Safety and antitumour activity of cadonilimab, an anti-PD-1/CTLA-4 bispecific antibody, for patients with advanced solid tumours (COMPASSION-03): a multicentre, open-label, phase 1b/2 trial

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For the Chinese translation of the abstract see **Online** for appendix 1

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Summary

Background Immune checkpoint inhibitors targeting PD-1 or CTLA-4 individually have shown substantial clinical benefits in the treatment of malignancies. We aimed to assess the safety and antitumour activity of cadonilimab monotherapy, a bispecific PD-1/CTLA-4 antibody, in patients with advanced solid tumours.

Methods This multicentre, open-label, phase 1b/2 trial was conducted across 30 hospitals in China. Patients aged 18 years or older with histologically or cytologically confirmed, unresectable advanced solid tumours, unsuccessful completion of at least one previous systemic therapy, and an Eastern Cooperative Oncology Group performance status of 0 or 1 were eligible for inclusion. Patients who had previously received anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment were not eligible for inclusion. In the dose escalation phase of phase 1b, patients received intravenous cadonilimab at 6 mg/kg and 10 mg/kg every 2 weeks. In the dose expansion phase of phase 1b, cadonilimab at 6 mg/kg and a fixed dose of 450 mg were given intravenously every 2 weeks. In phase 2, cadonilimab at 6 mg/kg was administered intravenously every 2 weeks in three cohorts: patients with cervical cancer, oesophageal squamous cell carcinoma, and hepatocellular carcinoma. The primary endpoints were the safety of cadonilimab in phase 1b and objective response rate in phase 2, based on the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The safety analysis was done in all patients who received at least one dose of cadonilimab. Antitumour activity was assessed in the full analysis set for the cervical cancer cohort, and in all patients with measurable disease at baseline and who received at least one dose of cadonilimab in the oesophageal squamous cell carcinoma and hepatocellular carcinoma cohorts. The study is registered on ClinicalTrial.gov, NCT03852251, and closed to new participants; follow-up has been completed.

Findings Between Jan 18, 2019, and Jan 8, 2021, 240 patients (83 [43 male and 40 female] in phase 1b and 157 in phase 2) were enrolled. Phase 2 enrolled 111 female patients with cervical cancer, 22 patients with oesophageal squamous cell carcinoma (15 male and seven female), and 24 patients with hepatocellular carcinoma (17 male and seven female). During dose escalation, no dose-limiting toxicities occurred. Grade 3–4 treatment-related adverse events occurred in 67 (28%) of 240 patients; the most frequent grade 3 or worse treatment-related adverse events were anaemia (seven [3%]), increased lipase (four [2%]), decreased bodyweight (three [1%]), decreased appetite (four [2%]), decreased neutrophil count (three [1%]), and infusion-related reaction (two [1%]). 17 (7%) patients discontinued treatment due to treatment-related adverse events. 54 (23%) of 240 patients reported serious treatment-related adverse events, including five patients who died (one due to myocardial infarction; cause unknown for four). In phase 2, in the cervical cancer cohort, with a median follow-up of 14·6 months (IQR 13·1–17·5), the objective response rate was 32·3% (32 of 99; 95% CI 23·3–42·5). In the oesophageal squamous cell carcinoma cohort, with a median follow-up of 17·9 months (IQR 4·0–15·1), the objective response rate was 18·2% (four of 22; 95% CI 5·2–40·3). In the hepatocellular carcinoma cohort, with a median follow-up of 19·6 months (IQR 8·7–19·8), the objective response rate was 16·7% (four of 24; 95% CI 4·7–37·4).

Interpretation Cadonilimab showed an encouraging tumour response rate, with a manageable safety profile, suggesting the potential of cadonilimab for the treatment of advanced solid tumours.

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Research in context

Evidence before this study

We searched PubMed from Jan 1, 2013, to March 31, 2023, using the search terms "solid tumours AND phase II AND (immunotherapy OR immune checkpoint OR anti-CTLA-4 OR anti-PD-1 OR CTLA-4 inhibitor OR PD-1 inhibitor)", which yielded 337 results; we excluded reviews and meta-analyses. We identified one relevant phase 2 study investigating dual PD-1 and CTLA-4 checkpoint blockade with the balstilimab and zalifrelimab combination as second-line treatment for advanced cervical cancer, which reported promising and durable clinical activity with favourable tolerability. The phase 1–2 CheckMate-040 and CheckMate-032 clinical trials had reported that the combination of nivolumab (an anti-PD-1 checkpoint inhibitor) and ipilimumab (a CTLA-4 checkpoint inhibitor) had a manageable safety profile and promising antitumour activity, with durable response in patients with hepatocellular carcinoma (CheckMate-040) and metastatic oesophagogastric cancer (CheckMate-032). A high dose of ipilimumab was shown to be associated with improved tumour response and survival benefit in various malignancies, but the therapeutic dose is low due to immune-related adverse events.

Added value of this study

Cadonilimab is a tetravalent, PD-1/CTLA-4 bi-specific antibody with a crystallisable fragment (Fc)-null design. To the best of our knowledge, this is the first report to show a promising activity and favourable safety profile of cadonilimab in patients with solid tumours especially in those with recurrent or metastatic cervical cancer.

Implications of all the available evidence

These findings support the potential use of cadonilimab monotherapy in patients with advanced solid tumours, especially in those with advanced cervical cancer, with an encouraging objective response rate, overall survival, and favourable safety profile. These results also support further investigation of cadonilimab as a monotherapy and in combination with other therapies; clinical trials assessing the effectiveness of cadonilimab in patients with cervical cancer (NCT04982237), hepatocellular carcinoma (NCT04728321), non-small-cell lung cancer (NCT04646330), and gastric adenocarcinoma (NCT05008783) are underway.

Introduction

Immune checkpoint inhibitors have emerged as a standard treatment option for a wide range of tumour types.[1] Regulatory approvals have primarily focused on two inhibitory pathways: PD-1 and CTLA-4.[2] Several anti-PD-1 antibodies have been approved worldwide for the treatment of various cancers. Monotherapy with certain anti-PD-1 antibodies has shown substantial antitumour efficacy in specific cancers. For example, dostarlimab has shown efficacy in patients with mismatch repair deficient or microsatellite instability-high colorectal cancer.[3] However, the efficacy of anti-PD-1 monotherapy has been inadequate in some studies. CTLA-4 is a transmembrane protein expressed on the surfaces of activated T cells and regulatory T cells. It binds to CD80 and CD86 molecules on antigen-presenting cells or tumour cells, leading to the suppression of host T-cell activation and immune surveillance.[4] The distinct and non-overlapping mechanisms used by tumours to evade the immune system through CTLA-4 and PD-1 pathways have made combined blockade of both pathways an attractive clinical strategy. The combination of PD-1 and CTLA-4 blockade has substantially improved overall survival in several cancer types.[5–8] However, the therapeutic dose of an anti-CTLA-4 monoclonal antibody is low due to dose-dependent immune-related adverse events, and the efficacy of dual blockade of PD-1 and CTLA-4 has been shown in only a few cancer types. Therefore, there is an urgent need for novel approaches that can enhance PD-1 and CTLA-4 blockade while improving the safety profile.[9]

Cadonilimab is a first-in-class bispecific antibody that targets both PD-1 and CTLA-4. Preclinical studies have shown that its tetravalent design enhances its high binding activity in the tumour microenvironment. With no Fc binding, cadonilimab could eliminate a series of functions mediated by the Fc receptor, which contribute to a poor safety profile in clinical settings.[10] In a phase 1a/1b study conducted in Australia, cadonilimab showed a favourable safety profile and promising antitumour activity when administered at doses of 4 mg/kg or higher in patients with solid tumours.[11]

We aimed to assess the safety and activity of cadonilimab monotherapy in a phase 1b/2 study (phase 1b was conducted in patients with solid tumours and phase 2 was conducted in patients with cervical cancer, oesophageal squamous cell carcinoma, and hepatocellular carcinoma).

Methods

Study design and participants

COMPASSION-03 was a multicentre, open-label, phase 1b/2 trial of cadonilimab monotherapy in patients with solid tumours and cadonilimab in combination with chemotherapy in patients with advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma. Since the data from the combination treatment cohort are not yet mature, the results of combined therapy in patients with gastric or gastro-oesophageal junction adenocarcinoma will be reported separately at a later date. The cadonilimab monotherapy study consisted of two phases: phase 1b (dose escalation and dose expansion) was conducted in

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See Online for appendix 2

patients with solid tumours and phase 2 was conducted in patients with cervical cancer, oesophageal squamous cell carcinoma, and hepatocellular carcinoma. This study was conducted across 30 hospitals in China (the complete list of hospitals is provided in appendix 2 p 10). Eligible patients were aged 18 years or older with histologically or cytologically confirmed unresectable advanced solid tumours, unsuccessful completion of at least one previous systemic treatment, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a life expectancy of more than 3 months, and at least one measurable lesion as per the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1. Laboratory tests required to assess eligibility included a haematology test, blood chemistry, cardiac function, urinalysis, coagulation, and thyroid function. During the screening phase of the study, disease progression was confirmed by the investigators on the basis of CT or MRI scans during or after the most recent treatment. In phase 2, for the cervical cancer cohort, eligible patients had to have received no more than two previous systemic therapies for recurrent or metastatic cervical cancer. If chemotherapy was received as neoadjuvant treatment, adjuvant treatment, and concomitant with radiotherapy used in the non-recurrent or metastatic setting, this was not counted as previous systemic therapy. PD-L1 expression status was analysed in archival tumour biopsy specimens with the validated PD-L1 immunohistochemistry 22C3 pharmDx assay (Agilent Technologies, Santa Clara, USA).[12] For the oesophageal squamous cell carcinoma and hepatocellular carcinoma cohorts, eligible patients had to have received no more than one previous systemic therapy for advanced disease. Patients who had previously received immune checkpoint inhibitors (including anti-PD-1, anti-PD-L1, and anti-CTLA-4 therapies) were excluded from the study. The comprehensive list of inclusion and exclusion criteria is provided in the study protocol (appendix 2). Information about sex or gender and race or ethnicity was self reported.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. The study protocol was reviewed and approved by relevant institutional review boards or ethics committees at each hospital. All patients provided written informed consent.

Procedures

The dose of cadonilimab in this study was determined on the basis of the first-in-human study of cadonilimab conducted in Australia (NCT03261011), which assessed cadonilimab monotherapy at doses from 0·2 mg/kg to 10 mg/kg intravenously every 2 weeks, and found that 6 mg/kg every 2 weeks could be used in future studies.[11] Therefore, in the present study, the regimen of 6 mg/kg intravenously every 2 weeks was used and 10 mg/kg intravenously every 2 weeks was also explored to assess the safety of cadonilimab in Chinese patients.

The dose escalation phase followed a 3+3 design, where two dose levels, 6 mg/kg and 10 mg/kg, were used.[13] Initially, three patients were enrolled and received the initial dose level. If none of these three patients had dose-limiting toxicities, the study escalated to the next dose level. In the event that one patient had a dose-limiting toxicity, an additional three patients would be enrolled at the current dose level. The specific definitions of dose-limiting toxicities are provided in the study protocol (appendix 2). Dose-limiting toxicities were assessed within 28 days after the first dose of cadonilimab. If no dose-limiting toxicities were observed at the dose level of 6 mg/kg every 2 weeks, the dose expansion phase would commence with expanded enrolment. This analysis was done in 21 patients from phase 1b (appendix 2 p 4). This analysis was done after the patients in phase 1b had been recruited and the blood samples from these patients had been collected. According to the pharmacokinetics analysis, 6 mg/kg and a fixed dose of 450 mg showed a similar pharmacokinetics profile. Considering that a fixed dose would be convenient to administer in clinical settings, 450 mg was also chosen in the dose expansion phase to evaluate the activity and safety of cadonilimab. In phase 2 of the study, antitumour activity was evaluated in three selected tumour types (cervical cancer, oesophageal squamous cell carcinoma, and hepatocellular carcinoma). All patients received cadonilimab 6 mg/kg intravenously every 2 weeks until disease progression, intolerable toxicity, investigator decision, or withdrawal of consent (whichever occurred first). Treatment with cadonilimab was planned to last no longer than 24 months.

Tumour assessments were conducted with CT or MRI scans. In phase 1b, assessments were done at baseline, every 6 weeks within 54 weeks after enrolment, then every 12 weeks (±7 days). For phase 2, assessments were conducted every 8 weeks for 56 weeks, and then every 12 weeks (±7 days) thereafter until initiation of subsequent antitumour therapy, disease progression, withdrawal of informed consent, death, or study closure. In phase 1b, imaging assessments were done by investigators for the oesophageal squamous cell carcinoma and hepatocellular carcinoma cohorts. In the cervical cancer cohort, imaging assessments were carried out by a masked independent radiology review committee. If radiographical evidence of disease progression was observed, clinically stable patients could continue receiving cadonilimab until progressive disease was confirmed on a subsequent scan at least 4 weeks later. Dose reductions of cadonilimab were not permitted during the study. Survival assessments were conducted every 3 months after treatment discontinuation. For patients who discontinued the study due to toxicities or confirmed disease progression, follow-up would be

continued until death, withdrawal of consent, loss of follow-up, or the end of the study, whichever occurred first. Laboratory assessments included haematology tests, blood chemistry tests, cardiac function, urinalysis, coagulation tests, and thyroid function tests. The haematology test, blood chemistry test, cardiac function, and urinalysis were performed on day 1 before dosing at each treatment cycle; the coagulation and thyroid function tests were done every 2 cycles. Adverse events occurring during the study were recorded at each follow-up and graded with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0. All adverse events were reported until 30 days after the last dose of study treatment or initiation of other antitumour therapy, and all serious adverse events and immune-related adverse events were reported until 90 days after the last dose of study treatment or initiation of other antitumour therapy. All data were collected at the study sites with the sponsor's electronic data capture and management system (Akeso Biopharma; Zhongshan, China).

Serum concentrations of cadonilimab were measured by a validated enzyme-linked immunosorbent assay (Molecular Device VERSA max and SpectraMax 340PC384, San Jose, CA, USA). Circulating quantities of T cells expressing the Ki67 and receptor occupancy of cadonilimab were monitored with qualified flow cytometry-based assays (BD Biosciences, FACSCelesta, San Jose, CA, USA). Antidrug antibodies to cadonilimab were detected with an electrochemiluminescent immunoassay by the use of Meso Scale Discovery technology (Rockville, MD, USA). The detailed methods used in the pharmacokinetic–pharmacodynamic analysis and the immunogenicity assessment are provided in appendix 2 (pp 2–3).

Outcomes

In phase 1b, the primary endpoint was the safety of cadonilimab. The secondary endpoint in phase 1b was the antitumour activity of cadonilimab (objective response rate, disease control rate, duration of response, time to response, and progression-free survival assessment done with Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1). In phase 2, the primary endpoint for the cervical cancer cohort was the objective response rate assessed by the independent radiology review committee according to RESCIST (version 1.1). For the oesophageal squamous cell carcinoma and hepatocellular carcinoma cohorts, the primary endpoint was the objective response rate assessed by investigators with RESCIST (version 1.1). The objective response rate was defined as the proportion of patients who had a confirmed complete response or partial response as their best overall response. Secondary endpoints included the duration of response, disease control rate, time to response, progression-free survival, overall survival, pharmacokinetic assessment, and the immunogenicity assessment. The duration of response was defined as the time from the first documentation of confirmed response (complete response or partial response) to the first documentation of progressive disease or death due to any cause, whichever occurred first. The disease control rate was defined as the proportion of patients who achieved a confirmed complete response or partial response or stable disease as their best overall response. Time to response was defined as the time from the first dose administration of cadonilimab to the first documentation of confirmed complete response or partial response. Progression-free survival was defined as the time from the start of treatment until documentation of disease progression or death from any cause, whichever

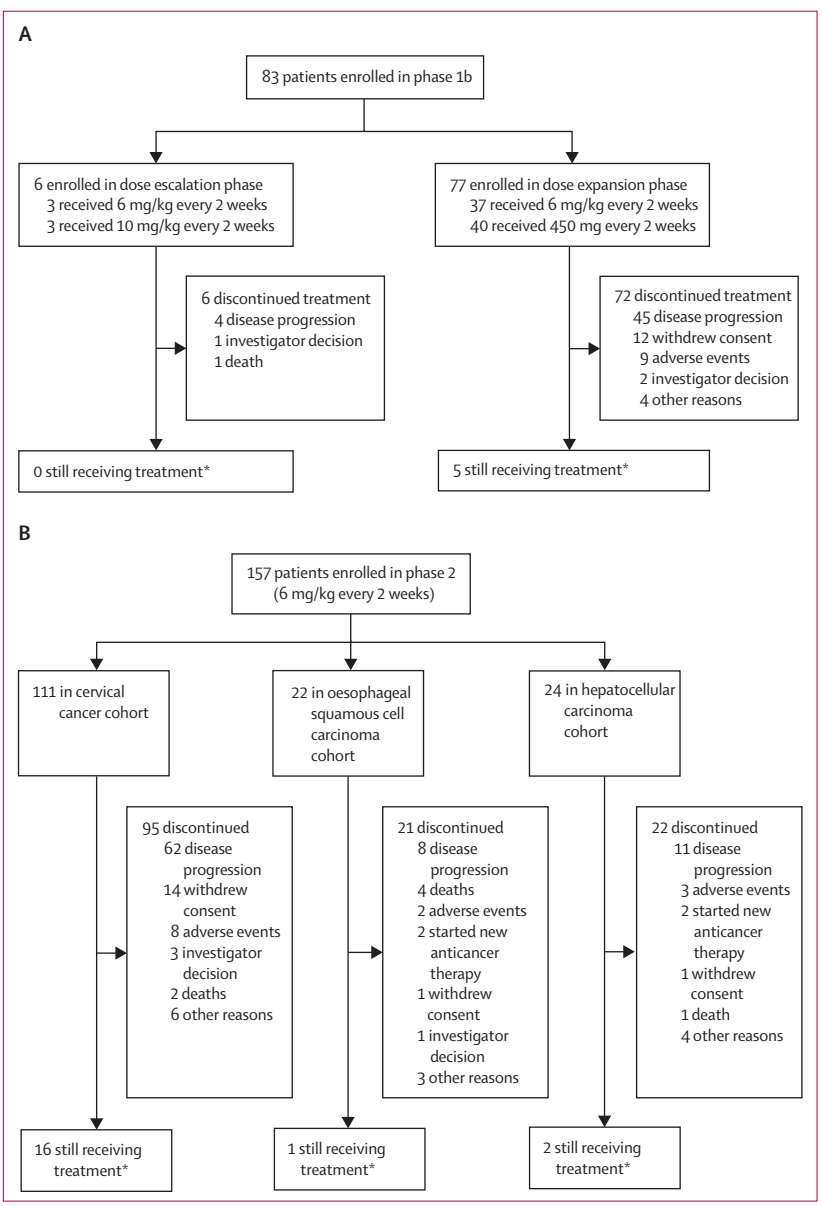


Figure 1: **Trial profile**
(A) Patients enrolled in the phase 1b trial. (B) Patients enrolled in the phase 2 trial. *As of Jan 7, 2022, for the cervical cancer cohort, and May 6, 2022, for the other cohorts.

occurred first. Overall survival was defined as the time from the start of treatment until death from any cause. Exploratory endpoints included pharmacodynamic biomarkers, the correlation between PD-L1 expression and antitumour response, and antitumour activity assessed with immune-related RECIST (irRECIST). As data collection was not mandatory for tumour response with irRECIST, the available data were not sufficient for this analysis; therefore, the results of tumour response based on irRECIST are not reported here. The assessment of cadonilimab in combination with oxaliplatin and capecitabine as first-line therapy in gastric cancer will be reported separately at a later date.

Statistical analysis

The number of patients enrolled in the dose escalation phase was determined with the conventional 3+3 design with two dose levels. The dose expansion cohorts had the potential to enrol up to 80 patients, with a maximum of 40 patients per dose level. For the cervical cancer cohort in phase 2, it was estimated that 110 patients with cervical cancer would need to be enrolled. This number was chosen to ensure there would be at least 100 patients in the full analysis set, meeting the requirements of the China National Medical Products Administration (NMPA) while ensuring the lower limit of the 95% CI of the objective response rate would be higher than 10% for moderate effect sizes. For the oesophageal squamous cell carcinoma and hepatocellular carcinoma cohorts, a sample size of 30 was assumed for each cohort, expanding the original study for exploratory purposes only.

The safety population comprised all patients who received at least one dose of cadonilimab. Dose-limiting toxicities were evaluated in all patients who received at least 80% of the planned dose during the dose escalation

	Phase 1b				Phase 2		
	6 mg/kg every 2 weeks (n=40)	10 mg/kg every 2 weeks (n=3)	450 mg every 2 weeks* (n=40)	Total (n=83)	Cervical cancer (n=111)	Oesophageal squamous cell carcinoma† (n=22)	Hepatocellular carcinoma (n=24)
Sex							
Male	23 (58%)	1 (33%)	19 (48%)	43 (52%)	0	15 (68%)	17 (71%)
Female	17 (42%)	2 (67%)	21 (52%)	40 (48%)	111 (100%)	7 (32%)	7 (29%)
Age (years)							
Median (IQR)	58 (54–62)	58 (56–68)	56 (49–64)	56 (51–63)	52 (45–58)	63 (59–67)	51 (44–56)
Range	32–68	56–68	26–75	26–75	27–73	49–73	27–68
<65 years	35 (88%)	2 (67%)	30 (75%)	67 (81%)	105 (95%)	12 (55%)	22 (92%)
≥65 years	5 (12%)	1 (33%)	10 (25%)	16 (19%)	6 (5%)	10 (45%)	2 (8%)
ECOG performance status							
0	9 (22%)	0	13 (32%)	22 (27%)	48 (43%)	7 (32%)	14 (58%)
1	31 (78%)	3 (100%)	27 (68%)	61 (73%)	63 (57%)	15 (68%)	10 (42%)
Smoking history							
Never smoker	18 (45%)	2 (67%)	23 (58%)	43 (52%)	108 (97%)	8 (36%)	14 (58%)
Current smoker	22 (55%)	1 (33%)	17 (42%)	40 (48%)	3 (3%)	14 (64%)	10 (42%)
Previous lines of systemic cancer therapy							
0	0	1 (33%)	3 (7%)	4 (5%)	1 (1%)	0	7 (29%)
1	14 (35%)	2 (67%)	16 (40%)	32 (39%)	70 (63%)	17 (77%)	17 (71%)
2	17 (43%)	0	9 (22%)	26 (31%)	40 (36%)	0	0
≥3	9 (22%)	0	10 (25%)	19 (23%)	0	0	0
PD-L1 combined positive score							
<1	7 (18%)	2 (67%)	15 (37%)	24 (29%)	20 (18%)	5 (23%)	13 (54%)
≥1	2 (5%)	1 (33%)	2 (5%)	5 (6%)	69 (62%)	11 (50%)	5 (21%)
Missing	30 (75%)	0	23 (58%)	53 (64%)	22 (20%)	6 (27%)	6 (25%)
Not available	1 (2%)	0	0	1 (1%)	0	0	0
Histopathological type							
Adenocarcinoma	..	..	..	..	5 (4%)	..	..
Squamous cell carcinoma	..	..	..	..	103 (93%)	..	..
Adenosquamous carcinoma	..	..	..	..	3 (3%)	..	..

Data are n (%), unless otherwise stated; percentages have been rounded up, so they might not total 100. Histopathologyical type was only tested in the cervical cancer cohort in phase 2. ECOG=Eastern Cooperative Oncology Group. *Two patients with previous systemic cancer therapy missing data on number of previous lines of therapy. †Five patients with previous systemic cancer therapy missing data on number of previous lines of therapy.

Table 1: **Baseline characteristics of participants**

phase (appendix 2). Antitumour activity was analysed in all patients with measurable disease at baseline who received at least one dose of cadonilimab, except for the cervical cancer cohort. For the cervical cancer cohort, according to the requirements of the NMPA, antitumour activity was assessed in the full analysis set, which included patients with measurable disease at baseline (assessed by independent radiology review committee), diagnosed as having relapsed or refractory cervical cancer (appendix 2 p 26), and without previous treatment with anti-PD-1, anti-PD-L1, and anti-CTLA-4 therapies. Safety was summarised descriptively. The objective response rate was estimated, and the 95% CI was calculated with the Clopper-Pearson method. For secondary endpoints with binary or proportion outcomes, the Clopper-Pearson method was used. The Kaplan-Meier method was used to evaluate time-to-event outcomes such as progression-free survival, overall survival, and duration of response. In phase 2, progression-free survival and overall survival were evaluated at 6 months and 12 months in all cohorts, and overall survival at 18 months was evaluated in the cervical cancer cohort. Additionally, in the cervical cancer cohort, response, median and 12-month progression-free survival, and median and 12-month overall survival were evaluated for the PD-L1 positive subgroup of patients, as was response for the PD-L1 negative subgroup. All of these analyses were prespecified. The 95% CI of the median event time was calculated with the Brookmeyer-Crowley method. For progression-free survival and duration of response, a patient was considered to be censored if no progressive disease or death was reported before the data cutoff date (Jan 7, 2022, for the cervical cancer cohort, and May 6, 2022, for the other disease cohorts and patients in phase 1b). For overall survival, a patient was considered censored if no death was reported before the data cutoff date. The administrative censoring was assumed to be random (ie non-informative). Detailed censoring rules are provided in appendix 2 (p 8). Data from pharmacodynamics analysis were presented by dose cohort along with descriptive statistics. The pharmacokinetic parameters were presented as medians and IQRs. A post-hoc analysis was conducted to explore the correlation between pharmacokinetics exposure of cadonilimab and clinical safety (appendix 2 p 2). All statistical analyses were done with SAS (version 9.4).

This trial is registered with ClinicalTrial.gov (NCT03852251).

Role of the funding source

The funder of the study worked with the investigators and participated in study design, data collection, data analysis, data interpretation, and writing of the report. All authors reviewed and approved the manuscript for publication.

Results

Between Jan 18, 2019, and Jan 8, 2021, 240 patients were enrolled (83 in phase 1b and 157 in phase 2; figure 1). Patient demographics and baseline disease characteristics are summarised in table 1. The types of solid tumours included in phase 1b are shown in appendix 2 (p 11). During dose escalation, no dose-limiting toxicities occurred. In phase 2, 111 female patients were enrolled in the cervical cancer cohort, 17 male and seven female patients in the hepatocellular carcinoma cohort, and 15 male and seven female patients in the oesophageal squamous cell carcinoma cohort.

All 240 patients were included in the safety analyses. Treatment-related adverse events of any grade were reported in 217 (90%) of 240 patients. Grade 3 or worse treatment-related adverse events were reported by 67 (28%) patients, with the most common being anaemia (seven [3%]), decreased appetite (four [2%]), increased lipase (four [2%]), decreased bodyweight (three [1%]), decreased neutrophil count (three [1%]), and infusion-related reaction (two [1%]; tables 2, 3). The incidence of treatment-related serious adverse events was 23% (54 of 240). The most commonly reported treatment-related serious adverse events were abnormal hepatic function (four [2%]) and immune-mediated myocarditis (three [1%]). 17 (7%) patients permanently discontinued cadonilimab due to treatment-related adverse events (appendix 2 p 21). Five (2%) deaths due to treatment-related adverse events were reported; the cause of death was myocardial infarction in one patient and unknown in four patients. 122 (51%) of 240 patients had immune-related adverse events, with grade 3 or worse immune-related adverse events reported in 33 (14%) patients. 27 (11%) patients had serious immune-related adverse events, and seven (3%) patients had immune-related adverse events leading to permanent discontinuation. No immune-related adverse events leading to death were reported. Details of treatment-related adverse events and immune-related adverse events are shown in appendix 2 (pp 12–13). Grade 1–2 treatment-emergent adverse events (occurring in more than 10% of patients) and all grade 3 or worse treatment-emergent adverse events are summarised in appendix 2 (pp 14–20). The most common events, including those that were treatment-related and those that were not, included anaemia (96 [40%]), increased aspartate aminotransferase (54 [23%]), increased alanine aminotransferase (50 [21%]), hypothyroidism (50 [21%]), decreased bodyweight (47 [20%]), decreased white blood cell count (44 [18%]), proteinuria (43 [18%]), pyrexia (41 [17%]), rash (39 [16%]), decreased neutrophil count (30 [13%]), diarrhoea (29 [12%]), hypoalbuminaemia (27 [11%]), increased blood creatine phosphokinase (25 [10%]), and upper respiratory tract infection (24 [10%]).

All 83 patients enrolled in phase 1b were evaluable for tumour response (table 4). At data cutoff, the median follow-up period was 19·5 months (IQR 4·3–18·0).

	6 mg/kg every 2 weeks (n=40)			10 mg/kg every 2 weeks (n=3)			450 mg every 2 weeks (n=40)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
All treatment-related adverse events	34 (85%)	8 (20%)	4 (10%)	3 (100%)	0	0	35 (88%)	9 (23%)	1 (3%)
Rash	9 (23%)	0	0	2 (67%)	0	0	8 (20%)	1 (3%)	0
Increased alanine aminotransferase	9 (23%)	1 (3%)	0	0	0	0	6 (15%)	0	0
Anaemia	8 (20%)	0	0	1 (33%)	0	0	6 (15%)	1 (3%)	0
Increased blood bilirubin	8 (20%)	0	1 (3%)	0	0	0	1 (3%)	1 (3%)	0
Increased aspartate aminotransferase	7 (18%)	1 (3%)	0	0	0	0	10 (25%)	0	0
Asthenia	7 (18%)	0	0	0	0	0	6 (15%)	0	0
Nausea	6 (15%)	0	0	0	0	0	3 (8%)	0	0
Decreased white blood cell count	6 (15%)	0	0	0	0	0	0	0	0
Increased conjugated bilirubin	6 (15%)	0	1 (3%)	0	0	0	3 (8%)	0	0
Proteinuria	5 (13%)	0	0	0	0	0	8 (20%)	1 (3%)	0
Hypothyroidism	5 (13%)	0	0	1 (33%)	0	0	5 (13%)	0	0
Increased blood thyroid stimulating hormone	5 (13%)	0	0	1 (33%)	0	0	5 (13%)	0	0
Decreased neutrophil count	5 (13%)	0	0	0	0	0	1 (3%)	0	0
Increased blood creatine phosphokinase	3 (8%)	1 (3%)	0	1 (33%)	0	0	6 (15%)	0	0
Pyrexia	3 (8%)	0	0	1 (33%)	0	0	4 (10%)	0	0
Pruritus	2 (5%)	0	0	1 (33%)	0	0	5 (13%)	0	0
Increased lipase	2 (5%)	0	0	1 (33%)	0	0	2 (5%)	1 (3%)	0
Increased amylase	2 (5%)	1 (3%)	0	0	0	0	4 (10%)	0	0
Diarrhoea	2 (5%)	0	0	0	0	0	4 (10%)	0	0
Increased troponin I	1 (3%)	0	0	1 (33%)	0	0	2 (5%)	0	0
Increased blood creatine phosphokinase myocardial band	1 (3%)	1 (3%)	0	0	0	0	1 (3%)	0	0
Increased C-reactive protein	0	0	0	0	0	0	0	1 (3%)	0
Increased urine bilirubin	0	1 (3%)	0	0	0	0	0	0	0
Decreased bodyweight	3 (8%)	1 (3%)	0	0	0	0	1 (3%)	1 (3%)	0
Ileus	0	0	0	0	0	0	0	1 (3%)	0
Sluggishness	0	1 (3%)	0	0	0	0	0	0	0
Immune thrombocytopenia	0	1 (3%)	0	0	0	0	0	0	0
Hyperthyroidism	1 (3%)	0	1 (3%)	0	0	0	1 (3%)	0	0
Nephrotic syndrome	0	0	0	0	0	0	0	1 (3%)	0
Hypoalbuminaemia	0	0	0	0	0	0	2 (5%)	1 (3%)	0
Diabetic ketoacidosis	0	0	1 (3%)	0	0	0	0	0	0
Hyperkalaemia	0	0	0	0	0	0	0	1 (3%)	0
Hypokalaemia	0	0	1 (3%)	0	0	0	0	0	0
Acute myocardial infarction	0	1 (3%)	0	0	0	0	0	0	0
Immune-mediated myocarditis	1 (3%)	0	0	0	0	0	0	1 (3%)	0
Myocarditis	0	0	1 (3%)	0	0	0	0	0	0
Pneumonitis	0	1 (3%)	0	0	0	0	0	0	0
Respiratory failure	0	0	0	0	0	0	0	0	1 (3%)
Respiratory tract haemorrhage	0	0	0	0	0	0	0	1 (3%)	0
Infusion-related hypersensitivity reaction	0	0	0	0	0	0	0	1 (3%)	0

Data are n (%). Grade 1–2 treatment-related adverse events occurring in at least 10% of patients and grade 3–5 treatment-related adverse events occurring in at least 2% of patients in phase 1b are shown.

Table 2: **Treatment-related adverse events in phase 1b**

Six (7·2%; 95% CI 2·7–15·1) of 83 patients had an objective response.

In phase 2, 103 (93%) of 111 patients had squamous cell carcinoma in the cervical cancer cohort. 99 (89%) of 111 patients were evaluable for tumour response by the independent radiology review committee assessment, after exclusion of two patients who had no measurable disease at baseline, nine patients who did not meet the criteria for recurrent or refractory cervical cancer, and one patient who had received anti-PD-1 treatment. At data cutoff, the median follow-up period was 14·6 months (IQR 13·1–17·5). 14 (14%) of 99 patients

	Cervical cancer (n=111)			Oesophageal squamous cell carcinoma (n=22)			Hepatocellular carcinoma (n=24)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
All treatment-related adverse events	100 (90%)	26 (23%)	4 (4%)	19 (86%)	7 (32%)	0	21 (88%)	6 (25%)	1 (4%)
Anaemia	32 (29%)	6 (5%)	0	6 (27%)	0	0	2 (8%)	0	0
Hypothyroidism	23 (21%)	0	0	8 (36%)	0	0	5 (21%)	0	0
Increased alanine aminotransferase	19 (17%)	1 (1%)	0	2 (9%)	0	0	7 (29%)	0	0
Increased aspartate aminotransferase	17 (15%)	1 (1%)	0	4 (18%)	0	0	7 (29%)	0	0
Decreased white blood cell count	17 (15%)	1 (1%)	0	5 (23%)	0	0	9 (38%)	0	0
Hyperthyroidism	16 (14%)	0	0	1 (5%)	0	0	3 (13%)	0	0
Pyrexia	14 (13%)	0	0	1 (5%)	0	0	2 (8%)	0	0
Diarrhoea	13 (12%)	1 (1%)	0	3 (14%)	0	0	0	0	0
Rash	12 (11%)	0	0	3 (14%)	1 (5%)	0	2 (8%)	0	0
Hypoalbuminaemia	12 (11%)	0	0	0	1 (5%)	0	0	0	0
Decreased neutrophil count	11 (10%)	1 (1%)	0	4 (18%)	1 (5%)	0	5 (21%)	1 (4%)	0
Increased blood creatine phosphokinase	8 (7%)	1 (1%)	0	4 (18%)	1 (5%)	0	1 (4%)	0	0
Increased C-reactive protein	6 (5%)	0	0	3 (14%)	0	0	0	0	0
Increased blood lactate dehydrogenase	5 (5%)	0	0	0	0	0	4 (17%)	0	0
Decreased platelet count	4 (4%)	1 (1%)	0	0	0	0	5 (21%)	1 (4%)	0
Infusion-related reaction	2 (2%)	0	1 (1%)	0	0	0	5 (21%)	1 (4%)	0
Pneumonitis	2 (2%)	0	0	3 (14%)	0	0	1 (4%)	0	0
Decreased bodyweight	11 (10%)	1 (1%)	0	1 (5%)	0	0	0	0	0
Increased blood creatinine	9 (8%)	1 (1%)	0	0	0	0	1 (4%)	0	0
Increased gamma-glutamyltransferase	8 (7%)	1 (1%)	0	0	0	0	1 (4%)	0	0
Increased lipase	8 (7%)	1 (1%)	0	2 (9%)	1 (5%)	0	1 (4%)	1 (4%)	0
Increased blood creatine phosphokinase myocardial band	8 (7%)	1 (1%)	0	0	0	0	1 (4%)	0	0
Abnormal hepatic function	2 (2%)	1 (1%)	0	0	0	0	2 (8%)	1 (4%)	0
Decreased appetite	8 (7%)	4 (4%)	0	0	0	0	0	0	0
Increased troponin T	3 (3%)	1 (1%)	0	0	0	0	0	0	0
Glucose urine present	1 (1%)	0	0	0	0	0	0	1 (4%)	0
Decreased haemoglobin	1 (1%)	1 (1%)	0	0	0	0	0	0	0
Decreased blood corticotrophin	0	0	0	0	1 (5%)	0	0	0	0
Decreased cortisol	0	0	0	0	1 (5%)	0	0	0	0
Hypopituitarism	0	0	0	0	1 (5%)	0	0	0	0
Adrenal insufficiency	0	1 (1%)	0	0	0	0	0	0	0
Immune-mediated hyperthyroidism	1 (1%)	1 (1%)	0	0	0	0	0	0	0
Immune thrombocytopenia	0	0	1 (1%)	0	0	0	0	0	0
Hypokalaemia	4 (4%)	1 (1%)	0	0	0	0	0	0	0
Hyponatraemia	1 (1%)	1 (1%)	0	0	0	0	0	0	0
Acute myocardial infarction	0	0	0	0	0	0	0	0	0
Immune-mediated myocarditis	0	1 (1%)	0	0	0	0	0	0	0
Renal impairment	4 (4%)	0	1 (1%)	0	0	0	0	0	0
Pneumonia	3 (3%)	1 (1%)	0	0	0	0	0	0	0
Immune-mediated pneumonitis	2 (2%)	0	1 (1%)	0	0	0	0	0	0
Gastritis	1 (1%)	1 (1%)	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0	0
Myocarditis	0	0	0	0	1 (5%)	0	0	0	0
Obstructive airways disorder	0	0	0	0	1 (5%)	0	0	0	0
Tracheo-oesophageal fistula	0	0	0	0	1 (5%)	0	0	0	0
Anaphylactic shock	0	0	0	0	0	0	0	0	1 (4%)
Bronchitis	0	1 (1%)	0	0	0	0	0	0	0
Dyspnoea	0	1 (1%)	1 (1%)	0	0	0	0	0	0

(Table 3 continues on next page)

	Cervical cancer (n=111)			Oesophageal squamous cell carcinoma (n=22)			Hepatocellular carcinoma (n=24)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)									
Immune-mediated myositis	0	1 (1%)	0	0	0	0	0	0	0
Venous thrombosis	0	1 (1%)	0	0	0	0	0	0	0
Immune-mediated hepatitis	0	1 (1%)	0	0	0	0	0	0	0
Vaginal haemorrhage	0	1 (1%)	0	0	0	0	0	0	0

Data are n (%). Grade 1–2 treatment-related adverse events occurring in at least 10% of patients and grade 3–5 treatment-related adverse events occurring in at least 2% of patients in phase 2 are shown. Three (3%) grade 5 events occurred in the cervical cancer cohort (one acute myocardial infarction and two deaths); two (9%) grade 5 events occurred in the oesophageal squamous cell carcinoma cohort (two deaths); and no grade 5 events occurred in the hepatocellular carcinoma cohort.

Table 3: **Treatment-related adverse events in phase 2**

	Phase 1b (n=83)	Phase 2 (n=145)		
		Cervical cancer (n=99)	Oesophageal squamous cell carcinoma (n=22)	Hepatocellular carcinoma (n=24)
Objective response	6 (7·2%; 2·7–15·1)	32 (32·3%; 23·3–42·5)	4 (18·2%; 5·2–40·3)	4 (16·7%; 4·7–37·4)
Complete response	0	14 (14%)	0	0
Partial response	6 (7%)	18 (18%)	4 (18%)	4 (17%)
Duration of response, months	NR (10·4–NE)	NR (7·4–NE)	10·2 (7·5–NE)	NR (3·6–NE)
Disease control	35 (42·2%; 31·4–53·5)	51 (51·5%; 41·3–61·7)	11 (50·0%; 28·2–71·8)	15 (62·5%; 40·6–81·2)
Stable disease	29 (35%)	19 (19%)	7 (32%)	11 (46%)
Progression-free survival, months	1·6 (1·3–3·0)	3·7 (1·9–6·3)	3·5 (1·8–6·2)	3·7 (1·8–9·9)
Overall survival, months	15·2 (9·4–21·9)	NR (11·3–NE)	9·4 (4·2–NE)	NR (14·5–NE)

Data are n (%; 95% CI), n (%), or median (95% CI). NR=not reached. NE=not estimable.

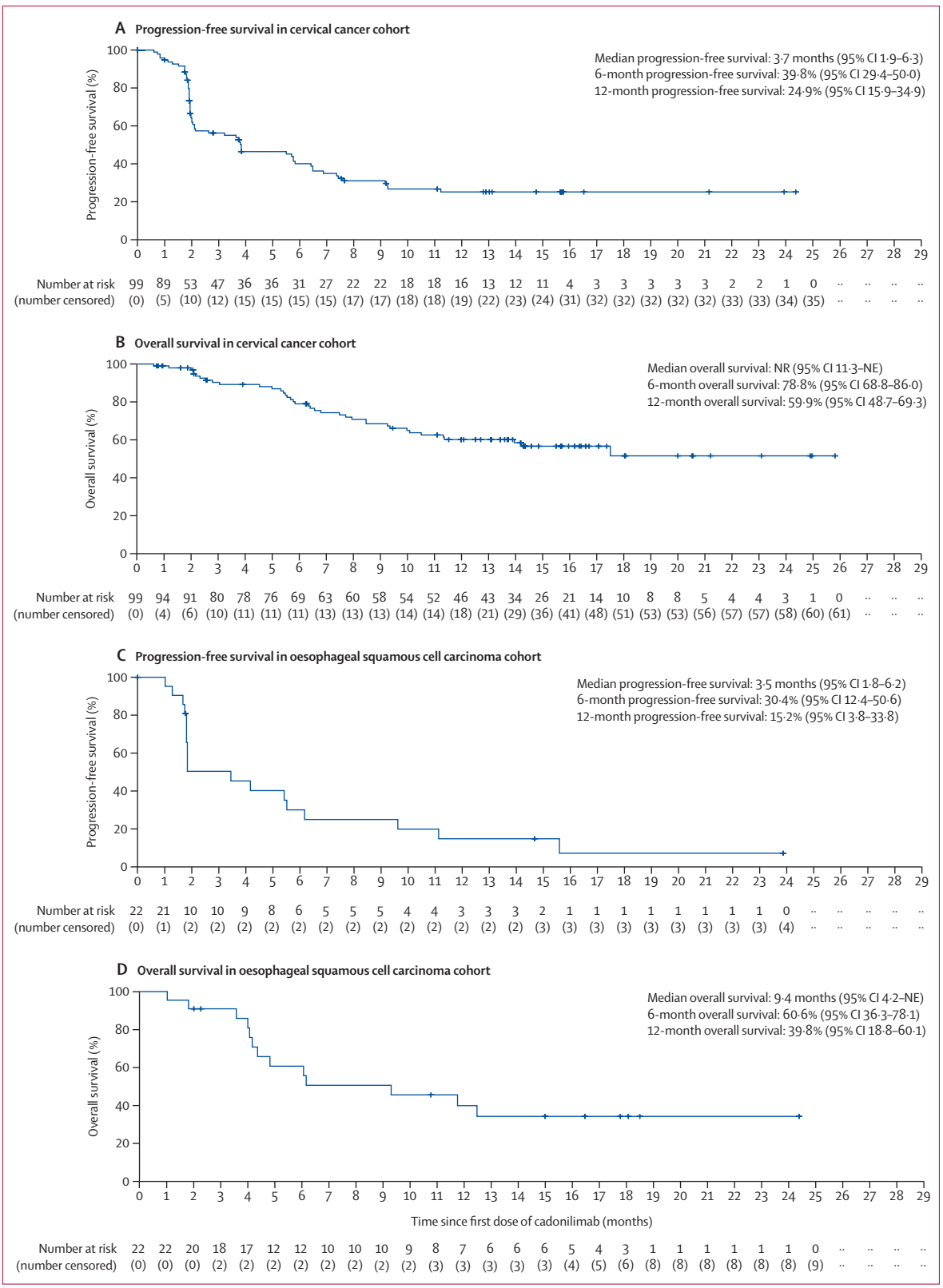
Table 4: **Summary of antitumour activity of cadonilimab**

had a complete response and 18 (18%) patients had a partial response, resulting in an objective response rate of 32·3% (32 of 99; 95% CI 23·3–42·5) and a disease control rate of 51·5% (51 of 99; 95% CI 41·3–61·7; table 4). 64 (65%) patients had a progression event and 38 (38%) died. Median progression-free survival was 3·7 months (95% CI 1·9–6·3; figure 2A), and median overall survival was not reached (95% CI 11·3 to not estimable; figure 2B; table 4). Estimated 12-month overall survival was 59·9% (95% CI 48·7–69·3), and the 18-month overall survival was 51·2% (95% CI 36·8–63·9). Of the 63 patients with cervical cancer and a PD-L1 combined positive score of 1 or higher, 11 (17%) had complete response and 16 (25%) had a partial response, resulting in an objective response rate of 42·9% (27 of 63; [95% CI 30·5–56·0]). In these patients, median progression-free survival was 5·8 months (95% CI 3·1–9·1), 12-month progression-free survival was 30·0% (95% CI 18·1–42·9), median overall survival was not reached (95% CI 17·5 to not estimable), and 12-month overall survival was 66·8% (95% CI 53·0–77·4). Notably, tumour responses were also observed in patients with PD-L1 combined positive score less than 1, with an objective response rate of 16·7% (three of 99 [95% CI 3·6–41·1]).

All 22 patients with oesophageal squamous cell carcinoma were evaluable for response. Four (18%) patients had a partial response, and the objective response rate was 18·2% (four of 22; 95% CI 5·2–40·3) with a median follow up of 17·9 months (IQR 4·0–15·1; table 4). 18 (82%) patients had a progression event and 13 (59%) patients died. Median progression-free survival was 3·5 months (95% CI 1·8–6·2; figure 2C), and median overall survival was 9·4 months (95% CI 4·2–NE; figure 2D; table 4).

All 24 patients with hepatocellular carcinoma were evaluable for tumour response. Four (17%) patients had a partial response, resulting in an objective response rate of 16·7% (four of 24; 95% CI 4·7–37·4) with a median follow up of 19·6 months (IQR 8·7–19·8; table 4). 16 (67%) patients had a progression event and eight (33%) patients died. Median progression-free survival was 3·7 months (95% CI 1·8–9·9; figure 2E), and median overall survival was not reached (95% CI 14·5–NE; figure 2F; table 4). Details of the duration of follow-up for progression-free survival and overall survival for the three cohorts are shown in appendix 2 (p 9). The subsequent anticancer treatments are summarised in appendix 2 (p 22).

Pharmacokinetic parameters at the first and fifth administration of cadonilimab in phase 1b are summarised in appendix 2 (pp 4–5). The pharmacokinetic parameters in 6 mg/kg and fixed dose of 450 mg cohorts were similar. The correlation analysis was conducted to assess the relationship between cadonilimab exposure and the safety profile; this analysis was done in 240 patients, three in the 10 mg/kg group, 197 in the 6 mg/kg group, and 40 in the 450 mg/kg group (appendix 2 p 23). The frequency of adverse events did not increase with increased drug exposure (10 mg/kg; appendix 2 p 23). The occupancy of cadonilimab on PD-1 and CTLA-4 of peripheral blood T cells reached approximately 80% at day 8 and was maintained (analysis done in ten patients; appendix 2 p 24). The



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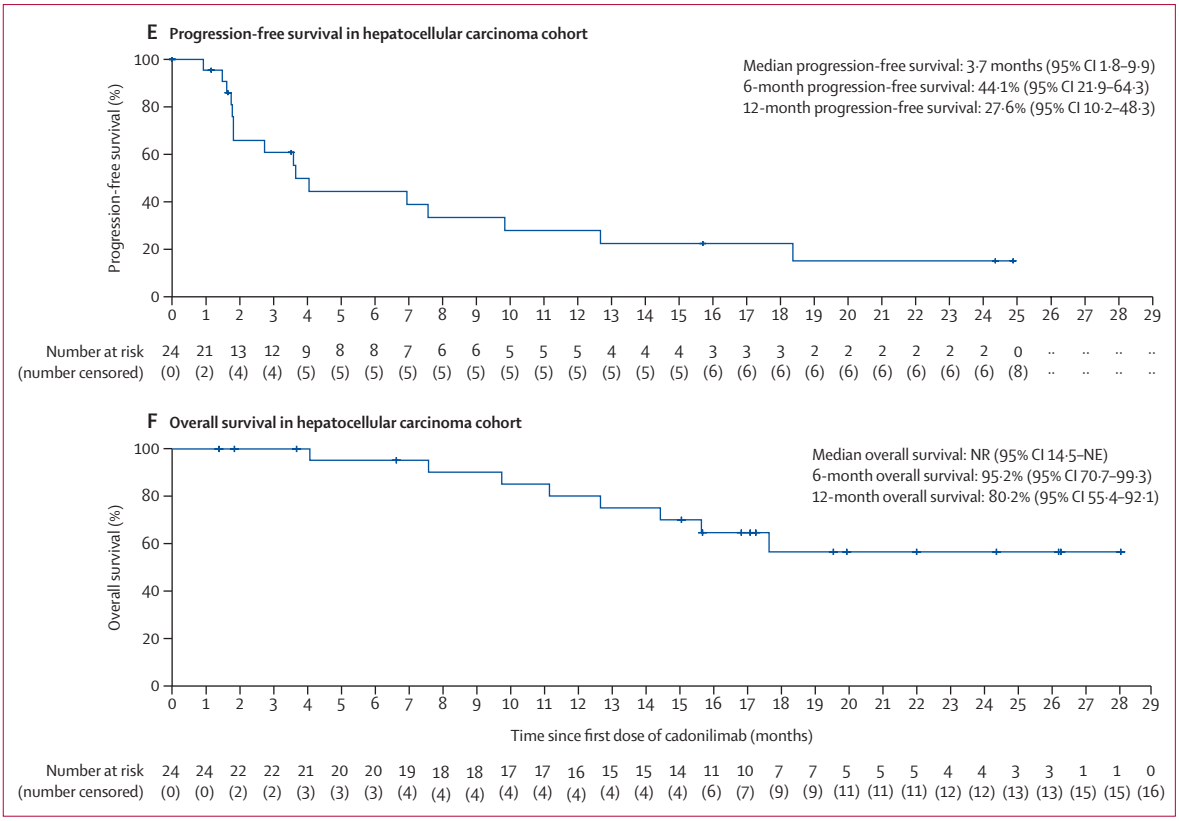

Figure 2: **Kaplan-Meier estimation of survival outcomes as per RECIST version 1.1 in the cervical cancer, oesophageal squamous cell carcinoma, and hepatocellular carcinoma cohorts in phase 2**

Progression-free survival (A) and overall survival (B) in the cervical cancer cohort, progression-free survival (C) and overall survival (D) in the oesophageal squamous cell carcinoma cohort, and progression-free survival (E) and overall survival (F) in the hepatocellular carcinoma cohort are shown. NE=not estimable. NR=not reached.

post-dose baseline ratio of $CD4^{+}Ki67^{+}$ T cells reached its peak on day 8 after the initial administration of cadonilimab (analysis done in ten patients; appendix 2 p 25). The detailed results of the immunogenicity analysis, which was done in 201 patients, are provided in appendix 2 (pp 6–7).

Discussion

In this phase 1b/2 study, cadonilimab showed a manageable safety profile, and encouraging antitumour activity in patients with advanced solid tumours, particularly in those with recurrent or metastatic cervical cancer. Haematological toxicities (eg, anaemia and decreased white blood cell count), abnormal hepatic function (eg increased alanine aminotransferase and aspartate aminotransferase), and immune-related endocrine toxicities, such as hypothyroidism and hyperthyroidism, commonly occurred. Notably, most treatment-related adverse events were grade 1 or 2. No unexpected adverse events were observed during the study. The high incidence of anaemia, characterised by a decline in haemoglobin concentrations, is believed to be primarily caused by non-immune-mediated haemolysis. This type of anaemia might be associated with factors such as poor baseline bone marrow reserves and tumour-related disease consumption.

Cadonilimab showed a comparable safety profile to that observed with combination therapy with nivolumab and ipilimumab, when low-dose ipilimumab (1 mg/kg) was used in patients with cervical cancer and hepatocellular carcinoma. In the preliminary results of the Checkmate 358 study, in 46 patients with cervical cancer the frequency of grade 3 or worse treatment-related adverse events was 29%.[14] In the Checkmate 040 study, which included 97 patients with hepatocellular carcinoma who were treated with 1 mg/kg ipilimumab-based regimens, the incidence of grade 3 or worse treatment-related adverse events was 29–31%.[15] The incidence of grade 3 or worse treatment-related adverse events in the present study was 28%. Another phase 2 study evaluating the combination of balstilimab and zalifrelimab as second-line treatment for patients with advanced cervical cancer reported an overall incidence of grade 3 or worse treatment-related adverse events of 20%,[16] lower than that reported in the present study. The overall incidence of immune-related adverse events with cadonilimab in the current study was 51%, which was consistent with the incidence of immune-related adverse

events observed in the balstilimab and zalifrelimab combination study, which reported an incidence of immune-mediated adverse events of 44·5%.[16] In comparison with MEDI5752, another bispecific anti-PD-1/CTLA-4 antibody, cadonilimab showed a favourable safety profile. In the first-in-human study of 86 patients who received MEDI5752 monotherapy, the incidence of grade 3–4 treatment-related adverse event was 38%, and the most common grade 3–4 adverse events of special interest were dermatitis or rash (five [6%] of 86) and hepatic events (15 [17%]). The incidence of diarrhoea or colitis of any grade was 11% (nine patients), with grade 3–4 events occurring in two (2%) patients.[17] In the present study, the incidence of grade 3 or worse treatment-related adverse events (28%) was lower than that reported for MEDI5752, and was similar to the data reported in the first-in-human study of MGD019, another bispecific anti-PD-1/CTLA-4 antibody, which had a frequency of grade 3 or worse treatment-related adverse events of 24%.[18] In our study, the frequency of diarrhoea and rash was very low, with only one patient reporting grade 3 or worse immune-related diarrhoea and two patients reporting grade 3 or worse rash. These adverse events are commonly associated with CTLA-4 blockade. Comparatively, in patients with metastatic melanoma treated with ipilimumab monotherapy, the incidence of diarrhoea of any grade was 27·5% and that of grade 3–4 diarrhoea was 4·6%.[19] Myocarditis, pneumonitis, and hepatitis are commonly reported fatal toxic events related to immune checkpoint inhibitor therapy;[20,21] in our study, two (1%) patients reported grade 3 or worse treatment related myocarditis, two (1%) patients reported grade 3 or worse treatment related abnormal hepatic function, and one patient reported grade 3 or worse treatment related pneumonitis. The favourable safety profile of cadonilimab might be due to its high binding avidity with PD-1 and CTLA-4, which contributes to its mechanism of action on tumours. An Fc-null design and absence of binding to Fc receptors might also contribute to the low toxicities observed in this trial.[10]

Cervical cancer ranks second among malignancies in female patients.[22] The US Food and Drug Administration has approved pembrolizumab for the treatment of advanced cervical cancer with disease progression during or after chemotherapy based on the findings of the KEYNOTE-158 trial, in which pembrolizumab showed an objective response rate of 12·2% in all patients and 14·3% in PD-L1-positive patients.[23] In the CheckMate 358 trial,[24] the objective response rate in patients who had previously received systemic therapy for recurrent or metastatic disease was 23·1% in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg group versus 36·4% in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg group, median progression-free survival was 3·6 months (95% CI 1·9–5·1) versus 5·8 months (3·5–17·2), and median overall survival was 10·3 months (95% CI 7·9–15·2) versus 25·4 months (17·5–NR). In the study of combination therapy with balstilimab and zalifrelimab in patients with cervical cancer, the objective response rate was 25·6% (32·8% in PD-L1-positive patients), median progression-free survival was 2·7 months (95% CI 1·5–3·7), and median overall survival was 12·7 months (95% CI 8·8–17·6).[16] In the cervical cancer cohort in the present study, the objective response rate was 32·3%; median progression-free survival was 3·71 months, and median overall survival was not reached. Notably, in 63 patients with PD-L1 combined positive score of 1 or higher, the objective response rate was 42·9% and the median progression-free survival was 5·75 months, but median overall survival was not reached. Although cross-study comparisons must be interpreted with caution, these results suggest that cadonilimab showed encouraging activity in the treatment of cervical cancer, especially in terms of the objective response rate and long-term survival benefit, but further follow-up is required to confirm these findings. On the basis of these results, cadonilimab has been approved by the NMPA for the treatment of advanced cervical cancer in China.

One limitation of this study was the small sample size of the hepatocellular carcinoma and oesophageal squamous cell carcinoma cohorts, which restricted interpretation of antitumour activity. Another limitation of study is the absence of randomised control groups. A randomised controlled trial of cadonilimab in patients with cervical cancer is ongoing (NCT04982237).

In the present study, cadonilimab showed a high objective response rate in patients with cervical cancer and showed durable survival benefits in patients with solid tumours, which might be attributed to its dual blockade of PD-1 and CTLA-4 immune checkpoints. Previous studies have reported improved tumour response and survival benefits when a high dose of ipilimumab was used in both monotherapy and combination therapy approaches.[24,25–28] However, the high dose of ipilimumab often leads to significant toxicities, thus limiting its clinical utility. In this study, cadonilimab showed a favourable safety profile while maintaining antitumour activity. Several studies in patients with cervical cancer (NCT04982237), hepatocellular carcinoma (NCT04728321), non-small-cell lung cancer (NCT04646330), and gastric adenocarcinoma (NCT05008783) are underway.

Contributors

JJ, XW, XG, NX, ZLi, LS, KJ, and ZZ conceived and designed the study. XG was responsible for the project administration and writing of the manuscript. NX was responsible for study conceptualisation. ZLi was responsible for study conceptualisation and data interpretation and was responsible for the hepatocellular carcinoma cohort. LS was responsible for study conceptualisation, data interpretation, and review and editing of the manuscript. KJ was responsible for the oesophageal squamous cell carcinoma cohort. ZZ was responsible for the cervical cancer cohort. All authors recruited patients and collected data. XG, JJ, and LS accessed and verified the data. WL, WS, ZMW, BL, and MX were primarily involved in the study and played a substantial role in study design, data collection, data analysis, data interpretation, and writing of the report. All authors interpreted the data and reviewed and approved the final version of the submitted report and are accountable for all aspects of the report.

Declaration of interests
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Data sharing
De-identified individual participant data that underlie the results reported here are available from the trial investigators and sponsors upon written request 24 months after publication of the Article. Enquiries should be made via email to the corresponding authors. Akeso Biopharma will not share data dictionaries or data from identified participants. The study protocol is available in appendix 2.

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