

Genomic Alterations Without Approved 1L Targeted Therapies in Patients With aNSCLC PD-L1 ≥50% Treated With Immunotherapy

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Conclusions

- Patients with aNSCLC PD-L1 ≥50% treated with IO + chemotherapy were younger, had better ECOG PS, and had greater metastatic burden compared with patients treated with IO monotherapy
- The prevalence of non-AGAs (i.e., other important clinically relevant alterations not targetable in 1L) aligned with expectations
 - TP53* and *KRAS* (73% and 44% of patients, respectively) were most prevalent
 - KEAP1* and *STK11* were observed in 9.5% and 8.5% of patients
- Among patients with PD-L1 ≥50% aNSCLC without *EGFR*, *ALK*, or *ROS1* mutations, alterations in key genes (*KEAP1*, *STK11*, *KRAS*, *TP53*) were not independently associated with rwOS or rwTTP upon treatment with IO monotherapy or IO + chemotherapy
- While the association was not statistically significant, *KEAP1*/*STK11* alterations showed consistent directional associations with poorer survival that warrant further evaluation in larger cohorts
- Baseline demographic and clinical characteristics remained the dominant determinants of outcomes, underscoring the need for improved risk stratification and identification of novel therapies for high-risk subgroups

Introduction

- Immunotherapy-based regimens are standard first-line (1L) treatment for patients with advanced non-small cell lung cancer (aNSCLC) and programmed cell death ligand 1 (PD-L1) tumor proportion score (TPS) ≥50% who lack actionable genomic alterations (AGAs)^{1–3}
 - As the landscape of biomarker-directed therapies continues to evolve, the definition of "actionable" has expanded over time; for this study, AGAs were operationally defined as *EGFR*, *ALK*, and *ROS1* alterations
- Although PD-L1 expression (≥50%) can provide insights into whether patients may preferentially benefit from immunotherapy, additional factors may account for non-responding patients⁴
- Many tumors lacking actionable genomic alterations instead harbor alterations in tumor suppressor genes, such as *TP53*, *STK11*, and *KEAP1*. Current evidence suggests that alterations in these genes may be associated with poor prognosis⁵
- The association of these alterations with clinical outcomes among patients with PD-L1 ≥50% receiving anti-PD-(L)1-based regimens remains unclear
- This study evaluated the real-world prevalence of key genomic alterations and their associations with outcomes among patients with aNSCLC receiving anti-PD-(L)1-based regimens in the United States

Study Limitations

- Data limitations: Real-world electronic health record data may be incomplete or lack sufficient detail for study analyses
- Generalizability of study results: Oncology practices included in this study are part of the database's oncology practice network, and results may not be generalizable to other populations
- Biomarker testing: Testing requirements may introduce immortal time bias, and liquid biopsy false negatives may lead to biomarker misclassification

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Methods

- Real-world data were extracted from the Flatiron Health-Foundation Medicine NSCLC Clinico-Genomic Database
- Patients with aNSCLC who initiated 1L anti-PD-(L)1-based therapy between January 1, 2018, and June 30, 2025; had PD-L1 TPS ≥50%; and had no canonical targetable alterations (specifically, *EGFR*, *ALK*, or *ROS1*) were included
 - Inclusion and exclusion criteria are shown in **Table 1**
- Prevalence of key non-AGAs (i.e., other important clinically relevant alterations not targetable in 1L, specifically *STK11*, *KEAP1*, *KRAS*, *TP53*) was quantified to characterize genomic distribution in the 1L immunotherapy (IO)–treated population
- The prognostic effect of each non-AGA was assessed using Kaplan–Meier analyses comparing real-world overall survival (rwOS) and time to progression (rwTTP) between patients with alteration-positive aNSCLC and those with wild-type aNSCLC
- The predictive effect of non-AGAs was evaluated using Cox proportional hazards models evaluating treatment (IO monotherapy vs IO + chemotherapy), alteration status, and treatment-by-alteration interaction terms
- Multivariable Cox models were used to identify demographic, clinical, and composite mutational profiles associated with rwOS, rwTTP, and real-world response rate (rwRR) overall and stratified by 1L treatment regimen

Table 1. Eligibility Criteria

Inclusion Criteria	- Patients in the Q3 2025 Flatiron Health-Foundation Medicine NSCLC CGDB - Patients with a diagnosis of aNSCLC on or after January 1, 2018 1L treatment with any IO-based therapy (inclusive of IO monotherapy and IO + chemotherapy) on or after January 1, 2018 - Has no AGAs (<i>EGFR</i>, <i>ALK</i>, <i>ROS1</i>) before the start of 1L therapy - Has evidence of PD-L1 TPS testing and a result ≥50% before the start of 1L therapy^a - Initiated 1L therapy at least 6 months before the data cutoff date
Exclusion Criteria	- Patients with another primary cancer diagnosis (except for non-melanoma skin cancer) at any time 1L therapy initiated >120 days after aNSCLC diagnosis, as a proxy for possible misclassifications of 1L treatment due to out of network treatment - Histology not otherwise specified

1L, first-line; AGA, actionable genomic alteration; aNSCLC, advanced non-small cell lung cancer; CGDB, Clinico-Genomic Database; IO, immunotherapy; Q3, third quarter; TPS, tumor proportion score.
^aTested using PD-L1 assay (22C3).

Results

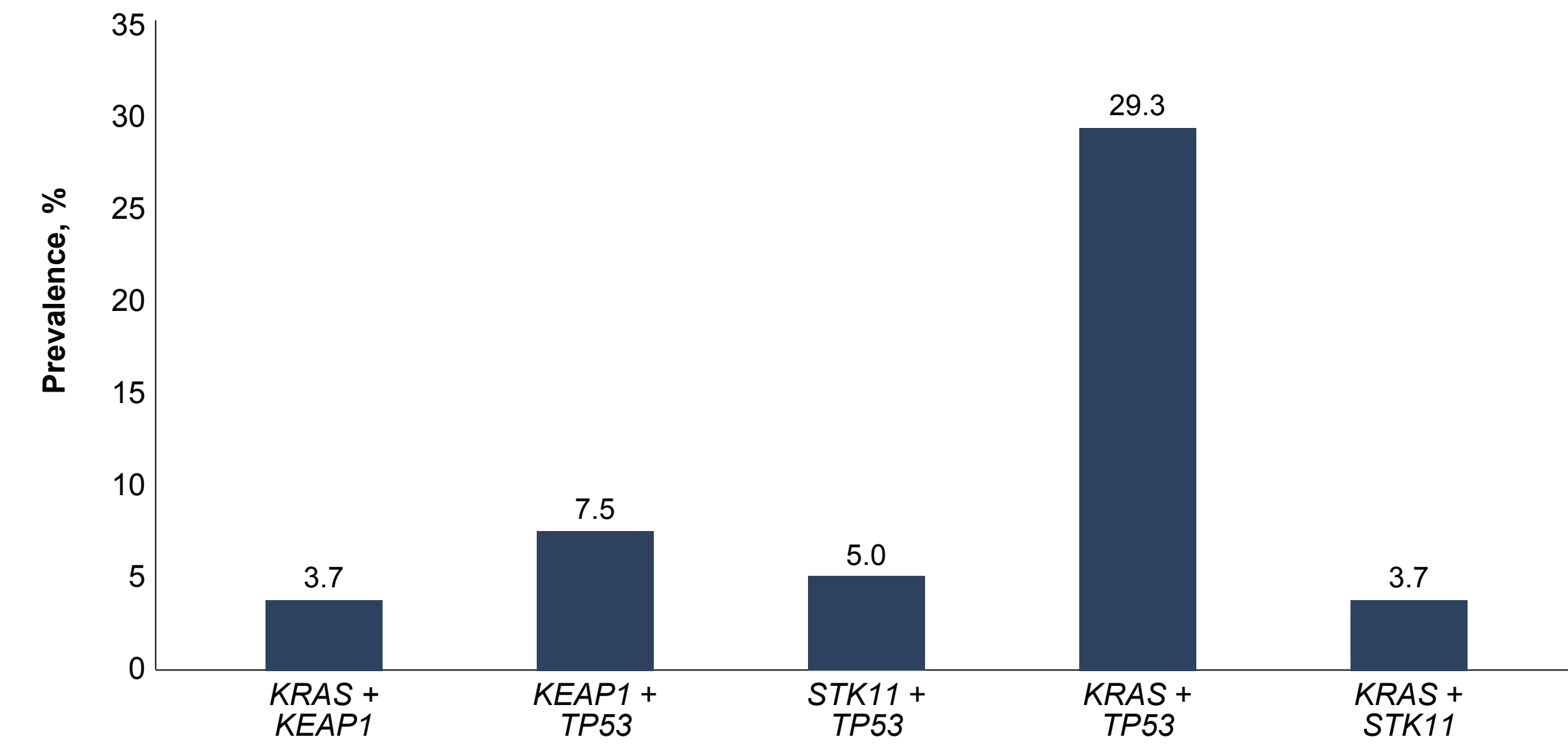
- This real-world analysis included 1240 patients (anti-PD-[L]1 monotherapy, n=744; anti-PD-[L]1 + chemotherapy, n=496) with a median follow-up of 13.3 months (interquartile range [IQR], 4.5–31.0)
- Median age was 71 years (IQR, 63–77); 48.6% were male (**Table 2**), 66.3% were White, 1.4% were Asian, 92.5% had a smoking history, and 79.4% had non-squamous histology
- The overall prevalence of *TP53*, *KRAS*, *KEAP1*, and *STK11* alterations was 73.3%, 43.9%, 9.5%, and 8.5%, respectively

Table 2. Baseline Demographic and Disease Characteristics

Characteristic	Overall (N=1240)	IO Monotherapy (n=744)	IO + Chemotherapy (n=496)
Median age, years	71.0	73.0	68.0
Female, n (%)	637 (51.4)	399 (53.6)	238 (48.0)
Non-AGAs, n (%)			
<i>KEAP1</i> (1205 tested)	114 (9.5)	60 (8.1)	54 (10.9)
<i>KRAS</i> (1237 tested)	543 (43.9)	319 (42.9)	224 (45.2)
<i>STK11</i> (1230 tested)	104 (8.5)	53 (7.1)	51 (10.3)
<i>TP53</i> (1237 tested)	907 (73.3)	548 (73.7)	359 (72.4)
PD-L1 score, n (%)			
50%–89%	672 (54.2)	398 (53.5)	274 (55.2)
≥90%	568 (45.8)	346 (46.5)	222 (44.8)
ECOG PS, n (%)			
0–1	764 (61.6)	452 (60.8)	312 (62.9)
≥2	271 (21.9)	183 (24.6)	88 (17.7)
Unknown/not documented	205 (16.5)	109 (14.7)	96 (19.4)

AGA, actionable genomic alteration; ECOG PS, Eastern Cooperative Oncology Group performance status; IO, immunotherapy; PD-L1, programmed cell death ligand 1.

Figure 1. Prevalence of Co-occurring Non-AGAs in Genes of Interest



AGA, actionable genomic alteration.

- There was frequent co-occurrence of *KRAS*/*TP53* (29.3%) and *KEAP1*/*TP53* (7.5%) (**Figure 1**). Other alterations without approved therapies included *MTAP* loss (12.9%), *PIK3CA* (10.9%), *RBM10* (10.0%), and *SMARCA4* (4.3%)

Clinical and Demographic Predictors of rwOS

- After multivariable adjustment within the anti-PD-(L)1 monotherapy group, a higher hazard of mortality was associated with older age, no smoking history, squamous histology, poor Eastern Cooperative Oncology Group performance status (ECOG PS), and brain metastases (**Figure 2**)
- Within the anti-PD-(L)1 + chemotherapy group, higher hazard of mortality was associated with male sex, poor ECOG PS, and higher tumor burden (number of metastatic sites ≥3; **Figure 3**)

Genomic Predictors of rwOS and rwTTP

- KEAP1*, *STK11*, *KRAS*, or *TP53* status was not significantly associated with rwOS in either treatment group
- A non-significant numerical trend toward increased mortality was observed in patients with *KEAP1*- or *STK11*-positive aNSCLC with PD-L1 ≥50% receiving IO + chemotherapy, and in those with *STK11*-positive aNSCLC with PD-L1 ≤50% receiving IO monotherapy
 - KEAP1*-positive: IO monotherapy, HR 1.05 (95% CI, 0.73; 1.50); IO + chemotherapy, HR 1.38 (95% CI, 0.96; 1.98)
 - STK11*-positive: IO monotherapy, HR 1.43 (95% CI, 0.99; 2.06); IO + chemotherapy, HR 1.34 (95% CI, 0.91; 1.98)
- This remained consistent in rwOS multivariable models after stratifying *KRAS* mutations by *G12C* status
- Mutation status for *KEAP1*, *STK11*, *KRAS*, and *TP53* did not significantly affect rwTTP in either the IO monotherapy or IO + chemotherapy subgroup

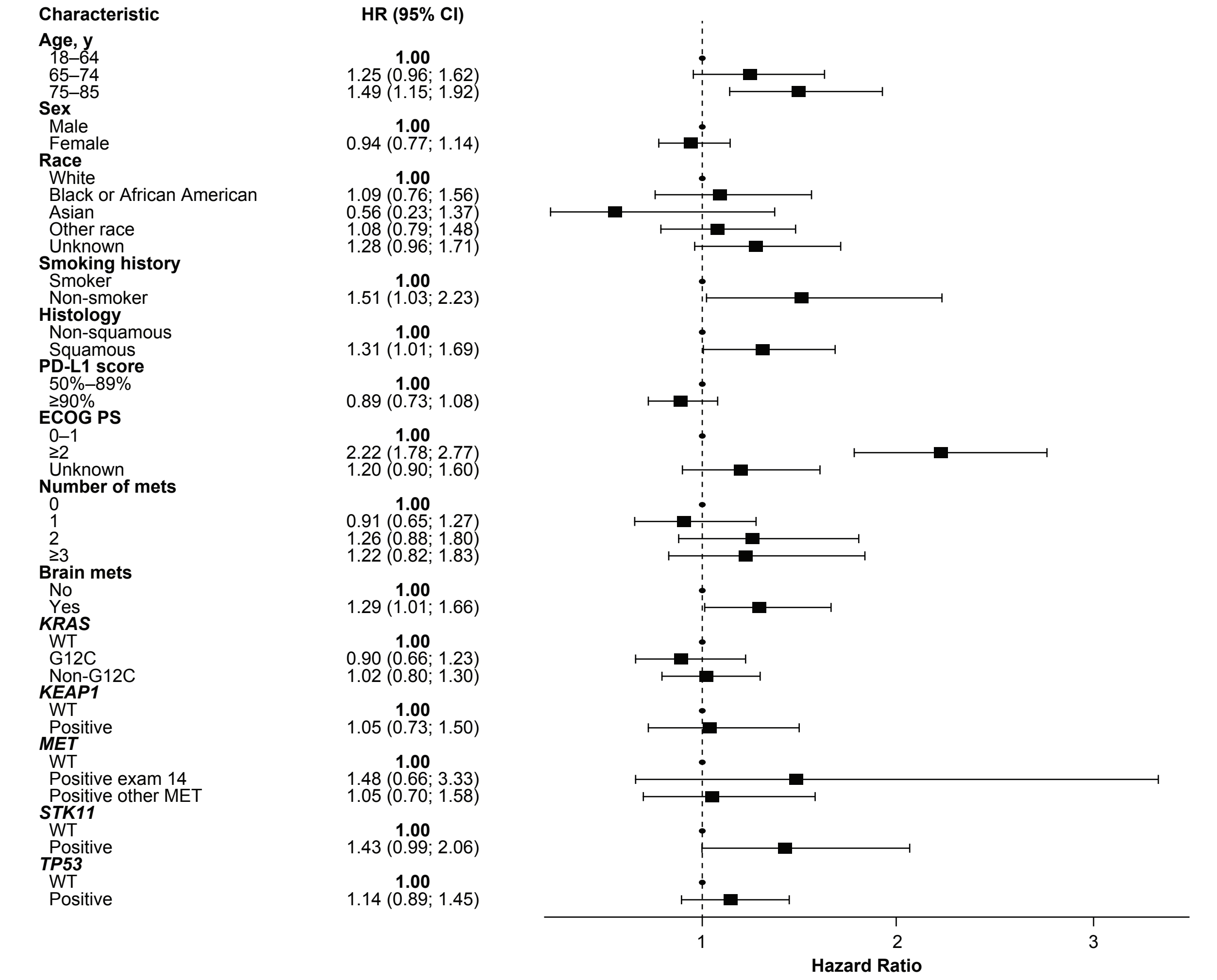
Table 3. rwRR by Non-AGA Status

Non-AGA Status	IO Monotherapy		IO + Chemotherapy	
	n	rwRR (95% CI), %	n	rwRR (95% CI), %
Overall	744	39.8 (36.2; 43.4)	496	60.9 (56.4; 65.2)
<i>KEAP1</i>				
WT	565	39.6 (35.6; 43.8)	377	62.1 (57.0; 67.0)
Positive	60	33.3 (21.7; 46.7)	54	50.0 (36.1; 63.9)
<i>STK11</i>				
WT	590	39.7 (35.7; 43.7)	391	62.7 (57.7; 67.5)
Positive	53	32.1 (19.9; 46.3)	51	49.0 (34.8; 63.4)
<i>KEAP1</i> and <i>STK11</i>				
Both WT	533	40.3 (36.1; 44.6)	343	63.3 (57.9; 68.4)
Both positive	13	23.1 (5.0; 53.8)	13	46.2 (19.2; 74.9)

AGA, actionable genomic alteration; HR, hazard ratio; IO, immunotherapy; rwRR, real-world response rate; WT, wild-type.

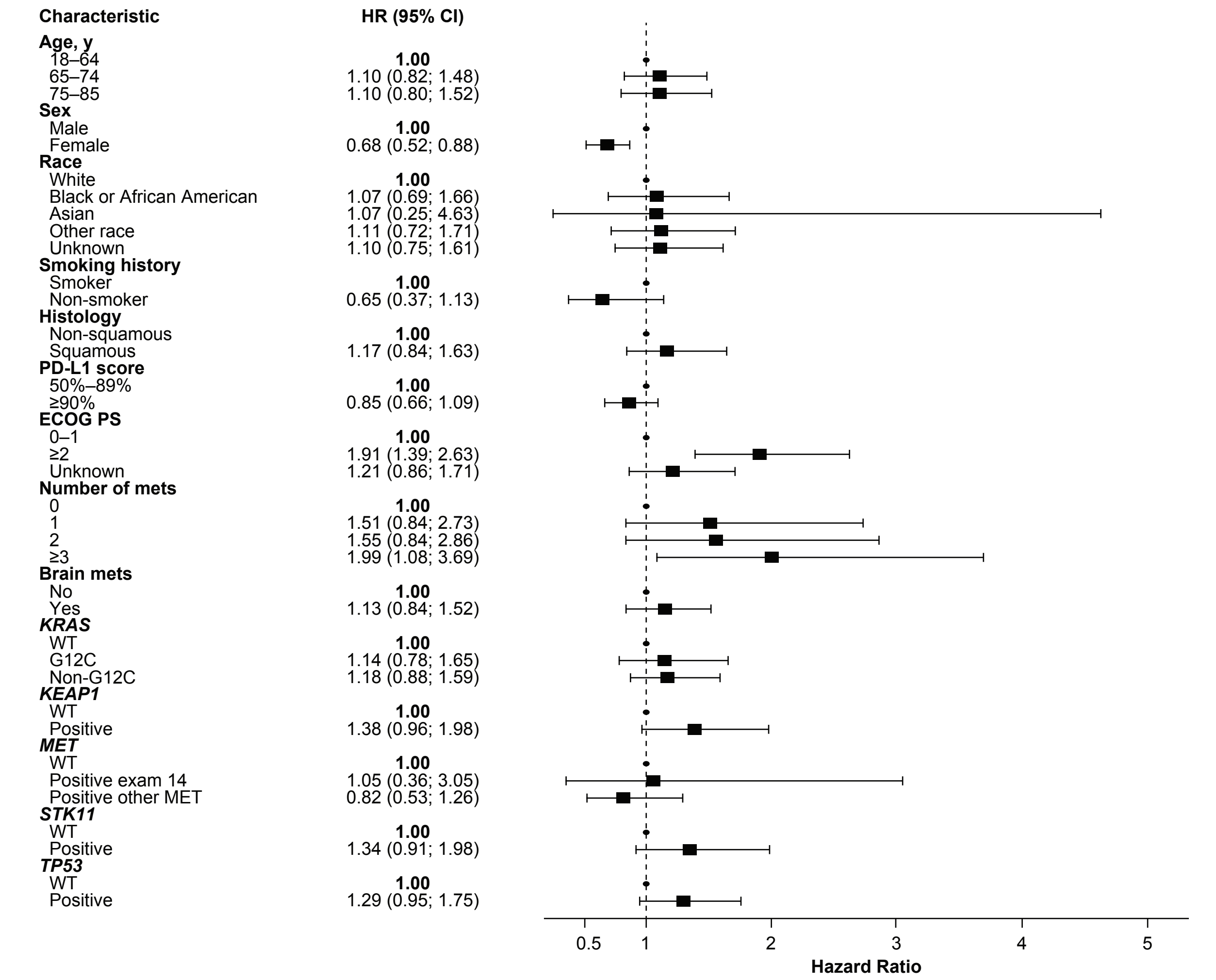
- Across all patients, those treated with IO + chemotherapy demonstrated a higher rwRR than patients treated with IO monotherapy (60.9% vs 39.8%)
- Across treatment groups, patients with *KEAP1*- and *STK11*-mutation–positive aNSCLC had lower rwRR than patients without these mutations with greater differences in response rates observed among those receiving IO + chemotherapy compared with those receiving IO monotherapy (**Table 3**)

Figure 2. rwOS in Patients Treated With IO Monotherapy



ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IO, immunotherapy; mets, metastasis; PD-L1, programmed cell death ligand 1; rwOS, real-world overall survival; WT, wild type.

Figure 3. rwOS in Patients Treated With IO + Chemotherapy



ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IO, immunotherapy; mets, metastasis; PD-L1, programmed cell death ligand 1; rwOS, real-world overall survival; WT, wild type