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Clinical Benefit of Glasdegib in Combination With Azacitidine or Low-Dose Cytarabine in Patients With Acute Myeloid Leukemia

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BACKGROUND

- Azacitidine (AZA) is an important treatment option for older patients with newly diagnosed acute myeloid leukemia (AML).
  - In a phase 3 trial, the median overall survival (OS) for AZA was 10.4 months and the rate of complete remission (CR) was 20%.[1]
  - Attempts to improve efficacy with combination therapy has resulted in Cycle 2 dose delays due to cytopenic complications.
- The Hedgehog (Hh) signaling pathway is aberrantly activated in AML, promoting leukemic stem cell maintenance.[2]
- Inhibition of Hh signaling has been shown to reduce leukemic stem cell growth and increase sensitivity to chemotherapy.[3]
- Glasdegib is a once-daily, oral, small-molecule inhibitor of the Hh signaling pathway.
- In the United States, glasdegib in combination with low-dose cytarabine (LDAC) is approved for the treatment of patients with AML ineligible for intensive chemotherapy.[4]
  - In a phase 2 trial with AML and myelodysplastic syndromes (MDS), glasdegib + LDAC demonstrated superior OS, higher rates of CR, and a manageable safety profile vs LDAC alone.[5]
- As the Hh signaling pathway is not essential for normal adult hematopoiesis, treatment with glasdegib may target leukemic stem cells while limiting cytopenias and cytopenic complications.[3,5,6]

OBJECTIVE

- To evaluate the safety profile of glasdegib in combination with AZA or LDAC in patients with newly diagnosed AML, with a focus on Hh pathway inhibitor class effects, cytopenias, infections, and dose delays.

METHODS

Study Design, Patients, and Treatments

- The study population for this analysis consisted of patients with AML who were ineligible for intensive chemotherapy enrolled in 2 clinical trials: BRIGHT MDS & AML 1012 (NCT02367456) and BRIGHT AML 1003 (NCT01546038).
- **BRIGHT MDS & AML 1012** (BRIGHT 1012) is an ongoing open-label, multicenter, phase 1b study.
  - Patients (aged ≥18 years) with newly diagnosed AML, higher risk MDS, and chronic myelomonocytic leukemia who elected AZA treatment received glasdegib + AZA.
    - Glasdegib 100 mg, once daily, was administered continuously in combination with AZA (75 mg/m^2/day) on Days 1–7 of a 28-day cycle.
- **BRIGHT AML 1003** (BRIGHT 1003) was an open-label, randomized, multicenter, phase 1b study for which methods have been previously published.[7]
  - Patients (aged ≥55 years) with newly diagnosed AML who were ineligible for intensive chemotherapy were randomized to receive glasdegib + LDAC or LDAC alone.
    - Glasdegib 100 mg was administered once daily, orally, in 28 cycles on a continuous basis.
    - LDAC 20 mg was administered twice daily for 10 days, every 28 days.
- The data cut-off for BRIGHT AML 1003 was October 11, 2018. The data cut-off for BRIGHT AML & MDS 1012 was September 11, 2019.

Outcomes

- To minimize bias due to imbalances in duration of treatment in each trial, safety outcomes are reported within the first 90 days and after 90 days.
- Efficacy was also assessed in each trial; the outcomes presented here include the rate of remission (CR and CR with incomplete hematologic response [CRi]), OS, transfusion independence, and cell lineage recovery (absolute neutrophil count [ANC], hemoglobin, and platelets).

RESULTS

Patients and Treatments

- Baseline characteristics and duration of treatment for patients enrolled in both studies are shown in **Table 1**.

Table 1: Baseline Characteristics

	BRIGHT 1012	BRIGHT 1003	
Patients Randomized	**Glas + AZA N=30**	**Glas + LDAC N=78**	**LDAC Alone N=38**
Male, n (%)	18 (60.0)	59 (75.6)	23 (60.5)
Age, median (range), yr	74 (56–87)	77 (64–92)	76 (58–83)
Race, n (%)			
White	22 (73.3)	75 (96.2)	38 (100.0)
Black	1 (3.3)	1 (1.3)	0
Asian	1 (3.3)	2 (2.6)	0
Other/unknown	6 (20.0)	0	0
Disease history, n (%)			
De novo	19 (63.3)	38 (48.7)	18 (47.4)
Secondary	11 (36.7)	40 (51.3)	20 (52.6)
ELN risk category*, n (%)			
Favorable	2 (6.7)	5 (6.4)	3 (7.9)
Intermediate	9 (30.0)	48 (61.5)	19 (50.0)
Adverse	18 (60.0)	25 (32.1)	16 (42.1)
Unknown	1 (3.3)	0	0
Median follow-up time, mo (95% CI)	11.5 (9.9–12.5)	43.4 (39.7–49.1)	42.0 (NE–NE)
Patients receiving ≥1 study dose	**N=30**	**N=75**	**N=36**
Median treatment duration, cycles (range)	5 (1–15)	3 (1–44)	2 (1–9)
ANC <500/μL†	10 (33.3)	39 (52.0)	12 (33.3)
ANC <1000/μL†	14 (46.7)	50 (66.7)	21 (58.3)
Bone marrow blasts, %			
Median (range)	32.0 (9.0–90.0)	41.0 (16.0–99.0)	46.0 (13.0–95.0)
Hemoglobin <9 g/dL†	19 (63.3)	47 (62.7)	18 (50.0)
Platelets <50,000/μL†	16 (53.3)	43 (57.3)	27 (75.0)

* Based on ELN AML genetic risk stratification (2010 for 1003 and 2017 for 1012). † For baseline blood counts, all patients with baseline measurements are included. Reported as the proportion of all treated patients, n (%). AML=acute myeloid leukemia; ANC=absolute neutrophil count; AZA=azacitidine; CI=confidence interval; ELN=European LeukemiaNet; Glas=glasdegib; LDAC=low-dose cytarabine; NE=not evaluable

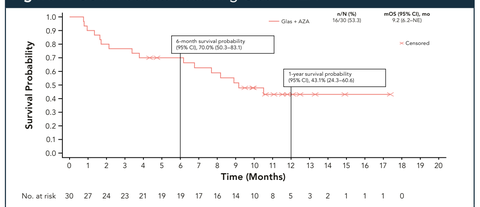
Safety

- The incidence of select treatment-emergent adverse events (TEAEs) is shown in **Table 2**.
  - TEAEs thought to be linked to the inhibition of the Hh pathway in normal tissue (muscle spasms, dysgeusia, alopecia) were <30% with glasdegib treatment.
  - The incidence of TEAEs associated with cytopenias, bleeding, and infection did not appear worse with glasdegib + LDAC or glasdegib + AZA vs LDAC alone.

Efficacy

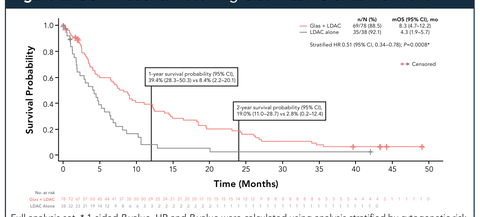
- For patients receiving glasdegib + AZA, 20% achieved CR; 3.3% achieved CRi.
- Median OS was 9.2 (95% CI, 6.2–not evaluable) months with glasdegib + AZA (**Figure 1**).
  - This preliminary estimate is based on 16/30 (53.3%) observed events with only 11.5 months' median follow-up, and therefore, the median OS could change as the OS data matures.
- For glasdegib + LDAC and LDAC alone, 19.2% and 2.6% of patients achieved CR; 5.1% and 2.6% achieved CRi.
- Median (95% CI) OS was 8.3 (4.7–12.2) months and 4.3 (1.9–5.7) months with glasdegib + LDAC and LDAC alone, respectively (**Figure 2**).
  - This estimate is based on very mature OS data, with approximately 90% OS events observed.

Figure 1: OS in Patients Receiving Glas + AZA



AZA=azacitidine; CI=confidence interval; Glas=glasdegib; mOS=median OS; NE=not evaluable; OS=overall survival

Figure 2: OS in Patients Receiving Glas + LDAC or LDAC Alone



Full analysis set. * 1-sided *P* value. HR and *P* value were calculated using analysis stratified by cytogenetic risk factor (good/intermediate vs poor).
CI=confidence interval; Glas=glasdegib; HR=hazard ratio; LDAC=low-dose cytarabine; mOS=median OS; OS=overall survival

Table 2: Cytopenias, Infections, and Hh Pathway Inhibitor Class Effects During the First 90 Days and After 90 Days

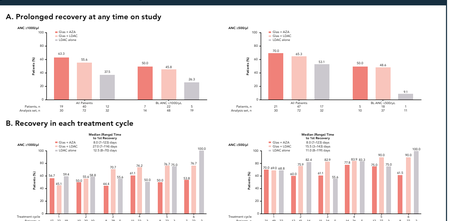
	BRIGHT 1012	BRIGHT 1003	
Select TEAEs of any Grade, n (%)	**Glas + AZA N=30**	**Glas + LDAC N=75**	**LDAC Alone N=36**
During the first 90 days			
Alopecia	1 (3.3)	3 (4.0)	0
Anemia	6 (20.0)	33 (44.0)	15 (41.7)
Diarrhea	12 (40.0)	13 (17.3)	9 (25.0)
Dysgeusia	7 (23.3)	15 (20.0)	1 (2.8)
Febrile neutropenia	7 (23.3)	23 (30.7)	8 (22.2)
Hemorrhage*	7 (23.3)	9 (12.0)	10 (27.8)
Muscle spasms	8 (26.7)	11 (14.7)	2 (5.6)
Nausea	18 (60.0)	22 (29.3)	4 (11.1)
Neutropenia	1 (3.3)	5 (6.7)	5 (13.9)
Pneumonia	1 (3.3)	14 (18.7)	9 (25.0)
Sepsis	1 (3.3)	4 (5.3)	5 (13.9)
Thrombocytopenia	1 (3.3)	23 (30.7)	9 (25.0)
Vomiting	12 (40.0)	15 (20.0)	3 (8.3)
After 90 days	N=19	N=43	N=14
Alopecia	0	4 (9.3)	0
Anemia	2 (10.5)	13 (30.2)	3 (21.4)
Diarrhea	5 (26.3)	14 (32.6)	1 (7.1)
Dysgeusia	1 (5.3)	6 (14.0)	0
Febrile neutropenia	3 (15.8)	4 (9.3)	1 (7.1)
Hemorrhage*	2 (10.5)	8 (18.6)	0
Muscle spasms	0	10 (23.3)	0
Nausea	2 (10.5)	9 (20.9)	0
Neutropenia	0	9 (20.9)	1 (7.1)
Pneumonia	0	8 (18.6)	3 (21.4)
Sepsis	1 (5.3)	1 (2.3)	1 (7.1)
Thrombocytopenia	0	10 (23.3)	2 (14.3)
Vomiting	2 (10.5)	4 (9.3)	0

The ≤90-day analysis included all treated patients. The >90-day analysis included patients who received ≥1 dose of study drug after Day 63 (Day 91 with a 28-day window for TEAEs).
* All preferred terms with hemorrhage are included.
AZA=azacitidine; Glas=glasdegib; Hh=Hedgehog; LDAC=low-dose cytarabine; TEAE=treatment-emergent adverse event

Cell Lineage Recovery

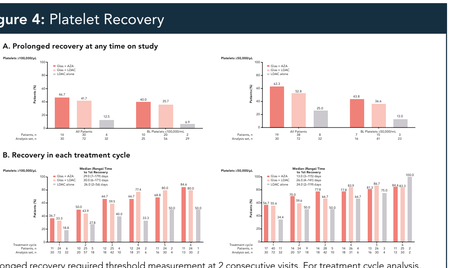
- Bone marrow recovery of ANC, hemoglobin, and platelet counts at 2 thresholds was seen following glasdegib treatment, regardless of baseline counts (**Figures 3–5**).
  - Recovery occurred as early as Cycle 1 in a meaningful proportion of patients, and generally continued to improve during subsequent cycles in the remaining patients at risk.

Figure 3: ANC Recovery



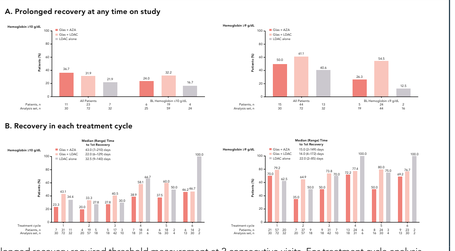
Prolonged recovery required threshold measurement at 2 consecutive visits. For treatment cycle analysis, 1 threshold measurement was required; all patients were included regardless of BL levels but each cycle only included remaining patients at risk in that cycle.
ANC=absolute neutrophil count; AZA=azacitidine; BL=baseline; Glas=glasdegib; LDAC=low-dose cytarabine

Figure 4: Platelet Recovery



Prolonged recovery required threshold measurement at 2 consecutive visits. For treatment cycle analysis, 1 threshold measurement was required; all patients were included regardless of BL levels but each cycle only included remaining patients at risk in that cycle.
AZA=azacitidine; BL=baseline; Glas=glasdegib; LDAC=low-dose cytarabine

Figure 5: Hemoglobin Recovery During Cycles 1–6

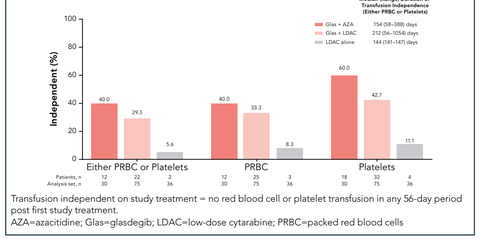


Prolonged recovery required threshold measurement at 2 consecutive visits. For treatment cycle analysis, 1 threshold measurement was required; all patients were included regardless of BL levels but each cycle only included remaining patients at risk in that cycle.
AZA=azacitidine; BL=baseline; Glas=glasdegib; LDAC=low-dose cytarabine

Transfusions

- Transfusion independence was achieved by >25% of patients receiving glasdegib (**Figure 6**).

Figure 6: Transfusion Independence During the Studies



Transfusion independent on study treatment = no red blood cell or platelet transfusion in any 56-day period post first study treatment.
AZA=azacitidine; Glas=glasdegib; LDAC=low-dose cytarabine; PRBC=packed red blood cells

Dose Delays

- Few patients (<10%) had Cycle 2 dose delays due to adverse events (AEs) in Cycle 1 (**Table 3**).

Table 3: Cycle 2 Dose Delays

	BRIGHT 1012	BRIGHT 1003	
n* (%)	**Glas + AZA N=30**	**Glas + LDAC N=75**	**LDAC Alone N=36**
Patients starting Cycle 2	23 (76.7)	60 (80.0)	24 (66.7)
No delay	21 (91.3)	56 (93.3)	21 (87.5)
With delay	2 (8.7)	4 (6.7)	3 (12.5)
Adverse event	2 (8.7)	4 (6.7)	1 (4.2)
Other	0	0	2 (8.3)

Delay = ≥1 week. * Percentage of patients starting Cycle 2 for patients with or without delays.
AZA=azacitidine; Glas=glasdegib; LDAC=low-dose cytarabine

CONCLUSIONS

- In the context of the response and survival benefit of adding glasdegib to either AZA or LDAC in the treatment of patients with newly diagnosed AML ineligible for intensive chemotherapy, glasdegib-based combinations demonstrated:
  - Similar rates of Hh pathway inhibitor–related AEs, which may or may not worsen over time but remain <30%.
  - Limited cytopenias (3–44%) in ≤90 days, reducing to 0–30% in >90 days, and low rates of pneumonia (<20%) or sepsis (<6%).
  - Recovery of ANC (>50% of patients), platelets (>40% of patients), and hemoglobin (>30% of patients), with recoveries as early as Cycle 1.
  - Packed red blood cells and platelet transfusion independence in one-third to over half of patients, even in patients with baseline cytopenias.
  - Limited Cycle 2 dose delays (<10%).
- By targeting leukemic stem cells while sparing normal hematopoiesis, glasdegib-based combinations may be effective AML agents for improving survival without substantial marrow suppression and attendant cytopenic complications.
- These data warrant further combination studies with glasdegib. Glasdegib is currently in phase 3 clinical development for newly diagnosed AML therapy in combination with AZA or 7 + 3 intensive chemotherapy (NCT03416179).

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