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ADISINSIGHT REPORT

Enlonstobart: First Approval

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Abstract
Enlonstobart (Enshuxing®), a recombinant, fully humanised immunoglobulin G4 monoclonal antibody targeted against programmed cell death protein 1 (PD-1), is being developed by the CSPC Pharmaceutical Group for the treatment of advanced cervical cancer and other solid tumours. Enlonstobart received its first approval (a conditional marketing authorisation) in June 2024, in China, for use in patients with recurrent or metastatic programmed cell death ligand 1 (PD-L1)-positive cervical cancer who have failed previous platinum-containing chemotherapy. Phase III clinical evaluation of enlonstobart for use as first-line treatment (in combination with chemotherapy ± bevacizumab) in patients with recurrent or metastatic PD-L1-positive cervical cancer is also underway in China. Additionally, phase II clinical development of enlonstobart (as a part of combination therapy) for use against a range of other solid tumour types is continuing. This article summarises the milestones in the development of enlonstobart leading to this first approval for recurrent or metastatic cervical cancer.

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Enlonstobart (Enshuxing®): Key Points

An anti-PD-1 monoclonal antibody is being developed by the CSPC Pharmaceutical Group for the treatment of advanced cervical cancer and other solid tumours

Received its first approval on 28 June 2024 in China

Approved for use in patients with recurrent or metastatic PD-L1-positive cervical cancer who have failed previous platinum-containing chemotherapy

1 Introduction

Enlonstobart (Enshuxing®), a recombinant, fully humanised immunoglobulin G4 (IgG4) monoclonal antibody targeted against programmed cell death protein 1 (PD-1) [1], is being developed in China by the CSPC Pharmaceutical Group for the treatment of advanced cervical cancer and other solid tumours [2, 3]. The binding of PD-1, a transmembrane receptor protein expressed on T-cells, to its ligands, programmed cell death ligand 1 and ligand 2 (PD-L1 and PD-L2), can inhibit T-cell proliferation and cytokine production [4]. In some cancers, modulation of PD-1/PD-L1 signalling is a mechanism for tumours to evade an antigen-specific T-cell immunological response [4]. Enlonstobart binds to and inhibits PD-1, blocking the interaction between the receptor and its ligands, thereby reversing PD-1/PD-L1 signalling pathway-mediated immunosuppression, resulting in the activation of T-cells and T-cell-mediated immune responses against tumour cells [1–3].

Enlonstobart received its first approval (a conditional marketing authorisation) on 28 June 2024, in China, for use in patients with recurrent or metastatic PD-L1-positive cervical cancer who have failed previous platinum-containing chemotherapy [1–3]. Conditional approval was granted based on objective response rate (ORR) and duration of response (DoR) data from a single-arm phase II clinical trial (NCT04886700). The full approval in this indication is dependent on the confirmation in ongoing clinical trials of the clinical benefits of enlonstobart therapy.

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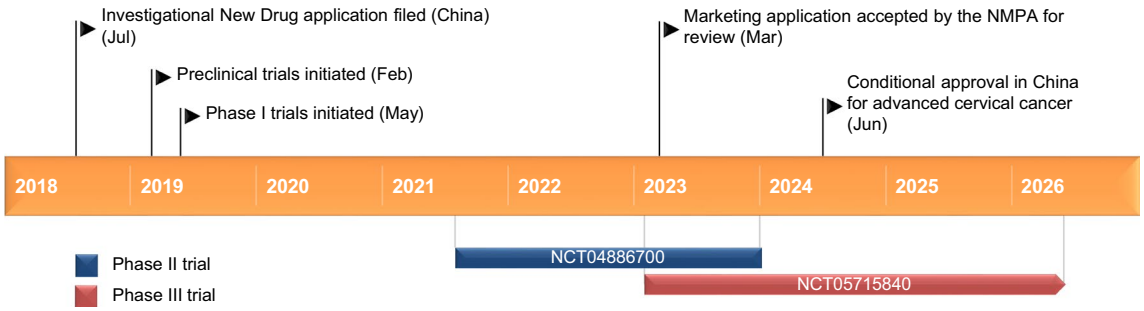

Key milestones in the development of enlonstobart. *NMPA* National Medical Products Administration (China)

Enlonstobart is administered by intravenous infusion, with a recommended dosage of enlonstobart 240 mg once every 2 weeks, with treatment to continue until the occurrence of disease progression or intolerable toxicity [1]. No dose adjustment is required for patients with mild or moderate renal impairment or mild hepatic impairment; use of enlonstobart is not recommended in patients with moderate or severe hepatic impairment. Enlonstobart should be used with caution in elderly patients (aged ≥ 65 years). Given the potential for pharmacodynamic drug interactions, systemic corticosteroids and other immunosuppressive agents should be avoided before initiating enlonstobart therapy. Local prescribing information should be consulted for guidelines on the use of treatment interruption or permanent discontinuation for the management of adverse reactions [1]. Atypical responses (e.g. temporary tumour enlargement or the appearance of new lesions during the first few months of treatment, followed by tumour shrinkage) may be observed with enlonstobart therapy. Even if there is preliminary evidence of disease progression on imaging, if the patient's clinical symptoms are improving or stable, continued treatment with enlonstobart may be considered (based on the judgement of overall clinical benefit) until disease progression is confirmed [1].

Enlonstobart is currently under phase III clinical evaluation in China for use as first-line treatment (in combination with chemotherapy ± bevacizumab) in patients with recurrent or metastatic PD-L1-positive cervical cancer [2]. Additionally, phase II clinical development of enlonstobart (as a part of combination therapy) is continuing in China for use against a range of other solid tumour types, including advanced triple-negative breast cancer and metastatic colorectal cancer [2].

1.1 Company Agreements

Enlonstobart was originally developed by Hangzhou Sumgen Biotech [5]. In 2019, the rights and interests relating to enlonstobart in China were transferred to the CSPC Pharmaceutical Group.

2 Scientific Summary

Enlonstobart is a fully humanised immunoglobulin G4 monoclonal antibody targeted against PD-1 [1].

2.1 Pharmacodynamics

Enlonstobart binds PD-1 with high affinity, thereby blocking the interaction between PD-1 and the ligands PD-L1 and PD-L2 [1]. Rapid activation of CD3+, CD4+ and CD8+ T-cells was observed in patients with advanced tumours who were administered a single dose of enlonstobart 1–10 mg/kg. With such dosing, the mean PD-1 receptor occupancy rate was > 80%, with occupancy maintained at this level for approximately 3 weeks. Similar, and generally stable, levels of PD-1 receptor occupancy were achieved with multiple doses of enlonstobart every 2 weeks [1].

2.2 Pharmacokinetics

After a single intravenous dose in Chinese patients with advanced tumours, exposure to enlonstobart was dose proportional over a range of 1 mg/kg to 10 mg/kg in a phase I study (NCT03852823) [1]. Steady-state plasma concentrations were reached after six doses with 2-weekly dosing. After a single dose of enlonstobart 240 mg in patients with advanced tumours, maximum plasma concentrations were reached in a mean time of 1.4 h, the geometric mean volume of distribution was 5.27 L, the geometric mean clearance was 0.69 L/day, and the geometric mean drug half-life was 5.76 days [1].

Age (range 23–84 years), body weight (range 29–98 kg), mild hepatic impairment, mild to moderate renal impairment, anti-drug antibody positivity, PD-L1 expression, tumour type and Eastern Cooperative Oncology Group (ECOG) score had no clinically relevant effects on enlonstobart pharmacokinetics based on population pharmacokinetic analysis [1].

Features and properties of enlonstobart

Alternative names	Enshuxing®; 恩舒幸®; SG-001; SYSA-1802
Class	Antineoplastics; immunotherapies; monoclonal antibodies
Mechanism of action	PD-1 receptor antagonism; antibody-dependent cell cytotoxicity; T-lymphocyte stimulation
Route of administration	Intravenous infusion
Pharmacodynamics	Binds PD-1 with high affinity, thereby blocking the interaction between PD-1 and the ligands PD-L1 and PD-L2, resulting in rapid activation of CD3+, CD4+ and CD8+ T-cells
Pharmacokinetics	After a single dose of enlonstobart 240 mg: mean T_{max} = 1.4 h; geometric mean volume of distribution = 5.27 L; geometric mean clearance = 0.69 L/day; geometric mean $t_{½}$ = 5.76 days
Most common adverse events	Anaemia, increased aspartate aminotransferase, rash, increased alanine aminotransferase, decreased white blood cell count, decreased neutrophil count, hypothyroidism, proteinuria
ATC codes	
WHO ATC code	L01F-F (PD-1/PD-L1 inhibitors)
EphMRA ATC code	L1G5 (Monoclonal antibody antineoplastics, PD-1/PD-L1)

PD-1 programmed cell death protein 1, *PD-L1/-L2* programmed cell death ligand 1/ligand 2, $t_{½}$ half-life, T_{max} time to maximum concentration

2.3 Therapeutic Trials

Enlonstobart demonstrated promising anti-tumour activity in a multicentre, single-arm, phase II trial (NCT04886700) in adults with PD-L1-positive (combined positive score ≥ 1) recurrent or metastatic cervical cancer who had failed platinum-based chemotherapy [6]. Patients in the trial received enlonstobart 240 mg intravenously every 2 weeks for up to 24 months or until disease progression or intolerable toxicity. At a median follow-up of 13.95 months, among patients in the full analysis set (FAS) population (n = 100), the independent review committee (IRC)-assessed confirmed ORR; primary endpoint) was 28.0% (95% CI 19.48–37.87) and the disease control rate (complete or partial response or stable disease) was 54.0% (95% CI 43.74–64.02) [1]. Two patients had a complete response and 26 patients had a partial response. The median DoR was 16.62 months (95% CI 10.81 to not reached) and the median progression-free survival (PFS) was 2.99 months (95% CI 2.23–6.90). At data cut-off, median overall survival was not reached; the 6-month and 12-month overall survival rates were 76.2% (95% CI 66.32–83.47) and 67.1% (95% CI 56.53–75.62).

In the FAS population, patients had a median age of 53.0 years (range 26–72), a median time since diagnosis of cervical cancer of 20.90 months (range 4.0–138.3), and an ECOG performance status of 0 (34%) or 1 (66%) [1]. The majority (94%) of patients had cervical squamous cell carcinoma, 5% had adenocarcinoma and 1% had adenosquamous carcinoma; 88% of patients had distant metastases at baseline. All patients had received at least one prior line of platinum-based chemotherapy, 26% had received second-line systemic therapy, 11% had received third- or greater-line systemic therapy, 92% had received radiotherapy, and 33% had received bevacizumab. Patients had to have at least one measurable lesion at baseline. Responses were assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 and required confirmation after ≥ 4 weeks.

Enlonstobart earlier demonstrated promising anti-tumour activity in patients with recurrent or metastatic cervical cancer in a multicentre, single-arm, phase 1b trial (NCT03852823) expansion cohort [7]. In total, 91 patients with recurrent or metastatic cervical cancer who had failed at least one prior line of chemotherapy were enrolled and treated with intravenous enlonstobart 240 mg every 2 weeks for up to 24 months or until disease progression or intolerable toxicity. In the FAS population (n = 91), the IRC-assessed ORR (primary efficacy endpoint) was 25.3% (95% CI 16.7–35.5) and the disease control rate was 63.7% (95% CI 53.0–73.6). Three patients had a complete response and 20 patients had a partial response. The median DoR had not been reached at data cut-off; the 12-month DoR rate was 62.4% (95% CI 35.7–80.5). Although responses were observed in patients both with PD-L1-positive and PD-L1-negative tumours, subgroup analyses in the phase Ib trial suggested that PD-L1 expression could be a predictor of enlonstobart effectiveness. In patients with PD-L1-positive (n = 43) and PD-L1-negative (n = 45) tumours, respectively, the ORRs were 30.2% (95% CI 17.2–46.1) and 20.0% (95% CI 9.6–34.6) and the median PFS was 7.1 months (95% CI 4.1–17.1) and 4.3 months (95% CI 26.2–6.2).

The dose regimen used in both the phase II and phase Ib trials was determined on the basis of efficacy and safety data from the phase Ia portion of the NCT03852823 trial, in patients with advanced tumours [7].

Key clinical trials of enlonstobart (CSPC Pharmaceutical Group and subsidiaries)

Identifier	Indication	Phase	Drug(s)	Location	Status
NCT05715840	Recurrent or metastatic PD-L1-positive cervical cancer	III	Enlonstobart; paclitaxel; cisplatin; carboplatin; bevacizumab; placebo	China	Recruiting
NCT04886700	Recurrent or metastatic PD-L1-positive cervical cancer	II	Enlonstobart	China	Active
NCT05068141	Advanced triple-negative breast cancer	II	Enlonstobart; nab-paclitaxel	China	Recruiting
NCT06089330	Metastatic colorectal cancer	II	Enlonstobart; becotatug; irinotecan; regorafenib	China	Not yet recruiting
NCT04983550	Relapsed epithelial ovarian cancer	II	Enlonstobart; liposomal doxorubicin	China	Not yet recruiting
NCT06136988	Unresectable oesophageal squamous carcinoma	I/II	Enlonstobart; albumin-bound docetaxel; cisplatin; paclitaxel	China	Not yet recruiting
NCT06132217	Advanced solid tumours	I/II	Enlonstobart; simmitinib	China	Not yet recruiting
NCT05508659	Advanced solid tumours	I/II	Enlonstobart; duvelisib	China	Not yet recruiting
NCT03852823	Advanced solid tumours	I	Enlonstobart	China	Active

PD-L1 programmed cell death ligand 1

2.4 Adverse Events

Enlonstobart monotherapy has an acceptable safety and tolerability profile, based on data from the NCT04886700 and NCT03852823 clinical trials [1, 6, 7]. Across the trials, 329 patients with advanced cancers (204 with cervical cancer) received enlonstobart (including 289 patients who received enlonstobart at a dose of 240 mg every 2 weeks) for a median duration of 3.25 months [1]. The most common (incidence ≥ 10%) adverse reactions in the pooled analysis were anaemia, increased aspartate aminotransferase (AST), rash, increased alanine aminotransferase (ALT), decreased white blood cell count, decreased neutrophil count, hypothyroidism and proteinuria. Grade ≥ 3 adverse reactions were reported in 25.2% of patients in the pooled analysis.

In the phase II NCT04886700 trial, with a median exposure to enlonstobart of 2.89 months, the most common adverse reactions (all grades, incidence ≥ 10%) were anaemia (22.4%), decreased white blood cell count (19.6%), increased AST (18.7%), increased ALT (15.9%), decreased neutrophil count (15.0%), hypothyroidism (15.0%) and hyperthyroidism (11.2%) [1]. Grade ≥ 3 adverse reactions were experienced by 28.0% of patients in the phase II trial; the most common (incidence ≥ 2%) grade ≥ 3 adverse reactions were anaemia (6.5%), decreased white blood cell count (3.7%), decreased neutrophil count (2.8%), increased γ-glutamyl transferase (2.8%) and increased ALT (2.8%). Four patients (3.7%) permanently discontinued enlonstobart treatment due to adverse reactions (one case each of pulmonary artery thrombosis, autoimmune anaemia, immune-mediated haemorrhagic erosive gastritis and immune-mediated enterocolitis; all grade 3); 17 patients (15.9%) had treatment with enlonstobart interrupted due to adverse reactions, most commonly due to increased ALT/AST.

2.5 Ongoing Clinical Trials

The safety and efficacy of enlonstobart in combination with chemotherapy (± bevacizumab) as first-line treatment in patients with recurrent or metastatic PD-L1-positive cervical cancer is being evaluated in a randomised, double-blind, placebo-controlled phase III trial (NCT05715840) [2]. Additionally, phase II clinical development of enlonstobart (as a part of combination therapy) is continuing in China for use against a range of other solid tumour types [2], including advanced triple-negative breast cancer (NCT05068141), metastatic colorectal cancer (NCT06089330), relapsed epithelial ovarian cancer (NCT04983550) and unresectable oesophageal squamous carcinoma (NCT06136988).

3 Current Status

Enlonstobart received its first approval on 28 June 2024, in China, for use in patients with relapsed or metastatic PD-L1-positive cervical cancer who have failed previous platinum-containing chemotherapy [2, 3].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-024-02119-z.

Declarations

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Ethics Approval, Consent to Participate, Consent to Publish, Availability of Data and Material, Code Availability Not applicable.

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