SUPPLEMENTAL APPENDIX

Mutant IDH1 Inhibitor Ivosidenib in Combination With Azacitidine for Newly Diagnosed Acute Myeloid Leukemia

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SUPPLEMENTAL METHODS

Dose-Finding Study Design

The ivosidenib dose-finding study utilized a standard 3 + 3 design, where a minimum of three eligible patients with an *IDH1* mutation were enrolled into cohort 1 to receive oral ivosidenib 500 mg once daily (QD) for 28 days plus azacitidine 75 mg/m^2/day subcutaneously on days 1-7 of each 28-day cycle.

Preliminary clinical data have shown ivosidenib to be well tolerated at total daily doses up to 1200 mg and the maximum tolerated dose was not reached. Based on a review of the available safety, pharmacokinetic/pharmacodynamic (PK/PD), and clinical activity data, 500 mg QD was selected as the starting dose for the phase Ib segment of this clinical trial. For ivosidenib, there was no dose escalation, but one dose de-escalation was allowed to Dose Level −1 (250 mg QD). The dose-review team reviewed the emerging safety data from the cohort to determine whether dose

de-escalation would occur. If none of the three patients experienced a dose-limiting toxicity (DLT), the recommended combination dose was confirmed by the dose-review team. An additional three patients were to be enrolled if one patient had a DLT. If two or more DLTs were declared in cohort 1, then cohort −1 was to be explored with ivosidenib at a dose of 250 mg QD and azacitidine 75 mg/m^2/day subcutaneously on days 1-7. If a cohort was expanded to six patients owing to a DLT, the recommended combination dose would be declared by the dose-review team at the dose level where no more than one of six patients experienced a DLT. Upon declaration of the recommended combination dose, an ivosidenib expansion cohort of 15 patients was to be enrolled for further evaluation.

The dose-review team reviewed all toxicities following the completion of cycle 1 to determine whether dose modification of azacitidine was warranted or additional cohorts were needed to further assess the safety of the combination.

DLTs were required to have commenced within 28 days of the first dose in a 28-day treatment cycle, to constitute a change from baseline irrespective of outcome, and be determined by the investigator to be related to treatment. DLTs for the recommended combination dose were evaluated during the first 28-day cycle for patients enrolled into the dose-escalation phase of the study. The DLT evaluation period began at the time the patient received one dose of the assigned treatment. DLTs were defined as all clinically significant nonhematologic toxicities of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 except for: any nonhematologic grade 3 laboratory abnormality that was asymptomatic and rapidly reversible (ie, returned to ≤ grade 1 within 4 days) and did not recur with continuation or resumption of treatment; grade 3 anorexia, diarrhea, nausea or vomiting lasting < 72 hours with optimal medical management; and grade 3 fatigue that resolved to

grade ≤ 2 within 4 days and did not recur at the same severity with continuation or resumption of treatment. Toxicity that was clearly and directly related to the primary disease or to another etiology was excluded from this definition. Because azacitidine has a well-characterized association with cytopenias and other hematologic toxicities, for the phase Ib portion, hematologic toxicities were not considered a DLT for ivosidenib and were mitigated through dose modification of azacitidine in subsequent cycles if required. The dose-review team were to review hematology laboratory data at the completion of each cohort to determine whether any events warranted a DLT designation.

Dose Modifications in the Expansion Cohort

Dosing interruptions, delays, and modifications were permitted to manage toxicities and/or augment treatment response during study treatment. Azacitidine and ivosidenib dosing could be interrupted concurrently, or either agent alone, depending on the attribution to an adverse event (AE) by the investigator.

For azacitidine, dose modifications followed common practice. Briefly, the first treatment cycle of azacitidine was given at 100% of the standard dose of 75 mg/m^2, regardless of a patient's laboratory values, provided that the patient was enrolled based on the inclusion and exclusion criteria. Patients were monitored for non-hematologic and hematologic toxicities. Any subject who experienced a non-hematologic AE of grade 3 or 4 that was an escalation from baseline status had azacitidine temporarily discontinued until the toxicity returned to less than grade 3. Azacitidine was permanently discontinued if the non-hematological toxicity persisted as grade 3 or 4 for more than 21 days despite the temporary interruption. Treatment with azacitidine is associated with anemia, neutropenia, and thrombocytopenia, particularly during the first 2 cycles, therefore complete blood counts were performed

as specified in the protocol to monitor toxicity. If hematologic toxicity was observed, dose modifications were made as described in Appendix Fig A2 depending on whether or not the patient had reduced baseline blood counts. If the dose of azacitidine was modified during the study and benefit was demonstrated at the reduced dose, that dose was maintained during subsequent cycles.

If toxicity was observed after initiation of ivosidenib at 500 mg QD and it was considered severe and possibly or probably related to treatment, dosing could be interrupted or delayed. Upon resolution of the toxicity, dosing could be resumed with a one-level dose reduction to 250 mg QD based on clinical judgment. Any patient unable to tolerate 250 mg QD of ivosidenib was to discontinue study treatment.

Patients experiencing QT prolongation while receiving ivosidenib were to be managed as follows:

- Levels of electrolytes (potassium, calcium, and magnesium) were checked and supplementation given to correct any values outside the normal range.
- Concomitant therapies were reviewed and adjusted as appropriate for medication with known QT prolonging effects.
- If no other cause was identified and the investigator believed it appropriate, particularly if QTc remained elevated (after the above measures had been implemented, or as determined by the investigator), ivosidenib dosing could be interrupted, and an ECG performed approximately 1 week after QT prolongation was first observed, or more frequently as clinically indicated.
- When ivosidenib dosing was held, rechallenge could be considered if QT prolongation had recovered or improved and the investigator believed it safe to do so; a reduced dose may be required per guidelines in the study protocol. Rechallenge was not permitted for grade 4 QT prolongation events.

At the earliest manifestations of suspected IDH differentiation syndrome (DS) patients were treated as follows:

- Administered corticosteroids at a suggested dose of 10 mg dexamethasone IV every 12 hours until disappearance of symptoms and signs, and for a minimum of 3 days.
- Administered hydroxyurea to control leukocytosis, if concurrent.
- Initiated furosemide, if clinically indicated.
- Initiated leukapheresis, if required.
- Temporarily held ivosidenib if clinical features could not be medically managed with the above measures.
- Once the signs and symptoms resolved, ivosidenib was reinitiated if study treatment was held.
- The dose of ivosidenib at reinitiation could be the same or reduced based on Investigator's judgement.

Patients experiencing leukocytosis were managed as follows:

- Temporary hold of study treatment only if symptoms could not be medically managed with the following:
    - Prompt initiation of hydroxyurea at up to a dose of 2000 or 3000 mg orally twice daily.
    - Prompt initiation of leukapheresis, if required.
- Treatment with hydroxyurea was allowed during treatment with ivosidenib/azacitidine for control of peripheral leukemic blasts in subjects with leukocytosis (white blood cells >30,000/µL).
- Once the symptoms resolved and the patient's clinical condition improved, ivosidenib was reinitiated if study treatment was held.

- The dose of ivosidenib at re-initiation could be the same or reduced based on Investigator's judgement.

Safety Assessments

Safety assessments included treatment-emergent AEs, serious AEs (SAEs), physical examination, Eastern Cooperative Oncology Group performance status, vital signs, electrocardiogram, hematology, and transfusions. Treatment-emergent AEs were defined as AEs between the time of first dose and 28 days after the last study treatment. Severity of AEs was graded using the CTCAE version 4.03. SAEs included those that resulted in death, were life threatening, led to hospitalization or prolongation of hospitalization, caused persistent or significant incapacity, or were considered to be an important medical event.

Pharmacokinetic and Pharmacodynamic Assessments

In the phase Ib expansion phase, peripheral blood was taken for PK assessments before dosing and at 0.5, 2, 3, 4, 6, and 8 hours after dosing on day 1 of cycles 1 and 2; an additional predose sample was taken on day 15 of cycle 1. The plasma PK profile of ivosidenib when administered with azacitidine was evaluated using a validated high-performance liquid chromatography/tandem mass spectrometric method.[1,2] PK analyses were performed using Phoenix WinNonlin version 8.1 (Pharsight, Inc., USA) using a noncompartmental approach.

Peripheral blood samples for analysis of D-2-hydroxyglutarate (2-HG) were collected at screening, on days 1 and 15 of cycles 1 and 2, and on day 1 from cycle 3 onwards. Plasma 2-HG concentrations were measured using a qualified liquid chromatography with tandem mass spectrometry method.[3]

Assessment of Clinical Activity

Endpoints included overall response rate (ORR), which included complete remission (CR), CR with incomplete hematologic or platelet recovery (CRi/CRp), morphologic leukemia-free state (MLFS), and partial remission (PR), and rates of CR, CR with partial hematologic recovery (CRh), and CR+CRh.

Time to CR and CR/CRh was defined as the time from the date of first dose to the date of first occurrence of CR or CR/CRh. Time to response was defined as the time from the date of first dose to the date of first occurrence of response, which includes CR, CRi, CRp, PR, and MLFS.

Duration of CR and CR+CRh was defined as time from the first documented CR or CR/CRh response to the first documented morphologic relapse according to modified International Working Group acute myeloid leukemia response criteria, or death due to any cause, whichever occurred first. Duration of response was defined as the time from the first documented CR, CRi/CRp, MLFS, or PR to the first documented morphologic relapse, progression, or death due to any cause, whichever occurred first.

Exploratory Analyses

Bone marrow mononuclear cells and peripheral blood mononuclear cells were processed centrally. Baseline comutations were assessed by next-generation sequencing (NGS) using the ACE Extended Cancer Panel (Personalis; Menlo Park, CA, USA), with 500X average target coverage for the full coding region of 1,400 genes (detection limit 2%). m*IDH1* variant allele frequency (VAF) was quantified through BEAMing digital PCR (dPCR) technology (OncoBEAM™; Sysmex Inostics, Baltimore, MD, USA) for assessment of R132 (C/G/L/S/H) alleles. This technique has a lower limit of detection for m*IDH1* alleles of 0.02-0.04% ($2\text{-}4 \times 10^{-4}$).[4] The

genomic DNA isolated from the bone marrow mononuclear cell and peripheral blood mononuclear cell samples met the minimum input material threshold (per assay specification) in order to obtain valid quantification of the fraction of mutant alleles to wild type alleles within each sample. If the minimum threshold of DNA is satisfied, the sensitivity of the BEAMing digital PCR assay allows for accurate detection of *IDH1* allelic frequencies from patient samples regardless of cellularity, including those deemed to be aplastic by the clinical investigator. *IDH1* mutation clearance was defined as m*IDH1* VAF reduction to below the limit of detection (0.02%-0.04%) for at least one on-study time point. These exploratory analyses were not pre-specified in the protocol.

Sample Size

The primary objectives of this small phase 1 study were to assess the safety and tolerability, and establish the recommended combination dose, of the ivosidenib and azacitidine combination. Per protocol, the dose-finding stage was to enroll approximately 24 patients across both the ivosidenib and enasidenib arms, and 15 patients were to be enrolled in the ivosidenib dose expansion phase to ensure acceptable toxicity at the recommended combination dose.

Based on a sample size of 18 patients treated at the recommended combination dose (ie, 15 subjects in dose expansion and ~3 subjects in dose escalation), there would be 95% probability of detecting one or more AEs with an underlying rate of 15%, and 85% probability of detecting 1 or more AEs with an underlying rate of 10%.

SUPPLEMENTAL RESULTS

Pharmacokinetic and Pharmacodynamic Findings

When administered in combination with azacitidine, ivosidenib 500 mg QD was rapidly absorbed, with median times to maximum plasma concentration of 3.0 hours and 2.5 hours following single and multiple doses, respectively. Ivosidenib exposure at steady state was higher than after a single dose. Mean accumulation ratios were 1.29 and 1.12 based on area under the curve and maximum plasma concentration, respectively, following 28 days of daily dosing.

Plasma 2-HG concentrations were substantially elevated at baseline in all patients except one. After one cycle of ivosidenib plus azacitidine, plasma 2-HG decreased from baseline to levels observed in healthy volunteers.[5] Baseline and steady-state 2-HG levels were comparable for patients who achieved a best overall response of CR or CRh and those with non-CR/CRh as best overall response (Appendix Fig A3).

REFERENCES

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2. Covance Inc.: Cross validation of a method for the determination of AG-120 in human plasma by HPLC with MS/MS detection, Covance 8378471, 2019
3. Covance Bioanalytical Service LLC: Qualification of a method for the determination of 2-hydroxyglutarate in human plasma by HPLC with MS/MS detection, 8373-474, 2019
4. Dressman D, Yan H, Traverso G, et al: Transforming single DNA molecules into fluorescent magnetic particles for detection and enumeration of genetic variations. Proc Natl Acad Sci U S A 100:8817-8822, 2003
5. Fan B, Mellinghoff IK, Wen PY, et al: Clinical pharmacokinetics and pharmacodynamics of ivosidenib, an oral, targeted inhibitor of mutant IDH1, in patients with advanced solid tumors. Invest New Drugs 38:433-444, 2020

FIG A1. Study design for the phase Ib dose-finding and expansion ivosidenib + azacitidine arm (N = 23; enrollment complete). The dose-finding phase had a standard 3 + 3 design. AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; CRi/CRp, CR with incomplete hematologic or platelet recovery; HMA, hypomethylating agent; m*IDH1*, mutant isocitrate dehydrogenase 1; MLFS, morphologic leukemia-free state; ND, newly diagnosed; ORR, overall response rate; PR, partial remission; QD, once daily; VAF, variant allele frequency. (*) ORR comprises CR, CRi/CRp, MLFS, and PR, per investigator-reported responses according to the modified International Working Group 2003 criteria for AML (Cheson BD, Bennett JM, Kopecky KJ, et al: Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 21:4642-4649, 2003). (†) CRh was derived by the sponsor and defined as CR except absolute neutrophil count > 0.5 × 10^9/L (500/μL) and platelet count > 50 × 10^9/L (50,000/μL).

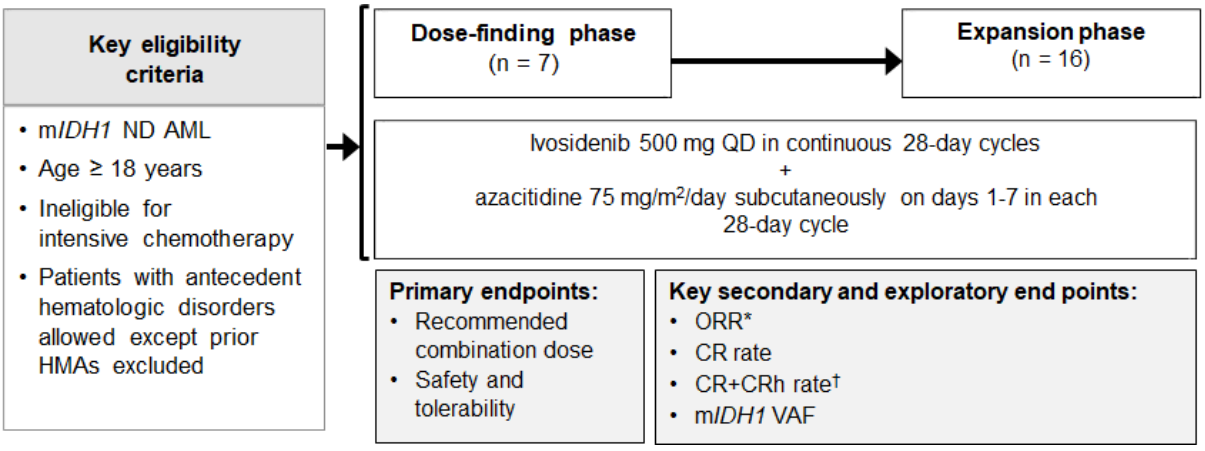
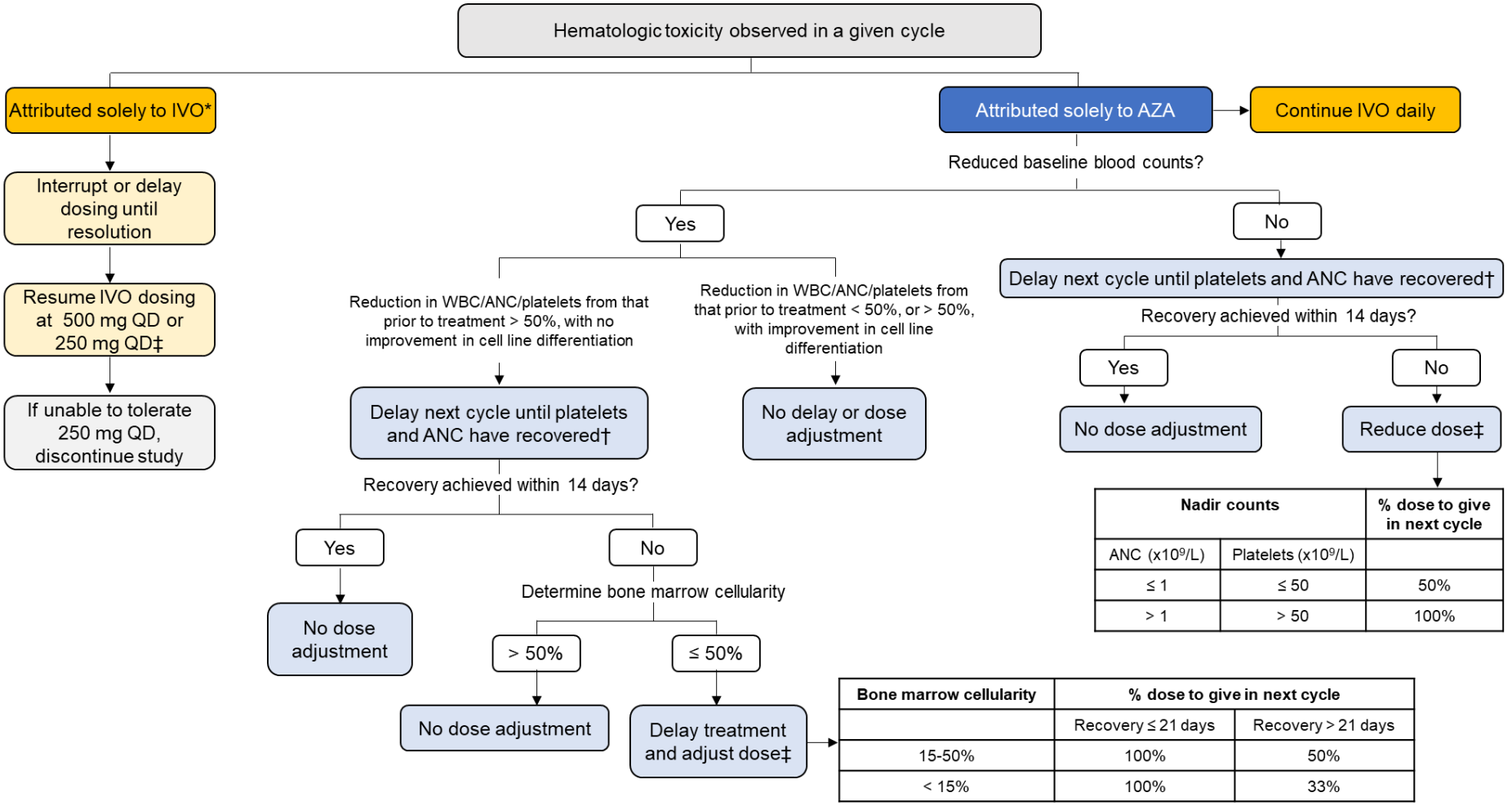


FIG A2. Ivosidenib and azacitidine dose modification guidelines for hematologic toxicity.* Initiation of a new cycle will start upon the ability to reinitiate the combination therapy and will begin upon the administration of the 7 days of subcutaneous azacitidine. If delay of > 28 days in start of next treatment cycle, medical monitor should be consulted for the risks and benefits of continuing ivosidenib or combination treatment. ANC, absolute neutrophil count; AZA, azacitidine; IVO, ivosidenib. (*) Ivosidenib dose modification guidelines shown are for any toxicity; no specific guidelines for managing hematologic toxicity with ivosidenib were included in the protocol because it is not considered to be a myelotoxic agent. (†) Recovery = counts ≥ nadir count + (0.5 x [baseline count – nadir count]). (‡) Reduced dose should be maintained during subsequent cycles unless toxicity develops.



Nadir counts		% dose to give in next cycle
ANC ($x10^9$/L)	Platelets ($x10^9$/L)	
≤ 1	≤ 50	50%
> 1	> 50	100%

Bone marrow cellularity	% dose to give in next cycle	
	Recovery ≤ 21 days	Recovery > 21 days
15-50%	100%	50%
< 15%	100%	33%

FIG A3. Ivosidenib dose modification guidance for AEs of special interest.

ECG, electrocardiogram; IVO, ivosidenib. (*) Reduced dose at discretion of the investigator; if benefit is observed at reduced dose level it should be maintained during subsequent cycles unless toxicity develops. (†) Dose cannot be re-escalated following dose reduction for Grade 3 QTcF prolongation unless the prolongation was associated with an electrolyte abnormality or concomitant medication.

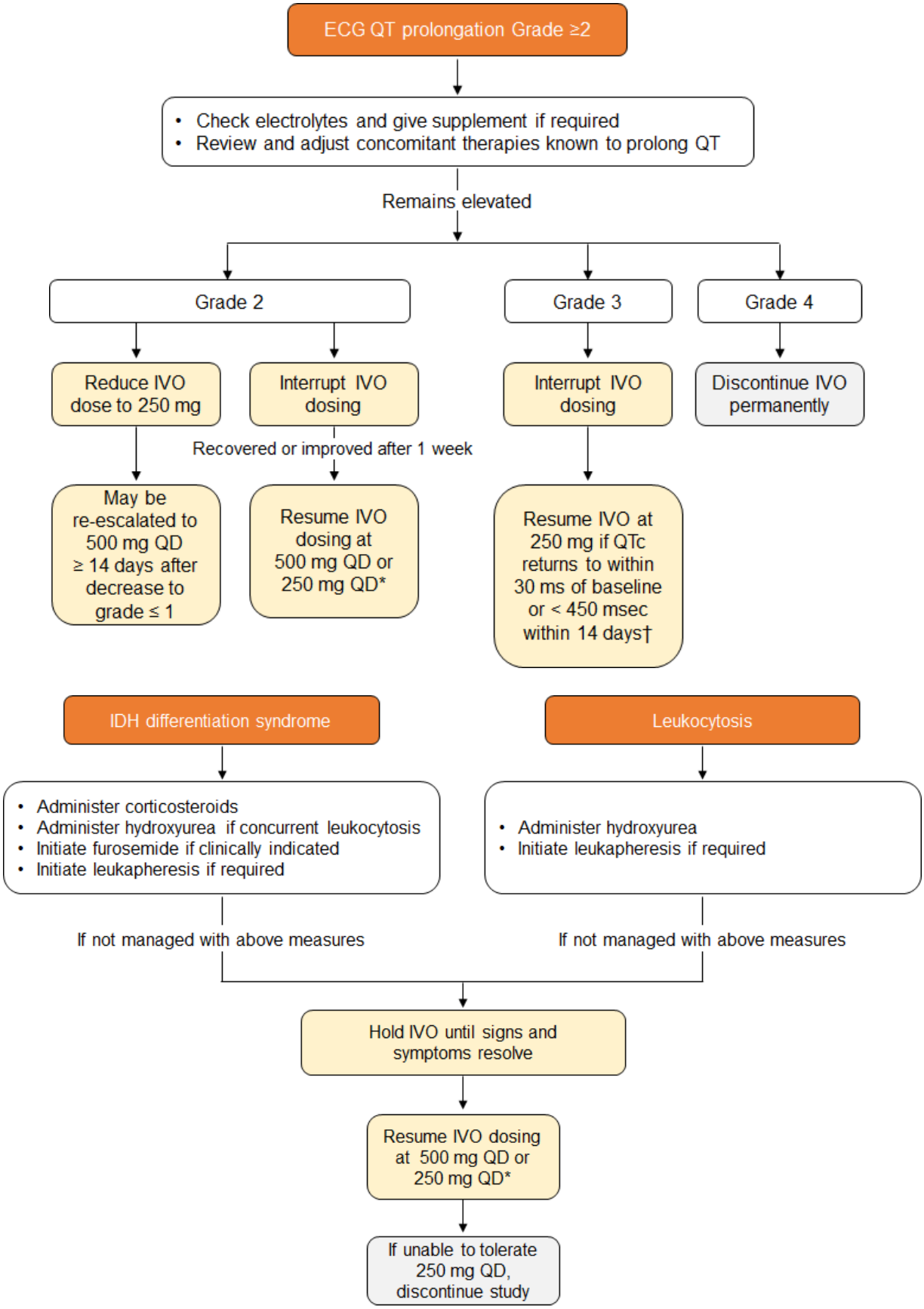

ECG QT prolongation Grade ≥2
• Check electrolytes and give supplement if required
• Review and adjust concomitant therapies known to prolong QT
Remains elevated
Grade 2
Grade 3
Grade 4
Reduce IVO dose to 250 mg
Interrupt IVO dosing
Interrupt IVO dosing
Discontinue IVO permanently
Recovered or improved after 1 week
May be re-escalated to 500 mg QD ≥ 14 days after decrease to grade ≤ 1
Resume IVO dosing at 500 mg QD or 250 mg QD*
Resume IVO at 250 mg if QTc returns to within 30 ms of baseline or < 450 msec within 14 days†
IDH differentiation syndrome
Leukocytosis
• Administer corticosteroids
• Administer hydroxyurea if concurrent leukocytosis
• Initiate furosemide if clinically indicated
• Initiate leukapheresis if required
• Administer hydroxyurea
• Initiate leukapheresis if required
If not managed with above measures
If not managed with above measures
Hold IVO until signs and symptoms resolve
Resume IVO dosing at 500 mg QD or 250 mg QD*
If unable to tolerate 250 mg QD, discontinue study

FIG A4. Plasma 2-HG concentration at (A) baseline and (B) cycle 2 day 1 by best overall response. Boxes indicate 25th percentile, median, and 75th percentile. Whiskers are plotted using Tukey's method. Dashed line represents the plasma 2-HG level (72.6 ng/mL) in normal healthy volunteers. CR, complete remission; CRh, CR with partial hematologic response; 2-HG, D-2-hydroxyglutarate.

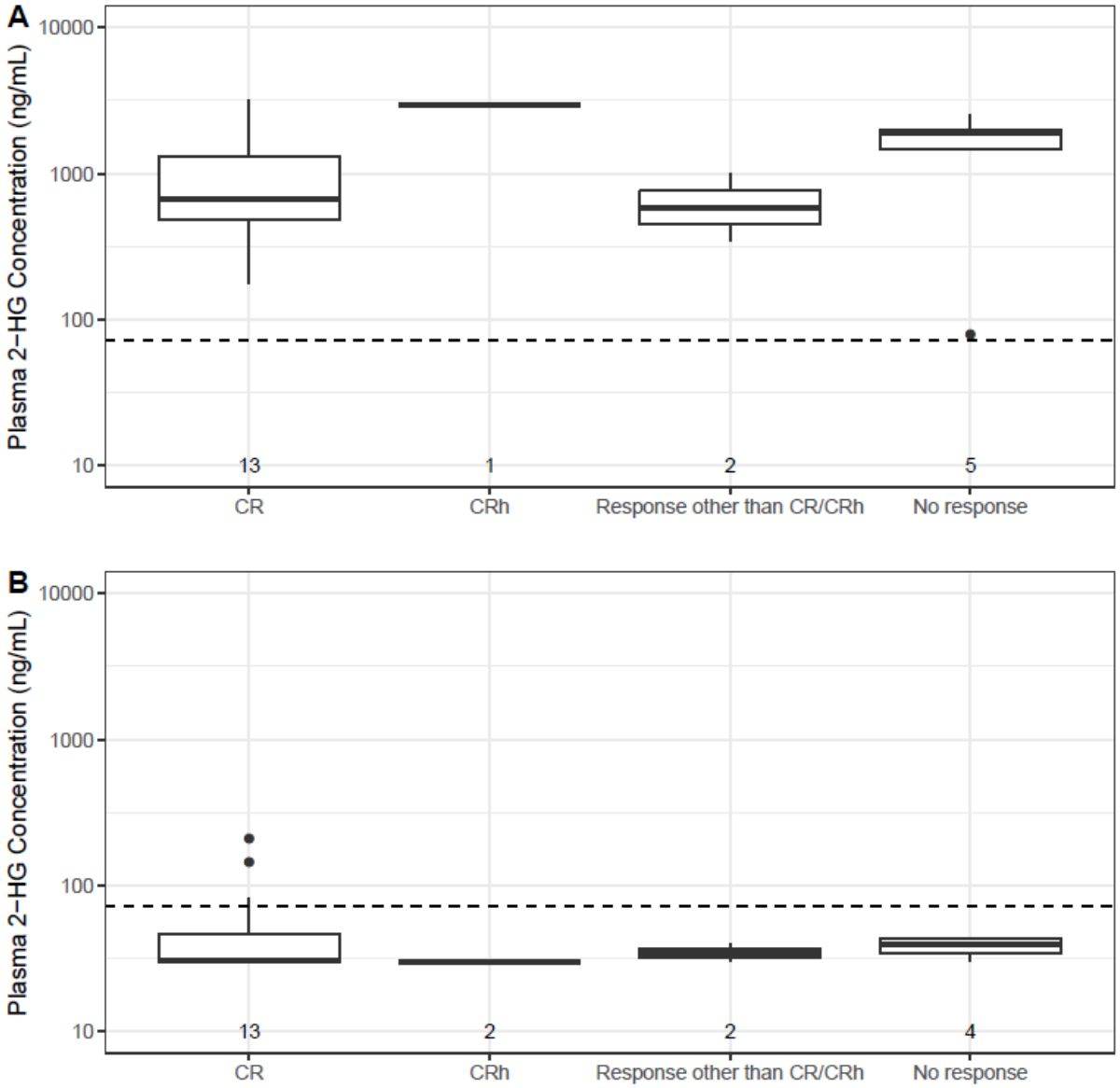


TABLE A1. Treatment-Emergent AEs of Any Grade Reported in ≥ 10% of Patients Receiving Ivosidenib + Azacitidine

	Ivosidenib + Azacitidine (N = 23)
Patients with ≥ 1 AE, No. (%)	23 (100)
Thrombocytopenia	15 (65.2)
Nausea	14 (60.9)
Diarrhea	13 (56.5)
Anemia	12 (52.2)
Constipation	12 (52.2)
Febrile neutropenia	10 (43.5)
Pyrexia	10 (43.5)
Vomiting	10 (43.5)
Fatigue	8 (34.8)
Hypokalemia	8 (34.8)
Dizziness	8 (34.8)
Insomnia	8 (34.8)
Back pain	7 (30.4)

Neutropenia	7 (30.4)
Cough	6 (26.1)
Decreased appetite	6 (26.1)
Electrocardiogram QT prolonged	6 (26.1)
Injection site erythema	5 (21.7)
Headache	5 (21.7)
Peripheral edema	5 (21.7)
Sepsis	5 (21.7)
Hypomagnesemia	4 (17.4)
Hyponatremia	4 (17.4)
IDH differentiation syndrome	4 (17.4)
Abdominal pain	4 (17.4)
Upper respiratory tract infection	4 (17.4)
Hypotension	4 (17.4)
Acute kidney injury	4 (17.4)
Leukocytosis[a]	4 (17.4)[b]
Gastroesophageal reflux disease	3 (13.0)
Asthenia	3 (13.0)

Noncardiac chest pain	3 (13.0)
Arthralgia	3 (13.0)
Muscular weakness	3 (13.0)
Pain in extremity	3 (13.0)
Dyspnea	3 (13.0)
Oropharyngeal pain	3 (13.0)
Cognitive disorder	3 (13.0)
Rash maculopapular	3 (13.0)
Anxiety	3 (13.0)
Confusional state	3 (13.0)
Visual impairment	3 (13.0)
Contusion	3 (13.0)

Abbreviations: AE, adverse event; IDH, isocitrate dehydrogenase.

[a]Combines the preferred terms of leukocytosis and hyperleukocytosis.

[b]Based on investigator assessment and includes investigator-reported grade 2 leukocytosis. The Common Terminology Criteria for Adverse Events version 4.03 only defines leukocytosis as an AE when grade = 3 (> 100,000/mm^3) or higher.

TABLE A2. Treatment-Related[a] Treatment-Emergent AEs of Any Grade Reported in ≥ 10% of Patients

	Patients (N = 23)		
	Ivosidenib	**Azacitidine**	**Ivosidenib and/or Azacitidine**
Any treatment-related AE, No. (%)	20 (87.0)	22 (95.7)	23 (100)
Nausea	12 (52.2)	13 (56.5)	13 (56.5)
Vomiting	5 (21.7)	5 (21.7)	7 (30.4)
Diarrhea	3 (13.0)	6 (26.1)	6 (26.1)
Neutropenia	4 (17.4)	6 (26.1)	6 (26.1)
ECG QT prolonged	6 (26.1)	1 (4.3)	6 (26.1)
Fatigue	5 (21.7)	6 (26.1)	6 (26.1)
Constipation	2 (8.7)	4 (17.4)	4 (17.4)
IDH differentiation syndrome	4 (17.4)	0	4 (17.4)
Thrombocytopenia	3 (13.0)	4 (17.4)	4 (17.4)
Anemia	2 (8.7)	3 (13.0)	3 (13.0)

Abbreviations: AE, adverse event; ECG, electrocardiogram; IDH, isocitrate dehydrogenase.

[a]Suspected by the investigator as being at least possibly related to study drug for either ivosidenib or azacitidine.

TABLE A3. Treatment-Emergent AEs Leading to Dose Modification of Ivosidenib and/or Azacitidine[a]

	Patients (N = 23)								
	Drug discontinuation			Dose interruption			Dose reduction		
	IVO only	AZA only	IVO and AZA	IVO only	AZA only	IVO and AZA	IVO only	AZA only	IVO and AZA
Patients with ≥ 1 AE, No. (%)	0	2 (8.7)	1 (4.3)	11 (47.8)	6 (26.1)	3 (13.0)	2 (8.7)	5 (21.7)	0 (0)
Enterobacter bacteremia	0	0	1 (4.3)	0	0	0	0	0	0
Thrombocytopenia	0	1 (4.3)	0	0	1 (4.3)	0	0	1 (4.3)	0
Fatigue	0	1 (4.3)	0	0	0	0	0	0	0
Febrile neutropenia	0	0	0	3 (13.0)	0	0	0	0	0
Neutropenia	0	0	0	1 (4.3)	2 (8.7)	1 (4.3)	0	3 (13.0)	0
Vomiting	0	0	0	2 (8.7)	1 (4.3)	0	0	0	0

IDH differentiation syndrome	0	0	0	0	0	1 (4.3)	0	0	0
Anemia	0	0	0	0	1 (4.3)	0	0	0	0
Leukocytosis	0	0	0	1 (4.3)	0	0	0	0	0
Leukopenia	0	0	0	0	1 (4.3)	0	0	0	0
Pyrexia	0	0	0	0	1 (4.3)	1 (4.3)	0	0	0
Asthenia	0	0	0	0	1 (4.3)	0	0	0	0
Chest discomfort	0	0	0	0	1 (4.3)	0	0	0	0
Sepsis	0	0	0	1 (4.3)	1 (4.3)	1 (4.3)	0	0	0
Bacteremia	0	0	0	1 (4.3)	0	0	0	0	0
Device related infection	0	0	0	1 (4.3)	0	0	0	0	0
Gastrointestinal infection	0	0	0	1 (4.3)	0	0	0	0	0

Pneumonia	0	0	0	1 (4.3)	0	0	0	0	0
Hyperglycemia	0	0	0	0	0	1 (4.3)	0	0	0
Hyperlipasemia	0	0	0	1 (4.3)	0	0	0	0	0
Atrial fibrillation	0	0	0	1 (4.3)	0	0	0	0	0
Hypoacusis	0	0	0	0	1 (4.3)	0	0	0	0
Abdominal pain upper	0	0	0	1 (4.3)	0	0	0	0	0
Anal fistula	0	0	0	1 (4.3)	0	0	0	0	0
Nausea	0	0	0	0	1 (4.3)	0	0	0	0
Cholecystitis	0	0	0	1 (4.3)	0	0	0	0	0
Blood creatinine increased	0	0	0	1 (4.3)	0	0	0	1 (4.3)	0
ECG QT prolonged	0	0	0	1 (4.3)	0	0	2 (8.7)	0	0

Syncope	0	0	0	1 (4.3)	0	0	0	0	0
Pruritis	0	0	0	1 (4.3)	0	0	0	0	0
Rash maculo-papular	0	0	0	1 (4.3)	0	0	0	0	0

Abbreviations: AE, adverse event; AZA, azacitidine; ECG, electrocardiogram; IVO, ivosidenib.

[a]Attribution to ivosidenib or azacitidine was by investigator.

FIG A5. Dose adjustments of azacitidine and ivosidenib during study. CR, complete remission; CRh, CR with partial hematologic response; 2-HG, D-2-hydroxyglutarate; CRi, complete remission with incomplete neutrophil recovery; CRp, complete remission with incomplete platelet recovery; HSCT, hematopoietic stem cell transplantation; MLFS, morphologic leukemia-free state; NA, not assessed; PR, partial remission; SD, stable disease.

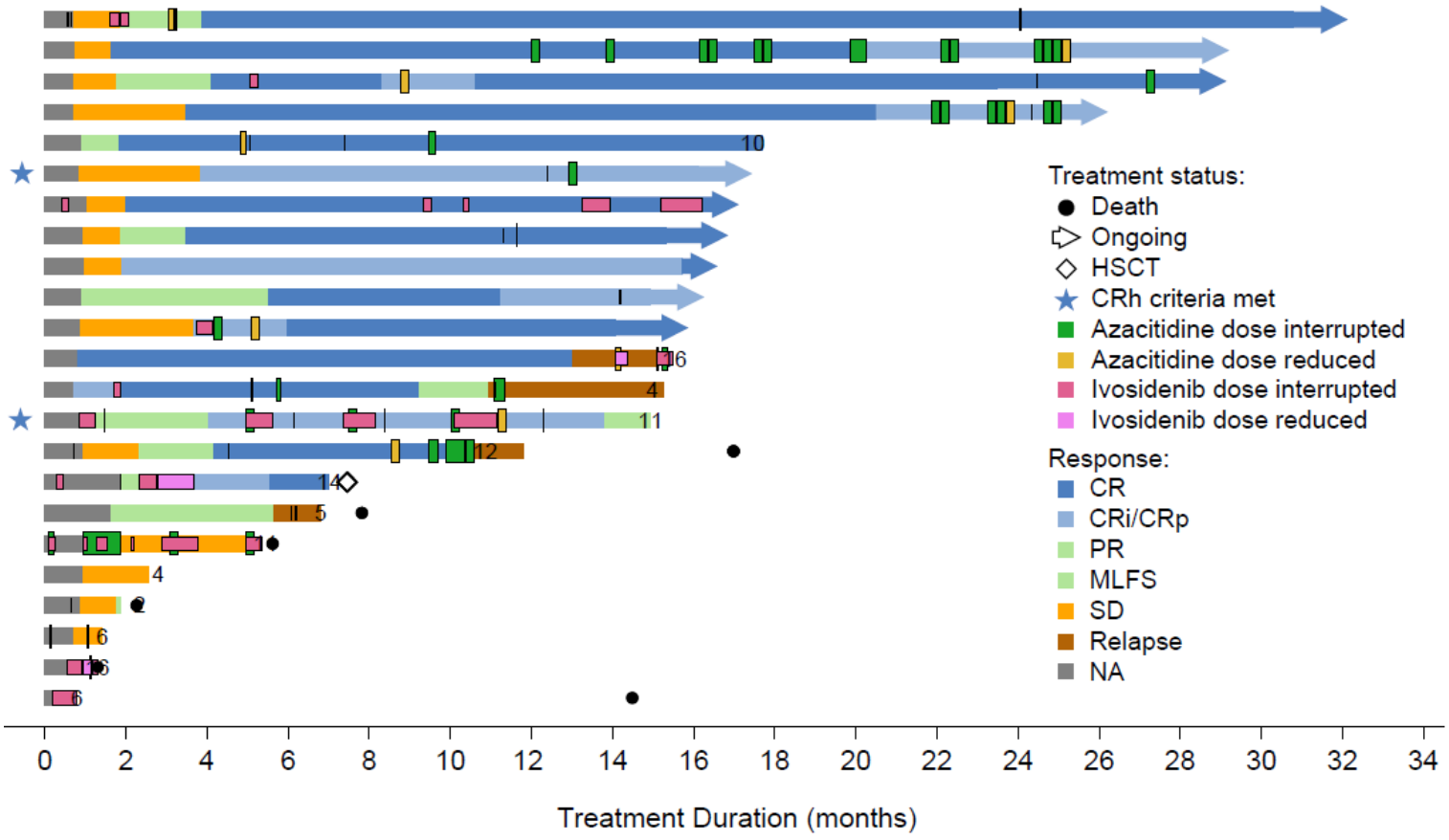
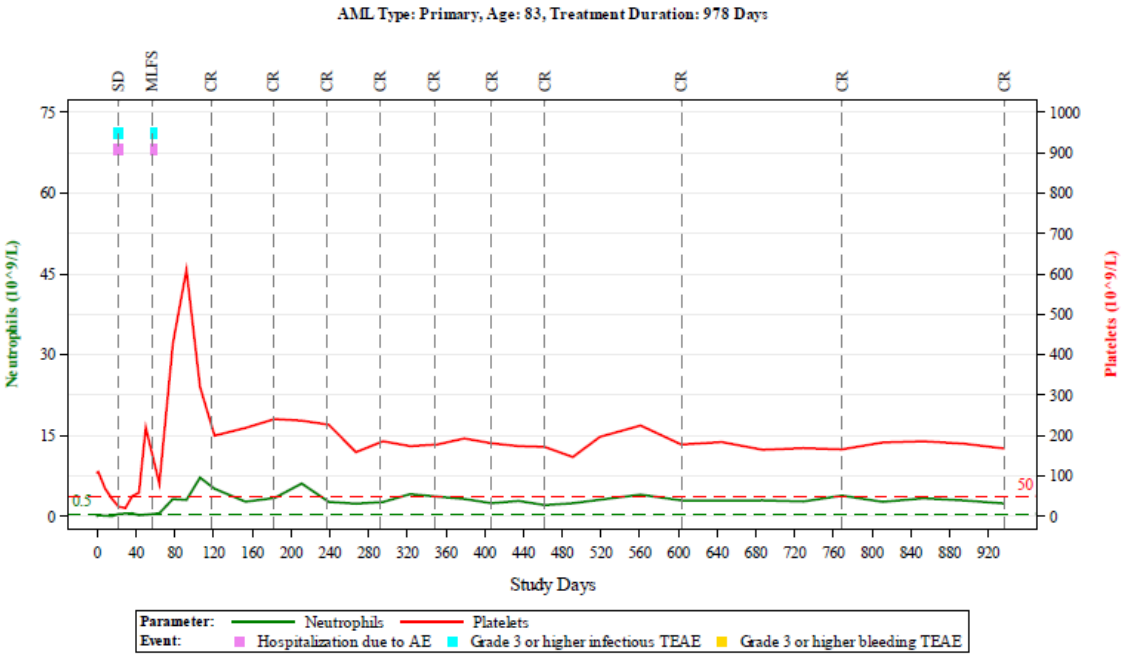
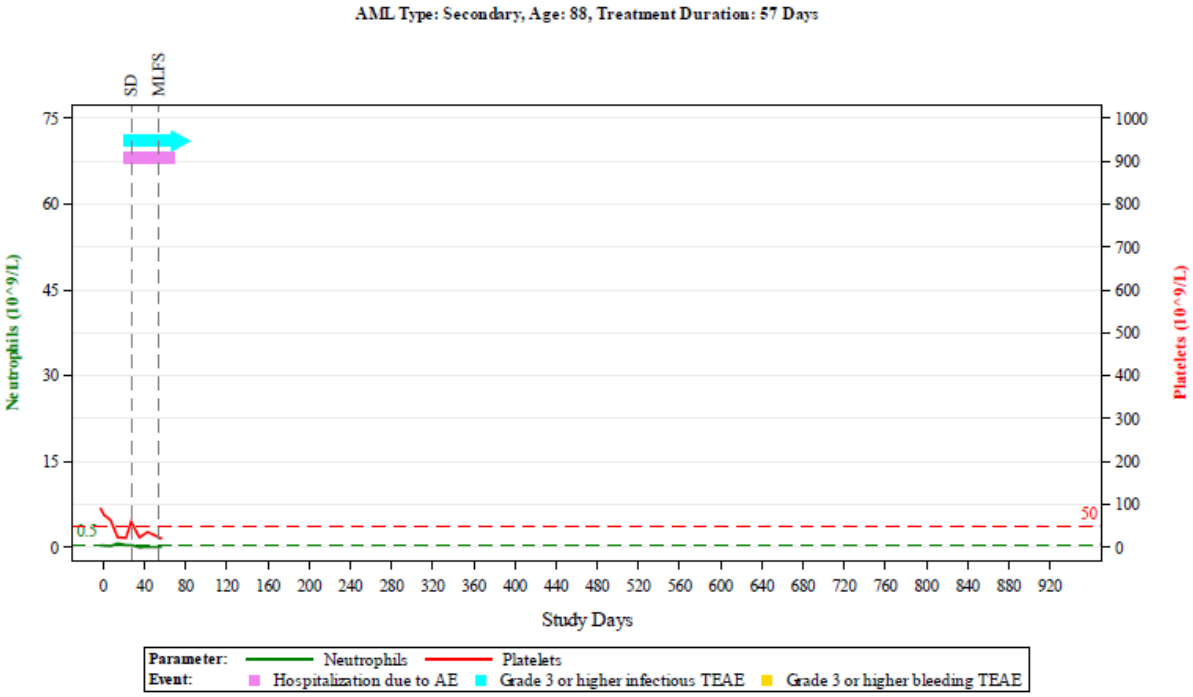
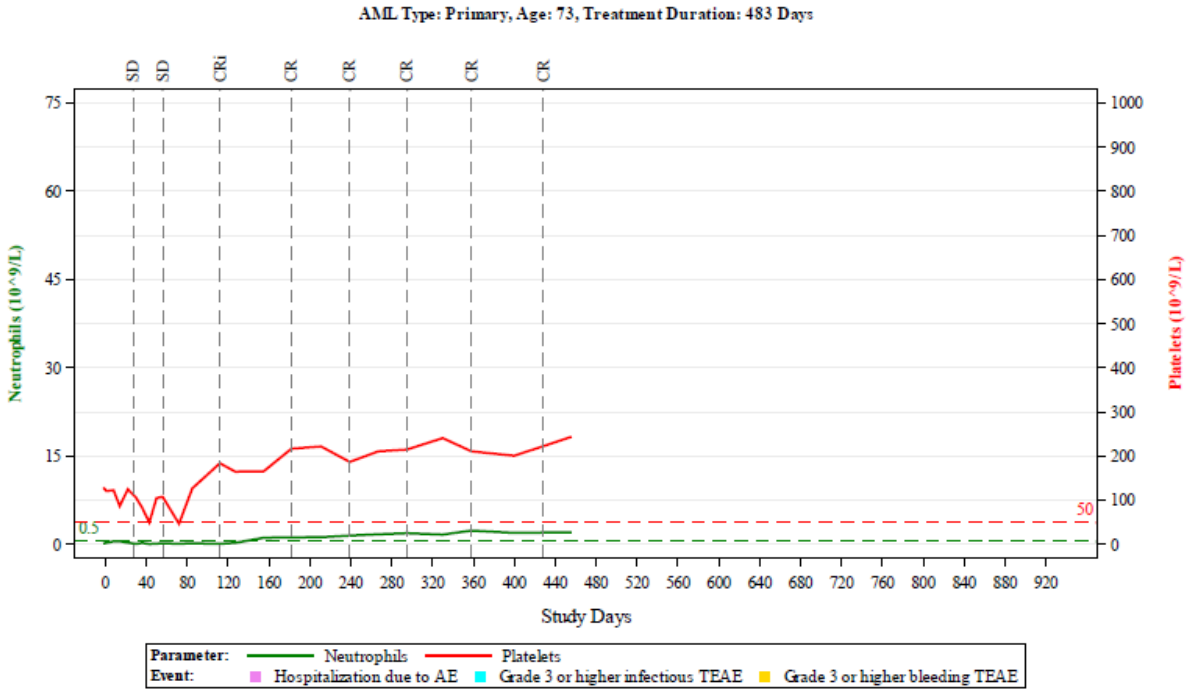
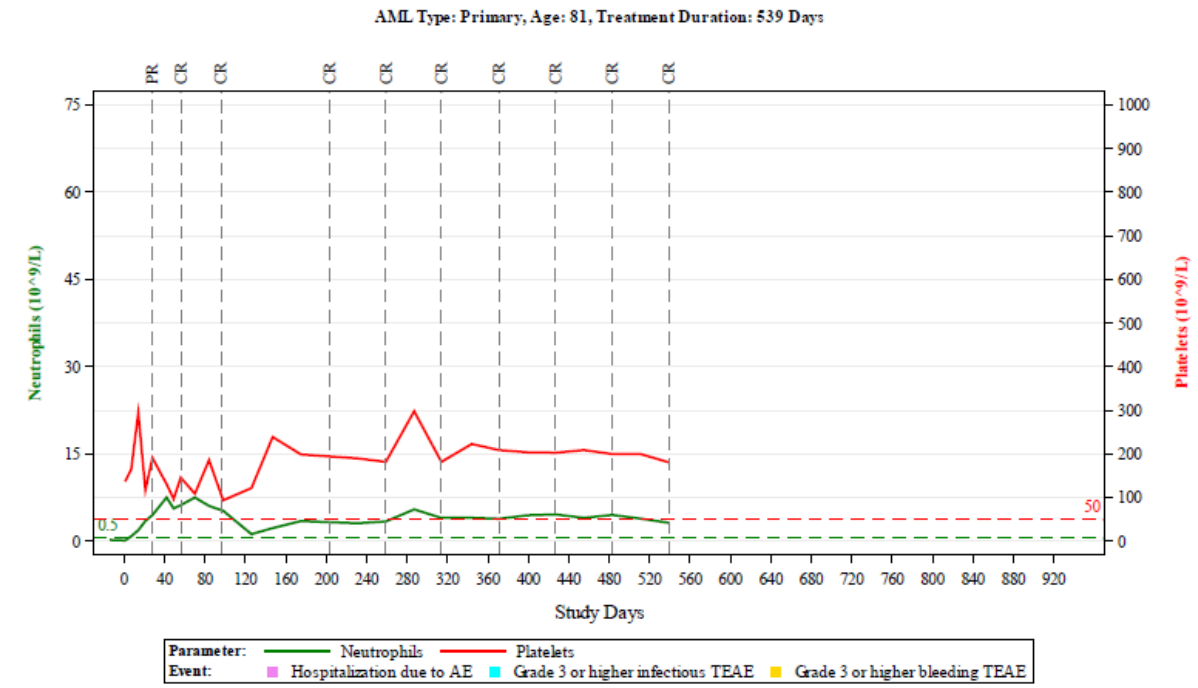


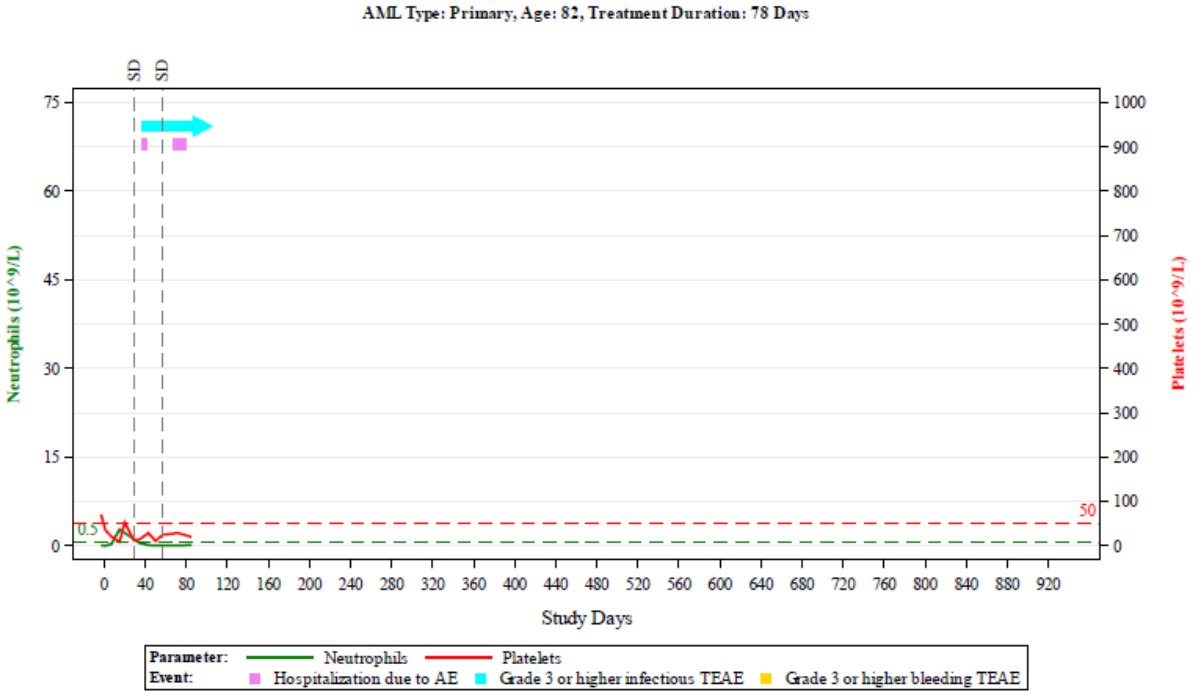
FIG A6. Plots of absolute neutrophil count and platelets with grade 3 or higher infectious/bleeding AEs and hospitalization for individual patients. Response over time is based on investigator assessments. AE, adverse event; AML, acute myeloid leukemia; CR, complete remission; CRi, complete remission with incomplete neutrophil recovery; CRp, complete remission with incomplete platelet recovery; MLFS, morphologic leukemia-free state; MR, morphologic relapse; NE, not evaluable; PR, partial remission; SD, stable disease; TEAE, treatment-emergent AE.

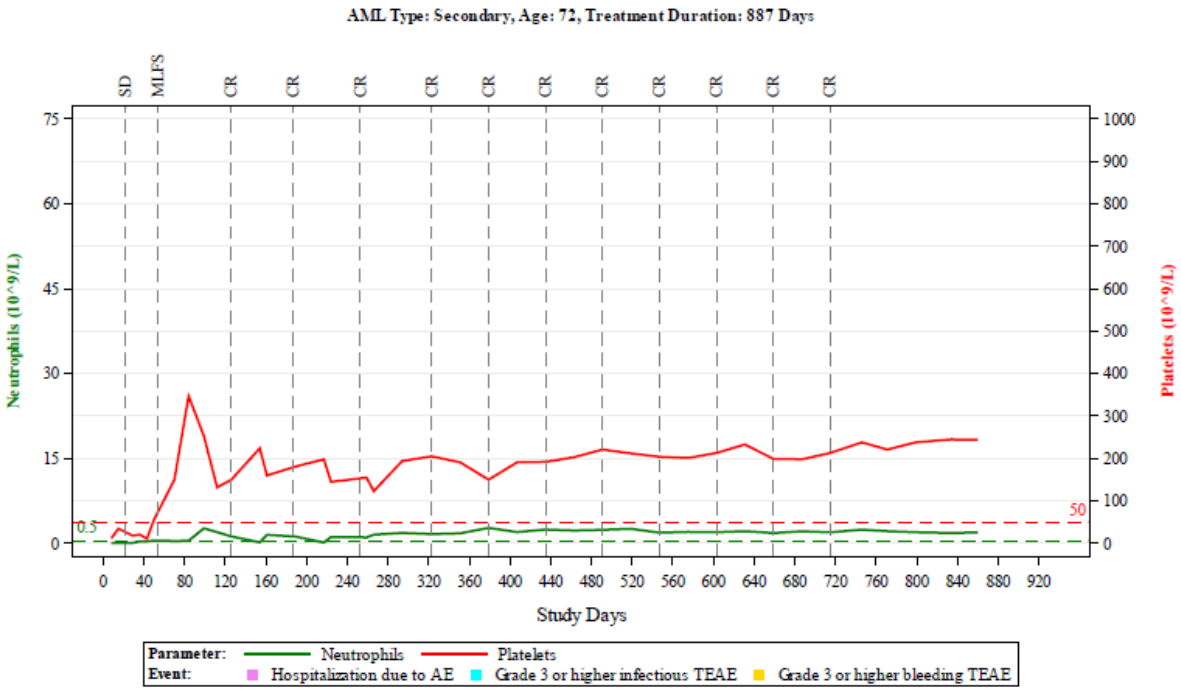


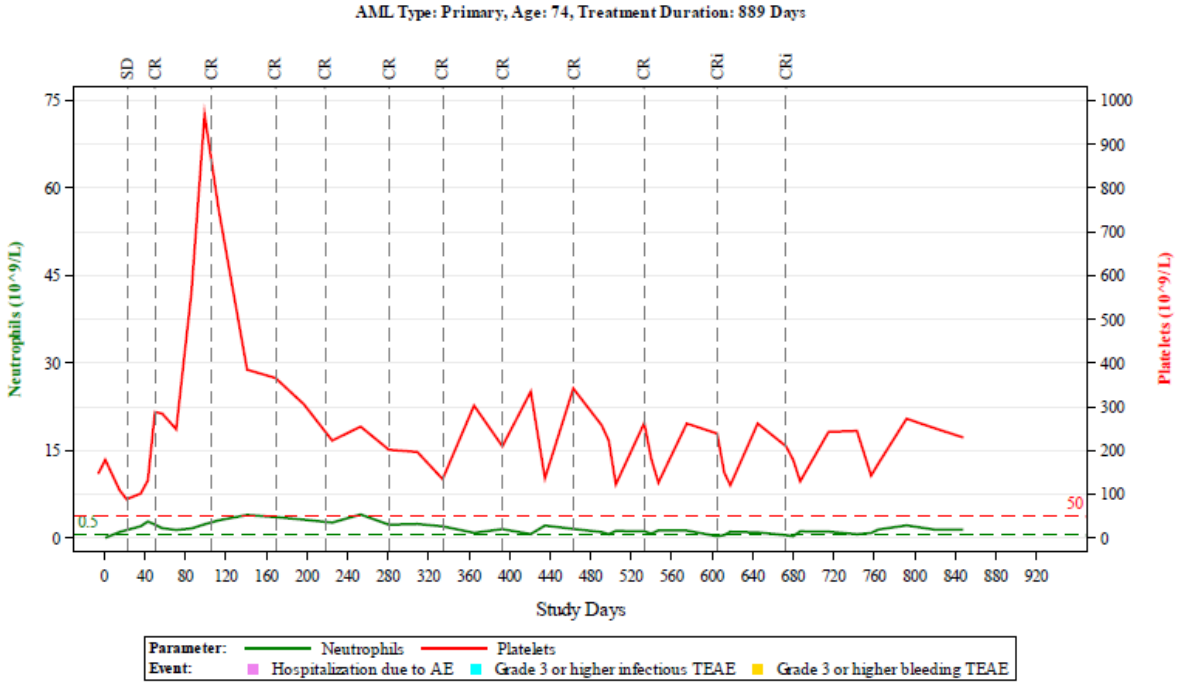

AML Type: Secondary, Age: 88, Treatment Duration: 57 Days
SD
MLFS
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

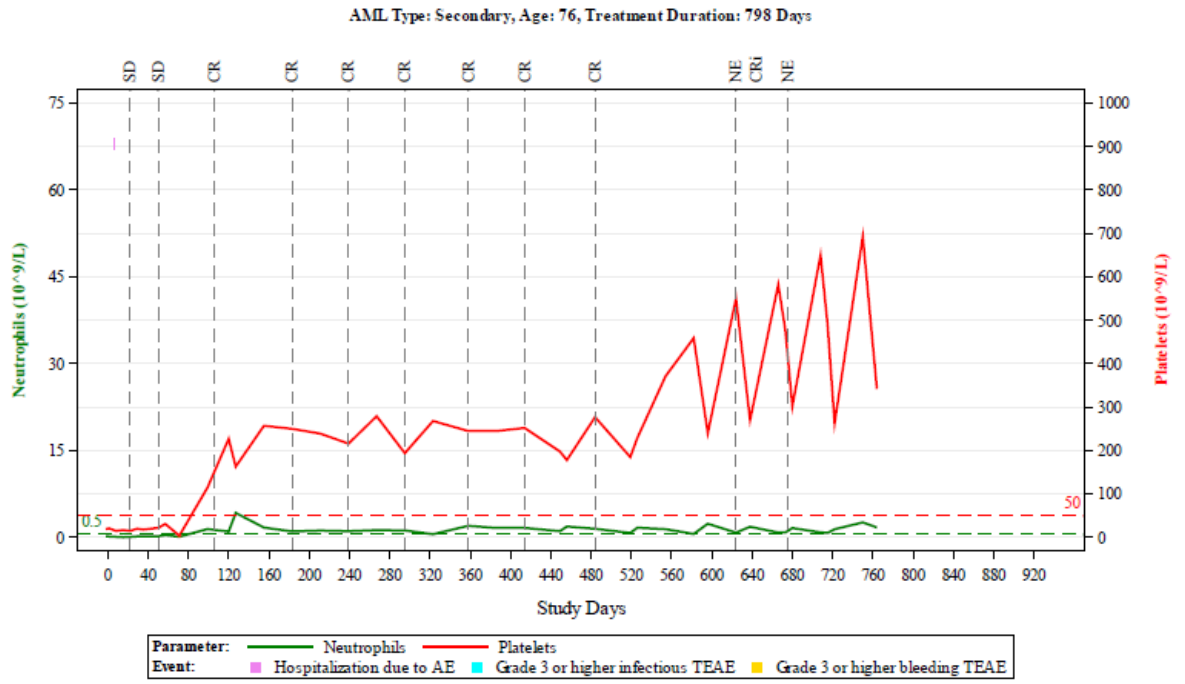

AML Type: Primary, Age: 73, Treatment Duration: 483 Days
SD
SD
CRi
CR
CR
CR
CR
CR
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

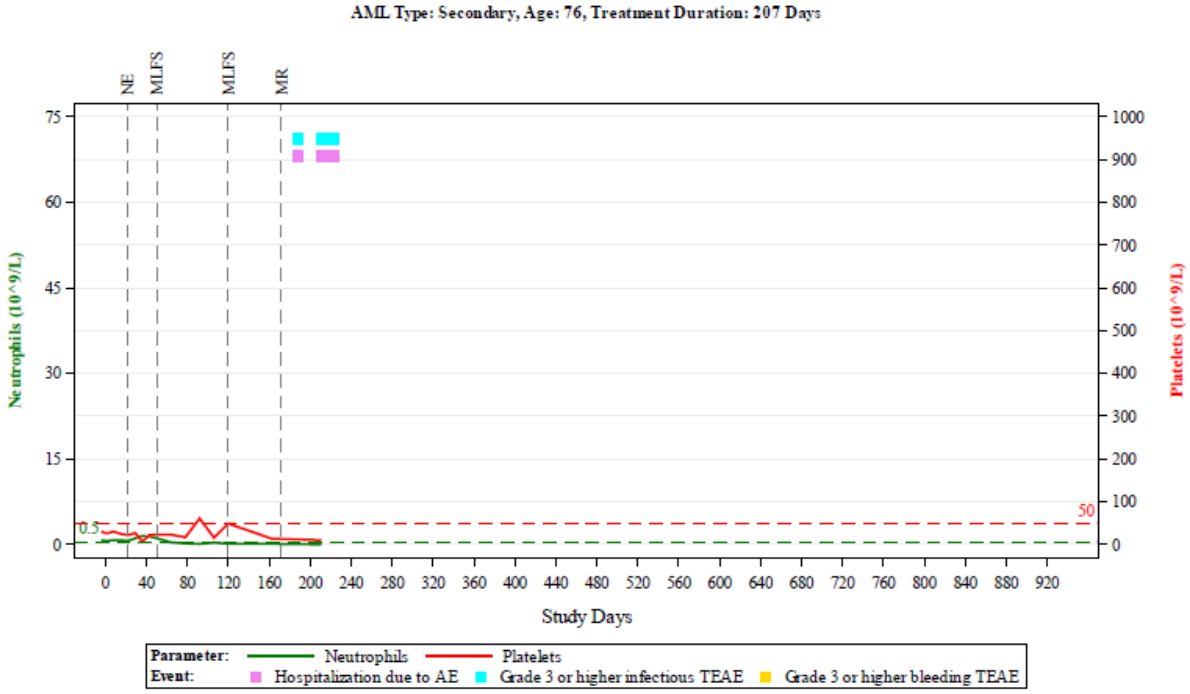

AML Type: Primary, Age: 81, Treatment Duration: 539 Days
PR
CR
CR
CR
CR
CR
CR
CR
CR
CR
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

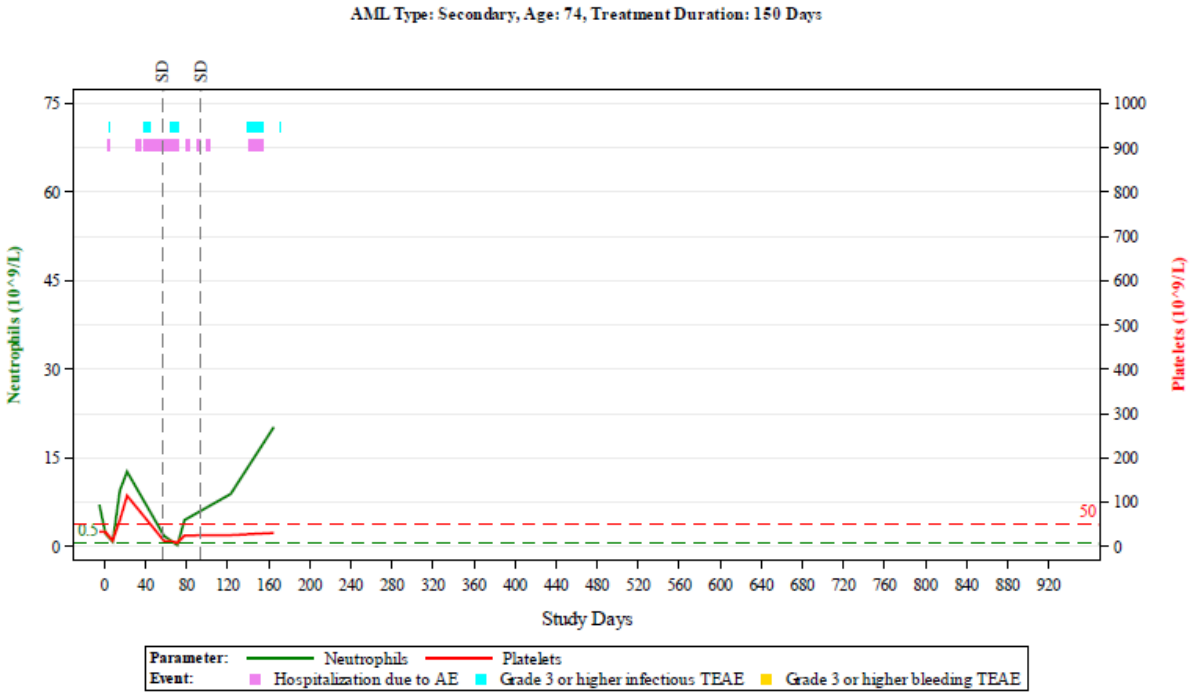

AML Type: Primary, Age: 82, Treatment Duration: 78 Days
SD
SD
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

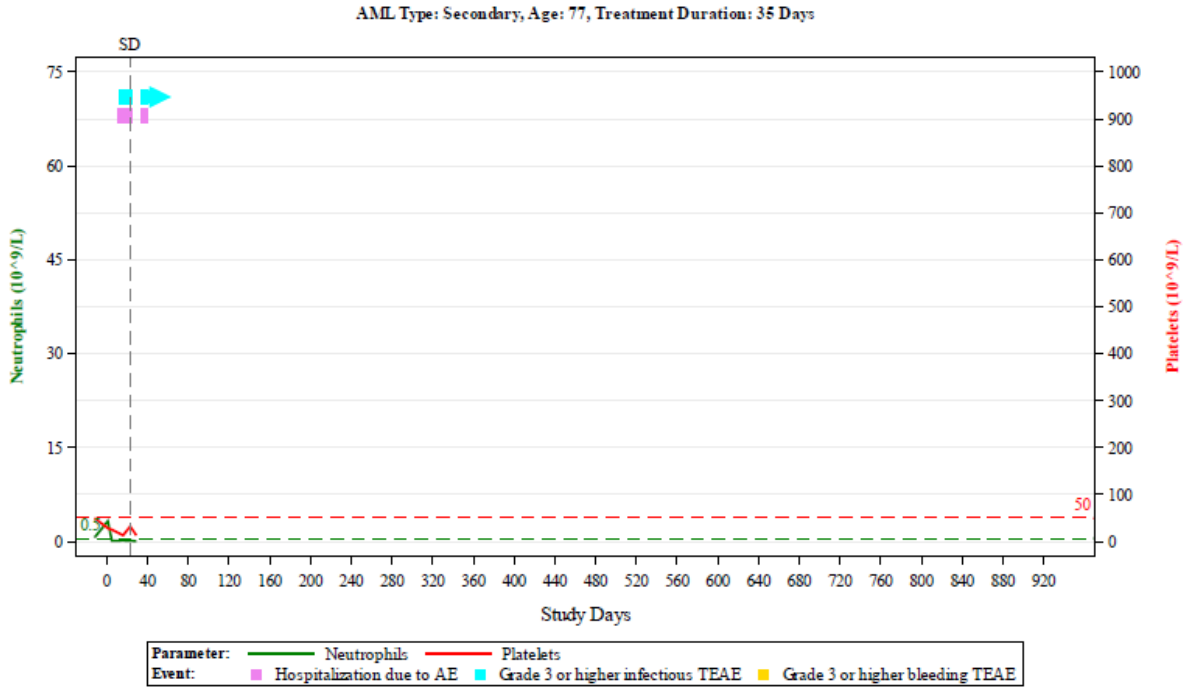

AML Type: Secondary, Age: 72, Treatment Duration: 887 Days
SD
MLFS
CR
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

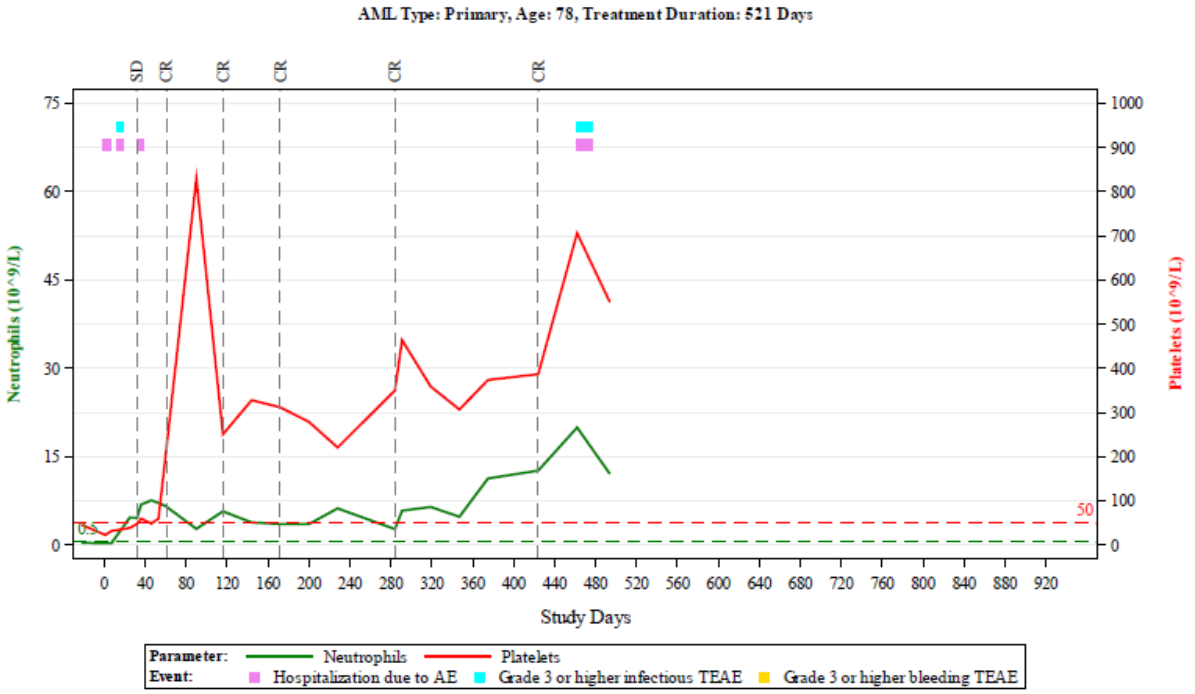

AML Type: Primary, Age: 74, Treatment Duration: 889 Days
SD
CR
CRi
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

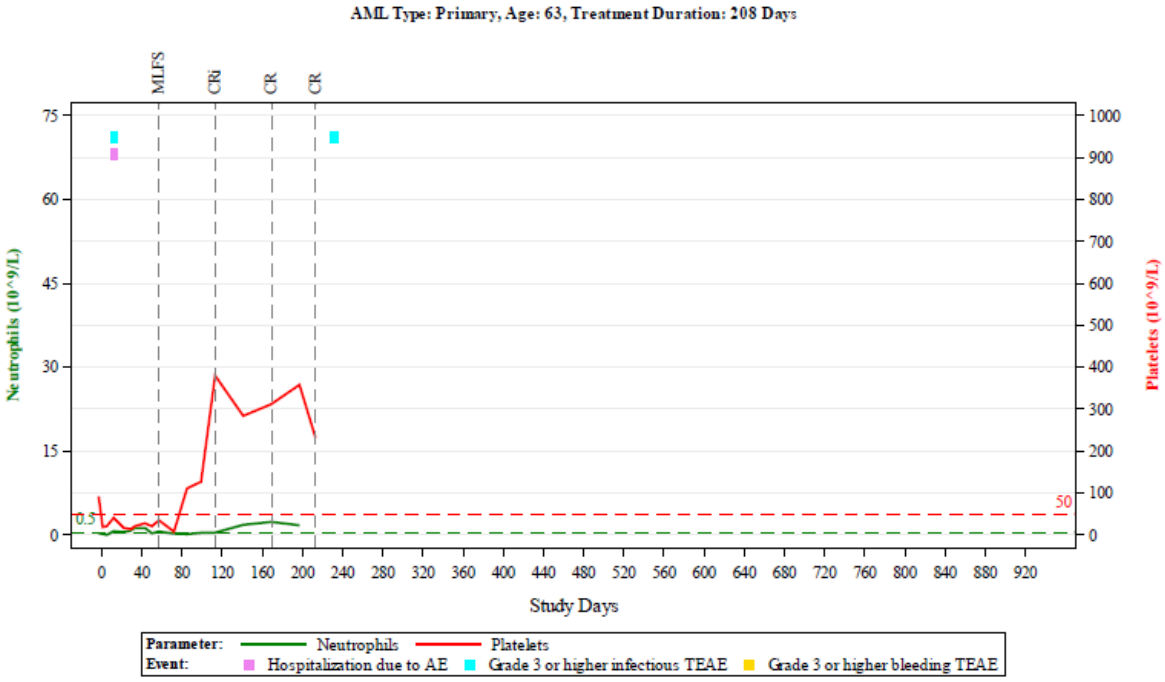

AML Type: Secondary, Age: 76, Treatment Duration: 798 Days
SD
SD
CR
CR
CR
CR
CR
CR
CR
NE
CRi
NE
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

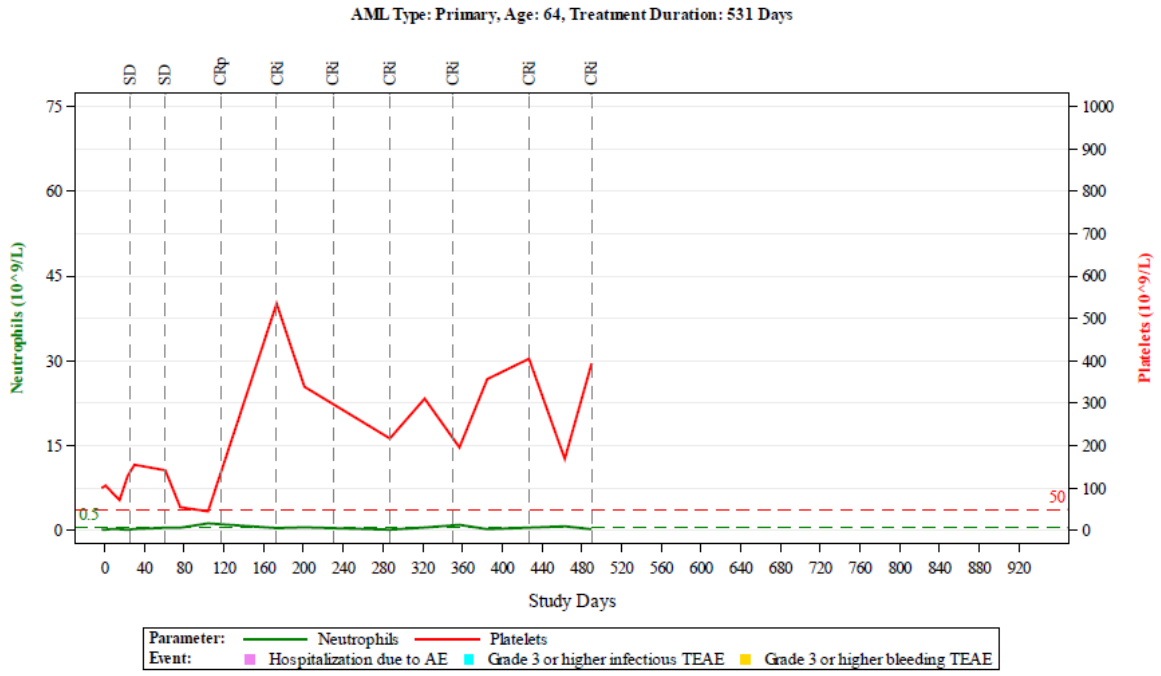

AML Type: Secondary, Age: 76, Treatment Duration: 207 Days
NE
MLFS
MLFS
MR
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

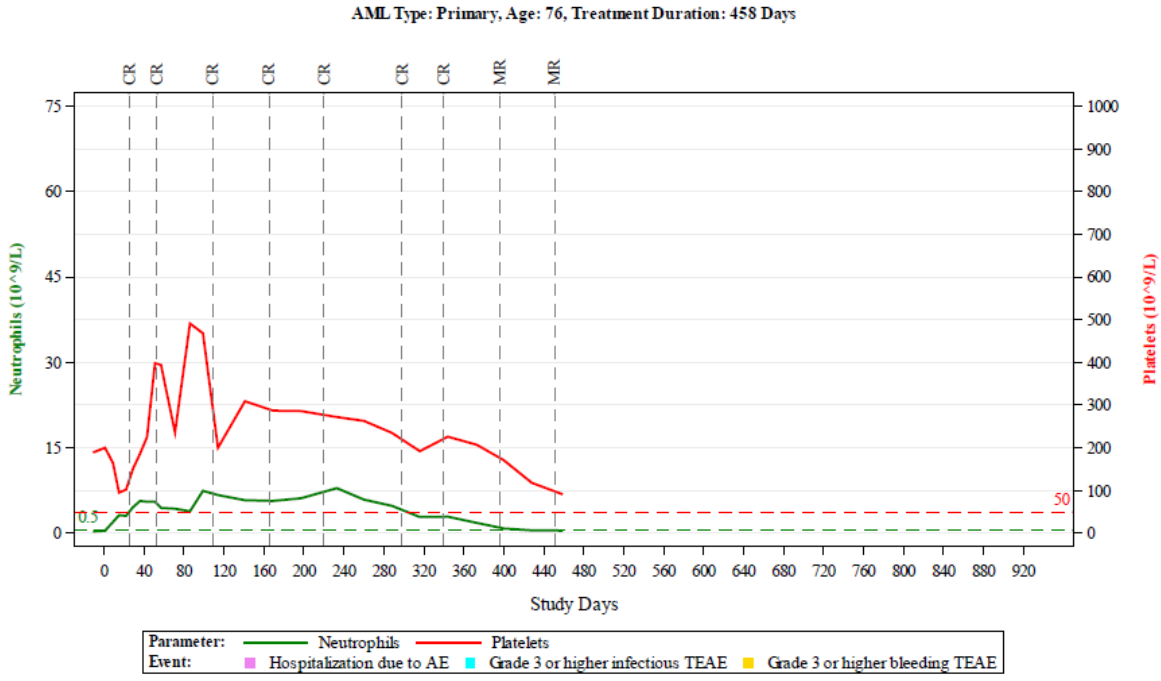

AML Type: Secondary, Age: 74, Treatment Duration: 150 Days
SD
SD
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

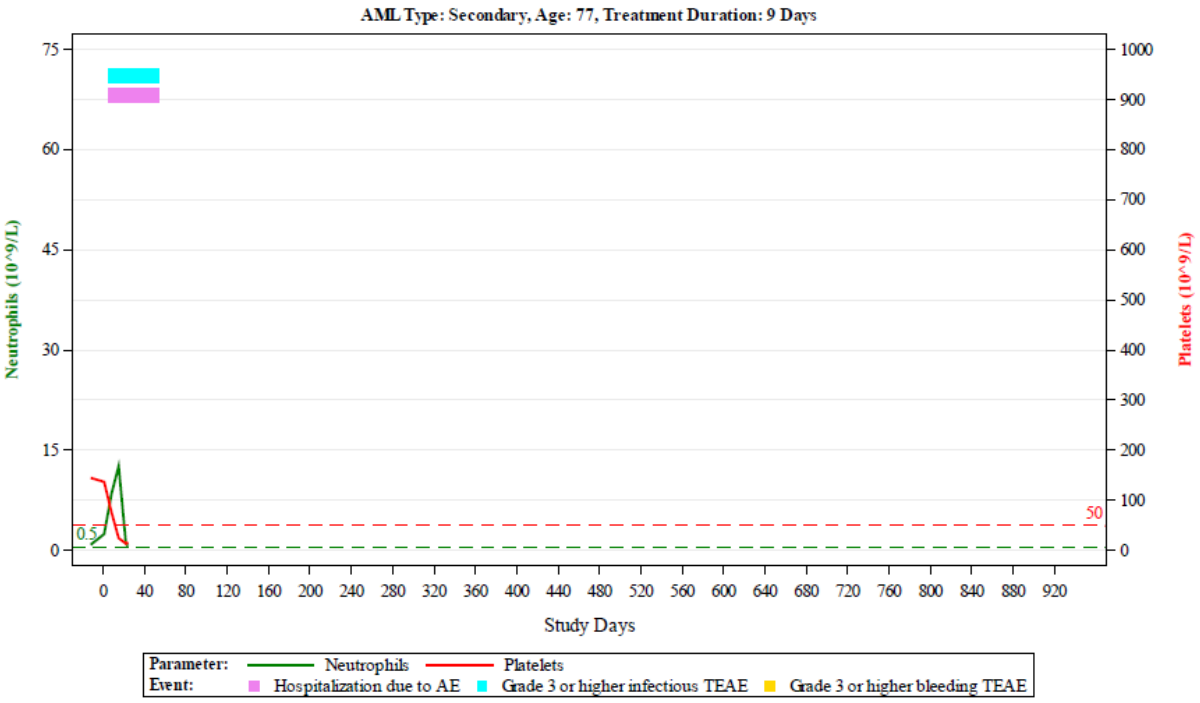

AML Type: Secondary, Age: 77, Treatment Duration: 35 Days
SD
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

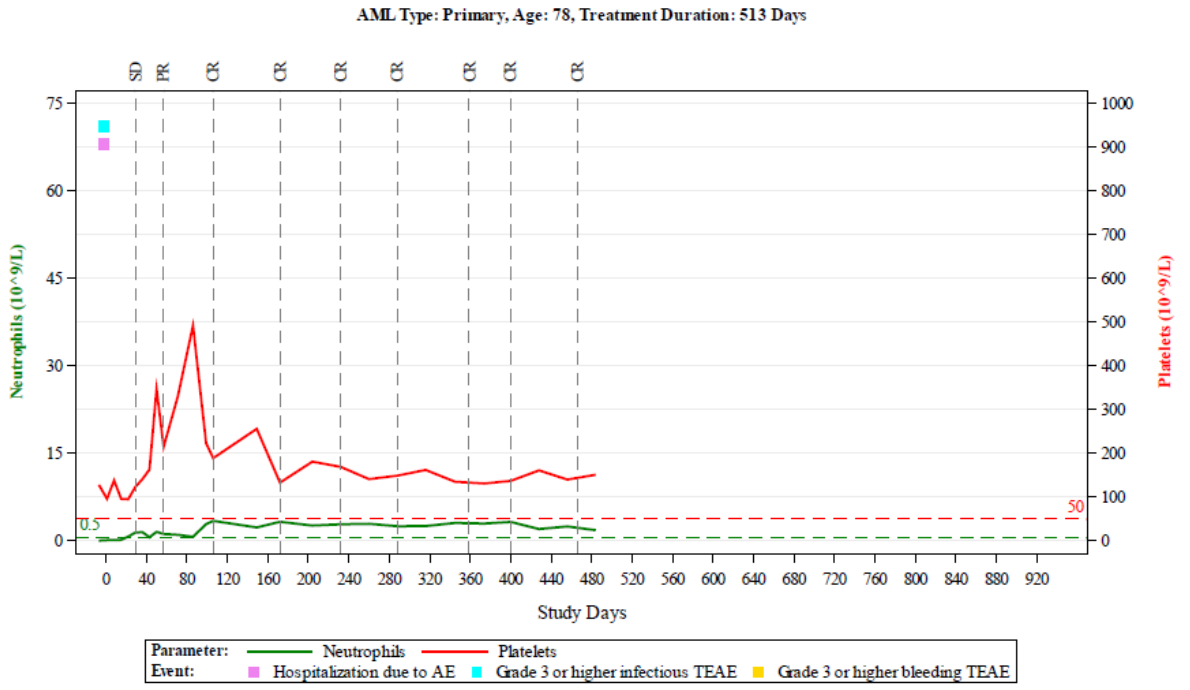

AML Type: Primary, Age: 78, Treatment Duration: 521 Days
SD
CR
CR
CR
CR
CR
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

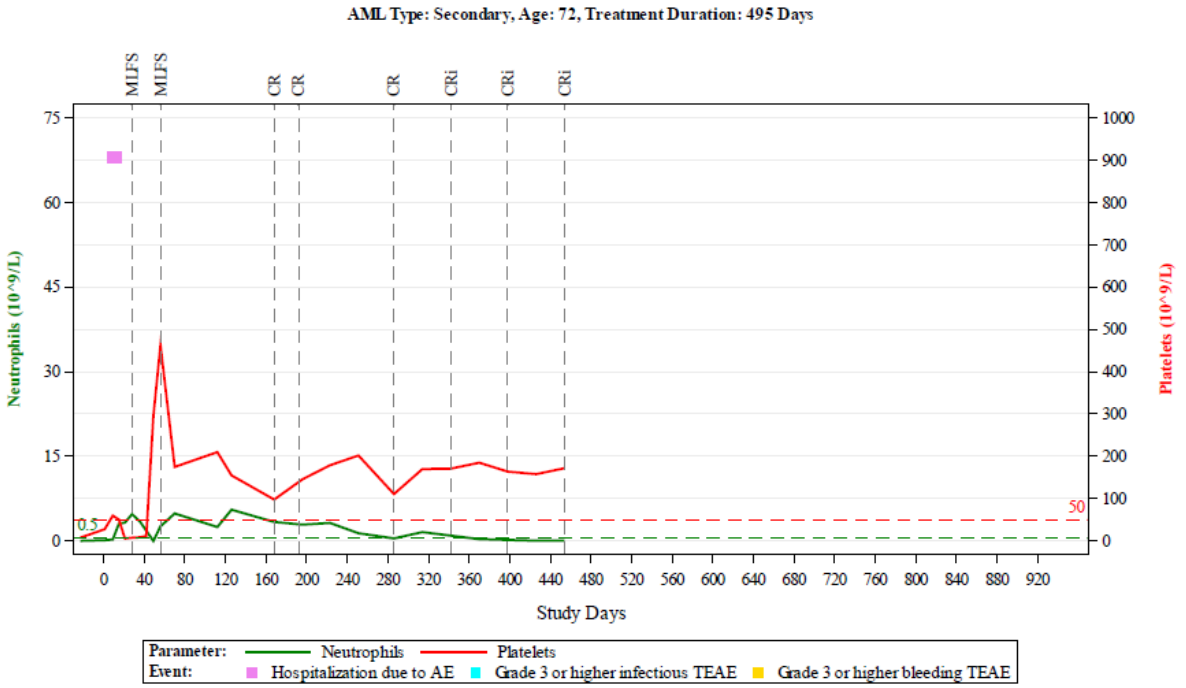

AML Type: Primary, Age: 63, Treatment Duration: 208 Days
MLFS
CRi
CR
CR
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

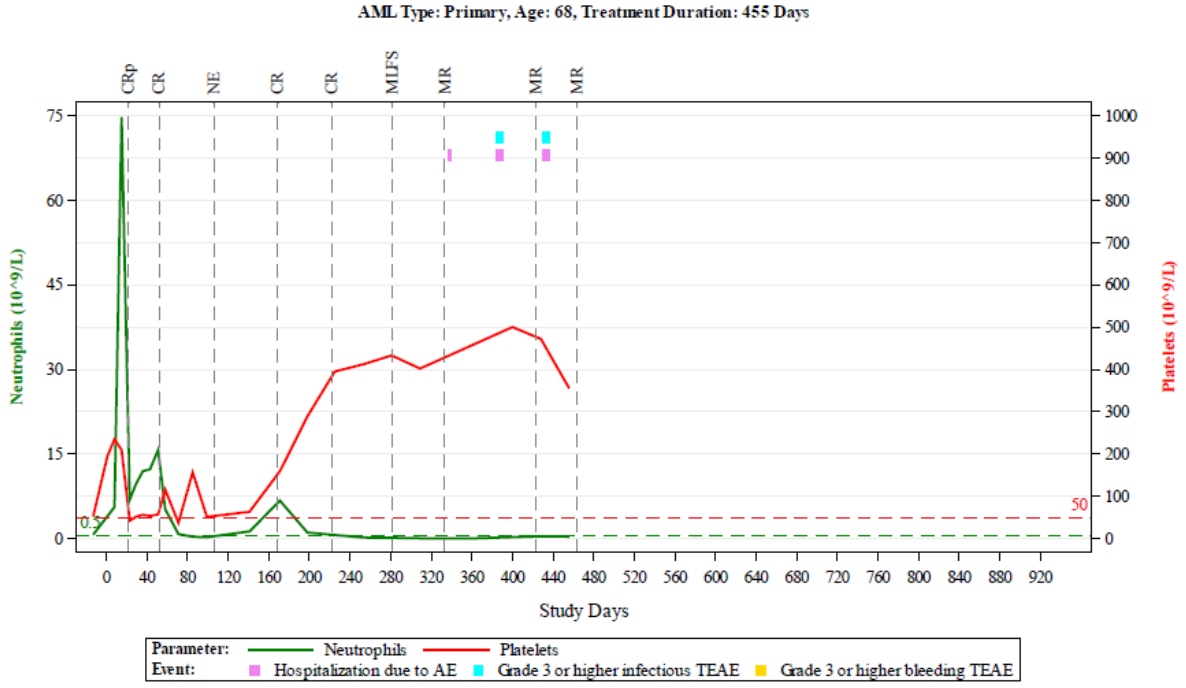

AML Type: Primary, Age: 64, Treatment Duration: 531 Days
SD
SD
CRp
CRi
CRi
CRi
CRi
CRi
CRi
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

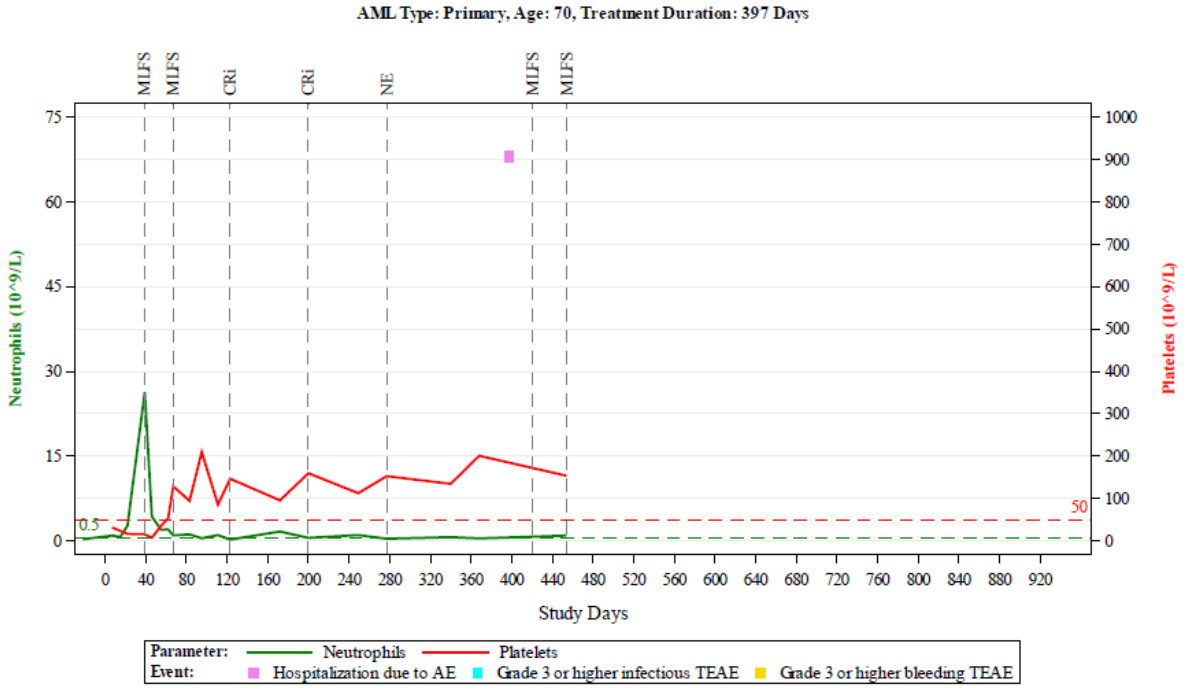

AML Type: Primary, Age: 76, Treatment Duration: 458 Days
CR
CR
CR
CR
CR
CR
CR
MR
MR
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

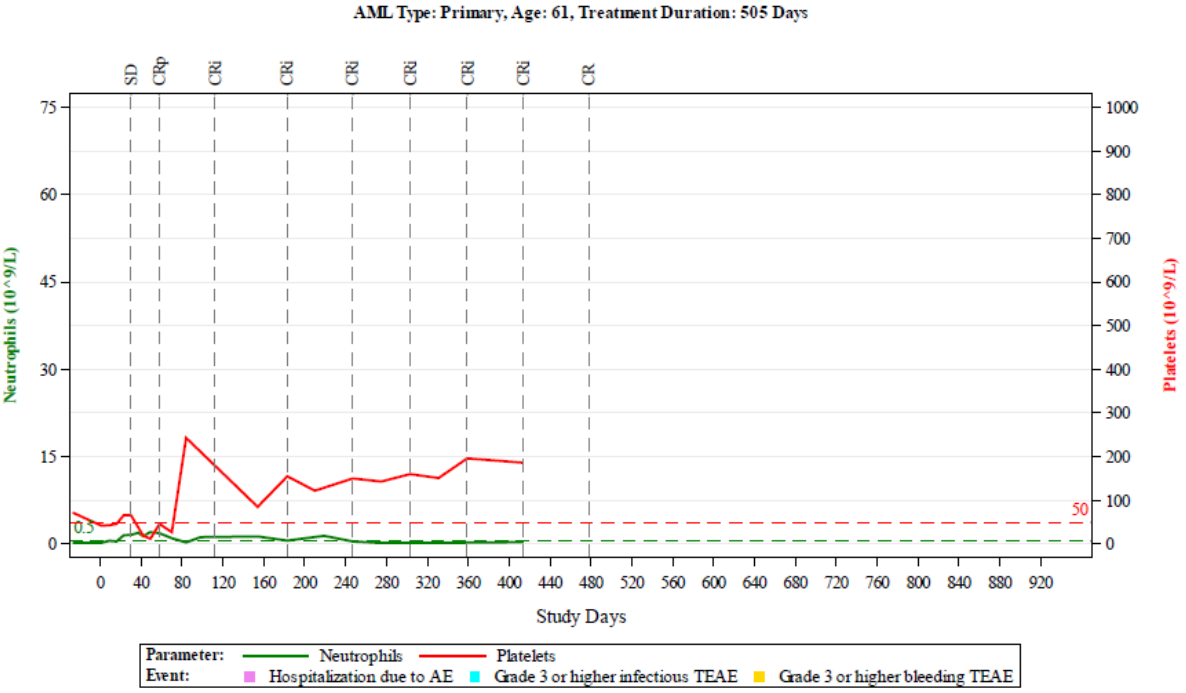

AML Type: Secondary, Age: 77, Treatment Duration: 9 Days
Neutrophils (10^9/L)
Platelets (10^9/L)
Study Days
0.5
50
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

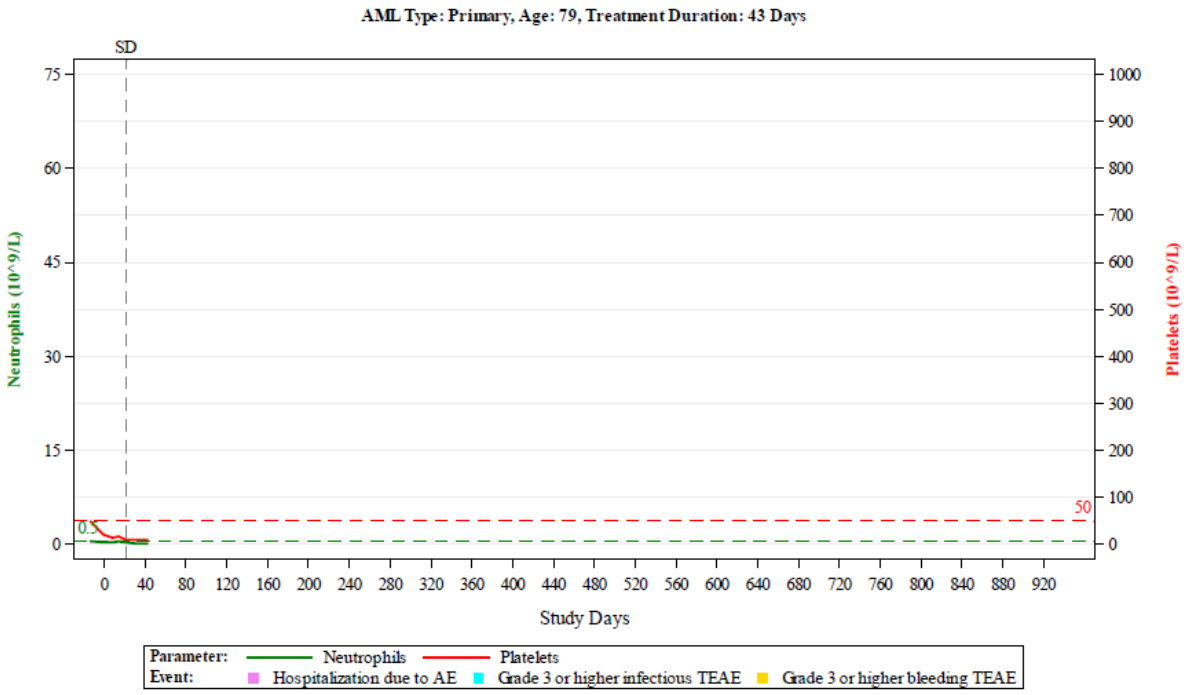

AML Type: Primary, Age: 78, Treatment Duration: 513 Days
SD
PR
CR
CR
CR
CR
CR
CR
CR
Neutrophils (10^9/L)
Platelets (10^9/L)
Study Days
0.5
50
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE


AML Type: Secondary, Age: 72, Treatment Duration: 495 Days
MLFS
MLFS
CR
CR
CR
CRi
CRi
CRi
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE


AML Type: Primary, Age: 68, Treatment Duration: 455 Days
CRp
CR
NE
CR
CR
MLFS
MR
MR
MR
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE


AML Type: Primary, Age: 70, Treatment Duration: 397 Days
MLFS
MLFS
CRi
CRi
NE
MLFS
MLFS
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE


AML Type: Primary, Age: 61, Treatment Duration: 505 Days
SD
CRp
CRi
CRi
CRi
CRi
CRi
CRi
CR
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE


AML Type: Primary, Age: 79, Treatment Duration: 43 Days
SD
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

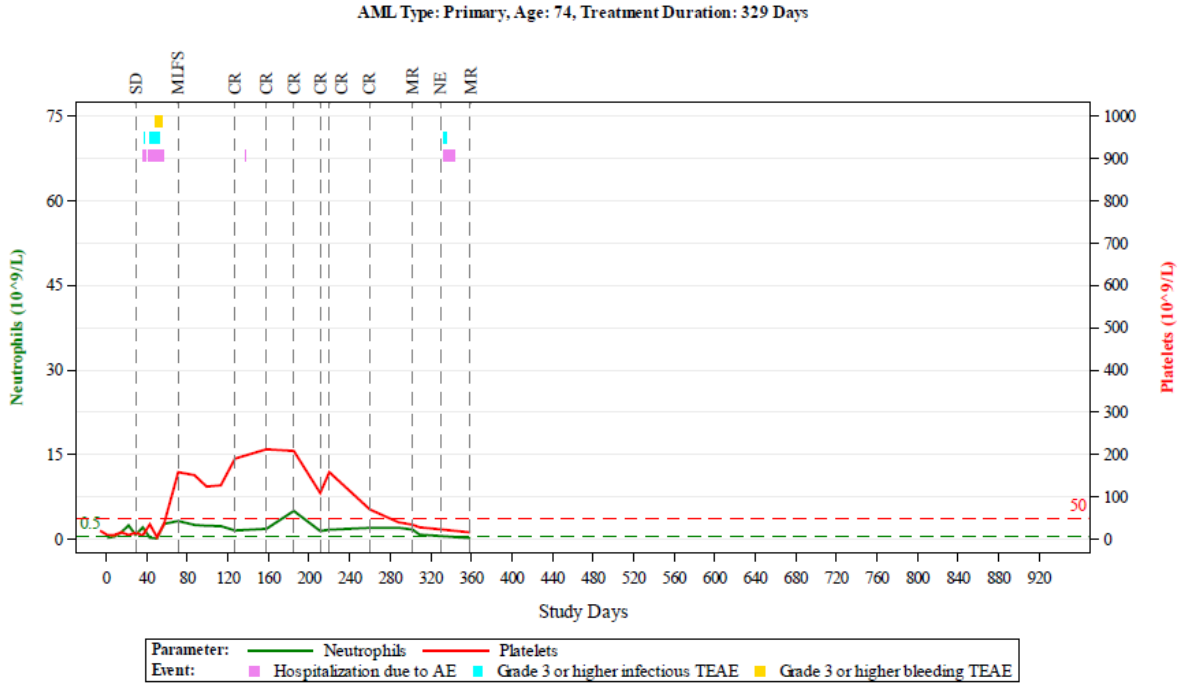
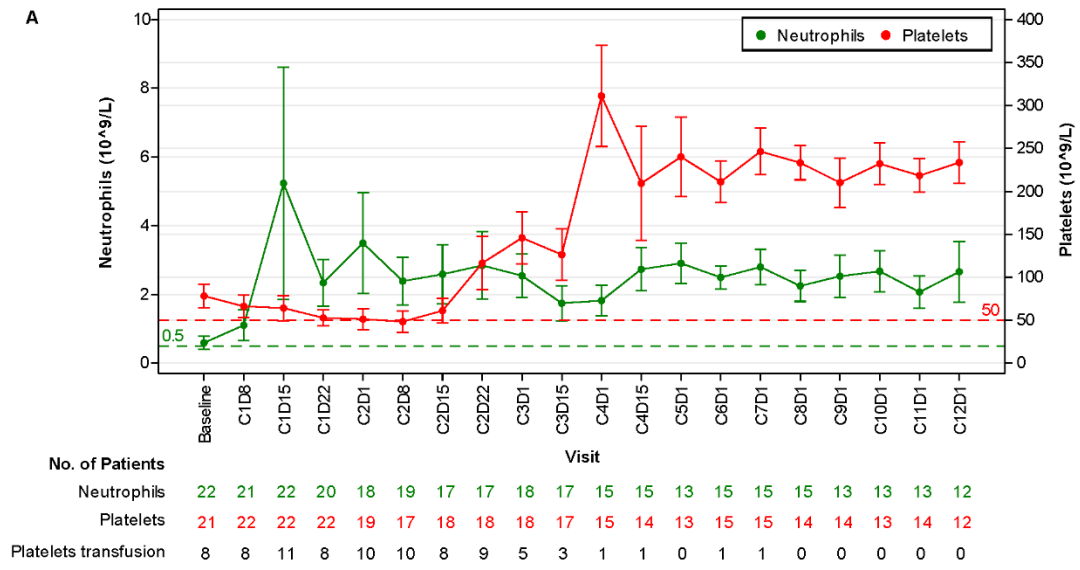
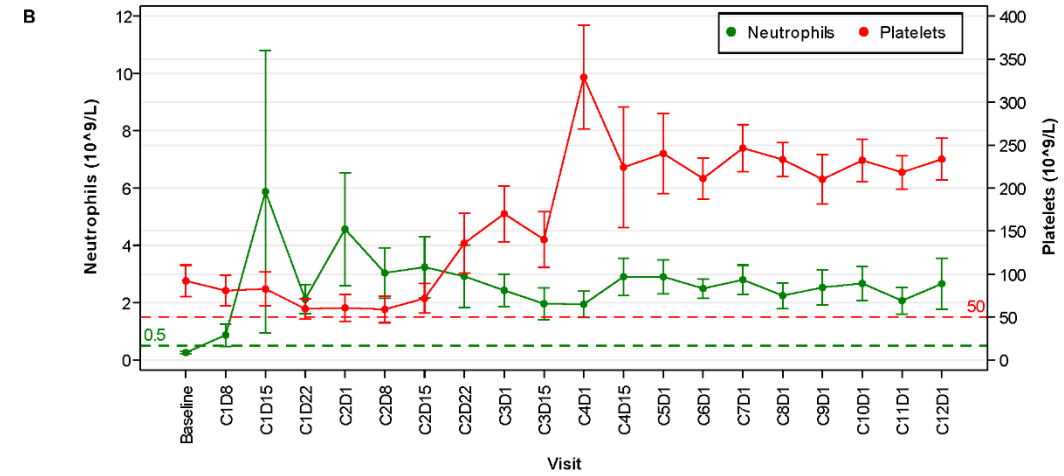

AML Type: Primary, Age: 74, Treatment Duration: 329 Days
SD
MLFS
CR
CR
CR
CR
CR
CR
MR
NE
MR
Neutrophils (10^9/L)
Platelets (10^9/L)
0.5
50
Study Days
Parameter: Neutrophils Platelets
Event: Hospitalization due to AE Grade 3 or higher infectious TEAE Grade 3 or higher bleeding TEAE

FIG A7. Changes in absolute neutrophil count (mean ± standard error) and platelet count (mean ± standard error) over study duration in the full analysis population (A), and in patients who achieved CR/CRh (B). Baseline was defined as the last available assessment before or on the study treatment start date. Dashed lines represent platelet and neutrophil thresholds for CRh. C, cycle; CR, complete remission; CRh, CR with partial hematologic recovery; D, day.



No. of Patients	Baseline	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22	C3D1	C3D15	C4D1	C4D15	C5D1	C6D1	C7D1	C8D1	C9D1	C10D1	C11D1	C12D1
Neutrophils	22	21	22	20	18	19	17	17	18	17	15	15	13	15	15	15	13	13	13	12
Platelets	21	22	22	22	19	17	18	18	18	17	15	14	13	15	15	14	14	13	14	12
Platelets transfusion	8	8	11	8	10	10	8	9	5	3	1	1	0	1	1	0	0	0	0	0



No. of Patients	Baseline	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22	C3D1	C3D15	C4D1	C4D15	C5D1	C6D1	C7D1	C8D1	C9D1	C10D1	C11D1	C12D1
Neutrophils	15	14	15	15	13	14	13	15	15	15	14	14	13	15	15	15	13	13	13	12
Platelets	14	15	15	15	14	13	14	15	15	15	14	13	13	15	15	14	14	13	14	12
Platelets transfusion	5	4	7	4	7	7	5	7	3	2	1	0	0	1	1	0	0	0	0	0

FIG A8. Overall survival. Tick marks indicate censored data. CI, confidence interval; NE, not estimable.

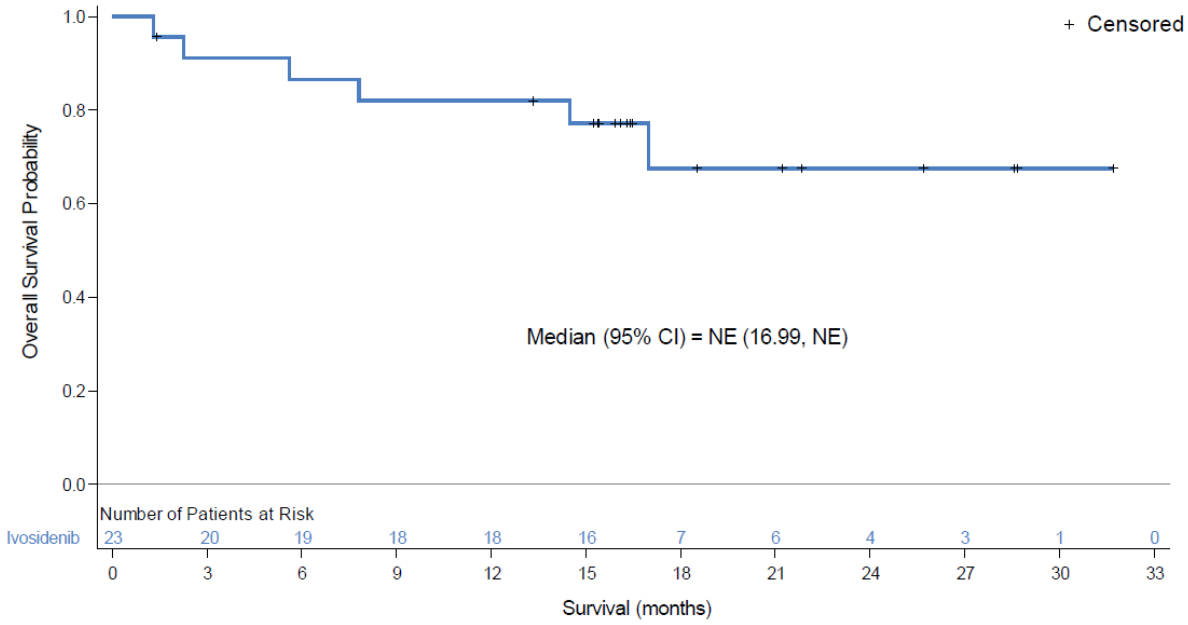


TABLE A4. Per-patient m*IDH1*-R132 Variant Detected and VAF in BMMCs and PBMCs by Next-Generation Sequencing (2% Limit of Detection)

		BMMCs		PBMCs	
BOR	**Time Point**	**Variant**	**VAF**	**Variant**	**VAF**
CR	Baseline	N/A	N/A	p.R132C	0.1
CR	Baseline	p.R132L	0.279	p.R132L	0.021
CR	Baseline	N/A	N/A	p.R132C	0.077
CR	Baseline	p.R132C	0.44	p.R132C	0.317
CR	Baseline	p.R132C	0.396	p.R132C	0.222
CR	Baseline	p.R132C	0.434	p.R132C	0.039
CR	Baseline	p.R132C	0.26	N/A	N/A
CR	Baseline	p.R132C	0.443	p.R132C	0.427
CR	Baseline	p.R132H	0.41	p.R132H	0.175
CR	Baseline	p.R132C	0.412	p.R132C	0.23
CR	Baseline	p.R132C	0.218	N/A	N/A
CR	Baseline	p.R132C	0.479	p.R132C	0.289
CR	Baseline	p.R132H	0.26	p.R132H	0.308
CR	Baseline	N/A	N/A	p.R132C	0.169

CRh	C1D15	N/A	N/A	p.R132L	0.06
CRh	Baseline	p.R132C	0.446	p.R132C	0.404
MLFS	Baseline	p.R132H	0.416	p.R132H	0.386
MLFS	Baseline	N/A	N/A	p.R132H	0.135
SD	Baseline	p.R132C	0.47	p.R132C	0.485
SD	Baseline	N/A	N/A	p.R132C	0.127
SD	Baseline	p.R132C	0.415	p.R132C	0.448
SD	Baseline	p.R132L	0.173	N/A	N/A
N/A	Baseline	p.R132C	0.433	p.R132C	0.286

Abbreviations: BMMC, bone marrow mononuclear cell; BOR, best overall response; C1D15, cycle 1 Day 15; CR, complete remission; CRh, complete remission with partial hematologic recovery; MLFS, morphologic leukemia-free state; N/A, not applicable (sample was not available for testing or sample failed during sequencing); PBMC, peripheral blood mononuclear cell; SD, stable disease; VAF, variant allele frequency.

FIG A9. Correlation of m*IDH1* VAF between BMMCs and PBMCs. VAFs from matched samples collected from both BMMCs and PBMCs were analyzed using the m*IDH1* BEAMing digital polymerase chain reaction assay. Longitudinal m*IDH1* VAF data were available from both BMMCs and PBMCs for 21 patients. A strong correlation was observed (Pearson correlation coefficient [*r*] = .919) between allelic frequencies detected in both sample types, including 99% (372/374) concordance in the mutation clearance calls made (mutation detected [MD]: *IDH1* mutation called VAF ≥ 0.02% to 0.04%; no mutation detected [NMD]: no *IDH1* mutation called ≤ 0.02% to 0.04%). The correlation was determined on a linear scale. BMMC, bone marrow mononuclear cell; m*IDH1*, mutant isocitrate dehydrogenase 1; PBMC, peripheral blood mononuclear cell; VAF, variant allele frequency.

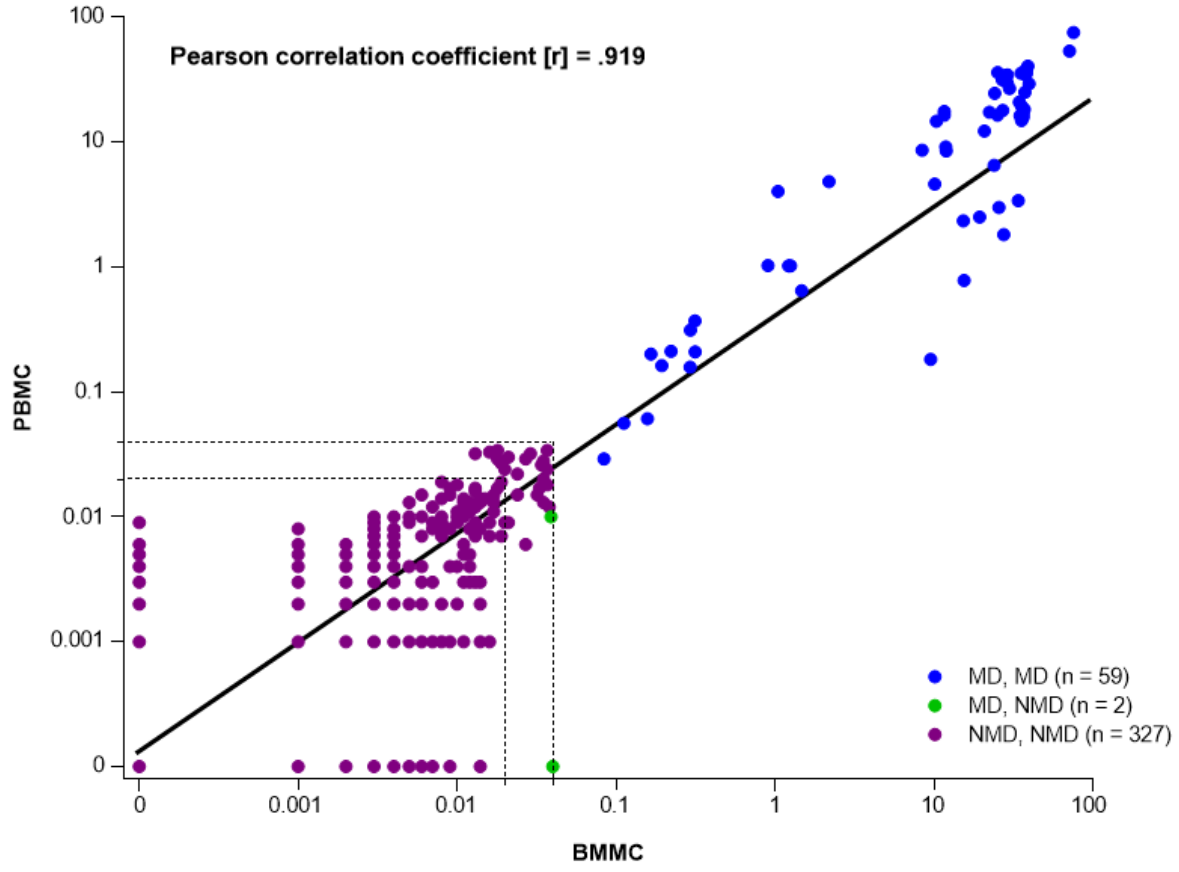
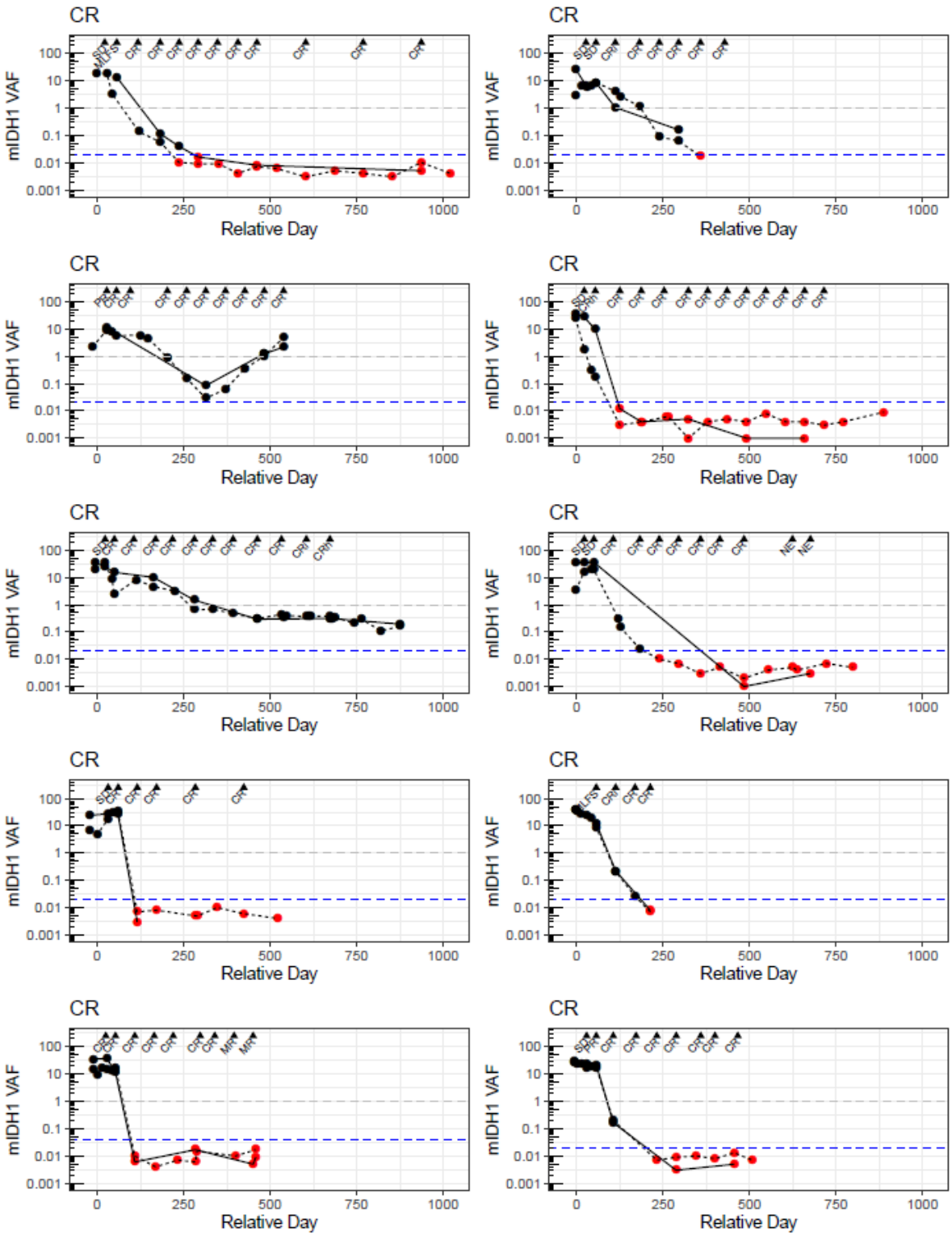
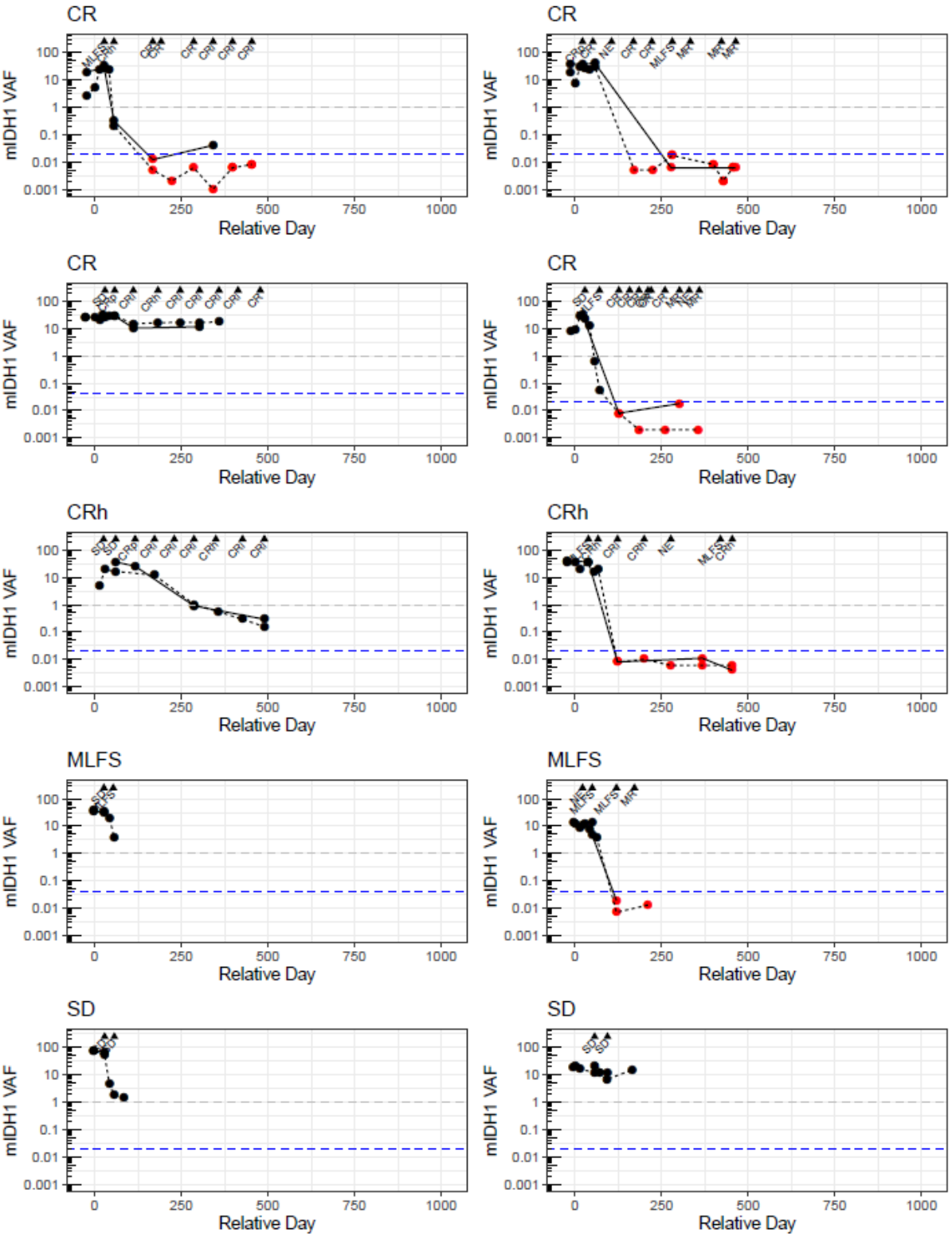
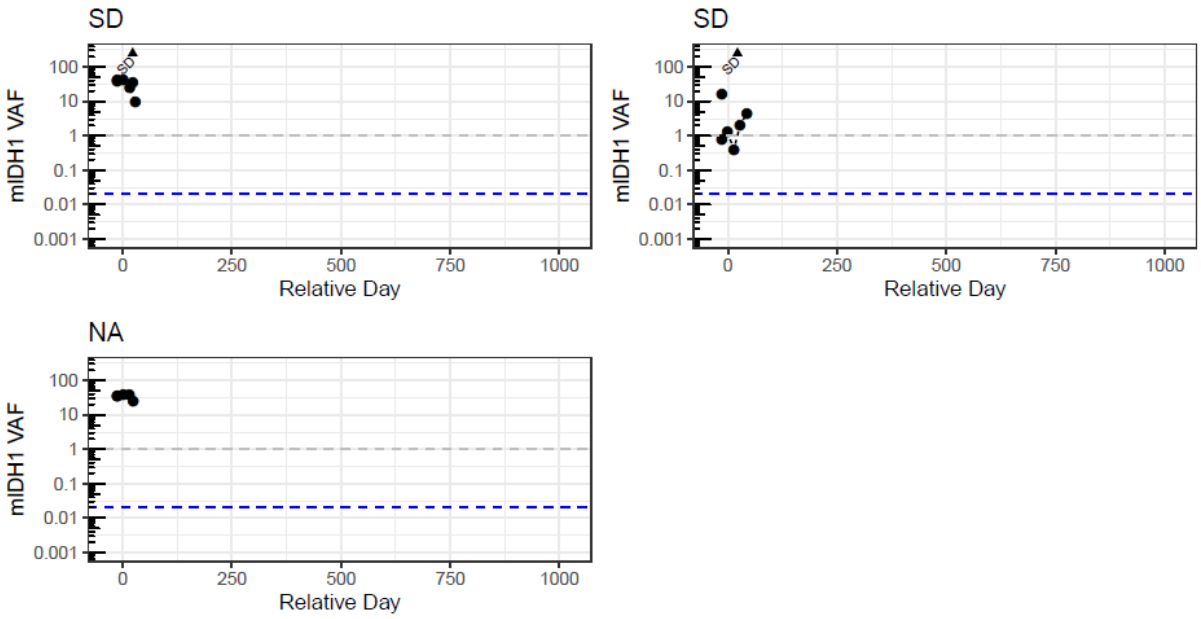


FIG A10. Longitudinal assessment of m*IDH1* clearance by BEAMing digital polymerase chain reaction assay in both bone marrow mononuclear cells (BMMCs) and peripheral blood mononuclear cells (PBMCs) for each patient receiving ivosidenib plus azacitidine (n = 23). Data were available from both BMMCs and PBMCs for 21 patients, including 16 with a best overall response of CR/CRh; two nonresponding patients had data from PBMCs only. Per-patient details are shown in individual plots, including the clinical response captured at each disease assessment, and a call on whether m*IDH1* was detected or not (black circle: m*IDH1* detected, VAF ≥ 0.02-0.04%; red circle: m*IDH1* not detected, VAF ≤ 0.02-0.04%). Solid lines in the plots show BMMC data and dashed lines show PBMC data. VAF cut-offs at the limit of detection (0.02-0.04%) and at 1% are represented by horizontal blue and gray dashed lines, respectively.


CR
mIDH1 VAF
Relative Day
100
10
1
0.1
0.01
0.001
0
250
500
750
1000


CR
CR
CR
CR
CRh
CRh
MLFS
MLFS
SD
SD
mIDH1 VAF
Relative Day
0
250
500
750
1000
100
10
1
0.1
0.01
0.001


SD
mIDH1 VAF
100
10
1
0.1
0.01
0.001
SD
0
250
500
750
1000
Relative Day
SD
mIDH1 VAF
100
10
1
0.1
0.01
0.001
SD
0
250
500
750
1000
Relative Day
NA
mIDH1 VAF
100
10
1
0.1
0.01
0.001
0
250
500
750
1000
Relative Day