Expert Review: DAURISMO™ (glasdegib) for the Treatment of Adults With Newly Diagnosed Acute Myeloid Leukemia Ineligible for Intensive Chemotherapy

JORGE E. CORTES, MD

Clinical Synopsis

For many years, nonintensive acute myeloid leukemia (AML) treatment options have been limited to single-agent low-dose cytarabine (LDAC) or hypomethylating agent (HMA) therapy.[1] The emergence of targeted agents and combination approaches has the potential to improve outcomes for patients ineligible for intensive chemotherapy.[2-4]

The Hedgehog (Hh) pathway, implicated preclinically in the maintenance of leukemic stem cells (LSCs), has emerged as a promising therapeutic target in AML.[5] In November 2018, the Hh pathway inhibitor glasdegib, in combination with LDAC, received US Food and Drug Administration (FDA) approval for the treatment of newly diagnosed AML in adult patients aged ≥ 75 years or who have comorbidities that preclude the use of intensive induction chemotherapy.[4] In a randomized trial, glasdegib combined with LDAC demonstrated superior overall survival (OS) compared with LDAC alone, significantly extending median OS (8.3 versus 4.3 months; hazard ratio [HR] = 0.46 [95% confidence interval {CI}, 0.30-0.71], *P* = 0.0002).[4] Serious adverse reactions (ARs) were reported in 79% of patients who received glasdegib plus LDAC compared with 78% of patients who received LDAC alone, and dose reductions associated with ARs in the glasdegib plus LDAC arm were reported in 26% of patients.[4,6]

With the emergence of new therapies, including mutation-targeted agents,[7] the AML treatment landscape is becoming increasingly complex, placing greater importance on a detailed patient workup to guide personalized treatment decisions. Appropriate candidates for nonintensive treatment may be selected based on many criteria, such as age ≥ 75 years and specific comorbidities.[8,9] Furthermore, patient choice and personal circumstance inform treatment decisions in the nonintensive setting. Glasdegib tablets plus subcutaneous LDAC can be administered at home, thereby providing a therapeutic option for patients who do not wish to be treated in an inpatient or clinic setting.

Glasdegib in combination with LDAC is a category 2A treatment option in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for certain adults with newly diagnosed AML who are not candidates for or decline intensive induction therapy.[10]

Pfizer developed this manuscript in conjunction with Dr Cortes. The discussion of glasdegib plus LDAC administration in clinical practice, therapy management, and patient cases reflects Dr Cortes' opinion on AML management in these specific situations.

SELECTED SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY: DAURISMO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. DAURISMO is embryotoxic, fetotoxic, and teratogenic in animals. Conduct pregnancy testing in females of reproductive potential prior to initiation of DAURISMO treatment. Advise females of reproductive potential to use effective contraception during treatment with DAURISMO and for at least 30 days after the last dose. Advise males of the potential risk of DAURISMO exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with DAURISMO and for at least 30 days after the last dose to avoid potential drug exposure.

Blood Donation: Advise patients not to donate blood or blood products while taking DAURISMO and for at least 30 days after the last dose, because their blood or blood products might be given to a female of reproductive potential.

Please see additional Important Safety Information on page 11 and full Prescribing Information, including BOXED WARNING and Medication Guide, here.

EXPERT REVIEW

Part 1. Introduction

AML is most frequently diagnosed among older patients (median age 68 years).[11] Advanced age is a predictor of poor outcomes,[12] and Surveillance, Epidemiology, and End Results (SEER) data from 2009-2015 indicate that patients aged ≥ 65 years have a 5-year relative survival rate of 7.9%.[13]

It has been reported that of AML patients who receive front-line induction therapy, approximately 40% do not receive intensive chemotherapy.[14] Selecting treatments for older adults involves consideration of performance status, comorbid conditions, cytogenetic and molecular profiles,[15] and history of antecedent hematologic disorder (AHD),[16] as well as patient choice, personal circumstance, and the balance between disease control and quality of life (QoL).[12,17]

New therapies for older patients remain a significant unmet need.[12,16,18] Until recently, treatment options for patients who decline or are ineligible for intensive chemotherapy have been limited to HMAs, such as decitabine or azacitidine, or LDAC.[1] Since 2017, 8 therapeutic agents have been approved by the FDA for the treatment of AML, but only 3 are indicated for this underserved population.[2-4,19-23] DAURISMO (glasdegib) and venetoclax were approved in November 2018 and ivosidenib was approved in May 2019 for *IDH1*-mutated cases.[2-4]

Part 2. Glasdegib Mechanism of Action and Clinical Data

Mechanism of Action

Glasdegib is a Hh pathway inhibitor that is indicated, in combination with LDAC, for the treatment of newly diagnosed AML in adult patients who are ≥ 75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy.[4] The Hh signaling pathway regulates self-renewal and differentiation of cells. It is highly active during embryogenesis, during which it guides organ and tissue development. In adults, the role of Hh signaling is limited to germ cell maturation in the reproductive system.[24,25] Preclinical research has suggested that inappropriate activation of the Hh pathway is associated with a variety of cancers, including AML.[25,26]

The Hh pathway plays a role in maintaining LSC quiescence and self-renewal.[5,25-27] These key characteristics of LSCs are theorized to contribute to chemoresistance and disease relapse.[5,27-29]

Preclinical data suggest that glasdegib inhibits Smoothened, a transmembrane protein involved in Hh signal transduction, and may contribute to the chemosensitization of LSCs by blocking LSC quiescence.[5,26] In a preclinical model of human AML, glasdegib plus LDAC inhibited tumor growth and reduced the percentage of AML blasts in the bone marrow (BM) to a greater extent than glasdegib or LDAC alone.[4] These results suggest that the 2 agents work synergistically, with glasdegib sensitizing dormant LSCs to the chemotherapeutic effects of LDAC.[4,26] It is important to note that preclinical and in vitro data may not necessarily correlate with clinical outcomes.

BRIGHT AML 1003 Trial

Trial Design

The BRIGHT AML 1003 trial was an open-label, multicenter, Phase II trial that evaluated the safety and efficacy of glasdegib in combination with LDAC. The trial enrolled 115 patients aged ≥ 55 years with newly diagnosed de novo AML or secondary acute myeloid leukemia (sAML) who were not eligible for intensive chemotherapy.[4] sAML was defined in the trial as AML evolving from myelodysplastic syndrome (MDS) or another AHD and AML occurring after previous cytotoxic therapy or radiation.[6]

Patients were required to meet at least 1 of the following criteria demonstrating ineligibility for intensive chemotherapy: age ≥ 75 years, severe baseline cardiac disease (left ventricular ejection fraction [LVEF] < 45%), baseline Eastern Cooperative Oncology Group performance status (ECOG PS) of 2, or baseline serum creatinine > 1.3 mg/dL.[4,6] Patients were stratified by cytogenetic risk (good/intermediate or poor) and randomized (2:1) to receive glasdegib plus LDAC (n = 77) or LDAC alone (n = 38) until disease progression or unacceptable toxicity.[4] In each 28-day cycle, glasdegib 100 mg was administered orally once daily on days 1-28 and LDAC 20 mg was administered subcutaneously twice daily on days 1-10.[4] The primary endpoint was OS and key secondary endpoints included response assessments.[6]

SELECTED SAFETY INFORMATION

QTc Interval Prolongation: Patients treated with DAURISMO can develop QTc prolongation and ventricular arrhythmias, including ventricular fibrillation and ventricular tachycardia. Of the 98 evaluable patients treated with DAURISMO 100 mg in combination with low-dose cytarabine in the clinical trial, 5% were found to have a QTc interval greater than 500 ms and 4% of patients had an increase from baseline QTc greater than 60 ms. The clinical trial excluded patients with baseline QTc of greater than 470 ms or with a history of long QT syndrome or uncontrolled cardiovascular disease. Monitor electrocardiograms (ECGs) and electrolytes. Concomitant use of DAURISMO with drugs known to prolong the QTc interval and CYP3A4 inhibitors may increase the risk of QTc interval prolongation. In patients with congenital long QT syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent ECG monitoring is recommended. Interrupt DAURISMO if QTc interval is >500 ms and discontinue permanently for patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Adverse Reactions: Most common adverse reactions associated with DAURISMO (incidence ≥20%) were anemia (43%), fatigue (36%), hemorrhage (36%), febrile neutropenia (31%), musculoskeletal pain (30%), edema (30%), thrombocytopenia (30%), nausea (29%), dyspnea (23%), decreased appetite (21%), dysgeusia (21%), mucositis (21%), constipation (20%), and rash (20%).

Please see additional Important Safety Information on page 11 and full Prescribing Information, including BOXED WARNING and Medication Guide, here.

Baseline Patient Characteristics

The 2 treatment arms of BRIGHT AML 1003 were generally balanced with respect to baseline demographics and disease characteristics. All patients in the trial had characteristics that made them difficult to treat with intensive chemotherapy **(Table 1)**.[4,6,17]

The BRIGHT AML 1003 trial included patients with significant comorbidities, and 65% of patients met ≥ 2 criteria for nonintensive treatment at baseline.[6] In the glasdegib plus LDAC arm, 61% of patients were aged ≥ 75 years, 53% had an ECOG PS of 2, 66% had severe cardiac disease, and 19% had serum creatinine > 1.3 mg/dL.[4] In addition, approximately half of the enrolled population had sAML (51%), including patients who had received 1 prior regimen for the treatment of MDS.[4,6] In the glasdegib plus LDAC arm, 28% of patients with sAML had been treated with a prior HMA for MDS.[4]

Efficacy

Overall Survival

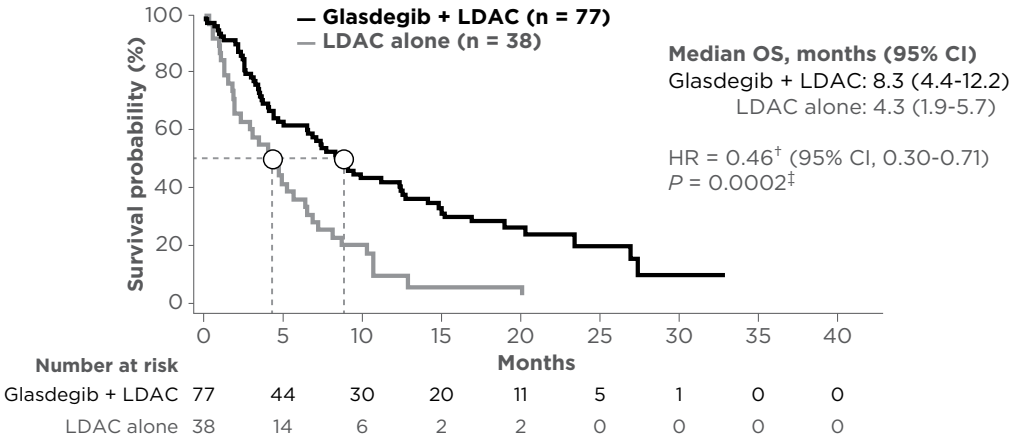
With a median follow-up of approximately 20 months, glasdegib plus LDAC significantly extended OS: median OS was 8.3 months versus 4.3 months with LDAC alone **(Figure 1)**.[4] The HR was 0.46, which represents a 54% reduction in the risk of death from any cause with the addition of glasdegib compared with LDAC alone.[4] The improvement in OS was consistent across prespecified cytogenetic subgroups.[6]

Table 1. Selected Patient Characteristics in the BRIGHT AML 1003 Trial

Baseline demographic and disease characteristics[4,6]	Glasdegib + LDAC (n = 77)	LDAC alone (n = 38)	Total (N = 115)
Criteria for nonintensive treatment, n (%)			
≥ 75 years, n (%)	47 (61)	23 (61)	70 (61)
ECOG PS 2	41 (53)	18 (47)	59 (51)
Serum creatinine > 1.3 mg/dL	15 (19)	5 (13)	20 (17)
Severe cardiac disease*	51 (66)	20 (53)	71 (62)
Number of criteria met, n (%)			
1	23 (30)	17 (45)	40 (35)
2	33 (43)	15 (40)	48 (42)
3	19 (25)	5 (13)	24 (21)
4	2 (3)	1 (3)	3 (3)

*Medical Dictionary for Regulatory Activities preferred terms for severe cardiac disease were determined by study team review of medical history. Patients may have had multiple applicable terms for severe cardiac disease (eg, LVEF < 45% by multigated acquisition scan or echocardiography at screening).

Figure 1. Overall Survival[4]



†HR based on the Cox proportional hazards model stratified by cytogenetic risk.
‡1-sided *P*-value from log-rank test stratified by cytogenetic risk.

SELECTED SAFETY INFORMATION

Drug Interactions: Co-administration with strong CYP3A4 inhibitors increased DAURISMO plasma concentrations, which may increase the risk of adverse reactions including QTc interval prolongation. Consider alternative therapies that are not strong CYP3A4 inhibitors during treatment with DAURISMO and monitor patients for increased risk of adverse reactions including QTc interval prolongation. Strong and moderate CYP3A4 inducers should be avoided due to decreased DAURISMO plasma concentrations, which may reduce efficacy. If concomitant use of moderate CYP3A4 inducers cannot be avoided, increase the DAURISMO dosage to 200 mg once daily (if the patient is taking 100 mg) and 100 mg once daily (if the patient is taking 50 mg) as tolerated. Co-administration of DAURISMO with QTc-prolonging drugs may increase the risk of QTc interval prolongation. Avoid co-administration of QTc-prolonging drugs with DAURISMO or replace with alternative therapies. If co-administration of a QTc-prolonging drug is unavoidable, monitor patients for increased risk of QTc interval prolongation.

Please see additional Important Safety Information on page 11 and full Prescribing Information, including BOXED WARNING and Medication Guide, here.

The probability of survival at 1 year was 39.9% (95% CI, 28.7-50.9) for glasdegib plus LDAC and 8.4% (95% CI, 2.2-20.1) for LDAC alone.[6] OS at 1 year was a prespecified exploratory endpoint, but there was no prespecified statistical procedure controlling for type 1 error (false positive) rate.

OS with glasdegib plus LDAC was also assessed across a range of patient subgroups, including age (≥ 75 years, < 75 years, and ≥ 65 years), baseline ECOG PS (0/1 and 2), baseline BM blast count (< 30% and ≥ 30%), European LeukemiaNet (ELN) risk group (intermediate-I, intermediate-II, and adverse) and disease history (de novo and sAML) **(Figure 3)**.[6]

sAML disease subtype and older age (≥ 75 years) are key subgroups of interest in which to assess the efficacy of glasdegib plus LDAC because they represent areas of high unmet need and comprise the majority of patients enrolled in the BRIGHT AML 1003 trial.[4,17] OS exploratory subgroup analyses were performed in patients with sAML and in patients aged ≥ 75 years, and are presented in **Part 3**.

Response Assessments

Response assessments were secondary endpoints of the BRIGHT AML 1003 trial **(Table 2)**, and most responses with glasdegib plus LDAC occurred within the first 6 months of treatment. More patients achieved complete response (CR) with glasdegib plus LDAC (18.2%) than LDAC alone (2.6%).[6] CR is the endpoint based on a patient's hematologic response that is most associated with clinical benefit in AML.

In the glasdegib plus LDAC arm, the median time to CR, complete response with incomplete blood count recovery (CRi), or morphologic leukemia-free state (MLFS) was 1.97 months (range, 1.08-7.59 months; n = 77).[6]

Best individual patient response by cycle (excluding stable disease [SD]) occurred in 12.5% of patients in cycle 1, 25.0% in cycle 2, 31.25% in cycle 3, and 31.25% in cycle 4 or later **(Figure 2)**. Twenty-eight percent (9/32) of patients treated with glasdegib plus LDAC achieved their best individual response at cycle 6 or later.[6]

These data support the glasdegib prescribing information recommendation to treat patients without unacceptable toxicity for a minimum of 6 cycles to allow time for clinical response.[4]

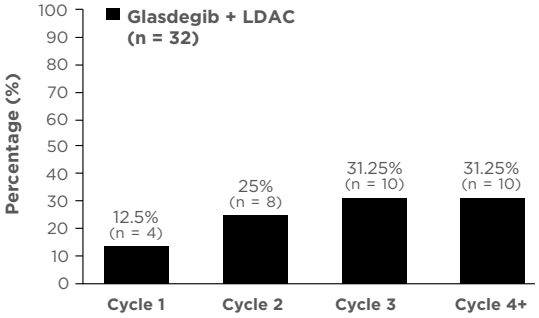
Table 2. Response Assessments[6]

These analyses were not powered to detect statistical significance. Small patient numbers and lack of multiplicity adjustments can be limitations of these analyses.

	Glasdegib + LDAC (n = 77)	LDAC alone (n = 38)
Secondary endpoints: protocol-defined response criteria		
CR, % (95% CI)	**18.2** (10.3-28.6); n = 14	**2.6** (0.1-13.8); n = 1
CRi, % (95% CI)	**6.5** (2.1-14.5); n = 5	**2.6** (0.1-13.8); n = 1
CR/CRi, % (95% CI)	**24.7** (15.6-35.8); n = 19	**5.3** (0.6-17.7); n = 2
MLFS, % (95% CI)	**2.6** (0.3-9.1); n = 2	–
PR, % (95% CI)	**6.5** (2.1-14.5); n = 5	–
Total, %	**33.8** (n = 26)	**5.3** (n = 2)

Figure 2. Time to Best Individual Patient Response by Cycle With Glasdegib + LDAC[6]*

Analyses were not prespecified and not powered to detect statistical significance. Small patient numbers and lack of multiplicity adjustments can be limitations of these analyses.



*Patient responses included CR, CRi, MLFS, partial remission (PR), partial remission with incomplete blood count recovery (PRi), and minor response (MR). SD was excluded.

SELECTED SAFETY INFORMATION

Lactation: Because of the potential for serious adverse reactions from DAURISMO in a breastfed child, advise women who are taking DAURISMO not to breastfeed or provide breast milk to infants or children during treatment and for at least 30 days after the last dose.

Renal Impairment: No dosage modification is recommended for patients with mild to severe renal impairment. Monitor patients with severe renal impairment (eGFR 15 to 29 mL/min) for increased risk of adverse reactions, including QTc interval prolongation, due to increased glasdegib concentrations.

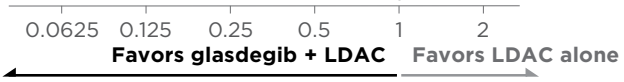
Blood Donation: Advise patients not to donate blood or blood products while taking DAURISMO and for at least 30 days after the last dose, because their blood or blood products might be given to a female of reproductive potential.

Please see additional Important Safety Information on page 11 and full Prescribing Information, including BOXED WARNING and Medication Guide, here.

Figure 3. Exploratory Overall Survival Analyses Across a Range of Patient Subgroups[6]

Subgroup analyses were not prespecified and not powered to detect statistical significance. There is a slight imbalance towards good/intermediate-risk cytogenetics in the glasdegib plus LDAC arm versus the LDAC arm. The HRs associated with each of these analyses are unreliable due to the very small sample sizes of each subgroup, and the CIs may not be interpretable. Therefore, these data could represent chance findings and should be interpreted with caution.

Subgroup	Number of events/ number of patients (n)		HR and 95% CI (log scale)
	Glasdegib + LDAC	LDAC alone	HR (95% CI)
AML population	58/77	35/38	0.459 (0.296-0.713)
Cytogenetic risk			
Good/intermediate cytogenetic risk	34/48	19/21	0.411 (0.229-0.736)
Poor cytogenetic risk	24/29	16/17	0.528 (0.273-1.022)
Age			
≥ 75 years	37/47	22/23	0.546 (0.319-0.936)
< 75 years	21/30	13/15	0.323 (0.150-0.694)
≥ 65 years	57/76	34/37	0.448 (0.289-0.696)
Gender			
Male	46/59	22/23	0.421 (0.247-0.717)
Female	12/18	13/15	0.475 (0.211-1.066)
Race			
White	56/75	35/38	0.450 (0.291-0.696)
Region			
North America	23/27	7/7	0.411 (0.162-1.043)
Europe	35/50	28/31	0.417 (0.250-0.696)
Baseline ECOG			
0 or 1	28/35	20/20	0.584 (0.323-1.056)
2	29/41	15/18	0.314 (0.163-0.607)
Baseline white blood cell count			
< 10	42/58	26/29	0.413 (0.249-0.685)
≥ 10	15/18	9/9	0.547 (0.220-1.362)
Baseline bone marrow blast count			
< 30%	12/17	10/10	0.138 (0.044-0.432)
≥ 30%	45/59	24/27	0.528 (0.318-0.876)
ELN risk groups			
Intermediate-I	20/27	10/11	0.335 (0.151-0.746)
Intermediate-II	14/20	6/8	0.896 (0.337-2.381)
Adverse	22/25	16/16	0.514 (0.264-1.000)
Disease history			
De novo	30/38	16/18	0.670 (0.362-1.239)
Secondary AML	28/39	19/20	0.288 (0.150-0.553)



The sample sizes for the subgroups of baseline age < 65 years, race other than white, and the prognostic risk factor as favorable were too small (n ≤ 10) for analysis.

The HR values presented were based on the unstratified analysis for all subgroups except for the AML population. Prognostic risk factor (good/intermediate versus poor) from interactive voice response system was used as a stratification factor in the stratified analysis for the AML population.

SELECTED SAFETY INFORMATION

QTc Interval Prolongation: Patients treated with DAURISMO can develop QTc prolongation and ventricular arrhythmias, including ventricular fibrillation and ventricular tachycardia. Of the 98 evaluable patients treated with DAURISMO 100 mg in combination with low-dose cytarabine in the clinical trial, 5% were found to have a QTc interval greater than 500 ms and 4% of patients had an increase from baseline QTc greater than 60 ms. The clinical trial excluded patients with baseline QTc of greater than 470 ms or with a history of long QT syndrome or uncontrolled cardiovascular disease. Monitor electrocardiograms (ECGs) and electrolytes. Concomitant use of DAURISMO with drugs known to prolong the QTc interval and CYP3A4 inhibitors may increase the risk of QTc interval prolongation. In patients with congenital long QT syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent ECG monitoring is recommended. Interrupt DAURISMO if QTc interval is >500 ms and discontinue permanently for patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Please see additional Important Safety Information on page 11 and full Prescribing Information, including BOXED WARNING and Medication Guide, here.

OS in Patients Who Did and Did Not Achieve CR

To evaluate the efficacy of glasdegib plus LDAC by disease response, an exploratory post hoc analysis of OS in patients who did or did not achieve CR was conducted. In the 14 patients who achieved a CR, median OS with glasdegib plus LDAC was 26.8 months (95% CI, 12.3-not reached). In the 63 patients who did not achieve a CR, median OS with glasdegib plus LDAC was 5.0 months (95% CI, 3.5-9.0).[6] Analyses of OS in CR-defined subgroups were not prespecified and not powered to detect statistical significance. Small patient numbers and lack of multiplicity adjustments can be limitations of these analyses. Response status is not a baseline characteristic and, therefore, not subject to randomization or stratification. These data are subject to length-biased sampling, which may lead to an overestimation of median survival.

Post hoc Analyses of Transfusion Independence

In addition to achieving CR or CRi, transfusion independence is clinically important for patients with AML who are not candidates for intensive chemotherapy. Transfusion independence was evaluated in all patients who received ≥ 1 study drug dose (N = 110) and was defined as at least 8 weeks without any type of packed red blood cell (PRBC) or platelet transfusion at any point in the study. Transfusion independence was not assessed at baseline. A post hoc analysis of the BRIGHT AML 1003 trial evaluated transfusion rates in the 2 treatment arms: 29.7% (n = 22/74) of patients in the glasdegib plus LDAC arm achieved transfusion independence versus 5.6% (n = 2/36) of patients in the LDAC alone arm. The exposure-adjusted rates of any transfusion were 0.0786 for glasdegib plus LDAC and 0.1555 for LDAC alone **(Figure 4)**.[6,30] Given the post hoc nature of this analysis and small patient numbers, the results should be interpreted with caution.

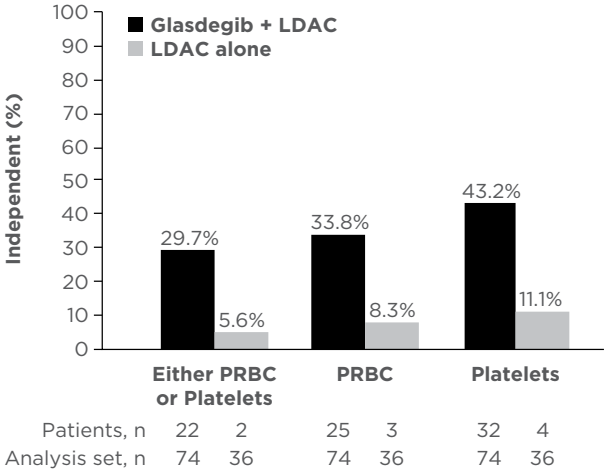
Safety Profile: Managing Therapeutic Benefits Versus Risks

ARs that occurred in ≥ 10% of patients within the first 90 days of treatment in the BRIGHT AML 1003 trial are listed in **Table 3**. Serious ARs as well as ARs leading to discontinuation or dose reduction were reported in patients who received glasdegib plus LDAC.[4] Serious ARs were reported in 79% of patients treated in the glasdegib plus LDAC arm and 78% of patients treated in the LDAC alone arm.[4,6] The most common (≥ 5%) serious ARs in patients receiving glasdegib plus LDAC compared with LDAC alone, respectively, were febrile neutropenia (29% versus 17%), pneumonia (23% versus 17%), hemorrhage (12% versus 7%), anemia (7% versus 0%), and sepsis (7% versus 15%).[4,6] In the glasdegib plus LDAC arm, 36% of patients discontinued treatment due to ARs.[4]

Figure 4. Post hoc Analyses of Transfusion Independence[6,30]

Analyses were post hoc and not powered to detect statistical significance. Small patient numbers and lack of multiplicity adjustments can be limitations of these analyses.

A **Transfusion-independent patients***



B **Exposure-adjusted transfusion rates***

	Glasdegib + LDAC (n = 74)	LDAC alone (n = 36)
Any transfusion	0.0786	0.1555
PRBC transfusion	0.0478	0.0789
Platelet transfusion	0.0308	0.0766

A) Transfusion independence was defined as patients who had ≥ 8 weeks (56 consecutive days) without any type of transfusion at any point in the study. All other patients were considered transfusion dependent. **B)** Exposure-adjusted transfusion rates were calculated as the sum of the number of on-study transfusions/total number of patient-days. Number of on-study transfusions includes transfusions from cycle 1, day 1 to the end of treatment. Total number of patient-days was the sum of the total time on treatment for all patients in each treatment arm.

*This post hoc analysis included all patients who received ≥ 1 study drug dose (N = 110).

SELECTED SAFETY INFORMATION

Adverse Reactions: Most common adverse reactions associated with DAURISMO (incidence ≥20%) were anemia (43%), fatigue (36%), hemorrhage (36%), febrile neutropenia (31%), musculoskeletal pain (30%), edema (30%), thrombocytopenia (30%), nausea (29%), dyspnea (23%), decreased appetite (21%), dysgeusia (21%), mucositis (21%), constipation (20%), and rash (20%).

Drug Interactions: Co-administration with strong CYP3A4 inhibitors increased DAURISMO plasma concentrations, which may increase the risk of adverse reactions including QTc interval prolongation. Consider alternative therapies that are not strong CYP3A4 inhibitors during treatment with DAURISMO and monitor patients for increased risk of adverse reactions including QTc interval prolongation. Strong and moderate CYP3A4 inducers should be avoided due to decreased DAURISMO plasma concentrations, which may reduce efficacy.

Please see additional Important Safety Information on page 11 and full Prescribing Information, including BOXED WARNING and Medication Guide, here.

Table 3. Adverse Reactions Occurring in ≥ 10% of Patients* Within the First 90 Days of Therapy[4]

Body system	Adverse reactions	Glasdegib + LDAC (n = 84)		LDAC alone (n = 41)	
		All grades, %	Grade ≥ 3, %	All grades, %	Grade ≥ 3, %
Blood and lymphatic system disorder	Anemia	43	41	42	37
	Hemorrhage	36	6	42	12
	Febrile neutropenia	31	31	22	22
	Thrombocytopenia	30	30	27	24
General disorders and administration site conditions	Fatigue	36	14	32	7
	Edema	30	0	20	2
	Mucositis	21	1	12	0
	Pyrexia	18	1	22	2
	Chest pain	12	1	2	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	30	2	17	2
	Muscle spasm	15	0	5	0
Gastrointestinal disorders	Nausea	29	1	12	2
	Constipation	20	1	12	0
	Abdominal pain	19	0	12	0
	Diarrhea	18	4	22	0
	Vomiting	18	2	10	2
Respiratory thoracic and mediastinal disorders	Dyspnea	23	11	24	7
	Cough	18	0	15	2
Metabolism and nutrition disorders	Decreased appetite	21	1	7	2
Nervous system disorders	Dysgeusia	21	0	2	0
	Dizziness	18	1	7	0
	Headache	12	0	10	2
Skin and subcutaneous tissue disorders	Rash	20	2	7	2
Infections and infestations	Pneumonia	19	15	24	22
Investigations	Hyponatremia	11	6	0	0
	Platelet count decreased	15	15	10	10
	Weight decreased	13	0	2	0
	White blood cell count decreased	11	11	5	2
Cardiac disorders	Atrial arrhythmia	13	4	7	2
Renal and urinary disorders	Renal insufficiency	19	5	10	0

*ARs with ≥ 10% incidence in the glasdegib plus LDAC arm or the LDAC arm are included. ARs included events that commenced within 28 days after the last treatment dose. ARs were graded according to NCI CTCAE version 4.0.
NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

SELECTED SAFETY INFORMATION

Drug Interactions (cont.): If concomitant use of moderate CYP3A4 inducers cannot be avoided, increase the DAURISMO dosage to 200 mg once daily (if the patient is taking 100 mg) and 100 mg once daily (if the patient is taking 50 mg) as tolerated. Co-administration of DAURISMO with QTc-prolonging drugs may increase the risk of QTc interval prolongation. Avoid co-administration of QTc-prolonging drugs with DAURISMO or replace with alternative therapies. If co-administration of a QTc-prolonging drug is unavoidable, monitor patients for increased risk of QTc interval prolongation.

Lactation: Because of the potential for serious adverse reactions from DAURISMO in a breastfed child, advise women who are taking DAURISMO not to breastfeed or provide breast milk to infants or children during treatment and for at least 30 days after the last dose.

Renal Impairment: No dosage modification is recommended for patients with mild to severe renal impairment. Monitor patients with severe renal impairment (eGFR 15 to 29 mL/min) for increased risk of adverse reactions, including QTc interval prolongation, due to increased glasdegib concentrations.

Please see additional Important Safety Information on page 11 and full Prescribing Information, including BOXED WARNING and Medication Guide, here.

The most frequent (≥ 2%) ARs that led to permanent discontinuation were pneumonia (6%), febrile neutropenia (4%), sepsis (4%), sudden death (2%), myocardial infarction (2%), nausea (2%), and renal insufficiency (2%).[4] Dose reductions due to ARs occurred in 26% of patients in the glasdegib plus LDAC arm, most commonly (≥ 2%) because of muscle spasms (5%), fatigue (4%), febrile neutropenia (4%), anemia (2%), thrombocytopenia (2%), and electrocardiogram (ECG) QT prolongation (2%).[4] The median duration of treatment was longer in the glasdegib plus LDAC arm at 2.73 months (range, 0.10-31.93 months; N = 84) compared with 1.54 months (range, 0.20-7.85 months; N = 41) in the LDAC alone arm.[4]

Therapy Management

In my institution, we educate patients on the expected and possible toxicities associated with glasdegib plus LDAC therapy, and instruct them on what to do in case of fever or other adverse events. My patients are scheduled to return to the clinic at least once weekly for blood tests and transfusions as required, so I can closely monitor and manage any ARs that emerge during treatment. In case of dysgeusia requiring management, I typically employ dose reduction as the first step. For muscle spasms, I recommend gentle exercise; in some instances tonic water or over-the-counter muscle cramp medicine may help. Calcium and/or potassium supplements may also help some patients with cramps, when appropriate. In the absence of unacceptable toxicity, I treat patients for a minimum of 6 cycles. During the course of therapy, I continually evaluate the risks and benefits of continuing treatment with glasdegib plus LDAC by monitoring disease response, tolerability, QoL, and transfusion requirements, as well as the patient's individual circumstances and treatment goals.

Part 3. Patient Cases (Adapted for Discussion Purposes)

Case 1. Newly Diagnosed De Novo AML

A 78-year-old man initially presented with persistent low-grade fever and a feeling of weakness. He had an ECOG PS of 2 and had been on and off antibiotics over the past few months due to several infections, including pneumonia. Degenerative joint disease caused him to have some limited mobility. The patient also had serious cardiac complications, including heart failure with reduced ejection fraction (< 40%), coronary artery disease, and a myocardial infarction that occurred 3 years previously.

His laboratory results showed a white blood cell (WBC) count of 2.3 × 10^9/L, an absolute neutrophil count (ANC) of 0.9 × 10^9/L, a hemoglobin of 9 g/dL, a hematocrit of 27%, a platelet count of 45,000 × 10^7/L, and a creatinine level of 2.2 mg/dL, which was indicative of renal impairment. Following a detailed workup, he was diagnosed with intermediate-risk AML (BM myeloblast count 26%; t(9;11) (p21.3;q23.3) and wild-type *NPM1* without *FLT3-ITD*). The patient expressed a preference for treatment at home because he lived far from the treatment center and had difficulty traveling.

Administration of Glasdegib Plus LDAC in Clinical Practice

The recommended dosage of glasdegib is 100 mg orally once daily on days 1-28 in combination with LDAC 20 mg subcutaneously twice daily on days 1-10 of each 28-day cycle in the absence of unacceptable toxicity or loss of disease control.[4] LDAC can either be administered at home by the patient or with the help of a caregiver, or can be administered in an inpatient/outpatient setting by a nurse.

Preparation of LDAC for use in clinical practice requires aseptic compounding of cytarabine into syringes, either by a hospital pharmacy, specialty pharmacy provider, or other compounding pharmacy. Once prepared, LDAC syringes are given to the patient directly (if hospital prepared) or are shipped either to the hospital or directly to the patient. The stability of LDAC varies according to the conditions in which it is stored, and syringes are generally labeled with a beyond use date. LDAC is typically supplied in 1 shipment of 20 syringes or 2 shipments of 10 syringes each.

In my experience, I expect that most of my patients can perform self-injection at home. A nurse provides LDAC subcutaneous injection training to the patient and/or caregiver. The nurse educates the patient on how to store LDAC, how to dispose of needles after injection, how to handle spills, what to do if any issues arise after injection, and when to call the doctor for help. The nurse also assists in the administration of the first dose in the clinic, and then the patient and/or caregiver can administer the remaining doses at home.

SELECTED SAFETY INFORMATION

Blood Donation: Advise patients not to donate blood or blood products while taking DAURISMO and for at least 30 days after the last dose, because their blood or blood products might be given to a female of reproductive potential.

QTc Interval Prolongation: Patients treated with DAURISMO can develop QTc prolongation and ventricular arrhythmias, including ventricular fibrillation and ventricular tachycardia. Of the 98 evaluable patients treated with DAURISMO 100 mg in combination with low-dose cytarabine in the clinical trial, 5% were found to have a QTc interval greater than 500 ms and 4% of patients had an increase from baseline QTc greater than 60 ms. The clinical trial excluded patients with baseline QTc of greater than 470 ms or with a history of long QT syndrome or uncontrolled cardiovascular disease. Monitor electrocardiograms (ECGs) and electrolytes. Concomitant use of DAURISMO with drugs known to prolong the QTc interval and CYP3A4 inhibitors may increase the risk of QTc interval prolongation. In patients with congenital long QT syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent ECG monitoring is recommended. Interrupt DAURISMO if QTc interval is >500 ms and discontinue permanently for patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Please see additional Important Safety Information on page 11 and full Prescribing Information, including BOXED WARNING and Medication Guide, here.

Is this patient a candidate for intensive chemotherapy?

Would glasdegib plus LDAC play a role in the management of this patient?

Because of this patient's cardiac comorbidities and poor general health, I do not think he would be a candidate for intensive chemotherapy or therapies associated with significant myelosuppression. I would consider alternative nonintensive treatment options.

Based on clinical data from the pivotal BRIGHT AML 1003 trial, glasdegib plus LDAC would be an appropriate treatment option for this patient. In the glasdegib plus LDAC arm of the trial, 61% of patients were aged ≥ 75 years, 53% of patients had an ECOG PS of 2, 62% of patients were intermediate risk, and 19% of patients had serum creatinine > 1.3 mg/dL.[4] Data from post hoc analyses of OS are available for subsets of patients, including those with each of these characteristics, in the BRIGHT AML 1003 trial **(Figure 3)**.[6] In the overall study population, median OS was 8.3 months with glasdegib plus LDAC versus 4.3 months with LDAC alone.[4] Median OS investigated in a post hoc analysis of patients aged ≥ 75 years was 8.8 months with glasdegib plus LDAC versus 4.9 months with LDAC alone. Small number of patients and lack of multiplicity adjustments may be limitations of these analyses **(Table 4)**.[4,6]

It is also important to consider this patient's ability to tolerate prolonged cytopenia as well as the impact of treatment on the need for transfusions. Achieving transfusion independence is an important clinical consideration for patients with AML who are ineligible for intensive chemotherapy because fewer transfusions may result in reduced need for clinic visits. In a post hoc analysis of the BRIGHT AML 1003 trial, the rate of transfusion independence was 29.7% in the glasdegib plus LDAC arm versus 5.6% in the LDAC alone arm **(Figure 4)**.[6,30] Given the post hoc nature and small patient numbers, these data may not be reliable.

Additionally, unlike HMAs, the glasdegib plus LDAC regimen offers the potential for treatment at home in line with the patient's wishes.

Table 4. Exploratory Overall Survival Subgroup Analyses[4,6]

Analyses of OS in the subgroup of patients with sAML and in age-defined subgroups were post hoc and not powered to detect statistical significance. Small patient numbers and a lack of multiplicity adjustments can be limitations of these analyses. HRs and CIs are provided for transparency. The HRs associated with these analyses are unreliable due to the very small sample size. The estimated median OS results in these exploratory subgroups may be biased due to censoring at the time of the analysis.

	Glasdegib + LDAC	LDAC alone
OS in patients with sAML*		
n/N (%)	39/77 (51%)	20/38 (49%)
Median (95% CI)	9.1 months (4.4-16.5)	4.1 months (1.5-6.4)
HR (95% CI)†	0.288 (0.150-0.553)	
OS in patients ≥ 75 years‡		
n/N (%)	47/77 (61%)	23/38 (61%)
Median (range)	8.8 months (4.4-11.1)	4.9 months (1.9-7.2)
HR (95% CI)†	0.546 (0.319-0.936)	

*sAML was defined in the trial as AML evolving from MDS or another AHD, and AML occurring after previous cytotoxic therapy or radiation.

†HR was based on the Cox proportional hazards model.

‡All patients in the BRIGHT AML 1003 trial were aged ≥ 55 years. Patients were eligible for the trial if they met at least 1 of the following criteria, which precluded the use of intensive chemotherapy: (a) aged ≥ 75 years; (b) severe cardiac disease (LVEF < 45%); (c) ECOG PS = 2; or (d) serum creatinine > 1.3 mg/dL.

SELECTED SAFETY INFORMATION

Adverse Reactions: Most common adverse reactions associated with DAURISMO (incidence ≥20%) were anemia (43%), fatigue (36%), hemorrhage (36%), febrile neutropenia (31%), musculoskeletal pain (30%), edema (30%), thrombocytopenia (30%), nausea (29%), dyspnea (23%), decreased appetite (21%), dysgeusia (21%), mucositis (21%), constipation (20%), and rash (20%).

Drug Interactions: Co-administration with strong CYP3A4 inhibitors increased DAURISMO plasma concentrations, which may increase the risk of adverse reactions including QTc interval prolongation. Consider alternative therapies that are not strong CYP3A4 inhibitors during treatment with DAURISMO and monitor patients for increased risk of adverse reactions including QTc interval prolongation. Strong and moderate CYP3A4 inducers should be avoided due to decreased DAURISMO plasma concentrations, which may reduce efficacy. If concomitant use of moderate CYP3A4 inducers cannot be avoided, increase the DAURISMO dosage to 200 mg once daily (if the patient is taking 100 mg) and 100 mg once daily (if the patient is taking 50 mg) as tolerated. Co-administration of DAURISMO with QTc-prolonging drugs may increase the risk of QTc interval prolongation. Avoid co-administration of QTc-prolonging drugs with DAURISMO or replace with alternative therapies. If co-administration of a QTc-prolonging drug is unavoidable, monitor patients for increased risk of QTc interval prolongation.

Please see additional Important Safety Information on page 11 and full Prescribing Information, including BOXED WARNING and Medication Guide, here.

Case 2. Newly Diagnosed sAML

An 80-year-old woman was diagnosed with MDS 1 year ago. She received local treatment with azacitidine for 6 cycles and experienced a CR. However, after 6 additional cycles, her disease progressed to sAML and she was referred for further evaluation and treatment.

She presented with flu-like symptoms, including fever, fatigue, and headache, as well as easy bruising. She had an ECOG PS of 2. Her medical history included severe chronic obstructive pulmonary disease and moderate renal impairment.

A complete blood count showed anemia, thrombocytopenia, and mild leukopenia (hemoglobin 9.4 g/dL, hematocrit 29%, platelet count 42,000 × 10^7/L, WBC count 3.5 × 10^9/L). Her BM blast count was 25%. Her cytogenetic and molecular profile revealed a normal cytogenetic karyotype and wild-type *NPM1* without *FLT3* or *IDH* mutations, indicating intermediate-risk disease. Her serum creatinine was 1.4 mg/dL, indicating moderate renal impairment. During her initial assessment and after a detailed discussion about her prognosis and treatment options, the patient mentioned that she would like to spend as much time as possible with her family and therefore would prefer to be treated in an outpatient setting.

What is the role of glasdegib plus LDAC in the management of sAML?

Given this patient's age, medical history, and preferences, I would look for a nonintensive treatment option that could reduce the amount of time spent at the treatment center and potentially help her live longer. Potential toxicities with more intensive regimens, including the risk of prolonged myelosuppression and tumor lysis syndrome, are also important considerations for this patient with moderate renal impairment. I would also try to minimize the need for transfusions and reduce the risk of infections. Because this patient was previously treated with azacitidine for MDS, I would select an alternate therapy to treat her sAML. An LDAC-based regimen, rather than an HMA-based regimen, would be my preferred approach. The glasdegib plus LDAC regimen also offers the potential for treatment in an outpatient setting, which is consistent with this patient's preference.

Based on clinical data from the BRIGHT AML 1003 trial, glasdegib plus LDAC would be an appropriate treatment option. Patients who had similar characteristics were enrolled in the study. In the glasdegib plus LDAC arm of BRIGHT AML 1003, 61% of patients were aged ≥ 75 years, 53% of patients had an ECOG PS of 2, 62% of patients had good/intermediate-risk disease, 51% of patients had sAML, and 28% of patients with sAML had received prior HMA treatment for MDS.[4] In addition to the primary OS analysis, OS was investigated in a post hoc analysis of patients with sAML. For these patients, the median OS was 9.1 months with glasdegib plus LDAC versus 4.1 months with LDAC alone **(Table 4)**.[4,6]

Conclusions

Until recently, treatment options for patients who decline or are ineligible for intensive chemotherapy have been limited to HMAs or LDAC.[1] The emergence of targeted agents and combination approaches has the potential to improve outcomes for these patients.[2-4]

The Hh pathway inhibitor glasdegib, in combination with LDAC, is an FDA-approved therapy for the treatment of newly diagnosed AML in adult patients aged ≥ 75 years or who have comorbidities that preclude the use of intensive induction chemotherapy.[4] In a randomized trial, glasdegib combined with LDAC demonstrated superior OS compared with LDAC alone, significantly extending median OS (8.3 versus 4.3 months; HR = 0.46 [95% CI, 0.30-0.71], *P* = 0.0002).[4] Serious ARs were reported in 79% of patients who received glasdegib plus LDAC compared with 78% of patients who received LDAC alone, and dose reductions associated with ARs in the glasdegib plus LDAC arm were reported in 26% of patients.[4,6] Glasdegib plus LDAC can be administered at home, thereby providing a therapeutic option for patients who do not wish to be treated in an inpatient or clinic setting.

SELECTED SAFETY INFORMATION

Lactation: Because of the potential for serious adverse reactions from DAURISMO in a breastfed child, advise women who are taking DAURISMO not to breastfeed or provide breast milk to infants or children during treatment and for at least 30 days after the last dose.
Renal Impairment: No dosage modification is recommended for patients with mild to severe renal impairment. Monitor patients with severe renal impairment (eGFR 15 to 29 mL/min) for increased risk of adverse reactions, including QTc interval prolongation, due to increased glasdegib concentrations.
Blood Donation: Advise patients not to donate blood or blood products while taking DAURISMO and for at least 30 days after the last dose, because their blood or blood products might be given to a female of reproductive potential.

Please see additional Important Safety Information on page 11 and full Prescribing Information, including BOXED WARNING and Medication Guide, here.

IMPORTANT SAFETY INFORMATION AND INDICATION

WARNING: EMBRYO-FETAL TOXICITY: DAURISMO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. DAURISMO is embryotoxic, fetotoxic, and teratogenic in animals. Conduct pregnancy testing in females of reproductive potential prior to initiation of DAURISMO treatment. Advise females of reproductive potential to use effective contraception during treatment with DAURISMO and for at least 30 days after the last dose. Advise males of the potential risk of DAURISMO exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with DAURISMO and for at least 30 days after the last dose to avoid potential drug exposure.

Blood Donation: Advise patients not to donate blood or blood products while taking DAURISMO and for at least 30 days after the last dose, because their blood or blood products might be given to a female of reproductive potential.

QTc Interval Prolongation: Patients treated with DAURISMO can develop QTc prolongation and ventricular arrhythmias, including ventricular fibrillation and ventricular tachycardia. Of the 98 evaluable patients treated with DAURISMO 100 mg in combination with low-dose cytarabine in the clinical trial, 5% were found to have a QTc interval greater than 500 ms and 4% of patients had an increase from baseline QTc greater than 60 ms. The clinical trial excluded patients with baseline QTc of greater than 470 ms or with a history of long QT syndrome or uncontrolled cardiovascular disease. Monitor electrocardiograms (ECGs) and electrolytes. Concomitant use of DAURISMO with drugs known to prolong the QTc interval and CYP3A4 inhibitors may increase the risk of QTc interval prolongation. In patients with congenital long QT syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent ECG monitoring is recommended. Interrupt DAURISMO if QTc interval is >500 ms and discontinue permanently for patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Adverse Reactions: Most common adverse reactions associated with DAURISMO (incidence ≥20%) were anemia (43%), fatigue (36%), hemorrhage (36%), febrile neutropenia (31%), musculoskeletal pain (30%), edema (30%), thrombocytopenia (30%), nausea (29%), dyspnea (23%), decreased appetite (21%), dysgeusia (21%), mucositis (21%), constipation (20%), and rash (20%).

Drug Interactions: Co-administration with strong CYP3A4 inhibitors increased DAURISMO plasma concentrations, which may increase the risk of adverse reactions including QTc interval prolongation. Consider alternative therapies that are not strong CYP3A4 inhibitors during treatment with DAURISMO and monitor patients for increased risk of adverse reactions including QTc interval prolongation. Strong and moderate CYP3A4 inducers should be avoided due to decreased DAURISMO plasma concentrations, which may reduce efficacy. If concomitant use of moderate CYP3A4 inducers cannot be avoided, increase the DAURISMO dosage to 200 mg once daily (if the patient is taking 100 mg) and 100 mg once daily (if the patient is taking 50 mg) as tolerated. Co-administration of DAURISMO with QTc-prolonging drugs may increase the risk of QTc interval prolongation. Avoid co-administration of QTc-prolonging drugs with DAURISMO or replace with alternative therapies. If co-administration of a QTc-prolonging drug is unavoidable, monitor patients for increased risk of QTc interval prolongation.

Lactation: Because of the potential for serious adverse reactions from DAURISMO in a breastfed child, advise women who are taking DAURISMO not to breastfeed or provide breast milk to infants or children during treatment and for at least 30 days after the last dose.

Renal Impairment: No dosage modification is recommended for patients with mild to severe renal impairment. Monitor patients with severe renal impairment (eGFR 15 to 29 mL/min) for increased risk of adverse reactions, including QTc interval prolongation, due to increased glasdegib concentrations.

Indication: DAURISMO is a hedgehog pathway inhibitor indicated, in combination with low-dose cytarabine, for the treatment of newly diagnosed acute myeloid leukemia (AML) in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.

References

1. Stone A, Zukerman T, Flaishon L, Yakar RB, Rowe JM. Efficacy outcomes in the treatment of older or medically unfit patients with acute myeloid leukaemia: a systematic review and meta-analysis. *Leuk Res*. 2019;82:36-42.
2. AbbVie receives US FDA accelerated approval for VENCLEXTA® (venetoclax) for treatment of newly-diagnosed acute myeloid leukemia patients ineligible for intensive chemotherapy [press release]. North Chicago, IL: AbbVie Inc.; November 21, 2018. https://news.abbvie.com/news/abbvie-receives-us-fda-accelerated-approval-for-venclexta-venetoclax-for-treatment-newly-diagnosed-acute-myeloid-leukemia-patients-ineligible-for-intensive-chemotherapy.htm. Accessed January 31, 2020.
3. Tibsovo [prescribing information]. Cambridge, MA: Agios Pharmaceuticals; 2019.
4. DAURISMO [prescribing information]. New York, NY: Pfizer Inc.; 2020.
5. Irvine DA, Copland M. Targeting hedgehog in hematologic malignancy. *Blood*. 2012;119(10):2196-2204.
6. Data on file, Pfizer Inc., New York, NY.
7. Lai C, Doucette K, Norsworthy K. Recent drug approvals for acute myeloid leukemia. *J Hematol Oncol*. 2019;12(1):100. doi:10.1186/s13045-019-0774-x.
8. Erba HP. Finding the optimal combination therapy for the treatment of newly diagnosed AML in older patients unfit for intensive therapy. *Leuk Res*. 2015;39(2):183-191.
9. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.
10. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V3.2020. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed January 29, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
11. Surveillance, Epidemiology, and End Results Program, National Cancer Institute. Cancer stat facts: leukemia – acute myeloid leukemia (AML). https://seer.cancer.gov/statfacts/html/amyl.html. Accessed January 31, 2020.
12. Ossenkoppele G, Löwenberg B. How I treat the older patient with acute myeloid leukemia. *Blood*. 2015;125(5):767-774.
13. Howlader N, Noone AM, Krapcho M, et al. SEER cancer statistics review (CSR) 1975-2016. https://seer.cancer.gov/csr/1975_2016/. Accessed January 31, 2020.
14. Medeiros BC, Pandya BJ, Hadfield A, et al. Treatment patterns in patients with acute myeloid leukemia in the United States: a cross-sectional, real-world survey. *Curr Med Res Opin*. 2019;35(5):927-935. doi:10.1080/03007995.2019.1578152.
15. Medeiros BC, Satram-Hoang S, Hurst D, Hoang KQ, Momin F, Reyes C. Big data analysis of treatment patterns and outcomes among elderly acute myeloid leukemia patients in the United States. *Ann Hematol*. 2015;94(7):1127-1138.
16. Boddu PC, Kantarjian HM, Ravandi F, et al. Characteristics and outcomes of older patients with secondary acute myeloid leukemia according to treatment approach. *Cancer*. 2017;123(16):3050-3060.
17. Klepin HD, Estey E, Kadia T. More versus less therapy for older adults with acute myeloid leukemia: new perspectives on an old debate. *Am Soc Clin Oncol Educ Book*. 2019;39:421-432.
18. Kumar CC. Genetic abnormalities and challenges in the treatment of acute myeloid leukemia. *Genes Cancer*. 2011;2(2):95-107.
19. Pfizer receives FDA approval for Mylotarg™ (gemtuzumab ozogamicin) [press release]. New York, NY: Pfizer Inc.; September 1, 2017. https://www.pfizer.com/news/press-release/press-release-detail/pfizer_receives_fda_approval_for_mylotarg_gemtuzumab_ozogamicin. Accessed January 31, 2020.
20. Vyxeos [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2019.
21. Rydapt [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp.; 2018.
22. Idhifa [prescribing information]. Summit, NJ: Celgene Corp.; 2017.
23. Xospata [prescribing information]. Northbrook, IL: Astellas Pharma US, Inc.; 2018.
24. Varjosalo M, Taipale J. Hedgehog: functions and mechanisms. *Genes Dev*. 2008;22(18):2454-2472.
25. Amakye D, Jagani Z, Dorsch M. Unraveling the therapeutic potential of the Hedgehog pathway in cancer. *Nat Med*. 2013;19(11):1410-1422.
26. Fukushima N, Minami Y, Kakiuchi S, et al. Small-molecule Hedgehog inhibitor attenuates the leukemia-initiation potential of acute myeloid leukemia cells. *Cancer Sci*. 2016;107(10):1422-1429.
27. Aberger F, Hutterer E, Sternberg C, Del Burgo PJ, Hartmann TN. Acute myeloid leukemia – strategies and challenges for targeting oncogenic Hedgehog/GLI signaling. *Cell Commun Signal*. 2017;15(1):8. doi:10.1186/s12964-017-0163-4.
28. Tabe Y, Konopleva M. Role of microenvironment in resistance to therapy in AML. *Curr Hematol Malig Rep*. 2015;10(2):96-103.
29. Thomas D, Majeti R. Biology and relevance of human acute myeloid leukemia stem cells. *Blood*. 2017;129(12):1577-1585.
30. Wang ES, Heuser M, Montesinos P, et al. Glasdegib with LDAC in newly diagnosed patients with acute myeloid leukemia (AML) unsuitable for intensive chemotherapy: effects on transfusions and marrow recovery vs LDAC alone. Poster PF272 presented at: European Hematology Association 24th Congress; June 13-16, 2019; Amsterdam, the Netherlands.

Please see additional Important Safety Information for DAURISMO (glasdegib) on page 11 and full Prescribing Information, including BOXED WARNING and Medication Guide, here.