

Immune correlates in a real-world EGFR-mutated non-small cell lung cancer cohort before and after first-line osimertinib

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INTRODUCTION

- Treatment with osimertinib has been shown to induce tumor microenvironment changes in *EGFR*-mutated non-small cell lung cancer (NSCLC)
- Optimal systemic therapy after osimertinib resistance is not well established
- We present immune biomarkers and cell infiltrates in tumor samples before and after osimertinib treatment in a retrospective, real-world cohort
- This investigation may inform drug development and patient selection for subsequent therapies

METHODS

- Patients with *EGFR* exon 19 deleted or L858R altered NSCLC treated with first-line (1L) osimertinib monotherapy who underwent DNA and RNA sequencing were identified in the Tempus database (N=525)
- Somatic gene testing include pathogenic/likely pathogenic short variants, copy number amplifications (>=8 copy numbers), biallelic deletions, and fusions
- RNA expression was normalized as transcripts per million (TPM) and reported as log2(TPM+1)
- Immune infiltration was estimated using quanTISEq deconvolution
- Tumor mutational burden (TMB) and PD-L1 were evaluated via DNA sequencing and immunohistochemistry
- Groups were compared using Chi-squared/Fisher’s and Wilcoxon rank sum tests for categorical and continuous variables, respectively

Figure 1. Study Cohort

Figure 1. The cohort included patient samples collected either in the treatment-naïve or post-osimertinib settings. Inclusion criteria were osimertinib monotherapy as 1L treatment, presence of an *EGFR* exon 19 deletion or L858R mutation, and osimertinib treatment initiation within one year of sample collection. **Table 1.** The cohort included 525 patients with *EGFR*-altered NSCLC who were treated with 1L osimertinib monotherapy. Median age at NSCLC diagnosis was 66 years (range 27 – 88). Patients were predominantly female (69%) and had a history of never-smoking (54%).

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SUMMARY

- TMB and PD-L1 expression were higher in post-osimertinib treatment tissue samples
- However, overall immune cell infiltration was paradoxically lower in post-treatment samples
- This may reflect immunosuppressive remodeling from acquired osimertinib resistance and may provide context for limited clinical activity of anti-PD-(L)1 therapies in second-line settings

RESULTS

Table 2. Immune Cell Infiltrates Pre- and Post-Osimertinib Treatment

	Overall N = 557	Pre-treatment N = 378	Post-treatment N = 179	p-value ¹
B cells				
Median (Q1, Q3)	3.37 (2.47, 4.99)	3.74 (2.63, 5.38)	2.79 (2.19, 3.76)	<0.001
Min, Max	0.15, 59.84	0.15, 59.84	0.33, 20.34	
Unknown	37	25	12	
Unknown	37	25	12	
Dendritic cells				
Median (Q1, Q3)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.2
Min, Max	0.00, 3.70	0.00, 3.70	0.00, 1.93	
Unknown	37	25	12	
Unknown	37	25	12	
M1 Macrophages				
Median (Q1, Q3)	8.79 (6.02, 12.74)	9.46 (6.41, 13.00)	8.14 (5.37, 12.01)	0.034
Min, Max	0.34, 51.64	0.78, 48.97	0.34, 51.64	
Unknown	37	25	12	
Unknown	37	25	12	
M2 Macrophages				
Median (Q1, Q3)	6.63 (4.38, 8.98)	7.03 (4.48, 9.08)	6.15 (3.90, 8.60)	0.06
Min, Max	0.00, 29.96	0.00, 22.66	0.00, 29.96	
Unknown	37	25	12	
Unknown	37	25	12	
Monocytes				
Median (Q1, Q3)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.7
Min, Max	0.00, 13.35	0.00, 4.78	0.00, 13.35	
Unknown	37	25	12	
Unknown	37	25	12	
NK cells				
Median (Q1, Q3)	2.92 (2.25, 3.58)	3.10 (2.45, 3.75)	2.52 (1.88, 3.22)	<0.001
Min, Max	0.58, 10.70	0.73, 10.70	0.58, 5.39	
Unknown	37	25	12	
Unknown	37	25	12	
Neutrophils				
Median (Q1, Q3)	8.80 (6.74, 11.07)	9.20 (7.08, 11.55)	8.03 (6.00, 10.01)	<0.001
Min, Max	0.00, 42.82	0.00, 36.96	0.00, 42.82	
Unknown	37	25	12	
Unknown	37	25	12	
Other				
Median (Q1, Q3)	60.88 (50.90, 68.68)	57.73 (49.27, 65.57)	66.48 (57.94, 73.15)	<0.001
Min, Max	0.00, 87.57	0.00, 86.12	0.00, 87.57	
Unknown	37	25	12	
Unknown	37	25	12	
CD4 T cells				
Median (Q1, Q3)	0.00 (0.00, 0.20)	0.00 (0.00, 0.79)	0.00 (0.00, 0.00)	0.002
Min, Max	0.00, 60.09	0.00, 60.09	0.00, 37.82	
Unknown	37	25	12	
Unknown	37	25	12	
CD8 T cells				
Median (Q1, Q3)	0.31 (0.00, 0.92)	0.45 (0.00, 1.13)	0.03 (0.00, 0.67)	<0.001
Min, Max	0.00, 9.32	0.00, 9.32	0.00, 5.36	
Unknown	37	25	12	
Unknown	37	25	12	
Tregs				
Median (Q1, Q3)	3.87 (2.64, 5.83)	4.27 (2.81, 6.20)	3.26 (2.25, 4.57)	<0.001
Min, Max	0.00, 18.14	0.49, 18.14	0.00, 14.37	
Unknown	37	25	12	
Unknown	37	25	12	

¹Wilcoxon rank sum test

Table 2. Among 10 immune cell subtypes assessed, infiltration of M1 macrophages, neutrophils, regulatory T, B, natural killer, and CD8+ T cells were significantly lower in post- than pre-treatment samples.

Figure 2. Somatic Landscape Pre- and Post- Osimertinib Treatment

Figure 2. In pre- and post-treatment samples, the most common mutations occurred in *TP53* (65% vs. 72%), *CDKN2A* (22% vs. 32%), *CDKN2B* (20% vs. 30%), *MTAP* (16% vs. 27%), and *RB1* (8% vs. 16%). Known mechanisms of resistance, such as the development of *MET* (0.3% vs. 16%) and *EGFR* C797S (0.5% vs. 7.8%) mutations, were also observed.

Figure 3. Immune Cell Correlates Pre- and Post-Osimertinib Treatment

Figure 3. Median (interquartile range) TMB was higher in post- than pre-treatment samples (4.74 [2.63, 6.84] vs. 3.68 [2.11, 5.79]; p<0.001). The frequency of high TMB (≥10 mut/mB) and PD-L1 expression (≥50%) was greater in post- than pre-treatment samples (11.1% vs. 3.7%, p=0.001; 31.4% vs. 14.7%, p<0.001).

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