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ADISINSIGHT REPORT

Glasdegib: First Global Approval

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Abstract
Glasdegib (DAURISMO™) is an oral inhibitor of the Hedgehog signalling pathway, the activation of which is associated with a number of malignancies. It has been developed by Pfizer and was approved in November 2018 in the USA for use in combination with low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukaemia (AML) in patients aged ≥ 75 years or those who have comorbidities that preclude use of intensive induction chemotherapy. Glasdegib is the first Hedgehog pathway inhibitor to be approved for AML in the USA. It received orphan designation for the treatment of AML in the USA in June 2017 and in the EU in October 2017, and for the treatment of myelodysplastic syndrome (MDS) in the USA in October 2017. It is also undergoing clinical development for use in select haematological and other malignancies, including MDS, in various countries worldwide. This article summarizes the milestones in the development of glasdegib leading to its use in combination with low-dose cytarabine for the treatment of newly-diagnosed AML in patients aged ≥ 75 years or those who have comorbidities that preclude use of intensive induction chemotherapy.

1 Introduction

Aberrant activation of the Hedgehog signalling pathway (which plays a key role not only in embryogenesis but also in maintenance and regeneration in adult tissues) is associated with a number of (haematological) malignancies [1]. Indeed, recent evidence suggests that the maintenance and expansion of malignant stem cells requires Hedgehog signalling, making the pathway a key therapeutic candidate [1].

Glasdegib (DAURISMO™) is the first Hedgehog pathway inhibitor to be approved (in November 2018) for acute myeloid leukaemia (AML) in the USA, where it is indicated for use in combination with low-dose cytarabine for the treatment of newly-diagnosed AML in patients aged ≥ 75 years or those who have comorbidities that preclude use of intensive induction chemotherapy [2–4]. Developed by Pfizer, glasdegib inhibits the Hedgehog pathway by binding to and inhibiting the transmembrane protein Smoothened (SMO) [3]. It is available as 25 and 100 mg tablets and its recommended dosage is 100 mg once daily administered orally (with or without food) in the absence of unacceptable toxicity or loss of disease control. Patients without unacceptable toxicity should be treated for a minimum of six cycles in order to allow time for a clinical response. Glasdegib carries a boxed warning pertaining to embryo-foetal toxicity, and local prescribing information should be consulted for detailed information regarding dose modifications for the management of adverse events, and patient monitoring [3].

Glasdegib received orphan designation for the treatment of AML in the USA in June 2017 [5] and in the EU in October 2017 [6], and for the treatment of myelodysplastic syndrome (MDS) in the USA in October 2017 [5]. It is undergoing clinical development for use in select haematological and other malignancies, including MDS, in various countries worldwide [7].

2 Scientific Summary

2.1 Pharmacodynamics

Glasdegib downregulated the expression of *GLI1* (a Hedgehog signalling pathway target gene), according to analyses of normal skin biopsies from 3 patients with haematological malignancies [8] and 15 patients with advanced solid

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through preclinical and clinical studies to market launch and beyond.

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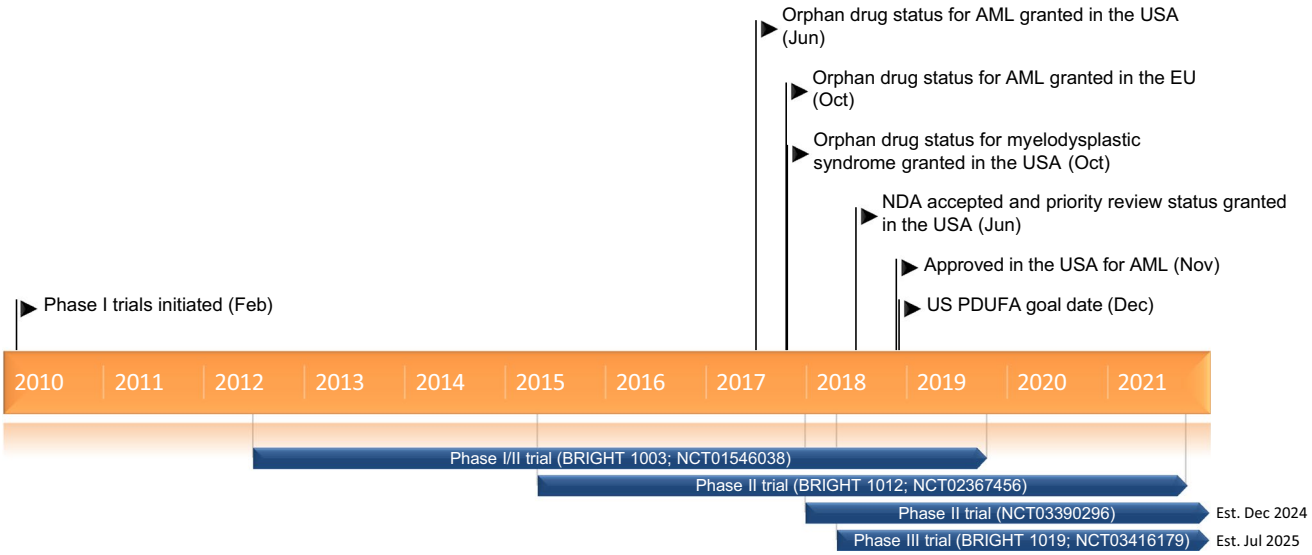


Key milestones in the development of glasdegib. *AML* acute myeloid leukaemia, *Est.* established, *NDA* New Drug Application, *PDUFA* Prescription Drug User Fee Act

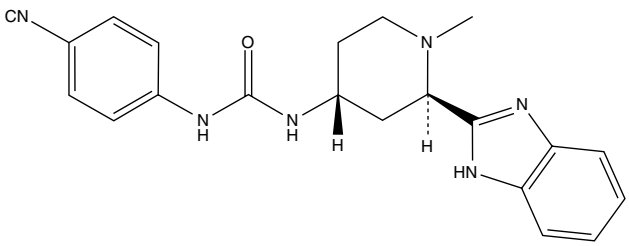
tumours [9] participating in phase I studies (NCT00953758 [8]; NCT01286467 [9]). Moreover, baseline *SMO*, *GLI1* and *PTC* expression was higher in patients responding to therapy with glasdegib (100 mg once daily) than in those who did not respond to therapy, while non-responders had higher post-therapy expression of these genes than responders in a phase II study in 35 patients with AML, chronic myelomonocytic leukaemia or MDS who have failed hypomethylating agent therapy (NCT01842646) [10]. Glasdegib plus low-dose cytarabine displayed antitumour activity in a murine xenotransplant model of human AML, inhibiting increases in tumour size and reducing the percentage of CD45+/CD33+ blasts in bone marrow to a greater extent than glasdegib or low-dose cytarabine alone [3].

Glasdegib is associated with concentration-dependent corrected QT (QTc) prolongation [3]. However, the effect does not appear to be large, according to a randomized, double-blind, four-way crossover, placebo- and open-label moxifloxacin-controlled study in 36 healthy volunteers (available as an abstract) [11]. At therapeutic and supratherapeutic plasma concentrations of glasdegib, the upper limits of the two-sided 90% CIs for all of the least-square mean differences between glasdegib and placebo were < 20 ms (with 20 ms considered to be the threshold for clinical concern in patients with cancer). Moreover, none of the subjects experienced an absolute Fridericia-corrected QT (QTcF) interval of ≥ 480 ms or an increase from baseline in the QTcF interval of ≥ 30 ms [11]. See Sect. 2.4 for a discussion on the effect of glasdegib on QTc interval in patients with AML. The concomitant administration of glasdegib and QTc prolonging drugs may increase the risk of QTc interval prolongation [3]. Local prescribing information should be consulted for detailed information regarding this potential drug interaction.

2.2 Pharmacokinetics

The pharmacokinetics of glasdegib are best described by a two-compartment model with first-order absorption, according to a population pharmacokinetic analysis of data (from an abstract) from 269 patients with advanced cancer who had received oral glasdegib 5–640 mg/day [12].

Glasdegib has a mean absolute bioavailability of 77% [3]. Once-daily oral glasdegib exhibited dose-proportional increases in area under the concentration–time curve (AUC) and maximum concentration (C_{max}) values over a 5–600 mg dose range (0.05–6-fold the recommended dose; see Sect. 1) in an open-label, multicenter, phase I study in 47 adults (aged ≥ 18 years) with haematological malignancies (NCT00953758) [8]. Steady state was reached by day 8 and the median accumulation ratio of glasdegib was in the range of 1.2–2.5 following multiple doses of glasdegib [8]. In the phase I part of a phase I/II study [NCT01546038



Chemical structure of glasdegib

Features and properties of glasdegib	
Alternative names	DAURISMO; PF 04; PF-04449913; PF-4449913
Class	Antineoplastics; benzimidazoles; phenylurea compounds; piperidines; small molecules
Mechanism of action	Hedgehog cell-signalling pathway inhibitors; SMO protein inhibitors
Route of administration	Oral
Pharmacodynamics	Inhibits the Hedgehog signalling pathway by binding to and inhibiting the transmembrane protein Smoothened
Pharmacokinetics	Exhibited dose-proportional increases in area under the concentration–time curve and maximum concentration (C_{max}) values; median time to C_{max} of 1.3–1.8 h; may be administered with or without food
Most frequent adverse events	Anaemia, febrile neutropenia, thrombocytopenia
ATC codes	
WHO ATC code	L (antineoplastic and immunomodulating agents)
	L01X-X63 (glasdegib)
EphMRA ATC code	L1X (all other antineoplastics)
Chemical name	*N*-[(2*R*,4*R*)-2-(1*H*-benzimidazol-2-yl)-1-methylpiperidin-4-yl]-*N*'-(4-cyanophenyl)urea

(BRIGHT 1003); see Sect. 2.3 for details], the median time to the glasdegib C_{max} was 1.3–1.8 h following the administration of glasdegib (100 mg once daily) in combination with low-dose cytarabine [13]. A high-fat, high-calorie meal reduced AUC from time 0 to infinity and C_{max} values by 16 and 31% [3] (see Sect. 1). In vitro, glasdegib is 91% bound to human plasma proteins [3].

Glasdegib is predominately metabolized by the cytochrome P450 (CYP)3A4 pathway, with minor contributions by CYP2C8 and UGT1A9 [3]. In a phase I study in six healthy volunteers (NCT02110342), glasdegib accounted for 69% of the total circulating drug-related material in the plasma [14]. Almost half (49%; 17% unchanged) and 42% (20% unchanged) of a single oral 100 mg dose of radiolabelled glasdegib was excreted in the urine and faeces [14]. The mean half-life of glasdegib is 17.4 h following 100 mg once-daily dosing in patients with haematological malignancies [3].

The pharmacokinetics of glasdegib were not affected to a clinically relevant extent by age (25–92 years), sex, race, bodyweight (43.5–145.6 kg), mild hepatic impairment, or mild to moderate renal impairment [3]. The effects of moderate and severe hepatic impairment, or severe renal impairment on the pharmacokinetics of glasdegib are not yet known [3]. According to an ongoing, open-label, multicentre, phase I study (NCT02038777), the pharmacokinetic profile of glasdegib in 13 Japanese patients with select advanced haematological malignancies was consistent with those in studies in non-Japanese patients [15].

Plasma glasdegib concentrations may be increased when glasdegib is coadministered with strong CYP3A inhibitors (e.g. ketoconazole) and decreased when glasdegib is coadministered with strong CYP3A inducers (e.g. rifampin) [3]. Local prescribing information should be consulted for detailed information regarding these and other potential drug interactions.

2.3 Therapeutic Trials

The addition of glasdegib to low-dose cytarabine was associated with a statistically significant and clinically relevant reduction in the risk of death compared with low-dose cytarabine alone in adults with previously untreated AML or high-risk MDS participating in the randomized arm of the phase II part of a phase I/II study [NCT01546038 (BRIGHT 1003)] [16]. At the time of the primary analysis (data cut-off date of 3 January 2017; median follow-up duration of 21.7 and 20.1 months in the glasdegib plus low-dose cytarabine and low-dose cytarabine groups), median overall survival (primary endpoint) was 8.8 months in the glasdegib plus low-dose cytarabine group ($n = 88$) and 4.9 in the low-dose cytarabine group ($n = 44$) [hazard ratio (HR) 0.51 (80% CI 0.39–0.67); $p = 0.0004$]. At this timepoint, 77.3 and 93.2% of patients in the respective groups had died, with disease progression the main cause of death. The 6- and 12-month probability of survival was 59.8 and 39.5% for glasdegib plus low-dose cytarabine and 38.2 and 9.5% for low-dose cytarabine alone. HRs for overall survival favoured glasdegib plus low-dose cytarabine over low-dose cytarabine alone in the cytogenetic risk (good/intermediate vs. poor; $n = 77$ and 55) and diagnosis (AML vs. MDS; $n = 116$ and 16) subgroups, although in patients with poor cytogenetic risk and those with MDS the benefit did not reach statistical significance [16]. Of note, results from a covariate-adjusted indirect analysis (available as an abstract) suggested that glasdegib plus low-dose cytarabine significantly prolonged overall survival compared with azacitidine [HR 0.492 (95% CI 0.287–0.843)] and decitabine [HR 0.540 (95% CI 0.324–0.900)] [17].

Glasdegib plus low-dose cytarabine demonstrated a significant advantage over low-dose cytarabine alone in investigator-assessed complete remission (CR) at the time of the

Key clinical trials of glasdegib

Drug(s)	Indication	Phase	Status	Location(s)	Identifier	Sponsor
Glasdegib	Acute myeloid leukaemia	I	Recruiting	Japan	NCT02038777	Pfizer
Glasdegib, azacitidine	Acute myeloid leukaemia, chronic myelomonocytic leukaemia or myelodysplastic syndrome	I	Recruiting	Multinational	NCT02367456 (BRIGHT 1012)	Pfizer
Glasdegib, low-dose cytarabine, cytarabine, decitabine, daunorubicin	Acute myeloid leukaemia or myelodysplastic syndrome	I/II	Active, not recruiting	Multinational	NCT01546038 (BRIGHT 1003)	Pfizer
Glasdegib	Graft-versus-host disease	I/II	Recruiting	Spain	NCT03415867 (GLAS)	Grupo Español de Trasplantes Hematopoyeticos y Terapia Celular
Glasdegib, temozolomide	Glioblastoma	I/II	Recruiting	Spain	NCT03466450 (GEINO 1602)	Grupo Español de Investigación en Neurooncología
Glasdegib, temozolomide	Glioblastoma	I/II	Not yet recruiting	Spain	NCT03529448 (GEINOCANN)	Grupo Español de Investigación en Neurooncología
Glasdegib, placebo	Myelofibrosis	II	Terminated	Japan, USA	NCT02226172 (SMOI)	Pfizer
Glasdegib, avelumab, azacitidine, gemtuzumab ozogamicin, utomilumab	Acute myeloid leukaemia	II	Recruiting	USA	NCT03390296	M.D. Anderson Cancer Center
Glasdegib	Acute myeloid leukaemia	II	Recruiting	USA	NCT01841333	University of Colorado, Denver
Glasdegib	Acute myeloid leukaemia, chronic myelomonocytic leukaemia or myelodysplastic syndrome	II	Completed	USA	NCT01842646	H. Lee Moffitt Cancer Center and Research Institute
Glasdegib, azacitidine, cytarabine, daunorubicin + cytarabine, placebo	Acute myeloid leukaemia	III	Recruiting	Multinational	NCT03416179 (BRIGHT 1019)	Pfizer

primary analysis (17.0 vs. 2.3%; $p < 0.05$) [16]. Moreover, patients receiving glasdegib plus low-dose cytarabine were fivefold more likely to achieve a CR than those receiving low-dose cytarabine alone [odds ratio 5.03 (80% CI 1.59–15.88); $p = 0.0152$]. In glasdegib plus low-dose cytarabine recipients achieving a CR, or a CR, a CR with an incomplete blood count recovery (CRi) or a morphological leukaemia-free state (MLFS), the median duration of response was 9.9 and 6.5 months. In the subgroup of patients with AML, an investigator-assessed overall response (OR; defined as the proportion of patients achieving a CR, CRi or MLFS) was achieved by 26.9% of 78 glasdegib plus low-dose cytarabine recipients and 5.3% of 38 low-dose cytarabine alone recipients. In the subgroup of patients with MDS, an OR (defined as the proportion of patients achieving a CR or a marrow CR) was achieved by 20.0% of 10 and 0% of 6 patients, respectively [16].

Glasdegib plus cytarabine and daunorubicin was associated with clinical activity in patients with AML or high-risk MDS participating in the nonrandomized arm of the phase II part of BRIGHT 1003 [18]. An investigator-assessed CR (primary endpoint) was achieved in 40.0% of 60 patients aged ≥ 55 years and in 88.9% of 9 patients aged < 55 years. Overall, median overall survival was 14.9 months and the 12-month survival probability was 66.6%. In patients aged ≥ 55 and < 55 years, median overall survival was 14.7 months and not estimable [18].

The maximum tolerated dosage of glasdegib was not reached in any of the treatment arms in the phase I part of BRIGHT 1003; thus, a 100 mg once daily dosage was selected for the phase II part of the study based on pharmacokinetic, efficacy and tolerability profiles [13].

BRIGHT 1003 is a phase I/II study [13, 16, 18]. In the open-label, multicentre, phase I part of this study, patients

ineligible for intensive chemotherapy received glasdegib plus low-dose cytarabine or glasdegib plus decitabine, while those eligible for intensive chemotherapy received glasdegib plus cytarabine and daunorubicin [13]. Glasdegib was administered orally at a dosage of 100 or 200 mg once daily on days 1–28 of each 28-day cycle [13]. In the phase II part of BRIGHT 1003 (conducted multinationally in the randomized arm or specifically in the USA in the non-randomized arm), patients ineligible for intensive chemotherapy (stratified by cytogenetic risk) were randomized to receive glasdegib plus low-dose cytarabine or low-dose cytarabine alone, while patients eligible for intensive chemotherapy received glasdegib plus cytarabine and daunorubicin [16, 18]. Glasdegib was administered orally at a dosage of 100 mg once daily on days 1–28 of each 28-day cycle. In both parts of the study, patients were treated until disease progression or unacceptable toxicity [16, 18]. In the randomized arm of the phase II part of BRIGHT 1003, the median number of cycles in the glasdegib plus low-dose cytarabine and low-dose cytarabine alone groups was three and two [16]. The primary analysis in the randomized arm of the phase II part of BRIGHT 1003 was conducted after 109 deaths (which corresponded to 118% of the prespecified total of ≥ 92 events) in the full analysis population [16]. The primary analysis in the nonrandomized arm of the phase II part of BRIGHT 1003 was conducted after 38 deaths in the full analysis population [18].

Glasdegib as monotherapy [8–10, 15, 19] has demonstrated variable preliminary clinical activity in phase I studies in patients with advanced solid tumours (NCT01286467) [9] and haematological malignancies (first-in human study [19]; NCT00953758 [8]; NCT02038777 [15]); and in a phase II study in patients with AML, chronic myelomonocytic leukaemia or MDS who have failed hypomethylating agent therapy (NCT01842646) [10]. Glasdegib in combination with chemotherapy (azacitidine [20], cytarabine plus daunorubicin [13], decitabine [13], low-dose cytarabine [13]) has also demonstrated variable preliminary clinical activity in a phase I study in patients with AML with 20–30% bone marrow blasts, chronic myelomonocytic leukaemia or MDS [NCT02367456 (BRIGHT 1012)] [20]; and in the phase I part of BRIGHT 1003 in patients with AML or high-risk MDS [13].

2.4 Adverse Events

Glasdegib in combination with low-dose cytarabine had a manageable safety profile in adults with previously untreated AML or high-risk MDS participating in the randomized arm of the phase II part of BRIGHT 1003 [16]. Moreover, its safety and tolerability profile was generally consistent between Japanese and non-Japanese patients, according to an ongoing phase I study (NCT02038777) [15].

In the randomized arm of the phase II part of BRIGHT 1003 [patients had received glasdegib plus low-dose cytarabine ($n = 84$) or low-dose cytarabine alone ($n = 41$) for a median of 2.7 and 1.5 months], grade 3–4 treatment-emergent adverse events (TEAEs) occurred in 64.3% of glasdegib plus low-dose cytarabine recipients and 56.1% of low-dose cytarabine alone recipients and grade 5 TEAEs in 28.6 and 41.5% of patients [16]. The most frequently reported (occurring in > 10% of patients in either treatment group and with a numerically higher incidence in the glasdegib plus low-dose cytarabine group than the low-dose cytarabine alone group) grade 3 or 4 TEAEs were anaemia (41.7 vs. 36.6% of patients), febrile neutropenia (35.7 vs. 24.4%), thrombocytopenia (31.0 vs. 24.4%), pneumonia (16.7 vs. 14.6%) and fatigue (14.3 vs. 4.9%). Of note, grade 5 anaemia, fatigue, febrile neutropenia and thrombocytopenia were not observed; the incidence of grade 5 pneumonia was generally similar between the respective treatment groups (7.1 vs. 7.3%). Grade 3–5 treatment-related adverse events (TRAEs) were observed in 65.5% of glasdegib plus low-dose cytarabine recipients and 34.1% of low-dose cytarabine alone recipients, with fatigue being the most frequently reported grade 3–5 TRAE (in 10.7 and 2.4% of patients) [16].

TEAEs resulting in dose reduction or interruption of the study medication were reported in 26.2 and 56.0% of glasdegib plus low-dose cytarabine recipients and 0 and 31.7% of low-dose cytarabine alone recipients [16]. Serious TEAEs occurred in 78.6 and 78.0% of patients receiving glasdegib plus low-dose cytarabine or low-dose cytarabine alone, with febrile neutropenia (28.6 vs. 17.1%) and pneumonia (22.6 vs. 17.1%) being the most frequently reported (in ≥ 15% of patients) serious TEAEs. Of note, in the glasdegib plus low-dose cytarabine group, three (3.6%) patients had a serious acute kidney injury (with the injury in one patient considered related to glasdegib) and one (1.2%) patient had serious muscle spasms (which were considered related to glasdegib). Permanent treatment discontinuation because of TEAEs occurred in 35.7 and 46.3% of patients receiving glasdegib plus low-dose cytarabine or low-dose cytarabine alone, with 10.7 and 7.3% of patients discontinuing treatment because of TRAES [16].

Elevated alanine aminotransferase, aspartate aminotransferase and/or total bilirubin levels (most of which were grade 1–2 in severity) occurred in nine and five patients receiving glasdegib plus low-dose cytarabine or low-dose cytarabine alone [16]. No patient had concurrent elevations of all enzymes and no elevations in liver enzymes led to permanent treatment discontinuation [16].

A mean QTcF interval of > 480 ms and/or a mean increase from baseline in QTcF of > 60 ms was seen in nine and five patients receiving glasdegib plus low-dose cytarabine or low-dose cytarabine alone [16]. QTcF prolongation

of > 500 ms occurred in 6.0% of 83 glasdegib plus low-dose cytarabine recipients and 11.8% of 17 low-dose cytarabine alone recipients. Dose interruption because of glasdegib-related ECG QT prolongation and permanent dose reduction because of treatment-related ECG QT prolongation each occurred in two patients. No patient experienced Torsades de Pointes [16]. Of note, patients with a baseline QTc of > 470 ms or with a history of long QT syndrome or uncontrolled cardiovascular disease were excluded from this study [3].

Therapy with glasdegib in combination with low-dose cytarabine was generally well tolerated in the nonrandomized arm of the phase II part of BRIGHT 1003 [18] and in the phase I part of BRIGHT 1003 [13]. The safety profile of glasdegib plus low-dose cytarabine was consistent with that seen in patients with AML receiving chemotherapy [18] and as expected during Hedgehog signalling pathway inhibitor therapy and chemotherapy [13].

2.5 Ongoing Clinical Trials

An open-label, multicenter, phase I study [NCT02367456 (BRIGHT 1012)] evaluating the efficacy and safety of glasdegib in combination with azacitidine is currently recruiting patients with AML with 20–30% bone marrow blasts, chronic myelomonocytic leukaemia or MDS. There are several ongoing phase I/II studies of glasdegib for the treatment of AML [NCT01546038 (BRIGHT 1003)], graft-versus-host disease [NCT03415867 (GLAS)] and glioblastoma [NCT03466450 (GEINO 1602); NCT03529448 (GEINOCANN)]. In addition, a number of ongoing phase II studies are assessing glasdegib for the treatment of AML (NCT03390296; NCT01841333). The phase II SMOI study (NCT02226172) in patients with myelofibrosis was terminated early.

BRIGHT 1019 (NCT03416179) comprises two randomized, double-blind, multinational, phase III studies evaluating the efficacy of glasdegib versus placebo, both in combination with intensive or non-intensive (azacitidine) chemotherapy [21]. BRIGHT 1019 was initiated in April 2018 and is planning to enrol 720 patients with previously untreated AML [21].

3 Current Status

Glasdegib received its first global approval on 21 November 2018 in the USA for use in combination with low-dose cytarabine for the treatment of newly-diagnosed AML in patients aged ≥ 75 years or those who have comorbidities that preclude use of intensive induction chemotherapy.

Compliance with Ethical Standards

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Conflicts of interest During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the author on the basis of scientific completeness and accuracy. Sheridan Hoy is a salaried employee of Adis/Springer, is responsible for the article content and declares no relevant conflicts of interest.

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