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Tislelizumab plus chemotherapy for patients with *EGFR*-mutated non-squamous non-small cell lung cancer who progressed on EGFR tyrosine kinase inhibitor therapy

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ABSTRACT

Background Treatment options are limited for epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) after treatment failure with EGFR tyrosine kinase inhibitors (TKIs). This multicenter open-label, phase II study aims to evaluate the efficacy and safety of tislelizumab plus chemotherapy (cohort 1, TIS+chemo) or tislelizumab plus chemotherapy and bevacizumab (cohort 2, TIS+chemo+ beva) in EGFR-mutated non-squamous NSCLC patients who progressed on EGFR TKI therapies. Here, the primary analysis of the TIS+chemo cohort is reported.

Methods In the TIS+chemo cohort, patients with EGFR-sensitizing mutations with prior EGFR TKI failure received tislelizumab plus carboplatin and nab-paclitaxel as induction treatment, followed by maintenance with tislelizumab plus pemetrexed. The primary endpoint was 1-year progression-free survival (PFS) rate. The planned sample size was 66 with a historical control of 7%, an expected value of 20%, a one-sided α of 0.05, and a power of 85%.

Results Between July 11, 2020 and December 13, 2021, 69 patients were enrolled. As of June 30, 2022, the median follow-up was 8.2 months. Among the 62 patients in the efficacy analysis set, estimated 1-year PFS rate was 23.8% (90% CI 13.1% to 36.2%), and its lower bound of 90% CI was higher than the historical control of chemotherapy (7%), which met the primary endpoint. The median PFS was 7.6 (95% CI 6.4 to 9.8) months. Median overall survival (OS) was not reached (95% CI 14.0 to not estimable), with a 1-year OS rate of 74.5% (95% CI 56.5% to 86.0%). The objective response rate and disease control rate were 56.5% (95% CI 43.3% to 69.0%) and 87.1% (95% CI 76.1% to 94.3%), respectively. Patients who had progressed on first-generation/second-generation and third-generation EGFR-TKIs at baseline had shorter PFS than those who progressed on first-generation/second-generation EGFR-TKIs (median 7.5 vs 9.8 months, p=0.031). Patients with positive ctDNA had shorter PFS (median 7.4 vs 12.3 months, p=0.031) than those with negative ctDNA. No grade 5 treatment-emergent adverse events (TEAEs) were observed. Grades 3–4 TEAEs occurred in 40.6% (28/69) of patients. Grades 3–4 immune-related AEs occurred in 5 (7.2%) patients.

Conclusion The study met the primary endpoint for the TIS+chemo cohort. Tislelizumab plus chemotherapy is effective with an acceptable safety profile for *EGFR*-mutated non-squamous NSCLC after EGFR TKI failure.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The combination approach of PD-(L)1 antibody, platinum-based doublet chemotherapy and VEGF inhibitors represents a promising approach for patients who progressed on prior epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapies. However, concerns for the use of the combination in clinical practice may be related to its toxicity.

⇒ The exploration of combinations with lower toxicities is needed to improve the efficacy–risk balance for this patient population.

WHAT THIS STUDY ADDS

⇒ Tislelizumab plus carboplatin and nab-paclitaxel displays promising efficacy and favorable toxicity in patients who progressed on prior EGFR TKI therapies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of the TIS+chemo cohort provide evidence for the exploration of lower toxicity combinations; the TIS+chemo+ beva cohort was initiated and recruited to evaluate the efficacy and safety of tislelizumab plus nab-paclitaxel and bevacizumab.

BACKGROUND

Lung cancer is the leading cause of cancer death globally.[1] The epidemiology in Asian populations is different from that in Western populations, with a high incidence of epidermal growth factor receptor

(EGFR)-activating gene mutations in up to 47% of lung adenocarcinoma cases.[2–4] EGFR tyrosine kinase inhibitors (TKIs) are the standard initial treatment for patients with *EGFR*-mutated non-squamous non-small cell lung cancer (NSCLC).[5 6] Despite high initial response rates, almost all patients inevitably develop resistance to EGFR TKIs, and median progression-free survival (PFS) ranges from 8.0 to 19.3 months with first-line TKI treatment.[7–10] For those who had disease progression on first-generation or second-generation TKIs without the T790M mutation and those who progressed after receiving a third-generation TKI, treatment options are limited,[10] and among them, platinum-based chemotherapy is still the standard therapy in this setting.[10] However, it offers a low response rate and minimal survival benefits.[11] Therefore, novel treatment options are needed for patients with *EGFR*-mutated NSCLC who progressed on prior EGFR TKI therapy.

In recent decades, immune checkpoint inhibitors (ICIs) have revolutionized the treatment for patients with advanced or metastatic NSCLC without driver gene mutations.[12] Despite disappointing results with PD-(L)1 antibody monotherapy for TKI-resistant *EGFR*-mutated metastatic NSCLC,[13] the combination approach of PD-(L)1 antibody, chemotherapy, and VEGF inhibitors may represent a promising approach in this setting. A subgroup analysis of the phase III IMpower150 study first showed that the PD-L1 inhibitor atezolizumab plus bevacizumab and chemotherapy (ABCP regimen) had good efficacy in patients with metastatic *EGFR*-mutated NSCLC who failed prior TKI therapy.[14] Recently, the phase III ORIENT-31 trial reported that sintilimab combined with bevacizumab biosimilar IBI305 plus chemotherapy could significantly prolong PFS compared with chemotherapy alone in this patient population.[15] However, even though the combination produced survival benefits, concerns for the use of the combination in clinical practice may be related to its toxicity considering the high rate of grade 3 or worse adverse events and treatment withdrawal. Therefore, the exploration of combinations with lower toxicities is urgently needed to improve the efficacy–risk balance for this patient population.

Tislelizumab is a humanized PD-1 monoclonal antibody with a high binding affinity for PD-1 and has been engineered to minimize Fcγ receptor binding on macrophages.[16 17] It has shown improved efficacy when combined with chemotherapy and is generally well tolerated in patients with *EGFR* wild-type (*EGFR*-wt) advanced NSCLC.[18 19] With the aim of exploring a regimen with a favorable efficacy–risk balance, this study included a comprehensive patient population who progressed after EGFR TKIs to evaluate the efficacy and safety of tislelizumab plus chemotherapy (cohort 1, TIS+chemo) or tislelizumab plus platinum-free chemotherapy and bevacizumab (cohort 2, TIS+chemo+beva). Here, we reported the primary analysis results of the TIS+chemo cohort.

METHODS

Study design and participants

This is a multicenter open-label, single-arm, phase II study with two cohorts to evaluate tislelizumab plus chemotherapy with or without bevacizumab in NSCLC patients who had progressed on prior TKIs. The study was conducted at six sites in China. Tislelizumab plus carboplatin and nab-paclitaxel was evaluated in cohort 1 (TIS+chemo), which had completed enrolment and is the focus of this article. After cohort 1 was recruited, cohort 2 (TIS+chemo+beva) was recruited to evaluate tislelizumab plus nab-paclitaxel and bevacizumab. This cohort is currently in the recruitment stage, and the results of cohort 2 will be reported separately once fully accrued. This study is registered with ClinicalTrials.gov, NCT04405674, and remains open as participants are actively being recruited in cohort 2.

Eligible patients were aged 18–75 years with histologically and/or cytologically confirmed locally advanced or metastatic non-squamous NSCLC (stage IIIB/C per AJCC eighth edition), ECOG PS of 0–1, and with *EGFR* sensitizing mutations who failed from prior EGFR TKIs including patients that progressed on (1) first-generation or second-generation EGFR TKIs with the absence of *EGFR* T790M mutation, (2) first-generation or second-generation EGFR TKIs with positive T790M mutation followed by third-generation EGFR TKI, or (3) third-generation EGFR TKI treatment as first-line therapy. A 14-day washout period was required before the initiation of the study treatment after EGFR TKI treatment. Patients were excluded if they had previously received immune checkpoint blockade therapies (eg, anti-PD-1, anti-PD-L1, CTLA-4) or systematic platinum-based chemotherapy for advanced disease.

Procedures/study treatment regimen

Patients in the TIS+chemo cohort (cohort 1) received intravenous tislelizumab 200 mg plus carboplatin area under the curve 5 mg/mL and nab-paclitaxel 260 mg/m^2 at day 1 for four cycles as induction therapy. Each cycle was 3 weeks. Following the induction phase, patients continued tislelizumab 200 mg and pemetrexed 500 mg/m^2 every 3 weeks as maintenance therapy. Treatment was continued for up to 24 months (including both the induction phase and maintenance phase) or until disease progression, intolerable toxicity, or no clinical benefit, whichever occurred first.

Endpoints and assessments

The primary endpoint was the 1-year PFS rate. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), PFS, overall survival (OS), and duration of response (DOR).

Tumor responses were assessed by the investigators using radiographic imaging per RECIST V.1.1 criteria. Scans were performed at baseline and then every 6 weeks (±7 days) during the first 6 months, every 9 weeks (±7 days) for the next 6 months, and every 12 weeks

(±7 days) thereafter until disease progression, withdrawal of informed consent or death.

Adverse events were continually monitored throughout the study from the time of informed consent to 90 days after the last dose or until initiation of new anticancer treatment, whichever occurred first. For immune-related adverse events (irAEs), evaluation and recording lasted until 90 days after the last dose of tislelizumab. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE V.5.0).

Next-generation sequencing

Next-generation sequencing (NGS) was performed in a CLIA-certified and CAP-accredited laboratory (Geneseeq Technology, Nanjing, China) as previously described.[20] In brief, circulating tumor DNA (ctDNA) from plasma collected at C1D1 was extracted. Hybridization enrichment was performed with customized xGen lockdown probes (Integrated DNA Technologies) targeting 425 cancer-relevant genes (Geneseeq). The target-enriched libraries were on-bead PCR amplified, purified, and then sequenced on the HiSeq4000 NGS platform (Illumina) to a mean sequencing depth of 5783X.

Mutation calling

Paired-end reads were aligned to the reference human genome (build hg19) using the Burrows-Wheeler Aligner,[21] followed by PCR deduplication (Picard, https://broadinstitute.github.io/picard/) and local realignment around indels and base quality score recalibration using GATK3.[22] SNVs and indels were identified using VarScan2[23] and were further filtered as follows: (1) read depth <20 and base quality <15; (2) variant allele frequency (VAF) <0.55% and variant reads <3 for hotspot mutations, and VAF<1% and variant reads <5 for other mutations; (3) >1% population frequency in the 1000G or ExAC database; and (4) through an internal database of recurrent sequencing errors. CNVs were analyzed with CNVkit,[24] with depth ratio cut-offs of above 2.0 and below 0.6. ctDNA positive or negative status was determined based on the presence or absence of detected genetic alterations.

Statistical analysis

The sample size of the TIS+chemo cohort was calculated based on the primary end point (1-year PFS rate) with a historical control of 7% of the chemotherapy arm in the IMPESS study.[11] A total of 66 patients were required to provide 85% power to show the higher efficacy of tislelizumab plus chemotherapy with a target 1-year PFS rate of 20% vs 7% of standard chemotherapy with a one-sided α of 0.05.

Efficacy was evaluated in the efficacy analysis set (EAS), which included patients receiving ≥1 dose of tislelizumab or chemotherapy and having completed ≥1 post-treatment tumor assessment unless treatment was discontinued before the first tumor assessment due to clinical disease progression or death. The 1-year PFS rate was estimated using the Kaplan-Meier method; corresponding 90% CIs were calculated based on Greenwood's formula.[25] Median PFS, OS, and DOR were estimated using the Kaplan-Meier method, and their two-sided 95% CIs were estimated using the Brookmeyer and Crowley method. The Clopper-Pearson method was used to calculate 95% CIs for ORR and DCR. The safety analysis set included all patients who received any dose of tislelizumab or chemotherapy. Safety results are presented descriptively.

Comparisons between groups were performed using Fisher's exact test for discrete variables and the Wilcoxon rank-sum test for continuous variables. For survival analyses, Kaplan-Meier curves were compared using the log-rank test, and HRs were calculated by the Cox proportional hazards model. A two-sided $p<0.05$ was considered significant. P values were adjusted for multiple hypothesis testing using the false discovery rate (FDR) adjustment method as appropriate. An adjusted $p<0.1$ was considered significant. Statistical tests were conducted with SAS V.9.4 and R V.3.5.2.

RESULTS

Patient characteristics

Between July 11, 2020 and December 13, 2021, a total of 110 patients were screened for enrolment, and 69 patients were enrolled in the TIS+chemo cohort (figure 1). The baseline demographics and disease characteristics of the TIS+chemo cohort are listed in table 1. Overall, the median age was 58 years (range: 33.0–76.0), and 38 (55.1%) patients were male. A total of 29.0% of patients were current or former smokers. 18.8% had stable brain metastases at baseline. The most common *EGFR* mutation types at diagnosis were mostly as expected, with exon 19 deletion and exon 21 L858R each contributing nearly half of the group (56.5% and 40.6%, respectively); 29.0% harbored exon 20 T790M mutation before enrolment. All patients received EGFR TKIs before starting the study therapy. Almost half (49.3%) of patients had progressed on third-generation EGFR TKIs after failure to respond to first-generation or second-generation EGFR TKI therapies. A total of 31.9% of patients received prior antiangiogenic treatment, and 17.4% were previously treated with systematic chemotherapy for advanced NSCLC.

As of June 30, 2022, the median study follow-up was 8.2 months (range, 0.03–22.0). A total of 23.2% (n=16) of patients remained on treatment. Fifty-three (76.8%) patients stopped study treatment, and the reasons for discontinuation included mainly disease progression (n=34, 49.3%), patient decisions (n=7, 10.1%), adverse events (n=6, 8.7%), and investigator decisions (n=4, 5.8%). Overall, the median duration of treatment was 24.4 weeks (range, 0.1–87.3), and the median number of tislelizumab treatment cycles was 8 (range, 1–23).

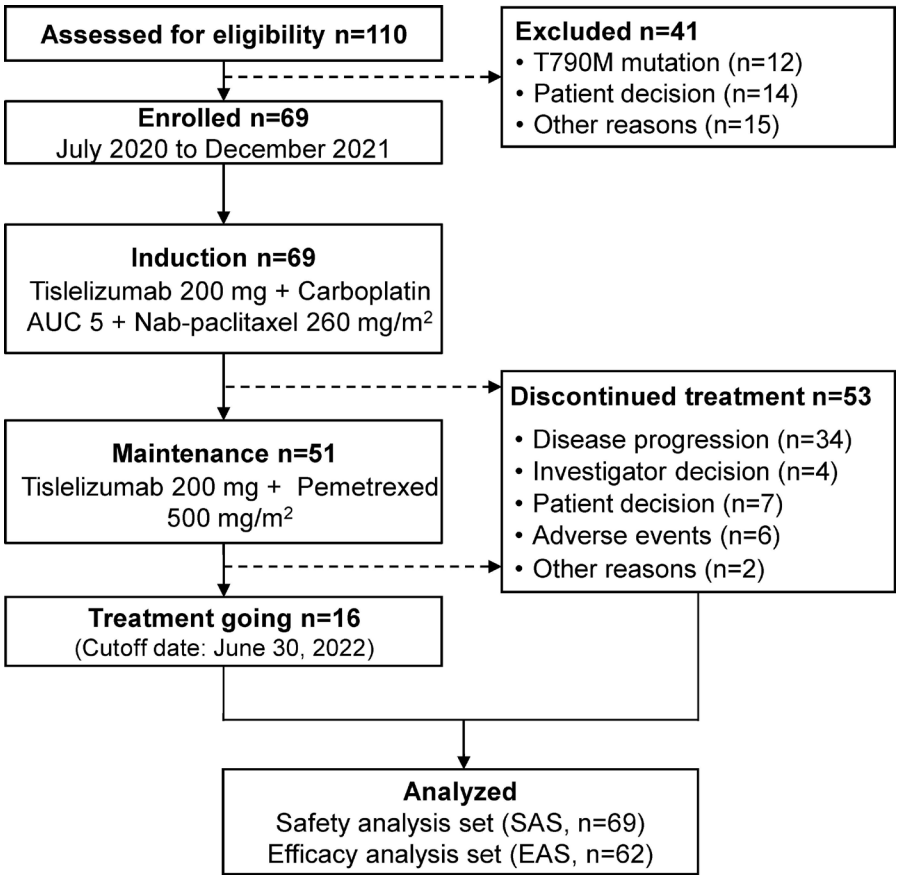

Figure 1 Patient flow and disposition.

Efficacy

Among the 62 patients in the EAS, the estimated 1-year PFS rate was 23.8% (90% CI 13.1% to 36.2%), and its lower bound of 90% CI was higher than the historical control of chemotherapy (7%), which met the primary endpoint. The median PFS was 7.6 (95% CI 6.4 to 9.8) months. Median OS was not reached (95% CI 14.0 months to not estimable (NE)). The 1-year OS rate was 74.5% (95% CI 56.5% to 86.0%). Kaplan-Meier analyses of PFS and OS survival curves are shown in figure 2.

The univariate analysis of PFS is shown in figure 3A. Smoking status, T790M mutation, prior antiangiogenic therapy, and prior systematic chemotherapy were not associated with PFS. Patients who had progressed on first-generation/second-generation and third-generation EGFR-TKIs had shorter PFS than those who failed only first-generation/second-generation EGFR-TKIs (median 7.5 vs 9.8, HR 2.17 (95% CI 1.07 to 4.42), p=0.031; figure 3A,B). Only seven patients progressed on first-line third-generation EGFR TKIs, and the median PFS was 5.7 (95% CI 1.4 to NE) months (figure 3B). Patients with exon 21 L858R mutation displayed a trend toward better PFS compared with patients with EGFR exon 19 deletion (median 10.1 vs 7.0 months, HR 0.50 (95% CI 0.26 to 1.04), p=0.056; figure 3C).

The ORR was 56.5% (95% CI 43.3% to 69.0%), with 35 patients achieving partial response (PR; including 4 unconfirmed PR) (online supplemental table S1, figure S1). Thirty-three patients (94.3%, out of 35 patients with BOR as PR) achieved a treatment response during the induction phase (online supplemental figure S2). Fifteen patients (45.5%, 15/33) showed further remission during the maintenance phase; 7 (21.2%, 7/33) patients achieved further tumor shrinkage of >10%. DCR was achieved by 54 (87.1%, 95% CI 76.1% to 94.3%) of 62 patients. The median time to response was 1.7 (95% CI 1.2 to 7.7) months. The median DOR was 6.1 (95% CI 4.7 to 10.3) months. The treatment response of each subgroup is shown in online supplemental table S1.

Safety and tolerability

Treatment-emergent adverse events (TEAEs) of any grade occurred in 65 (94.2%) patients. Grades 3–4 TEAEs occurred in 28 (40.6%) patients (online supplemental table S2). None of the patients experienced grade 5 TEAEs. Treatment-related adverse events (TRAEs) occurred in 65 (94.2%) patients. A total of 39.1% (27/69) experienced grades 3–4 TRAEs. As shown in table 2, the most common grades 3–4 TRAEs were decreased neutrophil count (17.4%), anemia (10.1%), decreased platelet count (10.1%), and decreased white cell count (8.7%). Grades 3–4 TRAEs occurred in 29.0% and 18.8% of patients during the induction phase and maintenance phase, respectively (online supplemental table S3). The incidence of adverse events tended to be higher during the induction phase than during the maintenance phase,

Table 1 Patient characteristics

	SAS (N=69)	EAS (N=62)
Age	58.0 (33.0, 76.0)	58.0 (33.0, 76.0)
BMI, kg/m^2	23.2 (16.5, 30.8)	23.1 (16.5, 30.8)
Sex, n (%)		
Male	38 (55.1)	33 (53.2)
Female	31 (44.9)	29 (46.8)
Ethnicity	69 (100)	62 (100)
Chinese	69 (100)	62 (100)
ECOG PS		
0	3 (4.3)	3 (4.8)
1	66 (95.7)	59 (95.2)
Smoking status		
Current or former smokers	20 (29.0)	17 (27.4)
Never smoked	49 (71.0)	45 (72.6)
Tumor histology		
Adenocarcinoma	68 (98.6)	61 (98.4)
NSCLC not otherwise specified	1 (1.4)	1 (1.6)
Site of metastasis		
Liver	8 (11.6)	5 (8.1)
CNS	13 (18.8)	11 (17.7)
Bone	24 (34.8)	22 (35.5)
Disease stage		
IIIB	2 (2.9)	2 (3.2)
IV	67 (97.1)	60 (96.8)
Prior EGFR mutation type		
Exon 19 deletion	39 (56.5)	35 (56.5)
Exon 21 L858R	28 (40.6)	26 (41.9)
Others*	2 (2.9)	1 (1.6)
EGFR T790M mutation		
Positive	20 (29.0)	18 (29.0)
Negative/unknown	49 (71.0)	44 (71.0)
Prior antitumor treatment		
Neoadjuvant/adjuvant	10 (14.5)	8 (12.9)
1L systematic therapy	65 (94.2)	59 (95.2)
2L systematic therapy	32 (46.4)	29 (46.8)
Prior EGFR TKI treatment		
First/second G TKI	26 (37.7)	23 (37.1)
Third G TKI	9 (13.0)	7 (11.3)
First/second G TKI+ third G TKI	34 (49.3)	32 (51.6)
Prior anti-angiogenesis treatment		
Yes	22 (31.9)	18 (29.0)
No	47 (68.1)	44 (71.0)
Prior systematic chemotherapy†		
Yes	12 (17.4)	11 (17.7)
No	57 (82.6)	51 (82.3)

Data are the median (range) and n (%).
*Others including patients with G719X or L861Q mutation.
†Patients received prior monotherapy or limited courses of doublet chemotherapy for advanced NSCLC.
CNS, central nervous system; EAS, efficacy analysis set; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; G, generation; 1L, first line; 2L, second line; NSCLC, non-small cell lung cancer; SAS, safety analysis set; TKI, tyrosine kinase inhibitor.

with mainly hematological toxicities related to carboplatin and nab-paclitaxel. TEAEs leading to treatment discontinuation occurred in 4 (5.8%) patients. Serious adverse events (SAEs) were reported in 13 (18.8%) patients. Grade 3 or 4 SAEs were reported in eight patients.

irAEs developed in 19 (27.5%) patients. Most of these events were grades 1–2 in severity (table 2). Grade 3 or 4 irAEs occurred in 5 (7.2%) patients. The most common (≥2 patients) irAEs were rash, immune-mediated

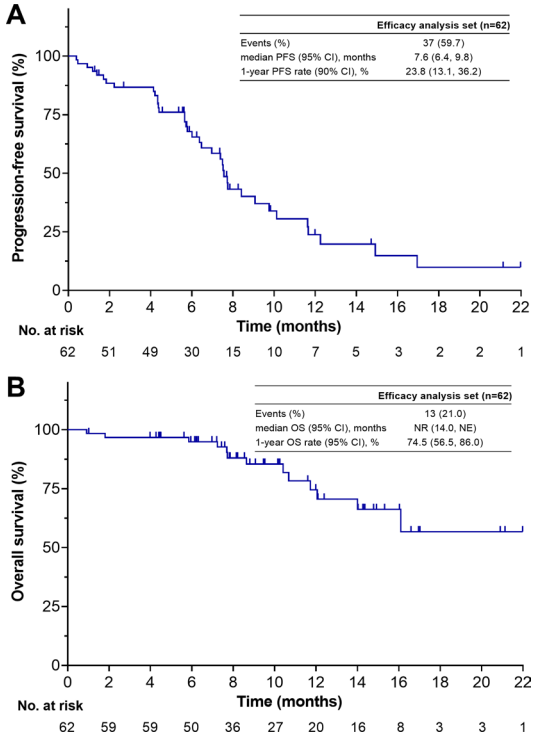

Figure 2 Kaplan-Meier plots for PFS (A) and OS (B). NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival.

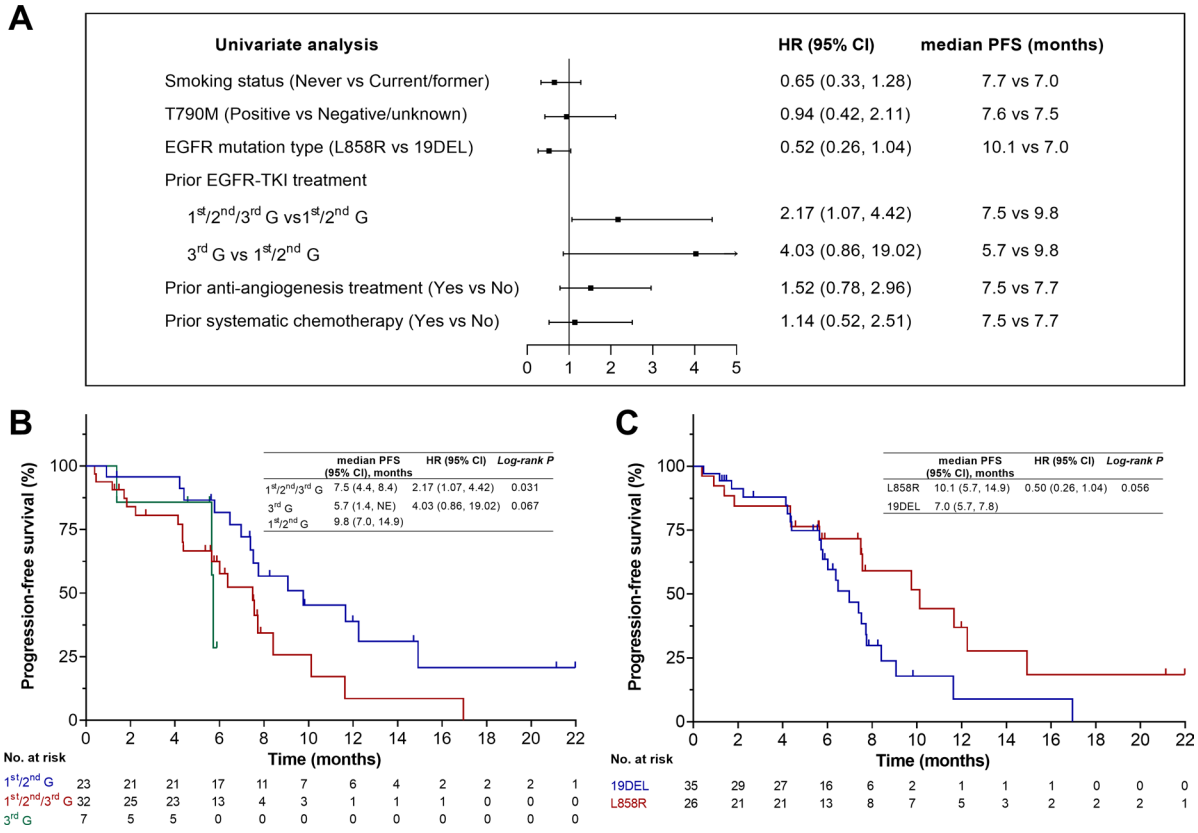

Figure 3 Univariate analysis of progression-free survival (PFS). (A) Forest plot of the association between clinicopathological variables and PFS; (B) Kaplan-Meier plot for PFS per prior EGFR-TKI treatment; (C) Kaplan-Meier plot for PFS per the EGFR mutation type (L858R vs 19DEL). 19DEL, 19 deletion; G, generation; NE, not estimable.

pulmonary disease, decreased platelet count, and decreased free thyroxine (table 2).

Genomic profiling in association with treatment efficacy

NGS was performed on baseline plasma samples from 57 patients in the EAS to detect ctDNA. The overall positive ctDNA detection rate was 75.4% (43/57). Patients with positive ctDNA had shorter PFS (median 7.4 vs 12.3 months, p=0.031; figure 4A) and OS (median 16.1 months vs NR; figure 4B) than those with negative ctDNA. Taking into consideration the VAF of EGFR (with a cut-off of 12%, online supplemental figure S3A,B), we found that patients with negative ctDNA exhibited the most favorable outcome, with PFS (online supplemental figure S3C) and OS (online supplemental figure S3D) significantly longer than those with high EGFR VAF (mPFS=12.3 vs 5.0, p=0.018; mOS=NR vs 14.0, p=0.007), as well as a trend toward longer PFS than those with low EGFR VAF (mPFS=12.3 vs 7.5, p=0.063; mOS=NR vs NR, p=0.29).

Among 43 patients with positive ctDNA in the EAS, 7 (16.3%) patients developed EGFR-dependent resistance mechanisms (T790M+C797S or T790M+L718Q), and 9 (20.9%) patients had downstream/bypass pathway activation (eg, KRAS G12C mutation, MET amplification, PTEN loss, ERBB2/PIK3CA activation). The mechanism of resistance was unknown in the other 27 patients (62.8%; figure 4C). Notably, no significant differences in PFS (figure 4D) and OS (figure 4E) were observed between patients with known and unknown EGFR TKI resistance mechanisms. Regarding the OS results, the data are preliminary, and longer follow-up is needed to obtain robust results.

We further evaluated the relationship between comutated genes and clinical outcomes. Our results showed that single-gene alterations in *PIK3CA* or *CTNNB1* were associated with poor prognosis (online supplemental table S4). Patients with mutations in *PIK3CA* (median PFS=4.1 vs 7.5 months, p=0.004; FDR adjusted p=0.018) or *CTNNB1* (median PFS=2.2 vs 7.5 months, p=0.004; FDR adjusted p=0.018) had worse PFS than those with wild-type genes (figure 4F,G; online supplemental table S4).

Additional exploratory analyses were conducted to evaluate the relationship between bTMB and clinical outcomes. The results showed that the levels of bTMB were comparable among patients with different treatment responses (online supplemental figure S4A). Moreover, increasing cut-off points of the bTMB score were not associated with PFS outcomes (online supplemental figure S4B).

DISCUSSION

In this study, the combination of tislelizumab plus chemotherapy had a favorable efficacy in patients with

Table 2 Most common (≥10%) TRAEs and irAEs (≥2 patients)

	Any grade	Grades 3–4
TRAEs		
Any TRAEs	65 (94.2)	27 (39.1)
Anemia	42 (60.9)	7 (10.1)
Decreased white cell count	36 (52.2)	6 (8.7)
Decreased neutrophil count	31 (44.9)	12 (17.4)
Decreased platelet count	28 (40.6)	7 (10.1)
Alopecia	23 (33.3)	0
Increased aspartate aminotransferase	20 (29.0)	0
Nausea	17 (24.6)	0
Hypoesthesia	15 (21.7)	0
Increased alanine aminotransferase	14 (20.3)	1 (1.4)
Rash	14 (20.3)	1 (1.4)
Hypercholesterolemia	13 (18.8)	0
Decreased lymphocyte count	13 (18.8)	4 (5.8)
Decreased hemoglobin	12 (17.4)	2 (2.9)
Constipation	10 (14.5)	0
Decreased appetite	10 (14.5)	0
Asthenia	9 (13.0)	0
Hypokalemia	8 (11.6)	1 (1.4)
Hyponatremia	8 (11.6)	0
Hypertriglyceridaemia	8 (11.6)	0
Increased blood lactate dehydrogenase	7 (10.1)	0
irAEs		
Any irAEs	19 (27.5)	5 (7.2)
Rash	8 (11.6)	1 (1.4)
Immune-mediated pulmonary disease	2 (2.9)	0
Decreased platelet count	2 (2.9)	2 (2.9)
Decreased free thyroxine	2 (2.9)	0

Data are n (%).
irAEs, immune-related adverse events; TRAEs, treatment-related adverse events.

advanced or metastatic *EGFR*-mutated NSCLC who had disease progression after previous EGFR TKI treatment. It met the protocol-defined primary outcome for the TIS+chemo cohort with a 1-year PFS rate of 23.8% (90% CI 13.1% to 36.2%), which was higher than the 7% of chemotherapy in the IMPRESS study.[11] The median PFS was 7.6 months (95% CI 6.4 to 9.8). The combination was generally well tolerated; TEAEs at grade 3–4 occurred in 40.6% of patients, and 4 (5.8%) patients had treatment withdrawal due to AEs. Additionally, clinically meaningful PFS and promising treatment responses were observed consistently in all subgroups.

At the time the current study was designed, only subgroup analysis of *EGFR*-positive patients of the IMpower150 study showed that ABCP produced a superior efficacy than the standard of care.[14] Subsequently, data on PD-1 antibody plus chemotherapy with or without VEGF inhibitors accumulated in patients who failed prior EGFR TKI therapies. In a phase II study, toripalimab plus carboplatin and pemetrexed reported a median PFS of 7.0 months as second-line treatment in patients treated with previous first-generation or second-generation EGFR-TKIs.[26] As the only phase III study in this setting, ORIENT-31 demonstrated, compared with chemotherapy alone, significantly prolonged PFS with sintilimab plus IBI305 (a bevacizumab biosimilar) plus chemotherapy (median 6.9 vs 4.3 months, HR 0.46 (95% CI 0.34 to 0.64), p<0.0001) and sintilimab plus chemotherapy (median 5.5 vs 4.3 months, HR 0.723, (95% CI 0.552 to 0.948); p=0.0181).[15 27] In line with these studies, we found that tislelizumab plus carboplatin and nab-paclitaxel was an effective treatment option with a median PFS of 7.6 (95% CI 6.4 to 9.8) months, which was even comparable with the combination of sintilimab plus IBI305 plus chemotherapy in ORIENT-31. Given the limited sample size and single-arm design, the results should be interpreted with caution. Nevertheless, all the studies indicated that patients who progressed after TKI therapy could benefit from the combination of PD-(L)1 antibody and chemotherapy.

We chose nab-paclitaxel plus carboplatin as the chemotherapy backbone in this study. The phase III CA031 trial showed that nab-paclitaxel plus carboplatin significantly improved the objective response rate compared with solvent-based paclitaxel plus carboplatin (33% vs 25%) in advanced NSCLC, and significantly reduced the occurrence of grade≥3 neuropathy, neutropenia, arthralgia, and myalgia.[28] In addition, albumin-bound paclitaxel does not require hormone pretreatment, which could avoid immunosuppression and thus maximize the efficacy of immunotherapy. The combination of nab-paclitaxel and carboplatin was selected as the combined chemotherapy backbone in phase III clinical studies of PD-(L)1 inhibitors, such as KEYNOT 407,[29] RATIONALE 307,[18] IMpower 130,[30] CHOICE 01,[31] and KEYNOTE 355.[32] In a dose-finding study, every 3-week treatment of nab-paclitaxel showed similar clinical benefit and safety profiles with weekly treatments.[33] In this cohort, we chose 260 mg/m^2 every 3 weeks of nab-paclitaxel for combination with the anti-PD-1 antibody. In addition, maintenance therapy with pemetrexed was chosen per the JMEN study, which demonstrated a survival benefit with good tolerability of switch-maintenance pemetrexed therapy.[34]

It is important to note that this treatment regimen has a favorable toxicity profile compared with previous reports of the combination of PD-(L)1 antibody plus chemotherapy and VEGF inhibitors. In ORIENT-31, grade≥3 TEAEs were reported in 55% of patients treated with sintilimab and IBI305 plus pemetrexed and cisplatin; 17% required withdrawal from treatment.[15] In the ABCP

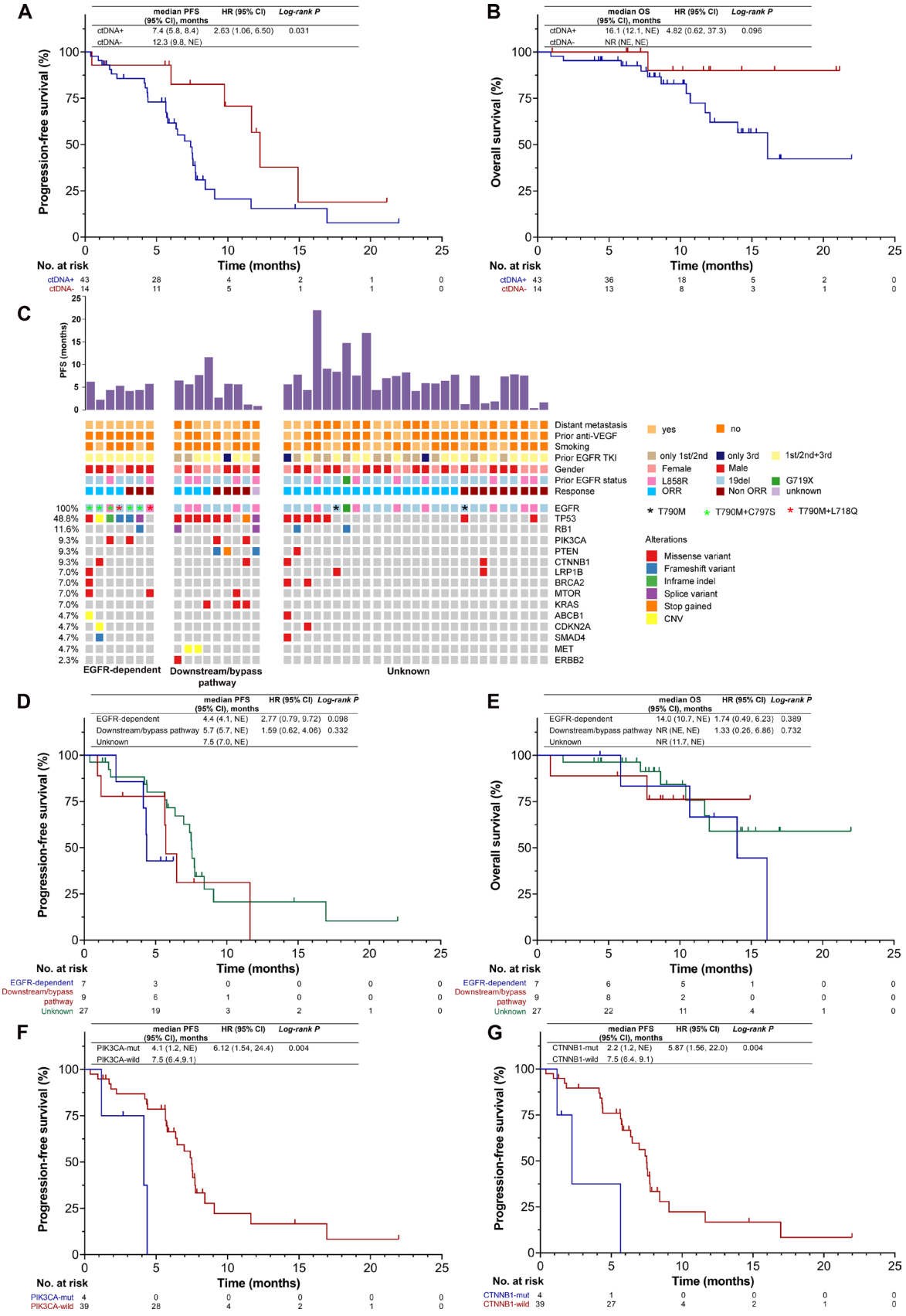

Figure 4 Genomic profiling in association with treatment efficacy. (A) PFS and (B) OS of patients with positive ctDNA versus negative ctDNA; (C) Mutational landscape of baseline plasma samples in 43 patients with positive ctDNA; (D) PFS and (E) OS of patients with different mechanisms of resistance to EGFR TKIs; (F) PFS in patients with PIK3CA mutation versus wild-type; (G) PFS in patients with CTNNB1 mutation versus wild-type. CNV, copy number variation; mut, mutation; NE, not estimable; NR, not reached; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; wild, wild-type.

arm of IMpower 150, 55.7% of patients developed grades 3–4 TRAEs, and 32.6% required withdrawal from treatment.[35] In this study, tislelizumab plus carboplatin and nab-paclitaxel displayed a trend of a low rate of grades 3–4 TEAEs (40.6%) and treatment withdrawal related to AEs (5.8%), which was similar to those with sintilimab plus chemotherapy in ORIENT-31 (grades 3–4 TEAEs: 46.2%; treatment withdrawal related to AEs: 10.3%). The incidence of pneumonitis was comparable with such combinations in patients with EGFR-wt NSCLC, such as 9% in RATIONALE 304 and 4.4% in KEYNOTE 189. In addition, no new safety signals were observed compared with previous studies of such regimens in *EGFR*-wt NSCLC patients.[18 19] The favorable toxicity profile may be partially related to the combination strategy without bevacizumab. In addition, this study excluded patients with interstitial lung disease that might be associated with pervious EGFR TKI treatment. A wash-out period was required after TKI treatment; a 2-week wash-out period was used before initiating tislelizumab plus chemotherapy in our study.

With advances in targeted therapy in recent decades, such as the approval of third-generation TKIs and the expansion of TKI-based treatment options, patients who progressed after TKI treatment became more complex. An increasing number of patients received third-generation TKIs, were treated with previous antiangiogenic therapy, or received limited cycles of chemotherapy before TKI treatment. In this study, comprehensive patient populations were included, which were close to NSCLC patients with EGFR TKI resistance in the real world. We further analyzed the relationship between patient characteristics and efficacy. Our results showed that smoking history, T790M mutation, prior antiangiogenesis, and prior chemotherapy for advanced disease were not associated with PFS or antitumor response. Interestingly, we found that patients who had progressed on first-generation/second-generation and third-generation EGFR-TKIs at baseline had shorter PFS than those who failed only first-generation/second-generation EGFR-TKIs (median 7.5 vs 9.8, p=0.031). For patients with the exon 21 L858R mutation, a tendency toward better PFS was observed compared with patients with the EGFR exon 19 deletion (median 10.1 vs 7.0 months, p=0.056). The observations were consistent with other reports.[15 26] In the TIS+chemo cohort, seven patients progressed after first-line third-generation TKI treatment. A favorable ORR of 57.1% was achieved in these patients, while the median PFS was 5.7 (95% CI 1.4 to NE) months. This may be related to the limited sample size, and thus needs further evaluation in a larger patient number.

As a non-invasive tool, ctDNA represents an attractive source of genetic material that enables assessment and dynamic monitoring of immunotherapy response. In this study, we found that 75.4% (43/57) of patients in the EAS had detectable ctDNA at baseline, and positive ctDNA was associated with unfavorable PFS, which was in line with previous findings.[36 37] Monitoring ctDNA dynamics in patients treated with ICIs could open the door to a broader application of biomarker-directed ICIs.[38] Therefore, in cohort 2 of our trial, ctDNA assays will be conducted both at baseline and during study treatment. The mechanisms of acquired resistance to TKI treatment are highly complex. Possible mechanisms include EGFR-dependent and downstream/bypass pathway mechanisms. However, nearly half of the resistance mechanisms remain unknown.[39] In our study, the mechanism of resistance was unknown in 62.8% of patients; while 16.3% developed EGFR-dependent resistance, and 20.9% had downstream/bypass pathway activation. We further analyzed whether resistance mechanisms were related to efficacy. Notably, no significant differences in PFS or OS were observed between patients with known and unknown EGFR TKI resistance mechanisms. Moreover, although limited by the small number of mutation-positive patients, our study identified alterations in *PIK3CA* and *CTNNB1* as potential genetic predictors for worse PFS. *PIK3CA* may predict a poor response to immunotherapy by driving immune evasion because of an altered immune microenvironment.[40 41] Patients with mutant *CTNNB1* also had a poor response to ICIs, likely due to the reduction in activated immune cells.[42] Future large-scale studies are needed to confirm the predictive value of *PIK3CA* and *CTNNB1*.

This study had several limitations. First, the study is a single-arm phase II trial with a limited number of patients. Second, the primary endpoint was assessed by investigators, and bias may exist in the absence of a central blinded review of PFS. Third, although we included comprehensive patient populations, such as patients with prior chemotherapy and with anti-angiogenic treatment, the sample size was relatively small in each subgroup. Therefore, the results should be cautiously interpreted, and validation in a larger patient population is needed.

CONCLUSIONS

In summary, the study met the primary endpoint for the TIS+chemo cohort. Compared with historical chemotherapy data, tislelizumab plus chemotherapy has better efficacy with an acceptable safety profile for patients with *EGFR*-mutated non-squamous NSCLC after EGFR TKI failure.

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