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Venetoclax and azacitidine for younger acute myeloid leukemia patients independent of fitness for intensive chemotherapy

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subjects, collected data and edited the manuscript; MLA, AK, CM, MS, MAS, CM, TB, JT, NC, SV and JAG enrolled and treated subjects and edited the manuscript; CJ edited the manuscript; MB, MG, NW, DA, JS, ZP and JZ interpreted data and edited the manuscript.

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Abstract

Venetoclax (ven)+azacitidine (aza) is the standard of care for newly-diagnosed acute myeloid leukemia (AML) patients who are not candidates for intensive chemotherapy (IC). Because prognostic factors for ven/aza and IC differ, an AML patient fit for IC may derive more benefit from ven/aza. We therefore designed a trial for younger, newly-diagnosed AML patients with non-favorable risk disease to receive ven/aza regardless of “fitness” for IC. We aimed to understand toxicity and efficacy in this population, and retrospectively compared outcomes to matched IC patients. Newly-diagnosed non-favorable risk patients ≤60 were enrolled and received ven, dose escalated to 600mg/dailyx28 days, with aza 75mg/m2x7 days on a 28-day cycle. Subjects were encouraged to move expeditiously to allogeneic stem cell transplant (ASCT) in first remission. Thirty-six subjects enrolled. Median age was 49 (22-59). Grade ≥3 neutropenia(42%), anemia(33%), thrombocytopenia(53%) and febrile neutropenia(36%) were common. The overall response rate (ORR) was 25/36 (69%) with 19 (53%) complete remissions; 68% of responders achieved MRD-negativity. Most subjects (53%) bridged to ASCT, and the majority of non-responders were successfully salvaged with IC. The median progression-free-survival (PFS) and overall survival (OS) have not been reached (median follow-up 2.9 years). Compared to IC matched controls, the ORR, ASCT rate and PFS were significantly improved (69% vs 44% [p=0.0495], 53% vs 28% [p-0.0290] and not reached vs 60.8 months [p=0.007]). Hospital days, transfusions and infectious complications were significantly reduced for ven/aza subjects. Ven/aza is feasible for newly-diagnosed, younger, non-favorable risk AML patients, and appears at least as effective as IC.

Introduction

Venetoclax (ven) with azacitidine (aza) is the standard of care for newly diagnosed patients with acute myeloid leukemia (AML) who are unfit for intensive chemotherapy (IC) due to age or comorbidities(1). Treatment guidelines recommend that patients who are candidates for IC should receive this upfront therapy(2). However, in an era in which more than one effective therapy for AML exists, the decision to administer IC only because a patient is able to withstand it should be scrutinized(3).

Furthermore, biological disease-related prognostic factors do not necessarily correlate with “fitness” for IC; “fit” patients may have biological factors that make them unlikely to benefit from IC, even if they are able to survive it. As knowledge surrounding biological risk factors for outcomes evolves to be treatment context-dependent(4, 5), it is clear that favorable and adverse risk factors for IC are not necessarily favorable and adverse risk factors for ven/aza(6). Patients with favorable risk disease per the European Leukemia Network (ELN) criteria(7) may be cured with IC and without an allogeneic stem cell transplant (ASCT) leading to a strong recommendation that eligible patients pursue this treatment(8). However, ELN intermediate and adverse risk patients are typically consolidated with ASCT in first remission, with curative intent(8). With the introduction of ven/aza for patients “unfit” for IC, we questioned whether this might represent a safer, equally efficacious therapy to allow a patient, regardless of their “fitness” for IC, to achieve a remission and proceed to a potentially curative ASCT. In addition, IC can be associated with prolonged hospitalization, debilitating infections that can derail ASCT, and worse quality of life for patients. For all of these reasons, we designed and conducted an investigator-initiated, multi-center pilot study of ven/aza for newly diagnosed younger AML patients with non-favorable risk disease. We report here these outcomes, and a matched-control analysis of patients who were treated with IC.

Methods

Patients

Newly-diagnosed untreated patients aged 18-59, independent of “fitness” for IC, with non-favorable risk disease(9) enrolled. Originally, only adverse risk patients were permitted; a

subsequent amendment allowed intermediate risk patients. Initially, patients with monocytic disease were permitted to enroll; after a planned interim analysis showed inferior outcomes, they were prospectively excluded.

Study Design

This was a prospective, multi-institutional investigator-initiated trial (NCT03573024) approved by the Colorado Multiple Institutional Review Board. The primary endpoint was overall response rate (ORR): complete remission (CR) + CR with incomplete recovery of blood counts (CRi) + morphological leukemia free state (MLFS). Secondary endpoints included the measurable residual disease (MRD) negativity, overall survival (OS), progression free survival (PFS) and toxicity. Stopping rules for futility, based on expectations for IC patients, were planned such that the study was to be suspended if the probability of ORR fell below 55%, using O'Brien Fleming(10) with an observed ORR of 2/6 in Stage 1, 7/12 in Stage 2, 19/27 in stage 3 and 25/36 in stage 4. After stage 3, 18/27 responded; the study was temporarily held. A subsequent analysis showed subjects with monocytic disease had a lower response rate (4/8, 50%) compared to others (14/20, 70%), and the protocol was amended to continue accrual after excluding monocytic subjects. "Monocytic" was defined using French-American-British (FAB) morphologic criteria for M4 and M5 (11), as well as, when available, evidence of monocytic differentiation by expression of at least two of the following markers: CD14, CD64, CD11b and CD11c. Baseline characteristics of the clinical and genetic features of the monocytic subjects and matched controls are shown in Supplemental Table 1.

Treatment

Subjects received aza 75 mg/m^2 IV d1-7/28-day cycles. Ven was escalated to 600 mg on days 1-4. Ven dose adjustments for CYP3A4 inhibitors occurred, targeting dose equivalence of 600mg. Interruptions allowing count recovery, with growth factor as needed, occurred. CR/CRi/MLFS by cycle 2 was required to continue. After at least MLFS that was MRD+, subjects could receive up to 3 additional cycles (consolidation). Once subjects achieved MRD$^-$, they received MRD$^-$ maintenance (5 days aza and 28 days 400mg ven). Subjects with MRD after 4 cycles remained on 7 days aza and 600 mg ven

(Figure 1). All subjects were encouraged to proceed to ASCT expeditiously after response.

After induction, the start of consolidation or maintenance could proceed in the absence of possibly/related > grade 2 non-hematologic toxicity. In the presence of possibly/related > grade 2 non-hematologic toxicity, venetoclax was interrupted until resolution to grade 1 and then resumed at the current dose (first occurrence) or dose reduced (second occurrence) per the study protocol. The third episode of >grade 3 neutropenia/thrombocytopenia that lasted >14 days required a reduction of venetoclax to 21/28 days. Grade 3 neutropenia with infection or fevers, or grade 4 neutropenia lasting > 42 days, resulted in a venetoclax interruption; the protocol also stated cycles may be delayed for any grade of hematologic toxicity. Please see Supplemental Files for full study protocol.

Study Assessments

Adverse events (AEs) were graded per the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Responses were assessed per ELN 2017. *RAS* pathway was defined as mutations in *NRAS*, *KRAS*, *PTPN11, NF1* or *CBL*. MRD was measured by multidimensional flow cytometry; negativity was <0.01%(12). AML with myelodysplasia-related changes (AML-MRC) was defined per the International Consensus Classification(13).

Statistical Analysis

PFS for responders was the time from diagnosis to progression, death or last follow-up; for non-responders the event date was date of diagnosis. OS was the time from diagnosis to death or last follow-up. Kaplan-Meier estimate of survival function calculated median survival time and its 95% confidence interval (CI). Conditional Cox regression methods, conditioning on case-control matches, compared survival. McNemar's test was used for binary outcomes. Categorical outcomes >two levels used kappa analysis. For continuous outcomes, linear mixed models conditioning on case-control matches compared outcomes. Wilcoxon Signed Rank was used when normality conditions were not met.

Subjects were matched 1:1 to historical controls treated from June 2013 to June 2024 at respective institutions. Controls were newly-diagnosed patients who received IC; matching was based on age within five years and ELN 2017(9) risk.

Results

Thirty-six subjects were accrued between November 2018 and October 2024. The median age was 49 years (range 22-59), 56% were female, 22% (8/36) had secondary AML (known prior MDS or therapy-related), 56% (20/36) had AML-MRC, 81% (29/36) were adverse risk and 19% (7/36) were intermediate risk by ELN 2017 criteria(9). See Table 1 for baseline characteristics of all subjects. The median number of cycles completed was 2 (range 0-6). Four subjects had a second induction cycle after not responding to the first cycle. Ten subjects had consolidation cycle #1, four had consolidation cycle #2 and two had consolidation cycle #3. Five subjects had maintenance cycles, all of which were MRD^- cycles; three subjects had one cycle, one subject had two cycles and one subject had three cycles. The median days of venetoclax during induction cycle #1 was 28 (range 14-28); 28 days was also the median days of venetoclax for subjects who completed consolidation cycles 1 and 2 and maintenance. The median number of days between the first and second cycle was 15 (range 7-42); between cycles 2 and 3 the median days between cycles was 28 days (14-35). The median number of cycles to first response was 1 (range 1-2) and the median number of cycles to best response was 1 (range 1-2).

Safety

There were 1,031 unique AEs. The most common ≥grade 3 hematologic AEs were neutropenia (42%), anemia (33%), thrombocytopenia (53%) and febrile neutropenia (36%). The most common non-hematologic ≥grade 3 AEs were mucositis/oral pain (19%), hypoxia (17%) and respiratory failure (11%). Tumor lysis syndrome occurred in 1 subject (grade 3). Table 2 includes the incidence of ≥grade 3 AEs regardless of attribution that occurred in ≥1 subjects. There were 2 deaths in the first 30 days (6%).

Efficacy

The ORR was 69% (25/36); 19 patients (53%) achieved CR, 2 (6%) achieved a CRi and 4 (11%) achieved MLFS. Seventeen subjects (47%) achieved MRD-negative responses (17/25 responders, 68%), and MRD negativity was achieved after a median of 1 cycle (range 1-4). The median duration of response (DOR) was not reached (95% CI: NR, NR) and median duration of CR was not reached (95% CI: NR, NR) (Supplemental Figure 1). Nineteen subjects (53%) were bridged to ASCT in first remission after ven/aza (Table 3).

Eleven subjects (31%) were refractory to treatment. Two were not salvaged, one due to death and the other due to refusal of further therapy. Nine subjects were salvaged with IC, including 7+3 (N=4), fludarabine/cytarabine/idarubicin/G-CSF/venetoclax (FLAG/IDA/VEN) (N=2), FLAG/IDA (N=1), 7+3 with midostaurin (N=1), and liposomal daunorubicin/cytarabine (N=1). Of the 9 who were salvaged, 7 achieved a response (N=4 CR, N=2 CRi, N=1 MLFS); two were refractory. Five ultimately proceeded to ASCT and 3 remain alive.

Five subjects who responded relapsed before ASCT; all were relatively early (median 98 days, range 35-125 days). All received IC salvage (N=3 7+3, N=1 FLAG/IDA/VEN, N=1 mitoxantrone/etoposide/cytarabine [MEC] with a novel therapy); 1/5 responded (N=1 CR) and 2 ultimately received ASCT and remain alive.

The median PFS and OS have not been reached (Figure 2). The respective 95% CIs were 29 days, NR and 123 days, NR. Median follow-up time was 2.9 years (95% CI: 1.4, 4.5).

Response outcomes were assessed by disease and molecular characteristics. Using the 4-gene molecular prognostic risk signature system(4), the ORR for higher benefit subjects was 18/23 (78%), 5/9 (56%) for intermediate benefit subjects and 2/4 (50%) for the lower benefit group (Supplemental Table 2). The 20 subjects with AML with MRC (13) had an ORR of 70% (14/20) with a 45% CR rate (9/20). Median DOR was not reached (95% CI: 127 days, NR), and median OS was not reached (95% CI: 151 days, NR) (Supplemental Figure 2). In contrast, subjects with monocytic AML had a 50% ORR (4/8), median DOR

was 136.5 days (95% CI: 64 days, NR), and median OS was 313.5 days (95% CI: 60 days, NR) (Supplemental Figure 3). Of the monocytic non-responders, 3/4 had KMT2A gene rearrangements, while 1/4 monocytic responders had this chromosomal abnormality. Two of four monocytic responders and 2/4 monocytic non-responders had *RAS* pathway mutations; no monocytic patients had an *NPM1* mutation in this non-favorable risk population. Subjects categorized by the 4-gene prognostic score(4) had marginally distinct OS outcomes, acknowledging the limitations of small numbers (higher benefit median OS=NR, 95% CI: [662, NR], intermediate benefit median OS=NR, 95% CI: [114, NR], lower benefit median OS=214.5 days, 95% CI: [48, NR]; logrank p=0.07; Figure 3).

Case-control matched comparison

Subjects were retrospectively compared to a dataset of historical patients treated with first-line IC; each subject was matched 1:1 with a patient at their own institution based on age +/- 5 years and ELN risk. The median age for this control group was 46 (range 19-59); 58% were female and 14/36 (39%) had secondary AML. Baseline characteristics are shown in Table 1, with comparisons made to the group of study subjects. Of note, 12/36 (33%) of patients did not have comprehensive genomic testing given they were treated before this was available.

Controls had an ORR of 44% (16/36); 10 patients (28%) achieved CR, 2 (11%) achieved CRi, 2 (6%) achieved MLFS. Given the earlier time period in which many of these patients were treated, MRD assessments were not done consistently and are not reported. Death within the first 30 days occurred in four patients (11%). Ten patients (28%) were bridged to ASCT in first remission after IC. The median duration of response was NR (95% CI: 123, NR), and the median duration of complete remission was NR (95% CI: 198, NR) (Supplemental Figure 1C and D).

Twenty patients were refractory to IC; 3 (15%) died in the first 30 days, prior to salvage treatment. Seventeen were salvaged, 12 with high-intensity chemotherapy regimens (N=3 high-dose cytarabine, N=6 clofarabine/cytarabine/G-CSF, N=1 FLAG/IDA/VEN,

N=1 MEC + novel therapy, N=1 clofarabine + cytarabine), and five with lower-intensity therapies (N=2 ven/aza, N=2 decitabine, N=1 menin inhibitor). Of these, nine (53%) responded to their first salvage (N=5 CR, N=3 CRi, N=1 MLFS). Eleven of the refractory patients proceeded to ASCT, and six remain alive.

Two patients relapsed after IC and before ASCT; both relapses occurred early (duration of response 84 and 75 days). One patient was salvaged with cytarabine/cladribine/cytarabine/G-CSF/mitoxantrone and did not respond; they did not proceed to ASCT and did not survive. The other patient was salvaged with ven/aza; they achieved a CR, proceeded to ASCT and remain alive.

When trial subjects and matched controls were compared, there was a significant difference in ORR (69% vs 44%, respectively; p = 0.0495) (Table 3). Given the high rate of non-response, controls had a median PFS of 0 (0, 123); ven/aza subjects had a significantly longer median PFS (p=0.007). There was no significant difference in median OS between subjects (NR) and matched controls (5.0 years); p=0.3206 (Supplemental Figure 4). Significantly more subjects were bridged to ASCT compared to controls (53% vs 28%, p=0.029) (Table 3).

There were significant reductions in days spent in the hospital (9 vs 30, p<0.0001), and the number of units of platelets (3.5 vs 11, p<0.0001) and red blood cells (4 vs 9, p<0.0001) transfused in the first 30 days in ven/aza subjects compared to controls. In addition, there were fewer infectious complications in the first 30 days (43% vs 94%, p<0.0001) in study subjects (Table 3). Deaths in the first 30 days did not differ significantly between groups (6% for subjects and 11% for controls, p=0.321).

Discussion

Ven/aza represented a clinical improvement for patients ineligible for IC(1), but restricting this therapy to this population, based on the premise that all who are likely to survive IC are likely to benefit from it, is ill-conceived in an era in which there is more than one effective treatment. This clinical trial was the first to query whether ven/aza is at least as

effective, and potentially less toxic, than IC in newly diagnosed non-favorable risk IC-eligible patients. In this small, uncontrolled study, we show that use of ven/aza in this population results in high response rates, deep remissions, frequent ASCT and the possibility of long-term OS. Compared with age- and risk-matched controls who received first-line IC, there appeared to be no compromise in clinical outcomes for the study subjects; in fact, ORR, patients who received ASCT and PFS were all significantly improved in the retrospective matched comparison. The most common AEs were largely hematologic toxicities that occurred in similar proportion to that reported in the definitive trial(1), and there was not a higher than expected rate of infectious or bleeding complications. Indeed, when compared with matched controls, there were large favorable differences in length of inpatient stay, infectious complications and transfusion support.

There is understandable concern, given the long history of IC in our field, that up-front ven/aza, if it fails in this population, may prohibit “fit” patients from receiving an IC regimen. However, we report here that nearly all refractory subjects were salvaged with IC, most successfully. A strategy to routinely use IC as the salvage option could reserve this more toxic therapy for those who truly need it. However, this would need to be carefully weighed against other experiences suggesting IC can be compromised when prior lower intensity therapies were administered for antecedent myelodysplastic syndromes(14-16). Furthermore, while this protocol defined “refractory” as lack of response to two cycles of ven/aza, there was discomfort in recommending a second cycle for non-responders when these patients were eligible for IC; only 4/13 who were refractory to the first cycle of induction remained on the study and received a second cycle. Future studies should consider how best to define “refractory” to ven/aza.

Analyses that can identify a group of patients with poor outcomes from IC who show particular benefit from ven/aza can be uniquely helpful in the clinical setting(6). One relatively large group for whom this contrast appears to apply is for patients with secondary-type AML (including those with prior MDS, therapy-related AML or MDS-related features). In this subset of 23 subjects (64% of the total population) the ORR was 17/23 (74%) while for the 21 controls the ORR was 7/21 (33%) ($p=0.0069$); with respect

to median OS, it was NR (95% CI: 250 days, NR) for the subjects and 572 days (95% CI: 250 days, NR) for the controls (p=0.032). Conversely, identifying features that carry negative prognostic significance for ven/aza but not IC are equally valuable. After a pre-planned interim analysis revealed inferior responses in patients with monocytic disease biology, at a time when it was being increasingly recognized that this was a poor prognostic factor for ven/aza(17-19), the study was amended to exclude these patients and accrual was completed. Unlike other risk factors that have negative prognostication for patients with IC as well ven/aza, such as *TP53* mutations or MECOM gene rearrangements, monocytic disease biology is not typically considered to be a risk factor for IC. Therefore, it was determined that monocytic patients who could receive IC should. We would recommend such a design for any ongoing or future randomized studies.

Results from the ongoing randomized study of ven/aza versus IC (NCT04801797) were recently presented in abstract form (Fathi et al, 2025); this very important study began three years after our study commenced accrual. While eligibility criteria differed (our study included only younger subjects, allowed those with *FLT3* mutations and ultimately excluded subjects with monocytic disease), the reported ORR for ven/aza (76%) and IC (53%) were similar to our reported results, as were favorable outcomes with respect to length of hospitalization. In addition, a recent study for newly diagnosed patients 18-59 who were randomized to receive ven/decitabine induction versus IC reported response rates for ven/decitabine that were non-inferior with less toxicity(20); however, subjects assigned to ven/decitabine received IC consolidation (up to 4 cycles of high-dose cytarabine consolidation), making it difficult to ascertain from this study whether a fully non-IC regimen is feasible for this population. A Markov analysis suggested ven/aza might be preferred for younger adverse risk, but not intermediate risk(21), patients, similar to the findings of a retrospective comparison study(6).

At the time this trial was conceived, it was thought that a higher dose of ven might be tolerated by this patient population and may help improve efficacy. Earlier phase ven/aza studies escalated to 600 mg of ven and beyond(22), and the labeled ven dose with low dose cytarabine is 600 mg(23). The toxicity profile, particularly for hematologic toxicity,

did not appear more severe for study subjects than what has been previously reported, with ≥grade 3 neutropenia, thrombocytopenia and febrile neutropenia rates of 42%, 53% and 36% for this study, respectively, and 42%, 45% and 30%, respectively, in the definitive phase 3 study of 400 mg of ven with aza(1). Despite this, we see no reason to promulgate the 600 mg dose of ven in this population and would recommend future studies be done with the standard 400 mg dose.

If the ultimate strategy for these patients is ASCT, one could reasonably question whether the use of ven/aza is as effective as IC for post-ASCT outcomes. Primarily, one could look to the success rate of ven/aza versus IC for effectively bridging patients to ASCT; our study suggests ven/aza is more successful at this outcome, whether due to its higher response rate or a reduction in early morbidity and mortality. Putting this aside and only evaluating post-ASCT outcomes for all of those who proceed to ASCT, no prospective head-to-head data comparing ven/aza and IC exist. However, very promising long-term data for older patients who proceed to ASCT after ven/aza have been reported(24), and retrospective comparisons do not show obvious signs of deficiency for ven/aza bridging strategies compared with IC(25). Only a prospective study can adequately answer this question.

This study was small and non-randomized, limiting the applicability of these findings to larger populations. In addition, the retrospective matching analysis was not a pre-specified analysis, and the IC patients were mostly treated in a slightly earlier era. Thus, small differences in practice patterns, including supportive care, salvage regimens and ASCT eligibility, may have skewed the comparison favorably toward ven/aza.

In summary, ven/aza for younger newly diagnosed AML patients given regardless of fitness for IC in a mostly adverse risk population resulted in an ORR of 69%, CR rate of 53%, most subjects bridging successfully to ASCT and median OS not yet reached with a median follow-up of nearly three years. Those with monocytic disease features were ultimately excluded because of lower response rates. ORR, PFS and ASCT rates were

higher compared to matched controls who received IC, with significant decreases in hospitalization, transfusion needs and infectious complications.

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Table 1: Baseline characteristics of study subjects (cases) and matched historical controls, with statistical comparisons

Variable	Cases*	Controls**	Matched Analysis p-value
	N = 36	N = 36	
Sex			
Female	20 (55.6%)	21 (58.3%)	0.8084†
Male	16 (44.4%)	15 (41.7%)	
Age			0.8791‡
Median	49	45.5	
Baseline Blasts			0.388‡
Median	46	50	
Treatment-related	3 (8.3%)	8 (22.2%)	0.0588†
Median year of diagnosis (range)	2022 (2018-2024)	2017 (2013-2024)	< 0.0001‡
Known Prior MDS	5 (13.9%)	6 (16.7%)	0.7630†
Monocytic	8 (22.2%)	16 (44.4%)	0.0593†
Complex cytogenetics	15 (41.7%)	15 (41.7%)	1.000†
Monosomal	6 (16.7%)	10 (27.8%)	0.2850†
KMT2A gene rearrangement	6 (16.7%)	9 (25.0%)	0.4054†
MDS-related per WHO(26)	20 (55.6%)	15 (48.4%)	0.5271†
4 gene signature(4)			Statistical comparisons not attempted due to missing data for controls
Higher benefit	23 (63.9%)	15 (62.5%)	
Intermediate benefit	9 (25.0%)	7 (29.2%)	
Lower benefit	4 (11.1%)	2 (8.3%)	
Unclassifiable	0	12 (33%)	
ELN Group(9)			
Adverse	29 (80.6%)	29 (80.6%)	1.000†
Intermediate	7 (19.4%)	7 (19.4%)	
RAS pathway	8	9	

	(22.2%)	(34.0%)	Statistical comparisons not attempted due to missing data for controls
PTPN11	3 (8.3%)	3 (13.0%)	
NPM1	1 (2.8%)	1 (3.0%)	
IDH1/2	11 (30.6%)	3 (13.0%)	
TP53	4 (11.1%)	2 (8.0%)	
ASXL1	5 (14%)	2 (8.0%)	
RUNX1	5 (13.9%)	7 (29.0%)	
FLT3 ITD	4 (11.1%)	1 (4.0%)	

*Cases=study subjects who received venetoclax+azacitidine
**Controls=retrospectively matched controls who received intensive chemotherapy
†McNemar's test
‡Paired T-test
§Kappa test
RAS pathway=NRAS, KRAS, CBL, PTPN11 and NF1
MDS=myelodysplastic syndrome
KMT2a=lysine methyltransferase 2A
WHO=World Health Organization
ELN=European leukemia network
ITD=internal tandem duplication

Table 2: Adverse events regardless of causation, that were grade 3 or greater and occurred in more than one study subject

Adverse Event Description	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)	≥Grade 3 (%)
Hematologic				
Anemia	10 (28%)	2 (6%)	0	12 (33%)
Febrile Neutropenia	13 (36%)		0	13 (36%)
Neutropenia	7 (19%)	8 (22%)	0	15 (42%)
Thrombocytopenia	9 (25%)	10 (28%)	0	19 (53%)
Non Hematologic				
Bronchopulmonary hemorrhage	1 (3%)	1 (3%)		2 (6%)
Dyspnea	2 (6%)	0	0	2 (6%)
Fatigue	2 (6%)	0	0	2 (6%)
Headache	2 (6%)	0	0	2 (6%)
Hypermagnesemia	2 (6%)	0	0	2 (6%)
Rash	2 (6%)	0	0	2 (6%)
Mucositis/oral pain	7 (19%)	0	0	7 (19%)
Hypoxia	5 (14%)	1 (3%)	0	6 (17%)
Respiratory failure	0	3 (8%)	1 (3%)	4 (11%)
Septic shock	1 (3%)	0	1 (3%)	2 (6%)
Cellulitis	2 (6%)	0	0	2 (6%)
Syncope	2 (6%)	0	0	2 (6%)

Table 3: Efficacy outcomes for study subjects and controls

Variable	Cases	Controls	Matched Analysis p-value
Overall response rate (%)	25/36 (69%)	16/36 (44%)	0.0495†
Complete response (%)	19 (58%)	10 (28%)	0.1083†
Complete response with incomplete recovery of blood counts (%)	2 (6%)	4 (11%)	0.4142†
Complete response and complete response with incomplete recovery of blood counts (%)	21 (58%)	14 (39%)	0.1083†
Morphologic leukemia free state (%)	4 (11%)	2 (6%)	0.4142†
Refractory (%)	11 (31%)	20 (56%)	0.0495†
Bridged to ASCT (%)	19 (53%)	10 (28%)	0.0290†
Median progression free survival (95% CI)	NR, (29, NR)	0 (0, 123)	0.0071‡
Median overall survival (95% CI)	NR, (389, NR)	1825, (283, NR)	0.3206‡
Death in first 30 days (%)	2 (6%)	4 (11%)	0.3206†
Median days in hospital in the first 30 days (interquartile range)	9 (5, 16)	30 (26.5, 30)	< 0.0001§
Median units of platelets transfused in the first 30 days (interquartile range)	3.5 (0, 8)	11 (6.5, 23.5)	< 0.0001§
Median units of red blood cells transfused in the first 30 days (interquartile range)	4 (1, 7.5)	9 (7, 11.5)	< 0.0001§
Experienced infectious complications in the first 30 days (%)	15 (43%)	34 (94%)	< 0.0001§

†McNemar's test
‡Cox regression
§Wilcoxon signed rank
ASCT=allogeneic stem cell transplantation
NR=not reached

Figure Legends

Figure 1: Outline of study schema

Figure 2: Time to event outcomes for all study subjects. A)Overall survival; B) Progression free survival

Figure 3: Median overall survival of study subjects stratified by the 4-gene classifier prognostic system for venetoclax+azacitidine

Figure 1

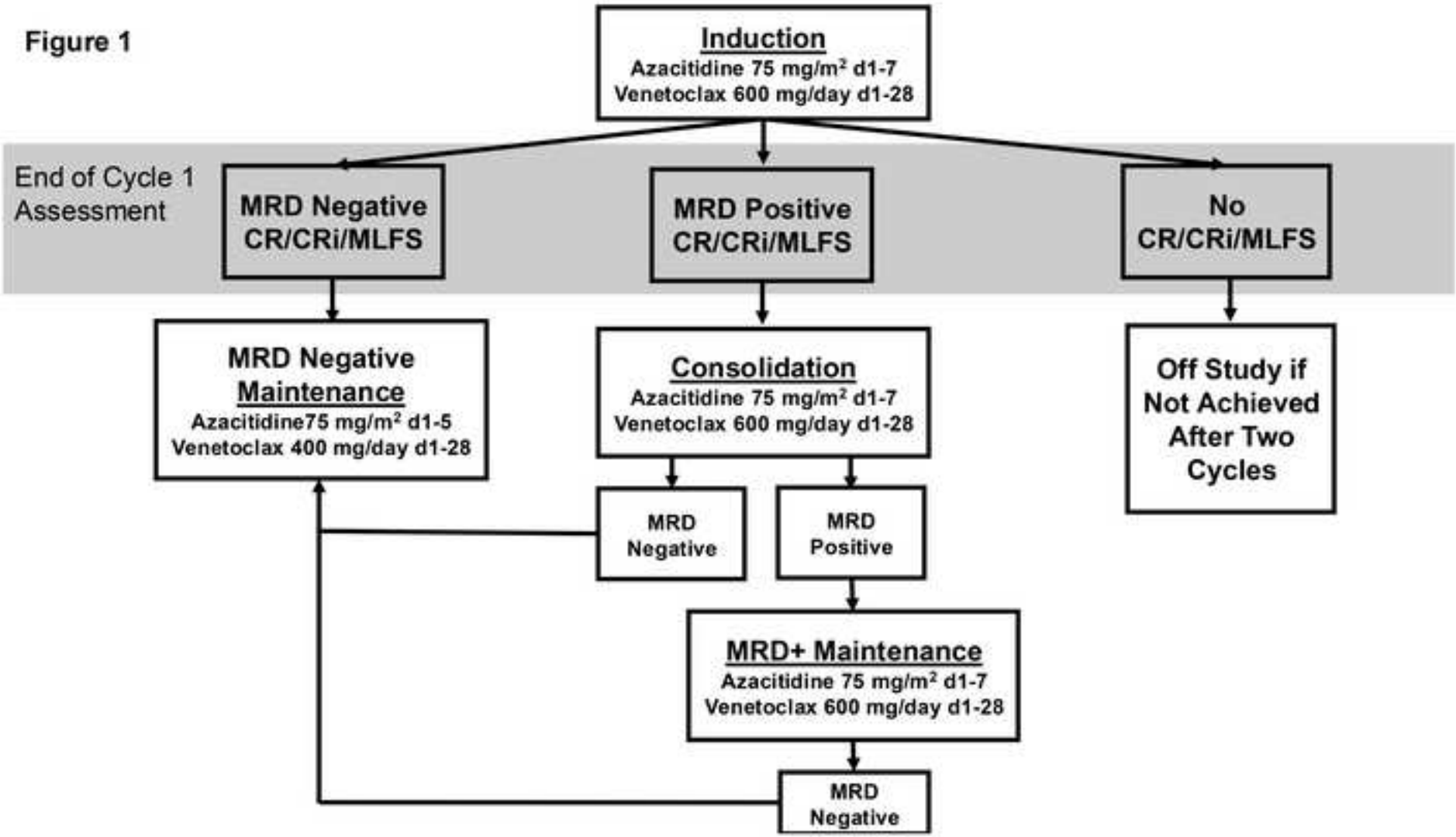

Figure 2

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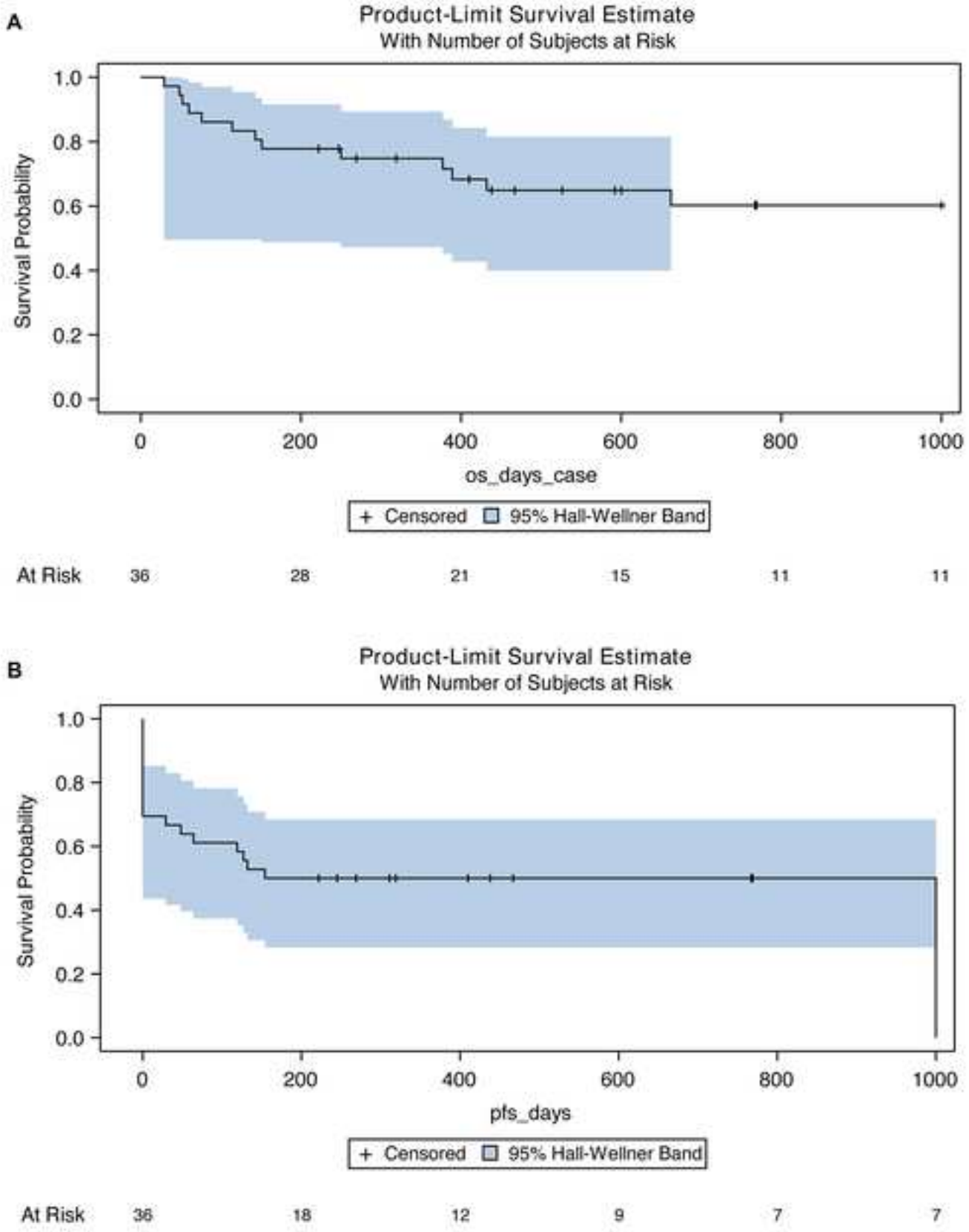

Figure 3

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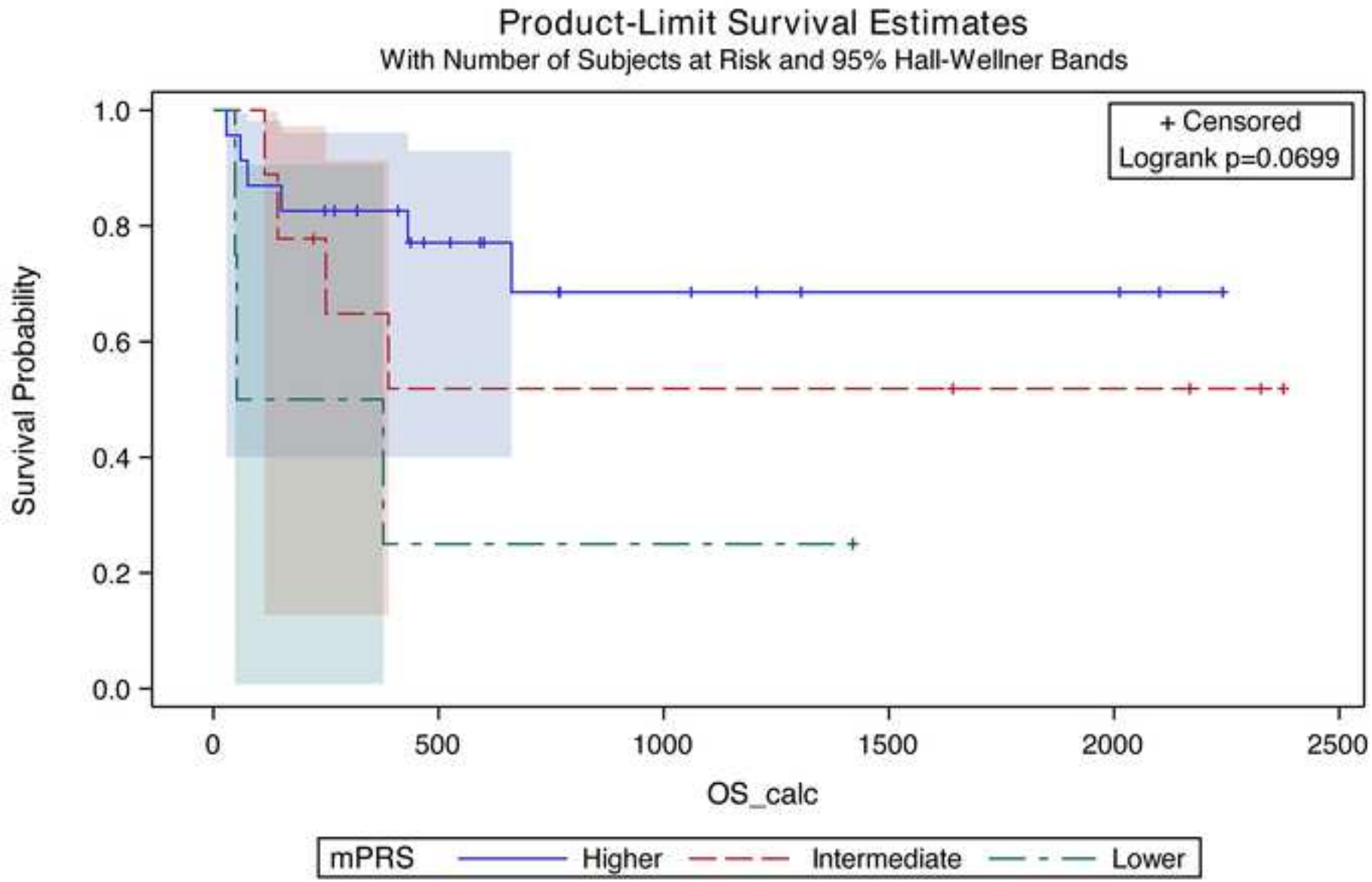


Supplemental Table 1: Baseline clinical and genetic features of the eight study subjects and 16 matched controls with monocytic disease features

Subject/ Control*	Sex	Age	Baseline Blasts (%)	KMT2A	Mutational Profile	ELN† Risk Group(7)	Molecular Prognostic Risk Signature(4)	Best Response	Salvage Therapy and Response
Subject 1	F	22	70	Y	NRAS	N/A	Intermediate	CR	N/A
Subject 2	M	36	42	N	IDH2, ASXL1, NRAS, PTPN11, SMC1A	N/A	Intermediate	CR	N/A
Subject 3	M	33	50	Y	FLT3 TKD, NRAS, ETV6, U2AF1, KRAS, NF1	N/A	Intermediate	No Response	7+3 with FLT3 inhibitor; CR
Subject 4	F	42	82	Y	KRAS, NF1	N/A	Intermediate	No Response	7+3; no response
Subject 5	M	54	70	N	TP53	N/A	Lower	CR	N/A
Subject 6	M	56	90	Y	NONE	N/A	Higher	No Response	No further therapy
Subject 7	M	22	28	N	SF3B1, RUNX1	N/A	Higher	CR	N/A
Subject 8	M	38	95	N	NRAS, NF1, ASXL1	N/A	Intermediate	No Response	7+3; CRi
Control 1	F	25	78	Y	EZH2, PML	Adverse	N/A	CR	N/A
Control 2	M	19	90	Y	ASXL1	Adverse	N/A	CR	N/A
Control 3	M	28	100	Y	KRAS, RUNX1	Adverse	N/A	CRi	N/A
Control 4	F	31	50	N	NRAS, RUNX1	Adverse	N/A	CRi	N/A
Control 5	M	28	80	Y	NONE	Adverse	N/A	CRi	N/A
Control 6	F	43	30	N	NOT DONE	Adverse	N/A	No Response	GCLAC; no response
Control 7	F	46	33	Y	NONE	Adverse	N/A	CR	N/A
Control 8	M	47	80	Y	IDH2, RUNX1, DNMT3A	Adverse	N/A	No Response	Azacitidine + venetoclax; CRi
Control 9	F	55	80	N	NOT DONE	Adverse	N/A	MLFS	N/A
Control 10	M	57	30	N	U2AF1, PTPN11, TET2, ASXL1	Adverse	N/A	No Response	No further therapy
Control 11	M	56	80	N	NOT DONE	Adverse	N/A	CR	N/A

Control 12	M	48	80	N	NOT DONE	Adverse	N/A	CR	N/A
Control 13	F	54	62	N	PTPN11, U2AF1	Intermediate	N/A	CR	N/A
Control 14	F	56	55	N	NONE	Adverse	N/A	No Response	Menin inhibitor; CRi
Control 15	F	55	45	N	DNMT3A, NRAS, TP53	Adverse	N/A	No Response	No further therapy
Control 16	F	30	49	Y	KRAS	Intermediate	N/A	No Response	Decitabine; no response

*Subjects were study participants and received venetoclax + azacitidine; controls were treated with intensive chemotherapy regimens

†European Leukemia Network

CR=complete remission

CRi=complete remission with incomplete recovery of blood counts

MLFS=morphologic leukemia free state

GLCAC=GCSF+clofarabine+cytarabine

Supplemental Table 2: Response rates for study subjects stratified by the 4-gene molecular prognostic risk signature(4)

	Overall Response Rate	Complete Remission	Complete Remission with Incomplete Recovery of Blood Counts	Morphologic Leukemia Free State	No Response
Higher Benefit (N=23)	18/23 (78%)	13/23 (57%)	2 (9%)	3 (13%)	5 (22%)
Intermediate Benefit (N=9)	5/9 (56%)	5/9 (56%)	0	0	4/9 (44%)
Lower Benefit (N=4)	2/4 (50%)	1/4 (25%)	0	1/4 (25%)	2/4 (50%)

Supplemental Figure Legends

Supplemental Figure 1: Response duration in study subgroups. A)Median duration of response (inclusive of complete remission, complete remission with incomplete recovery of blood counts and morphologic leukemia free state) in study subjects. B)Median duration of complete remission in study subjects. C)Median duration of response in controls. D)Median duration of complete remission in controls.

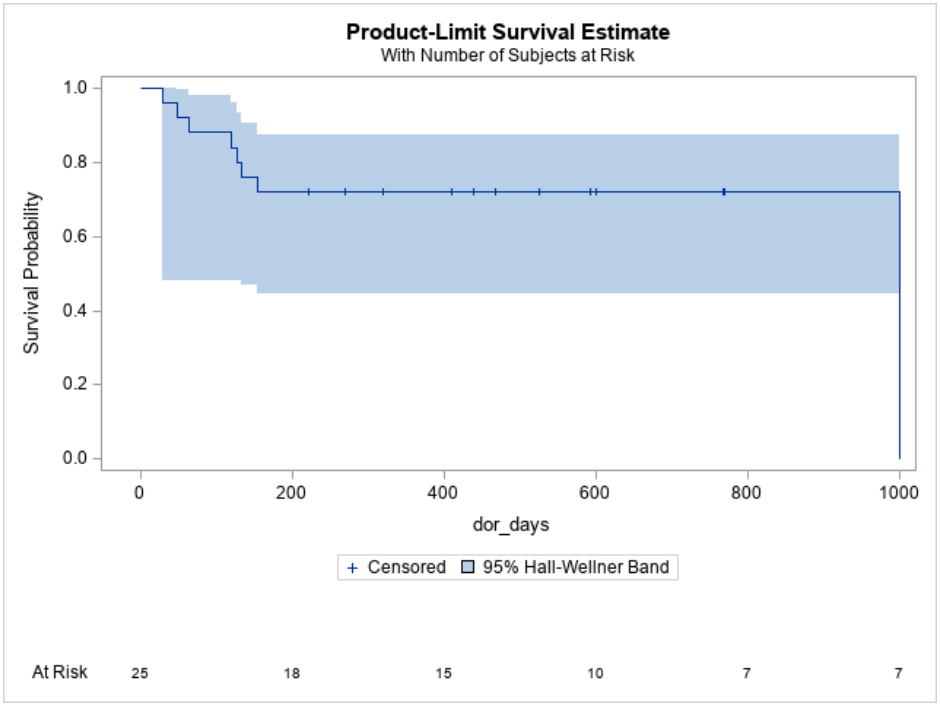
Supplemental Figure 2: Subjects with myelodysplasia-related changes: A)Median duration of response and B)Median overall survival

Supplemental Figure 3: Subjects with monocytic acute myeloid leukemia: A)Median duration of response and B)Median overall survival

Supplemental Figure 4: Study subjects compared with matched historical controls who received intensive chemotherapy: A)Overall survival and B) progression free survival

Suppl Figure 1

A



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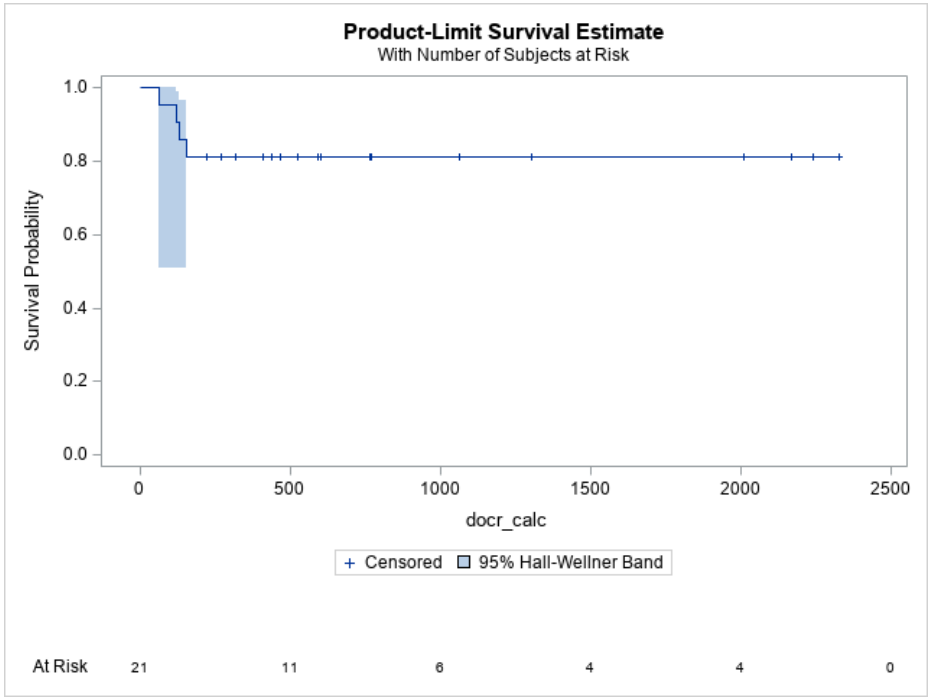

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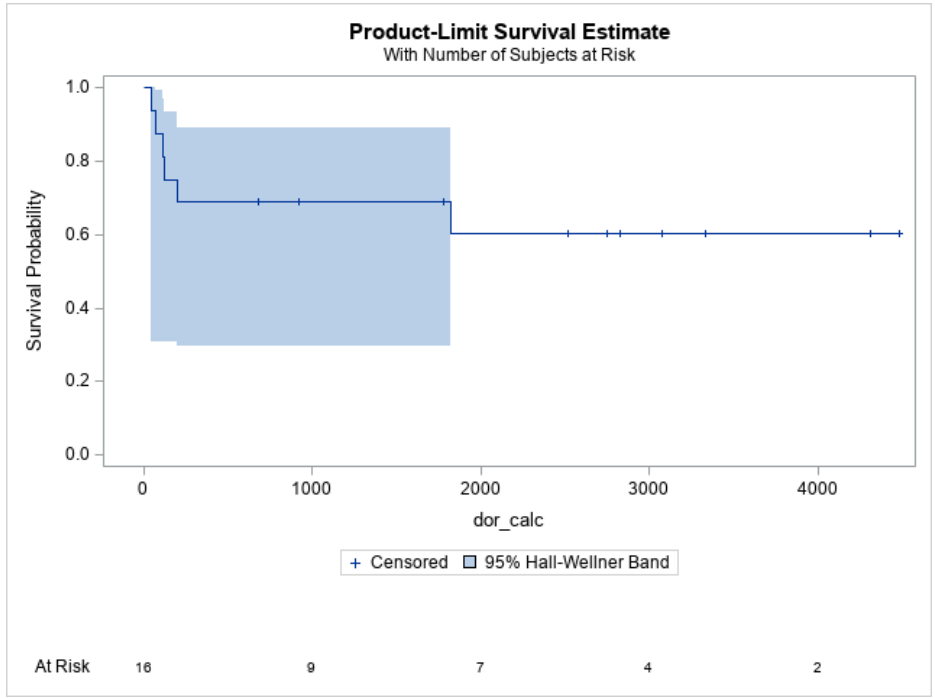

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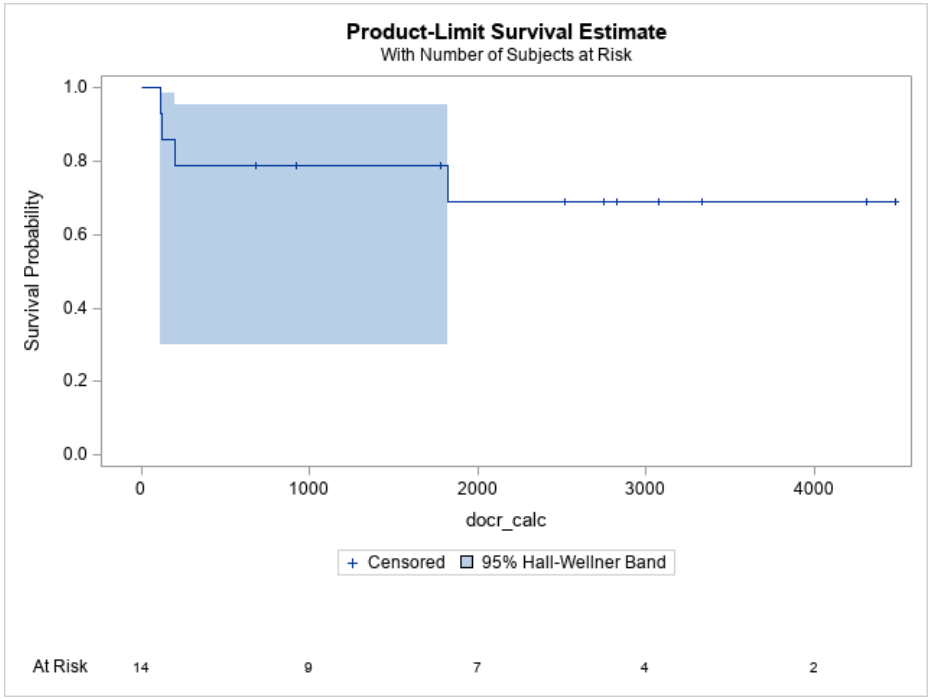
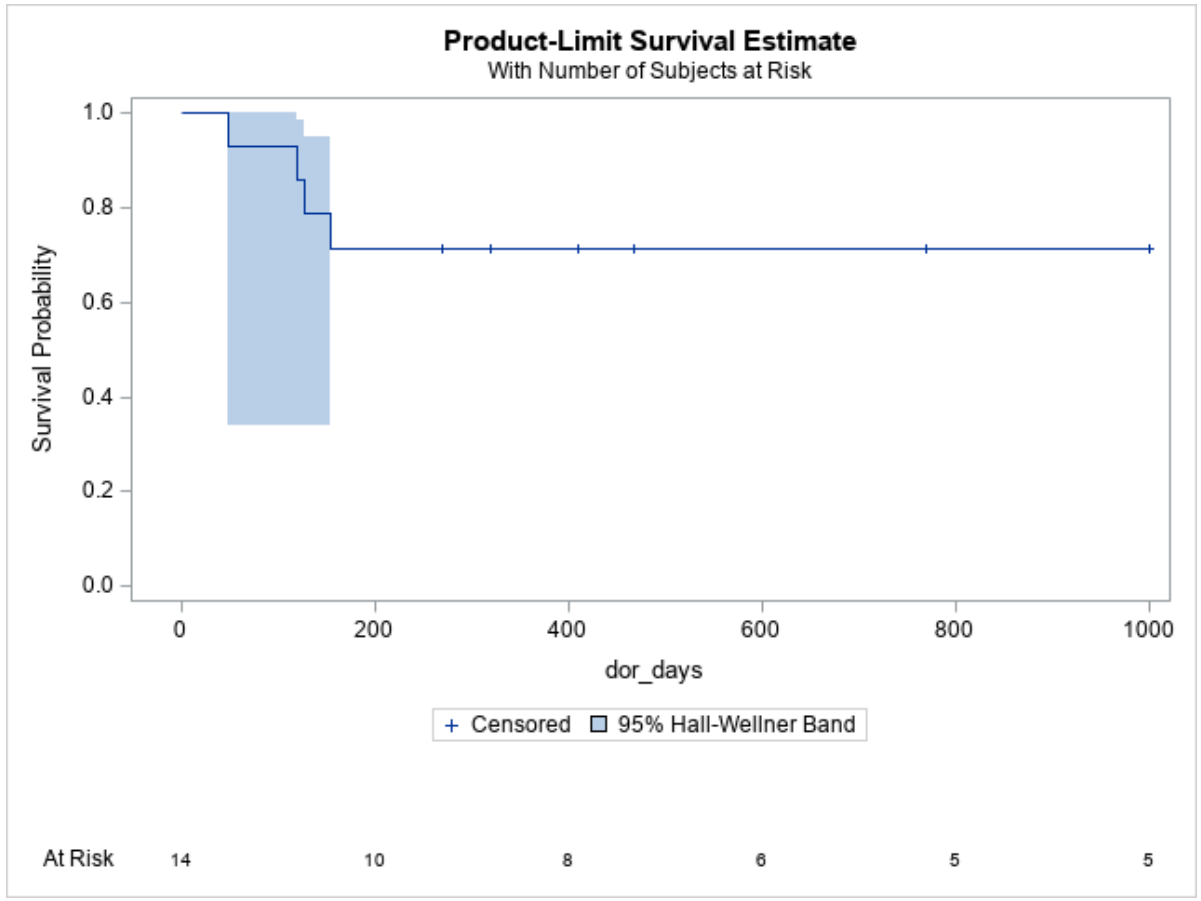


Supplemental Figure 2

A



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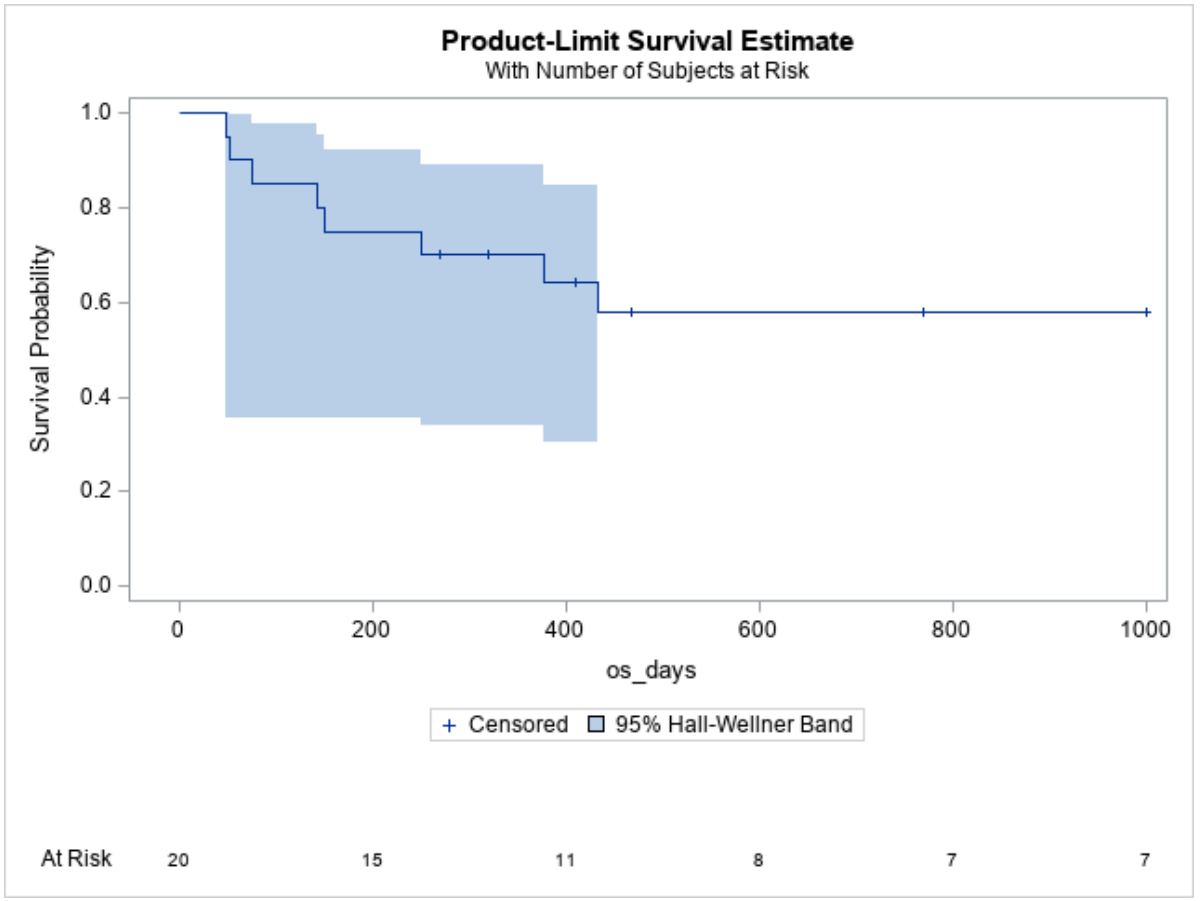
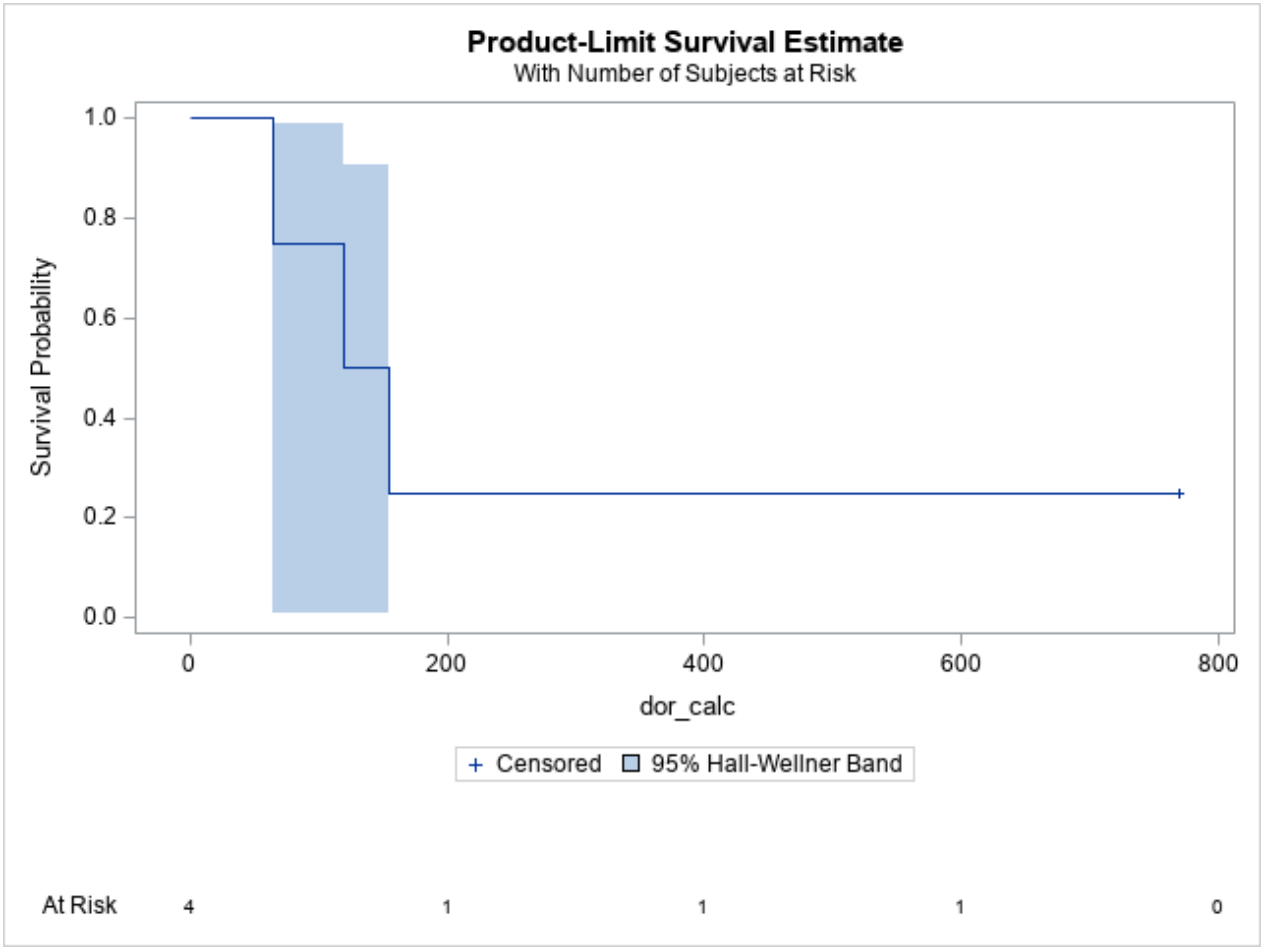


Supplemental Figure 3

A



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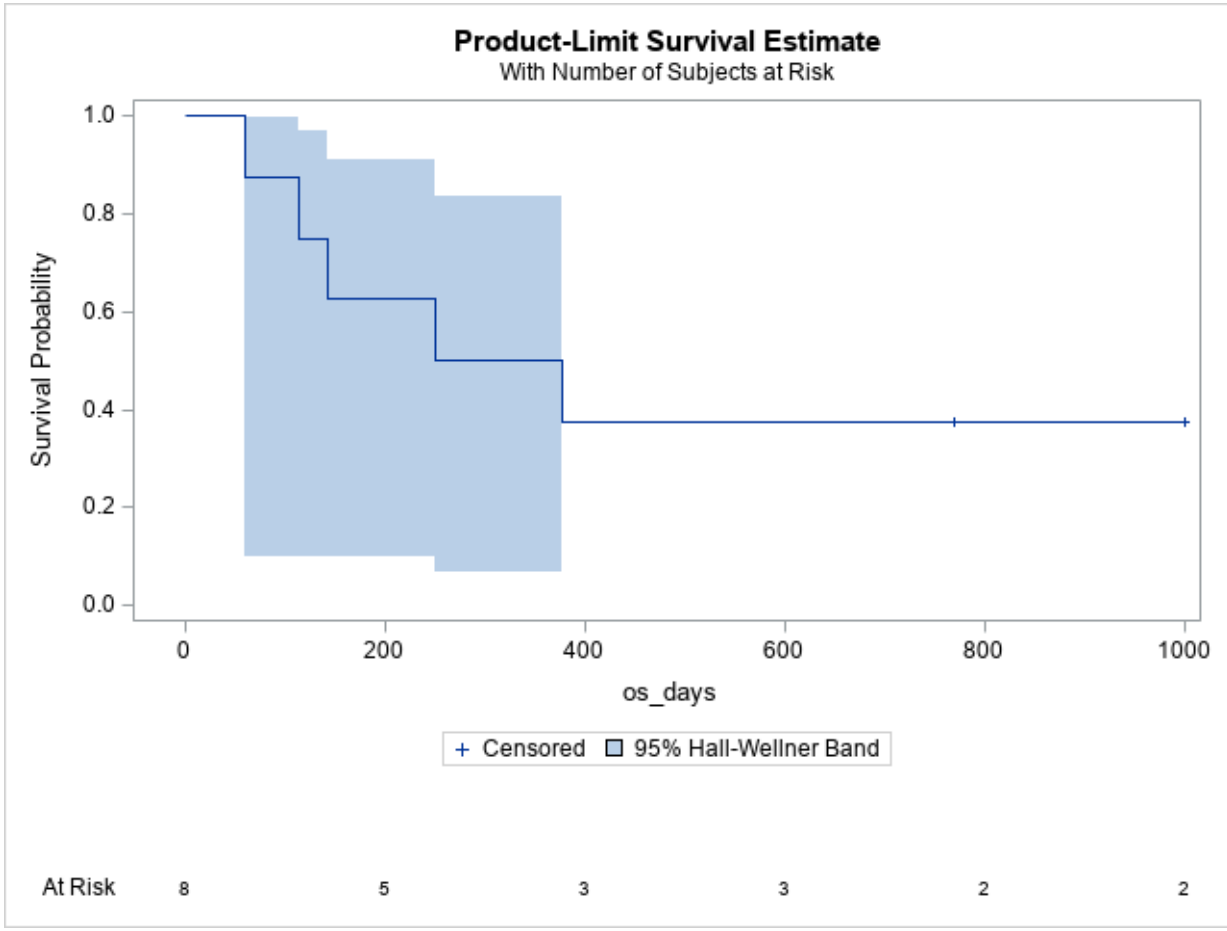
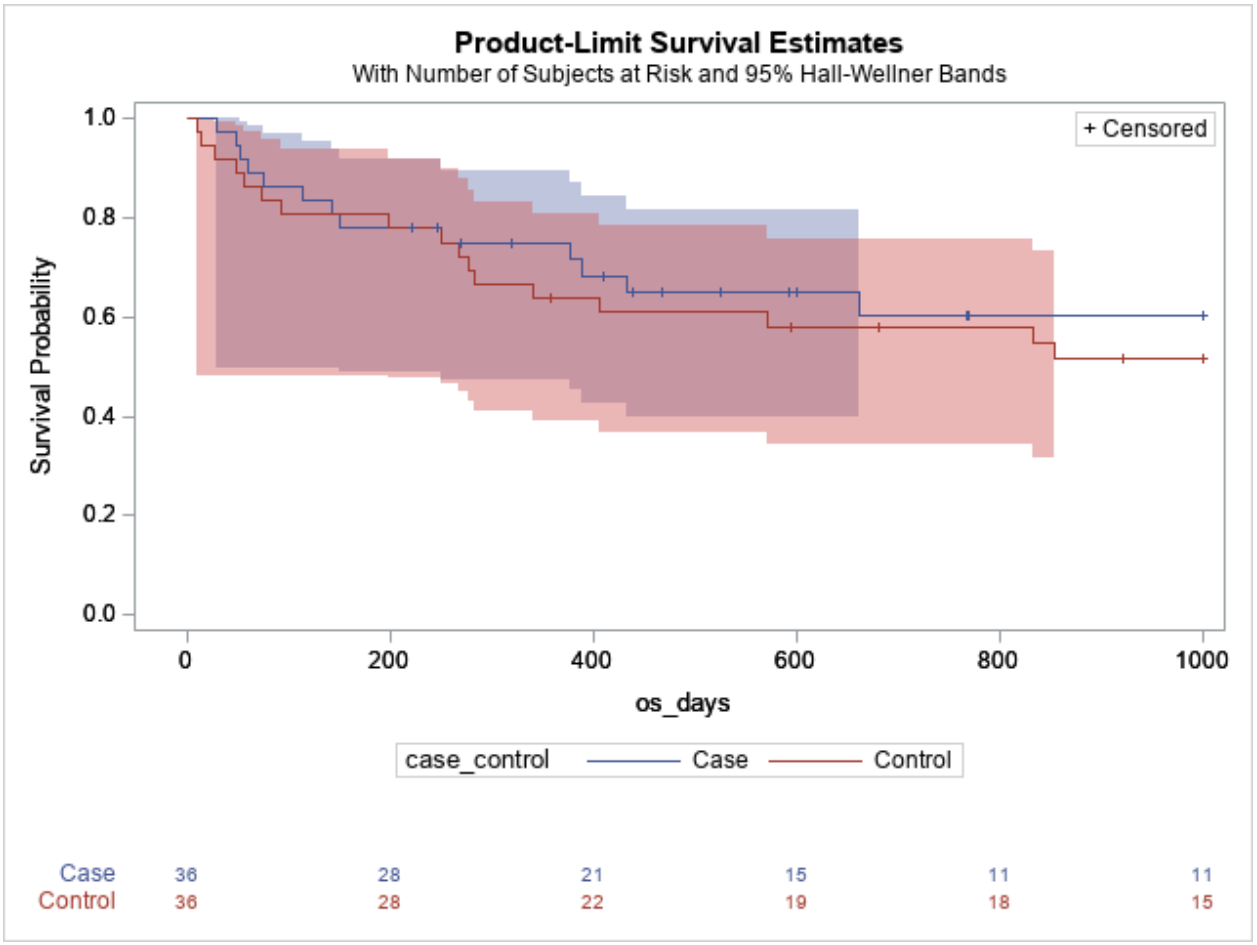


Supplemental Figure 4

A)



B)