# Use of TMB and PD-L1 to Predict Outcomes of Checkpoint Inhibitor Treatment

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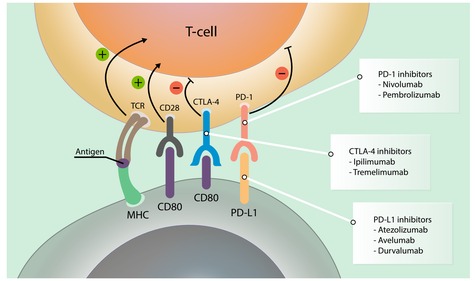
356P

## BACKGROUND

- Inhibition of immune checkpoints such as programmed cell death ligand 1 (PD-L1), programmed death-ligand 2 (PD-L2), programmed cell death protein 1 (PD-1), or cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) is a powerful approach for the treatment of many cancers (Figure 1).[1]

**Figure 1. Mechanism of Action of Immune Checkpoint Inhibitors**




MHC = major histocompatibility complex; TCR = T-cell receptor.
Adapted from de Mello et al. (2017).[2]

- Although the use of checkpoint inhibitory therapy has shown promise, not all patients respond to these therapies, so it is important to identify biomarkers that can predict clinical response.[3]
- Tumor mutational burden (TMB), also known as tumor mutational load (TML), is a measure of the number of mutations within a tumor genome, sometimes defined as the total number of nonsynonymous point mutations per coding area of a tumor genome.[4]
- The potential value of TMB and/or PD-L1 biomarkers to enhance the prediction of which patients are most likely to respond to checkpoint inhibitors that target programmed cell death protein or PD-L1 has been explored in multiple studies.[3,5]

## OBJECTIVE

- The objective of this targeted literature review was to compile and integrate data available for TMB and/or PD-L1 to examine the potential of these assessments to predict response to checkpoint inhibitors.

## METHODS

- A targeted literature review was performed to a prespecified protocol.
- Searches were performed of the MEDLINE, Embase, and BIOSIS electronic medical databases from August 2007 to April 2018. Search terms used combinations of free text and Medical Subject Heading terms. Terms relating to TMB, PD-L1, PD-1, CTLA-4, precision medicine, cancer, and drugs of interest were used. No language or geographical limitations were applied.
- Meeting abstracts for the American Association for Cancer Research, the Molecular Medicine Tri-Conference, and the European Society for Medical Oncology (2015-2018) and the Society for Immunotherapy of Cancer and the American Society of Clinical Oncology (2016-2018) were searched to identify more recent studies.
- In addition, we manually searched the reference lists of relevant systematic reviews and meta-analyses published in the 2 years prior to the search date for further studies of interest.
- The following inclusion and exclusion were used:
  - Inclusion: Adults with any tumor type; treated with ipilimumab, tremelimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab; randomized, nonrandomized, and observational studies investigating biomarkers such as TMB or the checkpoint inhibitors PD-L1, PD-1, and CTLA-4 that reported at least one outcome of the following: overall survival (OS), progression-free survival (PFS), time to progression, overall response rates, response rates, or relapse-free survival.
  - Exclusion: Studies in children; studies that did not have a treatment or outcome of interest, studies with a sample size of fewer than 50; articles published before 2007 or abstracts published before 2015.

## RESULTS

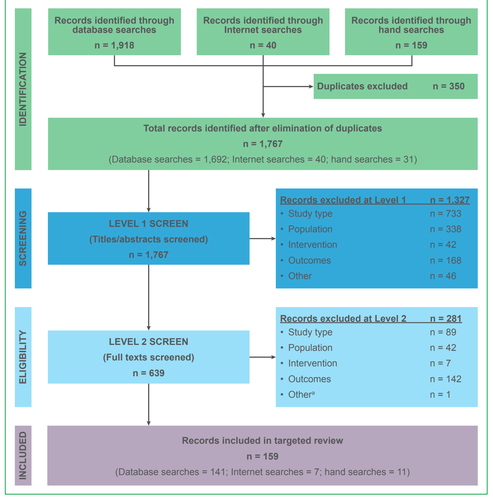
- A total of 2,768 titles and abstracts and 681 full-text publications were screened, and 102 primary studies and 111 secondary articles were included (Figure 2).
- Of the 102 primary studies, 27 were identified in non-small cell lung cancer (NSCLC), 41 in melanoma, 10 in urothelial cancer, and 5 for renal cancer indications. Studies also were identified in other cancer types (e.g., colorectal, breast, and gastric cancer and Merkel cell carcinoma [MCC]).
- Table 1 summarizes the indications included in the identified studies by intervention.
- Identified TMB data as a predictor for NSCLC and melanoma outcomes are presented in this poster. A summary of the information identified for PD-L1 is also provided.

**Table 1. Indications Included in Identified Studies by Intervention**

| Drug | Indication(s) |
|---|---|
| **CTLA-4 inhibitors** | |
| Ipilimumab | Melanoma (n = 24), NSCLC (n = 3), mCRC (n = 1), SCLC (n = 1), RCC (n = 1), pancreatic (n = 1) |
| Tremelimumab | Melanoma (n = 3) |
| **PD-1 inhibitors** | |
| Nivolumab | NSCLC (n = 14), melanoma (n = 14), RCC (n = 3), urothelial (n = 2), SCCHN (n = 1), GC (n = 1), mCRC (n = 1), Hodgkin's disease (n = 1), SCLC (n = 1) |
| Pembrolizumab | Melanoma (n = 9), NSCLC (n = 6), urothelial (n = 2), mCRC (n = 2), GC (n = 1), breast cancer (n = 1), SCCHN (n = 1) |
| **PD-L1 inhibitors** | |
| Atezolizumab | NSCLC (n = 6), melanoma (n = 2), urothelial (n = 3), RCC (n = 2) |
| Avelumab | NSCLC (n = 1), MCC (n = 1), urothelial (n = 1) |
| Durvalumab | NSCLC (n = 2), urothelial (n = 1) |

GC = gastric cancer; mCRC = metastatic colorectal cancer; RCC = renal cell cancer; SCCHN = squamous-cell carcinoma of the head and neck; SCLC = small cell lung cancer.

**Figure 2. PRISMA Diagram for Study Inclusion and Exclusion**




### Non-Small Cell Lung Cancer Tumor Mutational Burden Data

- Five of the identified NSCLC studies reported OS and PFS data for populations using TMB as a biomarker (Table 2).
- The most frequently applied TMB cutoff points were ≥ 10, ≥ 16, and ≥ 20 mutations per megabase; however, the studies that used these cutoff points used different definitions of TMB (blood or tissue based).
- A TMB of ≥ 10 mutations per megabase was shown to be an effective biomarker in the CheckMate 227 study.[5]

### Melanoma Tumor Mutational Burden Data

- Only three melanoma studies reported OS or PFS data using TMB as a biomarker (Table 3).
- Yaghmour et al.[6] reported that OS was higher in patients with a TMB in the top quintile (median genomic alterations = 16.5) than OS in patients with a TMB in the lower quintiles (median genomic alterations = 2) (hazard ratio [HR] = 3.29; 95% confidence interval [CI], 0.75-25.53).

### Non-Small Cell Lung Cancer Programmed Cell Death Ligand 1 Data

- Seventeen studies reported OS or PFS data in patients with NSCLC and with PD-L1 as a biomarker.[6-21]
- The cutoff values for PD-L1 expression in tumor and immune cells ranged from < 1% to ≥ 50%; not all of the studies reported the cutoff used.
- PD-L1 appears to be an appropriate biomarker for predicting response for all NSCLC types except for squamous-cell NSCLC. However, prediction of response was not a prespecified analysis in some PD-L1 studies; other studies had small sample sizes and wide CIs.

### Melanoma Programmed Cell Death Ligand 1 Data

- Five studies reported OS or PFS data using PD-L1 as a biomarker.[22-26]
- Median OS was significantly higher in patients with PD-L1 ≥ 1% than in patients with PD-L1 < 1% in the pembrolizumab KEYNOTE-001 and KEYNOTE-006 trials, with a HR between 0.55 and 0.83.[25,26]

**Table 2. Tumor Mutation Burden as Predictor of Non-Small Cell Lung Cancer Outcome: OS and PFS Data**

| | | | | OS | | PFS | |
|---|---|---|---|---|---|---|---|
| **Trial/Author (Year)** | **Subpopulation or Population** | **Treatment** | **No. of Patients** | **Median (95% CI), Months** | **HR (95% CI)** | **Median (95% CI), Months** | **HR (95% CI)** |
| **CheckMate 026** | | | | | | | |
| Carbone et al. (2017)[10] | High TMB | NIVO 3 mg/kg Q2W | 47 | 18.3 (11.4-NE) | 1.1 (0.64-1.88) | 9.7 (5.1-NE) | 0.62 (0.38-1.0) |
| Socinski et al. (2016)[11] | | Platinum-based chemotherapy Q3W | 60 | 18.8 (11.3-NE) | | 5.8 (4.2-8.5) | |
| | Low or medium TML | NIVO 3 mg/kg Q2W | 111 | 12.7 (9.9-16.1) | 0.99 (0.71-1.4) | 4.1 (2.8-5.4) | 1.82 (1.3-2.55) |
| | | Platinum-based chemotherapy Q3W | 94 | 13.2 (9.5-15.2) | | 6.9 (5.5-8.6) | |
| **CheckMate 227** | | | | | | | |
| Hellmann et al. (2018)[5] | TMB ≥ 10 mutations per mb | NIVO + IPI | 139 | NR | NR | 7.2 (5.5-13.2) | 0.58 (97.5% CI, 0.41-0.81) |
| | | Chemotherapy | 160 | NR | NR | 5.5 (4.4-5.8) | |
| | TMB < 10 mutations per mb | NIVO + IPI | 191 | NR | NR | 3.2 (2.7-4.3) | 1.07 (0.84-1.35) |
| | | Chemotherapy | 189 | NR | NR | 5.5 (4.3-5.6) | |
| **OAK**[a] | | | | | | | |
| Rittmeyer et al. (2017)[27] | TMB ≥ 10 | ATEZO vs. DTX | 251 | NR | 0.69 (NR) | NR | 0.73 (NR) |
| Gadgeel et al. (2017)[28] | TMB ≥ 16 | | 158 | NR | 0.64 (NR) | NR | 0.65 (NR) |
| Barlesi et al. (2016)[29] | TMB ≥ 20 | | 105 | NR | 0.65 (NR) | NR | 0.61 (NR) |
| Hida et al. (2018)[30] | | | | | | | |
| Gandara et al. (2017)[31] | | | | | | | |
| **POPLAR**[a] | | | | | | | |
| Fehrenbacher et al. (2016)[32] | TMB ≥ 10 | ATEZO vs. DTX | 96 | NR | 0.59 (NR) | NR | 0.68 (NR) |
| Smith et al. (2016)[33] | TMB ≥ 16 | | 63 | NR | 0.56 (NR) | NR | 0.57 (NR) |
| Mazieres et al. (2016)[34] | TMB ≥ 20 | | 42 | NR | 0.51 (NR) | NR | 0.58 (NR) |
| Vansteenkiste et al. (2015)[35] | | | | | | | |
| Spira et al. (2015)[36] | | | | | | | |
| Gandara et al. (2017)[31] | | | | | | | |
| Yaghmour (2016)[6] | TML: top quintile | ≥ First line, NIVO or IPI | 50 (overall patients) | NR | 3.29 (0.75-25.53) | NR | NR |
| | TML: other quintiles | | | NR | | NR | NR |
| **B-F1RST** | | | | | | | |
| Velcheti (2018)[37] | Blood-based TMB ≥ 12 | ATEZO | 22 | NR | NR | 3 | 0.95 (90% CI, 0.55-1.63) |
| | Blood-based TMB < 12 | | 36 | NR | NR | 3.2 | |
| | Blood-based TMB ≥ 14 | | 14 | NR | NR | 3.4 | 0.73 (90% CI, 0.39-1.39) |
| | Blood-based TMB < 14 | | 44 | NR | NR | 3.2 | |
| | Blood-based TMB ≥ 16 | | 11 | NR | NR | 9.5 | 0.49 (90% CI, 0.23-1.04) |
| | Blood-based TMB < 16 | | 47 | NR | NR | 2.8 | |
| | Blood-based TMB ≥ 20 | | 8 | NR | NR | 9.5 | 0.23 (90% CI, 0.08-0.62) |
| | Blood-based TMB < 20 | | 50 | NR | NR | 2.7 | |

ATEZO = atezolizumab; DTX = docetaxel; IPI = ipilimumab; mb = megabase; NE = could not be estimated/not reached; NIVO = nivolumab; NR = not reported; Q2W = every 2 weeks; Q3W = every 3 weeks.

[a] Blood-based TBM.

**Table 3. Tumor Mutation Burden as Predictor of Melanoma Outcome: OS and PFS Data**

| | | | | OS | | PFS | |
|---|---|---|---|---|---|---|---|
| **Trial/Author (Year)** | **Subpopulation or Population** | **Treatment** | **No. of Patients** | **Median (95% CI), Months** | **HR (95% CI)** | **Median (95% CI), Months** | **HR (95% CI)** |
| Johnson et al. (2016)[38] | High (> 23.1 mutations per mb) | NIVO, PEM, and ATEZO | 65 | NE | NR | NE | NR |
| | Intermediate (3.3-23.1 mutations per mb) | | 65 | 9.9 (NR) | NR | 2.9 (NR) | NR |
| | Low (< 3.3 mutations per mb) | | 65 | 12.3 (NR) | NR | 2.8 (NR) | NR |
| Roszik et al. (2016)[39] | Predicted TML ≤ 100 | IPI | 19 | 19.14 (NR) | 0.35 (0.16-0.77) | NR | NR |
| | Predicted TML > 100 | | 57 | Undefined (NR) | | NR | NR |
| Yaghmour et al. (2016)[6] | TML: top quintile | NIVO, PEM, and IPI | 50 (overall patients) | NR | 3.29 (0.75-25.53) | NR | NR |
| | TML: other quintiles combined | | | NR | | NR | NR |

## DISCUSSION

- The majority of TMB and PD-L1 data were identified for NSCLC, melanoma, and urothelial cancers.
- At present, there is no standard, harmonized definition of TMB or methodology for calculating this parameter.
- Even in the absence of a standardized definition or threshold for TMB determination, a clear predictive trend for TMB and PD-L1 was identified in NSCLC and melanoma studies but was not observed for cancers such as renal, breast, or gastric cancer or MCC in this data set.
- Optimal use of TMB as a predictive marker may require some indication-specific adjustments to accommodate the biology of disease. However, effective use of TMB across tumor types may be feasible if an appropriate threshold can be identified.
- For some indications, additional/other biomarkers may enhance the ability to enable prediction of whether a treatment will be successful for a patient or patient group.

## CONCLUSIONS

- On the basis of the data in this review, assessment of TMB and PD-L1 biomarker expression may enhance the prediction of response to checkpoint inhibition in some tumors, such as NSCLC and melanoma.
- In this rapidly growing area of research, further exploratory biomarkers are being investigated—such as TILs, immunoprofiling (e.g., effector T cells or regulatory T cells), epigenetic signatures, T-cell receptor repertoire, proteomics, microbiome, and metabolomics—and may provide additional guidance and insight on the potential efficacy of a treatment in a given patient.

## REFERENCES

See handout or QR code for references.

## CONTACT INFORMATION

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