# Efficacy and Safety of Venetoclax Plus Azacitidine for Patients With Treatment-Naive High-Risk Myelodysplastic Syndromes

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## Supplementary Methods

Core Clinical Response Criteria (CR, PR, mCR, SD, and PD) were defined based on modified International Working Group 2006 criteria plus additional requirements.

**Complete remission (CR):** all of the following requirements needed to be met at the time of assessment: bone marrow blasts ≤5%; hemoglobin ≥11 g/dL in one complete blood count (CBC) on the day of bone marrow aspirate or at least once within the following 3 weeks, unsupported by transfusion; platelets ≥100 × $10^9$/L in one CBC on the day of bone marrow aspirate or at least once within the following 3 weeks, unsupported by platelet transfusions; neutrophils ≥1 × $10^9$/L in one CBC on the day of bone marrow aspirate or at least once within the following 3 weeks, unsupported by G-CSF; no blasts in peripheral blood on the day of bone marrow aspirate, or in any subsequent CBCs leading up to and including the day all peripheral blood recovery criteria were met. Each of these peripheral blood criteria needed confirmation at least one additional time at 4 or more weeks after the CBC that first fulfilled these requirements. Bone marrow confirmation was not required for CR.

**Partial remission (PR)**: all of the following requirements needed to be met at the time of assessment: bone marrow blasts >5% and reduced to ≤50% of baseline value, peripheral blood requirements identical to CR, including confirmation after 4 weeks.

**Marrow complete remission (mCR):** all of the following requirements needed to be met: baseline bone marrow blast >5%, assessment bone marrow blasts ≤5% and reduced to ≤50% of baseline value, criteria from CR or PR not met.

**Progressive disease (PD):** two criteria needed to be satisfied.

For the first criterion, one at least one of the following needed to be met: 1) Bone marrow blasts >5% and higher than previous evaluation by at least 5%; 2) progression to AML (≥20% blasts); 3) appearance of previously absent leukemic blasts in peripheral blood; 4) absolute neutrophil count <1 × $10^9$/L and 50% below best unsupported on-study value; 5) platelet count <100 × $10^9$/L and 50% below best unsupported on-study value; 6) hemoglobin <11g/dL, and ≥2 g/dL reduction from best unsupported on-study value; 7) increase of the volume of transfused red blood cells by more than 30% in an 8-week period; 8) increase of the number of transfused platelet units by more than 30% in an 8-week period. In case of criteria 4-8, no reasonable alternative explanation such as drug toxicity should be identified.

The second criterion was the PD confirmation. One of the following needed to occur after the first criterion for PD was met: 1) no further disease assessments on peripheral blood and/or bone marrow could be performed for any reason; 2) additional disease assessments on peripheral blood and/or bone marrow performed ≥2 weeks after the first PD criterion was met to confirm PD; 3) subject continued onto a post-treatment anti-cancer therapy within three months of first PD criterion being met and there was an absence of improvement in original laboratory findings during this period.

**Stable disease (SD):** criteria for CR, mCR, or PR not met, and criteria for PD not met within the next 8 weeks after the evaluation day.

**Transfusion independence at baseline.** The baseline transfusion independence was defined as no transfusion 8 weeks prior to or on the date of the first dose of the study drug per modified IWG 2006 criteria. Transfusion dependence at baseline was defined as absence of transfusion independence at baseline. This study did not employ LTB/HTB definitions proposed in IWG 2018 HI criteria.

**Hematologic improvement (HI)**: Erythroid response (erythroid HI) was defined for patients who were either transfusion dependent during the past 8 weeks or who had pretreatment Hgb < 11 g/dL due to other known other reasons as: no transfusions of packed red blood cells (RBC) or whole blood during the past 8 weeks of treatment and hemoglobin increase by ≥1.5 g/dL compared to baseline; or reduction of RBC or whole blood transfusion units by ≥4 units over each 8 week period (only transfusions given for hemoglobin <9 g/dL were counted in RBC transfusion evaluation); or development of transfusion independence in patients who needed transfusions for hemoglobin <9 g/dL. Platelet response (platelet HI) was defined as: an absolute increase of ≥30 × $10^9$/L platelets (unsupported*); or for patients with pretreatment <20×$10^9$/L platelets, a doubling of pretreatment value increasing to >20 × $10^9$/L platelets (unsupported*); or development of platelet transfusion independence. Independence of platelet transfusions was defined as no platelet transfusion in a period of 8 weeks or more after evaluation date. Neutrophil response (neutrophil HI) was defined as at least a doubling (increase by ≥100%) of the pretreatment neutrophil count and an absolute increase of unsupported* neutrophils >0.5 × $10^9$/L. Erythroid, platelet, and neutrophil responses required confirmation at 8 weeks or later. (*In the context of peripheral blood hematology laboratory values, unsupported hemoglobin refers to the absence of RBC/whole blood transfusion within the past 21 days; unsupported platelets refers to the absence of platelet transfusion within the past 3 days; unsupported neutrophils refers to the absence of medication with G-CSF, or GM-CSF within the last 3 days, or pegylated GCSF within the last 7 days).

**Erythroid transfusion independence:** Patients that needed transfusions for hemoglobin of 9 g/dL or lower during the past 8 weeks predating the evaluation date, and did not need those transfusions for a period of 8 weeks or more after the evaluation date.

**Platelet transfusion independence:** Patients that required a platelet transfusion during the 8 weeks prior to the evaluation date, and did not require a platelet transfusion in a period of 8 weeks or more after the evaluation date.

**Somatic Mutations**: 37 genes included in the Archer™ VARIANTPlex™ Core Myeloid Panel were *ABL1, ANKRD26, ASXL1, BCOR, BRAF, CALR, CBL, CEBPA, CSF3R, DDX41, DNMT3A, ETNK1, ETV6, EZH2, FLT3, GATA1, GATA2, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NPM1, NRAS, PHF6, PTPN11, RUNX1, SETBP1*, *SF3B1, SRSF2, STAG2, TET2, TP53, U2AF1, WT1,* and *ZRSR2*.

**Supplementary Table 1. Guidelines for subsequent cycle delay and dose modification**

| Type of treatment adjustment | Conditions when indicated |
|---|---|
| **Subsequent treatment cycle** | |
| Subsequent cycle delay | Patients with ongoing adverse events grade ≥ 2 and clinically significant in the opinion of the physician. |
| Subsequent cycle restart | • Patients whose adverse event grade has reduced to ≤ 1 or to baseline or<br>• Physician determines that restarting is necessary for disease control |
| **Dose modification** | |
| Dose reduction | • After previous treatment interruption or delay of subsequent treatment cycle<br>• Patient who initiated treatment cycle with ANC ≥ 1.5 × $10^9$/L and platelets ≥ 75 × $10^9$/L and have a previous response of PR or better if<br>o subsequent ANC nadir < 500 × $10^6$/L (0.5 x $10^9$/L) or<br>o platelets nadir < 50 × $10^9$/L, if baseline was > 100 × $10^9$/L or<br>o platelets < 50% if baseline was ≤ 100 × $10^9$/L |
| Dose increase | Patients whose adverse event resulted in the prior dose reduction has not reoccurred at the same grade under the reduced dose, or were determined to be unrelated to the treatment drug |

**Supplementary Table 2. Dose modifications for hematologic toxicity**

| | Azacitidine | Venetoclax |
|---|---|---|
| Planned dose level | 75 mg/$m^2$ x 7 days | 400 mg x 14 days |
| 1st dose reduction | 50 mg/$m^2$ x 7 days | 400 mg x 14 days |
| 2nd dose reduction | 36 mg/$m^2$ x 7 days | 400 mg x 14 days |
| 3rd dose reduction | 36 mg/$m^2$ x 7 days | 400 mg x 7 days |

**Supplementary Table 3. Venetoclax dose modifications for co-administration with CYP3A inhibitors**

| Venetoclax initial target dose | Venetoclax dose if co-administered with a moderate CYP3A inhibitor | Venetoclax dose if co-administered with a strong CYP3A inhibitor |
|---|---|---|
| 100 mg | 50 mg | 10 mg |
| 200 mg | 100 mg | 20 mg |
| 300 mg | 150 mg | 30 mg |
| 400 mg | 200 mg | 50 mg |

**Supplementary Table 4. IPSS prognostic score at baseline**

| Characteristic | Venetoclax 400 mg (14 days/cycle) + azacitidine 75 mg/m$^2$ (7 days/cycle) N = 107 |
|---|---|
| IPSS prognostic score, n (%)* | |
| Intermediate 1 | 11 (10.4) |
| Intermediate 2 | 70 (66.0) |
| High | 25 (23.6) |
| Missing | 1 |

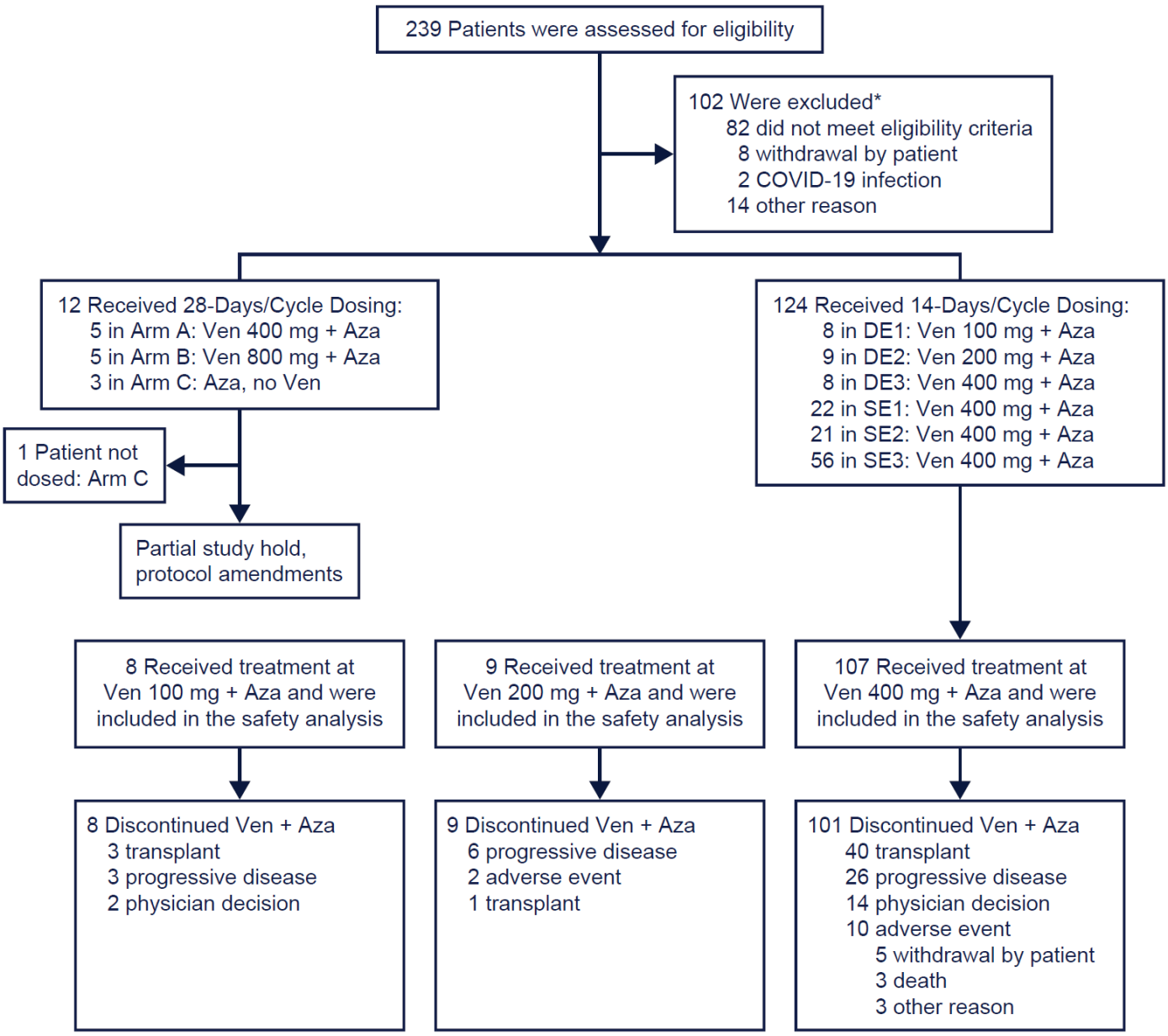
*IPSS prognostic score is based on % blasts, cytogenetics, and cytopenias.
IPSS, International Prognostic Scoring System.

**Supplementary Table 5. OS in patients who received SCT post-study by best response to venetoclax**

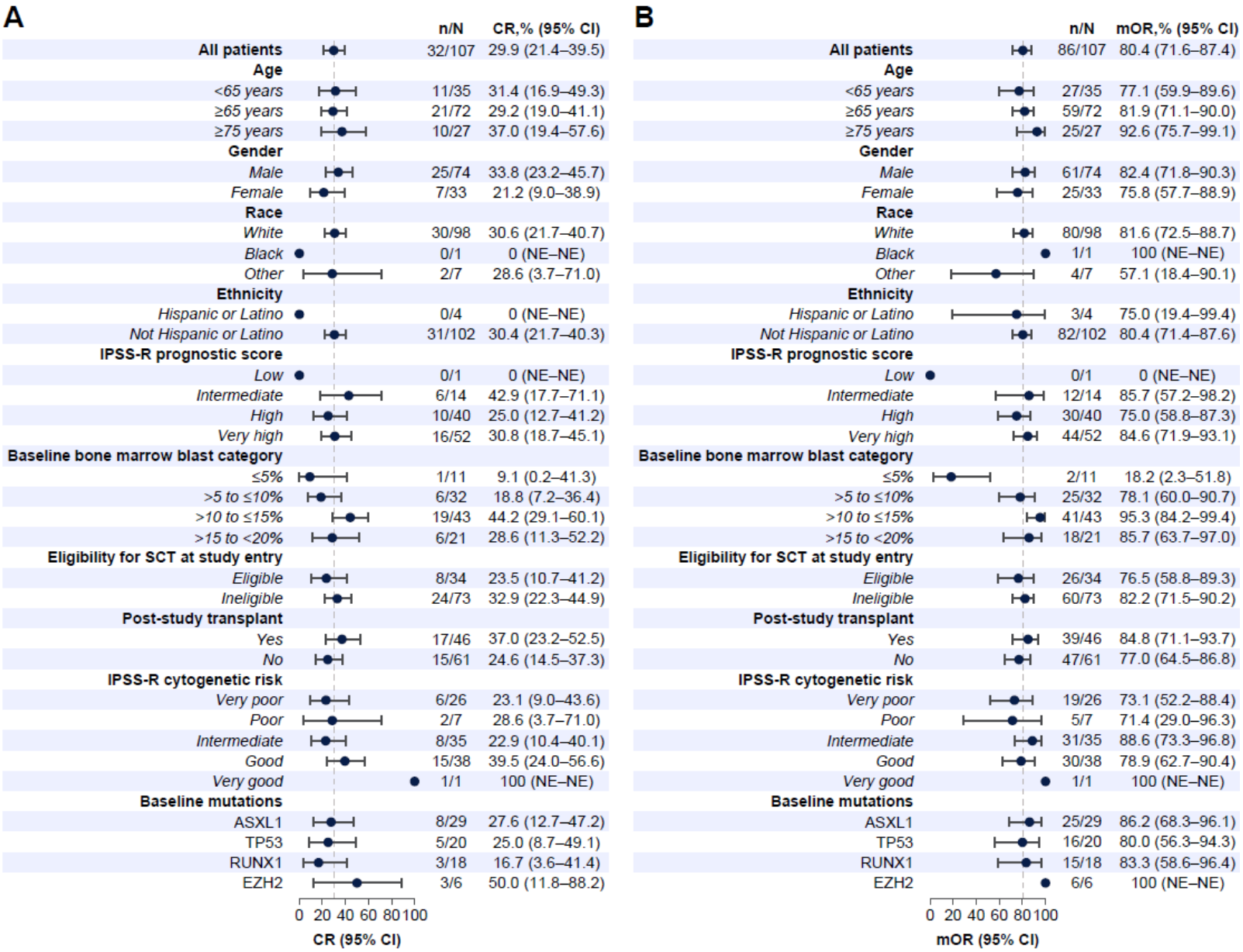
| | Achieved CR (n=17) | Achieved mCR (n=22) |
|---|---|---|
| Median OS (95% CI) | NR (18.1-NR) | NR (17.7-NR) |
| 12-Month Survival Estimate (95% CI) | 88.2% (60.6%-96.9%) | 81.8% (58.5%-92.8%) |
| 24-Month Survival Estimate (95% CI) | 70.6% (43.1%-86.6%) | 72.7% (49.1%-86.7%) |

CR, complete remission; mCR, marrow complete remission; NR, not reached; SCT, stem cell transplant; OS, overall survival.

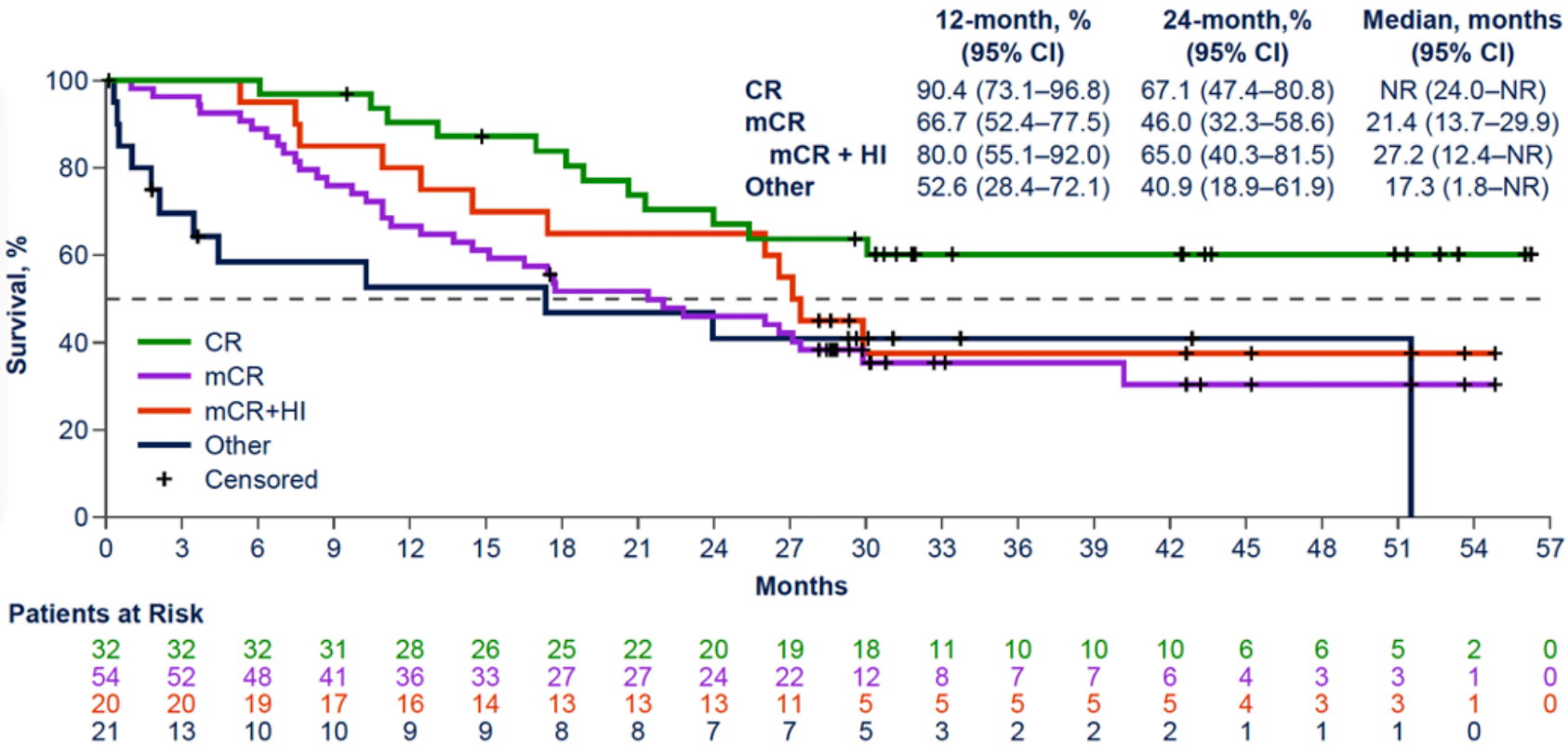
**Supplementary Figure 1. Diagram showing patient flow**. *Patients were counted under each reason; therefore, the sum is greater than the overall number of discontinuations. Aza, azacitidine; DE, dose escalation cohort; SE, safety expansion cohort; Ven, venetoclax.



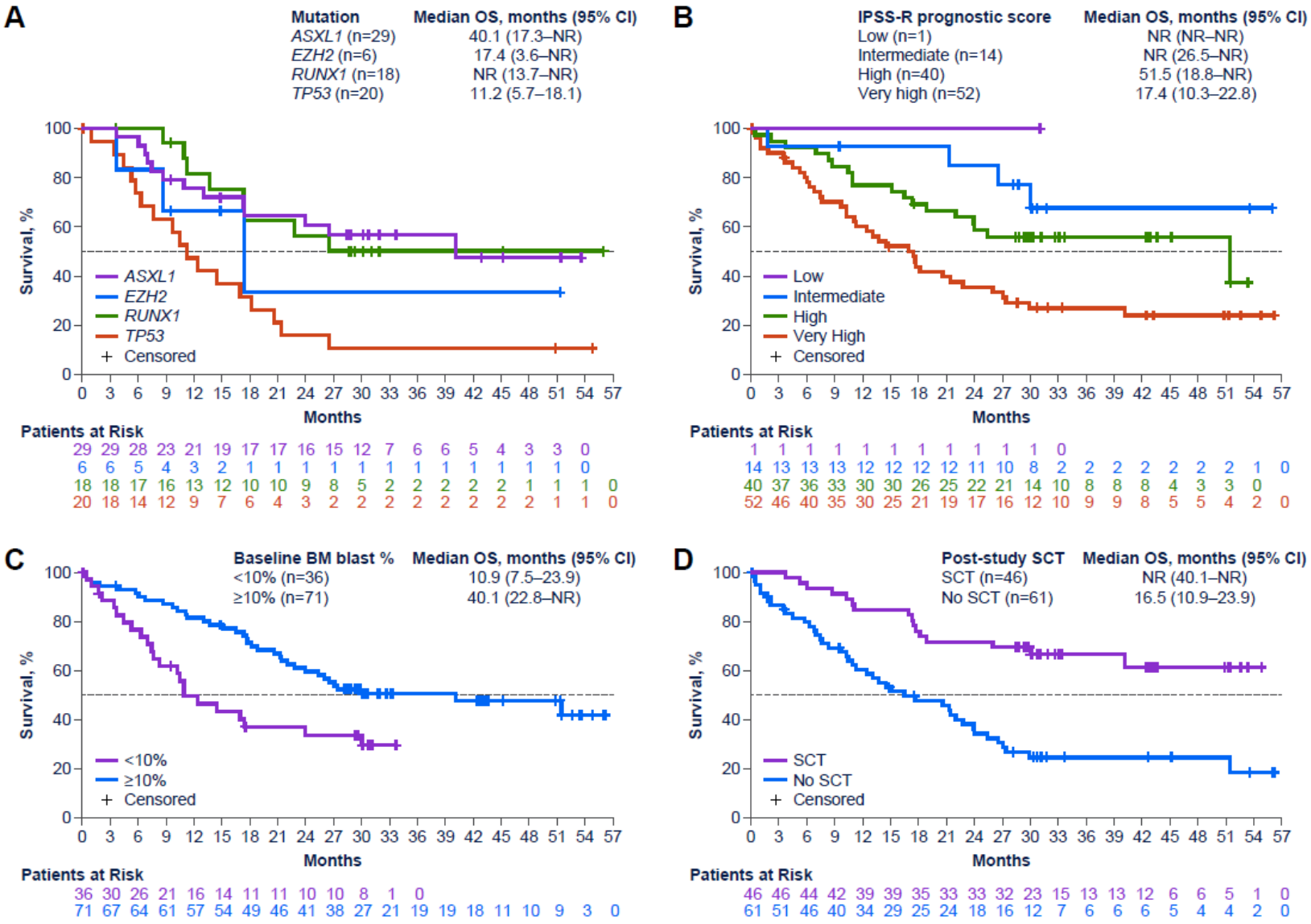
**Supplementary Figure 2. Rates of complete remission (A) and modified overall response (B) by subgroup with venetoclax 400 mg for 14 days + azacitidine**. CR, complete remission; IPSS-R, Revised International Prognostic Scoring System; mOR, modified overall response; NE, not estimable; SCT, stem cell transplant.



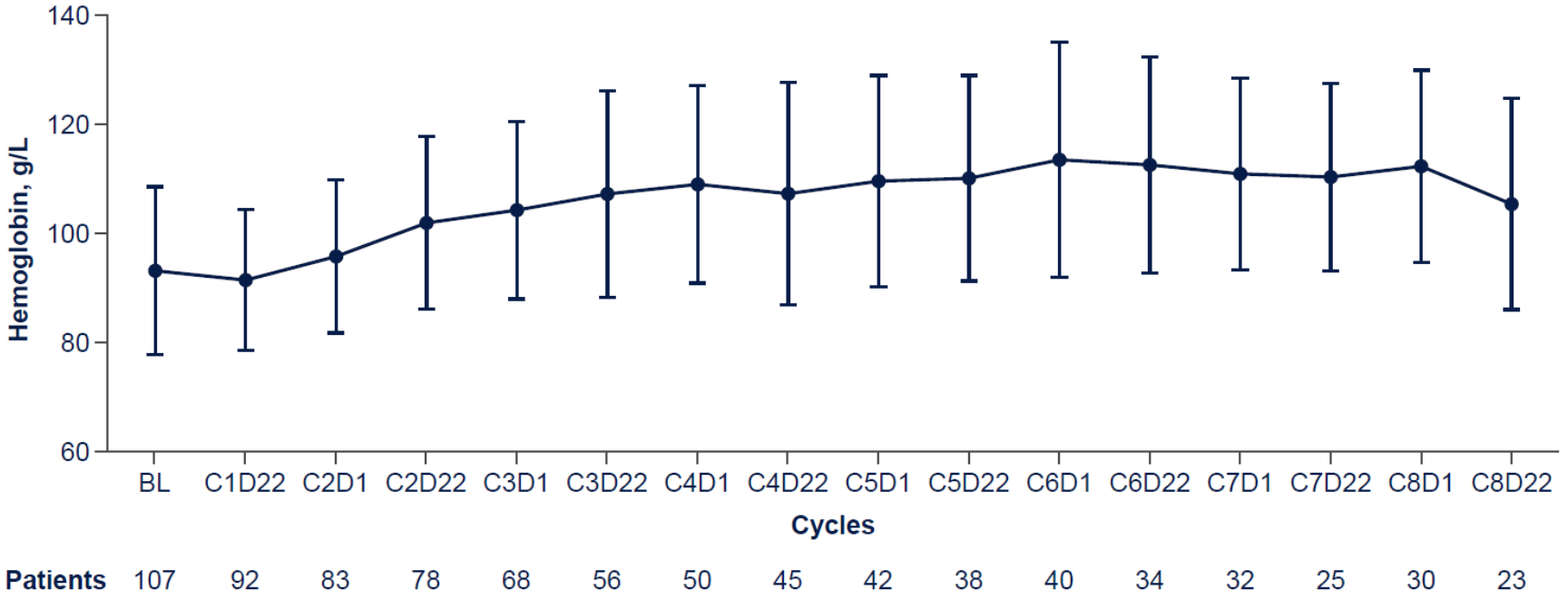
**Supplementary Figure 3. Overall survival by best response to treatment with venetoclax 400 mg for 14 days + azacitidine**.
CR, complete remission; HI, hematologic improvement; mCR, marrow complete remission; NR, not reached.



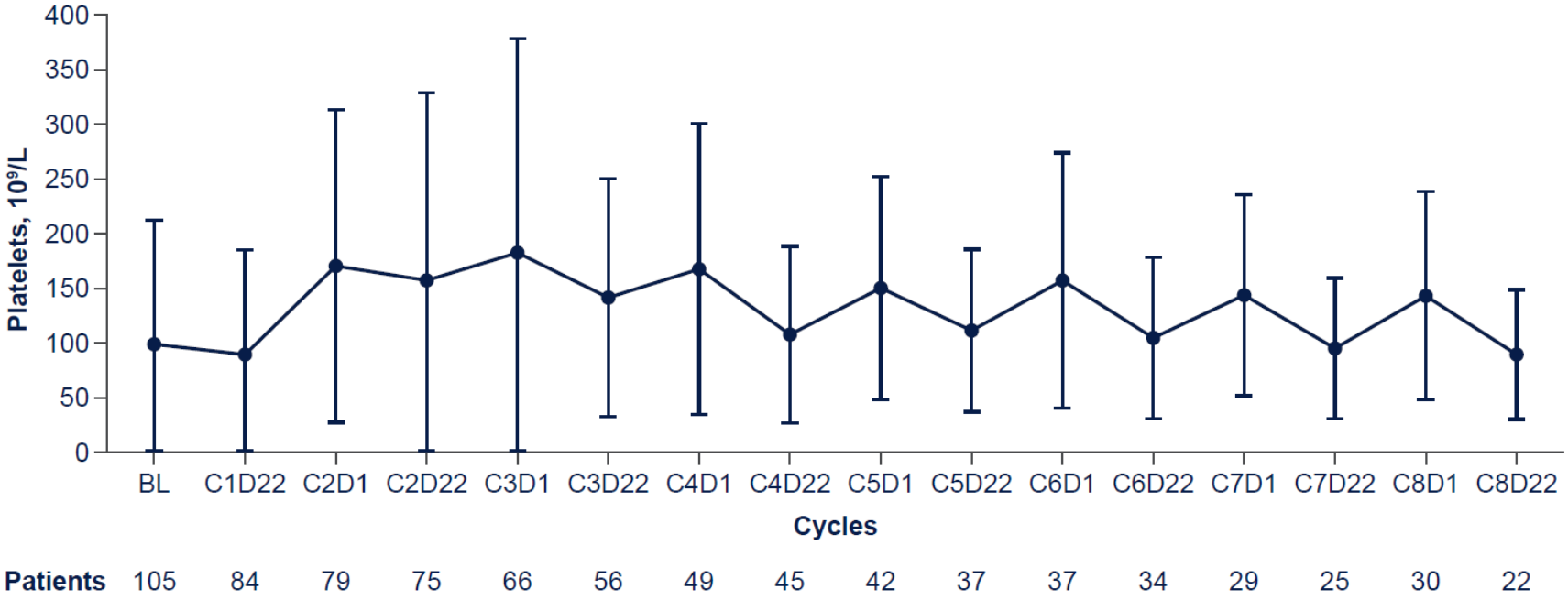
**Supplementary Figure 4. Overall survival by mutation subgroup (A), by IPSS-R score (B), by baseline bone marrow blast level (C), and by post-study SCT status (D) with venetoclax 400 mg for 14 days + azacitidine**. IPSS-R, Revised International Prognostic Scoring System; mOS, median overall survival; NR, not reached.



**Supplementary Figure 5. Mean (± standard deviation) hemoglobin over time in all patients treated with venetoclax 400 mg for 14 days + azacitidine 75mg/m$^2$**. Aza, azacitidine; BL, baseline; C, cycle, D, day.



**Supplementary Figure 6. Mean (± standard deviation) platelet count over time in all patients treated with venetoclax 400 mg for 14 days + azacitidine 75mg/m$^2$**. Aza, azacitidine; BL, baseline; C, cycle, D, day.



**Supplementary Figure 7. Mean (± standard deviation) neutrophils over time in all patients treated with venetoclax 400 mg for 14 days + azacitidine 75mg/m$^2$**. Aza, azacitidine; BL, baseline; C, cycle, D, day.