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ORIGINAL REPORT

Long-Term Follow-Up of Autotransplantation Trials for Multiple Myeloma: Update of Protocols Conducted by the Intergroupe Francophone du Myelome, Southwest Oncology Group, and University of Arkansas for Medical Sciences

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ABSTRACT

Purpose
The purpose of this study was to update outcomes of autotransplantation trials for myeloma conducted by the Intergroupe Francophone du Myelome (IFM), the Southwest Oncology Group, and the University of Arkansas for Medical Sciences (Total Therapy [TT]).

Methods
IFM90 (N = 194), IFM04 (N = 402), IFM9902 (N = 692), IFM9904 (N = 197), S9321 (N = 817), TT1 (N = 231), TT2 (N = 668), and TT3 (N = 303) were updated, and results were compared with original reports.

Results
Superior survival with single transplantation versus standard therapy in IFM90 was confirmed ($P = .004$), and a trend in favor of tandem versus single transplantation was maintained in IFM94 ($P = .08$). S9321 data were validated, with comparable survival in single transplantation and standard treatment arms ($P = .35$). A survival benefit from thalidomide maintenance in IFM9902 was not confirmed ($P = .39$) but emerged for the thalidomide arm of TT2 ($P = .04$). On multivariate analysis, survival was superior in TT2, TT3, and IFM9902 (all $P < .001$); tandem transplantations were superior to both single transplantations and standard therapies ($P < .001$), as were tandem transplantations with added thalidomide versus trials without thalidomide ($P < .001$). Postrelapse survival (PRS) was superior when initial event-free survival (EFS) exceeded 1280 days and when tandem transplantations had been administered, whereas PRS was shorter when EFS lasted 803 days or less and when trials had included thalidomide and bortezomib.

Conclusion
These long-term follow-up data of transplantation trials provide a crucial framework of reference for outcome reporting of novel agent–based trials reportedly exhibiting remarkable short-term efficacy approaching high-dose therapy results.

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INTRODUCTION

Survival of patients with multiple myeloma has been extended markedly as a result of autotransplantation-supported high-dose melphalan therapy[1-5] and the availability of novel agents.[6-11] The results of clinical trials are usually reported in line with original statistical objectives focusing on differences in complete response rate and event-free survival (EFS) between treatment arms or vis-à-vis historical controls. In the initial report on Total Therapy (TT) 2, overall survival (OS) was not prolonged in patients randomly assigned to the experimental arm with thalidomide, although both complete response and EFS were superior to results obtained on the control arm.[5] With an additional 38 months of follow-up (now at 80 months), however, OS is also significantly extended ($P = .04$) despite discontinuation of thalidomide for toxicity reasons by nearly 80% within 2 years.[12] This observation motivated us to update the results of major transplantation trials conducted by the authors of this report to determine whether earlier outcome estimates could be confirmed.

PATIENTS AND METHODS

Eight trials are covered in this report. Intergroupe Francophone du Myelome (IFM) trial IFM90 compared a single

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	IFM90 (N = 194)		IFM94 (N = 402)		IFM9902 (N = 692)		IFM9904 (N = 197)		S9321 (N = 817)		TT1 (N = 231)		TT2 (N = 668)		TT3 (N = 303)	
	No./Total No. of Patients	%	No./Total No. of Patients	%	No./Total No. of Patients	%	No./Total No. of Patients	%	No./Total No. of Patients	%	No./Total No. of Patients	%	No./Total No. of Patients	%	No./Total No. of Patients	%
Age ≥ 65 years	3/194	2	0/402	0	16/692	2	8/197	4	61/817	7	21/231	9	136/668	20	84/303	28
Albumin < 3.5 g/dL	63/194	32	113/402	28	202/692	29	100/197	51	293/817	36	62/231	27	119/664	18	78/303	26
B2M ≥ 3.5 mg/L	88/194	45	173/402	43	194/692	28	167/197	85	407/817	50	95/229	41	243/668	36	136/303	45
B2M > 5.5 mg/L	46/194	24	75/402	19	88/692	13	76/197	39	233/817	29	43/229	19	122/668	18	65/303	21
DS stage > I	177/177	100	371/402	92	627/680	92	182/188	97	602/817	74	215/229	94	580/668	87	272/303	90
ISS stage																
I	63/168	38	177/383	46	361/641	56	20/150	13	254/763	33	110/229	48	374/664	56	138/303	46
II	61/168	36	133/383	35	197/641	31	73/150	49	275/763	36	76/229	33	169/664	25	100/303	33
III	44/168	26	73/383	19	83/641	13	57/150	38	234/763	31	43/229	19	121/664	18	65/303	21
Cytogenetic abnormalities (any time before enrollment)	NA		NA		NA		NA		NA		74/221	33	197/661	30	100/302	33
Median follow-up (live patients), years	7.4		11.6		5.7		5.0		8.4		15.6		7.2		3.9	
Median time since last follow-up (live patients), months	120.5		4.4		3.9		4.1		32.5		1.2		1.0		0.6	

Abbreviations: IFM, Intergroupe Francophone du Myelome; TT, Total Theapy; B2M, β_2-microglobulin; DS, Durie/Salmon; NA, not applicable.

transplantation with standard chemotherapy.[1] IFM94 compared tandem and single transplantation.[3] IFM9902, which studied standard-risk myeloma, used tandem transplantation and randomly assigned patients to one of three maintenance arms (none, pamidronate, or pamidronate plus thalidomide).[13] IFM9904, which studied high-risk myeloma (high β_2-microglobulin [B2M] and deletion 13), evaluated tandem transplantations with a higher melphalan dose of 220 mg/m^2 and added anti–interleukin-6 monoclonal antibody.[14] Southwest Oncology Group trial S9321 randomly assigned patients to either single transplantation in support of melphalan plus total-body irradiation or the M2 regimen after vincristine, doxorubicin, and dexamethasone induction.[15] TT1 was a phase II study of tandem transplantation followed by interferon maintenance.[16] TT2 randomly assigned patients up front to receive or not to receive thalidomide and, compared with TT1, added consolidation chemotherapy after tandem transplantation and applied dexamethasone pulsing for the first year of maintenance with interferon.[5] TT3 was a phase II trial building on TT2 with bortezomib added to the thalidomide arm of TT2 but with two instead of four cycles each of induction and consolidation therapy before and after tandem transplantations, whereas maintenance included bortezomib-thalidomide-dexamethasone in the first year and thalidomide-dexamethasone in years 2 and 3.[17] Cancer Research and Biostatistics received data updates of IFM trials as of July 2008, of S9321 as of February 2009, and of all three TT trials as of April 2009. The individual protocols had been reviewed and approved by both centralized and individual institutional review boards. All patients had signed a written informed consent before protocol enrollment, in keeping with the Helsinki Declaration.

Patient characteristics revealed protocol-specified differences in upper age limit (Table 1). The distribution of patients across prognostic variable cut points varied, so that International Staging System–based stage II and III classification ranged from 44% to 87%. The proportions of patients with low albumin and high B2M levels based on the International Staging System are also portrayed; low albumin (< 3.5 g/dL) was present in 51% of patients enrolled onto IFM9904 and in only 18% enrolled onto TT2; high B2M (> 5.5 mg/dL) was documented in 29% of patients enrolled onto S9321 and in 39% enrolled onto IFM9904 but in only 13% enrolled onto IFM9902. Current median follow-up times were as short as 3.9 years in TT3 and approached 16 years in TT1, for an overall median of 6.1 years. The median times since last follow-up also varied widely, ranging from a short 0.6 months in TT3 to a long 120.5 months in IFM90.

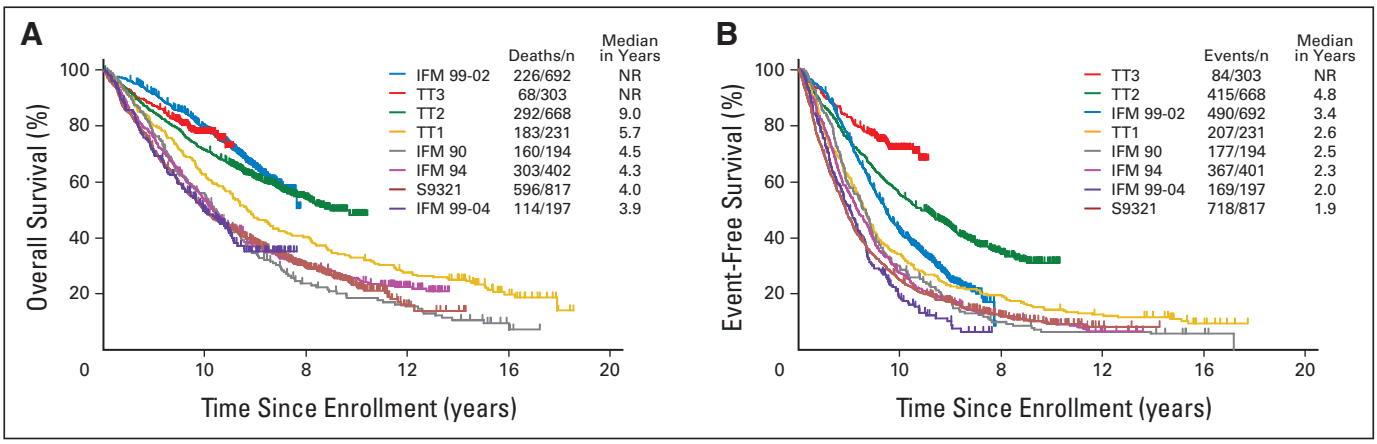

Fig 1. Kaplan-Meier plots of (A) overall and (B) event-free survival outcomes. IFM, Intergroupe Francophone du Myelome; TT, Total Therapy; S, Southwest Oncology Group; NR, not reported.

Clinical trial end points included OS and EFS, both of which were dated from initiation of protocol therapy or from treatment random assignment, as indicated. Events included death from any cause in OS and, additionally, relapse in EFS. Patients were censored for OS and EFS when alive and event free, respectively, as of last contact.

Statistical methods included Kaplan-Meier plots of OS and EFS.[18] Log-rank statistics were used to compare survival outcomes between treatment and prognostic subgroups.[19] Cox regression analysis was applied to determine the relative prognostic implications of baseline variables and treatment protocols in both univariate and multivariate models.[20]

RESULTS

Figure 1 depicts OS and EFS for all trials reported. In the IFM90, IFM94, S9321, and TT1 trials, survival outcomes extended beyond 10 years. Thus, 10-year OS and EFS estimates were 33% and 14% in TT1, 26% and 9% in IFM94 (both arms combined), 19% and 6% in IFM90 (both arms combined), and 22% and 18% in S9321 (both arms combined), respectively. For the remaining trials, 5-year OS and EFS estimates were 78% and 71% in TT3, 66% and 50% in TT2 (both arms combined), 73% and 34% in IFM9902 (all three arms combined), and 42% and 13% in IFM9904, respectively. Reiterating Kaplan-Meier analyses from early phases through completion of patient accrual and progressively extending follow-up times revealed superimposable OS plots for all trials examined (Data Supplement Fig 1), suggesting consistency of patient characteristics throughout the accrual time periods, patient follow-up, and therapeutic management. Thus, we failed to detect instances where initially more promising results deteriorated with longer follow-up.

Results of individual randomized trials are portrayed in Data Supplement Figure 2. In IFM90, both OS and EFS remain significantly prolonged for the transplantation arm versus standard treatment arm (Data Supplement Fig 2A), whereas trends remain for both OS and EFS in favor of tandem versus single transplantation in IFM94 (Data Supplement Fig 2B). Both arms of S9321 remain virtually superimposable in terms of OS, but a trend has emerged in favor of transplantation for EFS (Data Supplement Fig 2C). Regarding TT2, a significant advantage in favor of the thalidomide arm has now emerged for OS ($P = .04$; Data Supplement Fig 2D). However, the original OS advantage of thalidomide in IFM9902 is no longer apparent (comparing the two arms without thalidomide *v* thalidomide-containing maintenance, $P = .39$; Data Supplement Fig 2E); the current analysis pertains to the 88% of patients who also had interphase fluorescence hybridization data.

Table 2. Univariate and Multivariate Analyses of Baseline and Treatment Features Associated With Survival Outcomes in Context of Individual Trials

Variable	No./Total No. of Patients	%	Overall Survival		
			HR	95% CI	P*
Univariate analysis					
TT1	231/3,508	7	0.98	0.84 to 1.15	.838
TT2	668/3,508	19	0.66	0.58 to 0.75	< .001
TT3	303/3,508	9	0.54	0.42 to 0.70	< .001
S9321	821/3,508	23	1.60	1.45 to 1.76	< .001
IFM90	194/3,508	6	1.47	1.25 to 1.73	< .001
IFM94	402/3,508	11	1.32	1.17 to 1.49	< .001
IFM9902	692/3,508	20	0.53	0.46 to 0.61	< .001
IFM9904	197/3,508	6	1.51	1.25 to 1.82	< .001
Age ≥ 60 years	985/3,508	28	1.34	1.21 to 1.48	< .001
Albumin < 3.5 g/dL	893/3,367	27	1.42	1.29 to 1.57	< .001
B2M ≥ 3.5 mg/L	1,504/3,422	44	1.80	1.64 to 1.97	< .001
B2M > 5.5 mg/L	745/3,422	22	1.94	1.76 to 2.15	< .001
Hgb < 10 g/dL	1,188/3,422	35	1.59	1.45 to 1.75	< .001
LDH ≥ ULN	955/3,178	30	1.41	1.27 to 1.56	< .001
Multivariate†					
TT2	662/3,077	22	0.63	0.53 to 0.75	< .001
TT3	303/3,077	10	0.47	0.35 to 0.63	< .001
S9321	734/3,077	24	1.25	1.07 to 1.46	.004
IFM90	131/3,077	4	1.30	1.04 to 1.63	.023
IFM94	357/3,077	12	1.21	1.01 to 1.44	.037
IFM9902	544/3,077	18	0.52	0.43 to 0.64	< .001
Age ≥ 60 years	862/3,077	28	1.49	1.33 to 1.66	< .001
Albumin < 3.5 g/dL	808/3,077	26	1.15	1.03 to 1.28	.011
B2M ≥ 3.5 mg/L	1,320/3,077	43	1.39	1.25 to 1.55	< .001
Hgb < 10 g/dL	1,060/3,077	34	1.18	1.06 to 1.31	.003
LDH ≥ ULN	924/3,077	30	1.41	1.27 to 1.57	< .001

Abbreviations: HR, hazard ratio; TT, Total Therapy; IFM, Intergroupe Francophone du Myelome; B2M, β_2-microglobulin; Hgb, hemoglobin; LDH, lactate dehydrogenase; ULN, upper limit of normal.

*P values were determined using Wald χ^2 test in Cox regression. Multivariate results were not statistically significant at $P = .05$ level. All univariate P values were reported regardless of significance.

†Multivariate model used stepwise selection with entry level of $P = .1$, and variables remained if they met the $P = .05$ level. A multivariate $P > .05$ indicates a variable forced into model with significant variables chosen using stepwise selection. Variables considered for multivariate model were TT2, TT3, S9321, IFM90, IFM94, IFM9902, IFM9904, age ≥ 60 years, albumin < 3.5 g/dL, B2M ≥ 3.5 mg/L, Hgb < 10 g/dL, and LDH ≥ 190 U/L.

Table 3. Univariate and Multivariate Analyses of Variables Associated With Postrelapse Survival, Including Baseline Characteristics, Length of Initial EFS, and Availability of Thalidomide and Bortezomib

Variable	No./Total No. of Patients	%	Postrelapse Survival		
			HR	95% CI	P[a]
Univariate					
TT1	164/2,059	8	0.86	0.72 to 1.03	.098
TT2	276/2,059	13	0.88	0.75 to 1.04	.146
TT3	47/2,059	2	1.92	1.32 to 2.80	< .001
S9321	515/2,059	25	1.03	0.92 to 1.16	.601
IFM90	139/2,059	7	1.45	1.20 to 1.74	< .001
IFM94	326/2,059	16	1.25	1.10 to 1.44	.001
IFM99-02	446/2,059	22	0.63	0.54 to 0.74	< .001
IFM99-04	146/2,059	7	1.32	1.07 to 1.64	.009
Tandem transplantation[b]	1,240/2,059	60	0.81	0.73 to 0.90	< .001
Tandem transplantation with thalidomide[c]	161/2,059	8	1.17	0.94 to 1.45	.151
Thalidomide available at start of protocol[d]	915/2,059	44	0.79	0.71 to 0.89	< .001
Age ≥ 65 years	1,166/2,050	57	1.12	1.00 to 1.24	.045
Albumin < 3.5 g/dL	552/1,971	28	1.19	1.06 to 1.34	.004
B2M ≥ 3.5 mg/L	914/2,003	46	1.48	1.33 to 1.64	< .001
B2M > 5.5 mg/L	459/2,003	23	1.61	1.42 to 1.82	< .001
Hgb < 10 g/dL	755/2,010	38	1.30	1.16 to 1.44	< .001
LDH ≥ ULN	586/1,850	32	1.35	1.20 to 1.52	< .001
EFS ≤ 803 days (median)	1,030/2,059	50	1.84	1.65 to 2.05	< .001
EFS ≥ 1,280 days (quartile 4)	515/2,059	25	0.45	0.39 to 0.53	< .001
Multivariate 1[e,f]					
TT3	47/1,777	3	1.53	1.04 to 2.23	.029
IFM90	94/1,777	5	1.27	1.01 to 1.61	.045
IFM9902	353/1,777	20	0.57	0.47 to 0.69	< .001
Age ≥ 65 years	948/1,777	53	1.38	1.21 to 1.58	< .001
B2M > 5.5 mg/L	394/1,777	22	1.35	1.18 to 1.54	< .001
LDH ≥ ULN	563/1,777	32	1.29	1.14 to 1.46	< .001
EFS ≤ 803 days (median)	878/1,777	49	1.43	1.25 to 1.64	< .001
EFS > 1,280 days (quartile 4)	450/1,777	25	0.57	0.47 to 0.69	< .001
Multivariate 2[g]					
Tandem transplantation[b]	1,080/1,777	61	0.79	0.70 to 0.90	< .001
Tandem transplantation with thalidomide[c]	161/1,777	9	1.46	1.16 to 1.83	.001
Age > 65 years	948/1,777	53	1.30	1.15 to 1.47	< .001
B2M > 5.5 mg/L	394/1,777	22	1.40	1.23 to 1.60	< .001
LDH > ULN	563/1,777	32	1.25	1.11 to 1.42	< .001
EFS < 803 days (median)	878/1,777	49	1.44	1.26 to 1.66	< .001
EFS > 1,280 days (quartile 4)	450/1,777	25	0.59	0.49 to 0.72	< .001
Multivariate 3[h]					
Thalidomide available at start of protocol[d]	772/1,777	43	0.71	0.62 to 0.81	< .001
TT3 (bortezomib available at start of protocol)	47/1,777	3	2.04	1.38 to 3.01	< .001
Age > 65 years	948/1,777	53	1.33	1.18 to 1.51	< .001
B2M > 5.5 mg/L	394/1,777	22	1.42	1.25 to 1.62	< .001
LDH > ULN	563/1,777	32	1.28	1.13 to 1.45	< .001
EFS < 803 days (median)	878/1,777	49	1.44	1.26 to 1.65	< .001
EFS > 1,280 days (quartile 4)	450/1,777	25	0.59	0.49 to 0.71	< .001

Abbreviations: EFS, event-free survival; HR, hazard ratio; TT, Total Therapy; IFM, Intergroupe Francophone du Myelome; B2M, β_2-microglobulin; Hgb, hemoglobin; LDH, lactate dehydrogenase; ULN, upper limit of normal.

[a] P values were determined using Wald χ^2 test in Cox regression. Multivariate results were not statistically significant at $P = .05$ level. All univariate P values were reported regardless of significance.

[b] Tandem transplantation includes patients enrolled onto TT1, TT2, TT3, IFM9902, and IFM 9904 and patients randomly assigned to receive a tandem transplantation on IFM94.

[c] Tandem transplantation with thalidomide includes patients enrolled onto TT3 and the thalidomide arm of TT2.

[d] Thalidomide available at start of protocol includes patients enrolled onto TT2, TT3, IFM9902, and IFM9904.

[e] Multivariate models used stepwise selection with entry level of $P = .1$, and variables remained if they met the $P = .05$ level. A multivariate $P > .05$ indicates a variable forced into model with significant variables chosen using stepwise selection.

[f] Variables considered for the multivariate 1 analysis included TT2, TT3, IFM90, IFM94, IFM9902, IFM9904, S9321, age ≥ 65 years, albumin < 3.5 g/dL, B2M > 5.5 mg/L, Hgb < 10 g/dL, LDH ≥ ULN, EFS ≤ 803 days (median), and EFS ≥ 1,280 days (quartile 4).

[g] Variables considered for the multivariate 2 analysis included tandem transplantation, tandem transplantation with thalidomide, age ≥ 65 years, albumin < 3.5 g/dL, B2M > 5.5 mg/L, Hgb < 10 g/dL, LDH ≥ ULN, EFS ≤ 803 days (median), and EFS ≥ 1,280 days (quartile 4).

[h] Variables considered for the multivariate 3 analysis included thalidomide available at start of protocol, TT3 (bortezomib available at start of protocol), age ≥ 65 years, albumin < 3.5 g/dL, B2M > 5.5 mg/L, Hgb < 10 g/dL, LDH ≥ ULN, EFS ≤ 803 days (median), and EFS ≥ 1,280 days (quartile 4).

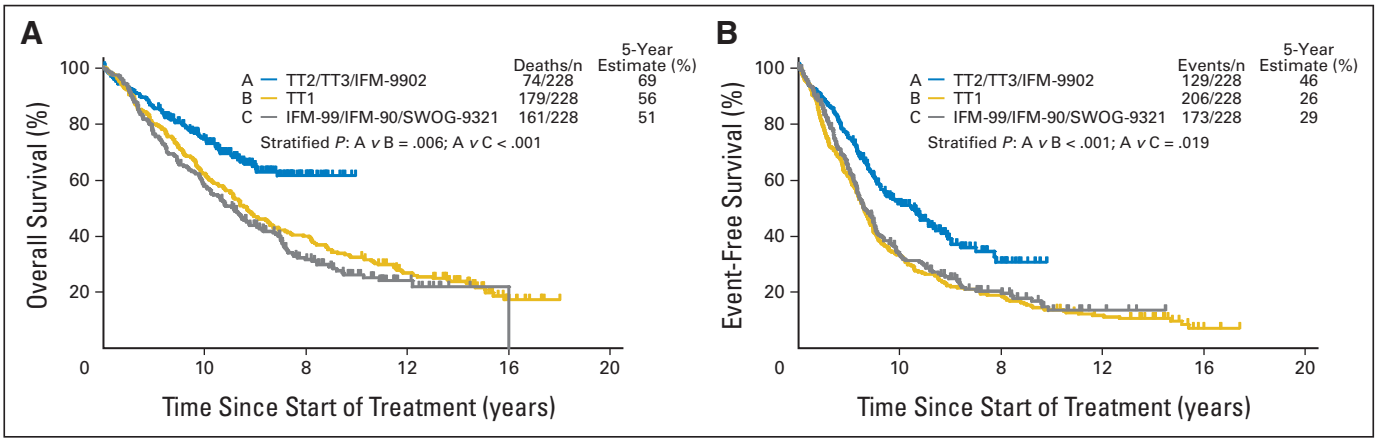

Fig 2. (A,B) Pair-mate analyses of patients matched on albumin, β_2-macroglobulin (B2M), lactate dehydrogenase (LDH), and hemoglobin (Hb). TT, Total Therapy; IFM, Intergroupe Francophone du Myelome; SWOG, Southwest Oncology Group.

Next, we performed univariate and multivariate analyses to determine which pretreatment parameters and which protocols were significantly linked to OS (Table 2). Independent adverse features included advanced age, low albumin and hemoglobin, and high B2M and lactate dehydrogenase (LDH); TT2, IFM9902, and TT3 protocols each conferred lower hazard ratio (HR) values (Table 2). Tandem transplantations as a group yielded superior results compared with single transplantations and standard-dose therapies (HR = 0.61, $P < .001$), and adding thalidomide to tandem transplantations was superior to tandem transplantations without thalidomide (HR = 0.69, $P < .001$; Table 3).

To portray individual trial comparisons, protocol patients were matched on the four variables identified as independently affecting OS on multivariate analysis (albumin < 3.5 g/dL, B2M ≥ 3.5 mg/L, LDH ≥ upper limit of normal, and hemoglobin < 10 g/dL), which was accomplished in three sets of 228 patients each, with one set representing the three trials with independently superior OS (TT3, TT2, and IFM9902; Table 2). The best outcomes were recorded in this category (TT3, TT2, and IFM9902), resulting in 8-year OS and EFS estimates of 62% and 31%, respectively, contrasting with similar inferior outcomes of 36% and 20%, respectively, for the two other categories (TT1; and IFM9904, IFM94, IFM90, and S9321; both $P < .001$; Fig 2).

Because of the long time span over which the protocols were executed, we examined postrelapse survival (PRS) to account for greater access to novel agents in more recently conducted trials. Thus, later trials' superior OS may have resulted from the availability of better salvage regimens rather than the impact of the original treatment. The following 5-year PRS estimates were recorded: 35% for IFM9902 and TT1, 29% for S9321, 27% for IFM9904 and TT2, 22% for IFM94, and 14% for IFM90 and TT3 ($P < .001$; Fig 3). IFM90 and TT1 participants had least access to thalidomide, which became available in 1997, but PRS after TT1 was far superior to PRS after IFM90. Patients in IFM94 and S9321 should have had equal access to thalidomide, perhaps explaining similar PRS. The availability of bortezomib and lenalidomide for salvage treatment around the year 2000 likely benefited patients treated on TT2, IFM9902, and IFM9904. The short PRS in patients who experienced treatment failure after TT3 may be attributable to the up-front use of all myeloma-active treatment ingredients, thus curtailing salvage efforts at relapse.

We also performed a multivariate analysis to capture variables independently linked to PRS, including baseline characteristics (relapse characteristics were only available in TT trials), individual trials, and the length of preceding EFS (Table 3). Older age and higher levels of baseline B2M (> 5.5 mg/L) and LDH had adverse impacts on PRS; preceding EFS equal to or shorter than the median (803 days) was another adverse feature, whereas long EFS (fourth quartile, ≥ 1,280 days) reduced the hazard of PRS. Regarding individual protocols, IFM90 and TT3 both resulted in shorter PRS, whereas IFM9902 trial participation conferred superior PRS. Tandem transplantation significantly reduced the PRS hazard compared with single transplantation and standard chemotherapy, and thalidomide as part of tandem transplantations was an independent favorable feature for PRS. Availability of thalidomide at protocol start (IFM9902, TT2, and TT3) was associated with a low HR (HR = 0.71, $P < .001$), whereas the availability of bortezomib in TT3 was associated with poor PRS (HR = 2.04, $P < .001$). Long preceding EFS retained its favorable impact on PRS.

DISCUSSION

This report represents, to our knowledge, the first international effort at systematically updating trial results reported earlier. Several important observations were made. First, outcomes were remarkablyconsistent when reiterative Kaplan-Meier plots were executed. Second, more recent trials had increased 10-year OS estimates, from

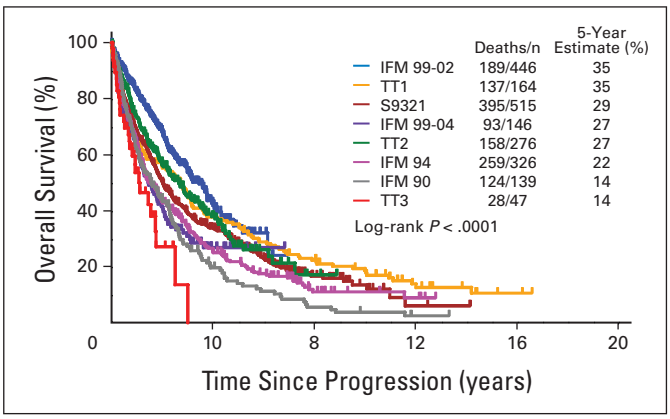

Fig 3. Post-relapse survival outcomes. IFM, Intergroupe Francophone du Myelome; TT, Total Therapy; S, Southwest Oncology Group.

20% to 30% in IFM90, IFM94, S9321, and TT1% to 50% in TT2, which was confirmed by multivariate and pair-mate analyses. On the basis of EFS data showing steep improvements when comparing IFM9902 with TT2 and TT3, further gains in 10-year OS are likely to ensue with TT3. Third, among randomized trials, consistency was observed in OS for S9321 and IFM90 and, trend-wise, for IFM94. In contrast, with longer follow-up, thalidomide's initially observed survival benefit when used as maintenance therapy in IFM9902 could not be confirmed, whereas a significant survival improvement from its up-front use in TT2 emerged with a significant delay of almost 8 years after 80% of patients had discontinued its use. Another trial has also reported on thalidomide's benefit in maintenance therapy,[21] which, in the case of the Tunisian study, could not be validated with longer follow-up.[22,23] The late manifestation of thalidomide's survival benefit in TT2 remains an enigma but is not unprecedented in cancer therapy, because higher dose equivalents of glucocorticoids in pediatric acute lymphoblastic leukemia have long-ranging cure effects.[24] Fourth, we also examined the variables impacting PRS, which was longer when prior EFS was sustained for at least 3.5 years, when tandem transplantations were used, and when thalidomide was included in the trial design (IFM9902, TT2, and TT3); the up-front use of bortezomib in TT3 adversely affected PRS. However, OS from protocol start was favorably affected by tandem transplantations, thalidomide with tandem transplantations, and TT3 that included bortezomib. Finally, in light of the steadily improving outcomes in myeloma, with 10-year survival estimates of 50% or higher as in TT2, the collective impact of successive interventions during induction, consolidation, and maintenance phases of treatment demands longer follow-up than currently practiced for survival effects to be appreciated, especially because complete response rates exceeding 50% can be regularly achieved with novel agent combinations even without transplantation. We hope that our work will encourage other groups to update their results so that the full impact of therapeutic trial interventions can be appreciated.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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