Ivosidenib or enasidenib combined with standard induction chemotherapy is well tolerated and active in patients with newly diagnosed AML with an IDH1 or IDH2 mutation: initial results from a phase 1 trial

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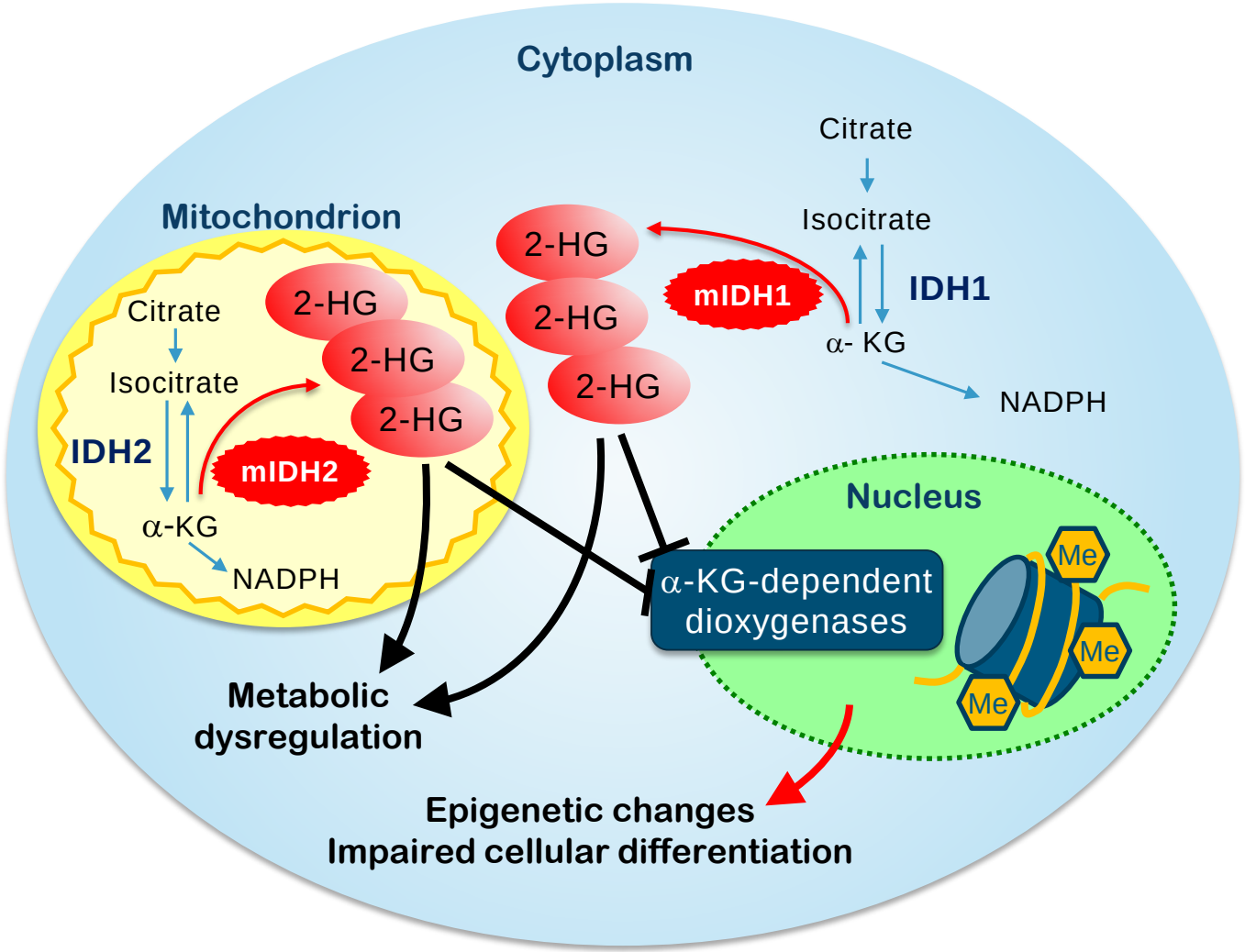
Introduction

- Mutant IDH (mIDH) 1 or 2 is seen in ~15–20% of patients with AML
- mIDH results in accumulation of 2-HG, leading to DNA and histone hypermethylation and a block in differentiation
- Ivosidenib (AG-120) and enasidenib (AG-221) are oral inhibitors of mIDH1 and mIDH2, respectively
- Given the single agent activity of ivosidenib and enasidenib in R/R AML, the safety and efficacy of these agents are being explored in earlier lines of therapy in combination with standard induction and consolidation regimens



Study summary: NCT02632708

Primary objective

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

Study design

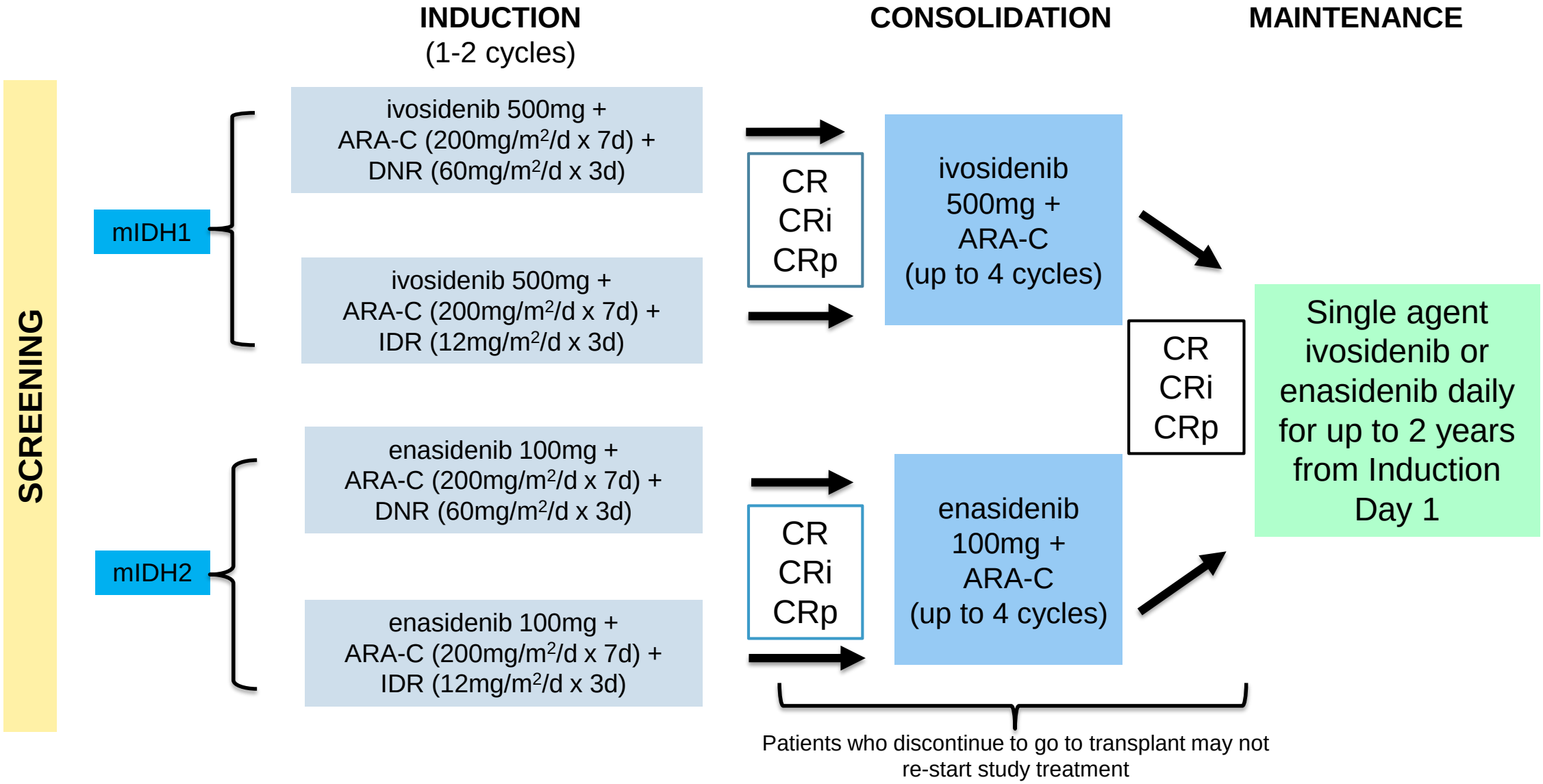
- "6+6" design to test safety of ivosidenib and enasidenib during induction
  - Six DLT-evaluable patients enrolled into each induction cohort (DNR, IDR) in parallel
  - After ivosidenib and enasidenib doses deemed safe, each induction cohort expanded to include up to 30 patients each

Key inclusion/exclusion criteria

- ≥18 years of age
- Previously untreated AML (*de novo* or secondary) with locally documented IDH1 and/or IDH2 mutation
- No prior chemotherapy for AML
  - Hydroxyurea allowed for control of the peripheral blast count in patients with leukocytosis
  - Patients with sAML may have had previous treatment for MDS or other AHD, including hypomethylating agents

DNR = daunorubicin; IDR = idarubicin

Study design



Patient characteristics

Baseline characteristics	Ivosidenib (AG-120) + chemotherapy (n=32)	Enasidenib (AG-221) + chemotherapy (n=56)
Age in years, median (range)	60.5 (24–76)	63 (32–76)
<60, n (%)	15 (47)	21 (38)
≥60, n (%)	17 (53)	35 (62)
Sex (male/female), n	18/14	31/25
AML type, n (%)		
De novo	22 (69)	32 (57)
Secondary (sAML)	10 (31)	24 (43)
Prior hypomethylating agent therapy	4 (40)[a]	15 (63)[a]
IDH1 mutation type[b], n (%)		
R132	30 (94)	n/a
Other	2 (6)	n/a
IDH2 mutation type[b], n (%)		
R140	n/a	39 (70)
R172	n/a	17 (30)
Risk status based on cytogenetics and molecular abnormalities[c], n (%)		
Favorable	8 (25)	4 (7)
Intermediate	13 (41)	25 (45)
Poor	11 (34)	20 (36)
Unknown	-	7 (13)
Comutations[b], n (%)		
FLT3-ITD	3 (9)	7 (13)
FLT3-TKD	1 (3)	1 (2)
NPM1	13 (41)	7 (13)
CEBPA	1 (3)	3 (5)

Grade ≥3 non-hematologic AEs in >5% of patients during induction period, regardless of attribution

	Ivosidenib (AG-120) + CT (n=32)	Enasidenib (AG-221) + CT (n=56)
Patients with >1 grade 3 or higher TEAE, n (%)	30 (94)	51 (91)
Febrile neutropenia	19 (60)	35 (63)
Blood bilirubin increased	3 (9)	5 (9)
Hypertension	3 (9)	5 (9)
Colitis	3 (9)	3 (5)
Alanine aminotransferase increased	3 (9)	1 (2)
Aspartate aminotransferase increased	3 (9)	-
Lung infection	2 (6)	3 (5)
Hyperglycemia	2 (6)	1 (2)
Abdominal Infection	2 (6)	-
Acute kidney injury	2 (6)	1 (2)
Hypokalemia	2 (6)	2 (4)
Metabolic acidosis	2 (6)	1 (2)
Decreased appetite	2 (6)	-
Hypoxia	2 (6)	-
Leukocytosis	2 (6)	-
Multiple organ dysfunction syndrome	2 (6)	-
Sepsis	2 (6)	2 (4)
Bacteremia	1 (3)	5 (9)
Diarrhea	1 (3)	4 (7)

Additional safety summary

- 30-day and 60-day mortality rates:
  - Both 6% in ivosidenib-treated patients
  - 5% and 7%, respectively, in enasidenib-treated patients
  - No deaths related to ivosidenib or enasidenib, as assessed by the investigator
- 1 DLT noted in enasidenib+daunorubicin+cytarabine cohort
  - Persistent Grade 4 thrombocytopenia in the absence of residual leukemia on Day 42 of induction
- No DLTs noted in either ivosidenib induction cohort

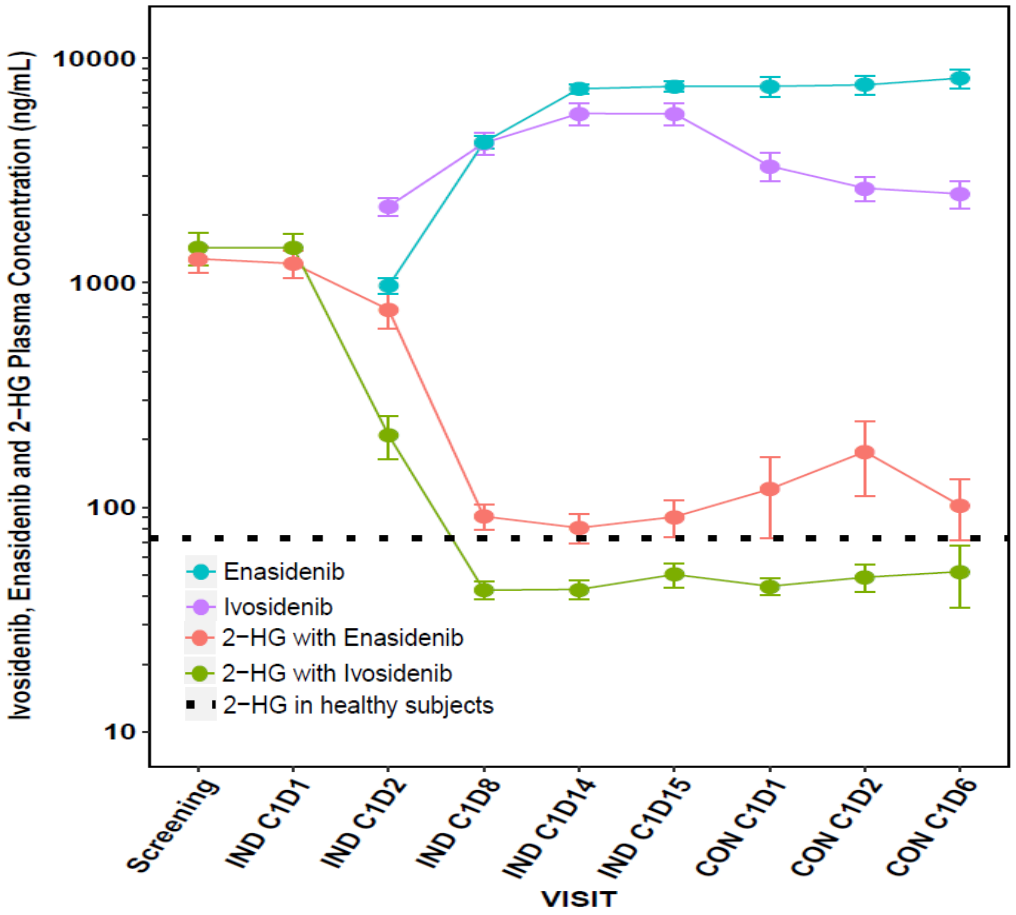
Hematologic recovery from induction therapy

	Ivosidenib (AG-120) + CT		Enasidenib (AG-221) + CT	
	n	Median - days (95% CI)	n	Median - days (95% CI)
Time to ANC recovery >500/µL				
Overall	20	28.5 (27,34)	29	34 (29,35)
De novo	15	28 (26,32)	14	32.5 (29,42)
sAML	5	35 (23,63)	15	34 (28,35)
Time to platelet recovery >50,000/µL				
Overall	20	28 (26,34)	29	33 (29,50)
De novo	15	27 (25,32)	14	29 (25,35)
sAML	5	38 (27,NE)	15	50 (29,74)

To be included in count recovery analyses, patients must have achieved CR, CRi, CRp, or MLFS by Day 28 (±7 days) of the first cycle of induction therapy. Patients with persistent disease and/or those who received a 2nd induction cycle were not included.

Plasma PK/PD in patients treated with ivosidenib or enasidenib + chemotherapy

Mean trough concentrations of ivosidenib and enasidenib, and concentrations of 2-HG (± SD)



- PK/PD data with ivosidenib or enasidenib is similar across daunorubicin and idarubicin induction cohorts
- Ivosidenib and enasidenib exposures are comparable to single agent ivosidenib and enasidenib exposures in Studies AG120-C-001 and AG221-C-001, respectively
- Plasma trough concentrations of both ivosidenib and enasidenib reach steady-state levels by Day 14 of Induction Cycle 1
- Plasma 2-HG concentrations are reduced by as much as 99%, and fall within the range observed in healthy volunteers in the majority of patients by Day 14 of Induction Cycle 1

Best overall response summary

	Ivosidenib (AG-120) + CT			Enasidenib (AG-221) + CT		
Response, n (%)	All (n=30)	*De novo* (n=21)	sAML (n=9)	All (n=50)	*De novo* (n=27)	sAML (n=23)
CR+CRi/CRp	23 (77)	19 (91)	4 (44)	31 (62)	18 (67)	13 (57)
CR	19 (63)	15 (71)	4 (44)	25 (50)	16 (59)	9 (39)
CRi/CRp	4 (13)	4 (19)	-	6 (12)	2 (7)	4 (17)
MLFS	1 (3)	-	1 (11)	10 (20)	4 (15)	6 (26)
PR	2 (7)	1 (5)	1 (11)	-	-	-
Persistent disease	2 (7)	1 (5)	1 (11)	5 (10)	2 (7)	3 (13)
NE	2 (7)	-	2 (22)	4 (8)	3 (11)	1 (4)

Best response from any time on study is shown

CR = complete response; CRi = CR with incomplete hematologic recovery; CRp = CR with incomplete platelet recovery; MLFS = morphologic leukemic-free state for patients with AML; PR = partial response; Persistent disease = stable disease + disease progression; NE = not evaluable

Conclusions

- The combination of ivosidenib or enasidenib with standard AML induction therapy is safe and well tolerated in this patient population, many of whom had secondary AML and received prior therapy with an HMA
  - Some patients with sAML treated with enasidenib have exhibited a prolonged time to platelet count recovery
    - The longer time to platelet recovery may reflect the reduced hematopoietic reserve of patients with sAML
    - An alternative dosing schedule with enasidenib is being explored to investigate any potential interaction with induction chemotherapy
- Preliminary response data are consistent with expectations for 7+3 induction chemotherapy in newly diagnosed AML patients with mIDH
- A randomized phase 3 trial is planned to assess the efficacy of ivosidenib or enasidenib combined with standard induction therapy in patients with newly diagnosed AML with mIDH

Acknowledgements

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