AGILE: A global, randomized, double-blind, phase 3 study of ivosidenib + azacitidine versus placebo + azacitidine in patients with newly diagnosed acute myeloid leukemia with an *IDH1* mutation

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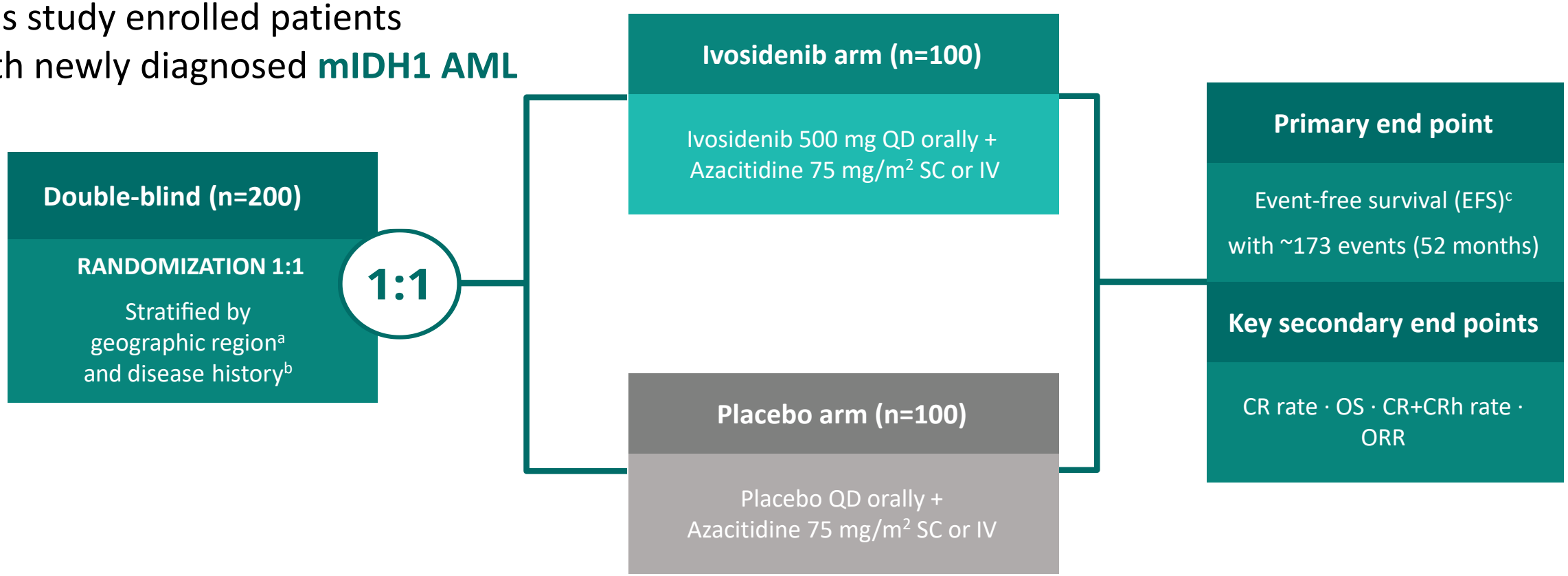
AGILE: study design and end points

This study enrolled patients with newly diagnosed **mIDH1 AML**



- As of the data cutoff date for this analysis (March 18, 2021), 146 patients have been randomized (IVO+AZA, n=72; PBO+AZA, n=74).
  - As of 12May2021, the IDMC recommended to halt enrollment based on a noted difference in clinical importance between the treatment groups, not related to safety.
    - A total of 148 patients were enrolled at 155 active sites in 20 countries.

[a]Geographic regions: US/Canada; Western Europe, Israel and Australia; Japan; and Rest of the World. [b]Disease history: de novo vs secondary AML
[c]**EFS is defined as the time from randomization until treatment failure, relapse from remission, or death from any cause, whichever occurs first. Treatment failure is defined as failure to achieve CR by week 24**
CR = complete remission; CRh = complete remission with partial hematologic recovery; IDMC = independent data monitoring committee; IV = intravenously; ORR = objective response rate; OS = overall survival; PBO = placebo; QD = once daily; SC = subcutaneously

Baseline demographic and disease characteristics

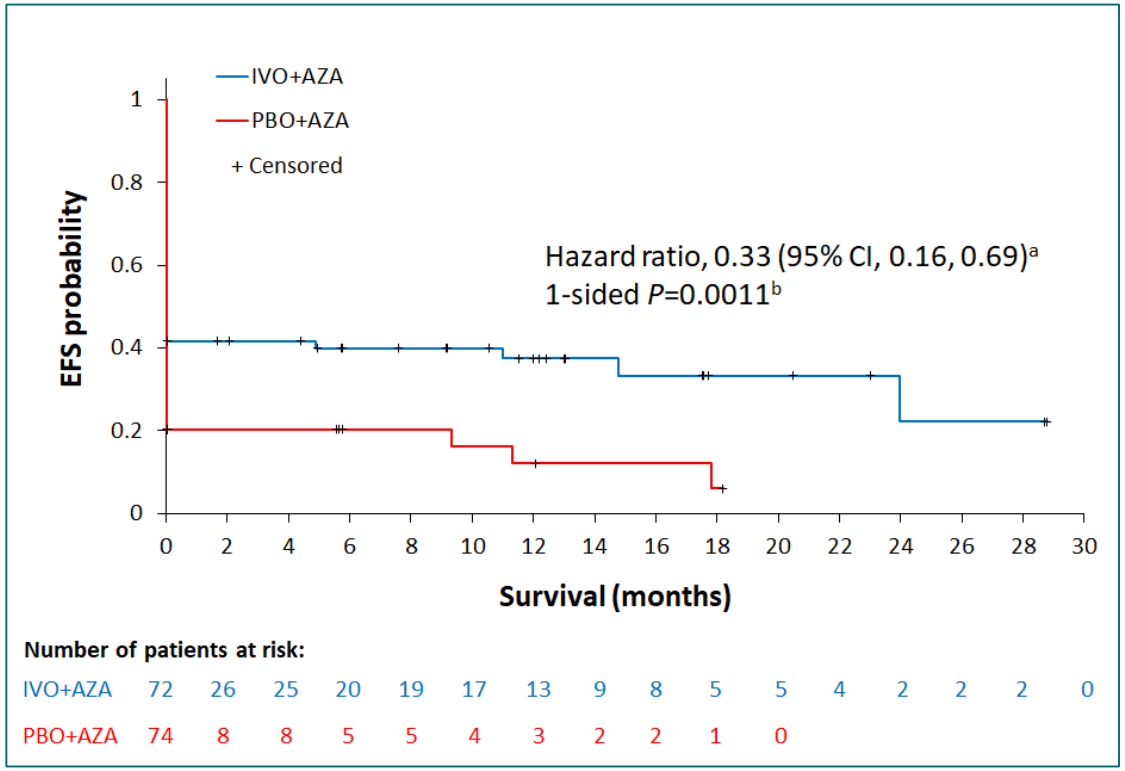
Characteristic	IVO+AZA (n=72)	PBO+AZA (n=74)
Median (range) age, years	76 (58–84)	75.5 (45–94)
Sex, n (%)		
Male/Female	42 (58.3)/30 (41.7)	38 (51.4)/36 (48.6)
ECOG PS score, n (%)		
0/1/2	14 (19.4)/32 (44.4)/26 (36.1)	10 (13.5)/40 (54.1)/24 (32.4)
Disease history (per investigator), n (%)		
De novo AML	54 (75.0)	53 (71.6)
Secondary AML[a]	18 (25.0)	21 (28.4)
Median (range) m*IDH1* VAF in BMA, % (range)[b]	36.7 (3.1–50.5)	35.5 (3.0–48.6)
Cytogenetic risk, n (%)[c]		
Favorable/intermediate/poor	3 (4.2); 48 (66.7); 16 (22.2)	7 (9.5); 44 (59.5); 20 (27.0)
Median (range) bone marrow blasts, %	54 (20–95)	48.0 (17–100)

[a]Secondary AML included patients with treatment-related AML, with history of MDS, or with history of MPN. [b]IVO+AZA, n=49; PBO+AZA, n=58; VAF was quantified by next-generation sequencing. [c]Cytogenetic risk status was reported as other or missing for 5 patients (6.9%) in the IVO+AZA arm and 3 patients (4.1%) in the PBO+AZA arm

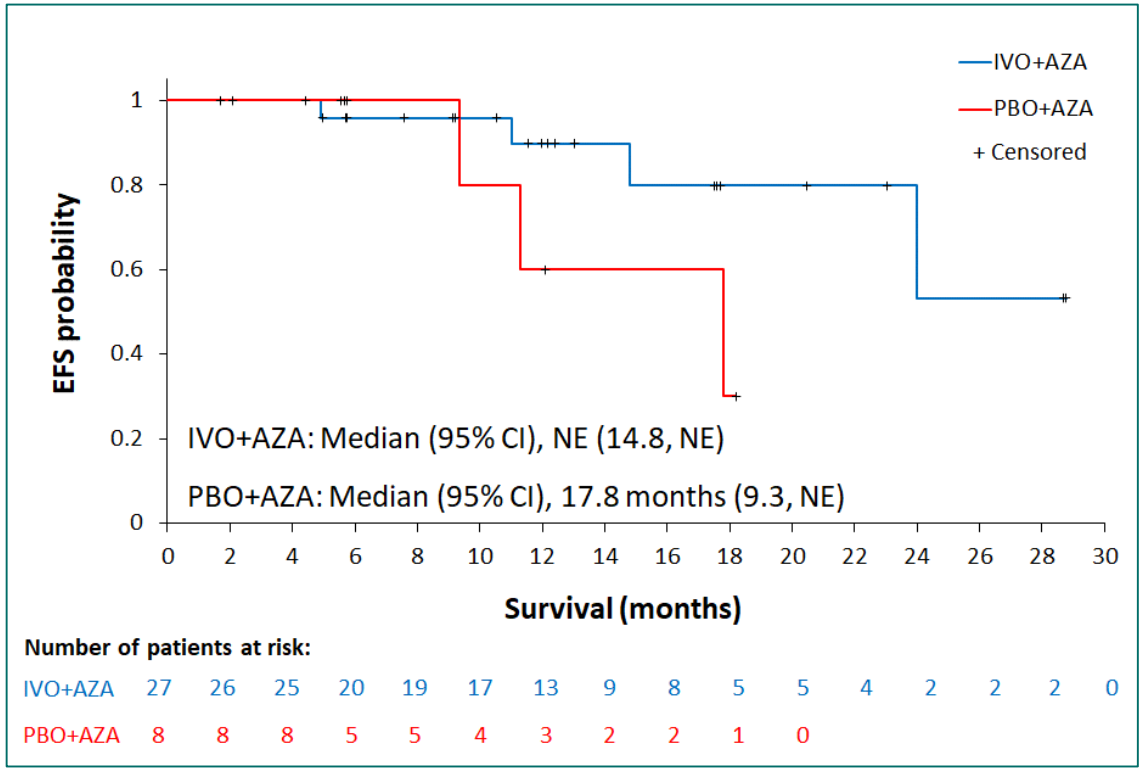
BMA = bone marrow aspirate; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MDS = myelodysplastic syndrome; MPN = myeloproliferative neoplasms; VAF = variant allele frequency

IVO+AZA significantly improves EFS in mIDH1 AML

EFS in the intent-to-treat population



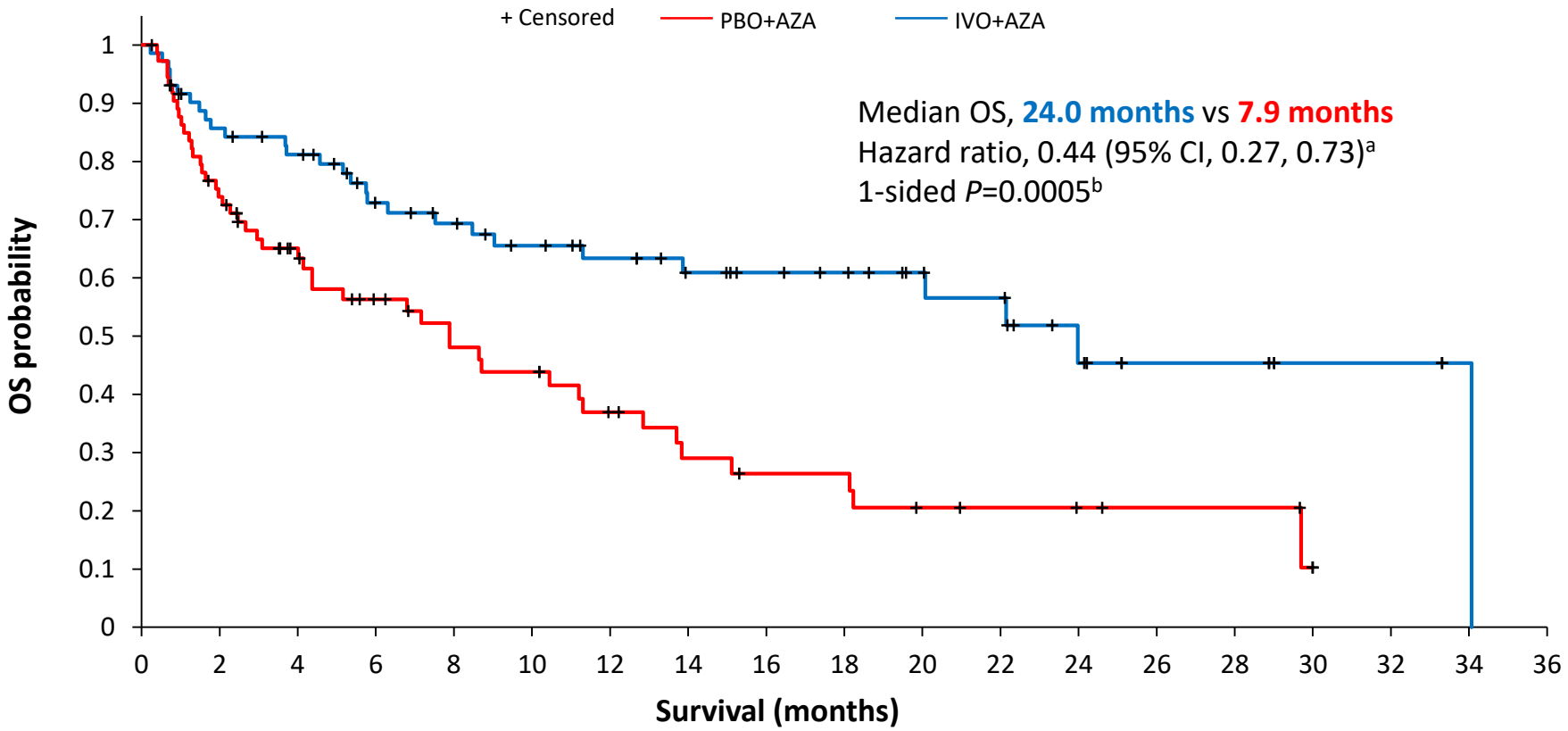
EFS among patients who achieved CR by 24 weeks



- Patients who did not achieve CR by week 24 were considered to have had an event at day 1 of randomization.
- EFS benefit was consistent across subgroups: de novo status, region, age, baseline ECOG PS score, sex, race, baseline cytogenetic risk status, WHO classification of AML, baseline white blood cell count, baseline percentage of bone marrow blasts.

[a]Hazard ratio was estimated using a Cox's proportional hazards model stratified by the randomization stratification factors
[b]*P* value was calculated from the one-sided log-rank test stratified by the randomization stratification factors
NE = not estimable; WHO = World Health Organization

IVO+AZA significantly improves OS in mIDH1 AML



Number of patients at risk:

PBO+AZA	74	53	38	29	23	21	15	11	9	9	6	5	4	3	3	0		
IVO+AZA	72	58	53	42	38	33	29	24	21	19	15	13	7	4	4	2	2	1

- OS benefit was consistent across subgroups: de novo status, region, age, baseline ECOG PS score, sex, race, baseline cytogenetic risk status, WHO classification of AML, baseline white blood cell count, baseline percentage of bone marrow blasts.

[a]Hazard ratio was estimated using a Cox's proportional hazards model stratified by the randomization stratification factors
[b]*P* value was calculated from the one-sided log-rank test stratified by the randomization stratification factors

IVO+AZA improved clinical and hematologic response in mIDH1 AML

Response rates	IVO+AZA (n=72)	PBO+AZA (n=74)
CR rate, n (%) [95% CI]	34 (47.2) [35.3, 59.3]	11 (14.9) [7.7, 25.0]
Odds ratio (95% CI); 1-sided *P* value	4.8 (2.2, 10.5); *P*<0.0001	
Median duration of CR (95% CI), months	NE (13.0, NE)	11.2 (3.2, NE)
Median time to CR (range), months	4.3 (1.7–9.2)	3.8 (1.9–8.5)
CR+CRh rate, n (%) [95% CI]	38 (52.8) [40.7, 64.7]	13 (17.6) [9.7, 28.2]
Odds ratio (95% CI); 1-sided *P* value	5.0 (2.3, 10.8); *P*<0.0001	
Median duration of CR+CRh (95% CI), months	NE (13.0, NE)	9.2 (5.8, NE)
Median time to CR+CRh (range), months	4.0 (1.7–8.6)	3.9 (1.9–7.2)
ORR, n (%) [95% CI]	45 (62.5) [50.3, 73.6]	14 (18.9) [10.7, 29.7]
Odds ratio (95% CI); 1-sided *P* value	7.2 (3.3, 15.4); *P*<0.0001	
Median duration of response (95% CI), months	22.1 (13.0, NE)	9.2 (6.6, 14.1)
Median time to first response (range), months	2.1 (1.7–7.5)	3.7 (1.9–9.4)

[a]Assessed by BEAMing Digital PCR (limit of detection 0.02–0.04%) in patients with at least one on-treatment sample available. [b]N being the total number of patients with available biomarker samples in the corresponding category. [c]Total number of patients with available biomarker samples in the corresponding treatment group

BMMC = bone marrow mononuclear cell; PCR = polymerase chain reaction

Treatment-emergent adverse events (TEAEs)

	IVO+AZA (n=71)		PBO+AZA (n=73)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE, n (%)	70 (98.6)	66 (93.0)	73 (100)	69 (94.5)
Any hematologic TEAEs, n (%)	55 (77.5)	50 (70.4)	48 (65.8)	47 (64.4)
Most common hematologic TEAEs (>20%[a]), n (%)				
Anemia	22 (31.0)	18 (25.4)	21 (28.8)	19 (26.0)
Febrile neutropenia	20 (28.2)	20 (28.2)	25 (34.2)	25 (34.2)
Neutropenia	20 (28.2)	19 (26.8)	12 (16.4)	12 (16.4)
Thrombocytopenia	20 (28.2)	17 (23.9)	15 (20.5)	15 (20.5)
Most common TEAEs (>20%[a]), n (%)				
Nausea	30 (42.3)	2 (2.8)	28 (38.4)	3 (4.1)
Vomiting	29 (40.8)	0	19 (26.0)	1 (1.4)
Diarrhea	25 (35.2)	1 (1.4)	26 (35.6)	5 (6.8)
Pyrexia	24 (33.8)	1 (1.4)	29 (39.7)	2 (2.7)
Constipation	19 (26.8)	0	38 (52.1)	1 (1.4)
Pneumonia	17 (23.9)	16 (22.5)	23 (31.5)	21 (28.8)
Bleeding, n (%)	29 (40.8)	4 (5.6)	21 (28.8)	5 (6.8)
Infections, n (%)	20 (28.2)	15 (21.1)	36 (49.3)	22 (30.1)

- TEAEs of special interest with IVO+AZA vs PBO+AZA included grade ≥2 differentiation syndrome (14.1% vs 8.2%) and grade ≥3 QT prolongation (9.9% vs 4.1%[b]).
- Infections were less common with IVO+AZA (28.2%) compared with PBO+AZA (49.3%).
- There were no deaths deemed related to treatment.

[a]>20% cutoff used for any-grade TEAEs based on IVO+AZA
[b]QT prolongation with PBO+AZA includes electrocardiogram QT prolonged (2.7%) and syncope (1.4%)

Summary

- **IVO+AZA significantly improved EFS, OS, and clinical response (CR, CR+CRh, ORR) compared with PBO+AZA in patients with newly diagnosed m*IDH1* AML ineligible for intensive induction chemotherapy.**
- **The safety profile of IVO+AZA was favorable and TEAEs were manageable, with fewer infections reported, relative to PBO+AZA.**
- **HRQoL was favored in the IVO+AZA arm compared with PBO+AZA.**
- **These data demonstrate the clinical benefit of IVO+AZA in this difficult-to-treat m*IDH1* AML population.**

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Disclosures

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