


# BMJ Open Prospective, multicentre, single-arm phase II trial of pembrolizumab combined with carboplatin and pemetrexed in elderly patients with advanced, non-squamous non-small cell lung cancer

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## ABSTRACT

**Introduction** Triplet regimen of carboplatin or cisplatin with pemetrexed and pembrolizumab is a standard treatment for patients with advanced, chemo-naïve, non-squamous non-small cell lung cancer. However, subgroup analysis for patients aged  $\geq 75$  years indicated that elderly patients who received the triplet regimen may have had shorter survival times than if they had chemotherapy alone (HR of 2.09). Treatments in the elderly are not always as effective or safe as for non-elderly patients, so there remains concern over whether the triplet regimen can be widely used in the elderly.

**Methods and analysis** This is a single-arm, prospective, multicentre phase II study. The primary endpoint is set as the overall response rate according to *Response Evaluation Criteria in Solid Tumors* V.1.1. Secondary endpoints are progression-free survival, disease control rate and safety. This trial will enrol 22 patients.

**Ethics and dissemination** This study was approved by the Wakayama Medical University Central Review Board on 2 December 2019 (approval number: W-32). Patients have been enrolled since February 2020. As the study will complete accrual in January 2022, results will be submitted for publication in peer-reviewed medical journals within 2023 and international scientific meetings. This study will provide significant information on whether the triplet regimens are clinically beneficial to elderly patients.

**Trial registration number** Japan Registry of Clinical Trials (jRCTs051190095).

## INTRODUCTION

The KEYNOTE 189 trial was a randomised phase III trial designed to compare triplet regimen of cisplatin or carboplatin (CBDCA), pemetrexed (PEM) and pembrolizumab with cisplatin or CBDCA and PEM. It elucidated superiority of the triplet regimen in overall survival (OS) and progression-free survival (PFS).<sup>1</sup> The triplet regimen is recognised

## Strengths and limitations of this study

- This is a prospective, multicentre, single arm phase II study to evaluate the efficacy and safety of triple combination of carboplatin (CBDCA), pemetrexed (PEM) and pembrolizumab in elderly patients ( $\geq 75$  years) with non-squamous non-small cell lung cancer (non-sq).
- First planned prospective study to assess the additional efficacy of immune-checkpoint inhibitors combined with platinum doublet in elderly patients with lung cancer.
- Criteria for reduction, postponement and cessation of CBDCA and PEM have been defined, they were not in KEYNOTE 189 trial, and this has enabled us to properly evaluate efficacy and safety through a typical, established method.
- Although this is a small sized, single arm, multi-institutional phase II study, results obtained from 22 participants will confer significant information to determine treatment plans for elderly patients with advanced non-sq.

worldwide as standard treatment for patients with advanced, chemo-naïve, non-squamous non-small cell lung cancer (non-sq). However, in the triplet-regimen patients  $\geq 75$  years of age, the HR for OS is 2.09 (0.84–5.23) and PFS is 1.73 (0.77–3.90).

In pooled analysis of KEYNOTE 010, KEYNOTE 024 and KEYNOTE 042, pembrolizumab monotherapy significantly prolonged OS compared with chemotherapy with HR 0.76 for programmed death-ligand 1 (PD-L1)  $\geq 1\%$  and HR 0.46 for PD-L1  $\geq 50\%$  in patients  $\geq 75$  years of age.<sup>2</sup> Most recently, a CBDCA/PEM combination therapy was reported in a phase III study of non-sq patients  $\geq 75$  years

with median PFS of 6.4 months and 0.9% treatment-related death.<sup>3</sup> These studies clarified that the therapies have no major safety or efficacy issues in an elderly population. Considering this, and that only 17% of deaths in patients aged  $\geq 75$  years in KEYNOTE 189 study were treatment-related, the most appropriate reason for the high HR for OS and PFS at  $\geq 75$  years is the imbalance of complication-related deaths. However, the efficacy and safety of this triplet regimen for the elderly requires prospective evaluation. The current prospective study could, therefore, have clinical significance in evaluation of the additional efficacy and safety of pembrolizumab when combined with CBDCA and PEM in elderly, chemotherapy-naïve, patients with non-sq. This is the first prospective trial of immune-checkpoint inhibitors combined with chemotherapy that targets the elderly. If additional efficacy and safety of pembrolizumab can be demonstrated in this prospective study, the value of the triplet regimen for elderly patients will be much increased.

#### Aim of the study

The main objective of this study is to evaluate additional efficacy by adding pembrolizumab to the CBDCA/PEM

combination in elderly patients ( $\geq 75$  years) that have non-sq as a first line setting.

#### STUDY DESIGN

This study is a single-arm, prospective, multicentre phase II study conducted in four facilities in Japan. The protocol scheme is shown in [figure 1](#). Study duration will be 3 years.

#### Endpoints

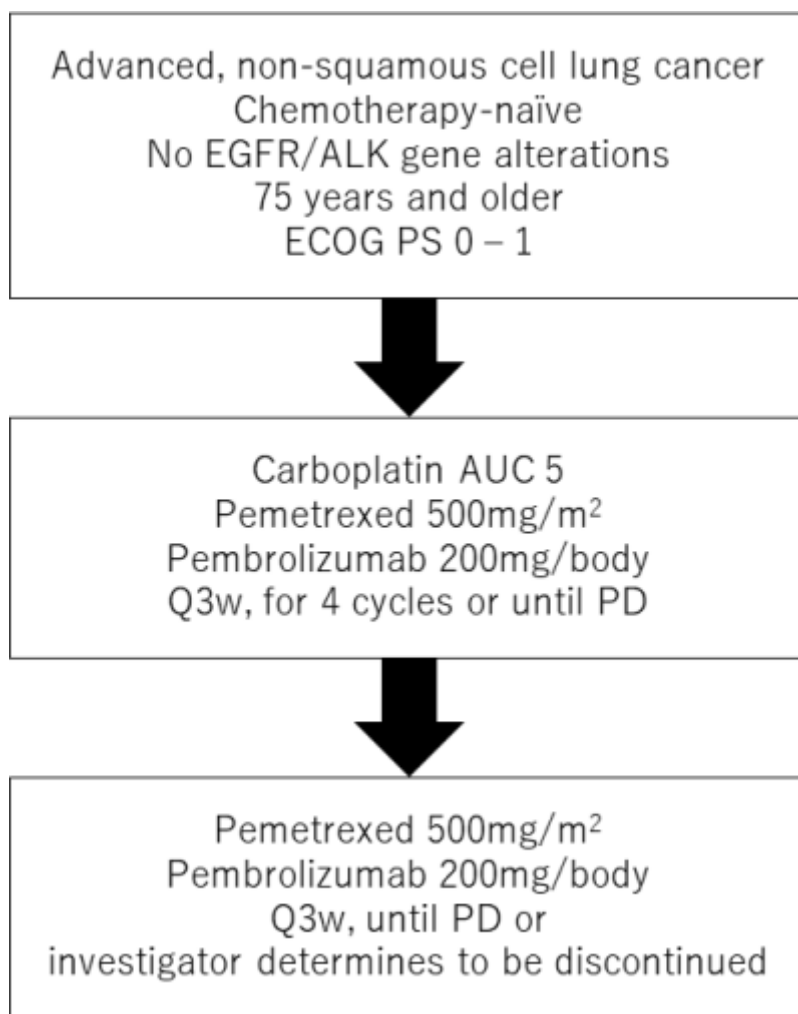
Primary endpoint is set as the overall response rate using the *Response Evaluation Criteria in Solid Tumors (RECIST)* V.1.1. Secondary endpoints are PFS, OS and safety.

#### Eligibility criteria of the participants

##### Inclusion criteria

Patients are required to fulfil all the following criteria:

1. Have histologically or cytologically confirmed non-sq. When pathologically mixed, non-squamous cell type must be dominant.
2. Be in advanced stage (IIIB, C and IV) or recurrence after surgical resection and not adaptable for curative radiotherapy.



**Figure 1** Protocol scheme of this study. AUC, area under the curve; ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PD, progressive disease; PS, performance status.

3. Be negative for both of epidermal growth factor receptor gene mutations and anaplastic lymphoma kinase (ALK) gene alterations.
4. Negative or unknown for ROS1 and BRAF gene alterations.
5. Have no previous systemic anticancer treatment (neo-adjuvant or adjuvant chemotherapy) is allowed when final administration was more than 6 months before.
6. Have adequate renal function (a creatinine clearance of  $\geq 45$  mL/min using Cockcroft-Gault equation).
7. Have measurable lesions according to evaluation by an investigator or radiologist based on RECIST V.1.1. Previously irradiated target lesions are considered measurable if disease progression is confirmed.
8. Are expected to survive for longer than 3 months.
9. Provide written informed consent to participate in the study.

#### Exclusion criteria

Patients are excluded if they meet any of all the following criteria:

1. Obvious interstitial pneumonia confirmed by CT.
2. Have received radiotherapy to the lungs exceeding 30 Gy within 6 months before registration.
3. Underwent palliative radiation therapy within 7 days before registration.
4. Have symptomatic brain metastases.
5. Have active double cancer (within 2 years).
6. Have active hepatitis B or C.
7. Have history of HIV.
8. Have uncontrolled pleural effusion or ascites.
9. Aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) cannot be suspended (except when using aspirin of  $\leq 1.3$  g/day) for 5 days (8 days for long-acting drugs, such as piroxicam).
10. Have active autoimmune disease (patients who need systemic administration of corticosteroids in excess of 10 mg/day in terms of prednisolone, or treatment with an immunosuppressant).
11. Cannot, or do not receive folic acid or vitamin B12 replacement therapy.

#### Discontinuation criteria

Interventions are discontinued if patients meet any of all the following criteria:

1. Disease progression or death.
2. Grade 3 or higher adverse event deemed by the investigator to be unacceptable.
3. Interstitial lung disease/pneumonitis grade 2 or higher.
4. If adverse events cannot be controlled by hormone replacement therapy or insulin replacement.
5. The administration criteria of pembrolizumab are not satisfied on day 106 after the discontinuation of chemotherapy on day 43 (see below).
6. Investigator determines that protocol treatment cannot be continued in consideration of safety.

#### Background data

Patient background data are collected prospectively for all patients including sex, age, performance status, comorbidities, smoking history, allergies, gene alterations, PD-L1 expression on tumours and history of treatments for cancer.

#### Interventions

Patients receive CBDCA (area under the curve (AUC) 5.0), PEM (500 mg/m<sup>2</sup>) and pembrolizumab (200 mg/body) every 3 weeks. After four cycles, PEM and pembrolizumab will be continued until disease progression or the investigator determines that protocol treatment should be discontinued. AUC is calculated based on the Calvert formula.

Starting criteria for the first and after second courses are shown in [table 1](#). Administration criteria for chemotherapy (CBDCA/PEM) and pembrolizumab after the second course are independent. If the criteria are not met, investigators are required to repeat the test and confirm that the criteria are met before starting treatment. Even if the starting criteria are met, the investigator may postpone any or all of CBDCA, PEM and pembrolizumab when postponement is considered necessary for safety by a principal investigator. For pembrolizumab, the treatment can be paused if patients require tapering of the steroid used to treat the adverse event until the steroid dose is reduced to  $\leq 10$  mg/day in prednisone.

If an adverse event corresponding to the dose reduction criteria ([table 2](#)) is observed within the treatment course, the dose of CBDCA and/or PEM should be reduced at the start of the next course according to the dose reduction method shown in [table 3](#). If the dose reduction criteria are met two or more times, the dose is reduced based on the dose at the time when the dose reduction criteria are met. If a three-stage dose reduction from the initial dose is required (two dose reductions and further dose reductions are required), treatment is discontinued. If the investigator or coinvestigator determines that toxicity is clearly causal to one of the two chemotherapy agents, it is appropriate to reduce the dose of that drug alone and not the other drugs. If the investigator determines that the toxicity is causally related to both chemotherapeutic agents, the dose is reduced for both agents according to the recommended dose adjustment shown in [table 3](#).

CBDCA, PEM and pembrolizumab will be discontinued when the discontinuation criteria shown in [table 4](#) are met. Discontinuation of CBDCA, PEM and pembrolizumab is independently determined. In addition, if CBDCA and PEM require a third dose adjustment according to dose reduction criteria shown in [table 3](#), or if the criteria for chemotherapy administration for the second and subsequent courses are not met until day 43 (day 1 is a day when the previous course started), CBDCA and/or PEM will be discontinued. If the criteria for pembrolizumab administration for the second and subsequent courses are not met until day 106, pembrolizumab will be discontinued. Any treatment will be discontinued

**Table 1** Starting criteria for first and after second cycle of carboplatin, pemetrexed and pembrolizumab

	First cycle	After second cycle	
Treatment	All	CBDCA, PEM	Pembrolizumab
ECOG PS	0–1	0–2	0–2
Neutrophils (/mm <sup>3</sup> )	≥1500	≥1500	N/A
Haemoglobin (g/L)	0.8	0.8	N/A
Platelet (/L)	≥100×10 <sup>9</sup>	≥100 ×10 <sup>9</sup>	N/A
AST, ALT	≤100 (≤150 when with liver metastasis)	≤100 (≤150 when with liver metastasis)	N/A
Total bilirubin (mg/dL)	≤2	≤2	N/A
Creatinine clearance	≥45 mL/min	≥45 mL/min	N/A
Constipation, appetite loss, nausea, vomit, oral mucositis, fatigue, phlebitis	N/A	≥Grade 2	N/A
Other medication related non-haematological adverse events except for hyponatraemia, alopecia, weight loss	N/A	≥Grade 1	N/A
Pneumonitis	N/A	Grade 0	See below
Immune-related adverse events (eg, pneumonitis, hepatitis, colitis, endocrine disorder*, eye disorder, myocarditis, neuropathy, etc.)	N/A	N/A	≤Grade 1
Amylase increase, hyperglycaemic, skin disorder	N/A	N/A	≤Grade 2
Immune-related cerebromeningitis	N/A	N/A	Grade 0
Non-haematological adverse events	N/A	N/A	≤Grade 2

\*Hypothyroidism, hypopituitarism (ACTH secretion deficiency) and type 1 diabetes that are stable with hormone replacement therapy can be administered.

ACTH, adrenocorticotropic hormone; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CBDCA, carboplatin; ECOG, Eastern Cooperative Oncology Group; N/A, not applicable; PEM, pemetrexed; PS, performance status.

if the investigator or research investigator determines it necessary. The detailed schedule for study participants is presented in [figure 2](#).

### Supportive therapy

There is no specified supportive therapy in this study. While patients are recommended to avoid NSAIDs

for 5 days from 2 days before the day of administration of PEM to 2 days after the administration, they are not excluded, even if NSAIDs are used.

### Follow-up and assessment

Evaluations will be conducted every 6 weeks (±2 weeks) until the end of four courses, and once every 9 weeks (±2

**Table 2** Dose reduction criteria for carboplatin and pemetrexed

Platelet (/L)	Neutrophil (/mm <sup>3</sup> )	CBDCA	PEM
Haematological adverse events			
≥50×10 <sup>9</sup>	≥500	No reduction	No reduction
≥50×10 <sup>9</sup>	<500	1 dose down	1 dose down
<50×10 <sup>9</sup> without bleeding	Any	1 dose down	1 dose down
<50×10 <sup>9</sup> with bleeding	Any	2 dose down	2 dose down
Any	<1000 and fever (≥38.5°C)	2 dose down	1 dose down
Non-haematological adverse events			
Nausea, vomit, appetite loss	Grade 4	1 dose down	1 dose down
Diarrhoea	Grade 3 or 4	No reduction	1 dose down
Enanthema	Grade 3 or 4	No reduction	2 dose down
Neurological toxicity	Grade 3 or 4	1 dose down	1 dose down
AST/ALT	Grade 3	1 dose down	1 dose down
	Grade 4	Discontinue	Discontinue
Others	Grade 4	1 dose down	1 dose down

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CBDCA, carboplatin; PEM, pemetrexed.

**Table 3** Dose reduction method for carboplatin and pemetrexed

	1 dose down	2 dose down	3 dose down
CBDCA (AUC)	AUC 3.75	AUC 2.5	Discontinue
PEM (500 mg/m <sup>2</sup> )	375	250	Discontinue

AUC, area under the curve; CBDCA, carboplatin; PEM, pemetrexed.

weeks) after that. For follow-up of patients who discontinued protocol treatment, examination and efficacy evaluation will be performed at the discretion of each investigator. If the protocol treatment is discontinued for reasons other than disease progression; however, the prescribed evaluation of the treatment efficacy should be performed every three ( $\pm 2$ ) weeks until confirmation of disease progression, start of post-treatment, or the end of the follow-up period. Evaluations will be confirmed by an expert committee. All adverse events are assessed with *Common Terminology Criteria for Adverse Events* V.4.0.

### Statistical analysis

The primary endpoint is the overall response rate. Calculate point to be estimated are those of response rate and two-sided 90% CI. We expect that the response rate in the elderly will be about 45% in point estimates based on KEYNOTE 189. An accurate CI based on the binomial distribution is used for the interval estimation of the response rate.

Secondary endpoints are OS, PFS and safety. Median values for OS and PFS are estimated using the Kaplan-Meier method, and 95% CIs are calculated using the Greenwood method. For safety, the frequency of all adverse events and the worst grade are calculated. Summary of statistics for the most abnormally low value or the most abnormally high value of each item of the haematological test, and biochemical test data are collected.

### Sample size calculation

The response rate of CBDCA/PEM was 18.9% in KEYNOTE 189 (95% CI 13.8% to 25.0%)<sup>1</sup> and 22.6% (95% CI 12.9% to 35.0%) in other phase II trial which treated only elderly ( $\geq 70$ ).<sup>4</sup> The response rate of CBDCA/PEM combined with pembrolizumab was 47.6% (95% CI

42.6% to 52.5%) in KEYNOTE 189.<sup>1</sup> In line with these, the threshold was defined as 20% and the expectation is defined as 45%. With alpha error of 0.1 (both sides) and power of 0.90, 19 cases are calculated to be necessary. Considering deviation cases, 22 cases were set as target registration numbers.

### Patients and public involvement

Neither patients, nor members of the public were directly involved in construction of this study. However, we believe assessment of benefits of pembrolizumab in addition to CBDCA and PEM in patients with  $\geq 75$  years is publicly important.

### Informed consent

All participants will be informed of the purpose of the study, the plan of intervention, the benefits and the possible risks to the participants, after which they will sign the patient consent form. All candidates will be given sufficient time to consider whether they would like to participate in this study. Patients participating in the study will be allowed, at any stage, to withdraw from the study without restrictions.

### Participating institutions

Wakayama Medical University Hospital, Wakayama National Hospital, National Hospital Organization Minami Wakayama Medical Center and Naga Municipal Hospital.

### Data storage and security data

Data are collected via electronic data capturing system hosted by the Wakayama Medical University Clinical Trial Center with a secure web interface. Study investigators or those designated as such use strictly controlled personal electronic signatures (IDs and passwords) to login to the electrical data capture (EDC) system. The accuracy of all data input is confirmed by study investigators. Hard copy will be stored in a cabinet with a lock in a secure location. Access to records and data will be limited to study related persons.

### Monitoring

This trial will employ centralised monitoring. Monitoring will be performed annually by each dataset collected via the EDC system to evaluate and improve study progress

**Table 4** Treatment cessation criteria for CBDCA, PEM and pembrolizumab

	CBDCA	PEM	Pembrolizumab
Immune-related adverse events (hepatitis, eye disorder, myocarditis, neuropathy)	N/A	N/A	$\geq$ Grade 3
Immune-related adverse events (diarrhoea, colitis, panhypopituitarism, pancreatitis, skin disorders)	N/A	N/A	$\geq$ Grade 4
Treatment related adverse events (pneumonitis)	$\geq$ Grade 1	$\geq$ Grade 1	$\geq$ Grade 2
Immune-related cerebromeningitis	N/A	N/A	$\geq$ Grade 1
Allergic reaction	$\geq$ Grade 3	$\geq$ Grade 3	$\geq$ Grade 3

CBDCA, carboplatin; PEM, pemetrexed; N/A, not applicable.

Treatment cycle	Enrolment	Treatment Cycles (3-week-cycles)								End of treatment	Follow-up
		1	2	3	4	5	6	7	8+		
Scheduling window (Days)	-14 to 0	+7	+7	+7	+7	+7	+7	+7	+7		
<b>Enrolment</b>											
Eligibility screen	×										
Informed consent	×										
<b>Assessments</b>											
Performance Status	×	×	×	×	×	×	×	×	×	×	
Physical examination	×	×	×	×	×	×	×	×	×	×	
Blood test	×	×	×	×	×	×	×	×	×	×	
Vital signs and weight	×	×	×	×	×	×	×	×	×	×	
Tumour imaging	×			×		×			×	×	
Adverse events		×	×	×	×	×	×	×	×	×	
Survival status											×
<b>Interventions</b>											
Carboplatin		×	×	×	×						
Pemetrexed		×	×	×	×	×	×	×	×	×	
Pembrolizumab		×	×	×	×	×	×	×	×	×	

**Figure 2** The schedule of enrolment, interventions and assessments. Tumour imaging is scheduled at 6, 12 weeks and then every 9 weeks ( $\pm 14$  days).

and quality. Monitoring consists of checking data as necessary, and individual facilities may be contacted to enter or add any missing data.

## DISCUSSION

Elderly people, usually defined as  $\geq 70$  years or  $\geq 75$  years, are thought to require different treatment strategies to non-elderly people. In this population, combination of gemcitabine and vinorelbine cannot surpass each individual agent in its antitumour effect,<sup>5</sup> and significant superiority of the combination of docetaxel and cisplatin over docetaxel alone could not be shown. Subsequently, phase III studies showed that combination of CBDCA and paclitaxel significantly prolonged survival compared with gemcitabine or vinorelbine alone,<sup>6</sup> but treatment-related deaths when patients were treated by CBDCA and paclitaxel were as frequent as 4.4% in this study. Considering these data about double agents combined regimens, there are remaining concerns about the clinical benefits of the regimen of combined triple agents in elderly patients.

In this study, with reference to the KEYNOTE 189 study protocol, the criteria for dose reduction, cessation, postponement and resumption of CBDCA and PEM were specified, which was left to the discretion of the attending physician in the KEYNOTE 189 study protocol. We believe that assessing efficacy and safety in the elderly in a well-established and typical way is useful for a fair assessment.

A limitation of this study is the small number of cases. The main purpose of this study; however, is to evaluate the efficacy of adding pembrolizumab to the combination of CBDCA and PEM, and we hypothesised increase of response rate from 20% to 45%, which are referred from the KEYNOTE 189 trial, and calculated number of

enrolments. We therefore believe that this number of cases is sufficient to achieve the main purpose.

Taken together, if the current study reaches its primary endpoint, it will suggest that pembrolizumab can add additive efficacy when combined with CBDCA and PEM in elderly patients. Safety information concerning prospectively enrolled and periodically evaluated elderly patients will be highly valuable.

## ETHICS AND DISSEMINATION

The study is designed and implemented according to good clinical practice and conducted in accordance with the Declaration of Helsinki. It was approved by the Wakayama Medical University Central Review Board on 2 December 2019 (approval number: W-32). Patients have been enrolled since February 2020. As the study will complete accrual in January 2022, results will be published within 2023. This study will provide important information whether triplet regimens of pembrolizumab, CBDCA and PEM would be clinically beneficial in elderly patients. For participants, results of this study will be announced by their physicians.

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