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ADISINSIGHT REPORT

Gilteritinib: First Global Approval

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Abstract
Gilteritinib (Xospata®) is an orally available small molecule receptor tyrosine kinase inhibitor developed by Astellas Pharma in collaboration with Kotobuki Pharmaceutical for the treatment of acute myeloid leukaemia (AML) harbouring FMS-like tyrosine kinase 3 (FLT3) mutations. Gilteritinib inhibits FLT3 (STK1 or FLK2), AXL (UFO or JTK11) and anaplastic lymphoma kinase (ALK or CD246). Gilteritinib inhibits FLT3 signalling in cells expressing FLT3 internal tandem duplication (ITD), tyrosine kinase domain mutation FLT3-D835Y and the double mutant FLT3-ITD-D835Y, thereby inducing apoptosis. Gilteritinib also binds to and inhibits the wild-type and mutated forms of ALK, resulting in reduced tumour cell proliferation in cancer cell types that overexpress the mutation. Gilteritinib is approved in Japan for the treatment of relapsed or refractory AML with *FLT3* mutation. Recently, it was also approved in the USA for the treatment of adult patients who have relapsed or refractory AML with a *FLT3* mutation, as detected by an FDA-approved test. Clinical development of gilteritinib is underway in several countries worldwide. Development for non-small cell lung cancer and solid tumours has been discontinued.

1 Introduction

Acute myeloid leukaemia (AML) is an aggressive haematological malignancy characterized by a block in myeloid differentiation, and proliferation of immature myeloid progenitor cells [1, 2]. It is a disease of acquired and occasionally inherited single or multiple genetic alterations, such as chromosomal translocations and somatic mutations, which produce the characteristic features of AML [3, 4]. FMS-like tyrosine kinase 3 (FLT3) is a tyrosine kinase receptor usually expressed in early myeloid progenitors that is thought to play a key role in the differentiation and maturation of haematopoietic precursors [2, 4]. Binding of FLT3 to the FLT3 ligand results in dimerization at the membrane, autophosphorylation and activation of downstream signalling pathways via intermediary proteins (e.g. RAS, MEK, PI3K, AKT, STAT-5), leading to growth and differentiation [2]. Approximately 20–30% of patients with AML have constitutively activated FLT3 because of internal tandem duplication (ITD) mutation, which is associated with higher rates of relapse and relatively poor clinical outcomes [2, 4]. Approximately 7% of patients with AML have point mutations in the activation loop of the FLT3 tyrosine kinase domain (TKD) [2, 4]. *FLT3*-TKD mutations have no characteristic clinical signature or prognostic effect, but may be very significant clinically as they represent a mechanism of resistance to FLT3 tyrosine kinase inhibitors [4]. Efforts to improve outcomes in patients with *FLT3* mutations led to the development of inhibitors of mutant FLT3, including the relatively non-specific first-generation FLT3 inhibitors sorafenib, midostaurin and sunitinib, and the more potent and selective second-generation FLT3 inhibitors, including gilteritinib (Xospata®). FLT3 inhibitors are also classified into type I and II inhibitors based on their interaction with FLT3, with type I inhibitors active in cells bearing either ITD or TKD mutations (e.g. sunitinib, midostaurin, gilteritinib), whereas type II inhibitors are active in cells with ITD, but not TKD, mutations (e.g. sorafenib, quizartinib) [5].

Gilteritinib is a small molecule multiple receptor tyrosine kinase inhibitor developed by Astellas Pharma in collaboration with Kotobuki Pharmaceutical for the treatment of *FLT3*-mutation positive AML. Gilteritinib received its first global approval in Japan for the treatment of relapsed or refractory *FLT3*-mutation positive AML, as assessed by an approved in vitro diagnostic assay

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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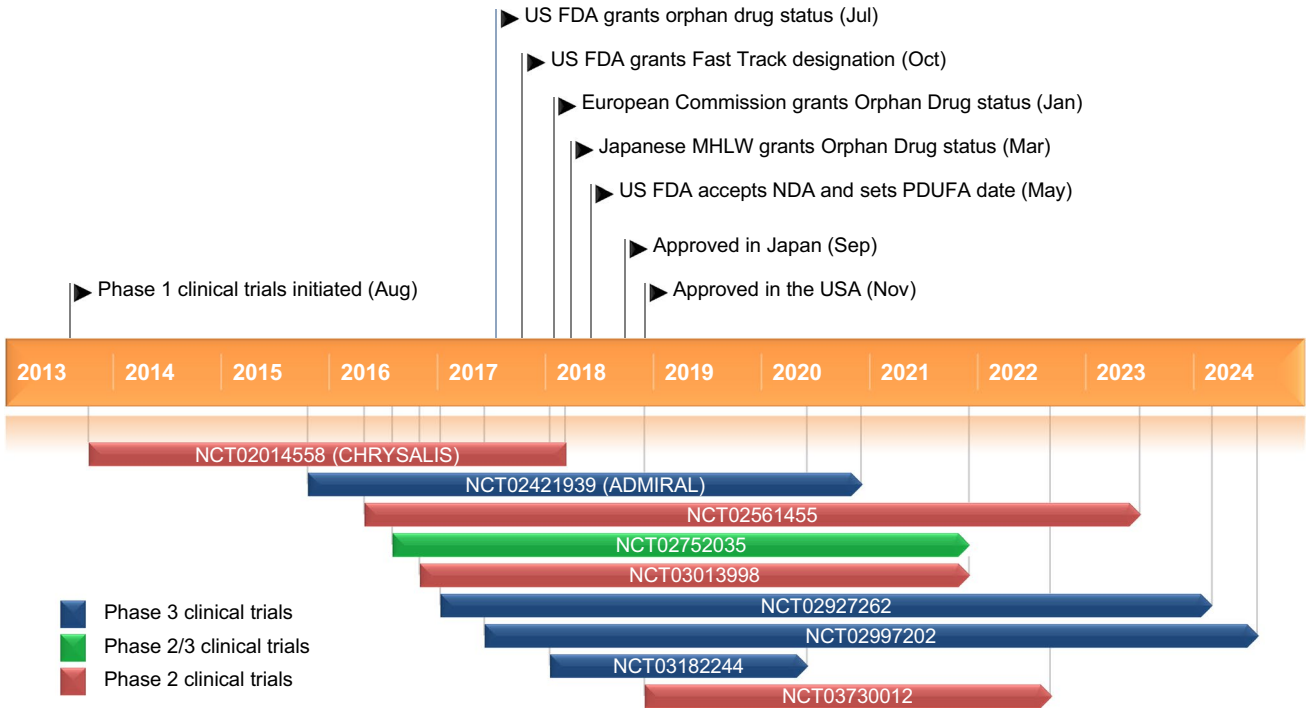


Key milestones in the development of gilteritinib for the treatment of patients with relapsed or refractory AML with a *FLT3*-mutation. *MHLW* Ministry of Health, Labor and Welfare, *NDA* new drug application, *PDUFA* Prescription Drug User Fee Act

(Leukostrat CDx *FLT3* mutation test) [6–8]. Gilteritinib has also been approved by the US FDA for the treatment of adults who have relapsed or refractory AML with a *FLT3*-mutation, as detected by an FDA-approved test (LeukoStrat CDx FLT3 Mutation Assay) [9, 10]. The recommended dosage of gilteritinib is 120 mg administered orally once daily [7, 10]. This article summarizes the milestones in the development of gilteritinib leading to its approval in this indication.

1.1 Company Agreements

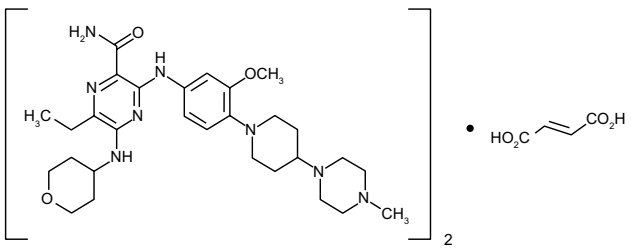
Astellas Pharma and Kotobuki Pharmaceutical entered into a research collaboration for the development of gilteritinib. Astellas has the exclusive global rights to develop, manufacture and commercialise the product [11].

2 Scientific Summary

2.1 Pharmacodynamics

Gilteritinib, a pyrazinecarboxamide derivative, is a selective inhibitor of multiple receptor tyrosine kinases, including FLT3 and AXL (geometric mean 50% inhibitory concentration 0.29 and 0.73 nmol/L, respectively) [12, 13]. In vitro gilteritinib inhibited FLT3 receptor signalling and cell proliferation in cells lines expressing FLT3 [12, 13]. Gilteritinib (a type I inhibitor) demonstrated potent activity against FLT3 with ITD and TKD mutations, including point mutations known to confer resistance to type II inhibitors and, to a lesser degree, against the F691 gatekeeper mutation [12, 13]. Computational modelling indicated that gilteritinib binds to FLT3 at the ATP binding site, far from the D835 position in the activation loop; it hydrophobically interacts with FLT3 at the 691 position [13].

In vitro and animal studies showed that gilteritinib inhibits phosphorylation of FLT3 and its downstream targets [13]. In vivo gilteritinib distributed at high levels in tumours and was associated with durable inhibition of phosphorylated FLT3 and STAT5, resulting in tumour regression (xenograft model) and decreased leukaemic burden and prolonged survival (intra-bone transplantation model of FLT3 driven AML) [13]. In a first-in-human, open-label, phase 1/2 study in patients with relapsed or refractory AML



Chemical structure of gilteritinib

(NCT02014558), treatment with gilteritinib 120 mg/day was associated with substantial (> 90%), rapid (within 24 h) and sustained FLT3 phosphorylation inhibition, as assessed by a plasma inhibitory activity assay [10, 14].

Gilteritinib in combination with chemotherapy had superior antitumour efficacy to that of chemotherapy alone in preclinical studies [15, 16]. Gilteritinib with cytarabine and daunorubicin enhanced chemotherapy-induced apoptosis in a leukaemia cell line and induced tumour regression (including complete regression) in a leukaemia xenograft model [15]. In comparison, only tumour growth inhibition was observed with cytarabine and daunorubicin alone. Sequential treatment with gilteritinib for 1 week followed by treatment with cytarabine and daunorubicin was also associated with xenograft tumour regression, with the final tumour volume being similar to that with concomitant gilteritinib and chemotherapy [15]. In another study, gilteritinib with azacitidine enhanced azacitidine-induced apoptosis in a leukaemia cell line, partly by reducing the expression of anti-apoptotic proteins (e.g. MCL-1, BCL2L10, survivin). The combination also inhibited tumour growth in a leukaemia xenograft model to a greater extent than gilteritinib or azacitidine alone (94 vs. 71 and 0%) [16].

In addition, in vitro gilteritinib in combination with the novel dual PI3 kinase/histone deacetylase inhibitor CUDC-907 had synergistic anti-leukaemic effects in FLT3-ITD AML cell lines and FLT3-ITD primary patient samples, as indicated by greater apoptosis with the combination than with either agent alone [17]. When combined with gilteritinib, CUDC-907 time-dependently abolished gilteritinib-induced expression of FLT3 in FLT3-ITD AML cell lines. Moreover, gilteritinib combined with CUDC-907 cooperatively inhibited the PI3K/AKT, JAK/STAT and RAS/RAF pathways and prevented escape through alternate pathways [17].

In a pilot immunohistochemical study in bone marrow biopsies of patients prior to and during treatment with FLT3 inhibitors (including gilteritinib), activated FLT3 levels were not found to be predictive of clinical response [18].

Next-generation sequencing identified two patterns of acquired resistance in patients receiving gilteritinib ≥ 80 mg/day in the first-in-human phase 1/2 study (NCT02014558): clone swapping (i.e. original FLT3 mutation is lost and mutations in other genes are acquired) and clonal evolution (i.e. baseline mutations in FLT3 and other genes persist, but additional mutations are acquired, resulting in clonal expansion) [19]. The most common mechanism of acquired resistance to gilteritinib was treatment-emergent RAS mutation, which may occur via clonal selection for FLT3-wildtype or clonal evolution of FLT3-mutated cells [20]. In vitro, a NRAS expressing leukaemia cell line was resistant to both gilteritinib and the MEK inhibitor trametinib, but remained sensitive to the two drugs in combination, suggesting the potential for combined therapy to prevent or delay the development of resistance [20].

Gilteritinib was not associated with large (20 ms) mean increases in the corrected QT (QTc) interval [10]. In the phase 1/2 study (NCT02014558) a maximum post-baseline QTcF interval longer than > 500 ms was reported in 4% (11/252) of patients and 9% (22/252) patients had a change from baseline in maximum QTcF of > 60 ms [14].

2.2 Pharmacokinetics

Gilteritinib exposure increased dose-proportionally over a dose-range of 20–450 mg once daily (0.17 to 3.75 times the recommended dosage) in patients with relapsed or refractory AML, [10]. At steady state, the mean peak plasma concentration (C_{max}) and area under the concentration-time curve (AUC) from 0 to 24 h for gilteritinib was 374 ng/mL and 6943 ng·h/mL, respectively. In the fasted state, the time to C_{max} (t_{max}) was approximately 4–6 h after dose administration. Steady-state plasma levels were reached within 15 days and drug accumulation was approximately 10-fold. Gilteritinib may be administered with or without food; coadministration of single-dose gilteritinib 40 mg with a high-fat meal in healthy subjects decreased gilteritinib C_{max} by 26% and AUC by < 10%, and prolonged t_{max} by 2 h relative to administration in the fasted state. Gilteritinib may be extensively distributed; the mean population estimated apparent central and peripheral volume of distribution values were 1092 L and 1100 L, respectively. In vitro, approximately 94% of gilteritinib is bound to human plasma proteins, primarily to human serum albumin [10].

In vitro, gilteritinib is primarily metabolized by CYP3A4. In humans, its primary metabolites at steady state include M17 (formed via *N*-dealkylation and oxidation) and M16 and M10 (both formed via *N*-dealkylation), none of which exceeded 10% of overall exposure to the parent drug [10]. Gilteritinib is eliminated largely (65%) in faeces; 16% of a dose was recovered in the urine as unchanged drug and metabolites. The estimated half-life of gilteritinib is 113 h and the estimated apparent clearance is 14.85 L/h [10].

The pharmacokinetics of gilteritinib are not affected by age (20–87 years), sex, race, mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, and mild [creatinine clearance(CL_{CR}) 50–80 mL/min] or moderate (CL_{CR} 30–50 mL/min) renal impairment to a clinically significant extent [10]. The effects of severe hepatic (Child-Pugh class C) or severe renal ($CL_{CR} \leq 29$ mL/min) impairment on the pharmacokinetics of gilteritinib have not been assessed.

Features and properties of gilteritinib

Alternative names	ASP-2215; ASP2215 hemifumarate; gilteritinib fumarate; XOSPATA®
Class	Amides; aniline compounds; antineoplastics; piperazines; piperidines; pyrans; pyrazines; small molecules
Mechanism of action	FLT3, anaplastic lymphoma kinase and AXL receptor tyrosine kinase inhibitor
Route of administration	Oral
Pharmacodynamics	Inhibits FLT3 phosphorylation and downstream signal transduction, resulting in the inhibition of AML cell proliferation
	Not associated with a large (> 500 ms) mean increase in the corrected QT interval
Pharmacokinetics	Peak plasma concentration reached in ≈ 4 to 6 h and steady state plasma levels in 15 days
	Eliminated largely (64.5%) in faeces; estimated half-life 113 h and estimated apparent clearance 14.85 L/h
Adverse reactions in patients with R/R AML	
Most frequent any grade	Myalgia/arthralgia, increased levels of transaminases, fatigue/malaise, fever, non-infectious diarrhoea, dyspnoea, oedema, rash, pneumonia
Most frequent grade ≥ 3	Pneumonia, increased levels of transaminases, dyspnoea
Nonhaematological serious	Pneumonia, sepsis, fever, dyspnoea, renal impairment
ATC codes	
WHO ATC code	L01X-E54 (gilteritinib)
EphMRA ATC code	L1 (antineoplastics); L1H (protein kinase inhibitor antineoplastics)
Chemical name	2-Pyrazinecarboxamide, 6-ethyl-3-[[3-methoxy-4-[4-(4-methyl-1-piperazinyl)-1-piperidinyl] phenyl] amino]-5-[(tetrahydro-2*H*-pyran-4-yl) amino]-, (2*E*)-2-butenedioate (2:1)

AML acute myeloid leukaemia, *R/R* relapsed/ refractory, *FLT3* FMS-like tyrosine kinase 3

Concomitant use of gilteritinib with combined P-glycoprotein (P-gp) and strong CYP3A inducers should be avoided as combined use decreases gilteritinib exposure, which may decrease the efficacy of gilteritinib [10]. The combined use of gilteritinib and strong CYP3A inhibitors increases gilteritinib exposure; therefore, alternative therapies to strong CYP3A inhibitors should be considered. If coadministration of these agents is unavoidable, patients should be monitored frequently for gilteritinib-associated adverse reactions, and in patients with serious or life-threatening toxicity, gilteritinib dosage should be reduced or interrupted. The efficacy of drugs that target $5HT_{2B}$ receptor or sigma non-specific receptor (e.g. escitalopram, fluoxetine) may be reduced if coadministered with gilteritinib; therefore, concomitant use of these agents should be avoided, unless necessary [10].

2.3 Therapeutic Trials

2.3.1 In Relapsed or Refractory AML

2.3.1.1 ADMIRAL Study The ongoing randomized, open-label, multicentre, phase 3 ADMIRAL study (NCT02421939) is assessing the efficacy and safety of gilteritinib versus salvage chemotherapy in patients with *FLT3*-mutated AML relapsed after or refractory to first-line chemotherapy [21]. The study has enrolled 371 adults with relapsed or refractory AML harbouring a *FLT3* ITD, D835 or 1836 mutation, as assessed by the LeukoStrat CDx FLT3 mutation assay [10, 21, 22]. In the first interim analysis, 28% (40/142) of patients receiving oral gilteritinib (starting dose 120 mg once daily) had achieved complete remission (CR) or complete remission with partial haematological recovery (CRh); the CR and CRh rates were 19 and 9%, respectively [7]. CR was defined as an absolute neutrophil count $\geq 1.0 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, normal marrow differential with < 5% blasts, patients must be red blood cells (RBC) and platelet transfusion independent and have no evidence of extramedullary leukaemia [10]. CRh was defined as marrow blasts < 5%, partial haematological recovery absolute neutrophil count $\geq 0.5 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L, patients must have no evidence of extramedullary leukaemia and cannot be classified as CR [10].

When only responses prior to hematopoietic stem cell transplantation (HSCT) were included in the response rates, the CR/CRh rate at the interim analysis (median follow-up 4.6 months) was 21% (29/138) [10]. The median time to first response in patients who achieved a CR/CRh was 3.6 months [10]. The CR and CRh rates were 12 and 9% respectively, and the median durations of response (DOR) for CR and CRh were 8.6 and 2.9 months. In patients with *FLT3*-ITD or *FLT3*-ITD/TKD mutations, the CR/CRh rate was 23% (29/126), while no patient with a *FLT3*-TKD mutation alone achieved a CR/CRh. Of the patients dependent on RBC and platelet transfusions at baseline 31% (33/106) became independent of transfusions during any 56-day post-baseline period, and of the patients independent of RBC

and platelet transfusions at baseline, 53% (17/32) remained transfusion-independent during any 56-day post-baseline period. Fourteen patients were still in remission at the time of the first interim DOR analysis [10].

2.3.1.2 CHRYSALIS Study In the first-in-human, open-label, phase 1/2, dose-escalation and dose-expansion CHRYSALIS study (NCT02014558), the maximum tolerated dose (MTD) of gilteritinib was established as 300 mg/day [14]. Between October 2013 and August 2015, 252 adults with relapsed or refractory AML received gilteritinib (20, 40, 80, 120, 200, 300 or 450 mg) once daily in one of seven dose-escalation ($n=23$) or dose-expansion ($n=229$) cohorts. Of the 249 patients in the full analysis set, 40% (100 patients) achieved a response, with 8% (19 patients) achieving CR, 4% (10 patients) achieving CR with incomplete platelet recovery (CRp), 18% (46 patients) achieving CRh, and 10% (25 patients) achieving partial remission (PR). Among patients with a composite CR (CRc, i.e. sum of patients with CR, CRh or CRp; $n=75$), two patients received the 20 mg/day dosage, seven the 80 mg/day dosage, 27 the 120 mg/day dosage, 36 the 200 mg/day dosage and three the 300 mg/day dosage. The median duration of response was 17 weeks (20 weeks in *FLT3* mutation-positive patients and 12 weeks in *FLT3* wildtype patients) and the median overall survival (OS) was 25 weeks (30 weeks in *FLT3* mutation-positive patients and 17 weeks in *FLT3* wildtype patients). Based on uniform in vivo target inhibition and high proportion of patients achieving overall response (55%), gilteritinib 120 mg/day dosage was selected as the starting dose for future studies [14].

Gilteritinib induced deep molecular responses that correlated with clinical response and improved OS in patients with *FLT3*-mutated relapsed or refractory AML, suggesting that the FLT3-ITD signal ratio may predict clinical benefit with gilteritinib therapy [23]. In an exploratory analysis of CHRYSALIS, of the 147 patients who received gilteritinib 120 or 200 mg/day and were *FLT3* mutation-positive, 80 were evaluable for molecular response, as assessed by next-generation sequencing (a novel MRD assay that is being validated [24]). The CRc in these 80 patients was 55% and during response 20 patients had an ITD signal ratio of $\leq 10^{-2}$ [18 patients with a signal ratio of $\leq 10^{-3}$, i.e. major molecular response (MMR); 13 patients with $\leq 10^{-4}$, i.e. minimum residual disease (MRD)-negative]. Of the evaluable patients, 60 did not achieve a molecular response, 62 did not achieve MMR and 67 patients were MRD-positive. The median OS in patients with molecular response, MMR or MRD-negative status was significantly longer than that in patients who did not achieve a molecular response, MMR or MRD-positive status (417 in the three groups vs. 199, 213 and 213 days; $p \leq 0.003$) [23].

In an analysis of MRD in 95 patients who were *FLT3* mutation-positive and received gilteritinib ≥ 80 mg/day, 14% (13/95) of patients achieved MRD-negative status and 52% (49/95) had a best overall response of CRc [25]. The median OS in patients who achieved CRc and were MRD-negative (11 patients) was significantly longer than that in patients who achieved CRc but were MRD-positive (168.7 vs. 36.1 weeks; $p=0.004$). None of the patients who received gilteritinib < 80 mg/day were MRD negative. Of the patients who were *FLT3* mutation-positive and received gilteritinib 120 mg/day, 23% (13/56) achieved a best overall response of CR/CRh; these patients had a median OS of 70.6 weeks and a 52-week survival probability of 67%. In comparison, patients who did not achieve CR/CRh had a median OS of 32.4 weeks and a 52-week survival probability of 20% [25]. Another analysis in 25 *FLT3* mutation-positive patients showed that the differentiation response to gilteritinib (≥ 80 mg/day) was strongly enriched among patients with *NPM1* and *DNMT3A* mutations [26].

2.3.1.3 In Japanese Patients An open-label phase 1 dose-escalation study (NCT02181660) in Japanese patients (aged ≥ 18 years) established the MTD dose of gilteritinib as 200 mg/day [27]. The study enrolled 24 Japanese patients with relapsed or refractory AML who received gilteritinib 20, 40, 80, 120, 200 or 300 mg once daily in one of six dose escalation cohorts. The overall response rate (ORR) in patients with *FLT3* mutation was 80% (4/5), with one patient each achieving CRp and PR, and two patients achieving CRh. In patients with wildtype *FLT3*, the ORR was 36% (4/11), with one patient achieving CR, two achieving CRp and one achieving PR [27].

2.3.2 In Newly Diagnosed AML

An ongoing, open-label, multicentre, three-arm, two-stage, phase 2/3 study (NCT02752035) is assessing the efficacy and safety of gilteritinib alone, gilteritinib plus azacitidine and azacitidine alone in newly diagnosed patients with *FLT3*-mutated AML who were ineligible for intensive induction chemotherapy [28, 29]. The study plans to enrol ≈ 540 patients [28]. The first stage of the study assessed the appropriate dose of gilteritinib in combination with azacitidine in the safety cohort, with patients receiving escalating doses of gilteritinib 80 or 120 mg/day on days 1–28 in combination with subcutaneous or intravenous azacitidine 75 mg/m^2 on days 1–7 [29]. As of June 2018, of the 15 patients in the safety cohort (14 *FLT3* mutation-positive patients), eight had a treatment duration of > 6 months, six remained on treatment and nine discontinued treatment [four patients died and one patient each withdrew because of relapse, adverse event (AE), physician decision, sponsor decision or subject decision]. One dose-limiting toxicity (DLT; tumour lysis syndrome) was reported in the observation period in one patient receiving gilteritinib 80 mg/day plus azacitidine. No DLTs were reported in patients receiving gilteritinib 120 mg/day

plus azacitidine and it was decided to proceed with this dose in the randomized stage of the study. The ORR in the safety cohort was 80% (12/15), with 10 (67%) patients achieving CRc (CR in four patients and CRh in six patients) and two patients (13%) achieving PR [29].

An ongoing open-label, dose escalation/expansion phase 1 study (NCT02236013) is assessing the safety (including DLT and MTD) and efficacy (exploratory objective) of gilteritinib in combination with induction and consolidation chemotherapy (7 + 3 induction schedule and high-dose cytarabine consolidation), followed by single-agent gilteritinib as maintenance therapy in patients with newly diagnosed AML [30, 31]. Oral gilteritinib 40, 80, 120 or 200 mg/day was administered in the dose-escalation phase following a 3 + 3 design [30, 31]. Patients received ≤ 2 cycles of a 7 + 3 induction regimen (cytarabine 100 mg/m^2/day on days 1–7 plus idarubicin 12 mg/m^2/day on days 1–3) plus gilteritinib once daily on days 4–17 (schedule 1) and subsequently changed to days 8–21 (schedule 2)]; daunorubicin 90 mg/m^2/day on days 1–3 was used as an alternative anthracycline [31]. During consolidation patients received cytarabine (1.5 g/m^2 every 12 h on days 1, 3 and 5) and gilteritinib once daily on days 1–14 at the induction dose for ≤ 3 cycles [30, 31]. Patients in the dose-expansion cohort received gilteritinib at the recommended expansion dose established during dose escalation. After consolidation or transplantation with stable engraftment, patients received gilteritinib once daily as maintenance therapy in 28-day cycles for ≤ 26 cycles [30, 31].

As of July 2018, 62 patients (60 in the safety analysis set) had been enrolled in this study, of which 32 were *FLT3* mutation-positive (23 with *FLT3*-ITD) [31]. In the dose-escalation phase, two patients in the gilteritinib 40 mg/day cohort who received gilteritinib on days 1–14 had DLTs (neutropenia, thrombocytopenia, decreased ejection fraction); no other DLTs were reported at this dosage after the gilteritinib induction schedule was changed to gilteritinib administration on days 8–21. Two patients receiving gilteritinib 200 mg/day had DLTs (neutropenia, neutropenic enterocolitis). Gilteritinib 120 mg/day was established as the MTD and the recommended expansion dose. In the response evaluable population, all *FLT3* mutation-positive patients receiving gilteritinib 120 mg/day ($n = 22$) achieved an investigator-assessed CRc regardless of regimen (schedule 1, or schedule 2 with daunorubicin; enrolment is underway for the schedule 2 cohort with idarubicin). In the schedule 1 plus idarubicin cohort, 94% of patients achieved CR and 6% achieved CRp, while in the schedule 2 plus daunorubicin cohort, 60% of patients achieved CR and 40% achieved CRh [31].

Key clinical trials of gilteritinib

Drug(s)	Indication	Phase	Status	Location(s)	Identifier	Sponsor
Gilteritinib, placebo	FLT3-ITD AML	3	Recruiting	Worldwide	NCT02997202; 2215-CL-0304; 2016-001061-83; BMT CTN 1506	Astellas Pharma Inc
Gilteritinib, placebo	FLT3-ITD AML	3	Recruiting	Worldwide	NCT02927262; 2215-CL-0302; 2016-001643-39	Astellas Pharma Inc
Gilteritinib, LoDAC, MEC, FLAG	R/R *FLT3*-mutated AML	3	Recruiting	Asian countries, Russian Federation	NCT03182244; 2215-CL-0303	Astellas Pharma Inc
Gilteritinib, LoDAC, AZA, MEC, FLAG-IDA	R/R *FLT3*-mutated AML	3	Ongoing	Worldwide	NCT02421939; 2215-CL-0301; 2015-000140-42; ADMIRAL	Astellas Pharma Inc
Gilteritinib, azacitidine	Newly diagnosed *FLT3*-mutated AML	2/3	Recruiting	Worldwide	NCT02752035; 2215-CL-0201; 2015-001790-41	Astellas Pharma Inc
Gilteritinib	R/R *FLT3*-mutated AML	EAP	No longer available	UK, Italy, Australia	NCT03409081; 2215-CL-9200	Astellas Pharma Inc
Gilteritinib	Paediatric pt with refractory *FLT3*-mutated AML	EAP	No longer available		NCT03315299; CHLA-17-00428	Children's Hospital Los Angeles
Gilterinib	R/R *FLT3*-mutated AML or *FLT3*-mutated AML in CR with MRD	EAP	Available	USA, Canada, Japan	NCT03070093; 2215-CL-9100	Astellas Pharma Inc.
Gilteritinib	R/R AML	1/2	Completed	USA, Italy, Germany	NCT02014558; 2215-CL-0101; CHRYSALIS	Astellas Pharma Inc
Gilteritinib, other targeted agents	AML	1/2	Recruiting	USA	NCT03013998; BAML-16-001	Beat AML, LLC
Gilteritinib plus atezolizumab	R/R *FLT3*-mutated AML	1/2	Planned	Not known	NCT03730012; 2215-CL-1101	Astellas Pharma Inc
Gilteritinib	AML, advanced solid tumours	1/2	Ongoing	USA	NCT02561455; 2215-CL-0109	Astellas Pharma Inc
Gilteritinib	R/R AML	1	Completed	Japan	NCT02181660; 2215-CL-0102	Astellas Pharma Inc
Gilteritinib, IDA, AraC, DNR	Newly diagnosed AML	1	Recruiting	USA	NCT02236013; 2215-CL-0103	Astellas Pharma Inc
Gilteritinib, Venetoclax	R/R AML	1	Recruiting	USA	NCT03625505; M16-802	AbbVie
Gilteritinib	Advanced solid tumours	1	Completed	USA	NCT02456883; 2215-CL-0105	Astellas Pharma Inc
Gilteritinib, IDA, AraC	Newly diagnosed AML	1	Ongoing	Japan	NCT02310321; 2215-CL-0104	Astellas Pharma Inc

AML acute myeloid leukaemia, *AraC* cytarabine, *AZA* azacitidine, *CR* complete remission, *DNR* daunorubicin, *EAP* expanded access programme, *FLAG* granulocyte colony stimulating factor, fludarabine, cytarabine, *FLT3* FMS-like tyrosine kinase 3, *IDA* idarubicin, *ITD* internal tandem repeat, *LoDAC* low-dose cytarabine, *MEC* mitoxantrone, etoposide cytarabine, *MRD* minimal residual disease, *pt* patient, *R/R* relapsed/refractory

2.4 Adverse Events

2.4.1 In Relapsed or Refractory AML

Oral gilteritinib 120 mg/day had a generally manageable tolerability profile in 292 patients with relapsed or refractory AML (median exposure 3 months) [10]. Adverse reactions resulted in the discontinuation of therapy in 8% of gilteritinib recipients. The most common (incidence ≥ 30%) any-grade adverse reactions with gilteritinib were myalgia/arthralgia (42%), increased levels of transaminases (41%), fatigue/malaise (40%), fever (35%), non-infectious diarrhoea (34%), dyspnoea (34%), oedema (34%), rash (30%) and pneumonia (30%). The most common (incidence ≥ 10%) grade ≥ 3 adverse reactions with gilteritinib were pneumonia (23%), increased levels of transaminases (16%) and dyspnoea (12%), and the most common (incidence ≥ 5%) non-haematological serious adverse reactions were pneumonia (19%), sepsis (13%), fever (13%), dyspnoea (7%) and renal impairment (5%). Other clinically significant adverse reactions in patients receiving gilteritinib included QT prolongation (7%), cardiac failure (4%), pericardial effusion (3%), pericarditis (2%), differentiation syndrome (1%), anaphylactic reaction (1%) and posterior encephalopathy syndrome (1%). The US prescribing information carries warnings and precautions related to the risk of posterior reversible encephalopathy syndrome, QT prolongation and pancreatitis [10].

2.4.2 In Newly-Diagnosed AML

In the safety cohort of the ongoing, open-label, phase 2/3 study (NCT02752035), 80% (12/15) of patients receiving gilteritinib 80 or 120 mg/day experienced adverse events considered at least possibly related to treatment, including anaemia (seven patients), febrile neutropenia and nausea (six patients each), and increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (ALT), constipation, diarrhoea, neutropenia, thrombocytopenia and pyrexia (five patients each) [29]. Grade ≥ 3 adverse events included febrile neutropenia (six patients), and anaemia and neutropenia (five patients each); serious adverse events reported in > 2 patients were febrile neutropenia (five patients), and anaemia and pyrexia (three patients each). No treatment-related deaths were reported in patients receiving gilteritinib, and of the 13 patients with post-baseline laboratory data, none had any potentially clinically significant increase in the levels of AST or ALT [i.e. levels of > 3 times the upper limit of normal (ULN)] or total bilirubin (i.e. levels of > 2 time the ULN), or a maximum post-baseline QTcF interval of > 500 ms [29].

In the safety analysis set ($n = 60$) of the ongoing open-label, dose escalation/expansion phase 1 study (NCT02236013), grade ≥ 3 adverse events occurring in > 10% of patients receiving gilteritinib 40–200 mg/day were febrile neutropenia (63%), thrombocytopenia (18%), decreased platelet count (17%) and neutropenia (15%) [31]. Serious treatment-related adverse events occurring in more than one patient were febrile neutropenia (nine patients) and small intestinal obstruction, lung infection, sepsis and decreased ejection fraction (two patients each).

2.5 Companion Diagnostic

LeukoStrat CDx FLT3 Mutation Assay, a polymerase chain reaction-based in vitro diagnostic test for use as a companion diagnostic to Astellas Pharma's gilteritinib has been developed by Invivoscribe Technologies in collaboration with Astellas Pharma. In April 2015, Invivoscribe Technologies entered into an agreement with Astellas Pharma for the development of the companion diagnostic [32]. The test is designed to detect ITD mutations and the TKD mutations D835 and I836 in genomic DNA extracted from mononuclear cells obtained from peripheral blood or bone marrow aspirates of patients diagnosed with AML. The gilteritinib companion diagnostic is approved in Japan and the USA for the diagnosis of AML with a FLT3 mutation [8, 9].

2.6 Ongoing Clinical Trials

In addition to the ongoing studies discussed in Sect. 2.3, several phase 1–3 studies are currently underway. Recruitment is underway in a randomized, double-blind, multicentre, placebo-controlled phase 3 study (NCT02997202) assessing the efficacy and safety of gilteritinib versus placebo as maintenance therapy following allogeneic HSCT in patients with *FLT3*-ITD AML in first morphologic CR. The study plans to enrol 346 patients; the primary endpoint is relapse-free survival and secondary endpoints include OS, event-free survival, and safety and tolerability. Another randomized, double-blind, multicentre, placebo-controlled phase 3 study (NCT02927262) is recruiting 354 patients to assess the efficacy and safety of gilteritinib versus placebo as maintenance therapy after induction/consolidation therapy in patients with *FLT3*-ITD AML in first CR. The primary endpoint is relapse-free survival and secondary endpoints include OS, event-free survival, and safety and tolerability. A third randomized, open-label, multicentre phase 3 study (NCT03182244) is recruiting 318 participants to evaluate the efficacy and safety of gilteritinib versus salvage chemotherapy in patients with relapsed or refractory *FLT3*-mutated AML in Asia and Russia. The primary endpoint is OS and secondary endpoints include event-free survival, CR, leukaemia-free survival, and safety and tolerability.

An expanded access programme (EAP; NCT03409081) aims to provide access to gilteritinib for adults with

FLT3-mutated AML who have relapsed, are refractory or in CR, while another EAP (NCT03315299) will provide access to gilteritinib for a single paediatric patient (12–15 year old female) with refractory *FLT3*-mutated AML without access to comparable or alternative therapy. A third EAP (NCT03070093) will provide expanded access to gilteritinib for subjects with *FLT3*-mutated relapsed or refractory AML or *FLT3*-mutated AML in CRc with MRD without access to comparable or alternative therapy.

Several other studies are underway, including a phase 1/2 study of biomarker-based treatment of AML sponsored by the Leukemia and Lymphoma Society (Beat AML; NCT03013998), a phase 1/2 study assessing the efficacy and safety of gilteritinib in combination with atezolizumab in patients with relapsed or refractory *FLT3*-mutated AML (NCT03730012), an open-label phase 1b study to assess safety and efficacy of venetoclax in combination with gilteritinib in patients with relapsed or refractory AML (NCT03625505) and a phase 1/2 rollover study that will provide access to continued treatment for patients who participated in other gilteritinib clinical trials (NCT02561455).

3 Current Status

Gilteritinib received its first global approval on 21 Sep 2018 for the treatment of relapsed or refractory AML with a *FLT3* mutation in Japan [6]. Gilteritinib was subsequently approved in the USA on 28 November 2018 for the treatment of adults who have relapsed or refractory AML with a *FLT3*-mutation, as detected by an FDA-approved test (LeukoStrat CDx FLT3 Mutation Assay).

Compliance with Ethical Standards

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