Clinical Cancer Research

Tumor Mutation Burden and Efficacy of EGFR-Tyrosine Kinase Inhibitors in Patients with *EGFR*-Mutant Lung Cancers

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Abstract

Purpose: Tumor mutation burden (TMB) is a biomarker of response to immune checkpoint blockade (ICB). The impact of TMB on outcomes with targeted therapies has not been explored.

Experimental Design: We identified all patients with metastatic *EGFR* exon19del or L858R-mutant lung cancers treated with first/second-generation EGFR tyrosine kinase inhibitors (TKIs) with pretreatment next-generation sequencing data (MSK-IMPACT assay). The effect of TMB on time-to-treatment discontinuation (TTD) and overall survival (OS) were evaluated in univariate and multivariate analyses. *EGFR* wild-type lung adenocarcinoma samples were used for comparison.

Results: Among 153 patients with *EGFR*-mutant lung cancer, TMB was lower compared with EGFR wild-type (n = 1,849; median 3.77 vs. 6.12 mutations/Mb; $P < 0.0001$) with a broad range (0.82–17.9 mutations/Mb). Patients with *EGFR*-mutant lung cancer whose tumors had TMB in the high tertile had shorter TTD (HR, 0.46; $P = 0.0008$) and OS (HR, 0.40; $P = 0.006$) compared with patients with low/intermediate TMB. Evaluating by median TMB, there was significantly shorter TTD and OS for patients with higher TMB (TTD, $P = 0.006$; OS, $P = 0.03$). In multivariate analysis, TTD and OS remained significantly longer in the low/intermediate tertile compared with high TMB (HR = 0.57, $P = 0.01$; HR = 0.50, $P = 0.02$, respectively). In paired pretreatment and post-progression samples, TMB was increased at resistance (median 3.42 vs. 6.56 mutations/Mb; $P = 0.008$).

Conclusions: TMB is negatively associated with clinical outcomes in metastatic patients with *EGFR*-mutant lung cancer treated with EGFR-TKI. This relationship contrasts with that seen in lung cancers treated with immunotherapy.

See related commentary by Cheng and Oxnard, p. 899

Introduction

Multiple groups have demonstrated the correlation between elevated somatic tumor mutation burden (TMB) and the increased efficacy of immune checkpoint blockade (ICB) response in lung cancers (1, 2) and other tumor types (2–8). The implication of TMB in other treatment settings, such as targeted therapy in oncogene-driven cancers, is unknown.

Approximately 20% of patients with non–small cell lung cancers (NSCLC) harbor an activating somatic mutation in the *epidermal growth factor receptor* (*EGFR*) gene (9–11), the most common of which are exon 19 deletion (ex19del) or the exon 21 substitution of arginine to leucine at amino acid 858 (L858R) mutation (10, 12). Small-molecule tyrosine kinase inhibitors (TKIs) against EGFR can be broadly delineated into first/second-generation TKIs (erlotinib/afatanib/gefitinib) and third-generation TKIs (osimertinib). First/second-generation EGFR-TKIs were the only available standard first-line therapy options for patients with *EGFR*-mutant lung cancers until recently (13), and are associated with a high response rate (~70%) and median progression–free survival (PFS) of 9 to 12 months (13–20). Still, there is a wide variation in the duration of response and survival in these patients, but no clinical or molecular markers are currently routinely used to estimate the likely benefit of TKI-based therapy.

Although increased TMB is correlated with improved outcomes with immunotherapy, we hypothesized an inverse relationship with efficacy of targeted therapy in patients with *EGFR*-mutant lung cancers, proposing that additional mutations represent potential pathways for resistance to targeted therapies. To explore this hypothesis, we identified all patients with *EGFR*-mutant lung cancers treated with EGFR-TKIs for whom TMB was available from

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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doi: 10.1158/1078-0432.CCR-18-1102

Translational Relevance

Tumor mutation burden (TMB) is an emerging predictive biomarker for response to immune checkpoint blockade in patients with lung cancer, but the impact of TMB on molecularly targeted therapies is unknown. In patients with *EGFR*-mutant lung cancers, we found an inverse relationship between TMB and clinical benefit of EGFR-tyrosine kinase inhibitors (EGFR-TKIs) as assessed by overall survival and time to treatment discontinuation. We speculate that increased TMB is associated with increased prevalence of resistance pathways. Consistent with this mechanism, we find that mutations in *TP53* are significantly more common in patients with high TMB and that *EGFR*-mutant tumors have higher TMB at the time of progression on EGFR-TKI compared with pretreatment. These data further refine the understanding of TMB and its varied, treatment context-specific, impact across lung cancers and provides additional guidance for predicting the durability of response to EGFR-TKIs.

targeted next-generation sequencing (NGS) (MSK-IMPACT), which has recently been demonstrated to closely estimate TMB derived from exome data (21, 22).

Materials and Methods

This study was undertaken at Memorial Sloan Kettering Cancer Center (New York, NY) in accordance with the United States Common Rule and was approved by the institutional review board. All patients involved provided informed written consent for analysis. We identified patients with metastatic *EGFR*-mutant lung cancers with sensitizing ex19del or L858R variants treated with first-/second-generation EGFR-TKIs (erlotinib, gefitinib, or afatanib) as initial TKI therapy. We then identified those patients that had targeted NGS with MSK-IMPACT (integrated mutation profiling of actionable cancer targets; ref. 23) performed on pre-EGFR–TKI tumor tissue. For comparison, 1,849 patients profiled by MSK-IMPACT from January 2014 to March 2018 with histologically proven lung adenocarcinoma that were *EGFR* wild-type were analyzed for TMB. An additional cohort of 62 lung adenocarcinomas with *EGFR* variants of unknown significance [VUS; defined as single nucleotide variants (SNV) or insertion/deletions without known targetable potential] were also analyzed for TMB to compare the effect of TMB among different classes of *EGFR*-mutations.

MSK-IMPACT is an FDA-approved NGS platform, in which tumor and normal DNA undergo targeted hybridization capture and deep-coverage NGS to detect somatic mutations, copy number changes, and select gene fusions in a custom gene panel of 341 (version 1), 410 (version 2), or 468 (version 3) genes (10, 22, 23). TMB was defined as the total number of nonsynonymous single nucleotide or insertion/deletion mutations divided by the coding region captured in each panel (341 genes, 0.98 Mb; 410 genes, 1.06 Mb; 468 genes, 1.22 Mb). Our group has recently demonstrated that information from targeted NGS testing with the MSK-IMPACT platform allows derivation of an accurate estimate of TMB compared with whole-exome sequenicng (21).

TMB was stratified by tertiles and by median within the *EGFR*-mutant cohort. Tertiles are described as low ($\leq$2.83 mutations/Mb), intermediate (2.84–4.85 mutations/Mb), and high (>4.85 mutations/Mb). Time to treatment discontinuation (TTD) was defined as the time from start of EGFR-TKI to last dose administered. Overall survival (OS) was defined as date of start of EGFR-TKI to date of death or last follow up. Differences in outcomes across TMB defined subgroups were analyzed using the Mann–Whitney test and the Wilcoxon signed-rank test was used for paired comparisons. Fisher exact test was used to compare the proportions. For survival analyses, Kaplan–Meier curves were compared using the Mantel–Cox log-rank test and HRs were calculated using Mantel–Haenszel method. Multivariate cox proportional hazards model analysis was performed integrating *TP53* mutation status, *EGFR* allele, and TMB.

Results

TMB in *EGFR*-mutant NSCLC

Samples collected between January 2010 and September 2017 from 3,077 patients with lung cancers underwent MSK-IMPACT testing, of whom 783 (25%) of the patients tested were found to have an *EGFR*-mutation. Of those patients, 153 met all criteria for the study population (had *EGFR* ex19del or L858R mutations, were targeted therapy naïve, were treated with first- or second-generation EGFR-TKIs and had confirmed metastatic disease at the time of NGS testing; Supplementary Fig. S1; Supplementary Table S1).

Of the 153 patients with *EGFR*-mutant lung cancer, 62% were never-smokers, 39% had an L858R mutation and 92% were treated with erlotinib as their first EGFR-TKI (Table 1; Supplementary Table S2). The median follow-up time in the cohort was 24 months. TMB was lower in patients with *EGFR*-mutant lung cancers compared with *EGFR* wild-type NSCLC (Mann–Whitney $P < 0.0001$; Fig. 1A). TMB in the L858R cohort was higher compared with ex19del (Mann–Whitney $P = 0.003$; Fig. 1B), despite no difference in smoking status (Fisher exact test $P = 0.23$) or presence of *TP53* comutation (Fisher exact test $P = 1.0$). There was a broad range of TMB within *EGFR*-mutant NSCLCs (range of 0.82–17.9 mutations/Mb), with distinct molecular landscape and rate of comutations (Fig. 1C).

Impact of TMB on TTD and OS

To assess the impact of TMB on the outcomes of patients with *EGFR*-mutant NSCLC, we divided the cohort into three groups [tertiles: low ($\leq$2.83 mutations/Mb), intermediate (2.84–4.85 mutations/Mb), high (>4.85 mutations/Mb)] based on TMB. In patients with *EGFR*-mutant lung cancers treated with EGFR-TKIs, TTD was the longest among patients with low or intermediate TMB compared with those with high TMB (medians of 17, 16, and 10 months, respectively; log-rank $P = 0.0003$; Fig. 1D). OS was improved in those with low or intermediate compared with high TMB (medians of 41, 37, and 21 months, respectively; log-rank $P = 0.02$; Fig. 1E). TTD and OS were similarly improved when patients were grouped above and below the median TMB (median TTD 17 vs. 10 months; HR, 0.56; 95% CI, 0.37–0.84; log-rank $P = 0.006$; median OS 41 vs. 29 months; HR, 0.52; 95% CI, 0.28–0.94; log-rank $P = 0.03$; Supplementary Fig. S2A and S2B).

Within several subgroups, TTD and OS were improved in those with low or intermediate TMB compared with those with high TMB (Fig. 2A and B), including within never-smokers (log-rank TTD, $P = 0.0007$; OS, $P = 0.02$) suggesting that smoking status was not the sole explanation for

Table 1. Patient characteristics. Clinical and molecular features of patients overall, and stratified by TMB tertile: low (≤2.83 mutations/Mb), intermediate (2.84–4.85 mutations/Mb), and high (>4.85 mutations/Mb).

	Total ($n = 153$)	1st tertile (≤2.83; $n = 60$)	2nd tertile (≤4.85; $n = 42$)	3rd tertile (>4.85; $n = 51$)
Median age (range)	64 (24–89)	63 (34–88)	66 (37–88)	65 (25–89)
Sex				
Female	101 (66%)	42 (70%)	30 (71%)	28 (55%)
Male	52	18	12	23
Smoking status				
Never	95 (62%)	39 (65%)	29 (69%)	27 (53%)
Ever (median pack years; range)	58 (10; 0.5–74)	21 (8; 3–74)	13 (6; 3–24)	24 (10; 0.5–46)
Year EGFR-TKI start				
2014 and earlier	36 (24%)	14 (23%)	12 (29%)	10 (20%)
2015	54 (35%)	24 (40%)	17 (40%)	14 (27%)
2016–2017	63	22	13	27
Mutation				
L858R	59 (39%)	16 (27%)	26 (62%)	27 (53%)
Exon 19 deletion	94	44	16	24
TKI used				
Erlotinib	141 (92%)	55 (92%)	38 (90%)	48 (94%)
Gefitinib	1	—	—	1
Afatanib	11	5	4	2
Oligoprogression[a]	15 (10%)	3 (5%)	9 (21%)	3 (6%)
Median TMB (range)	3.77 (0.43–17.92)	2.04 (0.82–2.83)	4.08 (3.06–4.72)	6.60 (4.92–17.92)

[a]Oligoprogression defined as radiographic/clinical progression of disease in ≤ 2 anatomic sites.

variation in TMB or outcomes. Unlike TMB, smoking status did not independently affect TTD or OS (log-rank TTD, $P = 0.25$; OS, 0.13). As we have previously demonstrated, *TP53* comutations were associated with inferior outcomes (24, 25). When looking at the *TP53* comutant cohort, there remained a significant difference in OS and TTD within the low/intermediate versus high TMB groups (log-rank TTD, $P = 0.02$; OS, $P = 0.02$), showing that *TP53* mutation status was not independently responsible for the differences in OS and TTD observed in the tertiles.

TMB and molecular landscape of EGFR-mutant NSCLC

We also examined the distribution of common comutations in the pre-EGFR–TKI samples in the context of TMB to determine whether known mechanisms were enriched in those with high TMB. Overall, 89 patients (59%) had concurrent *TP53* mutations and these were more common among patients with high TMB compared with low/intermediate TMB (53/102, 52%; 36/51, 71%, Fisher exact test $P = 0.037$; Supplementary Fig. S3). *PIK3CA* mutations were numerically, but not significantly, more common in those with high TMB (10/51, 14%; 9/102, 9%, Fisher exact test $P = 0.07$), while concurrent *SMARCA4* mutations were more common in those with high TMB (7/51, 14%; 3/102, 3%, Fisher exact test $P = 0.016$).

Multivariable analysis

To examine the effect of TMB on TTD and OS in the context of potential confounding variables associated with both TMB and outcomes, we performed multivariate analyses of TMB (low or intermediate vs. high), *TP53* status (wild-type vs. mutant), and *EGFR* allele (ex19del vs. L858R). Given that low and intermediate tertiles had overlapping outcomes in univariate analysis, these groups were combined for further evaluation. Low/intermediate TMB remained significantly correlated with improved TTD (HR, 0.57; 95% CI, 0.37–0.87; $P = 0.009$) and OS (HR, 0.50; 95% CI, 0.27–0.91; $P = 0.025$; Fig. 2C and D). When examined in multivariate analysis with TMB stratified > versus ≤ median, TTD was significantly improved in those with < median TMB (HR, 0.65; 95% CI, 0.43–0.99; $P = 0.038$), but OS was not significantly different (HR, 0.59; 95% CI, 0.31–1.11; $P = 0.10$; Supplementary Fig. S2C and S2D).

Differential resistance mechanisms by TMB

In the 30 patients who had MSK IMPACT testing performed on paired tissue taken pre-EGFR-TKI and at the time of resistance, TMB was significantly higher at resistance (median 3.42 vs. 6.56 mutations/Mb; Wilcoxon signed-rank test $P = 0.008$; Fig. 3A). In addition, 84 patients who progressed on EGFR-TKI underwent evaluation for T790M (using either ctDNA testing for *EGFR* T790M mutation, tissue PCR for T790M, and/or repeat MSK-IMPACT testing) and a T790M mutation was found in 45 patients (54%). The pretreatment TMB of patients who ultimately developed T790M resistance was numerically but not significantly lower compared with those without T790M mediated resistance (median 3.77 vs. 4.77 mutations/Mb; Mann–Whitney $P = 0.057$; Fig. 3B). In the 30 patients with pre- and post-EGFR-TKI paired NGS, each distinct non-T790M mechanism of acquired resistance occurred too infrequently to determine any relationship based on pretreatment TMB (Supplementary Table S3). Among 54 patients with tissue evaluated pathologically, one was found to have small-cell transformation at the time of EGFR-TKI resistance.

Discussion

TMB is an emerging predictive marker of ICB response (26), but its utility in other treatment paradigms such as targeted therapy has not previously been explored. In this analysis, we evaluated the utility of TMB as a predictive biomarker in *EGFR*-mutant lung cancers. Even though the absolute value of TMB observed in this *EGFR*-mutant lung cancer population is (as expected) less than that seen in patients with unselected lung cancer (21, 26, 27), we found a clinically meaningful diversity of TMB within this oncogene-defined group. We observed a negative relationship between TMB and clinical benefit, defined as time-to-treatment discontinuation and OS.

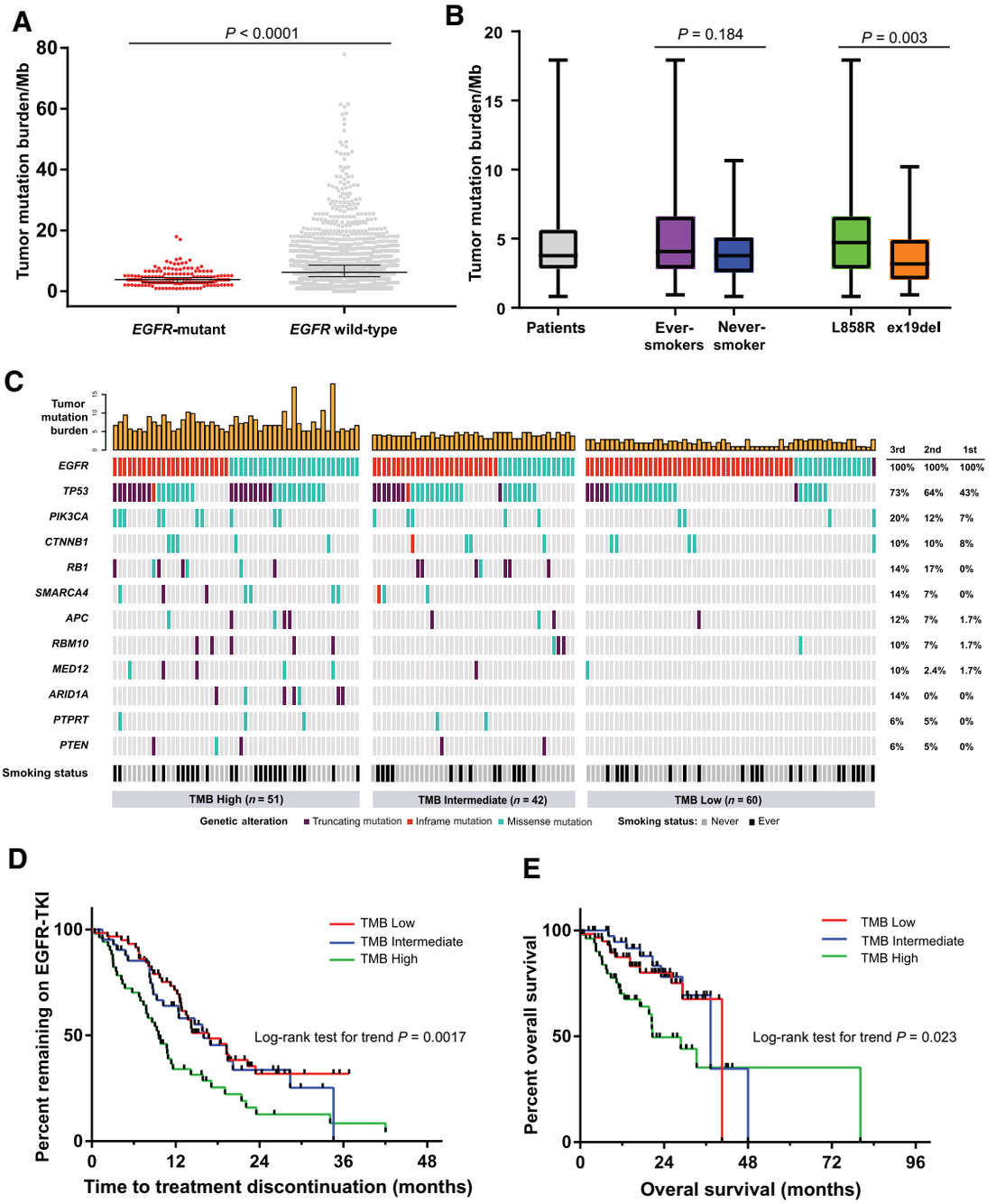
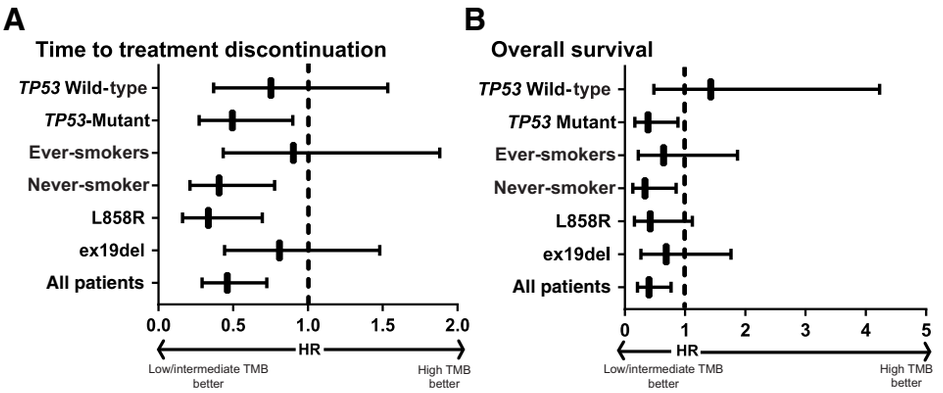


Figure 1.

A, Evaluation of patients with *EGFR*-mutant ($n = 153$) versus *EGFR* wild-type ($n = 1{,}849$) lung cancer. The horizontal line indicates the median and brackets the TMB intertertile range (tertiles: *EGFR*-mutant $\leq$ 2.83, 2.84–4.85, > 4.85 mutations/Mb; *EGFR* wild-type $\leq$ 4.08, 4.09–8.49, > 8.49 mutations/Mb). The median TMB for *EGFR*-mutant patients was 3.77 versus 6.12 mutations/Mb in *EGFR* wild-type patients (Mann–Whitney $P < 0.0001$). **B,** TMB in the ever-smoker group ($n = 58$) was similar to the never-smoker group ($n = 95$; median 4.08 vs 3.77 mutations/Mb; Mann–Whitney $P = 0.184$). TMB of patients with L858R ($n = 59$) was higher compared with exon 19 deletion (median 4.72 vs. median 3.17 mutations/Mb; Mann–Whitney $P = 0.003$). **C,** oncoprint for patients by TMB tertile. **D,** time to treatment discontinuation (TTD) evaluated by TMB: (lowest tertile: 16.7 months; intermediate: 16.0 months; high: 9.6 months; log-rank for trend $P = 0.002$). When evaluated by low/intermediate versus high TMB, the median TTD was 16.7 and 9.6 months, respectively, (HR, 0.46; 95% CI, 0.29–0.72; log-rank $P = 0.0008$). **E,** OS was significantly different when evaluated by tertiles (median OS of low TMB: 40.6 months; intermediate: 37.3 months; high: 20.6 months; log-rank for trend $P = 0.02$).



C Time to treatment discontinuation

Covariates	Hazard Ratio	95% CI of HR	*P*
TMB (Low/intermediate vs. high)	0.570	0.374–0.869	**0.0090**
TP53 (Mutant vs. wild-type)	1.299	0.857–1.969	0.2180
EGFR (L858R vs. ex19del)	1.442	0.959–2.169	0.0789

D Overall survival

Covariates	Hazard Ratio	95% CI of HR	*P*
TMB (Low/intermediate vs. high)	0.495	0.268–0.915	**0.0248**
TP53 (Mutant vs. wild-type)	1.471	0.776–2.786	0.2367
EGFR (L858R vs. ex19del)	1.462	0.797–2.684	0.2198

Figure 2.

A, HR (Mantel–Haenszel method) and *P* value (log-rank) for subgroups evaluating time to treatment discontinuation (TTD) stratified by low/intermediate versus high TMB. The low/intermediate TMBs for each subgroup analyzed were: *TP53*-mutant ≤ 5.66, *TP53* wild-type ≤ 4.30, ever smokers ≤ 6.60, never-smoker ≤ 4.72, *EGFR* L858R ≤ 5.66, *EGFR* ex19del ≤ 4.10 mutations/Mb. HR for TTD in each cohort were found to be: *TP53* mutant 0.49 (95% CI, 0.27–0.90; $P = 0.02$), *TP53* wild-type 0.75 (95% CI, 0.37–1.53; $P = 0.43$), ever-smokers 0.90 (95% CI, 0.43–1.88; $P = 0.78$), never-smoker 0.41 (95% CI, 0.21–0.78; $P = 0.006$), *EGFR* L858R 0.33 (95% CI, 0.16–0.69; $P = 0.003$), *EGFR* ex19del 0.81 (95% CI, 0.44–1.48; $P = 0.49$); **B,** HR for OS in each cohort was found to be: *TP53* mutant 0.38 (95% CI, 0.17–0.88; $P = 0.02$), *TP53* wild-type 1.42 (95% CI, 0.48–4.23; $P = 0.52$), ever smokers 0.64 (95% CI, 0.22–1.87; $P = 0.42$), never-smoker 0.33 (95% CI, 0.13–0.85; $P = 0.02$), *EGFR* L858R 0.42 (95% CI, 0.16–1.12; $P = 0.08$), *EGFR* ex19del 0.69 (95% CI, 0.27–1.76; $P = 0.43$). **C** and **D,** multivariate Cox proportional HR analysis for TTD and OS examining TMB (low/intermediate vs. high TMB), *TP53* status, and *EGFR* allele.

In the context of ICB, the relationship between increased TMB and response to treatment is hypothesized to be related to the increased tumor-specific neoantigen burden. In contrast, in the context of targeted therapy, we hypothesized that the elevated TMB would correlate with an increased pace with which a resistant mechanism and/or subclone would, under

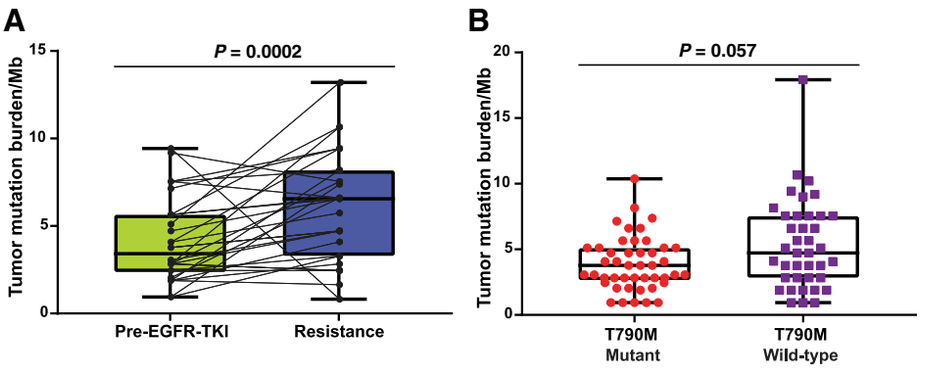


Figure 3.

A, In 30 patients who underwent next-generation sequencing at EGFR-TKI resistance with MSK-IMPACT, TMB was increased on the post-EGFR-TKI sample (median 3.42 pre-TKI vs. 6.56 mutation/Mb at resistance, Wilcoxon test $P = 0.0002$). Paired samples are linked by gray lines. **B,** 84 patients underwent *EGFR* T790M testing at the time of resistance to first/second-generation EGFR-TKI and 45 were found to have acquired a T790M mutation. The median TMB from the pre-EGFR-TKI sample of those that acquired T790M at resistance versus those that did not was 3.77 versus 4.72 mutations/Mb, respectively (Mann–Whitney $P = 0.057$).

the selective pressure of targeted therapy, lead to clinical resistance. Supporting this hypothesis, we found in patients with paired tumors analyzed pre- and post-EGFR-TKI that TMB is significantly increased post-EGFR-TKI. We also found that *TP53* mutation, a predictor of shorter time to progression, (25) is indeed more common among those with high TMB, but that the association between high TMB and poor outcomes remains significant even after adjusting for *TP53* status in multivariate analysis. Only one patient had small-cell transformation and did not have a meaningful contribution to the increased TMB seen at resistance. Examining the mechanisms determining relative molecular heterogeneity within *EGFR*-mutant lung cancers should continue to be evaluated.

It is also intriguing that the initial TMB of patients that ultimately develop T790M resistance trended toward being lower compared with other mechanisms of resistance, highlighting the distinct biology and fate of *EGFR*-mutant lung cancers based on pretreatment TMB and tumor heterogeneity. Given the relatively low number of patients with paired pre- and post-EGFR-TKI NGS ($n = 30$), we are unable to reach firm conclusions on the effect TMB may have on the pattern of acquired resistance mechanisms.

Although our report is the first to examine the impact of TMB on outcomes in patients with *EGFR*-mutant lung cancers, analogous results were found by Blakely and collaegues, which used cfDNA analysis of 74 patients with *EGFR*-mutant NSCLC to determine total alteration burden (inclusive of amplifications) and found that clinical nonresponse to EGFR-TKI was associated with higher alteration burden (28). However, not all patients were treatment naïve in that analysis, which may select for the increased number of alterations in posttreatment samples (as evidenced by the increase in TMB in posttreatment samples). Only patients with pretreatment tissue used for molecular analysis were used in our report.

It may be tantalizing to consider if the findings in this report, with increased TMB at the time of resistance to EGFR-TKI, may propose that use of ICBs after TKIs in *EGFR*-mutant lung cancers could be more effective. We speculate, however, that this strategy will not be successful. We propose that it is largely the emergence of initially subclonal mutations that drive the increase in TMB posttreatment, and that these mutations may increase overall TMB but not effective immunogenicity (8).

Our study has several important limitations. Although we analyzed OS, we used TTD as a surrogate for disease control. Given the routine continuation of EGFR-TKIs beyond initial progression in this disease, TTD represents a clinically relevant endpoint in this disease which has been shown to correlate closely with progression-free survival (29). In addition, we focused only on those patients treated with first/second-generation EGFR-TKI as initial targeted therapy as there is the most mature follow-up data for these treatments. With the adoption of osimertinib into the first-line setting (13), further research will be needed to validate these findings in the third-generation EGFR-TKI. Further assessment in other oncogene-addicted lung cancers as well as other tumor types will be of interest to determine the breadth of applicability of TMB on outcomes with targeted therapy. Ultimately, a prospective assessment of the impact of TMB will be important to conclude if the association seen here is predictive or prognostic of improved outcomes.

In conclusion, we find a negative relationship between TMB and outcomes with targeted therapy in patients with *EGFR*-mutant lung cancers. Our findings thus further expand the potential role of TMB as a meaningful molecular feature in lung cancers.

Disclosure of Potential Conflicts of Interest

A. Drilon reports receiving speakers bureau honoraria from AstraZeneca, Roche Genentech, and Pfizer. M.G. Kris is a consultant/advisory board member for AstraZeneca, Regeneron, and Pfizer. C.M. Rudin is a consultant/advisory board member for AbbVie, AstraZeneca, Bristol–Myers Squibb, Celgene, Genentech, and Harpoon. M. Ladanyi is a consultant/advisory board member for Bristol Myers Squibb, AstraZeneca, and Merck. G.J. Riely is a consultant/advisory board member for Genentech and Merck. H. Yu reports receiving commercial research grants from AstraZeneca, Pfizer, Daiichi, Novartis, and Lilly, and is a consultant/advisory board member for AstraZeneca. M.D. Hellmann is a consultant/advisory board member for Merck, Bristol–Myers Squibb, AstraZeneca, Genentech/Roche, Mirati, Syndax, Jannsen, and Shattuck and received commercial research grants from Bristol-Myers Squibb. No potential conflicts of interest were disclosed by the other authors.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Offin, H. Rizvi, A. Ni, F. Sanchez-Vega, B.T. Li, A. Drilon, M.G. Kris, N. Schultz, M.E. Arcila, M. Ladanyi, G.J. Riely, H. Yu, M.D. Hellmann

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Acknowledgments

This research was supported in part by the NCI of the NIH (T32 CA009207 and P30 CA008748); M.D. Hellmann is a Damon Runyon Clinical Investigator supported (in part) by the Damon Runyon Cancer Research Foundation (CI-98-18) and Druckenmiller Center for Lung Cancer Research at MSKCC.

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Received April 10, 2018; revised June 6, 2018; accepted July 10, 2018; published first July 25, 2018.

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