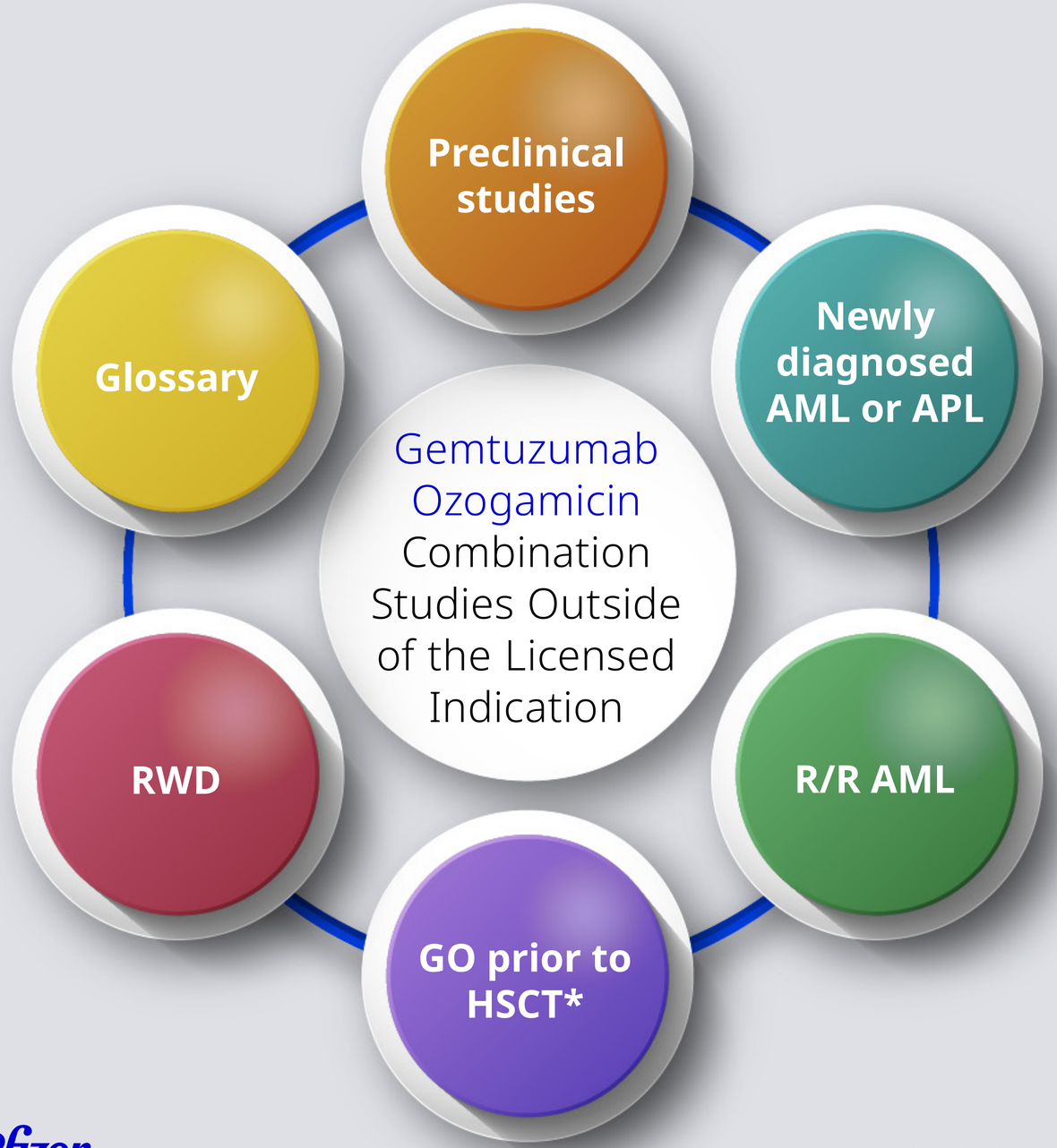
Gemtuzumab Ozogamicin Combination Studies Outside of the Licensed Indication

October 2021

Start



*Not all studies are outside of the GO licensed indication.

Gemtuzumab Ozogamicin Combination Studies Outside of the Licensed Indication

The clinical landscape of AML is continuing to expand, with multiple targeted therapeutic options now available. In this rapidly evolving landscape, there is a need to explore the efficacy and safety of novel treatment combinations and sequencing strategies.

This resource provides a summary of studies with GO in novel combinations outside of the licensed indication, and also a summary of studies investigating the use of GO in patients proceeding to transplant.

Links to additional resources that support the content presented in the compendium have been included throughout

Studies With GO in Novel Combinations Outside of the Licensed Indication: Preclinical Studies

Preclinical studies

Agents	Study name	Cell model	GM number	ISR/CRC	Results available
GO + talazoparib	Addition of the PARPi talazoparib to GO significantly enhances anti-leukemic activity in human CD33+ AML[1]	Human CD33+ AML cell lines		N/A	Yes
GO + M3814	DNA-PK inhibitor M3814 as a new combination partner of GO in the treatment of AML[2]	Molm-13, MV4-11, HL-60 cells		N/A	Yes
Calicheamicin	A CRISPR-based screen to identify genetic determinants of calicheamicin sensitivity[3]	ML1, HL-60, TF1 cells	WI234561	N/A	No

RESOURCE LINK:

1. Giorgi M, et al. EHA 2020. Poster presentation (Abstract EP495).

2. Carr MI, et al. *Front Oncol*. 2020;10:127.

3. Data on file. Pfizer Inc., New York, NY.

Addition of the PARP Inhibitor Talazoparib to GO Significantly Enhances Anti-Leukemic Activity in Human CD33+ AML

Preclinical studies

Cell and xenograft models	Treatment regimen	Efficacy data	Safety data
Human AML cell lines	**GO:** 10^{-12} to 10^{-4} µg/ml **Talazoparib:** 10^{-10} to 10^{-5} µg/ml Combination regimen dependent on cell line and experimental method	**GO and talazoparib monotherapy** • Dose-dependent decrease in cell proliferation **GO + talazoparib vs single-agent therapy** • Significantly decreased AML cell viability • Induced significant apoptosis, DNA damage, and PARP trapping	
Xenograft studies NSG mice engrafted with luciferase-labeled human CD33+ AML cells	**GO + talazoparib alone or in combination** **GO:** 1 µg/kg (1×/week for 3 weeks) **Talazoparib:** 0.1 and 0.33 mg/kg (5 days/week)	**GO (0.1 µg/kg) + talazoparib (0.33 mg/kg) vs vehicle control** • Significantly reduced tumor burden • No change in OS **GO (1 µg/kg) + talazoparib (0.33 mg/kg) vs single-agent therapy** • Significantly improved OS ($P < 0.05$)	Well tolerated with no significant weight loss or early morbidity

RESOURCE LINK:
Giorgi M, et al. EHA 2020. Poster presentation (Abstract EP495).

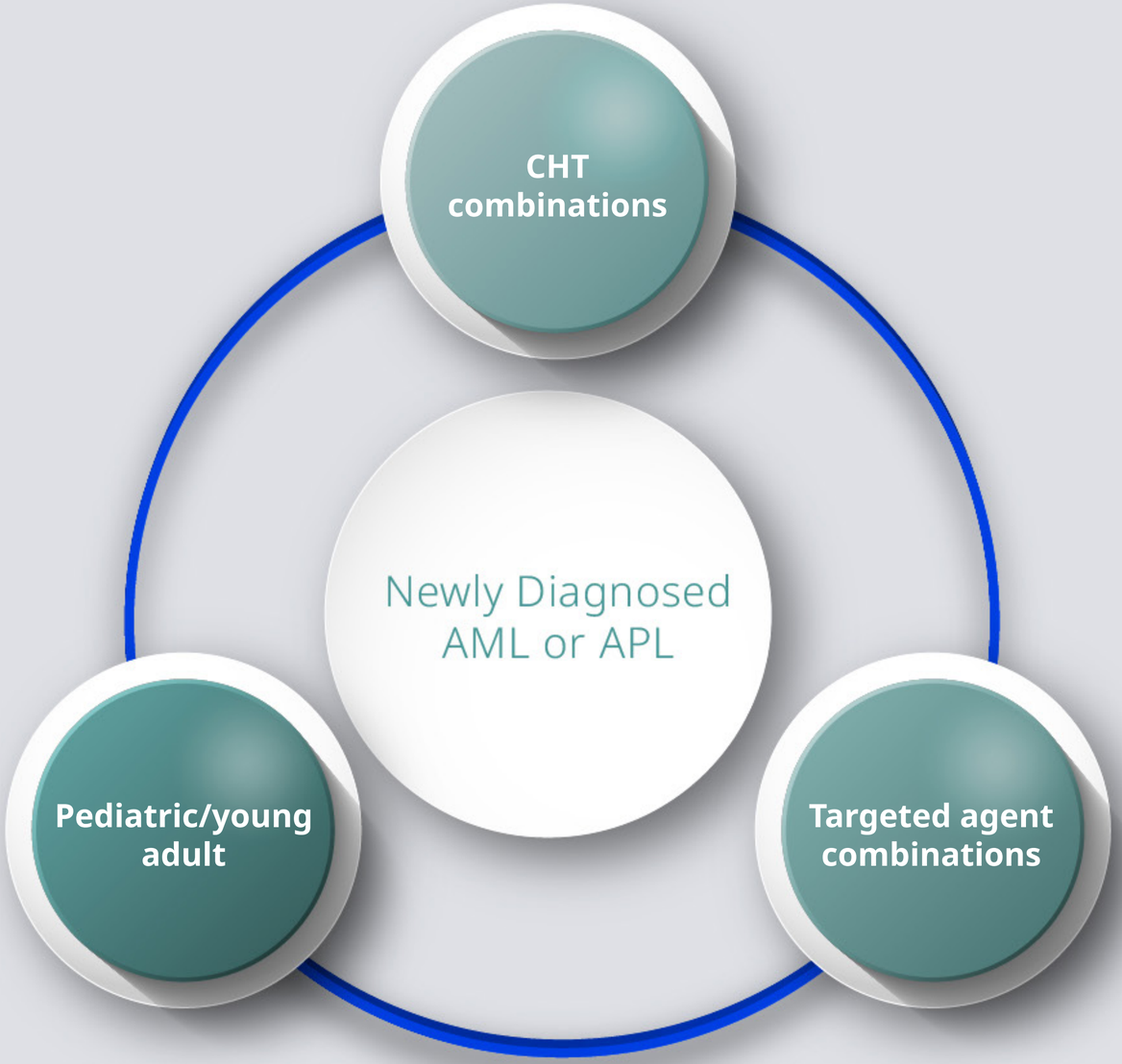
DNA-PK Inhibitor, M3814 As a New Combination Partner of GO in the Treatment of AML*

Preclinical studies

Xenograft models	Treatment regimen	Efficacy data	Safety data
MV4-11 (n = 10) • H2d Rag2d mice injected with tumor cells • Tumors were left to reach 65-180 mm^3 and mice were randomized into groups of equal mean tumor volume (170 mm^3) prior to treatment	**GO + M3814 alone and in combination:** **GO:** 0.1 mg/kg (single dose) **M3814:** 100 mg/kg (daily)	**M3814 alone vs vehicle control:** No significant effect on tumor volume **GO alone:** Complete response, n = 3; tumor outgrowth, n = 7 **GO + M3814:** Complete response, 70% (n = 7)	**Body weight:** Minimal effects with GO + M3814
HL60 (n = 9) • Hsd:Athymic Nude-Foxn1^{nu} mice injected with tumor cells • Tumors were left to reach 94-284 mm^3 and mice were randomized into groups of equal mean tumor volume (170 mm^3) prior to treatment	**GO + M3814 alone and in combination:** **GO:** 1.0 mg/kg (single dose) **M3814:** 100 mg/kg (daily)	**M3814 alone vs vehicle control:** No significant effect on tumor volume **GO alone:** Complete response, n = 3; tumor outgrowth, n = 6 **GO + M3814:** Complete response, 89% (n = 8)	**Body weight:** Minimal effects with GO + M3814

RESOURCE LINK:
Carr MI, et al. *Front Oncol*. 2020;10:127.

*Merck KGaA study.


CHT combinations
Newly Diagnosed AML or APL
Pediatric/young adult
Targeted agent combinations

Studies With GO in Novel Combinations Outside of the Licensed Indication:
Newly Diagnosed AML/APL

CHT combinations

Agents	Study name	Eligible ages	Phase	Estimated or actual enrolment	Start date	Estimated PCD/SCD	Status	NCT number/ GM number	ISR/ CRC	Study results available
GO + standard CHT, glasdegib + HiDAC	DA + GO in either single or fractionated dose in induction therapy and HiDAC + glasdegib vs HiDAC + placebo in post-remission therapy in patients with AML (GnG)	≥ 60	3	252 (E)	Apr 2021	Dec 2023/ Mar 2024	Recruiting	NCT04093505*	CRC	No
GO + standard CHT, HSCT, glasdegib	Phase 3 study to assess the impact of GO in combination with standard CHT, in the levels of MRD and the role of glasdegib as a post-transplant maintenance in adult patients aged 18-60 years with previously untreated, de novo, fav–intermediate AML (GIMEMA AML 1819)	18-60	3	414 (E)	Sep 2020	Apr 2023/ Apr 2027	Recruiting	NCT04168502* GM 53234457	ISR	No
GO + AraC	GO + AraC vs Ida + AraC in elderly patients with AML Mylofrance 4 (ALFA1401)	60-80	2/3	225 (E)	Nov 2015	Apr 2019/ Nov 2020	Follow-up	NCT02473146* WI180467	ISR	No
Flu + AraC + filgrastim-sndz + GO + Ida hydrochloride	Fludarabine phosphate, AraC, filgrastim-sndz, GO, and idarubicin hydrochloride in treating patients with newly diagnosed AML or high-risk MDS	≥ 18	2	200 (E)	Apr 2007	Apr 2022/ Apr 2022	Recruiting	NCT00801489*	N/A	Yes
AZA + GO	AZA + GO as induction and post-remission therapy in patients aged ≥ 60 years with previously untreated non-M3 AML	≥ 60	2	133 (A)	Dec 2008	Jun 2013 (PCD)	Active, not recruiting	NCT00658814*	N/A	Yes
GO + AraC + Flu + Ida	Induction, consolidation and intensification therapy for patients < 66 years with previously untreated CD33+ AML (MYFLAI07)	18-65	2	130 (A)	Mar 2008	Mar 2009/ Mar 2013	Completed	NCT00909168*	N/A	Yes
GO + AraC + G-CSF + cladribine + mitoxantrone	Single- or fractionated-dose GO with cladribine, AraC, G-CSF, and mitoxantrone (CLAG-M) in treating participants with previously untreated AML or high-grade myeloid neoplasm	≥ 18	1/2	66 (A)	Sep 2018	Jul 2021/ Jul 2025	Active, not recruiting	NCT03531918* WI236712	ISR	Yes

In studies where multiple treatment arms are being investigated, only the GO treatment arm has been included.
*Clinical trials available at https://clinicaltrials.gov/. Accessed June 9-11, 2021.

Phase 2 Study of FLAG-GO vs FLAG-Ida in Newly Diagnosed Patients With CBF AML

CHT combinations

Treatment regimen	Comparator arm	Patient population	Efficacy data (GO vs comparator)	Safety data (GO vs comparator)
FLAG-GO **Induction (1 cycle)** **FLAG:** **Flu:** 30 mg/m^2 (D1-5) **AraC**: 2 g/m^2 (D1-5) **G-CSF**: 5 µg/kg (D1-5) **GO**: 3 mg/m^2 (D1) **Consolidation** **FLAG*** **GO**: 3 mg/m^2 given in 2 of 6 planned cycles	**FLAG-Ida** **Induction (1 cycle)** **FLAG** **Flu:** 30 mg/m^2 (D1-5) **AraC:** 2 g/m^2 (D1-5) **G-CSF:** 5 µg/kg (D1-5) **Ida:** 6 mg/m^2 (D3-4) **Consolidation:** **FLAG*** **Ida:** 6 mg/m^2 given in 1 of 6 planned cycles	FLAG-GO, n = 50 Median age, 47 years (range 19-76) FLAG-Ida, n = 103 Median age, 47 years (range 19-78) CBF-AML	**CR/CRi:** 96% vs 100% **Molecular responses**: MR3 after induction: 65% vs 40% (P = 0.01); MR4 at the end of therapy: 92% vs 56% (P < 0.001) **MVA:** MR3 after induction and MR4 at the end of therapy were significantly associated with extended RFS (HR 0.412 [95% CI, 0.189-0.897]; P = 0.026; and HR 0.3 [95% CI, 0.15-0.63]; P = 0.001, respectively) **RFS** was significantly improved with FLAG-GO vs FLAG-Ida (P = 0.015) **5-year RFS:** 87% vs 67%	**Early death:** 4% vs 0

NCT information

*Consolidation FLAG: 30 mg/m^2 Flu (D1-3) + 2 g/m^2 AraC (D1-3) + 5 µg/kg G-CSF (D1-5).

NCT00801489

RESOURCE LINK:
Borthakur GM, et al. ASH 2018. Oral presentation (Abstract 290).

Phase 2 Study of AZA and GO As Induction and Post-remission Therapy in Older Patients With Non-M3 AML

CHT combinations

Treatment regimen	Comparator arm	Patient population	Efficacy data (good-risk vs poor-risk)	Safety data (good-risk vs poor-risk)
AZA + GO **Induction** **AZA:** 75 mg/m^2 (D1-7) **GO:** 3 mg/m^2 (D8) **Consolidation (1 cycle)*** **AZA:** 75 mg/m^2 (D1-7) **GO:** 3 mg/m^2 (D8) **Maintenance (4 cycles)*** **AZA:** 75 mg/m^2 every 28 days	N/A, single-arm study	Patients aged ≥ 60 years, stratified into good-risk and poor-risk groups Good-risk, n = 79; Median age, 71 years (range 60-88) sAML, n = 27 Poor-risk, n = 54; Median age, 75 years (range 70-87)	**CR/CRi:** 44.3% vs 35.2% **Median RFS:** 8.3 months vs 7 months **mOS:** 11 months vs 11 months	**Grade ≥ 3 nonhematologic AEs:** 68.4% vs 68.5% **VOD:** 0% vs 0% **Fatal toxicities:** 5.1%† vs 9.3%‡

NCT information

*For patients who achieved CR/CRi.
†n = 4: 2 due to disease progression, 1 due to infection, and 1 due to sudden death.
‡n = 5: 2 due to infection, 1 due to multiorgan failure, 1 due to neutropenic fever and multiorgan failure, and 1 due to respiratory failure and hypoxia.

NCT00658814

RESOURCE LINK:
Nand S, et al. *Blood*. 2013;122(20):3432-3439.

Phase 2 Study of FLAI + Low-Dose GO As Induction Therapy in CD33-Positive AML: Final Results and Long-term Outcomes (MYFLAI07)

CHT combinations

Treatment regimen	Comparator arm	Patient population	Efficacy data	Safety data
FLAI-GO **Induction** **GO:** 3 mg/m^2 (D6) **FLAI:** 25 mg/m^2 Flu + 2 g/m^2 AraC (D1-D5) + 10 mg/m^2 Ida (D1, D3, and D5) **Consolidation** AC-IDA and HiDAC	N/A, single-arm study	n = 130 CD33+ (expression > 20%) Median age of patients was 52 years (range 18-65)	**ORR:** 85% (CR, 82% [n = 106/130] ; PR, 3% [n = 4/130]) **Complete molecular remission (assessed by *WT1* expression)*:** 51% (n = 54/106) UVA and MVA showed molecular response significantly improved OS and DFS (OS: *P* = 0.0005 [UVA] and *P* = 0.027 [MVA]; DFS: *P* = 0.0003 [UVA] and *P* = 0.03 [MVA]) **Proceeded to HSCT:** 64% **mOS and mDFS:** 63 and 61 months **1-year OS and DFS:** 80% and 77% **2-year OS and DFS:** 63% and 58% **5-year OS and DFS:** 52% and 52%	**Deaths during induction:** 3% **Infections:** 43% (including 2 deaths) **Liver toxicity:** Grade 2: 7%; Grade 3: 1% **VOD:** No VOD occurred during chemotherapy or after alloHSCT **Median time to recovery, days (range):** Platelet (> 50 × 10^9/l): 25 (18-44) Neutrophil (> 1 × 10^9/l): 24 (19-40)

NCT information

NCT00909168

RESOURCE LINK:
Candoni A, et al. *Am J Hematol.* 2018;93(5):655-663.

*Complete molecular remission defined as W*T1* < 70 copies.

Phase 1 Trial of Cladribine, HiDAC, G-CSF, and Dose-Escalated Mitoxantrone (CLAG-M) + GO in Adults With Newly-Diagnosed AML or Other High-Grade Myeloid Neoplasm

CHT combinations

Treatment regimen	Comparator arm	Patient population	Efficacy data	Safety data
CLAG-M + GO*	N/A, single-arm study	Patients fit for iCHT	Evaluable patients, n = 18	**GO1 (n = 6)**
CLAG-M **Cladribine:** 5 mg/m^2/D (D1-5) **AraC:** 2 g/m^2/D (D1-5) **G-CSF:** 300 µg (weight < 76 kg) or 480 µg/D (weight ≥ 76 kg) (D0-5) **Mitoxantrone:** 18 mg/m^2/D (D1-3)		Median age, 66 years (range 28-77), n = 18	**CR/CRi:** 83% (95% CI, 59%-96%), (n = 15)	• **DLTs:** Grade 3 LV systolic dysfunction (n = 1)
GO dose-escalated cohorts over 2 dose levels: **GO1:** 3 mg/m^2 (D1) **GO3:** 3 mg/m^2 (D1, D4, and D7)†		Newly diagnosed AML, n = 14; HG-MN, n = 4	**CR:** 72% (n = 13) **CRi:** 11% (n = 2)	**GO3 (RP2D) (n = 12)** • **DLTs:** Grade 4 aminotransferase level increase (n = 1); Grade 3 posterior reversible encephalopathy syndrome (n = 1); Grade 3 intracranial hemorrhage (n = 1)
		ELN 2017 genetic risk stratification: Favorable, n = 7; Intermediate, n = 4; Adverse, n = 7	**MRD-negativity:** **CR/CRi:** 72% (49%-88%), (n = 13)	**Evaluable patients (n = 18)** • **ANC recovery (1000/µl):** 88% (n = 16). Median time to recovery, 35 days (range 24-48) • **Platelet count recovery (100,000/ml):** 72% (n = 13); median time to recovery 31 days (range 26-48) • **Deaths < 56 days of induction:** 0% • **Most common AEs:** infections, neutropenic fever, hypertension, LV systolic dysfunction
		GO1, n = 6 GO3, n = 12		

NCT information

*A second course of CLAG-M without GO was given if MRD-negative CR/CRi was not achieved.
†GO3 was selected as the recommended phase 2 dose.

NCT03531918

RESOURCE LINK:
Godwin CD, et al. *Blood.* 2019;134(suppl 1):3892.

Studies With GO in Novel Combinations Outside of the Licensed Indication:
Newly Diagnosed AML/APL

Targeted agent combinations

Agents	Study name	Eligible ages	Phase	Estimated or actual enrolment	Start date	Estimated PCD/SCD	Status	NCT number/ GM number	ISR/ CRC	Study results available
GO + CPX-351	GO + CPX-351 in subjects aged ≥ 55 years with AML (CPX GO)	≥ 55	1	30 (E)	Aug 2019	Sep 2022/ Sep 2026	Recruiting	NCT03878927* WI242507	ISR	No
GO + ATRA + Ida + AraC + etoposide + pegfilgrastim	CHT + ATRA ± GO in patients with AML and *NPM1* gene mutation (AMLSG 09-09)	≥ 18	3	588 (E)	Feb 2010	Sep 2021/ Sep 2021	Active, not recruiting	NCT00893399* WS935976	ISR	Yes
GO + ATRA + ATO, mercaptopurine + methotrexate	GO and combination CHT in treating patients with previously untreated APL (SWOG 0535)	18-120	2	78 (A)	Nov 2007	Jun 2017/ Jun 2017	Completed	NCT00551460*	N/A	Yes
GO + ATO + ATRA	Phase 2 study of treatment of APL with ATRA, ATO and GO	≥ 10	2	150 (E)	Oct 2011	Dec 2021/ Dec 2021	Recruiting	NCT01409161* WS900799	ISR	Yes
GO + standard CHT + midostaurin	Midostaurin + GO + standard CHT in 1L AML (MODULE, ph 1) with transition to phase 2 study of midostaurin + GO in 1L standard therapy for fit *FLT3*-mutated AML (MAGMA)	18-75 (MODULE) 18-60 (MAGMA)	1/2	154 (E)	Sep 2020	Apr 2021/ Apr 2028	Recruiting	NCT04385290* WI238023	ISR	No
GO + standard CHT + midostaurin, alloHSCT	Testing the combination of standard induction therapy with GO and midostaurin as a novel approach to treating patients with newly diagnosed *FLT3*-mutated AML	≥ 18	1	24 (E)	Mar 2019	Jan 2023/ Jan 2025	Recruiting	NCT03900949* WI237938	ISR	No
GO (1 dose vs 2 doses) + standard CHT + HiDAC + midostaurin[1]	DA + GO in 1 or 2 doses in induction + HiDAC consolidation followed by midostaurin monotherapy as maintenance therapy for 1 year in non-transplanted patients with *FLT3* ITD or TKD mutations (AML-19)[1,2]	Aged ≥ 18 and eligible for iCHT[2]		50 (E)[1,2,†]	Oct 2020[2]	–	Recruiting[2]	NCT00091234 53026553	N/A	No

In studies where multiple treatment arms are being investigated, only the GO treatment arm has been included.
*Clinical trials available at https://clinicaltrials.gov/. Accessed June 9-11, 2021.
†250 patients expected to be enrolled will be randomized to receive DA + 1 or 2 doses of GO; approximately 50 patients with an *FLT3* mutation will receive midostaurin.[2]

RESOURCE LINK:

1. Data on file. Pfizer Inc., New York, NY.
2. AML-Hub.com. Updates from NCRI AML18 and AML 19 trials. Available at https://aml-hub.com/medical-information/updates-from-ncri-aml18-and-aml-19-trials. Accessed August 2, 2021.

Phase 3 Study of Chemotherapy in Combination With ATRA ± GO in Patients Aged ≥ 18 years With AML and *NPM1* Gene Mutation (AMLSG 09-09)

Targeted agent combinations

Treatment regimen	Comparator arm	Patient population	Efficacy data (GO vs comparator)	Safety data (GO vs comparator)
GO + iCHT **Induction (2 cycles)** **GO:** 3 mg/m^2 (D1) **Ida:** 12 mg/m^2 (D1, D3, D5)* **AraC:** 100 mg/m^2 continuous IV (D1-7) **Etoposide:** 100 mg/m^2 (D1-3)*,† **ATRA:** 45 mg/m^2 (D6-8) and 15 mg/m^2 (D9-21) **Consolidation (3 cycles)‡,§:** **GO:** 3 mg/m^2 (D1 cycle 1 only) HiDAC ATRA Pegfilgrastim	**iCHT** **Induction (2 cycles)** **Ida:** 12 mg/m^2 (D1, D3, D5)* **AraC:** 100 mg/m^2 continuous IV (D1-7) **Etoposide:** 100 mg/m^2 (D1-3)*,† **ATRA:** 45 mg/m^2 (D6-8) and 15 mg/m^2 (D9-21) **Consolidation (3 cycles)‡,§:** HiDAC ATRA Pegfilgrastim	n = 588 *NPM1*-mutated AML GO arm, n = 292 Median age, 58.6 years (range 18.4-82.3) Standard arm, n = 296 Median age 58.7 years (range 20.9-80.2)	**CR/CRi:** 85.3% vs 88.5% **Death during induction therapy:** n = 30 (10.3%) vs n = 17 (5.7%) **EFS:** • **2-year EFS rates:** 58.1% (95% CI, 52.5%-64.4%) vs 52.6% (95% CI, 47%-58.9%) – Females: HR 0.67 (95% CI, 0.49-0.92) – Males: HR 1.08 (95% CI, 0.77-1.51) – Age > 70 years: HR 1.22 (95% CI, 0.76-1.95) • **Age-stratified HR** (≤ 60 years vs > 60 years): 0.83 (95% CI, 0.65-1.04; *P* = 0.1) **CIR/CID in patients achieving CR/CRi within the protocol:** • **2-year CIR rates:** 25.5% (95% CI, 19.7%-31.2%) vs 36.9% (95% CI, 30.8%-43.0%) • **Age-stratified HR** (≤ 60 years vs > 60 years): 0.66 (95% CI, 0.49-0.88; *P* = 0.005) • **2-year CID rates:** 8.3% (95% CI, 1.8%-11.8%) vs 7.1% (95% CI, 3.9%-10.3%) **WBC recovery, median:** After first induction: 23 days vs 24 days (*P* = 0.003) After second induction: 21 days vs 20 days (*P* = 0.51) **Platelet recovery, median:** After first induction: 24 days vs 23 days (*P* = 0.18) After second induction: 25 days vs 20 days (*P* < 0.001)	**Mortality rate during induction:** GO arm: 10.3% Standard arm: 5.7%

NCT information

*Reduced to D1 and D3 in induction cycle 2 and for patients aged > 60 years.
†Reduced from 3 to 2 days for all patients in the induction cycle 2 by amendment in April 2011 as a result of prolonged hematologic recovery in both arms.
‡For patients in CR or CRi, 3 cycles of consolidation therapy were intended.
§Cytarabine 3 g/m^2 every 12 hours on D1-3 for patients 18-60 years, 1 g/m^2 every 12 hours on D1-3 for patients > 60 years; ATRA 15 mg/m^2/D PO D4-21; pegfilgrastim 6 mg subcutaneously on D8.

NCT00893399

RESOURCE LINK:
Schlenk RF, et al. *J Clin Oncol*. 2020;38(6):623-632.

A Phase 2 Study of ATRA, ATO, and GO in Patients Aged ≥ 18 Years With High-Risk APL (SWOG 0535)

Targeted agent combinations

Treatment regimen	Comparator arm	Patient population	Efficacy data (GO vs comparator)	Safety data (GO vs comparator)
GO + ATRA + ATO **Induction** **GO:** 9 mg/m^2 (D1) **ATRA:** 45 mg/m^2/D (D1-CR) **ATO:** 0.15 mg/kg/D (D10-CR) **Consolidation 1&2** Patients in CR will receive **ATO**: 0.15 mg/kg/D × 25 days **Consolidation 3&4** **DNR:** 50 mg/m^2 (D1-3) **Consolidation 5&6** **GO:** 9 mg/m^2 (D1) **Maintenance (1 year)** **ATRA:** 45 mg/m^2/D × 7 days (every 14 days) **6-MP:** 60 mg/m^2/D **Methotrexate:** 20 mg/m^2 (once per week)	N/A, single-arm study	n = 70 High-risk APL Median age, 46.5 years (range 19.1-86.3)	**Overall response to therapy (CR):** 86% **EFS:** • KM-determined 3-year EFS rate: 78% (95% CI, 67%-86%) vs historical protocol-specified rate: 50% • 3-year EFS rate by binary EFS endpoints: 74% (95% CI, 62%-84%) **3-year OS:** 86% (95% CI, 75%-92%) **3-year relapse-free survival:** 91% (95% CI, 80%-96%) **CIR at 3 years post CR:** 7.1% (95% CI, 2.2% to 15.8%)	**Mortality rate during induction:** 11% (95% CI, 5%-21%) (within 6 weeks of initiating therapy) No reported cases of VOD **Most common Grade 3-5 TEAE:** Febrile neutropenia • Induction, 41% • Consolidation, 53% • Maintenance, 4%

NCT information

NCT00551460

RESOURCE LINK:
Lancet JE, et al. *Blood Adv*. 2020;4(8):1683-1689.

Long-term Outcomes of ATRA + ATO + GO in Patients Aged ≥ 10 Years With APL

Targeted agent combinations

Treatment regimen	Comparator arm	Patient population	Efficacy data	Safety data
GO + ATRA + ATO (high-risk patients, WBC > 10 × 10^9/l) **Induction:** **ATRA:** 45 mg/m^2/D until CR **ATO:** 0.15 mg/kg/D until CR **GO:** 9 mg/m^2 (D1)* **Consolidation (28-day cycles)** **ATRA:** 45 mg/m^2/D (14 days) **ATO:** 0.15 mg/kg/D (5 days/week)	**ATRA + ATO** (low-risk patients, WBC ≤ 10 × 10^9/l) **Induction** **ATRA:** 45 mg/m^2/D until CR **ATO:** 0.15 mg/kg/D until CR **Consolidation (28-day cycles)** **ATRA:** 45 mg/m^2/D (14 days) **ATO:** 0.15 mg/kg/D (5 days/week)	n = 187 Newly diagnosed APL Median age, 50 years (range 14-84) High risk at baseline (n = 53): • Received GO: 45 (83%) Low risk at baseline of developing leukocytosis with induction (n = 96): • Received GO: n = 60	**5-year survival, full cohort:** EFS: 85% DFS: 96% OS: 88% **5-year survival, low-risk cohort:** EFS: 89% DFS: 99% OS: 89% **5-year survival, high-risk cohort:** EFS: 81% DFS: 89% OS: 86%	**Most common treatment-related Grade 3 and 4 adverse events:** • Infections: 23.5% (n = 44) • QT prolongation: 7.5% (n = 14) • Hemorrhage: 5% (n = 10)

NCT information

*For a brief period, 12 mg/m^2 IDA on D1 was administered instead of GO due to transient GO unavailability.

Long-term follow-up of 3 prospective studies including NCT01409161

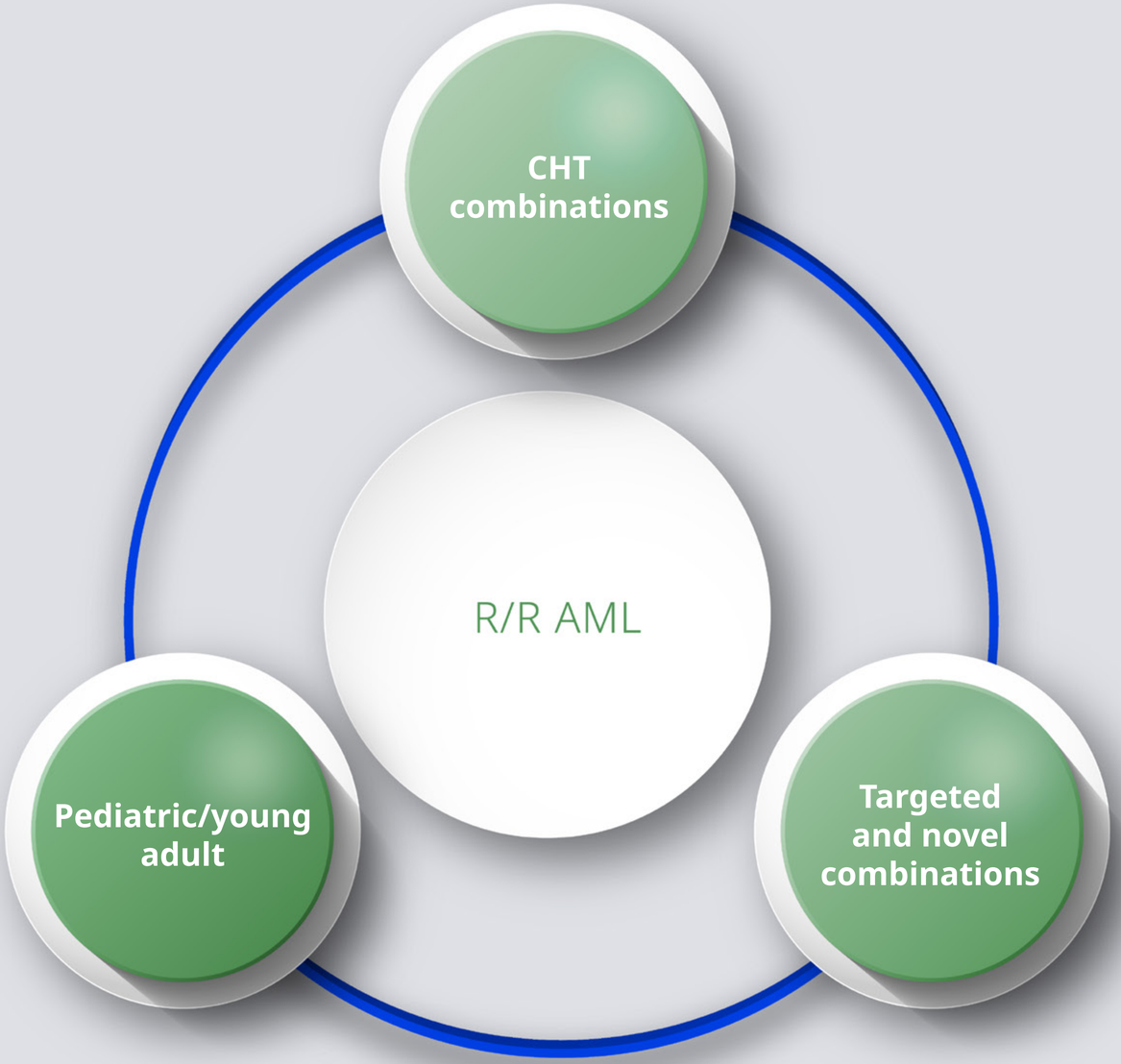
RESOURCE LINK:
Abaza Y, et al. *Blood*. 2017;129(10):1275-1283.

Studies With GO in Novel Combinations Outside of the Licensed Indication:
Pediatric Newly Diagnosed AML/APL

Pediatric/ young adult

Agents	Study name	Eligible ages	Phase	Estimated or actual enrolment	Start date	Estimated PCD/SCD	Status	NCT number/ GM number	ISR/ CRC	Study results available
DNR + AraC (3+10) + GO + atovaquone	Atovaquone (Mepron®) + conventional CHT for de novo AML (ATACC AML)	≥ 1 month < 21 years	1	26 (A)	Jul 2018	Sep 2020/ Oct 2025	Active, not recruiting	NCT03568994*	N/A	No
GO + AraC + mitoxantrone or GO + L-DNR + AraC	International randomized phase 3 clinical trial in children with AML (Myechild01)	≤ 17	3	700 (E)	Apr 2016	Dec 2031/ Dec 2032	Recruiting	NCT02724163*	CRC	No
GO + ATO + ATRA	Treatment study for children and adolescents with high-risk APL (ICC APL study 02)	< 18	2	89 (E)	Oct 2019	Oct 2022/ Oct 2024	Recruiting	NCT04793919* WI216205	ISR	No
Low-risk AML: AraC + DNR + erwinase + etoposide + GO High-risk AML: AraC + DNR + erwinase + etoposide + GO + sorafenib + HSCT	CHOA-AML: A pilot study for newly diagnosed pediatric patients with AML	< 21	Pilot study	8 (A)	Jan 2020	Aug 2021/ Aug 2021	Active, not recruiting	NCT04326439*	N/A	No
GO + CPX-351, GO + 7+3, gilteritinib + GO + 7+3, CPX-351 + gilteritinib + GO	Study to compare standard CHT to therapy with CPX-351 and/or gilteritinib for patients with newly diagnosed AML with or without *FLT3* mutations	≤ 22	3	1400 (E)	Jul 2020	Sep 2027/ Sep 2027	Recruiting	NCT04293562*	N/A	No

In studies where multiple treatment arms are being investigated, only the GO treatment arm has been included.
*Clinical trials available at https://clinicaltrials.gov/. Accessed June 9-11, 2021.


CHT combinations
R/R AML
Pediatric/young adult
Targeted and novel combinations

Studies With GO in Novel Combinations Outside of the Licensed Indication: R/R AML

CHT combinations

Agents	Study name	Eligible ages	Phase	Estimated or actual enrolment	Start date	Estimated PCD/SCD	Status	NCT number/ GM number	ISR/ CRC	Study results available
GO + mitoxantrone + etoposide	Phase 2 study of the combination of mitoxantrone, etoposide and GO (MEGO) for patients with AML refractory to initial standard induction therapy	18-75	2	53 (E)	Feb 2019	Oct 2024/ Nov 2024	Recruiting	NCT03839446*/ 51825151	N/A	No
GO + cladribine + AraC + G-CSF	CLAG-GO for patients with persistent, R/R AML	≥ 18	2	39 (E)	Nov 2019	Jun 2022/ Feb 2023	Recruiting	NCT04050280* WI230769	ISR	No
GO + decitabine	Decitabine and GO in AML and H-R MDS	≥ 16	2	43 (A)	Apr 2009	Aug 2012/ Aug 2012	Completed	NCT00882102*	N/A	Yes ›
GO + 5-azacitidine	Combination 5-azacitidine and GO therapy for treatment of relapsed AML	18-90	1/2	50 (A)	Jul 2005	Sep 2014/ Sep 2014	Completed	NCT00766116*	N/A	Yes ›

In studies where multiple treatment arms are being investigated, only the GO treatment arm has been included.
*Clinical trials available at https://clinicaltrials.gov/. Accessed June 9-11, 2021.

Phase 2 Study of GO + DEC in Newly Diagnosed and Relapsed AML, and High-Risk MDS Patients Aged ≥ 18 Years

CHT combinations

Treatment regimen	Comparator arm	Patient population	Efficacy data	Safety data
GO + DEC **Induction*** **GO:** 3 mg/m^2 (D5) **DEC:** 20 mg/m^2 (D1-5) **Post-induction (≤ 5 cycles)**† **GO:** 3 mg/m^2 (D5) **DEC:** 20 mg/m^2 (D1-5) **Maintenance (≤ 24 cycles)**‡ DEC alone every 4-8 weeks	N/A, single-arm study	n = 110 Median age, 70 years (range 27-89) AML, n = 84; HR-MDS, n = 22; MF, n = 4 High-risk cytogenetics, n = 44 (40%) *FLT3*mt, n = 11 (of 95 tested) (12%) Patients enrolled into 4 pre-defined groups: **Group 1 (n = 28):** R/R AML with CRD < 1 year; age 62 years (range 26-83) **Group 2 (n = 5):** R/R AML with CRD > 1 year, age 83 years (64-68) **Group 3 (n = 57):** Untreated, unfit AML (n = 40), MDS or MF (n = 17); age 70 years (range 42-87) **Group 4 (n = 20):** AML evolving from MDS, R/R MDS, or MF; age 70 years (range 32-82)	**Overall population (n = 110)** • **CR/CRi:** 35% (n = 39); Median duration, 5.8 months (range 1-41) **CR/CRi, n/N (%):** • Group 1: 5/18 (18%) • Group 2: 3/5 (60%) • Group 3: AML, 18/40 (45%): HR-MDS, 5/15 (33%) • Group 4: 7/20 (35%) **Median OS, months** • Group 1: 3.5 • Group 2: 8.0 • Group 3: AML, 7.0; HR-MDS, 5.7 • Group 4: 7.2	**Overall population** • **Grade 3/4 toxicities, n (%):** – Most common: neutropenic fever, 50 (45) – Gastrointestinal and mucosal bleeding, 8 (7) • **VOD:** No cases of VOD or treatment-related Grade 3-4 liver function abnormalities **8-week mortality** • Group 1: 11% • Group 2: 0% • Group 3: 15% • Group 4: 15%

NCT information

*Patients whose BM at D14 showed BM cellularity ≥ 20% and ≥ 5% blasts received an additional 5-day course of DEC, beginning on D15.
†Patients with response or no obvious progression (without DEC at D15).
‡Patients who maintained CR or CRi at the end of post-induction therapy.

NCT00882102

RESOURCE LINK:
Daver N, et al. *Leukemia*. 2016;30(2):268-273.

Phase 1/2 Study of GO in Combination With AZA in Patients Aged > 18 Years With R/R AML

CHT combinations

Treatment regimen	Comparator arm	Patient population	Efficacy data	Safety data
AZA + GO **Phase 1 – to determine MTD** **AZA:** 75 mg/m^2 • Cohort 1 (n = 6): D1-2 • Cohort 2 (n = 4): D1-4 • Cohort 3 (n = 4): D1-6 **GO:** 6 mg/m^2 (2 doses 14 days apart) **Phase 2 - MTD** **AZA:** 75 mg/m^2 (D1-6) **GO:** 6 mg/m^2 (D7, D21)	N/A, single-arm study	n = 50* Previous number of relapses ≥ 2: 24% (n = 12) Prior HSCT: 34% (n = 17) Median age, years (range) • Phase 1 (n = 14): 66 (39-82) • Phase 2 (n = 36): 63.5 (29-76) Median number of prior therapies, n (range): • Phase 1: 1 (1-3) • Phase 2: 1 (1-3) Unfavorable karyotype at diagnosis, n • Phase 1: 3 • Phase 2: 6	**All patients** **CR/CRp:** 24% (n = 12) **Phase 1** **ORR:** cohort 1, 0%; cohort 2, 25% (n = 1) cohort 3, 50% (n = 2) **Phase 2 (n = 36)**† **Total CR:** 25% (n = 9) **CR:** 11% (n = 4) **CRp:** 14% (n = 5) In the 3 cohorts, prior alloHSCT and cytogenetic risk were not predictive of response‡	**Phase 1** **DLTs:** n = 0 **Phase 2** **Most common Grade 3/4 AEs (occurring in ≥ 4 patients):** • Febrile neutropenia, n = 28 • Gram-positive infections, n = 5 • Pneumonia, n = 4 • Electrolyte abnormalities, n = 4 **Grade 3/4 liver function abnormalities:** n = 2 **Hepatic SOS:** n = 0

NCT information

*Fifty-one patients provided written consent; however, 1 patient did not receive any investigational therapy and was excluded from the analyses.
†Evaluable patients, n = 36. However, 5 patients withdrew consent before the response assessment and 4 patients died.
‡Unplanned post hoc analysis of outcomes.

NCT00766116

RESOURCE LINK:
Medeiros BC, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(5):346-352.

Studies With GO in Novel Combinations Outside of the Licensed Indication: R/R AML

Targeted and novel combinations

Agents	Study name	Eligible ages	Phase	Estimated or actual enrolment	Start date	Estimated PCD/SCD	Status	NCT number/ GM number	ISR/ CRC	Study results available
GO + pracinostat	Pracinostat in combination with GO (PraGO) in patients with R/R AML	≥ 18	1	18 (E)	May 2019	May 2022/ Mar 2023	Recruiting	NCT03848754* WI243940	ISR	No
GO + VEN	Study of the safety and efficacy of GO + VEN in patients with R/R CD33+ AML: big ten cancer research consortium BTCRC-AML17-113[1]	≥ 18	1b	24 (E)	Sep 2019	Oct 2021/ Oct 2022	Recruiting	NCT04070768* WI234149	ISR	No
GO + AZA + VEN or GO + AZA + avelumab or GO + glasdegib	OX40, VEN, avelumab, glasdegib, GO, and AZA in treating patients with R/R AML	≥ 18	1b/2	138 (E)	Dec 2017	Dec 2023/ Dec 2024	Recruiting	NCT03390296*	CRC	Yes
GO + bortezomib + AraC	TEAM-trial: targeting epigenetic therapy resistance in R/R AML with bortezomib (TEAM)	18-100	2	50 (E)	Oct 2019	Dec 2021/ Dec 2021	Recruiting	NCT04173585* WI218218	ISR	No
GO + talazoparib	Talazoparib and GO for the treatment of CD33+ R/R AML[2]	≥ 18	1/2	20 (E)	Jul 2020	Feb 2022/ Feb 2023	Recruiting	NCT04207190* 53593673	ISR	No
GO + CPX-351	CPX-351 and GO in treating patients with R/R AML	≥ 18	1	33 (E)	Jul 2019	Jul 2022/ Jul 2023	Recruiting	NCT03904251* WI240677	ISR	No
GO + CPX-351	CPX-351 and GO in treating patients with R/R AML high-risk MDS	≥ 18	2	50 (E)	Nov 2018	Nov 2022/ Nov 2022	Recruiting	NCT03672539*	N/A	Yes
GO + CPX-351	GO + CPX-351 in subjects aged ≥ 55 years with AML (CPX GO)	≥ 55	1	30 (E)	Aug 2019	Sep 2022/ Sep 2026	Recruiting	NCT03878927* WI242507	ISR	No
GO, non-engraftment DLI	Fractionated GO followed by non-engraftment DLI for R/R AML	≥ 18	2	18 (E)	Dec 2019	Mar 2021/ Mar 2022	Recruiting	NCT03374332* WI231684	ISR	No
GO + AraC + gilteritinib	Phase 2 study of GO-cytarabine-gilteritinib combination in adults with *FLT3*-mutated R/R AML (AGORA-1)[3]	-	2	50 (E)	–	–	Contracting	- 61277773	N/A	No
GO + vorinostat + AZA	Vorinostat, AZA, and GO for older patients with R/R AML	≥ 50	1/2	52 (A)	May 2009	Jul 2013/ Sep 2013	Completed	NCT00895934*	N/A	Yes

In studies where multiple treatment arms are being investigated, only the GO treatment arm has been included.
*Clinical trials available at https://clinicaltrials.gov/. Accessed June 9-11, 2021.

RESOURCE LINK:

1. Arain S, et al. *J Clin Oncol*. 2020;38(suppl 15):TPS7566.

2. Przespolewski A. *Blood*. 2020;138(suppl 1):20-21.

3. Data on file. Pfizer Inc., New York, NY.

Targeted and novel combinations

Phase 1b/2 Multi-Arm Combination Study in Patients With R/R AML

Treatment regimen	Comparator arm	Patient population	Efficacy data	Safety data
Multi-arm, parallel cohort study to evaluate various novel combinations of agents, including 3 treatment arms that include GO:	N/A	Aged ≥ 18 with R/R AML or AML from antecedent hematological malignancy previously treated with HMA		
AZA + VEN + GO (Arm A) **AZA:** 75 mg/m^2 (D1-7) **VEN:** 400 mg (Cycle 1, D1-28; Cycle 2, D1-21) **GO:** 3 mg/m^2 (D8)*		n = 20 Median age, 65 years (range 27-84) Prior VEN exposure, n = 8 Poor risk, n = 12	**Response** • **Entire cohort (n = 20):** CR/CRi, 40%; CR/CRi/MLFS, 55% • **No prior VEN (n = 12):** CR/CRi, 50%; CR/CRi/MLFS, 75% • **Prior VEN (n = 8):** CR/CRi, 25%; CR/CRi/MLFS, 25% **mDOR:** 4.1 months (range 3.5-5.3+) **mOS:** 7.3 months **HSCT rate:** n = 3 (15% overall; 27% of responders)	No DLTs were observed in the initial 6-patient safety lead-in cohort
AZA + avelumab + GO (Arm C) **AZA:** 75 mg/m^2 (D1-7) **Avelumab:** 10 mg/kg (D1, D14)† **GO:** 3 mg/m^2 (D8)*		n = 6 (5 evaluable) Median age, 56 years (range 26-79) Prior VEN exposure, n = 6 Poor risk, n = 3	**Response** • **CR:** 17% (n = 1)	No DLTs were observed
Glasdegib + GO (Arm E) **Glasdegib:** 100 mg (D1-28) **GO:** 3 mg/m^2 (D1, D4, D7)*		n = 5	**Response:** n = 0	Grade 3 mucositis (n = 1), possibly related to GO

NCT information

The study included 5 treatment arms, only treatment arms that included GO are included.
*Maximum dose 4.5 mg.
†Maximum dose 2000 mg.

NCT03390296

RESOURCE LINK:
Short NJ, et al. ASH 2020. Poster presentation (Abstract 1791).

CPX-351 + GO in Patients With CD33+ R/R AML, Post-HMA Failure HR-MDS and Newly Diagnosed sAML With Prior HMA therapy

Targeted and novel combinations

Treatment regimen[1]	Comparator arm[1]	Patient population[1]	Efficacy data	Safety data
CPX-351-GO **Induction*** CPX-351 (D1, D3, and D5) GO: 3 mg/m^2 (D1) **Consolidation (≤ 2 cycles)**† CPX-351 (D1 and D3) GO‡: 3 mg/m^2 (D1) **Maintenance** GO monotherapy (D1 Q6W) in cases of persistent MRD	N/A, single-arm, single-institution study	n = 20 Median age, 70 years (range 23-76) sAML, 65% (n = 13) De novo AML, 15% (n = 3) tAML, 20% (n = 4) Complex cytogenetics, 35% (n = 7) Median number of prior treatments, 2 (range 1-7)	**Response**[1] • ORR: 40% (n = 8) • CR/CRi: 30% (n = 6) • PR: 10% (n = 2) • NR: 60% (n = 12) **Median CRD:** 10.5 months[1] **mOS:** 7.2 months[1] **6-month OS:** 52%[1] **Molecular response:** 50% (n = 4) of responding patients were MRD-negative[2]	**Most common Grade ≥ 3 AEs (≥ 15%)**[1]**:** • Neutropenic fever: 80% (n = 16) • Bacteremia: 35% (n = 7) • Lung infection: 20% (n = 4) • Sepsis: 20% (n = 4) Five patients died within 60 days of treatment[2] **Time to blood count recovery, median in days (range)**[1]**:** • ANC > 0.5 × 10^9/l: 30 (30-56) • ANC > 1 × 10^9/l: 40 (31-74) • Platelets > 50 × 10^9/l: 40 (33-46) • Platelets > 100 × 10^9/l: 43 (34-53)

NCT information

*Patients who did not achieve CR or CRi after first induction could receive a second induction of CPX-351 (D1 and D3) + GO, 3 mg/m^2 (D1).
†Patients with CR or CRi could receive ≤ 2 consolidation cycles after ≥ 4 weeks from the start of the last cycle with CPX-351.
‡GO was only administered in second consolidation if there was evidence of MRD.

NCT03672539

RESOURCE LINK:

1. Ramos-Perez JM, et al. ASH 2020. Poster presentation (Abstract 987).

2. Ramos-Perez JM, et al. *Blood*. 2020;138(suppl 1):32-34.

Phase 1/2 Study of GO in Combination With Vorinostat and AZA in Patients Aged ≥ 50 Years With R/R AML

Targeted and novel combinations

Treatment regimen	Comparator arm	Patient population	Efficacy data	Safety data
AZA + vorinostat + GO **Phase 1: Dose level 1*** **AZA:** 75 mg/m^2/D (D1-7) **Vorinostat** 200 mg/D (D1-9) **GO:** 3 mg/m^2 (D8) **Dose levels 2 and 3*** As per dose level 1 with vorinostat increased to 300 mg and 400 mg respectively **Dose level 4* (Phase 2 dose level - MTD)** As per dose level 1 with **GO:** 3 mg/m^2 (D4 and D8)	N/A	AML requiring therapy for first relapse (remission duration ≤ 12 months) All patients, n = 52; median age, 64.8 years (range 50.2-78.9) Primary refractory disease at time of study entry, n = 29 • Prior therapies: – 7+3, n = 13 – Repeated 7+3, n = 4 – HiDAC regimens, n = 11 – LDAC/clofarabine, n = 1 Phase 2 dose level, n = 43	Phase 2 dose level (n = 43): **Best response post-induction, n (%)** • **CR:** – Without MRD: 10 (23.3) – With MRD: 8 (18.6) • **CRi:** – Without MRD: 8 (18.6) – With MRD: 2 (4.7) • **CR + CRi:** 18 (41.9) • **MLFS:** 0	**Overall population DLTs** • Dose levels 1-3: 0% • Dose level 4: death due to sepsis after Cycle 1, n = 1 Phase 2 dose level (n = 43) **Early death**: n = 4 (9%) **Death in aplasia:** n = 1 (2.4%) **Resistant disease:** n = 24 (55.8%)

NCT information

*If there was clear evidence of persistent leukemia (≥ 20% blasts, no hypercellularity) on D15, the first cycle was repeated. In all other patients, a second cycle was begun if peripheral blood counts had recovered and/or toxicities had resolved to ≤ Grade 2.

NCT00895934

RESOURCE LINK:
Walter RB, et al. *Hematologica*. 2014;99(1):54-59.

Studies With GO in Novel Combinations Outside of the Licensed Indication: R/R AML

Pediatric/young adult

Agents	Study name	Eligible ages	Phase	Estimated or actual enrolment	Start date	Estimated PCD/SCD	Status	NCT number/ GM number	ISR/ CRC	Study results available
GO + bulsulfan + cyclophosphamide, alloHSCT	Immunochemotherapy and alloHSCT in patients with high-risk CD33+ AML/MDS	≤ 25	2	25 (E)	Nov 2011	Jun 2021/ Jun 2022	Recruiting	NCT02221310*	N/A	No

In studies where multiple treatment arms are being investigated, only the GO treatment arm has been included.
*Clinical trials available at https://clinicaltrials.gov/. Accessed June 9-11, 2021.

GO prior to HSCT

Studies With GO Prior to HSCT

Agents	Study name	Eligible ages	Phase	Enrolment	Status	Study results available
GO, HSCT	Prior GO exposure in adults with AML does not increase hepatic VOD risk after HSCT: a CIBMTR analysis[1]	≥ 18	N/A	685	Completed	Yes
GO, HSCT	Risk of SOS in HSCT after prior GO treatment: a retrospective study from the ALWP of the EBMT[2]	≥ 18	N/A	146	Completed	Yes
GO, HSCT	Prior treatment with GO and the risk of VOD after HSCT[3]	≥ 3	N/A	44	Completed	Yes
GO + AraC + DNR	Fractionated GO combined with Ara-C and DNR as salvage therapy in very high-risk AML patients[4]	≥ 18	N/A	24	Completed	Yes
GO + AraC + DNR or Ida or mitoxantrone	Fractionated GO in association with high-dose CHT: a bridge to HSCT in R/R AML[5]	≥ 16	N/A	58	Completed	Yes
GO + AraC + mitoxantrone + ATRA	Salvage therapy with high-dose cytarabine and mitoxantrone in combination with ATRA and GO in AML refractory to first induction therapy[6]	≥ 18	2	93	Completed	Yes

RESOURCE LINK:

1. Ho VT, et al. *Biol Blood Marrow Transplant*. 2020;26(5):884-892.
2. Battipaglia G, et al. *Bone Marrow Transplant*. 2017;52(4):592-599.
3. Chevalier P, et al. *Bone Marrow Transplant*. 2010;45(1):165-170.
4. Paubelle E, et al. *Ann Hematol*. 2017;96(3):363-371.
5. Debureaux PE, et al. *Bone Marrow Transplant*. 2020;55(2):452-460.
6. Hütter-Krönke M, et al. *Hematologica*. 2016;101(7):839-845.

Studies Investigating the Use of Gemtuzumab Ozogamicin in Patients Proceeding to Transplant* (1)

GO prior to HSCT

	Treatment pre-HSCT	Patient population	Efficacy data	Safety data
RWD: Retrospective, matched cohort (2008-2011)[1]	**Induction** GO (median dose† 9.5 mg, range 3.0-33.0 mg) + CHT‡	AlloHSCT after GO, n = 137; control, n = 548 Median age: GO exposure, 42 years (range 18-73) Matched controls, 38 years (range 18-74) Disease status: GO exposure: CR1, 33%; CR ≥ 2, 30%; relapse/primary induction failure, 37% Matched controls: CR1, 33%; CR ≥ 2, 30%; relapse/primary induction failure, 37%	**5-year OS:** 38% in both GO and control arm	**VOD:** Cumulative incidence at 100 days (95% CI): • VOD (GO vs control): 4% (1-7) vs 3% (1-6) • Severe VOD (GO vs control): 3% (2-5) vs 1% (0-2) In MVA, GO exposure was not associated with an increased risk of VOD (OR 1.10 [95% CI, 0.43-2.81]; *P* = 0.85)
RWD: Retrospective, multicenter (2002-2012)[2]	**Induction** GO (median dose§ 3 mg/m^2, range 3-9 mg/m^2) + CHT (n = 127) or as a single agent (n = 10)‡	HSCT after GO, n = 146 Median age, 50 years (range 19-70); 11% sAML Disease status: CR1, 37%; CR2, 29%; active disease, 34%	**5-year LFS:** 37%; 5-year OS: 40% **Impact of time to HSCT after GO on OS** • HSCT ≤ 3.5 months vs > 3.5 months after last GO dose: OS was not significantly different (*P* = 0.16) • HSCT ≤ 1 month after last GO dose: OS was significantly worse (*P* = 0.032)	**VOD:** Mild, n = 2; moderate, n = 6; severe, n = 6 (death n = 3) • Incidences were not significantly different for patients with an interval of ≤ 3.5 months between GO and HSCT compared with the others • There was a trend for increased risk of VOD in patients undergoing HSCT ≤ 1 month after their last GO dose (*P* = 0.06)

*Studies with < 10 patients who received GO and proceeded to transplant, or with limited transplant population-specific data were not included.
†Among patients with available dosing data, n = 58.
‡FDA/EMA approved dosage and administration.
§Among patients with available dosing data, n = 137.

RESOURCE LINK:

1. Ho VT, et al. *Biol Blood Marrow Transplant.* 2020;26(5):884-892.

2. Battipaglia G, et al. *Bone Marrow Transplant*. 2017;52(4):592-599.

Studies Investigating the Use of Gemtuzumab Ozogamicin in Patients Proceeding to Transplant* (2)

GO prior to HSCT

	Treatment pre-HSCT	Patient population	Efficacy data	Safety data
RWD: Retrospective, multicenter (2001-2008)[1]	**Induction** GO 9 mg/m^2 D4 + AraC + mitoxantrone (n = 36),[†] or other combinations of CHT (n = 8)	HSCT after GO, n = 44 Median age, 50 years (range 3-67); 14% sAML Disease status: CR1, 29.5%; CR2, 38.5%; CR3, 7%; advanced, refractory, or persistent disease, 25%	**2-year LFS:** 38%; 2-year OS: 45%	**VOD:** Incidence of VOD was 7% (n = 3) • 8.3% (n = 2/24) in patients with a short GO–allograft interval (≤ 4.2 months) vs 5% (n = 1/20) for all others (*P* = NS) • 10.5% (n = 2/19) in patients with a ≤ 3.5-month GO–allograft interval vs 4% (n = 1/25) for all others (*P* = NS)
RWD: Retrospective single-center (2013-2015)[2]	**Induction** GO 3 mg/m^{2,‡} (D1, 4, and 7) 7+3[§] Proceeded to alloHSCT: n = 13 (54%)	R/R AML, n = 24 Median age, 55.3 years (range 22.2–70.1) 67% de novo AML 33% sAML	**CR rate (overall population):** 50% (95% CI, 28-72) **mOS (overall population):** 6.7 months (95% CI, 3.3-19.2) OS was significantly higher in patients who received alloHSCT than in non-transplanted patients (*P* = 0.02) **1-year OS post alloHSCT:** 51% (95% CI, 21-74) vs 11% (95% CI, 1-38) in the absence of alloHSCT	**VOD:** No VOD was reported after alloHSCT

RESOURCE LINK:

1. Chevalier P, et al. *Bone Marrow Transplant*. 2010;45(1):165-170.

2. Paubelle E, et al. *Ann Hematol*. 2017;96(3):363-371.

*Studies with < 10 patients who received GO and proceeded to transplant, or with limited transplant population-specific data were not included.
[†]AraC 1 g/m^2/12h D1-5 and mitoxantrone 12 mg/m^2 D1-3. GO was dose-reduced to 4.5 mg/m^2 in 1 patient and mitoxantrone was omitted in 3 patients.
[‡]Maximum dose 5 mg.
[§]FDA/EMA approved dosage and administration.

Studies Investigating the Use of Gemtuzumab Ozogamicin in Patients Proceeding to Transplant* (3)

GO prior to HSCT

	Treatment pre-HSCT	Patient population	Efficacy data	Safety data
RWD: Retrospective, single-center (2009-2017)[1]	**Induction** GO 3 mg/m^{2,†} (D1, 4, and 7)‡ AraC§ + DNR, Ida, or mitoxantrone¶ **Consolidation** Patients in CR also received GO **Proceeded to alloHSCT:** n = 28 (48%)	R/R AML (n = 58) Median age, 56 years (range 16-74) 74% de novo AML 26% sAML	ORR: 67% MRD negativity (after first treatment cycle): Achieved in 41% of 46 patients with an MRD target LFS at 2 years (transplanted patients): 57% (range 36.3-77.5) OS at 2 years (transplanted patients): 69% (range 49.3-88.7)	**VOD:** 5 cases of VOD occurred during transplant (3 moderate and 2 very severe) No VOD-related deaths occurred
Phase 2. Primary refractory AML[2]	**Induction** GO 3 mg/m^{2,‡} (D1, 4, and 7) 7+3§ **Proceeded to alloHSCT:** n = 13 (54%)	Refractory AML (n = 93) Median age, 48 years (range 22-62) 83% de novo AML 17% sAML	ORR (overall population): 61% (n = 57) mOS (overall population): 16.0 months 4-year OS rate (overall population): 32% (95% CI, 24%-43%) • 4-year OS rates were significantly higher in patients who received alloHSCT (n = 71), 39% (95% CI, 29%-52%) than in non-transplanted patients (n = 22), 7% (95% CI, 1%-42%); *P* = 0.0006	**Incidence of SOS after alloHSCT:** • Overall: 12.7% (9/71) • Moderate/severe: 8.5% **Liver toxicity:** Grade 4/5 was not observed **30-day mortality:** 3% (n = 3)

*Studies with < 10 patients who received GO and proceeded to transplant, or with limited transplant population specific data were not included.
†Maximum dose 5 mg.
‡FDA/EMA approved dosage and administration.
§1 g/m^2 twice daily on D1-5.
¶DNR 60 mg/m^2 D1-3 *or* Ida 12 mg/m^2 D1-3 or mitoxantrone 12 mg/m^2 D1-3.
‖AraC 3 g/m^2 every 12 hours D1-3 + mitoxantrone 12 mg/m^2 D2 and D3 + ATRA 45 mg/m^2 D4-6 and 15 mg/m^2 D7-28

RESOURCE LINK:

1. Debureaux PE, et al. *Bone Marrow Transplant*. 2020;55(2):452-460.
2. Hütter-Krönke M, et al. *Hematologica*. 2016;101(7):839-845.

RWD

Studies With GO in Novel Combinations Outside of the Licensed Indication: RWD

Agents	Study name	Eligible ages	Enrolment	Status	Study results available
Flu + AraC + GO + HSCT	Fludarabine, cytarabine, and fractionated GO followed by HSCT for 1L refractory AML in children[1]	< 18	8	Completed	Yes
Flu + AraC + Ida + GO, Flu + AraC + Ida	FLAI-GO vs FLAI in patients with CBF-AML[2]	≥ 18	37	Completed	Yes
Flu + AraC + Ida + GO, Flu + AraC + Ida	FLAI-GO as 1L treatment for patients with cytogenetically normal AML, according to *NPM1* and *FLT3*-ITD mutational status[3]	< 65	148	Completed	Yes

RESOURCE LINK:

1. Penel-Page M, et al. *Pediatr Blood Cancer*. 2020;67(6):e283051.

2. Gottardi M, et al. *Hematol Rep*. 2017;9(3):7029.

3. Mineto P, et al. EHA 2020. Poster presentation (Abstract EP573).

Flu, AraC, and Fractioned GO Followed by HSCT for 1L Refractory AML in Children

RWD

RWD study (retrospective 2013-2018)

Treatment regimen	Comparator arm	Patient population	Efficacy data (GO vs comparator)	Safety data (GO vs comparator)
FLA-GO **GO:** 3 mg/m^2 (D1, D7) **AraC:** 2000 mg/m^2 (D 1-5) **Flu:** 30 mg/m^2 (D 1-5)	N/A, single-arm study	n = 8 Refractory AML, pediatric Median age, 14.5 years (range 11.1-17.5)	• 5/8 achieved CR • 1/8 had MRD < 10^{-2} but without hematologic response • All patients underwent HSCT	• 1 patient with moderate allergy to GO, relieved by steroids and antihistamine • 11 episodes of febrile neutropenia of 13 courses

RESOURCE LINK:
Penel-Page M, et al. *Pediatr Blood Cancer*. 2020;67(6):e283051.

FLAI-GO vs FLAI in Patients With CBF AML

RWD

	Treatment regimen	Comparator arm	Patient population	Efficacy data (GO vs comparator)	Safety data (GO vs comparator)
RWD study: Retrospective 2006-2009 (FLAI-GO) and 2003-2006/2010-2013 (FLAI)	**FLAI-GO**[1] **Induction** **FLAI** **Flu:** 30 mg/m^2 (D1-5) **AraC:** 2 g/m^2 (D1-5) **Ida:** 10 mg/m^2 (D1, D3, and D5) **GO:** 3 mg/m^2 (D6) **Consolidation** 2 HiDAC-based cycles	**FLAI** **Induction** **FLAI** **Flu:** 30 mg/m^2 (D1-5) **AraC:** 2 g/m^2 (D1-5) **Ida:** 10 mg/m^2 (D1, D3, and D5) **Consolidation** 2 HiDAC-based cycles*	FLAI-GO, n = 12 Median age, 46.3 years (range 29-67) FLAI, n = 25 Median age, 41.3 years (range 18-66) CBF-AML	**CR after induction** 100% vs 88%; *P* = 0.540 **MRD-negativity:** Achievement of MRD-negativity (100% of the 4 patients analyzed vs 63% of the 13 patients analyzed) was of pivotal prognostic importance (*P* < 0.001 for OS, DFS, and EFS) **HSCT rate:** After induction: 7/12 vs 7/25 After relapse and CR2: 2/3 vs 7/10 **5-year OS:** 69.4% vs 48.6%; *P* = 0.202 **5-year DFS:** 54.7% vs 42.4%; *P* = 0.327 **5-year EFS:** 54.7% vs 36.9%; *P* = 0.136 **mDFS:** NR vs 14.7 months	No deaths during induction

RESOURCE LINK:
Gottardi M, et al. *Hematol Rep*. 2017;9(3):7029.

*Overall dose 24 g/m^2/cycle.

GO + FLAI As 1L Treatment for Patients Aged < 65 Years With Cytogenetically Normal AML, According to *NPM1* and *FLT3*-ITD Mutational Status

RWD

	Treatment regimen	Comparator arm	Patient population	Efficacy data (GO vs comparator)	Safety data (GO vs comparator)
RWD study (retrospective 2008-2018)	**FLAI-GO** **FLAI*** **Flu:** 30 mg/m^2 (D1-5) **AraC:** 2 g/m^2 (D1-5) **Ida:** 10 mg/m^2 (D1, D3, and D5) **GO:** 3 mg/m^2 single dose (day not stated)	**FLAI** **FLAI*** **Flu:** 30 mg/m^2 (D1-5) **AraC:** 2 g/m^2 (D1-5) **Ida:** 10 mg/m^2 (D1, D3, and D5)	n = 148 AML with ≥ 1 *FLT3*-ITD or *NPM1*mt molecular alteration *FLT3*-ITD, n = 33 *NPM1*mt, n = 65 *FLT3*-ITD/*NPM1*mt, n = 50 Median age, 50 years (range 18-65) FLAI-GO arm, n = 42	**Overall 3-year OS:** 59.5% (median NR) • *FLT3*-ITD: 66.7% vs 46.6% ($P < 0.03$) – The addition of GO improved outcomes in *FLT3*-ITD patients. This effect was more pronounced in *FLT3*-ITD/*NPM1*wt patients (n = 33) median OS, NR (P = NS) **Overall CR rate:** 85% after FLAI induction. No difference between patients receiving and not receiving GO	**Overall 60-day mortality:** 3%, not significantly affected by GO

*For patients who achieved CR, Flu was omitted in the second induction cycle and IDA increased to 12 mg/m^2.

RESOURCE LINK:
Mineto P, et al. EHA 2020. Poster presentation (Abstract EP573).

Glossary (A-G)

1L = first line

6-MP = 6-mercaptopurine

A = actual

AC-IDA = intermediate doses of cytarabine and idarubicin

AE = adverse event

ALL = acute lymphoblastic leukemia

alloHSCT = allogeneic hematopoietic stem cell transplantation

ALWP = Acute Leukemia Working Party

AML = acute myeloid leukemia

ANC = absolute neutrophil count

APL = acute promyelocytic leukemia

AraC = cytarabine

ATO = arsenic trioxide

ATRA = all-*trans* retinoic acid

AZA = azacitidine

BM = bone marrow

BSC = best supportive care

CBF-AML = core binding factor acute myeloid leukemia

CG = center grant

CHT = chemotherapy

CI = confidence interval

CIBMTR = Center for International Blood & Marrow Transplant Research

CID = cumulative incidence of death

CIR = cumulative incidence of relapse

CLAG-GO = cladribine, AraC, G-CSF and GO

CLAG-M = cladribine, HiDAC, G-CSF and dose-escalated mitoxantrone

CR = complete remission

CR1 = first complete remission

CR2 = second complete remission

CR3 = third complete remission

CRC = clinical research collaboration

CRD = CR duration

CRi = complete remission with incomplete hematologic recovery of peripheral blood counts

CRISPR = clustered regularly interspaced short palindromic repeats

CRp = complete remission with incomplete peripheral blood recovery

D = day

DA = daunorubicin, cytarabine

DEC = decitabine

DFS = disease-free survival

DLI = donor lymphocyte infusion

DLT = dose-limiting toxicities

DNR = daunorubicin

E = estimated

EBMT = European Group for Blood and Marrow Transplantation

EFS = event-free survival

ELN = European Leukemia Net

FLA = fludarabine and cytarabine

FLAG = fludarabine, cytarabine and granulocyte colony-stimulating factor

FLAI = fludarabine, cytarabine, idarubicin

Flu = fludarabine

G-CSF = granulocyte colony-stimulating factor

GM = grant management

GO = gemtuzumab ozogamicin

Glossary (H-Z)

HG-MN = high-grade myeloid neoplasm
HiDAC = high-dose cytarabine
HMA = hypomethylating agent
HR = hazard ratio
HR-MDS = high-risk myelodysplastic syndrome
HSCT = hematopoietic stem cell transplantation
iCHT = intensive chemotherapy
Ida = idarubicin
ITD = internal tandem duplication
ISR = investigator-sponsored research
KM = Kaplan-Meier
LDAC = low-dose cytarabine
L-DNR = liposomal daunorubicin
LFS = leukemia-free survival
LV = left ventricular
M3 AML = acute promyelocytic leukemia
mDFS = median disease-free survival
MDS = myelodysplastic syndrome
MF = myelofibrosis
MLFS = morphologic leukemia-free state
mOS = median OS
MR3 = qPCR ≤ 0.1
MR4 = qPCR ≤ 0.01
MRD = minimal residual disease
Mt = mutant
MTD = maximum tolerated dose
MVA = multivariate analysis
N/A = not applicable
NCT = National Clinical Trial
NR = not reached
NS = not significant
NSG = NOD scid gamma
ORR = overall response rate
OS = overall survival
PARP = poly (ADP-ribose) polymerase
PARPi = PARP inhibitor
PCD = primary completion date
PO = orally
PR = partial response
PK = protein kinase
Q6W = every 6 weeks
qPCR = quantitative polymerase chain reaction
RFS = relapse-free survival
R/R = relapsed or refractory
RP2D = recommended phase 2 dose
RWD = real-world data
sAML = secondary AML
SCD = study completion date
SOS = sinusoidal obstructive syndrome
TEAE = treatment-emergent adverse events
TKD = tyrosine kinase domain
UVA = univariate analysis
VEN = venetoclax
VOD = veno-occusive disease
WBC = white blood count
wt = wild-type