Integrating Clinicopathologic and Genomic Features to Identify Patients at Risk of Earlier Progression to First-Line Osimertinib in EGFR-Mutant NSCLC

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Background: With the recent approvals of the FLAURA2 and MARIPOSA regimens in *EGFR*-mutant non-small cell lung cancer (NSCLC), identifying the clinico-genomic features predictive of suboptimal outcomes with first-line osimertinib monotherapy is critical in guiding upfront treatment selections.

Methods: This is a multicenter retrospective study enrolling patients with advanced NSCLC harboring common *EGFR* mutations (exon 19 deletions [ex19del], L858R) treated with first-line osimertinib monotherapy across 12 centers. Clinicopathologic and genomic features were correlated with real-world progression-free survival (rwPFS). Comprehensive baseline genomic data on tumor tissue were available for DFCI and MSKCC.

Results: A total of 1327 patients were enrolled; median age was 67 years-old, 62.5% had an ex19del, 51.5% had *TP53* mutated ($TP53^{MUT}$, n=829 with *TP53* available on baseline tumor tissue). In the whole cohort, with median follow-up of 45.1 months (95%CI 42.3-47.9), median rwPFS was 16.0 months (95%CI 15.0-17.3), median overall survival was 37.0 months (95%CI 34.9-39.6). **Table 1** shows baseline clinicopathologic features associated with rwPFS.

The strongest predictors of very-early (<6 months) PFS in a multivariable model were PD-L1 (adjusted HR [aHR] 1.74 for ≥50% versus 0%), ECOG-PS (aHR 1.63 for 1 versus 0; aHR 2.26 for 2 versus 0), *TP53* (aHR 1.36 for $TP53^{MUT}$ versus $TP53^{WT}$) (all p<0.001).

Looking separately at ex19del and L858R, $TP53^{MUT}$ was associated with shorter rwPFS in ex19del (aHR 1.67, p<0.001) but not in L858R (aHR 1.08, p=0.6), after adjusting for histology, ECOG-PS, metastatic sites, PD-L1, age, sex.

The most common co-mutations detected (comprehensive genomic analysis for DFCI+MSKCC, n=313) were in *TP53* (67%), *RB1* (10%), *RBM10* (9%). *RBM10* mutations were enriched in L858R (18.5%) versus ex19del (3.3%) (p<0.001). At median follow up of 38.2 months (95%CI 34.9-43.4), loss-of-function mutations in *KMT2D* (HR 8.5, p<0.001), *RB1* (HR 1.75, p=0.01), *TP53* (HR 1.41, p=0.01), *CREBBP* (HR 3.03, p=0.01), *ATM* (HR 2.4, p=0.02*), RBM10* (HR 1.5, p=0.04) predicted shorter rwPFS.

Next, we investigated the role of concurrent tumor suppressor gene (*TSG*) alterations (*RBM10, CREBBP, BRCA1/2, PTEN, SMAD4, SMARCA4, ARID1A, ATM, APC, NF1, RB1, CDKN2A, KMT2D, KEAP1, ARID2*, *STK11*) in the same cohort. Combining *TP53* and *TSG,* patients with $TP53^{MUT}$ plus at least one TSG^{MUT} had the shortest rwPFS compared to $TP53^{WT}$-TSG^{WT}, $TP53^{MUT}$-TSG^{WT} *and* $TP53^{WT}$-TSG^{MUT} (11.4, 21.9, 17.1, 17.4 months, respectively, p=0.004).

Conclusions: In this multicenter real-world cohort, baseline $TP53^{MUT}$, PD-L1≥50%, ECOG-PS ≥1 were the strongest predictors of very-early progression to first-line

osimertinib. Integrating *TP53* with *TSG* profiling further refined risk stratification, identifying patients with very short rwPFS.

Table 1. Univariable and multivariable analyses for rwPFS to first-line osimertinib considering baseline clinicopathologic features.

Variable	Median rwPFS (months)	Univariable HR (95%CI)	p-value	Multivariable HR (95%CI)	p-value
EGFR mutation					
Ex19del-ref vs L858R	17.5 vs 13.9	1.32 (1.16-1.50)	< 0.001	1.23 (1.02-1.49)	0.03
Sex					
Female-ref vs Male	17.5 vs 13.9	1.20 (1.05-1.37)	0.007	1.30 (1.07-1.58)	0.008
History of smoking					
Ever-ref vs never	15.1 vs 16.3	0.95 (0.83-1.08)	0.4	0.58 (0.70-1.03)	0.1
Race					
Asian-ref vs others	15.8 vs 18.4	0.94 (0.67-1.30)	0.7	1.10 (0.68-1.78)	0.7
Asian-ref vs white	15.8 vs 16.0	1.01 (0.83-1.22)	0.9	1.12 (0.83-1.52)	0.4
Age					
>65 years-old-ref versus <65 years-old	17.3 vs 15.2	1.18 (1.04-1.33)	0.01	1.17 (0.96-1.41)	0.1
Histology					
Adenocarcinoma-ref vs Others	16.3 vs 8.7	1.94 (1.35-2.7)	<0.001	2.53 (1.47-4.38)	<0.001
ECOG-PS					
0-ref vs 1	19.4 vs 15.3	1.28 (1.11-1.47)	<0.001	1.24 (1.02-1.52)	0.03
0-ref vs ≥ 2	19.4 vs 10.2	2.08 (1.66-2.59)	<0.001	2.09 (1.52-2.87)	<0.001
Brain metastasis					
No-ref vs Yes	18.6 vs 13.1	1.47 (1.29-1.67)	<0.001	1.31 (1.08-1.59)	0.007
Liver metastasis					
No-ref vs Yes	17.3 vs 11.2	1.56 (1.32-1.85)	<0.001	1.20 (0.92-1.55)	0.17
Bone metastasis					
No-ref vs Yes	18.8 vs 14.0	1.42 (1.26-1.61)	<0.001	1.22 (1.01-1.48)	0.04
PD-L1 TPS					
<1%-ref vs 1-49%	18.7 vs 14.9	1.16 (1.01-1.36)	0.04	1.12 (0.91-1.36)	0.28
<1%-ref vs ≥50%	18.7 vs 11.0	1.73 (1.42-2.11)	<0.001	1.87 (1.43-2.45)	<0.001
Baseline *TP53* status on tumor tissue					
Wild-type-ref vs Mutated	20.0 vs 12.7	1.51 (1.28-1.88)	<0.001	1.37 (1.13-1.66)	0.001