Drugs (2022) 82:469–475
https://doi.org/10.1007/s40265-022-01680-9

ADISINSIGHT REPORT

Olverembatinib: First Approval

Sohita Dhillon[1]

Published online: 23 February 2022

Abstract
Olverembatinib (HQP1351) is an oral, third-generation BCR-ABL1 tyrosine kinase inhibitor (TKI) developed by Ascentage Pharma for the treatment of chronic myeloid leukaemia (CML), acute myeloid leukaemia, acute lymphoblastic leukaemia (ALL) and solid tumours, including gastrointestinal stromal tumours (GIST). Olverembatinib is an ATP binding-site inhibitor of wild type BCR-ABL1 kinase and a broad spectrum of BCR-ABL1 mutants, including mutant T315I, which confers resistance against all first- and second-generation TKIs. In November 2021, olverembatinib received its first approval in China for the treatment of adult patients with TKI-resistant chronic-phase CML (CML-CP) or accelerated-phase CML (CML-AP) harbouring the T315I mutation, as confirmed by a validated diagnostic test. Clinical studies are underway in the US for CML and precursor cell ALL, and in China for solid tumours, including GIST. This article summarizes the milestones in the development of olverembatinib leading to this first approval for the treatment of CML-CP or CML-AP.

Digital Features for this AdisInsight Report can be found at https://doi.org/10.6084/m9.figshare.19111685

Olverembatinib: Key Points

An oral, third-generation BCR-ABL1 TKI developed by Ascentage Pharma for the treatment of haematological malignancies, including CML-CP and CML-AP, and solid tumours, such as GIST

Received its first approval on 24 November 2021 in China

Approved for use in adults with TKI-resistant CML-CP or CML-AP harbouring the T315I mutation

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

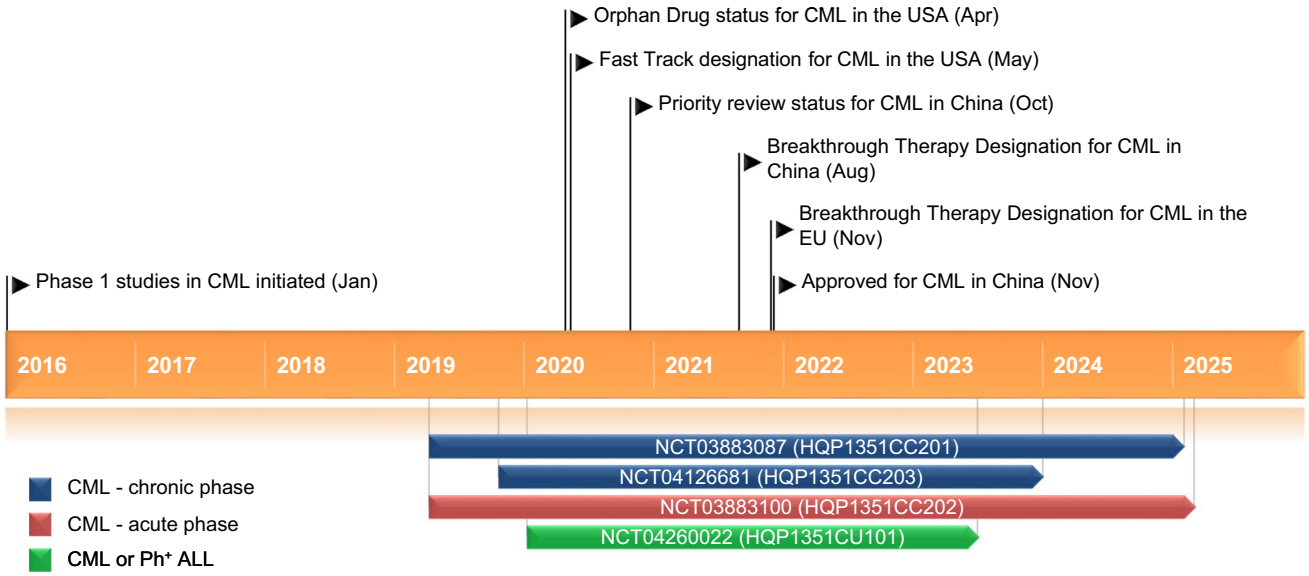
✉ Sohita Dhillon
dru@adis.com

[1] Springer Nature, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand

1 Introduction

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasia caused by constitutively active BCR-ABL1 fusion tyrosine kinase [1, 2]. The essential role of BCR-ABL1 kinase activity for oncogenic transformation in CML led to the development of targeted tyrosine kinase inhibitors (TKIs), which are currently the mainstay of CML treatment [2, 3]. Imatinib was the first BCR-ABL1 TKI to be developed and approved for use [1, 3]. However, resistance to TKI therapy, in many instances through BCR-ABL1 kinase domain point mutations, remained a challenge [4]. To overcome the limitation of imatinib-resistance, several second-generation TKIs (e.g. nilotinib, dasatinib, bosutinib) were developed, which have partially overlapping resistance profiles [2]. However, mutations of T315I (the "gatekeeper mutation") remained a common gap in coverage, conferring resistance to first- and second-generation TKIs [2]. This led to the development of third-generation TKIs (e.g. ponatinib), which have been developed to retain efficacy against the T315I mutation [2].

Olverembatinib (HQP1351) is one such third-generation TKI targeting BCR-ABL1, FLT3, KIT, and other kinases, developed by Ascentage Pharma for the treatment of patients with CML, acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), and solid tumours, including gastrointestinal stromal tumours (GIST). Olverembatinib is an oral, ATP binding-site inhibitor designed to effectively



Key milestones in the development of olverembatinib for the treatment of chronic myeloid leukaemia. *CML* chronic myeloid leukaemia; *Ph*$^+$ *ALL* Philadelphia chromosome-positive acute lymphoblastic leukaemia

target wild type BCR-ABL1 kinase and a broad spectrum of BCR-ABL1 mutants, including T315I, the highly refractory gatekeeper mutation [1, 3, 5, 6]. It is the first third-generation TKI to be developed in China, where currently no third-generation TKIs are available [3]. In November 2021 [7], olverembatinib received its first approval in China for the treatment of adult patients with TKI-resistant chronic-phase CML (CML-CP) or accelerated-phase CML (CML-AP) harbouring the T315I mutation as confirmed by a validated diagnostic test [8]. The recommended dosage is 40 mg once every 2 days (once every other day), taken orally with meals, until the disease progresses or the patient no longer tolerates the treatment [8]. Clinical studies are underway in the US for CML and precursor cell ALL, and in China for solid tumours, including GIST.

1.1 Company Agreements

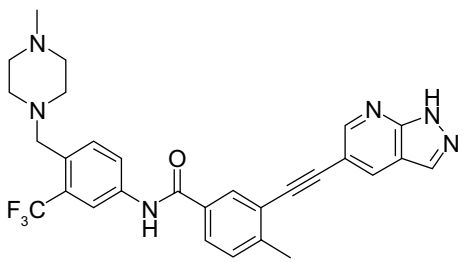
In 2013, Guangzhou Institutes of Biomedicine and Health (GIBH) transferred all patents and exclusive rights for the development of olverembatinib to Healthquest Pharma [9]. In December 2016, Ascentage Pharma acquired Healthquest Pharma [10]. In January 2019, Ascentage Pharma entered into a research and development agreement with The University of Texas MD Anderson Cancer Center for the clinical development of Ascentage Pharma's apoptosis-targeted and TKI candidates, including olverembatinib [11]. In July 2021, Ascentage Pharma and Innovent Biologics entered into a multifaceted strategic collaboration, which includes joint commercialization of olverembatinib in China [12].

2 Scientific Summary

2.1 Pharmacodynamics

Olverembatinib is a BCR-ABL1 TKI that tightly binds to the ATP binding sites of native BCR-ABL1 and multiple BCR-ABL1 mutants [binding affinities (K_d) of 0.18–3.2 nM], including the most refractory gatekeeper mutant T315I [5]. Olverembatinib binds to both the phosphorylated and non-phosphorylated forms of BCR-ABL1 kinase (K_d 0.32 and 0.34 nM, respectively), as well as to several other kinases, including KIT, FLT3, fibroblast growth factor receptor 1 (FGFR1), and platelet-derived growth factor receptor α (PDGFRα) [5, 13]. Olverembatinib induced G0/G1 phase arrest and apoptosis in leukaemia cells [13] and GIST cells [14].

Olverembatinib dose-dependently suppressed the activation of BCR-ABL1 and downstream CRKL and STAT5 proteins in BCR-ABL-positive human CML cells in vitro [5]. A dose-dependent reduction in CRKL phosphorylation was



Chemical structure of olverembatinib

Features and properties of olverembatinib

Alternative names	APG 1351; D 824; GZD 824; HQP 1351
Class	Antineoplastics; benzamides; fluorinated hydrocarbons; piperazines; pyrazoles; pyridines; small molecules
Mechanism of action	Inhibits wild type BCR-ABL1 kinase and a broad spectrum of BCR-ABL mutants (including T315I), as well as other kinases including KIT, FLT3, FGFR1 and PDGFRα
Route of administration	Oral
Pharmacodynamics	Tightly binds to the ATP-binding sites of native BCR-ABL and multiple BCR-ABL mutants, including T315I
	Binds to both the phosphorylated and non-phosphorylated forms of BCR-ABL kinase
	Binds to and inhibits other kinases, such as KIT, FLT3, FGFR1 and PDGFRα and their mutant kinases
	Dose-dependently suppresses the activation of BCR-ABL and downstream CRKL and STAT5
	Suppresses proliferation of leukaemia cells expressing native or mutant BCR-ABL or mutant FLT3 in vitro and in xenograft models
	Versus ponatinib, it exhibits more potent or equivalent antiproliferative activity in imatinib-resistant and -sensitive GIST cell lines, and greater antitumour activity in xenograft models from imatinib-resistant GIST cancer cell lines
Pharmacokinetics	Peak plasma concentration 4-8 h after dosing
	Slight to moderate accumulation on day 27 after multiple dosing
	Mean terminal elimination half-life 17.5 to 42.5 h
Common AEs	
Haematological	Thrombocytopaenia, anaemia, leukopaenia, neutropaenia
Non-haematological	Skin pigmentation, hypocalcaemia, proteinuria, hypertriglyceridaemia, hyperphosphataemia, arthralgia, fatigue, increased creatinine kinase, increased aspartate aminotransferase, increased alanine aminotransferase
ATC codes	
WHO ATC code	L01X-E (protein kinase inhibitors)
EphMRA ATC code	L1X (all other antineoplastics)
Chemical name	4-Methyl-*N*-[4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]-3-[2-(1H-pyrazolo[3,4-b]pyridin-5-yl) ethynyl]benzamide

AE, adverse events, *AML*, acute myeloid leukaemia, *FGFR1* fibroblast growth factor receptor 1, *GIST* gastrointestinal stromal tumour, *PDGFRα* and platelet-derived growth factor receptor α

also observed in peripheral blood mononuclear cells from patients with TKI-resistant CML who received olverembatinib in a phase 1 study (HQP1351-SJ002; Sect. 2.3.2), with ≥ 50% reduction in phosphorylation observed with doses of 12–60 mg [15]. Olverembatinib inhibited both wild-type and various mutant KIT kinases in a biochemical assay [14], suppressed the phosphorylation of FLT3, FGFR1, PDGFRα and their downstream signalling in leukaemia cells [13], and inhibited both the SRC kinase and PI3K/AKT pathways in precursor ALL (pre-B ALL) cells (thereby inhibiting proliferation) [16].

Olverembatinib potently suppressed proliferation of leukaemia cells expressing BCR-ABL1, including K562 and Ku812 human CML cells and SUB-B15 human ALL cells (IC_{50} values of 0.21, 0.13 and 2.5 nM, respectively) in vitro [5]. Olverembatinib also suppressed proliferation of leukaemia cells harbouring *FLT3*, *FGFR1* and *PDGFRα* mutations [13, 17] and B cell precursor ALL (pre-B ALL) cells in vitro [16]. In vivo, olverembatinib suppressed the growth of tumours driven by native and mutant BCR-ABL in mouse xenograft or allograft models of human leukaemia, and provided significant survival benefit in an allograft leukaemia mouse model [5]. Olverembatinib suppressed the growth of *FLT3-ITD* mutant AML xenograft tumours [13, 18] and prolonged survival of tumour-bearing mice [18]. Proliferation of primary cells isolated from the bone marrow of patients with AML (seven had native FLT3 and one had *FLT3-ITD-E654D* mutation) [13] and the growth of pre-B ALL cells in patient-derived xenograft mouse models [16] were also inhibited with olverembatinib.

Compared with the third-generation BCR-ABL1 and KIT inhibitor ponatinib, olverembatinib exhibited more potent or equivalent antiproliferative activity in both imatinib-resistant and -sensitive GIST cell lines, and exhibited slightly better antitumour activity in xenograft models derived from imatinib-resistant GIST cancer cell lines [14]. In KIT mutant GIST cell lines, olverembatinib appeared to inhibit phosphorylation of KIT and its downstream proteins (e.g. AKT, ERK1/2, STAT3) to a greater extent than ponatinib or imatinib. Olverembatinib also appeared to have stronger inhibitory effects on colony formation, migration and cell invasion, as well as cell cycle arrest and cell apoptosis than ponatinib or imatinib in GIST cell lines [14].

In addition, in preclinical studies synergistic antitumour effects were observed with olverembatinib plus the allosteric inhibitor asciminib [19], the BCL-2 inhibitor lisaftoclax [18], and the MDM2-p53 antagonist APG-115 [20].

2.2 Pharmacokinetics

Pharmacokinetic properties of olverembatinib are based on data from an open-label, multicentre, phase 1 dose-escalation study (HQP1351-SJ002) conducted in China involving adults with CML-CP or CML-AP who were resistant to or intolerant of first- or second-generation TKIs (Sect. 2.3.2) [21]. Olverembatinib exposure (area under the drug concentration-time curve and peak plasma drug concentration) increased in an approximately dose proportional manner following oral administration of olverembatinib doses of 1–60 mg. Peak olverembatinib concentration was reached four to 8 h after dosing. Following multiple dosing, a slight to moderate accumulation of olverembatinib was observed on day 27. Olverembatinib elimination appeared to be linear, with a mean terminal elimination half-life of 17.5–42.5 h [21].

A population pharmacokinetic analysis based on data from 65 patients showed that the pharmacokinetics of olverembatinib are best described by a two-compartment model with first-order absorption and first-order elimination. Olverembatinib pharmacokinetics were significantly affected by total bilirubin, aspartate aminotransferase (AST) and albumin levels [22].

2.3 Therapeutic Trials

2.3.1 Pivotal Phase 2 Studies

Oral olverembatinib was efficacious in heavily TKI-pretreated patients with T315I-mutated CML-CP or CML-AP who were participating in two pivotal, ongoing, open-label, multicentre, single-arm, studies HQP1351CC201 (NCT03883087) and HQP1351CC202 (NCT03883100). Patients received olverembatinib 40 mg once every other day in a 28-day cycle for 24 months [6].

As of data cutoff (25 August 2020), study HQP1351CC201 had enrolled 41 patients (median age 47 years) with CML-CP, of whom 32 (78%) had completed ≥ 12 treatment cycles [6]. After a median follow-up of 13 (3.1–16.3) months, 75.6% of patients (31 of 41 evaluable) had experienced major cytogenetic response (MCyR; primary endpoint), with 28 (68.3%) CCyRs. Major molecular response (MMR) was achieved among 23 of 41 patients (56.1%). Furthermore, of the 31 evaluable patients who did not have a complete haematological response (CHR) at baseline, 31 (100%) achieved CHR following olverembatinib treatment. The 12-month progression-free survival (PFS) rate was 89.3% (95% CI 73.9–95.8%), and OS was 100% (95% CI 100–100%) [6].

As of data cutoff (27 July 2020), study HQP1351CC202 had enrolled 23 patients (median age 41 years) with CML-AP, of whom 14 (61%) had completed ≥ 12 treatment cycles [6]. After a follow-up of 13.5 months, 73.9% (17 of 23 evaluable) of patients who did not have responses at baseline had experienced MaHR (primary endpoint) with olverembatinib, including 65.2% patients with CHR and 8.7% with no evidence of leukaemia (NEL); MCyR was achieved among 52.2% (12 of 23 evaluable) of patients and CCyR among 11 (47.8%). Nine of 23 (39.1%) patients achieved MMR. The 12-month PFS rate was 74.1% (95% CI 48.2–88.4%), and the OS was 91.3% (95% CI 69.5–97.8%) at this time point [6].

2.3.2 Phase 1 Study

Olverembatinib demonstrated potent anti-leukaemic activity in adults with CML-CP or CML-AP resistant to or intolerant

Key clinical trials of olverembatinib conducted by Ascentage Pharma

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Olverembatinib	CML-CP	2	Active, not recruiting	China	NCT03883087; HQP1351CC201
Olverembatinib	CML-AP	2	Active, not recruiting	China	NCT03883100; HQP1351CC202
Olverembatinib, best available therapy	CML-CP	2	Active, not recruiting	China	NCT04126681; HQP1351CC203
Olverembatinib	CML or Ph^+ ALL	1b	Ongoing	China, USA	NCT04260022; HQP1351CU101
Olverembatinib	CML	1	Completed	China	HQP1351-SJ002; SJ002
Olverembatinib	GIST or other solid tumours	1	Recruiting	China	NCT03594422; SJ-0003

AP acute phase; *CML* chronic myeloid leukaemia; *CP* chronic phase; GIST gastrointestinal stromal tumour; *Ph^+ ALL* Philadelphia chromosome-positive acute lymphoblastic leukaemia

of first- or second-generation TKIs who were participating in an open-label, multicentre, phase 1 dose-escalation study (HQP1351-SJ002) conducted in China [23]. Patients in 11 dose cohorts received olverembatinib 1–60 mg once every other day in 28-day cycles. A total of 101 patients (median age 40 years) with CML-CP (n = 86) or CML-AP (n = 15) were enrolled, of whom 62.4% (63/101) harboured a T315I mutation; 17.8% (18/101) of patients were treated with olverembatinib for > 3 years and 5% (5/101) for > 4 years [23]. The maximum tolerated dose of olverembatinib was determined to be 50 mg and the recommended phase 2 dose (RP2D) was 40 mg [22].

As of data cutoff (2 February 2021), 97.0% of patients without baseline responses had CHR, 62.1% had CCyR and 51.0% had MMR after a median follow-up of 30.8 months. In patients with CML-CP and T315I mutations, 100% achieved CHR, 83.7% achieved MCyR and 71.2% achieved MMR after treatment with olverembatinib; the 36-month PFS rate was 96.3%. In patients with CML-AP and T315I mutations, 80% had CHR, 54.5% had MCyR and 54.5% had MMR; the 36-month PFS rate was 71.4%. In patients who had received olverembatinib for > 4 years, the CHR, MCyR, CCyR and MMR rates were 100%, 100%, 80% and 60%, respectively; the mean 36- and 48-month PFS rates were both 100% and the 60-month PFS rate was not reached. Olverembatinib was efficacious regardless of baseline BCR-ABL1 mutational status [23]. An exposure-efficacy analysis using MCyR data from 89 patients with CML (78 with CML-CP and 11 with CML-AP) showed a clear efficacy-response relationship, with increased probability of achieving MCyR at 6 months with increasing average olverembatinib dose [22].

2.4 Adverse Events

Olverembatinib had an acceptable tolerability profile in heavily TKI-pretreated patients with T315I-mutated CML-CP or CML-AP who were participating in the two pivotal phase 2 studies (HQP1351CC201 and HQP1351CC202; Sect. 2.3.1) [6].

In study HQP1351CC201 in patients with CML-CP, the most common any grade and grade 3 or 4 treatment-related haematological AEs with olverembatinib were thrombocytopaenia (70.7% and 48.8%, respectively), anaemia (61% and 26.8%), leukopaenia (43.9% and 17.1%) and neutropaenia (36.6% and 19.5%) [6]. The most common treatment-related non haematological any grade AEs with olverembatinib included skin pigmentation (56.1%) and increased levels of creatine kinase (51.2%), alanine aminotransferase (39.0%) and aspartate aminotransferase (34.1%), most of which were mild or moderate in severity. No deaths were reported in the study [6].

In study HQP1351CC202 in patients with CML-AP, the most common any grade and grade 3 or 4 treatment-related AEs with olverembatinib were thrombocytopaenia (73.9% and 56.5%, respectively), anaemia (60.9% and 34.8%), leukopaenia (56.5% and 30.4%) and neutropaenia (26.1% and 21.7%) [6]. Serious AEs in patients receiving olverembatinib included thrombocytopaenia (17.4%) and anaemia (13.0%). Common non-haematological AEs with olverembatinib included skin pigmentation (69.6%), hypocalcaemia (52.2%), proteinuria (47.8%), hypertriglyceridaemia (56.5%), hyperphosphataemia (47.8%) and arthralgia (34.8%), most of which were mild or moderate in severity [6].

The tolerability profile of olverembatinib in the phase 1 dose-escalation study (HQP1351-SJ002) in patients with TKI-resistant CML-CP or CML-AP was generally similar to that observed in the phase 2 studies. Most treatment-related AEs with olverembatinib were of mild or moderate severity [23]. Common any grade treatment-related non-haematological AEs in patients receiving olverembatinib were skin hyperpigmentation (86.1%), hypertriglyceridaemia (59.4%) and proteinuria (58.4%), and the most common haematological AEs were thrombocytopaenia (77.2%), anaemia (41.6%) and leukopaenia (22.8%). The most common grade ≥ 3 treatment-related non-haematological AEs were hypertriglyceridaemia (10.9%), pyrexia (6.9%) and proteinuria (5.0%), and haematological AEs with olverembatinib were thrombocytopaenia (51.5%), leukopeania (20.8%) and anaemia (15.8%) [23]. An exposure-safety analysis using a cell life-span model showed a significant dose response relationship between the olverembatinib average dose and the incidence of grade ≥ 3 reductions in platelet count [22]. However, the phase 1 dose-escalation study (HQP1351-SJ002) showed that the incidences of treatment-related AEs generally decreased over time, while responses (efficacy) increased over time [23].

2.5 Ongoing Clinical Trials

In addition to the ongoing studies discussed in Sect. 2.3, a pivotal, randomized, open label phase 2 study (NCT04126681) is underway to evaluate the efficacy of olverembatinib versus best available therapy (hydroxyurea or IFN-based therapy or homoharringtonine, imatinib/dasatinib/nilotinib) in 144 patients with CML-CP who are resistant to and/or intolerant of first- and second-generation TKIs. The primary outcome measure of the study is event-free survival.

Also underway is an open-label phase 1b bridging study (NCT04260022) to evaluate the pharmacokinetic properties, RP2D, efficacy and safety of olverembatinib in patients with CML-CP, CML-AP, CML-blast phase or Philadelphia chromosome-positive ALL (with or without the T315I mutation) who are resistant to or intolerant of ≥ 3 TKIs. Eligible patients are being randomized to receive oral olverembatinib

30, 40 or 50 mg ($n = 10$ per group) once every other day in 28-day cycles [24].

Recruitment is underway for an open-label, multicentre, phase 1 study (NCT03594422) to determine the RP2D (primary objective), and to assess the safety, tolerability, pharmacokinetic and preliminary anti-tumour activity (secondary objectives) of olverembatinib in ~ 30 patients with GIST or other solid tumours.

3 Current Status

Olverembatinib received its first approval on 24 November 2021 in China for the treatment of adult patients with TKI-resistant CML-CP or CML-AP harbouring the T315I mutation, as confirmed by a validated diagnostic test [7, 8].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-022-01680-9.

Declarations

Funding The preparation of this review was not supported by any external funding.

Authorship and conflict 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 authors on the basis of scientific completeness and accuracy. Sohita Dhillon is a contracted employee of Adis International Ltd/Springer Nature and declares no relevant conflicts of interest. All authors contributed to the review and are responsible for the article content.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

References

1. Alves R, Goncalves AC, Rutella S, et al. Resistance to tyrosine kinase inhibitors in chronic myeloid leukemia-from molecular mechanisms to clinical relevance. Cancers. 2021;13(19):4820.
2. Braun TP, Eide CA, Druker BJ. Response and resistance to BCR-ABL1-targeted therapies. Cancer Cell. 2020;37(4):530–42.
3. Javidi-Sharifi N, Hobbs G. Future directions in chronic phase CML treatment. Curr Hematol Malig Rep. 2021;16(6):500–8.
4. Shoukier M, Kubiak M, Cortes J. Review of new-generation tyrosine kinase inhibitors for chronic myeloid leukemia. Curr Oncol Rep. 2021;23(8):91.
5. Ren X, Pan X, Zhang Z, et al. Identification of GZD824 as an orally bioavailable inhibitor that targets phosphorylated and nonphosphorylated breakpoint cluster region-Abelson (Bcr-Abl) kinase and overcomes clinically acquired mutation-induced resistance against imatinib. J Med Chem. 2013;56(3):879–94.
6. Jiang Q, Dayu S, Zongru L, et al. Updated results of pivotal phase 2 trials of olverembatinib (HQP1351) in patients (pts) with tyrosine kinase inhibitor (TKI)-resistant BCR-ABL1 T315I-mutated chronic- and accelerated-phase chronic myeloid leukemia (CML-CP and CML-AP). Blood. 2021;138(Suppl 1):3598.
7. Ascentage Pharma. Ascentage Pharma and Innovent Biologics announce approval for China's first third-generation BCR-ABL TKI olverembatinib, marking a clinical breakthrough in the treatment of chronic myeloid leukemia [media release]. 30 Nov 2021. https://www.ascentagepharma.com/press-releases/ascentage-pharma-and-innovent-biologics-announce-approval-for-chinas-first-third-generation-bcr-abl-tki-olverembatinib-marking-a-clinical-breakthrough-in-the-treatment-of-chronic-myeloid-leu-2/.
8. Ascentage Pharma. Olverembatinib (HQP1351): Chinese prescribing information. 2021
9. Guangzhou Institutes of Biomedicine and Health Chinese Academy of Sciences. http://english.gibh.cas.cn/Comment/201305/t20130527_102502.html. Accessed 20 Dec 2021.
10. Ascentage Pharma. 2019 Annual report. https://www.ascentagepharma.com/wp-content/uploads/2020/08/2020041700666.pdf. Accessed 20 Dec 2021.
11. Ascentage Pharma, MD Anderson Cancer Center. Ascentage Pharma and MD Anderson Cancer Center announce strategic alliance in cancer drug development [media release]. 6 Jan 2019. https://www.ascentagepharma.com/news/press-releases/.
12. Innovent Biologics. Ascentage Pharma and Innovent Biologics reach multifaceted strategic agreement totaling US$245 million including commercialization of olverembatinib (HQP1351) in China, joint clinical development of lisaftoclax (APG-2575) and equity investment [media release]. 14 Jul 2021. https://www.ascentagepharma.com/news/press-releases/.
13. Wang Y, Zhang L, Tang X, et al. GZD824 as a FLT3, FGFR1 and PDGFRα inhibitor against leukemia in vitro and in vivo. Transl Oncol. 2020;13(4):100766.
14. Liu X, Wang G, Yan X, et al. Preclinical development of HQP1351, a multikinase inhibitor targeting a broad spectrum of mutant KIT kinases, for the treatment of imatinib-resistant gastrointestinal stromal tumors. Cell Biosci. 2019;9:88.
15. Jiang Q, Huang XJ, Chen Z, et al. Safety and efficacy of HQP1351, a 3rd generation oral BCR-ABL inhibitor in patients with tyrosine kinase inhibitor-resistant chronic myelogenous leukemia: preliminary results of phase I study [abstract]. Blood. 2018;132(Suppl. 1):791.
16. Ye W, Jiang Z, Lu X, et al. GZD824 suppresses the growth of human B cell precursor acute lymphoblastic leukemia cells by inhibiting the SRC kinase and PI3K/AKT pathways. Oncotarget. 2017;8(50):87002–15.
17. Jiang K, Tang X, Guo J, et al. GZD824 overcomes FGFR1-V561F/M mutant resistance in vitro and in vivo. Cancer Med. 2021;10(14):4874–84.
18. Fang DD, Zhu H, Tang Q, et al. FLT3 inhibition by olverembatinib (HQP1351) downregulates MCL-1 and synergizes with BCL-2 inhibitor lisaftoclax (APG-2575) in preclinical models of FLT3-ITD mutant acute myeloid leukemia. Transl Oncol. 2021;15(1):101244.
19. Wang G, Lv J, Tang C, et al. ATP-site inhibitor olverembatinib, HQP1351, enhanced the effect of allosteric inhibitor on the resistance conferred by the compound mutations of BCR-ABL [abstract]. Cancer Res. 2021;81(13 Suppl):1463.
20. Fang DD, Tang Q, Wang Q, et al. Synergy of tyrosine kinase inhibitor HQP1351 and MDM2-P53 antagonist, APG-115, in preclinical models of FLT3 mutant and TP53 wild-type acute myeloid leukemia [abstract]. Cancer Res. 2020;80(16 Suppl):4217.
21. Jiang Q, Huang X, Chen Z, et al. An updated safety and efficacy results of phase 1 study of HQP1351, a novel 3rd generation of BCR-ABL tyrosine kinase inhibitor (TKI), in patients

with TKI resistant chronic myeloid leukemia [abstract]. Blood. 2019;134(Suppl 1):493.
22. Lu M, Deng C, Xiong Y, et al. Exposure-response (E-R) analysis of olverembatinib (HQP1351) in Chinese patients with chronic myeloid leukemia (CML) [abstract]. Blood. 2020;136(Suppl 1):5–6.
23. Jiang Q, Shi D, Li Z, et al. Updated safety and efficacy results of phase 1 study of olverembatinib (HQP1351), a novel third-generation BCR-ABL tyrosine kinase inhibitor (TKI), in patients with TKI-resistant chronic myeloid leukemia (CML) [abstract plus presentation]. Blood. 2021;138(Suppl 1):311.
24. Jabbour EJ, Kantarjian H, Issa GC, et al. Trial in Progress: Phase 1b bridging study of the pharmacokinetics (PK), safety, and efficacy of orally administered olverembatinib (HQP1351) in patients with refractory chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ ALL) [abstract]. Blood. 2021;138(Suppl 1):2551.