Serplulimab: First Approval

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Abstract
Serplulimab (汉斯状®) is an intravenously administered anti-PD-1 antibody being developed by Shanghai Henlius Biotech, Inc. for the treatment of solid tumours. Anti-PD-1 immunotherapies, such as serplulimab, can stimulate immune responses by relieving PD-1-related immunosuppression. Serplulimab received its first approval on 25 Mar 2022 in China for the treatment of adult patients with advanced unresectable or metastatic microsatellite instability-high (MSI-H) solid tumours that have failed to respond to previous standard treatments. This article summarizes the milestones in the development of serplulimab leading to this first approval in the treatment of MSI-H solid tumours in adults.

Serplulimab (汉斯状®): Key points
An anti-PD-1 monoclonal antibody is being developed by Shanghai Henlius Biotech, Inc. for the treatment of solid tumours
Received its first approval on 25 Mar 2022 in China
Approved for use in the treatment of adult patients with advanced unresectable or metastatic MSI-H solid tumours that have failed to respond to previous standard treatments

1 Introduction
Microsatellites are short repeating DNA sequences, which in cells with microsatellite instability (MSI), can increase or decrease in length following DNA replication [1]. MSI has been implicated in the tumorigenesis for a range of solid cancers, including in tumours that exhibit an MSI-high (MSI-H) phenotype. Immunotherapies targeting programmed cell death protein 1 (PD-1) have been successfully utilized in the treatment of MSI-H tumours [1].

Serplulimab (汉斯状®) is a fully humanized anti-PD-1 IgG4 antibody being developed by Shanghai Henlius Biotech, Inc. for the treatment of adult patients with advanced unresectable or metastatic MSI-H solid tumours that have failed to respond to previous standard treatments [1], including in patients with advanced colorectal cancer, gastric cancer, endometrial cancer and other solid tumours [2]. Serplulimab is being assessed as a treatment for other solid tumours, including small cell lung cancer, squamous and non-squamous non-small cell lung cancer, oesophageal carcinoma, gastric cancer, colorectal cancer and head and neck squamous cancer [2]. The recommended dosage of serplulimab is 3 mg/kg administered via intravenous infusion once every 2 weeks until disease progression or unacceptable toxicity [3]. Serplulimab is not recommended in patients who have moderate or severe hepatic impairment or kidney disease [3].

1.1 Company Agreements
PT Kalbe Genexine Biologics entered into a collaboration agreement and an exclusive licencing agreement with Shanghai Henlius Biotech, Inc. in Sep 2019 for the commercialisation rights of serplulimab in the Philippines, Indonesia, Malaysia, Singapore, Thailand, Laos, Myanmar, Cambodia, Brunei and Vietnam [4, 5].
2 Scientific Summary

2.1 Pharmacodynamics

Serplulimab is a competitive inhibitor of PD-1, with binding regions that overlap with nivolumab and pembrolizumab (other PD-1 inhibitors) at the PD-L1 binding site [6]. Serplulimab, nivolumab and pembrolizumab have high affinities for human PD-1 with affinity constants in the nanomolar range (K_D 2.42 nM, 11.9 nM and 8.04 nM, respectively). In cell assays, serplulimab blocked the interaction between PD-1 and its ligands PD-L1 and PD-L2 (IC50 4.36 nM and 6.46 nM, respectively) and inhibited T cell proliferation and stimulation in a dose-dependent manner. In vivo, dose-dependent inhibition of tumour growth by serplulimab was demonstrated, which was comparable to that by nivolumab and pembrolizumab. Furthermore, serplulimab exhibited a synergistic effect in inhibiting tumour growth when administered with a bevacizumab biosimilar [6].

2.2 Pharmacokinetics

Serplulimab is completely absorbed after intravenous infusion [3]. Based on population pharmacokinetic analyses, the volume of distribution of serplulimab in cancer patients is 5.61 L. The baseline clearance of serplulimab in cancer patients is 0.219 L/d, and the lowest clearance is 0.697-times the baseline clearance. The time to reach half of the maximum change in clearance is 125 d. The half-life is 17.9 d after the first dose and 23.0 d at steady state. The pharmacokinetics of serplulimab have not been studied in children or adolescents, or in patients with hepatic impairment or kidney disease [3].

2.3 Therapeutic Trials

The primary endpoint was objective response rate (ORR) assessed by an independent radiological review committee (IRRC) using RECIST version 1.1 criteria, which was 39.7% in the main efficacy analysis population with 68 patients with MSI-H solid tumours, including 3 patients (4.4%) who achieved a complete response (CR) [7]. In this single-arm, open-label, phase II trial (NCT03941574), 108 patients with unresectable or metastatic MSI-H solid tumours aged 18–75 years received intravenous treatment with serplulimab 3 mg/kg once every 2 weeks for up to 2 years or until disease progression, unacceptable toxicity or patient withdrawal [7]. Colorectal cancer was the most common cancer reported in evaluable patients [7]. The median overall survival (OS), progression-free survival (PFS) and duration of response (DOR) were not yet reached as of the latest data cut-off (10 Jul 2021); the median follow-up duration was 13.5 months [7].

Median OS was significantly prolonged with serplulimab than with placebo [15.4 vs 10.9 months; hazard ratio (HR) 0.63, 95% CI 0.49–0.82; p < 0.001] in patients with extensive-stage small cell lung cancer (interim analysis of primary endpoint) [8]. In this international, double-blind, multicenter, phase III trial (NCT04063163) patients with extensive-stage small cell lung cancer who had not received prior systemic therapy were randomized to receive serplulimab 4.5 mg/kg (n = 389) or placebo (n = 196) intravenously once every 3 weeks; all patients received carboplatin and etoposide intravenously once every 3 weeks for up to four cycles. Disease progression was assessed by IRRC using RECIST version 1.1 criteria. In secondary analyses, median PFS was significantly longer in the serplulimab group than the placebo group (5.8 vs 4.3 months; HR 0.47, 95% CI
Features and properties of serplulimab

- **Alternative names:** Hansizhuang®, siluli dankang zhushaye, HLX10
- **Class:** Antineoplastics, antivirals, immunotherapies, monoclonal antibodies
- **Mechanism of action:** Inhibits PD-1-related immunosuppression, thereby stimulating an immune response against tumours
- **Route of administration:** Intravenous
- **Pharmacodynamics:**
  - $K_d$ 2.42 nM for human PD-1; $IC_{50}$ 4.36 nM against PD-1/PD-L1, 6.46 nM against PD-1/PD-L2
- **Pharmacokinetics:**
  - $V_d$ 5.61 L; $CL$ initially 0.219 L/d; $t_\frac{1}{2}$ 17.9 d after first dose and 23.0 d at steady state
- **Adverse reactions:**
  - Most frequent grade ≥ 3 reactions: Anaemia, hypertension, liver injury, elevated bilirubin, elevated AST, decreased neutrophil count and decreased lymphocyte count
- **ATC codes:**
  - WHO ATC code: J05 (antivirals for systemic use), L01X-C (monoclonal antibodies)
  - EphMRA ATC code: J5B (antivirals, excluding anti-HIV products), L1G (monoclonal antibody antineoplastics)
- **Chemical name:** Immunoglobulin G4 (228-proline), anti-(human programmed cell death protein 1) (human-mus musculus monoclonal HLX10 gamma4-chain), disulfide with human-mus musculus monoclonal HLX10 kappa-chain, dimer

One patient (7.7%) receiving serplulimab 3 mg/kg achieved partial response and four patients (30.8%) receiving serplulimab 0.3 or 3 mg/kg (two patients for each dose group) achieved stable disease in a pooled analysis of three phase I studies in solid tumours (NCT0346875, NCT03757936 and NCT03952403) [11]. Patients were treated with biweekly intravenous infusions of serplulimab 0.3–10 mg/kg during these trials [11].

### 2.4 Adverse Events

The safety and tolerability of serplulimab were assessed in 320 patients in 6 clinical studies [3]. 79.1% of patients were treated with serplulimab 3 mg/kg and the median treatment duration was 2.84 months. The incidence of all grade ≥ 3 adverse reactions was 41.9%. In descending order, the most common reactions were anaemia, hypertension, liver injury, blood bilirubin increased, aspartate aminotransferase increased, neutrophil count decreased, lymphocyte count decreased, γ-glutamyltransferase increased and white blood cell count decreased; the incidences of the individual reactions were not reported. Immune-related reactions of special interest reported with serplulimab included skin reactions (any-grade incidence 8.4%), hepatitis (2.8%), nephritis (2.8%), pancreatitis (2.8%), thrombocytopenia (2.8%), pneumonitis (2.2%), diarrhoea (2.5%), colitis (0.9%), and myocarditis (0.9%); immune-related reactions of the endocrine system included hypothyroidism (10.0%), hyperthyroidism (5.0%), thyroiditis (0.9%), hypopituitarism (0.6%) and hyperglycemia or diabetes mellitus (0.6%) [3].

One hundred and eight adult patients with advanced unresectable or metastatic MSI-H solid tumours were treated with serplulimab in the pivotal NCT03941574 trial, in which the most common (incidence ≥ 3%) grade ≥ 3 adverse reactions were anaemia (9.3%), intestinal obstruction (5.6%),...
hepatic function abnormal (4.6%), pneumonitis (4.6%), \( \gamma \)-glutamyltransferase increased (4.6%), blood bilirubin increased (4.6%), hyponatremia (3.7%) and aspartate aminotransferase increased (3.7%) \[3\]. Serplulimab was discontinued in 37 patients (34.3%) due to adverse reactions, most commonly due to pneumonitis, abnormal liver function, bilirubin increased, platelet count decreased and intestinal obstruction. Treatment was permanently discontinued due to adverse reactions in 4 patients (3.7%) \[3\].

### 2.5 Ongoing Clinical Trials

There are ongoing trials that are investigating serplulimab for the treatment of solid tumours, including trials that are assessing combination therapies with other drugs which are being developed by Shanghai Henlius Biotech, Inc., such as HLX04 (a bevacizumab biosimilar) and HLX07 (a cetuximab biobetter).

There are four active trials investigating serplulimab in solid tumours, including NCT04033354 in squamous non-small cell lung cancer (phase III; serplulimab plus carboplatin and nab-paclitaxel vs placebo plus carboplatin and nab-paclitaxel), NCT04063163 in extensive-stage small cell lung cancer (phase III; serplulimab plus carboplatin and etoposide vs placebo plus carboplatin and etoposide), NCT03958890 in locally advanced/metastatic oesophageal squamous cell carcinoma (phase III; serplulimab plus cisplatin and fluorouracil vs placebo plus cisplatin and fluorouracil vs placebo plus cisplatin and fluorouracil vs placebo plus...
fluorouracil) and NCT03973112 in advanced hepatocellular carcinoma (phase II; serplulimab plus HLX04).

Six trials assessing serplulimab are currently recruiting patients, including NCT03941574 in MSI-H or mismatch repair deficient solid malignant tumours (phase II; serplulimab), NCT04976647 in squamous non-small cell lung cancer (phase II; serplulimab plus HLX07, carboplatin and nab-paclitaxel vs serplulimab plus carboplatin and nab-paclitaxel vs serplulimab plus HLX07), NCT03952403 in non-squamous non-small cell lung cancer (phase III; serplulimab ± HLX04 plus carboplatin and metemodex vs carboplatin and metemodex), NCT04139135 in gastric cancer (phase III; serplulimab plus oxaliplatin and tegafur/gimeracin/otetacil vs placebo plus oxaliplatin and tegafur/gimeracin/otetacil), NCT05246982 in gastric or gastroesophageal junction cancer (phase II; HLX07 plus serplulimab, capcitabine and oxaliplatin vs HLX07) and NCT04547166 in metastatic colorectal cancer (phase II/III; serplulimab plus HLX04, capcitabine and oxaliplatin vs placebo plus bevacizumab, capcitabine and oxaliplatin).

Trials investigating serplulimab which are not yet recruiting include NCT05354700 in extensive stage small cell lung cancer (phase II; HLX07 plus serplulimab, carboplatin and etoposide), NCT05353257 in limited-stage small cell lung cancer (phase III; serplulimab plus carboplatin/cisplatin-etoposide and concurrent radiotherapy vs placebo plus carboplatin/cisplatin-etoposide and concurrent radiotherapy), NCT05221658 in oesophageal squamous cell or oesophageal adenocarcinoma (phase II; HLX07 plus serplulimab, cisplatin and fluorouracil vs HLX07), NCT05239650 in colorectal cancer (phase II; HLX07 plus serplulimab and HLX04 vs HLX07 plus bevacizumab, carboplatin and oxaliplatin vs placebo plus bevacizumab, carboplatin and oxaliplatin vs placebo plus bevacizumab, carboplatin and oxaliplatin vs placebo plus bevacizumab, carboplatin and oxaliplatin vs placebo plus bevacizumab).

3 Current Status

Serplulimab received its first approval on 25 Mar 2022 for the treatment of adult patients with advanced unresectable or metastatic MSI-H solid tumours that have failed to respond to previous standard treatments in China [1].

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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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