Table of Contents

[Supplementary Tables 2](#_Toc131410989)

[Supplementary Table 1. Formulas of Accuracy Metrics 2](#_Toc131410990)

[Supplementary Table 2. Breakdown of Cancer Types in the Data set 3](#_Toc131410991)

[Supplementary Table 3. Breakdown of Biomarkers in the Data Set 4](#_Toc131410992)

[Supplementary Table 4. Meta-Analysis Estimates of Biomarkers Across All Cancer Types 5](#_Toc131410993)

[Supplementary Table 5. Meta-Analysis Estimates of Biomarkers by Cancer Types 6](#_Toc131410994)

[Supplementary Table 6. References of Studies Included in Analyses 8](#_Toc131410995)

[Supplementary Figures 14](#_Toc131410996)

[Supplementary Figure. Literary Review Description 14](#_Toc131410997)

## Supplementary Tables

## Supplementary Table 1. Formulas of Accuracy Metrics

|  |  |
| --- | --- |
| **Metric** | **Formula** |
| False discovery rate |  |
| False negative rate |  |
| False omission rate |  |
| False positive rate |  |
| Negative predictive value |  |
| Positive predictive value |  |
| Sensitivity |  |
| Specificity |  |

FN, false negatives; FP, false positives; TN, true negatives; TP, true positives.

## Supplementary Table 2. Breakdown of Cancer Types in the Data set

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Cancer** | **Biomarkers** | **Studies** | **Cohorts** | **Subjects** | **%** |
| NSCLC | PD-L1 IHC, TMB, multimodal, TGS | 28 | 32 | 6556 | 29.47 |
| Melanoma | Multimodal, TMB, TGS, PD-L1 IHC, MB, mIHC/IF, others | 21 | 24 | 2828 | 22.11 |
| Multiple cancers | TMB, multimodal, TGS, PD-L1 IHC, MB | 10 | 10 | 973 | 10.53 |
| Urothelial | PD-L1 IHC, imAEs/AESIs, CD8+, TGS | 9 | 9 | 2967 | 9.47 |
| Head and neck | PD-L1 IHC, multimodal, TMB, TGS | 8 | 8 | 1260 | 8.42 |
| RCC | PD-L1 IHC, TGS, TMB, IMDC | 8 | 8 | 2130 | 8.42 |
| MCC | CD8+, mIHC/IF, PD-L1 IHC | 4 | 4 | 217 | 4.21 |
| Breast | PD-L1 IHC | 3 | 3 | 715 | 3.16 |
| Colon | PD-L1 IHC | 3 | 3 | 342 | 3.16 |
| Gastric/GEJ | PD-L1 IHC | 3 | 3 | 325 | 3.16 |
| SCLC | PD-L1 IHC, TMB | 3 | 3 | 338 | 3.16 |
| HCC | PD-L1 IHC | 2 | 3 | 313 | 2.11 |
| Cervical | PD-L1 IHC | 1 | 1 | 84 | 1.05 |
| Esophageal | PD-L1 IHC, CD8+ | 1 | 1 | 34 | 1.05 |
| Ovarian | Biomarker not analyzed | 1 | 1 | 63 | 1.05 |
| Prostate | PD-L1 IHC | 1 | 1 | 199 | 1.05 |

AESI, adverse event of special interest; GEJ, gastroesophageal junction; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; imAE, immune-mediated adverse event; IMDC, International Metastatic RCC Database Consortium Risk Score; MB, microbiome signature MCC, Merkel cell carcinoma; mIHC/IF, fluorescent multiplex IHC; NSCLC, non–small cell lung cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer; TGS, T-cell–related gene signature; TMB, tumor mutational burden.

## Supplementary Table 3. Breakdown of Biomarkers in the Data Set

AESI, adverse event of special interest; IHC, immunohistochemistry; imAE, immune-mediated adverse event; IMDC, International Metastatic RCC Database Consortium Risk Score; MCC, mIHC/IF, fluorescent multiplex IHC; TGS, T-cell–related gene signature; TMB, tumor mutational burden.

|  |  |  |  |
| --- | --- | --- | --- |
| **Biomarker** | **Studies** | **Cohorts** | **Subjects** |
| PD-L1 IHC | 76 | 79 | 14,914 |
| TMB | 15 | 19 | 1936 |
| Multimodal | 5 | 6 | 577 |
| TGS | 4 | 4 | 726 |
| CD8+ | 3 | 3 | 255 |
| mIHC/IF | 3 | 4 | 201 |
| IMDC | 2 | 2 | 547 |
| Microbiome signature | 2 | 2 | 128 |
| imAEs/AESIs | 1 | 1 | 1747 |

## Supplementary Table 4. Meta-Analysis Estimates of Biomarkers Across All Cancer Types

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Biomarker** | **Cohortsa** | **AUC (95% CI)** | **Sensitivity (95% CI)** | **FPR (95% CI)** | **Specificity (95% CI)** | **FNR (95% CI)** |
| CD8+ | 3 | 0.63 (0.4-0.67) | 0.56 (0.32-0.77) | 0.35 (0.14-0.64) | 0.65 (0.36-0.86) | 0.44 (0.23-0.68) |
| TGS | 6 | 0.58 (0.49-0.64) | 0.65 (0.5-0.78) | 0.5 (0.39-0.62) | 0.5 (0.38-0.61) | 0.35 (0.22-0.5) |
| Microbiome signature | 3 | 0.83 (0.37-0.98) | 0.58 (0.21-0.88) | 0.1 (0.01-0.5) | 0.9 (0.5-0.99) | 0.42 (0.12-0.79) |
| mIHC/IF | 7 | 0.71 (0.63-0.83) | 0.75 (0.53-0.89) | 0.36 (0.25-0.48) | 0.64 (0.52-0.75) | 0.25 (0.11-0.47) |
| Multimodal | 9 | 0.69 (0.62-0.73) | 0.56 (0.45-0.67) | 0.26 (0.17-0.38) | 0.74 (0.62-0.83) | 0.44 (0.33-0.55) |
| PD-L1 IHC | 95 | 0.63 (0.61-0.65) | 0.6 (0.55-0.64) | 0.39 (0.35-0.44) | 0.61 (0.56-0.65) | 0.4 (0.36-0.45) |
| TMB | 29 | 0.68 (0.64-0.72) | 0.59 (0.52-0.66) | 0.33 (0.28-0.38) | 0.67 (0.62-0.72) | 0.41 (0.34-0.48) |

**a**Total number of cohorts. Less than 10% of the studies had separate discovery and validation cohorts.

AUC, area under the curve; FNR, false negative rate; FPR, false positive rate; IHC, immunohistochemistry; mIHC/IF, fluorescent multiplex IHC; TGS, T-cell–related gene signature; TMB, tumor mutational burden.

## Supplementary Table 5. Meta-Analysis Estimates of Biomarkers by Cancer Types

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Cancer** | **Biomarker** | **Cohortsa** | **AUC (95% CI)** | **Sensitivity (95% CI)** | **FPR (95% CI)** | **Specificity (95% CI)** | **FNR (95% CI)** |
| Breast | PD-L1 IHC | 4 | 0.48 (0.43-0.76) | 0.4 (0.29-0.52) | 0.27 (0.09-0.58) | 0.73 (0.42-0.91) | 0.6 (0.48-0.71) |
| Colon | PD-L1 IHC | 4 | 0.54 (0.33-0.62) | 0.37 (0.23-0.53) | 0.36 (0.29-0.44) | 0.64 (0.56-0.71) | 0.63 (0.47-0.77) |
| Gastric/GEJ | PD-L1 IHC | 4 | 0.65 (0.5-0.71) | 0.5 (0.22-0.78) | 0.28 (0.11-0.55) | 0.72 (0.45-0.89) | 0.5 (0.22-0.78) |
| HCC | PD-L1 IHC | 4 | 0.65 (0.6-0.72) | 0.52 (0.27-0.77) | 0.32 (0.19-0.49) | 0.68 (0.51-0.81) | 0.48 (0.23-0.73) |
| Head and neck | PD-L1 IHC | 8 | 0.61 (0.57-0.67) | 0.65 (0.5-0.77) | 0.5 (0.31-0.68) | 0.5 (0.32-0.69) | 0.35 (0.23-0.5) |
| Melanoma | Microbiome signature | 3 | 0.83 (0.37-0.98) | 0.58 (0.21-0.88) | 0.1 (0.01-0.5) | 0.9 (0.5-0.99) | 0.42 (0.12-0.79) |
| Melanoma | mIHC/IF | 5 | 0.66 (0.59-0.83) | 0.62 (0.43-0.78) | 0.37 (0.24-0.52) | 0.63 (0.48-0.76) | 0.38 (0.22-0.57) |
| Melanoma | Multimodal | 4 | 0.65 (0.63-0.74) | 0.64 (0.51-0.75) | 0.38 (0.3-0.46) | 0.62 (0.54-0.7) | 0.36 (0.25-0.49) |
| Melanoma | PD-L1 IHC | 15 | 0.63 (0.53-0.69) | 0.58 (0.44-0.71) | 0.38 (0.25-0.51) | 0.62 (0.49-0.75) | 0.42 (0.29-0.56) |
| Melanoma | TMB | 6 | 0.74 (0.61-0.88) | 0.73 (0.64-0.81) | 0.27 (0.12-0.51) | 0.73 (0.49-0.88) | 0.27 (0.19-0.36) |
| MCC | PD-L1 IHC | 5 | 0.63 (0.49-0.69) | 0.75 (0.52-0.9) | 0.62 (0.31-0.85) | 0.38 (0.15-0.69) | 0.25 (0.1-0.48) |
| Multiple cancers | PD-L1 IHC | 5 | 0.67 (0.52-0.77) | 0.62 (0.43-0.78) | 0.36 (0.23-0.51) | 0.64 (0.49-0.77) | 0.38 (0.22-0.57) |
| Multiple cancers | TMB | 4 | 0.8 (0.71-0.83) | 0.82 (0.59-0.93) | 0.3 (0.2-0.43) | 0.7 (0.57-0.8) | 0.18 (0.07-0.41) |
| NSCLC | Multimodal | 3 | 0.71 (0.5-0.81) | 0.43(0.23-0.65) | 0.12 (0.04-0.31) | 0.88 (0.69-0.96) | 0.57 (0.35-0.77) |
| NSCLC | PD-L1 IHC | 29 | 0.66 (0.63-0.69) | 0.63 (0.57-0.68) | 0.37 (0.3-0.45) | 0.63 (0.55-0.7) | 0.37 (0.32-0.43) |
| NSCLC | TMB | 14 | 0.71 (0.66-0.75) | 0.6 (0.47-0.71) | 0.3 (0.25-0.36) | 0.7 (0.64-0.75) | 0.4 (0.29-0.53) |
| Ovarian | Others | 3 | 0.66 (0.41-0.75) | 0.5 (0.29-0.72) | 0.3 (0.17-0.48) | 0.7 (0.52-0.83) | 0.5 (0.28-0.71) |
| RCC | PD-L1 IHC | 7 | 0.59 (0.57-0.65) | 0.6 (0.53-0.66) | 0.46 (0.38-0.53) | 0.54 (0.47-0.62) | 0.4 (0.34-0.47) |
| RCC | TMB | 6 | 0.59 (0.55-0.64) | 0.49 (0.31-0.68) | 0.34 (0.19-0.54) | 0.66 (0.46-0.81) | 0.51 (0.32-0.69) |
| SCLC | PD-L1 IHC | 3 | 0.59 (0.25-0.84) | 0.59 (0.13-0.93) | 0.45 (0.1-0.85) | 0.55 (0.15-0.9) | 0.41 (0.07-0.87) |
| Urothelial | PD-L1 IHC | 9 | 0.68 (0.63-0.71) | 0.53 (0.35-0.71) | 0.3 (0.23-0.39) | 0.7 (0.61-0.77) | 0.47 (0.29-0.65) |

AUC, area under the curve; FNR, false negative rate; FPR, false positive rate; GEJ, gastroesophageal junction; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; MCC, Merkel cell carcinoma; mIHC/IF, fluorescent multiplex IHC; NSCLC, non–small cell lung cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer; TMB, tumor mutational burden.

**a**Total number of cohorts. Less than 10% of the studies had separate discovery and validation cohorts.

## Supplementary Table 6. References of Studies Included in Analyses

|  |  |
| --- | --- |
| 1 | Adams S, Schmid P, Rugo HS, et al. Pembrolizumab monotherapy for previously treated metastatic triple-negative breast cancer: cohort A of the phase II KEYNOTE-086 study. *Ann Oncol*. 2019;30(3):397-404. doi:10.1093/annonc/mdy517 |
| 2 | Antonarakis ES, Piulats JM, Gross-Goupil M, et al. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: multicohort, open-label phase II KEYNOTE-199 study. *J Clin Oncol*. 2020;38(5):395-405. doi:10.1200/JCO.19.01638 |
| 3 | Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016;17(7):883-895. doi:10.1016/S1470-2045(16)30098-5. Published corrections appear in *Lancet Oncol*. 2016;17(7):e270 and 2019;20(2):e70. |
| 4 | Balar AV, Galsky MD, Rosenberg JE, et al; IMvigor210 Study Group. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet*. 2017;389(10064):67-76. doi:10.1016/S0140-6736(16)32455-2. Published correction appears in *Lancet*. 2017;390(10097):848. |
| 5 | Bauml J, Seiwert TY, Pfister DG, et al. Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: results from a single-arm, phase II study. *J Clin Oncol*. 2017;35(14):1542-1549. doi:10.1200/JCO.2016.70.1524 |
| 6 | Bellmunt J, de Wit R, Vaughn DJ, et al; KEYNOTE-045 Investigators. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376(11):1015-1026. doi:10.1056/NEJMoa1613683 |
| 7 | Bonta I, Isac JF, Meiri E, Bonta D, Rich P. Correlation between tumor mutation burden and response to immunotherapy. *J Clin Oncol.* 2017;35(15\_suppl):abstr e14579. doi:10.1200/JCO.2017.35.15\_suppl.e14579 |
| 8 | Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627-1639. doi:10.1056/NEJMoa1507643 |
| 9 | Campesato LF, Barroso-Sousa R, Jimenez L, et al. Comprehensive cancer-gene panels can be used to estimate mutational load and predict clinical benefit to PD-1 blockade in clinical practice. *Oncotarget*. 2015;6(33):34221-34227. doi:10.18632/oncotarget.5950 |
| 10 | Carbone DP, Reck M, Paz-Ares L, et al; CheckMate 026 Investigators. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med*. 2017;376(25):2415-2426. doi:10.1056/NEJMoa1613493 |
| 11 | Choueiri TK, Motzer RJ, Rini BI, et al. Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. *Ann Oncol*. 2020;31(8):1030-1039. doi:10.1016/j.annonc.2020.04.010 |
| 12 | Chow LQM, Haddad R, Gupta S, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort. *J Clin Oncol*. 2016;34(32):3838-3845. doi:10.1200/JCO.2016.68.1478 |
| 13 | Chung HC, Lopez-Martin JA, Kao SC-H, et al. Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158. *J Clin Oncol*. 2018;36(15\_suppl):abstr 8506. doi:10.1200/JCO.2018.36.15\_suppl.8506 |
| 14 | Chung HC, Ros W, Delord J-P, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2019;37(17):1470-1478. doi:10.1200/JCO.18.01265 |
| 15 | Cohen EEW, Soulières D, Le Tourneau C, et al; KEYNOTE-040 investigators. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet*. 2019;393(10167):156-167. doi:10.1016/S0140-6736(18)31999-8. Published correction appears in *Lancet*. 2019;393(10167):132. |
| 16 | Cristescu R, Mogg R, Ayers M, et al. Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy. *Science*. 2018;362(6411):eaar3593. doi:10.1126/science.aar3593. Published correction appears in *Science*. 2019;363(6430):eaax1384. |
| 17 | Daud AI, Hamid O, Ribas A, et al. Abstract CT104: antitumor activity of the anti-PD-1 monoclonal antibody MK-3475 in melanoma (MEL): correlation of tumor PD-L1 expression with outcome. *Cancer Res*. 2014;74(19\_suppl):CT104. doi:10.1158/1538-7445.AM2014-CT104 |
| 18 | Daud AI, Wolchok JD, Robert C, et al. Programmed death-ligand 1 expression and response to the anti-programmed death 1 antibody pembrolizumab in melanoma. *J Clin Oncol*. 2016;34(34):4102-4109. doi:10.1200/JCO.2016.67.2477 |
| 19 | Dirix LY, Takacs I, Jerusalem G, et al. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. *Breast Cancer Res Treat*. 2018;167(3):671-686. doi:10.1007/s10549-017-4537-5 |
| 20 | El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389(10088):2492-2502. doi:10.1016/S0140-6736(17)31046-2 |
| 21 | Maher VE, Fernandes LL, Weinstock C, et al. Analysis of the association between adverse events and outcome in patients receiving a programmed death protein 1 or programmed death ligand 1 antibody. *J Clin Oncol*. 2019;37(30):2730-2737. doi:10.1200/JCO.19.00318 |
| 22 | Eng C, Kim TW, Bendell J, et al; IMblaze370 Investigators. Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol*. 2019;20(6):849-861. doi:10.1016/S1470-2045(19)30027-0. Published correction appears in *Lancet Oncol*. 2019;20(6):e293. |
| 23 | Färkkilä A, Gulhan DC, Casado J, et al. Immunogenomic profiling determines responses to combined PARP and PD-1 inhibition in ovarian cancer. *Nat Commun*. 2020;11(1):1459. doi:10.1038/s41467-020-15315-8. Published correction appears in *Nat Commun*. 2020;11(1):2543. |
| 24 | Fehrenbacher L, Spira A, Ballinger M, et al; POPLAR Study Group. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet*. 2016;387(10030):1837-1846. doi:10.1016/S0140-6736(16)00587-0 |
| 25 | Felip E, de Braud FG, Maur M, et al. Ceritinib plus nivolumab in patients with advanced ALK-rearranged non–small cell lung cancer: results of an open-label, multicenter, phase 1B study. *J Thorac Oncol*. 2020;15(3):392-403. doi:10.1016/j.jtho.2019.10.006 |
| 26 | Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2016;375(19):1856-1867. doi:10.1056/NEJMoa1602252 |
| 27 | Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *JAMA Oncol*. 2018;4(5):e180013. doi:10.1001/jamaoncol.2018.0013. Published correction appears in *JAMA Oncol*. 2019;5(4):579 |
| 28 | Gadgeel S, Rodríguez-Abreu D, Speranza G, et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non–small-cell lung cancer. *J Clin Oncol*. 2020;38(14):1505-1517. doi:10.1200/JCO.19.03136 |
| 29 | Gandara DR, Paul SM, Kowanetz M, et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. *Nat Med*. 2018;24(9):1441-1448. doi:10.1038/s41591-018-0134-3 |
| 30 | Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al; KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078-2092. doi:10.1056/NEJMoa1801005 |
| 31 | Gandhi L, Balmanoukian A, Hui R, et al. Abstract CT105: MK-3475 (anti-PD-1 monoclonal antibody) for non-small cell lung cancer (NSCLC): antitumor activity and association with tumor PD-L1 expression. *Cancer Res.* 2014;74(19\_suppl):CT105. doi:10.1158/1538-7445.AM2014-CT105 |
| 32 | Garon EB, Rizvi NA, Hui R, et al; KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372(21):2018-2028. doi:10.1056/NEJMoa1501824 |
| 33 | Scott SN, Shepherd FA, Antonia SJ, et al. First-line nivolumab (anti-PD-1; BMS-936558, ONO-4538) monotherapy in advanced NSCLC: safety, efficacy, and correlation of outcomes with PD-L1 status. *J Clin Oncol*. 2014;32(15\_suppl):8024–8024. doi:10.1200/jco.2014.32.15\_suppl.8024 |
| 34 | Giraldo NA, Nguyen P, Engle EL, et al. Multidimensional, quantitative assessment of PD-1/PD-L1 expression in patients with Merkel cell carcinoma and association with response to pembrolizumab. *J Immunother Cancer*. 2018;6(1):99. doi:10.1186/s40425-018-0404-0 |
| 35 | Goodman AM, Kato S, Bazhenova L, et al. Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. *Mol Cancer Ther*. 2017;16(11):2598-2608. doi:10.1158/1535-7163.MCT-17-0386 |
| 36 | Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science*. 2018;359(6371):97-103. doi:10.1126/science.aan4236 |
| 37 | Grosso J, Horak CE, Inzunza D, et al. Association of tumor PD-L1 expression and immune biomarkers with clinical activity in patients (pts) with advanced solid tumors treated with nivolumab (anti-PD-1; BMS-936558; ONO-4538). *J Clin Oncol.* 2013;31(15\_suppl):abstr 3016. doi:10.1200/jco.2013.31.15\_suppl.3016 |
| 38 | Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med*. 2019;381(21):2020-2031. doi:10.1056/NEJMoa1910231 |
| 39 | Hellmann MD, Callahan MK, Awad MM, et al. Tumor mutational burden and efficacy of nivolumab monotherapy and in combination with ipilimumab in small-cell lung cancer. *Cancer Cell*. 2018;33(5):853-861.e4. doi:10.1016/j.ccell.2018.04.001. Published correction appears in *Cancer Cell*. 2019;35(2):329. |
| 40 | Hellmann MD, Nathanson T, Rizvi H, et al. Genomic features of response to combination immunotherapy in patients with advanced non-small-cell lung cancer. *Cancer Cell*. 2018;33(5):843-852.e4. doi:10.1016/j.ccell.2018.03.018 |
| 41 | Hellmann MD, Ciuleanu T-E, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med*. 2018;378(22):2093-2104. doi:10.1056/NEJMoa1801946 |
| 42 | Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387(10027):1540-1550. doi:10.1016/S0140-6736(15)01281-7 |
| 43 | Herbst RS, Soria J-C, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature*. 2014;515(7528):563-567. doi:10.1038/nature14011 |
| 44 | Horn L, Spigel DR, Vokes EE, et al. Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cancer: two-year outcomes from two randomized, open-label, phase III trials (CheckMate 017 and CheckMate 057). *J Clin Oncol*. 2017;35(35):3924-3933. doi:10.1200/JCO.2017.74.3062 |
| 45 | Hui R, Garon EB, Goldman JW, et al. Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced non-small cell lung cancer: a phase 1 trial. *Ann Oncol*. 2017;28(4):874-881. doi:10.1093/annonc/mdx008 |
| 46 | Janjigian YY, Bendell J, Calvo E, et al. CheckMate-032 study: efficacy and safety of nivolumab and nivolumab plus ipilimumab in patients with metastatic esophagogastric cancer. *J Clin Oncol*. 2018;36(28):2836-2844. doi:10.1200/JCO.2017.76.6212. Published correction appears in *J Clin Oncol*. 2019;37(5):443. |
| 47 | Johnson DB, Bordeaux J, Kim JY, et al. Quantitative spatial profiling of PD-1/PD-L1 interaction and HLA-DR/IDO-1 predicts improved outcomes of anti-PD-1 therapies in metastatic melanoma. *Clin Cancer Res*. 2018;24(21):5250-5260. doi:10.1158/1078-0432.CCR-18-0309 |
| 48 | Johnson DB, Frampton GM, Rioth MJ, et al. Targeted next generation sequencing identifies markers of response to PD-1 blockade. *Cancer Immunol Res*. 2016;4(11):959-967. doi:10.1158/2326-6066.CIR-16-0143 |
| 49 | Kato K, Doki Y, Ura T, et al. Long-term efficacy and predictive correlates of response to nivolumab in Japanese patients with esophageal cancer. *Cancer Sci*. 2020;111(5):1676-1684. doi:10.1111/cas.14380 |
| 50 | Kaufman HL, Russell JS, Hamid O, et al. Updated efficacy of avelumab in patients with previously treated metastatic Merkel cell carcinoma after ≥1 year of follow-up: JAVELIN Merkel 200, a phase 2 clinical trial. *J Immunother Cancer*. 2018;6(1):7. doi:10.1186/s40425-017-0310-x |
| 51 | Kaufman HL, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(10):1374-1385. doi:10.1016/S1470-2045(16)30364-3 |
| 52 | Kefford R, Ribas A, Hamid O, et al. Clinical efficacy and correlation with tumor PD-L1 expression in patients (pts) with melanoma (MEL) treated with the anti-PD-1 monoclonal antibody MK-3475. *J Clin Oncol*. 2014;32(15\_suppl):abstr 3005. doi:10.1200/jco.2014.32.15\_suppl.3005 |
| 53 | Khagi Y, Goodman AM, Daniels GA, et al. Hypermutated circulating tumor DNA: correlation with response to checkpoint inhibitor-based immunotherapy. *Clin Cancer Res*. 2017;23(19):5729-5736. doi:10.1158/1078-0432.CCR-17-1439 |
| 54 | Langer CJ, Gadgeel SM, Borghaei H, et al; KEYNOTE-021 Investigators. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol*. 2016;17(11):1497-1508. doi:10.1016/S1470-2045(16)30498-3 |
| 55 | Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23-34. doi:10.1056/NEJMoa1504030. Published correction appears in *N Engl J Med*. 2018;379(22):2185. |
| 56 | Larkin J, Minor D, D’Angelo S, et al. Overall survival in patients with advanced melanoma who received nivolumab versus investigator’s choice chemotherapy in CheckMate 037: a randomized, controlled, open-label phase III trial. *J Clin Oncol*. 2018;36(4):383-390. doi:10.1200/JCO.2016.71.8023 |
| 57 | Loo K, Tsai KK, Mahuron K, et al. Partially exhausted tumor-infiltrating lymphocytes predict response to combination immunotherapy. *JCI Insight*. 2017;2(14):e93433. doi:10.1172/jci.insight.93433 |
| 58 | Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science*. 2018;359(6371):104-108. doi:10.1126/science.aao3290 |
| 59 | McDermott DF, Huseni MA, Atkins MB, et al. Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. *Nat Med*. 2018;24(6):749-757. doi:10.1038/s41591-018-0053-3. Published correction appears in *Nat Med*. 2018;24(12):1941. |
| 60 | McGregor BA, McKay RR, Braun DA, et al. Results of a multicenter phase II study of atezolizumab and bevacizumab for patients with metastatic renal cell carcinoma with variant histology and/or sarcomatoid features. *J Clin Oncol*. 2020;38(1):63-70. doi:10.1200/JCO.19.01882 |
| 61 | Mehra R, Seiwert TY, Gupta S, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012. *Br J Cancer*. 2018;119(2):153-159. doi:10.1038/s41416-018-0131-9 |
| 62 | Mok TSK, Wu Y-L, Kudaba I, et al; KEYNOTE-042 Investigators. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393(10183):1819-1830. doi:10.1016/S0140-6736(18)32409-7 |
| 63 | Motzer RJ, Tannir NM, McDermott DF, et al; CheckMate 214 Investigators. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378(14):1277-1290. doi:10.1056/NEJMoa1712126 |
| 64 | Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380(12):1103-1115. doi:10.1056/NEJMoa1816047 |
| 65 | Muro K, Chung HC, Shankaran V, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. *Lancet Oncol*. 2016;17(6):717-726. doi:10.1016/S1470-2045(16)00175-3 |
| 66 | Nghiem P, Bhatia S, Lipson EJ, et al. Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. *J Clin Oncol*. 2019;37(9):693-702. doi:10.1200/JCO.18.01896 |
| 67 | Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol*. 2018;36(8):773-779. doi:10.1200/JCO.2017.76.9901 |
| 68 | Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2017;18(9):1182-1191. doi:10.1016/S1470-2045(17)30422-9. Published correction appears in *Lancet Oncol*. 2017;18(9):e510. |
| 69 | Patel MR, Ellerton J, Infante JR, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. *Lancet Oncol*. 2018;19(1):51-64. doi:10.1016/S1470-2045(17)30900-2. Published correction appears in *Lancet Oncol*. 2018;19(7):e335. |
| 70 | Paz-Ares L, Luft A, Vicente D, et al; KEYNOTE-407 Investigators. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379(21):2040-2051. doi:10.1056/NEJMoa1810865 |
| 71 | Plimack ER, Bellmunt J, Gupta S, et al. Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): a non-randomised, open-label, phase 1b study. *Lancet Oncol*. 2017;18(2):212-220. doi:10.1016/S1470-2045(17)30007-4 |
| 72 | Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med*. 2015;372(21):2006-2017. doi:10.1056/NEJMoa1414428. Published correction appears in *N Engl J Med*. 2018;379(22):2185. |
| 73 | Powles T, Eder JP, Fine GD, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature*. 2014;515(7528):558-562. doi:10.1038/nature13904 |
| 74 | Powles T, O’Donnell PH, Massard C, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. *JAMA Oncol*. 2017;3(9):e172411. doi:10.1001/jamaoncol.2017.2411 |
| 75 | Puzanov I, Dummer R, Schachter J, et al. Efficacy based on tumor PD-L1 expression in KEYNOTE-002, a randomized comparison of pembrolizumab (Pembro; MK-3475) versus chemotherapy in patients (pts) with ipilimumab-refractory (IPI-R) advanced melanoma (MEL). *J Clin Oncol*. 2015;33(15\_suppl):abstr 3012. doi:10.1200/jco.2015.33.15\_suppl.3012 |
| 76 | Ready N, Hellmann MD, Awad MM, et al. First-line nivolumab plus ipilimumab in advanced non-small-cell lung cancer (CheckMate 568): outcomes by programmed death ligand 1 and tumor mutational burden as biomarkers. *J Clin Oncol*. 2019;37(12):992-1000. doi:10.1200/JCO.18.01042 |
| 77 | Riaz N, Havel JJ, Makarov V, et al. Tumor and microenvironment evolution during immunotherapy with nivolumab. *Cell*. 2017;171(4):934-949.e16. doi:10.1016/j.cell.2017.09.028 |
| 78 | Rini BI, Powles T, Atkins MB, et al; IMmotion151 Study Group. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. *Lancet*. 2019;393(10189):2404-2415. doi:10.1016/S0140-6736(19)30723-8 |
| 79 | Rittmeyer A, Barlesi F, Waterkamp D, et al; OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389(10066):255-265. doi:10.1016/S0140-6736(16)32517-X. Published correction appears in *Lancet*. 2017;389(10077):e5. |
| 80 | Rizvi H, Sanchez-Vega F, La K, et al. 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. *J Clin Oncol*. 2018;36(7):633-641. doi:10.1200/JCO.2017.75.3384. Published correction appears in *J Clin Oncol*. 2018;36(16):1645. |
| 81 | 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*. 2015;348(6230):124-128. doi:10.1126/science.aaa1348 |
| 82 | Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372(4):320-330. doi:10.1056/NEJMoa1412082 |
| 83 | 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*. 2016;387(10031):1909-1920. doi:10.1016/S0140-6736(16)00561-4 |
| 84 | Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science*. 2018;359(6371):91-97. doi:10.1126/science.aan3706 |
| 85 | Schmid P, Adams S, Rugo HS, et al; IMpassion130 Trial Investigators. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379(22):2108-2121. doi:10.1056/NEJMoa1809615 |
| 86 | Shah MA, Kojima T, Hochhauser D, et al. Efficacy and safety of pembrolizumab for heavily pretreated patients with advanced, metastatic adenocarcinoma or squamous cell carcinoma of the esophagus: the phase 2 KEYNOTE-180 study. *JAMA Oncol*. 2019;5(4):546-550. doi:10.1001/jamaoncol.2018.5441 |
| 87 | Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2017;18(3):312-322. doi:10.1016/S1470-2045(17)30065-7 |
| 88 | Singal G, Miller PG, Agarwala V, et al. Analyzing biomarkers of cancer immunotherapy (CIT) response using a real-world clinico-genomic database. *Ann Oncol*. 2017;28(suppl 5):v404-v405. doi:10.1093/annonc/mdx376.005 |
| 89 | Socinski MA, Jotte RM, Cappuzzo F, et al; IMpower150 Study Group. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378(24):2288-2301. doi:10.1056/NEJMoa1716948 |
| 90 | Spigel DR, Gettinger SN, Horn L, et al. Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2013;31(15\_suppl):8008. doi:10.1200/jco.2013.31.15\_suppl.8008 |
| 91 | Taube JM, Klein A, Brahmer JR, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. *Clin Cancer Res*. 2014;20(19):5064-5074. doi:10.1158/1078-0432.CCR-13-3271 |
| 92 | Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454. doi:10.1056/NEJMoa1200690 |
| 93 | Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature*. 2014;515(7528):568-571. doi:10.1038/nature13954 |
| 94 | Tykodi SS, Donskov F, Lee JL, et al. First-line pembrolizumab (pembro) monotherapy in advanced clear cell renal cell carcinoma (ccRCC): updated results for KEYNOTE-427 cohort A. *J Clin Oncol*. 2019;37(15\_suppl):4570. doi:10.1200/JCO.2019.37.15\_suppl.4570 |
| 95 | Uemura M, Tomita Y, Miyake H, et al. Avelumab plus axitinib vs sunitinib for advanced renal cell carcinoma: Japanese subgroup analysis from JAVELIN Renal 101. *Cancer Sci*. 2020;111(3):907-923. doi:10.1111/cas.14294 |
| 96 | Wang L, Saci A, Szabo PM, et al. EMT- and stroma-related gene expression and resistance to PD-1 blockade in urothelial cancer. *Nat Commun*. 2018;9(1):3503. doi:10.1038/s41467-018-05992-x |
| 97 | Weber JS, D’Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2015;16(4):375-384. doi:10.1016/S1470-2045(15)70076-8 |
| 98 | Weber JS, Reiney Kudchadkar R, Yu B, et al. Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. *J Clin Oncol*. 2013;31(34):4311-4318. doi:10.1200/JCO.2013.51.4802 |
| 99 | Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2017;377(14):1345-1356. doi:10.1056/NEJMoa1709684. Published correction appears in *N Engl J Med*. 2018;379(22):2185 |
| 100 | Zhu AX, Finn RS, Edeline J, et al; KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol*. 2018;19(7):940-952. doi:10.1016/S1470-2045(18)30351-6. Published correction appears in *Lancet Oncol*. 2018;19(9):e440. |

## Supplementary Figures

## Supplementary Figure. Literary Review Description



Studies were excluded if data for 2x2 contingency table between biomarker and treatment response were not available. Please refer to the Methods section for more information about contingency tables.