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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**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% vs. 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.
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). 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, and specifically in NSCLC, programmed death-ligand 1 (PD-L1) expression. Most trials in NSCLC have demonstrated increased response rates in tumors with greater PD-L1 expression, but enrichment of responses is incomplete. 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, bladder cancer, NSCLC, and mismatch repair–deficient tumors.

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.

We hypothesized that TMB determined by targeted NGS 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. 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. 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) were used.

**MSK-IMPACT sequencing**

The MSK-IMPACT assay was performed as previously described. 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. Mean sequencing coverage across all tumor samples was 744×, with minimum depth of coverage of 91×. Samples were run through a custom pipeline to identify somatic alterations, including mutations and copy number alterations. Data are available through the cbioPortal for Cancer Genomics. 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.

**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 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. MuTect was used to generate single-nucleotide variant (SNV) calls by using slightly modified default parameters. The complete listing of the source code for the variant detection pipeline is available online. The Genome Analysis Toolkit is available online. The results were validated using the OncoKB database.

**Key points**

- 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) were used.
- 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.
- Tumor samples used for MSK-IMPACT were collected before immunotherapy treatment in 204 patients (85%).
- 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 and variants of unknown significance. Reported percentages include all variants unless otherwise noted.
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- MuTect was used to generate single-nucleotide variant (SNV) calls by using slightly modified default parameters.
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Key points

- Eighty-four tumors had tissue evaluated for PD-L1 expression, which was reported as the percentage of tumor cells with membranous staining.
- The top 50 genes ordered by increasing P values were reported, with significant associations after correcting for the false discovery rate (FDR) highlighted.
- Demographic features of the current patient cohort are similar to the overall group of patients treated with anti–PD-(L)1 therapy.
- To determine whether targeted NGS could accurately quantify 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 ρ = 0.86; P < .001).
- 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.
- Survival outcomes among patients with advanced NSCLC not treated with immunotherapy did not correlate with increasing TMB; in fact, an inverse relationship between TMB and survival was identified.

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 log₂(odds ratio) versus log₂(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.

- 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. 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 ρ = 0.86; P < .001; Figure 1A). By using data from targeted NGS, TMB was greater in patients with DCB than with NDB (median, 8.5 vs. 6.6 SNVs/Mb; P = .0062) and in patients with CR/PR versus SD versus PD (median, 8.5 vs. 6.6 SNVs/Mb; P = .0151; Figure 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% vs. 25.1%; P = .009; PFS HR, 1.38; P = .024. The rate of DCB and PFS were also improved among those in the top decile of TMB in the cohort (Figure 1C and D). By contrast, survival outcomes among patients with advanced NSCLC not treated with immunotherapy16 did not correlate with increasing TMB; in fact, an inverse relationship between TMB and survival was identified.

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 vs. 0.11; P = .007; Figure 1E). Of note, despite a negative association with response to ICIs, FGA had...
### TABLE 1 - Patient characteristics

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

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; 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. Mutations in KRAS were common (n = 83), and the rate of DCB was similar in this group compared with the overall study cohort (36%). 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). 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 (Figure 2). 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 melanoma. 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. 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; this patient had PD).

Recently, hyperprogression with anti–PD-1 therapy has been reported in patients treated with ICI and was associated with MDM2/MDM4 amplifications. In the current series, MDM2/MDM4 amplifications were identified in eight patients, 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% vs. ≥1%; HR, 0.526; P = .011. No correlation was found...
between PD-L1 and TMB (Spearman \( r = 0.1915; P = .08 \); Figure 3A) or PD-L1 and FGA (Spearman \( r = -0.1273; P = .25 \); Figure 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; Figure 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 (Figure 3D).

We also evaluated whether mutations in individual altered genes were associated with PD-L1 expression (stratified as ≥ 1% vs. < 1%). **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 ICI, with the odds of DCB improving with increasing thresholds. Because there was no positive
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Key points

- 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.

- We found that the FGA was highest among patients who derived the least benefit from ICI. Despite this inverse association, FGA and TMB were modestly but positively associated with each other, consistent with a previous report.

- Mutations in EGFR were underrepresented among patients with DCB, which is likely related to the association of EGFR mutations with never smokers and resulting low TMB.

- 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.

- Alterations in B2M and JAK2 have been described as mediating acquired resistance in patients with melanoma treated with PD-1 blockade.

- 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.

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, 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. 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 resistance, consistent with cases of acquired resistance mediated through defective interferon gamma signaling. 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.
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 has become increasingly routine, particularly in patients with lung cancer.\textsuperscript{15,16,35} Furthermore, consistent with recent reports that analyzed the same patient tumors for targeted NGS and WES,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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 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,\textsuperscript{36} multiplexed protein expression,\textsuperscript{37} T-cell receptor clonality,\textsuperscript{38} and others will need to be considered together to realize more fully the potential for precision immunotherapy.

Key points

- A recent report described that in panels with genomic coverage < 0.5 Mb, the accuracy of TMB determined by targeted NGS diminishes.
- 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.
- As a result of variations in panels as well as 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.

References