Drugs (2025) 85:699–706
https://doi.org/10.1007/s40265-025-02160-6

ADISINSIGHT REPORT

Iparomlimab and Tuvonralimab: First Approval

Susan J. Keam[1]

Accepted: 5 February 2025 / Published online: 1 April 2025
© Springer Nature Switzerland AG 2025

Abstract
Iparomlimab and tuvonralimab (齐倍安®) is a bifunctional combination of anti-programmed death receptor-1 (PD-1)/anti-cytotoxic T lymphocyte-associated protein-4 (CTLA-4) monoclonal antibodies (mAbs) being developed by Qilu Pharmaceutical Co., Ltd for the treatment of advanced, solid, malignant tumours. In September 2024, iparomlimab and tuvonralimab was granted conditional approval (based on surrogate endpoints) for the treatment of patients with recurrent or metastatic cervical cancer who have failed previous platinum-based chemotherapy. This article summarizes the milestones in the development of iparomlimab and tuvonralimab leading to this first approval for the treatment of patients with recurrent or metastatic cervical cancer who have failed previous platinum-based chemotherapy.

Digital Features for this AdisInsight Report can be found at https://doi.org/10.6084/m9.figshare.28347014.

Iparomlimab and Tuvonralimab (齐倍安®): Key Points

A bifunctional combination of anti-PD-1/anti-CTLA-4 mAbs being developed by Qilu Pharmaceutical for the treatment of advanced, solid, malignant tumours

Received its first approval (conditional approval based on surrogate endpoints) on 26 September 2024 in China

Approved for use in patients with recurrent or metastatic cervical cancer who have failed previous platinum-based chemotherapy

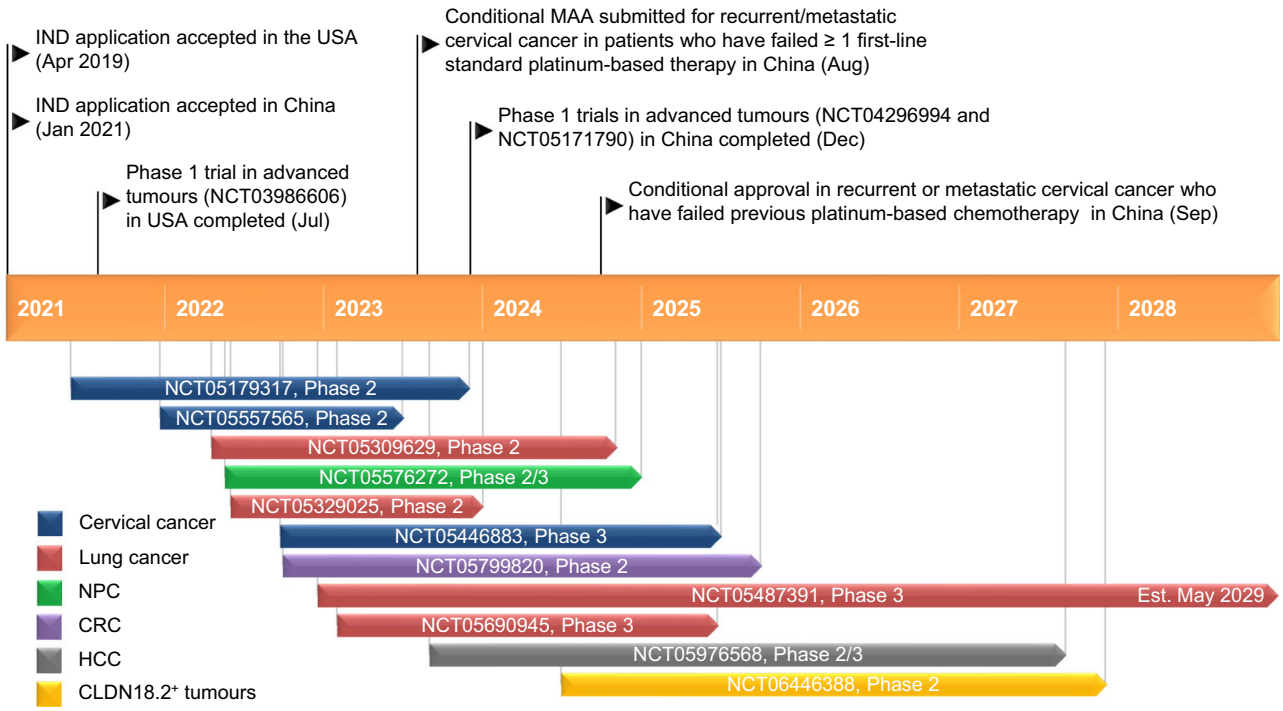
This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch and beyond.

✉ Susan J. Keam
dru@adis.com

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

1 Introduction

The development of cancer immunotherapies, and in particular immune checkpoint inhibitors, has significantly changed the treatment of solid malignant tumours in the last decade [1–3]. Checkpoint inhibitors modulate immune system cellular interactions with tumour cells, and anti-programmed death receptor-1/anti-programmed death receptor-ligand 1 (anti-PD-1/anti-PD-L1) and anti-cytotoxic T lymphocyte-associated protein-4 (CTLA-4) monoclonal antibodies (mAbs) have been shown to stimulate or reactivate/amplify anti-tumour T cell response, restoring functional activity [1, 2, 4]. Anti-PD-1/anti-PD-L1 mAbs have shown good efficacy as monotherapy or in combination with anti-CTLA-4 mAbs, with or without chemotherapy, in a range of solid tumours [5], including cervical cancer [2], non-small-cell cancer (NSCLC) [3, 6], small cell lung cancer (SCLC) [3], nasopharyngeal cancer (NPC) [7, 8], hepatocellular cancer (HCC) [1] and colorectal cancer (CRC) [9]. Compared with monotherapy, treatment with the combination of an anti-PD-1/anti-PD-L1 mAb and an anti-CTLA-4 mAb significantly improves overall response and survival in many of these cancers due to synergistic activity, but is associated with increased immune response adverse events that are predominantly due to anti-CTLA-4 activity [1–3, 5]. Consequently, combination regimens that have a reduced dose of an anti-CTLA-4 mAb are of interest [3, 5].



Key milestones in the development of iparomlimab and tuvonralimab for the treatment of advanced solid tumours. *CLDN* Claudin, *CRC* colorectal cancer, *HCC* hepatocellular cancer, *IND* investigational new drug, *MAA* marketing authorization application, *NPC* nasopharyngeal cancer

Iparomlimab and tuvonralimab (齐倍安®) is a bifunctional combination of anti-PD-1 and anti-CTLA-4 mAbs being developed by Qilu Pharmaceutical Co., Ltd for the treatment of advanced, solid, malignant tumours [10, 11]. Iparomlimab and tuvonralimab contains a mixture of full length anti-huPD-1 IgG4 (iparomlimab) and anti-huCTLA-4 IgG1 (tuvonralimab) mAbs expressed in a fixed ≈2:1 ratio from a single cell line using the MabPair® platform [5, 12–16]. MabPair® technology uses a molecular engineering approach to control cognate pairing of antibody light chains and heavy chains during the assembly of two antibodies in the same cell line. The relative ratio of the two antibodies is predefined and each antibody is individually engineered to achieve optimal target coverage, effector function and pharmacokinetics [12, 15, 16]. Tuvonralimab has been engineered to have a shorter half-life ($t_{1/2}$) than other available anti-CTLA-4 mAbs to reduce exposure and decrease the risk of immune-related adverse events [5, 12–14]. Unlike bispecific mAbs, iparomlimab and tuvonralimab consists of two separate mAb components, has a flexible mAb ratio and tunable pharmacokinetics [16]. Compared to a combination of two mAbs targeting different immune checkpoint pathways [e.g. nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA-4)], iparomlimab and tuvonralimab is a single product assembled in the same cell line, with reduced toxicity because of the shorter $t_{1/2}$ of the anti-CTLA-4 mAb [16].

In September 2024, iparomlimab and tuvonralimab was granted conditional approval (based on surrogate endpoints) in China for the treatment of adult patients with recurrent or metastatic cervical cancer who have failed previous platinum-containing chemotherapy. [4, 10, 11]. Full approval of this indication in China will depend on confirmation of iparomlimab and tuvonralimab clinical benefits in ongoing confirmatory clinical trials [4]. The recommended dose of iparomlimab and tuvonralimab is 5 mg/kg administered as an intravenous (IV) infusion over 30–60 mins every 3 weeks until disease progression or unacceptable toxicity occurs [4]. Patients administered iparomlimab and tuvonralimab may experience immune-related adverse events (including severe and fatal events) during treatment and after discontinuing the product, and should be closely monitored for signs and symptoms of these adverse events. Most immune-related adverse events are reversible and can be managed by interrupting treatment and administering corticosteroid treatment, and/or supportive care, or non-corticosteroid immunosuppressants. In the event of severe immune-related adverse reactions, immune-related adverse reactions that do not respond to treatment, or recurrent or persistent adverse reactions, it may be necessary permanently discontinue treatment with iparomlimab and tuvonralimab [4]. Iparomlimab and tuvonralimab is not recommended for use in patients with moderate or severe hepatic impairment or severe renal

impairment, as it has not been investigated in these patient populations. Based on the mechanism of action and pharmacological and toxicological research data, iparomlimab and tuvonralimab is not recommended during pregnancy unless the clinical benefits outweigh the risks [4].

2 Scientific Summary

2.1 Pharmacodynamics

Iparomlimab and tuvonralimab specifically targets and simultaneously binds to PD-1 and CTLA-4, blocking the PD-1/PD-L1 and CTLA-4/B7 signalling pathways and reversing the inhibitory effect of both checkpoint signalling pathways on T lymphocytes, restoring functional activity and anti-tumour response [4]. Tuvonralimab-mediated CTLA-4 blocking also kills regulatory T (Treg) cells in the tumour, which increases the ratio of effector T cells to Treg cells in the tumour site and results in tumour cell death [4]. In vitro, iparomlimab and tuvonralimab showed inhibitory PD-1 and CTLA-4 activity comparable with that of individual anti-PD-1 and anti-CTLA-4 agents. Compared with individual agents, iparomlimab and tuvonralimab showed synergistic effects on interleukin 2 (IL-2) production by human peripheral blood mononuclear cells (PBMCs) in response to staphylococcal enterotoxin B stimulation assays, and on human CD8+ T cells in response to cytomegalovirus-restimulation assays [5, 16]. In humanized mouse tumour models, iparomlimab and tuvonralimab administration enhanced human T cell expansion and inhibited tumour growth [5, 16].

In two phase 1 dose-escalation/dose expansion trials in patients with advanced malignant tumours, administration of IV iparomlimab and tuvonralimab 0.3–10 mg/kg (NCT04296994) [13] or 0.3–5 mg/kg (NCT03986606) [14] every 3 weeks achieved a sustained > 90% PD-1 receptor occupancy rate on circulating CD3+ T cells in all treatment groups throughout the treatment cycle [4, 5, 13, 14]. Proliferation of Ki67+ cells in CD4+ and CD8+ T cell populations and expansion of ICOS+ CD4+ T cells (a surrogate for CTLA-4 blockade) was greater with the 5 and 10 mg/kg doses than the 0.3, 1 and 3 mg/kg doses [5, 13].

2.2 Pharmacokinetics

The pharmacokinetics of iparomlimab and tuvonralimab in patients with advanced malignant solid tumours were linear and exposure was dose-proportional after IV administration of iparomlimab and tuvonralimab 0.3–10 mg/kg once every 3 weeks in a population pharmacokinetic analysis based on clinical trials conducted in China [4, 5, 13]. Steady state is reached after the 7th dose of iparomlimab and the 2nd dose of tuvonralimab. At steady state, the iparomlimab accumulation ratio is 1.9, while tuvonralimab accumulation is negligible. The mean volume of distribution at steady state ($V_{d,ss}$) was 4.27 L for iparomlimab and 2.92 L for tuvonralimab. At steady state, the mean $t_{1/2}$ of iparomlimab is 17.5 d and mean clearance (CL) is 0.24 L/d, and the mean $t_{1/2}$ of tuvonralimab is 6.2 d and the mean CL is 0.48 L/d [4].

2.3 Therapeutic Trials

2.3.1 Cervical Cancer

Treatment with IV iparomlimab and tuvonralimab 5 mg/kg every 3 weeks showed promising efficacy in a phase 2 trial (NCT05557565; DUBHE-C-206) conducted in China in patients with recurrent/metastatic cervical cancer who had failed ≥ 1 platinum-containing standard treatment and were immunotherapy-naive [4, 17]. In the full analysis set (FAS) population ($n = 147$), the independent imaging review committee (IRC)-assessed confirmed objective response rate (cORR) [primary endpoint] was 33.3% (49/147 patients; 2 CR, 47 PR) [4]. Median duration of response (DoR) was not reached, and the 6- and 12-month DoR rates were 78.3% and 71.0%. Median progression-free survival (PFS) was 5.4 months and the 6- and 12-month PFS rates were 45.3% and 29.6%. Median overall survival (OS) was 17.1 months, and the 6- and 12-month OS rates were 83.9% and 64.4% [4]. Among patients who were PD-L1-positive [combined positive score (CPS) ≥ 1] at baseline, IRC-assessed cORR was 36.5% (38/104 patients), and among those who were PD-L1- negative (CPS < 1) at baseline, IRC-assessed cORR was 25.6% (11/43) [4]. At enrolment, 37% of patients had received ≥ 2 lines of systemic treatment, 40% had used bevacizumab, and 91% had received radiotherapy. 71% of patients had a positive baseline PD-L1 and 29% had a negative PD-L1 score [4, 17]. At data cut-off (28 October 2023), the median follow-up duration was 17.5 months, and the last enrolled patient completed 12.0 months of follow-up [4]. The target ORR was 25%, and an ORR < 15% was considered ineffective [17].

First-line treatment of recurrent/metastatic cervical cancer with 6 cycles of IV iparomlimab and tuvonralimab 5 mg/kg every 3 weeks plus paclitaxel and cisplatin/carboplatin with/without bevacizumab followed by iparomlimab and tuvonralimab with/without bevacizumab maintenance showed promising anti-tumour activity in a Chinese phase 2 trial in immunotherapy-naive patients (NCT05179317; DUBHE-C-204) [18]. A cORR of 75.0% (21/28 patients; 4 CR, 17 PR) was achieved in the iparomlimab and tuvonralimab, paclitaxel plus

Features and properties of iparomlimab and tuvonralimab

Alternative names	齐倍安®; PSB205; QL1706
Class	Antineoplastics; Immunotherapies; Monoclonal antibodies; Recombinant fusion proteins
Mechanism of action	Antibody-dependent cell cytotoxicity; Programmed cell death 1 receptor antagonists; Cytotoxic T-lymphocyte antigen 4 inhibitors; T lymphocyte stimulants
Route of administration	IV
Pharmacodynamics	Specifically and simultaneously targets and binds to PD-1 and CTLA-4 and reverses inhibitory effect of both checkpoint signalling pathways on T lymphocytes Tuvonralimab-mediated CTLA-4 blocking also kills Treg cells in the tumour, increasing the ratio of effector T cells to Treg cells in the tumour site Inhibitory PD-1 and CTLA-4 activity comparable with individual anti-PD-1, anti-CTLA-4 agents Synergistic effects on IL-2 production by human PBMC in response to SEB and on human CD8+ T cells in response to CMV > 90 % PD-1 receptor occupancy rate throughout treatment cycle
Pharmacokinetics	Steady state reached after iparomlimab 7th dose and tuvonralimab 2nd dose; Steady state accumulation ratio 1.9 (iparomlimab), negligible (tuvonralimab); Mean $V_{d,ss}$ 4.27 L (iparomlimab), 2.92 L (tuvonralimab); mean $t_{1/2}$ 17.5 d (iparomlimab), 6.2 d (tuvonralimab); mean CL 0.24 L/d (iparomlimab), 0.48 L/d (tuvonralimab)
Adverse events (monotherapy)	
Most fre-quent	Rash, hypothyroidism, hyperthyroidism, pruritus, fatigue, anaemia, ↑ AST, ↑ ALT
Immune-related	Endocrine toxicity, skin adverse reactions, pneumonitis, pancreatic-related toxicity, myocarditis, thrombocytopenia, anaemia, skeletal muscle toxicity, gastrointestinal toxicity, ocular toxicity, nephrotoxicity, myelosuppression, neurotoxicity, oral mucositis
Occasional	Infusion-related reactions
ATC codes	
WHO ATC code	L01F (Monoclonal antibodies and antibody drug conjugates)
EphMRA ATC code	L1G (Monoclonal Antibody Antineoplastics)

cisplatin/carboplatin arm and cORR 76.7% (23/30; 3 CR, 20 PR) was achieved in the iparomlimab and tuvonralimab, paclitaxel plus cisplatin/carboplatin plus bevacizumab arm [18]. Median PFS in the respective arms was 14.3 and 16.4 months (15.1 months in the overall population) and median OS in either arm was not reached. Median follow-up duration was 27.0 months [18]. In the cervical cancer cohort who received IV iparomlimab and tuvonralimab 5 mg/kg every 3 weeks in a Chinese phase 1/1b trial in patients with advanced solid tumours (NCT04296994 and NCT0517790), ORR was 27.3% (15/55 patients) in the overall population and 28.3% (15/53) in the immunotherapy-naive population [5].

2.3.2 Other Solid Tumours

In a phase 2 trial of IV iparomlimab and tuvonralimab 5 mg/kg every 3 weeks plus platinum doublet chemotherapy with or without bevacizumab in patients with advanced NSCLC conducted in China (NCT05329025; DUBHE-L-201) [6, 19], a cORR of 45% (27/60 patients; all PR) and median PFS of 6.8 months was achieved in the subgroup of patients with wild-type EGFR (median follow-up 12.6 months) [6]. In the subgroup of patients with mutated EGFR (Cohort 5), cORR was 54.8% (17/31; all PR), median PFS was 8.5 months and median OS was 26.5 months (median follow-up 29.5 months) [19]. Most patients had stage IV cancer at trial entry and all were immunotherapy-naive [6]. In the NSCLC cohort who received IV iparomlimab and tuvonralimab 5 mg/kg every 3 weeks in the Chinese phase 1/1b trial in patients with advanced solid tumours (NCT04296994 and NCT0517790), ORR was 14.0% (17/121 patients) in the overall population and 24.2% (16/66) in those who were immunotherapy-naive [5].

In a phase 2 trial (NCT05309629) in patients with extensive-stage small-cell lung cancer (ES-SCLC) conducted in China [20], first-line treatment with IV iparomlimab and tuvonralimab 5 mg/kg plus etoposide and carboplatin every 3 weeks for 4–6 cycles, followed by iparomlimab and tuvonralimab maintenance treatment achieved a cORR of 89.7% (all PR; $n = 39$ evaluable) at data cut-off (median iparomlimab and tuvonralimab treatment duration of 5.9 months) [20]. Median DoR was 4.5 months, median PFS was 5.7 months, with 3- and 6-month PFS rate of 94.8% and 44.7%, respectively. At a median 6.2 months' follow-up, median OS had not been reached [20]. In the SCLC cohort who received IV

iparomlimab and tuvonralimab 5 mg/kg every 3 weeks in the Chinese phase 1/1b trial in patients with advanced solid tumours (NCT04296994 and NCT0517790), the ORR was 23.1% (6/26 patients) [5].

In the phase 2 part of a phase 2/3 study of first-line IV iparomlimab and tuvonralimab 7.5 mg/kg every 3 weeks with bevacizumab and/or XELOX in patients with advanced HCC (NCT05976568; DUBHE-H-308) [21] [median follow-up 7.9 months], the ORR was 35.5% (1 CR; 10 PR) in the iparomlimab and tuvonralimab plus bevacizumab and chemotherapy arm ($n = 31$), 36.7% (11 PR) in the iparomlimab and tuvonralimab plus bevacizumab arm ($n = 30$) and 36.7% (11 PR) in the iparomlimab and tuvonralimab plus chemotherapy arm ($n = 30$). The ORR in the reference arm (sintilimab plus bevacizumab; $n = 29$) was 20.7% (6 PR). The 6-month PFS rate in the respective treatment arms were 79.0%, 64.3%, 57.7% and 49.5% [21]. In a phase 1b/2 trial evaluating IV iparomlimab and tuvonralimab 5 mg/kg plus bevacizumab every 3 weeks or IV iparomlimab 200 mg plus bevacizumab every 3 weeks (NCT05603039) as first-line treatment in advanced HCC in China, the ORR was 38.3% (18/47 evaluable patients) in the iparomlimab and tuvonralimab arm and 15.4% (4/26) in the iparomlimab arm. Median PFS in the respective treatment groups were 6.7 months and 5.4 months [22].

First-line treatment of recurrent/metastatic NPC with IV iparomlimab and tuvonralimab 5 mg/kg every 3 weeks in combination with gemcitabine and cisplatin for 4–6 cycles followed by iparomlimab and tuvonralimab maintenance therapy achieved an ORR of 82.1% (23/28 evaluable patients; 1 CR, 22 PR) in a Chinese phase 2 trial (NCT05576272; DUBHE-N-302) [8]. Median DoR was 14.1 months, median PFS was 12.5 months and median OS was not reached. In patients with high level PD-L1 expression (CPS ≥ 50; $n = 13$), ORR was 92.3% and median PFS was 16.2 months. Median follow-up was 15.5 months [8]. In the NPC cohort who received IV iparomlimab and tuvonralimab 5 mg/kg every 3 weeks in the phase 1/1b Chinese trial in patients with advanced solid tumours (NCT04296994 and NCT0517790), ORR was 24.5% (27/110 patients) in the overall population and 38.7% (24/62) in immunotherapy-naive patients [5].

In a phase 2 Chinese trial (NCT05490719) in patients with inoperable locally advanced oesophageal squamous cell carcinoma (SCC) [$n = 39$], administration of 2 cycles of IV paclitaxel, cisplatin and iparomlimab and tuvonralimab 5 mg/kg every 3 weeks with concurrent radiotherapy (50.4 Gy/28 fractions) followed by iparomlimab and tuvonralimab maintenance therapy achieved a median PFS of 13.99 months; the 12-month PFS and OS rates were 62.1% and 86.2%, respectively (median follow-up 12.2 months). Patients with PD-L1-positive tumours [tumour proportion score (TPS) ≥ 5%: 41.0%; CPS ≥ 10: 56.4%] had significantly longer PFS than those with PD-L1-negative tumours (TPS ≥ 5% vs TPS < 5%: $p = 0.03$; CPS ≥ 10 vs CPS < 10: $p = 0.014$] [23].

In a phase 2 Chinese trial (NCT05799820) in patients with untreated, unresectable locally advanced or metastatic CRC (n = 59) [24], treatment with IV iparomlimab and tuvonralimab 5 mg/kg every 3 weeks achieved a cORR (primary endpoint) of 62.5% (5 PR) in the cohort of patients (n = 8) with microsatellite instability (MSI)-high tumours regardless of *RAS/BRAF* status, and treatment with IV iparomlimab and tuvonralimab 5 mg/kg plus bevacizumab and XELOX every 3 weeks achieved a cORR of 70.6% (36 PR) in the cohort of wild-type *RAS/BRAF* patients (n = 51) with microsatellite stable (MSS)/MSI-low tumours. Median DoR was not reached in either cohort. Median follow-up was 10.7 months across both cohorts [24].

2.4 Adverse Events

In patients with solid tumours ($n = 666$), most of whom ($n = 616$) received treatment with iparomlimab and tuvonralimab 5 mg/kg every 3 weeks as monotherapy in phase 1 (NCT04296994; NCT0517790) and phase 2 (NCT05557565) clinical trials, the incidence of adverse reactions (any grade) was 77.5% [4]. The most common adverse reactions (any grade; incidence ≥ 10%) were rash (19.8%), hypothyroidism (16.1%), hyperthyroidism (13.2%), pruritus (12.6%), fatigue (12.5%), anaemia (12.5%), increased AST (12.2%) and increased ALT (11.3%). Adverse reactions ≥ grade 3 were reported in 25.4% of patients; the most frequent (incidence ≥ 1%) were anaemia (4.4%), decreased lymphocyte count (2.7%), lung inflammation (1.8%), increased lipase (1.5%), decreased platelet count (1.5%), increased AST (1.4%), infectious pneumonia (1.4%), rash (1.2%), increased γ-GT (1.2%), decreased neutrophil count (1.2%), fatigue (1.1%) and increased ALT (1.1%) [4]. Immune-related adverse reactions included endocrine toxicity [hypothyroidism (15.8%), hyperthyroidism (13.2%), thyroiditis (1.1%), hyperglycemia (3.2%), type 1 diabetes (0.2%), hypophysitis (0.5%), hypopituitarism (0.8%), adrenal insufficiency (0.8%)], skin adverse reactions (10.8%), pneumonitis (3.6%), pancreatic-related toxicity (3.2%), myocarditis (1.2%), thrombocytopenia (1.2%), anaemia (0.9%), skeletal muscle toxicity (0.8%), gastrointestinal toxicity [diarrhoea (0.3%), colitis (0.3%), gastritis (0.3%) hepatitis (0.5%)], ocular toxicity (0.3%), nephrotoxicity (0.2%), myelosuppression (0.2%), neurotoxicity (0.2%) and oral mucositis (0.2%) [4]. Infusion-related reactions

Key clinical trials of iparomlimab and tuvonralimab (Qilu Pharmaceutical Co., Ltd)

Drug(s)	Indication	Phase	Status	Location	Identifier
Iparomlimab and tuvonralimab, bevacizumab, platinum-based chemotherapy, placebo	Recurrent/metastatic cervical cancer	3	Recruiting	China	NCT05446883; DUBHE-C-301
Iparomlimab and tuvonralimab, platinum-based chemotherapy, placebo	Resected stage II/IIIb NSCLC	3	Recruiting	China	NCT05487391; DUBHE-L-304
Iparomlimab and tuvonralimab, tislelizumab, platinum-based chemotherapy	PD-L1-negative advanced/metastatic NSCLC	3	Recruiting	China	NCT05690945; DUBHE-L-303
Iparomlimab and tuvonralimab, bevacizumab, platinum-based chemotherapy, sintilimab	Advanced HCC	2/3	Recruiting	China	NCT05976568; DUBHE-H-308
Iparomlimab and tuvonralimab, camrelizumab, platinum-based chemotherapy	Recurrent/metastatic NPC	2/3	Active	China	NCT05576272; DUBHE-N-302
Iparomlimab and tuvonralimab, bevacizumab, platinum-based chemotherapy	Recurrent/metastatic cervical cancer	2	Completed	China	NCT05179317; DUBHE-C-204
Iparomlimab and tuvonralimab	Recurrent/metastatic cervical cancer	2	Completed	China	NCT05557565; DUBHE-C-206
Iparomlimab and tuvonralimab, bevacizumab, platinum-based chemotherapy	Advanced NSCLC	2	Completed	China	NCT05329025; DUBHE-L-201
Iparomlimab and tuvonralimab, platinum-based chemotherapy	ES-SCLC	2	Completed	China	NCT05309629
Iparomlimab and tuvonralimab, bevacizumab, platinum-based chemotherapy	Advanced/metastatic CRC	2	Recruiting	China	NCT05799820
Iparomlimab and tuvonralimab, QLS31905, platinum-based or standard chemotherapy	CLDN18.2+ advanced solid tumours	2	Recruiting	China	NCT06446388

occurred in 8.3% of patients (55/666 patients), all of whom recovered after appropriate treatment. Treatment was suspended in 3 patients and permanently discontinued in 9 patients [4].

In two clinical trials of iparomlimab and tuvonralimab (NCT05171790; NCT05557565), the incidence of iparomlimab antidrug antibodies (ADAs) was 33.5% (61/182 patients) and tuvonralimab ADAs was 34.1% (62/182). ADAs for iparomlimab and tuvonralimab had no effect on iparomlimab and tuvonralimab efficacy and safety [4].

2.5 Ongoing Clinical Trials

Several trials of iparomlimab and tuvonralimab are recruiting: phase 3 trials in recurrent or metastatic cervical cancer (NCT05446883; DUBHE-C-301), completely resected stage II-IIIB NSCLC (NCT05487391; DUBHE-L-304) [25], and PD-L1-negative advanced or metastatic NSCLC (NCT05690945; DUBHE-L-303) [26]; a phase 2/3 trial in advanced HCC (NCT05976568; DUBHE-H-308); a phase 2 trial in unresectable, locally advanced or metastatic CRC (NCT05799820); and a phase 2 trial of QLS31905 (a Claudin18.2/CD3 bi-specific antibody) and/or iparomlimab and tuvonralimab plus chemotherapy in Claudin18.2-positive malignant solid tumours (NCT06446388). A phase 2/3 trial in NPC (NCT05576272; DUBHE-N-302) is ongoing. A phase 1b/3 trial of iparomlimab and tuvonralimab as perioperative treatment in patients with untreated MSI-high/defective mismatch repair, resectable CRC (NCT0668576) is planned. Investigator-sponsored trials of iparomlimab and tuvonralimab include phase 2 studies in advanced oesophageal SCC (NCT05490719), platinum-resistant recurrent ovarian cancer (NCT06509971), high-risk, triple-negative early breast cancer (NCT06404736), high-risk, estrogen receptor-positive/HER2-negative early breast cancer (NCT06404463), and unresectable locally advanced or metastatic pancreatic cancer (NCT06313970).

3 Current Status

Iparomlimab and tuvonralimab received its first approval (a conditional approval based on surrogate endpoints) on 26 September 2024 for use in patients with recurrent or metastatic cervical cancer who have failed previous platinum-based chemotherapy in China [4, 27, 28].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-025-02160-6.

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. Susan J. Keam is a contracted employee of Adis International Ltd/Springer Nature, and declares no relevant conflicts of interest. All authors contributed to this article and are responsible for its content.

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

References

1. Ramai D, Shapiro A, Facciorusso A, et al. Immune checkpoint inhibitor therapy for hepatocellular carcinoma. Ann Gastroenterol. 2022;35(6):568–76.
2. Xie Y, Kong W, Zhao X, et al. Immune checkpoint inhibitors in cervical cancer: current status and research progress. Front Oncol. 2022;12: 984896.
3. Cheng W, Kang K, Zhao A, et al. Dual blockade immunotherapy targeting PD-1/PD-L1 and CTLA-4 in lung cancer. J Hematol Oncol. 2024. https://doi.org/10.1186/s13045-024-01581-2.
4. Qilu Pharmaceutical. Iparomlimab and tuvonralimab: Chinese prescribing information. 2024. https://www.hnysfww.com/data/m_c/1728497267153795099.pdf. Accessed 18 Oct 2024
5. Zhao Y, Ma Y, Zang A, et al. First-in-human phase I/Ib study of QL1706 (PSB205), a bifunctional PD1/CTLA4 dual blocker, in patients with advanced solid tumors. J Hematol Oncol. 2023. https://doi.org/10.1186/s13045-023-01445-1.
6. Huang Y, Yang Y, Zhao Y, et al. QL1706 (anti-PD-1 IgG4/CTLA-4 antibody) plus chemotherapy with or without bevacizumab in advanced non-small cell lung cancer: a multi-cohort, phase II study. Signal Transduct Target Ther. 2024. https://doi.org/10.1038/s41392-023-01731-x.
7. American Cancer Society. Treatment options by stage of nasopharyngeal cancer. 2024. https://www.cancer.org/. Accessed 22 Nov 2024.
8. Huang Y, Zhao S, Qu S, et al. Safety and efficacy of iparomlimab and tuvonralimab in combination with gemcitabine and cisplatin as first-line treatment for patients with recurrent or metastatic nasopharyngeal carcinoma: a multicenter, single-arm, phase 2 trial (DUBHE-N-302) [abstract no. 6026 plus poster]. J Clin Oncol. 2024;42(16 Suppl).
9. American Cancer Society. Immunotherapy for colorectal cancer. 2024. https://www.cancer.org/. Accessed 22 Nov 2024.
10. Qilu Pharmaceutical. Qilu Pharmaceutical's blockbuster class 1 new drug has been approved for marketing, and it is expected to make new breakthroughs in the treatment of cervical cancer [media release]. 30 Sep 2024. https://www.qilu-pharma.com/.
11. Sound Biologics. Sound Biologics announces breakthrough approval of PSB205 by the National Medical Products Administration in China [media release]. 16 Oct 2024. https://www.soundbiologics.com/.
12. Fanslow WC, Liu Z, Hu ZH, et al. Development of PSB205, a bifunctional MabPair product that targets PD-1 and CTLA-4 [abstract no. 4069]. Cancer Res. 2019;79(13 Suppl).
13. Zhang L, Zhao HY, Ma YX, et al. Development and preliminary clinical activity of QL1706 (PSB205), a combination of anti-PD1 and anti-CTLA-4 antibodies manufactured together as a single product [abstract no. CT119 plus poster]. Cancer Res. 2021;81(13 Suppl).
14. Chugh R, Wang J, Olszanski A, et al. Safety of dual checkpoint-blockade with PSB205, an anti-PD-1/CTLA4 monoclonal antibody combination, manufactured and dispensed as a single product: a phase 1 study [abstract no. 2611 plus poster]. J Clin Oncol. 2022;40(16 Suppl).
15. Sound Biologics. MabPair™ Platform. 2024. https://www.soundbiologics.com/. Accessed 19 Nov 2024.
16. Liu Z, Hu Z, Shen M, et al. Development of MabPair technology, a novel platform for bifunctional antibody product [abstract and poster]. 2019. https://www.soundbiologics.com/. Accessed 20 Nov 2024.
17. Lou H, Zhou Y, Li D, et al. Efficacy and safety of iparomlimab and tuvonralimab in previously treated patients with recurrent or metastatic cervical cancer: a multicenter, open-label, single-arm, phase 2 clinical trial (DUBHE-C-206) [abstract no. 251 plus presentation]. Int J Gynecol Cancer. 2024;34(Suppl 1):A5.
18. Liu N, Yang Z, Tang D, et al. First-line iparomlimab and tuvonralimab (QL1706) + chemotherapy (chemo) ± bevacizumab (BEV) for recurrent or metastatic cervical cancer (r/mCC): updated results of the phase II DUBHE-C-204 study (abstract no 373O plus presentation). Ann Oncol. 2024;35(Suppl 4):S1544.
19. Fang W, Yang Y, Zhao Y, et al. Iparomlimab and tuvonralimab (QL1706) plus chemotherapy and bevacizumab for epidermal growth factor receptor inhibitor (EGFRi)-resistant, EGFR-mutant, advanced non-small cell lung cancer (NSCLC): updated results from Cohort 5 in the DUBHE-L-201 study [abstract no. 646P plus poster]. Ann Oncol. 2024;35(Suppl 4):S1646.
20. Fan Y, Wang Z, Yang R, et al. Safety and efficacy of QL1706 plus carboplatin/etoposide (EC) as first-line (1L) treatment for extensive-stage small-cell lung cancer (ES-SCLC): the results from a phase II single-arm study [abstract no. 8525 plus poster]. J Clin Oncol. 2023;41(16 Suppl).
21. Qin S, Fan J, Yang F, et al. Iparomlimab and tuvonralimab (QL1706) with bevacizumab and/or chemotherapy in first-line (1L) treatment of advanced hepatocellular carcinoma (aHCC): a randomized, open-label, phase II/III study (DUBHE-H-308) [abstract no. LBA38 plus presentation]. Ann Oncol. 2024;35(Suppl 2):S1229-S30.
22. Bi F, Zhang Y-q, Gu S, et al. An open-label, multicenter, adaptive, phase Ib/II study of QL1706 or QL1604 plus bevacizumab as first-line treatment in patients with advanced hepatocellular carcinoma [abstract no. 4077 plus poster]. J Clin Oncol. 2023;41(16 Suppl).
23. Zhang W, Zhang T, Chen X, et al. Iparomlimab and tuvonralimab (QL1706) with definitive chemoradiotherapy for locally advanced esophageal squamous cell carcinoma: an open-label phase II study [abstract no. 1414P plus poster]. Ann Oncol. 2024;35(Suppl 2):S883.
24. Li J, Bai Y, Li Y, et al. Efficacy and safety of iparomlimab and tuvonralimab (QL1706) in untreated metastatic colorectal cancer (mCRC) [abstract no. 77P plus poster]. Ann Oncol. 2024;35(Suppl 4):S1434.
25. Zhu Y, Jiang T, Fang L, et al. A randomized, double blinded, multicenter phase 3 study of platinum-based chemotherapy with or without QL1706 as adjuvant therapy in completely resected stage II-IIIb NSCLC [abstract no. TPS8606 plus poster]. J Clin Oncol. 2023;41(16 Suppl).
26. Zhang L, Huang Y, Fang L, et al. A phase III, multicenter, double-blinded, randomized, active-controlled study on the efficacy and safety of QL1706 with chemotherapy (CT) as first-line therapy for PD-L1-negative advanced or metastatic non-small-cell lung cancer (NSCLC) [abstract no. TPS9139 plus poster]. J Clin Oncol. 2023;41(16 Suppl).

27. National Medical Products Administration. Iparomlimab and tuvonralimab injection: approval notice. 2024. https://www.nmpa.gov.cn/. Accessed 25 Nov 2024.
28. National Medical Products Administration. Iparomlimab and tuvonralimab injection: conditional approval announcement. 2024. https://www.nmpa.gov.cn/zhuanti/cxylqx/cxypxx/20240930101946184.html. Accessed 25 Nov 2024.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.