Pimtespib: First Approval

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Abstract

Pimtespib (Jeselhy®) is an oral small molecule inhibitor of the α and β isoforms of heat shock protein 90 (HSP90). HSP90α and HSP90β regulate the stability and activity of a number of proteins that are crucial for tumour development. Pimtespib is being developed by Taiho Pharmaceutical for the treatment of solid tumours, including gastrointestinal stromal tumour (GIST), and in June 2022 it received its first approval in Japan for GIST that has progressed after chemotherapy. Pimtespib is undergoing phase I development for the treatment of solid tumours in the EU and the USA. This article summarizes the milestones in the development of pimtespib leading to this first approval for GIST that has progressed after chemotherapy.

1 Introduction

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal tumour of the gastrointestinal tract (occurring more frequently in the stomach and small intestine and more rarely in the oesophagus) [1, 2]. Its formation involves genetic changes in one of several genes: ≈ 80% and ≈ 10% of GIST cases are associated with mutations in the KIT and platelet-derived growth factor receptor α (PDGFRα) genes, which encode receptor tyrosine kinases [2]. Given the general resistance of GIST to conventional chemotherapy, the introduction of tyrosine kinase inhibitors (TKIs) revolutionized GIST treatment [3]. However, most patients with an initial clinical response to first-line TKI therapy with imatinib eventually experience disease progression [3], usually subsequent to the emergence of secondary KIT mutations [4]. In such cases, subsequent lines of TKI therapy, including newer generation TKIs (e.g. sunitinib, regorafenib) are of limited clinical benefit [3].

A molecular chaperone is ‘any protein that interacts with, stabilizes or helps another protein to acquire its functionally active conformation, without being present in their final structure’ [5]. Among the molecular chaperones that generally participate in de novo protein folding and refolding is heat shock protein 90 (HSP90) [5]. HSP90 has four isoforms: α, β, glucose related protein 94 (GRP94) and tumour necrosis factor receptor-associated protein 1 (TRAP1) [6, 7]. HSP90α and HSP90β regulate the stability and activity of a number of proteins [including the receptor tyrosine kinases ALK, FLT3, KIT, MET and PDGFRα and the growth factor receptor epidermal growth factor receptor (EGFR)] crucial for tumour development [5–9]. Thus, it is considered a promising target for the treatment of certain cancers [5].

Pimtespib (Jeselhy®) is an orally administered inhibitor of HSP90α and HSP90β being developed by Taiho Pharmaceutical for the treatment of solid tumours, including GIST [8–10]. On 20 June 2022, it received its first approval...
in Japan for GIST that has progressed after chemotherapy [9, 10]. Its target population is patients who have already received treatment with imatinib, sunitinib and regorafenib [10].

Pimitespib is available as 40 mg tablets and should be taken on an empty stomach [10]; Sect. 2.2. The recommended adult dosage is 160 mg once daily for 5 consecutive days followed by 2 days of no treatment in a repeating 7-day cycle. Local prescribing information should be consulted for information regarding dose modification recommendations in the event of adverse events (AEs) [9, 10]. The use of pimitespib is contraindicated in patients with a history of hypersensitivity to the ingredients of the drug [10]. Pimitespib may impair reproductive function. Patients should use appropriate contraception during and for a period of time after the administration of pimitespib. The drug should be used in pregnant or potentially pregnant women only if the therapeutic benefit outweighs the risks, and should be avoided in breastfeeding women. The efficacy and safety of pimitespib as an adjunct therapy to surgery or when administered concomitantly with other antineoplastic agents have not been established [10]. Pimitespib is undergoing phase I development for the treatment of solid tumours in the EU and the USA [11].

2 Scientific Summary

2.1 Pharmacodynamics

Pimitespib is a potent and selective small molecule inhibitor of HSP90α and HSP90β [8]. In a biochemical assay, it potently inhibited the binding of geldanamycin (an HSP90 inhibitor) to HSP90α and HSP90β [mean inhibitory constant (Ki) 34.7 and 21.3 nmol/L] but did not inhibit GRP94 and TRAP1 (mean Ki > 50,000 and > 50,000 nmol/L) [8]. In human colorectal carcinoma cell lines, pimitespib inhibited HSP90α and HSP90β at a concentration of 300,000 nmol/L but did not inhibit GRP94 at a concentration of 3,000,000 nmol/L [8]. Pimitespib reduced phosphorylated KIT levels in the Golgi apparatus, inhibited proliferation and induced apoptosis in imatinib-naïve and -resistant GIST cell lines, and reduced phosphorylated EGFR levels and suppressed the growth of gefitinib-naïve and gefitinib-resistant EGFR-mutated lung cancer cell lines [12].

Oral pimitespib displayed potent antitumour activity along with the depletion of multiple HSP90 client proteins in human tumour xenograft mouse and rat models [8, 12]. In the rat model, antitumour activity was demonstrated without detectable ocular toxicities (a notable HSP90-related AE; Sect. 2.4), with the distribution of pimitespib greater in tumours and plasma than in the retina (from which it was eliminated within 24 h). Pimitespib also exhibited antitumour activity against an orthotopic human lung cancer xenograft mouse model expressing EGFR [8].

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In a first-in-human, open-label, multinational, phase I study in patients with advanced solid tumours, oral pimtespib 4.8–107.5 mg/m² once daily induced HSP70 protein expression (a pharmacodynamic marker of HSP90 inhibitors) in a dose-dependent manner [13].

2.2 Pharmacokinetics

Taking pimtespib with a high-fat meal increased systemic exposure to the drug relative to administration in fasted conditions; pimtespib should therefore be taken on an empty stomach (i.e. at least 1 h before or 2 h after a meal) [10].

The pharmacokinetics of oral pimtespib were initially assessed in a first-in-human, multinational phase I study in patients with advanced solid tumours [13]. Systemic exposure to pimtespib was dose proportional over a dose range of 4.8–150.5 mg/m²; there was no unexpected accumulation in pimtespib exposure between days 1 and 8 of the first treatment cycle [13]. Pimtespib (administered as a 160 mg dose once daily to Japanese patients with advanced solid tumour) reached its maximum concentration in a mean of 3.87 h on day 1 and 2.98 h on day 5 [10].

In vitro, pimtespib binds to plasma proteins (mostly serum albumin) extensively (93.1–93.6%) and is metabolized mainly via carboxylesterase 1 [10]. In patients with advanced solid tumours receiving oral pimtespib, the parent drug (2.2% of the dose), amide hydrolysate and N-demethylated drug were detected in the urine up to 24 h following administration. Pimtespib dosages of 160 mg once daily had a mean half-life of 11.22 h on day 1 and 10.40 h on day 5 [10].

In vitro, pimtespib is a BCRP and P-gp substrate and inhibits BCRP, P-gp and OATP1B1 [10]. It displays CYP3A, MATE1 and MATE2-K inhibitory effects; thus, the exposure of drugs that serve as CYP3A (e.g. midazolam) and MATE1 and MATE2-K (e.g. metformin) substrates may increase when coadministered with pimtespib [10].

2.3 Therapeutic Trials

2.3.1 Phase III Study

Oral pimtespib significantly reduced the risk of disease progression or death relative to placebo in Japanese patients (aged ≥ 20 years) with previously treated advanced GIST participating in the randomized, double-blind, placebo-controlled treatment period of a multicentre, phase III study (CHAPTER-GIST-301; JapicCTI-184094) [14]. CHAPTER-GIST-301 enrolled patients who had previously received treatment with imatinib, sunitinib and regorafenib, or were intolerant to the most recent of these therapies. Patients enrolled in the double-blind period received (under fasting conditions) pimtespib 160 mg/day or placebo for 5 consecutive days followed by 2 days off treatment per week in 21-day cycles until disease progression, unacceptable toxicity, withdrawal of consent or investigator-determined discontinuation [14].

After a median follow-up duration of 8.0 months for pimtespib and 7.0 months for placebo (data cut-off date 23 June 2020), median blinded central radiological review (BCRR)-assessed progression-free survival (PFS) [primary endpoint] was 2.8 months in the pimtespib group (n = 58) and 1.4 months in the placebo group (n = 28) [hazard ratio (HR) 0.51 (95% CI 0.30–0.87); p = 0.006] [14]. These results were consistent with those of an investigator analysis [HR 0.58 (95% CI 0.33–1.02); p = 0.028]. Moreover, HRs for this endpoint favoured pimtespib over placebo in the KIT exon 9 mutation detected, KIT exon 11 mutation detected, and KIT exon 13/14 or 17/18 mutation detected subgroups, although the benefit did not reach statistical significance. At the time of this analysis, 73 BRCC-PFS events (46 in the pimtespib group and 27 in the placebo group) had occurred. One pimtespib recipient and 17 placebo recipients experienced...
BCRR-confirmed disease progression during the double-blind period and crossed over into an open-label period, during which those originally assigned to placebo received pimitespib 160 mg/day while those originally assigned to pimitespib continued therapy at the same or a lower dose. The median PFS achieved by the patients originally assigned to placebo was 2.7 months [14].

Fourth-line therapy with pimitespib significantly reduced the risk of death relative to placebo according to an analysis designed to correct for crossover bias by using the rank-preserving structural failure time (RPSFT) method [14]. Median overall survival (OS) was 13.8 months in the pimitespib group and 7.6 months in the RPSFT-adjusted placebo group [HR 0.42 (95% CI 0.21–0.85); p = 0.007]. In the unadjusted OS analysis, median OS was 13.8 months with pimitespib and 9.6 months with placebo [HR 0.63 (95% CI 0.32–1.21); p = 0.081]. Although no patient in either treatment group achieved a BCRR- assessed complete response (CR) or partial response (PR) in this study, the BCRR-assessed disease control rate (i.e. a CR, PR or stable disease for ≥ 12 weeks) was 27.6% with pimitespib and 21.4% with placebo. The median time to BCRR-assessed disease progression was 2.8 months in the pimitespib group and 1.4 months in the placebo group [HR 0.67 (95% CI 0.41–1.09); p = 0.052] [14].

In CHAPTER-GIST-301, dose interruptions (≤ 21 days) and dose reductions (to 120, 80 or 40 mg/day) were permitted for the management of AEs, with the study drug discontinued if dose interruptions of > 21 days were necessary [14]. BCRR-assessed PFS was defined as the period between the date of randomization until the date of radiological disease progression or death by any cause, whichever occurred first. OS was defined as the period between the date of randomization until the date of death by any cause [14].

### 2.3.2 Phase II Study

Oral pimitespib demonstrated clinical benefits in Japanese patients (aged ≥ 20 years) with previously treated advanced GIST refractory to imatinib, sunitinib and regorafenib who were participating in an open-label, noncomparative phase II study (JapicCTI-163182) [15]. Patients (n = 40) received (under fasting conditions) pimitespib 160 mg/day for 5 consecutive days followed by 2 days off treatment per week in 21-day cycles until disease progression, unacceptable AEs or withdrawal of consent. At the data cut-off date of 9 June 2017 (median treatment duration of 77.5 days), centrally assessed median PFS (primary endpoint) was 4.4 months and median OS was 11.5 months. The progression-free rate at 12 weeks was 73.4%, the objective response rate was 0% and the disease control rate was 85.0%; 85.0% of patients had stable disease for 6 weeks [15].

### 2.3.3 Phase I Studies

Pimitespib showed promise as a treatment for advanced solid tumours, including heavily pretreated GIST, in patients participating in a first-in-human, open-label, multinational, phase I, dose-escalation and -expansion study (NCT02965885; JapicCTI-142444) [13]. In the dose-escalation period of this study, patients received oral pimitespib 4.8–150.5 mg/m² once daily or 107.5–295.0 mg/m² every other day in 21-day cycles. The maximum tolerated doses (MTDs) were 107.5 mg/m² once daily and 210.7 mg/m² once every other day. With no correlation between body surface area and oral clearance identified, the dosages for the dose-expansion period were determined to be 160 mg once daily or 340 mg every other day. Moreover, as most of the patients who received once-daily pimitespib at the MTD developed treatment-related AEs (TRAEs) during the first cycle and thus required drug interruption, the administration schedule was modified to once daily for 5 consecutive days followed by 2 days of no treatment in 7-day cycles for the dose-expansion period. Treatment in both periods was continued until disease progression, the occurrence of unacceptable AEs or withdrawal of informed consent [13].

Across both periods of NCT02965885, therapy with oral pimitespib resulted in confirmed PRs in one patient with advanced GIST and two patients with non-small cell lung cancer (NSCLC) [13]. The responses were durable: 239 days in the patient with GIST without a detectable KIT mutation, 173 days in the patient with NSCLC without detectable ALK and EGFR mutations and 463 days (at the time of data cut-off) in the patient with NSCLC with an EGFR exon 19 deletion mutation. Disease control (i.e. PR or stable disease for 12 weeks) was achieved by 27% of 60 patients [13].

Preliminary efficacy with oral pimitespib in combination with intravenous nivolumab was displayed in patients with colorectal cancer and other solid tumours participating in an open-label, multicentre, phase I, dose-escalation and -expansion study (EPOC1704) [16]. Enrolled patients had colorectal cancer (n = 29), gastric cancer (n = 8), sarcoma (n = 5), NSCLC (n = 1) or melanoma (n = 1). They initially received pimitespib (80–160 mg once daily) monotherapy for 2 weeks, after which intravenous nivolumab 3 mg/kg every 2 weeks was added to the treatment regimen. Overall, median PFS was 3.0 months and the objective response rate was 14% [16].
2.4 Adverse Events

Oral pimtespib had a manageable safety profile in patients with previously treated advanced GIST participating in CHAPTER-GIST-301 [14]. Moreover, its safety profile in this study was consistent with that seen in the phase II study [15].

Although almost all (93.1%) of 58 pimtespib recipients (vs 39.3% of 28 placebo recipients) in CHAPTER-GIST-301 experienced TRAEs of any grade, few (5.2% vs 0% with placebo) experienced a TRAE leading to permanent discontinuation; most AEs were manageable with dose modification [14]. The most frequently reported (incidence ≥ 30%) TRAEs of any grade in the pimtespib and placebo groups were diarrhoea (74.1% vs 14.3% of patients) and decreased appetite (31.0% vs 7.1%). Most (79.1%) of the diarrhoea events were reversible (median time to resolution of 33 days). Grade ≥ 3 TRAEs occurred in 25.9% and 3.6% of patients in the pimtespib and placebo groups; treatment-related serious AEs were reported in six (10.3%) pimtespib recipients. During the double-blind period of this study, dose reductions and interruptions owing to TRAEs occurred in 34.5% and 58.6% of pimtespib recipients and 0% and 7.1% of placebo recipients. There were no treatment-related deaths in CHAPTER-GIST-301. One AE leading to death was reported during the study in a pimtespib recipient (tumour haemorrhage), but was deemed unrelated to the study medication [14].

Eye disorders have been commonly reported with several HSP90 inhibitors [14]. In CHAPTER-GIST-301, grade 2 retinal vein occlusion (n = 1) and grade 2 visual impairment (n = 1) were reported with pimtespib therapy. Both vision abnormalities resolved following treatment discontinuation and dose interruption/reduction, respectively. The most common visual abnormality was grade 1 night blindness (13.8% of patients); most resolved (median time to resolution of 21 days) and did not require dose modification or treatment discontinuation [14].

Combination therapy with oral pimtespib plus intravenous nivolumab was associated with a manageable safety profile; there were no dose-limiting toxicities at any dose level [16].

2.5 Ongoing Clinical Trials

A noncomparative phase II study (JapicCTI-163182) is underway in Japan to evaluate the efficacy and safety of pimtespib in adults with advanced GIST following disease progression on or intolerance to imatinib, regorafenib or sunitinib. In addition, the randomized, open-label, phase I CHAPTER-GIST-101 study (NCT05245968) in Japan is currently recruiting patients to assess the maximum tolerated dose, pharmacokinetics, efficacy and safety of pimtespib in combination with imatinib in adults with advanced GIST who are considered refractory to imatinib.

3 Current Status

Pimtespib received its first approval on 20 June 2022 in Japan for GIST that has progressed after chemotherapy [9, 10].

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