# Outcome heterogeneity of *TP53*-mutated myeloid neoplasms and the role of allogeneic hematopoietic cell transplantation

*TP53* mutations are present in up to 20% of patients with *de novo* myeloid neoplasms (MN) and nearly 40% with myeloid neoplasm post cytotoxic therapy (MN-pCT). They are frequently associated with a complex karyotype (CK) and poor responses to therapy.[1-3] There are currently no effective targeted therapies for *TP53*-MN. Since standard cytotoxic regimens are seldom successful in achieving remission and may result in significant toxicity, the treatment paradigm has recently shifted to less intensive therapies such as hypomethylating agents (HMA). Even though the overall response rate has improved significantly with HMA alone or in combination with venetoclax, most patients succumb to their disease.[4,5] Allogeneic hematopoietic cell transplantation (alloHCT) remains the only curative option for patients with high-risk MN. Even though some patients achieve long-term survival, the outcomes after alloHCT are disappointing.[3,6] Thus, it is unclear if the standard of care alloHCT is an appropriate treatment for patients with *TP53*-MN given potentially serious morbidity and mortality, particularly in older patients.[7]

We performed a single-center retrospective review of adult patients with *TP53*-MN evaluated at Johns Hopkins between November 2015 and February 2020. The clinical characteristics are included in Table 1. The clinical next-generation sequencing (NGS) panel including 59 genes commonly mutated in myeloid malignancies was used to identify *TP53* mutations, as previously described (*Online Supplementary Table S1*).[8] We identified 93 patients including 22 with *de novo* acute myeloid leukemia (AML), 15 with AML, myelodysplasia-related (AML-MR), 23 with myelodysplastic neoplasms (MDS), 29 with MN-pCT, two with myeloproliferative neoplasm (MPN), and two with MDS/MPN. DNA was extracted from diagnostic bone marrow specimens or peripheral blood leukocytes. The identification of somatic variants has been performed as previously described.[8] Despite our stringent filtering criteria, the germline origin of some variants could not have been entirely excluded.

Overall, 79 of 93 (85%) patients received therapy: 20 (25.3%) were treated with HMA alone, 30 (38.0%) with HMA + venetoclax, ten (12.7%) with HMA + others, 15 (19.0%) with intensive chemotherapy, two (2.5%) with an immunomodulatory drug, one (1.3%) with ivosidenib and one (1.3%) with a JAK2 inhibitor. Twenty-nine (36.7%) patients received non-myeloablative alloHCT with post-transplant cyclophosphamide (Figure 1A).

*TP53* variants included missense, truncating, splice-site mutations, and insertions/deletions. Missense variants were more common, and several recurrent mutations were

**Table 1.** Clinical characteristics of the *TP53*-myeloid neoplasm cohort.

| Variable | Overall N=93 | alloHCT N=29 | Therapy no alloHCT N=50 | No therapy N=14 | *P* |
|---|---|---|---|---|---|
| Age in years, median (range) | 67 (59-73) | 62 (53-67) | 68 (60-73) | 76 (70-84) | <0.0001 |
| Sex, N (%) | | | | | |
| F | 38 (40.9) | 13 (44.8) | 18 (36.0) | 7 (50.0) | 0.54 |
| M | 55 (59.1) | 16 (55.2) | 32 (64.0) | 7 (50.0) | |
| Diagnosis, N (%) | | | | | |
| AML | 22 (23.7) | 8 (27.6) | 13 (26.0) | 1 (7.1) | 0.31 |
| AML-MR | 15 (16.1) | 5 (17.2) | 9 (18.0) | 1 (7.1) | 0.69 |
| MDS | 23 (24.7) | 4 (13.8) | 11 (22.0) | 8 (57.1) | 0.01 |
| MDS/MPN overlap | 2 (2.2) | 2 (6.9) | 0 (0) | 0 (0) | 0.21 |
| MPN | 2 (2.2) | 0 (0) | 2 (4.0) | 0 (0) | 0.66 |
| MN-pCT (AML) | 10 (10.8) | 4 (13.8) | 4 (8.0) | 2 (14.3) | 0.58 |
| MN-pCT (MDS) | 19 (20.4) | 6 (20.7) | 11 (22.0) | 2 (14.3) | 0.94 |
| Cytogenetics, N (%) | | | | | |
| Complex | 73 (78.5) | 22 (75.9) | 42 (84.0) | 9 (64.3) | 0.54 |
| Non-complex | 16 (17.2) | 6 (20.7) | 7 (14.0) | 3 (21.4) | |
| Not available | 4 (4.3) | 1 (3.4) | 1 (2.0) | 2 (14.3) | |

alloHCT: allogeneic hematopoietic cell transplantation; AML: acute myeloid leukemia; AML-MR: acute myeloid leukemia myelodysplasia-related; MDS: myelodysplastic neoplasms; MPN: myeloproliferative neoplasms; MN-pCT: myeloid neoplasm post cytotoxic therapy.

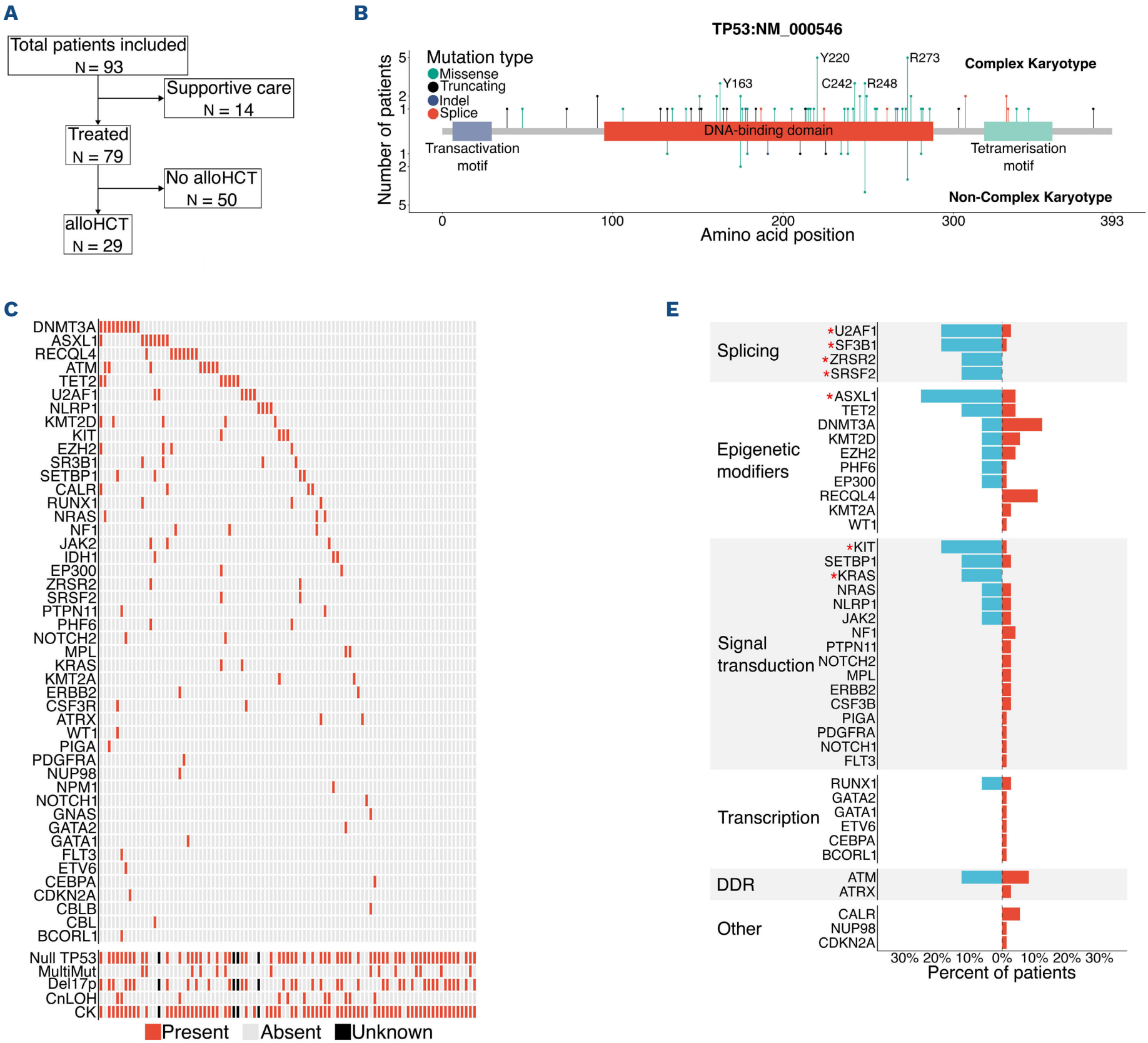


**Figure 1. *TP53*-myeloid neoplasm cohort, molecular and cytogenetic characteristics of patients.** (A) The study cohort and treatments. (B) Lollipop plot representing the *TP53* mutations grouped by the presence or absence of complex karyotype (CK). The amino acid changes are provided for recurring mutations observed in 3 or more patients with CK. (C) Oncoprint representing the gene mutations per patient, the presence of CK and *TP53* null phenotypes as determined by multiple mutations, del(17p), and copy neutral loss of heterozygosity (CN-LOH). (D) Distribution of the number of mutations per patient according to CK. *TP53* null causes are represented by red and not null by blue dots. (E) Bar-plot representing the relative number of non-*TP53* mutations according to CK. The mutated genes with significantly different distribution between CK (blue bars) and non-CK (red bars) are marked with asterisks. DDR: DNA damage response.

observed, specifically R175, Y220, R248, and R273 (Figure 1B; *Online Supplementary Table S2*). Karyotype results were available from 89 of 93 (95.7%) patients. Of those, 73 (78.5%) patients had CK. Sixty-two (66.6%) patients had biallelic *TP53* aberration (null phenotype): 14 (15.1%) patients with biallelic *TP53* mutations, 37 (41.6%) with deletion 17p, and 11 (12.0%) with copy-neutral loss-of-heterozygosity (CN-LOH) involving chromosome 17p (Figure 1C). As expected, CK was significantly associated with *TP53* null phenotype compared to monoallelic mutations (56/62 [90.3%] *vs*. 17/26 [65.4%], respectively; *P*=0.01).

Additional somatic mutations in presumptive cancer driver genes were seen in 65 of 81 (80.2%) of patients with *TP53* mutations. *DNMT3A, ASXL1, RECQL4, ATM, TET2*, and *U2AF1* were among the most commonly mutated genes (Figure 1C; *Online Supplementary Table S3*). The presence of CK was associated with lower mutational burden compared to non-CK patients (*P*< 0.01; Figure 1D). Next, we sought to determine, whether mutations in genes involved in distinct cellular processes were significantly more common in patients with *TP53* and CK. The mutations in genes involved in mRNA splicing and chromatin modifications such as *ASXL1* were significantly associated with *TP53* and CK (Figure 1E). Even though the outcomes of patients with *TP53* mutations are generally poor, some studies report 10-20% long-term survival after alloHCT. We analyzed the outcome of all patients with *TP53* mutations, regardless of the karyotype results. Fourteen of the 93 patients (15%) were offered supportive care only, while remission induction was attempted in 79 (85%) patients. Complete remission or complete remission with incomplete hematological recovery (CR/CRi) was achieved in 25 of 79 (31.6%) patients. Twenty-nine (36.7%) patients received non-myeloablative alloHCT with post-transplant cyclophosphamide; 22 (75.9%) in CR/CRi and seven (24.1%) with residual disease. (Table 1; Figure 1A). The median survival was significantly better in patients treated with alloHCT compared to those who did not proceed to alloHCT (18.9 *vs*. 4.1 months, respectively; *P*<0.0001; Figure 2A). A significantly higher CR/CRi rate among alloHCT recipients compared to the non-alloHCT arm may have contributed to the observed difference in survival (75.9% *vs*. 6.8%, respectively). The median survival was similar between supportive care and therapy-only groups (2.5 *vs*. 4.1 months; *P*=0.94; Figure 2A). Since the *TP53* null phenotype is almost uniformly associated with genomic instability and CK, we sought to examine the effect of CK on alloHCT outcome. The median overall survival was significantly better in patients with *TP53* mutations and non-CK compared to patients with CK (not reached *vs*. 13.7 months; *P*=0.01; Figure 2B). We previously showed that mobilized peripheral blood (PB) and a more intensive conditioning regimen with 400 cGy total body radiation (TBI) appeared to be associated with improved outcomes in T-cell lymphomas and myelofibrosis compared to our standard

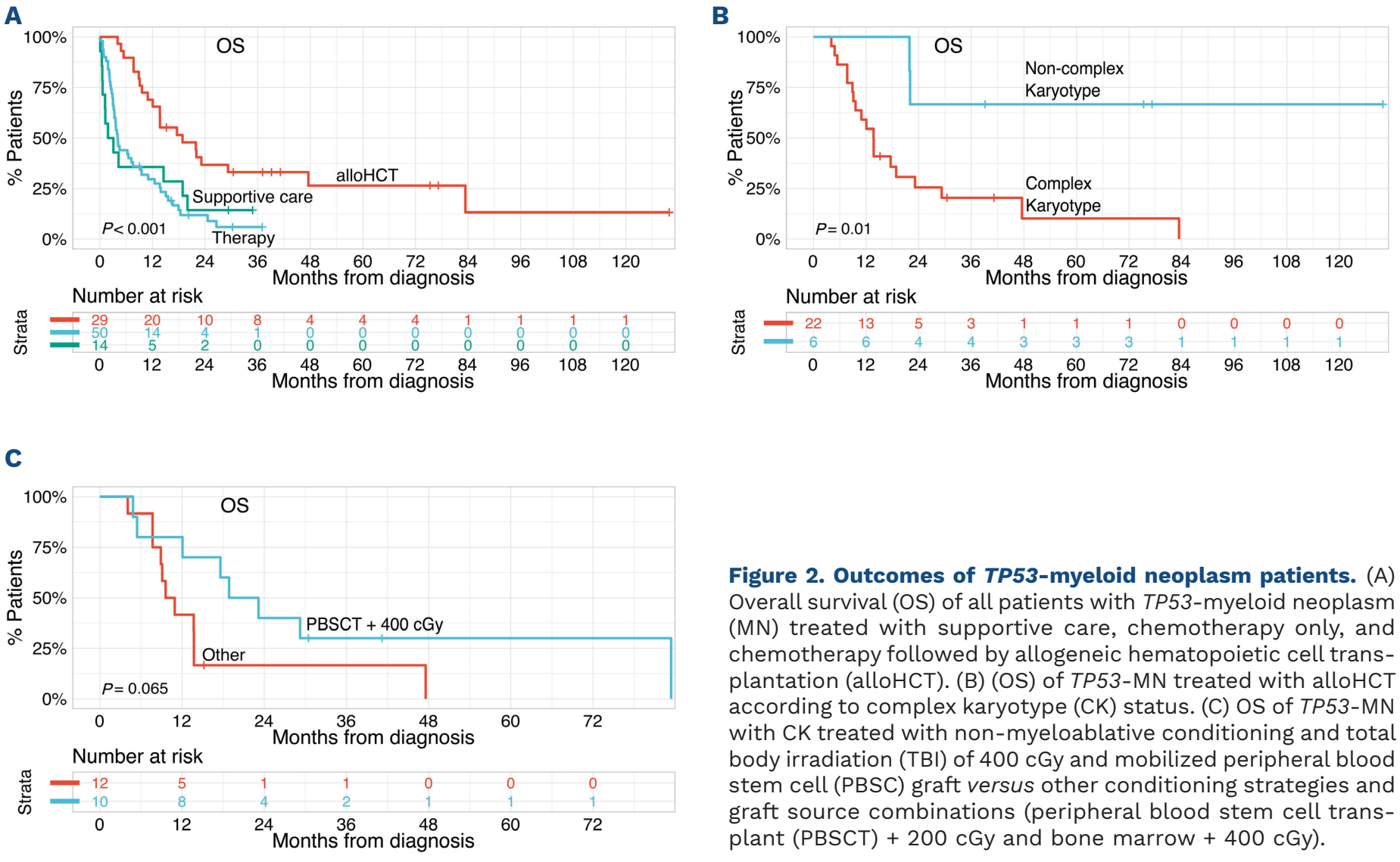


**Figure 2. Outcomes of *TP53*-myeloid neoplasm patients.** (A) Overall survival (OS) of all patients with *TP53*-myeloid neoplasm (MN) treated with supportive care, chemotherapy only, and chemotherapy followed by allogeneic hematopoietic cell transplantation (alloHCT). (B) (OS) of *TP53*-MN treated with alloHCT according to complex karyotype (CK) status. (C) OS of *TP53*-MN with CK treated with non-myeloablative conditioning and total body irradiation (TBI) of 400 cGy and mobilized peripheral blood stem cell (PBSC) graft *versus* other conditioning strategies and graft source combinations (peripheral blood stem cell transplant (PBSCT) + 200 cGy and bone marrow + 400 cGy).

bone marrow (BM) allografts and 200 cGy TBI.[9,10] Thus, we compared the outcome of *TP53*-CK patients who received PB and 400 cGy to those who received other conditioning strategies. Although not statistically significant, the median overall survival was longer in patients who received PB and 400 cGy (21.0 *vs*. 10.3 months; *P*=0.065; Figure 2C).

Consistent with prior reports, we observed that *TP53*-MN is a heterogeneous group of myeloid malignancies characterized by diverse responses to therapies and outcomes.[11] Complete loss of *TP53* function, and not merely a presence of *TP53* somatic variant, appears to mark the high-risk disease. While the presence of one wild-type allele is likely sufficient for an adequate DNA damage response and apoptosis, a null phenotype often leads to genome instability and CK.[12] Thus, CK, appears to be an ultimate consequence of a complete loss of TP53 function.[13]

Although morphological remission can be achieved in *TP53*-MN and CK, relapse is usually inevitable. Since traditional cytotoxic induction chemotherapies rely predominantly on intact DNA damage response pathway to induce apoptosis, low CR rates are not surprising.[14] Thus, therapies such as HMA alone or in combination with venetoclax appear to be more effective. With these contemporary and often less toxic approaches, approximately half of the patients will achieve clinically meaningful responses and suitable candidates are often offered consolidation with alloHCT. The reported long-term survival after alloHCT in *TP53*-MN varies widely between the studies from as high as 25% to under 5%.[3,6] This difference is likely due to the biological heterogeneity of *TP53*-MN.[13] Our results demonstrate that the alloHCT outcome greatly depended on the karyotype. Patients with *TP53*-MN and CK treated with alloHCT had a median OS of 13.7 months while it was not reached in patients with non-CK. Additionally, most patients with TP53 mutations and CK relapsed within 12 months post-alloHCT. Modification of the conditioning regimen and graft source may result in better disease control and augmentation of the antileukemic effect of the graft, respectively.[15] Like we previously showed in other high-risk diseases, higher TBI dose and the use of PB allografts may result in longer survival after alloHCT.[9,10] Given the poor outcome with a standard alloHCT in patients with *TP53*-CK, novel approaches focused either on improving the immune effect of the graft or targeted maintenance therapies will be critical to improving outcomes.

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**Disclosures**

No conflicts of interest to disclose.

**Contributions**

SP, SDH and LPG designed the study. SP, SDH and AA collected and annotated clinical data. SP and SDH performed variant filtering and analyzed molecular data. JAW, TJ, WBD, GTP, GG, AED, IG, BDS, TK, CS, KS, MJL and RJJ analyzed and interpreted clinical data. SP, SDH, RJJ and LPG wrote and edited the manuscript. All authors critically reviewed the manuscript and approved the final version.

**Data-sharing statement**

Data are available on request from the corresponding author.

## References

1. Weinberg OK, Siddon A, Madanat YF, et al. TP53 mutation defines a unique subgroup within complex karyotype de novo and therapy-related MDS/AML. Blood Adv. 2022;6(9):2847-2853.
2. Rücker FG, Schlenk RF, Bullinger L, et al. TP53 alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. Blood. 2012;119(9):2114-2121.
3. Lindsley RC, Saber W, Mar BG, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. N Engl J Med. 2017;376(6):536-547.
4. Pollyea DA, Pratz KW, Wei AH, et al. Outcomes in patients with poor-risk cytogenetics with or without TP53 mutations treated with venetoclax and azacitidine. Clin Cancer Res. 2022;28(24):5272-5279.
5. Döhner H, Dolnik A, Tang L, et al. Cytogenetics and gene mutations influence survival in older patients with acute myeloid leukemia treated with azacitidine or conventional care. Leukemia. 2018;32(12):2546-2557.
6. Murdock HM, Kim HT, Denlinger N, et al. Impact of diagnostic genetics on remission MRD and transplantation outcomes in

older patients with AML. Blood. 2022;139(24):3546-3557.
7. Versluis J, Lindsley RC. Transplant for TP53-mutated MDS and AML: because we can or because we should? Hematology. 2022;2022(1):522-527.
8. Gondek LP, Zheng G, Ghiaur G, et al. Donor cell leukemia arising from clonal hematopoiesis after bone marrow transplantation. Leukemia. 2016;30(9):1916-1920.
9. Sterling CH, Hughes MS, Tsai H-L, et al. Allogeneic blood or marrow transplantation with post-transplantation cyclophosphamide for peripheral T cell lymphoma: the importance of graft source. Transplant Cell Ther. 2023;29(4):267.e1-267.e5.
10. Jain T, Tsai H-L, DeZern AE, et al. Post-Transplantation cyclophosphamide-based graft-versus-host disease prophylaxis with nonmyeloablative conditioning for blood or marrow transplantation for myelofibrosis. Transplant Cell Ther. 2022;28(5):259.e1-259.e11.
11. Short NJ, Montalban-Bravo G, Hwang H, et al. Prognostic and therapeutic impacts of mutant TP53 variant allelic frequency in newly diagnosed acute myeloid leukemia. Blood Adv. 2020;4(22):5681-5689.
12. Jasek M, Gondek LP, Bejanyan N, et al. TP53 mutations in myeloid malignancies are either homozygous or hemizygous due to copy number-neutral loss of heterozygosity or deletion of 17p. Leukemia. 2010;24(1):216-219.
13. Bernard E, Nannya Y, Hasserjian RP, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. Nat Med. 2020;26(10):1549-1556.
14. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med. 2016;374(23):2209-2221.
15. Hourigan CS, Dillon LW, Gui G, et al. Impact of conditioning intensity of allogeneic transplantation for acute myeloid leukemia with genomic evidence of residual disease. J Clin Oncol. 2020;38(12):1273-1283.