Immune checkpoint inhibitors (ICI) block PD-1/PD-L1.

ICI reactivate immune response to tumor cells by inhibiting the interaction action of PD-L1 and PD-1.

Immune checkpoint inhibitors (ICI): a type of immunotherapy that block immune checkpoint proteins from binding with partner proteins.

PD-1: receptor often on the surface of immune cells, inhibitor of both adaptive and innate immune responses

PD-L1: protein that has a broader presence, including on the tumor cells.

PD-1/PD-L1 pathway controls the induction and maintenance of immune tolerance within the tumor microenvironment.

Efficacy: **primary outcome**: Objective response rate (ORR) to anti-PD-1/anti-PD-L1 therapies ~ 24%.

Clinical benefit (CB) if ORR is not available.

Adverse Events (AE): 16% patients experience significant toxicity (colitis and endocrine organ dysfunction).

Responses: determined using Response evaluation criteria in solid tumors (RECIST) or modified RECIST

<https://recist.eortc.org/>

Discriminate responders and nonresponders:

1. Whether PD-L1/PD-1 protein expression
2. Tumor mutational burden (TMB)
3. Immune-mediated AE (imAEs)
4. Microbiome signature

Results are inconsistent.

1. Patient Population
2. Sample collection and processing
3. Technology platforms
4. Biomarker thresholds
5. Specific ICI used
6. Limited sample size

Meta-analysis: 100 studies and 18792 patients.

Biomarkers: 9 classes, 3 frequently observed: (PD-L1 protein expression, TMB, multimodal biomarkers.)

* **PD-L1 protein expression**: greater than the expression threshold > more likely to respond to treatment
* **TMB**: DNA mutations across tumor genome. Median TMB was a commonly reported threshold for assessing response to ICIs. Above the threshold was indicative of an increased likelihood of response to treatment.
* **T cell-related gene signatures (TGSs)**:
* Epithelial-mesenchymal transition-related gene expression correlated with T-cell infiltration
* Total RNA and mRNA.
* **CD8+**:
* **Microbiome signature**
* **AEs of special interest and imAEs**
* **Multimodal biomarkers.**
* **International Metastatic RCC Database Consortium (IMDC) risk score**

Meta-analysis to determine:

* Discriminatory potential for each biomarker across multiple cancer types
* Discriminatory potential for each biomarker for each cancer type

**Report AUC**: Binary test outcomes, such as sensitiv­ity and specificity, rely on a threshold for determining the optimal test per­formance. This threshold often creates a tradeoff between certain values, and simply averaging values across studies with different thresholds can confound results. To address this, we implemented the summary-receiving operating characteristic curve (**ROC curve** **same as AUC**) approach. AUC was calculated from bivariate models. Confidence intervals were estimated using bootstrapping.

Model: Linear mixed effects model.

**A minimum of 3 studies, or 500 patients were required to perform each meta-analysis.**

**If one study report multiple thresholds for the same biomarker**: only the threshold with the greatest accuracy were reported.

# Discussion

Challenge:

1. Only 24% (95% CI, 21%-28%) of patients respond to these treatments.
2. No consensus exists regarding which of these biomarkers is capable of or has the potential to be clinically useful.

Achievement of this meta-analysis:

1. More studies, more patients
2. More biomarkers including novel biomarkers
3. Bivariate linear mixed models: provide more accurate estimates

Findings that were consistent with other studies:

1. PD-L1 HIC, TMB, and MIHC/IF had better discriminatory ability than randomly guess (AUC>0.5).
2. TMB had better discriminatory ability than PD-L1 expression.
3. MIHC/IF is a new biomarker which has been investigated only in 2 cancer types (melanoma and Merkel cell carcinoma).
4. Multimodal biomarkers has consistent discriminatory ability across studies of melanoma, but a large variation among studies of non–small cell lung cancer (NSCLC).

Future plan:

1. An important metric, positive predictive value (PPV) was not reported. PPV is a measure of the probability of the outcome given a positive biomarker result. However, PPV is influenced by the prevalence of responders and is therefore highly dependent on tumor type and many other factors.
2. Those findings should be validated in an independent cohort for prediction in the future.