Adebrelimab or placebo plus carboplatin and etoposide as first-line treatment for extensive-stage small-cell lung cancer (CAPSTONE-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Outline

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Background

- Adebrelimab (SHR-1316) is a novel humanised IgG4 monoclonal antibody against PD-L1.
- In a phase 1 trial in patients with solid advanced tumours,
  - Adebrelimab showed preliminary antitumour activity and acceptable safety, with no dose limiting toxicity reported up to a dose of 20 mg/kg every 3 weeks; in addition, dose-proportional exposure was observed at the dose range of 3–20 mg/kg, every 3 weeks.
- In a phase 2 trial of oesophageal squamous cell cancer, the clinical efficacy and tolerability of adebrelimab was shown in combination with chemotherapy.

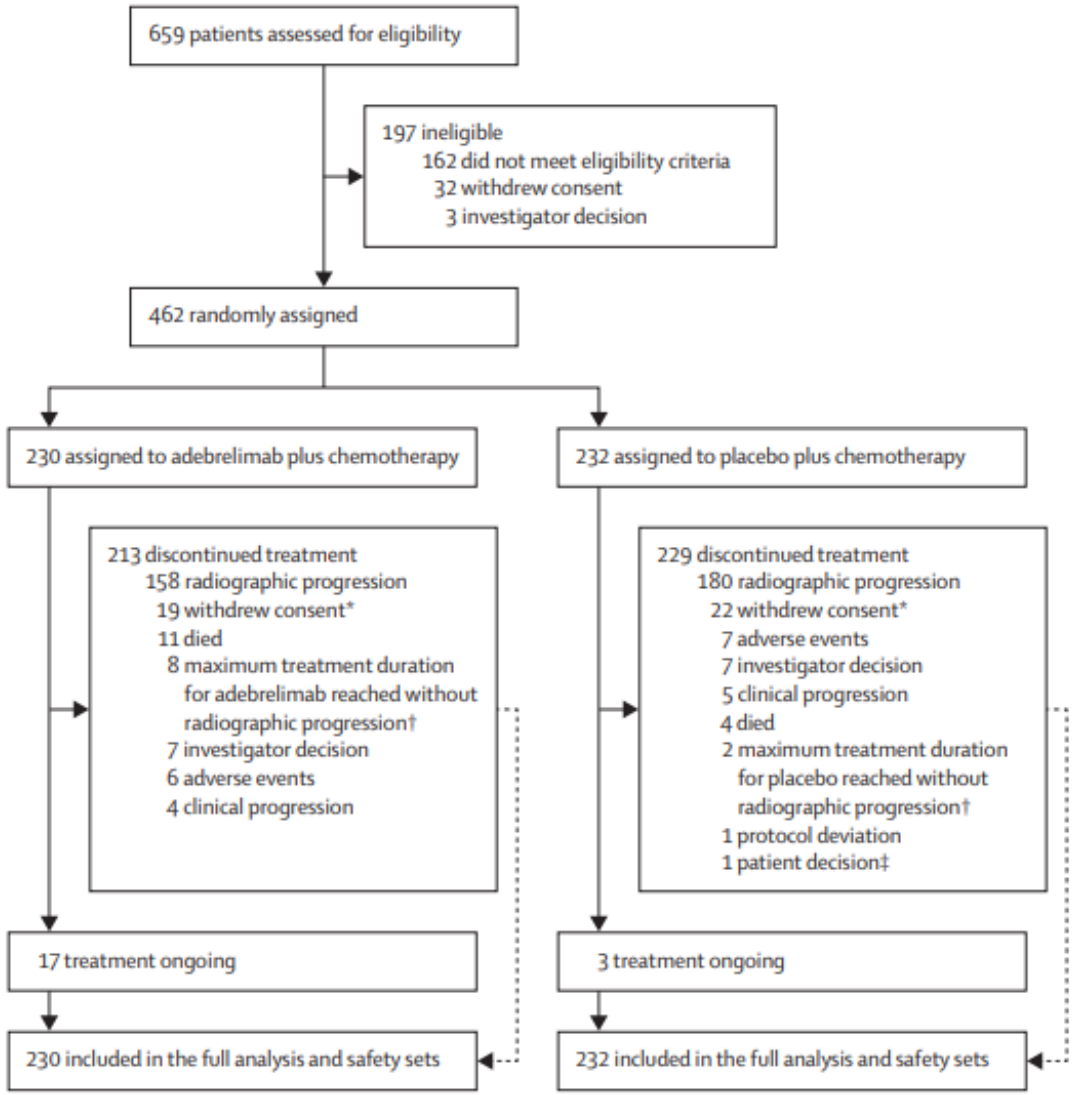
Aim

- To assess the efficacy and safety of adebrelimab (SHR-1316), a novel anti-PD-L1 antibody, with standard chemotherapy as a first-line treatment for ES-SCLC

Methods

- Randomised, double-blind, placebo-controlled, phase 3 trial, done in 47 tertiary hospitals in China.
- Key inclusion criteria were
  - Patients aged 18–75 years, with previously untreated histologically or cytologically confirmed ES-SCLC and ECOG performance status of 0–1.
- Eligible patients were randomly assigned (1:1) to receive
  - four to six cycles of carboplatin (area under the curve of 5 mg/mL per min, day 1 of each cycle) and
  - etoposide (100 mg/m^2 of body-surface area, on days 1–3 of each cycle) with either
  - adebrelimab (20 mg/kg, day 1 of each cycle) or matching placebo, followed by maintenance therapy with adebrelimab or placebo.
  - 659 patients were screened for inclusion, of whom 462 (70%) were eligible for inclusion: 230 (50%) were randomly assigned to the adebrelimab group and 232 (50%) were assigned to the placebo group.
  - All treatments were given intravenously in 21-day cycles.
  - Randomisation was done using a centralised interactive web response system with a block size of four, stratified by liver metastases, brain metastases, and lactate dehydrogenase concentration.

Trial profile



*Five (2%) patients in the adebrelimab group and seven (3%) patients in the placebo group withdrew due to the COVID-19 pandemic. †The maximum duration of treatment allowed for adebrelimab or placebo was 2 years per protocol. ‡Started new antitumour treatment at local hospital without confirmed evidence of radiographical progression

Baseline characteristics

	Adebrelimab group (n=230)	Placebo group (n=232)
Age, years		
Median (IQR)	62 (55–66)	62 (56–67)
<65	155 (67%)	147 (63%)
≥65	75 (33%)	85 (37%)
Sex		
Male	184 (80%)	188 (81%)
Female	46 (20%)	44 (19%)
ECOG performance status		
0	33 (14%)	30 (13%)
1	197 (86%)	202 (87%)
Smoking history		
Never smoked	50 (22%)	53 (23%)
Former smoker	180 (78%)	178 (77%)
Current smoker	0	1 (<1%)
Disease stage		
III	8 (3%)	6 (3%)
IV	222 (97%)	226 (97%)
Lactate dehydrogenase at enrolment		
≤ULN	116 (50%)	115 (50%)
>ULN	114 (50%)	117 (50%)
Brain metastases		
Yes*	5 (2%)	5 (2%)
No	225 (98%)	227 (98%)
Liver metastases		
Yes	73 (32%)	74 (32%)
No	157 (68%)	158 (68%)
PD-L1 tumour proportion score		
<1%	196 (85%)	200 (86%)
≥1%	24 (10%)	20 (9%)
Not evaluable	10 (4%)	12 (5%)

Outcome

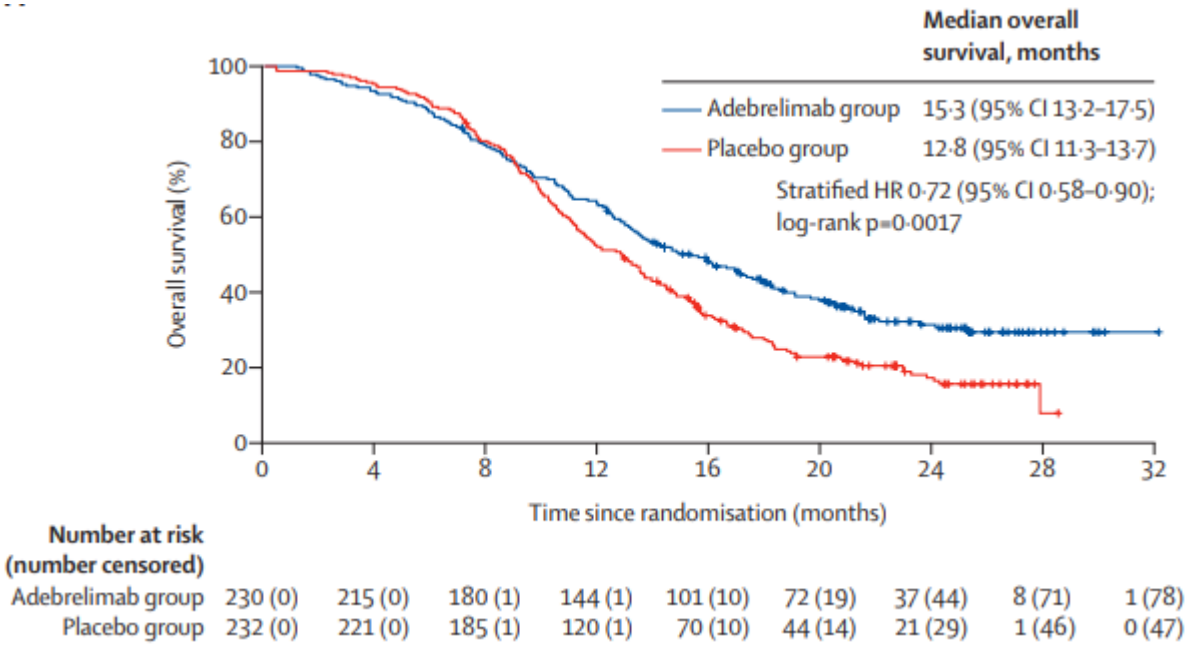
- Primary endpoint
    - overall survival, defined as time from randomisation to death from any cause.
- Secondary endpoints were
    - PFS (time from randomisation to RECIST-defined disease progression or death, whichever occurred first),
    - ORR (proportion of patients with confirmed complete or partial response),
    - duration of response (time from first complete or partial response to first disease progression or death),
    - DCR (proportion of patients with complete or partial disease or stable disease lasting for at least 4 weeks),
    - PFS at 6 months and 12 months (all as assessed by the BICR and investigator),
    - OS at 12 months and 24 months, and safety.

Results

- **Median overall survival** was significantly longer in the adebrelimab group (15·3 months [95% CI 13·2–17·5]) than in the placebo group (12·8 months [11·3–13·7]; HR 0·72 [95% CI 0·58–0·90]; one-sided p=0·0017.
- **overall survival rates** were
  - **62·9% (95% CI 56·3–68·8) in the adebrelimab group** versus 52·0% (45·4–58·2) in the placebo group at 12 months and
  - **31·3% (24·9–37·9) in the adebrelimab** group versus 17·2% (12·1–23·0) in the placebo group at 24 months.

Kaplan-Meier curve of overall survival.

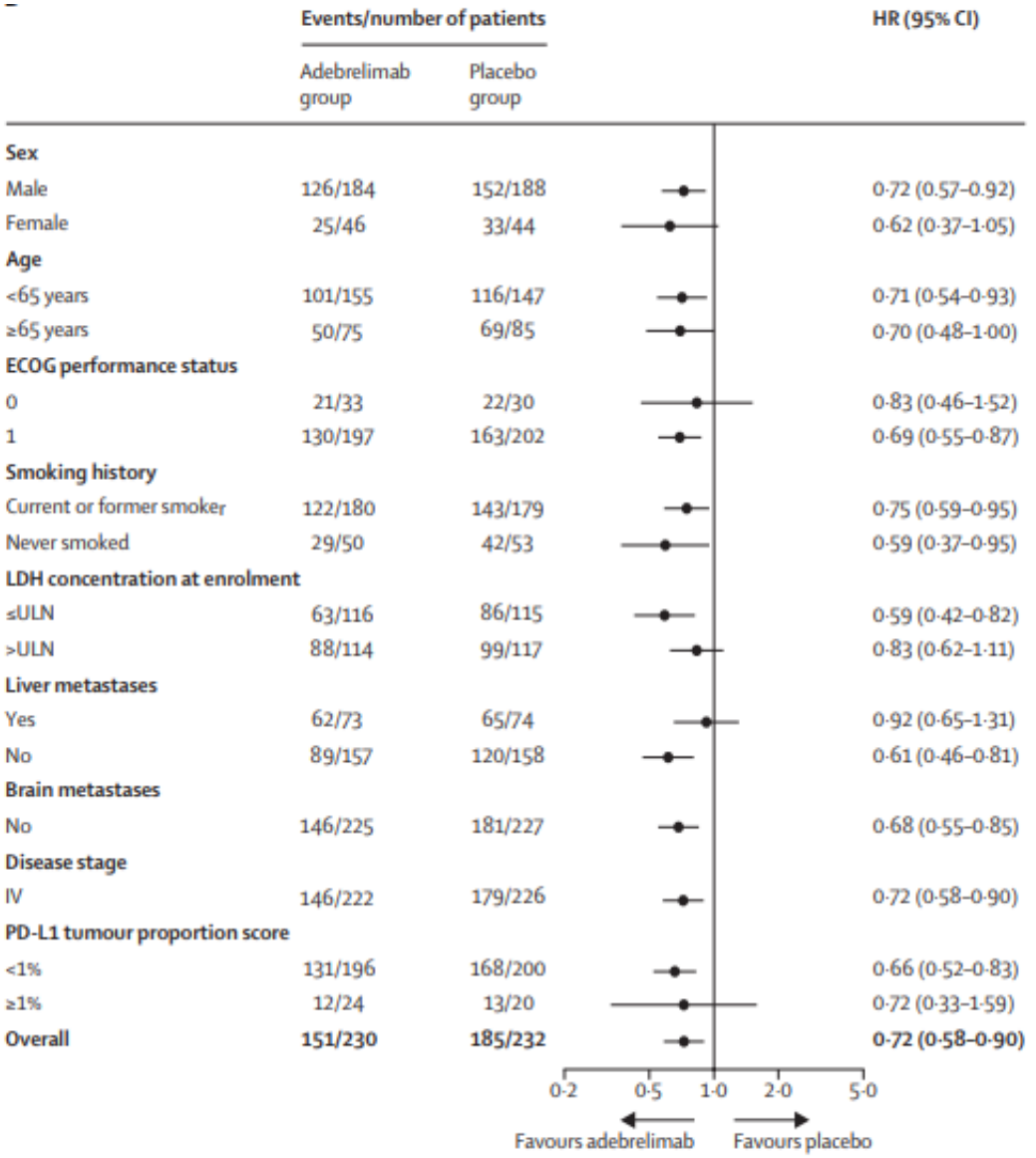
Crosses denote censored patients



Number at risk (number censored)									
Adebrelimab group	230 (0)	215 (0)	180 (1)	144 (1)	101 (10)	72 (19)	37 (44)	8 (71)	1 (78)
Placebo group	232 (0)	221 (0)	185 (1)	120 (1)	70 (10)	44 (14)	21 (29)	1 (46)	0 (47)

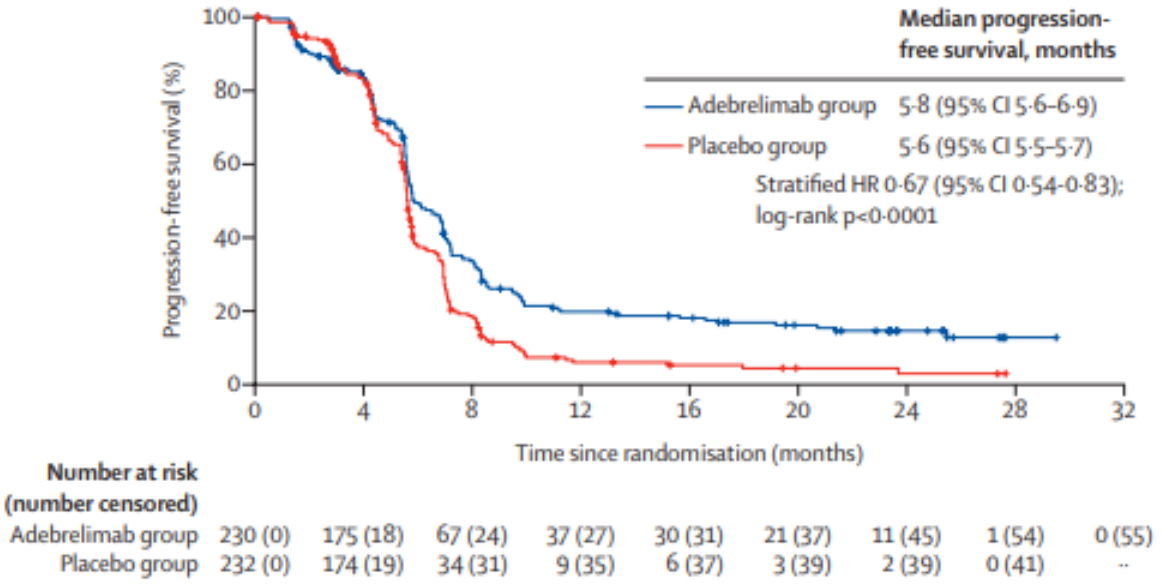
Results

- With a cutoff at 28·6 months (the minimum of the longest follow-up time for a patient in either group),
  - **the restricted mean survival time was 16·8 months (95% CI 15·6–18·0) in the adebrelimab group** and 14·5 months (13·5–15·5) in the placebo group.
  - Overall survival results across predefined subgroups are shown in fig



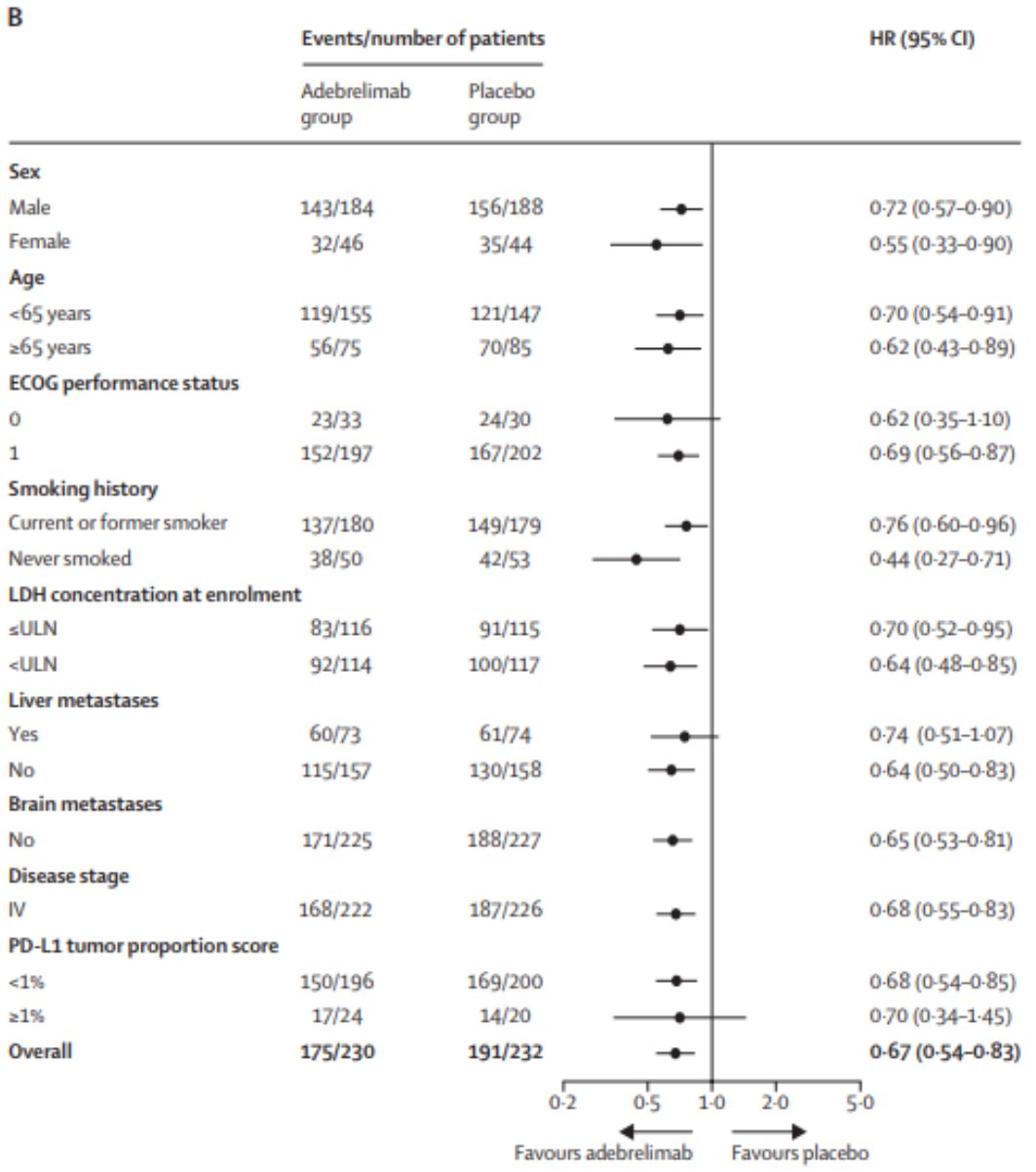
Results

- According to the assessment of PFS according to BICR,
  - 175 (76%) of 230 patients in the adebrelimab group and 191 (82%) of 232 patients in the placebo group had disease progression or died.
- The PFS rate was
  - **49·4% (95% CI 42·4–56·0) in the adebrelimab group versus 37·3% (30·7–43·9) in the placebo group** at 6 months and 19·7% (14·5–25·5) versus 5·9% (3·1–10·1) at 12 months



Results

- Analyses of progression-free survival by the investigators were similar to the findings of the BICR assessment.
- Progression-free survival across predefined subgroups is shown in figure.



Treatment-related adverse events

- AEs occurred in 229 (100%) patients in the adebrelimab group and 229 (99%) patients in the placebo group;
- Grade 3 or worse treatment related AEs occurred in 197 (86%) patients in the adebrelimab group and 197 (85%) patients in the placebo group

	Adebrelimab group (n=230)				Placebo group (n=232)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any treatment-related adverse event	32 (14%)	85 (37%)	110 (48%)	2 (1%)	32 (14%)	110 (47%)	85 (37%)	2 (1%)
Neutrophil count decreased	44 (19%)	82 (36%)	92 (40%)	0	45 (19%)	103 (44%)	72 (31%)	0
White blood cell count decreased	111 (48%)	99 (43%)	7 (3%)	0	127 (55%)	78 (34%)	10 (4%)	0
Platelet count decreased	103 (45%)	65 (28%)	23 (10%)	0	113 (49%)	56 (24%)	22 (9%)	0
Alanine aminotransferase increased	90 (39%)	5 (2%)	0	0	69 (30%)	4 (2%)	0	0
Aspartate aminotransferase increased	78 (34%)	2 (1%)	1 (<1%)	0	56 (24%)	4 (2%)	0	0
γ-glutamyltransferase increased	24 (10%)	4 (2%)	0	0	22 (9%)	1 (<1%)	0	0
Anaemia	131 (57%)	63 (27%)	1 (<1%)	0	141 (61%)	66 (28%)	0	0
Nausea	90 (39%)	2 (1%)	0	0	107 (46%)	0	0	0
Vomiting	58 (25%)	2 (1%)	0	0	53 (23%)	1 (<1%)	0	0
Constipation	40 (17%)	0	0	0	42 (18%)	0	0	0
Alopecia	102 (44%)	0	0	0	98 (42%)	0	0	0
Decreased appetite	63 (27%)	5 (2%)	0	0	60 (26%)	2 (1%)	0	0
Hypoalbuminaemia	26 (11%)	0	0	0	24 (10%)	0	0	0
Asthenia	41 (18%)	1 (<1%)	0	0	44 (19%)	1 (<1%)	0	0
Hypothyroidism	28 (12%)	0	0	0	21 (9%)	0	0	0
Hyponatraemia	13 (6%)	3 (1%)	2 (1%)	0	8 (3%)	4 (2%)	2 (1%)	0
Hypertension	6 (3%)	6 (3%)	0	0	2 (1%)	2 (1%)	0	0
Hypokalaemia	6 (3%)	2 (1%)	2 (1%)	0	11 (5%)	0	0	0
Pneumonia	7 (3%)	3 (1%)	0	0	2 (1%)	1 (<1%)	0	0
Lymphocyte count decreased	4 (2%)	3 (1%)	2 (1%)	0	4 (2%)	1 (<1%)	3 (1%)	0
Febrile neutropenia	0	3 (1%)	2 (1%)	0	0	0	2 (1%)	0
Myelosuppression	0	0	2 (1%)	0	1 (<1%)	0	3 (1%)	0

Treatment-related adverse events

- The most common grade 3 or 4 treatment-related adverse events in both groups were haematological adverse events, including
  - decreased neutrophil count (174 [76%] patients in the adebrelimab group and 175 [75%] in the placebo group),
  - decreased WBC count (106 [46%] vs 88 [38%]),
  - decreased platelet count (88 [38%] vs 78 [34%]), and anemia (64 [28%] vs 66 [28%]).
- Treatment-related AEs led to discontinuation of any treatment component in 12 (5%) patients in the adebrelimab group and nine (4%) patients in the placebo group, with decreased platelet count being the most common reason in both groups (three [1%] patients in the adebrelimab group and two [1%] patients in the placebo group.
- Treatment-related SAEs occurred in 89 (39%) patients in the adebrelimab group and 66 (28%) patients in the placebo group; all events with an incidence of 2% or more (in either group) were haematological adverse events and hepatic function test abnormalities .
- Fatal AEs possibly related to study treatment were reported in two (1%) patients in the adebrelimab group (respiratory failure and ILDs or pneumonia) and two (1%) patients in the placebo group (multiple organ dysfunction and unknown cause of death).

Treatment-related adverse events

- Immune-mediated AEs of any grade were reported in 64 (28%) patients in the adebrelimab group and 40 (17%) patients in the placebo group;
  - Most frequent events were hypothyroidism (21 [9%] patients in the adebrelimab group and 13 [6%] in the placebo group), and hepatic laboratory abnormalities (17 [7%] patients in the adebrelimab group and 12 [5%] patients in the placebo group.
- Grade 3 or worse immune mediated adverse events occurred in
  - 11 (5%) patients in the adebrelimab group and seven (3%) patients in the placebo group; hepatic laboratory abnormalities and pneumonitis (four [2%] patients each) occurred in 1% or more of patients in the adebrelimab group.


THANK YOU