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## Outcomes in patients with multiple myeloma with *TP53* deletion after autologous hematopoietic stem cell transplant

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### Abstract

*TP53* gene deletion is associated with poor outcomes in multiple myeloma (MM). We report the outcomes of patients with MM with and without *TP53* deletion who underwent immunomodulatory drug (IMiD) and/or proteasome inhibitor (PI) induction followed by autologous hematopoietic stem cell transplant (auto-HCT). We identified 34 patients with MM and *TP53* deletion who underwent IMiD and/or PI induction followed by auto-HCT at our institution during 2008-2014. We compared their outcomes with those of control patients (n=111) with MM without *TP53* deletion. Median age at auto-HCT was 59 years in the *TP53*-deletion group and 58 years in the control group (P=0.4). Twenty-one patients (62%) with *TP53* deletion and 69 controls (62%) achieved at least partial remission before auto-HCT (P=0.97). Twenty-three patients (68%) with *TP53* deletion and 47 controls (42%) had relapsed disease at auto-HCT (P=0.01). Median progression-free survival was 8 months for patients with *TP53* deletion and 28 months for controls (P<0.001). Median overall survival was 21 months for patients with *TP53* deletion and 56 months for controls (P<0.001). On multivariate analysis of both groups, *TP53* deletion (hazard ratio 3.4, 95% confidence interval 1.9-5.8, P<0.001) and relapsed disease at auto-HCT (hazard ratio 2.0, 95% confidence interval 1.2-3.4, P=0.008) were associated with a higher risk of earlier progression. In MM patients treated with PI and/or IMiD drugs, and auto-HCT, *TP53* deletion and relapsed disease at the time of auto-HCT are independent predictors of progression. Novel approaches should be evaluated in this high-risk population.

**Conflicts of interest:** The authors have no potential conflicts of interest to declare.

#### Author Contributions

S.G. and M.Q. designed the study, analyzed the data and wrote the manuscript; S.S., G.R. and R.D. prepared the data; R.S. performed the statistical analysis; G.L, J.E.B., N.S., Q.B., K.P., F.B., S.P., C.H., U.P., J.J.S., E.E.M., R.Z.O., R.C. reviewed and interpreted the data, and edited the manuscript; and all authors approved the final manuscript.

## Keywords

High risk multiple myeloma; autologous stem cell transplantation; TP53 gene deletion; deletion chromosome 17

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## Introduction

The *TP53* gene is a well-characterized tumor suppressor that transcriptionally regulates cell cycle progression and apoptosis and is mapped to 17p13.[1] Deletion of *TP53* gene can be detected by conventional cytogenetics (deletion of 17p) or by fluorescence in situ hybridization (FISH). In multiple myeloma, 17p deletion is a clinical indicator of very poor prognosis.[2-5] *TP53* deletion in multiple myeloma is rare at diagnosis, occurring at rates from 2% to 11% in different studies.[4, 6] However, the incidence of *TP53* deletion increases as the disease advances, occurring in up to half of patients with advanced-stage disease,[5, 7] which suggests that *TP53* deletion plays an essential role in disease progression.[4, 5, 8] Indeed, clonal evolution studies using FISH indicate that *TP53* deletion in multiple myeloma occurs most commonly in subclones.[9] Patients with multiple myeloma and *TP53* deletion generally have an aggressive disease course, with a higher prevalence of extramedullary disease and hypercalcemia and shorter overall survival (OS) and progression-free survival (PFS).[3-5, 10] Subgroup analyses from several randomized trials in multiple myeloma have shown poor outcomes in patients with 17p deletion, even after treatment with immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and autologous hematopoietic stem cell transplant (auto-HCT).[4, 11-13] The optimal treatment strategy for this high-risk group remains unknown.

In this study, we evaluated clinical outcomes in patients with multiple myeloma and *TP53* deletion, identified by FISH studies, who received PIs and/or IMiDs and auto-HCT at our institution. We then evaluated the association between various factors, including *TP53* deletion, and risk of disease progression.

## Methods

### Patients and Study Design

We queried our departmental database to identify consecutive patients with multiple myeloma with a *TP53* deletion who underwent auto-HCT at our institution from January 2008 through December 2014. We used an electronic algorithm to identify a matched control group of multiple myeloma patients, from our departmental database, who did not have *TP53* deletion and underwent auto-HCT during the same period. The controls were matched to the *TP53* deletion cases by age and response to the last therapy before auto-HCT. The ratio of cases to controls used was 3:1. The primary endpoints of this study were 2-year PFS rate and 2-year OS rate. The secondary endpoint was the best response after auto-HCT.

### TP53 Deletion

*TP53* deletion was determined by FISH analysis of bone marrow aspirates. FISH for each case was performed with the protocol employed in the Clinical Cytogenetics Laboratory at

The University of Texas MD Anderson Cancer Center using the LSI *TP53* Spectrum Orange probe from Abbott Molecular Inc. This probe contains DNA sequences specific to the *TP53* gene, mapped to the 17p13.1 region of chromosome 17, and can detect *TP53* gene deletions. The cutoff to define a positive test for *TP53* gene deletion with this probe with a 95% ( $P < 0.05$ ) confidence limit was 6.2%. [14]

## Response and Outcome Definitions

Post-transplant response was assessed at day 100 after auto-HCT. Response and progression were assessed according to the International Myeloma Working Group uniform response criteria. [15] Toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count of more than  $0.5 \times 10^9/L$ . Platelet engraftment was defined as the first of 7 consecutive days with a platelet count of more than 20,000  $\mu L$  without a platelet transfusion.

## Statistical Analysis

Time to event was assessed from the day of auto-HCT. OS and PFS were estimated by the Kaplan-Meier method. The incidence of disease progression was estimated with death in the absence of disease considered a competing risk. For OS, death from any cause was considered an event, while for PFS, death or progression was considered an event. [16] Pearson  $\chi^2$  and Fisher exact tests were used to compare differences between categorical variables, and the rank-sum test was used to compare the distribution of continuous variables. Cox proportional hazards regression analysis was used to compare the OS and PFS rates between the *TP53*-deletion and control groups and to evaluate predictors of disease progression on univariate and multivariate analysis. Analyses were performed using STATA software (2009; StataCorp, College Station, TX).

## Results

### Patient Characteristics

Patient and disease characteristics are summarized in Table 1. We identified 34 patients with multiple myeloma with *TP53* deletion, who were categorized as the *TP53* group, and 111 matched patients with multiple myeloma without *TP53* deletion, who were categorized as the control group. Twenty-one patients (62%) in the *TP53* group and 69 patients (62%) in the control group had achieved at least a partial response to their last therapy before auto-HCT. Of note, 23 patients (68%) in the *TP53* group, in contrast to 47 patients (42%) in the control group, had experienced relapse before auto-HCT. Therapies used for pre-transplant induction and post-transplant maintenance are summarized in table 1. Most patients in both groups received a PI-containing regimen before auto-HCT (*TP53*: 32 patients [94%], control: 91 patients [82%],  $P = 0.08$ ). There was no difference between the groups in pre-transplant IMiD exposure (*TP53*: 24 patients [71%], control: 84 patients [76%],  $P = 0.55$ ) or the use of post-transplant maintenance therapy (*TP53*: 19 patients [56%], control: 70 patients [63%],  $P = 0.4$ ). Among the 15 patients (44%) who did not receive maintenance therapy in the *TP53* group, the reasons were: early disease progression ( $n = 10$ ), low blood

counts (n = 2), early death (n = 1), patient refusal (n = 1), and allogeneic hematopoietic stem cell transplant immediately after the auto-HCT (n = 1).

### Engraftment and Toxicity

The median number of CD34+ hematopoietic stem cells infused was  $4.32 \times 10^6$ /kg of body weight for the *TP53* group and  $4.37 \times 10^6$ /kg of body weight for the control group. All patients in the control group and 33 (97%) patients in the *TP53* group. One patient in the *TP53* group failed to engraft and subsequently died owing to the graft failure and disease progression. The median times to neutrophil and platelet engraftment were 11 days for both groups. CTCAE grade 3-4 adverse events were observed in 22 patients (65%) in the *TP53* group and 69 patients (62%) in the control group (Table 1S). Infections were the most common grade 3-4 adverse events (*TP53*: 20 patients [59%], control: 62 patients [56%]). This was followed by hypotension (*TP53*: five patients [15%], control: seven patients [6%]). One patient in the *TP53* group died of congestive heart failure 85 days post-transplant, and no patients in the control group died of transplant-related complications during the first 100 days post-transplant.

### Response After Auto-HCT

Post-transplant responses are shown in Table 1S. The overall response rate at 100 days post-transplant (partial response, very good partial response, complete response, or stringent complete response) was 82% in the *TP53* group and 92% in the control group. Fifteen patients (44%) in the *TP53* group and 65 patients (59%) in the control group had an upgrade in their response post-transplant compared to the last response pre-transplant. Two patients (9%) in the *TP53* group and four patients (4%) in the control group had evidence of progressive disease at day 100 post-transplant.

Among the patients who received maintenance therapy post-transplant (*TP53*: 19 patients, control: 70 patients), seven patients (39%) in the *TP53* group and 26 patients (37%) in the control group had an upgrade in their response after maintenance therapy compared to their response at day 100 post-transplant.

### Survival

The median follow-up in surviving patients was 16 months (range 1.5-69 months) in the *TP53* group and 25 months (range 0.9-78 months) in the control group. The median PFS time was 8 months in the *TP53* group and 28 months in the control group, and the 2-year PFS rate was 14% in the *TP53* group and 55% in the control group ( $P < 0.001$ ) (Figure 1A). The median OS time was 21 months in the *TP53* group and 56 months in the control group, and the 2-year OS rate was 43% in the *TP53* group and 87% in the control group ( $P < 0.001$ ) (Figure 1B). The causes of death are summarized in Table 1S. The most common cause of death in both groups was disease progression.

### Risk of Progression Among Patients with *TP53* Deletion

In the *TP53* group, on univariate analysis, no factors were significantly associated with a higher risk of disease progression, including age, response before auto-HCT, time from diagnosis to auto-HCT, International Staging System stage, conditioning regimen,

cytogenetic features, and prior exposure to PIs or IMiDs. There was a trend toward higher rates of disease progression in patients with *TP53* deletion who had relapsed disease at the time of auto-HCT; however, this trend was not statistically significant (Table 2S).

### Univariate and Multivariate Analysis of Risk of Progression in Both Groups

We then assessed the independent effects of *TP53* deletion and other factors on the risk of disease progression in the combined cohort of patients with *TP53* deletion and controls (Table 2). On univariate analysis, the presence of *TP53* deletion and relapsed disease at the time of auto-HCT were the only factors associated with a significantly higher risk of disease progression. These two factors remained significantly associated with disease progression risk on multivariate analysis and were also associated with shorter PFS and OS (Figure 2).

## Discussion

The presence of *TP53* deletion in patients with multiple myeloma is associated with a poor prognosis, [17-21] and the optimal management of these high-risk cases remains controversial.[2] In this study, we retrospectively analyzed the clinical outcomes and response to therapy in patients with multiple myeloma and *TP53* deletion, identified by FISH studies, who received PI- and/or IMiD-containing induction followed by auto-HCT. We compared these patients' clinical outcomes with those of a matched control group of patients with multiple myeloma without *TP53* deletion. Although both groups received induction therapy with PIs and/or IMiDs followed by auto-HCT and in most cases maintenance therapy and despite similar overall response rates following auto-HCT and similar toxic effects, the *TP53* group had significantly worse survival outcomes. This difference was due primarily to a higher risk of progression in the *TP53* group (median PFS 8 months in the *TP53* group vs. 28 months in the control group). Indeed, the most common cause of death in the *TP53* group was disease progression, with only one patient dying of transplant-related complications.

We then sought to identify risk factors within the *TP53* group that could affect the risk of progression. On univariate analysis of the *TP53* group alone, the only factor associated, although not significantly, with a higher risk of progression was having relapsed disease at the time of the transplant. Age, International Staging System stage, response to last therapy before auto-HCT, and a pre-transplant induction containing a combination of PI and IMiD did not significantly affect the risk of disease progression in this group. This result was confirmed on multivariate analysis of both groups, in which the presence of *TP53* deletion and having relapsed disease at the time of the transplant were the only independent risk factors associated with a higher risk of disease progression. Moreover, patients with *TP53* deletion who had relapsed disease at the time of the transplant had worse outcomes than those who received the transplant as consolidation after initial induction, highlighting the worse outcomes in patients who develop *TP53* deletion later in their disease course than in those who *TP53* deletion found at the time of initial diagnosis. Overall, patients with *TP53* deletion early or late in their disease course had worse outcomes than their control group counterparts.

The ability of novel drugs followed by auto-HCT and maintenance therapy to overcome the negative effects of high-risk cytogenetic features in multiple myeloma remains debatable.[2] The HOVON-65/GMMG-HD4 trial suggested that the adverse impact of 17p deletion could be reduced by incorporating bortezomib in both pre-transplant induction and post-transplant maintenance therapy.[12] Similarly, the Italian Group for Hematologic Diseases in Adults (GIMEMA) suggested that pre-transplant bortezomib, thalidomide, and dexamethasone (VTD) induction could overcome the poor prognostic impact of high-risk cytogenetic features, including 17p deletion.[13] Also, the Myeloma Institute at the University of Arkansas for Medical Sciences reported that Total Therapy 3, which incorporated VTD in induction, consolidation, and maintenance, overcame the adverse impact of *TP53* deletion.[22] However, other studies failed to show the benefit of novel agents and auto-HCT in patients with 17p deletion. A phase III trial by the Spanish Myeloma Group (PETHEMA-GEM), in contrast to the GIMEMA study, found that VTD was unable to overcome the poor prognostic impact of 17p deletion in high-risk multiple myeloma.[11] Likewise, the Intergroupe Francophone du Myélome (IFM) trial IFM-2005-01, which reported on the use of bortezomib plus dexamethasone versus vincristine, doxorubicin, and dexamethasone (VAD) induction followed by auto-HCT, did not show improvement in PFS or OS in a subgroup of patients with 17p deletion receiving the bortezomib-based induction regimen (4-year OS 50% in patient with 17p deletion vs. 79% in patients without 17p deletion).[17] In our retrospective analysis, although all patients had prior exposure to a PI and/or an IMiD, the PFS and OS rates were significantly lower in the *TP53* group whether the *TP53* deletion was detected at diagnosis or at relapse.

These results clearly demonstrate that there is significant room for improvement in the transplant management of multiple myeloma with *TP53* deletion. Although post-transplant maintenance, as described by the Hemato-oncology Foundation for Adults in the Netherlands (HOVON) group, may help abrogate the risk associated with *TP53* deletion, other transplant-specific approaches may improve outcomes further. Improved CR rates post-transplant are associated with an improved 5-year OS rate of up to 80% at 5 years.[23] Additionally, the depth of response in patients with *TP53* deletion may be more significant than in intermediate- or standard-risk disease. One study by Haessler et al. demonstrated improved OS in a small number of patients whose disease had 17p deletion who attained a CR after receiving a tandem auto-transplant, although this benefit was not seen in the low-risk group.[24] The Bologna 96 study demonstrated higher CR rates in patients with multiple myeloma who received tandem auto-transplants than in those who received single auto-transplants (33% with single vs. 47% with tandem,  $P = 0.008$ ), making tandem auto-SCT a promising approach for the treatment of high-risk disease where a CR may be beneficial.[25] While cytogenetic features were not evaluated in this study, its results led to the creation of a phase III randomized trial, CTN 0702, comparing tandem transplants versus single transplants versus single transplants followed by lenalidomide, bortezomib, and dexamethasone (RVD) consolidation. All patients received lenalidomide maintenance. This protocol has closed to accrual, and the results may inform whether tandem auto-HCT may be beneficial in a subgroup of patients.

Our study reported here has weaknesses inherent to a retrospective analysis, including patient heterogeneity and selection bias. However, we tried to overcome these limitations by



using a matched control arm of patients who were treated during the same time period. Even with this matching, the proportion of patients with relapsed disease was higher in the *TP53* group than in the control group, which may have adversely affected the outcomes in the *TP53* group.

A number of treatment approaches are being explored for patients with multiple myeloma with *TP53* deletion. Some centers recommend intense up-front combination therapy (e.g., lenalidomide, bortezomib, and dexamethasone (RVD) followed by up-front auto-HCT to maximize CR rates, and then by PI-based maintenance therapy to maintain the response.[26] Allogeneic HCT, although controversial, is being explored in clinical trials.[27, 28] Currently, the Bone and Marrow Transplant Clinical Trials Network is conducting a multicenter phase II study (BMT CTN 1302, or NCT02440464) investigating the utility of frontline allogeneic HCT in patients with multiple myeloma with high-risk cytogenetics. Additionally, novel conditioning regimens, such as the busulfan and melphalan regimen, currently under investigation at MD Anderson Cancer Center, may improve CR rates and other outcomes in patients with high-risk multiple myeloma. Other emerging approaches include the use of monoclonal antibodies such as elotuzumab and daratumumab that have shown responses in patients with 17p deletion.[29, 30] Cellular therapy directed against clonal plasma cells is another promising approach.[31, 32] Finally, novel approaches of targeting intracellular pathways, such as MDM2 in patients with 17p deletion, are also being explored.[33]

In conclusion, we found that patients with *TP53* deletion continue to have poor outcomes with the current approach of PI-based induction followed by auto-HCT and that *TP53* deletion and relapsed disease at the time of auto-HCT are each associated with a higher risk of progression. Novel treatments are needed for these high-risk cases.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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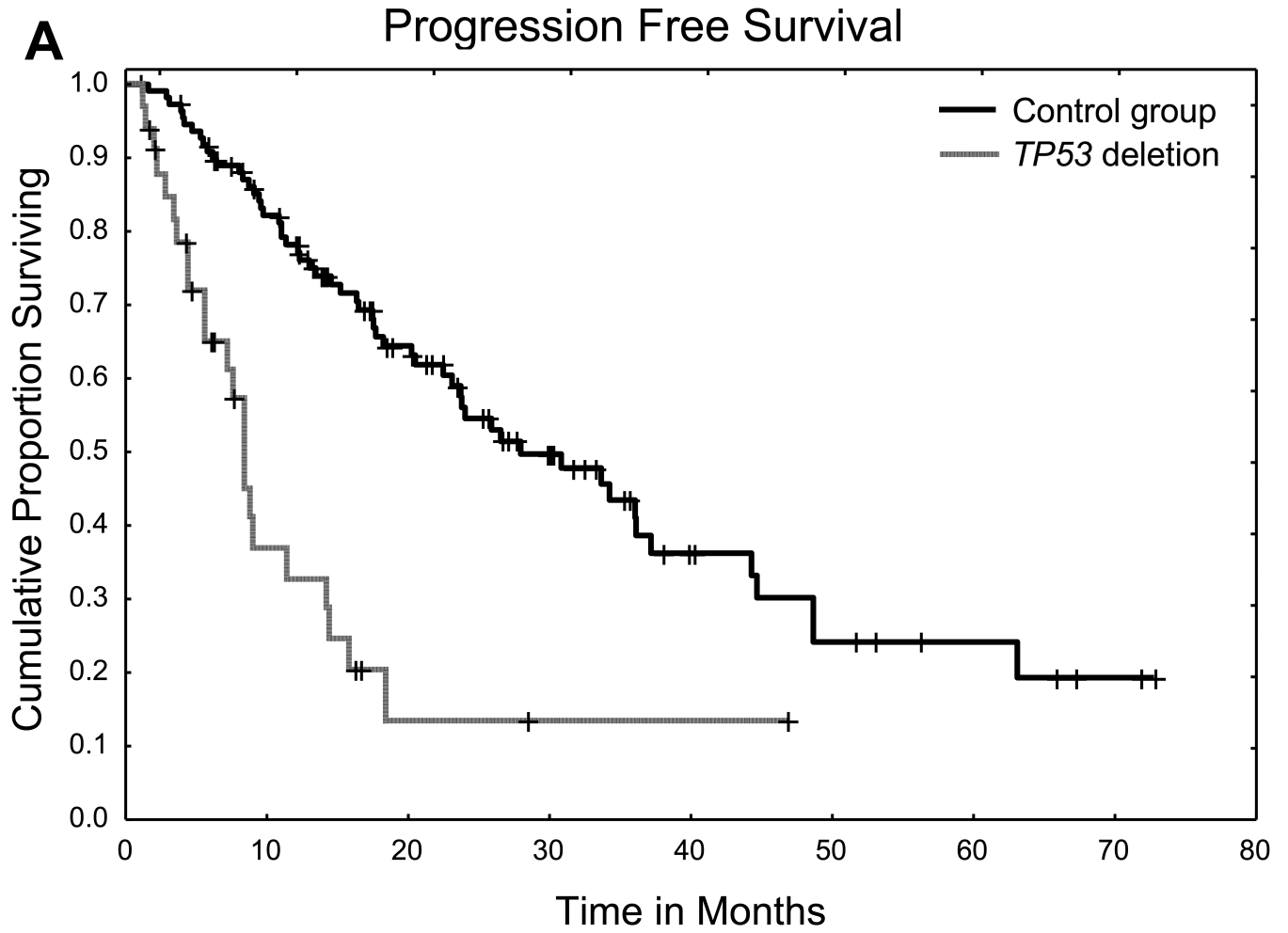
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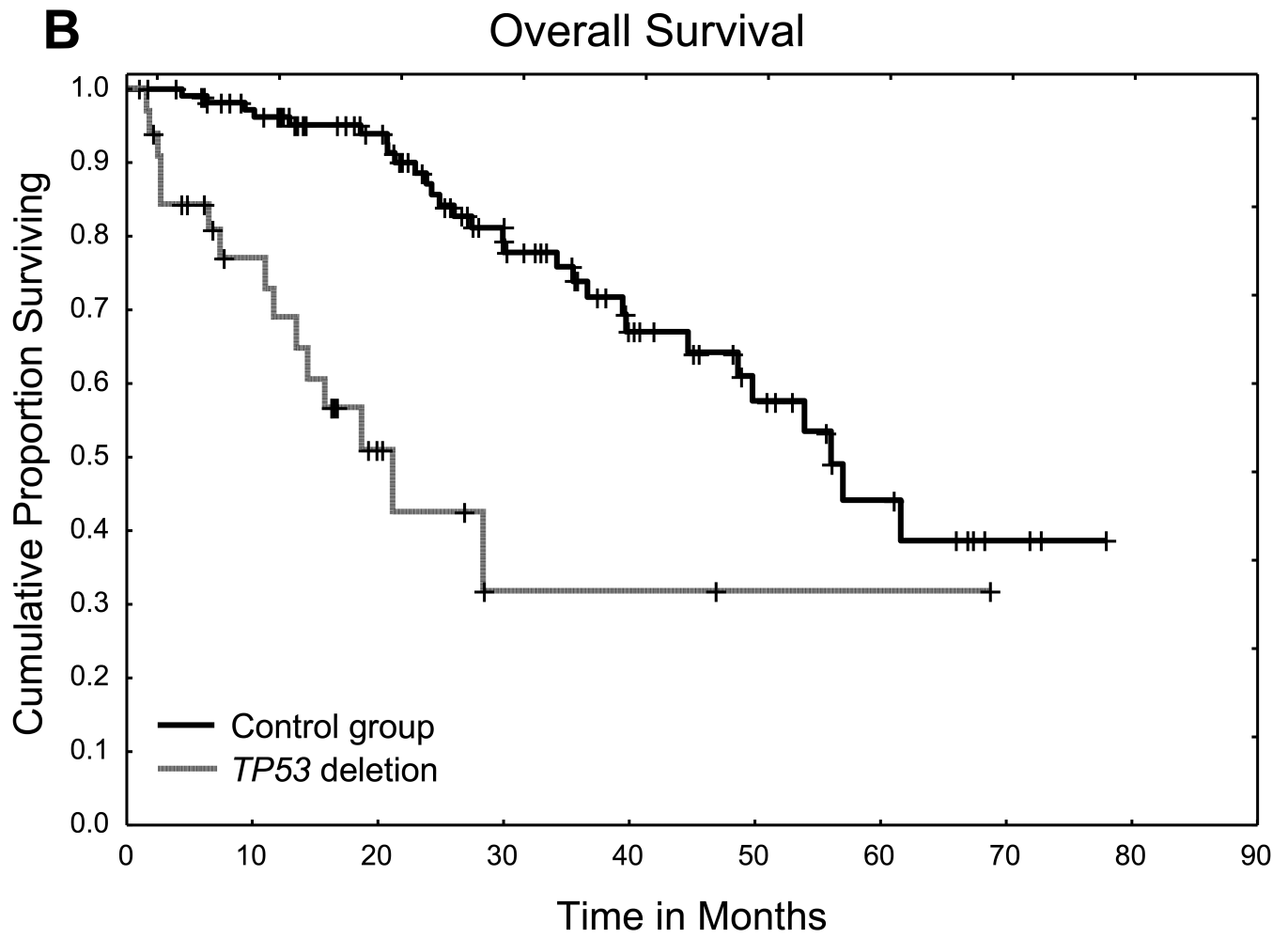


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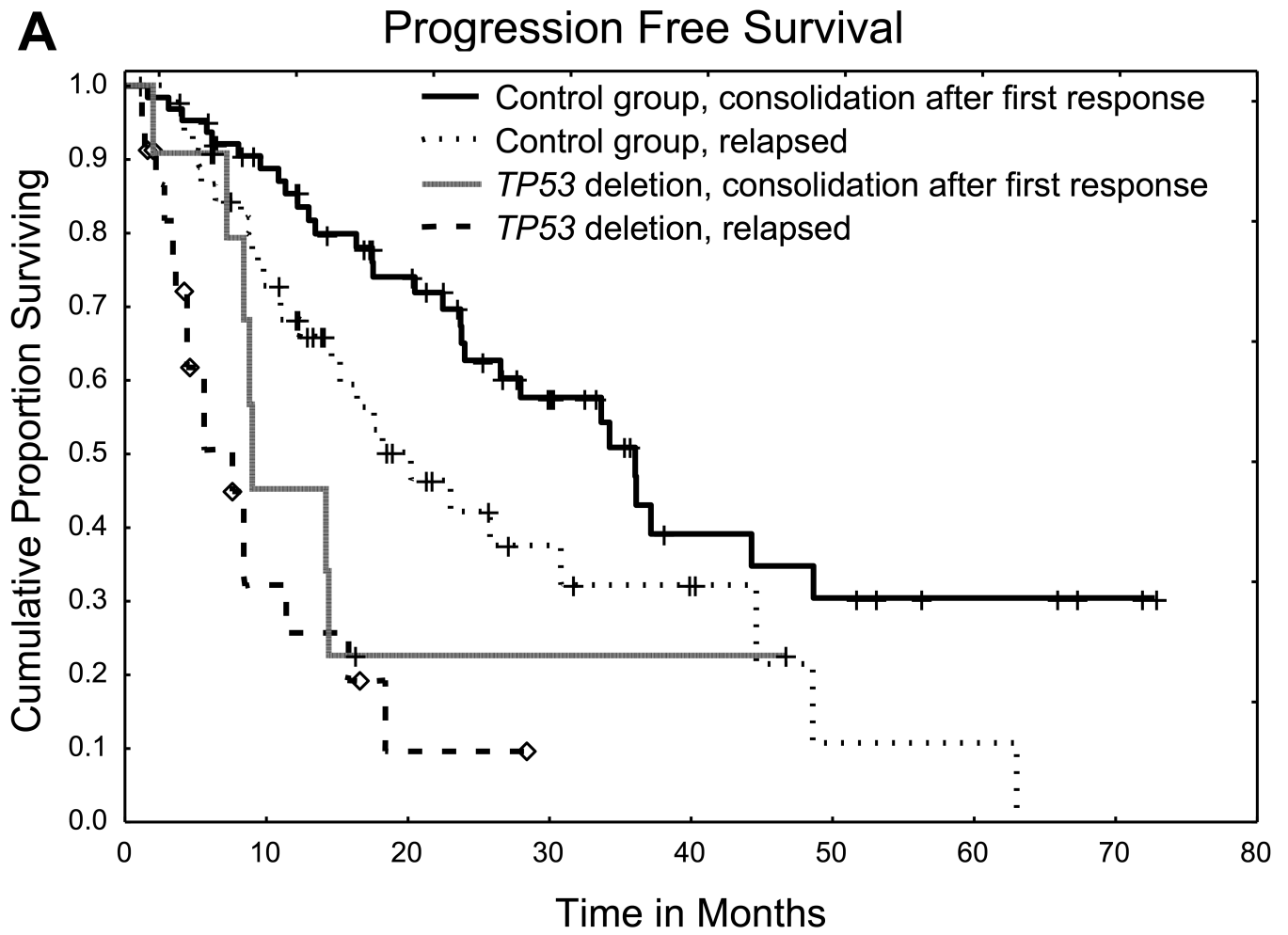
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**Figure 1.**  
 A. Progression free survival for patients with *TP53* deletion and controls  
 B. Overall survival for patients with *TP53* deletion and controls

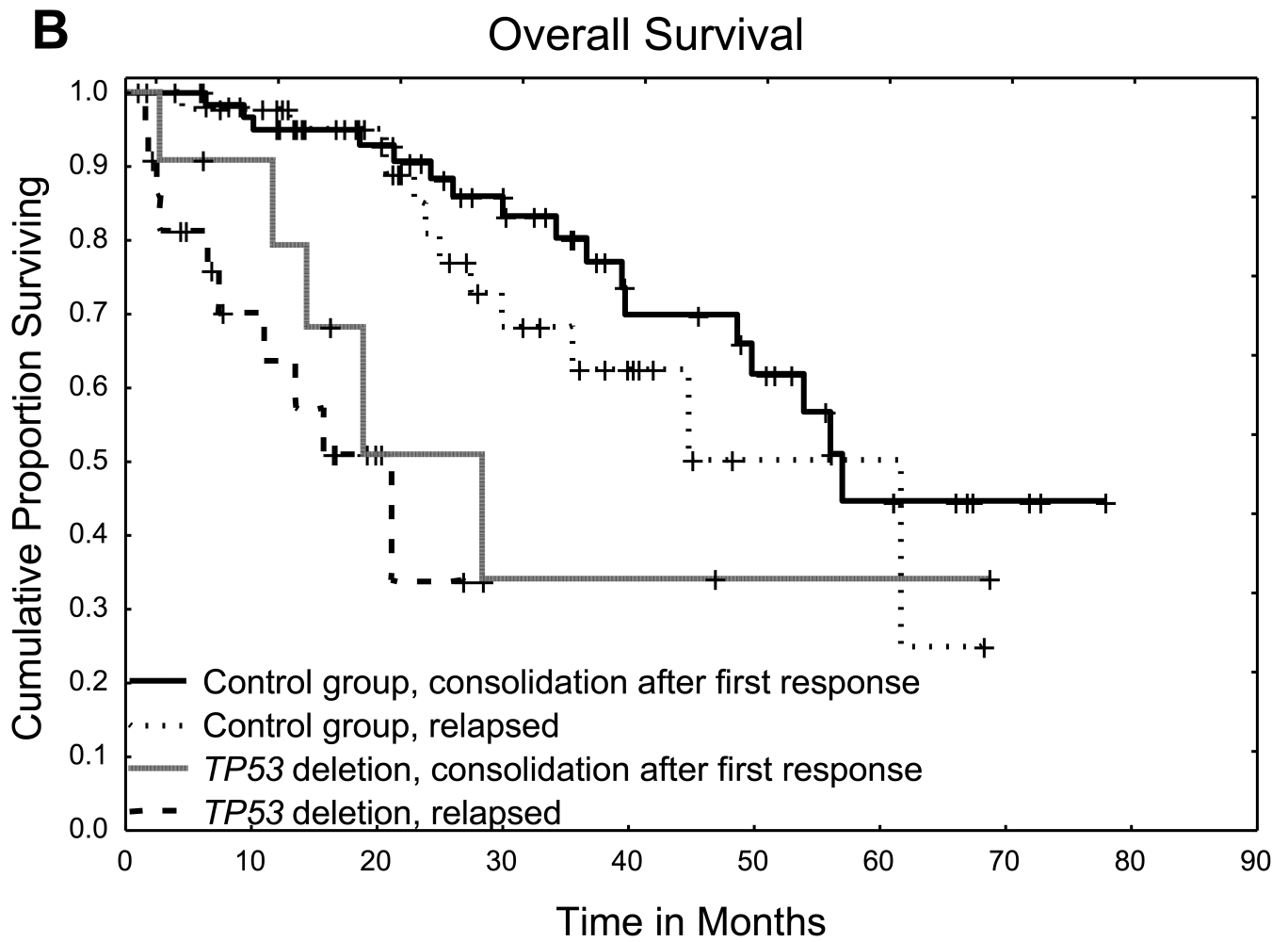


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**Figure 2.**

A. Progression free survival for patients with TP53 deletion and controls according to disease status at time of transplant

B. Overall survival for patients with TP53 deletion and controls according to disease status at time of transplant

**Table 1**

## Transplant outcomes

<b>Outcome</b>	<b>TP53 deletion group (n = 34)</b>	<b>Control group (n = 111)</b>	<b>P value</b>
<b>Median follow-up duration, mo (range)</b>	<b>16 (1.5-69)</b>	<b>25 (0.9-78)</b>	
<b>Response, no. (%)</b>			
Overall response (PR/VGPR/CR)	28 (82)	103 (92)	0.07
sCR	2 (6)	24 (22)	
CR and near CR	8 (24)	19 (17)	
VGPR	11 (32)	35 (32)	
PR	7 (21)	25 (23)	
Stable disease	4 (12)	4 (4)	
Progressive disease	2 (6)	4 (4)	
<b>Transplant-related deaths at 100 days, no.</b>	<b>1</b>	<b>0</b>	<b>0.05</b>
<b>Grade 3-4 toxic effects, no. (%)</b>			<b>0.8</b>
Infection	20 (59)	62 (56)	
Hypotension	5 (15)	7 (6)	
Pulmonary toxic effects	0	5 (5)	
Elevation of liver enzymes	2 (6)	3 (3)	
Gastrointestinal effects	2 (6)	5 (5)	
Renal impairment	1 (3)	3 (3)	
<b>Median OS, mo</b>	<b>21</b>	<b>56</b>	
<b>Two-year OS rate, % (95% CI)</b>	<b>43 (20-63)</b>	<b>87 (78-93)</b>	<b>&lt;0.001</b>
<b>Median PFS, mo</b>	<b>8</b>	<b>28</b>	
<b>Two-year PFS rate, % (95% CI)</b>	<b>14 (3-32)</b>	<b>55 (43-64)</b>	<b>&lt;0.001</b>
<b>Cause of death, no. (%)</b>	<b>15 (44)</b>	<b>29 (26)</b>	
Disease progression	14 (41)	27 (24)	
Toxic effects	1 (3)	0	
Secondary malignancy	0	1 (1)	
Prior malignancy (prostate cancer)	0	1 (1)	

PR: partial response; VGPR: very good partial response; CR: complete response; sCR: stringent complete response; SD: stable disease; PD: progressive disease.



**Table 2**

Univariate and multivariate analysis of risk of progression at 2 years among patients with *TP53* deletion and controls (n = 145)

Factor	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
<i>TP53</i> deletion (ref: absence of <i>TP53</i> deletion)	3.8	2.2-6.7	<0.001	3.4	1.9-5.8	<0.001
Age above 60 years (ref: 60 years)	0.9	0.5-1.5	0.7			
Time from diagnosis to auto-HCT of less than 1 year (ref: >1 year)	1.6	0.98-2.7	0.06			
Relapsed disease at time of transplant (ref: other)	2.3	1.4-3.9	0.001	2.0	1.2-3.4	0.008
Less than PR as last response before transplant (ref: other)	1.1	0.6-1.8	0.8			
Conditioning regimen (melphalan vs. others)	0.9	0.5-1.5	0.7			

Ref: reference; CI: confidence interval; PR: partial response.

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