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ORIGINAL REPORT

Molecular Determinants of Response to Anti–Programmed Cell Death (PD)-1 and Anti–Programmed Death-Ligand 1 (PD-L1) Blockade in Patients With Non–Small-Cell Lung Cancer Profiled With Targeted Next-Generation Sequencing

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ABSTRACT

Purpose
Treatment of advanced non–small-cell lung cancer with immune checkpoint inhibitors (ICIs) is characterized by durable responses and improved survival in a subset of patients. Clinically available tools to optimize use of ICIs and understand the molecular determinants of response are needed. Targeted next-generation sequencing (NGS) is increasingly routine, but its role in identifying predictors of response to ICIs is not known.

Methods
Detailed clinical annotation and response data were collected for patients with advanced non–small-cell lung cancer treated with anti–programmed death-1 or anti–programmed death-ligand 1 [anti-programmed cell death (PD)-1] therapy and profiled by targeted NGS (MSK-IMPACT; n = 240). Efficacy was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and durable clinical benefit (DCB) was defined as partial response/stable disease that lasted > 6 months. Tumor mutation burden (TMB), fraction of copy number–altered genome, and gene alterations were compared among patients with DCB and no durable benefit (NDB). Whole-exome sequencing (WES) was performed for 49 patients to compare quantification of TMB by targeted NGS versus WES.

Results
Estimates of TMB by targeted NGS correlated well with WES ($\rho = 0.86$; $P < .001$). TMB was greater in patients with DCB than with NDB ($P = .006$). DCB was more common, and progression-free survival was longer in patients at increasing thresholds above versus below the 50th percentile of TMB (38.6% *v* 25.1%; $P < .001$; hazard ratio, 1.38; $P = .024$). The fraction of copy number–altered genome was highest in those with NDB. Variants in *EGFR* and *STK11* associated with a lack of benefit. TMB and PD-L1 expression were independent variables, and a composite of TMB plus PD-L1 further enriched for benefit to ICIs.

Conclusion
Targeted NGS accurately estimates TMB and elevated TMB further improved likelihood of benefit to ICIs. TMB did not correlate with PD-L1 expression; both variables had similar predictive capacity. The incorporation of both TMB and PD-L1 expression into multivariable predictive models should result in greater predictive power.

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ASSOCIATED CONTENT

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Appendix

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) have dramatically changed the therapeutic landscape for patients with a multitude of advanced cancers, including non–small-cell lung cancer (NSCLC).[1-6] Because only a subset of patients with lung cancer respond to ICIs, an urgent need exists to develop clinically practical tools to identify the subset of patients most likely to derive clinical benefit.

To date, the only Food and Drug Administration–approved predictive biomarkers are mismatch repair deficiency,[7] and specifically in

NSCLC, programmed death-ligand 1 (PD-L1) expression.[6] Most trials in NSCLC have demonstrated increased response rates in tumors with greater PD-L1 expression, but enrichment of responses is incomplete.[1,6] Our group and others have demonstrated that a greater somatic mutation burden is associated with a greater likelihood of response to immunotherapy in several tumor types, including melanoma,[8,9] bladder cancer,[10] NSCLC,[11,12] and mismatch repair–deficient tumors.[7,13] These studies established the importance of tumor mutation burden (TMB) as a biomarker that may be relevant across tumor types. However, most studies have used whole-exome sequencing (WES) to quantify TMB, a methodology that is not currently feasible or expedient at the scale of a clinical setting. By contrast, genomic profiling of tumors by using targeted next-generation sequencing (NGS) is increasingly routine. At Memorial Sloan Kettering Cancer Center (MSKCC), a custom hybridization capture-based NGS assay (Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets [MSK-IMPACT])[14] has been used to analyze > 10,000 tumors.[15]

We hypothesized that TMB determined by targeted NGS may associate with response to immunotherapy in patients with NSCLC. To address this hypothesis, we examined 240 patients with NSCLC profiled by targeted NGS and who were treated with anti–PD-1 or anti–PD-L1 [anti–PD-(L)1]–based therapy. A subset of tumors from these patients also were analyzed by WES to examine the correlation of TMB derived by both methods. Secondary analyses included an examination of associations of other molecular features obtained from targeted NGS, such as copy number alterations and specific genes, with response or resistance to ICIs as well as the relationship between TMB and PD-L1 expression.

METHODS

Patients

After MSKCC institutional review board approval, patients with advanced NSCLC treated with anti–PD-(L)1 monotherapy or in combination with anti–cytotoxic T-cell lymphocyte-4 (anti–CTLA-4) between April 2011 (the first date on which a patient with NSCLC was treated with ICI at our center) and January 2017 (the last date to have begun therapy to permit enough time for at least one response assessment before database lock in May 2017) were identified. Patients with tumors molecularly profiled by MSK-IMPACT were included. A prespecified sample size was not determined. Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was used to assess efficacy; scans were reviewed by a thoracic radiologist (D.H., A.P., or N.L.) prospectively in patients treated as part of clinical trials or retrospectively in patients treated outside a clinical trial (Appendix Fig A1, online only). Patients who were not evaluable radiologically were excluded. Progression-free survival (PFS) was assessed from the date the patient began immunotherapy to the date of progression. Patients who had not progressed were censored at the date of their last scan; cases retrospectively adjudicated to not be progressive disease (PD) per RECIST but determined in real-time by the treating clinician as PD were considered as events. In addition to response defined by RECIST, efficacy also was defined as durable clinical benefit (DCB; complete response [CR]/partial response [PR] or stable disease [SD] that lasted > 6 months) or no durable benefit (NDB, PD or SD that lasted ≤ 6 months[12]; Appendix Fig A2, online only). Patients who had not progressed and were censored before 6 months of follow-up were considered not evaluable. Overall survival (OS) was calculated from treatment start date. Patients who did not die were censored at the date of last contact.

To provide a comparison cohort, patients with NSCLC who had undergone MSK-IMPACT testing between January 2014 and March 2017 and were not treated with any immunotherapy (non-ICI NSCLC; n = 1,836) were identified. For comparisons specifically related to OS, which was calculated from the date of recurrent or metastatic disease, a subset of these patients with non-ICI NSCLC with advanced-stage lung adenocarcinoma (non-ICI advanced stage; n = 608[16]) were used (Appendix Fig A1).

MSK-IMPACT Sequencing

The MSK-IMPACT assay was performed as previously described.[14] Briefly, DNA was extracted from tumors and patient-matched blood samples. Bar-coded libraries were generated and sequenced and targeted all exons and select introns of a custom gene panel of 341 (56 patients; version 1), 410 (164 patients; version 2), or 468 (20 patients, version 3) genes (Appendix Table A1, online only). Mean sequencing coverage across all tumor samples was 744×, with minimum depth of coverage of 91×. Samples were run through a custom pipeline[14] to identify somatic alterations, including mutations and copy number alterations. Data are available through the cBioPortal for Cancer Genomics.[17] To normalize somatic nonsynonymous TMB across panels of various sizes, the total number of mutations was divided by the coding region captured in each panel, which covered 0.98, 1.06, and 1.22 megabases (Mb) in the 341-, 410-, and 468-gene panels, respectively (Appendix Fig A3, online only). The fraction of copy number–altered genome (FGA) was defined as the fraction of genome with $\log_2$ copy number gain > 0.2 or loss < −0.2 relative to the size of the genome with copy number profiled. Tumor samples used for MSK-IMPACT were collected before immunotherapy treatment in 204 patients (85%; Appendix Table A2, online only).

Gene and Pathway Analysis

Individual genes were queried for enrichment among groups of DCB, NDB, and non-ICI NSCLC. Analysis included both previously described oncogenic or likely oncogenic variants as reported by OncoKB[18] and variants of unknown significance. Reported percentages include all variants unless otherwise noted. Slides for one patient were stained for immunohistochemistry (IHC) with β2 microglobulin (B2M; polyclonal, 1 μg/mL; DAKO, Copenhagen, Denmark) on a BOND RX (Leica Biosystems, Wetzlar, Germany) after 30 minutes of antigen retrieval in Leica ER2 buffer by Bond Polymer Refine Detection.

WES

A subset of patients (n = 49) had tumor/normal tissue profiled by both MSK-IMPACT and WES. The same tissue sample was used for both analyses in 40 patients; 36 were from the same DNA aliquot. Enriched exome libraries were sequenced on a HiSeq platform (Illumina, San Diego, CA) to generate paired-end reads (2 × 76 base pairs) to a target of 150× mean coverage (44 sequenced at Broad Institute, Cambridge, MA; five sequenced at MSKCC). The mean target coverage was 232× in tumor and 125× in normal sequences; mean target coverage < 60× in tumor or < 30× in normal sequences were excluded. For each patient, a binary alignment map file was produced by aligning tumor and normal sequences to the b37 human genome build with decoy contigs added. Additional indel realignment, base-quality score recalibration, and duplicate-read removal were performed by using the Genome Analysis Toolkit.[19] MuTect was used to generate single-nucleotide variant (SNV) calls by using slightly modified default parameters[20] (Appendix Table A3, online only). The complete listing of the source code for the variant detection pipeline is available online.[21] The Genome Analysis Toolkit HaplotypeCaller was used to detect indels.[22]

PD-L1 Testing

Eighty-four tumors had tissue evaluated for PD-L1 expression, which was reported as the percentage of tumor cells with membranous staining. Several antibodies, which have largely been shown to be similar,[23] were used, including 22C3 (n = 24; DAKO), 28-8 (n = 10; DAKO), and E1L3N (n = 50; Cell Signaling, Danvers, MA).

Statistical Analysis

Differences in TMB and FGA were examined by using the Mann-Whitney *U* test for two-group comparisons or the Kruskal-Wallis exact test for three-group comparisons. The Fisher's exact test was used to compare proportions. For survival analyses, Kaplan-Meier curves were compared by using the log-rank test, and hazard ratios (HRs) were calculated by using the Mantel-Haenszel test. Correlations were examined by the Spearman rank correlation coefficients. Receiver operating characteristic curves that plotted sensitivity and 1-specificity of continuous variables and rate of DCB were assessed by generating the area under the curve (AUC). An unbiased analysis of enrichment in frequency of altered genes within individual groups were examined by plotting the $\log_2$(odds ratio) versus $\log_2$(Fisher's exact test *P* value). The top 50 genes ordered by increasing *P* values were reported, with significant associations after correcting for the false discovery rate (FDR) highlighted. All reported *P* values are two-sided. All statistical analyses were performed with R version 3.3.3 software (www.r-project.org).

RESULTS

Mutation Burden and Somatic Molecular Features Associated With Immunotherapy Benefit

Since 2011, 759 patients with NSCLC have been treated with anti–PD-(L)1 therapy alone or in combination with anti–CTLA-4 therapy at MSKCC, of whom 398 (52%) have been profiled by MSK-IMPACT. Of these, 240 (60% of those molecularly profiled, 32% of all patients treated) were radiologically evaluable for response and are included in this analysis. Demographic features of the current patient cohort (Table 1) are similar to the overall group of patients treated with anti–PD-(L)1 therapy (Appendix Table A4, online only). Forty-nine patients (20%) had CR/PR; 69 (29%) had DCB. The median TMB was 7.4 SNVs/Mb (range, 0.8 to 91.8 SNVs/Mb).

To determine whether targeted NGS could accurately quantitate TMB in NSCLC, we compared TMB quantified by MSK-IMPACT and WES in a subset of patients. In patients profiled with both targeted NGS and WES (n = 49), TMB assessed by targeted NGS was highly correlated with TMB assessed by WES (Spearman $\rho = 0.86$; $P < .001$; Fig 1A). By using data from targeted NGS, TMB was greater in patients with DCB than with NDB (median, 8.5 *v* 6.6 SNVs/Mb; $P = .0062$) and in patients with CR/PR versus SD versus PD (median, 8.5 *v* 6.6 *v* 6.6 SNVs/Mb; $P = .0151$; Fig 1B).

We examined how increasing cut points of TMB affected rates of DCB and PFS to ICI treatment. When TMB was stratified into increasing quartiles, rates of DCB and PFS improved with increasing TMB (Figs 1C and 1D); improved DCB rate and PFS were seen in those with TMB above versus below the 50th percentile (DCB rate, 38.6% *v* 25.1%; $P = .009$ [Appendix Fig A4, online only]; PFS HR, 1.38; $P = .024$ [Appendix Fig A5, online only]). The rate of DCB and PFS were also improved among those in the top decile of TMB in the cohort (Figs 1C and 1D). By contrast, survival outcomes among patients with advanced NSCLC not treated with immunotherapy[16] did not correlate with increasing TMB; in fact, an inverse relationship between TMB and survival was identified (Appendix Fig A6, online only).

In addition, FGA was lowest in patients with DCB and significantly higher in those with NDB than in those with non-ICI NSCLC (median, 0.16 *v* 0.11; $P = .007$; Fig 1E). Of note, despite a negative association with response to ICIs, FGA had a modest but significantly positive association with TMB (Appendix Fig A7, online only).

Table 1. Patient Characteristics

Characteristic	No. (%)
No. of patients	240
Median age, years (range)	66 (22-92)
Sex	
Male	118 (49)
Female	122 (51)
Histology	
Adenocarcinoma	186 (78)
Squamous	34 (14)
Other	20 (8)
Smoking status	
Ever	193 (80)
Never	47 (20)
Line of therapy	
First	51 (21)
Second	127 (53)
Third or more	62 (26)
Treatment	
PD-(L)1, monotherapy	206 (86)
PD-(L)1 + CTLA-4 combination therapy	34 (14)
Treatment setting	
Clinical trial	54 (23)
Standard of care	186 (78)
Best overall response	
CR/PR	49 (20)
SD	83 (35)
PD	108 (45)
Clinical benefit	
DCB	69 (29)
NDB	158 (66)
Not evaluable (< 6 months follow-up)	13 (5)
Actionable mutations	
EGFR	17 (7)
ALK	2 (1)
BRAF	5 (2)
ROS1	7 (3)
RET	2 (1)
MET	7 (3)

Abbreviations: CR, complete response; CTLA-4, cytotoxic T-cell lymphocyte-4; DCB, durable clinical benefit; NDB, no durable benefit; PD, progressive disease; PD-(L)1, programmed cell death-1 or programmed death-ligand 1; PR, partial response; SD, stable disease.

Gene Alterations Associated With Response and Resistance to Immunotherapy

We next assessed whether mutations in individual genes were associated with response or resistance to ICI treatment. First, we examined the frequency of common oncogenic driver mutations found in NSCLC and their association with clinical benefit from ICI treatment.[24] Mutations in *KRAS* were common (n = 83), and the rate of DCB was similar in this group compared with the overall study cohort (36%; Fig 2). Those with *EGFR* mutations rarely experienced DCB (7%) and were significantly underrepresented in the DCB group compared with the non-ICI NSCLC group (FDR-adjusted $P = .013$ Appendix Fig A8, online only). *STK11* was significantly enriched in the NDB group compared with the non-ICI NSCLC group (FDR-adjusted $P = .007$).

We also examined the prevalence and impact of alterations in genes associated with antigen presentation on response to immunotherapy (Fig 2; Appendix Fig A9, online only). Truncating mutations in the gene encoding *B2M* and deleterious mutations in *JAK1* and *JAK2* have recently been identified as mechanisms that lead to primary and acquired resistance to anti–PD-1 treatment in

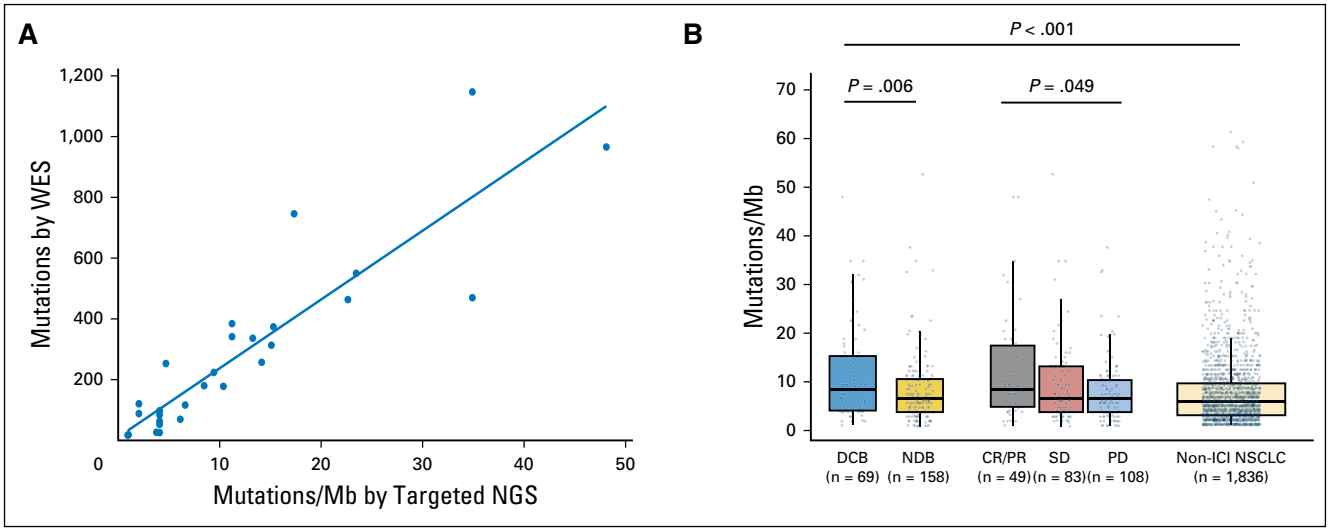

Fig 1. Somatic molecular features associated with response to immunotherapy. (A) Tumor mutation burden (TMB) assessed by targeted next-generation sequencing (NGS) correlates with TMB assessed by whole-exome sequencing (WES; n = 49, Spearman ρ = 0.86; *P*, .001). Individual tumors are shown as dots. The line depicts the best fit. (B) Somatic nonsynonymous TMB is greater in durable clinical benefit (DCB) versus no durable benefit (NDB; median, 8.5 v 6.6 single-nucleotide variants/megabase [Mb]; *P* = .006) and is significantly different in those with complete response (CR)/partial response (PR) versus stable disease (SD) versus progressive disease (PD; median, 8.5 v 6.6 v 6.6 single-nucleotide variants/Mb; *P* = .049). The distribution of TMB in patients with non–immune checkpoint inhibitor (ICI)–treated non–small-cell lung cancer (NSCLC) are shown for reference. TMB in patients with DCB was similar to those with CR/PR (*P* = .85) and greater in those with non-ICI NSCLC (*P*, .001). Box plots represent medians, interquartile ranges, and vertical lines extend to the 95th percentiles. TMB of individual patients are represented with light dots. (C) Odds ratio (OR) of DCB with increasing cut points of TMB.25th (OR, 1.75), 50th (OR, 2.02), 75th (OR, 2.06), and 90th (OR, 3.24) percentiles. The 0 percentile (white bar) is shown for reference of all patients (default OR, 1). The odds of DCB increase significantly above the 50th percentile of TMB. (D) Individual Kaplan-Meier curves of progressionfree survival (PFS) above each percentile at increasing thresholds of TMB. PFS in patients with NSCLC treated with anti–programmed cell death-1– or anti–programmed deathligand 1–based therapy increaseswith increases inTMB. (E) Fraction of copy number–altered genome (FGA) inDCBversusNDB(median, 0.08 v 0.15;*P* = .129) and PR/CR versus SD versus PD (median, 0.09 v 0.11 v 0.16; *P* = .479). FGA is enriched among those with PD or NDB compared with non-ICI NSCLC (*P* = .004 and .002, respectively).

melanoma.[7,25,26] In the current cohort, likely deleterious *B2M* mutations were rare, occurring in only one patient who had an S40* mutation in *trans* with a Q28L mutation of uncertain significance and loss of B2M expression in tumor cells by IHC (Appendix Fig A10, online only). As of August 2017, this patient has achieved an early response to PD-1 therapy that has been ongoing for 8.9 months. Mutations in *JAK2* also were uncommon (n = 2), with only one tumor having a homozygous deleterious mutation (a loss-of-function splice mutation on one allele paired with loss of heterozygosity; Appendix Fig A11, online only); this patient had PD.

Recently, hyperprogression with anti–PD-1 therapy[27] has been reported in patients treated with ICI and was associated with *MDM2/MDM4* amplifications.[28] In the current series, *MDM2/MDM4* amplifications were identified in eight patients (Appendix Fig A12, online only), and PFS was not substantially different in this group compared with the overall patient cohort (HR, 1.4; *P* = .44).

PD-L1 Expression and TMB

PD-L1 expression was available for 84 patients, of whom 43 (51%) had ≥ 1% expression. Consistent with prior reports, PD-L1 expression was associated with improved PFS (PD-L1, 0% *v* ≥ 1%; HR, 0.526; *P* = .011; Appendix Fig A13, online only). No correlation was found between PD-L1 and TMB (Spearman ρ = 0.1915; *P* = .08; Fig 3A) or PD-L1 and FGA (Spearman ρ = −0.1273; *P* = .25; Fig 3B). Considered as continuous variables, PD-L1 and TMB had a similar predictive impact on the likelihood of DCB (TMB AUC, 0.601; PD-L1 AUC, 0.646; Fig 3C). When considered as a composite variable, patients with high TMB (greater than the group median) and PD-L1 positivity (≥ 1% expression) had a 50% rate of DCB, whereas the presence of only one or neither variable was associated with a lower rate of DCB (Fig 3D). We also evaluated whether mutations in individual altered genes were associated with PD-L1 expression (stratified as ≥ 1% *v* < 1%; Appendix Fig A14, online only). *SKT11* was the most enriched gene in the PD-L1–negative cohort, but this association was not statistically significant (FDR-adjusted *P* = .27).

DISCUSSION

To our knowledge, we describe the largest series to date to explore the molecular determinants of response to ICIs and the first series to evaluate the role of molecular features derived from targeted NGS in determining response or resistance to anti–PD-(L)1–based therapy in patients with advanced NSCLC. TMB assessed by targeted NGS was significantly associated with improved benefit among patients with NSCLC treated with ICIs, with the odds of DCB improving with increasing thresholds. Because there was no positive correlation between increasing TMB and survival in a cohort of patients not treated with ICIs, we demonstrate that the effect of TMB is predictive rather than prognostic. In fact, survival among patients with high TMB is worse in the absence of ICI, which also highlights the clinical value of ICI to improve survival and overcome naturally poor prognostic features.

Although TMB has been a major focus of biomarker studies, other molecular features also have been hypothesized to influence

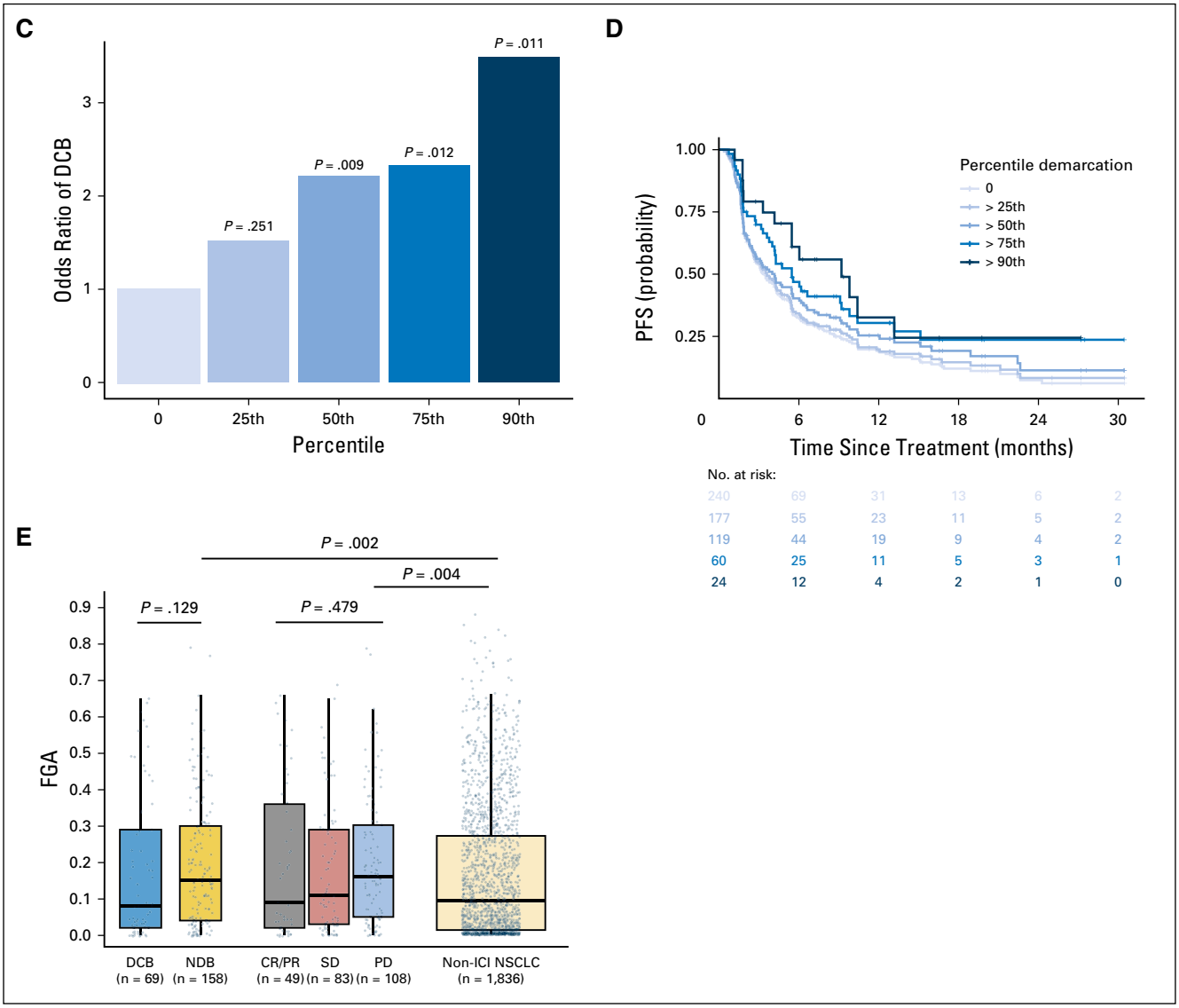

Fig 1. (Continued).

the likelihood of clinical benefit from ICIs. Aneuploidy was shown recently to reduce response to immunotherapy in patients with melanoma.[29,30] These reports largely focused on patients treated with CTLA-4 therapy and hypothesized that aneuploidy negatively correlates with the presence of cytotoxic immune infiltrates that may subsequently lead to poor survival outcomes in these patients. Similarly, we found that the FGA was highest among patients who derived the least benefit from ICIs. Despite this inverse association, FGA and TMB were modestly but positively associated with each other, consistent with a previous report.[29] Given the growing concordance of data that support aneuploidy and lack of response to ICIs, additional work is needed to explore the underlying mechanism and impact of its interaction with TMB.

Beyond summary metrics, such as TMB and FGA, we also examined the impact of specific gene alterations on benefit from ICI. In an unbiased analysis, few additional genes were significantly associated with DCB and NDB. Mutations in *EGFR* were underrepresented among patients with DCB, which is likely related to the association of *EGFR* mutations with never smokers[31] and resulting low TMB. Other actionable mutations in lung cancer also were found in low frequency in the current data set (Table 1). Future analysis is needed to clarify the activity of immunotherapy and whether TMB is similarly relevant in these patients. Alterations in *STK11* also were associated with lack of benefit, which is consistent with recent reports that described low tumor inflammation in murine models and human tumors with STK11 alterations.[32,33]

We also explored specific alterations that have been previously purported to affect response to ICI. For example, amplifications in *MDM2* and *MDM4* have been associated with hyperprogression,[27] although this was not seen in the current cohort. Separately, alterations in *B2M* and *JAK2* have been described as mediating acquired resistance in patients with melanoma treated with PD-1 blockade.[26] Although our study was not designed to examine acquired resistance (where selective pressure from ICI may increase the frequency of these variants), we identified one patient with a deleterious homozygous *JAK2* mutation in a setting of primary

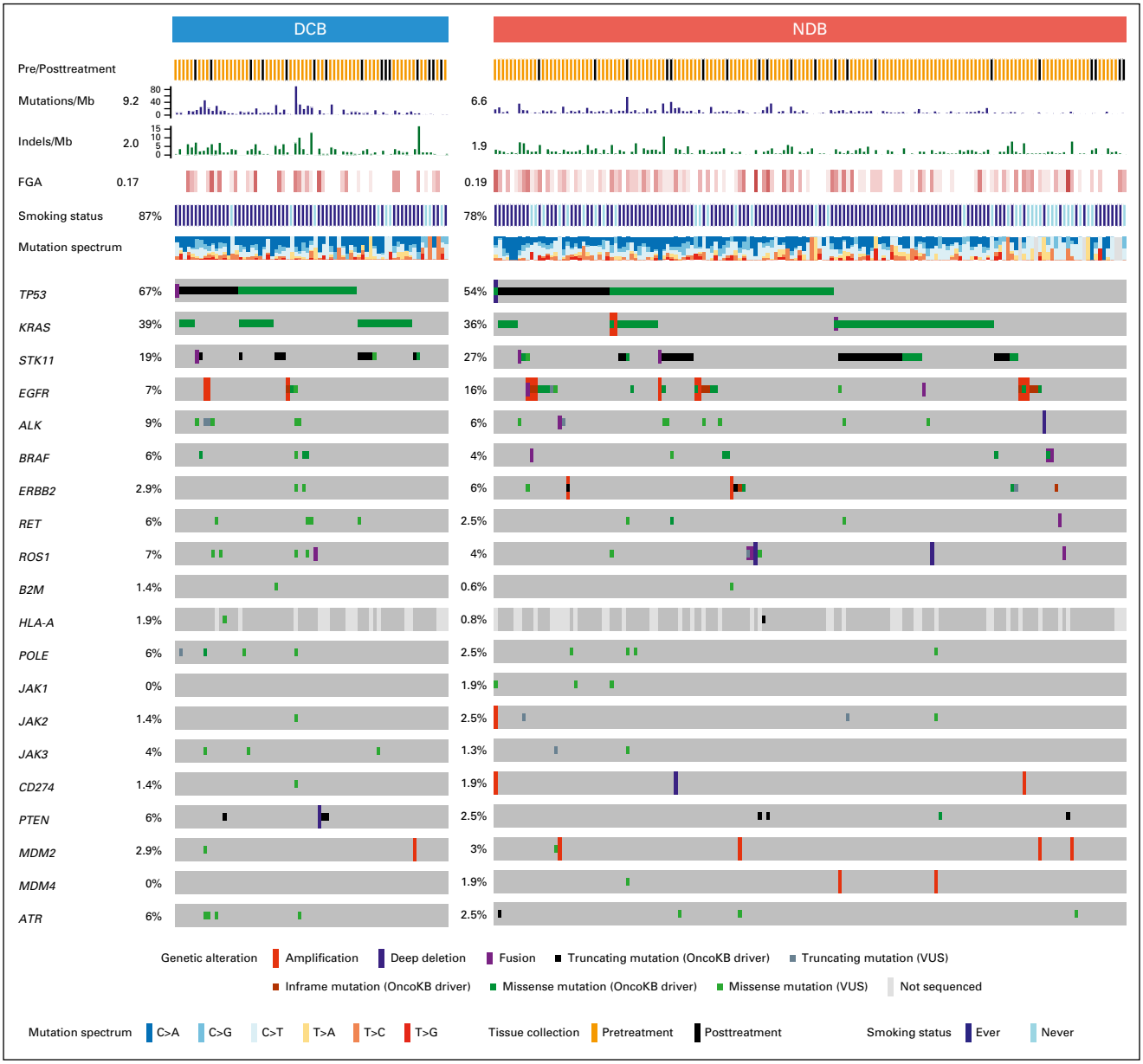

Fig 2. Genes associated with response and resistance to immunotherapy. OncoPrint that depicts alterations in preselected genes of interest in durable clinical benefit (DCB) and no durable benefit (NDB) groups. Reported frequencies include a composite of all alterations for each gene across all groups (single-nucleotide variants, indels, fusions, amplifications, deletions). Predicted functional impact of genetic alterations are described as known in OncoKB or variants of unknown significance (VUSs). Summary rows of each case at top include annotation for whether samples were obtained before or after initiation of immune checkpoint inhibitor (ICI) therapy, mutations/megabase (Mb; histogram), indels/Mb (histogram), frequencies of fraction of copy number–altered genome (FGA; lowest to highest FGA, white to dark red), smoking, and mutation spectrum. Events where information is unknown (eg, gene not covered in panel tested) are depicted in light gray on the OncoPrint.

resistance, consistent with cases of acquired resistance mediated through defective interferon gamma signaling.[25,34] Of note, the one patient with two *trans* mutations in *B2M* and loss-of-protein expression confirmed by IHC has an ongoing PR to therapy and a mutation rate of 48 SNVs/Mb.

Overall, although MSK-IMPACT examines several hundred cancer-associated genes, we did not observe novel associations between mutation in individual genes and response or resistance to ICI, which may reflect that current targeted NGS panels were constructed for the purpose of identifying targetable oncogenes and, thus, may not include the key genetic determinants of immunotherapy response. However, because these panels can be readily amended to include additional probes to expand the genetic landscape surveyed (eg, the MSK-IMPACT panel has increased from 341 genes at inception to currently 468 genes), a future effort to include genes specifically related to immunogenomics is likely to be fruitful. In addition, continued emphasis on approaches such as WES and whole-genome sequencing for ongoing discovery is important.

One of the critiques of WES as a prospective tool for examining predictors of response to ICI to aid in clinical decision making is that it is not optimized for use in routine clinical practice. By contrast, the use of targeted NGS to guide treatment

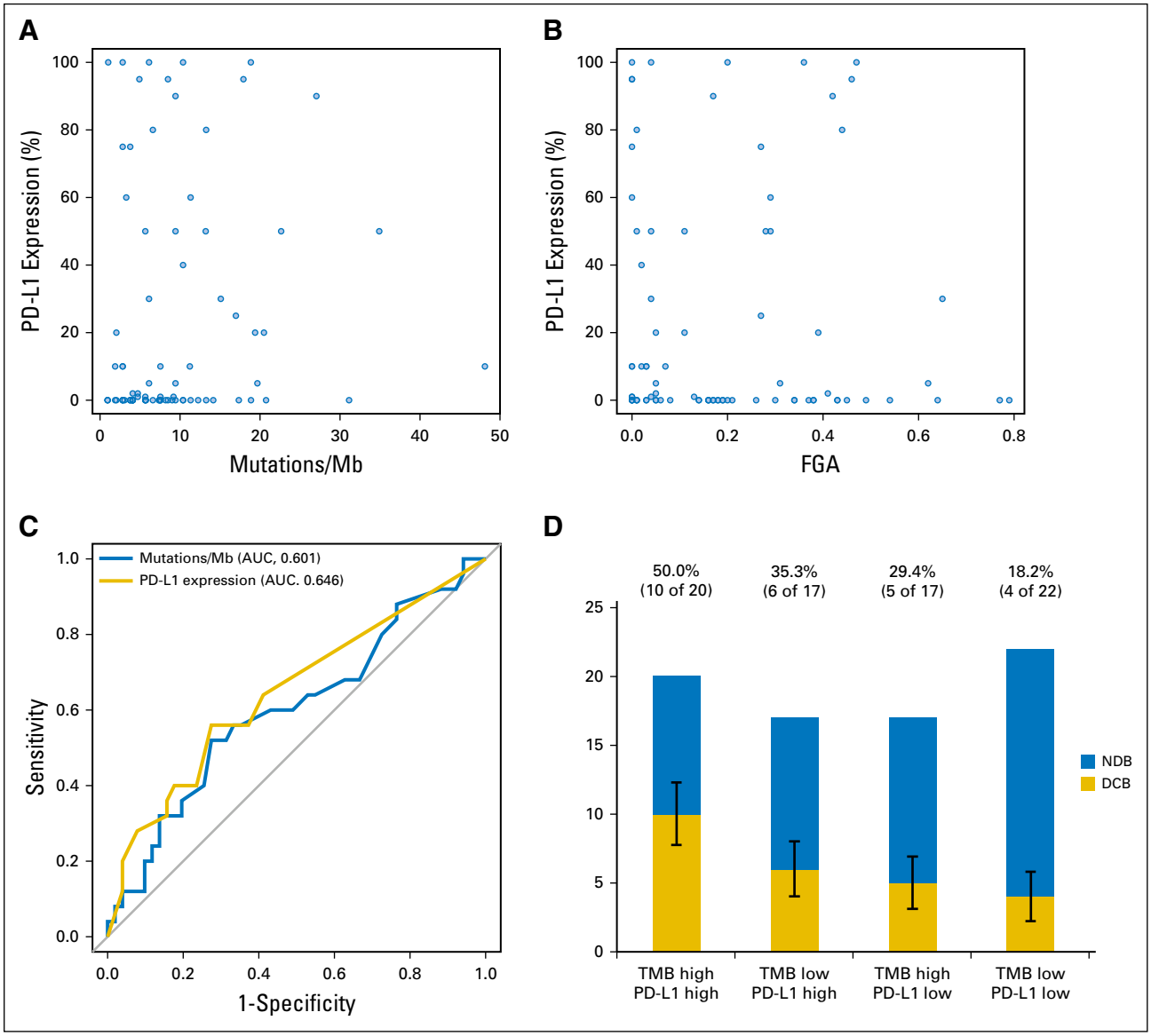

Fig 3. Comparison of programmed death-ligand 1 (PD-L1) expression with tumor mutation burden (TMB) and fraction of copy number–alteration genome (FGA). (A) Scatter plot of TMB and PD-L1 expression. TMB does not correlate with percent PD-L1 expression (n = 84; Spearman $\rho = 0.192$; $P = .081$). Dots represent individual tumors, and the line represents the best fit. (B) Scatter plot of FGA versus percent PD-L1 expression. No correlation exists between FGA and PD-L1 expression (n = 84; Spearman $\rho = 0.127$; $P = .25$). Dots represent individual tumors. (C) Receiver operating characteristic curve of sensitivity versus 1-specificity of durable clinical benefit (DCB) at varying levels of TMB (area under the curve [AUC], 0.601; $P = .078$) and PD-L1 expression (AUC, 0.646; $P = .014$). Results depict only those patients with available data for both TMB and PD-L1 (n = 84). (D) A histogram depicts the proportion of DCB among patients in groups defined by a composite variable of TMB (stratified above and below the median as low *v*high) and PD-L1 expression (stratified into 0% or ≥ 1% groups as low *v*high). Rate of DCB is lowest in patients low for both variables (18%), intermediate in patients high for one variable (29% to 35%), and highest in patients high for both variables (50%). Error bars show the SE of the percentage. Mb, megabase.

has become increasingly routine, particularly in patients with lung cancer.[15,16,35] Furthermore, consistent with recent reports that analyzed the same patient tumors for targeted NGS and WES,[15,35] we found that TMB quantified by targeted NGS closely correlated with TMB as quantified by WES. However, not all NGS panels may be well suited to estimate TMB; in particular, caution may be needed when using smaller panels. A recent report described that in panels with genomic coverage < 0.5 Mb, the accuracy of TMB determined by targeted NGS diminishes.[35]

Despite the consistent relevance of TMB and PD-L1 as predictive biomarkers of response to ICI across series, neither is fully sensitive or specific. We found that TMB and PD-L1 expression were independent variables that both associated with benefit as previously seen.[11] It seems that TMB is similarly meaningful as PD-L1 expression, but a composite of both variables may be most helpful in identifying with precision patients most likely to benefit.

The current study had a moderate sample size, which may limit the power of conclusions, especially when considering multiple variables and subgroup analyses. Nonetheless, this analyzed cohort is representative of the overall patient population treated with ICI at our institution (Appendix Table A4). Although clinical outcomes were derived retrospectively in some patients, inclusion of both the clinical trial and the real-world clinical experience of patients who receive ICI makes results generalizable

across various treatment settings. Finally, because this study used a single targeted NGS panel at our institution, the analysis does not attempt to specify a universally applicable cut point of TMB for derived benefit and instead highlights a trend that demonstrates an increase in benefit with increasing TMB. As a result of variations in panels as well as of differences in informatics methods, a relevant numerical cut point would need to be assay specific and distinct to specific clinical situations.

In conclusion, given the remarkable antitumor activity of ICIs coupled with advances in targeted sequencing approaches to routinely molecularly profile tumors, we determined the utility of targeted NGS in identifying patients who most benefit from ICI. We found that TMB determined by targeted NGS strongly correlates with TMB as determined by WES, is associated with clinical benefit, and is independent of PD-L1 expression with similar predictive capacity. Other molecular features derived from targeted NGS may also refine the predictive capacity of these tools. Moving forward, multiple orthogonal biomarkers, integrating DNA sequencing, transcriptomics,[36] multiplexed protein expression,[37] T-cell receptor clonality,[38] and others will need to be considered together to realize more fully the potential for precision immunotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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REFERENCES

1. Garon EB, Rizvi NA, Hui R, et al: Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 372:2018-2028, 2015
2. Borghaei H, Paz-Ares L, Horn L, et al: Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 373: 1627-1639, 2015
3. Brahmer J, Reckamp KL, Baas P, et al: Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373: 123-135, 2015
4. Fehrenbacher L, Spira A, Ballinger M, et al: Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): A multicentre, open-label, phase 2 randomised controlled trial. Lancet 387:1837-1846, 2016
5. Herbst RS, Baas P, Kim DW, et al: Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. Lancet 387:1540-1550, 2016
6. Reck M, Rodríguez-Abreu D, Robinson AG, et al: Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375:1823-1833, 2016
7. Le DT, Durham JN, Smith KN, et al: Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357:409-413, 2017
8. Snyder A, Makarov V, Merghoub T, et al: Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 371:2189-2199, 2014
9. Van Allen EM, Miao D, Schilling B, et al: Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science 350: 207-211, 2015
10. Rosenberg JE, Hoffman-Censits J, Powles T, et al: Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: A single-arm, multicentre, phase 2 trial. Lancet 387:1909-1920, 2016
11. Carbone DP, Reck M, Paz-Ares L, et al: First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 376:2415-2426, 2017
12. Rizvi NA, Hellmann MD, Snyder A, et al: Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 348:124-128, 2015
13. Le DT, Uram JN, Wang H, et al: PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 372:2509-2520, 2015
14. Cheng DT, Mitchell TN, Zehir A, et al: Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): A hybridization capture-based next-generation sequencing clinical assay for solid tumor molecular oncology. J Mol Diagn 17:251-264, 2015
15. Zehir A, Benayed R, Shah RH, et al: Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 23:703-713, 2017
16. Jordan EJ, Kim HR, Arcila ME, et al: Prospective comprehensive molecular characterization of lung adenocarcinomas for efficient patient matching to approved and emerging therapies. Cancer Discov 7: 596-609, 2017
17. CBioPortal for Cancer Genomics: Non-small-cell lung cancer (MSK, JCO 2018). http://www.cbioportal.org/study?id=nsclc_pd1_msk_2018
18. Chakravarty D, Gao J, Phillips SM, et al: OncoKB: A precision oncology knowledge base. Precision Oncol 2017:1-16, 2017
19. Cibulskis K, McKenna A, Fennell T, et al: ContEst: Estimating cross-contamination of human samples in next-generation sequencing data. Bioinformatics 27:2601-2602, 2011
20. Cibulskis K, Lawrence MS, Carter SL, et al: Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. Nat Biotechnol 31:213-219, 2013
21. GitHub: soccin/BIC-variants_pipeline. https://github.com/soccin/BIC-variants_pipeline
22. Van der Auwera GA, Carneiro MO, Hartl C, et al: From FastQ data to high confidence variant calls: The Genome Analysis Toolkit best practices pipeline. Curr Protoc Bioinformatics 43:11.10.1-11.10.33, 2013
23. Rimm DL, Han G, Taube JM, et al: A prospective, multi-institutional, pathologist-based assessment of 4 immunohistochemistry assays for PD-L1 expression in non-small cell lung cancer. JAMA Oncol 3:1051-1058, 2017
24. Kris MG, Johnson BE, Berry LD, et al: Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 311: 1998-2006, 2014
25. Shin DS, Zaretsky JM, Escuin-Ordinas H, et al: Primary resistance to PD-1 blockade mediated by JAK1/2 mutations. Cancer Discov 7:188-201, 2017
26. Zaretsky JM, Garcia-Diaz A, Shin DS, et al: Mutations associated with acquired resistance to PD-1 blockade in melanoma. N Engl J Med 375:819-829, 2016
27. Champiat S, Dercle L, Ammari S, et al: Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. Clin Cancer Res 23:1920-1928, 2017
28. Kato S, Goodman A, Walavalkar V, et al: Hyperprogressors after immunotherapy: Analysis of genomic alterations associated with accelerated growth rate. Clin Cancer Res 23:4242-4250, 2017
29. Davoli T, Uno H, Wooten EC, et al: Tumor aneuploidy correlates with markers of immune evasion and with reduced response to immunotherapy. Science 355:355, 2017
30. Roh W, Chen PL, Reuben A, et al: Integrated molecular analysis of tumor biopsies on sequential CTLA-4 and PD-1 blockade reveals markers of response and resistance. Sci Transl Med 9:9, 2017
31. Govindan R, Ding L, Griffith M, et al: Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell 150:1121-1134, 2012
32. Koyama S, Akbay EA, Li YY, et al: STK11/LKB1 deficiency promotes neutrophil recruitment and proinflammatory cytokine production to suppress T-cell activity in the lung tumor microenvironment. Cancer Res 76:999-1008, 2016

33. Skoulidis F, Byers LA, Diao L, et al: Co-occurring genomic alterations define major subsets of KRAS-mutant lung adenocarcinoma with distinct biology, immune profiles, and therapeutic vulnerabilities. Cancer Discov 5:860-877, 2015

34. Garcia-Diaz A, Shin DS, Moreno BH, et al: Interferon receptor signaling pathways regulating PD-L1 and PD-L2 expression. Cell Reports 19:1189-1201, 2017

35. Chalmers ZR, Connelly CF, Fabrizio D, et al: Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 9:34, 2017

36. Ayers M, Lunceford J, Nebozhyn M, et al: IFN-γ-related mRNA profile predicts clinical response to PD-1 blockade. J Clin Invest 127:2930-2940, 2017

37. Nghiem PT, Bhatia S, Lipson EJ, et al: PD-1 Blockade with pembrolizumab in advanced Merkel-cell carcinoma. N Engl J Med 374:2542-2552, 2016

38. Tumeh PC, Harview CL, Yearley JH, et al: PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 515:568-571, 2014

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Molecular Determinants of Response to Anti–Programmed Cell Death (PD)-1 and Anti–Programmed Death-Ligand 1 (PD-L1) Blockade in Patients With Non–Small-Cell Lung Cancer Profiled With Targeted Next-Generation Sequencing

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Appendix

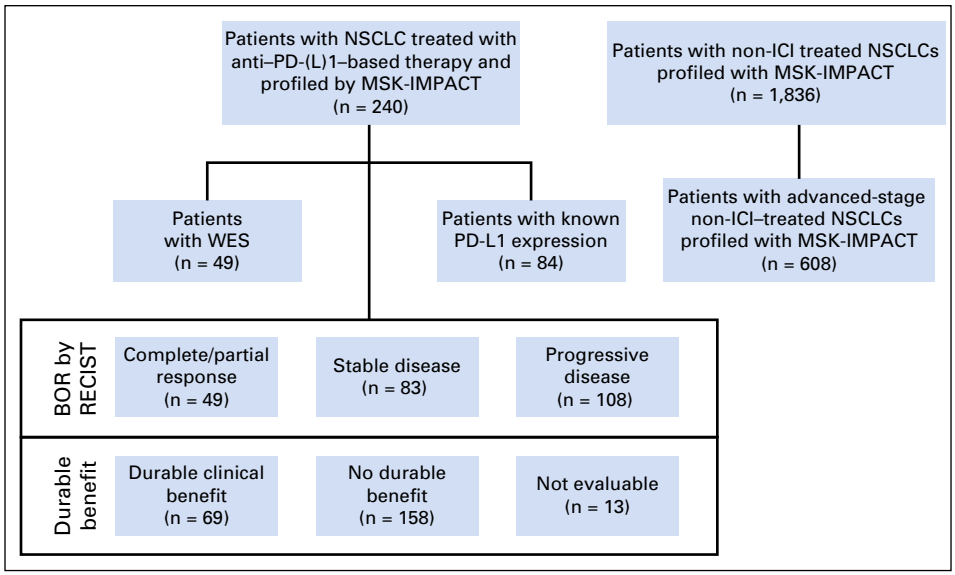

Fig A1. Flow of patients with non–small-cell lung cancer (NSCLC). These patients were treated with anti–programmed cell death-1 or anti–programmed death-ligand 1 [PD-(L)1] therapy from April 2011 through January 2017 and profiled with Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) panels are shown on the left. Patients with NSCLC profiled with MSK-IMPACT who have not been treated with immunotherapy (non–immune checkpoint inhibitors [ICIs]) are shown on the right. BOR, best overall response; RECIST, Response Evaluation Criteria in Solid Tumors; WES, whole-exome sequencing.

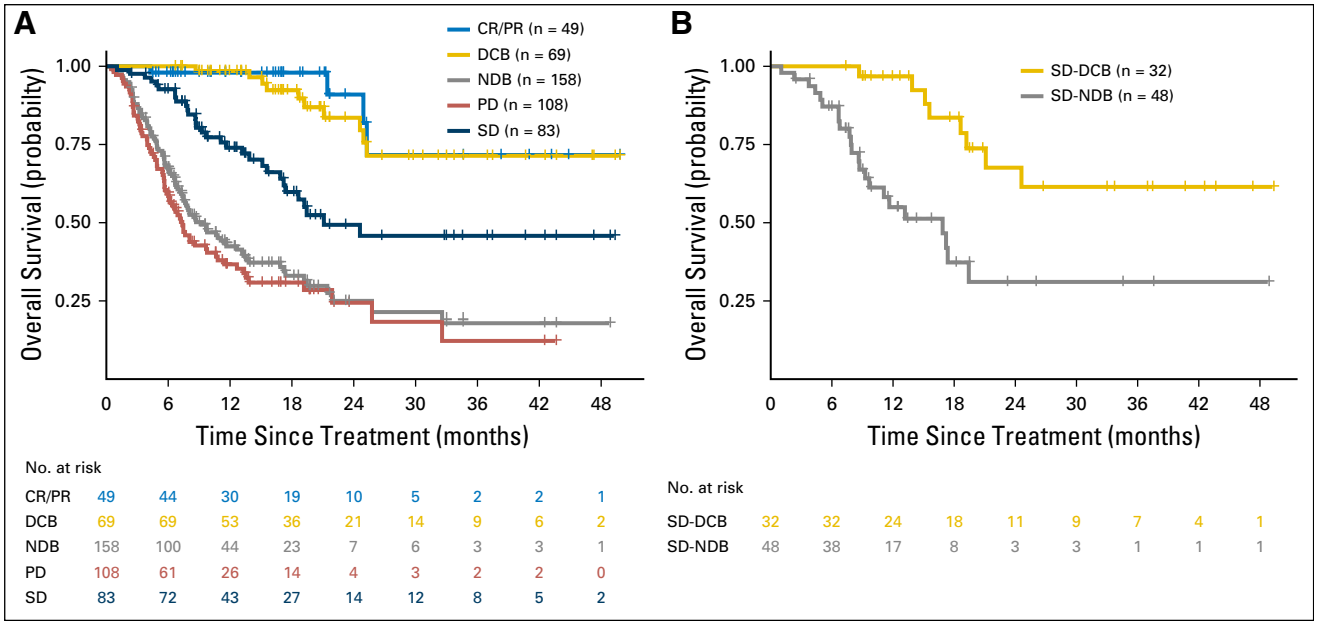

Fig A2. Durable clinical benefit (DCB)/no durable benefit (NDB) compared with Response Evaluation Criteria in Solid Tumors (RECIST)–defined benefit. DCB and NDB are clinically useful, simple, binary outcomes to categorize those who benefit or not from immunotherapy. These groups have survival outcomes similar to RECIST-defined complete response (CR)/partial response (PR) or progressive disease (PD) while also incorporating meaningful distinction of those with stable disease (SD) who are benefiters or not. (A) Overall survival of patients with DCB/NDB or CR/PR, SD, or PD. Survival of DCB closely mirrors that of CR/PR, and NDB mirrors patients with PD. (B) A focus just on patients with SD shows a significant difference in overall survival stratified by DCB and NDB ($P < .001$). RECIST-defined SD, therefore, is an intermediate group that is comprised by a "true" benefit (progression-free survival [PFS] > 6 months) and not a "true" benefit (PFS < 6 months). Therefore, dichotomizing outcomes by duration of benefit more explicitly captures the major contribution of benefit from immunotherapy (durability), removes patients with uncommon short-lived responses, and improves adjudication of those with RECIST-defined SD, a heterogeneous group that comprises true benefit or not of immunotherapy.

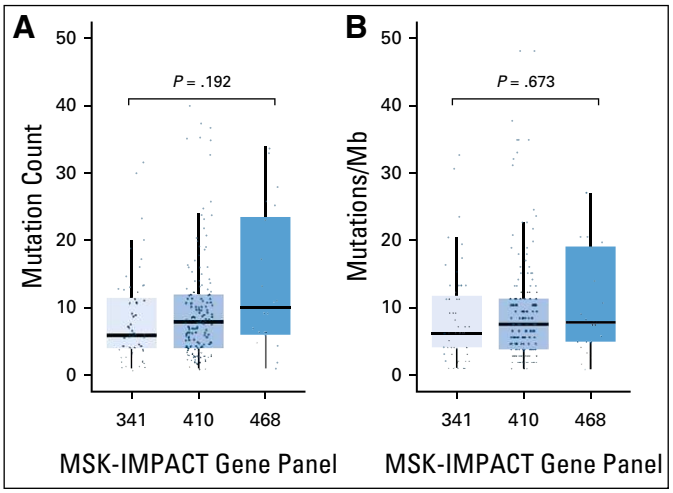

Fig A3. Range of mutation burden across varying sizes of targeted next-generation sequencing panels. (A) Absolute nonsynonymous missense mutation count reported for tumors assessed by using the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) 341-, 410-, and 486-gene panels. Increasing absolute mutation burden is seen with increasing numbers of genes tested (median of six, eight, and nine and a half mutations in the 341-, 410-, and 486-gene panels, respectively; $P = .192$). (B) The mutation rate normalized by the size of the coding region covered. This correction results in similar mutation rates across each panel (median, 6.1, 7.5, and 7.8 per megabase [Mb] in the 341-, 410-, and 486-gene panels, respectively; $P = .673$).

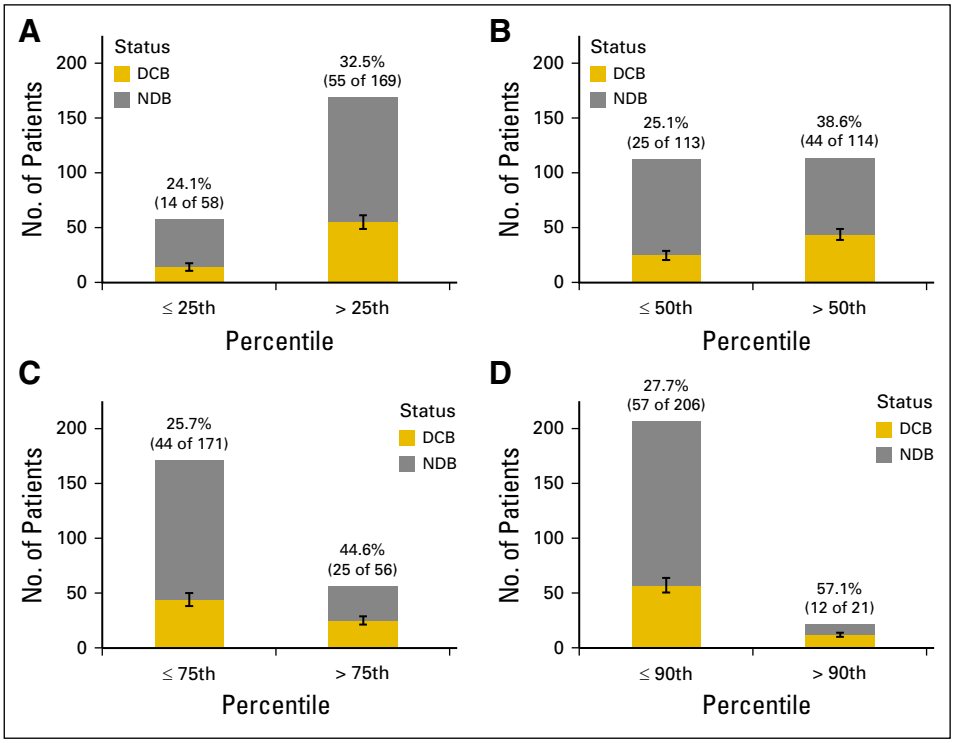

Fig A4. Proportion of durable clinical benefit (DCB) above or below the (A) 25th, (B) 50th, (C) 75th, and (D) 90th percentiles of tumor mutation burden. Percentages of DCB in each group are reported above each bar. Error bars show the SE of the percentage. NDB, no durable response.

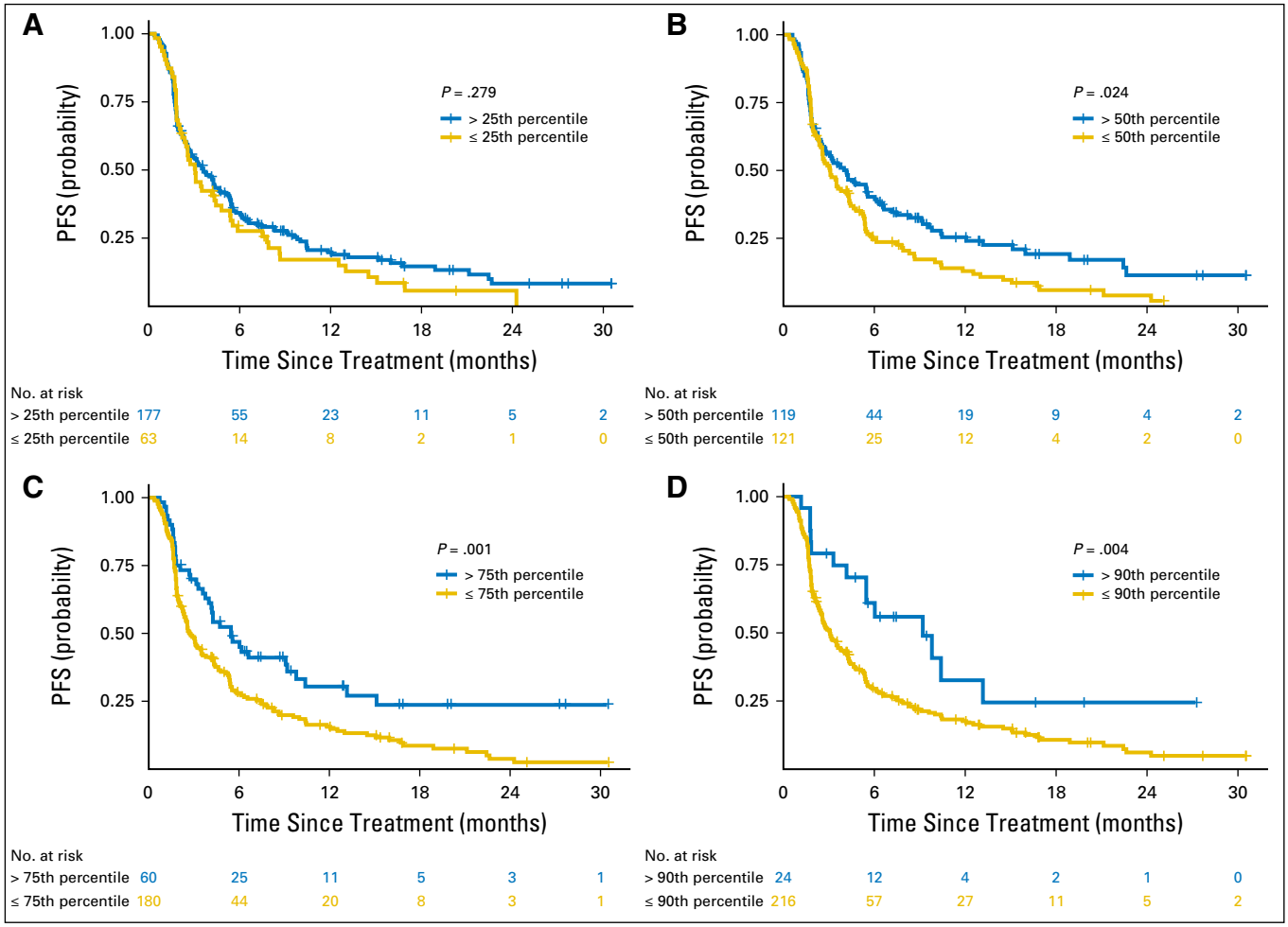

Fig A5. Progression-free survival (PFS) of patients with tumor mutation burden above or below the (A) 25th, (B) 50th, (C) 75th, and (D) 90th percentiles. The hazard ratios for PFS at each cut point were as follows: 25th percentile, 1.19 ($P = .279$); 50th percentile, 1.38 ($P = .024$); 75th percentile, 1.74 ($P = .001$); 90th percentile, 2.05 ($P = .004$).

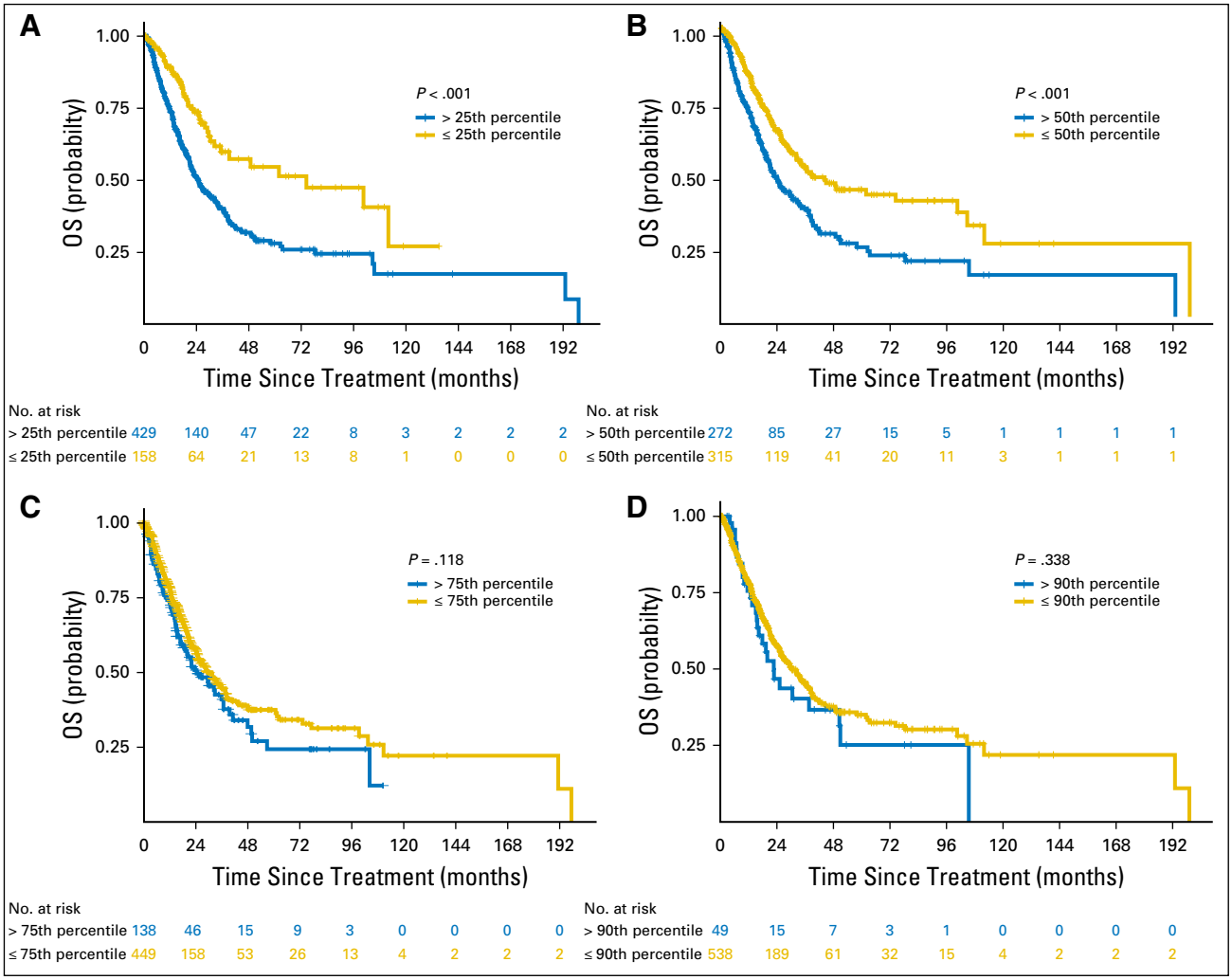

Fig A6. Overall survival (OS) of patients with advanced-stage lung adenocarcinoma not treated with immunotherapy. Survival is shown on the basis of tumor mutation burden above or below the (A) 25th, (B) 50th, (C) 75th, and (D) 90th percentiles within the non–immune checkpoint inhibitor non–small-cell lung cancer advanced-stage cohort (n = 609). The hazard ratios for OS at each cut point were as follows: 25th percentile, 0.49 ($P < .001$); 50th percentile, 0.58 ($P < .001$); 75th percentile, 0.81 ($P = .118$); and 90th percentile, 0.82 ($P = .338$).

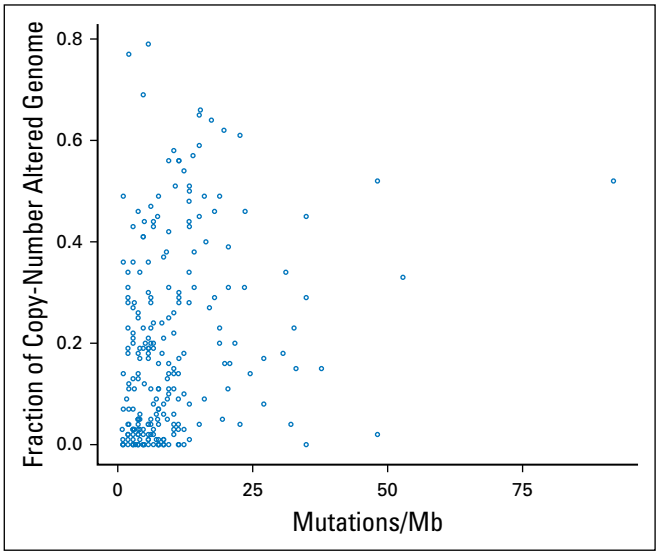

Fig A7. Scatter plot of tumor mutational burden versus fraction of copy number–altered genome in individual tumors (n = 240; Spearman $\rho = 0.31$; $P < .001$). Mb, megabase.

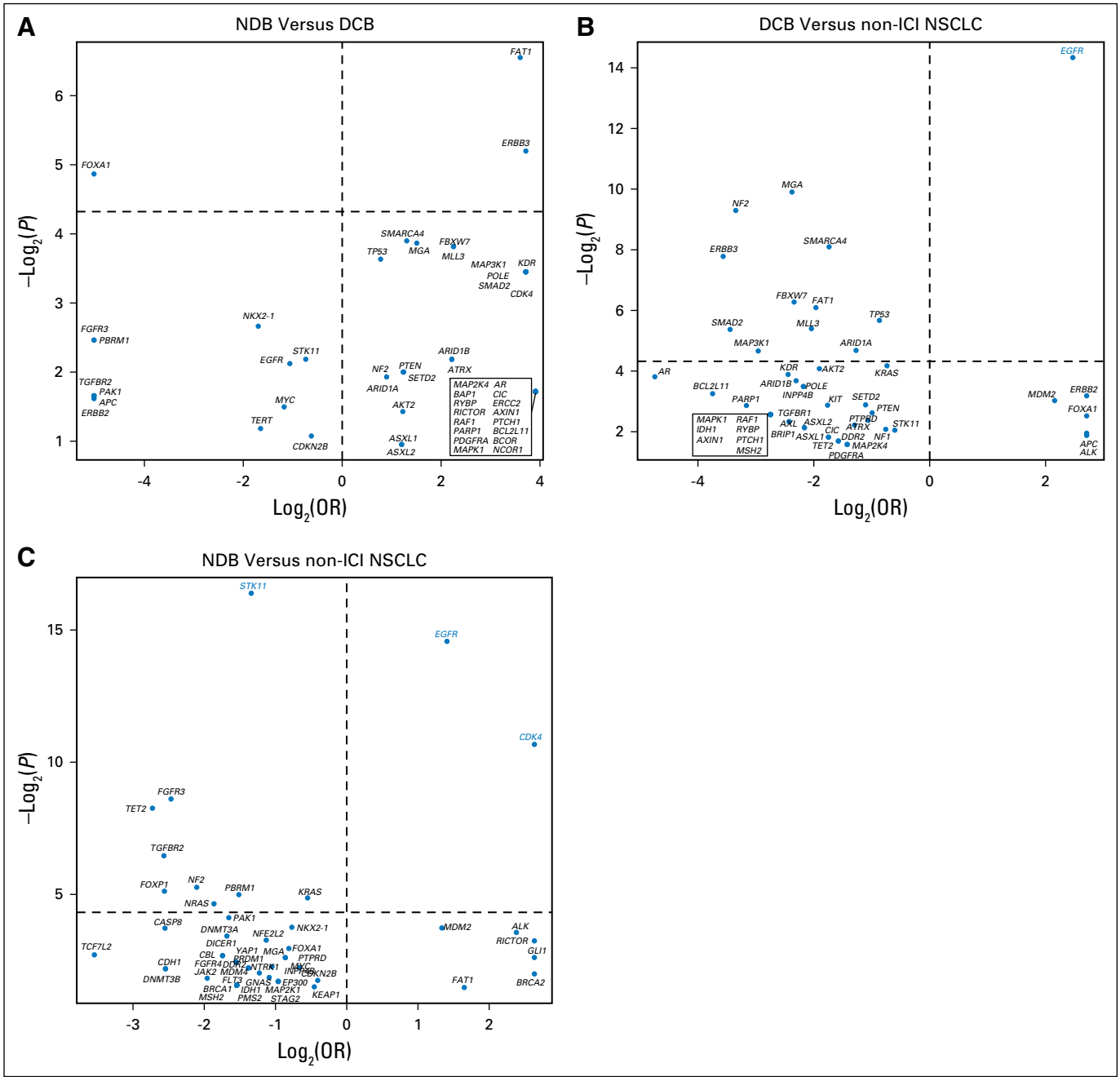

Fig A8. Log_2(odds ratio [OR]) and $–log_2$(*P* value) for enrichment of individual altered genes deemed oncogenic or likely oncogenic by OncoKB in group comparisons of (A) durable clinical benefit (DCB) versus no durable benefit (NDB), (B) DCB versus non–immune checkpoint inhibitor (ICI) non–small-cell lung cancer (NSCLC), and (C) NDB versus non-ICI NSCLC. The top 50 genes in each comparison are depicted, with adjusted *P* values used. Genes labeled in red were significantly enriched after correcting for the false discovery rate.

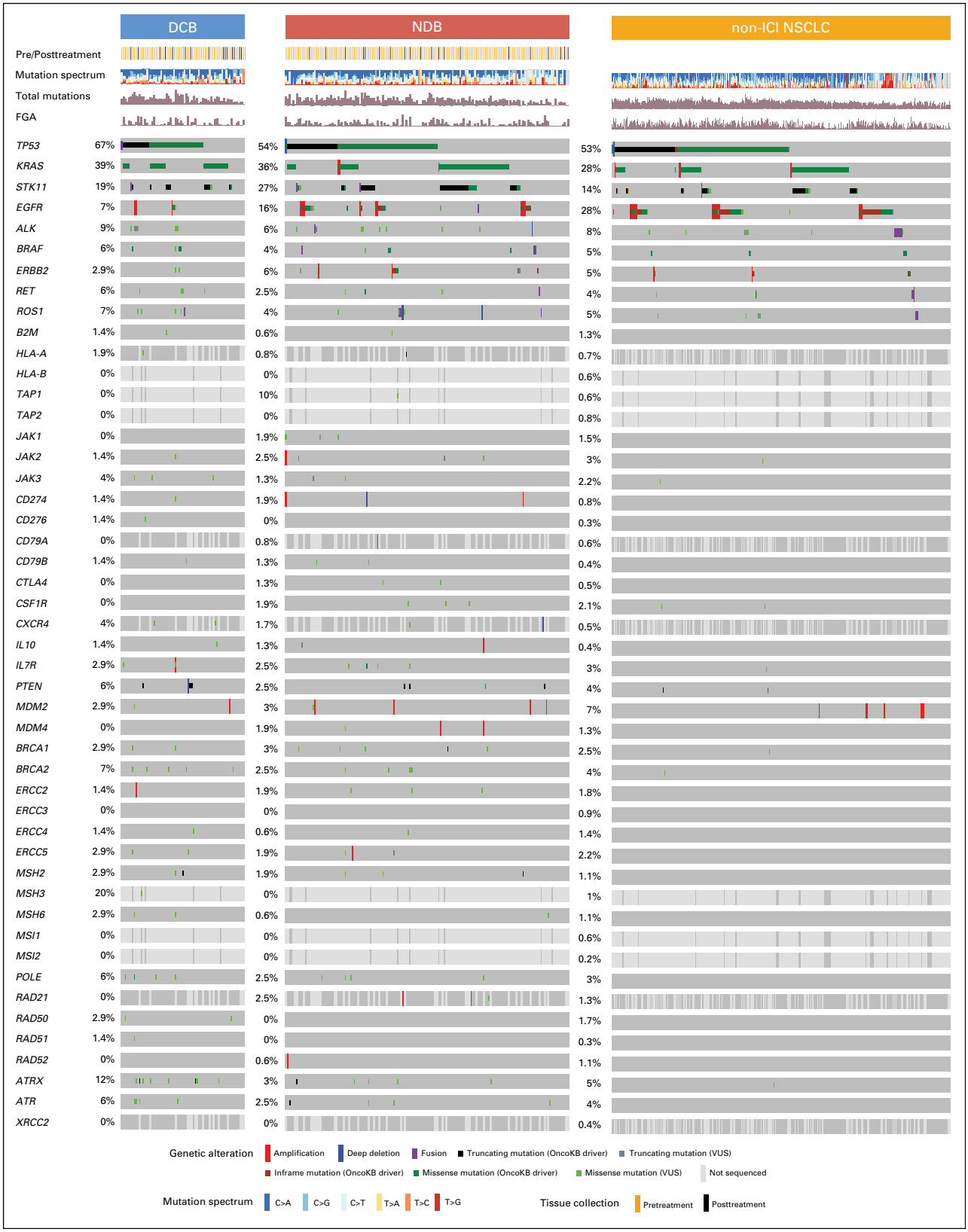

Fig A9. OncoPrint that depicts durable clinical benefit (DCB), no durable benefit (NDB), and non–immune checkpoint inhibitor (ICI) non–small-cell lung cancer (NSCLC) with an expanded list of preselected genes of interest, including oncogenic drivers in NSCLC, genes involved in antigen presentation, genes involved in modulating immune responses to cancer, genes previously reported to associate with response/resistance to programmed death-1 blockade, and genes involved in DNA repair. Genes shown in light gray were not sequenced as part of the MSK-IMPACT (Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets) panel. VUS, variant of unknown significance.

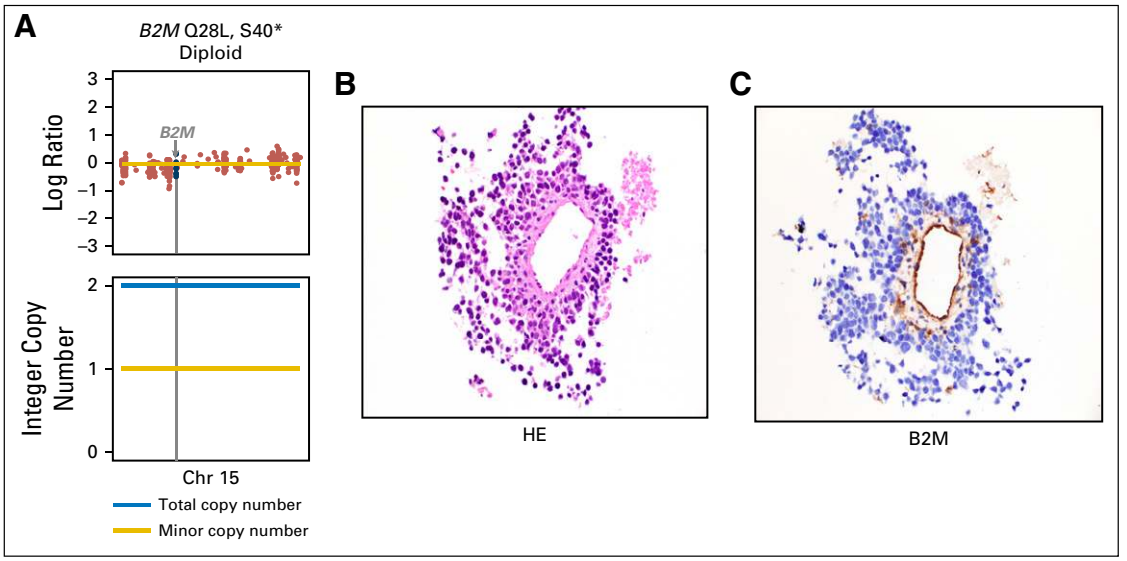

Fig A10. β2 microglobulin (*B2M*) mutation found in one patient that occurred in *trans* with one mutation on each allele. (A) The top plot shows overall copy number segmentations across the chromosome (Chr), with the vertical line highlighting the *B2M* gene position. The bottom plot shows the integer copy number, with the black line depicting the total integer copy number and the red line depicting minor copy number. (B) The hematoxylin and eosin (HE) stain (magnification, ×40) shows large tumor cells circumferentially around a central vessel. (C) B2M immunohistochemistry (magnification, ×40) shows selective loss of expression in tumor cells with retention of expression in normal endothelium and within scattered lymphocytes and histiocytes.

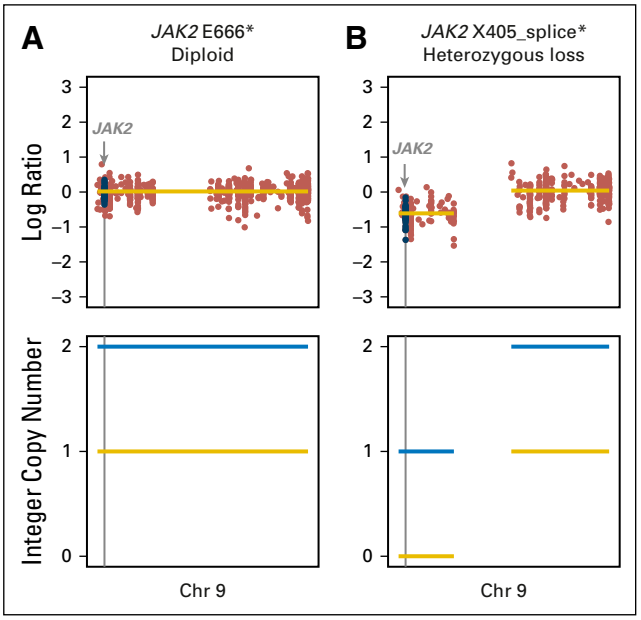

Fig A11. *JAK2* mutations were found in two patients. (A) A heterozygous mutation in *JAK2* with the wild-type allele retained. (B) A homozygous loss-of-function mutation in *JAK2* with loss of the wild-type allele occurring in a patient with primary progression to programmed death-1 blockade. Chr, chromosome.

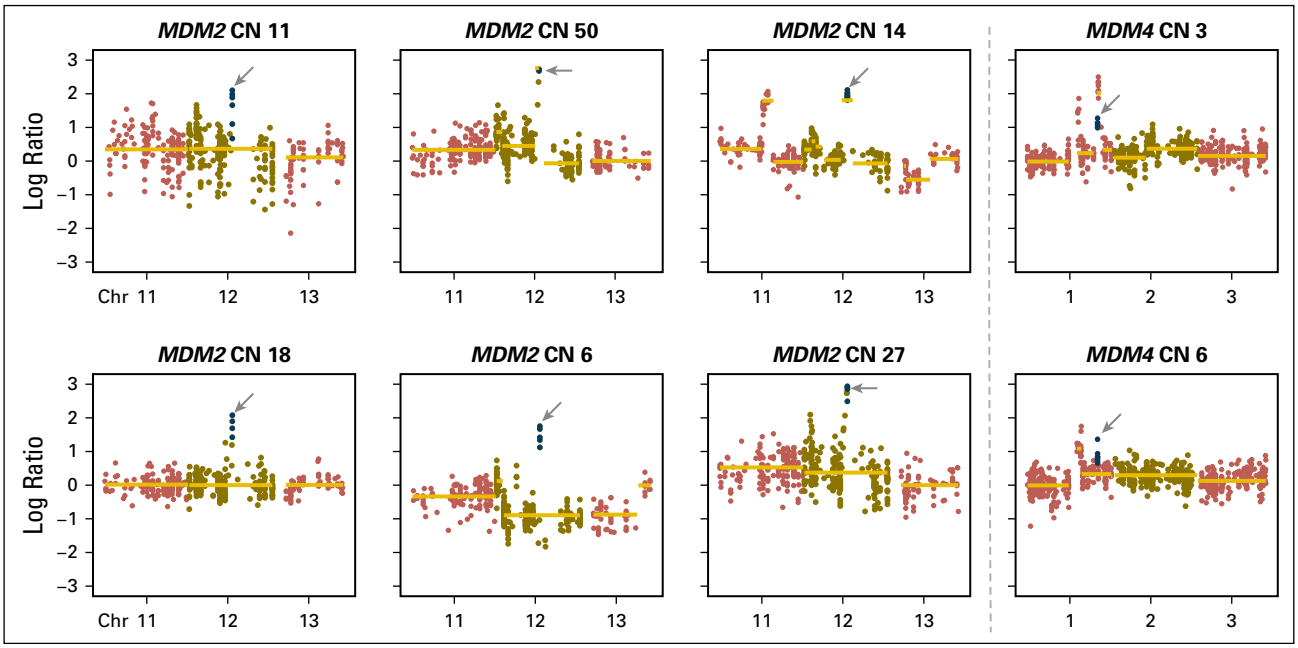

Fig A12. Amplifications in *MDM2* or *MDM4* were found in eight patients. Each plot shows the copy number (CN) log ratio of the overall CN segmentations across chromosomes (Chr). Estimated integer CNs are reported for each patient and calculated by FACETS. One patient had durable clinical benefit and five of eight patients had > 2 months progression-free survival. The patient with the greatest amplification had rapid progression. The progression-free survival curve of patients with *MDM2* or *MDM4* amplifications are compared with those with *MDM2*/*MDM4* wild type (hazard ratio, 1.4; $P = .44$).

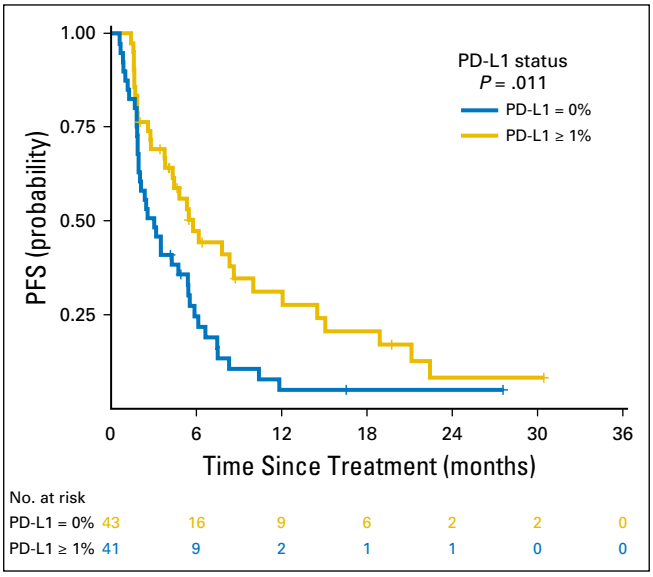

Fig A13. Progression-free survival (PFS) curve of patients with a programmed death-ligand 1 (PD-L1) expression of 0% compared with a PD-L1 expression ≥ 1% (hazard ratio, 0.53; $P = .01$).

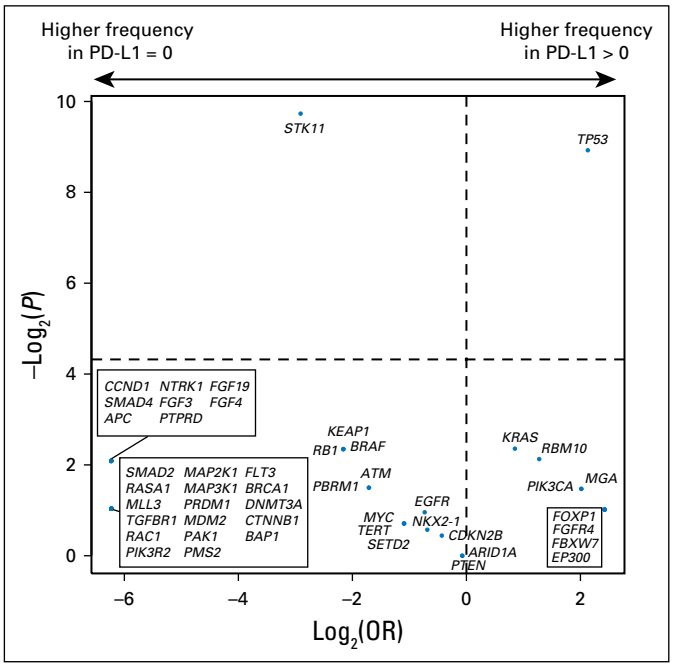

Fig A14. Log_2(odds ratio [OR]) and $–log_2$(*P* value) for enrichment of individual altered genes deemed oncogenic or likely oncogenic by OncoKb in the programmed death-ligand 1 (PD-L1)–positive versus PD-L1–negative subgroup. The top 50 genes in each comparison are depicted, with the false discovery rate–adjusted *P* values used.

Table A1. Gene Lists for MSK-IMPACT Versions 1 (341 Genes), 2 (410 Genes), and 3 (468 Genes)

Gene Symbol	Gene Description	Version of Panel First Included
ABL1	c-Abl oncogene 1, nonreceptor tyrosine kinase	Version 1
ACVR1	Activin A receptor, type I	Version 2
AGO2	Eukaryotic translation initiation factor 2C, 2	Version 3
AKT1	v-Akt murine thymoma viral oncogene homolog 1	Version 1
AKT2	v-Akt murine thymoma viral oncogene homolog 2	Version 1
AKT3	v-Akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma)	Version 1
ALK	Anaplastic lymphoma receptor tyrosine kinase	Version 1
ALOX12B	Arachidonate 12-lipoxygenase, 12R type	Version 1
ANKRD11	Ankyrin repeat domain 11	Version 2
APC	Adenomatous polyposis coli	Version 1
AR	Androgen receptor	Version 1
ARAF	v-Raf murine sarcoma 3611 viral oncogene homolog	Version 1
ARID1A	AT-rich interactive domain 1A (SWI-like)	Version 1
ARID1B	AT-rich interactive domain 1B (SWI1-like)	Version 1
ARID2	AT-rich interactive domain 2 (ARID, RFX-like)	Version 1
ARID5B	AT-rich interactive domain 5B (MRF1-like)	Version 1
ASXL1	Additional sex combs like 1 (*Drosophila*)	Version 1
ASXL2	Additional sex combs like 2 (*Drosophila*)	Version 1
ATM	Ataxia telangiectasia mutated	Version 1
ATR	Ataxia telangiectasia and Rad3 related	Version 1
ATRX	Alpha thalassemia/mental retardation syndrome X-linked	Version 1
AURKA	Aurora kinase A	Version 1
AURKB	Aurora kinase B	Version 1
AXIN1	Axin 1	Version 1
AXIN2	Axin 2	Version 1
AXL	AXL receptor tyrosine kinase	Version 1
B2M	Beta-2 microglobulin	Version 1
BABAM1	Chromosome 19 open reading frame 62	Version 3
BAP1	BRCA1 associated protein-1 (ubiquitin carboxy-terminal hydrolase)	Version 1
BARD1	BRCA1 associated RING domain 1	Version 1
BBC3	BCL2 binding component 3	Version 1
BCL10	B-cell CLL/lymphoma 10	Version 2
BCL2	B-cell CLL/lymphoma 2	Version 1
BCL2L1	BCL2-like 1	Version 1
BCL2L11	BCL2-like 11 (apoptosis facilitator)	Version 1
BCL6	B-cell CLL/lymphoma 6	Version 1
BCOR	BCL6 corepressor	Version 1
BIRC3	Baculoviral IAP repeat-containing 3	Version 2
BLM	Bloom syndrome, RecQ helicase-like	Version 1
BMPR1A	Bone morphogenetic protein receptor, type IA	Version 1
BRAF	v-Raf murine sarcoma viral oncogene homolog B1	Version 1
BRCA1	Breast cancer 1, early onset	Version 1
BRCA2	Breast cancer 2, early onset	Version 1
BRD4	Bromodomain containing 4	Version 1
BRIP1	BRCA1 interacting protein C-terminal helicase 1	Version 1
BTK	Bruton agammaglobulinemia tyrosine kinase	Version 1
CALR	Calreticulin	Version 2
CARD11	Caspase recruitment domain family, member 11	Version 1
CARM1	Coactivator-associated arginine methyltransferase 1	Version 3
CASP8	Caspase 8, apoptosis-related cysteine peptidase	Version 1
CBFB	Core-binding factor, beta subunit	Version 1
CBL	Cas-Br-M (murine) ecotropic retroviral transforming sequence	Version 1
CCND1	Cyclin D1	Version 1
CCND2	Cyclin D2	Version 1
CCND3	Cyclin D3	Version 1
CCNE1	Cyclin E1	Version 1
CD274	CD274 molecule	Version 1
CD276	CD276 molecule	Version 1
CD79A	CD79a molecule, immunoglobulin-associated alpha	Version 2
CD79B	CD79b molecule, immunoglobulin-associated beta	Version 1
CDC42	Cell division cycle 42 (GTP binding protein, 25 kDa)	Version 3
CDC73	Cell division cycle 73, Paf1/RNA polymerase II complex component, homolog (*Saccharomyces cerevisiae*)	Version 1
CDH1	Cadherin 1, type 1, E-cadherin (epithelial)	Version 1
CDK12	Cyclin-dependent kinase 12	Version 1
CDK4	Cyclin-dependent kinase 4	Version 1

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Table A1. Gene Lists for MSK-IMPACT Versions 1 (341 Genes), 2 (410 Genes), and 3 (468 Genes) (continued)

Gene Symbol	Gene Description	Version of Panel First Included
CDK6	Cyclin-dependent kinase 6	Version 1
CDK8	Cyclin-dependent kinase 8	Version 1
CDKN1A	Cyclin-dependent kinase inhibitor 1A (p21, Cip1)	Version 1
CDKN1B	Cyclin-dependent kinase inhibitor 1B (p27, Kip1)	Version 1
CDKN2A	Cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	Version 1
CDKN2B	Cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4)	Version 1
CDKN2C	Cyclin-dependent kinase inhibitor 2C (p18, inhibits CDK4)	Version 1
CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha	Version 2
CENPA	Centromere protein A	Version 2
CHEK1	CHK1 checkpoint homolog (*Schizosaccharomyces pombe*)	Version 1
CHEK2	CHK2 checkpoint homolog (*S pombe*)	Version 1
CIC	Capicua homolog (*Drosophila*)	Version 1
CREBBP	CREB binding protein	Version 1
CRKL	v-Crk sarcoma virus CT10 oncogene homolog (avian)-like	Version 1
CRLF2	Cytokine receptor-like factor 2	Version 1
CSDE1	Cold shock domain containing E1, RNA-binding	Version 3
CSF1R	Colony-stimulating factor 1 receptor	Version 1
CSF3R	Colony-stimulating factor 3 receptor (granulocyte)	Version 2
CTCF	CCCTC-binding factor (zinc finger protein)	Version 1
CTLA4	Cytotoxic T-lymphocyte-associated protein 4	Version 1
CTNNB1	Catenin (cadherin-associated protein), beta 1, 88 kDa	Version 1
CUL3	Cullin 3	Version 1
CXCR4	Chemokine (C-X-C motif) receptor 4	Version 2
CYLD	Cylindromatosis (turban tumor syndrome)	Version 3
CYSLTR2	Cysteinyl leukotriene receptor 2	Version 3
DAXX	Death domain–associated protein	Version 1
DCUN1D1	DCN1, defective in cullin neddylation 1, domain containing 1 (*S cerevisiae*)	Version 1
DDR2	Discoidin domain receptor tyrosine kinase 2	Version 1
DICER1	Dicer 1, ribonuclease type III	Version 1
DIS3	DIS3 mitotic control homolog (*S cerevisiae*)	Version 1
DNAJB1	DnaJ (Hsp40) homolog, subfamily B, member 1	Version 2
DNMT1	DNA (cytosine-5-)-methyltransferase 1	Version 1
DNMT3A	DNA (cytosine-5-)-methyltransferase 3 alpha	Version 1
DNMT3B	DNA (cytosine-5-)-methyltransferase 3 beta	Version 1
DOT1L	DOT1-like, histone H3 methyltransferase (*S cerevisiae*)	Version 1
DROSHA	Drosha, ribonuclease type III	Version 3
DUSP4	Dual specificity phosphatase 4	Version 3
E2F3	E2F transcription factor 3	Version 1
EED	Embryonic ectoderm development	Version 1
EGFL7	EGF-like domain, multiple 7	Version 1
EGFR	Epidermal growth factor receptor	Version 1
EIF1AX	Eukaryotic translation initiation factor 1A, X-linked	Version 1
EIF4A2	Eukaryotic translation initiation factor 4A2	Version 2
EIF4E	Eukaryotic translation initiation factor 4E	Version 2
ELF3	E74-like factor 3 (ets domain transcription factor, epithelial-specific)	Version 3
EP300	E1A binding protein p300	Version 1
EPAS1	Endothelial PAS domain protein 1	Version 3
EPCAM	Epithelial cell adhesion molecule	Version 1
EPHA3	EPH receptor A3	Version 1
EPHA5	EPH receptor A5	Version 1
EPHA7	EPH receptor A7	Version 2
EPHB1	EPH receptor B1	Version 1
ERBB2	v-Erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)	Version 1
ERBB3	v-Erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)	Version 1
ERBB4	v-Erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)	Version 1
ERCC2	Excision repair cross-complementing rodent repair deficiency, complementation group 2	Version 1
ERCC3	Excision repair cross-complementing rodent repair deficiency, complementation group 3 (xeroderma pigmentosum group B complementing)	Version 1
ERCC4	Excision repair cross-complementing rodent repair deficiency, complementation group 4	Version 1

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Table A1. Gene Lists for MSK-IMPACT Versions 1 (341 Genes), 2 (410 Genes), and 3 (468 Genes) (continued)

Gene Symbol	Gene Description	Version of Panel First Included
ERCC5	Excision repair cross-complementing rodent repair deficiency, complementation group 5	Version 1
ERF	Ets2 repressor factor	Version 3
ERG	v-Ets erythroblastosis virus E26 oncogene homolog (avian)	Version 1
ERRFI1	ERBB receptor feedback inhibitor 1	Version 2
ESR1	Estrogen receptor 1	Version 1
ETV1	Ets variant 1	Version 1
ETV6	Ets variant 6	Version 1
EZH1	Enhancer of zeste homolog 1 (*Drosophila*)	Version 3
EZH2	Enhancer of zeste homolog 2 (*Drosophila*)	Version 1
FAM123B	Family with sequence similarity 123B	Version 1
FAM175A	Family with sequence similarity 175, member A	Version 1
FAM46C	Family with sequence similarity 46, member C	Version 1
FAM58A	Family with sequence similarity 58, member A	Version 3
FANCA	Fanconi anemia, complementation group A	Version 1
FANCC	Fanconi anemia, complementation group C	Version 1
FAT1	FAT tumor suppressor homolog 1 (*Drosophila*)	Version 1
FBXW7	F-box and WD repeat domain containing 7	Version 1
FGF19	Fibroblast growth factor 19	Version 1
FGF3	Fibroblast growth factor 3	Version 1
FGF4	Fibroblast growth factor 4	Version 1
FGFR1	Fibroblast growth factor receptor 1	Version 1
FGFR2	Fibroblast growth factor receptor 2	Version 1
FGFR3	Fibroblast growth factor receptor 3	Version 1
FGFR4	Fibroblast growth factor receptor 4	Version 1
FH	Fumarate hydratase	Version 1
FLCN	Folliculin	Version 1
FLT1	Fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor)	Version 1
FLT3	Fms-related tyrosine kinase 3	Version 1
FLT4	Fms-related tyrosine kinase 4	Version 1
FOXA1	Forkhead box A1	Version 1
FOXL2	Forkhead box L2	Version 1
FOXO1	Forkhead box O1	Version 2
FOXP1	Forkhead box P1	Version 1
FUBP1	Far upstream element (FUSE)–binding protein 1	Version 1
FYN	FYN oncogene related to SRC, FGR, YES	Version 2
GATA1	GATA binding protein 1 (globin transcription factor 1)	Version 1
GATA2	GATA binding protein 2	Version 1
GATA3	GATA binding protein 3	Version 1
GLI1	GLI family zinc finger 1	Version 2
GNA11	Guanine nucleotide binding protein (G protein), alpha 11 (Gq class)	Version 1
GNAQ	Guanine nucleotide binding protein (G protein), q polypeptide	Version 1
GNAS	GNAS complex locus	Version 1
GPS2	G protein pathway suppressor 2	Version 2
GREM1	Gremlin 1	Version 1
GRIN2A	Glutamate receptor, ionotropic, *N*-methyl D-aspartate 2A	Version 1
GSK3B	Glycogen synthase kinase 3 beta	Version 1
H3F3A	H3 histone, family 3A	Version 2
H3F3B	H3 histone, family 3B (H3.3B)	Version 2
H3F3C	H3 histone, family 3C	Version 1
HGF	Hepatocyte growth factor (hepapoietin A; scatter factor)	Version 1
HIST1H1C	Histone cluster 1, H1c	Version 1
HIST1H2BD	Histone cluster 1, H2bd	Version 1
HIST1H3A	Histone cluster 1, H3a	Version 2
HIST1H3B	Histone cluster 1, H3b	Version 1
HIST1H3C	Histone cluster 1, H3c	Version 2
HIST1H3D	Histone cluster 1, H3d	Version 2
HIST1H3E	Histone cluster 1, H3e	Version 2
HIST1H3F	Histone cluster 1, H3f	Version 2
HIST1H3G	Histone cluster 1, H3g	Version 2
HIST1H3H	Histone cluster 1, H3h	Version 2
HIST1H3I	Histone cluster 1, H3i	Version 2
HIST1H3J	Histone cluster 1, H3j	Version 2
HIST2H3C	Histone cluster 2, H3c	Version 2
HIST2H3D	Histone cluster 2, H3d	Version 2

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Table A1. Gene Lists for MSK-IMPACT Versions 1 (341 Genes), 2 (410 Genes), and 3 (468 Genes) (continued)

Gene Symbol	Gene Description	Version of Panel First Included
HIST3H3	Histone cluster 3, H3	Version 2
HLA-A	Major histocompatibility complex, class I, A	Version 2
HLA-B	Major histocompatibility complex, class I, B	Version 3
HNF1A	HNF1 homeobox A	Version 1
HOXB13	Homeobox B13	Version 2
HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene homolog	Version 1
ICOSLG	Inducible T-cell costimulator ligand	Version 1
ID3	Inhibitor of DNA binding 3, dominant negative helix-loop-helix protein	Version 2
IDH1	Isocitrate dehydrogenase 1 (NADP+), soluble	Version 1
IDH2	Isocitrate dehydrogenase 2 (NADP+), mitochondrial	Version 1
IFNGR1	Interferon gamma receptor 1	Version 1
IGF1	Insulin-like growth factor 1 (somatomedin C)	Version 1
IGF1R	Insulin-like growth factor 1 receptor	Version 1
IGF2	Insulin-like growth factor 2 (somatomedin A)	Version 1
IKBKE	Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase epsilon	Version 1
IKZF1	IKAROS family zinc finger 1 (Ikaros)	Version 1
IL10	Interleukin 10	Version 1
IL7R	Interleukin 7 receptor	Version 1
INHA	Inhibin, alpha	Version 2
INHBA	Inhibin, beta A	Version 2
INPP4A	Inositol polyphosphate-4-phosphatase, type I, 107 kDa	Version 1
INPP4B	Inositol polyphosphate-4-phosphatase, type II, 105 kDa	Version 1
INPPL1	Inositol polyphosphate phosphatase-like 1	Version 3
INSR	Insulin receptor	Version 1
IRF4	Interferon regulatory factor 4	Version 1
IRS1	Insulin receptor substrate 1	Version 1
IRS2	Insulin receptor substrate 2	Version 1
JAK1	Janus kinase 1	Version 1
JAK2	Janus kinase 2	Version 1
JAK3	Janus kinase 3	Version 1
JUN	Jun proto-oncogene	Version 1
KDM5A	Lysine (K)–specific demethylase 5A	Version 1
KDM5C	Lysine (K)–specific demethylase 5C	Version 1
KDM6A	Lysine (K)–specific demethylase 6A	Version 1
KDR	Kinase insert domain receptor (a type III receptor tyrosine kinase)	Version 1
KEAP1	Kelch-like ECH-associated protein 1	Version 1
KIT	v-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	Version 1
KLF4	Kruppel-like factor 4 (gut)	Version 1
KMT2B	Myeloid/lymphoid or mixed-lineage leukemia 4	Version 3
KMT5A	SET domain containing (lysine methyltransferase) 8	Version 3
KNSTRN	Chromosome 15 open reading frame 23	Version 3
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	Version 1
LATS1	LATS, large tumor suppressor, homolog 1 (*Drosophila*)	Version 1
LATS2	LATS, large tumor suppressor, homolog 2 (*Drosophila*)	Version 1
LMO1	LIM domain only 1 (rhombotin 1)	Version 1
LYN	v-Yes-1 Yamaguchi sarcoma viral related oncogene homolog	Version 3
MALT1	Mucosa associated lymphoid tissue lymphoma translocation gene 1	Version 2
MAP2K1	Mitogen-activated protein kinase kinase 1	Version 1
MAP2K2	Mitogen-activated protein kinase kinase 2	Version 1
MAP2K4	Mitogen-activated protein kinase kinase 4	Version 1
MAP3K1	Mitogen-activated protein kinase kinase kinase 1	Version 1
MAP3K13	Mitogen-activated protein kinase kinase kinase 13	Version 1
MAP3K14	Mitogen-activated protein kinase kinase kinase 14	Version 2
MAPK1	Mitogen-activated protein kinase 1	Version 1
MAPK3	Mitogen-activated protein kinase 3	Version 2
MAPKAP1	Mitogen-activated protein kinase–associated protein 1	Version 3
MAX	MYC-associated factor X	Version 1
MCL1	Myeloid cell leukemia sequence 1 (BCL2-related)	Version 1
MDC1	Mediator of DNA-damage checkpoint 1	Version 1
MDM2	Mdm2 p53 binding protein homolog (mouse)	Version 1
MDM4	Mdm4 p53 binding protein homolog (mouse)	Version 1
MED12	Mediator complex subunit 12	Version 1

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Table A1. Gene Lists for MSK-IMPACT Versions 1 (341 Genes), 2 (410 Genes), and 3 (468 Genes) (continued)

Gene Symbol	Gene Description	Version of Panel First Included
MEF2B	Myocyte enhancer factor 2B	Version 1
MEN1	Multiple endocrine neoplasia I	Version 1
MET	Met proto-oncogene (hepatocyte growth factor receptor)	Version 1
MGA	MAX gene associated	Version 2
MITF	Microphthalmia-associated transcription factor	Version 1
MLH1	MutL homolog 1, colon cancer, nonpolyposis type 2 (*Escherichia coli*)	Version 1
MLL	Myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, *Drosophila*)	Version 1
MLL2	Myeloid/lymphoid or mixed-lineage leukemia 2	Version 1
MLL3	Myeloid/lymphoid or mixed-lineage leukemia 3	Version 1
MPL	Myeloproliferative leukemia virus oncogene	Version 1
MRE11A	MRE11 meiotic recombination 11 homolog A (*S cerevisiae*)	Version 1
MSH2	MutS homolog 2, colon cancer, nonpolyposis type 1 (*E coli*)	Version 1
MSH3	MutS homolog 3 (*E coli*)	Version 3
MSH6	MutS homolog 6 (*E coli*)	Version 1
MSI1	Musashi homolog 1 (*Drosophila*)	Version 3
MSI2	Musashi homolog 2 (*Drosophila*)	Version 3
MST1	Macrophage stimulating 1 (hepatocyte growth factor-like)	Version 2
MST1R	Macrophage stimulating 1 receptor (c-met-related tyrosine kinase)	Version 2
MTOR	Mechanistic target of rapamycin (serine/threonine kinase)	Version 1
MUTYH	MutY homolog (*E coli*)	Version 1
MYC	v-Myc myelocytomatosis viral oncogene homolog (avian)	Version 1
MYCL1	v-Myc myelocytomatosis viral oncogene homolog 1, lung carcinoma derived (avian)	Version 1
MYCN	v-Myc myelocytomatosis viral related oncogene, neuroblastoma derived (avian)	Version 1
MYD88	Myeloid differentiation primary response gene (88)	Version 1
MYOD1	Myogenic differentiation 1	Version 1
NBN	Nibrin	Version 1
NCOA3	Nuclear receptor coactivator 3	Version 2
NCOR1	Nuclear receptor corepressor 1	Version 1
NEGR1	Neuronal growth regulator 1	Version 2
NF1	Neurofibromin 1	Version 1
NF2	Neurofibromin 2 (merlin)	Version 1
NFE2L2	Nuclear factor (erythroid-derived 2)–like 2	Version 1
NFKBIA	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	Version 2
NKX2-1	NK2 homeobox 1	Version 1
NKX3-1	NK3 homeobox 1	Version 1
NOTCH1	Notch 1	Version 1
NOTCH2	Notch 2	Version 1
NOTCH3	Notch 3	Version 1
NOTCH4	Notch 4	Version 1
NPM1	Nucleophosmin (nucleolar phosphoprotein B23, numatrin)	Version 1
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog	Version 1
NSD1	Nuclear receptor binding SET domain protein 1	Version 1
NTHL1	nth endonuclease III-like 1 (*E coli*)	Version 3
NTRK1	Neurotrophic tyrosine kinase, receptor, type 1	Version 1
NTRK2	Neurotrophic tyrosine kinase, receptor, type 2	Version 1
NTRK3	Neurotrophic tyrosine kinase, receptor, type 3	Version 1
NUF2	NUF2, NDC80 kinetochore complex component, homolog (*S cerevisiae*)	Version 3
NUP93	Nucleoporin 93 kDa	Version 2
PAK1	p21 protein (Cdc42/Rac)–activated kinase 1	Version 1
PAK7	p21 protein (Cdc42/Rac)–activated kinase 7	Version 1
PALB2	Partner and localizer of BRCA2	Version 1
PARK2	Parkinson protein 2, E3 ubiquitin protein ligase (parkin)	Version 1
PARP1	Poly (ADP-ribose) polymerase 1	Version 1
PAX5	Paired box 5	Version 1
PBRM1	Polybromo 1	Version 1
PDCD1	Programmed cell death-1	Version 1
PDCD1LG2	Programmed cell death-1 ligand 2	Version 3
PDGFRA	Platelet-derived growth factor receptor, alpha polypeptide	Version 1
PDGFRB	Platelet-derived growth factor receptor, beta polypeptide	Version 1
PDPK1	3-Phosphoinositide–dependent protein kinase-1	Version 1

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Table A1. Gene Lists for MSK-IMPACT Versions 1 (341 Genes), 2 (410 Genes), and 3 (468 Genes) (continued)

Gene Symbol	Gene Description	Version of Panel First Included
PGR	Progesterone receptor	Version 2
PHOX2B	Paired-like homeobox 2b	Version 1
PIK3C2G	Phosphoinositide-3-kinase, class 2, gamma polypeptide	Version 1
PIK3C3	Phosphoinositide-3-kinase, class 3	Version 1
PIK3CA	Phosphoinositide-3-kinase, catalytic, alpha polypeptide	Version 1
PIK3CB	Phosphoinositide-3-kinase, catalytic, beta polypeptide	Version 1
PIK3CD	Phosphoinositide-3-kinase, catalytic, delta polypeptide	Version 1
PIK3CG	Phosphoinositide-3-kinase, catalytic, gamma polypeptide	Version 1
PIK3R1	Phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	Version 1
PIK3R2	Phosphoinositide-3-kinase, regulatory subunit 2 (beta)	Version 1
PIK3R3	Phosphoinositide-3-kinase, regulatory subunit 3 (gamma)	Version 1
PIM1	Pim-1 oncogene	Version 1
PLCG2	Phospholipase C, gamma 2 (phosphatidylinositol-specific)	Version 2
PLK2	Polo-like kinase 2	Version 1
PMAIP1	Phorbol-12-myristate-13-acetate-induced protein 1	Version 1
PMS1	PMS1 postmeiotic segregation increased 1 (*S cerevisiae*)	Version 1
PMS2	PMS2 postmeiotic segregation increased 2 (*S cerevisiae*)	Version 1
PNRC1	Proline-rich nuclear receptor coactivator 1	Version 1
POLD1	Polymerase (DNA directed), delta 1, catalytic subunit 125 kDa	Version 2
POLE	Polymerase (DNA directed), epsilon	Version 1
PPARG	Peroxisome proliferator–activated receptor gamma	Version 3
PPM1D	Protein phosphatase, Mg2+/Mn2+ dependent, 1D	Version 2
PPP2R1A	Protein phosphatase 2, regulatory subunit A, alpha	Version 1
PPP4R2	Protein phosphatase 4, regulatory subunit 2	Version 3
PPP6C	Protein phosphatase 6, catalytic subunit	Version 2
PRDM1	PR domain containing 1, with ZNF domain	Version 1
PRDM14	PR domain containing 14	Version 3
PREX2	Phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 2	Version 3
PRKAR1A	Protein kinase, cAMP-dependent, regulatory, type I, alpha (tissue specific extinguisher 1)	Version 1
PRKCI	Protein kinase C, iota	Version 3
PRKD1	Protein kinase D1	Version 3
PTCH1	Patched 1	Version 1
PTEN	Phosphatase and tensin homolog	Version 1
PTP4A1	Protein tyrosine phosphatase type IVA, member 1	Version 3
PTPN11	Protein tyrosine phosphatase, nonreceptor type 11	Version 1
PTPRD	Protein tyrosine phosphatase, receptor type, D	Version 1
PTPRS	Protein tyrosine phosphatase, receptor type, S	Version 1
PTPRT	Protein tyrosine phosphatase, receptor type, T	Version 1
RAB35	RAB35, member RAS oncogene family	Version 2
RAC1	Ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)	Version 1
RAC2	Ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2)	Version 3
RAD21	RAD21 homolog (*S pombe*)	Version 2
RAD50	RAD50 homolog (*S cerevisiae*)	Version 1
RAD51	RAD51 homolog (RecA homolog, *E coli*) (*S cerevisiae*)	Version 1
RAD51C	RAD51 homolog C (*S cerevisiae*)	Version 1
RAD51L1	RAD51-like 1 (*S cerevisiae*)	Version 1
RAD51L3	RAD51-like 3 (*S cerevisiae*)	Version 1
RAD52	RAD52 homolog (*S cerevisiae*)	Version 1
RAD54L	RAD54-like (*S cerevisiae*)	Version 1
RAF1	v-Raf-1 murine leukemia viral oncogene homolog 1	Version 1
RARA	Retinoic acid receptor, alpha	Version 1
RASA1	RAS p21 protein activator (GTPase activating protein) 1	Version 1
RB1	Retinoblastoma 1	Version 1
RBM10	RNA binding motif protein 10	Version 1
RECQL	RecQ protein-like (DNA helicase Q1-like)	Version 3
RECQL4	RecQ protein-like 4	Version 1
REL	v-Rel reticuloendotheliosis viral oncogene homolog (avian)	Version 1
RET	Ret proto-oncogene	Version 1
RFWD2	Ring finger and WD repeat domain 2	Version 1
RHEB	Ras homolog enriched in brain	Version 2
RHOA	Ras homolog gene family, member A	Version 1
RICTOR	RPTOR independent companion of MTOR, complex 2	Version 1
RIT1	Ras-like without CAAX 1	Version 1

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Table A1. Gene Lists for MSK-IMPACT Versions 1 (341 Genes), 2 (410 Genes), and 3 (468 Genes) (continued)

Gene Symbol	Gene Description	Version of Panel First Included
RNF43	Ring finger protein 43	Version 1
ROS1	c-Ros oncogene 1, receptor tyrosine kinase	Version 1
RPS6KA4	Ribosomal protein S6 kinase, 90 kDa, polypeptide 4	Version 1
RPS6KB2	Ribosomal protein S6 kinase, 70 kDa, polypeptide 2	Version 1
RPTOR	Regulatory associated protein of MTOR, complex 1	Version 1
RRAGC	Ras-related GTP binding C	Version 3
RRAS	Related RAS viral (r-ras) oncogene homolog	Version 3
RRAS2	Related RAS viral (r-ras) oncogene homolog 2	Version 3
RTEL1	Regulator of telomere elongation helicase 1	Version 3
RUNX1	Runt-related transcription factor 1	Version 1
RXRA	Retinoid X receptor, alpha	Version 3
RYBP	RING1 and YY1 binding protein	Version 1
SDHA	Succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	Version 1
SDHAF2	Succinate dehydrogenase complex assembly factor 2	Version 1
SDHB	Succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	Version 1
SDHC	Succinate dehydrogenase complex, subunit C, integral membrane protein, 15 kDa	Version 1
SDHD	Succinate dehydrogenase complex, subunit D, integral membrane protein	Version 1
SESN1	Sestrin 1	Version 3
SESN2	Sestrin 2	Version 3
SESN3	Sestrin 3	Version 3
SETD2	SET domain containing 2	Version 1
SF3B1	Splicing factor 3b, subunit 1, 155 kDa	Version 1
SH2B3	SH2B adaptor protein 3	Version 2
SH2D1A	SH2 domain containing 1A	Version 1
SHOC2	Soc-2 suppressor of clear homolog (*Caenorhabditis elegans*)	Version 3
SHQ1	SHQ1 homolog (*S cerevisiae*)	Version 1
SLX4	SLX4 structure-specific endonuclease subunit homolog (*S cerevisiae*)	Version 3
SMAD2	SMAD family member 2	Version 1
SMAD3	SMAD family member 3	Version 1
SMAD4	SMAD family member 4	Version 1
SMARCA4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4	Version 1
SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	Version 1
SMARCD1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 1	Version 1
SMO	Smoothened homolog (*Drosophila*)	Version 1
SMYD3	SET and MYND domain containing 3	Version 3
SOCS1	Suppressor of cytokine signaling 1	Version 1
SOS1	Son of sevenless homolog 1 (*Drosophila*)	Version 3
SOX17	SRY (sex determining region Y)-box 17	Version 1
SOX2	SRY (sex determining region Y)-box 2	Version 1
SOX9	SRY (sex determining region Y)-box 9	Version 1
SPEN	Spen homolog, transcriptional regulator (*Drosophila*)	Version 1
SPOP	Speckle-type POZ protein	Version 1
SPRED1	Sprouty-related, EVH1 domain containing 1	Version 3
SRC	v-Src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)	Version 1
SRSF2	Serine/arginine-rich splicing factor 2	Version 2
STAG2	Stromal antigen 2	Version 1
STAT3	Signal transducer and activator of transcription 3 (acute-phase response factor)	Version 2
STAT5A	Signal transducer and activator of transcription 5A	Version 2
STAT5B	Signal transducer and activator of transcription 5B	Version 2
STK11	Serine/threonine kinase 11	Version 1
STK19	Serine/threonine kinase 19	Version 3
STK40	Serine/threonine kinase 40	Version 1
SUFU	Suppressor of fused homolog (*Drosophila*)	Version 1
SUZ12	Suppressor of zeste 12 homolog (*Drosophila*)	Version 1
SYK	Spleen tyrosine kinase	Version 1
TAP1	Transporter 1, ATP-binding cassette, subfamily B (MDR/TAP)	Version 3
TAP2	Transporter 2, ATP-binding cassette, subfamily B (MDR/TAP)	Version 3
TBX3	T-box 3	Version 1
TCEB1	Transcription elongation factor B (SIII), polypeptide 1 (15 kDa, elongin C)	Version 2

(continued on following page)

Table A1. Gene Lists for MSK-IMPACT Versions 1 (341 Genes), 2 (410 Genes), and 3 (468 Genes) (continued)

Gene Symbol	Gene Description	Version of Panel First Included
TCF3	Transcription factor 3 (E2A immunoglobulin enhancer binding factors E12/E47)	Version 2
TCF7L2	Transcription factor 7-like 2 (T-cell specific, HMG-box)	Version 2
TEK	TEK tyrosine kinase, endothelial	Version 3
TERT	Telomerase reverse transcription	Version 1
TET1	Tet oncogene 1	Version 1
TET2	Tet oncogene family member 2	Version 1
TGFBR1	Transforming growth factor, beta receptor 1	Version 1
TGFBR2	Transforming growth factor, beta receptor II (70/80 kDa)	Version 1
TMEM127	Transmembrane protein 127	Version 1
TMPRSS2	Transmembrane protease, serine 2	Version 1
TNFAIP3	Tumor necrosis factor, alpha-induced protein 3	Version 1
TNFRSF14	Tumor necrosis factor receptor superfamily, member 14 (herpesvirus entry mediator)	Version 1
TOP1	Topoisomerase (DNA) I	Version 1
TP53	Tumor protein p53	Version 1
TP53BP1	Tumor protein p53-binding protein 1	Version 3
TP63	Tumor protein p63	Version 1
TRAF2	TNF receptor-associated factor 2	Version 2
TRAF7	TNF receptor-associated factor 7	Version 1
TSC1	Tuberous sclerosis 1	Version 1
TSC2	Tuberous sclerosis 2	Version 1
TSHR	Thyroid-stimulating hormone receptor	Version 1
U2AF1	U2 small nuclear RNA auxiliary factor 1	Version 1
UPF1	UPF1 regulator of nonsense transcripts homolog (yeast)	Version 3
VEGFA	Vascular endothelial growth factor A	Version 2
VHL	von Hippel-Lindau tumor suppressor	Version 1
VTCN1	V-set domain containing T-cell activation inhibitor 1	Version 1
WHSC1	Wolf-Hirschhorn syndrome candidate 1	Version 3
WHSC1L1	Wolf-Hirschhorn syndrome candidate 1–like 1	Version 3
WT1	Wilms tumor 1	Version 1
WWTR1	WW domain–containing transcription regulator 1	Version 3
XIAP	X-linked inhibitor of apoptosis	Version 1
XPO1	Exportin 1 (CRM1 homolog, yeast)	Version 1
XRCC2	X-ray repair complementing defective repair in Chinese hamster cells 2	Version 2
YAP1	Yes-associated protein 1	Version 1
YES1	v-Yes-1 Yamaguchi sarcoma viral oncogene homolog 1	Version 1
ZFHX3	Zinc finger homeobox 3	Version 2
ZRSR2	Zinc finger (CCCH type), RNA-binding motif and serine/arginine rich 2	Version 2

Abbreviation: MSK-IMPACT, Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets.

Table A2. Detailed Clinical Characteristics of Patients

Patient ID	Gene Panel	Mean Tumor Coverage	Tissue Sample Taken Pre- or Posttreatment	Histology	Sex	Age	Smoking Status*	Prior Lines of Therapy†	Treatment‡	PFS (months)	Event§	BOR‖	DCB
1	IMPACT341	428	Pre	ADC	F	58	Ever	1	Combo	27.20	0	CR	DCB
2	IMPACT341	905	Pre	ADC	M	60	Ever	4	Mono	14.50	1	PR	DCB
3	IMPACT341	1,346	Pre	ADC	F	68	Ever	1	Mono	4.17	1	SD	NDB
4	IMPACT341	618	Pre	SQCLC	M	77	Ever	3	Mono	0.60	1	PD	NDB
5	IMPACT341	699	Pre	LC-NE	M	66	Ever	2	Combo	1.63	1	PD	NDB
6	IMPACT468	486	Pre	SQCLC	M	67	Ever	3	Mono	4.93	0	PR	NE
7	IMPACT341	418	Pre	SQCLC	M	71	Never	2	Mono	1.20	1	PD	NDB
8	IMPACT341	1,201	Pre	ADC	M	66	Ever	6	Mono	1.73	1	PD	NDB
9	IMPACT341	369	Pre	ADC	M	42	Never	1	Mono	1.50	1	PD	NDB
10	IMPACT341	990	Post	ADC	M	57	Never	1	Combo	11.83	1	SD	DCB
11	IMPACT341	438	Post	ADC	F	49	Ever	1	Combo	2.33	1	SD	NDB
12	IMPACT410	817	Pre	ADC	F	68	Ever	3	Mono	5.47	1	SD	NDB
13	IMPACT410	966	Pre	ADC	M	58	Ever	6	Mono	2.57	1	PD	NDB
14	IMPACT341	549	Pre	ADC	F	73	Ever	1	Mono	10.00	1	SD	DCB
15	IMPACT341	433	Post	SQCLC	M	64	Ever	1	Combo	3.80	1	SD	NDB
16	IMPACT341	532	Post	ADC	M	79	Never	3	Mono	5.27	1	SD	NDB
17	IMPACT410	979	Pre	ADC	F	58	Never	7	Mono	3.50	1	PD	NDB
18	IMPACT410	839	Pre	ADC	F	59	Never	3	Mono	2.10	1	PD	NDB
19	IMPACT341	540	Pre	ADC	M	65	Ever	1	Combo	22.43	1	SD	DCB
20	IMPACT341	728	Post	LC-NE	F	44	Ever	2	Mono	1.17	1	PD	NDB
21	IMPACT341	1,189	Pre	ADC	M	53	Ever	2	Mono	13.17	1	PR	DCB
22	IMPACT341	861	Pre	NOS	M	62	Ever	3	Mono	5.33	1	SD	NDB
23	IMPACT341	534	Pre	ADC	M	71	Ever	3	Mono	1.87	1	PD	NDB
24	IMPACT341	580	Pre	ADC	F	50	Ever	1	Combo	30.43	0	CR	DCB
25	IMPACT341	758	Pre	ADC	F	55	Never	3	Mono	0.67	1	PD	NDB
26	IMPACT341	551	Pre	ADC	F	48	Never	6	Mono	3.07	1	PD	NDB
27	IMPACT341	722	Pre	ADC	F	74	Ever	2	Combo	4.63	1	PR	NDB
28	IMPACT341	748	Pre	ADC	F	60	Ever	2	Mono	1.77	1	PD	NDB
29	IMPACT341	439	Pre	ADC	M	70	Ever	3	Mono	4.20	1	SD	NDB
30	IMPACT341	358	Pre	ADC	F	31	Never	3	Mono	3.03	1	PD	NDB
31	IMPACT341	159	Pre	ADC	M	80	Ever	2	Mono	1.30	1	PD	NDB
32	IMPACT341	623	Pre	SQCLC	F	64	Ever	3	Mono	25.03	0	PR	DCB
33	IMPACT341	819	Pre	ADC	F	71	Ever	3	Mono	9.60	1	PR	DCB
34	IMPACT341	690	Pre	ADC	M	66	Ever	3	Mono	1.27	1	PD	NDB
35	IMPACT410	1,232	Pre	SQCLC	M	71	Never	2	Mono	2.57	1	SD	NDB
36	IMPACT341	628	Pre	ADC	F	69	Ever	3	Mono	2.77	1	PD	NDB
37	IMPACT341	342	Pre	SQCLC	F	73	Ever	2	Mono	4.27	1	PR	NDB
38	IMPACT341	892	Post	ADC	F	75	Never	7	Mono	1.93	1	PD	NDB
39	IMPACT341	1,494	Pre	ADC	M	57	Never	2	Mono	1.77	1	SD	NDB
40	IMPACT341	692	Pre	SQCLC	F	74	Ever	3	Mono	5.37	1	SD	NDB
41	IMPACT341	737	Pre	ADC	M	66	Ever	3	Mono	2.10	1	PD	NDB
42	IMPACT341	608	Post	SQCLC	M	43	Ever	1	Mono	7.50	1	SD	DCB
43	IMPACT341	282	Pre	ADC	M	67	Ever	1	Combo	7.90	1	PR	DCB
44	IMPACT341	727	Post	ADC	F	37	Never	1	Mono	1.07	1	PD	NDB
45	IMPACT341	1,086	Pre	LC-NE	M	53	Ever	1	Combo	27.60	0	CR	DCB
46	IMPACT341	760	Pre	ADC	F	67	Ever	2	Mono	8.10	0	PR	DCB
47	IMPACT410	776	Pre	ADC	F	64	Ever	2	Mono	15.03	0	PR	DCB
48	IMPACT341	91	Pre	ADC	F	68	Ever	1	Mono	4.43	1	SD	NDB
49	IMPACT341	112	Pre	NOS	M	62	Ever	3	Mono	1.80	1	PD	NDB
50	IMPACT341	757	Pre	ADC	F	66	Ever	2	Mono	1.57	1	PD	NDB
51	IMPACT410	738	Pre	ADC	F	61	Ever	2	Mono	15.97	1	PR	DCB
52	IMPACT341	613	Pre	ADC	M	80	Ever	1	Mono	8.30	1	PR	DCB
53	IMPACT341	777	Pre	ADC	F	61	Ever	3	Mono	1.57	1	PD	NDB
54	IMPACT341	1,045	Pre	ADC	F	55	Ever	4	Mono	1.03	1	PD	NDB
55	IMPACT341	678	Pre	ADC	F	40	Never	4	Mono	0.37	1	PD	NDB
56	IMPACT341	430	Pre	ADC	M	73	Ever	3	Mono	1.63	1	PD	NDB
57	IMPACT341	509	Pre	ADC	M	22	Never	3	Combo	4.33	1	SD	NDB
58	IMPACT341	200	Pre	ADC	F	51	Ever	2	Mono	2.57	1	PD	NDB
59	IMPACT341	438	Pre	ADC	F	73	Ever	2	Mono	6.63	1	SD	DCB
60	IMPACT341	970	Pre	SQCLC	M	56	Ever	1	Mono	1.17	1	PD	NDB
61	IMPACT341	462	Pre	ADC	M	56	Ever	4	Mono	0.73	1	PD	NDB
62	IMPACT341	839	Pre	ADC	F	81	Never	5	Mono	6.13	1	SD	DCB
63	IMPACT410	1,021	Pre	ADC	M	80	Ever	4	Mono	3.60	1	SD	NDB
64	IMPACT410	951	Pre	ADC	M	53	Ever	5	Mono	5.57	1	SD	NDB
65	IMPACT410	620	Pre	SQCLC	F	67	Ever	2	Mono	1.83	1	SD	NDB
66	IMPACT410	765	Pre	SQCLC	M	63	Never	2	Mono	0.77	1	PD	NDB

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Table A2. Detailed Clinical Characteristics of Patients (continued)

Patient ID	Gene Panel	Mean Tumor Coverage	Tissue Sample Taken Pre- or Posttreatment	Histology	Sex	Age	Smoking Status*	Prior Lines of Therapy†	Treatment‡	PFS (months)	Event§	BOR‖	DCB
67	IMPACT410	550	Pre	ADC	M	60	Ever	6	Mono	19.77	0	PR	DCB
68	IMPACT410	689	Pre	ADC	M	69	Ever	2	Mono	5.53	1	SD	NDB
69	IMPACT410	745	Pre	ADC	F	73	Never	4	Combo	4.23	0	SD	NE
70	IMPACT410	684	Post	SQCLC	M	58	Ever	2	Mono	6.17	1	SD	DCB
71	IMPACT410	743	Pre	ADC	F	57	Ever	1	Combo	30.47	0	PR	DCB
72	IMPACT410	530	Pre	ADC	F	92	Never	5	Mono	8.67	1	SD	DCB
73	IMPACT410	1,018	Pre	ADC	F	60	Ever	1	Mono	9.20	1	SD	DCB
74	IMPACT410	513	Post	ADC	M	59	Ever	1	Mono	8.33	1	SD	DCB
75	IMPACT410	429	Pre	ADC	F	68	Ever	3	Mono	0.87	1	PD	NDB
76	IMPACT410	859	Post	ADC	F	57	Never	2	Mono	10.40	1	PR	DCB
77	IMPACT410	708	Pre	ADC	M	58	Ever	2	Mono	3.10	1	SD	NDB
78	IMPACT410	643	Post	ADC	F	66	Ever	1	Mono	5.47	1	SD	NDB
79	IMPACT341	818	Pre	ADC	F	44	Never	5	Mono	0.40	1	PD	NDB
80	IMPACT341	654	Pre	ADC	M	73	Ever	3	Mono	2.80	1	PD	NDB
81	IMPACT410	866	Pre	ADC	F	47	Never	5	Mono	5.83	0	PR	NE
82	IMPACT410	693	Pre	ADC	F	58	Ever	1	Combo	5.13	1	SD	NDB
83	IMPACT410	437	Pre	ADC	M	61	Ever	2	Mono	3.17	1	SD	NDB
84	IMPACT410	496	Pre	ADC	M	75	Ever	5	Mono	4.63	1	PD	NDB
85	IMPACT410	544	Pre	ADC	F	59	Never	3	Mono	1.80	1	PD	NDB
86	IMPACT410	836	Pre	ADC	M	75	Ever	2	Mono	1.83	1	PD	NDB
87	IMPACT410	305	Pre	ADC	M	62	Ever	1	Mono	3.30	1	PD	NDB
88	IMPACT410	566	Pre	ADC	M	82	Never	2	Mono	1.57	1	PD	NDB
89	IMPACT410	201	Pre	ADC	F	62	Ever	2	Mono	4.00	1	SD	NDB
90	IMPACT410	959	Pre	SQCLC	M	40	Ever	2	Mono	1.07	1	PD	NDB
91	IMPACT410	726	Pre	SQCLC	M	67	Never	2	Mono	1.67	1	PD	NDB
92	IMPACT410	756	Pre	ADC	M	73	Ever	3	Mono	20.20	0	PR	DCB
93	IMPACT410	595	Pre	NOS	F	52	Ever	2	Mono	20.00	0	PR	DCB
94	IMPACT410	580	Pre	ADC	M	86	Never	3	Mono	1.8	1	PD	NDB
95	IMPACT410	677	Pre	ADC	F	63	Ever	2	Mono	0.67	1	PD	NDB
96	IMPACT410	662	Pre	SQCLC	M	58	Ever	1	Mono	10.47	1	SD	DCB
97	IMPACT410	515	Pre	ADC	F	69	Ever	2	Mono	1.83	1	PD	NDB
98	IMPACT410	1,049	Pre	ADC	F	69	Ever	3	Mono	4.37	1	SD	NDB
99	IMPACT410	1,223	Post	SQCLC	M	54	Never	1	Combo	1.83	1	PD	NDB
100	IMPACT410	965	Post	ADC	F	68	Never	1	Combo	15.07	1	SD	DCB
101	IMPACT410	539	Pre	SQCLC	M	55	Ever	2	Mono	1.83	1	PD	NDB
102	IMPACT410	202	Pre	ADC	M	67	Ever	3	Mono	1.23	1	PD	NDB
103	IMPACT410	839	Pre	ADC	M	73	Ever	3	Mono	16.90	1	SD	DCB
104	IMPACT410	709	Pre	ADC	M	47	Ever	2	Mono	6.57	1	SD	DCB
105	IMPACT410	1,384	Post	ADC	M	67	Ever	4	Mono	21.13	1	PR	DCB
106	IMPACT410	472	Pre	ADC	F	81	Ever	2	Mono	1.73	1	PD	NDB
107	IMPACT410	622	Pre	ADC	M	79	Ever	2	Mono	10.43	1	SD	DCB
108	IMPACT410	846	Post	ADC	M	64	Ever	5	Mono	1.80	1	PD	NDB
109	IMPACT410	1,406	Pre	SQCLC	M	59	Ever	2	Mono	3.23	1	PD	NDB
110	IMPACT410	248	Pre	ADC	F	81	Ever	2	Mono	8.63	0	SD	DCB
111	IMPACT410	921	Pre	SQCLC	F	71	Never	2	Mono	12.53	1	SD	DCB
112	IMPACT410	742	Pre	ADC	F	81	Ever	2	Mono	1.17	1	PD	NDB
113	IMPACT410	1,121	Post	ADC	M	60	Ever	1	Mono	18.90	1	SD	DCB
114	IMPACT410	1,146	Post	ADC	F	62	Never	2	Mono	7.80	1	PR	DCB
115	IMPACT410	752	Pre	ADC	F	53	Ever	2	Mono	4.73	1	SD	NDB
116	IMPACT410	885	Pre	ADC	M	62	Never	1	Mono	3.50	1	SD	NDB
117	IMPACT410	661	Pre	ADC	F	55	Never	3	Mono	1.80	1	PD	NDB
118	IMPACT410	586	Pre	ADC	F	63	Ever	2	Mono	0.73	1	SD	NDB
119	IMPACT410	923	Pre	ADC	F	51	Never	2	Combo	15.30	0	PR	DCB
120	IMPACT410	178	Pre	ADC	M	45	Never	2	Mono	5.40	1	SD	NDB
121	IMPACT410	747	Pre	ADC	F	60	Ever	2	Mono	1.60	1	PD	NDB
122	IMPACT410	1,288	Pre	ADC	M	63	Ever	2	Mono	4.33	1	SD	NDB
123	IMPACT410	301	Pre	ADC	M	86	Ever	2	Mono	1.97	1	PD	NDB
124	IMPACT410	483	Pre	SQCLC	M	70	Ever	1	Combo	1.67	1	PD	NDB
125	IMPACT410	1,100	Pre	ADC	F	68	Ever	2	Mono	2.70	1	PD	NDB
126	IMPACT410	704	Pre	NOS	F	48	Ever	2	Mono	7.37	0	PR	DCB
127	IMPACT410	901	Pre	ADC	M	66	Ever	1	Mono	4.27	1	SD	NDB
128	IMPACT410	882	Pre	ADC	M	65	Ever	2	Mono	9.37	0	PR	DCB
129	IMPACT410	691	Pre	ADC	F	66	Ever	3	Mono	1.63	1	PD	NDB
130	IMPACT410	597	Pre	ADC	M	68	Ever	3	Mono	1.00	1	PD	NDB
131	IMPACT410	263	Pre	ADC	M	83	Ever	1	Combo	1.63	1	PD	NDB
132	IMPACT410	919	Post	ADC	F	42	Ever	2	Mono	1.87	1	PD	NDB

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Table A2. Detailed Clinical Characteristics of Patients (continued)

Patient ID	Gene Panel	Mean Tumor Coverage	Tissue Sample Taken Pre- or Posttreatment	Histology	Sex	Age	Smoking Status*	Prior Lines of Therapy†	Treatment‡	PFS (months)	Event§	BOR‖	DCB
133	IMPACT410	513	Pre	ADC	M	76	Ever	2	Mono	1.70	1	PD	NDB
134	IMPACT410	851	Pre	ADC	F	58	Ever	1	Mono	8.77	0	PR	DCB
135	IMPACT410	861	Pre	ADC	F	66	Ever	2	Mono	15.90	0	PR	DCB
136	IMPACT410	760	Pre	LC-NE	F	55	Ever	3	Mono	2.57	1	PD	NDB
137	IMPACT410	519	Pre	ADC	F	56	Ever	2	Mono	12.87	0	SD	DCB
138	IMPACT410	673	Pre	ADC	F	85	Ever	2	Mono	2.37	1	SD	NDB
139	IMPACT410	902	Pre	ADC	M	76	Ever	2	Mono	2.07	0	PR	NE
140	IMPACT410	780	Pre	ADC	M	82	Ever	2	Mono	1.03	1	PD	NDB
141	IMPACT410	744	Pre	ADC	F	69	Ever	2	Mono	1.63	1	PD	NDB
142	IMPACT410	1,213	Pre	ADC	M	73	Ever	2	Mono	1.17	1	PD	NDB
143	IMPACT410	785	Post	ADC	M	77	Ever	2	Mono	1.17	1	PD	NDB
144	IMPACT410	719	Post	ADC	M	76	Never	1	Combo	24.27	1	SD	DCB
145	IMPACT410	1,219	Post	NOS	F	37	Ever	2	Combo	6.33	1	SD	DCB
146	IMPACT410	712	Pre	ADC	F	76	Never	3	Mono	2.60	1	PD	NDB
147	IMPACT410	827	Pre	ADC	F	68	Ever	2	Mono	12.07	1	PR	DCB
148	IMPACT410	420	Pre	NOS	F	69	Ever	2	Mono	1.63	1	PD	NDB
149	IMPACT410	707	Pre	ADC	F	50	Ever	2	Mono	2.50	1	PD	NDB
150	IMPACT410	698	Pre	ADC	F	71	Never	1	Mono	1.93	1	PD	NDB
151	IMPACT410	465	Pre	SQCLC	F	74	Ever	2	Mono	15.13	1	SD	DCB
152	IMPACT410	1,118	Pre	ADC	M	57	Ever	1	Mono	3.17	1	PD	NDB
153	IMPACT410	788	Post	ADC	M	66	Ever	2	Mono	2.10	0	SD	NE
154	IMPACT410	876	Pre	ADC	F	77	Ever	2	Mono	0.90	1	PD	NDB
155	IMPACT410	989	Post	ADC	F	67	Ever	4	Mono	1.17	1	PD	NDB
156	IMPACT410	1,022	Pre	ADC	F	65	Never	2	Mono	1.40	1	PD	NDB
157	IMPACT410	636	Post	ADC	M	73	Ever	1	Combo	9.10	1	SD	DCB
158	IMPACT410	1,174	Pre	ADC	M	64	Never	2	Mono	1.87	0	SD	NE
159	IMPACT410	1,029	Pre	LC-NE	M	76	Ever	2	Mono	1.33	1	PD	NDB
160	IMPACT410	1,102	Pre	NOS	M	63	Ever	1	Mono	1.40	1	PD	NDB
161	IMPACT410	543	Pre	ADC	F	74	Ever	3	Mono	3.07	1	PD	NDB
162	IMPACT410	718	Pre	ADC	F	46	Ever	1	Mono	1.60	1	PD	NDB
163	IMPACT410	209	Post	ADC	M	83	Ever	2	Combo	22.63	1	PR	DCB
164	IMPACT410	973	Pre	SQCLC	M	74	Ever	2	Mono	1.87	1	SD	NDB
165	IMPACT410	649	Pre	SQCLC	M	66	Ever	2	Mono	3.47	0	PR	NE
166	IMPACT410	828	Pre	ADC	F	75	Ever	2	Mono	7.47	1	SD	DCB
167	IMPACT410	1,002	Pre	ADC	F	76	Ever	2	Combo	1.00	1	PD	NDB
168	IMPACT410	558	Pre	ADC	F	80	Ever	2	Mono	16.57	0	PR	DCB
169	IMPACT410	919	Post	ADC	M	62	Ever	1	Combo	13.00	1	SD	DCB
170	IMPACT410	1,224	Pre	ADC	M	69	Ever	3	Mono	1.03	1	SD	NDB
171	IMPACT410	606	Pre	ADC	M	60	Ever	2	Mono	1.73	1	PD	NDB
172	IMPACT410	227	Pre	ADC	F	64	Ever	6	Mono	5.53	1	SD	NDB
173	IMPACT410	696	Pre	ADC	F	32	Never	2	Mono	2.73	1	PD	NDB
174	IMPACT410	709	Pre	ADC	M	79	Ever	2	Mono	11.97	0	PR	DCB
175	IMPACT410	777	Pre	SQCLC	M	72	Ever	2	Mono	2.60	1	PD	NDB
176	IMPACT410	1,088	Post	ADC	F	62	Ever	1	Mono	2.20	1	PD	NDB
177	IMPACT410	403	Pre	NOS	F	74	Ever	2	Mono	2.47	1	PD	NDB
178	IMPACT410	1,196	Pre	ADC	F	55	Ever	2	Mono	7.17	1	SD	DCB
179	IMPACT410	948	Post	ADC	F	68	Ever	1	Combo	8.63	1	SD	DCB
180	IMPACT410	448	Pre	ADC	F	59	Ever	5	Mono	5.40	1	SD	NDB
181	IMPACT410	803	Pre	ADC	F	48	Ever	2	Combo	1.57	1	PD	NDB
182	IMPACT410	893	Pre	ADC	F	50	Ever	2	Mono	6.30	0	SD	DCB
183	IMPACT410	972	Pre	ADC	F	54	Ever	2	Mono	10.40	1	SD	DCB
184	IMPACT410	1,367	Pre	ADC	M	66	Ever	2	Mono	5.87	1	SD	NDB
185	IMPACT410	1,238	Pre	SQCLC	M	80	Ever	2	Mono	16.73	0	PR	DCB
186	IMPACT410	1,025	Pre	ADC	F	58	Ever	2	Mono	1.63	1	PD	NDB
187	IMPACT410	589	Pre	ADC	M	39	Ever	2	Mono	7.53	0	PR	DCB
188	IMPACT410	631	Pre	ADC	F	50	Ever	2	Mono	16.80	0	PR	DCB
189	IMPACT410	556	Pre	ADC	F	72	Ever	2	Mono	3.10	1	PD	NDB
190	IMPACT410	1,073	Pre	SQCLC	M	68	Ever	2	Mono	5.77	1	SD	NDB
191	IMPACT410	553	Pre	ADC	M	73	Ever	2	Mono	2.03	1	PD	NDB
192	IMPACT410	1,357	Pre	LC-NE	M	67	Ever	2	Combo	2.77	0	PR	NE
193	IMPACT410	733	Pre	ADC	M	78	Ever	1	Mono	9.80	1	SD	DCB
194	IMPACT410	1,001	Pre	ADC	M	51	Ever	2	Mono	5.43	1	PD	NDB
195	IMPACT410	313	Pre	ADC	F	55	Ever	2	Mono	0.83	1	PD	NDB
196	IMPACT410	881	Pre	ADC	F	42	Never	3	Combo	1.27	1	PD	NDB
197	IMPACT410	1,215	Pre	ADC	F	55	Ever	2	Mono	2.30	1	SD	NDB
198	IMPACT410	806	Pre	ADC	F	62	Never	2	Mono	1.70	1	PD	NDB

(continued on following page)

Table A2. Detailed Clinical Characteristics of Patients (continued)

Patient ID	Gene Panel	Mean Tumor Coverage	Tissue Sample Taken Pre- or Posttreatment	Histology	Sex	Age	Smoking Status*	Prior Lines of Therapy†	Treatment‡	PFS (months)	Event§	BOR‖	DCB
199	IMPACT410	1,170	Pre	LC-NE	M	55	Ever	2	Mono	1.80	1	PD	NDB
200	IMPACT410	732	Pre	ADC	F	58	Ever	2	Mono	2.47	1	PD	NDB
201	IMPACT410	913	Post	ADC	F	60	Never	3	Mono	1.83	1	PD	NDB
202	IMPACT410	920	Post	ADC	F	74	Ever	2	Mono	2.27	1	PD	NDB
203	IMPACT410	1,071	Pre	SQCLC	M	76	Ever	2	Mono	2.10	1	PD	NDB
204	IMPACT410	1,053	Pre	ADC	F	56	Ever	2	Combo	1.53	1	PD	NDB
205	IMPACT410	884	Pre	ADC	F	71	Ever	1	Mono	2.27	1	PD	NDB
206	IMPACT410	353	Pre	ADC	F	77	Ever	3	Mono	4.20	0	PR	NE
207	IMPACT410	883	Pre	ADC	M	72	Ever	2	Mono	5.37	1	SD	NDB
208	IMPACT410	1,021	Pre	ADC	M	72	Never	2	Combo	3.50	1	SD_	NDB
209	IMPACT410	811	Pre	ADC	F	72	Ever	2	Combo	12.80	0	PR	DCB
210	IMPACT410	634	Post	ADC	M	68	Ever	2	Mono	1.77	1	PD	NDB
211	IMPACT410	456	Pre	ADC	M	66	Ever	2	Mono	1.70	1	PD	NDB
212	IMPACT410	734	Pre	NOS	M	81	Ever	2	Mono	4.80	1	SD	NDB
213	IMPACT410	906	Pre	ADC	M	69	Ever	2	Mono	4.27	1	SD	NDB
214	IMPACT410	977	Pre	ADC	M	54	Ever	2	Mono	7.20	0	PR	DCB
215	IMPACT410	682	Pre	ADC	F	59	Ever	1	Mono	11.30	0	PR	DCB
216	IMPACT410	918	Pre	ADC	M	57	Ever	2	Mono	1.70	1	PD	NDB
217	IMPACT410	802	Pre	ADC	F	50	Never	3	Mono	2.90	1	PD	NDB
218	IMPACT410	1,007	Post	ADC	M	79	Never	2	Mono	3.60	1	SD	NDB
219	IMPACT410	765	Pre	SQCLC	M	71	Ever	2	Mono	2.00	1	SD	NDB
220	IMPACT410	1,071	Pre	ADC	F	69	Ever	2	Combo	5.43	1	SD	NDB
221	IMPACT410	365	Pre	ADC	M	83	Ever	1	Mono	3.77	1	SD	NDB
222	IMPACT468	655	Pre	SQCLC	M	74	Ever	2	Mono	1.70	1	SD	NDB
223	IMPACT468	375	Pre	ADC	F	64	Ever	2	Mono	0.60	1	PD	NDB
224	IMPACT468	1,150	Pre	SQCLC	F	65	Ever	1	Mono	4.67	0	PR	NE
225	IMPACT468	540	Pre	SQCLC	M	63	Ever	2	Mono	8.83	0	SD	DCB
226	IMPACT468	446	Pre	NOS	F	65	Ever	2	Mono	1.87	1	PD	NDB
227	IMPACT468	1,048	Pre	ADC	M	83	Ever	1	Mono	6.03	1	SD	DCB
228	IMPACT468	809	Post	ADC	F	69	Ever	2	Mono	2.37	1	PD	NDB
229	IMPACT468	893	Pre	NOS	M	67	Ever	1	Mono	6.43	0	PR	DCB
230	IMPACT468	786	Pre	SQCLC	F	53	Ever	2	Mono	7.10	0	PR	DCB
231	IMPACT468	749	Pre	ADC	M	64	Ever	2	Mono	16.73	1	PR	DCB
232	IMPACT468	942	Pre	NOS	F	88	Ever	1	Mono	4.07	0	PR	NE
233	IMPACT468	231	Pre	ADC	M	62	Ever	2	Combo	3.43	1	SD	NDB
234	IMPACT468	994	Post	ADC	M	51	Ever	2	Mono	1.83	1	PD	NDB
235	IMPACT468	1,215	Pre	ADC	F	56	Ever	2	Mono	4.17	1	SD	NDB
236	IMPACT468	737	Post	SQCLC	F	66	Ever	2	Mono	1.63	1	PD	NDB
237	IMPACT468	813	Pre	ADC	M	72	Ever	1	Mono	5.50	0	PR	NE
238	IMPACT468	874	Pre	ADC	F	68	Never	2	Mono	2.67	1	PD	NDB
239	IMPACT468	1,126	Pre	ADC	M	76	Ever	1	Mono	1.87	1	SD	NDB
240	IMPACT468	725	Pre	NOS	F	88	Ever	1	Mono	4.13	0	PR	NE

Abbreviations: ADC, adenocarcinoma; BOR, best overall response; CR, complete response; DCB, durable clinical benefit; F, female; IMPACT, Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets panel; LC-NE, large-cell neuroendocrine carcinoma; M, male; NOS, non–small-cell lung cancer not otherwise specified; NCB, no clinical benefit; NE, not evaluable for benefit posttreatment (samples taken after beginning of treatment); PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SQCLC, squamous cell carcinoma.

*Patient-reported smoking status.

†Prior courses of cytotoxic chemotherapy.

‡Mono, anti–programmed death-1 or anti–programmed death-ligand 1 [anti–PD-(L)1] monotherapy; combo, anti–PD-(L)1 + anti–cytotoxic T-cell lymphocyte-4 combination therapy.

§Event (1) or censor (0) for PFS.

‖By Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Table A3. WES Metrics and Comparison With Targeted Next-Generation Sequencing

Patient ID	Time Point of Tissue Sample Used	Same Tissue Sample Used for WES and MSK-IMPACT?*	Same DNA Aliquot Used for WES and MSK-IMPACT?*	Mean Tumor Coverage (WES)	Mean Normal Coverage (WES)	TMB† (WES)	TMB† (MSK-IMPACT)
2	Pretreatment	1	0	206	76	19	1.020408163
10	Pretreatment	0	0	267	102	98	4.081632653
12	Pretreatment	1	1	212	97	464	22.641509430
19	Pretreatment	1	1	308	238	342	11.224489800
24	Pretreatment	1	1	193	126	337	13.265306120
25	Pretreatment	1	1	223	96	64	4.081632653
28	Pretreatment	1	1	309	102	550	23.469387760
30	Pretreatment	1	1	216	98	89	2.040816327
37	Pretreatment	1	1	263	148	374	15.306122450
38	Pretreatment	0	0	139	126	54	4.081632653
43	Pretreatment	1	1	198	154	121	2.040816327
45	Pretreatment	1	0	209	126	746	17.346938780
46	Pretreatment	1	1	309	162	385	11.224489800
47	Pretreatment	1	1	475	179	224	9.433962264
50	Pretreatment	1	1	278	94	70	6.122448980
52	Pretreatment	1	0	196	120	27	4.081632653
62	Pretreatment	1	1	274	124	85	4.081632653
65	Pretreatment	1	1	198	122	470	34.905660380
67	Pretreatment	1	1	373	89	966	48.113207550
70	Pretreatment	0	0	230	132	314	15.094339620
71	Pretreatment	1	1	380	146	181	8.490566038
72	Pretreatment	1	1	204	108	28	3.773584906
73	Pretreatment	1	0	246	137	1147	34.905660380
74	Pretreatment	0	0	165	65	179	10.377358490
82	Pretreatment	1	1	191	103	254	4.716981132
84	Pretreatment	1	1	233	162	117	6.603773585
91	Pretreatment	1	1	400	121	258	14.150943400
94	Pretreatment	1	1	86	84	18	0.943396226
100	Pretreatment	0	1	203	133	1	3.773584906
105	Pretreatment	0	0	173	194	228	5.660377358
109	Pretreatment	1	1	224	75	334	10.377358490
113	Pretreatment	0	0	210	141	124	9.433962264
116	Pretreatment	1	1	238	168	48	6.603773585
121	Pretreatment	1	1	228	153	227	5.660377358
122	Pretreatment	1	1	309	92	91	4.716981132
132	Pretreatment	0	0	104	92	51	4.716981132
136	Pretreatment	1	1	349	127	165	7.547169811
141	Pretreatment	1	1	77	140	135	13.207547170
142	Pretreatment	1	1	79	137	296	15.094339620
144	Pretreatment	0	0	295	112	30	2.830188679
146	Pretreatment	1	1	291	142	57	2.830188679
152	Pretreatment	1	1	90	119	226	5.660377358
155	Pretreatment	1	1	317	104	751	23.584905660
159	Pretreatment	1	1	92	125	170	5.660377358
163	Pretreatment	1	1	219	188	207	7.547169811
174	Pretreatment	1	1	722	151	171	8.490566038
176	Pretreatment	1	1	84	94	124	2.830188679
179	Pretreatment	0	0	204	142	67	2.830188679
190	Pretreatment	1	1	93	86	227	6.603773585

Abbreviations: MSK-IMPACT, Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets; TMB, tumor mutation burden; WES, whole-exome sequencing.

*1 = yes; 0 = no.

†Nonsynonymous mutation burden rate normalized by megabase covered.

Table A4. Baseline Demographic Features of MSK-IMPACT Versus All Patients Treated With PD-(L)1–Based Therapy at Memorial Sloan Kettering Cancer Center

Patient Characteristic	MSK-IMPACT, No. (%)	All NSCLC, No. (%)	*P*
No. of patients	240	759	
Median age, years (range)	66 (22-92)	66 (22-93)	.32
Sex			.85
Male	118 (49)	368 (48)	
Female	122 (51)	391 (52)	
Histology			.98
Adenocarcinoma	186 (78)	586 (77)	
Squamous	34 (14)	121 (16)	
Other	20 (8)	52 (7)	
Smoking status			.41
Ever	193 (80)	629 (83)	
Never	47 (20)	131 (17)	
Line of therapy			.78
First	51 (21)	183 (24)	
Second	127 (53)	351 (46)	
Third or more	62 (26)	225 (30)	
Treatment			.54
PD-(L)1, monotherapy	206 (86)	663 (87)	
PD-(L)1 + CTLA-4, combination therapy	34 (14)	96 (13)	

Abbreviations: CTLA-4, cytotoxic T-cell lymphocyte-4; MSK-IMPACT, Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets; NSCLC, non–small-cell lung cancer; PD-(L)1, programmed death-1 or programmed death-ligand 1.