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ORIGINAL ARTICLE

Atezolizumab plus carboplatin and nab-paclitaxel versus carboplatin and nab-paclitaxel as treatments for Chinese, treatment-naïve, stage IV, non-squamous, non-small-cell lung cancer patients: A retrospective analysis

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Abstract

The IMpower trials reported significant effects of atezolizumab-containing chemotherapies on Caucasian patients. Chinese patients differ from their Western counterparts in terms of driver mutations, etiologies, and regimen tolerance. In China, atezolizumab-containing chemotherapies are not cost-effective. Atezolizumab addition triggers grade >3 adverse events. Here, we evaluated the effectiveness and the safety profile of atezolizumab plus carboplatin and nab-paclitaxel compared to carboplatin and nab-paclitaxel in treatment-naïve Chinese patients with confirmed stage IV, non-squamous, non-small-cell lung cancer. All patients completed six cycles of 1200 mg of atezolizumab/3 weeks plus 6 mg/ml/min area-under-the-curve carboplatin/3 weeks plus 100 mg/m^2 nab-paclitaxel/week (n = 115; ACN cohort) or 6 mg/ml/min area-under-the-curve carboplatin/3 weeks plus 100 mg/m^2 nab-paclitaxel/week (n = 130; CNP cohort). The progression-free survival (12.98 ± 2.57 months vs. 10.89 ± 2.18 months, p < .0001) and overall survival (38.04 ± 19.8 months vs. 33.59 ± 87 months, p = .012) of patients in the ACN cohort were higher than those of patients in the CNP cohort after 48 weeks of follow-up. A total of 97 (84%) patients in the ACN cohort and 94 (72%) in the CNP cohort developed grade ≥3 adverse events (p = .030). A total of 84 (73%) patients from the ACN cohort and 107 (82%) from the CNP cohort died during 48 weeks of follow-up (p = .091). The addition of atezolizumab to carboplatin and nab-paclitaxel enhanced progression-free and overall survival but increased the risk of grade ≥3 adverse events in Chinese, treatment-naïve, stage IV, non-squamous, non-small-cell lung cancer patients who completed treatment (Level of Evidence: III; Technical Efficacy Stage: 4).

Abbreviations: ACN cohort, patients had received 1200 mg intravenously atezolizumab/3 weeks plus 6 mg/ml/min area under the curve carboplatin/3 weeks plus 100 mg/m^2 intravenously nab-paclitaxel/ week; CNP cohort, patients had received 6 mg/ml/min area under the curve carboplatin/3 weeks plus 100 mg/m^2 intravenously nab-paclitaxel/ week; EMA, European Medicines Agency; PD-1, cell death protein 1; PD-L1, ligands of cell death protein 1; RECIST, Response Evaluation Criteria in Solid Tumors; SD, standard deviation; USFDA, United States Food and Drugs Administration.

KEYWORDS
atezolizumab, carboplatin, chemotherapy, immunotherapies, nab-paclitaxel, non-small-cell lung cancer

1 | INTRODUCTION

Platinum-based chemotherapy is the traditional first-line treatment for advanced-stage, non-small-cell lung cancer.[1,2] Another option is platinum-based chemotherapy with bevacizumab.[1] Patients of advanced stage should be treated with tyrosine kinase inhibitors.[1] Novel treatment approaches include immunotherapies.[3] Although many treatments are available, the overall survival is unsatisfactory.

Atezolizumab is a monoclonal antibody that inhibits the binding of ligands of cell death protein 1 (PD-L1) to cell death protein 1 (PD-1) and protein B7.1 (CD80), restoring anticancer immunity.[4–7], The POPLAR[8,9] and OAK[10] trials reported improved overall survival of non-small-cell lung cancer patients treated previously with other chemotherapies who received atezolizumab monotherapy. The IMpower130[11] and the IMpower150[12] trials found that atezolizumab plus chemotherapies improved the overall and progression-free survival of Caucasian, non-squamous, non-small-cell, stage IV lung cancer patients not previously treated with other chemotherapies. Atezolizumab assists chemotherapy by releasing immunogenic tumor antigens.[13] The United States Food and Drug Administration (USFDA) and the European Medicines Agency (EMA) recommend atezolizumab plus chemotherapy for patients with non-small-cell lung cancer lacking epidermal growth factor receptor mutations or anaplastic lymphoma kinase rearrangements.[14] The application of Western lung cancer treatment guidelines to Chinese patients is problematic, Chinese non-small-cell lung cancer patients differ from those of Western countries in several ways. The driver mutations differ (epidermal growth factor receptor mutations are more common and anaplastic lymphoma kinase rearrangements less common in Asians). The etiologies differ, as do the tolerances to treatment regimens.[15] The current Chinese Society of Clinical Oncology guidelines[16] do not recommend atezolizumab plus chemotherapy as the first-line treatment for patients with non-small-cell lung cancer lacking epidermal growth factor receptor mutations or anaplastic lymphoma kinase rearrangements. Thus, Chinese patients do not receive atezolizumab.

The effects of atezolizumab plus chemotherapies were reported in the IMpower130[11] and IMpower150[12] trials on Caucasians, neither the effectiveness nor adverse effects of atezolizumab plus chemotherapies have been tested in Chinese patients. It was thus necessary to evaluate the synergistic or additive effect of atezolizumab when added to chemotherapies in Chinese, non-small-cell, lung cancer patients. Often, patients acquire resistance to therapies; responses do not endure.[11] Immunogenic tumor antigens do not differ between cancer and normal cells.[17] Moreover, in China, atezolizumab plus chemotherapy was not cost-effective when used to treat treatment-naïve, stage IV, non-squamous, non-small-cell, lung cancer patients.[18,19] The responses to atezolizumab plus chemotherapy depend on patient condition, and thus vary.[14] Camrelizumab plus carboplatin plus pemetrexed improved the progression-free survival of Chinese, non-squamous, non-small-cell lung cancer patients,[20] but camrelizumab was approved in China on 31 May 2019 for the treatment of Hodgkin lymphoma only (not treatment-naïve cancer).[21] Atezolizumab addition to chemotherapy triggers grade >3 adverse events in non-squamous, non-small-cell, lung cancer patients.[22]

We evaluated the effectiveness and safety of atezolizumab plus carboplatin and nab-paclitaxel compared to carboplatin plus nab-paclitaxel in Chinese, treatment-naïve, stage IV, non-squamous, non-small-cell lung cancer patients.

2 | MATERIALS AND METHODS

2.1 | Ethics approval and consent to participate

The study protocol was approved by the Rongchang District People's Hospital Review Board and the Chinese Society of Clinical Oncology (approval no. RDPHCL1524 dated 25 July 2021). The study adhered to the law of China and the 2008 Declaration of Helsinki. As the work was retrospective, the need for informed patient consent was waived.

2.2 | Study population

A total of 271 patients aged ≥18 years with cytopathologically or histopathologically confirmed, stage IV, non-squamous, non-small-cell lung cancers; of 0 or 1 Eastern Cooperative Oncology Group performance status; and who had not previously received chemotherapy for stage IV disease, underwent chemotherapy at the Department of Oncology of Rongchang District People's Hospital, Chongqing, China, and referring hospitals from 1 September 2015 to 2 January 2016. Among these, four patients did not complete the six cycles; one patient ceased chemotherapy (on physician advice); seven died during treatment; and 14 received other chemotherapies (not carboplatin and nab-paclitaxel). These 26 patients were excluded from analysis. Data on progression-free and overall survival, death, and treatment-associated adverse events for 245 patients were collected from institutional records. A flow diagram of the study is shown in Figure 1.

2.3 | Treatment

A total of 115 patients received 1200 mg of atezolizumab intravenously every 3 weeks plus 6 mg/ml/min area-under-the-curve carboplatin every 3 weeks plus 100 mg/m^2 intravenous nab-paclitaxel every week. All patients received a total of six cycles. These patients constituted the ACN cohort. A total of 130 patients received 6 mg/ml/min area-under-the-curve carboplatin every 3 weeks plus 100 mg/m^2

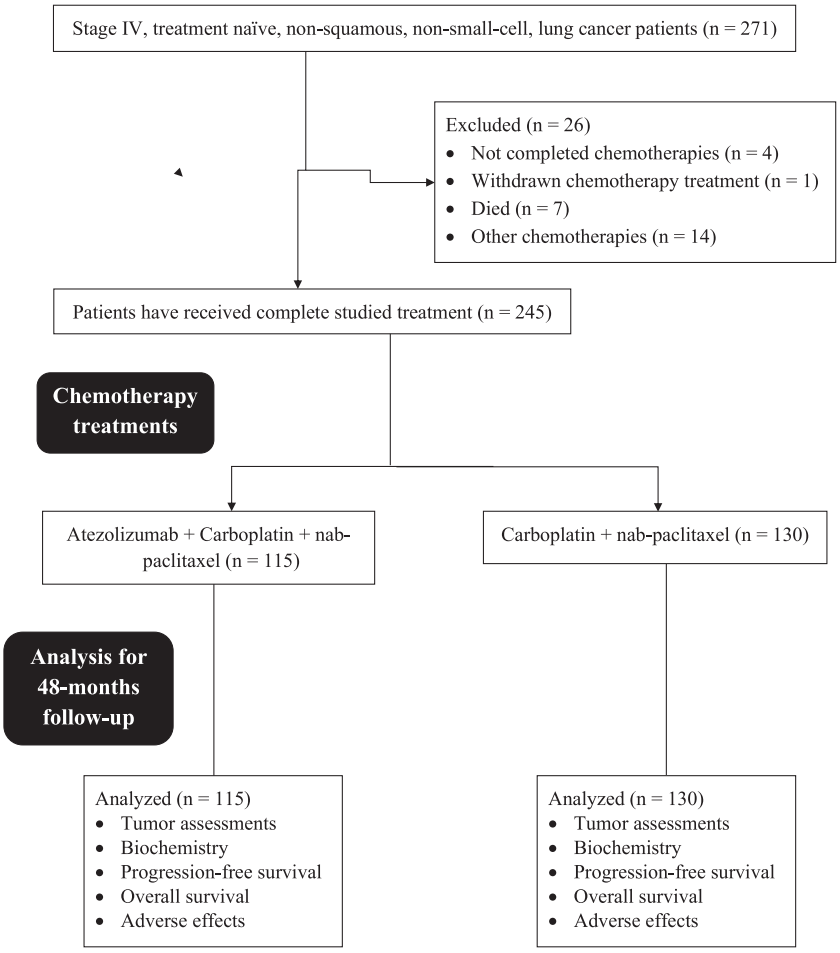

FIGURE 1 A flow diagram of the retrospective analysis

intravenous nab-paclitaxel every week. All patients received a total of six cycles. These patients constituted the CNP cohort. Corticosteroids were administered in both cohorts when necessary. Patients in the CNP cohort did not receive atezolizumab because of its high cost.

2.4 | Tumor assessments

Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 was used to evaluate all tumors before treatment commencement and every 3 weeks thereafter.

2.5 | Biochemistry

Serum chemistry and hematology tests were performed every 3 to 48 weeks after the completion of chemotherapy or death.

2.6 | Adverse events

Treatment-associated adverse events were assessed during 66 weeks from the start of chemotherapy. All events were graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events, ver. 5.0 (NCCN guidelines ver. 5, 2021)[23].

2.7 | Outcome measures

Progression-free and overall survival were assessed during the 66 weeks from the start of chemotherapy treatment as functions of PD-L1 expression.[11]

2.8 | PD-L1 expression

The Ventana PD-L1 (SP142) assay system (Ventana Medical Systems) was used to assess PD-L1 expression as follows: PD-L1-high, PD-L1 expressed by ≥50% of tumor cells or ≥10% of tumor-infiltrating immune cells; PD-L1-low, PD-L1 expressed by ≥1% but <50% of tumor cells or ≥1% but <10% of tumor-infiltrating immune cells; and PD-L1-negative, PD-L1 expression by <1% of tumor cells or <1% of tumor-infiltrating immune cells.[11]

2.9 | Statistical analysis

InStat 3.01 (GraphPad Software) was used for statistical analysis. The Fisher exact test or chi-squared test of independence was used to compare categorical variables, and the unpaired *t*-test to compare continuous variables. Non-parametric tests were used to compare

survival. The stratified log-rank test was employed to compare progression-free and overall survival. A p-value < .05 was taken to indicate significance.

3 | RESULTS

3.1 | Demographic and clinical conditions

The demographic and clinical parameters prior to treatment commencement did not differ significantly between the cohorts (Table 1, all $p > .05$).

3.2 | Outcome measures

The progression-free survival of patients in the ACN cohort was 12.98 ± 2.57 months (range 8–20 months) and that of the CNP cohort 10.89 ± 2.18 months (range 7–15 months) ($p < .0001$). Twelve months after the completion of treatment, 59 (51%) patients in the ACN cohort and 33 (25%) in the CNP cohort survived without progression (Figure 2A, $p < .0001$). The overall survival of patients in the ACN cohort was 38.04 ± 19.8 months (minimum 20 months) and that of patients in the CNP cohort 33.59 ± 87 months (minimum 20 months) ($p = .012$). At 36 months after the completion of treatment, 56 (49%) patients from the ACN cohort and 37 (28%) from the CNP cohort survived (with or without disease) (Figure 2B, $p = .002$). Further, 84 (73%) patients in the ACN cohort and 107 (82%) in the CNP cohort died during 12 weeks of treatment and 48 weeks of follow-up. More CNP than ACN cohort patients died but statistical significance was not attained ($p = .091$). Detailed outcomes are shown in Figure 3.

For patients with liver metastases or with epidermal growth factor receptor mutations or anaplastic lymphoma kinase rearrangements (genomic aberrations), the progression-free and overall survival of patients in the ACN cohort were not significantly better than those of the CNP cohort (all $p > .05$).

3.3 | Adverse events

All-grade adverse events were encountered in 115 (100%) patients in the ACN cohort and 130 (100%) in the CNP cohort. Overall, 97 (84%) patients in the ACN cohort and 94 (72%) in the CNP cohort developed grade ≥3 adverse events ($p = .030$); these are listed in Table 2.

4 | DISCUSSION

At 12 months after treatment, the number of patients exhibiting progression-free survival in the ACN cohort was twice that in the CNP cohort; this was also true at 36 months (i.e., on completion of treatment), consistent with the IMpower130[11] and IMpower150[12] trials in Caucasians and two meta-analyses.[22,24] However, in the cited trials, about 7% of patients were Asian,all of our patients were South and East Asians. Atezolizumab creates an environment allowing the immune system to tackle lung cancer.[25] The addition of atezolizumab to carboplatin and nab-paclitaxel enhances progression-free survival and overall survival in Chinese, treatment-naïve, stage IV, non-squamous, non-small-cell lung cancer patients. We lack data on the etiologies and regimen tolerance. We explored whether the addition of immunotherapy to chemotherapy was safe in Chinese patients.

The progression-free and overall survival of patients in the ACN cohort were higher than those in the CNP cohort except for patients with liver metastases or with epidermal growth factor receptor mutations or anaplastic lymphoma kinase rearrangements (genomic aberrations). These results are consistent with those of the IMpower130[11] and the IMpower150[12] trials in Caucasians and one meta-analysis,[24] but not another meta-analysis.[22] The latter meta-analysis included only small numbers of patients with genomic aberrations (type I error). The addition of atezolizumab to carboplatin and nab-paclitaxel afforded important clinical advantages but not in patients with liver metastases or epidermal growth factor receptor mutations or anaplastic lymphoma kinase rearrangements (genomic aberrations). We found no significant differences between patients with liver metastases or genetic abnormalities. However, given the limited number of cases, we cannot be certain that no difference exists.

We found more grade ≥3 adverse events in the ACN than the CNP cohort, consistent with the results of the IMpower130[11] and the IMpower150[12] trials in Caucasians, and one meta-analysis[22] but not another meta-analysis.[24] The very high patient numbers in the latter meta-analysis[24] introduced a type II error. Atezolizumab addition to carboplatin and nab-paclitaxel chemotherapies triggered grade ≥3 adverse events in Chinese, treatment-naïve, stage IV, non-squamous, non-small-cell lung cancer patients.

We prescribed nab-paclitaxel rather than paclitaxel; this removed the need for steroid premedication (prescribing information for Abraxan, Celgene Corp.)[26]. Steroids attenuate the immune system.[11] To maximize the effects of carboplatin and atezolizumab, nab-paclitaxel was preferred to paclitaxel.

The limitations of our work include its retrospective nature. This was not a randomized clinical trial. Even when nab-paclitaxel was prescribed, most patients (>75%) required corticosteroids. The reasons why corticosteroids were needed are unclear, as are the effects thereof (if any) on atezolizumab action. We cite the IMpower130[11] and the IMpower150[12] trials. However, the survival analyses and patient inclusion criteria of these trials differed from ours, the trials enrolled intention-to-treat populations. Our results are limited to patients who completed treatment. As the work was retrospective, the selection bias in play when patients were assigned to the ACN or CNP cohort is a major limitation. Financial concerns may have affected the choice of treatment, but the judgments of attending physicians and other factors may also have been in play. Multivariate analysis is needed to minimize the impact of such factors.

TABLE 1 Demographic and clinical data prior to treatment commencement

Parameters	Cohorts		
	ACN	CNP	
Treatment	Atezolizumab + carboplatin + nab-paclitaxel	Carboplatin + nab-paclitaxel	Comparisons
Number of patients	115	130	*p*-value
Sex			
Male	63 (55)	68 (52)	.703
Female	52 (45)	62 (48)	
Ethnicity			
Han Chinese	106 (92)	122 (94)	.873
Mongolian	8 (7)	7 (5)	
Tibetan	1 (1)	1 (1)	
Age (years)			
<65	51 (44)	59 (45)	.898
≥65	64 (56)	71 (55)	
Mean ± *SD*	60.12 ± 12.11	61.22 ± 11.19	
Liver metastases			
Present	13 (11)	19 (15)	.456
Absent	102 (89)	111 (85)	
Bone metastases			
Present	28 (24)	32 (25)	.999
Absent	87 (76)	98 (75)	
Eastern Cooperative Oncology Group performance status			
0	29 (25)	48 (37)	.144
1	85 (74)	81 (62)	
2	1 (1)	1 (1)	
Smoking status			
Never	69 (60)	80 (62)	.968
Previous	45 (39)	49 (37)	
Current	1 (1)	1 (1)	
Adenocarcinoma	106 (92)	116 (89)	.513
Adenocarcinoma with neuroendocrine features	1 (1)	3 (2)	.625
Adenosquamous tumor	2 (2)	2 (2)	.999
Bronchioloalveolar carcinoma	1 (1)	2 (2)	.999
Large cell tumor	2 (2)	4 (3)	.687
Sarcomatoid tumor	3 (3)	3 (2)	.999
Patients with epidermal growth factor receptor mutations or anaplastic lymphoma kinase rearrangements (genomic aberrations)	10 (9)	7 (5)	.327
Ligand of cell death protein 1 expression			
High	25 (22)	31 (24)	.060
Low	47 (41)	35 (27)	
Negative	43 (37)	64 (49)	
Corticosteroid use	88 (77)	98 (75)	.882

(Continues)

TABLE 1 (Continued)

Parameters	Cohorts		
	ACN	CNP	
Treatment	Atezolizumab + carboplatin + nab-paclitaxel	Carboplatin + nab-paclitaxel	Comparisons
Number of patients	115	130	*p*-value
Follow-up time (months)			
Minimum	18	18	.129
Maximum	48	48	
Mean ± *SD*	20.1 ± 5.2	21.3 ± 6.9	

Note: Continuous variables are presented as means ± standard deviations (*SD*s) and categorical variables as frequencies (percentages). The Fisher exact test or the chi-squared test of independence was used to compare categorical variables; the unpaired *t*-test employed to compare continuous variables. A *p*-value < .05 was considered significant.

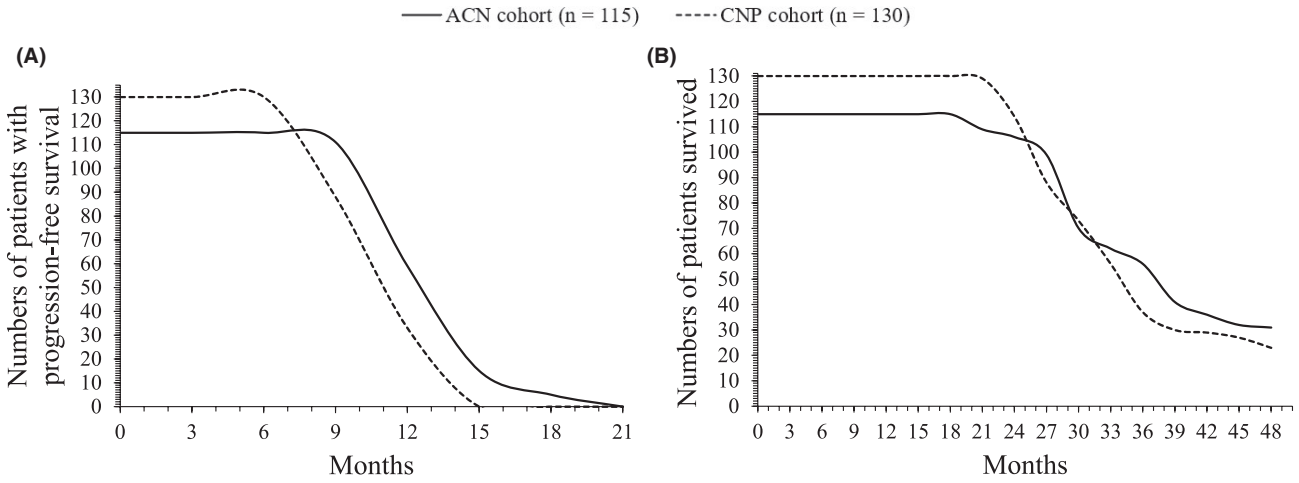

FIGURE 2 Effects of treatment. (A) Progression-free survival. (B) Overall survival

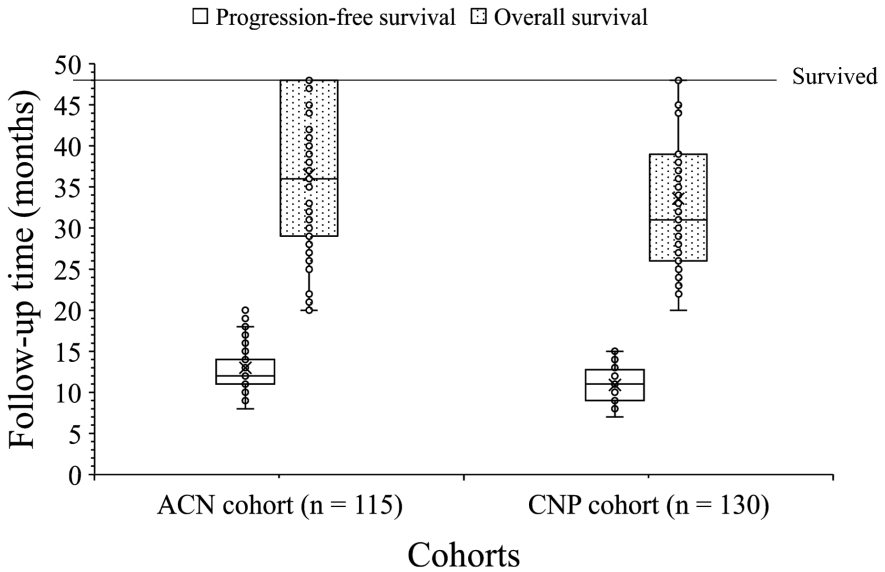

FIGURE 3 Outcomes

TABLE 2 Treatment-associated adverse events during 66 weeks after treatment commencement

	Cohorts							
Event	ACN				CNP			
Numbers of patients	115				130			
Grade	1 or 2	3	4	5	1 or 2	3	4	5
Neutropenia	16 (14)	22 (19)	15 (13)	2 (2)	22 (17)	25 (19)	9 (7)	1 (1)
Anemia	26 (23)	33 (29)	1 (1)	0 (0)	35 (27)	24 (18)	2 (2)	0 (0)
Thrombocytopenia	20 (17)	7 (6)	4 (3)	0 (0)	24 (18)	7 (5)	4 (3)	0 (0)
Reduced white blood cell count	6 (5)	5 (4)	1 (1)	0 (0)	5 (4)	3 (2)	1 (1)	0 (0)
Fatigue	38 (33)	7 (6)	1 (1)	0 (0)	38 (29)	8 (6)	1 (1)	0 (0)
Diarrhea	31 (27)	7 (6)	1 (1)	0 (0)	25 (19)	7 (5)	1 (1)	0 (0)
Nausea	46 (40)	4 (3)	1 (1)	0 (0)	52 (40)	5 (4)	1 (1)	0 (0)
Vomiting	23 (20)	3 (3)	1 (1)	0 (0)	25 (19)	4 (3)	1 (1)	0 (0)
Loss of appetite	25 (22)	4 (3)	0 (0)	0 (0)	21 (16)	5 (4)	1 (1)	0 (0)
Constipation	20 (17)	3 (3)	1 (1)	0 (0)	20 (15)	2 (2)	0 (0)	0 (0)
Hypomagnesaemia	15 (13)	2 (2)	1 (1)	0 (0)	13 (10)	1 (1)	0 (0)	0 (0)
Alopecia	40 (35)	0 (0)	0 (0)	0 (0)	38 (29)	0 (0)	0 (0)	0 (0)
Dysgeusia	12 (10)	0 (0)	0 (0)	0 (0)	7 (5)	0 (0)	0 (0)	0 (0)

Note: The figures are frequencies (percentages). Some patients experienced more than one event. All events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

5 | CONCLUSIONS

The addition of atezolizumab to carboplatin and nab-paclitaxel increased the progression-free and overall survival of Chinese, treatment-naïve, stage IV, non-squamous, non-small-cell lung cancer patients who completed treatment, except in patients with liver metastases and those with epidermal growth factor receptor mutations or anaplastic lymphoma kinase rearrangements (genomic aberrations). The addition of atezolizumab to carboplatin and nab-paclitaxel chemotherapies caused grade ≥3 adverse events in Chinese, treatment-naïve, stage IV, non-squamous, non-small-cell lung cancer patients. Our findings may be of interest to Chinese oncologists. We explored the benefits afforded by the addition of immunotherapy to chemotherapy in patients with advanced non-small cell lung cancer. These may differ by race, as may the toxicities.

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DISCLOSURE

The authors declared that they have no conflict of interest or any other competing interest regarding results and/ or discussion reported in the research.

AUTHOR CONTRIBUTIONS

All authors have read and approved the manuscript for publication. YC was a project administrator, contributed to supervision, visualization, literature review, resources, validation, and methodology of the study. SK contributed to the methodology, literature review, conceptualization, resources, and software of the study. MY contributed to investigation, data curation, formal analysis, and the literature review of the study, draft, and edited the manuscript for intellectual content. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study are not publicly available (institutional policy on legal and ethical grounds) and will make available from the corresponding author on reasonable request.

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