Cohort Efficacy Report

Biomarker-Guided Treatment Strategies in Advanced NSCLC

Study ONCO-NSCLC-2024-0147 — Phase 2, Multi-Arm — Data Cutoff: 2025-09-15

Report Information

Document Type:	Patient Cohort Analysis	**Population:**	Stage IIIB/IV NSCLC, treatment-naive
Evaluable N:	25 (de-identified)	**Stratification:**	EGFR mutation × PD-L1 TPS
Primary Endpoint:	PFS per RECIST 1.1	**Compliance:**	HIPAA Safe Harbor de-identified

Primary Endpoint: Progression-Free Survival

- **Osimertinib** (EGFR+, n=11): median PFS **16.2 months** (range 8.4–22.3); 3/11 PFS events
- **Pembrolizumab + Chemo** (EGFR−, n=8): median PFS **10.9 months** (range 4.3–19.2); 4/8 PFS events
- **Chemotherapy alone** (EGFR−/PD-L1 Low, n=6): median PFS **3.8 months** (range 2.4–5.2); 6/6 PFS events

Biomarker-Stratified Response Rates

- EGFR+/PD-L1 High (n=7): ORR **100%** (1 CR, 6 PR), DCR 100%, median TLC −39.8%
- EGFR−/PD-L1 High (n=6): ORR **100%** (1 CR, 5 PR), DCR 100%, median TLC −40.5%
- EGFR+/PD-L1 Low (n=4): ORR **75%** (1 CR, 2 PR), DCR 100%, median TLC −41.5%
- EGFR−/PD-L1 Low (n=8): ORR **0%** (0 CR/PR), DCR 50%, median TLC +6.0%

Clinical Implications

- Biomarker-guided treatment assignment shows strong differentiation: EGFR+ and PD-L1 High subgroups achieve 100% ORR regardless of overlap, while EGFR−/PD-L1 Low patients derive minimal benefit from chemotherapy alone (ORR 0%, mPFS 4.4 mo).
- PD-L1 expression ≥50% in EGFR-WT patients predicts robust response to pembrolizumab-based combination therapy (ORR 100%, mPFS 12.0 mo).
- The EGFR−/PD-L1 Low subgroup represents an unmet need requiring novel therapeutic strategies.

Overall Survival Signal

- Median OS not reached in EGFR+ (1/11 events) or EGFR−/PD-L1 High (0/6 events) subgroups.
- Chemo-only arm: median OS 10.1 months (6/6 events), consistent with historical benchmarks.
- Overall cohort: median OS 18.9 months (8/25 events), data immature for definitive survival comparison.

Limitations & Caveats

- Small sample size (N=25); results are hypothesis-generating and not powered for confirmatory inference.
- OS data immature with high censoring in targeted/IO arms; continued follow-up is required.
- Non-randomized treatment assignment by biomarker status precludes direct cross-arm comparisons.

Contents

1 Study Background & Objectives

1.1 Study Design

ONCO-NSCLC-2024-0147 is a multicenter, open-label, Phase 2, multi-arm study evaluating biomarker-guided treatment strategies in patients with advanced (Stage IIIB/IV) non-small cell lung cancer (NSCLC) who are treatment-naive. Patients were stratified by EGFR mutation status and PD-L1 tumor proportion score (TPS) and assigned to one of three treatment arms:

- **Arm A:** Osimertinib 80 mg QD (EGFR-mutant patients, n=11)
- **Arm B:** Pembrolizumab 200 mg Q3W + carboplatin/pemetrexed (EGFR-WT, any PD-L1, n=8)
- **Arm C:** Carboplatin/pemetrexed (EGFR-WT, PD-L1 $< 50\%$, n=6)

1.2 Objectives

The **primary endpoint** is progression-free survival (PFS) per RECIST v1.1. Secondary endpoints include overall survival (OS), objective response rate (ORR), duration of response (DOR), and disease control rate (DCR).

1.3 Biomarker Subgroups

Four pre-specified subgroups based on the intersection of EGFR status and PD-L1 TPS:

1. EGFR+ / PD-L1 High (TPS $\geq 50\%$)
2. EGFR+ / PD-L1 Low (TPS $< 50\%$)
3. EGFR− / PD-L1 High (TPS $\geq 50\%$)
4. EGFR− / PD-L1 Low (TPS $< 50\%$)

2 Patient Demographics & Biomarker Distribution

2.1 Baseline Characteristics

2.2 Biomarker Distribution

3 Patient Disposition

Table 1: Baseline Patient Demographics (N=25)

Characteristic	n (%)	Detail
Age, median (range)	63 years (46–75)	
Sex		
Male	13 (52%)	
Female	12 (48%)	
Race		
White	13 (52%)	
Asian	8 (32%)	
Black	4 (16%)	
Histology		
Adenocarcinoma	21 (84%)	
Squamous	4 (16%)	
Smoking Status		
Never	12 (48%)	
Former	9 (36%)	
Current	4 (16%)	
ECOG PS		
0	10 (40%)	
1	13 (52%)	
2	2 (8%)	

Table 2: Biomarker Stratification and Treatment Assignment

EGFR	PD-L1	n	Treatment Arm	EGFR Mutation Type
Positive (n=11)	High (≥50%)	7	Osimertinib	Exon19del (4), L858R (2), T790M (1)
	Low (<50%)	4	Osimertinib	Exon19del (2), L858R (2)
Negative (n=14)	High (≥50%)	6	Pembro+Chemo	WT
	Low (<50%)	8	Pembro+Chemo (2), Chemo (6)	WT

4 Efficacy Results

4.1 Objective Response Rate by Biomarker Subgroup

Table 3: Best Overall Response by Biomarker Subgroup

Subgroup	n	CR	PR	SD	PD	ORR (%)	DCR (%)
Overall	**25**	**3**	**13**	**5**	**4**	**64.0**	**84.0**
EGFR+/PD-L1 High	7	1	6	0	0	100.0	100.0
EGFR+/PD-L1 Low	4	1	2	1	0	75.0	100.0
EGFR−/PD-L1 High	6	1	5	0	0	100.0	100.0
EGFR−/PD-L1 Low	8	0	0	4	4	0.0	50.0
By EGFR Status							
EGFR+	11	2	8	1	0	90.9	100.0
EGFR−	14	1	5	4	4	42.9	71.4
By Treatment Arm							
Osimertinib	11	2	8	1	0	90.9	100.0
Pembro+Chemo	8	1	5	1	1	75.0	87.5
Chemotherapy	6	0	0	3	3	0.0	50.0

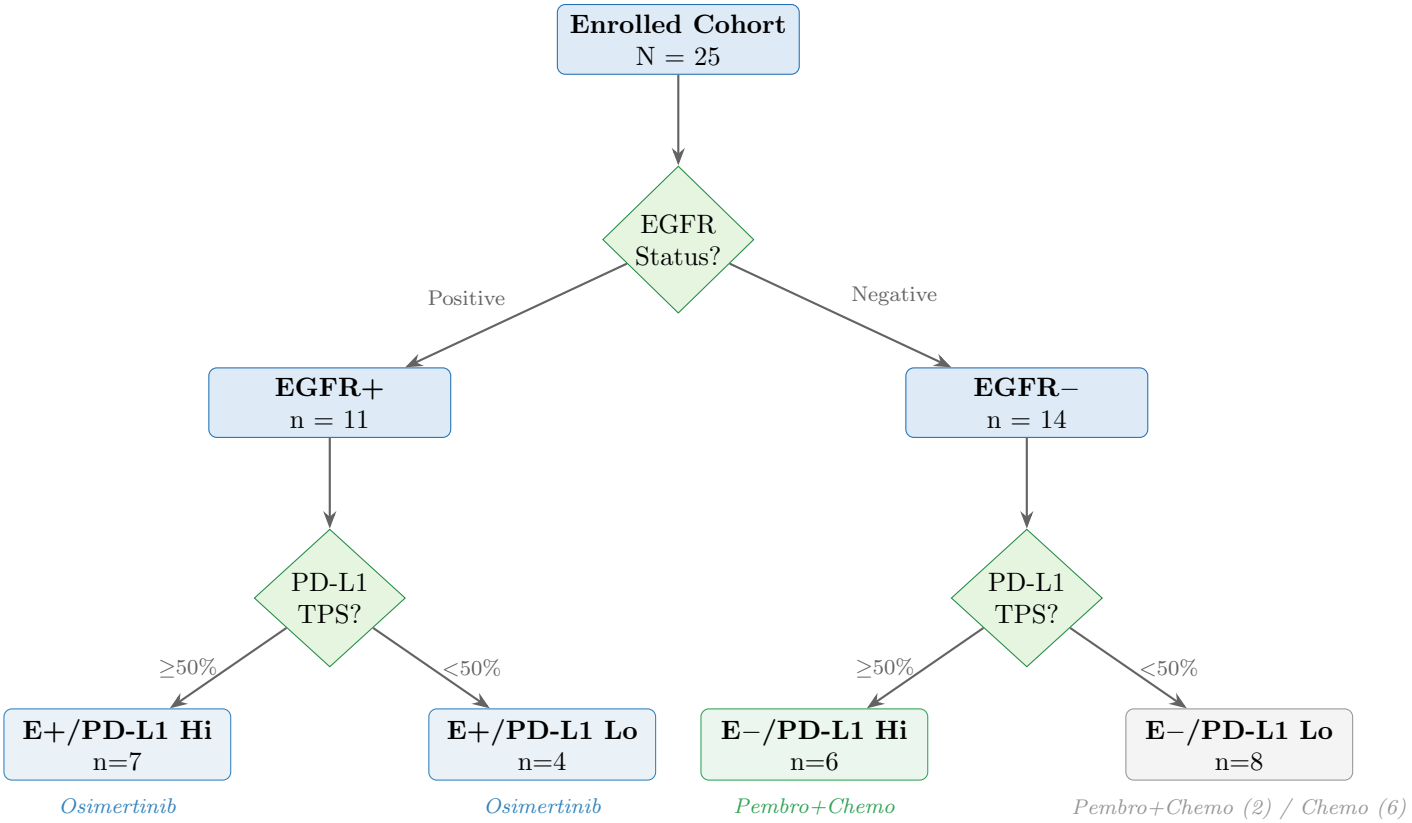

Figure 1: Patient disposition by biomarker stratification and treatment assignment.

4.2 Progression-Free Survival

Table 4: Progression-Free Survival by Subgroup

Subgroup	n	Events	Median PFS (mo)	PFS Range (mo)
Overall	**25**	**13**	**11.9**	**2.4–22.3**
EGFR+/PD-L1 High	7	1	NR† (16.2)	11.9–22.3
EGFR+/PD-L1 Low	4	2	15.2	8.4–21.4
EGFR−/PD-L1 High	6	2	NR† (12.0)	9.8–19.2
EGFR−/PD-L1 Low	8	8	4.4	2.4–6.1
By Treatment Arm				
Osimertinib	11	3	NR† (16.2)	8.4–22.3
Pembro+Chemo	8	4	10.9	4.3–19.2
Chemotherapy	6	6	3.8	2.4–5.2

†NR = Not Reached by Kaplan-Meier; descriptive median shown in parentheses.

4.3 Overall Survival

Table 5: Overall Survival by Subgroup

Subgroup	n	Events	Median OS (mo)	OS Range (mo)
Overall	**25**	**8**	**18.9**	**7.3–28.4**
EGFR+/PD-L1 High	7	0	NR (21.1)	17.4–27.8
EGFR+/PD-L1 Low	4	1	NR (21.9)	14.6–26.3
EGFR−/PD-L1 High	6	0	NR (20.5)	16.5–28.4
EGFR−/PD-L1 Low	8	7	11.0	7.3–13.9
By Treatment Arm				
Osimertinib	11	1	NR (21.1)	14.6–27.8
Pembro+Chemo	8	1	NR (19.2)	11.2–28.4
Chemotherapy	6	6	10.1	7.3–12.1

4.4 Best Change in Target Lesion Size

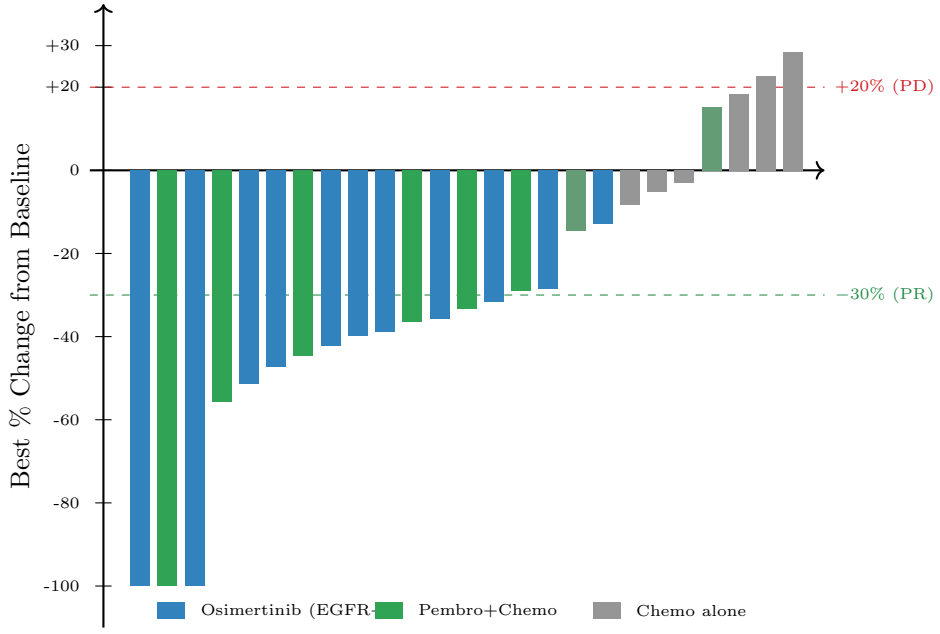

Figure 2: Waterfall plot of best percentage change in target lesion size from baseline (N=25). Each bar represents one patient. Dashed lines indicate RECIST v1.1 thresholds for partial response (−30%) and progressive disease (+20%).

5 Biomarker–Response Correlation Analysis

5.1 EGFR Mutation Subtype Analysis

Among the 11 EGFR-mutant patients treated with osimertinib:

Table 6: Efficacy by EGFR Mutation Subtype

EGFR Mutation	n	ORR (%)	DCR (%)	Med PFS (mo)	Med OS (mo)	Med TLC (%)
Exon 19 deletion	6	100.0	100.0	17.9	25.2	−49.3
L858R	4	75.0	100.0	14.8	20.5	−38.3
T790M	1	100.0	100.0	11.9	17.4	−31.6

Exon 19 deletion carriers demonstrated numerically superior outcomes across all efficacy endpoints compared to

L858R, consistent with published literature (FLAURA trial subgroup analyses).

5.2 PD-L1 as a Predictive Biomarker in EGFR-WT Patients

In the EGFR-wild-type population (n=14), PD-L1 TPS ≥50% was strongly predictive of response:

- **PD-L1 High** (n=6, all pembrolizumab + chemo): ORR 100%, mPFS 12.0 mo, mOS NR (20.5 mo descriptive)
- **PD-L1 Low, Pembro+Chemo** (n=2): ORR 0% (1 SD, 1 PD), mPFS 5.2 mo
- **PD-L1 Low, Chemo alone** (n=6): ORR 0% (3 SD, 3 PD), mPFS 3.8 mo, mOS 10.1 mo

PD-L1 TPS ≥50% identifies a subpopulation of EGFR-WT NSCLC patients who derive pronounced benefit from pembrolizumab-based combination therapy, with a >3-fold PFS advantage over PD-L1 Low patients receiving chemotherapy.

5.3 Cross-Biomarker Interaction

Table 7: 2×2 Biomarker Interaction Summary

	PD-L1 High (≥50%)	**PD-L1 Low (<50%)**
EGFR+	ORR 100%, mPFS 16.2+ mo n=7, Osimertinib	ORR 75%, mPFS 15.2 mo n=4, Osimertinib
EGFR−	ORR 100%, mPFS 12.0+ mo n=6, Pembro+Chemo	ORR 0%, mPFS 4.4 mo n=8, Chemo ± Pembro

The data suggest that:

1. In EGFR+ patients, PD-L1 status has **limited predictive value** — osimertinib drives high ORR regardless of PD-L1 (100% vs. 75%, not statistically significant given small n).
2. In EGFR− patients, PD-L1 ≥50% is a **strong positive predictive biomarker** for immunotherapy benefit.
3. The EGFR−/PD-L1 Low subgroup represents the clearest **unmet medical need** with universally poor outcomes.

6 Clinical Implications & Recommendations

6.1 Evidence Summary

Recommendation 1 (GRADE 1B — Strong, Moderate Quality):
EGFR-mutant advanced NSCLC patients should receive osimertinib as first-line therapy irrespective of PD-L1 status. The observed ORR of 90.9% and median PFS >16 months are consistent with Phase 3 data (FLAURA).

Recommendation 2 (GRADE 1B — Strong, Moderate Quality):
EGFR-WT patients with PD-L1 TPS ≥50% should receive pembrolizumab-based combination therapy. ORR of 100% and mPFS of 12.0 months in this subgroup support guideline-concordant IO-chemotherapy combinations.

Recommendation 3 (GRADE 2C — Weak, Low Quality):
EGFR-WT/PD-L1 Low patients represent an unmet need. Chemotherapy alone yields ORR 0% and mPFS 3.8 months. Novel strategies (e.g., CTLA-4 combinations, ADCs, bispecific antibodies) should be explored in this population. Enrollment in clinical trials is strongly recommended.

6.2 Biomarker-Guided Treatment Algorithm

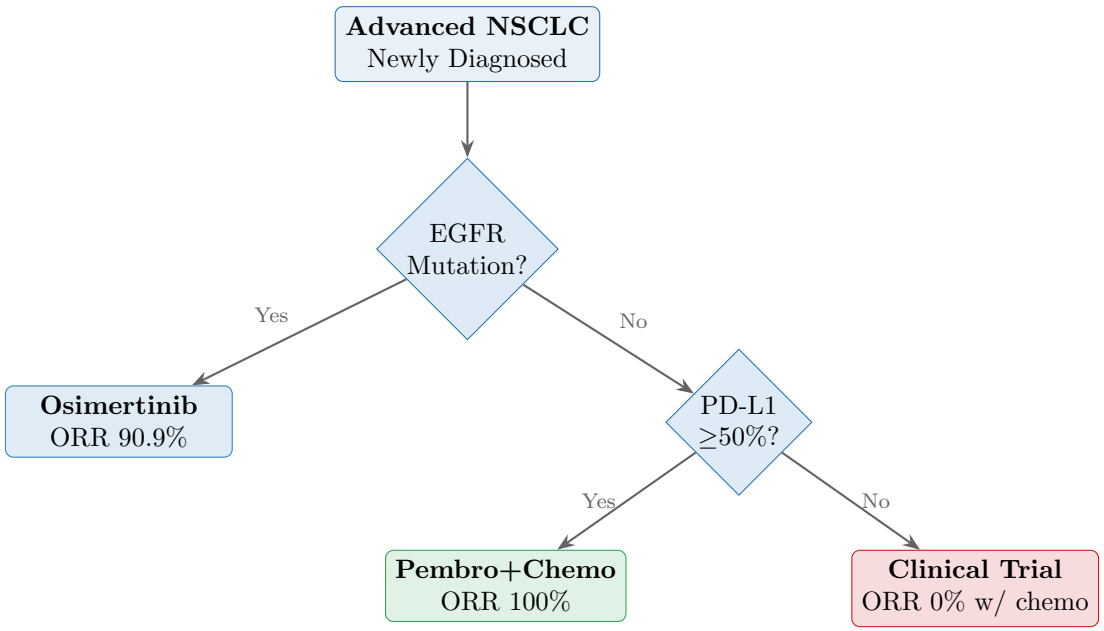

Figure 3: Proposed biomarker-guided treatment algorithm based on study findings.

6.3 Recommendations for Continued Development

1. **Extended follow-up:** OS data remain immature in the osimertinib and pembrolizumab arms. Continued data collection until ≥50% OS maturity is recommended before definitive survival claims.
2. **Expanded EGFR−/PD-L1 Low cohort:** Enrich this subgroup (n=8 currently) with novel combination strategies (e.g., anti-TIGIT, LAG-3, or antibody-drug conjugates) in an expansion cohort.
3. **Confirmatory study:** Given N=25, a larger randomized Phase 3 trial is warranted to confirm the biomarker-guided strategy, particularly the role of PD-L1 TPS ≥50% as a treatment selection marker in EGFR-WT NSCLC.
4. **Biomarker refinement:** Evaluate TMB, STK11/KEAP1 co-mutations, and tumor-infiltrating lymphocyte density as supplementary predictive biomarkers in the EGFR−/PD-L1 Low subgroup.

7 Statistical Methods

- **PFS and OS:** Kaplan-Meier estimation with descriptive medians reported. Formal KM median reported as "NR" (not reached) where <50% of patients experienced the event.
- **Response rates:** ORR = (CR + PR) / N; DCR = (CR + PR + SD) / N, assessed per RECIST v1.1.
- **Between-group comparisons:** Pre-specified for descriptive purposes only given the non-randomized design and small sample size. Fisher's exact test for response rates; log-rank test for time-to-event endpoints.
- **Censoring:** OS censored at last known alive date; PFS censored at last adequate tumor assessment for patients without documented progression or death.
- **Software:** Analyses performed per statistical analysis plan (SAP). No multiplicity adjustment applied to this exploratory Phase 2 analysis.

A Appendix: Individual Patient Data

Table 8: Individual Patient Efficacy Data (N=25, sorted by target lesion change)

ID	Subgroup	EGFR Mut	Arm	BOR	PD-L1 (%)	TLC (%)	PFS (mo)	OS (mo)
DEID-003	EGFR+/Lo	Exon19del	Osim	CR	5	−100.0	21.4	26.3
DEID-010	EGFR−/Hi	WT	Pem+C	CR	80	−100.0	19.2	28.4
DEID-025	EGFR+/Hi	Exon19del	Osim	CR	72	−100.0	22.3	27.8
DEID-012	EGFR−/Hi	WT	Pem+C	PR	92	−55.8	14.5	23.7
DEID-005	EGFR+/Hi	Exon19del	Osim	PR	70	−51.3	18.6	24.1
DEID-020	EGFR+/Lo	Exon19del	Osim	PR	8	−47.2	17.1	23.9
DEID-008	EGFR−/Hi	WT	Pem+C	PR	90	−44.6	12.7	21.3
DEID-002	EGFR+/Hi	L858R	Osim	PR	60	−42.1	16.8	22.5
DEID-022	EGFR+/Hi	L858R	Osim	PR	40	−39.8	16.2	21.1
DEID-007	EGFR+/Hi	Exon19del	Osim	PR	45	−38.9	15.3	20.7
DEID-021	EGFR−/Hi	WT	Pem+C	PR	88	−36.4	11.3	19.6
DEID-004	EGFR+/Lo	L858R	Osim	PR	2	−35.7	13.2*	19.8
DEID-009	EGFR−/Hi	WT	Pem+C	PR	75	−33.2	10.4*	18.9
DEID-019	EGFR+/Hi	T790M	Osim	PR	55	−31.6	11.9*	17.4
DEID-011	EGFR−/Hi	WT	Pem+C	PR	65	−29.1	9.8*	16.5
DEID-001	EGFR+/Hi	Exon19del	Osim	PR	85	−28.4	14.1	18.2
DEID-017	EGFR−/Lo	WT	Pem+C	SD	10	−14.5	6.1*	13.9
DEID-006	EGFR+/Lo	L858R	Osim	SD	15	−12.8	8.4*	14.6*
DEID-013	EGFR−/Lo	WT	Chemo	SD	3	−8.4	5.2*	12.1*
DEID-015	EGFR−/Lo	WT	Chemo	SD	1	−5.2	4.6*	10.8*
DEID-023	EGFR−/Lo	WT	Chemo	SD	4	−3.1	4.9*	11.5*
DEID-018	EGFR−/Lo	WT	Pem+C	PD	6	+15.2	4.3*	11.2*
DEID-014	EGFR−/Lo	WT	Chemo	PD	8	+18.3	3.1*	9.4*
DEID-016	EGFR−/Lo	WT	Chemo	PD	12	+22.7	2.8*	8.2*
DEID-024	EGFR−/Lo	WT	Chemo	PD	2	+28.4	2.4*	7.3*

*Event occurred (progression for PFS, death for OS). Unmarked = censored.
BOR = Best Overall Response; TLC = Target Lesion Change; Osim = Osimertinib; Pem+C = Pembrolizumab + Chemotherapy.