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## Supplementary Tables

## Supplementary Table 1. Formulas of Accuracy Metrics

|  |  |
| --- | --- |
| **Metric** | **Formula** |
| False discovery rate | $$\frac{FP}{TP+FP}$$ |
| False negative rate  | $$\frac{FN}{TP+FN}$$ |
| False omission rate  | $$\frac{FN}{TN+FN}$$ |
| False positive rate | $$\frac{FP}{TN+FP}$$ |
| Negative predictive value | $$\frac{TN}{TN+FN}$$ |
| Positive predictive value | $$\frac{TP}{TP+FP}$$ |
| Sensitivity | $$\frac{TP}{TP+FN}$$ |
| Specificity | $$\frac{TN}{TN+FP}$$ |

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 |
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| 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. |
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| 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 |
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| 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 |
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| 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  |
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## 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.