Ivosidenib or enasidenib combined with standard induction and consolidation chemotherapy in patients with newly diagnosed AML with an IDH1 or IDH2 mutation is safe, effective, and leads to MRD-negative complete remissions

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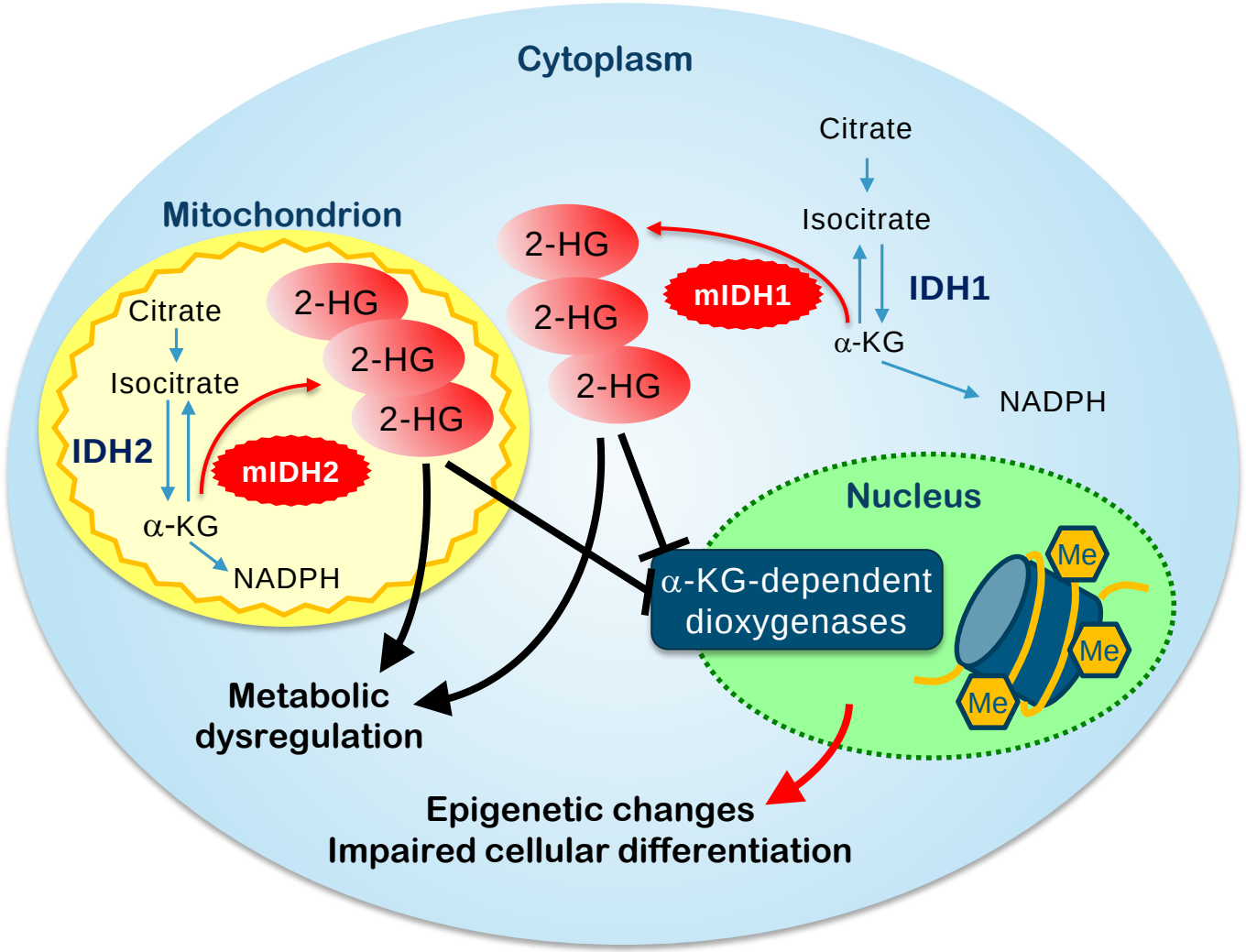
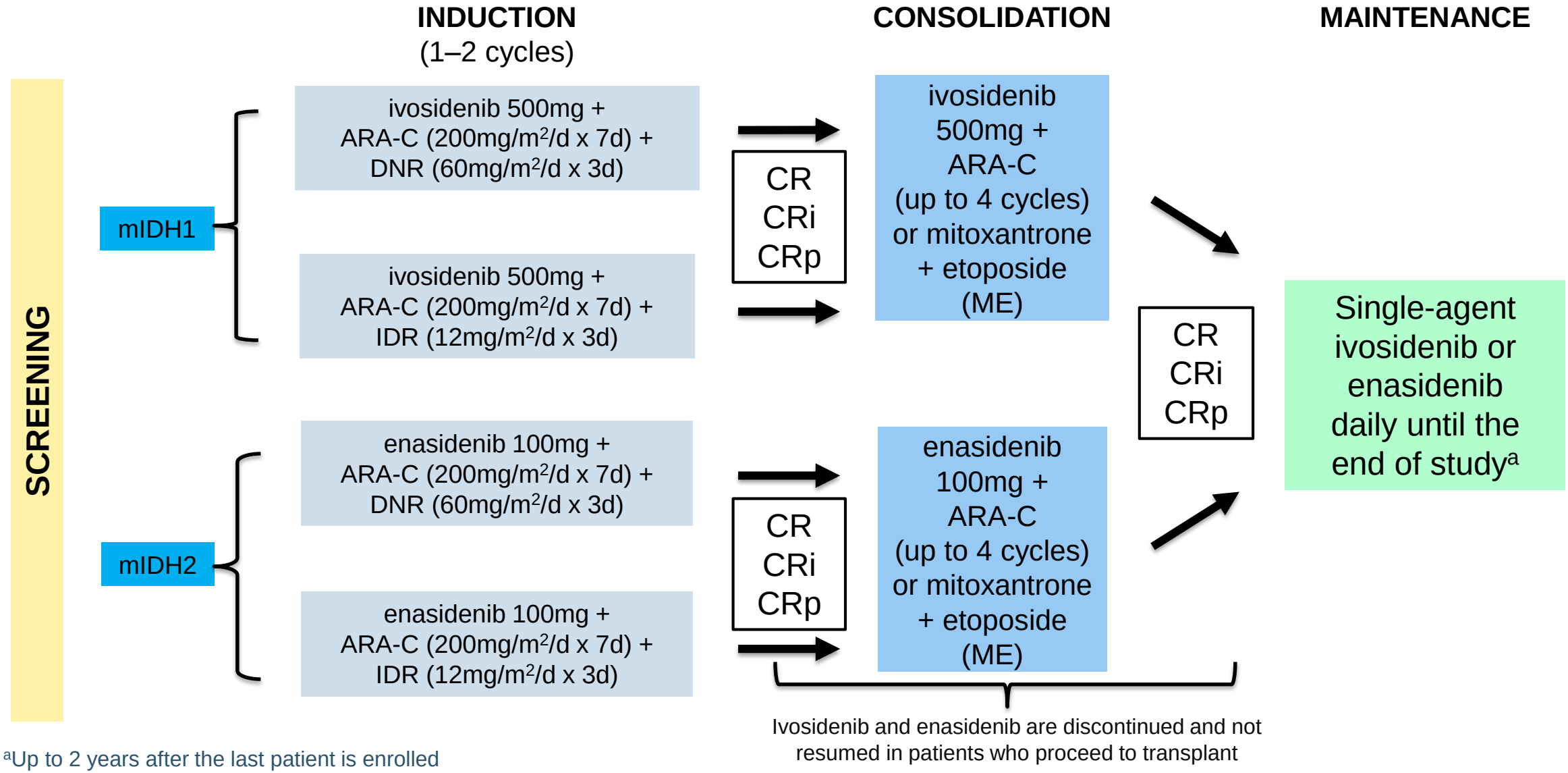
Introduction

- Mutant IDH (mIDH) 1 or 2 is seen in ~15–20% of patients with AML
- Ivosidenib (AG-120) and enasidenib (AG-221) are oral inhibitors of mIDH1 and mIDH2, respectively
- Both ivosidenib and enasidenib are approved for treatment of relapsed or refractory AML with an IDH1 or IDH2 mutation, respectively
- These agents are now being explored in combination with standard induction and consolidation chemotherapy



Study design



[a]Up to 2 years after the last patient is enrolled

ARA-C = cytarabine; DNR = daunorubicin; IDR = idarubicin

Study summary

Primary objective

- Safety and tolerability of ivosidenib or enasidenib when administered with standard induction and consolidation chemotherapy

Secondary, exploratory objectives

- Clinical activity of ivosidenib or enasidenib in combination with AML induction and consolidation therapy
- Evaluation of measurable residual disease (MRD) using flow cytometry and IDH mutation clearance (MC) using digital PCR

Study design

- "6+6" design to test the safety of ivosidenib or enasidenib when combined with daunorubicin- or idarubicin-based induction chemotherapy, followed by cohort expansion
- An alternative regimen in which enasidenib dosing started on Day 8 of Induction Cycle 1 rather than on Day 1 was explored in a small (n=25) cohort of patients with mIDH2

Key inclusion/exclusion criteria

- ≥18 years of age
- Previously untreated AML (*de novo* or sAML) with locally documented IDH1 and/or IDH2 mutation
- No prior chemotherapy for AML
  - Patients with sAML may have had previous treatment for MDS or other antecedent hematologic disorder, including hypomethylating agents

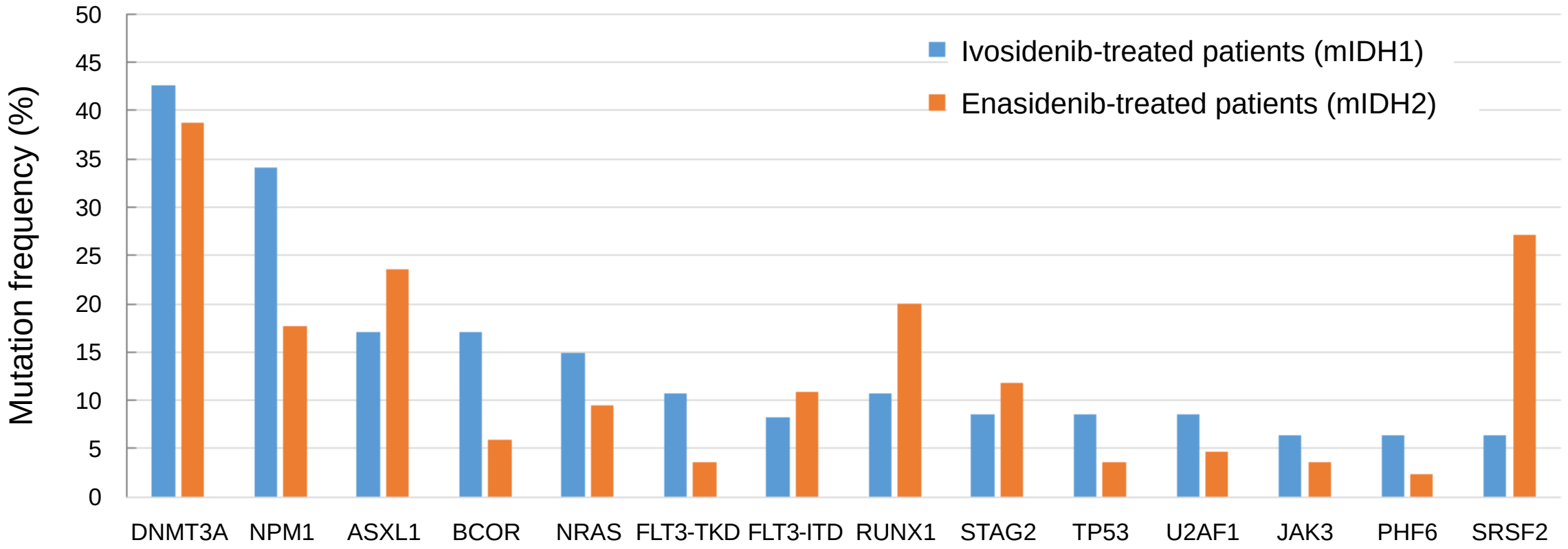
sAML = secondary AML

Patient characteristics

Baseline characteristics	Ivosidenib (AG-120) + chemotherapy (n=60)	Enasidenib (AG-221) + chemotherapy (n=93)
Age in years, median (range)	62.5 (24–76)	63 (27–77)
<60, n (%)	21 (35)	34 (37)
≥60, n (%)	39 (65)	59 (63)
Sex, male, n (%)	30 (50)	52 (56)
AML type, n (%)		
De novo	42 (70)	59 (63)
sAML	18 (30)	34 (37)
% of sAML patients who rec'd prior hypomethylating agent therapy	4 (22)	17 (50)
IDH1 mutation type,[a,b] n (%)		
R132	57 (95)	2 (2)
Other or unknown	3 (5)	2 (2)
IDH2 mutation type,[a,b] n (%)		
R140	1 (2)	65 (70)
R172	2 (3)	23 (25)
Other or unknown	-	5 (5)
Risk status based on cytogenetics and molecular abnormalities,[c] n (%)		
Favorable	12 (20)	11 (12)
Intermediate	26 (43)	46 (49)
Poor	20 (33)	29 (31)
Unknown	2 (3)	7 (8)

[a]Per site local testing. [b]Patients with dual IDH1 and IDH2 mutations were assigned to ivosidenib or enasidenib on the basis of the IDH mutation with the higher allele burden. [c]Per NCCN Guidelines Version 2.2016

Baseline co-mutation rates



- DNMT3A, NPM1, ASXL1, and BCOR were the most commonly occurring baseline co-mutations in mIDH1 patients
- DNMT3A, SRSF2, ASXL1, and RUNX1 were the most commonly occurring baseline co-mutations in mIDH2 patients

Patient disposition

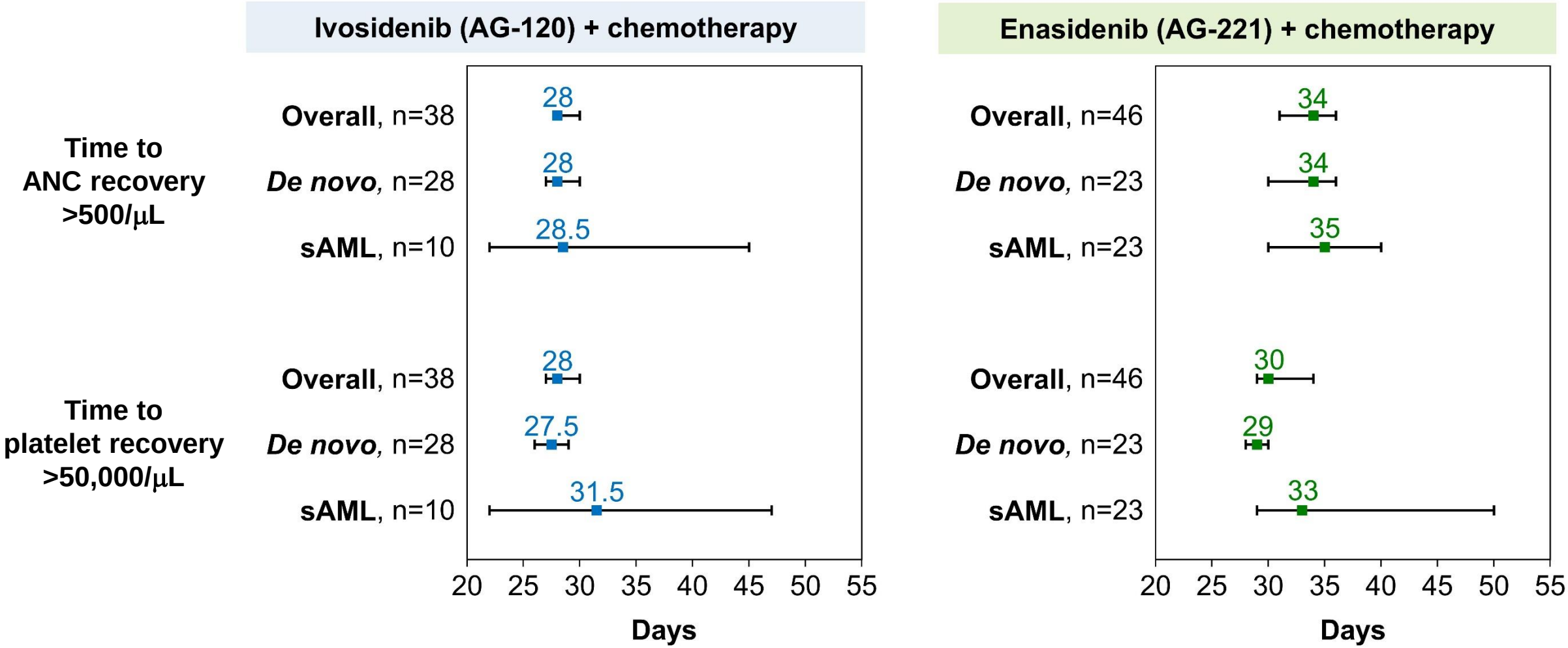
	Ivosidenib (AG-120) + chemotherapy (n=60)	Enasidenib (AG-221) + chemotherapy (n=93)
Dosed in induction period, n (%)	**60 (100)**	**93 (100)**
Ongoing in induction period	9 (15)	0 (0)
Dosed in consolidation period, n (%)	**28 (47)**	**45 (48)**
Ongoing in consolidation period	8 (13)	4 (4)
Dosed in maintenance period, n (%)	**11 (18)**	**18 (19)**
Ongoing in maintenance period	8 (13)	9 (10)
Treatment discontinuation total, n (%)	**33 (55)**	**78 (84)**
Reasons for discontinuation, n (%)		
Hematopoietic stem cell transplant	17 (52)	41 (53)
Death	1 (3)	4 (5)
Adverse event	8 (24)	11 (14)
Progressive disease	4 (12)	7 (9)
Patient/Physician decision	2 (6)	9 (12)
Other	1 (3)	6 (8)

AEs of interest, 30-day and 60-day mortality rates

Grade ≥3 AE of interest, regardless of attribution, n (%)	Induction period	
	Ivosidenib (AG-120) + chemotherapy (n=60)	Enasidenib (AG-221) + chemotherapy (n=93)
IDH differentiation syndrome	2 (3)	1 (1)
Leukocytosis	-	-
QT interval prolongation	1 (2)	-
Blood bilirubin increased	4 (7)	13 (14)

Mortality rates, n (%)	Ivosidenib (AG-120) + chemotherapy (n=60)	Enasidenib (AG-221) + chemotherapy (n=93)
30-day mortality	3 (5)	5 (5)
60-day mortality	5 (8)	8 (9)

Hematologic recovery from induction therapy



The symbol and the numerical value represent the median in days and the lines represent the 95% confidence intervals

For enasidenib-treated patients, the count recovery analysis only includes those patients who started enasidenib on Day 1 of induction cycle 1

Summary of best overall response in efficacy-evaluable patients[a]

Response,[b] n (%)	Ivosidenib (AG-120) + chemotherapy			Enasidenib (AG-221) + chemotherapy		
	All (n=49)	*De novo* (n=34)	sAML (n=15)	All (n=89)	*De novo* (n=56)	sAML (n=33)
CR+CRi/CRp	**39 (80)**	31 (91)	8 (53)	**64 (72)**	43 (77)	21 (64)
CR	**35 (71)**	27 (79)	8 (53)	**50 (56)**	36 (64)	14 (42)
CRi/CRp	**4 (8)**	4 (12)	-	**14 (16)**	7 (13)	7 (21)
MLFS	**3 (6)**	1 (3)	2 (13)	**11 (12)**	6 (11)	5 (15)
PR	**1 (2)**	-	1 (7)	**1 (1)**	-	1 (3)
Treatment failure	**6 (12)**	2 (6)	4 (27)	**13 (15)**	7 (13)	6 (18)

[a]Patients who have at least one post-baseline response assessment on or after Induction Day 21 or who discontinued treatment before having a response assessment

[b]Best response from any time on study is shown

CR = complete response; CRi/CRp = CR with incomplete hematologic recovery or incomplete platelet recovery; MLFS = morphologic leukemia-free state for patients with AML; PR = partial response; treatment failure = stable disease + disease progression + discontinuation before response assessment + discontinuation with best response of not evaluable

IDH1 mutation clearance (MC) and measurable residual disease (MRD) in ivosidenib-treated patients

IDH1-MC by digital PCR	
Best response	**IDH1-MC, n (%)**
CR/CRi/CRp, n=29	12 (41)

MRD by flow cytometry	
Best response	**MRD-negative, n (%)**
CR/CRi/CRp, n=17	15 (88)

Of the **12** ivosidenib-treated patients who achieved IDH1-MC:

- **10** patients achieved MC following induction
- **2** patients achieved MC during or after consolidation

Of the **15** ivosidenib-treated patients who became MRD-negative:

- **12** patients became MRD-negative following induction
- **3** patients became MRD-negative during or after consolidation

IDH1 mutation clearance (IDH1-MC) is assessed by digital PCR technology (Sysmex Inostics Inc) and is defined as a reduction in the m*IDH1* variant allele frequency to a level below the limit of detection (0.02–0.04%) for ≥1 on-treatment time point on or after Day 21 of induction

MRD in bone marrow aspirates is analyzed using multi-parameter flow cytometry with “different from normal” approach. MRD-negative is defined as no identification of abnormal myeloid blast, monocyte or maturing myeloid population

IDH2 mutation clearance (MC) and measurable residual disease (MRD) in enasidenib-treated patients

IDH2-MC by digital PCR	
Best response	**IDH2-MC, n (%)**
CR/CRi/CRp, n=59	15 (25)

MRD by flow cytometry	
Best response	**MRD-negative, n (%)**
CR/CRi/CRp, n=20	9 (45)

Of the **15** enasidenib-treated patients who achieved IDH2-MC:

- **11** patients achieved MC following induction
- **4** patients achieved MC during or after consolidation

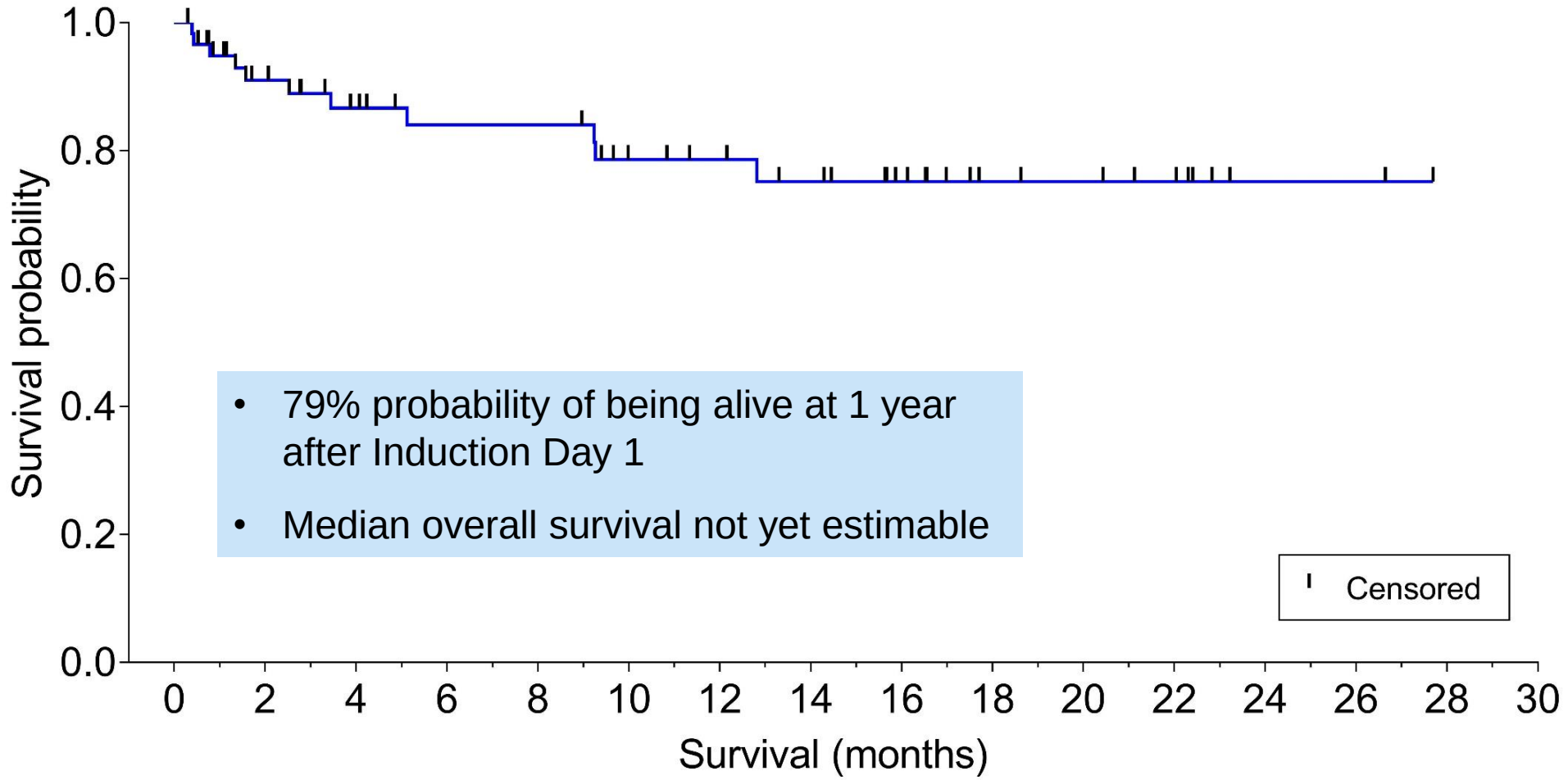
Of the **9** enasidenib-treated patients who became MRD-negative:

- **7** patients became MRD-negative following induction
- **2** patients became MRD-negative during or after consolidation

IDH2 mutation clearance (IDH2-MC) is assessed by digital PCR technology (Sysmex Inostics Inc) and is defined as a reduction in the m*IDH2* variant allele frequency to a level below the limit of detection (0.02–0.04%) for ≥1 on-treatment time point on or after Day 21 of induction

MRD in bone marrow aspirates is analyzed using multi-parameter flow cytometry with “different from normal” approach. MRD-negative is defined as no identification of abnormal myeloid blast, monocyte or maturing myeloid population

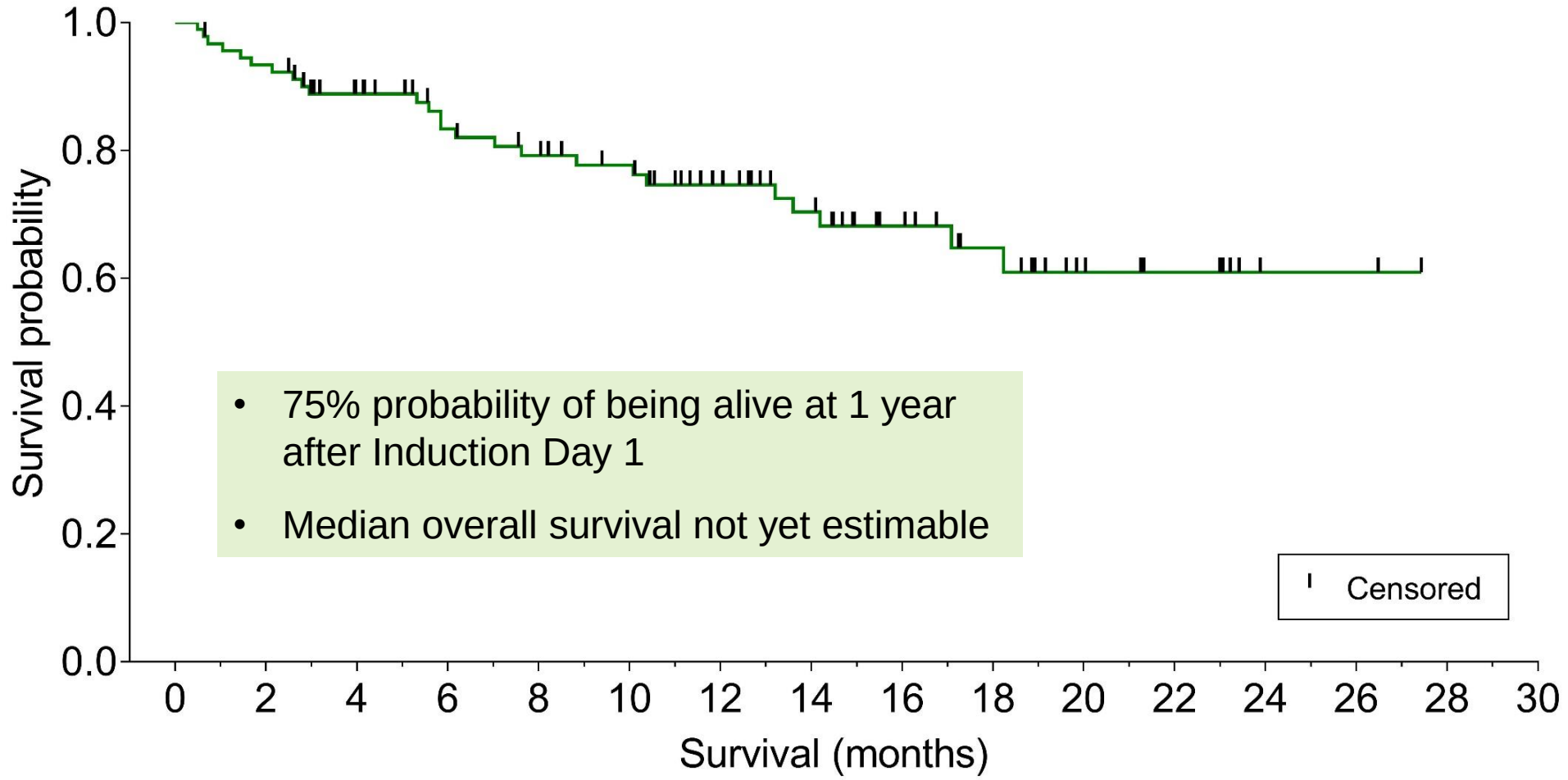
Overall survival in ivosidenib-treated patients



- 79% probability of being alive at 1 year after Induction Day 1
- Median overall survival not yet estimable

Number of patients at risk	60	52	45	40	37	33	32	32	32	31	26	25	24	22	21	19	16	12	10	9	9	8	7	3	2	2	2	1

Overall survival in enasidenib-treated patients



- 75% probability of being alive at 1 year after Induction Day 1
- Median overall survival not yet estimable

Number of patients at risk	91	87	84	76	71	68	61	59	56	52	51	46	41	36	33	25	23	20	17	13	10	9	7	6	2	2	2	1

Conclusions

- The combination of ivosidenib or enasidenib with standard induction and consolidation therapy is safe and well tolerated in patients with newly diagnosed AML and an IDH mutation
- The remission rates observed with these combinations are encouraging, especially in this population of older, high-risk patients
- In the subset of patients who achieved a CR, CRi, or CRp:
  - Ivosidenib was associated with elimination of MRD by flow cytometry in 88% of patients and with IDH1-MC in 41% of patients
  - Enasidenib was associated with elimination of MRD by flow cytometry in 45% of patients and with IDH2-MC in 25% of patients
- The overall survival rates are robust, with ≥75% 1-year survival in both ivosidenib-treated and enasidenib-treated patients
- The benefit of adding ivosidenib or enasidenib to induction and consolidation followed by single-agent maintenance therapy for patients with newly diagnosed AML and an IDH mutation will be further evaluated in an upcoming randomized phase 3 trial

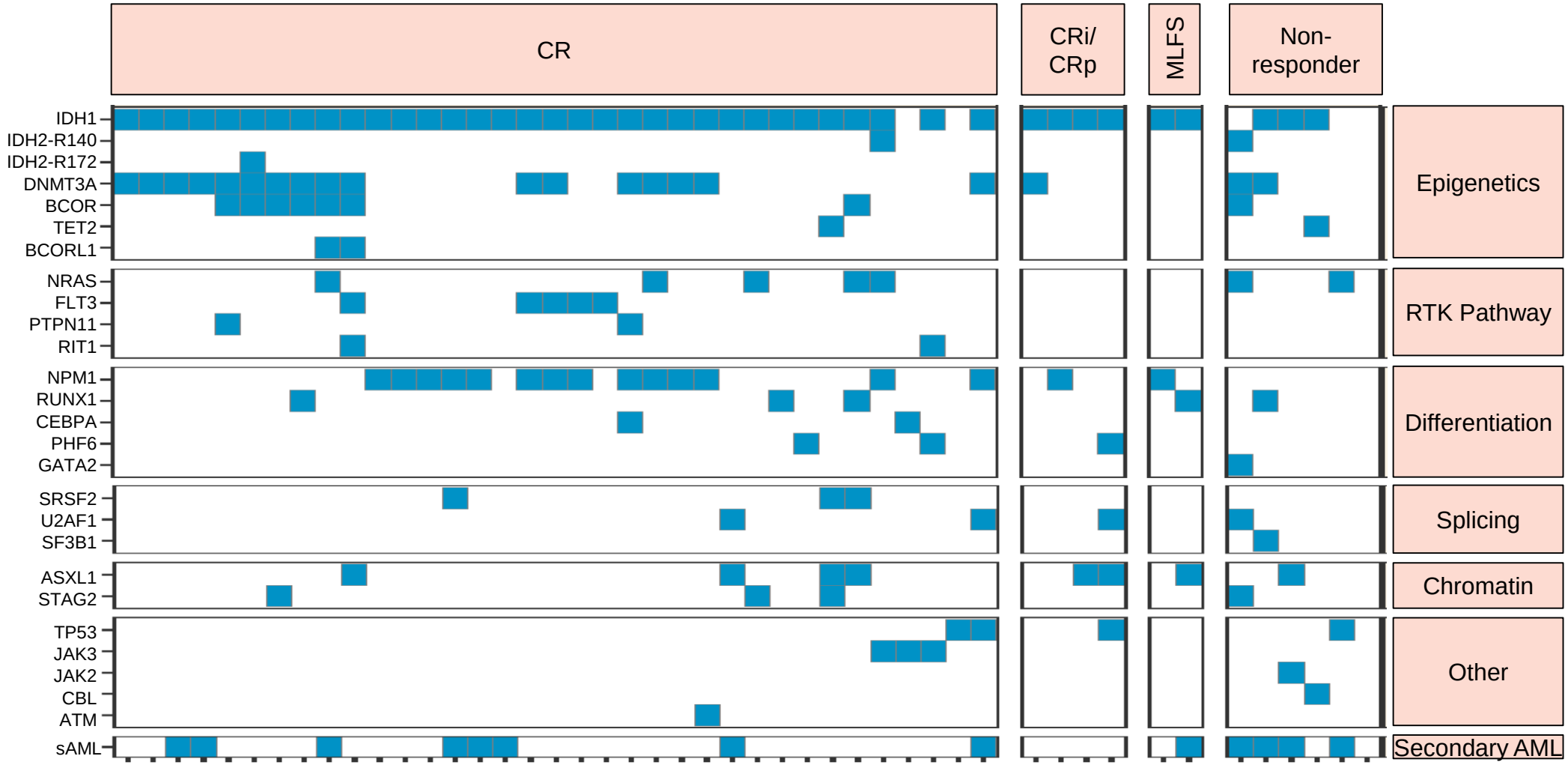
Acknowledgments

- We would like to thank the patients who volunteered to take part in this study, the principal investigators, their staff, and their institutions

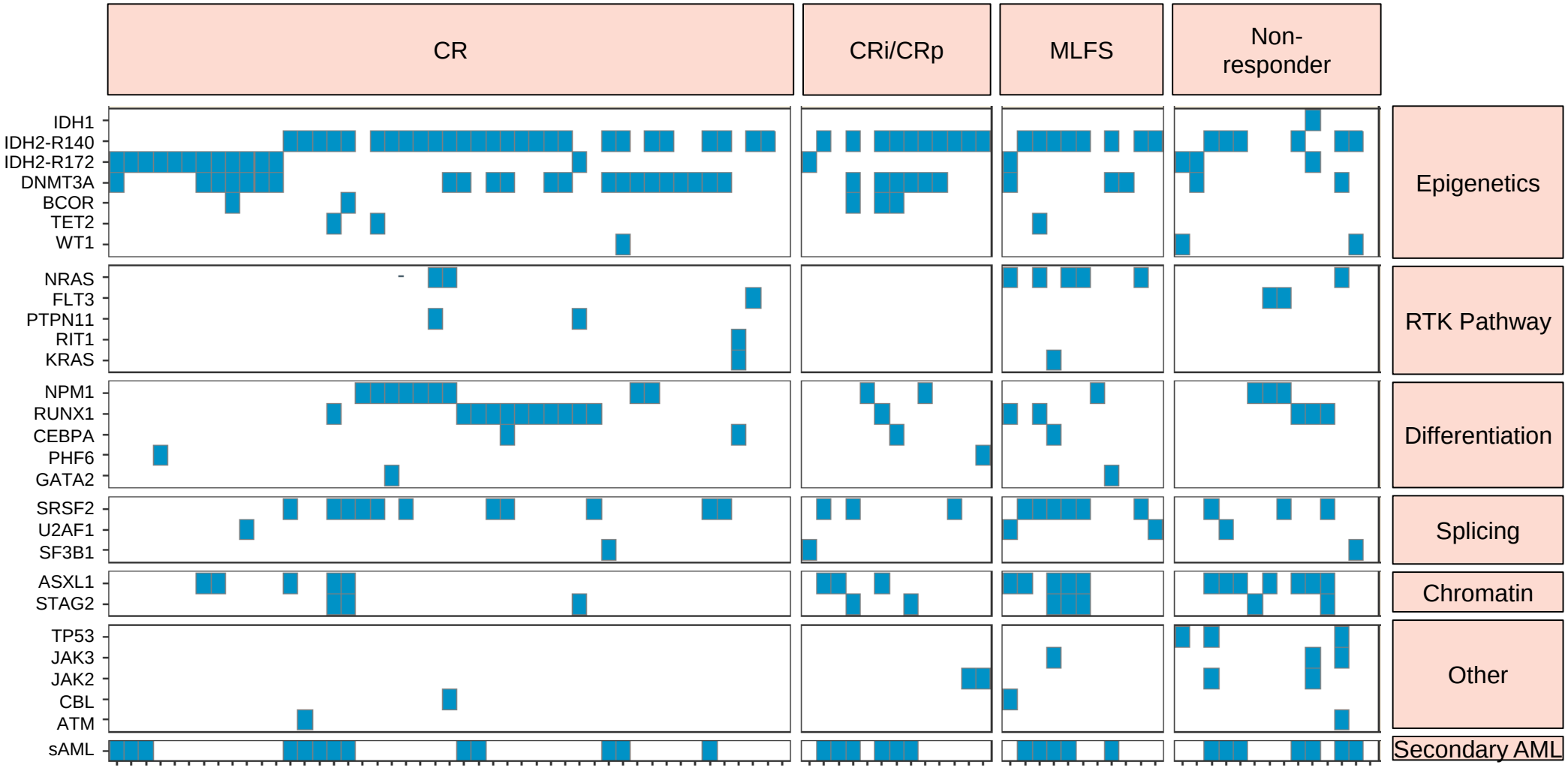
- Disclosure: This clinical study is funded by Agios Pharmaceuticals, Inc. and Celgene Corporation

BACK-UP SLIDES

Ivosidenib (AG-120) baseline co-mutation heatmap



Enasidenib (AG-221) baseline co-mutation heatmap



Grade ≥3 non-hematologic TEAEs in ≥10% of patients during induction and/or consolidation periods, regardless of attribution

TEAE, n (%)	Induction period		Consolidation period	
	Ivosidenib + chemotherapy (n=60)	Enasidenib + chemotherapy (n=93)	Ivosidenib + chemotherapy (n=28)	Enasidenib + chemotherapy (n=45)
Patients with ≥1 grade 3 or higher TEAE	57 (95)	86 (93)	25 (89)	41 (91)
Febrile neutropenia	37 (62)	57 (61)	10 (36)	17 (38)
Hypophosphatemia	8 (13)	11 (12)	-	3 (7)
Hypokalemia	6 (10)	8 (9)	1 (4)	5 (11)
Colitis	6 (10)	3 (3)	-	-
Hypertension	6 (10)	6 (7)	-	2 (4)
Blood bilirubin increased	4 (7)	13 (14)	1 (4)	6 (13)
Lung infection	3 (5)	10 (11)	2 (7)	4 (9)
Sepsis	4 (7)	4 (4)	3 (11)	7 (16)

Hematologic recovery from induction therapy

	Ivosidenib (AG-120) + chemotherapy		Enasidenib (AG-221) + chemotherapy	
	n	Median, days (95% CI)	n	Median, days (95% CI)
Time to ANC recovery >500/μL				
Overall	38	28 (28, 30)	46	34 (31, 36)
De novo	28	28 (27, 30)	23	34 (30, 36)
sAML	10	28.5 (22, 45)	23	35 (30, 40)
Time to platelet recovery >50,000/μL				
Overall	38	28 (27, 30)	46	30 (29, 34)
De novo	28	27.5 (26, 29)	23	29 (28, 30)
sAML	10	31.5 (22, 47)	23	33 (29, 50)