



Cadonilimab: First Approval

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Abstract

Cadonilimab (开坦尼[®]), a PD-1/CTLA-4 bi-specific antibody, is being developed by Akeso, Inc. for the treatment of a range of solid tumours, including cervical cancer, lung cancer, gastric/gastroesophageal junction cancer, oesophageal squamous cell cancer, liver cancer and nasopharyngeal cancer. Cadonilimab was approved in China in June 2022 for use in patients with relapsed or metastatic cervical cancer (r/mCC) who have progressed on or after platinum-based chemotherapy. This article summarizes the milestones in the development of cadonilimab leading to this first approval for the treatment of patients with r/mCC.

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Cadonilimab (开坦尼[®]): Key points

A PD-1/CTLA-4 bi-specific antibody being developed by Akeso, Inc. for the treatment of a wide range of solid tumours

Received its first approval on 29 June 2022 in China

Approved for use in patients with r/mCC who have progressed on or after platinum-based chemotherapy

1 Introduction

Over the last decade, immunotherapy has become an important part of managing many types of cancers [1–4]. The programmed cell death-1 (PD-1) receptor is predominantly expressed on the surface of activated T lymphocytes;

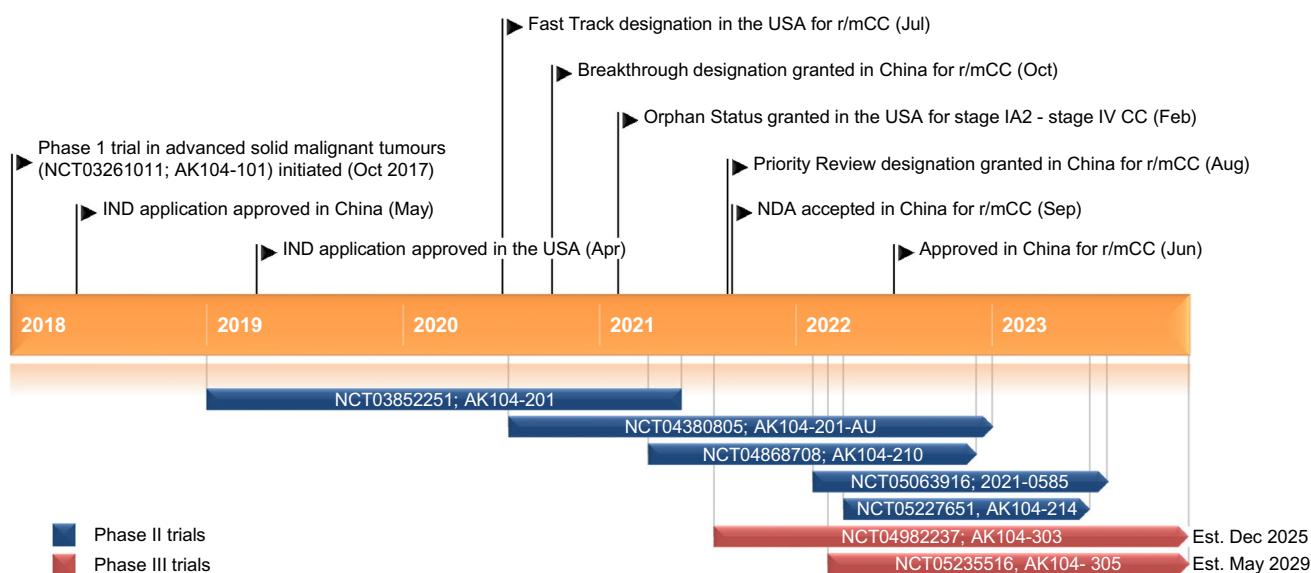
binding of PD-1 to its ligands PD-L1 and PD-L2 inhibits T cell proliferation and cytokine production. Cytotoxic T lymphocyte antigen-4 (CTLA-4) is expressed on the surface of activated CD4+ and CD8+ T cells; binding to its ligands B7.1 and B7.2 inhibits the activity of T cells and CTLA-4 is therefore a negative regulator of T cell activity. PD-L1 and PD-L2 are upregulated in some tumour cells and signalling via this pathway can inhibit the immune surveillance of tumours by activated T cells [5]. PD-1 and CTLA-4 co-express in tumour-infiltrating lymphocytes, but are not expressed in normal peripheral tissue lymphocytes [6]. Numerous PD1/PD-L1 and CTLA-4 blockers have been developed and have shown efficacy in broad range of cancers. Combination immunotherapy regimens using agents that block different receptors (e.g. PD-1 and CTLA-4) may have synergistic effects in some cancers; however, each agent has its own adverse events profile and when administered in combination, safety and tolerability issues may limit use [3, 4].

Cadonilimab (开坦尼[®]; AK104), a PD-1/CTLA-4 blocker being developed by Akeso, Inc. for use in cancer, is the first dual immune checkpoint inhibitor bi-specific antibody treatment to be approved [7]. In June 2022, cadonilimab was approved in China for the treatment of patients with relapsed or metastatic cervical cancer (r/mCC) who have progressed on or after platinum-based chemotherapy [5, 7, 8]. The approval is conditional, as it is based on surrogate endpoints; full approval for this indication will be contingent upon ongoing confirmatory trials [5]. Cadonilimab is also being investigated for use in several other major cancer types, including liver cancer, lung cancer, gastric cancer,

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Key milestones in the development of cadonilimab for the treatment of cervical cancer. *CC* cervical cancer, *IND* investigational new drug, *NDA* new drug application, *r/mCC* relapsed or metastatic cervical cancer

oesophageal squamous cell cancer and nasopharyngeal carcinoma [7]. The recommended dosage of cadonilimab is 6 mg/kg every 2 weeks as an intravenous infusion over \approx 60 mins until disease progression or intolerable toxicity [5]. An atypical response (e.g., temporary tumour enlargement or new lesions in the first months of treatment, followed by tumour shrinkage) may occur. If the patient is clinically stable or has sustained relief (even if there is preliminary evidence of disease progression on imaging), continued treatment may be considered (based on the judgement of the overall clinical benefit) until disease progression is confirmed. Cadonilimab is not recommended for use in patients with moderate or severe liver impairment or severe kidney impairment (because there are no clinical data in these patient groups) or during pregnancy; females of childbearing age should use effective contraception during treatment and for at least 4 months after the last dose. Since human IgG is secreted into breast milk, there may be potential risks to breastfeeding infants; consequently breastfeeding should be suspended during treatment and for at least 4 months after the last cadonilimab dose [5].

Immune-related adverse events can occur during or after treatment with cadonilimab [5]. Depending on the severity of the reaction, suspension of treatment and administration of corticosteroids is required until the immune-related adverse reaction improves to \leq grade 1; the corticosteroid dose should then be tapered over a period of at least 1 month until it is discontinued. If immune-related adverse reactions continue to worsen or do not improve, non-corticosteroid immunosuppressive therapy should be considered. Permanent discontinuation of cadonilimab is recommended for: all

grade 4 and some grade 3 immune-related adverse reactions; any recurrent immune-related grade 3 adverse reactions or grade 2 or 3 immune-related adverse reactions that do not improve to grade 0–1 within 12 weeks of the last cadonilimab dose; or if the corticosteroid dose fails to reduce to \leq 10 mg/day within 12 weeks of the last cadonilimab dose. Permanent discontinuation is also required if grade 3 or 4 infusion-related reactions or recurrent or persistent grade 3 or 4 adverse effects occur. Patients should be monitored for clinically significant immune-related adverse reactions: these include pneumonitis, gastrointestinal toxicity, hepatitis, thyroid disease, hyperglycaemia and type 1 diabetes, hypophysitis, adrenal insufficiency, skin adverse reactions, myocarditis, musculoskeletal toxicity, iridocyclitis, nephrotoxicity, pancreatic toxicity, neurotoxicity, and haematological toxicities, including thrombocytopenia [5].

1.1 Company Agreements

In February 2022, Akeso entered into a collaboration agreement with Shenzhen Chipscreen Biosciences to establish a clinical trial partnership to jointly conduct a phase 1b/2 trial of cadonilimab in combination with chiauranib (a highly selective Aurora B/VEGFR/PDGFR/c-Kit/CSF1R inhibitor developed to address drug resistance) for the treatment patients with extensive stage small cell lung cancer (ES-SCLC) that has progress on first-line combination PD-(L)1 inhibitor and platinum-based chemotherapy [9].

In August 2021, Akeso entered into a research partnership with Pfizer Inc. to jointly conduct a phase 2 trial of cadonilimab in combination with axitinib as first-line treatment

for advanced or metastatic clear cell renal cell carcinoma (ccRCC) [10].

2 Scientific Summary

2.1 Pharmacodynamics

Cadonilimab is a humanized bi-specific antibody that targets both PD-1 and CTLA-4 with a higher affinity for tumour-infiltrating lymphocytes in the tumour microenvironment compared with surrounding tissues [11]. Cell binding assays show that cadonilimab binds to PD-1 and CTLA-4 simultaneously and crosslinks cells expressing PD-1 and CTLA-4 [12]. Cadonilimab blocks PD-1 binding to PD-L1 and PD-L2 and CTLA-4 binding to B7-1 and B7-2 [13]. It is an IgG1 scaffold Fc-engineered antibody designed to eliminate binding to FcγRs and C1q and to minimise lymphocyte loss and antibody-dependent cytokine release from macrophages [12]. In cellular assays, cadonilimab showed no affinity for FcγRIa, FcγRIIa_H131, FcγRIIIa_V158, FcγRIIIa_F158 or C1q and did not elicit antibody-mediated cell-dependent cytotoxicity, complement-dependent cell-mediated cytotoxicity (both measured by lactate dehydrogenase release from 293TCTLA4-PD1 cells) or antibody-dependent cellular phagocytosis activity (measured by murine bone marrow-derived macrophage phagocytosis of CHO-K1-PD1-CTLA4 cells). Cadonilimab induced minimal secretion of interleukin (IL)-6 and IL-8 secretion by human macrophages in the presence of interferon-γ [12]. Administration of cadonilimab

in mouse models of cancer was associated with inhibition of tumour growth [5].

In patients with advanced solid tumours who were treated with cadonilimab 0.2–10.0 mg/kg every 2 weeks in a phase 1 trial (NCT03261011), peripheral CD4+ T cells showed dose-dependent increases in Ki-67 expression at day 8 (i.e. evidence of increased T cell proliferation) [13]. A receptor occupancy rate was 80% on peripheral T cells was evident at day 2 after administration of cadonilimab 6 mg/kg in patients with advanced solid tumours [5].

2.2 Pharmacokinetics

After a single dose of cadonilimab 0.2–25.0 mg/kg in patients with advanced malignant tumours ($n = 298$), increases in C_{max} and AUC_{14d} were dose proportional [5]. After repeated infusions of cadonilimab 6 mg/kg every 2 weeks, the mean accumulation ratios were 1.01 (C_{max}) and 1.06 (AUC). Based on population pharmacokinetics ($n = 436$ patients with advanced malignant tumours), the mean steady state V_d of cadonilimab was 6.23 L, the mean CL was 1.3 L/day and the mean $t_{1/2}$ was 4.76 days [5].

The pharmacokinetics of cadonilimab are not significantly affected by mild or moderate kidney impairment or mild liver impairment, according to a population pharmacokinetics analysis. There are insufficient data in patients with severe kidney impairment or moderate or severe liver impairment. Cadonilimab has not been studied in children or adolescents [5].

Features and properties of Cadonilimab

Alternative names	AK-104, 开坦尼®
Class	Antineoplastics; Bispecific antibodies; Immunotherapies
Mechanism of action	Antibody-dependent cell cytotoxicity; CTLA4 inhibitors; PD-1 antagonists; T lymphocyte stimulants
Route of administration	IV infusion
Pharmacodynamics	Binds to PD-1 and CTLA-4 simultaneously and crosslinks cells expressing PD-1 and CTLA-4; blocks PD-1 binding to PD-L1 and PD-L2 and CTLA-4 binding to B7-1 and B7-2. Does not bind to FcγRs and C1q; causes minimal lymphocyte loss and antibody-dependent cytokine release from macrophages. 80% receptor occupancy rate on peripheral T cells at day 2 after administration
Pharmacokinetics	Dose-proportional pharmacokinetics with no accumulation after repeated administration. Mean steady state V_d 6.23 L, mean CL 1.3 L/day, mean $t_{1/2}$ 4.76 days
Adverse reactions (most frequent)	
All grades (incidence $\geq 10\%$)	Rash, anaemia, hypothyroidism, increased AST, increased ALT, pruritus, fatigue, proteinuria
\geq Grade 3 (incidence $\geq 2\%$)	Infusion-related reactions, anaemia
Immune-related adverse reactions (incidence $\geq 1\%$)	Hypothyroidism, hyperthyroidism, skin adverse reactions, hyperglycaemia, other thyroid diseases, hepatitis, pneumonitis, musculoskeletal toxicity, diarrhoea and colitis
ATC codes	
WHO ATC code	L01 (Antineoplastic Agents)
EphMRA ATC code	L1 (Antineoplastics)

2.3 Therapeutic Trials

2.3.1 Cervical Cancer

Cadonilimab 6 mg/kg administered every 2 weeks for up to 2 years showed good antitumour efficacy in a phase 1b/2 study (NCT03852251) in patients with r/mCC who had failed previous platinum-containing chemotherapy [5, 6, 14]. The phase 2 cervical cancer cohort of this trial enrolled 111 patients, of whom 99 were evaluable (full analysis set); 63.6% were PD-L1 positive [combined positive score (CPS) ≥ 1] and 90.9% had distant metastases [5, 6]. At a median follow-up of 15.61 months in the evaluable population (data cut-off 7 January 2022), the objective response rate (ORR) was 31.3% (primary endpoint), the disease control rate (DCR) was 50.5% and the median duration of response (DoR) was not reached at cut-off (6- and 12-month DoR rates were 78.6% and 63.4%). 13.1% of patients showed complete remission. The median progression-free survival (PFS) duration was 3.71 months (6- and 12-month PFS rates were 39.0% and 24.4%); the median overall survival (OS) duration was not reached (6- and 12-month OS rates were 78.8% and 59.9%). The ORR in patients who were PD-L1 positive was 41.3% compared with 16.7% in those who were PD-L1 negative ($n = 18$; PD-L1 expression was unknown in an additional 18 patients) [5] 93.9% of those in the cervical cancer cohort had squamous cell carcinoma, 3% had adenosquamous carcinoma and 3% had adenocarcinoma. The last patient to enroll in this cohort completed at least 12 months of follow-up [5].

Cadonilimab in combination with current standard of care (platinum-based chemotherapy with or without bevacizumab) showed good antitumour activity as first-line treatment in patients with persistent, r/mCC in a phase 2 trial (NCT04868708) [15]. Patients were assigned to one of three cohorts: cadonilimab 15 mg/kg plus platinum-based chemotherapy (A-15; $n = 15$ evaluable patients); cadonilimab 10 mg/kg plus platinum-based chemotherapy (A-10; $n = 16$); or cadonilimab 10 mg/kg plus platinum-based chemotherapy and bevacizumab (B-10; $n = 14$). At data cut-off (18 April 2022) ORR was 66.7% in the A-15 group, 68.8% in the A-10 group, 92.3% in the B-10 group and 79.3% in the combined A-10 and B-10 groups; the corresponding DCRs were 100%, 93.8%, 100% and 96.6%, respectively. The median DoR was not reached in the A-15 and B-10 groups, and was 5.75 months in the A-10 group. The response to treatment occurred regardless of patient CPS status; in those who were PD-L1 CPS ≥ 1 ($n = 27$), ORR was 70.0%, 75.0%, 88.9% and 82.4% in the A-15, A-10, B-10 and A-10 + B-10 groups and in those who were CPS < 1 ($n = 17$), the respective ORRs were 60.0%, 62.5%, 100.0% and 75.0%. PFS and OS data were not mature at data cut-off [15].

2.3.2 Lung Malignancies

Cadonilimab plus anlotinib achieved an ORR of 62.5% (primary endpoint) and DCR of 100% in part 1 of a 2-part phase 1b/2 trial in treatment-naïve patients ($n = 8$ evaluable) with advanced non-small cell lung cancer (NSCLC) [NCT04646330]. In the subgroup of 5 patients with non-squamous NSCLC, the ORR was 80%. Patients had a PD-L1 tumour proportion score (TPS) $\geq 1\%$ at study entry and were administered cadonilimab 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks, plus once daily oral anlotinib 12 mg 2 weeks on/1 week off [16].

In the subgroup of patients with mesothelioma ($n = 15$ evaluable; data cut-off 10 Jul 2020) in a phase 1 dose-escalation trial of cadonilimab in patients with advanced solid tumours (NCT03261011), treatment with cadonilimab resulted in an ORR of 20.0% (primary endpoint); The 6-month PFS rate was 64.5%. 12 of 13 patients were anti-PD(L)-1 therapy naïve at study entry; cadonilimab dosages were 4 mg/kg, 6 mg/kg, 10 mg/kg or 450 mg every 2 weeks [17].

2.3.3 Gastrointestinal Malignancies

Cadonilimab plus platinum-based chemotherapy showed efficacy as first-line therapy in treatment-naïve patients with unresectable, advanced gastric/GEJ cancer in a phase 1b/2 dose-escalation trial (NCT03852251) [18]. In 88 evaluable patients (cut-off 13 Aug 2021), the ORR (primary endpoint) was 65.9%, DCR was 92.0% and the median DoR was 6.93 months. The median PFS was 7.10 months and median OS was 17.41 months. In patients who were PD-L1 CPS ≥ 1 , median OS was 17.41 months compared with 14.65 months in those with PD-L1 CPS < 1 [18]. Patients were enrolled regardless of PD-L1 status and received cadonilimab 4 mg/kg, 6 mg/kg or 10 mg/kg every 2 weeks or 10 mg/kg or 15 mg/kg every 3 weeks plus modified XELOX 2 weekly or XELOX 3 weekly. Median follow-up was 9.95 months [18].

The combination of cadonilimab and lenvatinib showed good antitumour activity as first-line therapy in a phase 2 trial (NCT04444167) in patients with unresectable hepatic cancer. Treatment with IV cadonilimab 6 mg/kg every 2 weeks plus oral lenvatinib once daily [$n = 18$ evaluable for antitumour activity (≥ 13 weeks follow-up)] achieved an ORR of 44.4% (primary endpoint) and a DCR of 77.8% (data cut-off 1 Feb 2021). The 6- and 12-month overall survival rates (data cut-off August 2021) were 94.1% and 83.6%; median PFS and OS had not been reached [14, 19].

2.3.4 Other Solid Tumours

Initial data from a phase 2 trial (NCT04220307) indicate that cadonilimab 6 mg/kg administered every 2 weeks has good antitumour activity in patients with metastatic nasopharyngeal cancer who had failed ≥ 2 lines of chemotherapy and had not had previous anti-PD-1/PD-L1 antibody treatment [1]. The confirmed

ORR (primary endpoint) was 30% ($n = 20$ evaluable patients) and DCR was 70%. In the subgroup of patients who were PD-L1 positive ($n = 8$), ORR was 50% compared with 16.7% in those who were PD-L1 negative ($n = 12$) [1].

Cadonilimab showed efficacy in a phase 1 dose escalation and expansion study in advanced or metastatic solid tumours

(NCT03261011). In those who received cadonilimab ≥ 2 mg/kg every 2 weeks ($n = 25$), the ORR was 24.0% (primary endpoint) and DCR was 44.0%. Patients ($n = 40$) were administered cadonilimab 0.2 mg/kg, 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 4.0 mg/kg or 6.0 mg/kg every 2 weeks; data cut-off was 24 September 2019 [13].

Key clinical trials of Cadonilimab

Drug(s)	Indication	Phase	Status	Location(s)	Sponsor	Identifier
Cadonilimab, bevacizumab, carboplatin, cisplatin, paclitaxel	Cervical cancer	3	Ongoing	China	Akeso	NCT04982237, AK104-303
Cadonilimab, placebo chemoradiotherapy	Cervical cancer	3	Recruiting	China	Akeso	NCT05235516, AK104-305
Cadonilimab	Cervical cancer	2	Ongoing	USA, Australia, New Zealand	Akeso	NCT04380805, AK104-201AU
Cadonilimab, carboplatin, pemetrexed, paclitaxel	Cervical cancer	2	Ongoing	China	Akeso	NCT04868708, AK104-210
Cadonilimab	Cervical cancer	2	Ongoing	China	Akeso	NCT05227651, AK104-214
Cadonilimab	Cervical cancer	2	Ongoing	USA	M. D. Anderson Cancer Center	NCT05063916, 2021-0585
Cadonilimab, placebo	Gastric or GEJ cancer	3	Ongoing	China	Akeso	NCT05008783, AK104-302
Cadonilimab, pulocimab, chemotherapy	Gastric or GEJ cancer	1/2	Recruiting	China	Akeso	NCT04982276, AK109-201
Cadonilimab, oxaliplatin, capecitabine	Gastric or GEJ cancer, solid tumours	1/2	Completed	China	Akeso	NCT03852251, AK104-201
Cadonilimab	MSI-H/dMMR gastric or colorectal cancer	2	Recruiting	China	Peking University	NCT04556253, IIT-002
Cadonilimab	MSI-H/dMMR colorectal cancer	1/2	Recruiting	China	Sun Yat-sen University	NCT05426005, CSWOG-C03
Cadonilimab, lenvatinib	Liver cancer	2	Ongoing	China	Akeso	NCT04728321, AK104-209
Cadonilimab, lenvatinib	Liver cancer	2	Recruiting	China	Akeso	NCT05319431, AK104-216
Cadonilimab, lenvatinib	Liver cancer	1/2	Completed	China	Akeso	NCT04444167, AK104-206
Cadonilimab	Nasopharyngeal cancer	2	Completed	China	Akeso	NCT04220307, AK104-204
Cadonilimab, docetaxel	NSCLC	2	Ongoing	China	Akeso	NCT05215067, AK104-215
Cadonilimab	NSCLC	2	Recruiting	China	Henan Cancer Hospital	NCT05377658, IIT-005
Cadonilimab, anlotinib	NSCLC	2	Recruiting	China	Akeso	NCT04544644, IIT-001, ChiCTR2000035993
Cadonilimab, anlotinib	NSCLC	1/2	Ongoing	China	Akeso	NCT04646330, AK104-208
Cadonilimab, carboplatin, pemetrexed, paclitaxel	NSCLC	1/2	Recruiting	China	Akeso	NCT04647344, AK104-207
Cadonilimab, axitinib	RCC	2	Recruiting	China	Akeso	NCT05256472, AK104-213
Cadonilimab	Ovarian cancer	2	Recruiting	China	Hunan Cancer Hospital	NCT05430906, AK104-IIT-003
Cadonilimab	MSI-H/dMMR solid tumours	2	Completed	China	Akeso	NCT04547101, AK104-205
Cadonilimab, pulocimab	Solid tumours	1/2	Ongoing	China	Akeso	NCT05142423, AK109-102
Cadonilimab, ligufalimab, chemotherapy	Solid tumours	1/2	Recruiting	China	Akeso	NCT05235542, AK117-204
Cadonilimab	Solid tumours	1/2	Completed	China	Akeso	NCT04172454, AK104-202
Cadonilimab	Solid tumours	1	Completed	Australia	Akeso	NCT03261011, AK104-101
Cadonilimab, dresbuxelimab	Solid tumours	1	Ongoing	Australia	Akeso	NCT04572152, AK119-102
Cadonilimab, AK 127	Solid tumours	1	Ongoing	Australia	Akeso	NCT05021120, AK127-101
Cadonilimab	Peripheral T-cell lymphoma	1/2	Completed	China	Akeso	NCT04444141, AK104-203

ES-SCLC extensive-stage small cell lung cancer, *GEJ* gastroesophageal junction, *MSI-H/dMMR* microsatellite instability-high/mismatch repair deficient, *NSCLC* non-small cell lung cancer, *RCC* renal cell cancer

2.4 Adverse Events

Adverse reactions of all grades were reported in 83.6% of patients ($n = 458$) with advanced solid tumours who participated in four single-agent trials of cadonilimab [NCT03261011 (AK104-101; $n = 119$), NCT03852251 (AK104-201; $n = 240$), NCT04172454 (AK104-202; $n = 68$) and NCT04220307 (AK104-204; $n = 31$) [5]. The most frequent adverse reactions (incidence $\geq 10\%$) were rash (23.1%), anaemia (16.4%), hypothyroidism (16.2%), increased AST (14.6%), increased ALT (13.8%), pruritus (10.9%), fatigue (10.3%) and proteinuria (10.0%). Grade 3 or higher adverse reactions occurred in 20.3% of patients, and these included infusion-related reactions (2.2%) and anaemia (2.0%) [5].

In the cohort of patients with r/mCC who received cadonilimab 6 mg/kg every 2 weeks in the phase 1b/2 trial [NCT03852251; $n = 111$] [5], adverse reactions of all grades were reported in most (91.9%) patients; those with an incidence $\geq 10\%$ were anaemia (36.0%), hypothyroidism (20.7%), increased AST (18.0%), increased ALT (16.2%), hyperthyroidism (16.2%), decreased white blood cell count (15.3%), hypoalbuminaemia (15.3%), rash (15.3%), diarrhoea (12.6%), fever (12.6%), increased brain natriuretic peptide (11.7%), decreased body weight (10.8%), decreased neutrophil count (10.8%) and hyperglycaemia (10.8%). Adverse reactions \geq grade 3 occurred in 27.9% of patients; those with an incidence $\geq 2\%$ were anaemia (6.3%) and loss of appetite (3.6%) [5].

Immune-related adverse reactions among 458 cadonilimab monotherapy recipients included hypothyroidism (19.9%), hyperthyroidism (13.3%), skin adverse reactions (8.7%), hyperglycaemia (3.5%), other thyroid diseases (2.6%), hepatitis (2.0%), pneumonitis (1.7%), musculoskeletal toxicity (1.3%), diarrhoea and colitis (1.1%), type 1 diabetes (0.9%), hypophysitis (0.9%), myocarditis (0.9%), pancreatic toxicity (0.9%), thrombocytopenia (0.9%), adrenal insufficiency (0.7%), other haematological toxicity (0.7%), gastritis (0.4%), iridocyclitis (0.2%), nephrotoxicity (0.2%) and neurotoxicity (0.2%). Infusion-related reactions or hypersensitivity reactions occurred in 9.2% of patients, and resulted in permanent treatment discontinuation in 2.6% [5].

In 288 evaluable cadonilimab monotherapy recipients from 3 clinical trials conducted in China, anti-drug antibodies (ADAs) due to treatment with cadonilimab developed in 5.6% of patients. The effects of ADAs on the pharmacokinetics, efficacy and safety of cadonilimab is unknown [5].

2.5 Ongoing Clinical Trials

There are numerous ongoing trials of cadonilimab as monotherapy or combination therapy. In cervical cancer, there are

two phase 3 trials [one in combination with concurrent chemoradiotherapy in locally advanced disease (NCT05235516) and the other in combination with platinum-based chemotherapy with or without bevacizumab as first-line therapy (NCT04982237)] and four phase 2 trials (NCT04868708; NCT05227651; NCT05063916; and NCT04380805) underway. In gastric/GEJ or colorectal cancer, a phase 3 trial in combination with chemotherapy as first-line treatment for gastric/GEJ cancer (NCT05008783), a phase 2 trial investigating perioperative use in MSI-H/dMMR locally advanced gastric or colorectal cancer (NCT04556253), a phase 1/2 trial in PD-1/PD-L1 blockade-refractory, MSI-H/dMMR, advanced colorectal cancer (NCT05426005) and a phase 1b/2 trial of cadonilimab plus pulocimab in gastric/GEJ cancer (NCT04982276) are ongoing. In hepatocellular cancer, a phase 3 trial of cadonilimab plus lenvatinib and TACE in the treatment of unresectable, non-metastatic hepatocellular carcinoma (NCT05319431) and a phase 2 trial of cadonilimab with or without lenvatinib in advanced hepatic cancer (NCT04728321) are underway. A phase 3 trial of cadonilimab in the treatment of early-stage hepatocellular carcinoma is ongoing (NCT05489289). Three phase 2 (NCT05377658; NCT05215067; NCT04544644) and two phase 1b/2 (NCT04646330; NCT04647344) trials are ongoing in patients with NSCLC, as are phase 2 studies in ccRCC (NCT05256472) and ovarian cancer (NCT05430906). Cadonilimab in combination with other investigational agents for the treatment of advanced solid tumours is being investigated in two ongoing phase 1b/2 trials [with pulocimab (NCT05142423) and with ligufalimab with or without chemotherapy (NCT05235542)] and two ongoing phase 1 trials [with AK127 (NCT05021120) and with dresbuxelimumab (NCT04572152)].

Two other phase 1b/2 studies of cadonilimab are planned: a trial in combination with the Aurora B/VEGFR/PDGFR/c-Kit/CSF1R inhibitor chiauranib for extensive stage small cell lung cancer [9] and a trial in combination with ivonescimab (a PD-1/VEGF bi-specific antibody) with or without chemotherapy in advanced NSCLC [20].

3 Current Status

Cadonilimab received its first approval on 29 June 2022 in China [8] for the treatment of patients with r/mCC who have progressed on or after platinum-based chemotherapy [5, 7].

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40265-022-01761-9>.

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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