan consolidation	295	42%
Putkonen, 2010	Non-randomised clinical trial	NDMM-TE	NA	37	57%
Korthals, 2012	Non-randomised clinical trial	NDMM-TE	HDT induction + ASCT, maintenance with interferon alpha or thalidomide	53	45%
Rawstron, 2013	Randomised clinical trial	NDMM-TE	CTd or CVAd + ASCT	397	86%
Ferrero, 2015	Non-randomised clinical trial	NDMM-TE	ASCT + VTd consolidation	39	68%
Ludwig, 2015	Randomised clinical trial	NDMM-TE	VTd or VTdC + SCT	42	81%
Cohen, 2016	Non-randomised clinical trial	NDMM-TE	ASCT + Bortezomib consolidation	19	68%
Solovev, 2016	Non-randomised clinical trial	NDMM-TE	ASCT+ Maintenance therapy with Bortezomib	52	48%

Chakraborty, 2017	Retrospective observational study	NDMM-TE	ASCT	185	56%
Popat, 2017	Non-randomised clinical trial	NDMM-TE	PAd induction + ASCT (arm 1)	27	26%
			PAd induction followed by no further treatment (arm 2)	50	36%
Oliva, 2017	Randomised clinical trial	NDMM-TE	VCd induction + VMP or HDM intensification + ASCT +/- VRD consolidation + LEN maintenance	316	76%
Schinke, 2017	Non-randomised clinical trial	NDMM-TE	VTd and PACE chemo + ASCT + consolidation (?) + VRD maintenance	109	35%
Austin, 2018	Retrospective observational study	NDMM-TE,	ASCT	124 (NDMM-TE)	47%
		RRMM		26 (RRMM)	62%
Clark, 2018	Non-randomised clinical trial	NDMM-TE	VRD induction + ASCT	25	72%
Gu, 2018	Non-randomised clinical trial	NDMM-TE	Bortezomib induction + ASCT	104	66%
Perrot, 2018	Randomised clinical trial	NDMM-TE	RVd	239	38%
Rossi, 2018	Non-randomised clinical trial	NDMM-TE	PAD induction	30	50%
Shah, 2018	Non-randomised clinical trial	NDMM-TE	Bortezomib or LEN induction + ASCT	25	48%
Solovev, 2018	Non-randomised clinical trial	NDMM-TE	Bortezomib induction + ASCT + LEN maintenance	37	62%

Avet-Loiseau, 2019	Randomised clinical trial	NDMM-TE	D-VTd or VTd	1085	54%
Gambella, 2019	Randomised clinical trial	NDMM-TE	LEN or with LEN + prednisone	73	73%
Hahn, 2019	Randomised clinical trial	NDMM-TE	ASCT + RVD consolidation + LEN maintenance	437	56%
Paiva, 2020	Randomised clinical trial	NDMM-TE	Induction with VRD + ASCT + consolidation with VRD	357	57%
Mateos, 2014	Randomised clinical trial	NDMM-TIE	VMP or VTP induction + bortezomib and thalidomide or bortezomib and prednisone maintenance	153	22%
De Tute, 2016	Randomised clinical trial	NDMM-TIE	RCda (arm 1)	154	16%
			CTda (arm 2)	143	11%
Sanchez-Vega, 2016	Non-randomised clinical trial	NDMM-TIE	VMP or VTP induction + bortezomib and thalidomide or bortezomib and prednisone maintenance	110	NA
Martinez-Lopez, 2017	Randomised clinical trial	NDMM-TIE	VMP + Rd or alternating VMP/Rd	73	20%
Bahlis, 2019	Randomised clinical trial	NDMM-TIE	D-Rd (arm 1)	369	29%
			Rd (arm 2)	368	8%
Facon, 2019	Randomised clinical trial	NDMM-TIE	KMP or VMP induction	327	23%
Li, 2019	Retrospective observational study	NDMM-TIE	VCd or BiCTd as induction and consolidation	123	25%

Mateos, 2019	Randomised clinical trial	NDMM-TIE	D-VMP (arm 1)	350	23%
			VMP (arm 2)	356	8%
Paiva, 2015	Non-randomised clinical trial	RRMM	Salvage therapy (different types of treatments, not specified)	31	42%
Avet-Loiseau, 2018 (Study 1)	Randomised clinical trial	RRMM	D-Vd (arm 1)	251	14%
			Vd (arm 2)	247	2%
Avet-Loiseau, 2018 (Study 2)	Randomised clinical trial	RRMM	D-Rd (arm 1)	286	31%
			Rd (arm 2)	283	6%
Yong, 2018	Randomised clinical trial	RRMM	KCd induction and carfilzomib maintenance or no maintenance	141	13%
Martinez-Sanchez, 2008	Non-randomised clinical trial	Undefined	VBCMP/ VBAD followed by high dose chemotherapy (melphalan 200 mg/m2) with autologous peripheral blood stem cell support	53	53%
Silvennoinen, 2014	Non-randomised clinical trial	Undefined	Induction therapy with bortezomib and dexamethasone + mobilization with cyclophosphamide and granulocyte colony-stimulating factor + ASCT	22	68%
Korde, 2015	Non-randomised clinical trial	Undefined	KRd with lenalidomide maintenance	45	32%
Fukomoto, 2016	Retrospective observational study	Undefined	ASCT in 37% of patients + either maintenance therapy with bortezomib + dexamethasone or no further therapy	78	44%

Flores-Montero, 2017	Retrospective observational study	Undefined	Salvage therapy (different types of treatments, not specified)	79	47%
Rasche, 2018	Non-randomised clinical trial	Undefined	Novel agents (unspecified) + ASCT	83	41%
Alonso, 2019	Retrospective observational study	Undefined	NA	84	65%


A
Study
No. of Patients
MRD negative
MRD positive
HR (95% CI)
NDMM TE
Swedin, 1998 10 0·21 [0·02, 2·02]
Rawstron, 2002 44 0·31 [0·13, 0·73]
Bakkus, 2004 50 0·27 [0·14, 0·55]
Paiva, 2008 295 0·28 [0·17, 0·43]
Putkonen, 2010 37 0·28 [0·11, 0·70]
Korthals, 2012 38 0·43 [0·20, 0·96]
Rawstron, 2013 287 0·56 [0·41, 0·75]
Ferrero, 2015 38 0·09 [0·03, 0·26]
Cohen, 2016 19 0·28 [0·10, 0·75]
Solovev, 2016 52 0·59 [0·35, 0·99]
Chakraborty, 2017 185 0·45 [0·31, 0·66]
Oliva, 2017 316 0·35 [0·19, 0·65]
Popat, 2017 (arm 1) 27 0·38 [0·13, 1·15]
Popat, 2017 (arm 2) 50 0·62 [0·31, 1·25]
Schinke, 2017 72 0·55 [0·22, 1·37]
Austin, 2018 (arm 1) 124 0·37 [0·13, 1·06]
Clark, 2018 25 0·13 [0·02, 0·81]
Gu, 2018 104 0·29 [0·13, 0·65]
Perrot, 2018 239 0·18 [0·12, 0·28]
Rossi, 2018 30 0·13 [0·03, 0·51]
Shah, 2018 25 0·15 [0·01, 2·23]
Solovev, 2018 37 0·50 [0·16, 1·53]
Avet−Loiseau, 2019 1085 0·31 [0·20, 0·49]
Gambella, 2019 73 0·19 [0·09, 0·41]
Hahn, 2019 437 0·48 [0·31, 0·74]
Paiva, 2020 357 0·21 [0·12, 0·36]
Summary Estimate (4056) 0·33 [0·28, 0·40]
NDMM TIE
Mateos, 2014 153 0·40 [0·25, 0·65]
De Tute, 2016 (arm 1) 154 0·41 [0·24, 0·71]
De Tute, 2016 (arm 2) 143 0·49 [0·26, 0·94]
Sanchez−Vega, 2016 110 0·36 [0·21, 0·60]
Martinez−Lopez, 2017 71 0·36 [0·16, 0·82]
Bahlis, 2019 (arm 1) 362 0·16 [0·07, 0·37]
Bahlis, 2019 (arm 2) 352 0·25 [0·09, 0·68]
Facon, 2019 225 0·26 [0·13, 0·52]
Li, 2019 123 0·29 [0·12, 0·69]
Mateos, 2019 (arm 1) 323 0·21 [0·11, 0·40]
Mateos, 2019 (arm 2) 334 0·30 [0·20, 0·46]
Summary Estimate (2350) 0·32 [0·27, 0·39]
RRMM
Paiva, 2015 31 0·36 [0·13, 0·98]
Austin, 2018 (arm 2) 26 0·49 [0·31, 0·78]
Avet−Loiseau, 2018 (study 1, arm 1) 251 0·17 [0·09, 0·33]
Avet−Loiseau, 2018 (study 1, arm 2) 247 0·18 [0·05, 0·57]
Avet−Loiseau, 2018 (study 2, arm 1) 277 0·28 [0·17, 0·44]
Avet−Loiseau, 2018 (study 2, arm 2) 251 0·37 [0·18, 0·79]
Yong, 2018 141 0·59 [0·33, 1·06]
Summary Estimate (1224) 0·34 [0·24, 0·47]
0
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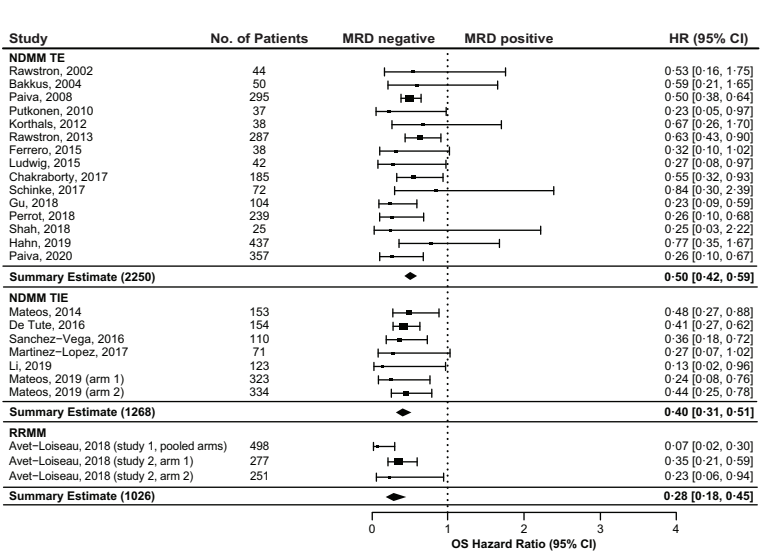
PFS Hazard Ratio (95% CI)


B
Study
No. of Patients
MRD negative
MRD positive
HR (95% CI)
NDMM TE
Rawstron, 2002 44 0·53 [0·16, 1·75]
Bakkus, 2004 50 0·59 [0·21, 1·65]
Paiva, 2008 295 0·50 [0·38, 0·64]
Putkonen, 2010 37 0·23 [0·05, 0·97]
Korthals, 2012 38 0·67 [0·26, 1·70]
Rawstron, 2013 287 0·63 [0·43, 0·90]
Ferrero, 2015 38 0·32 [0·10, 1·02]
Ludwig, 2015 42 0·27 [0·08, 0·97]
Chakraborty, 2017 185 0·55 [0·32, 0·93]
Schinke, 2017 72 0·84 [0·30, 2·39]
Gu, 2018 104 0·23 [0·09, 0·59]
Perrot, 2018 239 0·26 [0·10, 0·68]
Shah, 2018 25 0·25 [0·03, 2·22]
Hahn, 2019 437 0·77 [0·35, 1·67]
Paiva, 2020 357 0·26 [0·10, 0·67]
Summary Estimate (2250) 0·50 [0·42, 0·59]
NDMM TIE
Mateos, 2014 153 0·48 [0·27, 0·88]
De Tute, 2016 154 0·41 [0·27, 0·62]
Sanchez−Vega, 2016 110 0·36 [0·18, 0·72]
Martinez−Lopez, 2017 71 0·27 [0·07, 1·02]
Li, 2019 123 0·13 [0·02, 0·96]
Mateos, 2019 (arm 1) 323 0·24 [0·08, 0·76]
Mateos, 2019 (arm 2) 334 0·44 [0·25, 0·78]
Summary Estimate (1268) 0·40 [0·31, 0·51]
RRMM
Avet−Loiseau, 2018 (study 1, pooled arms) 498 0·07 [0·02, 0·30]
Avet−Loiseau, 2018 (study 2, arm 1) 277 0·35 [0·21, 0·59]
Avet−Loiseau, 2018 (study 2, arm 2) 251 0·23 [0·06, 0·94]
Summary Estimate (1026) 0·28 [0·18, 0·45]
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OS Hazard Ratio (95% CI)

A
Study
No. of Patients
MRD negative
MRD positive
HR (95% CI)
Sensitivity threshold 10⁻⁴
Rawstron, 2002 44 0·31 [0·13, 0·73]
Bakkus, 2004 50 0·27 [0·14, 0·55]
Paiva, 2008 295 0·28 [0·17, 0·43]
Putkonen, 2010 37 0·28 [0·11, 0·70]
Korthals, 2012 38 0·43 [0·20, 0·96]
Rawstron, 2013 287 0·56 [0·41, 0·75]
Ferrero, 2015 38 0·09 [0·03, 0·26]
Paiva, 2015 31 0·36 [0·13, 0·98]
Cohen, 2016 19 0·28 [0·10, 0·75]
De Tute, 2016 (arm 1) 154 0·41 [0·24, 0·71]
De Tute, 2016 (arm 2) 143 0·49 [0·26, 0·94]
Fukumoto, 2016 78 0·29 [0·09, 0·99]
Chakraborty, 2017 185 0·45 [0·31, 0·66]
Popat, 2017 (arm 1) 27 0·38 [0·13, 1·15]
Popat, 2017 (arm 2) 50 0·62 [0·31, 1·25]
Austin, 2018 (arm 1) 124 0·37 [0·13, 1·06]
Austin, 2018 (arm 2) 26 0·49 [0·31, 0·78]
Clark, 2018 25 0·13 [0·02, 0·81]
Rossi, 2018 30 0·13 [0·03, 0·51]
Yong, 2018 141 0·59 [0·33, 1·06]
Alonso, 2019 109 0·53 [0·28, 0·99]
Gambella, 2019 73 0·19 [0·09, 0·41]
Li, 2019 123 0·29 [0·12, 0·69]
Summary Estimate (2127) 0·38 [0·32, 0·45]
Sensitivity threshold 10⁻⁵
Mateos, 2014 153 0·40 [0·25, 0·65]
Silvennoinen, 2014 22 0·17 [0·05, 0·66]
Korde, 2015 44 0·22 [0·07, 0·69]
Sanchez−Vega, 2016 110 0·36 [0·21, 0·60]
Martinez−Lopez, 2017 71 0·36 [0·16, 0·82]
Oliva, 2017 316 0·35 [0·19, 0·65]
Schinke, 2017 72 0·55 [0·22, 1·37]
Avet−Loiseau, 2018 (study 1, arm 1) 251 0·17 [0·09, 0·33]
Avet−Loiseau, 2018 (study 1, arm 2) 247 0·18 [0·05, 0·57]
Avet−Loiseau, 2018 (study 2, arm 1) 277 0·28 [0·17, 0·44]
Avet−Loiseau, 2018 (study 2, arm 2) 251 0·37 [0·18, 0·79]
Gu, 2018 104 0·29 [0·13, 0·65]
Rasche, 2018 83 0·46 [0·18, 1·15]
Solovev, 2018 37 0·50 [0·16, 1·53]
Avet−Loiseau, 2019 1085 0·31 [0·20, 0·49]
Bahlis, 2019 (arm 1) 362 0·16 [0·07, 0·37]
Bahlis, 2019 (arm 2) 352 0·25 [0·09, 0·68]
Gambella, 2019 73 0·29 [0·14, 0·61]
Hahn, 2019 437 0·48 [0·31, 0·74]
Mateos, 2019 (arm 1) 323 0·21 [0·11, 0·40]
Mateos, 2019 (arm 2) 334 0·30 [0·20, 0·46]
Paiva, 2020 357 0·29 [0·18, 0·46]
Summary Estimate (5361) 0·31 [0·27, 0·36]
Sensitivity threshold 10⁻⁶
Flores−Montero, 2017[a] 79 0·11 [0·03, 0·51]
Dimopoulos, 2018 (arm 1) 286 0·41 [0·19, 0·90]
Dimopoulos, 2018 (arm 2) 283 0·15 [0·02, 1·09]
Perrot, 2018 239 0·18 [0·12, 0·28]
Facon, 2019 225 0·26 [0·13, 0·52]
Paiva, 2020[a] 357 0·21 [0·12, 0·36]
Summary Estimate (1469) 0·22 [0·16, 0·29]
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PFS Hazard Ratio (95% CI)
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Study
No. of Patients
MRD negative
MRD positive
HR (95% CI)
Sensitivity threshold 10⁻⁴
Rawstron, 2002 44 0·53 [0·16, 1·75]
Bakkus, 2004 50 0·59 [0·21, 1·65]
Paiva, 2008 295 0·50 [0·38, 0·64]
Putkonen, 2010 37 0·23 [0·05, 0·97]
Korthals, 2012 38 0·67 [0·26, 1·70]
Rawstron, 2013 287 0·63 [0·43, 0·90]
Ferrero, 2015 38 0·32 [0·10, 1·02]
De Tute, 2016 154 0·41 [0·27, 0·62]
Chakraborty, 2017 185 0·55 [0·32, 0·93]
Li, 2019 123 0·13 [0·02, 0·96]
Summary Estimate (1251) 0·50 [0·43, 0·60]
Sensitivity threshold 10⁻⁵
Mateos, 2014 153 0·48 [0·27, 0·88]
Sanchez−Vega, 2016 110 0·36 [0·18, 0·72]
Martinez−Lopez, 2017 71 0·27 [0·07, 1·02]
Schinke, 2017 72 0·84 [0·30, 2·39]
Avet−Loiseau, 2018 (study 1, pooled arms) 498 0·07 [0·02, 0·30]
Avet−Loiseau, 2018 (study 2, arm 1) 277 0·35 [0·21, 0·59]
Avet−Loiseau, 2018 (study 2, arm 2) 251 0·23 [0·06, 0·94]
Gu, 2018 104 0·23 [0·09, 0·59]
Hahn, 2019 437 0·77 [0·35, 1·67]
Mateos, 2019 (arm 1) 323 0·24 [0·08, 0·76]
Mateos, 2019 (arm 2) 334 0·44 [0·25, 0·78]
Summary Estimate (2630) 0·39 [0·31, 0·49]
Sensitivity threshold 10⁻⁶
Perrot, 2018 239 0·26 [0·10, 0·68]
Paiva, 2020[a] 357 0·26 [0·10, 0·67]
Summary Estimate (596) 0·26 [0·13, 0·51]
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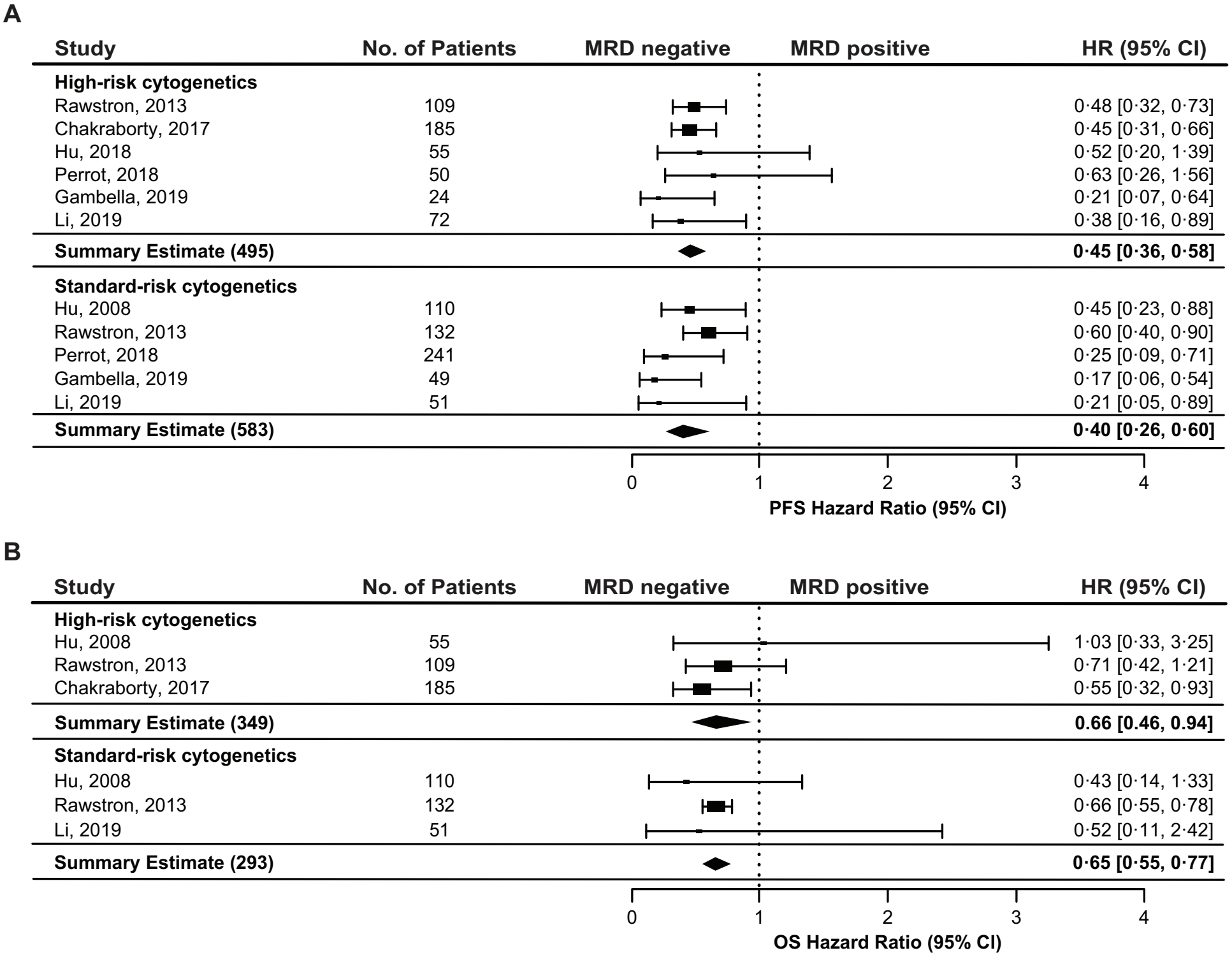
OS Hazard Ratio (95% CI)


A
Study
No. of Patients
MRD negative
MRD positive
HR (95% CI)
High-risk cytogenetics
Rawstron, 2013 109 0·48 [0·32, 0·73]
Chakraborty, 2017 185 0·45 [0·31, 0·66]
Hu, 2018 55 0·52 [0·20, 1·39]
Perrot, 2018 50 0·63 [0·26, 1·56]
Gambella, 2019 24 0·21 [0·07, 0·64]
Li, 2019 72 0·38 [0·16, 0·89]
Summary Estimate (495) 0·45 [0·36, 0·58]
Standard-risk cytogenetics
Hu, 2008 110 0·45 [0·23, 0·88]
Rawstron, 2013 132 0·60 [0·40, 0·90]
Perrot, 2018 241 0·25 [0·09, 0·71]
Gambella, 2019 49 0·17 [0·06, 0·54]
Li, 2019 51 0·21 [0·05, 0·89]
Summary Estimate (583) 0·40 [0·26, 0·60]
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PFS Hazard Ratio (95% CI)
B
Study
No. of Patients
MRD negative
MRD positive
HR (95% CI)
High-risk cytogenetics
Hu, 2008 55 1·03 [0·33, 3·25]
Rawstron, 2013 109 0·71 [0·42, 1·21]
Chakraborty, 2017 185 0·55 [0·32, 0·93]
Summary Estimate (349) 0.66 [0.46, 0.94]
Standard-risk cytogenetics
Hu, 2008 110 0·43 [0·14, 1·33]
Rawstron, 2013 132 0·66 [0·55, 0·78]
Li, 2019 51 0·52 [0·11, 2·42]
Summary Estimate (293) 0·65 [0·55, 0·77]
0
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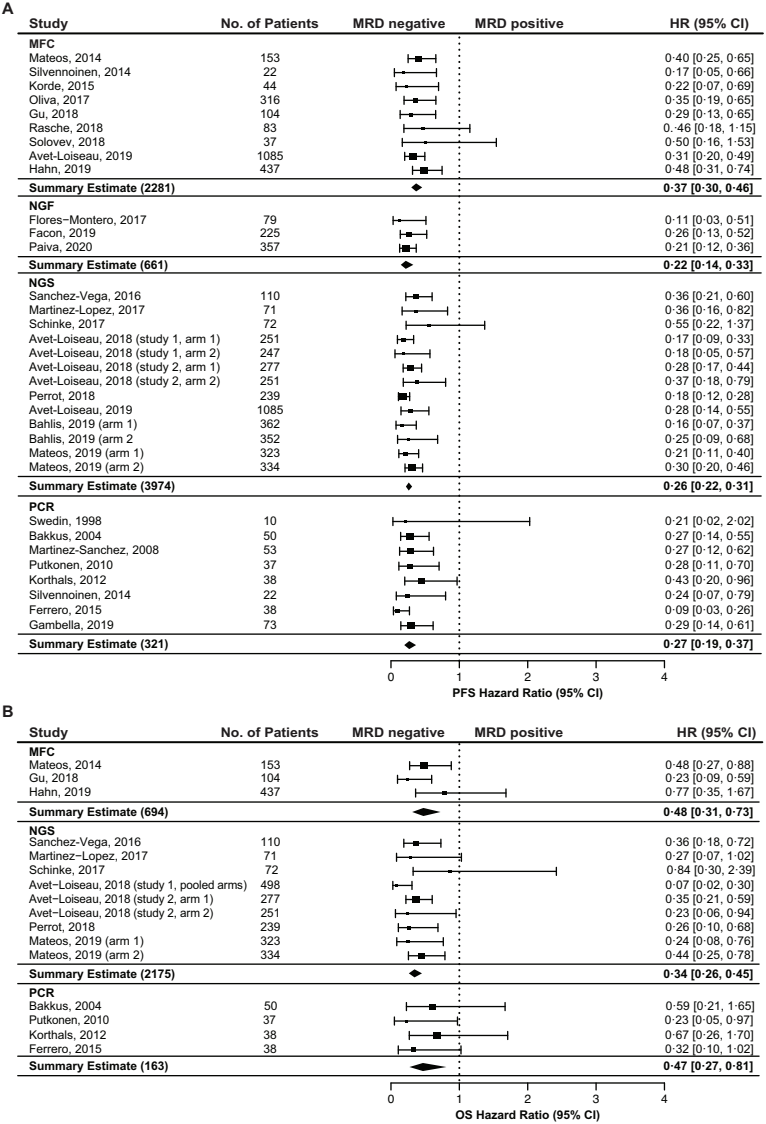
OS Hazard Ratio (95% CI)


A
Study
No. of Patients
MRD negative
MRD positive
HR (95% CI)
MFC
Mateos, 2014 153 0·40 [0·25, 0·65]
Silvennoinen, 2014 22 0·17 [0·05, 0·66]
Korde, 2015 44 0·22 [0·07, 0·69]
Oliva, 2017 316 0·35 [0·19, 0·65]
Gu, 2018 104 0·29 [0·13, 0·65]
Rasche, 2018 83 0.·46 [0·18, 1·15]
Solovev, 2018 37 0·50 [0·16, 1·53]
Avet-Loiseau, 2019 1085 0·31 [0·20, 0·49]
Hahn, 2019 437 0·48 [0·31, 0·74]
Summary Estimate (2281) 0·37 [0·30, 0·46]
NGF
Flores−Montero, 2017 79 0·11 [0·03, 0·51]
Facon, 2019 225 0·26 [0·13, 0·52]
Paiva, 2020 357 0·21 [0·12, 0·36]
Summary Estimate (661) 0·22 [0·14, 0·33]
NGS
Sanchez-Vega, 2016 110 0·36 [0·21, 0·60]
Martinez-Lopez, 2017 71 0·36 [0·16, 0·82]
Schinke, 2017 72 0·55 [0·22, 1·37]
Avet-Loiseau, 2018 (study 1, arm 1) 251 0·17 [0·09, 0·33]
Avet-Loiseau, 2018 (study 1, arm 2) 247 0·18 [0·05, 0·57]
Avet-Loiseau, 2018 (study 2, arm 1) 277 0·28 [0·17, 0·44]
Avet-Loiseau, 2018 (study 2, arm 2) 251 0·37 [0·18, 0·79]
Perrot, 2018 239 0·18 [0·12, 0·28]
Avet-Loiseau, 2019 1085 0·28 [0·14, 0·55]
Bahlis, 2019 (arm 1) 362 0·16 [0·07, 0·37]
Bahlis, 2019 (arm 2 352 0·25 [0·09, 0·68]
Mateos, 2019 (arm 1) 323 0·21 [0·11, 0·40]
Mateos, 2019 (arm 2) 334 0·30 [0·20, 0·46]
Summary Estimate (3974) 0·26 [0·22, 0·31]
PCR
Swedin, 1998 10 0·21 [0·02, 2·02]
Bakkus, 2004 50 0·27 [0·14, 0·55]
Martinez-Sanchez, 2008 53 0·27 [0·12, 0·62]
Putkonen, 2010 37 0·28 [0·11, 0·70]
Korthals, 2012 38 0·43 [0·20, 0·96]
Silvennoinen, 2014 22 0·24 [0·07, 0·79]
Ferrero, 2015 38 0·09 [0·03, 0·26]
Gambella, 2019 73 0·29 [0·14, 0·61]
Summary Estimate (321) 0·27 [0·19, 0·37]
0
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PFS Hazard Ratio (95% CI)
B
Study
No. of Patients
MRD negative
MRD positive
HR (95% CI)
MFC
Mateos, 2014 153 0·48 [0·27, 0·88]
Gu, 2018 104 0·23 [0·09, 0·59]
Hahn, 2019 437 0·77 [0·35, 1·67]
Summary Estimate (694) 0·48 [0·31, 0·73]
NGS
Sanchez-Vega, 2016 110 0·36 [0·18, 0·72]
Martinez−Lopez, 2017 71 0·27 [0·07, 1·02]
Schinke, 2017 72 0·84 [0·30, 2·39]
Avet−Loiseau, 2018 (study 1, pooled arms) 498 0·07 [0·02, 0·30]
Avet−Loiseau, 2018 (study 2, arm 1) 277 0·35 [0·21, 0·59]
Avet−Loiseau, 2018 (study 2, arm 2) 251 0·23 [0·06, 0·94]
Perrot, 2018 239 0·26 [0·10, 0·68]
Mateos, 2019 (arm 1) 323 0·24 [0·08, 0·76]
Mateos, 2019 (arm 2) 334 0·44 [0·25, 0·78]
Summary Estimate (2175) 0·34 [0·26, 0·45]
PCR
Bakkus, 2004 50 0·59 [0·21, 1·65]
Putkonen, 2010 37 0·23 [0·05, 0·97]
Korthals, 2012 38 0·67 [0·26, 1·70]
Ferrero, 2015 38 0·32 [0·10, 1·02]
Summary Estimate (163) 0·47 [0·27, 0·81]
0
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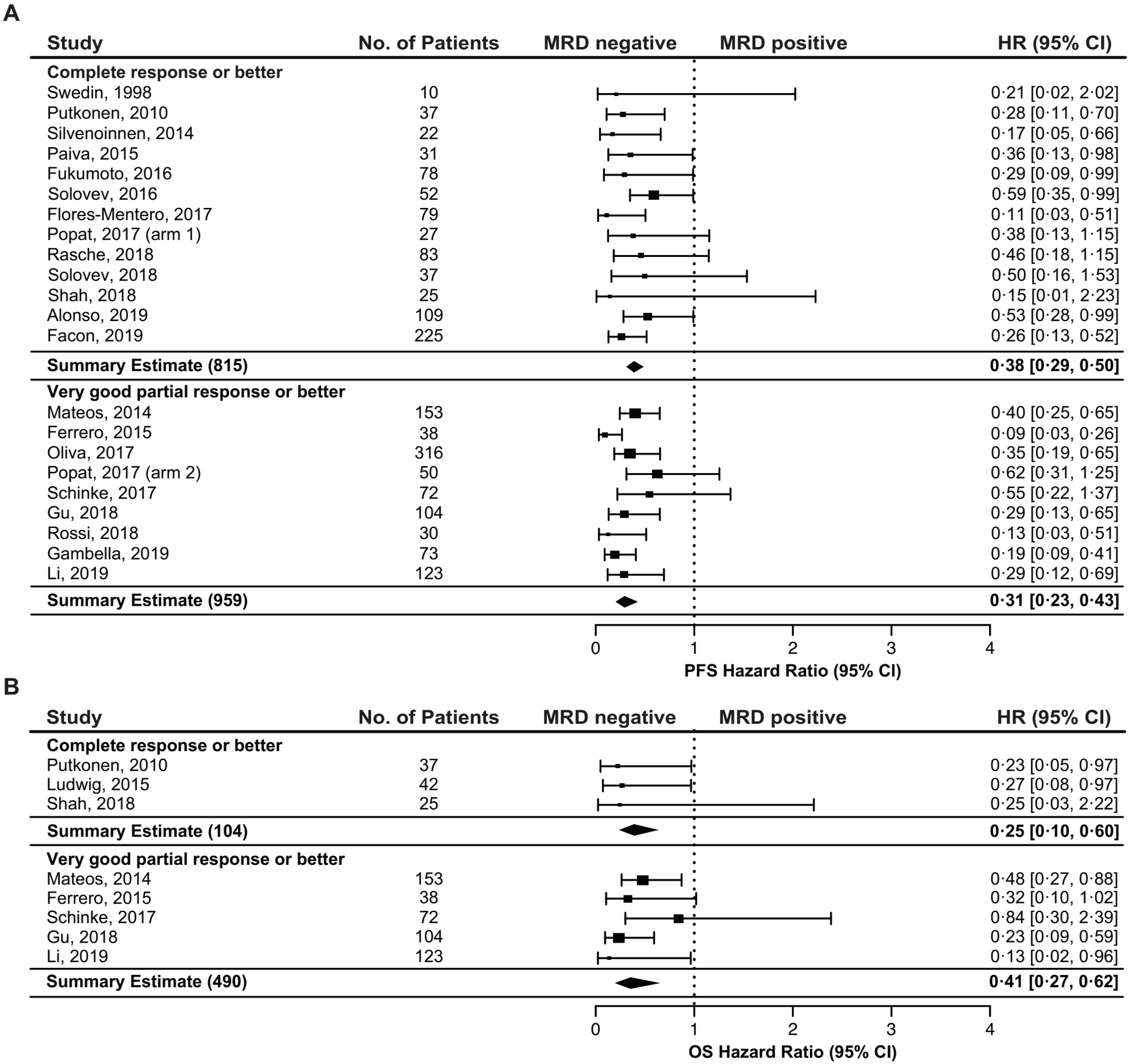
OS Hazard Ratio (95% CI)


A
Study
No. of Patients
MRD negative
MRD positive
HR (95% CI)
Complete response or better
Swedin, 1998 10 0·21 [0·02, 2·02]
Putkonen, 2010 37 0·28 [0·11, 0·70]
Silvenoinnen, 2014 22 0·17 [0·05, 0·66]
Paiva, 2015 31 0·36 [0·13, 0·98]
Fukumoto, 2016 78 0·29 [0·09, 0·99]
Solovev, 2016 52 0·59 [0·35, 0·99]
Flores-Mentero, 2017 79 0·11 [0·03, 0·51]
Popat, 2017 (arm 1) 27 0·38 [0·13, 1·15]
Rasche, 2018 83 0·46 [0·18, 1·15]
Solovev, 2018 37 0·50 [0·16, 1·53]
Shah, 2018 25 0·15 [0·01, 2·23]
Alonso, 2019 109 0·53 [0·28, 0·99]
Facon, 2019 225 0·26 [0·13, 0·52]
Summary Estimate (815) 0·38 [0·29, 0·50]
Very good partial response or better
Mateos, 2014 153 0·40 [0·25, 0·65]
Ferrero, 2015 38 0·09 [0·03, 0·26]
Oliva, 2017 316 0·35 [0·19, 0·65]
Popat, 2017 (arm 2) 50 0·62 [0·31, 1·25]
Schinke, 2017 72 0·55 [0·22, 1·37]
Gu, 2018 104 0·29 [0·13, 0·65]
Rossi, 2018 30 0·13 [0·03, 0·51]
Gambella, 2019 73 0·19 [0·09, 0·41]
Li, 2019 123 0·29 [0·12, 0·69]
Summary Estimate (959) 0·31 [0·23, 0·43]
0
1
2
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4
PFS Hazard Ratio (95% CI)
B
Study
No. of Patients
MRD negative
MRD positive
HR (95% CI)
Complete response or better
Putkonen, 2010 37 0·23 [0·05, 0·97]
Ludwig, 2015 42 0·27 [0·08, 0·97]
Shah, 2018 25 0·25 [0·03, 2·22]
Summary Estimate (104) 0·25 [0·10, 0·60]
Very good partial response or better
Mateos, 2014 153 0·48 [0·27, 0·88]
Ferrero, 2015 38 0·32 [0·10, 1·02]
Schinke, 2017 72 0·84 [0·30, 2·39]
Gu, 2018 104 0·23 [0·09, 0·59]
Li, 2019 123 0·13 [0·02, 0·96]
Summary Estimate (490) 0·41 [0·27, 0·62]
0
1
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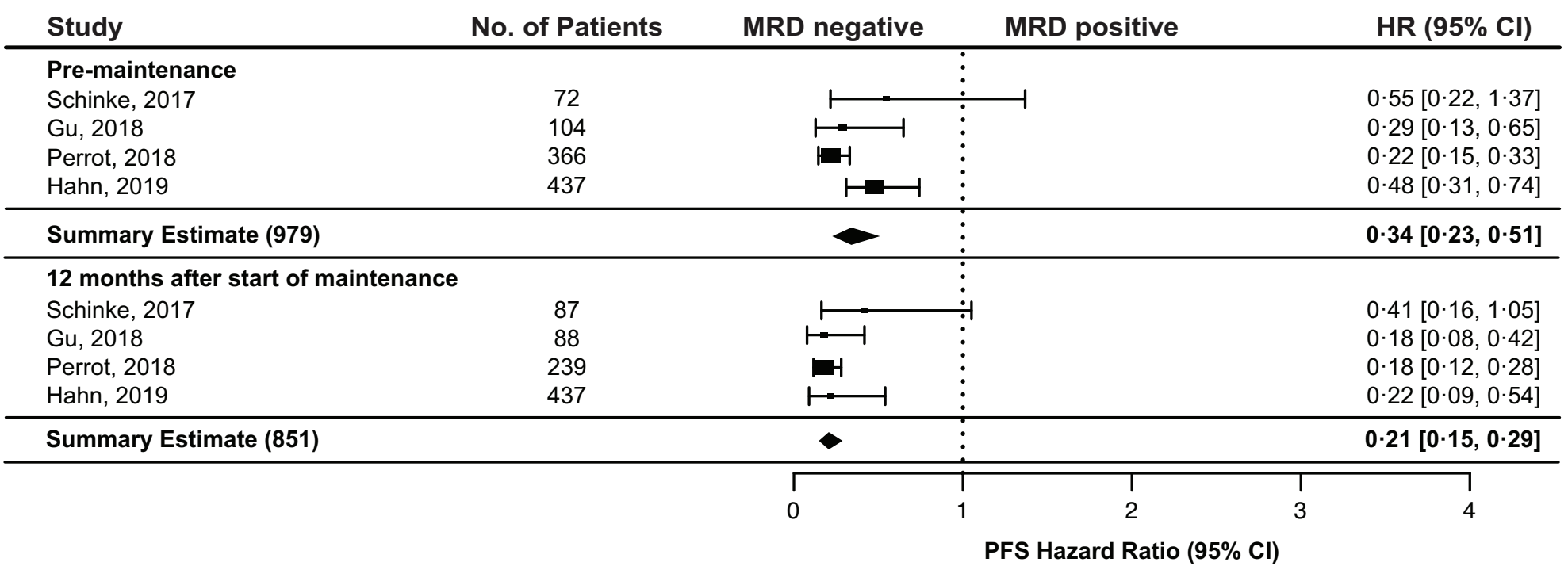
OS Hazard Ratio (95% CI)


Study
No. of Patients
MRD negative
MRD positive
HR (95% CI)
Pre-maintenance
Schinke, 2017
72
0·55 [0·22, 1·37]
Gu, 2018
104
0·29 [0·13, 0·65]
Perrot, 2018
366
0·22 [0·15, 0·33]
Hahn, 2019
437
0·48 [0·31, 0·74]
Summary Estimate (979)
0·34 [0·23, 0·51]
12 months after start of maintenance
Schinke, 2017
87
0·41 [0·16, 1·05]
Gu, 2018
88
0·18 [0·08, 0·42]
Perrot, 2018
239
0·18 [0·12, 0·28]
Hahn, 2019
437
0·22 [0·09, 0·54]
Summary Estimate (851)
0·21 [0·15, 0·29]
0
1
2
3
4
PFS Hazard Ratio (95% CI)