CCR Drug Updates

Clinical Cancer Research

FDA Approval Summary: Glasdegib for Newly Diagnosed Acute Myeloid Leukemia

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Abstract

On November 21, 2018, the FDA approved glasdegib (Daurismo; Pfizer), a small-molecule Hedgehog inhibitor, in combination with low-dose cytarabine (LDAC) for treatment of newly diagnosed acute myeloid leukemia (AML) in adults $\geq$ 75 years or with comorbidities that preclude use of intensive induction chemotherapy. Evidence of clinical benefit came from Study BRIGHT AML 1003, a randomized trial comparing glasdegib+LDAC with LDAC alone for treatment of newly diagnosed AML in 115 patients either $\geq$ 75 years old or $\geq$ 55 years old with preexisting comorbidities. Efficacy was established by improved overall survival (OS) with the combination compared with LDAC alone (HR, 0.46; 95% confidence interval, 0.30–0.71; one-sided stratified log-rank $P = 0.0002$). Median OS was 8.3 months with the combination and 4.3 months with LDAC alone. Common adverse reactions included cytopenias, fatigue, hemorrhage, febrile neutropenia, musculoskeletal pain, nausea, edema, dyspnea, decreased appetite, dysgeusia, mucositis, constipation, and rash. The label includes a boxed warning for embryo-fetal toxicity and a warning for QT interval prolongation. There is a limitation of use for patients with moderate-to-severe hepatic and severe renal impairment; trials studying glasdegib in these patient populations are required as a condition of this approval.

See related commentary by Fathi, p. 6015

Introduction

Acute myeloid leukemia (AML) occurs in patients of all ages but is primarily a disease of older adults, with a median age at diagnosis of 67 years (1). The current standard of care for patients with newly diagnosed AML includes intensive induction chemotherapy when treating with intent to cure. However, almost half of adults with newly diagnosed AML are not treated with intensive induction chemotherapy (2–4), presumably due to perception that toxicity may outweigh potential benefit. In an epidemiologic study, high early mortality was noted for patients $\geq$ 75 years with newly diagnosed AML, independent of treatment (5). The prognostic values of several comorbidity indices have been evaluated with inconsistent results (6). Although some variation may exist at the individual patient level regarding the ability to tolerate intensive chemotherapy, a formal consensus process among leukemia experts identified parameters that would preclude use of intensive induction chemotherapy, including age > 75 years, poor performance status, preexisting severe organ comorbidity, infection resistant to therapy, and cognitive impairment (7).

Recommended treatments for newly diagnosed AML in older patients or those with severe comorbidities include hypomethylating agents (HMA), low-dose cytarabine (LDAC), gemtuzumab ozogamicin (GO) for CD33-positive AML, venetoclax combinations, or best supportive care (BSC; ref. 8). Off-label use of HMAs and LDAC results in complete remission (CR) rates of 8% to 20% and median overall survival (OS) of 3 to 10 months (9–11). Venetoclax combinations and GO monotherapy are approved for this population. For GO, the CR rate was 15%, and median OS was 4.9 months (12). For venetoclax in combination with azacitidine, decitabine, or LDAC, the CR rates were 37%, 54%, and 21%, respectively (13). Only LDAC and GO have demonstrated a survival benefit compared with hydroxyurea or BSC, respectively (9, 12). Despite emerging nonintensive AML treatment options, there is still a clear need for alternatives for patients who cannot tolerate intensive chemotherapy.

Glasdegib, also known as PF-04449913, is a small-molecule inhibitor of Smoothened, a key protein in the Hedgehog (Hh) signaling pathway (14). *In vitro*, glasdegib inhibited Hh signaling with an IC_{50} of 5.2 nmol/L in a cell-based reporter gene assay. Activation of the Hh pathway has been implicated in hematologic malignancies. In a murine xenotransplant model of human AML, glasdegib was synergistic with low doses of cytarabine in inhibiting tumor growth and limiting the percentage of $CD45^+/CD33^+$ blasts in the marrow (14).

Herein, we provide a summary of FDA's review of the marketing application that led to approval of glasdegib+LDAC for treatment of adults with newly diagnosed AML who are $\geq$ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Clinical Pharmacology

Dose selection

The pharmacodynamic effects observed in patients included inhibition of GLI1 expression. The first-in-human study in patients with hematologic malignancies (NCT00953758) identified the MTD of glasdegib as 400 mg once daily. Inhibition of GLI1 expression was >90% at $\geq$ 100 mg and $\geq$80% at 50 mg. Thus, 100 mg was chosen as a safe and biologically effective dose to evaluate in Study BRIGHT AML 1003, allowing for increased glasdegib exposures when patients required coadministration of strong CYP3A inhibitors.

Pharmacokinetics

Glasdegib exhibited a dose proportional increase in exposure from 5 to 600 mg once daily. Steady-state plasma levels were reached by 8 days of daily dosing with median accumulation ratio of 1.2 to 2.5. Following 100 mg daily oral administration, glasdegib median time to peak plasma concentrations at steady-state ranged from 1.3 to 1.8 hours. There was no notable food effect on exposure, supporting the recommendation to administer glasdegib with or without food. The mean elimination half-life (±SD) following glasdegib 100 mg once daily was 17.4 (3.7) hours.

Population pharmacokinetics analysis showed that age, sex, race, body weight, mild-to-moderate renal impairment (RI) [creatinine clearance (CLcr) 30–89 mL/minute], or mild hepatic impairment [HI; total bilirubin $\leq$ upper limit of normal (ULN) and AST > ULN, or total bilirubin 1–1.5 $\times$ ULN and any AST] had no clinically meaningful effects on the pharmacokinetics of glasdegib. The effect of severe (CLcr 15–29 mL/minute) RI and moderate (total bilirubin 1.5–3 $\times$ ULN and any AST) and severe (total bilirubin > 3 $\times$ ULN and any AST) HI on the pharmacokinetics of glasdegib is unknown.

Drug interactions

Glasdegib is metabolized primarily by CYP3A4, and thus, concomitant strong CYP3A4 inhibitors and inducers will increase and decrease glasdegib plasma concentrations, respectively. In addition, coadministration with QTc-prolonging drugs may increase the risk of QTc interval prolongation with glasdegib.

Assessment of Efficacy

Clinical trial overview

Study BRIGHT AML 1003 (NCT01546038) was an open-label, multicenter, multipart trial that included a randomized phase II portion comparing glasdegib+LDAC with LDAC alone in adults $\geq$ 55 years with newly diagnosed AML or high-risk myelodysplastic syndrome (HR-MDS, a condition for which glasdegib is not indicated). Eligible patients must have met at least one of the following criteria: (i) age $\geq$ 75 years, (ii) severe cardiac disease (e.g., left ventricular ejection fraction < 45% at screening), (iii) baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2, or (iv) baseline serum creatinine > 1.3 mg/dL.

Patients were randomized 2:1 to receive glasdegib 100 mg orally once daily on days 1 to 28 and LDAC 20 mg subcutaneously twice daily on days 1 to 10 of a 28-day cycle or LDAC alone in 28-day cycles until disease progression or unacceptable toxicity. Randomization was stratified by baseline cytogenetic risk of poor (inv[3], t[6;9], 11q23, -5, -5q, -7, abnormal 17p, or complex karyotype) versus good/intermediate (all other cytogenetics).

The primary efficacy endpoint was OS. The study was designed assuming a median OS for LDAC of 5 months. A sample size of 132 subjects (92 OS events) was calculated to demonstrate an HR of 0.625 with 80% power at a one-sided alpha of 0.1. CR rate was a secondary endpoint. Response was assessed with bone marrow and peripheral blood assessments on cycle 3 day 1 and every third cycle thereafter, within 14 days of initial hematologic recovery in the peripheral blood (ANC > 1 Gi/L and platelets $\geq$ 100 Gi/L), and at end of treatment.

A total of 132 patients were randomized, 88 to glasdegib+LDAC (78 AML, 10 HR-MDS) and 44 to LDAC (38 AML, 6 HR-MDS). In the analysis of the primary endpoint in the intent-to-treat (ITT) population ($n = 132$), OS was superior on the glasdegib+LDAC arm compared with the LDAC arm [HR, 0.51; 95% confidence interval (CI), 0.34–0.77: one-sided P value 0.0004 stratified log-rank test]. Based on the small number of patients with MDS accrued, it was concluded there were insufficient data to establish efficacy for MDS. For further evaluations, the efficacy population was limited to 115 patients with confirmed AML.

Demographics and disposition of the patients with AML

The demographics of the efficacy population are shown in Table 1. In addition, 41 (36%) had pulmonary disease on medical history, but no grading was provided. Overall, 114 (99%) fulfilled the minimal age or comorbidities criteria expected for the proposed indication (see discussion in Regulatory Insights), but there were no patients at the extreme levels of the criteria (i.e. ECOG PS $\geq$ 3, creatinine clearance < 30 mL/minute, or total bilirubin > 1.5 times the ULN at baseline).

At the time of the primary efficacy analysis, the median follow-up was approximately 20 months. Four patients on the glasdegib+LDAC arm remained on therapy versus none on the LDAC alone arm. Reasons for treatment discontinuation included primary disease (47% glasdegib+LDAC vs. 45% LDAC), adverse reactions (AR; 31% vs. 39%), physician/patient decision (6% vs. 5%), and global deterioration in health (4% vs. 5%). Median

Table 1. Characteristics of randomized patients with newly diagnosed AML in Study BRIGHT AML 1003

	Glasdegib+LDAC ($n = 77$)	LDAC ($n = 38$)
Median age (range)	77 (64, 92) years	76 (58, 83) years
$\geq$75 years	47 (61%)	23 (61%)
Gender		
Male	59 (77%)	23 (61%)
Female	18 (23%)	15 (39%)
Race		
Caucasian	75 (97%)	38 (100%)
Black or African American	1 (1%)	0
Asian	1 (1%)	0
ECOG PS[a]		
0–1	35 (46%)	20 (53%)
2	41 (53%)	18 (47%)
Disease history		
De novo AML	38 (49%)	18 (47%)
Secondary AML	39 (51%)	20 (53%)
Prior HMA use	11 (14%)	6 (16%)
Cytogenetic risk		
Good/intermediate	48 (62%)	21 (55%)
Poor	29 (38%)	17 (45%)
Baseline severe cardiac disease	51 (66%)	20 (53%)
Baseline creatinine clearance < 45 mL/minute	8 (10%)	3 (8%)

[a]One patient on the glasdegib+LDAC arm had a missing ECOG PS.

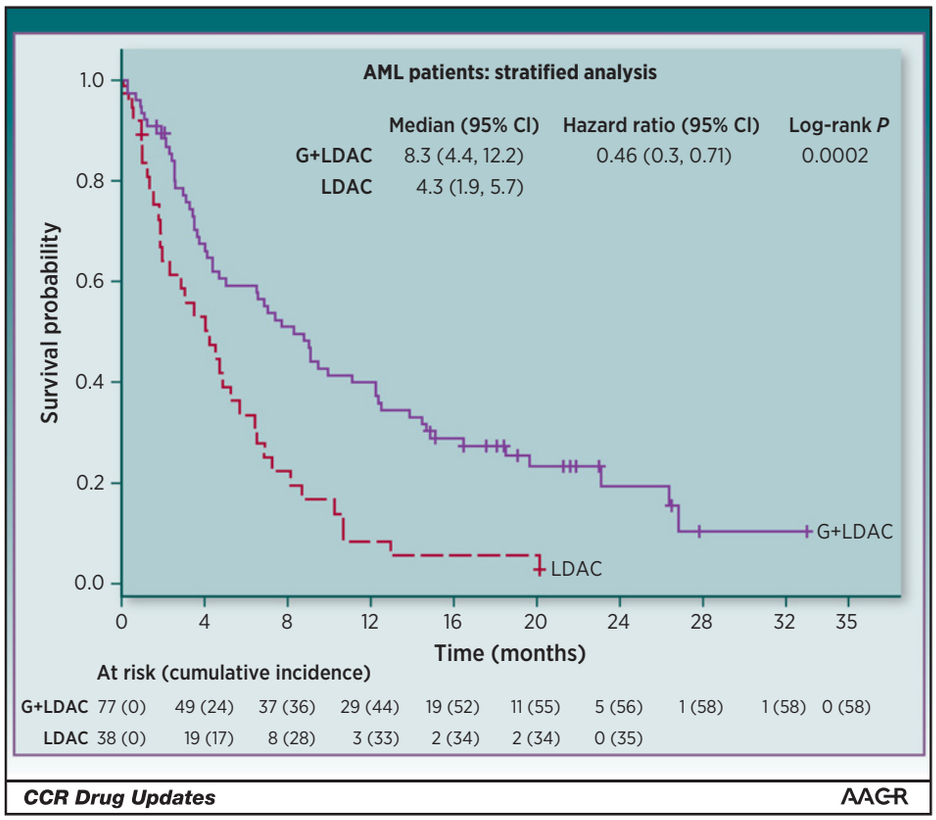

Figure 1.
OS. Kaplan–Meier plot of OS for patients with newly diagnosed AML on Study BRIGHT AML 1003. G, glasdegib.

duration of exposure was 2.6 (range, 0.1–32.0) months on glasdegib+LDAC and 1.3 (range, 0.2–7.9) months on LDAC. One patient on glasdegib+LDAC and none on LDAC proceeded to allogeneic hematopoietic stem cell transplantation.

Efficacy results for the patients with AML

Efficacy results are shown in Fig. 1 and Table 2. The study showed a survival benefit for the combination arm (HR, 0.46; 95% CI, 0.30–0.71; $P = 0.0002$). Improvement in OS was consistent across prespecified demographic and disease subgroups (see Supplementary Fig. S1). The results for the secondary endpoint, CR rate (Table 2), were supportive.

Table 2. Efficacy results in patients with newly diagnosed AML on Study BRIGHT AML 1003

Endpoint	Glasdegib+LDAC ($n = 77$)	LDAC ($n = 38$)
OS		
Median (95% CI)	8.3 months (4.4–12.2)	4.3 months (1.9–5.7)
HR (95% CI)[a]	0.46 (0.30–0.71)	
P value[b]	0.0002	
CR		
Number (%)	14 (18.2%)	1 (2.6%)
95% CI	(10.3–28.6)	(0.1–13.8)
Median time to CR (months) (range)	1.9 (1.2–5.6)	5.6
Median duration of CR (months) (range)	9.8 (0.03–27.6)	3.0

[a]HR based on the Cox proportional hazards model stratified by cytogenetic risk.
[b]One-sided *P* value from log-rank test stratified by cytogenetic risk.

Assessment of Safety

Nonclinical toxicology

FDA identified important safety risks based on analysis of nonclinical pharmacology and toxicology data. In rats and dogs administered glasdegib, toxicities were noted in the kidneys, liver (dog only), and growing bone, teeth, testis, and peripheral nerve (rat only). Additional findings included weight loss, decreased food consumption, alopecia, skin irritation, and tremors or twitching. In rats, minimal-to-mild hypercellularity of marrow and decreased cellularity of lymphoid tissues were observed. There was also a red cell mass loss and reticulocytosis, thought to be a consequence of oral ulcerations and hemorrhage. In addition, glasdegib was found to be teratogenic in rats and rabbits at maternal exposures approximately 0.6 and 3 times the human exposure, respectively, based on Cmax (rat) and AUC (rabbit) in embryo-fetal developmental toxicity studies. Lastly, a single-dose safety pharmacology study in dogs identified QTc prolongation as a toxicity.

Safety events

A total of 125 patients received treatment with glasdegib+LDAC ($n = 84$) or LDAC alone ($n = 41$) in the randomized portion of Study BRIGHT AML 1003. The median duration of exposure to study therapy in the safety population was 2.7 (range, 0.1–42.1) months on the glasdegib+LDAC arm versus 1.6 (range, 0.2–7.9) months on the LDAC arm. Given the shorter duration of therapy on the LDAC arm, FDA focused the safety analysis on the first 90 days of therapy, during which most patients were still receiving therapy on both treatment arms.

Table 3. Treatment-emergent ARs in the safety population[a] within the first 90 days of therapy

	Glasdegib+LDAC ($N = 84$)		LDAC ($N = 41$)	
Preferred term[b]	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Anemia	43%	41%	42%	37%
Fatigue	36%	14%	32%	7%
Hemorrhage	36%	6%	42%	12%
Febrile neutropenia	31%	31%	22%	22%
Edema	30%	0	20%	2%
Musculoskeletal pain	30%	2%	17%	2%
Thrombocytopenia	30%	30%	27%	24%
Nausea	29%	1%	12%	2%
Dyspnea	23%	11%	24%	7%
Decreased appetite	21%	1%	7%	2%
Dysgeusia	21%	0	2%	0
Mucositis	21%	1%	12%	0
Constipation	20%	1%	12%	0
Rash	20%	2%	7%	2%
Abdominal pain	19%	0	12%	0
Pneumonia	19%	15%	24%	22%
Renal insufficiency	19%	5%	10%	0
Cough	18%	0	15%	2%
Diarrhea	18%	4%	22%	0
Dizziness	18%	1%	7%	0
Pyrexia	18%	1%	22%	2%
Vomiting	18%	2%	10%	2%
Muscle spasms	15%	0	5%	0
Atrial arrhythmia	13%	4%	7%	2%
Weight decreased	13%	0	2%	0
Chest pain	12%	1%	2%	0
Headache	12%	0	10%	2%
Hyponatremia	11%	6%	0	0
White blood cell count decreased	11%	11%	5%	2%

[a]$N = 125$ adults with newly diagnosed AML or HR-MDS treated with glasdegib+LDAC or LDAC alone.
[b]Includes grouped terms. See Supplementary Table S1 for further information.

Six deaths (7%) were concluded to have potentially resulted from a direct toxicity of glasdegib+LDAC, and 5 (12%) deaths were due to toxicity on the LDAC arm. Proximate causes of death on the glasdegib+LDAC arm included sudden death ($n = 2$) and one case each of cardiac arrest, myocardial infarction, pneumonia, and unknown. All-cause 30-day mortality was 6% (95% CI, 2%–13%) on the glasdegib+LDAC arm and 12% (95% CI, 4%–26%) on the LDAC arm.

Glasdegib+LDAC was interrupted ≥1 day in 56% of patients (32% on LDAC alone), dose reduced in 26% (0% on LDAC alone), and discontinued prematurely in 36% (44% on LDAC alone) due to an AR. ARs leading to dose interruption in ≥ 5% on glasdegib+LDAC were febrile neutropenia, pneumonia, hemorrhage, fatigue, anemia, muscle spasms, pyrexia, and renal insufficiency. ARs leading to dose reduction in ≥ 2% included muscle spasms, fatigue, febrile neutropenia, QT interval prolongation, anemia, and thrombocytopenia. ARs resulting in discontinuation in ≥2% included pneumonia, sepsis, febrile neutropenia, myocardial ischemia, nausea, renal insufficiency, and sudden death.

Common ARs are listed in Table 3. The safety profile includes established Hh inhibitor class ARs. Additional Hh inhibitor class ARs in < 10% of patients included alopecia (6% glasdegib+LDAC vs. 0% LDAC) and dental disorders (5% glasdegib+LDAC vs. 0% LDAC). The cases of alopecia were grade 1 in severity, but less than half resolved (within 14 to 64 days). With follow-up after the first 90 days of therapy, muscle spasms and decreased appetite progressed from grades ≤ 2 to grade 3 or higher in some patients on the glasdegib+LDAC arm.

Common nonhematologic laboratory abnormalities that were more frequent on the glasdegib+LDAC arm included elevated creatinine, hyponatremia, elevated aspartate aminotransferase, hypomagnesemia, hyperkalemia, and elevated creatine phosphokinase (CPK; Supplementary Table S2). Grade ≥ 3 laboratory abnormalities were rare. Most laboratory abnormalities occurred within the first 2 months on therapy, but there appeared to be a cumulative effect on elevated creatinine, hypomagnesemia, elevated alanine aminotransferase, and elevated CPK.

Incidence of QTc interval prolongation was higher in the glasdegib+LDAC arm for any-grade (8% vs. 2%) or grade > 3 (4% vs. 2%) events. QTc prolongation was typically observed in the first month of therapy. Ventricular arrhythmias were rare (2%). In a substudy of 98 patients treated with glasdegib+LDAC in all portions of Study BRIGHT AML 1003, 5% were found to have a QTc interval > 500 msec and 4% had an increase from baseline QTc > 60 msec.

Regulatory Insights

The 4-month improvement in median OS on the glasdegib+LDAC arm and corroborating improvement in CR rate compared with LDAC alone in Study BRIGHT AML 1003 comprised the substantial evidence of efficacy for regular approval of glasdegib. There were three challenges presented by deficiencies in the study:

1. The statistical analysis plan prespecified inferential testing based on a one-sided alpha of 0.1, which is generally not accepted as evidence of efficacy. However, based on the observed outcome of clinically meaningful improvement in OS and a *P* value of 0.0004 in the primary analysis of OS in the ITT population, the FDA concluded that the results were persuasive.
2. The number of patients with MDS enrolled was too small to assess efficacy for this disease, so only the subgroup with AML was used to determine the approved indication. The additional analysis of OS in the AML subgroup also showed a strong treatment effect and a persuasive *P* value of 0.0002.
3. In part by design, the accrued population did not include patients with severe RI or moderate-to-severe HI, and no studies have been performed to determine safe dosing in patients with such organ impairment. Given that these comorbidities would preclude use of intensive chemotherapy, there is a Limitation of Use for the indication, and additional studies will be required postmarketing to resolve the knowledge gap.

With the approval of venetoclax for AML (13), there was a precedent for using age ≥ 75 years or specific comorbidities (baseline ECOG PS ≥ 2, severe cardiac, severe pulmonary disease, HI with bilirubin > 1.5 times the ULN, creatinine clearance < 45 mL/minute) to identify in an approved indication the intended population for which intensive induction chemotherapy is precluded. Notably, these criteria are less stringent than those proposed by Ferrara and colleagues (7), but FDA is open to looking at other criteria that may preclude the use of intensive chemotherapy.

The median duration of therapy was notably longer on the glasdegib+LDAC arm compared with the LDAC arm. The discrepancy was related to earlier discontinuations on the LDAC arm due to disease progression and ARs, inclusive of deaths. Furthermore, the median time to CR response was shorter on the glasdegib+LDAC arm compared with the LDAC arm. The discrepant durations of therapy led FDA to analyze safety data between the arms during the period of treatment overlap. Beyond this time period, FDA analyzed safety on the glasdegib+LDAC arm to determine whether certain ARs increased in incidence or severity. FDA has utilized a similar approach with other approved therapies, when compared with a control arm with a shorter duration of therapy (15).

The safety profile of glasdegib was like that reported for other Hh inhibitors. The established class potential for risks of embryo-fetal death or severe birth defects when administered to pregnant women led to a boxed warning for embryo-fetal toxicity and a Medication Guide to inform patients about risks and mitigation strategies. Preclinical studies of glasdegib also showed adverse changes in growing bone and teeth in rats. To address these risks, the intended population is restricted to adults, and the risks are described in the Pediatric Use section of the Prescribing Information (PI).

QT interval prolongation was associated with glasdegib administration in nonclinical testing, a QT study in healthy volunteers, and the clinical trial. QT prolongation was a potentially life-threatening toxicity identified by FDA listed under Warnings and Precautions in the PI. Patients with AML are frequently treated with drugs, especially antifungals, that are strong CYP3A inhibitors that may increase the risk of QT prolongation. Based on results in the clinical trial, the risk could be mitigated by monitoring ECGs and dose modifications, as outlined in the PI.

Conclusions

The benefit–risk analysis of the results of Study BRIGHT AML 1003 supported regular approval of glasdegib+LDAC for treatment of adults with newly diagnosed AML who are $\geq$ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy, with a Limitation of Use for patients with severe RI or moderate-to-severe HI. Although there was a survival benefit for the combination, it was clearly not curative, and how to incorporate use of this combination in practice will require further study.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The Editor handling the peer review and decision-making process for this article has no relevant employment associations to disclose.

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