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ORIGINAL RESEARCH

Taxanes Versus Pemetrexed After Osimertinib Resistance in EGFR-Mutated NSCLC: A Retrospective Cohort with Two-Model In Vitro Validation

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Purpose: To evaluate whether chemotherapy backbone selection influences outcomes in epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) after acquired resistance to osimertinib, addressing the absence of a preferred post-osimertinib chemotherapy approach.

Methods: Outcomes were retrospectively compared between taxane-based and pemetrexed-based chemotherapy using propensity score matching and multivariable Cox models; progression was stratified as gradual or dramatic. An exploratory in vitro assay compared chemosensitivity between osimertinib-resistant sublines and parental cells.

Results: After 1:1 matching, taxanes showed numerically longer progression-free survival (PFS; median 8.8 vs 7.9 months; hazard ratio [HR]: 0.71, 95% confidence interval [CI]: 0.48–1.03) and overall survival (OS; 18.8 vs 15.9 months; HR: 0.70, 95% CI: 0.45–1.09) versus pemetrexed, without statistical significance. In the gradual-progression cohort, outcomes were comparable. By contrast, in the dramatic-progression cohort, taxanes were associated with longer PFS (7.7 vs 6.4 months; HR: 0.51, 95% CI: 0.30–0.86; P=0.009) and OS (16.1 vs 12.7 months; HR: 0.54, 95% CI: 0.30–0.97; P=0.034). Multivariable analysis identified taxanes as an independent favorable factor in dramatic progression for PFS (adjusted hazard ratio [aHR]: 0.48, 95% CI: 0.27–0.84; P=0.011) and OS (aHR: 0.51, 95% CI: 0.27–0.96; P=0.036). Non-hematologic toxicities were more frequent with taxanes than pemetrexed (56/74, 75.7% vs 52/95, 54.7%). Additionally, osimertinib-resistant sublines exhibited reduced half-maximal inhibitory concentration (IC50) to taxanes versus parental cells (P<0.05).

Conclusion: Taxane-based chemotherapy was associated with more favorable outcomes than pemetrexed in dramatic progression after osimertinib resistance, with higher non-hematologic toxicity. These findings, supported by exploratory in vitro sensitivity, warrant prospective validation.

Keywords: osimertinib, acquired resistance, NSCLC, EGFR, chemosensitivity

Introduction

Lung cancer remains the leading cause of cancer mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for about 85% of cases.[1,2] Activating epidermal growth factor receptor (EGFR) mutations—predominantly exon 19 deletions and L858R—define a subset deriving substantial benefit from EGFR tyrosine kinase inhibitors (EGFR-TKIs).[3] Osimertinib, a third-generation, irreversible EGFR-TKI with central nervous system activity, is the standard first-line therapy for EGFR-mutant NSCLC given superior progression-free and overall survival versus earlier-generation TKIs.[4,5] Nonetheless, acquired resistance is nearly universal, creating an unmet need for effective

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post-progression strategies. In practice, platinum doublets or single-agent chemotherapy (eg, taxanes, pemetrexed, gemcitabine) are commonly used, yet head-to-head evidence guiding selection after osimertinib resistance remains limited.[6]

Osimertinib resistance arises through diverse and often overlapping mechanisms. On-target alterations include EGFR C797S and other tertiary mutations; off-target and bypass routes include MET or HER2 amplification, PIK3CA or BRAF mutations, KRAS activation, gene fusions, and histologic transformation to small-cell or squamous phenotypes.[7–9] Epithelial–mesenchymal transition (EMT), lineage plasticity, and microenvironmental remodeling also contribute to drug tolerance and resistance.[10–13] Although targeted approaches (eg, MET inhibition, amivantamab-based strategies, fourth-generation EGFR inhibitors, and combinations with anti-angiogenic or immune checkpoint agents) are being explored, many patients lack actionable alterations, and prospective data showing durable benefit across heterogeneous resistance contexts remain sparse.[3,6] Chemotherapy therefore retains a central role after osimertinib failure.

Both pemetrexed and taxanes are guideline-endorsed options post-osimertinib, but mechanistic considerations suggest that certain resistance states may favor microtubule-targeting agents. EMT, a recurrent feature of acquired EGFR-TKI resistance, remodels the cytoskeleton, increases microtubule dependence, and engages regulators (eg, AKT/FOXM1, Notch) that influence microtubule dynamics and mitotic vulnerability, providing a biologic rationale for heightened taxane activity in EMT-enriched settings.[14–16] Changes in tubulin isotypes and microtubule stability with EMT and lineage plasticity may further modulate drug–microtubule interactions,[10,12,17] while upregulation of efflux pumps (eg, ABCB1) can differentially impact chemotherapy classes.[18,19] These links remain hypothesis-generating, and comparative clinical and mechanistic evidence between pemetrexed and taxanes after osimertinib resistance is still lacking.

Clinically, post-EGFR-TKI progression patterns are heterogeneous and can be stratified as dramatic, gradual, or local, reflecting tumor kinetics, symptom burden, and disease dynamics that inform treatment selection.[20,21] Cohort data suggest that cytotoxic chemotherapy may benefit dramatic progression, whereas gradual progression may be managed with continued EGFR-TKI, lower-intensity chemotherapy, or local therapy.[22–24] Thus, evaluating whether progression patterns inform chemotherapy selection is warranted.

Accordingly, this study retrospectively compares taxane- versus pemetrexed-based chemotherapy after osimertinib resistance in EGFR-mutant NSCLC, with prespecified stratification by dramatic versus gradual progression. An exploratory in vitro analysis examines relative chemosensitivity to taxanes and pemetrexed in osimertinib-resistant sublines versus parental cells, and reporting follows STROBE (retrospective cohort) and MDAR (in vitro).

Materials and Methods

Patient Selection

We systematically searched the electronic databases at General Hospital of Southern Theater Command to identify eligible patients diagnosed with NSCLC from June 2020 to June 2024 (Figure 1). Inclusion criteria were: (1) histologically confirmed lung adenocarcinoma; (2) stage IIIB–IV disease (AJCC 8th edition);[25] (3) documented EGFR-sensitizing mutation (exon 19 deletion or L858R); (4) extensive (non-local) progression on osimertinib attributable to acquired resistance; and (5) receipt of ≥2 cycles of taxane- or pemetrexed-based chemotherapy with complete clinical data. Exclusion criteria included: (1) histologic transformation after osimertinib resistance; (2) fewer than 2 cycles of chemotherapy or lack of response assessment; and (3) incomplete clinical information. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments, and was approved by the institutional ethics committee (NZLLKZ2024107).

Treatment and Outcomes

We compared the effectiveness and safety of pemetrexed- versus taxane-based chemotherapy in advanced NSCLC after osimertinib resistance. Regimens were selected at treating physicians' discretion based on clinical judgment, prior therapies, and local practice. Within each backbone, patients could also receive platinum, programmed cell death protein 1 (PD-1) inhibitors, and/or bevacizumab; these concomitant treatments were not mutually exclusive. The chemotherapy

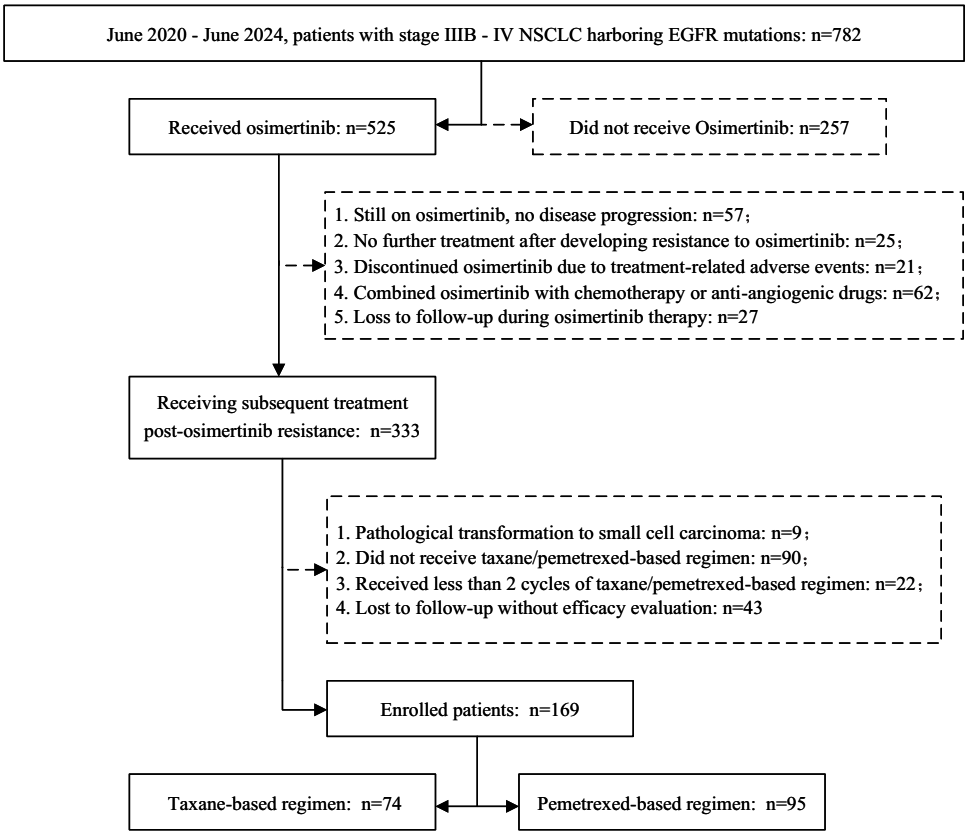

Figure 1 Flowchart of patient enrollment.

backbone was the primary exposure, with platinum, PD-1 inhibitors, and bevacizumab recorded, summarized, and incorporated in adjusted and sensitivity analyses.

Tumor response was assessed per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by a blinded, independent central review conducted by radiologists and medical oncologists; dual reads were performed, with senior adjudication of any discrepancies to ensure the final best overall response. Adverse events were abstracted from medical records and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. PFS was defined as the time from the initiation of post-osimertinib treatment to disease progression (PD) or death from any cause. OS was defined as the time from initiation of post-osimertinib treatment to death from any cause. Follow-up was completed by September 2025.

Progression-Pattern Classification

In our study, tumor progression after osimertinib resistance was classified into two types, based on the criteria proposed by Professor Yi-Long Wu.[20] Dramatic progression: (1) ≥3 months of disease control with EGFR-TKI; (2) a marked increase in target lesions with a non-target lesion score of ≥2; (3) a symptom score of 2. Gradual progression: (1) ≥6 months of disease control with EGFR-TKI; (2) no significant increase in tumor burden with a non-target lesion score of ≤2; (3) a symptom score of ≤1. All criteria were required for each category; cases not fully meeting criteria were reviewed by two investigators, with discrepancies resolved by consensus.

In vitro Exploratory Validation

PC-9 lung adenocarcinoma cells with EGFR exon 19 deletion and the gefitinib-resistant derivative PC-9/ZD (exon 19 deletion plus T790M) were obtained from Dr. Fumiaki Koizumi (National Cancer Center, Japan). An additional gefitinib-resistant line (PC-9/GR) was generated from parental PC-9 by prolonged gefitinib exposure. Cell identity was

verified by short tandem repeat profiling (June 26, 2019), and routine mycoplasma testing remained negative. Cells were maintained in RPMI-1640 (Gibco) supplemented with 10% FBS (Gibco) at 37°C in 5% CO_2. To derive osimertinib-resistant sublines, osimertinib was escalated from 0.1 to 3.2 μmol/L at 3–4-week intervals over approximately seven months, yielding PC-9/ZDOR and PC-9/GROR. These derivatives underwent targeted next-generation sequencing (NGS) with a 56-gene lung cancer panel (LungCore, Burning Rock Biotech, Guangzhou, China), showing loss of parental EGFR p.E746_A750del and T790M, with no detectable EGFR expression or amplification.

Paired comparisons (PC-9/ZD vs PC-9/ZDOR; PC-9/GR vs PC-9/GROR) were performed in 96-well plates. Cell viability was measured by CCK-8 to estimate half-maximal inhibitory concentration (IC50) and calculate resistance indices (RI), defined as IC50 (PC-9/ZDOR)/IC50(PC-9/ZD) and IC50 (PC-9/GROR)/IC50(PC-9/GR). Daily counts were used to generate growth curves and doubling times. All experiments were conducted in biological triplicate.

Statistical Analysis

Analyses were performed using GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, USA) and SPSS 25.0 (IBM Corp., Armonk, NY, USA). Baseline characteristics were compared using Mann–Whitney U tests (continuous) and Fisher's exact tests (categorical). Survival was estimated using the Kaplan–Meier test, with comparisons by log-rank. We performed 1:1 propensity-score matching (nearest-neighbour, no replacement, caliper 0.05) on sex, age, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), smoking history, EGFR mutation type, line of osimertinib therapy, progression pattern, clinical stage, brain and liver metastases, local consolidative therapy, and use of platinum, PD-1 inhibitors, and bevacizumab; balance was assessed using standardized mean differences (SMDs) of <0.1. Cox models provided adjusted hazard ratios (aHRs, 95% CI); covariates were prespecified by clinical relevance and pre-match imbalance (SMDs of >0.1), with variance inflation factors of <5 indicating no concerning collinearity. All tests were two-sided, with $P<0.05$ considered statistically significant.

Results

Patient Characteristics

Among 782 consecutive stage IIIB-IV EGFR-mutant NSCLC patients evaluated from June 2020 to June 2024, 525 received osimertinib; of these, 333 underwent subsequent therapy after developing resistance. Among the 333, 164 were excluded for small-cell transformation (n=9), absence of a taxane- or pemetrexed-based regimen (n=90), fewer than two cycles (n=22), or loss to follow-up without efficacy assessment (n=43). The final cohort comprised 169 patients, including 74 treated with taxane-based regimens and 95 with pemetrexed-based regimens; the study flow is shown in Figure 1. Of these, 42 (24.9%) underwent rebiopsy after progression on osimertinib, and NGS results were available for 30. NGS-defined resistance mechanisms and co-mutation profiles are summarized in Supplementary Table 1. After propensity-score matching, covariates were balanced between the taxane and pemetrexed groups (all $P>0.05$; SMD<0.1). Baseline characteristics before and after matching are summarized in Table 1.

Clinical Outcomes in the Overall Cohort Stratified by Progression Pattern

As of September 12, 2025, median follow-up was 22.7 months (95% CI: 20.5–24.9); disease progression occurred in 149/169 patients (88.2%) and death in 117 (69.2%). In the overall population, taxane-based chemotherapy was associated with longer PFS than pemetrexed (median 8.9 vs 7.8 months; HR: 0.69, 95% CI: 0.50–0.95; P=0.022; Figure 2A), while OS showed a borderline advantage with taxanes (17.7 vs 15.6 months; HR: 0.70, 95% CI: 0.48–1.01; P=0.052; Figure 2B). In analyses stratified by post-osimertinib progression type, the gradual-progression cohort showed broadly comparable PFS and OS between regimens (Figures 2C and D). By contrast, in the dramatic-progression cohort, taxane-based therapy was associated with longer PFS (7.8 vs 5.3 months; HR: 0.44, 95% CI: 0.28–0.69; $P<0.001$; Figure 2E) and directionally longer OS (16.1 vs 10.7 months; HR: 0.46, 95% CI: 0.28–0.75; P=0.001; Figure 2F).

Table 1 Baseline Characteristics of Patients in the Pemetrexed and Taxane Groups Before and After Propensity Score Matching

Characteristic	Before PSM (n=169)		P-value (SMD)	After PSM (n=124)		P-value (SMD)
	Pemetrexed (n=95)	Taxane (n=74)		Pemetrexed (n=62)	Taxane (n=62)	
Age grouping, n (%)			0.98 (0.03)			0.85 (0.07)
≥65 years	36 (37.9)	27 (36.5)		22 (35.5)	24 (38.7)	
<65 years	59 (62.1)	47 (63.5)		40 (64.5)	38 (61.3)	
Sex, n (%)			0.12 (0.27)			1.00 (0.03)
Male	49 (51.6)	48 (64.9)		37 (59.7)	38 (61.3)	
Female	46 (48.4)	26 (35.1)		25 (40.3)	24 (38.7)	
Smoking history, n (%)			0.88 (0.05)			0.83 (0.08)
Never	74 (77.9)	56 (75.7)		46 (74.2)	48 (77.4)	
Current or former	21 (22.1)	18 (24.3)		16 (25.8)	14 (22.6)	
ECOG-PS, n (%)			0.33 (0.19)			0.79 (0.09)
0-1	77 (81.1)	65 (87.8)		55 (88.7)	53 (85.5)	
≥2	18 (18.9)	9 (12.2)		7 (11.3)	9 (14.5)	
EGFR mutation type, n (%)			0.61 (0.10)			1.00 (0.03)
19del	49 (51.6)	42 (56.8)		35 (56.5)	36 (58.1)	
21L858R	46 (48.4)	32 (43.2)		27 (43.5)	26 (41.9)	
line of osimertinib therapy, n (%)			0.81 (0.06)			1.00 (0.00)
First-line	31 (32.6)	22 (29.7)		19 (30.6)	19 (30.6)	
≥second-line	64 (67.4)	52 (70.3)		43 (69.4)	43 (69.4)	
Progression pattern, n (%)			0.76 (0.07)			1.00 (0.00)
Dramatic	48 (50.5)	40 (54.1)		33 (53.2)	33 (53.2)	
Gradual	47 (49.5)	34 (45.9)		29 (46.8)	29 (46.8)	
Stage, n (%)						1.00 (0.05)
III	10 (10.5)	8 (10.8)	0.99 (0.01)	7 (11.3)	8 (12.9)	
IV	85 (89.5)	66 (89.2)		55 (88.7)	54 (87.1)	
Liver metastasis, n (%)	18 (18.9)	13 (17.6)	0.98 (0.04)	10 (16.1)	11 (17.7)	1.00 (0.04)
Brain metastasis, n (%)	26 (27.4)	22 (29.7)	0.87 (0.05)	17 (27.4)	18 (29.0)	1.00 (0.04)
Local consolidative therapy, n (%)	26 (27.4)	21 (28.4)	0.99 (0.02)	18 (29.0)	20 (32.3)	0.85 (0.07)
Combined platinum, n (%)	54 (56.8)	41 (55.4)	0.98 (0.03)	37 (59.7)	37 (59.7)	1.00 (0.00)
Combined PD-1 inhibitor, n (%)	32 (33.7)	25 (33.8)	1.00 (0.00)	18 (29.0)	19 (30.6)	1.00 (0.03)
Combined bevacizumab, n (%)	51 (53.7)	42 (56.8)	0.81 (0.06)	37 (59.7)	35 (56.5)	0.86 (0.06)

Abbreviations: PSM, propensity score matching; SMD, standardized mean difference; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; PD-1, programmed cell death protein 1.

Clinical Outcomes in Matched Patients Stratified by Progression Pattern

After 1:1 propensity-score matching, trends observed pre-match were largely preserved. In the overall matched cohort, taxane-based therapy showed numerically longer PFS (median 8.8 vs 7.9 months; HR: 0.71, 95% CI: 0.48–1.03; Figure 3A) and OS (18.8 vs 15.9 months; HR: 0.70, 95% CI: 0.45–1.09; Figure 3B) than pemetrexed, without statistical significance. Consistent with pre-match findings, outcomes in the gradual-progression subgroup remained broadly comparable across regimens (Figures 3C and D). In the dramatic-progression subgroup, the association between taxanes and improved outcomes persisted, with longer PFS (7.7 vs 6.4 months; HR: 0.51, 95% CI: 0.30–0.86; P=0.009; Figure 3E) and longer OS (16.1 vs 12.7 months; HR: 0.54, 95% CI: 0.30–0.97; P=0.034; Figure 3F).

Prognostic Factors in Matched Patients Stratified by Progression Pattern

Multivariable Cox models were fitted in the post-PSM cohorts to estimate aHRs for the chemotherapy backbone alongside prespecified covariates selected for clinical relevance and pre-matching imbalance (Table 2). In the gradual--progression subgroup, the chemotherapy backbone was not independently associated with PFS (aHR: 0.82, 95% CI:

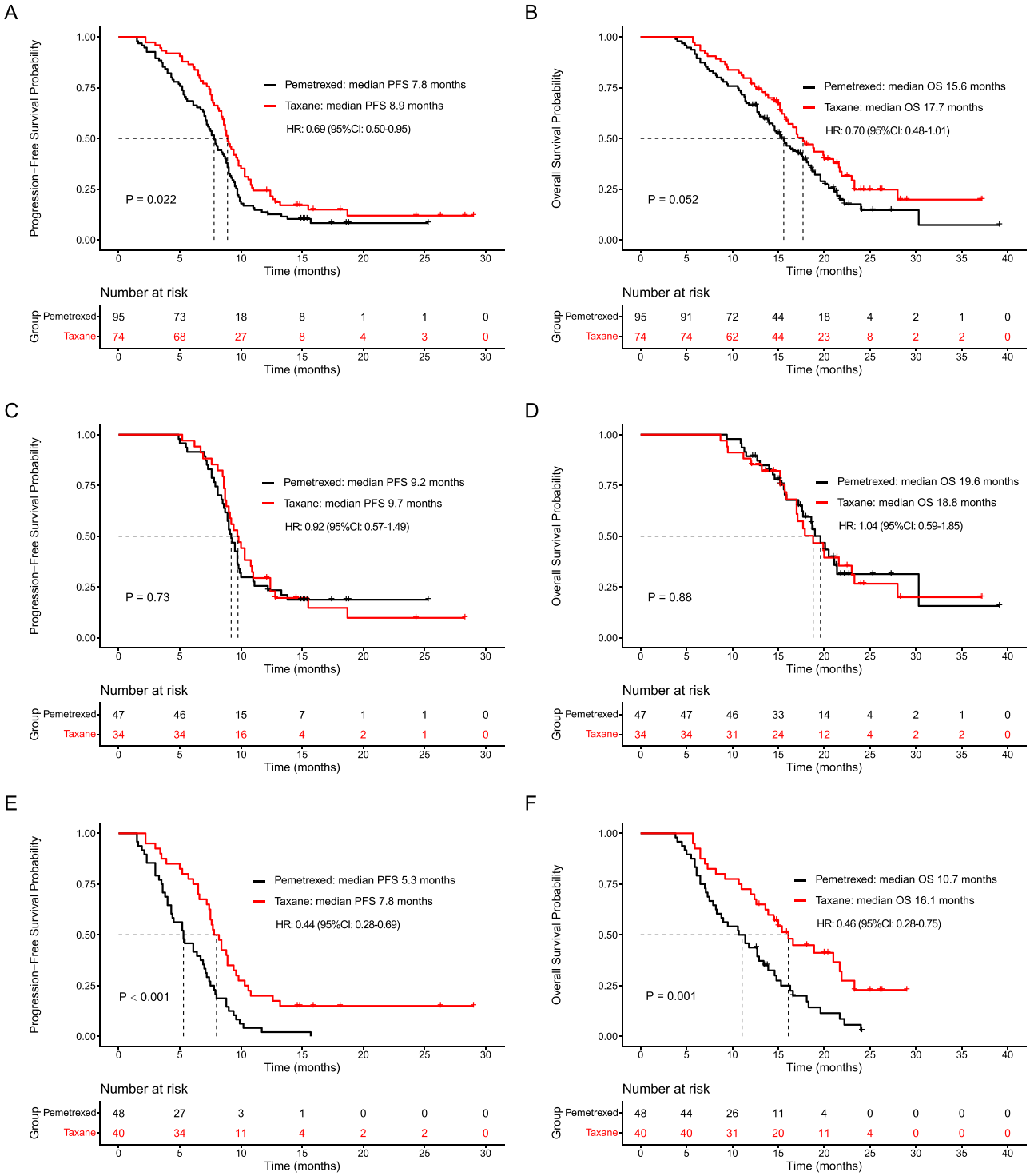

Figure 2 Kaplan–Meier curves before propensity-score matching comparing taxane- versus pemetrexed-based chemotherapy after osimertinib resistance in EGFR-mutated NSCLC: (**A**) PFS in the overall cohort; (**B**) OS in the overall cohort; (**C**) PFS in the gradual-progression subgroup; (**D**) OS in the gradual-progression subgroup; (**E**) PFS in the dramatic-progression subgroup; and (**F**) OS in the dramatic-progression subgroup.

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

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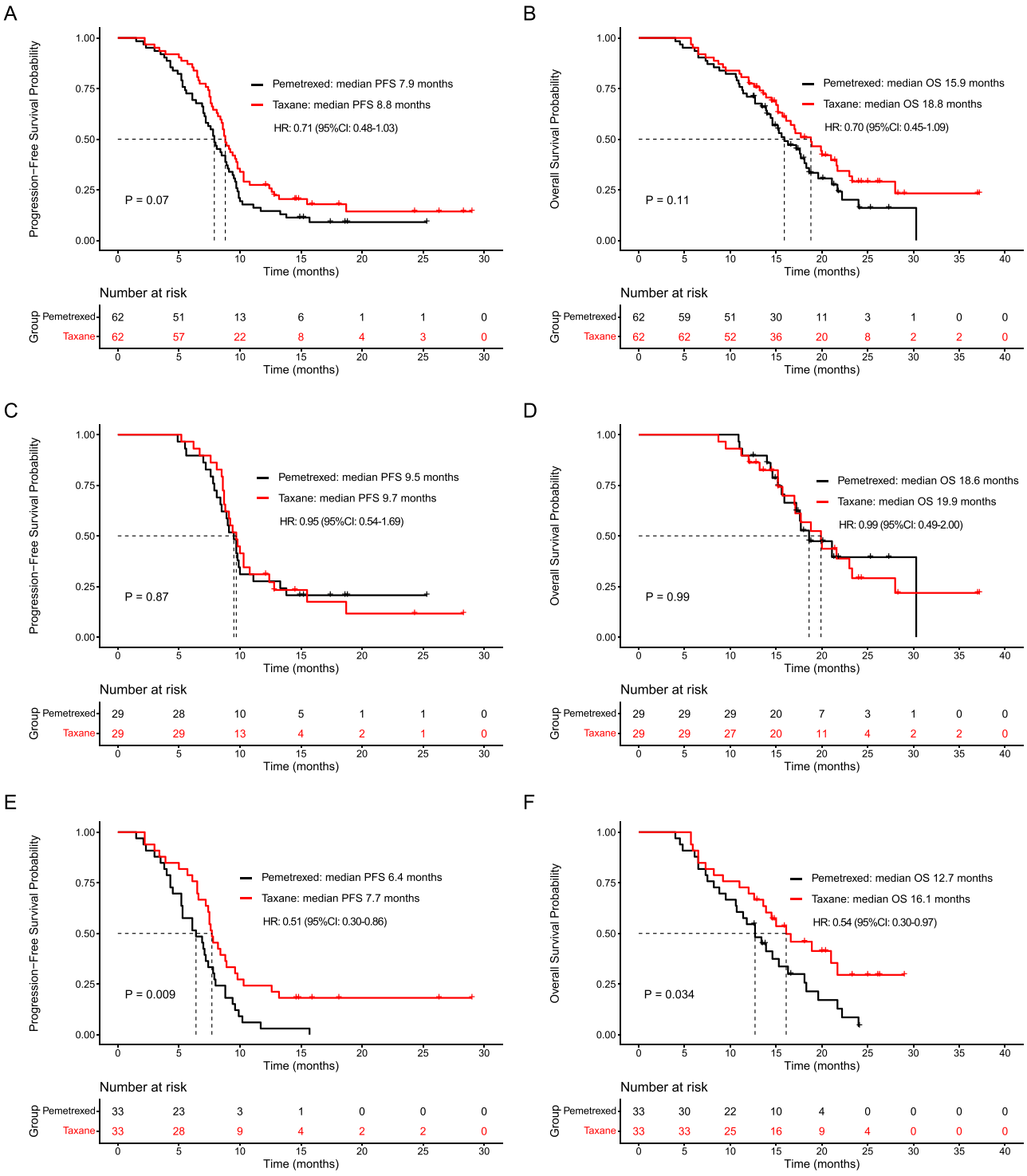

Figure 3 Kaplan–Meier curves after propensity-score matching comparing taxane- versus pemetrexed-based chemotherapy after osimertinib resistance in EGFR-mutated NSCLC: (**A**) PFS in the overall cohort; (**B**) OS in the overall cohort; (**C**) PFS in the gradual-progression subgroup; (**D**) OS in the gradual-progression subgroup; (**E**) PFS in the dramatic-progression subgroup; and (**F**) OS in the dramatic-progression subgroup.

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

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Table 2 Multivariable Predictors of PFS and OS in Matched Patients by Post-osimertinib Progression Pattern

Covariates	PFS		OS	
	aHR (95% CI)	P-value	aHR (95% CI)	P-value
Gradual-progression cohort:				
Chemotherapy backbone (taxane vs pemetrexed)	0.82 (0.43–1.56)	0.548	0.97 (0.45–2.09)	0.930
ECOG-PS (PS0-1 vs PS≥2)	1.54 (0.28–8.34)	0.615	0.70 (0.07–6.95)	0.757
EGFR mutation type (19del vs 21L858R)	0.46 (0.23–0.93)	0.030	0.55 (0.25–1.24)	0.148
Liver metastasis	3.64 (0.80–16.44)	0.094	2.22 (0.38–12.85)	0.373
Brain metastasis	1.26 (0.46–3.49)	0.652	3.31 (1.01–10.88)	0.048
Local therapy	0.74 (0.31–1.74)	0.489	1.02 (0.33–3.11)	0.977
Combined platinum	0.62 (0.33–1.16)	0.133	1.02 (0.47–2.22)	0.960
Combined PD-1 inhibitor	0.91 (0.41–2.05)	0.827	0.87 (0.30–2.56)	0.806
Combined bevacizumab	0.65 (0.35–1.23)	0.188	0.41 (0.19–0.89)	0.024
Dramatic-progression cohort:				
Chemotherapy backbone (taxane vs pemetrexed)	0.48 (0.27–0.84)	0.011	0.51 (0.27–0.96)	0.036
ECOG-PS (PS0-1 vs PS≥2)	0.22 (0.10–0.52)	0.001	0.22 (0.09–0.53)	0.001
EGFR mutation type (19del vs 21L858R)	0.83 (0.48–1.44)	0.508	0.72 (0.39–1.33)	0.291
Liver metastasis	3.17 (1.57–6.42)	0.001	2.66 (1.20–5.89)	0.016
Brain metastasis	2.02 (1.01–4.06)	0.047	1.32 (0.60–2.92)	0.489
Local therapy	0.88 (0.48–1.59)	0.667	0.82 (0.42–1.58)	0.555
Combined platinum	0.94 (0.51–1.71)	0.830	0.72 (0.37–1.42)	0.350
Combined PD-1 inhibitor	0.74 (0.41–1.34)	0.320	0.70 (0.36–1.33)	0.273
Combined bevacizumab	0.37 (0.21–0.66)	0.001	0.51 (0.28–0.95)	0.034

Notes: The aHR for the chemotherapy backbone was adjusted for the other covariates listed above.
Abbreviations: PFS, progression-free survival; OS, overall survival; aHR, adjusted hazard ratios; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; PD-1, programmed cell death protein 1.

0.43–1.56) or OS (aHR: 0.97, 95% CI: 0.45–2.09). By contrast, in the dramatic-progression subgroup, a taxane backbone was independently favorable for both PFS (aHR: 0.48, 95% CI: 0.27–0.84; P=0.011) and OS (aHR: 0.51, 95% CI: 0.27–0.96; P=0.036) compared with pemetrexed. Notably, the addition of bevacizumab was independently associated with longer OS in both subgroups.

Safety

Adverse events were compared between the taxane-based and pemetrexed-based regimens in the overall enrolled cohort (Table 3). Any-grade events were more frequent with the taxane backbone (64/74, 86.5% vs 63/95, 66.3%), whereas grade ≥3 events were broadly similar (10/74, 13.5% vs 11/95, 11.6%). The excess with taxanes was driven mainly by non-hematologic toxicities (56/74, 75.7% vs 52/95, 54.7%), with higher rates of alopecia (70.3% vs 20.0%), peripheral

Table 3 Treatment-Related Adverse Events in the Overall Cohort

Event, n (%)	Pemetrexed Group, n=95 (n, %)		Taxane Group, n=74 (n, %)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any	63 (66.3)	11 (11.6)	64 (86.5)	10 (13.5)
Hematologic	33 (34.7)	6 (6.3)	28 (37.8)	4 (5.4)
Leukopenia/neutropenia	19 (20.0)	4 (4.2)	22 (29.7)	3 (4.0)
Anemia	17 (17.9)	2 (2.1)	10 (13.5)	0 (0.0)
Thrombocytopenia	9 (9.5)	2 (2.1)	12 (16.2)	3 (4.0)

(*Continued*)

Table 3 (Continued).

Event, n (%)	Pemetrexed Group, n=95 (n, %)		Taxane Group, n=74 (n, %)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Non-hematologic	52 (54.7)	7 (7.4)	56 (75.7)	8 (10.8)
Fatigue	26 (27.4)	1 (1.0)	23 (31.1)	0 (0.0)
Alopecia	19 (20.0)	0 (0.0)	52 (70.3)	0 (0.0)
Nausea/vomiting	18 (18.9)	1 (1.0)	15 (20.3)	2 (2.7)
Decreased appetite	24 (25.3)	4 (4.2)	24 (32.4)	3 (4.0)
Diarrhea	7 (7.4)	1 (1.0)	17 (23.0)	0 (0.0)
Constipation	16 (16.8)	0 (0.0)	19 (25.7)	0 (0.0)
Peripheral neuropathy	5 (5.3)	0 (0.0)	45 (60.8)	4 (5.4)
Stomatitis	8 (8.4)	1 (1.0)	13 (17.6)	0 (0.0)
Arthralgia	4 (4.2)	0 (0.0)	13 (17.6)	1 (1.0)
Pruritus	8 (8.4)	1 (1.0)	11 (14.9)	0 (0.0)
Rash	6 (6.3)	0 (0.0)	7 (9.4)	1 (1.4)
ALT/AST increased	9 (9.5)	0 (0.0)	8 (10.8)	0 (0.0)
Led to dose reduction	16 (16.8)	–	13 (17.6)	–
Led to discontinuation	5 (5.3)	–	6 (8.1)	–
Led to death	2 (2.1)	–	1 (1.4)	–

neuropathy (60.8% vs 5.3%), and arthralgia (17.6% vs 4.2%), while hematologic events were comparable. Rates of treatment modification due to toxicity were similar between regimens: dose reduction (17.6% vs 16.8%), treatment discontinuation (8.1% vs 5.3%), and treatment-related death (1.4% vs 2.1%).

Exploratory Analysis: Chemotherapy Sensitivity After Acquisition of Osimertinib Resistance

Osimertinib-resistant derivatives (PC-9/ZDOR, PC-9/GROR) were established from PC-9/ZD and PC-9/GR as described in the Methods section. Compared with parental lines, resistant cells showed reduced sensitivity to osimertinib (Figure 4A) with similar proliferation kinetics (Figure 4B). Acquisition of osimertinib resistance was accompanied by increased sensitivity to taxanes, with IC50 for docetaxel and paclitaxel lower than those in the parental PC-9/ZD and PC-9/GR lines ($P<0.05$), whereas sensitivity to pemetrexed did not differ significantly ($P>0.05$) (Table 4).

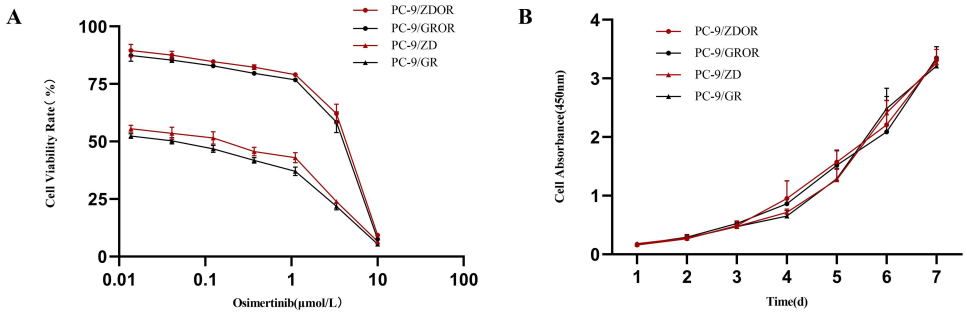

Figure 4 (**A**) Dose-response curves of osimertinib-induced cell viability in PC-9/ZD, PC-9/ZDOR, PC-9/GR, and PC-9/GROR cell lines; (**B**) Cell growth curves of PC-9/ZD, PC-9/ZDOR, PC-9/GR, and PC-9/GROR cell lines.

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Table 4 Drug Sensitivity of PC-9/ZDOR and PC-9/GROR Compared with Parental PC-9/ZD and PC-9/GR (n=3, $\bar{\chi} \pm s$)

Drug	PC-9/ZD IC50 (nmol/L)	PC-9/ZDOR IC50 (nmol/L)	P-value	RI	PC-9/GR IC50 (nmol/L)	PC-9/GROR IC50 (nmol/L)	P-value	RI
Docetaxel	0.463±0.049	0.152±0.031	0.0008	0.328	0.400±0.062	0.106±0.008	0.0027	0.265
Paclitaxel	2.205±0.225	1.19±0.001	0.0109	0.540	3.256±0.138	2.146±0.094	0.0007	0.659
Pemetrexed	51.89±6.698	55.23±1.341	0.4444	1.064	65.363±0.872	64.733±2.309	0.7364	0.990

Abbreviations: RI, Resistance Index, defined as IC50 (PC-9/ZDOR)/IC50 (PC-9/ZD) and IC50 (PC-9/GROR)/IC50 (PC-9/GR).

Discussion

This real-world analysis focused on EGFR-mutant NSCLC after osimertinib and examined whether progression patterns inform the association between chemotherapy backbone and outcomes after covariate balancing. Taxane-based regimens were linked to numerically longer PFS and OS than pemetrexed in both overall and matched cohorts, with no apparent difference in the gradual-progression subgroup, whereas the dramatic-progression subgroup showed a statistically significant association favoring taxanes. Exploratory in vitro findings were directionally concordant: osimertinib-resistant PC-9 sublines tended to show greater sensitivity to taxanes, whereas sensitivity to pemetrexed did not differ significantly.

For patients who develop resistance to third-generation EGFR-TKIs, the NCCN guidelines for NSCLC recommend repeat tissue biopsy and molecular testing to guide subsequent treatment decisions and elucidate resistance pathways.[26] However, approximately 30–65% of resistance mechanisms remain uncharacterized and, even when identified, many potential targets lack effective therapeutic options.[7,9] In real-world clinical settings, the rate of repeat biopsy and molecular retesting is often constrained by procedural risk and cost; in this cohort, only 42 patients underwent rebiopsy after osimertinib resistance. Consequently, treatment selection commonly depends on post-osimertinib progression patterns and overall clinical condition, with chemotherapy-based regimens applied accordingly.

Regarding chemotherapy recommendations for third-generation EGFR-TKI resistance, major guidelines generally extrapolate from EGFR-wild-type NSCLC, endorsing platinum doublets or single-agent taxanes, pemetrexed, or gemcitabine as options.[26–28] However, many pivotal chemotherapy trials predated routine EGFR-TKI use, leaving a gap for the post-TKI-resistant population.[29,30] Tang et al[31] reported that an osimertinib-resistant derivative of H1975 exhibited greater sensitivity to paclitaxel, whereas pemetrexed activity remained limited. Aligned with our cell-based observations, these findings suggest that cytotoxic drug sensitivity may shift after EGFR-TKI exposure in a drug-specific manner.

Current clinical research on systemic treatment strategies following resistance to third-generation EGFR-TKIs primarily focuses on exploring the efficacy of combining chemotherapy with anti-angiogenic agents and immunotherapy. Several recent immunotherapy-related clinical studies have utilized either taxane-based regimens or pemetrexed-based regimens, and the differences in their outcomes are worthy of thorough discussion. In IMpower150,[32] atezolizumab plus carboplatin, paclitaxel, and bevacizumab (ABCP) improved efficacy, with subgroup analyses suggesting longer OS in EGFR-mutant patients previously treated with TKIs. By contrast, ORIENT-31[33] used pemetrexed–cisplatin with sintilimab and prolonged PFS but did not significantly improve OS over chemotherapy alone. Similarly, CheckMate 722 and KEYNOTE-789, both with pemetrexed-based chemotherapy, did not demonstrate superior outcomes for chemo-immunotherapy versus chemotherapy alone.[34,35] Thus, the benefit of adding immunotherapy post-EGFR-TKI remains uncertain and may depend on the chemotherapy backbone and anti-angiogenic context.

A recent network meta-analysis of nine randomized trials (n=2,534) after EGFR-TKI failure found that chemotherapy plus anti–PD-1/PD-L1 and anti-VEGF (or bispecific PD-1/VEGF blockade) outperformed chemotherapy alone; bevacizumab plus chemotherapy also reduced progression risk, whereas chemo-immunotherapy without anti-angiogenic therapy yielded modest benefit and no objective response rate (ORR) gain.[36] Consistently, in multivariable analyses (Table 2), bevacizumab-containing combinations were associated with better OS in both progression subgroups, whereas adding immunotherapy was not an independent prognostic factor. These signals support cautiously tailoring bevacizumab with the chemotherapy backbone according to progression patterns, pending prospective validation.

This study has limitations. The ≥2-cycle inclusion criterion may introduce selection bias by excluding early progressors or those discontinuing as a result of toxicity, potentially enriching patients with better tolerance or disease biology. The nonrandomized design and physician-driven regimen choice raise the possibility of residual confounding despite propensity matching and multivariable adjustment. Outcomes may also be influenced by subsequent therapies (eg, anti-angiogenic agents, immunotherapy, later-line TKIs), which could differentially affect OS and attenuate backbone-specific effects. Moreover, the concomitant mutation landscape in post-osimertinib patients was not systematically catalogued or analyzed; such alterations may modulate chemotherapy sensitivity and introduce unmeasured bias. The in vitro component was limited to two PC-9–derived models, constraining generalizability across genotypes, resistance mechanisms, and cellular contexts. Accordingly, findings should be interpreted as associative and hypothesis-generating. Prospective, multicenter randomized trials, coupled with mechanistic preclinical validation (in vivo xenografts and additional EGFR-mutant cell lines), are needed prior to clinical adoption.

Conclusions

Taxane-based chemotherapy was associated with more favorable outcomes than pemetrexed in dramatic progression after osimertinib resistance, with higher non-hematologic toxicity. These findings, supported by exploratory in vitro sensitivity, warrant prospective validation.

Abbreviations

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; EMT, epithelial–mesenchymal transition; PD-1, programmed cell death protein 1; RECIST, Response Evaluation Criteria in Solid Tumors; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, disease progression; RI, resistance indices; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; SMD, standardized mean difference; aHR, adjusted hazard ratio; ORR, objective response rate; NGS, next-generation sequencing.

Data Sharing Statement

The data used in this study are available upon reasonable request from the corresponding authors, Juan Zhou and Bo Xie.

Ethic Approval

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments, and was approved by the Ethics Committee of the General Hospital of Southern Theater Command (approval number: NZLLKZ2024107), which waived the requirement for informed consent due to the anonymized use of clinical data.

Author Contributions

Ning Yang and Ning Wan are co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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