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A phase II trial of azacitidine with ipilimumab, nivolumab, or ipilimumab and nivolumab in previously untreated myelodysplastic syndrome

Ian M. Bouligny[1], Guillermo Montalban-Bravo[1], Koji Sasaki[1], Naval Daver[1], Elias Jabbour[1], Yesid Alvarado[1], Courtney D. DiNardo[1], Farhad Ravandi[1], Gautam Borthakur[1], Prithviraj Bose[1], Naveen Pemmaraju[1], Steven Kornblau[1], Tapan Kadia[1], Lucia Masarova[1], Koichi Takahashi[1], Michael Andreeff[1], Alexandre Bazinet[1], Hui Yang[1], Rashmi Kanagal-Shamanna[2], Chitra Hosing[3], Sherry Pierce[1], Meghan Meyer[1], Xuelin Huang[4], Guillermo Garcia-Manero[1*]

1. Department of Leukemia, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030
2. Department of Hematopathology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030
3. Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030
4. Department of Biostatistics, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030

*Corresponding author: Guillermo Garcia-Manero; ggarciam@mdanderson.org.

Running head: Azacitidine and Immunotherapy in MDS
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1. Letter to the Editor

Patients with high-risk myelodysplastic syndrome (MDS) have dismal prognoses. The standard of care for patients with high-risk MDS who cannot undergo an allogeneic stem cell transplant (SCT) is continuous treatment with a hypomethylating agent.[1-3] However, hypomethylating agents do not elicit a response in at least half of patients with MDS.[4] Thus, innovative therapies are necessary. In this clinical trial, we found modest clinical activity of immunotherapy in combination with azacitidine and increased toxicity associated with dual checkpoint blockade.

Hypomethylating agents increase the expression of programmed death-ligand 1 (PD-L1) and cytotoxic T- lymphocyte-associated protein 4 (CTLA4) in MDS cells.[5] PD-L1 is expressed on the surface of MDS cells resistant to hypomethylating agents, allowing for immune escape via T-cell evasion.[5] Hypomethylating agents also decrease the methylation of programmed cell death protein 1 (PD-1) promoters in $CD8^+$ T cells, increasing PD-1 expression.[6] Thus, combining PD-1 and CTLA4 blockade with hypomethylating agents may represent a successful treatment strategy for MDS.

Nivolumab and ipilimumab are fully human anti-PD-1 and anti-CTLA4 monoclonal antibodies, respectively. Whereas dual PD-1 and CTLA4 blockade is safe and effective in several tumor types,[7-9] the safety and efficacy of nivolumab and ipilimumab when administered with a hypomethylating agent in patients with MDS remain undefined.

This study was a sequential cohort, open-label, phase II trial involving previously untreated MDS (NCT02530463). Eligible patients were at least 18 years of age with treatment-naïve MDS according to the revised fourth edition of the World Health Organization criteria, with an Eastern Cooperative Oncology Group (ECOG) score of $\leq$2, adequate organ function, and less than 20% peripheral or bone marrow blasts. Patients received azacitidine-ipilimumab, azacitidine-nivolumab, or azacitidine-ipilimumab-nivolumab. We selected a sequential cohort design instead of a three-arm randomized design to assess the safety of the doublet regimens before enrolling patients into the triplet cohort. The

MD Anderson Institutional Review Board approved this study. All patients provided written informed consent according to the Declaration of Helsinki.

Patients received azacitidine 75 mg/m^2 intravenously (IV) on days 1–5 with nivolumab 3 mg/kg IV on days 6 and 20 in cohort 1; azacitidine 75 mg/m^2 IV on days 1–5 with ipilimumab 3 mg/kg IV on day 6 in cohort 2; azacitidine 75 mg/m^2 IV on days 1–5 with nivolumab 3 mg/kg IV and ipilimumab 1 mg/kg IV, both on day 6, in cohort 3. Patients continued the regimens until disease progression or intolerability.

The primary efficacy outcome was overall response, defined as complete response (CR), CR with limited count recovery (CR_L), or hematological improvement according to the International Working Group 2023 criteria.[10] The study was monitored using the Bayesian design described by Thall and Sung.[11] Differences in mean values between groups were compared using the Mann-Whitney *U* test or Fisher's exact test. Overall survival was estimated using the Kaplan-Meier method and compared using the log-rank test. Hazard ratios were estimated using a Cox proportional hazards model. All reported *P* values were two-sided, with significance evaluated at the 0.05 alpha level. Statistical analyses were performed with GraphPad Prism 10.1.1 and R 4.4.1 for macOS. Data were stored in the ERIS MDS REDCap database designed for MD Anderson.[12,13]

We enrolled 66 patients from September 2015 to June 2021 in three cohorts: 33 (50%) patients in the azacitidine-ipilimumab cohort, 20 (30%) in the azacitidine-nivolumab cohort, and 13 (20%) in the azacitidine-ipilimumab-nivolumab cohort (Table 1). More patients had Revised International Prognostic Scoring System (IPSS-R) very poor-risk disease than any other risk category (47%; p = 0.042). *TP53* mutations occurred significantly more frequently than did any other mutation (46%; p = 0.003). The median Molecular International Prognostic Scoring System (IPSS-M) score was very high (1.59 [range, – 1.55 to 4.08]). Overall, this trial included fit, older patients with high-risk cytogenetic and molecular characteristics.

The overall response rates (ORRs) were 27% (95% CI, 14%–44%) for azacitidine-ipilimumab, 55% (95% CI, 34%–74%) for azacitidine-nivolumab, and 54% (95% CI, 29%–77%) for azacitidine-ipilimumab-nivolumab (Table 2). CR was more frequent in the azacitidine-nivolumab cohort than in the azacitidine-ipilimumab cohort (40% versus 7%; $p = 0.009$). Among patients with 5% baseline blasts, the triplet approach of azacitidine-ipilimumab-nivolumab was associated with a better ORR compared to azacitidine-ipilimumab (55% versus 17%; $p = 0.048$).

We pooled the three cohorts and used a multiple logistic regression analysis to assess cytogenetic and molecular predictors of overall response in patients with ≥5% baseline blasts. Normal karyotypes were associated with an increased probability of response (odds ratio [OR], 9.39 [95% CI, 1.32–98.19]; $p = 0.036$), and *DNMT3A*^{mut} was associated with a reduced ORR (OR, 0.09 [95% CI, 0.004–0.638]; $p = 0.043$). In contrast, when we performed the response analysis in the overall cohort, irrespective of blast count, multiple logistic regression failed to identify significant cytogenetic or molecular predictors of overall response.

In a landmark analysis using the median time to SCT as the landmark, the median overall survival was 25.8 months for azacitidine-ipilimumab, 17.5 months for azacitidine-nivolumab, and 15.0 months for azacitidine-ipilimumab-nivolumab ($p = 0.224$) (Figure 1A). A Cox proportional hazards model using SCT as a time-varying covariate did not identify any significant differences in overall survival between treatment cohorts. The event-free survival was 12.1 months for azacitidine-ipilimumab, 13.7 months for azacitidine-nivolumab, and 11.9 months for azacitidine-ipilimumab-nivolumab ($p = 0.215$). In a landmark subgroup analysis, azacitidine-nivolumab was associated with better overall survival compared to azacitidine-ipilimumab for patients with IPSS-R intermediate-risk MDS (not reached versus 25.8 m.; $p = 0.049$) (Figure 1B). Overall survival curves stratified by IPSS-R and IPSS-M risk are presented in Supplementary Figures 2C and 2D.

We noticed a disparity in post-transplant outcomes among treatment cohorts. Following SCT, the overall survival was 49.6 months with azacitidine-ipilimumab and not reached with azacitidine-nivolumab with a median follow-up time of 88 months. In contrast, the overall survival of patients in the triplet cohort who underwent SCT was significantly shorter at 13.7 months (doublet versus triplet cohorts; $p = 0.008$) (Figure 1D).

Next, we pooled the cohorts and used a multivariate Cox proportional hazards model with SCT as a time-dependent covariate to assess the impact of baseline characteristics in addition to cytogenetic and molecular features on overall survival. Patients with monosomy 5 or loss of 5q had superior overall survival (hazard ratio, 0.24 [95% CI, 0.07–0.83]; $p = 0.024$). Conversely, patients with *TP53*^{mut} MDS had inferior overall survival (hazard ratio, 19.46 [95% CI, 2.50–151.53]; $p = 0.005$) (Supplementary Figure 1).

Azacitidine-ipilimumab-nivolumab had greater hematological toxicity than did azacitidine-ipilimumab, including significantly higher rates of leukopenia (100% versus 58%; $p = 0.004$) and neutropenia (100% versus 70%; $p = 0.022$) (Supplementary Table 1). The rates of grade 3 rash and pneumonitis were higher in the triplet cohort than in the combined doublet cohorts (23% versus 2%; $p = 0.021$ and 15% versus 4%; $p = 0.171$, respectively). These findings translated to more days hospitalized in the triplet cohort (27 d.) compared to patients in the azacitidine-ipilimumab (8 d.) or azacitidine-nivolumab (3 d.) cohorts ($p = 0.002$).

Overall, 29 (44%) patients had at least one immunotherapy-related adverse event (irAE). We saw no association between irAE incidence and the achievement of a response. Similarly, we observed no differences in overall survival between patients who did and did not experience an irAE (23.0 m. versus 16.2 m.; $p = 0.924$). However, we found that grade ≥2 pneumonitis was associated with worse overall survival (7.4 m. versus 22.7 m.; $p = 0.025$) (Figure 1F). Furthermore, we discovered that patients with pneumonitis of any grade were more likely to have *TP53*^{mut} MDS than patients without pneumonitis (86% vs 43%; $p = 0.047$).

Herein, we present data on the safety and efficacy of azacitidine-ipilimumab, azacitidine-nivolumab, and azacitidine-ipilimumab-nivolumab for patients with treatment-naïve MDS. We noted no differences in overall survival or event-free survival among the three treatment cohorts. However, in patients with IPSS- R intermediate-risk MDS, azacitidine-nivolumab produced better overall survival than did azacitidine- ipilimumab. Despite limited sample sizes, these findings imply that overall survival benefits differ among discrete IPSS-R risk categories for patients undergoing immunotherapy-based approaches.

Post-transplant survival was significantly worse for the triplet cohort than for the doublet cohorts. However, our sample sizes are limited, and our results should be interpreted cautiously. Yet, our data suggest that azacitidine-ipilimumab-nivolumab is associated with a higher risk of post-transplant mortality than the doublet regimens. While post-transplant immune complications may play a role in our observations of inferior survival for the triplet approach, more research is needed to determine the safety of immunotherapy-based combinations preceding SCT.

The doublet combinations appeared to be well tolerated, with irAE incidence rates similar to those reported in a large meta-analysis of 7936 patients treated with nivolumab or ipilimumab-nivolumab.[14] However, we emphasize the significantly increased toxicity associated with the triplet approach. Furthermore, in the overall study population, we discovered that patients with pneumonitis were enriched in mutated *TP53*, and that the incidence of pneumonitis was associated with shortened overall survival. Therefore, these findings raise awareness of the risk of irAEs, which may be increased in patients with $TP53^{mut}$ MDS.

In summary, azacitidine-nivolumab produced higher rates of CR and a nonsignificantly higher ORR in the overall study population than did the other two combinations. Azacitidine-nivolumab was also associated with a greater survival benefit for IPSS-R intermediate-risk MDS than azacitidine-ipilimumab. High-grade toxicities and hospitalization rates were considerably worse in the triplet

cohort than in the doublet cohorts, and the triplet regimen appeared to be associated with increased post-transplant mortality. Therefore, azacitidine in combination with PD-1 or CTLA4 blockade had modest activity in MDS; the triplet approach failed to improve overall survival and was associated with increased toxicity.

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Characteristic, n (%)	Azacitidine-ipilimumab (N = 33)	Azacitidine-nivolumab (N = 20)	Azacitidine-ipilimumab-nivolumab (N = 13)
Female	13 (39.4)	4 (20.0)	11 (84.6)
Median age at diagnosis, y. (range)	71 (45 – 86)	65 (39 – 83)	66 (46 – 72)
Median Charlson comorbidity index score (range)	4 (0 – 10)	4 (0 – 6)	4 (0 – 7)
Median ECOG at diagnosis (range)	1 (0 – 2)	1 (0 – 2)	1 (0 – 1)
Diagnostic entity			
MDS	28 (84.8)	13 (65.0)	13 (100)
MDS/MPN	0	2 (10.0)	0
CMML	5 (15.2)	5 (25.0)	0
Median hematological parameters at diagnosis (range)			
Blasts (%)	6 (1 – 18)	9 (1 – 18)	11 (1 – 19)
WBC (10^3/µL)	3.7 (0.6 – 46.1)	4.9 (1.1 – 25.1)	2.2 (1.1 – 7)
ANC (10^3/µL)	1.7 (0.1 – 24.0)	1.8 (0 – 16.8)	0.8 (0.2 – 3.2)
Hemoglobin (g/dL)	9.4 (5.2 – 16.1)	9.7 (5.0 – 15.2)	9.0 (6.1 – 13.3)
Platelets (10^3/µL)	92 (7 – 647)	53 (7 – 244)	81 (18 – 209)
Median number of cycles (range)	4 (0 – 12)	6 (2 – 76)	3 (1 – 7)
Procession to allogeneic SCT	9 (27.3)	4 (20.0)	4 (30.8)
IPSS-R cytogenetic risk group			
Good	7 (21.2)	7 (35.0)	2 (15.4)
Intermediate	7 (21.2)	2 (10.0)	1 (7.7)
Poor	7 (21.2)	0	2 (15.4)
Very poor	12 (36.4)	11 (55.0)	8 (61.5)
Median IPSS-R risk classification	High	Very high	Very high
Median IPSS-R score (range)	5.5 (2 – 9.5)	7 (1 – 9.5)	7 (4 – 10)
IPSS-M risk group[A]			
Very low	1 (8.3)	0	0
Low	4 (12.1)	2 (10.0)	0
Moderate low	1 (8.3)	1 (10.0)	0
Moderate high	3 (9.1)	2 (10.0)	2 (15.4)
High	7 (21.2)	4 (20.0)	3 (23.1)
Very high	16 (48.5)	11 (55.0)	7 (53.8)
Median IPSS-M score (range)	1.54 (-1.55 – 4.08)	1.57 (-1.34 – 3.60)	1.66 (0.25 – 3.38)
Molecular aberrations			
TP53	14 (42.4)	8 (40.0)	8 (61.5)
ASXL1	7 (21.9)	4 (20.0)	0
RUNX1	5 (15.6)	5 (25.0)	2 (15.4)
DNMT3A	4 (12.5)	4 (20.0)	4 (30.8)
TET2	4 (12.5)	7 (35.0)	2 (15.4)

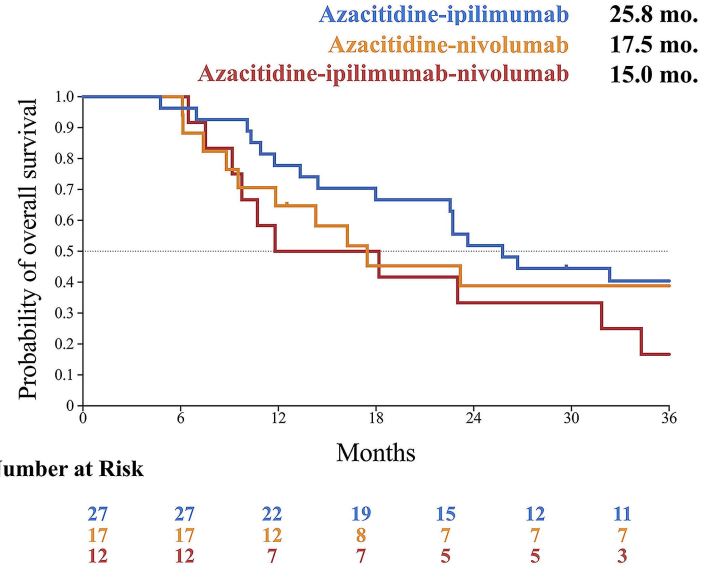
Table 1. Baseline characteristics of patients treated with azacitidine-ipilimumab, azacitidine-nivolumab, or azacitidine-ipilimumab-nivolumab.
A: IPSS-M risk group cohorts were based on availability of next-generation sequencing data at diagnosis.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; CMML, chronic myelomonocytic leukemia; WBC, white blood count; ANC, absolute neutrophil count.

Response category, n (%)	Azacitidine-ipilimumab (N = 30)[A]	Azacitidine-nivolumab (N = 20)	Azacitidine-ipilimumab-nivolumab (N = 13)
Complete remission	2 (6.7)	8 (40.0)	3 (23.1)
Complete remission with limited count recovery	2 (6.7)	0	3 (23.1)
Hematologic improvement	4 (13.3)	3 (15.0)	1 (7.7)
Marrow complete remission	9 (30.0)	4 (20.0)	3 (23.1)
No response	13 (43.3)	5 (25.0)	3 (23.1)
Overall response rate[B]	8 (26.7)	11 (55.0)	7 (53.8)
Subgroup Response Categories			
IWG 2023 ORR, blasts ≥5%	3/18 (16.7)	6/15 (40.0)	6/11 (54.5)
IWG 2023 ORR by IPSS-M risk			
Very low or low	3/5 (60.0)	2/2 (100.0)	—
Moderate low or moderate high	2/4 (50.0)	2/3 (66.7)	1/2 (50.0)
High or very high	3/20 (15.0)	6/15 (40.0)	5/10 (50.0)
IWG 2023 ORR, *TP53*^{mut}	3/13 (23.1)	5/8 (62.5)	2/8 (25.0)

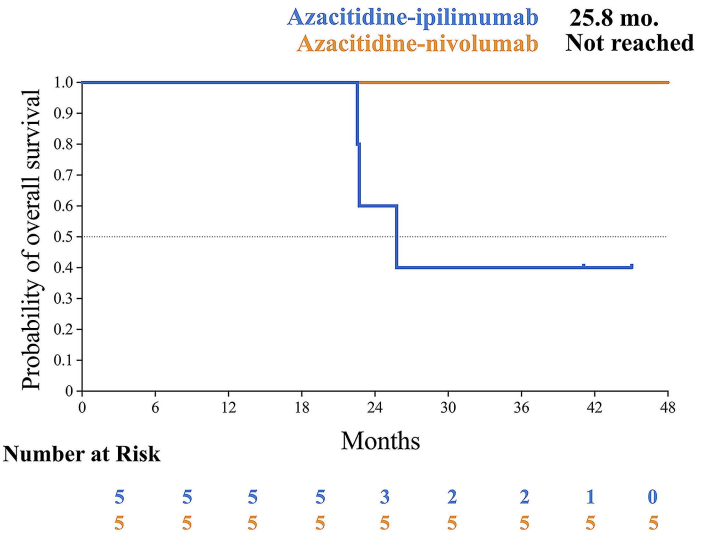
Table 2. IWG 2023 response rates of patients treated with azacitidine-ipilimumab, azacitidine-nivolumab, or azacitidine-ipilimumab-nivolumab.
A: Thirty of 33 patients were evaluable for response in the azacitidine-ipilimumab cohort.
B: The ORR was determined using the IWG 2023 criteria. The ORR was calculated as the sum of patients with CR, complete remission with limited count recovery, and hematological improvement.
Abbreviations: ORR, overall response rate; IWG 2023, International Working Group 2023 criteria; IPSS-M, Molecular International Prognostic Scoring System.

Figure 1. Time-to-event analyses of azacitidine-ipilimumab, azacitidine-nivolumab, or azacitidine-ipilimumab-nivolumab. (A) Landmark analysis of overall survival of azacitidine-ipilimumab, azacitidine-nivolumab, or azacitidine-ipilimumab-nivolumab (p = 0.224). (B) Landmark analysis of overall survival of patients with IPSS-R intermediate-risk disease treated with azacitidine-nivolumab versus azacitidine-ipilimumab (p = 0.049). (C) Landmark analysis of overall survival of patients who did and did not undergo SCT from first-line therapy, regardless of immunotherapy cohort (p = 0.200). (D) Overall survival of patients who underwent SCT after receiving doublet therapy versus triplet therapy (p = 0.008). (E) Progression to acute myeloid leukemia for all three cohorts. The probability of progression was significantly lower in the azacitidine-ipilimumab cohort (p = 0.011). (F) Overall survival of patients treated with azacitidine with immunotherapy who did and did not experience pneumonitis (p = 0.025).

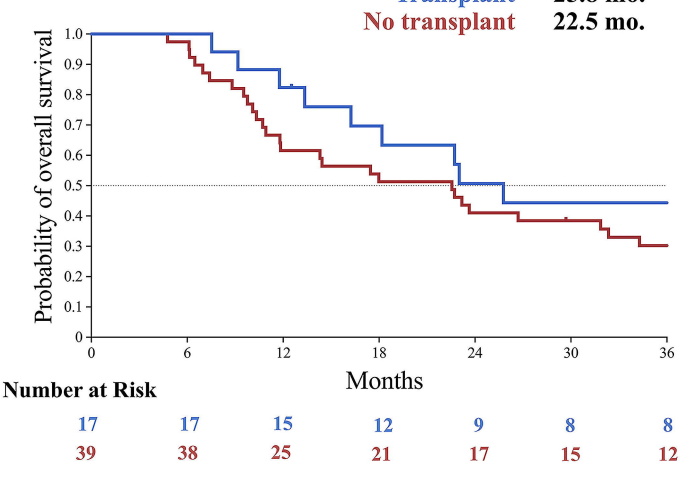
A. Overall Survival



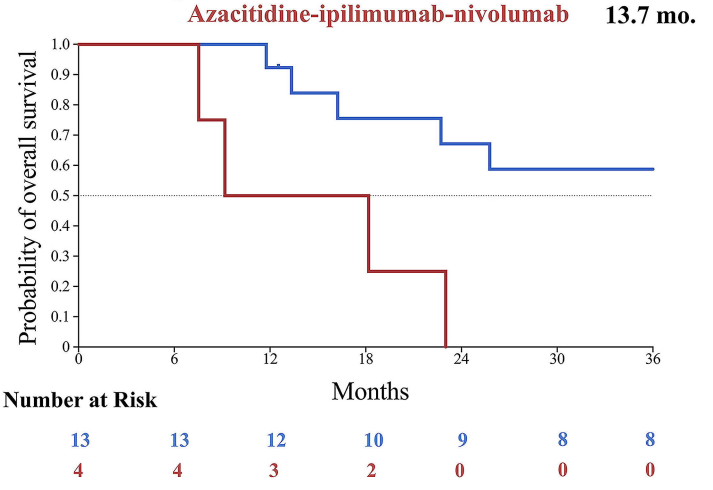
B. Overall Survival, IPSS-R Intermediate Risk



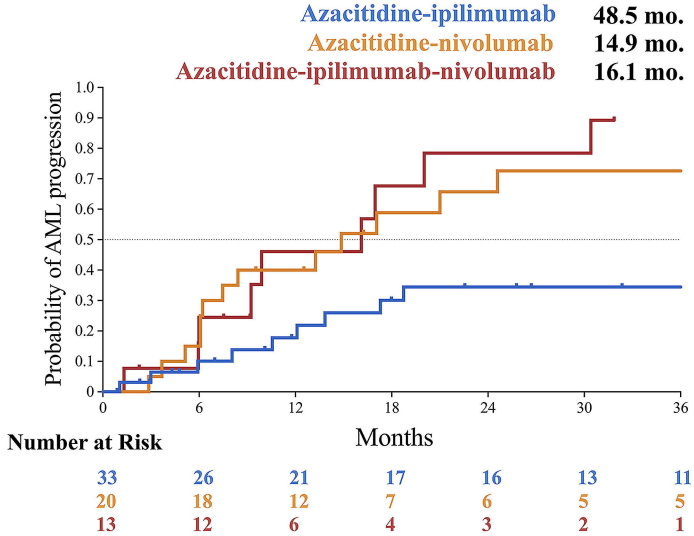
C. Overall Survival



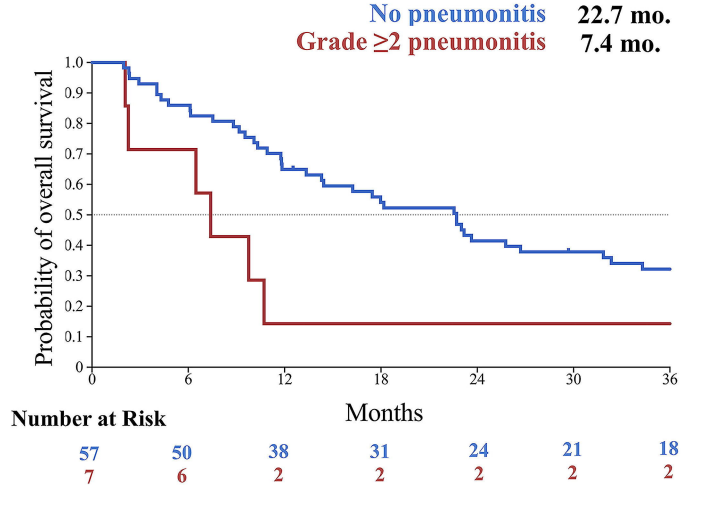
D. Overall Survival, Post-Transplant



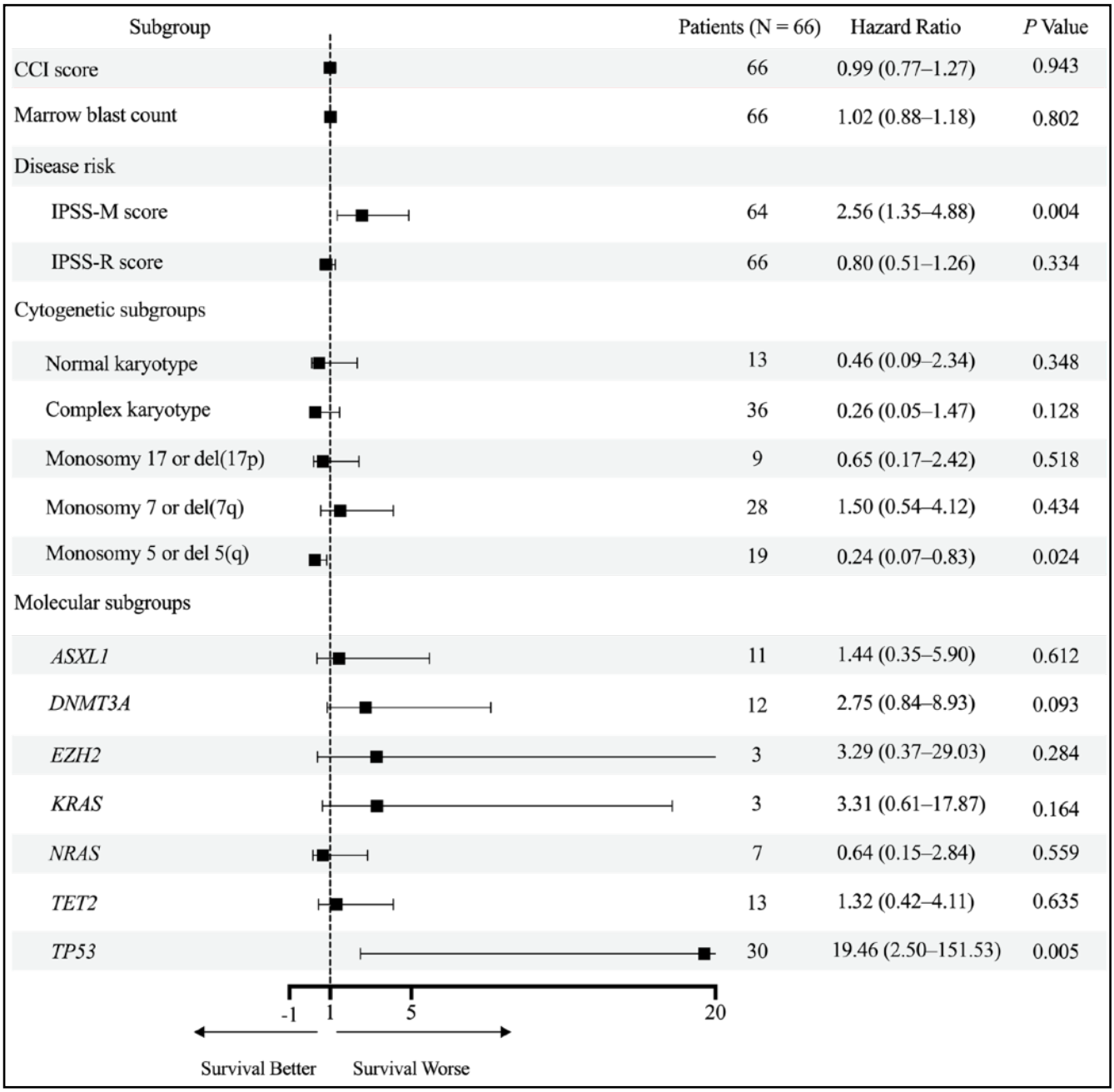
E. Time to AML Progression



F. Overall Survival



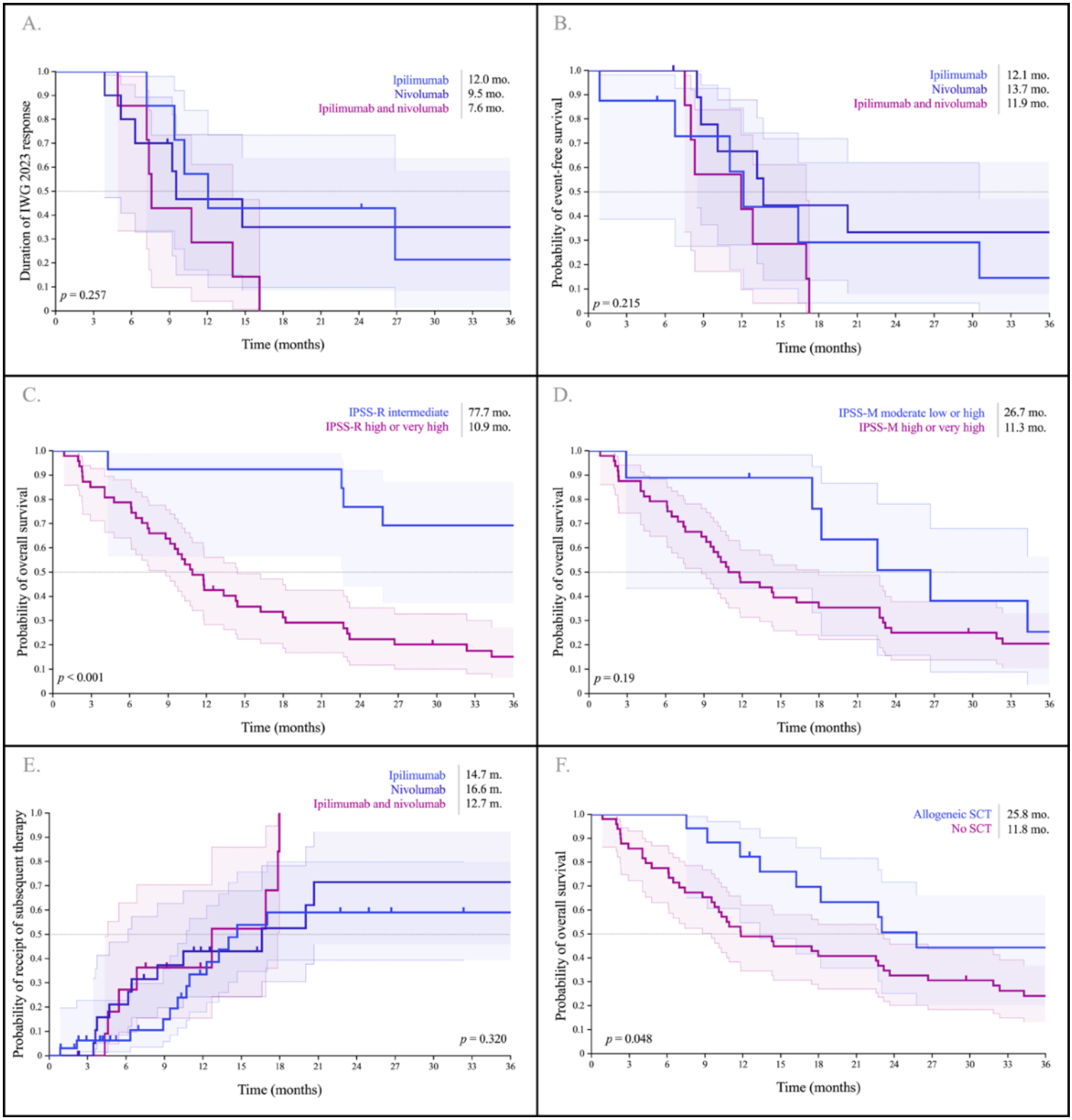
Supplementary Appendix



Supplementary Figure 1. Forest plot of predictors of overall survival with stem cell transplant as a time-dependent covariate for patients treated with azacitidine-ipilimumab, azacitidine-nivolumab, and azacitidine-ipilimumab-nivolumab. Sixty-four of 66 patients had next-generation sequencing performed prior to treatment.

	Azacitidine-ipilimumab (N = 33)	Azacitidine-nivolumab (N = 20)	Azacitidine-ipilimumab-nivolumab (N = 13)
Hematologic toxicities, grade ≥3 (%)			
Leukopenia	19 (57.6)	15 (75.0)	13 (100.0)
Neutropenia	23 (69.7)	17 (85.0)	13 (100.0)
Lymphocytopenia	14 (42.2)	8 (40.0)	11 (84.6)
Anemia	21 (63.6)	11 (55.0)	9 (69.2)
Thrombocytopenia	25 (75.8)	17 (85.0)	13 (100.0)
Non-hematologic toxicities, grade ≥3 (%)			
Neutropenic fever	6 (18.2)	4 (20.0)	6 (46.2)
Infection	7 (21.2)	9 (45.0)	6 (46.2)
Fatigue	0	0	0
Pneumonia	5 (15.2)	7 (35.0)	2 (15.4)
Pneumonitis	2 (6.1)	0	2 (15.4)
Respiratory failure or hypoxia	4 (12.1)	0	0
Hemorrhage	0	2 (10.0)	1 (7.7)
Abdominal pain	0	0	0
Vomiting	0	0	0
Diarrhea	0	0	0
Colitis	1 (3.0)	1 (5.0)	0
AST elevation	1 (3.0)	3 (15.0)	1 (7.7)
ALT elevation	2 (6.1)	3 (15.0)	2 (15.4)
Bilirubin elevation	0	1 (5.0)	0
Rash	1 (3.0)	0	3 (23.1)
Hyperthyroidism	0	0	0
Hypothyroidism	0	0	0
Creatinine increased	2 (6.1)	0	1 (7.7)
Death during induction (%)			
Death within 30 days	1 (3.0)	0	0
Death between 31 – 60 days	1 (3.0)	0	0

Supplementary Table 1. Grade ≥3 toxicities in patients treated with azacitidine-ipilimumab, azacitidine-nivolumab, and azacitidine-ipilimumab-nivolumab.
Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.



Supplementary Figure 2. Time-to-event analyses for patients treated with azacitidine-ipilimumab, azacitidine-nivolumab, and azacitidine-ipilimumab-nivolumab. **(A)** Duration of response among IWG 2023 responders for all three cohorts. **(B)** Probability of event-free survival in all three cohorts. **(C)** Overall survival stratified by IPSS-R intermediate-risk disease and high or very high-risk disease. All cohorts are pooled. **(D)** Overall survival stratified by IPSS-M moderate- or high-risk disease. All cohorts are pooled. **(E)** Median time to the next line of therapy for relapsed or refractory disease for all three cohorts. **(F)** Non-landmarked analysis of overall survival in patients that underwent SCT for all three cohorts.