Phase II Study of Thalidomide Plus Dexamethasone Induction Followed by Tandem Melphalan-Based Autotransplantation and Thalidomide-Plus-Prednisone Maintenance for Untreated Multiple Myeloma: A Southwest Oncology Group Trial (S0204)

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ABSTRACT

Purpose

Thalidomide-dexamethasone (THAL-DEX) is standard induction therapy for multiple myeloma (MM). Tandem melphalan-based transplantations have yielded superior results to single transplantations. Phase II trial S0204 was designed to improve survival results reported for the predecessor, phase III trial S9321 by 50%.

Patients and Methods

Newly diagnosed patients with MM were eligible for S0204 with THAL-DEX induction, tandem melphalan-based tandem transplantation, and THAL-prednisone maintenance.

Results

Of 143 eligible patients, 142 started induction, 73% completed first transplantation, 58% completed second transplantation, and 56% started maintenance. The quantity of stem cells required for two transplantations was reached in 88% of 111 patients undergoing collection, 74% of whom completed both transplantations. Partial response, very good partial remission, and complete response were documented after 12 months of maintenance therapy in 87%, 72%, and 22% of patients, respectively. During a median follow-up time of 37 months, 4-year estimates of event-free and overall survival were 50% and 64%, respectively. Survival outcomes were superior for International Staging System (ISS) stage 1 disease, when lactate dehydrogenase (LDH) levels were normal and a second transplantation was applied in a timely fashion.

Conclusion

Both overall survival ($P = .0002$) and event-free survival ($P < .0001$) were significantly improved with S0204 compared with S9321 when 121 and 363 patients, respectively, were matched on ISS stage and LDH.

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INTRODUCTION

The Southwest Oncology Group (SWOG) had chaired US Intergroup trial S9321 for previously untreated patients with symptomatic or progressive multiple myeloma (MM) and had observed no difference in overall survival (OS) and event-free survival (EFS) between the transplantation and standard treatment arms.¹ Compared with other published, randomized clinical trials that address standard versus high-dose therapy, the 7-year OS and EFS estimates of 42% and 16%, respectively, in the standard vincristine, carmustine (BCNU), melphalan, cyclophosphamide, and prednisone (VBMCP) arm of S9321 were virtually identical to

the 43% and 16%, respectively, reported for the transplantation arm of the IFM90 trial, which induced a complete response rate of 17% (ie, identical to results in both arms of S9321) compared with 5% in the control arm.²

Meanwhile, the IFM94 trial confirmed Arkansas phase II pilot data with Total Therapy 1,³ which demonstrated superior outcomes for tandem compared with single transplantation, although controversy persists about the outcomes.⁴ The Arkansas myeloma group then performed a prospective, randomized trial to address the role of up-front incorporation of thalidomide (THAL) into a tandem transplantation setting.⁵ Updated results revealed superior EFS and OS, especially among patients who

presented with metaphase cytogenetic abnormalities.⁶ It was in this setting that SWOG embarked on the first group tandem transplantation trial in the United States to determine whether S9321 results, in addition to feasibility and safety, could be improved. THAL-dexamethasone (DEX) was selected as induction therapy because of its relatively low frequency of serious toxicity and, thus, likelihood for high compliance with completion of both intended transplantations.⁷

PATIENTS AND METHODS

Patient Eligibility

Newly diagnosed patients with active or progressive MM age 18 to 65 years were eligible for this trial. Measurable disease required serum M-protein levels of at least 1.0 g/dL and urinary M-protein excretion of at least 200 mg per 24 hours. Patients with immunoglobulin M (IgM) myeloma had to have either 20% or greater bone marrow plasmacytosis or greater than three lytic lesions on skeletal survey. Patients with nonsecretory myeloma (ie, M-protein inadequate for measurement) were eligible if bone marrow plasmacytosis exceeded 20%.

Zubrod performance status could not exceed 2 unless it was solely based on bone pain. Adequate cardiac systolic ejection fraction (ie, echocardiogram or multigated angiogram $\geq 50\%$) and pulmonary function (forced expiratory

volume in 1 second and carbon monoxide diffusing capacity [both] $\geq 50\%$) were required during an examination within 42 days of registration.

Treatment Regimen

As depicted in Figure 1A, induction therapy consisted of three cycles, once every 5 weeks of THAL-DEX. The daily starting dose of THAL was 50 mg, which could be escalated weekly by 50 mg to a maximum of 400 mg/d. DEX was administered at 40 mg on days 1 through 4, 9 through 12, and 17 through 20 of each 35-day cycle. Peripheral-blood stem cell (PBSC) collection was performed with cyclophosphamide 1.0 g/m² intravenously over 45 to 60 minutes followed by daily granulocyte colony-stimulating factor 10 $\mu\text{g/kg}$ and granulocyte-macrophage colony-stimulating factor 500 $\mu\text{g/m}^2$ for 10 days. The intended CD34 target was 7.5×10^6 cells/kg for the safe conduct of two transplantations. A minimum of 2×10^6 CD34 cells/kg was required for a single transplantation, and patients who collected fewer than 2×10^6 CD34 cells/kg bypassed the transplantation procedure and proceeded to maintenance therapy.

The first transplantation regimen consisted of melphalan 140 mg/m² on day -1 followed by PBSC infusion on day 0 and granulocyte-macrophage colony-stimulating factor 500 μg subcutaneously on day 6. The second transplantation employed a higher melphalan dose of 200 mg/m² and was applied, preferably between 2 and 4 months, but no later than 6 months, after the first.

Maintenance consisted of daily THAL 50 mg/d (with permission to a maximum dose of 200 mg/d according to tolerance) plus prednisone 50 mg on

Fig 1. (A) S0204 regimen details. (B) CONSORT flow diagram. Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; G-CSF, granulocyte colony-stimulating factor; PBSC, peripheral-blood stem cell.

alternating days until disease progression or undue toxicity occurred. Treatment was started 70 to 90 days post-transplantation, once neutrophils exceeded $750/\mu\text{L}$ and platelets exceeded $20,000/\mu\text{L}$. All patients were observed until death or until 5 years after registration.

Laboratory Evaluation

Baseline studies included complete metabolic profile and blood count, coagulation profile, bone marrow aspirate and biopsy, and serum and urine M-protein quantitation. Staging was done according to SWOG criteria and to the more recently adopted International Staging System (ISS) criteria.⁸

For each transplantation, patients had to have a Zubrod performance status of 0 to 1 and adequate renal function (ie, serum creatinine of ≤ 3.0 mg/dL) determined within 14 days of transplantation. Patients had to have no evidence of progressive disease.

For the registration before maintenance (at 70 to 90 days post-transplant), hematologic function had to be adequate, as defined by granulocyte levels $\geq 750/\mu\text{L}$ and platelet count $\geq 20,000/\mu\text{L}$. There could be no evidence of progressive disease.

Response and Relapse Criteria

Classification of responses resembles those reported for the European Bone Marrow Transplant (EBMT) group by Blade et al.⁹ Complete remission (CR) was defined as disappearance of all evidence of serum and urine M-proteins on immunofixation electrophoresis. Remission (REM) was defined as at least 75% reduction in the serum M-protein concentration and at least 90% reduction and reduction in urinary M-protein excretion by at least 90% or to less than 0.2 g/d. In both CR and REM, bone marrow plasmacytosis could not exceed 5%. Partial remission (PR) required at least 50% reduction in the serum M-protein concentration and at least 50% reduction in daily urine M-protein excretion. Because of the recent acceptance of the French very good partial response (VGPR) category by the myeloma community at large, our article also reports on this outcome variable, which is defined as at least 90% reductions in both serum and urine M-protein markers.¹⁰

Relapse was defined as a doubling of the lowest recorded M-protein values; an increase beyond the levels required for REM and PR definitions; and, for CR, reappearance of any myeloma peak that had disappeared while on protocol treatment. For all response levels, the serum calcium had to remain normal, and the size and number of lytic skeletal lesions could not increase. Toxicities were graded with the National Cancer Institute Common Toxicity Criteria of Adverse Events, version 2.0.

Statistical Methods

OS was defined as the time from registration to death or was censored when patients were alive at last contact. EFS was defined as the time from registration to progression or death or was censored for those alive and without progression at last contact.¹¹ OS and EFS curves were estimated by the Kaplan-Meier method,¹² whereas the log-rank test was applied to compare survival outcomes.¹³ Cox regression analyses were applied to determine variables associated with outcomes, and response and transplantations examined were time-dependent covariates.¹⁴ The χ^2 test was used to compare the incidence of thromboses before and after protocol amendment.

The study was designed to have 82% power for detecting a 50% improvement in survival from a median of 4 years, as observed in SWOG S9321. If a constant hazard and exponential survival are assumed, the observed 4-year survival estimate of 64% in S0204 translates into a median survival of greater than 6 years. Details of S9321 have been published previously,¹ and these data were used in a pair-mate analysis performed with participants who were enrolled on the current S0204 trial and who were matched 3:1 on ISS stage and lactate dehydrogenase (LDH), the most significant independent, adverse variables for OS in S0204.

RESULTS

Patient Characteristics

Between July 2002 and October 2005, 147 patients with newly diagnosed, symptomatic, or progressive MM were registered, of

whom 143 were eligible and 142 started induction therapy. The characteristics of these 142 patients are typical of the past trial experience in SWOG. The median age was 57 years (range, 23 to 66 years); 83% were white, and 61% were men. Immunoglobulin isotypes included IgG in 62%, IgA in 15%, and only light chain in 11%. None had IgD myeloma; 12% had nonsecretory disease. Serum levels of B2M and C-reactive protein (CRP) exceeded 3.5 mg/dL in 44% and 0.8 mg/dL in 17%, respectively. ISS distribution included 48% of patients with ISS 1, 30% with ISS 2, and 22% with ISS 3. Anemia (ie, hemoglobin < 10 g/dL) was present in 37%, and renal function impairment (ie, creatinine > 2 mg/dL) was present in 6%. Hypercalcemia (ie, serum calcium > 10 mg/dL) was rare (13%), and elevation of LDH (ie, > 190 U/L) was noted in 29%. Cytogenetic abnormalities were recorded in 42% of 81 patients who had such information available. Bone marrow plasmacytosis that exceeded 30% was present in 67%.

Figure 1B depicts a CONSORT flow diagram that accounts for all patients enrolled and initiated in successive protocol phases, the present status of each, and the reason for study removal of each. Registration to PBSC collection occurred in 111 patients, a first transplantation was performed in 103 (73%), and a second transplantation was performed in 82 patients (58%). Ninety-one percent of second transplantations were performed within 4 months from the first application. Seventy-nine patients (56%) proceeded to maintenance, of whom 65 have since come off study.

Of 111 patients who underwent PBSC collection, 88% collected the PBSC quantity required to perform two transplantations (ie, $\geq 4 \times 10^6$ CD34 cells/kg), and 74% received two transplantations. The inability to proceed to second transplantation was due to low PBSC yield (which permitted single transplantation only in seven and no transplantation in two patients) and to patient or physician choices in seven and two patients, respectively. The excellent tolerance afforded timely application within a 4-month interval of a second transplantation in 91% of those who received this intervention.

Toxicities

One treatment-related death was observed during induction and one during the maintenance phase. Overall, grades 3 to 4 toxicities were observed in 59% during induction, 40% during PBSC collection, 90% with first transplantation, 94% with second transplantation (predominantly hematologic), and 69% during the maintenance phase of the trial. Infectious complications occurred in two thirds of patients during each of the two transplantation phases. The incidence of deep vein thrombosis decreased from 26% when THAL 100 mg was given to the first 23 patients to 9% as a result of reduction of the starting THAL dose to 50 mg, with weekly increments of 50 mg as tolerated to a maximum of 400 mg ($P = .02$).¹³ Twenty-seven percent reported neurologic toxicity of grade 3 or higher during THAL-prednisone maintenance.

Response and Survival Outcomes

The proportions of patients who achieved various response levels relevant to the four treatment phases of the trial are depicted in Figure 2A. Thus, at the end of induction therapy, 66% had achieved at least PR, including 14% who qualified for REM, 22% for VGPR, and 5% for CR status. The respective values for first post-transplantation and second post-transplantation time points were 79% and 81% for PR, 60% and 63% for REM, 48% and 53% for VGPR, and 11% and 12% for CR. Finally, at the end of the first year of maintenance, 87%

Fig 2. Response. (A) Cumulative best response by treatment step: The proportions of patients who achieved partial response (PR) and complete response (CR) status increased from 60% and 1% at the end of induction to 79% and 5% after the first transplantation and to 81% and 7% after the second transplantation. At the end of the first year of maintenance, 87% qualified for PR status and 21% for CR status. (B) Cumulative proportions of patients who responded (PR or CR). The median times to reach PR and very good partial response (VGPR) were 3 and 14 months, respectively, whereas the median had not yet been reached for those who entered CR status. (C) Duration of response by levels achieved and measured from their onset. Measured from onset of response, the 4-year estimates of patients remaining in PR, VGPR, and CR are 58%, 63%, and 78%, respectively. UCR, unconfirmed complete response; UVGPR, unconfirmed very good partial response; REM, remission $\geq$ 75% reduction in serum M-protein and/or $\geq$ 90% reduction in daily urinary M-protein excretion; UREM, unconfirmed REM; UPR, unconfirmed partial response.

qualified for PR, including 80% for REM, 72% for VGPR, and 22% for CR status. The cumulative proportions of patients who attained PR and CR over time are portrayed in Figure 2B, which demonstrates ultimate levels of PR and CR of 77% and 15%, respectively; the median times to reach PR and VGPR status were 3 and 14 months, respectively, whereas the median has not been reached for CR. Counted from the onset of the respective response levels, 58%, 63%, and 77% were estimated to remain without recurrence 4 years after achievement of PR, VGPR, and CR status, respectively (Fig 2C). During the median follow-up of 37 months, 15 patients have remained on study; 74 have remained event free; and 98 are alive, with 4-year estimates of 50% and 64% (Fig 3A). Examination of baseline prognostic variables and of post-therapy events (ie, response) and interventions (ie, first and second transplantations) as time-dependent covariates revealed ISS stage and LDH to be independently and significantly associated with both OS and EFS (Tables 1 and 2). The combined presence of ISS stage 1 and normal LDH identified 44 patients with an outstanding prognosis; only one patient died, whereas 10 suffered an event, which contrasts with poor outcomes among the three remaining combination subsets (Fig 3B). Whereas PR and VGPR did not independently affect OS and EFS, timely application of the second transplantation reduced the hazards of both death and any event by 80% and 69%, respectively. By applying a 4-month landmark analysis, 24-month survival and event-free survival rates were 91% and 75%, respectively, when two transplantations had been applied, as opposed to 70% and 49% in the remaining participants who had received just one cycle of high-dose therapy in that time frame (Fig 3C). Among patients who achieved less than VGPR status after the first transplantation, the post-landmark OS (and EFS, data not shown) was superior when such patients had received a second transplantation rather than moving on to maintenance without additional high-dose therapy (OS: $P = .04$; EFS: $P = .03$; Fig 3D). In addition, for EFS, there was a strong trend for those already in VGPR to have superior outcome when a second transplantation had been applied ($P = .06$). The improved outcome after a second transplantation for patients who had less than VGPR after the first transplantation could not be explained by an upgrade in the response level: among patients with less than VGPR at the time of first transplantation, 36% of patients (14 of 39) achieved at least VGPR status after the second transplantation, which was not different from the 23% (three of 13) when such second intervention had not been applied ($P = .3608$). The baseline characteristics of patients who received or did not receive two transplantations within the 4-month landmark were similar (data not shown); the observed superior OS after two transplantations when VGPR had not been attained was likely due to the therapeutic intervention.

In line with our stated protocol objectives, we also compared survival outcomes on this S0204 trial with those previously observed in S9321. S0204 affected OS and EFS, which were superior to outcomes observed in S9321, both when all patients were considered (Figs 4A and B) and when the analysis was restricted to 121 patients in S0204 and 363 in S9321 who had been matched on ISS stage and LDH as the two key variables associated with outcomes in S0204 (Figs 4C and D). The time on study was significantly longer than had been the case for S9321; thus, at 24 months, 79% of patients had remained on S0204 compared with only 15% on S9321 (Fig 4E), which strongly suggests better tolerance of S0204.

Fig 3. Overall and event-free survival outcomes. (A) All patients: The 4-year estimates of survival and event-free survival were 64% and 50%, respectively. (B) Overall survival according to International Staging System (ISS) stage and lactate dehydrogenase (LDH). The 4-year survival estimates were far superior in patients who presented with ISS stage 1 and normal LDH levels compared with the remainder. (C) Overall survival according to whether a second transplantation was administered within 4 months from the first transplantation. Overall survival was superior when patients had received a second transplantation within 4 months from the first high-dose intervention. (D) Overall survival according to timeliness of second transplantation and to level of response achieved within 4 months from first transplantation. Overall survival among patients who did not qualify for very good partial response (VGPR) status (ie, who had achieved remission [REM] or less after first transplantation), experienced a superior overall survival ($P = .04$) when a second transplantation had been applied within 4 months of the first transplantation. Patients qualifying for VGPR or better after first transplantation fared equally well whether two or one transplantation had been applied ($P = .60$).

DISCUSSION

Results reported herein indeed support the feasibility of performing tandem transplantations safely and effectively in the cooperative-group setting, as reviewed and summarized recently by Attal et al.¹⁵ Two published trials were selected for comparison with our S0204 results. After tandem transplantations, IMf99-02 randomly assigned patients to no maintenance, to pamidronate, or to pamidronate plus THAL.¹⁶ The VGPR rate of 67% on the THAL arm of IMf99-02 was similar to the 72% observed at the end of the first year of THAL maintenance with S0204. The 4-year OS and EFS estimates, counted from initiation of therapy, were 64% and 50%, respectively, for S0204 compared with 87% and 36%, respectively, for the THAL maintenance arm and 75% and 26%, respectively, for the other two arms of IMf99-02 (which were measured, how-

ever, from random assignment after second transplantation). We also examined S0204 outcomes in the context of the recently published Tunisian study that compared, after THAL plus DEX induction, the survival outcomes of patients randomly assigned between tandem transplantations without THAL maintenance versus single transplantation with THAL maintenance.¹⁷ The 3-year post-random assignment estimates (after PBSC collection) of OS and EFS were superior for the THAL arm at 85% and 85%, respectively, versus 65% and 57%, respectively, for the tandem transplantation arm without THAL maintenance. The results of this study have been the subject of some controversy. In a comparison of published 3-year OS and EFS data, Mehta¹⁸ pointed to the unexpectedly favorable performance of the Tunisian single transplantation arm and the comparatively poor survival after the tandem transplantation arm of this trial.¹⁸ Indeed, the 65% 3-year OS estimate in the

Table 1. Univariate Analyses of Baseline and Time-Dependent Post-Therapy Variables Associated With OS and EFS

Variable	Patients			Univariate Analyses					
	No.	Total No. Evaluated	%	OS			EFS		
				HR	95% CI	P*	HR	95% CI	P*
Sex, male	86	142	61	1.30	0.70 to 2.44	.403	1.15	0.70 to 1.88	.577
B2M $\geq$ 3.5 mg/dL	59	133	44	2.59	1.35 to 4.98	.004	2.05	1.24 to 3.38	.005
CRP $\geq$ 8 mg/L	20	121	17	2.09	1.01 to 4.30	.046	0.98	0.50 to 1.93	.950
Albumin < 3.5 g/dL	30	137	22	3.80	2.04 to 7.06	< .001	2.85	1.70 to 4.77	< .001
Hemoglobin < 10 g/dL	52	142	37	1.68	0.93 to 3.04	.088	1.64	1.01 to 2.64	.044
Creatinine > 2 mg/dL	8	142	6	1.25	0.39 to 4.05	.705	1.19	0.43 to 3.26	.739
Calcium $\geq$ 10 mg/dL	19	142	13	1.32	0.61 to 2.85	.474	1.27	0.66 to 2.42	.471
LDH > 190 U/L	39	135	29	2.09	1.14 to 3.84	.018	1.61	0.98 to 2.65	.063
Bone marrow plasmacytosis > 30%	91	136	67	1.46	0.73 to 2.91	.282	1.41	0.81 to 2.43	.221
ISS stage†									
2	38	128	30	3.63	1.55 to 8.48	.003	2.70	1.46 to 4.99	.003
3	28	128	22	4.27	1.74 to 10.48		2.49	1.27 to 4.90	
Transplantation‡									
First	103	142	73	0.39	0.20 to 0.74	.004	0.59	0.32 to 1.06	.079
Second	82	142	58	0.32	0.16 to 0.62	< .001	0.42	0.24 to 0.73	.002
Response‡									
CR	20	142	14	0.26	0.06 to 1.07	.062	0.49	0.19 to 1.23	.128
VGPR	70	142	49	0.37	0.19 to 0.74	.005	0.49	0.29 to 0.84	.009
PR	102	142	72	0.51	0.27 to 0.94	.030	0.76	0.45 to 1.29	.316

Abbreviations: OS, overall survival; EFS, event-free survival; HR, hazard ratio; CRP, C-reactive protein; LDH, lactate dehydrogenase; ISS, International Staging System; CR, complete remission; VGPR, very good partial remission; PR, partial remission.

*P from Wald χ^2 test in Cox regression.

†Reference, stage 1.

‡Time dependent.

Tunisian tandem transplantation arm appeared inferior to the 86% and 80%, respectively, reported for the control arms without THAL of IFM99-02¹⁶ and of the Arkansas Total Therapy 2 trials.⁵ Although VGPR rates and survival outcomes with S0204 were comparable to published results of other tandem transplantation studies that included THAL, the CR rate of only 21% was unexpectedly low but was similar to the 17% reported for both arms of S9321. Yet, survival outcomes with S0204 were significantly improved over historical data reported and updated here for S9321, which supports the role of VGPR status for survival outcomes.¹⁰

We confirmed the independent prognostic roles of ISS stage and LDH for both OS and EFS so that a combination of ISS stage and LDH permitted separation of patients into cohorts with markedly different outcomes. Timely application of the second high-dose melphalan intervention within 4 months from the first transplantation significantly improved both OS and EFS as measured from a 4-month landmark, which was also confirmed on multivariate analysis that considered the application of the second transplantation intervention as a time-dependent variable and, thus, included all patients.

Table 2. Multivariate Analyses of Baseline and Time-Dependent Post-Therapy Variables Associated With OS and EFS

Variable	Patients			Multivariate Analyses					
	No.	Total No. Evaluated	%	OS			EFS		
				HR	95% CI	P*	HR	95% CI	P*
Transplantation†									
First	93	121	77	1.63	0.56 to 4.69	.368	1.69	0.70 to 4.09	.241
Second	76	121	63	0.20	0.07 to 0.53	.001	0.31	0.15 to 0.66	.002
LDH > 190 U/L	32	121	26	3.27	1.54 to 6.96	.002	1.75	1.00 to 3.09	.052
ISS stage‡									
2	37	121	31	4.54	1.75 to 11.76	.003	2.79	1.47 to 5.28	.004
3	27	121	22	5.56	1.93 to 16.02		2.65	1.25 to 5.61	

Abbreviations: OS, overall survival; EFS, event-free survival; HR, hazard ratio; LDH, lactate dehydrogenase; ISS, International Staging System.

*P from Wald χ^2 test in Cox regression.

†Time dependent.

‡Reference, stage 1.

Fig 4. Comparisons of this tandem transplantation trial S0204 and a previous Intergroup trial S9321. (A) Overall survival (all patients) was superior on S0204 trial compared with the Intergroup trial S9321. (B) Event-free survival (all patients) was superior on S0204 trial compared with the Intergroup trial S9321. (C) Overall survival (pair mates, matched on ISS stage and LDH) was superior on S0204 compared with S9321 when patients were matched on ISS stage and LDH. (D) Event-free survival (pair mates, matched on ISS stage and LDH) was superior on S0204 compared with S9321 when patients were matched on ISS stage and LDH. (E) Time-on-study comparison between S0204 and S9321 trials. More patients remained on trial for a longer time span on S0204 compared with S9321.

Joint consideration of both timing of second transplantation and response status effectuated by the first high-dose therapy intervention revealed significant survival benefits in patients who did not qualify for VGPR status when a second transplantation was applied within 4 months. Although this seemingly confirms IFM94

trial interpretations of an exclusive benefit from a second high-dose therapy cycle in patients who had less than VGPR^{4,10} the superior outcome of patients who had less than VGPR and who received a second transplantation intervention in S0204 could not be linked to an upgrading of response status as in the IFM94 trial.

Up-front incorporation of bortezomib plus THAL into the Total Therapy 3 study improved the 3-year sustained CR rate to 90% from the 70% rate in Total Therapy 2.¹⁹ Because of a 10-year continuous CR rate of 20% in Total Therapy 1, and because of an estimated sustained CR rate of 40% in Total Therapy 2, we project a cure fraction in excess of 60% in Total Therapy 3.²⁰ These unsurpassed results form the basis for a confirmatory trial of Total Therapy 3 for younger patients in SWOG.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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