ORIGINAL ARTICLE

Camrelizumab in different PD-L1 expression cohorts of pre-treated advanced or metastatic non-small cell lung cancer: a phase II study

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Abstract

Background This phase II study evaluated camrelizumab in different PD-L1 expression cohorts of patients with previously treated advanced/metastatic non-small cell lung cancer (NSCLC; NCT03085069, registered March 21, 2017).

Methods Patients who progressed during/after chemotherapy were enrolled and divided into four cohorts based on PD-L1 tumor proportion score (TPS). Patients with *EGFR/ALK* alterations and PD-L1 TPS ≥ 50% were also eligible. All enrolled patients received camrelizumab at 200 mg IV Q2W. The primary endpoint was objective response rate.

Results A total of 146 patients were enrolled. As of data cutoff on Aug 20, 2020, the median follow-up was 29.5 months (95% CI 27.4–30.8). Objective response rate was 17.8% (95% CI 12.0–25.0) and improved with the increasing PD-L1 TPS (TPS < 1%, 12.2% [95% CI 5.7–21.8]; ≥ 1–< 25%, 19.4% [95% CI 7.5–37.5]; ≥ 25–< 50%, 36.4% [95% CI 10.9–69.2]; ≥ 50%, 23.3% [95% CI 9.9–42.3]). No response was observed in the five patients harboring *EGFR* mutations. Median progression-free survival was 3.2 months (95% CI 2.0–3.4), and patients with positive PD-L1 TPS had longer progression-free survival. Median overall survival was 14.8 months (95% CI 10.2–18.7). Treatment-related adverse events (TRAEs) of any grade occurred in 87.7% of patients, and 21.2% had grade ≥ 3 TRAEs.

Conclusion Camrelizumab showed improved efficacy compared with historical data of the second-line chemotherapy in pre-treated advanced/metastatic NSCLC. Patients with positive PD-L1 expression derived greater benefit from camrelizumab. Camrelizumab has a manageable safety profile.

Keywords Camrelizumab · PD-L1 · Immunotherapy · NSCLC · Phase II study

Abbreviations

CI	Confidence interval
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
HR	Hazard ratio
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand 1
RCCEP	Reactive Cutaneous Capillary Endothelial Proliferation
RECIST	Response Evaluation Criteria In Solid Tumors
TPS	Tumor proportion score

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide, with non-small cell lung cancer (NSCLC) as the predominant subtype [1, 2]. Before the availability of targeted therapy, chemotherapy was the standard treatment strategy for patients with NSCLC, with limited overall survival and poor adverse event profile [3]. Targeted therapy is effective in patients with oncogenic driver alterations, which accounts for only parts of NSCLCs [4–6]. Since blocking the binding of programmed cell death 1 (PD-1) to its ligands, programmed cell death ligand 1/2 (PD-L1/PD-L2) on tumor cells could stimulate T-cell response and hinder tumor cells

to escape immune surveillance [7, 8], so for patients without amenable alterations, immunotherapy is becoming a new treatment paradigm with promising survival outcomes. Although immunotherapy is commonly used in the first-line treatment of NSCLCs, it also shows encouraging anti-tumor activity as second-line therapy [9–14]. Therefore, developing reliable and validated biomarkers that stratify patients with different probabilities of response to immunotherapy is of great importance for clinical practice [15–18].

The correlation between PD-L1 expression and immunotherapeutic efficacy in second-line and beyond settings of NSCLC had been interrogated in several studies, but remains controversial. Pembrolizumab is superior to docetaxel in terms of progression-free survival in patients with PD-L1 tumor proportion score (TPS) ≥ 50%, but not in the total population (TPS ≥ 1%), as shown in KEYNOTE-010 study [12]. The magnitude of benefits from nivolumab versus docetaxel improved with the increasing PD-L1 expression in advanced non-squamous NSCLC whose tumors expressed PD-L1 (TPS ≥ 1%, hazard ratio [HR] for overall survival 0.59, HR for progression-free survival 0.70; ≥ 5%, 0.43, 0.54; and ≥ 10%, 0.40, 0.52), as revealed in CheckMate 057 study [10]. But this result was inconsistent with that from CheckMate 017 study which showed that the expression of the PD-L1 was neither prognostic nor predictive of benefit in squamous cell NSCLC and that from CheckMate 078 study which showed that the survival benefit with nivolumab was observed regardless of PD-L1 expression level [9, 11]. Both POPLAR and OAK study showed that the improvement of overall survival by atezolizumab versus docetaxel was associated with increase of PD-L1 expression, but the improvement of survival in PD-L1 low or undetectable subgroup by atezolizumab was only reported in OAK study [13, 14]. Thus, no clear evidence supported the use of PD-L1 expression to guide patient selection for immunotherapy in the second-line treatment.

Currently, there were no clinical trials specifically designed to explore the value of PD-L1 expression in guiding second-line immunotherapy of NSCLC. Therefore, we conducted this phase II trial, which offers a new trial design aiming to test different types of patients or treatments in an innovative and effective way, to assess the efficacy and safety of camrelizumab (a humanized IgG4 anti-PD-1 monoclonal antibody which has shown promising activity in multiple malignances [19–23]) in different PD-L1 expression cohorts of patients with previously treated advanced or metastatic NSCLC.

Materials and methods

Study design and participants

This was an open-label, single-arm, multicenter phase II study conducted at 14 medical centers in China. This study assessed efficacy of camrelizumab in different PD-L1 expression cohorts simultaneously to evaluate the correlation of camrelizumab with PD-L1 expression. We enrolled patients aged 18–80 years; with a histologically and cytologically confirmed NSCLC; had stage IIIb or IV disease according to International Association for the Study of Lung Cancer (IASLC) Staging Manual in Thoracic Oncology (the seventh edition); relapsed or progressed during/after platinum-based chemotherapy; provision of fresh tissue or core needle biopsy; with at least one measurable tumor lesion detected by computed tomography or magnetic resonance imaging according to Response Evaluation for Criteria for Solid Tumors (RECIST) version 1.1; and with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients with *EGFR* mutations or *ALK* gene rearrangements were eligible provided they had disease progression with at least one approved tyrosine kinase inhibitor and had PD-L1 expression of 50% or greater in tumor. Exclusion criteria were patients with previous treatment of anti-PD-1/PD-L1/PD-L2/CTLA-4 antibody, antitumor vaccine, immune-stimulatory antitumor agent, systemic corticosteroids or immunosuppression (within 14 days before the initiation of study treatment), those with central type lung cancer, interstitial pneumonitis, active tuberculosis, carcinomatous meningitis or central nervous system metastases.

Study treatments and assessments

Eligible patients were assigned to four cohorts based on PD-L1 TPS: PD-L1 TPS < 1%, TPS ≥ 1% and < 25%, TPS ≥ 25% and < 50%, and TPS ≥ 50%. Patients were intravenously given camrelizumab 200 mg every 2 weeks in each 4-week cycle until disease progression, intolerable toxic effects, physician decision or patient withdrawal. Dose reduction was not permitted. Dose delay which was defined as a delay in delivering treatment by at least 3 days was allowed to manage toxicities. When treatment-related adverse events (TRAEs) recovered to grade ≤ 1 or baseline status, the treatment would be re-started. Response (complete response/partial response) had to be confirmed at least 4 weeks after first noted. Tumor response was assessed at week 8 from the initiation of treatment and every 6 weeks thereafter using radiographic imaging according to RECIST, version 1.1. Adverse events were monitored continuously throughout the study period and assessed every 30 days after treatment discontinuation until 90 days after the last dose of study treatment. Adverse events were graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. The extent of PD-L1 expression in tumors was measured at a central laboratory with the PD-L1 immunohistochemistry 22C3 PharmDx assay (Dako, Carpinteria, CA) in accordance with the Manufacturer's instructions. PD-L1 expression was

quantified as TPS, which was defined as the percentage of viable tumor cells showing partial or complete membrane staining ($\geq 1^+$), relative to all viable tumor cells present in the sample [24]. The expression of PD-L1 was finally confirmed by pathologist group.

Outcomes

The primary endpoint was objective response rate, which was defined as the proportion of patients with a confirmed complete response or partial response as per RECIST, version 1.1. The secondary endpoints were duration of response (the time from first evidence of response to disease progression per RECIST 1.1 or death due to any cause), progression-free survival (the time from treatment initiation until disease progression per RECIST 1.1 or death due to any cause, which occurred first), 12-month overall survival rate (the probability of surviving during the first 12 months from treatment initiation), and safety.

Statistical analysis

On the basis of results of PD-L1 expression level, patients were assigned to one of the four PD-L1 expression study cohorts in a non-randomized manner. For each of the PD-L1 expression cohort, sample size was calculated using the exact method based on the primary endpoint of objective response rate. The desirable objective response rate ($p1$) and unacceptable objective response rate ($p0$) are 10% and 1% for TPS < 1% cohort, 20% and 4% for TPS $\geq$ 1–< 25% cohort, 25% and 5% for TPS $\geq$ 25–< 50% cohort, and 30% and 8% for TPS $\geq$ 50% cohort. With an alpha of 0.05 and power of 80%, the trial was conducted aiming to enroll a sample size of 42 in PD-L1 TPS < 1% cohort, 27 in TPS $\geq$ 1–< 25% cohort, 21 in TPS $\geq$ 25–< 50% cohort and 21 in TPS $\geq$ 50% cohort. To assess the preliminary anti-tumor activity of camrelizumab, each of the cohort was conducted using a two-stage study design. In the first stage, at least one response in the first 15 patients of each cohort was required for further cohort expansion; otherwise, the cohort would be closed for futility.

Patients administrated with one dose of study medication constituted the intent-to-treat population. We assessed both efficacy and safety in intent-to-treat population. Median progression-free survival, overall survival, and duration of response were estimated using the Kaplan–Meier method, with their 95% confidence intervals (CIs) calculated using Brookmeyer–Crowley method. The 12-month survival rate was also calculated using the Kaplan–Meier method, with its corresponding 95% CI calculated using the log–log transformation according to normal distribution approximation with back transformation to CI on the untransformed scale. The estimate of objective response rate was presented with

95% CI using the Clopper–Pearson method. All statistical analyses were conducted using SAS, version 9.4.

Results

Patients

Between May 24, 2017, and Aug 1, 2018, 260 participants were assessed for eligibility. A total of 146 patients were enrolled and received study treatment. Of them, 74 (50.7%) had a PD-L1 TPS of < 1%, 31 (21.2%) of $\geq$ 1–< 25%, 11 (7.5%) of $\geq$ 25–< 50%, and 30 (20.5%) of $\geq$ 50% (Fig. 1). In patients with TPS $\geq$ 50%, five participants harbored *EGFR* mutations and 25 did not.

Patient demographics and disease characteristics were well-balanced across different PD-L1 TPS populations at baseline (Table 1). Among them, the median age was 62 years (range 35–76); 78.8% (115/146) were males; 54.8% (80/146) had non-squamous cell carcinomas; and 45.2% (66/146) had squamous cell carcinomas; and 89.7% (131/146) had stage IV NSCLC.

Efficacy

At the time of data cutoff on Aug 20, 2020, the median follow-up was 29.5 months (95% CI 27.4–30.8). A total of 146 patients were included in the full analysis set. Five patients with TPS of < 1%, two with TPS of $\geq$ 1–< 25%, none with TPS of $\geq$ 25–< 50% and three with TPS of $\geq$ 50% were still continuing camrelizumab treatment. Subsequent anti-cancer therapy was received by 72 (49.3%) patients, with docetaxel-containing therapy (22, 15.1%) being the most common one.

Best change in sum of target lesion dimensions from baseline is shown in Fig. 2. No patient achieved complete response, 26 (17.8%) patients had partial response at their best response, 51 (34.9%) had stable disease, 54 (37.0%) had progressive disease, and overall response of 15 (10.3%) patients was not evaluable (Table 2). The objective response rate was 17.8% (95% CI 12.0–25.0), and disease control rate was 52.7% (95% CI 44.3–61.1). When grouped according to PD-L1 expression, the objective response rate was 12.2% (95% CI 5.7–21.8) in PD-L1 TPS < 1% population, 19.4% (95% CI 7.5–37.5) in TPS $\geq$ 1–< 25% population, 36.4% (95% CI 10.9–69.2) in TPS $\geq$ 25–< 50% population, and 23.3% (95% CI 9.9–42.3) in TPS $\geq$ 50% population. Objective response rate was improved with the increase of PD-L1 expression, and the greatest benefit was seen in patients with a PD-L1 TPS of $\geq$ 25–< 50%. In patients with TPS $\geq$ 50%, objective response was observed in 28.0% (95% CI 12.1–49.4) of patients without *EGFR* mutation, while no response occurred in patients with *EGFR* mutations. Subgroup analysis showed that objective response rate was
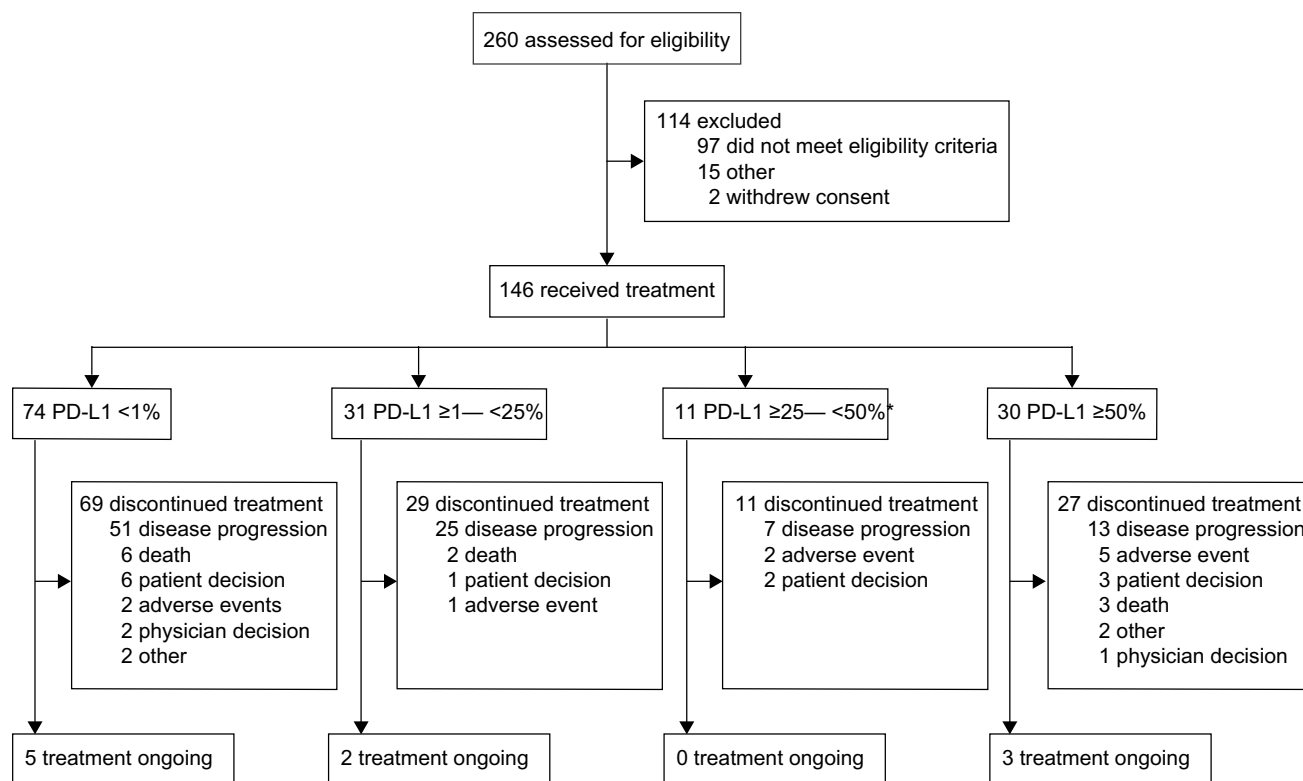
Fig. 1 Study profile. *Among the screened patients, proportion of patients with PD-L1 ≥ 25–< 50% was relatively lower. Number of patients in this cohort did not reach the planned sample size, when all other cohorts had already reached. But the pre-set objective response had been achieved with 11 patients. After comprehensive consideration, enrollment of this cohort was stopped

promising in nearly all subgroups irrespective of baseline characteristics (Table S1).

The responders had durable response (median 13.6 months, 95% CI 5.6–22.6; Table 2). A total of 127 (87.0%) patients had disease progression or died by the time of data cutoff. Median progression-free survival was 3.2 months (95% CI 2.0–3.4) (Fig. 3a). In cohorts of patients with different PD-L1 expression, the median progression-free survival was 2.1 months (95% CI 1.9–3.2) in those with TPS < 1%, 3.1 months (95% CI 1.8–4.9) in TPS ≥ 1–< 25%, 6.0 months (95% CI 1.6–not estimable) in TPS ≥ 25–< 50%, and 7.1 months (95% CI 2.0–11.4) in TPS ≥ 50%, indicating that patients with higher PD-L1 expression had numerically longer median progression-free survival. In patients with TPS ≥ 50%, those without *EGFR* mutation had more favorable median progression-free survival than those with *EGFR* mutations (7.6 months, 95% CI 2.0–16.8 vs. 1.7 months, 95% CI 1.2–not estimable).

A total of 98 (67.1%) deaths occurred in the entire cohort, and the median overall survival was 14.8 months (95% CI 10.2–18.7) (Fig. 3B). In patients with PD-L1 TPS < 1%, ≥ 1–< 25%, ≥ 25–< 50% and ≥ 50%, the median overall survival was 9.2 months (95% CI 6.5–15.4), 23.5 months (95% CI 11.6–not estimable), 32.3 months (95% CI 2.9–not estimable), and 19.3 months (95% CI 9.0–not estimable), respectively. Patients with PD-L1 TPS ≥ 25–< 50% had the longest median overall survival. The estimated 12-month and 18-month survival probability was 53.4% (95% CI 44.8–61.2) and 44.6 (95% CI 36.2–52.6), respectively.

Safety

The median number of cycles of camrelizumab administration was 3.5 (range 0.5–37.0). Treatment-related adverse events of any grade occurred in 87.7% (128/146) of patients (Table 3). The most common treatment-related adverse events were reactive cutaneous capillary endothelial proliferation (RCCEP; 111/146, 76.0%), hypothyroidism (23/146, 15.8%), increased aspartate aminotransferase (22/146, 15.1%), and proteinuria (18/146, 12.3%). Treatment-related adverse events of grade 3 or greater were reported in 21.2% (31/146) patients, with the most common being RCCEP (4/146, 2.7%), dyspnea (4/146, 2.7%), increased gamma-glutamyltransferase (3/146, 2.1%), increased amylase (3/146, 2.1%), and increased lipase (3/146, 2.1%). The percentage of patients with serious treatment-related adverse events was 17.1% (25/146). Treatment-related adverse events led to dose delay or interruption in 15.8%

Table 1 Baseline demographics and disease characteristics

	Cohorts by PD-L1 expression						All patients (n = 146)
	<1% (n = 74)	≥1–<25% (n = 31)	≥25–<50% (n = 11)	≥50%			
				Total (n = 30)	EGFR− (n = 25)	EGFR+ (n = 5)	
Age, median years (range)	62 (35–74)	61 (38–74)	64 (46–76)	59 (40–74)	59 (40–74)	57 (41–66)	62 (35–76)
Male	58 (78.4)	24 (77.4)	10 (90.9)	23 (76.7)	20 (80.0)	3 (60.0)	115 (78.8)
ECOG performance status							
0	5 (6.8)	1 (3.2)	0	2 (6.7)	2 (8.0)	0	8 (5.5)
1	69 (93.2)	30 (96.8)	11 (100)	28 (93.3)	23 (92.0)	5 (100)	138 (94.5)
Tumor histology							
Adenocarcinoma	43 (58.1)	18 (58.1)	3 (27.3)	14 (46.7)	9 (36.0)	5 (100)	78 (53.4)
Squamous cell carcinoma	30 (40.5)	13 (41.9)	7 (63.6)	16 (53.3)	16 (64.0)	0	66 (45.2)
Others	1 (1.4)	0	1 (9.1)	0	0	0	2 (1.4)
Disease stage							
IIIa	1 (1.4)	0	0	0	0	0	1 (0.7)
IIIb	8 (10.8)	4 (12.9)	1 (9.1)	1 (3.3)	0	1 (20.0)	14 (9.6)
IV	65 (87.8)	27 (87.1)	10 (90.9)	29 (96.7)	25 (100)	4 (80.0)	131 (89.7)
Metastases	74 (100)	31 (100)	11 (100)	30 (100)	25 (100)	5 (100)	146 (100)
Number of metastatic organs							
≤2	53 (71.6)	22 (71.0)	8 (72.7)	23 (76.7)	20 (80.0)	3 (60.0)	106 (72.6)
>2	21 (28.4)	9 (29.0)	3 (27.3)	7 (23.3)	5 (20.0)	2 (40.0)	40 (27.4)
Previous therapies							
Surgery	28 (37.8)	15 (48.4)	4 (36.4)	10 (33.3)	8 (32.0)	2 (40.0)	57 (39.0)
Chemotherapy	71 (95.9)	30 (96.8)	11 (100)	30 (100)	25 (100)	5 (100)	142 (97.3)
Radiotherapy	26 (35.1)	12 (38.7)	4 (36.4)	6 (20.0)	5 (20.0)	1 (20.0)	48 (32.9)
Adjuvant therapy	9 (12.2)	5 (16.1)	0	2 (6.7)	2 (8.0)	0	16 (11.0)
Neoadjuvant therapy	2 (2.7)	0	0	0	0	0	2 (1.4)

Data are presented in n (%), unless otherwise specified

(23/146) of patients and led to treatment discontinuation in 7.5% (11/146) of patients. Five (3.4%) deaths were considered as treatment-related, including two dyspnea, one pneumonitis, one respiratory failure, and one death from unknown cause. For the two patients with pneumonitis and respiratory failure, the possibility of immune-related pneumonitis cannot be excluded. The other two patients with dyspnea could not rule out the possibility of disease progression or pulmonary embolism. The correlation between the death from unknown cause and camrelizumab was unassessable. Therefore, the causes of all five deaths were not definitely related to treatment.

Discussion

To our knowledge, this is the first prospective study using such a trial design, which tests different types of patients or treatments in an innovative and effective way, to confirm the value of PD-L1 expression in the selection of potential patients for immunotherapy in second-line treatment of NSCLC. This is also the first prospective study to enroll *EGFR*-mutated patients in those with PD-L1 TPS ≥ 50% for immunotherapy and to show that *EGFR*-positive patients did not respond to camrelizumab. It has been reported that the response rate of first-line chemotherapy for NSCLC was 17–22% and overall survival was 7.4–8.2 months [3], while the response rate of second-line immunotherapy for NSCLC was about 17–30%, and the overall survival was approximately 9.2–13.8 months [10–14]. In our phase II study, the response rate (36.4%) and overall survival (32.3 months) of camrelizumab in higher PD-L1 expression cohorts were far beyond those of immunotherapy without patient selection.

Overall, camrelizumab demonstrated comparable efficacy with that of other immune checkpoint inhibitors in advanced/metastatic NSCLC. The confirmed objective response rate (17.8%, 95% CI 12.0–25.0), progression-free survival (3.2 months, 95% CI 2.0–3.4), and 12-month overall survival rate (53.4%, 95% CI 44.8–61.2) with
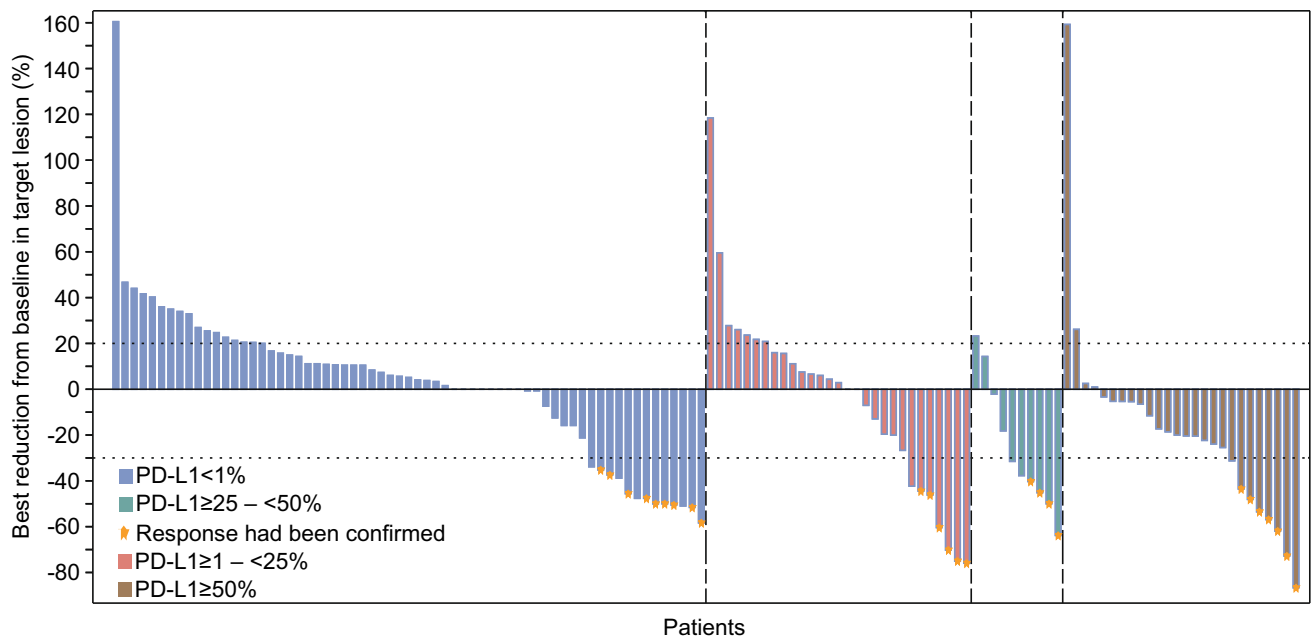
Fig. 2 Tumor response

Table 2 Summary of key efficacy results

	Cohorts by PD-L1 expression						All patients (n = 146)
	< 1% (n = 74)	≥ 1–< 25% (n = 31)	≥ 25–< 50% (n = 11)	≥ 50%			
				Total (n = 30)	EGFR− (n = 25)	EGFR+ (n = 5)	
Best overall response, n (%)							
PR	9 (12.2)	6 (19.4)	4 (36.4)	7 (23.3)	7 (28.0)	0	26 (17.8)
SD	24 (32.4)	10 (32.3)	5 (45.5)	12 (40.0)	10 (40.0)	2 (40.0)	51 (34.9)
PD	33 (44.6)	13 (41.9)	1 (9.1)	7 (23.3)	6 (24.0)	1 (20.0)	54 (37.0)
NE	8 (10.8)	2 (6.5)	1 (9.1)	4 (13.3)	2 (8.0)	2 (40.0)	15 (10.3)
Objective response rate, % (95% CI)	12.2 (5.7–21.8)	19.4 (7.5–37.5)	36.4 (10.9–69.2)	23.3 (9.9–42.3)	28.0 (12.1–49.4)	0	17.8 (12.0–25.0)
Disease control rate, % (95% CI)	44.6 (33.0–56.6)	51.6 (33.1–69.8)	81.8 (48.2–97.7)	63.3 (43.9–80.1)	68.0 (46.5–85.1)	40.0 (5.3–85.3)	52.7 (44.3–61.1)
Duration of response, months (95% CI)	8.3 (3.8–22.3)	27.1 (5.6–NE)	NR (2.8–NE)	15.1 (2.8–NE)	15.1 (2.8–NE)	NR	13.6 (5.6–22.6)

PR partial response, *SD* stable disease, *PD* progressive disease, *NE* not estimable, *NR* not reached

camrelizumab as second-line therapy were numerically similar as that reported with nivolumab, pembrolizumab, and atezolizumab (objective response rate, 14–18.0%; progression-free survival, 2.8–3.0 months; 12-month overall survival rate, 50–55%) [11, 13, 25], indicating that camrelizumab may be an efficacious treatment option for pretreated advanced/metastatic NSCLC.

As to the association between PD-L1 expression and efficacy of immunotherapy drugs in second-line and beyond setting, conclusions from previous studies have been discrepant [9, 10, 12–14]. In this study, we compared efficacies of camrelizumab across different PD-L1 TPS cohorts. Numerically, patients with positive PD-L1 expression derived greater benefit from camrelizumab
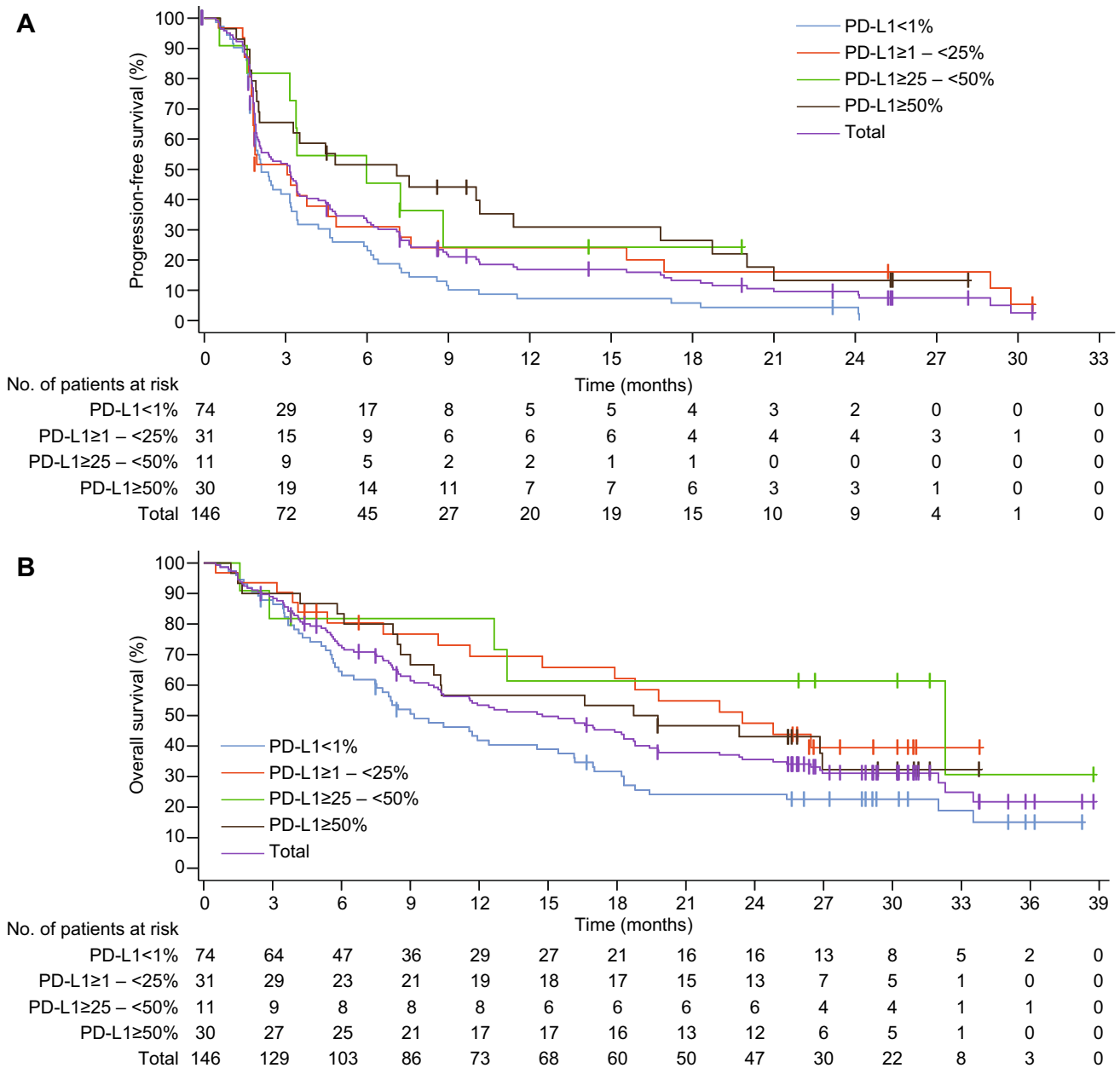
Fig. 3 Kaplan–Meier estimates of progression-free survival (**a**) and overall survival (**b**) in different PD-L1 expression cohorts

compared with historical data of the second-line chemotherapy, while efficacy of camrelizumab in patients with TPS < 1% was similar to that of second-line chemotherapy [11–13]. The observation that benefit from camrelizumab improved with the increase of PD-L1 expression was also echoed with other anti-PD-1/PD-L1 drugs in patients with advanced NSCLC [10, 12–14, 25–27]. In this study, we found patients with PD-L1 TPS ≥ 25–< 50% achieved higher objective response rate, median overall survival, and 12-month overall survival rate than other PD-L1 expression groups, and the correlation of progression-free survival and PD-L1 TPS was not fully synchronized

with the correlation of overall survival and PD-L1 TPS in this population, since patients in PD-L1 TPS ≥ 50% group had the longest progression-free survival than other groups. Two possible reasons might lead to such phenomenon. Firstly, TPS ≥ 50% group included five patients with *EGFR*-positive. They did not response to camrelizumab and progressed rapidly, resulting in a reduction in the efficacy of camrelizumab in TPS ≥ 50% group. Secondly, the number of patients varies among different PD-L1 TPS groups and TPS ≥ 25–< 50% group had only 11 patients. Therefore, a larger randomized, controlled, confirmative study is further needed to validate this result.

Table 3 Treatment-related adverse events occurring in > 5% of patients

	All patients (n = 146)	
	Any grade	Grade 3–5
All treatment-related adverse events*	128 (87.7)	31 (21.2)
RCCEP	111 (76.0)	4 (2.7)
Hypothyroidism	23 (15.8)	0
Aspartate aminotransferase increased	22 (15.1)	0
Proteinuria	18 (12.3)	0
Alanine aminotransferase increased	17 (11.6)	0
Decreased appetite	12 (8.2)	1 (0.7)
Amylase increased	11 (7.5)	3 (2.1)
Pruritus	11 (7.5)	0
Cough	10 (6.8)	0
Pyrexia	10 (6.8)	0
Asthenia	10 (6.8)	0
Anemia	10 (6.8)	2 (1.4)
Pneumonitis	9 (6.2)	3 (2.1)
Hyperthyroidism	9 (6.2)	0
Lipase increased	8 (5.5)	3 (2.1)
Hepatic function abnormal	8 (5.5)	0

Data are presented in n (%). RCCEP, Reactive cutaneous capillary endothelial proliferation. *The treatment-related adverse event refers to the correlation of the event with treatment was "definitely related", "possibly related", or "unassessable"

There is no evidence in this study suggesting *EGFR*-positive patients could obtain overall response to camrelizumab treatment. But among these patients with *EGFR* mutations, one with *EGFR* exon 20 insertion had a best overall response of stable disease, a progression-free survival of 8.7 months, and an overall survival of 24.8 months, while another stable disease patient with *EGFR* L858R showed a progression-free survival of 4.5 months and an overall survival of 26.4 months. This indicated that patients harboring some specific mutation types might achieve benefit to camrelizumab, and further studies are needed to verify this hypothesis.

Camrelizumab demonstrated a manageable safety profile, which was similar to other PD-1/PD-L1 inhibitors [11, 26], except for RCCEP. The occurrence frequency of RCCEP was consistent with that of other studies of camrelizumab monotherapy [23, 28, 29]. RCCEP is characterized by a tripartite growth cycle of proliferation, plateau and involution, and is not life-threatening or function-impairing. RCCEP is expected to disappear after termination of treatment [30, 31]. It was reported that patients developed RCCEP seemed to have higher response rate than those without RCCEP, but the conclusion needs further validation [30].

There are several limitations of this study. One limitation of this study is the lack of control group, which makes

it difficult to assess the correlation of PD-L1 expression and clinical benefits from camrelizumab versus chemotherapy. In addition, bias might be introduced owing to the unbalanced number of patients in each cohort.

Conclusions

In conclusion, camrelizumab improved efficacy compared with historical data of the second-line chemotherapy in previously treated advanced/metastatic NSCLC with positive PD-L1 expression. Patients with *EGFR* mutations may not benefit from camrelizumab even with PD-L1 > 50%. Camrelizumab has a manageable safety profile. This phase II data suggested that camrelizumab monotherapy might be a feasible option as second-line treatment for patients with previously treated advanced/metastatic NSCLC.

Declarations

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