Fludarabine, Cytarabine, Granulocyte Colony-Stimulating Factor, and Idarubicin With Gemtuzumab Ozogamicin Improves Event-Free Survival in Younger Patients With Newly Diagnosed AML and Overall Survival in Patients With *NPM1* and *FLT3* Mutations

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ABSTRACT

PURPOSE To determine the optimal induction chemotherapy regimen for younger adults with newly diagnosed AML without known adverse risk cytogenetics.

PATIENTS AND METHODS One thousand thirty-three patients were randomly assigned to intensified (fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin [FLAG-Ida]) or standard (daunorubicin and Ara-C [DA]) induction chemotherapy, with one or two doses of gemtuzumab ozogamicin (GO). The primary end point was overall survival (OS).

RESULTS There was no difference in remission rate after two courses between FLAG-Ida + GO and DA + GO (complete remission [CR] + CR with incomplete hematologic recovery 93% *v* 91%) or in day 60 mortality (4.3% *v* 4.6%). There was no difference in OS (66% *v* 63%; $P = .41$); however, the risk of relapse was lower with FLAG-Ida + GO (24% *v* 41%; $P < .001$) and 3-year event-free survival was higher (57% *v* 45%; $P < .001$). In patients with an *NPM1* mutation (30%), 3-year OS was significantly higher with FLAG-Ida + GO (82% *v* 64%; $P = .005$). *NPM1* measurable residual disease (MRD) clearance was also greater, with 88% versus 77% becoming MRD-negative in peripheral blood after cycle 2 ($P = .02$). Three-year OS was also higher in patients with a *FLT3* mutation (64% *v* 54%; $P = .047$). Fewer transplants were performed in patients receiving FLAG-Ida + GO (238 *v* 278; $P = .02$). There was no difference in outcome according to the number of GO doses, although *NPM1* MRD clearance was higher with two doses in the DA arm. Patients with core binding factor AML treated with DA and one dose of GO had a 3-year OS of 96% with no survival benefit from FLAG-Ida + GO.

CONCLUSION Overall, FLAG-Ida + GO significantly reduced relapse without improving OS. However, exploratory analyses show that patients with *NPM1* and *FLT3* mutations had substantial improvements in OS. By contrast, in patients with core binding factor AML, outcomes were excellent with DA + GO with no FLAG-Ida benefit.

ACCOMPANYING CONTENT

Appendix
Data Supplement
Protocol

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INTRODUCTION

The optimal induction regimen for younger patients with newly diagnosed AML is uncertain, although a 3 + 7 regimen of an anthracycline plus cytosine arabinoside (Ara-C) is regarded as a standard of care.[1] In the Medical Research Council AML15 trial, we observed a higher response rate and reduced relapse in patients treated with fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-Ida) compared with those treated with daunorubicin and Ara-C (DA) with or without etoposide (ADE), but no difference in overall survival (OS).[2] There was

CONTEXT

Key Objective

To compare a single dose versus fractionated schedule of gemtuzumab ozogamicin (GO) combined with standard or intensified induction chemotherapy (daunorubicin and Ara-C [DA] or fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin [FLAG-Ida]) in younger adults with AML.

Knowledge Generated

Fractionated GO did not improve outcomes compared with a single dose. The combination of GO with FLAG-Ida increased myelosuppression but also improved event-free survival (EFS) compared with DA + GO. There was evidence for an overall survival benefit in patients with *NPM1* and *FLT3* mutations not observed in other molecular subgroups, including core binding factor AML, where excellent outcomes were achieved with DA + GO.

Relevance *(S. Lentzsch)*

In the evolving landscape of treating *NPM1* and *FLT3* mutated AML patients, these data showing that FLAG-Ida + GO significantly improves the 3-year EFS in *NPM1* and *FLT3* mutated AML are promising. However, additional studies reflecting the current standard of care are needed.*

*Relevance section written by *JCO* Associate Editor Suzanne Lentzsch, MD, PhD.

more hematologic toxicity with FLAG-Ida, predominately after the second induction course, affecting delivery of consolidation therapy. Nevertheless, patients who received two courses of FLAG-Ida only had promising outcomes.

The AML15 study also demonstrated that the addition of gemtuzumab ozogamicin (GO) at a single dose of 3 mg/m² in induction but not consolidation improved OS.[3] This benefit was seen in patients with favorable and intermediate-risk cytogenetics. A study in older patients conducted by the ALFA group comparing DA with or without GO given in a fractionated schedule (days 1, 4, and 7) and in consolidation showed an improvement in event-free survival (EFS) leading to regulatory approval.[4,5] The survival benefit of GO was confirmed in a meta-analysis of five front-line trials; however, it remained unclear which scheduling was optimal.[6] ALFA0701 also suggested a survival benefit for GO in *NPM1*-mutated (*NPM1*^{mut}) AML, supported by measurable residual disease (MRD) analyses using reverse-transcription quantitative polymerase chain reaction showing that GO increased MRD negativity.[7] Subgroup analyses also suggested a benefit for patients with a *FLT3* mutation (*FLT3*^{mut}).[8]

The primary aim of the National Cancer Research Institute (NCRI) AML19 trial was to define the optimal induction chemotherapy regimen for younger patients with newly diagnosed AML without known adverse cytogenetics by comparing DA and FLAG-Ida combined with either a single dose or fractionated GO schedule. The fractionated schedule used two doses of GO because of toxicity concerns, particularly with FLAG-Ida, which had previously only been given with a single dose.[3] Secondary aims were to evaluate the impact of these regimens in molecular and cytogenetic subgroups, their effect on MRD clearance, and the benefit of consolidation after two courses of FLAG-Ida + GO.

PATIENTS AND METHODS

The NCRI AML19 trial (ISRCTN78449203) enrolled 1,498 patients generally age 16-60 years with newly diagnosed de novo or secondary AML or myelodysplastic syndrome (MDS)-EB2, not known to have adverse risk cytogenetics, between November 2015 and November 2020. Older patients (age older than 60 years) could be enrolled if considered fit for intensive therapy. Of patients enrolled, 19 later withdrew consent, leaving 1,479 randomly assigned between FLAG-Ida (n = 738) and DA (n = 741). Hydroxycarbamide was permitted for up to 7 days before treatment initiation. Previous azacytidine was permitted for the treatment of MDS but not of AML. Of the 1,479 patients, 1,033 were also randomly assigned to receive a single dose of GO on D1 (GO1, n = 514) or a fractionated schedule given on D1 and D4 (GO2, n = 519). The remaining patients did not enter the GO randomization either because of contraindication due to abnormal liver function, or because of a transient drug supply interruption.

Patients were designated as high-risk after course 1 if they had refractory disease, on the basis of a validated risk score,[9] or if they had a *FLT3*-internal tandem duplication (ITD) mutation and unmutated *NPM1*. After course 2, *NPM1*^{mut} patients could be designated HR if they had detectable MRD in the peripheral blood (PB).[10] After a protocol amendment in February 2018, patients without *NPM1* mutation who tested MRD-positive in the bone marrow (BM) by flow cytometry (>0.1%) were also designated high-risk.[11] Patients classified as high-risk after course 1 or course 2 were recommended for transplant and

could enter a randomization between CPX-351 and FLAG-Ida but are included in this analysis.

Patients who were not high-risk after cycle 1 received a second course of allocated induction without GO and if not high-risk after course 2 could receive up to two courses of high-dose cytarabine (HDAC) consolidation (3 g/m² twice daily on D1, 3, and 5, reduced to 1.5 g/m² for patients age older than 60 years). Patients in the FLAG-IDA arm who had completed two induction courses could enter a randomization to receive zero, one, or two courses of HDAC. Patients with core binding factor (CBF) AML and those with detectable MRD in the BM, either by flow cytometry or molecular assessment, were excluded from this randomization. No *FLT3* inhibition was used as midostaurin had not been approved when this study commenced.

The trial was approved by the Wales Multicentre Research Ethics Committee 3 (14/WA/1056) and conducted in accordance with the Declaration of Helsinki. Written consent was required for each randomization. A CONSORT diagram is shown in Figure 1. Figure 2 shows treatment schedules and trial schema. All randomizations used a 1:1 ratio. The AML19 study contained a number of other independent randomizations available to patients with specific disease characteristics. This paper reports only on those patients without known adverse karyotype at diagnosis who were randomly assigned between FLAG-Ida + GO and DA + GO; results of other randomizations will be reported separately.

Statistical Analyses

Primary analyses are by intention-to-treat, and the primary end point of the randomization was OS. End points were defined according to the revised International Working Group criteria.[12] OS was defined as the time from randomization (DA + GO *v* FLAG-Ida + GO) to death from any cause with those still alive censored at the date last seen. Final data cutoff was on May 17, 2022. Relapse-free survival (RFS) was calculated only for patients who achieved complete remission (CR) or CR with incomplete hematological recovery (CRi), and was measured from the date of CR/CRi until the date of relapse or death from any cause. EFS was measured in all patients and was defined as the time from randomization to the occurrence of the first of one of the following events: failure to achieve CR/CRi by end of course 2, relapse, or death from any cause. For the outcomes of OS, RFS, EFS, and CR/CRi achievement, multivariable analyses were adjusted by all stratification variables used at the time of randomization (sex, age group, performance status, baseline white blood cell count, and disease type).

RESULTS

Patients

Baseline characteristics are shown in Table 1. The median age was 51.5 years and 149 (14%) were age older than 60 years. Eighty-eight percent had de novo AML, 7% clinical secondary AML, and 5% MDS-EB2. Cytogenetic risk was favorable in 12%, intermediate in 75%, and adverse in 9%; the remaining had missing data. Of major molecular subgroups, 30% had *NPM1* and 26% *FLT3* ITD or tyrosine kinase domain (TKD) mutations, and 12% had either t(8;21)(q22;q22) or inv(16)(p13.1;q22) and were thus designated CBF AML. After the first cycle, 692 patients received course 2 of allocated induction (348 DA + GO, 344 FLAG-Ida + GO) and 179 were designated high-risk. After the second cycle, 35 patients were designated high-risk on the basis of MRD and 415 proceeded to HDAC consolidation, including 279 initially assigned DA + GO and 136 initially assigned FLAG-Ida + GO (Fig 1). Eighty-five patients entered the post FLAG-Ida consolidation randomization (54 of whom had received FLAG-Ida + GO and 31 FLAG-Ida alone).

Induction Response

In the comparison of GO1 versus GO2, there was no significant difference in response rates (Data Supplement, Table S1, online only) or survival; so, for comparisons of DA + GO versus FLAG-Ida + GO, results from GO1 and GO2 were combined. Response rate after two courses did not differ between DA + GO and FLAG-Ida + GO, with CR in 86.6% and 87.2% respectively, and overall response rate (CR plus CRi with incomplete count recovery, CRi) of 90.7% versus 93.0% (Table 2). Day 30 and 60 mortality were not different between DA + GO and FLAG-Ida + GO (D30; 2.9% *v* 3.1%; $P = .83$; D60; 4.6% *v* 4.3%; $P = .80$), neither was there a significant difference between GO1 and GO2 (D30; 2.15% *v* 3.3%; $P = .11$; D60; 3.3% *v* 5.6%; $P = .08$).

Toxicity

Greater hematologic toxicity was seen after the second course of FLAG-Ida when recovery of neutrophils and platelets was significantly delayed (Data Supplement, Table S2). There was no impact of GO dose on count recovery after course 1 for neutrophils (29 *v* 29 days; $P = .23$) or platelets (27 *v* 29 days; $P = .07$) for GO1 and GO2, respectively. The impact of the hematologic toxicity of the second course of FLAG-Ida was to diminish the proportion of patients continuing with HDAC as course 3 (40% of those not high-risk or entering consolidation randomization *v* 83% for DA) and course 4 (27% of the same group compared with 64% for DA).

Longer-Term Outcomes

Median follow-up by the reverse Kaplan-Meier method was 32 months. There was no difference in relapse between GO1 and GO2 (3-year cumulative incidence of relapse [CIR], 31% *v* 35%; $P = .24$; Data Supplement, Fig S1), neither was there a difference in OS (3-year OS 66% *v* 63%; hazard ratio [HR], 1.16 [95% CI, 0.95 to 1.439]; $P = .15$), EFS (3-year EFS 52% *v* 49%; HR, 1.09 [95% CI, 0.91 to 1.32]; $P = .09$), or death in remission (3-year cumulative incidence of death in remission

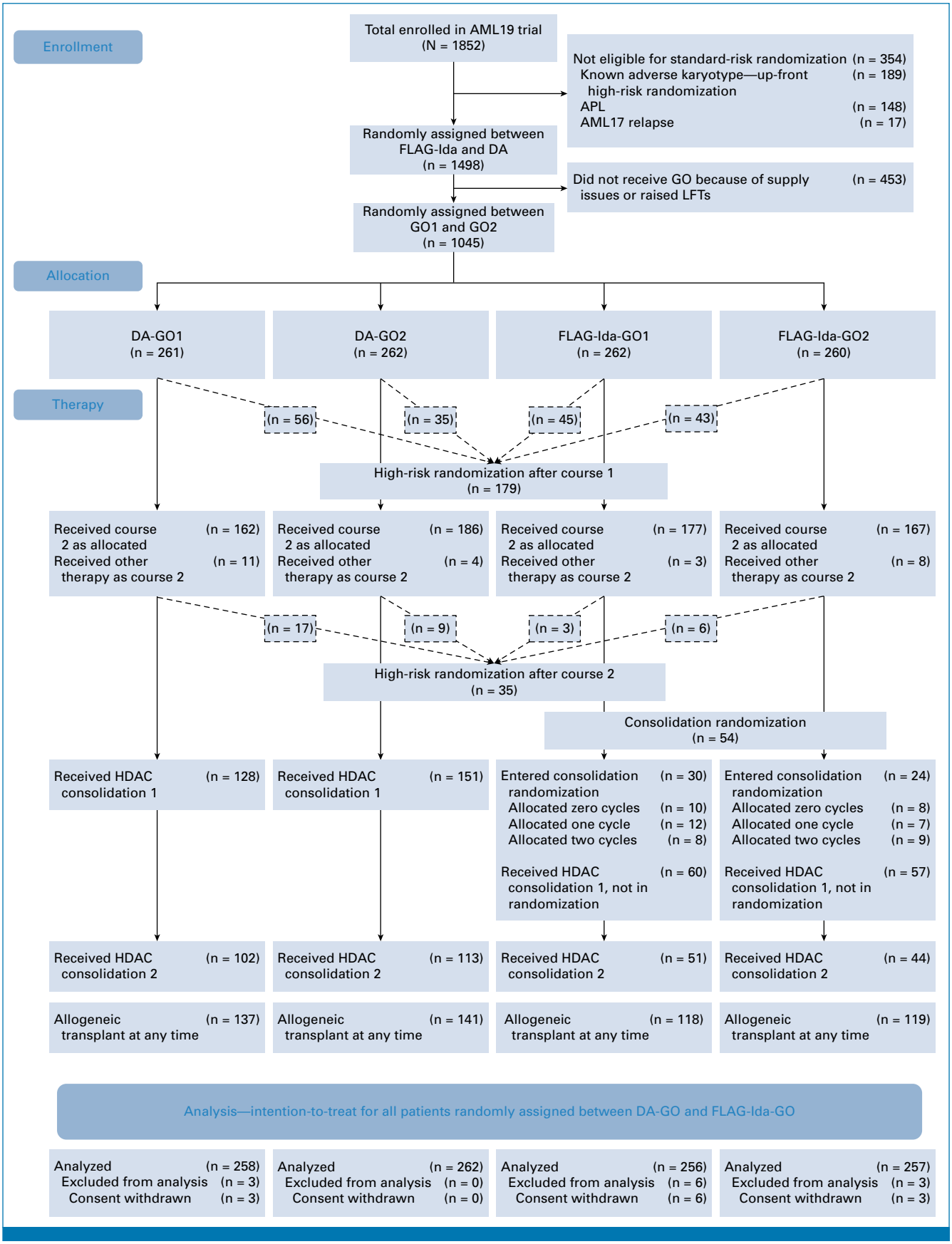
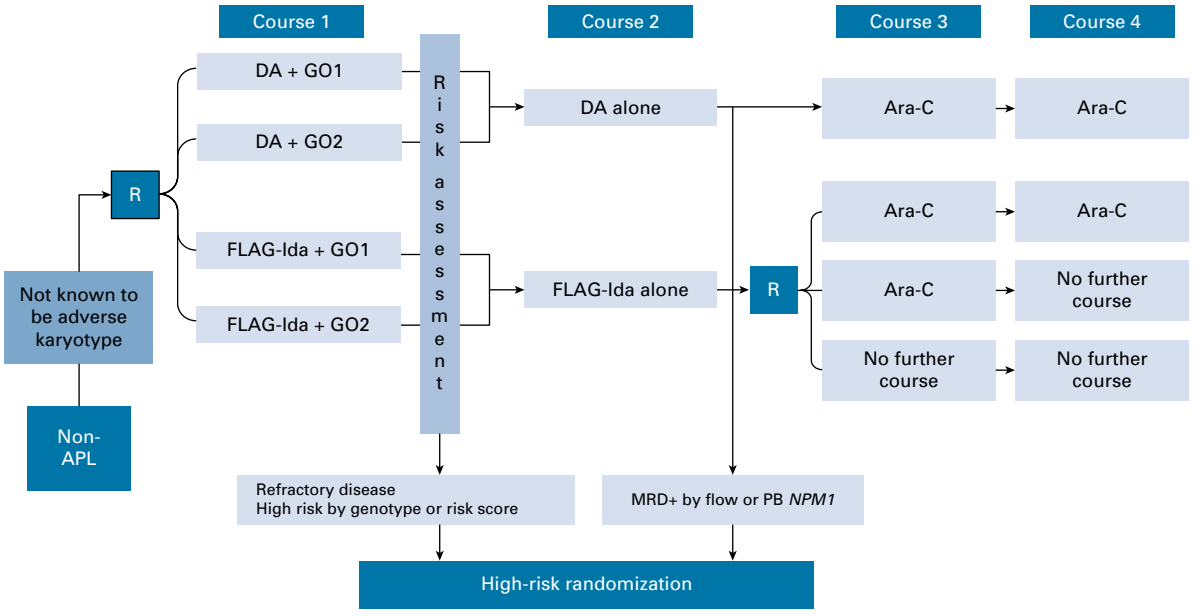


FIG 1. CONSORT diagram. APL, acute pyomyeloctic leukemia; DA, daunorubicin and Ara-C; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; GO, gemtuzumab ozogamicin; HDAC, high-dose cytarabine; LFT, liver function tests.



Treatment	Details	Changes/ Comments
DA 3 + 10 (course 1)	Daunorubicin 60 mg/m^2 IV once a day on days 1, 3, 5 Cytarabine 100 mg/m^2 IV once every 12 hours on days 1-10	
DA 3 + 8 (course 2)	Daunorubicin 50 mg/m^2 IV once a day on days 1, 3, 5 Cytarabine 100 mg/m^2 IV once every 12 hours on days 1-8	Commence course 2 if CR achieved, neutrophils >1.0 × 10^9/L, and platelets >80 × 10^9/L
FLAG-IDA (courses 1 and 2)	Fludarabine 30 mg/m^2 IV once a day on days 2-6 Cytarabine 2 g/m^2 IV (over 4 hours, 4 hours after fludarabine) once a day on days 2-6 G-CSF 263 µg (lenograstim) once a day on days 1-7 Idarubicin 8 mg/m^2 IV once a day on days 4, 5, 6	Cytarabine dose reduced to 1 g/m^2 for patients ≥60 years of age Omit G-CSF until the WCC has fallen to <30
Single-dose gemtuzumab ozogamicin (GO1)	3 mg/m^2 (no maximum dose) once a day on day 1 of course 1 (day 2 with FLAG-Ida)	WCC must be <30 × 10^9/L before starting. Can be reduced with hydroxycarbamide before commencing, and GO delayed until Day 4 Liver function tests must not exceed 2 × ULN
Fractionated gemtuzumab ozogamicin (GO2)	3 mg/m^2 (max 5 mg/d) once a day on days 1 and 4 of course 1 (days 2 and 5 with FLAG-Ida)	
HDAC (high-dose cytarabine)	Courses 3 and 4 Cytarabine 3 g/m^2 IV once every 12 hours by 4-hour infusion on days 1, 3, 5	Cytarabine dose reduced to 1 g/m^2 for patients ≥60 years of age

FIG 2. Trial schema and treatment protocols. APL, acute promyelocytic leukemia; CR, complete remission; DA, daunorubicin and Ara-C; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; G-CSF, granulocyte colony-stimulating factor; GO, gemtuzumab ozogamicin; HDAC, high-dose cytarabine; MRD, measurable residual disease; PB, peripheral blood; ULN, upper limit of normal; WCC, white cell count.

[CIDCR], 9.2% *v* 9.7%; *P* = .91), so again further outcome analyses were undertaken with GO doses combined.

FLAG-Ida + GO significantly reduced relapse (3-year CIR, 24% *v* 41%; *P* < .001; Table 2; Fig 3). EFS was significantly better with FLAG-Ida + GO compared with DA + GO (3-year EFS, 45% *v* 57%; HR, 0.73 [95% CI, 0.61 to 0.87]; *P* < .001) and did not vary by age, sex, performance status, or clinical disease category (Data Supplement, Fig S2), but there was no difference in OS (63% *v* 66%; HR, 0.92 [95% CI, 0.75 to 1.13]; *P* = .41; Figs 3A and 3B). This appeared to be consequent to a higher rate of successful salvage therapy for relapsed/refractory disease after DA + GO (Data Supplement, Fig S3). RFS also favored FLAG-Ida + GO (Table 2). CIDCR was greater with FLAG-Ida + GO (3-year CIDCR, 12% *v* 7.3%; *P* = .026; Fig 3D). The number of allogeneic transplants performed in CR1 and overall was lower after FLAG-Ida + GO (181 *v* 197 in CR1; *P* = .22; and 238 *v* 278 overall; *P* = .021; Table 2).

TABLE 1. Baseline Patient Characteristics

Characteristic	DA + GO1, No. (%)	DA + GO2, No. (%)	FLAG-Ida + GO1, No. (%)	FLAG-Ida + GO2, No. (%)
Total	258 (100)	262 (100)	256 (100)	257 (100)
Sex				
Male	132 (51)	134 (51)	130 (51)	132 (51)
Female	126 (49)	128 (49)	126 (49)	125 (49)
Age group, years				
<30	24 (9)	29 (11)	28 (11)	23 (9)
30-39	38 (15)	38 (15)	37 (14)	35 (14)
40-49	54 (21)	55 (21)	54 (21)	55 (21)
50-59	103 (40)	104 (40)	101 (39)	106 (41)
≥60	39 (15)	36 (14)	36 (14)	38 (15)
Type of disease				
De novo AML	227 (88)	233 (89)	226 (88)	228 (89)
Secondary AML	18 (7)	17 (6)	17 (7)	16 (6)
High-risk MDS	13 (5)	12 (5)	13 (5)	13 (5)
WBC ($\times 10^9$/L)				
<10	138 (53)	143 (55)	135 (53)	140 (54)
10 to <50	73 (28)	74 (28)	73 (29)	72 (28)
50 to <100	32 (12)	32 (12)	34 (13)	31 (12)
≥100	15 (6)	13 (5)	14 (5)	14 (5)
WHO performance status				
Normal activity	156 (60)	161 (61)	154 (60)	157 (61)
Restricted activity	86 (33)	86 (33)	86 (34)	86 (33)
In bed <50% waking hours	16 (6)	15 (6)	16 (6)	14 (5)
FLT3 ITD mutation				
Wild-type	209 (81)	209 (80)	194 (76)	196 (76)
Mutant	43 (17)	47 (18)	54 (21)	58 (23)
No result	3 (1)	3 (1)	3 (1)	0 (0)
FLT3 TKD mutation				
Wild-type	234 (91)	240 (92)	233 (91)	232 (90)
Mutant	19 (7)	17 (6)	15 (6)	21 (8)
No result	2 (1)	2 (1)	3 (1)	1 (0)
NPM1 mutation				
Wild-type	183 (71)	179 (68)	168 (66)	179 (70)
Mutant	72 (28)	79 (30)	82 (32)	75 (29)
No result	0 (0)	1 (0)	1 (0)	0 (0)
Cytogenetics				
Normal	119 (46)	140 (53)	109 (43)	123 (48)
Intermediate	61 (24)	74 (28)	74 (29)	50 (19)
Adverse	39 (15)	14 (5)	29 (11)	35 (14)
Core binding factor	31 (12)	24 (9)	33 (13)	33 (13)
No result	8 (3)	10 (4)	9 (4)	13 (5)
Molecular MRD marker				
NPM1 mutation	74 (29)	81 (31)	82 (32)	76 (30)
RUNX1::RUNX1T1	18 (7)	8 (3)	14 (5)	13 (5)
CBFβ::MYH11	12 (5)	16 (6)	19 (7)	19 (7)
KMT2A fusion	7 (3)	7 (3)	13 (5)	10 (4)
Other	6 (2)	11 (4)	8 (3)	16 (6)

Abbreviations: DA, daunorubicin and Ara-C; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; GO, gemtuzumab ozogamicin; ITD, internal tandem duplication; MDS, myelodysplastic syndrome; MRD, measurable residual disease; TKD, tyrosine kinase domain.

TABLE 2. Comparison of Outcomes Between DA + GO Versus FLAG-Ida + GO

Outcome	DA + GO	FLAG-Ida + GO	*P*
Response after cycle 1, No. (%)			
CR	343 (66)	387 (76)	.014
CRi	60 (11)	46 (9)	
ORR (CR + CRi)	403 (78)	433 (85)	
Best response after two cycles, No. (%)			
CR	449 (87)	446 (87)	.19
CRi	20 (3.9)	29 (5.7)	
ORR (CR + CRi)	469 (91)	475 (93)	
Early mortality, No. (%)			
Day 30	15 (2.9)	16 (3.1)	.83
Day 60	24 (4.6)	22 (4.3)	.80
Allogeneic transplant, No. (%)			
Allogeneic transplant at any time	278 (54)	238 (46)	.021
Allogeneic transplant in first response[a]	197 (42)	181 (38)	.22
Outcomes at 3 years, %			
OS	63	66	.41
EFS	45	57	<.001
RFS	52	64	.002
CIR	41	24	<.001
CIDCR	7.2	12	.026

Abbreviations: CIDCR, cumulative incidence of death in remission; CIR, cumulative incidence of relapse; CR, complete remission; CRi, XXX; DA, daunorubicin and Ara-C; EFS, event-free survival; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; GO, gemtuzumab ozogamicin; ORR, overall response rate; OS, overall survival; RFS, relapse-free survival.
[a]Percentage of patients achieving CR/CRi.

Outcomes in Molecularly Defined Subgroups

Thirty percent of patients (n = 308) were *NPM1*^{mut} and 26% (n = 275) *FLT3*^{mut} AML. In a planned exploratory subgroup analysis with no multiplicity adjustments, both an EFS benefit and an OS benefit were observed for FLAG-Ida + GO in patients with *NPM1*^{mut} (3-year EFS, 52.5% *v* 70.2%; 3-year OS, 82% *v* 64%; HR, 0.5 [95% CI, 0.31 to 0.81]; *P* = .005; Fig 4) and there was no difference in CIDCR by treatment arm (Data Supplement, Fig S4b). The OS benefit for FLAG-Ida + GO was also seen in *FLT3*^{mut} AML (3-year OS, 64% *v* 54%; HR, 0.67 [95% CI, 0.45 to 0.99]; *P* = .047) and was seen with both *FLT3*-ITD and TKD (Data Supplement, Figs S5A and S5B). There was no benefit for GO2 in either *NPM1*^{mut} or *FLT3*^{mut} subgroup (Data Supplement, Fig S6). The survival benefit for FLAG-Ida + GO within the *NPM1*^{mut} subgroup was seen in both *FLT3*^{mut} and *FLT3*^{wt} patients without statistically significant evidence of differential benefit on tests for heterogeneity (Fig 4; *P* = .08). FLAG-Ida + GO increased the number of patients who were MRD− in the PB after course 2 (PBPC2 MRD−, 88% *v* 77% with DA + GO; *P* = .02), as well as the number testing MRD− in the BM both after course 2 (56% *v* 37%; *P* = .004) and at the end of treatment (70% *v* 58%; *P* = .32; Data Supplement, Fig S7a). Among PBPC2 MRD− patients, the BM response was deeper in the FLAG-Ida + GO arm, with 60% also BM MRD− compared with 47% with DA + GO (*P* = .069; Data Supplement, Fig S7b). The same trend for a deeper BM MRD response was seen in those who were PBPC2 MRD+. The improved MRD response with FLAG-Ida + GO was seen in both *FLT3*^{mut} (PBPC2 MRD−, 83% *v* 68%) and *FLT3*^{wt} (PBPC2 MRD−, 92% *v* 82%).

Within the DA + GO arm, GO2 resulted in an increase in the proportion of patients testing PB PC2 *NPM1* MRD− (84% for GO2 *v* 69% for GO1; *P* = .04) but did not improve survival (3-year OS DA + GO2 70%, DA + GO1 74%). For *NPM1*^{mut} patients who were PBPC2 MRD+, 61% proceeded to transplant in CR and this did not differ by randomization. For these high-risk *NPM1*^{mut} patients, 3-year OS was 59%, and those randomly assigned to FLAG-Ida + GO had a trend to better survival than those allocated to DA + GO (3-year OS, 74% *v* 50%; HR, 0.52 [95% CI, 0.17 to 1.57]; Data Supplement, Fig S8). For PBPC2 MRD− patients, outcomes were excellent with both therapies, but here again survival was superior in patients treated with FLAG-Ida + GO (3-year OS, 90% *v* 78%; HR, 0.43 [95 CI, 0.22 to 0.87]; Data Supplement, Fig S8). There was no heterogeneity in the FLAG-Ida + GO benefit on the basis of MRD response (Data Supplement, Fig S9).

For patients with CBF AML, there was no EFS or OS benefit for FLAG-Ida + GO (3-year EFS, 72% *v* 77%; HR, 0.84 [95% CI, 0.4 to 1.76]; *P* = .64 and 3-year OS, 94% *v* 86%; HR, 2.04 [95% CI, 0.72 to 5.80]; *P* = .17 for DA + GO *v* FLAG-Ida + GO, respectively) and there was no benefit for GO2 (3-year OS,

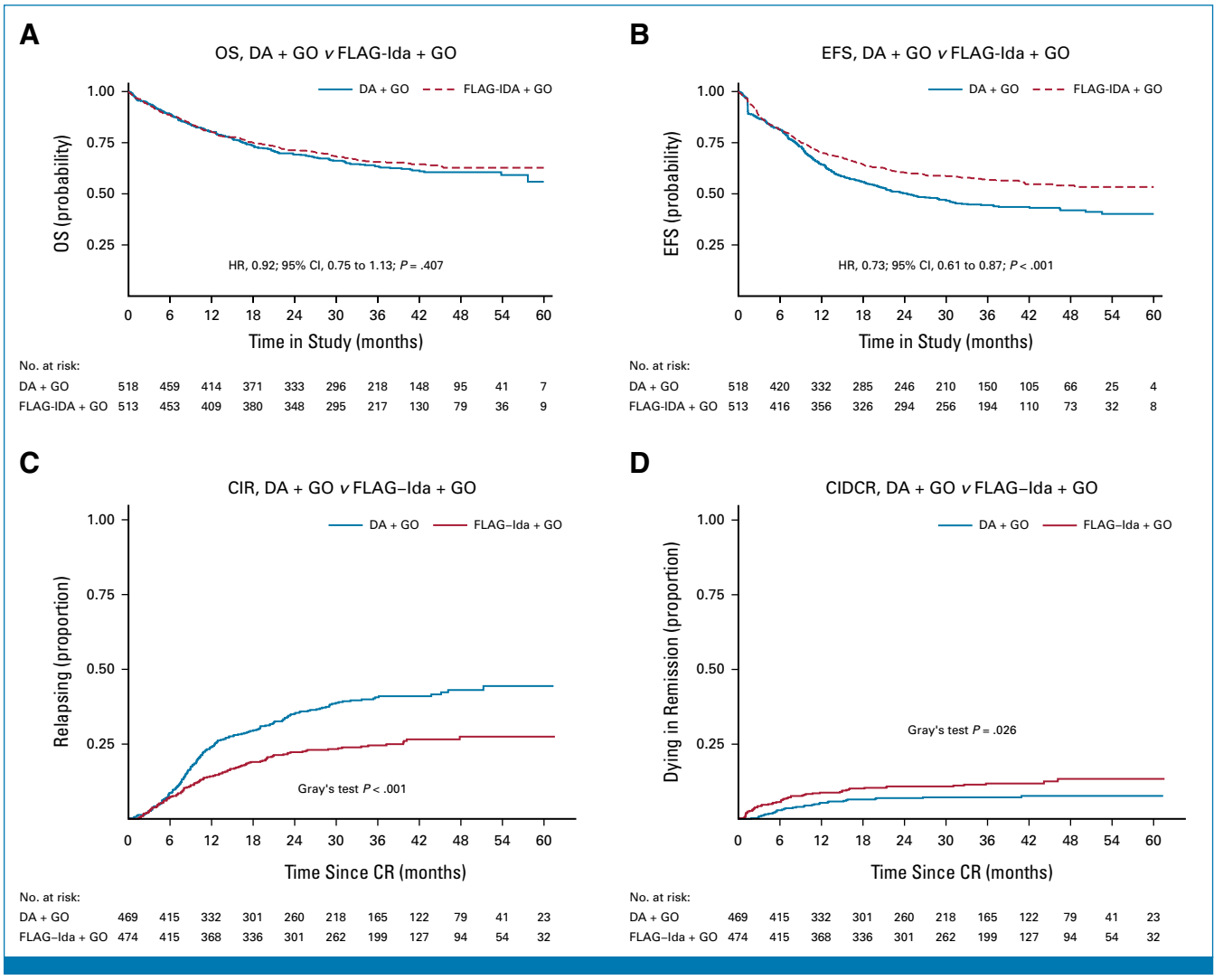


FIG 3. (A) OS, (B) EFS, (C) CIR, and (D) CIDCR by randomization arm (DA + GO *v* FLAG-Ida + GO). CIDCR, cumulative incidence of death in remission; CIR, cumulative incidence of relapse; CR, complete remission; DA, daunorubicin and Ara-C; EFS, event-free survival; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; GO, gemtuzumab ozogamicin; OS, overall survival.

91% GO1 *v* 89% GO2; HR, 1.67 [95% CI, 0.64 to 4.39]; $P = .29$). The best outcomes were achieved with DA + GO1 with 3-year OS of 96% (Data Supplement, Fig S10).

Consolidation

Patients who were in remission after two courses of FLAG-Ida or FLAG-Ida + GO could enter a randomization to receive no further consolidation, one course of HDAC, or two courses of HDAC. In the randomized comparison (n = 85), the demographics of the patients was balanced except fewer patients allocated no consolidation were *NPM1*^{mut} (Data Supplement, Table S3). When comparing the three arms, there was a significant difference in CIR ($P = .033$) and RFS ($P = .021$), with higher relapse in the one course arm but no difference in OS ($P = .18$) or CIDCR ($P = .8$; Data Supplement, Fig S11). In an exploratory nonrandomized comparison of treatment delivered in patients who were *NPM1*^{mut} and PBPC2 MRD– after two courses of FLAG-Ida + GO (n = 115), there was no evidence that OS or RFS was improved by consolidation (for zero, one, and two cycles of consolidation, respectively; 3-year OS, 90% *v* 83% *v* 93%; $P = .53$; 3-year RFS, 75% *v* 65% *v* 81%; $P = .14$; Data Supplement, Fig S12).

DISCUSSION

In this large, randomized study, we observed no survival benefit for fractionated over a single dose of GO. FLAG-Ida + GO significantly improved EFS and reduced relapse compared with DA + GO, although with greater myelosuppression and a higher risk of death in remission. These findings are consistent with the NCRI AML15 trial[2] but are in contrast to the results of the NCRI AML18 trial for older adults, where DA + GO2 improved OS. However, in that study, the benefit was restricted to patients age 60-70 years who were transplanted in CR1.[13] Consistent with AML18, we observed superior MRD clearance with fractionated GO2 when combined with DA.

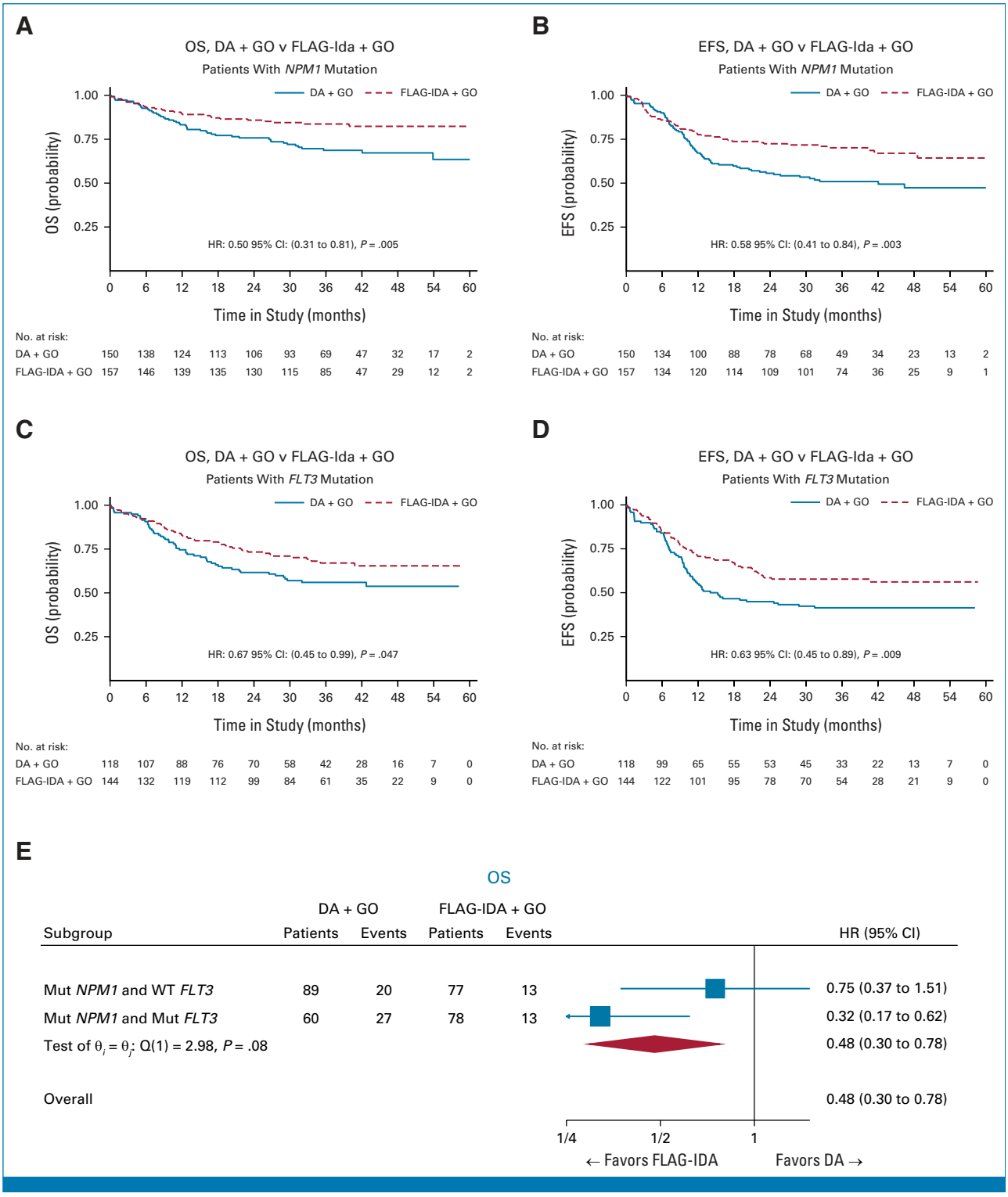


FIG 4. (A) OS and (B) EFS in *NPM1*-mutated AML, (C) OS and (D) EFS in *FLT3*-mutated AML, and (E) forest plot of OS in *NPM1*-mutated AML stratified by *FLT3* status. Unadjusted analysis of patients receiving GO1/GO2. Unadjusted analyses with DA as referent and *FLT3* grouping TKD and ITD patients receiving GO1/GO2. DA, daunorubicin and Ara-C; EFS, event-free survival; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; GO, gemtuzumab ozogamicin; HR, hazard ratio; ITD, internal tandem duplication; OS, overall survival; TKD, tyrosine kinase domain.

Although there was no OS benefit for FLAG-Ida + GO, there was evidence of a substantial EFS benefit, and an OS benefit was apparent in patients with *NPM1* and *FLT3* mutations where the treatment was well tolerated with no excess mortality. Of the many driver mutations documented in AML, *NPM1* and *FLT3* are among the most frequent.[14-16] In

this study, OS at 3 years for patients receiving FLAG-Ida + GO was 86% and 62% and in *NPM1*^{mut} and *FLT3*^{mut} disease, respectively, compared with 64% and 54% with DA + GO. For *FLT3*^{mut} patients, the standard of care is DA plus midostaurin,[1] which in the RATIFY trial gave a 3-year survival of 50%,[17] comparable with the 54% seen here with DA + GO without midostaurin. The result with DA + GO is consistent with previous reports of a GO benefit in *FLT3*^{mut} AML[8,18] but given the superior survival observed with FLAG-Ida + GO without a FLT3 inhibitor, studies combining FLAG-Ida + GO with midostaurin are warranted. In this context, we and others have shown that midostaurin can be safely combined with DA + GO,[19,20] and studies with FLAG-Ida + GO are planned. The survival benefit of FLAG-Ida + GO in *NPM1*^{mut} AML was supported by MRD analysis, where patients treated with FLAG-Ida + GO had faster, deeper clearance of *NPM1* transcripts than those receiving DA + GO. The AML17 study demonstrated that achievement of PBPC2 MRD negativity was associated with a greatly reduced risk of relapse and death.[10] Importantly, the FLAG-Ida + GO survival benefit in *NPM1*^{mut} patients was independent of *FLT3* mutation and PBPC2 MRD status. These findings are consistent with the observed lower BM MRD levels after course 2 with FLAG-Ida + GO regardless of PB MRD. The survival of *NPM1*^{mut} PB PC2 MRD+ patients in AML19 was improved compared with AML17 (where PC2 MRD status was not used to select patients for intensified treatment and early transplantation). Fewer transplants (15% reduction) were performed in the FLAG-Ida + GO arm overall compared with DA + GO, including fewer in CR1, reflecting the application of MRD negativity to guide transplant decisions and the reduced relapse risk with FLAG-Ida + GO.

GO given in combination with intensive chemotherapy has been reported to increase *NPM1* MRD negativity.[7,21] Our results are consistent with these findings and emphasize the interaction between GO and the chemotherapy backbone in eliminating MRD in *NPM1*^{mut} AML. Thus, for patients allocated DA chemotherapy, GO2 was more effective than GO1 in reducing MRD, whereas with the more intensive FLAG-Ida regimen, there was no benefit of GO2.

Previous studies have established the benefit of GO in patients with favorable-risk cytogenetics,[3,6] although the ALFA0701 trial included few such patients[4] and the question of the optimal dose and scheduling has been unresolved. We observed no survival benefit for GO2 in this group, neither was there benefit for FLAG-Ida, the best results being achieved with DA + GO1. Overall, these results illustrate significant heterogeneity among molecular types of AML in sensitivity to both induction chemotherapy and GO scheduling.

The question of what consolidation is required after two courses of FLAG-Ida + GO remains open. This randomized comparison showed no OS benefit from two courses of HDAC, although there was an increase in relapse risk with one consolidation course. In the nonrandomized comparison of *NPM1*^{mut} patients who were PB PC2 MRD− after two cycles of FLAG-Ida + GO, this treatment appears sufficient with an OS of 90% and no RFS benefit for those given consolidation. If treatment is discontinued in such cases, then ongoing MRD monitoring could be used for early identification and preemptive treatment of relapse. Novel maintenance treatment approaches are of interest in this situation[22,23] and warrant investigation. FLAG-Ida combined with venetoclax has been reported to produce high rates of CR and MRD negativity in newly diagnosed AML, including patients with *FLT3*^{mut}, further supporting the ongoing evaluation of intensive induction regimens in AML.[24]

In conclusion, in this randomized trial, we saw no benefit for fractionated GO and although FLAG-Ida + GO significantly improved EFS compared with DA + GO, there was no OS benefit. In exploratory analyses, there was evidence of a survival benefit in major subgroups, including patients with *NPM1* and *FLT3* mutations.

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DATA SHARING STATEMENT

Access to deidentified data and supporting documentation is available via formal application to Cardiff University via the corresponding authors. Cardiff University is committed to open access to deidentified clinical trial data.

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Fludarabine, Cytarabine, Granulocyte Colony-Stimulating Factor, and Idarubicin With Gemtuzumab Ozogamicin Improves Event-Free Survival in Younger Patients With Newly Diagnosed AML and Overall Survival in Patients With *NPM1* and *FLT3* Mutations

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