Supplementary Appendix

Inclusion and exclusion criteria of selected protocols are demonstrated below.

FLAG-IDA+VEN (NCT03214562)

Inclusion Criteria

1. Diagnosis of AML by WHO criteria. Patients with high risk MDS as defined by the presence of ≥ 10% blasts are also eligible at the discretion of the PI.
2. Patients ≥ 18 to ≤ 65 years. Patients older than 65 who are deemed fit to receive intensive chemotherapy by the treating physician will be eligible after discussion with the PI.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2
4. Adequate renal function including creatinine clearance ≥ 30 mL/min based on the Cockcroft-Gault equation.
5. Adequate hepatic function including total bilirubin ≤ 1.5x ULN unless increase is due to Gilbert's disease or leukemic involvement, and AST and/or ALT ≤ 3x ULN unless considered due to leukemic involvement
6. Ability to understand and provide signed informed consent
7. Male subjects must agree to refrain from unprotected sex and sperm donation from initial study drug administration until 90 days after the last dose of study drug.
8. Only patients who are relapsed, refractory, or intolerant of standard AML therapy will be eligible for Part 1 (minimum of 1 prior line of AML-directed therapy)

Exclusion Criteria

1. Patients with t(15;17) karyotypic abnormality or acute promyelocytic leukemia (FAB class M3-AML)
2. Patients having received any prior BCL2 inhibitor therapy
3. Subject has known active CNS involvement with AML
4. Patients with New York Heart Association (NYHA) Class III or IV congestive heart failure or LVEF < 40% by echocardiogram or multi-gated acquisition (MUGA) scan
5. Patients with a history of myocardial infarction within the last 6 months or unstable / uncontrolled angina pectoris or history of severe and/or uncontrolled ventricular arrhythmias
6. Patients with known infection with human immunodeficiency virus (HIV) or active Hepatitis B or C
7. Patients with known dysphagia, short-gut syndrome, or other conditions that would affect the ingestion or gastrointestinal absorption of drugs administered orally.
8. Subject has any other significant medical or psychiatric history that in the opinion of the investigator would adversely affect participation in this study.

9. Subject has a white blood cell count > 25 x 10^9/L. (Note: Hydroxyurea is permitted to meet this criterion.)
10. Nursing women, women of childbearing potential (WOCBP) with positive urine pregnancy test, or women of childbearing potential who are not willing to maintain adequate contraception. Appropriate method(s) of contraception include oral or injectable hormonal birth control, IUD, and double barrier methods (for example a condom in combination with a spermicide).

FLAG-IDA+VEN Induction and Consolidation Schedule:

FLAG-IDA Induction:

a. Fludarabine 30 mg/m2 intravenously over approximately 30 minutes daily on days 2, 3, 4, 5, 6
b. Cytarabine 1.5 g/m2 intravenously over approximately 4 hours daily starting 4 hours (+/- 3 hours) after the completion of fludarabine on days 2, 3, 4, 5, 6
c. Idarubicin 6 mg/m2 intravenously over approximately 15 to 30 minutes given following fludarabine administration on days 4 and 5φ
d. Filgrastim (GCSF) 5 mcg/kg (rounded to nearest vial size) daily on days 1, 2, 3, 4, 5, 6, 7. Alternatively, a single injection of pegylated filgrastim (Neulasta) 6 mg can be administered subcutaneously after day 5 to replace remaining injections of filgrastim.
e. Dose adjustment guidelines for renal insufficiency or liver dysfunction are provided in Table 1.
f. For patients not in remission after the first induction therapy cycle, a second re-induction can be administered using the same dosing as induction.

φ Idarubicin 8 mg/m2 intravenously over approximately 15 to 30 minutes given following fludarabine on days 4, 5, and 6 can be administered for newly diagnosed AML patients (Burnett A et al, JCO 2013)

FLAG-IDA Consolidation:

a. Fludarabine, cytarabine and filgrastim as during induction, except that fludarabine and cytarabine is administered for 3, rather than 5, days. Idarubicin may be administered as in the induction cycle +/- 2 days, in up to two post-remission cycles to be determined by the treating physician. Pegfilgrastim can be administered after day 3 to replace remaining injections of filgrastim.
b. In general, post-remission courses should begin once extramedullary toxicity has resolved, the neutrophil count has recovered to > 1000 x 10^9/L and platelet count to > 50,000 x 10^9/L after the previous course. In patients in remission with incomplete count recovery, consolidation cycles can begin at the discretion of the treating physician. Up to 4-6 consolidation cycles may be administered.
c. Dose adjustment guidelines for renal insufficiency and/or liver dysfunction are provided in Table 1.

d. For patients who develop symptomatic heart failure, cardiac ejection fraction ≤ 40%, or other cardiac concerns, idarubicin will be omitted in consolidation therapy.
e. Idarubicin will be held during any cycle the total bilirubin is ≥ 2 mg/dL.
f.

For any patient with significant comorbidities such as pulmonary disease, prolonged cytopenias, other complications, or at the discretion of the treating physician after discussion with the PI, if additional intensive chemotherapy cycles are not in the patients best interest, the treating physician may stop induction/consolidation prior to completion of all cycles and transition directly to venetoclax maintenance therapy.

Venetoclax will be administered on days 1-14 of induction and days 1-7 of each consolidation treatment cycle. Other dose adjustments during consolidation for the best interest of the patient will be allowed after discussion with the PI and documentation in the medical record. Part 1 will only enroll patients with relapsed/refractory AML.

CLIA+VEN and CLIA (NCT02115295)

Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Patients with a diagnosis of AML, Acute Biphenotypic Leukemia, or high risk MDS (>/= 10% blasts or IPSS >/= intermediate-2) will be eligible. Patients with CML in Myeloid Blast Phase are also eligible.
2. **For Frontline cohort (1 or 4):** No prior potentially-curative therapy for leukemia. Prior therapy with hydroxyurea, hematopoietic growth factors, azacytidine, decitabine, ATRA, or a total dose of cytarabine up to 2g (for emergency use for stabilization) is allowed. Patients deemed able to receive venetoclax (ie. insurance clearance) will be assigned to Frontline cohort 4. Patients with secondary AMLwho have been treated for their antecedent myeloid neoplasm will be enrolled into the separate **Secondary AML cohort.**
3. **For Salvage cohort:** Patients with previously treated, relapsed or refractory AML, Acute Biphenotypic Leukemia, or CML in Myeloid Blast Phase are eligible.
4. Age </= 65 years.
5. Adequate organ function as defined below:
   - liver function (bilirubin ≤ 2mg/dL, AST and/or ALT ≤3 x ULN – or ≤5 x ULN if related to leukemic involvement)
   - kidney function (creatinine ≤ 1.5 x ULN).
   - known cardiac ejection fraction of > or = 45% within the past 6 months
6. ECOG performance status of ≤ 2.
7. A negative urine pregnancy test is required within 1 week for all women of childbearing potential prior to enrolling on this trial.

8. Patient must have the ability to understand the requirements of the study and signed informed consent. A signed informed consent by the patient or his legally authorized representative is required prior to their enrollment on the protocol.

Exclusion Criteria

1. Pregnant women are excluded from this study because the agents used in this study have the potential for teratogenic or abortifacient effects. Because there is a potential risk for adverse events in nursing infants secondary to treatment of the mother with the chemotherapy agents, breastfeeding should also be avoided.
2. Uncontrolled intercurrent illness including, but not limited to active uncontrolled infection, symptomatic congestive heart failure (NYHA Class III or IV), unstable angina pectoris, clinically significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
3. Patient with documented hypersensitivity to any of the components of the chemotherapy program.
4. Men and women of childbearing potential who do not practice contraception. Women of childbearing potential and men must agree to use contraception prior to study entry and for the duration of study participation.

CLIA/CLIA+VEN induction/consolidation schedule:

Induction

Cladribine at a dose of 5 mg/m^2/day will be given IV over approximately 1 to 2 hours, daily on <u>days 1-5</u> combined with cytarabine at the appropriate dose noted below IV over 2 hours daily on <u>days 1-5</u>. The cytarabine should be initiated approximately 3-6 hours following the start of the cladribine infusion. Idarubicin will given at a dose of 10 mg/m^2/day IV over 30-60 minutes on <u>days 1-3</u>.

Induction – Cytarabine dose		
Age	**Cytarabine dose (cohorts 1-3)**	**Cytarabine dose (cohort 4 – addition of Venetoclax)**
Age < 60 years	2 grams/m^2	1.5 grams/m^2
Age > or = 60 years	1.5 grams/m^2	1 gram/m^2

Due to inter-individual differences in age, performance status, and fitness for intensive chemotherapy, dose-reductions are commonly implemented during induction per the treating physician's judgment. Therefore, in patients with a **PS=2** or **age ≥ 60 years**, the number of days of cladribine and araC may be reduced to **<u>4 days</u>**, or **<u>3 days</u>** in the judgment of the treating physician if it is in the best interest of the patient after discussion with the PI. Concomitantly, the number of days of idarubicin will be reduced to **<u>2 days</u>** (Idarubicin 10 mg/m^2/day IV over 30-60 minutes on days 1-2).

Venetoclax Dosing (For Patients in Cohort 4 only)
Patients treated in cohort 4 (Frontline, untreated AML patients receiving the addition of venetoclax to CLIA) may receive venetoclax for 7 days of each cycle starting on approximately day 2 (with flexible window to allow delaying start up to day 5). Missed doses do not need to be made up. Rationale or reason for interruptions should be documented in the medical record.

Consolidation

Cladribine 5 mg/m^2/day will be given IV over 1 to 2 hours on days 1-3 combined with cytarabine at a dose noted below IV over 2 hours daily on days 1-3. The cytarabine should be initiated approximately 3-6 hours following the start of the cladribine infusion. Idarubicin will be given at a dose of 8 mg/m^2/day IV over 30-60 minutes on days 1-2.

Consolidation – Cytarabine dose		
Age	**Cytarabine dose (cohorts 1-3)**	**Cytarabine dose (cohort 4 – addition of Venetoclax)**
Age < 60 years	1.5 grams/m^2	1 grams/m^2
Age > or = 60 years	1 grams/m^2	0.75 gram/m^2

One cycle of therapy is considered 4 weeks. Subsequent cycles may be started within 3-7 weeks after the start of the previous cycle depending on hematopoietic recovery (see section 6 for details) and resolution of toxicities in the judgment of the treating physician. Subsequent cycle delay beyond 7 weeks may be allowed after discussion with the principal investigator and documentation of the discussion.

Patients with progressive or proliferating disease requiring initiation of a subsequent cycle of chemotherapy prior to day 28 of a previous cycle may start therapy no earlier than day 21 of a previous cycle after discussion with the principal investigator and documentation of the discussion.

FIA/CIA (NCT01289457)

Inclusion/Exclusion Criteria:

Inclusion criteria:
1. Sign an IRB-approved informed consent document.
2. Age ≥18 years.
3. Diagnosis of AML [other than acute promyelocytic leukemia (APL)] with refractory/relapsed disease. Patients with newly diagnosed AML will be eligible if not a candidate for any frontline protocol chemotherapy. Patients with high-risk (intermediate-2 or high by IPSS or ≥10% blasts, previously treated or not, including CMML) MDS will be also eligible.

4. ECOG performance status of ≤ 3 at study entry.
5. Organ function as defined below (unless due to leukemia):
    a. Serum creatinine ≤ 3 mg/dL
    b. Total bilirubin ≤ 2.5 mg/dL
    c. ALT (SGPT) ≤ 3 x ULN or ≤ 5 x ULN if related to disease
6. Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days and must agree to practice acceptable contraceptive methods. Men must agree not to father a child and agree to use a condom if his partner is of child bearing potential.
7. Cardiac ejection fraction ≥ 40% (by either cardiac echo or MUGA scan). Documentation of recent (≤ 6 months from screening) outside reports is acceptable.

Exclusion Criteria:

1. Breast feeding females

FIA/CIA Induction

In the Phase II portion, patients will be randomized to receive

a. Clofarabine (dose selected based on Phase I portion) IV over approximately 1 hour daily for 5 days (days 1-5)
b. Idarubicin 10 mg/m^2 IV over approximately 30 minutes daily for 3 days (days 1-3)
c. Cytarabine 1 g/m^2 IV over approximately 2 hours daily for 5 days (days 1-5) Idarubicin will follow clofarabine by 1 to 2 hours and cytarabine will follow clofarabine by 3 to 6 hours.

or

a. Fludarabine 30 mg/m^2 IV over approximately 30 minutes daily for 5 days (days 1-5)
b. Idarubicin 10 mg/m2 IV over approximately 30 minutes daily for 3 days (days 1-3)
c. Cytarabine 1 g/m2 IV over approximately 2 hours daily for 5 days (days 1-5) Idarubicin will follow fludarabine by 1 to 2 hours and cytarabine will follow fludarabine by 3 to 6 hours.

The induction may be given over 4 days in patients ≥ 65 years and over 3 days in patients with PS ≥ 2, at the discretion of the treating physician.

Patients who have not achieved a complete remission following the induction course, can receive a second induction course to optimize response if possible. A second induction course at the same dose as the previous course should not be given until at least 28 days of course 1. If the bone marrow aspirate and/or biopsy(s) performed after the re-induction cycle reveals a remission marrow (CR/CRp), then the patient may proceed with consolidation at the discretion of the treating investigator. In addition, any clinically significant drug-related, non-hematologic toxicity experienced by a patient should return to ≤ grade 2 or the baseline grade before the patient continues treatment Should the patient not have achieved a remission after the reinduction course, he will be

taken off study for failure to respond, unless the patient has achieved clinical benefit, at which time further therapy on protocol may be permitted with approval from the PI.

FIA/CIA Consolidation

Patients in CR or CRp can continue with up to 6 consolidation cycles.

Clofarabine (dose selected based on Phase I portion) IV over approximately 1 hour daily for 3 days (days 1-3)
Idarubicin 8 mg/m^2 IV over approximately 30 minutes daily for 2 days (days 1-2)
Cytarabine 1 g/m^2 IV over approximately 2 hours daily for 3 days (days 1-3)

Or
Fludarabine 30 mg/m^2 IV over approximately 30 minutes daily for 3 days (days 1-3)
Idarubicin 8 mg/m^2 IV over approximately 30 minutes daily for 2 days (days 1-2)
Cytarabine 1 g/m^2 IV over approximately 2 hours daily for 3 days (days 1-3)

The consolidation may be given over 2 days in patients ≥ 65 years and/or with PS ≥ 2.

Cycles may be repeated every 3 to 10 weeks based on leukemia response and resolution of drug-related toxicities. Prior to each consolidation cycle, the ANC should be $\geq$ 1.0 x 10^9/L, and the platelet count should be $\geq$ 60 x 10^9/L (except for patients who are considered to have achieved a CRp following induction/reinduction and in whom the platelet count may be lower). Patients with borderline values for ANC and platelet count (value up to 10% lower than recommended) can still proceed with the next consolidation cycle if this is judged to be in the best interest of the patients and after discussion with the principal investigator. In addition, any drug-related non-hematologic toxicity experienced by the patient must return to $\leq$ grade 2 before receiving the next cycle. Doses missed or held during a cycle of treatment will not be made up and are recorded as being omitted. If patients experience multiple study drug-related toxicities or experience significant infections, dose adjustments may need to be made based on the most severe toxicity and based on the drug causing the toxicity.

Supplementary table S1: Overall characteristics of selected patients (N=312)

Parameter	IC+VEN (N=91)	IC (N=221)	FLAG-IDA +VEN (N=41)	CLIA +VEN (N=50)	FIA (N=74)	CLIA (N=108)	CIA (N=39)	*p-value*
Age	46 (18-65)	50 (18-66)	44 (20-65)	48 (18-64)	49 (18-66)	51 (21-65)	48 (19-60)	0.09
Sex (M)	47 (52)	99 (45)	19 (46)	28 (56)	39 (52)	45 (42)	15 (38)	
Bone marrow blast (%)	51 (1-85)	55 (6-96)	46 (4-85)	56 (1-84)	55 (11-96)	59 (6-93)	49 (11-92)	0.07
Extra-medullary leukemia	6 (7)	11 (5)	4 (10)	2 (4)	2 (3)	5 (5)	4 (10)	
AML type								
High Risk MDS	4 (4)	-	-	4 (8)	-	-	-	-
de novo AML	69 (76)	193 (87)	29 (71)	40 (80)	63 (85)	101 (94)	29 (74)	-
sAML/tAML	22 (24)	28 (12)	12 (29)	10 (20)	11 (15)	7 (6)	10 (26)	0.02
ELN Risk Group								
Favorable	24 (26)	40 (18)	8 (20)	16 (32)	12 (16)	25 (23)	3 (8)	0.12
Intermediate	31 (34)	77 (35)	15 (37)	16 (32)	29 (39)	30 (28)	18 (46)	1.0
Adverse	36 (40)	104 (47)	18 (44)	18 (36)	33 (45)	53 (49)	18 (46)	0.26
Cytogenetic Risk								
Favorable	1 (1)	1 (<1)	-	1 (2)	-	1 (<1)	-	0.50
Diploid	43 (47)	104 (47)	17 (41)	26 (52)	35 (47)	55 (51)	14 (36)	1.0
Other Intermediate	20 (22)	41 (19)	12 (29)	8 (16)	12 (16)	24 (22)	8 (21)	0.75
Adverse/Complex	21 (23)	64 (29)	11 (27)	10 (20)	25 (34)	23 (21)	16 (41)	0.33
Insufficient Mitoses/Unknown	6 (7)	7 (3)	1 (2)	5 (10)	2 (3)	5 (5)	1 (3)	0.22
KMT2A rearranged	9 (10)	17 (8)	5 (12)	4 (8)	3 (4)	8 (7)	6 (15)	0.51
Molecular Mutations								
***NPM1* Mutated**	24/91 (26)	59/216 (27)	6 (15)	18 (36)	15 (20)	38 (35)	6 (15)	0.88
***IDH1* Mutated**	7/84 (8)	15/182 (8)	3 (7)	4 (8)	7 (9)	8 (7)	-	1.0
***IDH2* Mutated**	12/91 (13)	29/182 (16)	7 (17)	5 (10)	6 (8)	23 (21)	-	0.59
***RUNX1* Mutated**	12/91 (13)	9/149 (6)	6 (15)	6 (12)	3 (4)	6 (6)	-	0.06
***ASXL1* Mutated**	8/91 (9)	22/180 (12)	3 (7)	5 (10	3 (4)	19 (18)	-	0.53
***TP53* Mutated**	5/91 (5)	15/184 (8)	4 (10)	1 (2)	5 (7)	8 (7)	2 (5)	0.62
***FLT3-TKD* Mutated**	12/91 (13)	12/216 (5)	5 (12)	7 (14)	5 (7)	5 (5)	2 (5)	0.034
***FLT3-ITD* Mutated**	13/91 (14)	62/218 (28)	2 (5)	11 (22)	15 (20)	42 (39)	5 (13)	0.008
Received FLT3-inhibitor	9/91 (10)	53/221 (24)	-	9 (18)	12 (16)	41 (38)	-	0.005

*Data displayed as N(%) or median (range). P-value shown for VEN+IC vs. IC only

Supplementary table S2: Characteristics by treatment arm of PSM population (N=279)

Characteristic*	**FLAG-IDA+VEN** N = 40	**CLIA+VEN** N = 45	**FIA** N = 67	**CLIA** N = 98	**CIA** N = 29
Age	44 (20 - 65)	48 (18 - 64)	49 (18 - 63)	54 (21 - 65)	44 (19 - 60)
Sex (M)	19 (48%)	25 (56%)	35 (52%)	41 (42%)	11 (38%)
Bone Marrow Blast (%)	46 (4 - 85)	64 (1 - 84)	55 (11 - 96)	60 (6 - 93)	47 (11 - 92)
AML Type					
De novo	29 (72%)	38 (84%)	59 (88%)	92 (94%)	25 (86%)
High-risk MDS	-	3 (6.7%)	-	-	-
sAML	6 (15%)	2 (4.4%)	4 (6.0%)	2 (2.0%)	2 (6.9%)
tAML	5 (12%)	2 (4.4%)	4 (6.0%)	4 (4.1%)	2 (6.9%)
ELN Risk Group					
Favorable	7 (18%)	14 (31%)	10 (15%)	20 (20%)	2 (6.9%)
Intermediate	15 (38%)	14 (31%)	27(40%)	26 (27%)	14 (48%)
Adverse	18 (45%)	17 (38%)	30 (45%)	52 (53%)	13 (45%)
Cytogenetics					
Favorable	-	1 (2.2%)	-	-	-
Diploid	16 (40%)	24 (53%)	31 (47%)	51 (52%)	11 (38%)
Other intermediate	12 (30%)	6 (13%)	10 (15%)	19 (19%)	6 (21%)
Adverse/Complex	11 (28%)	11 (24%)	24 (36%)	23 (23%)	11 (38%)
Insufficient/Unknown	1 (2.5%)	3 (6.7%)	1 (1.5%)	5 (5.1%)	1 (3.4%)
Molecular mutations					
***NPM1* Mutated**	5 / 40 (12%)	15 / 45 (33%)	13 / 67 (19%)	33 / 97 (34%)	5 / 27 (19%)
***IDH1* Mutated**	3 / 40 (7.5%)	4 / 45 (8.9%)	5 / 67 (7.5%)	7 / 98 (7.1%)	-
***IDH2* Mutated**	6 / 40 (15%)	4 / 45 (8.9%)	5 / 67 (7.5%)	18 / 98 (18%)	-
***FLT3*-D835 Mutated**	5 / 40 (12%)	7 / 45 (16%)	5 / 67 (7.5%)	5 / 98 (5.1%)	2 / 27 (7.4%)
***FLT3-ITD* Mutated**	1 / 40 (2.5%)	11 / 45 (24%)	14 / 67 (21%)	40 / 98 (41%)	4 / 28 (14%)
FLT3-inhibitor (Y)	-	9 / 45 (20%)	12 / 67 (18%)	39 / 98 (40%)	-
***RUNX1* Mutated**	6 / 40 (15%)	5 / 45 (11%)	3 / 40 (7.5%)	6 / 96 (6.2%)	-
***ASXL1* Mutated**	3 / 40 (7.5%)	5 / 45 (11%)	2 / 67 (3.0%)	18 / 96 (19%)	-
***TP53* Mutated**	4 / 40 (10%)	1 / 45 (2.2%)	5 / 56 (8.9%)	8 / 98 (8.2%)	2 / 2 (100%)

*Data displayed as N(%) or median (range)

Supplementary table S3: Responses by treatment arm of overall unmatched population (N=312)

Response Parameter*	IC+VEN (N=91)	IC (N=221)	FLAG-IDA +VEN (N=41)	CLIA +VEN (N=50)	FIA (N=74)	CLIA (N=108)	CIA (N=39)	p-value
Overall Response	87 (96)	190 (86)	40 (98)	47 (94)	62 (84)	94 (87)	34 (87)	0.02
Composite CR	83 (91)	190 (86)	36 (88)	47 (94)	62 (84)	94 (87)	34 (87)	0.3
Complete Response	72 (79)	174 (78)	30 (73)	42 (84)	55 (74)	88 (81)	31 (79)	
CRh	5 (5)	-	5 (12)	-	-	-	-	
CRi	6 (7)	16 (7)	1 (2)	5 (10)	7 (9)	6 (6)	3 (8)	
MRD-Negative CRc	70/80 (88)	93/154 (60)	33/35 (94)	37/45 (82)	34/57 (60)	59/87 (68)	0/10	<0.001
MLFS	4 (4)	-	4 (10)	-	-	-	-	
No response	3 (3)	26 (12)	1 (2)	2 (4)	11 (15)	11 (10)	4 (10)	
Unevaluable		1 (<1)	-	-	-	-	1 (3)	
Relapse	15 (17)	79 (42)	9 (23)	6 (13)	32 (52)	28 (30)	19 (56)	<0.001
MRD-negative CRc by *ELN Risk Group*								
Favorable	22 (92)	39 (98)	7 (88)	15 (94)	12 (100)	24 (96)	3 (100)	0.55
MRD-Negative CRc	20/22 (91)	28/33 (85)	7/7 (100)	13/15 (87)	8/11 (73)	20/22 (91)	-	0.69
Intermediate	28 (90)	68 (88)	13 (87)	15 (94)	23 (79)	28 (93)	17 (94)	1.0
MRD-Negative CRc	22/26 (85)	34/53 (64)	11/12 (92)	11/14 (79)	13/20 (65)	21/27 (78)	0/6 (0)	0.07
Adverse	33 (92)	83 (80)	16 (89)	17 (94)	27 (82)	42 (79)	14 (78)	0.13
MRD-Negative CRc	28/32 (88)	31/68 (46)	15/16 (94)	13/16 (81)	13/26 (50)	18/38 (47)	0/4 (0)	<0.001

*Data displayed as N(%) or median (range). P-value shown for VEN+IC vs. IC only

Supplementary table S4: Responses by molecular subgroups within PSM population (N=279)

Characteristic	**Overall**, N = 279	**IC**, N = 194	**VEN**, N = 85	**p-value**
***NPM1* mutated**				
Composite CR	69 / 71 (97%)	51 / 51 (100%)	18 / 20 (90%)	0.08
MRD-Negative CRc	50 / 62 (81%)	35 / 44 (80%)	15 / 18 (83%)	0.9
***IDH1* mutated**				
Composite CR	15 / 19 (79%)	10 / 12 (83%)	5 / 7 (71%)	0.6
MRD-Negative CRc	10 / 15 (67%)	6 / 10 (60%)	4 / 5 (80%)	0.6
***IDH2* mutated**				
Composite CR	26 / 33 (79%)	17 / 23 (74%)	9/ 10 (90%)	0.4
MRD-Negative CRc	22 / 26 (85%)	13 / 17 (76%)	9 / 9 (100%)	0.3
***FLT3*-TKD mutated**				
Composite CR	22 / 24 (92%)	11 / 12 (92%)	11 / 12 (92%)	0.9
MRD-Negative CRc	15 / 19 (79%)	4 / 8 (50%)	11 / 11 (100%)	**0.02**
***FLT3*-ITD mutated**				
Composite CR	64 / 70 (91%)	54 / 58 (93%)	10 /12 (83%)	0.3
MRD-Negative CRc	44 / 57 (77%)	37 / 47 (79%)	7 / 10 (70%)	0.7
***ASXL1* mutated**				
Composite CR	24 / 28 (86%)	17 / 20 (85%)	7 / 8 (88%)	0.9
MRD-Negative CRc	18 / 23 (78%)	11 / 16 (69%)	7 / 7 (100%)	0.3
***RUNX1* mutated**				
Composite CR	20 / 20 (100%)	9 / 9 (100%)	11 / 11 (100%)	1.0
MRD-Negative CRc	11 / 20 (55%)	1 / 9 (11%)	10 / 11 (91%)	**<0.001**
***TP53* mutated**				
Composite CR	17 / 20 (85%)	13 / 15 (87%)	4 /5 (80%)	0.9
MRD-Negative CRc	7/ 13 (54%)	4 / 9 (44%)	3 / 4 (75%)	0.6

*Data displayed as N(%)

Figure S1: Love plot depicting balance of variables before and after propensity score matching (A). Barplot depicting balance of molecular characteristics between the VEN+IC compared to the IC cohort after propensity score matching

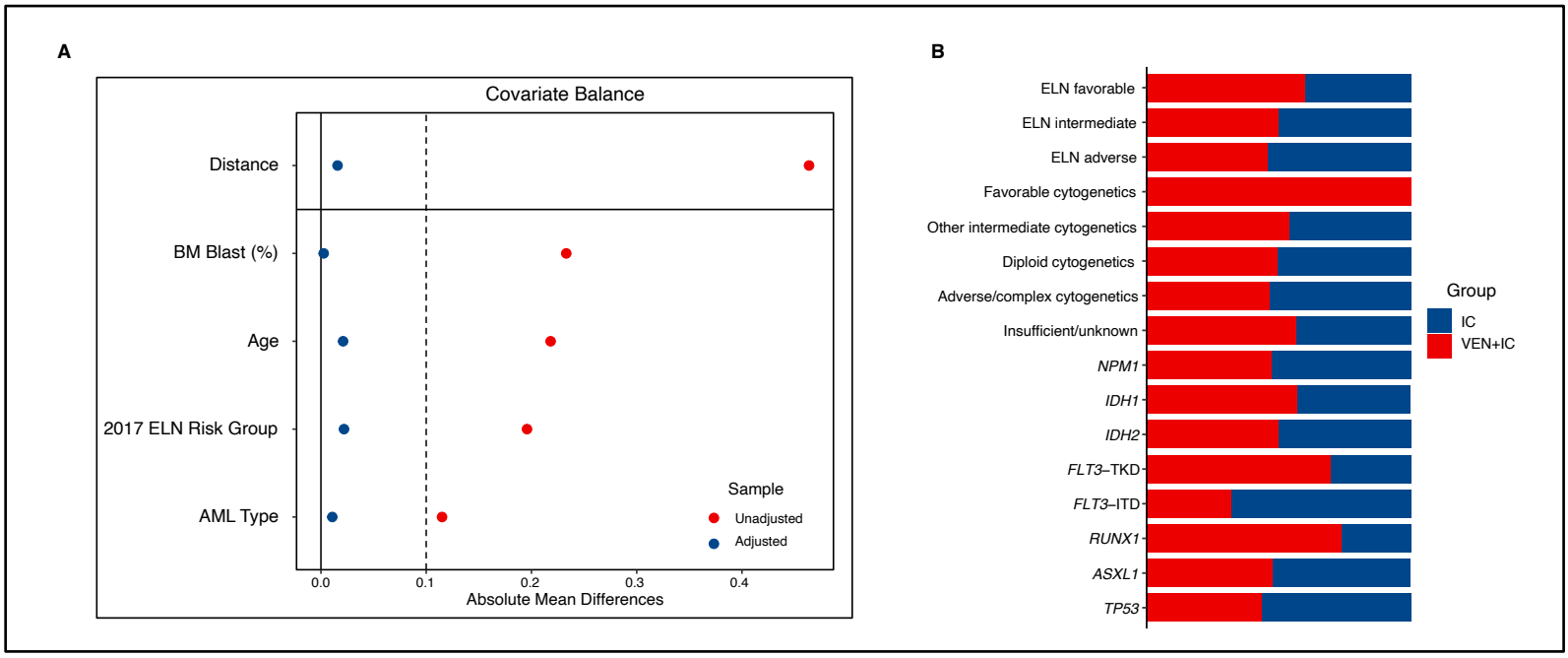

Figure S2: Overall and event-free survival within the PSM population by treatment arm within the VEN+IC (A and C) and within the IC cohort (B and D).

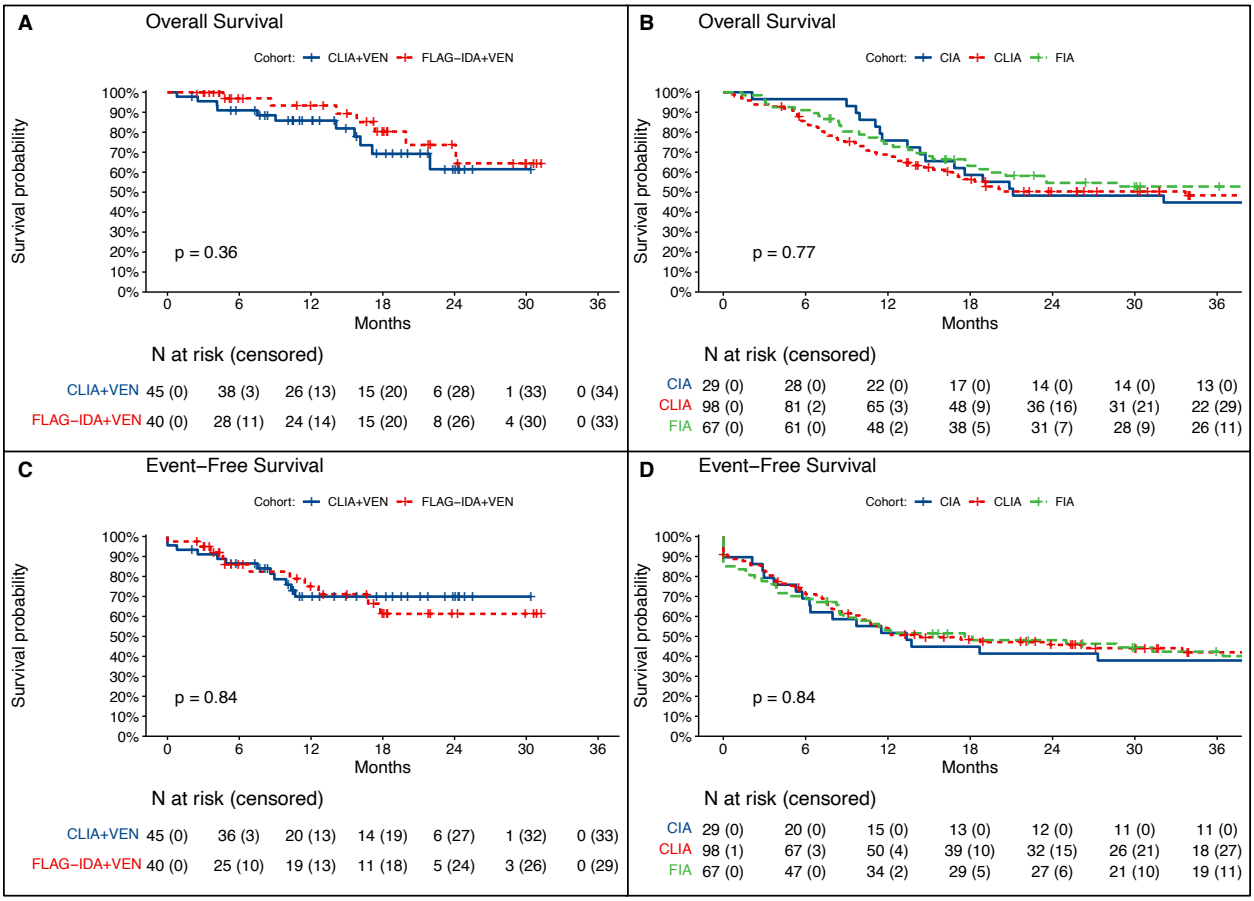

Figure S3: Survival based on treatment period among all propensity-score matched (PSM) patients (A) and among PSM patients treated within the IC cohort (B).

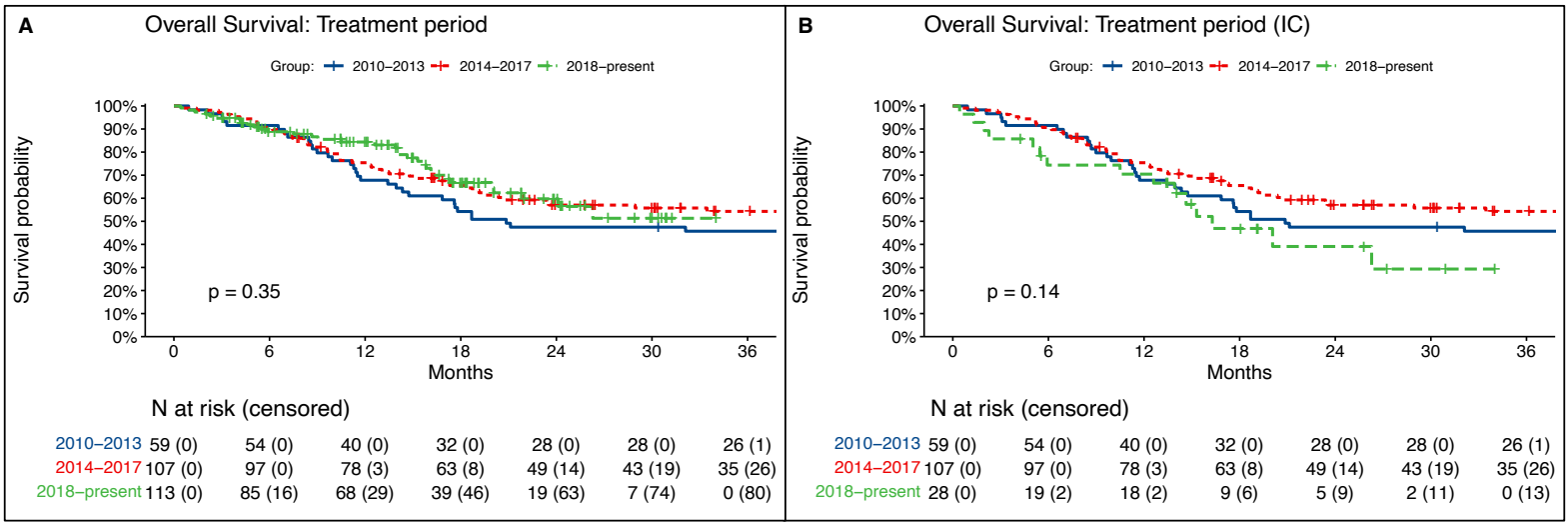

Figure S4: Oncoprint of all patients treated with VEN+IC (N=91) correlated with response and cytogenetics (A).

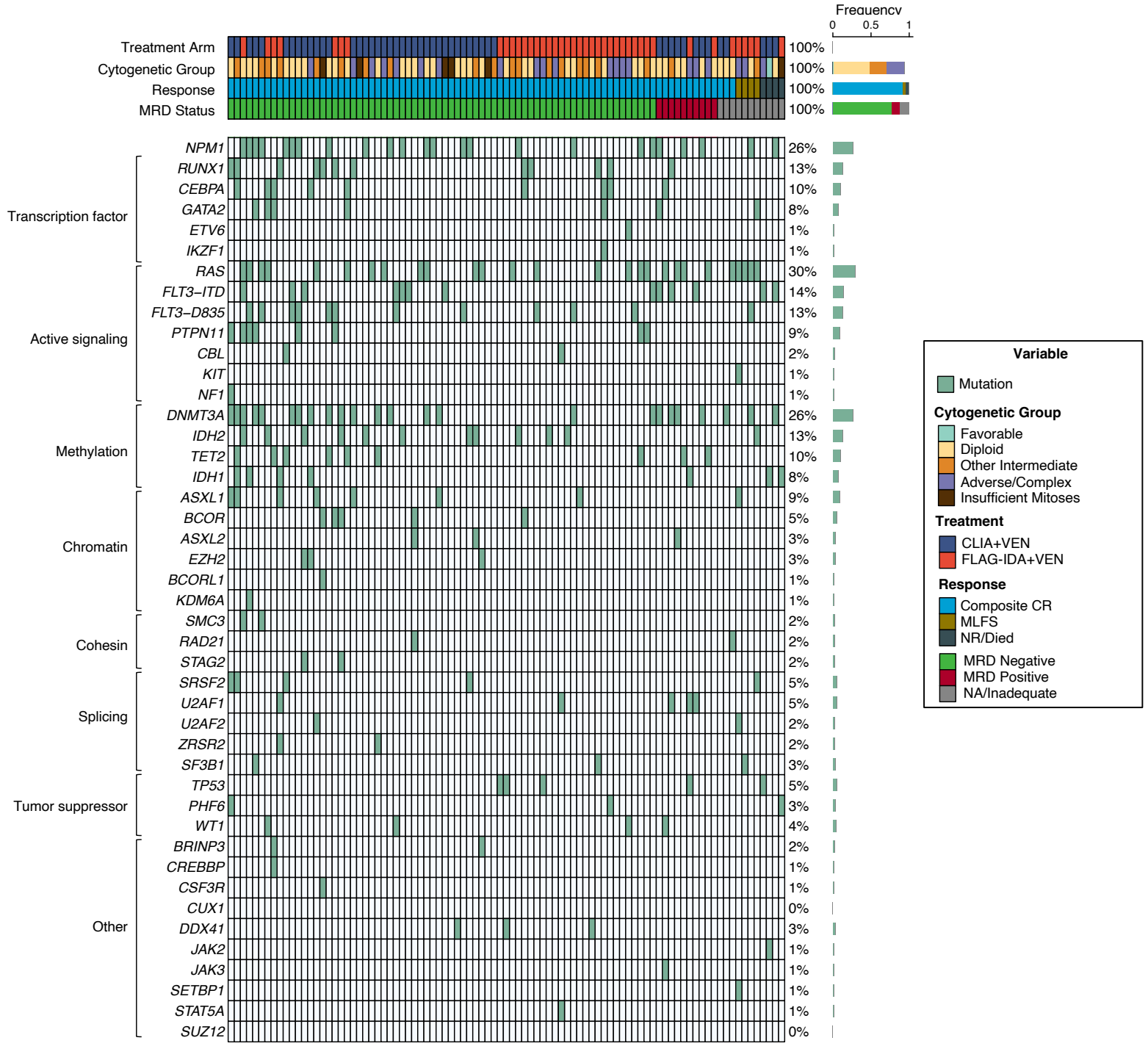

Figure S5: Overall survival based on molecular mutations within the VEN+IC cohort grouped by molecular pathway. Patients with tumor suppressor mutations (B) demonstrated inferior survival compared to wild-type patients, while mutations in other pathways had no significant impact on OS. Unstratified p-values based on log-rank test are displayed.

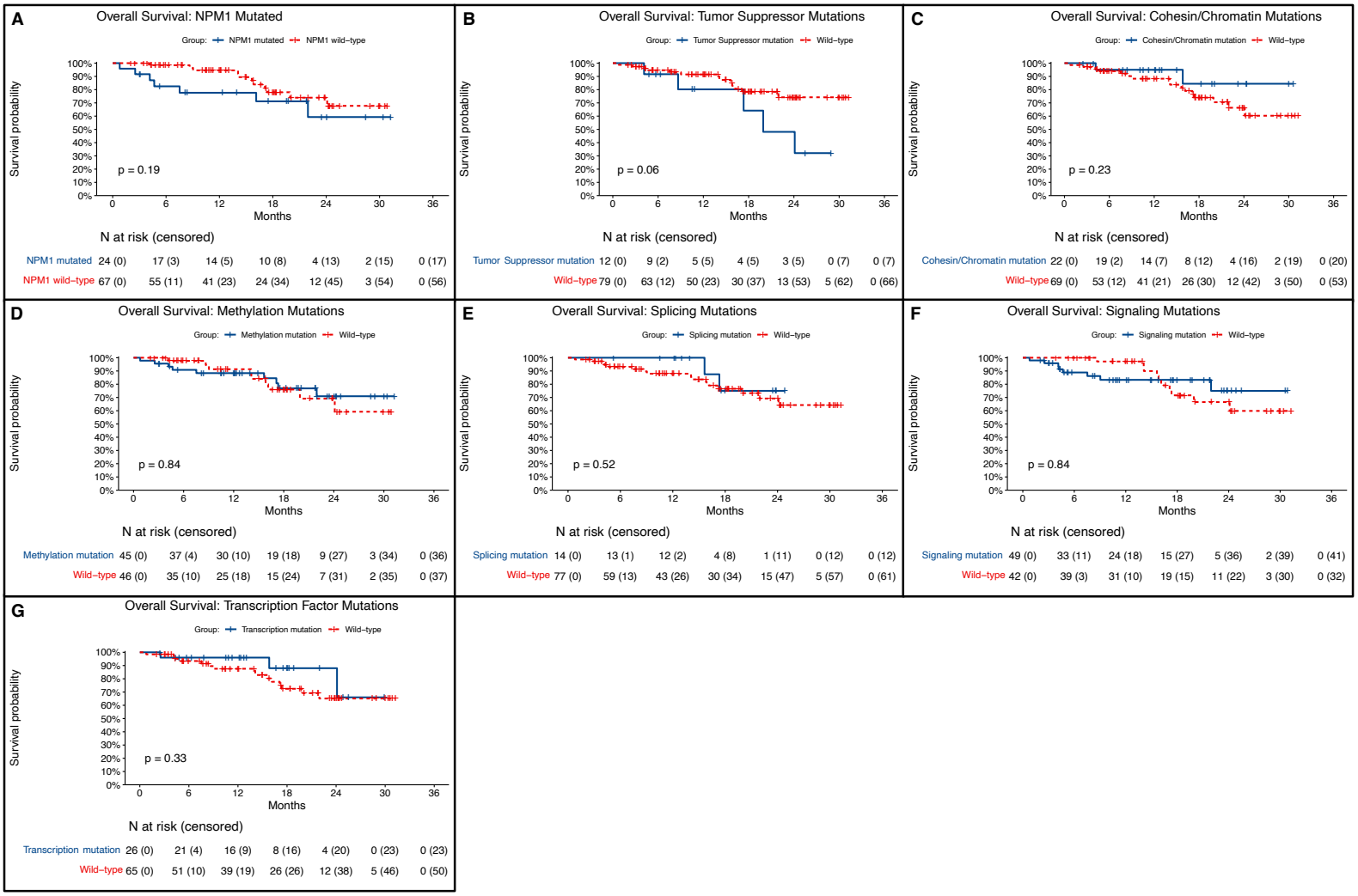

Figure S6: Survival based on *FLT3* mutation status (including TKD and ITD mutated patients) in the PSM population (A) and by each treatment cohort (B). Overall survival based on FLT3 inhibitor use (C) and by FLT3 inhibitor use within each respective treatment cohort (D).