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Original Article

Clinical effect of Almonertinib in treating epidermal growth factor receptor mutation-positive residual ground-glass opacities after stage I lung cancer resection

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Abstract: Objective: To investigate the clinical effect of Almonertinib in in patients with epidermal growth factor receptor (EGFR) mutation-positive residual ground-glass opacities following resection of stage I lung cancer. Methods: A retrospective analysis of 75 patients with EGFR mutation-positive residual ground-glass opacities post-stage I lung cancer surgery was conducted at Tianjin Medical University Cancer Institute and Hospital between January 2021 and December 2023. Patients were categorized into the control group (CG, n = 33, treated with pemetrexed and cisplatin) and the observation group (OG, n = 42, treated with Almonertinib). Cellular immune markers, tumor markers, CT nodule characteristics (size, density), malignancy risk scores before (T0) and after treatment (T1), treatment efficacy at T1, and adverse drug reactions were evaluated. Results: At T1, both groups showed an increase in CD3+ and CD4+ levels, and a decrease in CD8+ levels compared to T0. The OG group had significantly higher CD3+ and CD4+ levels and lower CD8+ levels compared to the CG group (all $P < 0.05$). Serum levels of IL-6, IL-8, and TNF-α decreased significantly in both groups at T1, with greater reductions observed in the OG group (all $P < 0.05$). Additionally, the OG group demonstrated a more substantial reduction in serum carcinoembryonic antigen, carbohydrate antigen 125, carbohydrate antigen 50, cytokeratin 19 fragment antigen 21-1, neuron-specific enolase, and carbohydrate antigen 19-9 levels compared to the CG group (all $P < 0.05$). Nodule size and density also decreased in both groups, with more significant reductions in the OG group at T1 (all $P < 0.05$). The Mayo and Brock model predictions indicated a significantly lower risk of malignancy at T1 in the OG group compared to T0 (all $P < 0.05$). The objective response rate (ORR) and disease control rate (DCR) were significantly higher in the OG group ($P < 0.05$), and adverse reaction rates were lower in the OG group compared to the CG group at T1 (all $P < 0.05$). Conclusion: Almonertinib demonstrates good clinical efficacy and safety for the treatment of EGFR mutation-positive residual ground-glass opacities following stage I lung cancer resection.

Keywords: Lung cancer, Almonertinib, epidermal growth factor receptor mutation, ground glass nodules, clinical efficacy, adverse reactions

Introduction

Lung cancer has the highest incidence among malignant tumors in China. In 2016, China reported approximately 828,000 new cases of lung cancer and nearly 657,000 deaths, accounting for 20.4% of total new cancer cases and 27.2% of cancer-related deaths, respectively [1]. By 2022, the number of new lung cancer cases had risen to 1.061 million, with 733,000 deaths, representing 22.0% incidence of all cancers and 28.5% of cancer-related mortality. Both of these are the highest rankings among malignant tumors [2].

Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases [3, 4]. The early symptoms of NSCLC, such as chest discomfort,

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cough, and fever, resemble those of common respiratory conditions, often leading to delayed diagnosis until intermediate or advanced stages [5]. Currently, surgical resection is the primary treatment for NSCLC, with radiotherapy and chemotherapy serving as adjuncts, particularly effective for early or mid-stage patients. However, in advanced stages, systemic metastasis is frequent, leading to poor treatment outcome [1, 6]. Studies indicate that patients with early-stage lung cancer have a 5-year survival rate exceeding 90%, whereas those with advanced disease have a survival rate of less than 15% [7].

Among early-stage lung cancer patients undergoing radical surgery, about 6% present with ground-glass nodules (GGNs) that cannot be resected concurrently [8]. Currently, no effective treatment exists for GGNs in western medicine. Postoperative pathology often reveals that GGNs represent early-stage lung adenocarcinoma, which typically does not require chemotherapy or radiotherapy. Only a small proportion of patients with large solid nodules or those with lymph node metastasis, require chemotherapy. There is no conclusive evidence supporting the benefit of molecular targeted therapy for GGN patients. However, for patients with compromised lung function, making surgery unfeasible, genetic testing is recommended to guide possible targeted therapy and prevent recurrence.

With the rapid advancement and widespread use of gene detection technology, numerous oncogenic driver genes have been identified. Among them, the epidermal growth factor receptor (EGFR) is the most common driver gene in patients with non-small cell lung cancer (NSCLC). Approximately 50% of Asian NSCLC patients and 15% of Caucasian NSCLC patients harbor mutations in the EGFR-tyrosine kinase domain [9-11]. Advances in understanding NSCLC driver genes and the development of targeted therapies have led to breakthroughs in treatment [12]. Compared to traditional chemotherapy, EGFR tyrosine kinase inhibitors (EGFR-TKIs) have demonstrated markedly prolonged intracranial disease control in EGFR-mutant NSCLC patients with brain metastases, establishing EGFR-TKIs as a standard treatment for EGFR-positive advanced lung cancer [13].

As a targeted therapy for NSCLC driver genes, EGFR-TKIs have significantly improved the prognosis of patients who can now be routinely treated with these inhibitors. However, most patients develop acquired resistance after about one year of first- or second-generation EGFR-TKI treatment, with approximately 60% exhibiting the EGFR T790M resistance mutation [14]. For patients with this mutation, third-generation EGFR-TKIs offer a more effective treatment option. Almonertinib, China's first third-generation EGFR-TKI, was the first to undergo first-line treatment research in a Chinese population, making it most representative of the clinical benefits for Chinese NSCLC patients [15, 16]. Currently, Almonertinib is widely used to treat advanced EGFR-mutant NSCLC [17, 18]; however, there is no literature on its use for treating residual ground-glass nodules in EGFR mutation-positive patients after stage I lung cancer resection. Therefore, this study retrospectively analyzed 75 patients with EGFR mutation-positive residual ground-glass nodules after stage I lung cancer resection who were treated with Almonertinib for at least six months. The aim was to explore the clinical efficacy of Almonertinib and provide a scientific basis for future treatment.

Materials and methods

Materials

A retrospective analysis was conducted on the clinical data of 75 patients with EGFR mutation-positive residual ground-glass nodules who underwent stage I lung cancer resection at Tianjin Medical University Cancer Institute and Hospital between January 2021 and December 2023. The patients were divided into an observation (OG) group (n = 33, treated with Almonertinib) and the control (CG) group (n = 42, treated with pemetrexed and cisplatin), based on the treatment method.

Inclusion criteria: (1) Diagnosis of stage I NSCLC confirmed by surgery, imaging, and pathologic analysis; (2) Age ≥ 18 years; (3) EGFR mutations confirmed by next-generation sequencing; (4) Thin-slice CT scan showing round or irregular lesions with a diameter ≤ 1 cm in other lung lobes or segments, exhibiting ground-glass opacity; (5) Complete clinical data available.

Exclusion criteria: (1) Patients with mental disorders or congenital heart disease; (2) Esti-

mated survival time < 3 months; (3) Patients unable to tolerate or cooperate with the treatment; (4) Pregnant or lactating patients; (5) Patients with other primary malignant tumors; (6) Patients with a history of targeted drug therapy.

This study was approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital.

Treatment methods

The control group (CG group) received pemetrexed and cisplatin. One month after surgery, following confirmation of stable physical condition, healed surgical incisions, and the absence of acute complications, patients began chemotherapy. On day 1 of each cycle, pemetrexed (Jiangsu Haosen Pharmaceutical Group Co., Ltd., Sinopharm H20093996) was administered intravenously at 500 mg/m^2, once daily. Cisplatin (Yunnan Plant Pharmaceutical Co., Ltd., H53021677) was infused intravenously at 75 mg/m^2 on days 1-3. Each chemotherapy cycle lasted 3 weeks, with a total of 6 cycles, and a review conducted after every 2 cycles.

The observation group (OG group) received Almonertinib targeted therapy in addition to the CG regimen. On the 7th day of cisplatin infusion, patients began oral Almonertinib (Jiangsu Haosen Pharmaceutical Group Co., Ltd., national drug approval H20200004, 55 mg/tablet) at 110 mg once daily. It was advised to take the medication at approximately the same time each day, with or without food. Chewing or crushing the tablet was discouraged, and doses missed by more than 12 hours were not to be made up. Patients were informed of potential side effects, such as rash, diarrhea, and stomatitis, and were advised on hygiene practices. For skin itching, patients were advised not to scratch, and skin cream or corticosteroid ointment was recommended for severe cases. Dietary recommendations included a light, non-spicy diet. Adjustments to the treatment were made as needed based on the patient's response and adverse reactions. Both groups continued treatment for 6 cycles.

Observation indicators

The primary indicators were as follows: (1) Immune Index: Peripheral venous blood (5 mL) was collected from patients after fasting for more than 8 hours, 1 day before treatment (T0) and 1 day after 3 months of treatment (T1). The levels of mature T lymphocytes (CD3+, CD4+, CD8+) were measured using flow cytometry with immunofluorescence labeling. (2) Inflammatory factors: The levels of interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α) were detected using a double antibody one-step sandwich enzyme-linked immunosorbent assay (ELISA) at T0 and T1. The assay kits were provided by Shanghai Jianglai Biological Co., Ltd. (No. JL14113, JL19291, JL19246). (3) Tumor markers: Levels of carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), carbohydrate antigen 50 (CA50), cytokeratin 19 fragment antigen 21-1 (CYFRA21-1), neuron-specific enolase (NSE), and carbohydrate antigen 19-9 (CA19-9) were measured using flow fluorescence luminescence on an automatic chemiluminescence analyzer (Shanghai Huanxi Medical Device Co., Ltd.) at T0 and T1. (4) CT findings: Thin-layer chest CT data at T0 and T1 were analyzed to assess changes in lung nodule size and density. The Mayo and Brock models were used to evaluate the probability of malignant risk of the nodules [19, 20]. (5) Efficacy determination [21]: After three treatment cycles, the effects were categorized as follows: Complete response (CR): Disappearance of all target lesions, with no new lesions, sustained for at least 4 weeks. Partial response (PR): A ≥ 50% reduction in the sum of the largest diameters of target lesions, sustained for at least 4 weeks. Stable disease (SD): Lesion reduction below PR thresholds or lesion expansion not exceeding 25-49% of the largest diameter. Progressive disease (PD): A < 25% reduction in lesion length. The overall response rate (ORR) was calculated as CR + PR, while the disease control rate (DCR) was defined as CR + PR + SD.

The secondary indicators included adverse reactions [22], such as rash, nausea, vomiting, and diarrhea. All adverse events were assessed according to the "International Adverse Reaction Evaluation System for Cancer Chemotherapy Drugs - Common Adverse Reaction Terminology Standards".

Statistical analysis

Data were analyzed by professional statisticians using GraphPad Prism 7.0 and SPSS 20.0

Table 1. Comparison of basic data

Items	OG group (n = 42)	CG group (n = 33)	t/χ^2	*P*
Age ($\bar{x}$ ± sd, years)	46.78 ± 14.52	47.03 ± 15.91	-0.71	0.943
Sex (n, %)			1.886	0.170
Males	27 (64.29)	16 (48.48)		
Females	15 (35.71)	17 (51.52)		
BMI ($\bar{x}$ ± sd, kg/m^2)	23.81 ± 2.13	23.43 ± 2.54	0.759	0.450
Course of disease ($\bar{x}$ ± sd, year)	2.16 ± 0.50	2.32 ± 0.43	1.462	0.148
Pathologic type (n, %)			0.112	0.945
Adenocarcinoma infiltrating	19 (45.24)	16 (48.48)		
Adenocarcinoma in situ	17 (40.48)	13 (39.39)		
Others	6 (14.28)	4 (12.13)		
Smoking history			0.640	0.424
Yes	23 (54.76)	15 (45.45)		
No	19 (45.24)	18 (54.56)		
Complicated with diabetes mellitus			1.566	0.211
Yes	12 (28.57)	14 (42.42)		
No	30 (71.43)	19 (57.58)		
Complicated with hypertension			3.544	0.060
Yes	18 (42.86)	21 (63.64)		
No	25 (57.14)	12 (36.36)		

Note: BMI: body mass index; CG group: control group; OG group: observation group.

software. Data following a normal distribution were expressed as mean ± standard deviation ($\bar{x}$±sd), and analyzed with a two-sample t-test. For non-normally distributed data, medians and interquartile ranges [M (P25, P75)] were used, and paired data were analyzed using the Wilcoxon signed-rank test. Categorical data were presented as frequencies or rates (%), and the χ^2 test was applied. A *P*-value of < 0.05 was considered significant.

Results

Comparison of basic information

A total of 75 patients were included in this study. Based on treatment methods, 42 patients were treated with Almonertinib (OG group), while 33 received pemetrexed and cisplatin (CG group). There were no significant differences between the groups regarding gender, pathological type, age, body mass index (BMI), smoking history, diabetes mellitus, or hypertension (all P > 0.05), indicating comparability (**Table 1**).

Comparison of immune indicators

At T1, CD3+ (66.41 ± 3.28 vs. 58.25 ± 2.37; 61.29 ± 3.16 vs. 58.40 ± 2.36) and CD4+ (46.90 ± 3.28 vs. 32.71 ± 2.43; 42.28 ± 3.05 vs. 33.07 ± 2.56) levels were higher in both OG and CG groups compared to T0, while CD8+ (22.59 ± 1.87 vs. 29.33 ± 2.49; 25.18 ± 2.15 vs. 30.02 ± 2.37) was lower. CD3+ and CD4+ levels were significantly higher in the OG group compared to the CG group, while CD8+ levels were lower in the OG group (P < 0.05), as shown in **Figure 1**.

Comparison of inflammatory factors

At T1, serum levels of IL-6 (5.26 ± 1.50 vs. 16.36 ± 4.09; 6.45 ± 2.77 vs. 16.28 ± 4.16), IL-8 (9.21 ± 2.70 vs. 21.94 ± 4.59; 13.50 ± 3.48 vs. 21.15 ± 4.08), and TNF-α (3.23 ± 0.82 vs. 16.03 ± 2.27; 5.61 ± 1.38 vs. 16.25 ± 2.36) were significantly lower in both groups compared to T0. However, the levels were significantly lower in the OG group compared to the CG group at T1 (P < 0.05), as shown in **Figure 2**.

Comparison of serum tumor markers

At T1, serum levels of CEA (10.47 ± 1.15 vs. 24.56 ± 2.39; 13.11 ± 1.29 vs. 25.13 ± 2.67), CA50 (13.55 ± 1.34 vs. 28.46 ± 2.67; 18.75 ± 1.51 vs. 29.19 ± 2.74), CA125 (38.40 ± 2.95 vs. 57.55 ± 4.56; 41.41 ± 3.16 vs. 58.03 ±

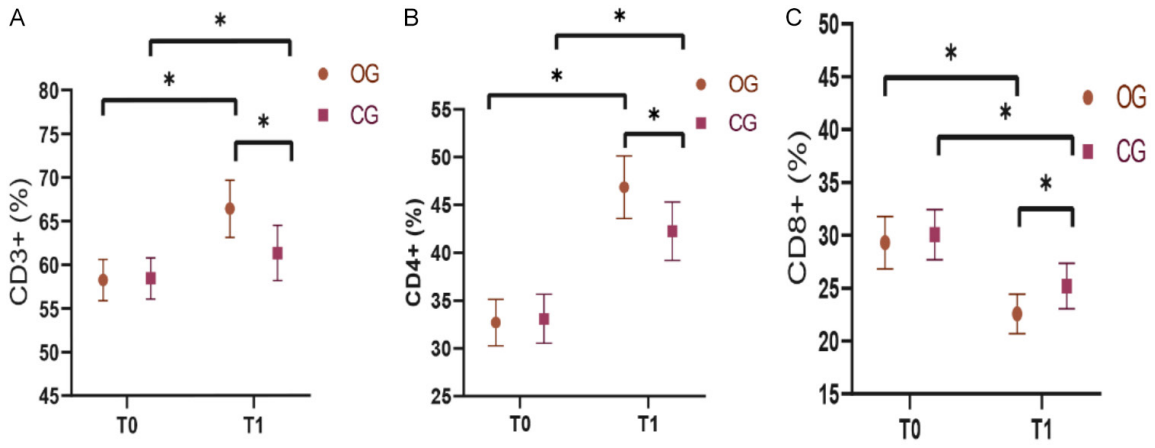

Figure 1. Comparison of immune indexes. Note: *P < 0.05; A: CD3+; B: CD4+; C: CD8+; CD: cluster of differentiation; CG: control group; OG: observation group.

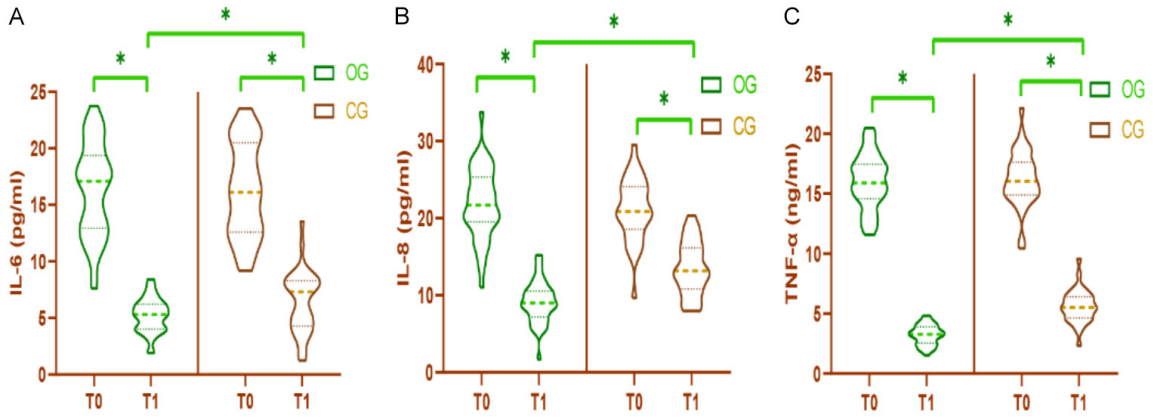

Figure 2. Comparison of inflammatory factor levels. Note: *P < 0.05; A: IL-6; B: IL-8; C: TNF-α; IL-6: Interleukin-6; IL-8: Interleukin-8; TNF-α: tumor necrosis factor-α; CG: control group; OG: observation group.

5.12), CYFRA21-1 (2.16 ± 0.51 vs. 5.28 ± 1.40; 3.92 ± 0.72 vs. 5.34 ± 1.39), NSE (6.65 ± 1.44 vs. 37.89 ± 6.37; 15.82 ± 3.26 vs. 38.18 ± 6.47), and CA19-9 (8.68 ± 1.85 vs. 38.96 ± 7.11) were significantly lower in both groups compared to T0, with the OG group showing more pronounced reductions than the CG group (all P < 0.05), as shown in **Figure 3**.

Comparison of nodule size and density

Compared to T0, both groups exhibited reductions in nodule size and density, with the OG group showing significantly greater reductions than the CG group at T1 (P < 0.05), as shown in **Table 2**. This suggests that Almonertinib effectively reduced the size and density of pulmonary nodules.

Malignant risk probability of pulmonary nodules

Using the Mayo and Brock models, the probability of malignant risk at T1 was significantly lower than at T0 in both groups (P < 0.05), as shown in **Table 3**. This indicates that Almonertinib may reduce the risk of lung cancer recurrence or progression.

Comparison of clinical efficacy evaluation

At T1, the ORR and DCR of the OG group were 52.38% and 80.95%, respectively, which were significantly higher than those of the CG group (21.21%, 57.58%; $\chi^2 = 7.570$, $\chi^2 = 4.087$; both P < 0.05). These results confirm the superior efficacy of Almonertinib treatment (**Table 4**).

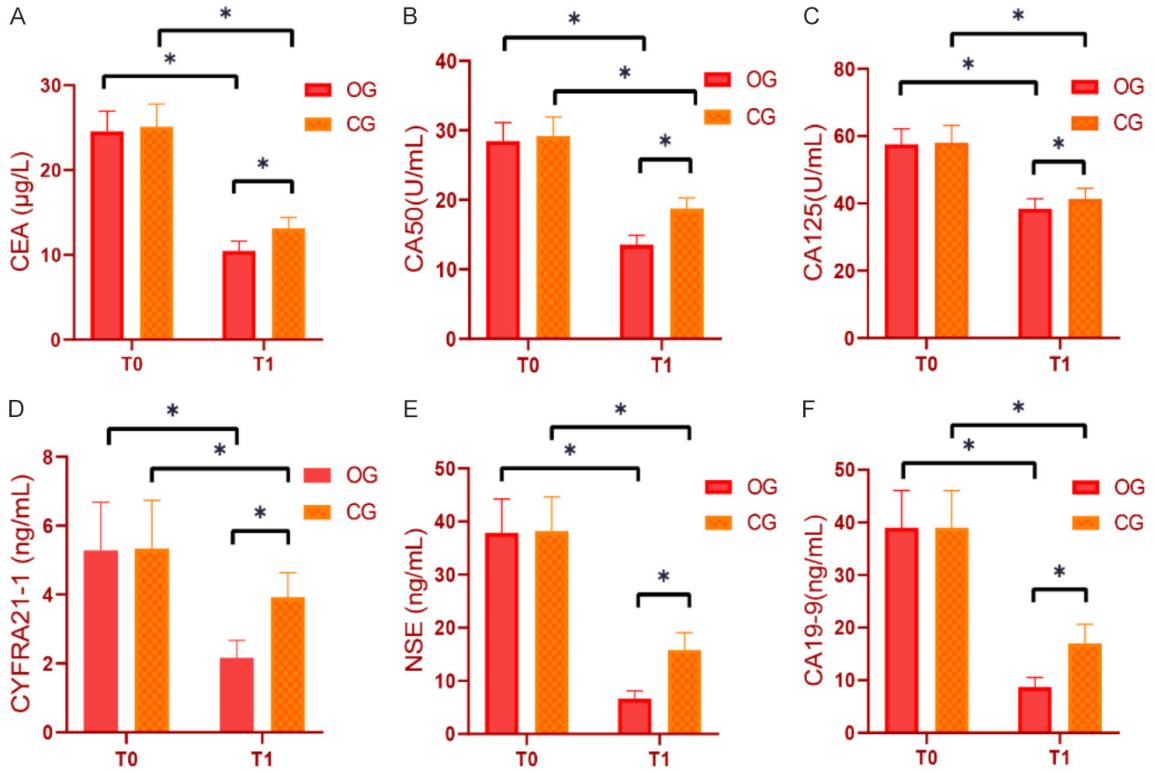

Figure 3. Comparison of serum tumor markers. Note: *P < 0.05; A: CEA; B: CA50; C: CA125; D: CYFRA21-1; E: NSE; F: CA19-9; CEA: carcinoembryonic antigen; CA50: carbohydrate antigen 50; CA125: carbohydrate antigen 125; CYFRA21-1: cyto-keratin 19 fragment antigen 21-1; NSE: neuron specific enolase; CA19-9: carbohydrate antigen 19-9; CG: control group; OG: observation group.

Table 2. Comparison of nodule size and nodule density ($\bar{x}$ ± sd)

Groups	Nodule size (mm)		Nodule density (HU)	
	T0	T1	T0	T1
OG group (n = 42)	12.63 ± 3.02	8.12 ± 2.26*	46.89 ± 10.12	21.56 ± 6.79*
CG group (n = 33)	12.45 ± 2.78	10.34 ± 2.47*	47.32 ± 9.56	37.18 ± 10.05*
t	0.255	-4.077	-0.211	-8.034
P	0.799	< 0.001	0.833	< 0.001

Note: VS the same group of T0: *P < 0.05. CG group: control group; OG group: observation group.

Comparison of adverse reactions

The adverse reaction rate in the OG group was 2.38%, significantly lower than the CG group's rate of 15.15% (χ^2 = 4.095, P = 0.043), indicating that Almonertinib treatment had better safety and higher patient tolerance (**Table 5**).

Discussion

Chronic inflammation is a key pathophysiologic feature of NSCLC. Studies have shown that IL-6 and IL-8 are associated with poor prognosis in NSCLC patients [23]. The results of this study demonstrated that levels of IL-6, TNF-α, and IL-8 were significantly lower in the OG group compared to the CG group at T1, suggesting that Almonertinib can significantly reduce pro-inflammatory factors in patients, thereby inhibiting tumor angiogenesis and slowing the progression of NSCLC.

Furthermore, CD3+, CD4+ and CD8+ are commonly used cellular immune markers to assess immune function, with unbalanced expression indicating immune dysfunction [24]. Impaired immune function can accelerate cancer progression and reduce drug tolerance [25]. Klum-

Table 3. Malignant risk probability of pulmonary nodules before and after treatment in patients with ground-glass nodules [M (P25, P75), %]

Model	Times	OG group (n = 42)	CG group (n = 33)	*Z*	*P*
Mayo model	T0	2.81 (2.08, 3.70)	2.93 (2.00, 3.89)	-1.564	0.118
	T1	2.05 (1.34, 4.06)	2.41 (1.46, 3.46)	-4.945	< 0.001
Z		-5.646	-4.048		
P		< 0.001	< 0.001		
Brock model	T0	0.96 (0.71, 1.31)	0.80 (0.44, 1.13)	-1.587	0.112
	T1	0.26 (0.14, 0.39)	0.43 (0.28, 0.67)	-2.207	0.027
Z		-5.390	-4.460		
P		< 0.001	< 0.001		

Note: CG group: control group; OG group: observation group.

Table 4. Comparison of clinical efficacy [n (%)]

Clinical efficacy	OG group (n = 42)	CG group (n = 33)	χ^2	*P*
CR	4 (9.52)	0 (0.00)		
PR	19 (45.24)	7 (21.21)		
SD	11 (26.19)	12 (36.36)		
PD	8 (19.05)	14 (42.42)		
ORR	22 (52.38)	7 (21.21)	8.677	0.003
DCR	34 (80.95)	19 (57.58)	4.872	0.027

Note: CG group: control group; OG group: observation group. CR: complete remission; PR: partial response; SD: stable disease; PD: progressive disease; ORR: Overall response rate; DCR: Disease control rate.

Table 5. Comparison of adverse reactions [n (%)]

Adverse Reaction	OG group (n = 42)	CG group (n = 33)	χ^2	*P*
Rash	1 (2.38)	2 (6.06)		
Nausea and vomiting	0 (0.00)	0 (0.00)		
Diarrhea	0 (0.00)	3 (9.09)		
Total rate	1 (2.38)	5 (15.15)	4.095	0.043

Note: CG group: control group; OG group: observation group.

per et al. [26] found that NSCLC patients exhibited a lower proportion of CD4+ T cells and NK cells, while CD8+ T cells were elevated, which improved following anti-tumor therapy. This study revealed that at T1, the OG group had higher levels of CD3+ and CD4+ and lower CD8+ levels compared to the CG group, aligning with previous findings. This suggests that Almonertinib promotes immune recovery, benefiting prognosis in patients with EGFR mutation-positive residual ground-glass nodules after stage I lung cancer resection. However, given that the immune microenvironment in EGFR-mutant patients is immunosuppressive, if resistance to Almonertinib develops, the immune microenvironment may shift, transforming the tumor into a "hot tumor" with enhanced immune function due to immune cell aggregation, but with diminished anticancer effects. Therefore, further studies are needed to validate these conclusions.

CEA, CA50, CA125, CYFRA21-1, NSE, and CA19-9 are common tumor markers associated with ovarian and lung cancers. These markers are typically expressed at low levels or are absent in healthy individuals, but their expression is significantly elevated in EGFR mutation-positive advanced NSCLC, with higher levels indicating more aggressive tumor invasion [27, 28]. This study showed that at T1, the OG group had higher ORR and DCR rates compared to the CG group, along with significantly lower serum levels of CEA, CA50, CA125, CYFRA21-1, NSE, and CA19-9, suggesting that Almonertinib offers superior therapeutic benefits for EGFR mutation-positive patients with residual ground-glass opacities post-stage I lung cancer surgery, possibly delaying disease progression more effectively. The reason for this may be that EGFR-TKIs significantly inhibit tyrosine kinase activity, promoting tumor cell apoptosis by blocking tumor neovascularization [29]. This effectively reduces tumor marker levels and slows disease progression.

Additionally, in this study, both nodule size and density decreased from T0 to T1 in both groups, with more significant reductions observed in the OG group compared to the CG group, indicating that Almonertinib can effectively reduce the volume and density of EGFR mutation-positive residual ground-glass nodules. This may be due to Almonertinib's highly efficient and selective third-generation irreversible EGFR-TKI action, wherein its electrophilic acrylamide acts as a Michael receptor, irreversibly binding to the corresponding ATP site and inhibiting EGFR phosphorylation. This prevents tumor cell proliferation and division, thereby reducing tumor growth and volume, and alleviating symptoms [17].

In this study, the Mayo model and Brock model were used to assess the malignant risk of pulmonary nodules. Both the ACCP lung cancer diagnosis and treatment guidelines [30] and the NCCN lung cancer screening guidelines [31] recommend the Mayo model for malignant risk assessment of pulmonary nodules. The Mayo model includes six independent lung cancer predictors: age, smoking history, history of thoracic malignancy (> 5 years before nodule detection), nodule diameter, spiculation, and upper lobe location. The Brock model, developed by Brock University, predicts the probability of malignant nodules based on CT signs, with an area under the receiver operating characteristic curve reaching 0.9 [32]. Its predictors include age, gender, family history of lung cancer, emphysema, nodule diameter, nodule characteristics, nodule number, upper lobe location, and spiculation. These two models complement each other in this study. The predictions from both models showed that Almonertinib reduced the malignant risk of nodules, suggesting that it may lower the likelihood of secondary surgery, benefitting patients' quality of life.

This study demonstrated that the OG group had superior overall efficacy and disease control rates compared to the CG group, confirming the potential of this therapeutic approach to improve disease management. Additionally, no serious adverse reactions associated with Almonertinib were observed. Most adverse events were mild, including rash, nausea, vomiting, diarrhea, and liver injury, indicating that Almonertinib is generally well tolerated and safe for patients with EGFR mutation-positive residual ground-glass nodules after stage I lung cancer resection. The low affinity of Almonertinib's degradation products for EGFR and their weak inhibitory effects likely contribute to the reduced incidence of common side effects, such as diarrhea and rash [33, 34]. However, despite the low incidence of adverse reactions, close monitoring is still necessary, and appropriate interventions should be taken when needed.

Drug resistance remains a major challenge for molecularly targeted therapies in clinical use [35]. Resistance during treatment can lead to diminished or ineffective therapeutic outcomes. Therefore, understanding the mechanisms of drug resistance in targeted therapies is crucial in order to develop new treatment strategies to overcome it. This study acknowledges its limitations, particularly its retrospective design, which introduces inherent biases. The sample size is also small, which restricts the generalizability of the findings. Future multicenter studies are needed to further validate these results.

Almonertinib offers significant therapeutic advantages for patients with EGFR-mutated residual ground-glass opacities following stage I lung cancer resection. It effectively reduces inflammatory factors and tumor marker levels, slows disease progression, and mitigates the negative impact of chemotherapy on immune function.

Disclosure of conflict of interest

None.

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References

[1] Zheng RS, Zhang SW, Sun KX, Chen R, Wang SM, Li L, Zeng HM, Wei WW and He J. Cancer statistics in China, 2016. Zhonghua Zhong Liu Za Zhi 2023; 45: 212-220.

[2] Zheng RS, Chen R, Han BF, Wang SM, Li L, Sun KX, Zeng HM, Wei WW and He J. Cancer incidence and mortality in China, 2022. Zhonghua Zhong Liu Za Zhi 2024; 46: 221-231.

[3] Chen P, Liu Y, Wen Y and Zhou C. Non-small cell lung cancer in China. Cancer Commun (Lond) 2022; 42: 937-970.
[4] Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, Bruno DS, Chang JY, Chirieac LR, D'Amico TA, Dilling TJ, Dowell J, Gettinger S, Gubens MA, Hegde A, Hennon M, Lackner RP, Lanuti M, Leal TA, Lin J, Loo BW Jr, Lovly CM, Martins RG, Massarelli E, Morgensztern D, Ng T, Otterson GA, Patel SP, Riely GJ, Schild SE, Shapiro TA, Singh AP, Stevenson J, Tam A, Yanagawa J, Yang SC, Gregory KM and Hughes M. NCCN guidelines insights: non-small cell lung cancer, version 2.2021. J Natl Compr Canc Netw 2021; 19: 254-266.
[5] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-249.
[6] Lahiri A, Maji A, Potdar PD, Singh N, Parikh P, Bisht B, Mukherjee A and Paul MK. Lung cancer immunotherapy: progress, pitfalls, and promises. Mol Cancer 2023; 22: 40.
[7] Maomao C, He L, Dianqin S, Siyi H, Xinxin Y, Fan Y, Shaoli Z, Changfa X, Lin L, Ji P and Wanqing C. Current cancer burden in China: epidemiology, etiology, and prevention. Cancer Biol Med 2022; 19: 1121-38.
[8] Lee K, Kim HR, Park SI, Kim DK, Kim YH, Choi S and Lee GD. Natural progression of ground-glass nodules after curative resection for non-small cell lung cancer. J Korean Med Sci 2021; 36: e266.
[9] Passaro A, Mok T, Peters S, Popat S, Ahn MJ and de Marinis F. Recent advances on the role of EGFR tyrosine kinase inhibitors in the management of NSCLC with uncommon, non exon 20 insertions, EGFR mutations. J Thorac Oncol 2021; 16: 764-773.
[10] Passaro A, Mok T, Peters S, Popat S, Ahn MJ and de Marinis F. Recent advances on the role of EGFR tyrosine kinase inhibitors in the management of NSCLC with uncommon, non exon 20 insertions, EGFR mutations. J Thorac Oncol 2021; 16: 764-773.
[11] Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, Heeroma K, Itoh Y, Cornelio G and Yang PC. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol 2014; 9: 154-62.
[12] Arbour KC and Riely GJ. Systemic therapy for locally advanced and metastatic non-small cell lung cancer: a review. JAMA 2019; 322: 764-774.
[13] Lee HJ, Jeong GH, Li H, Kim MS, Kim JS, Park SJ, Han YJ, Lee KH, Kronbichler A, Hong SH, Ghayda RA, Luchini C, Nottegar A, Koyanagi A, Smith L, Jacob L, Dragioti E, Radua J, Cargnin S, Terrazzino S, Thompson T, Yon DK, Lee SW, Yang JM, Wasuwanich P, Shin JI and Gamerith G. Efficacy and safety of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) monotherapy for advanced EGFR-mutated non-small cell lung cancer: systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2021; 25: 6232-6244.
[14] Huang J and Wang H. Targeted therapy and mechanism of drug resistance in non-small cell lung cancer with epidermal growth factor receptor gene mutation. Zhongguo Fei Ai Za Zhi 2022; 25: 183-192.
[15] Lu S, Wang Q, Zhang G, Dong X, Yang CT, Song Y, Chang GC, Lu Y, Pan H, Chiu CH, Wang Z, Feng J, Zhou J, Xu X, Guo R, Chen J, Yang H, Chen Y, Yu Z, Shiah HS, Wang CC, Yang N, Fang J, Wang P, Wang K, Hu Y, He J, Wang Z, Shi J, Chen S, Wu Q, Sun C, Li C, Wei H, Cheng Y, Su WC, Hsia TC, Cui J, Sun Y, Ou SI, Zhu VW and Chih-Hsin Yang J. Efficacy of Aumolertinib (HS-10296) in patients with advanced EGFR T790M+ NSCLC: updated post-national medical products administration approval results from the APOLLO registrational trial. J Thorac Oncol 2022; 17: 411-422.
[16] Li L. Two non-small cell lung cancer (NSCLC) patients with brain metastasis harboring epidermal growth factor receptor (EGFR) G719X and L861Q mutations benefited from aumolertinib: two cases report and review of the literature. Heliyon 2022; 8: e10407.
[17] Lu S, Dong X, Jian H, Chen J, Chen G, Sun Y, Ji Y, Wang Z, Shi J, Lu J, Chen S, Lv D, Zhang G, Liu C, Li J, Yu X, Lin Z, Yu Z, Wang Z, Cui J, Xu X, Fang J, Feng J, Xu Z, Ma R, Hu J, Yang N, Zhou X, Wu X, Hu C, Zhang Z, Lu Y, Hu Y, Jiang L, Wang Q, Guo R, Zhou J, Li B, Hu C, Tong W, Zhang H, Ma L, Chen Y, Jie Z, Yao Y, Zhang L, Jie W, Li W, Xiong J, Ye X, Duan J, Yang H, Sun M, Sun C, Wei H, Li C, Ali SM, Miller VA and Wu Q. AENEAS: a randomized phase III trial of Aumolertinib versus gefitinib as first-line therapy for locally advanced or metastatic non-small-cell lung cancer with EGFR exon 19 deletion or L858R mutations. J Clin Oncol 2022; 40: 3162-3171.
[18] Liu Y, Ge X, Pang J, Zhang Y, Zhang H, Wu H, Fan F and Liu H. Restricting glutamine uptake enhances NSCLC sensitivity to third-generation EGFR-TKI Almonertinib. Front Pharmacol 2021; 12: 671328.
[19] van Riel SJ, Ciompi F, Jacobs C, Winkler Wille MM, Scholten ET, Naqibullah M, Lam S, Prokop M, Schaefer-Prokop C and van Ginneken B. Malignancy risk estimation of screen-detected nodules at baseline CT: comparison of the Pan-

Can model, lung-RADS and NCCN guidelines. Eur Radiol 2017; 27: 4019-4029.
[20] Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD and Edell ES. The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. Arch Intern Med 1997; 157: 849-55.
[21] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.
[22] Liu K, Jiang G, Zhang A, Li Z and Jia J. Icotinib is as efficacious as gefitinib for brain metastasis of EGFR mutated non-small-cell lung cancer. BMC Cancer 2020; 20: 76.
[23] Giatromanolaki A, Harris AL, Banham AH, Contrafouris CA and Koukourakis MI. Carbonic anhydrase 9 (CA9) expression in non-small-cell lung cancer: correlation with regulatory FOXP3+T-cell tumour stroma infiltration. Br J Cancer 2020; 122: 1205-1210.
[24] Wu Z, Zheng Y, Sheng J, Han Y, Yang Y, Pan H and Yao J. CD3+CD4-CD8- (double-negative) T cells in inflammation, immune disorders and cancer. Front Immunol 2022; 13: 816005.
[25] Stankovic B, Bjørhovde HAK, Skarshaug R, Aamodt H, Frafjord A, Müller E, Hammarström C, Beraki K, Bækkevold ES, Woldbæk PR, Helland Å, Brustugun OT, Øynebråten I and Corthay A. Immune cell composition in human non-small cell lung cancer. Front Immunol 2019; 9: 3101.
[26] Klümper N, Saal J, Berner F, Lichtensteiger C, Wyss N, Heine A, Bauernfeind FG, Ellinger J, Brossart P, Diem S, Schmid S, Joerger M, Frueh M, Ritter M, Hölzel M, Flatz L and Bald T. C reactive protein flare predicts response to checkpoint inhibitor treatment in non-small cell lung cancer. J Immunother Cancer 2022; 10: e004024.
[27] Saad HM, Tourky GF, Al-Kuraishy HM, Al-Gareeb AI, Khattab AM, Elmasry SA, Alsayegh AA, Hakami ZH, Alsulimani A, Sabatier JM, Eid MW, Shaheen HM, Mohammed AA, Batiha GE and De Waard M. The potential role of MUC16 (CA125) biomarker in lung cancer: a magic biomarker but with adversity. Diagnostics (Basel) 2022; 12: 2985.
[28] Cheng C, Yang Y, Yang W, Wang D and Yao C. The diagnostic value of CEA for lung cancer-related malignant pleural effusion in China: a meta-analysis. Expert Rev Respir Med 2022; 16: 99-108.
[29] Almalki FA, Shawky AM, Abdalla AN and Gouda AM. Icotinib, Almonertinib, and Olmutinib: a 2D similarity/docking-based study to predict the potential binding modes and interactions into EGFR. Molecules 2021; 26: 6423.
[30] Mazzone PJ, Silvestri GA, Souter LH, Caverly TJ, Kanne JP, Katki HA, Wiener RS and Detterbeck FC. Screening for lung cancer: CHEST guideline and expert panel report. Chest 2021; 160: e427-e494.
[31] Wood DE, Kazerooni EA, Aberle D, Berman A, Brown LM, Eapen GA, Ettinger DS, Ferguson JS, Hou L, Kadaria D, Klippenstein D, Kumar R, Lackner RP, Leard LE, Lennes IT, Leung ANC, Mazzone P, Merritt RE, Midthun DE, Onaitis M, Pipavath S, Pratt C, Puri V, Raz D, Reddy C, Reid ME, Sandler KL, Sands J, Schabath MB, Studts JL, Tanoue L, Tong BC, Travis WD, Wei B, Westover K, Yang SC, McCullough B and Hughes M. NCCN Guidelines® Insights: lung cancer screening, version 1.2022. J Natl Compr Canc Netw 2022; 20: 754-764.
[32] McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, Yasufuku K, Martel S, Laberge F, Gingras M, Atkar-Khattra S, Berg CD, Evans K, Finley R, Yee J, English J, Nasute P, Goffin J, Puksa S, Stewart L, Tsai S, Johnston MR, Manos D, Nicholas G, Goss GD, Seely JM, Amjadi K, Tremblay A, Burrowes P, MacEachern P, Bhatia R, Tsao MS and Lam S. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med 2013; 369: 910-9.
[33] Yang JC, Camidge DR, Yang CT, Zhou J, Guo R, Chiu CH, Chang GC, Shiah HS, Chen Y, Wang CC, Berz D, Su WC, Yang N, Wang Z, Fang J, Chen J, Nikolinakos P, Lu Y, Pan H, Maniam A, Bazhenova L, Shirai K, Jahanzeb M, Willis M, Masood N, Chowhan N, Hsia TC, Jian H and Lu S. Safety, efficacy, and pharmacokinetics of Almonertinib (HS-10296) in pretreated patients with EGFR-mutated advanced NSCLC: a multicenter, open-label, phase 1 trial. J Thorac Oncol 2020; 15: 1907-1918.
[34] Zhang Y, Zhang Y, Niu W, Ge X, Huang F, Pang J, Li X, Wang Y, Gao W, Fan F, Li S and Liu H. Experimental study of Almonertinib crossing the blood-brain barrier in EGFR-mutant NSCLC brain metastasis and spinal cord metastasis models. Front Pharmacol 2021; 12: 750031.
[35] Jin H, Wang L and Bernards R. Rational combinations of targeted cancer therapies: background, advances and challenges. Nat Rev Drug Discov 2023; 22: 213-234.