

## ORIGINAL ARTICLE

# First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

L. Horn, A.S. Mansfield, A. Szczesna, L. Havel, M. Krzakowski, M.J. Hochmair, F. Huemer, G. Losonczy, M.L. Johnson, M. Nishio, M. Reck, T. Mok, S. Lam, D.S. Shames, J. Liu, B. Ding, A. Lopez-Chavez, F. Kabbinavar, W. Lin, A. Sandler, and S.V. Liu, for the IMpower133 Study Group\*

N Engl J Med 2018;379:2220-9.  
DOI: 10.1056/NEJMoa1809064

## RobotReviewer report

### Abstract

Here are the results from 1 PDFs. Risk of bias table

trial	design	n	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment
Horn L, 2018	RCT	201	+	+	+	+

## Characteristics of studies

### Horn L, 2018

- |              |  |
|--------------|--|
| Population   | <ol style="list-style-type: none"> <li>1. Patients Eligible patients were adults with histologically or cytologically confirmed extensive-stage small-cell lung cancer as defined according to the Veterans Administration Lung Study Group staging system (Table S1 in the Supplementary Appendix, available at NEJM.org), 16 measurable extensivestage small-cell lung cancer according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with higher numbers reflecting greater disability) who had not received previous systemic treatment for extensive-stage small-cell lung cancer.</li> <li>2. Key exclusion criteria were a history of autoimmune disease and previous treatment with CD137 agonists or immune-checkpoint blockade therapies.</li> <li>3. METHODS We conducted this double-blind, placebo-controlled, phase 3 trial to evaluate atezo-lizumab plus carboplatin and etoposide in patients with extensive-stage small-cell lung cancer who had not previously received treatment.</li> </ol> |
| Intervention | <ol style="list-style-type: none"> <li>1. Patients were randomly assigned to receive atezoliz,Ä umab plus carboplatin and etoposide (atezolizumab group) or placebo plus carboplatin and etoposide (placebo group); four 21,Ä day cycles of treatment were administered in the induction phase, after which patients received atezolizumab or placebo in a maintenance phase.</li> <li>2. Patients were randomly assigned in a 1:1 ratio to receive carboplatin and etoposide with either atezoliz-umab or placebo for four 21-day cycles (induction phase),</li> </ol>  |

followed by a maintenance phase during which they received either atezolizumab or placebo (according to the previous random assignment) until they had unacceptable toxic effects, disease progression according to Response Evaluation Criteria in Solid Tumors, version 1.1, or no additional clinical benefit.

3. Enrolled patients were assigned in a 1:1 ratio to receive, in the induction phase, four 21-day cycles of carboplatin (area under the curve of 5 mg per milliliter per minute, administered intravenously on day 1 of each cycle) and etoposide (100 mg per square meter of body-surface area, administered intravenously on days 1 through 3 of each cycle) with either atezolizumab (at a dose of 1200 mg, administered intravenously on day 1 of each cycle) or placebo (Fig.

1. The two primary end points were investigator-assessed progression-free survival and overall survival in the intention-to-treat population.
2. Key secondary end points included investigator-assessed objective response rate (according to RECIST) and the duration of response.
3. Kaplan, ÅiMeier methodology was used to estimate the probability of overall survival and progression-free survival, as well as to calculate the median time from randomization to death (for overall survival) and the median time from randomization to disease progression or death (for progression-free survival) for each group, and the Brookmeyer and Crowley method was used to construct the 95% confidence interval for the medians.

Outcomes

**Bias**

**Judgement**

**Support for judgement**

Random  
sequence  
generation

low

1. Randomization was performed with the use of a permuted-block randomization method (IxRS) and was stratified according to sex, ECOG performance-status score (0 or 1), and presence of brain metastases (yes or no).
2. Enrolled patients were assigned in a 1:1 ratio to receive, in the induction phase, four 21-day cycles of carboplatin (area under the curve of 5 mg per milliliter per minute, administered intravenously on day 1 of each cycle) and etoposide (100 mg per square meter of body-surface area, administered intravenously on days 1 through 3 of each cycle) with either atezolizumab (at a dose of 1200 mg, administered intravenously on day 1 of each cycle) or placebo (Fig.
3. Patients were randomly assigned to receive atezoliz, Å umab plus carboplatin and etoposide (atezolizumab group) or placebo plus carboplatin and etoposide (placebo group); four 21, Å day cycles of treatment were administered in the induction phase, after which patients received atezolizumab or placebo in a maintenance phase.

Allocation  
concealment

low

1. Patients were randomly assigned in a 1:1 ratio to receive carboplatin and etoposide with either atezoliz-umab or placebo for four 21-day cycles (induction phase), followed by a maintenance phase during which they received either atezolizumab or placebo (according to the previous random assignment) until they had unacceptable toxic effects, disease progression according to Response Evaluation Criteria in Solid Tumors, version 1.1, or no additional clinical benefit.
2. Randomization was performed with the use of a permuted-block randomization method (IxRS) and was stratified according to sex, ECOG performance-status score (0 or 1), and presence of brain metastases (yes or no).
3. Patients were randomly assigned to receive atezoliz, Å umab plus carboplatin and etoposide (atezolizumab group) or placebo plus carboplatin and etoposide (placebo group); four 21, Å day cycles of treatment were administered in the induction phase, after which patients received atezolizumab or placebo in a maintenance phase.

Blinding of participants and personnel

low

1. Patients were randomly assigned to receive atezolizumab plus carboplatin and etoposide (atezolizumab group) or placebo plus carboplatin and etoposide (placebo group); four 21-day cycles of treatment were administered in the induction phase, after which patients received atezolizumab or placebo in a maintenance phase.
2. Patients were randomly assigned in a 1:1 ratio to receive carboplatin and etoposide with either atezolizumab or placebo for four 21-day cycles (induction phase), followed by a maintenance phase during which they received either atezolizumab or placebo (according to the previous random assignment) until they had unacceptable toxic effects, disease progression according to Response Evaluation Criteria in Solid Tumors, version 1.1, or no additional clinical benefit.
3. The IMpower133 trial is a multinational, phase 1 (safety) and phase 3 (efficacy), double-blind, randomized, placebo-controlled trial.

Blinding of outcome assessment

low

1. METHODS We conducted this double-blind, placebo-controlled, phase 3 trial to evaluate atezolizumab plus carboplatin and etoposide in patients with extensive-stage small-cell lung cancer who had not previously received treatment.
2. Patients were randomly assigned in a 1:1 ratio to receive carboplatin and etoposide with either atezolizumab or placebo for four 21-day cycles (induction phase), followed by a maintenance phase during which they received either atezolizumab or placebo (according to the previous random assignment) until they had unacceptable toxic effects, disease progression according to Response Evaluation Criteria in Solid Tumors, version 1.1, or no additional clinical benefit.
3. For the analysis of progression-free survival, data for patients who were alive and had no disease progression were censored at the time of the last tumor assessment.