

# Unmet clinical needs in biomarker-guided immune checkpoint inhibitor treatment

## Introduction

### Problem Statement

Immune checkpoint inhibitors (ICIs) have transformed outcomes for patients with select tumor types, but benefit remains confined to a minority of the total patient population. Of the estimated 56% of patients eligible to receive ICI therapy based on current biomarker paradigms, only 20% exhibit an objective response.<sup>1</sup>

Predictive performance of FDA-approved biomarkers falls short of clinical need, and for many tumor types, no predictive biomarker exists at all.

## Current biomarkers have limited predictive value

ICI therapy includes antibodies such as anti-programmed cell death protein 1 ( $\alpha$ PD-1) or anti-cytotoxic T-lymphocyte-associated protein 4 ( $\alpha$ CTLA-4) that block inhibitory checkpoint signaling to restore anti-tumor immune activity. Programmed-death ligand 1 (PD-L1), microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), and tumor mutational burden high (TMB-H) are FDA-approved biomarkers used to determine ICI eligibility. PD-L1 was authorized alongside the earliest  $\alpha$ PD-1/ $\alpha$ PD-L1 approvals beginning in October 2015. MSI-H/dMMR became the first tissue-agnostic approval in oncology in May 2017,<sup>2</sup> and TMB-H followed as the second tissue-agnostic biomarker in June 2020.<sup>3</sup> These biomarkers fall into two mechanistic groups: (1) presence of a targetable, inhibitory immune checkpoint protein in the tumor (PD-L1), and (2) higher tumor neoantigen load (MSI-H/dMMR or TMB-H).

### Purpose

This white paper describes clinical uncertainty in treating patients with immunotherapy, focusing on populations for whom, despite FDA-approved biomarkers, current guidance does not provide a clear course of action.

This document outlines five persistent, literature-based gaps in biomarker-guided decision-making for ICI therapy:

1. The limited predictive accuracy of current biomarkers.
2. The absence of a tool to match patients with the ICI mechanism most likely to benefit them before treatment begins.
3. The lack of guidance for post-progression re-challenge decisions.
4. The absence of guidance for managing populations without an FDA-approved ICI indication who may respond.
5. Unresolved clinical equipoise in patients with immune dysregulation, liver metastases, or who may benefit from chemotherapy de-escalation.

MSI-H is typically assessed genomically, while dMMR is assessed by immunohistochemistry (IHC), but given their high concordance, the two are often used interchangeably. Standard biomarkers also differ in how their approvals apply across tumor types: PD-L1 approvals are tumor-type specific, and MSI-H/dMMR and TMB-H have both tissue-specific and tissue-agnostic approvals.

In the largest ICI biomarker meta-analysis to date (18,792 patients, 100 studies, including FDA-approved and non-approved indications), predictive accuracy varied by biomarker and tumor type (Figure 1).<sup>4,5</sup> This variability partly reflects differences in the tumor microenvironment (TME) between tumor types. For example, lung cancer is more T cell-inflamed while pancreatic cancer has a more suppressive TME<sup>6</sup>; this limits how well a single biomarker or threshold generalizes across tumor types. In practice, non-response persists across all 3 biomarkers: 44%, 59% and 66% of patients with MSI-H/dMMR, TMB-H, or PD-L1-positive tumors respectively do not respond to ICI treatment.<sup>5</sup>



## How is biomarker accuracy measured?

Biomarker accuracy is typically reported as the area under the receiver operating characteristic curve (AUC), a measure of how well a biomarker distinguishes responders from non-responders, where 1.0 indicates perfect discrimination and 0.5 indicates performance no better than chance. The AUC summarizes a biomarker's sensitivity and specificity across all possible thresholds. Sensitivity reflects the proportion of ICI responders correctly identified as positive, while specificity reflects the proportion of non-responders it correctly identifies as negative. The two are inherently in tension: because responders and non-responders overlap in biomarker values, no single threshold can maximize both.<sup>7</sup> A threshold set for high sensitivity captures most true responders but classifies more non-responders as positive; a threshold set for high specificity excludes most non-responders but risks denying treatment to patients who would have responded. This relationship is evident in Figure 1C and D where tumor types with high biomarker sensitivity have low specificity and vice versa.

## PD-L1

PD-L1 is the most widely studied ICI biomarker, given its direct role in the PD-1/PD-L1 axis targeted by many ICIs, but its ability to distinguish responders from non-responders remains limited. For FDA-approved indications, PD-L1's AUC ranges from 0.61 to 0.68. PD-L1 positivity is scored on a continuous 0-100 scale; any eligibility cutoff placed along that scale must balance sensitivity and specificity. This aligns with reported sensitivity and specificity ranges of 50-65% and 50-72%, respectively.<sup>4</sup> Consistent with this, in an analysis of all 45 FDA ICI approvals through April 2019, PD-L1 expression was not predictive of response in more than half of cases.<sup>8</sup> Assay complexity and variability, including inter-pathologist scoring differences, scoring approaches (tumor proportion score [TPS] vs combined positive score [CPS]), tumor-type-specific thresholds, assay clone, intra-biopsy heterogeneity due to sampling depth of serial sections, and tumor heterogeneity relative to routine biopsy sampling, can all contribute to false negatives and false positives (Figure 2). With these variables in play, the same tumor can be classified as PD-L1-positive on one platform and negative on another, especially for samples where PD-L1 expression is low. False positives can also occur; for example, PD-L1 expression can be induced adaptively by local IFN $\gamma$  signaling without reflecting a durable, therapeutically actionable anti-tumor response.<sup>9</sup>

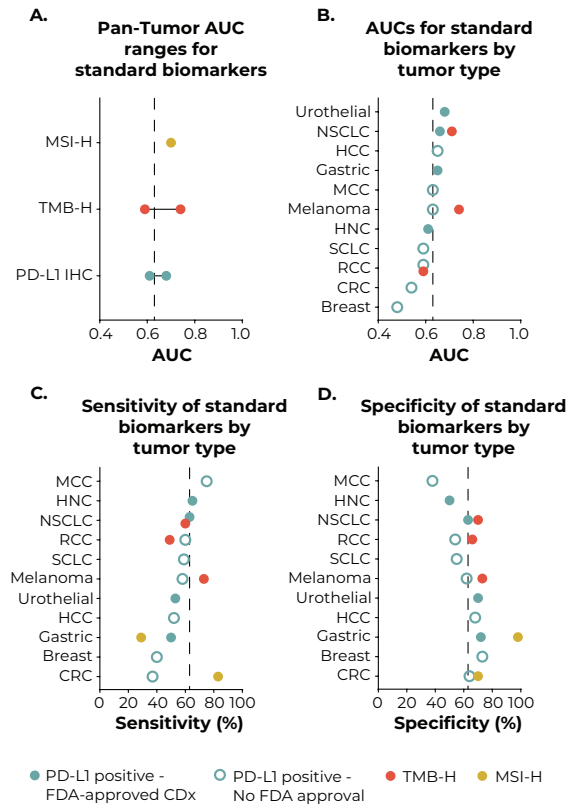


**Figure 1.** Predictive accuracy of standard ICI biomarkers by tumor type. (A) range of pan-tumor AUC estimates for PD-L1 and TMB-H across tumor types; MSI-H is shown as a single pooled estimate, as tumor-type-specific data were not reported. (B) AUC by tumor type, where available, ordered by PD-L1 performance (highest, urothelial carcinoma, to lowest, breast cancer). PD-L1 values are filled where an FDA-approved companion diagnostic exists for that indication and open where none exists; TMB-H, with tissue-agnostic approval, is shown uniformly. (C) Sensitivity (%) and (D) Specificity (%) by tumor type, using the same encoding as in (B). Dotted lines represent median values. Data are from Mariam et al. (PD-L1 [8,948 patients, 37 studies], TMB-H [2,128 patients, 14 studies]) and Shi et al. (MSI-H [5,322 patients, 49 studies]).

## MSI-H/dMMR

dMMR produces immune-recognizable somatic mutations, manifesting clinically as MSI. Unlike PD-L1, MSI-H/dMMR status is a binary yes/no, and favors specificity over sensitivity. Consistent with this, MSI-H/dMMR shows the highest specificity (90%) of the three FDA-approved biomarkers, although sensitivity is comparatively low (42%), yielding an extrapolated pooled AUC of ~0.7.<sup>4</sup> MSI-H/dMMR is the most robust biomarker to predict response to ICI in metastatic colorectal cancer (mCRC) and its approved indications extend beyond mCRC: pembrolizumab, a monoclonal antibody targeting PD-1, gained the earliest tissue-agnostic FDA approval for MSI-H/dMMR solid tumors in May 2017. This was the first tissue-agnostic approval in oncology based on biomarker presence rather than anatomic site.



It was based on pooled evidence from 149 patients with MSI-H/dMMR cancers (15 tumor types) across five single-arm trials,<sup>2</sup> including KEYNOTE-016, -164, -012, -028, and -158. However, objective response based on MSI-H/dMMR status is highly variable,<sup>10,11</sup> and only 5% of mCRCs are dMMR, leaving most patients with mCRC without an actionable biomarker.

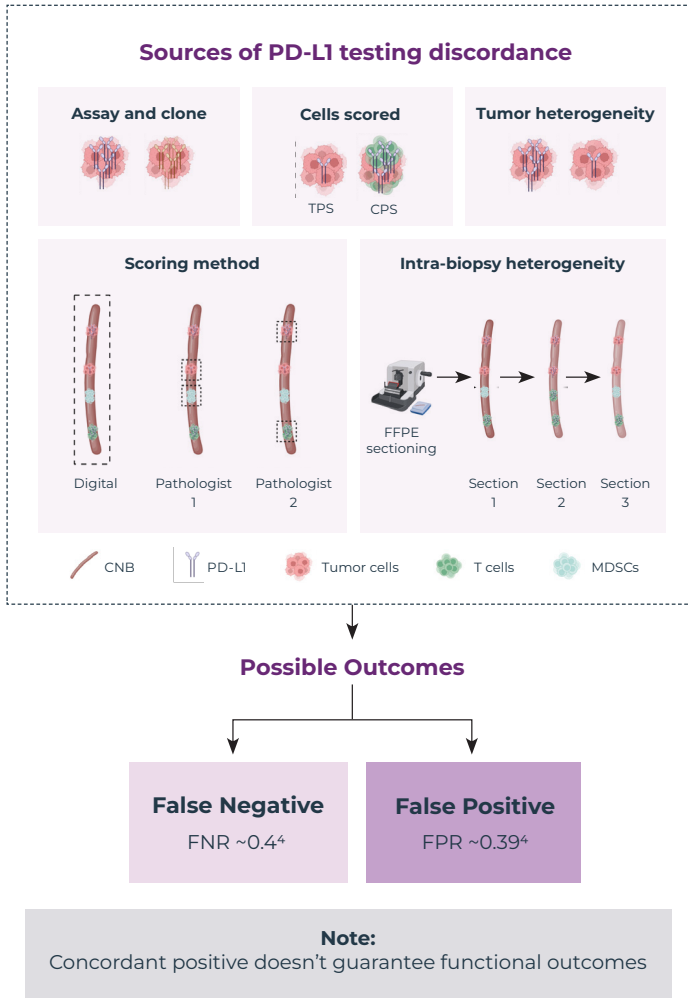


**Figure 2.** Sources of PD-L1 immunohistochemistry inconsistency and their relationship to test performance. PD-L1 status is typically assessed from a single core needle biopsy (CNB), but several independent variables can affect test outcomes: antibody clone/assay choice, scoring metric (TPS vs CPS), intratumor heterogeneity, scoring method (digital vs pathologist read), and sampling depth across serial biopsy sections. These sources of inconsistency can produce discordant results between methods, false negative, and false positive classifications. Pooled across cancer types, PD-L1 IHC carries a false negative rate (FNR) of 0.40 (95% CI 0.36-0.45) and a false positive rate (FPR) of 0.39 (95% CI 0.35-0.44) for predicting ICI response. Concordant, positive PD-L1 results do not guarantee response, since IHC captures static expression rather than functional anti-tumor immune activity. Data are from Mariam et al. (8,948 patients, 37 studies).

## TMB-H

In the context of tumor-immune interactions, the higher number of somatic mutations a tumor has, the more likely neoantigens are to form and contribute to immune activation. TMB is typically measured using whole-exome or panel-based sequencing, although sequencing panels, analysis methods, and cutoffs for high versus low TMB vary. In the pan-tumor meta-analysis by Mariam et al., TMB-H carried an AUC of 0.68 (95% CI 0.64-0.72) with 59% sensitivity and 61% specificity.<sup>4</sup> Clinical studies have also shown that TMB-H is associated with response to ICI specifically in non-small cell lung cancer (NSCLC) and melanoma,<sup>12,13</sup> although its predictive capacity across the broader range of solid tumors is less robust. This inconsistency reflects the fact that TMB is a proxy for neoantigen burden rather than a direct measure of immune recognition. TMB-H is often associated with certain mutational processes that generate immunogenic neoantigens, but the two are not interchangeable. For example, a subset of TMB-low metastatic NSCLC harboring certain mutational signatures still responds well to ICI, independent of PD-L1 status.<sup>14</sup>

## Inability to compare different ICI agents before starting treatment

PD-1/PD-L1, CTLA-4, and a growing number of newer targets, including lymphocyte-activation gene 3 (LAG-3) act at distinct stages of the immune response and through non-overlapping biological mechanisms. Neither CTLA-4 nor LAG-3 has a predictive biomarker to assess a tumor's potential to respond, yet LAG-3 blockade is already FDA-approved in melanoma. Translational work in melanoma has shown that CTLA-4 and PD-1 blockade produce largely distinct cellular and genomic signatures. Wei et al. demonstrated that CTLA-4 blockade predominantly expands CD4<sup>+</sup> helper T cells, while PD-1 blockade acts mainly on exhausted CD8<sup>+</sup> T cells.<sup>15</sup> Chen et al. found that responders to CTLA-4 versus PD-1 blockade showed largely non-overlapping patterns of immune gene upregulation in longitudinal tumor biopsies.<sup>16</sup> Research is needed to establish whether a single test can assess the potential for response across immunotherapy agents before treatment begins.



The absence of a comparative, mechanism-specific selection tool has implications extending beyond the treatment decision itself. A validated method for matching patients to the single-agent mechanism most likely to benefit them could support expanded indications for ICI agents. It would also give patients and clinicians a basis for weighing risk against expected benefit. For example, in melanoma, knowing in advance that a patient is more likely to respond to combined PD-1/PD-L1 + CTLA-4 blockade than to PD-1/PD-L1 blockade alone would ease the decision to accept the adverse safety profile of CTLA-4. In this sense, the unmet need is not just about matching patients to the most effective agent, but also about giving patients and clinicians the information needed to make the risk-benefit determination deliberately.

## Decision-making on post-progression re-challenge with ICI, either alone or combined with other agents

Many patients will experience disease progression after initially responding to ICI. Standard second-line therapeutic options are limited, and their utility is often extrapolated from trials performed prior to the widespread use of immunotherapy. Re-challenge with PD-1/PD-L1 inhibitors has been explored to re-engage the anti-tumor immune response. While complex mechanisms of resistance to immunotherapy make selection of a second-line treatment difficult, there is evidence of possible clinical benefit when a tumor is either re-challenged with the same mechanism of action<sup>17,18</sup> or a different mechanistic target.<sup>19</sup> Despite patients progressing on ICI or experiencing adverse events, a meta-analysis (2,343 patients, 41 studies) found that some patients still benefit from re-challenge (ORR = 19.4%).<sup>20</sup> Retrospective analyses have identified several factors associated with more favorable re-challenge outcomes, including a longer duration of first-line response, a longer treatment-free interval, and discontinuation of first-line therapy for reasons other than disease progression (eg, immune-related adverse event [irAE] management or a planned end of treatment course).<sup>18,21–23</sup> However, retrospective analysis of re-challenge strategies in different cancer types highlights the ongoing difficulty of predicting whether resistant tumors will respond to re-challenge, and no validated, prospective tool yet exists to integrate these factors into a single patient-selection framework.

Prospective identification of patients who will benefit from ICI re-challenge remains an unmet need. As in the first-line setting, PD-L1, while a valuable reference point in some cases, remains an imperfect biomarker for predicting response to re-challenge. PD-L1 expression can change over the course of first-line treatment, necessitating a dynamic approach to assess the tumor's potential to respond<sup>21</sup> (Figure 3).

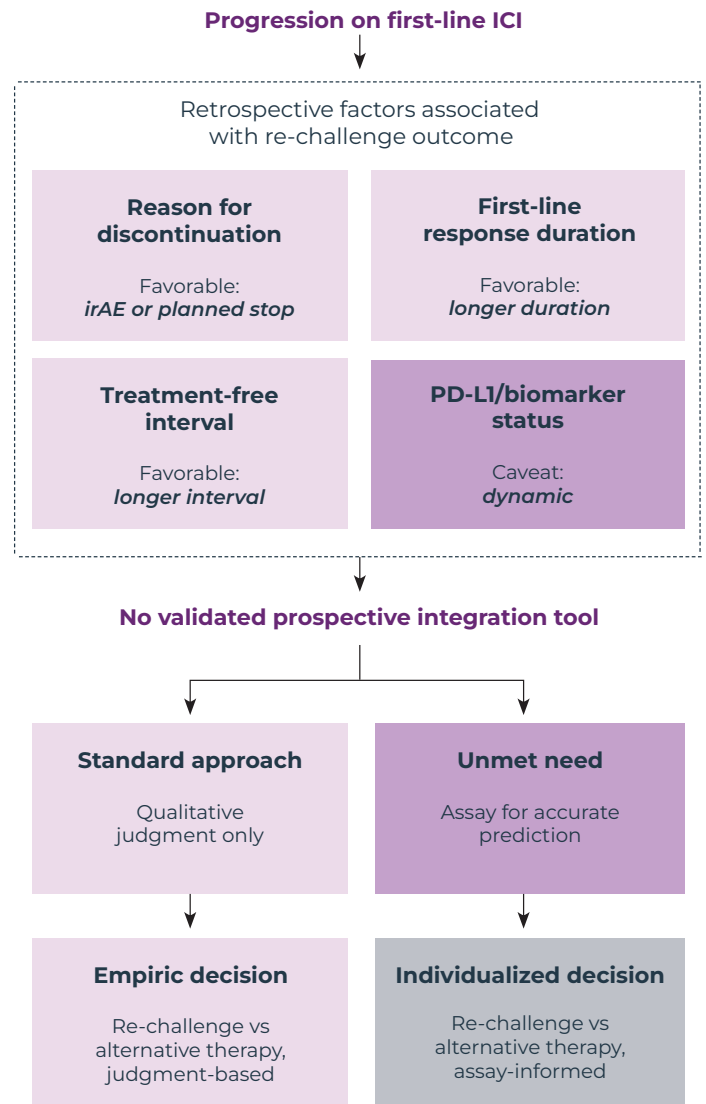


**Figure 3.** No validated tool exists to prospectively guide ICI re-challenge decisions after progression on first-line therapy. Retrospective analyses have identified factors associated with more favorable re-challenge outcomes: reason for treatment discontinuation, duration of first-line response, treatment-free interval, and PD-L1/biomarker status. No validated method integrates these factors into a prospective patient-selection framework. In the absence of such a tool, treatment decisions default to qualitative clinical judgment. An assay capable of accurately predicting re-challenge response would instead allow this decision to be individualized to each patient's tumor biology.



## Biomarker-negative patients are excluded from ICI eligibility despite evidence of response

Across the spectrum of metastatic solid tumors, the biomarkers used to guide ICI eligibility capture only some of the patients who will respond (Table 1). The following examples span CRC, NSCLC, hormone receptor positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer, endometrial cancer, esophageal squamous cell carcinoma (ESCC) and head and neck squamous cell carcinoma (HNSCC). Tumor types were included where a clinical study reported ORR for patients treated only with ICI, and where the tumor type has a biomarker-restricted FDA-approved indication for ICI. Metastatic patient counts reflect estimated US disease prevalence, not annual incidence.<sup>24,25</sup> In each, established biomarkers capture a subset of patients, excluding biomarker-negative patients who will respond.

### mCRC without liver metastases

Among patients with mCRC without liver involvement, roughly 95% are microsatellite stable (MSS) or mismatch repair proficient (pMMR),<sup>26</sup> an estimated 210,690 patients in the United States who are not eligible for ICI under current guidelines. A single-center retrospective study of patients who received either  $\alpha$ PD-1 or  $\alpha$ PD-L1 reported a 19.5% ORR in the MSS/pMMR population,<sup>27</sup> suggesting

that around 41,090 of these patients could benefit from ICI. The CCTG CO.26 trial (NCT02870920), evaluating the combination of  $\alpha$ PD-L1 (durvalumab) and  $\alpha$ CTLA-4 (tremelimumab) versus best supportive care in patients with heavily pretreated mCRC, reported an overall survival benefit for patients with MSS/pMMR tumors who received the combination ICI regimen.<sup>28</sup> Based on the results of this study, the Phase III BATMAN trial (CCTG CO.33, NCT07152821) was initiated to test the combination of  $\alpha$ PD-1 (balstilimab) and  $\alpha$ CTLA-4 (botensilimab) versus best supportive care in patients with MSS/pMMR mCRC. This trial was terminated for financial reasons rather than an efficacy or safety signal, with funds being re-allocated to the same regimen in the neoadjuvant setting for earlier-stage, resectable disease. This re-prioritization, away from the advanced/refractory setting where the diagnostic and treatment gap is most acute, underscores the need for dedicated study of ICI treatment outcomes in advanced MSS/pMMR CRC.

### NSCLC

About 57% of patients with metastatic NSCLC, 150,900 patients today, have tumors with PD-L1 TPS < 1%.<sup>29</sup> Pembrolizumab and atezolizumab monotherapy trials (KEYNOTE-001<sup>30</sup>; POPLAR/OAK<sup>31</sup>) have shown modest activity in PD-L1-negative disease (10.7% ORR<sup>30</sup>; 14-15% 4-year overall survival<sup>31</sup>), leaving an estimated 16,150 patients with PD-L1-negative NSCLC who could benefit from ICI treatment not considered based on current guidelines.

## Patients in the US with biomarker-negative metastatic cancer who could respond to ICI (from SEER prevalence data)

| Tumor type (metastatic) | ICI-ineligible biomarker/tumor type | Ineligible patients (based on prevalence) | Clinical study                    | Reported ORR | Potential # of responding patients |
|-------------------------|-------------------------------------|-------------------------------------------|-----------------------------------|--------------|------------------------------------|
| CRC (w/o liver mets)    | MSS/pMMR                            | 210,690                                   | Retrospective study <sup>27</sup> | 19.5%        | 41,090                             |
| NSCLC                   | PD-L1 TPS < 1                       | 150,900                                   | KEYNOTE-001 <sup>30</sup>         | 10.7%        | 16,150                             |
| Breast                  | HR+/HER2-                           | 118,540                                   | KEYNOTE-028 <sup>32</sup>         | 12%          | 14,230                             |
| Endometrial             | MSS/pMMR                            | 66,680                                    | GARNET <sup>34</sup>              | 15.4%        | 10,270                             |
| ESCC                    | PD-L1 CPS < 10                      | 3,770                                     | KEYNOTE-181 <sup>36</sup>         | 11.9%        | 450                                |
| HNSCC                   | PD-L1 CPS < 1                       | 8,300                                     | KEYNOTE-048 <sup>38</sup>         | 4.5%         | 370                                |
| <b>Total</b>            |                                     | <b>558,880</b>                            |                                   |              | <b>82,560</b>                      |

**Table 1.** Estimated US disease prevalence of patients without an actionable biomarker for ICI consideration, and those who could benefit by tumor type. For each tumor type, the "ICI-ineligible biomarker/tumor type" column defines the biomarker or tumor type without an FDA-approved ICI indication, and "Ineligible patients" reflects how many patients fall outside of biomarker-guided ICI eligibility. "Reported ORR" is the objective response rate of biomarker-negative cohorts from the published clinical trial data. "Potential # of responding patients" is the number of ineligible patients multiplied by reported ORR.



## HR+/HER2- metastatic breast cancer

HR+/HER2- breast cancer, which makes up approximately 70% of all metastatic breast cancer diagnoses<sup>24</sup> (an estimated 118,540 patients), is immunologically cold and unlikely to respond to ICI. This subgroup of breast cancer does not qualify for ICI treatment based on current guidelines. Despite this, the KEYNOTE-028 trial<sup>32</sup> of pembrolizumab in patients with HR+/HER2- advanced breast cancer showed an ORR of 12%. Although this represents a proportionally small subset of responders, it suggests that roughly 14,230 patients with metastatic breast cancer who are likely to respond to ICI are not eligible based on current guidelines.

## Endometrial cancer

Patients with MSS/pMMR endometrial cancer are currently excluded from ICI monotherapy indications, an estimated 66,680 patients in the United States.<sup>33</sup> The Phase I GARNET trial of dostarlimab monotherapy enrolled a cohort of MSS/pMMR patients alongside the MSI-H/dMMR cohort that supported initial approval and reported a 15.4% ORR in the pMMR population.<sup>34</sup> These results suggest that 10,270 patients with MSS/pMMR endometrial cancer could derive some benefit from ICI monotherapy despite falling outside the approved biomarker population.

## ESCC

ESCC is a less common but difficult-to-treat population, with an estimated 3,770 patients who are ineligible based on the current PD-L1 CPS  $\geq 10$  cutoff for pembrolizumab monotherapy.<sup>35</sup> The KEYNOTE-181 trial comparing pembrolizumab versus chemotherapy in metastatic ESCC showed an 11.9% ORR in the CPS  $< 10$  subgroup of the pembrolizumab cohort,<sup>36</sup> suggesting roughly 450 CPS  $< 10$  patients could still see benefit despite falling outside the approved threshold.

## HNSCC

HNSCC follows a similar pattern in the recurrent/metastatic setting. An estimated 8,300 patients with PD-L1 CPS  $< 1$  are ineligible for pembrolizumab monotherapy in the metastatic setting,<sup>37</sup> though KEYNOTE-048 showed a 4.5% ORR in this population<sup>38</sup> (roughly 370 patients who could benefit). The same CPS  $\geq 1$  threshold now also governs eligibility for the 2025 KEYNOTE-689-based neoadjuvant/adjuvant approval.<sup>39</sup> As perioperative ICI becomes standard of care for this CPS  $\geq 1$  population, patients with PD-L1-negative tumors remain ineligible.

## Clinical equipoise complicates ICI decision-making

Across landmark clinical trials, ICIs have generally demonstrated favorable safety profiles. However, many patients seen in routine practice would have been ineligible for those trials and were excluded from the safety and efficacy data that now informs standard use. As a result, uncertainty remains in managing patients with immune dysregulation, whether from autoimmune disease or post-transplant immunosuppression, or with liver metastases, which are associated with reduced ICI efficacy. Identifying which of these patients may still respond favorably to ICI therapy with an acceptable risk/benefit profile remains a significant unmet need in clinical practice today. The optimal degree of chemotherapy de-escalation following the addition of ICI to a regimen remains similarly undefined, despite its direct implications on patient risk and treatment burden.

## Opportunity for ICI use in patients with immune dysregulation due to autoimmune disease or transplant-related immune suppression

For patients with pre-existing autoimmune disease, there is concern that further immune stimulation with ICIs could exacerbate the underlying condition or lead to severe irAEs. A substantial portion of the population lives with autoimmune disease, and data on tolerability of ICI in these patients remain limited. Retrospective studies have shown that patients with pre-existing autoimmune disease, especially those not requiring high-dose steroids to manage disease, respond to ICI treatment at rates similar to those described in landmark clinical studies.<sup>40,41</sup> While irAEs occurred in a subset of these patients, the adverse events were easily resolved in most cases. These data underscore the need for individualized approaches to treatment selection rather than broad exclusion by convention.

Patients who undergo organ transplantation face an elevated risk of developing cancer, due in part to the immunosuppression required to maintain the graft. Treatment with ICIs in these patients may increase risk of transplant rejection. While prospective studies of ICI safety and efficacy in transplant recipients are lacking, a systematic review and individual-patient-data meta-analysis of 343 transplant recipients who received ICI therapy found that the objective response at 1 year was 31.6%.<sup>42</sup>



This is comparable to responses seen in patients who had not received transplants. Response varied by tumor type,<sup>42</sup> with patients with cutaneous squamous cell carcinoma (cSCC) achieving higher ORRs near 70%. Acute rejection occurred in 36.2% of patients and graft loss in 18.4%, with melanoma carrying a higher risk than cSCC<sup>42</sup>; however, emerging evidence suggests this risk can be mitigated to some degree. For example, maintenance immunosuppressive regimens built around mTOR inhibitors have been associated with lower risk of transplant rejection during ICI treatment.<sup>43</sup> These data indicate that transplant-related immunosuppression attenuates, but does not eliminate, the case for ICI therapy, reinforcing that exclusion by convention does not always track with demonstrated lack of benefit.

### **Organ-specific immune tolerance reduces, but does not eliminate, ICI benefit in patients with liver metastases**

ICI efficacy is measurably lower across tumor types when liver metastases are present.<sup>44-46</sup> The liver is an inherently tolerogenic organ, and liver metastases have been shown to drive systemic depletion of tumor-specific T cells,<sup>47</sup> offering a plausible mechanistic basis for reduced ICI response in this population. There are still cases in which patients with liver metastases respond to ICI. A secondary analysis of the CCTG CO.26 study of  $\alpha$ PD-L1 (durvalumab) plus  $\alpha$ CTLA-4 (tremelimumab) in MSS/pMMR mCRC found that while patients with liver metastases did not experience an overall survival benefit, the treatment was associated with improved progression-free survival and disease control rate.<sup>48</sup> Further, a meta-analysis of 30 randomized controlled trials and observational studies of ICI for advanced lung cancers found that both patients with small cell and non-small cell lung cancer with liver metastases benefited from ICI treatment, although the magnitude of benefit was lower than in patients without liver metastases.<sup>46</sup>

### **Chemotherapy de-escalation lacks a biomarker to guide patient selection**

ICI therapy is frequently administered in combination with chemotherapy. Improved methods for predicting response to ICI monotherapy could reduce chemotherapy exposure in patients unlikely to require it. Across tumor types, however, de-escalation strategies still rely on proxies (clinical risk stratification, pathologic response, or PD-L1 expression) rather than a biomarker that directly identifies the patients for whom ICI monotherapy is sufficient.

The two examples below, in NSCLC and breast cancer, illustrate this gap, and underscore that strong evidence is needed before a therapy is removed from a standard regimen.

In NSCLC with high PD-L1 expression (TPS  $\geq$  50), single-agent PD-1/PD-L1 blockade is an established first-line option, sparing chemotherapy in this biomarker-selected subgroup. However, network meta-analyses comparing ICI monotherapy with chemo-ICI combinations in this population report improved ORR and progression-free survival with the addition of chemotherapy.<sup>49</sup> Real-world comparative effectiveness data similarly suggest an incremental benefit from chemo-immunotherapy over monotherapy, with magnitude varying across patients,<sup>50</sup> suggesting that PD-L1 expression identifies candidates for chemotherapy omission imperfectly.

De-escalation strategies in breast cancer have focused on reducing chemotherapy intensity within chemo-ICI regimens. The KEYNOTE-522 regimen of carboplatin and paclitaxel followed by anthracycline/cyclophosphamide, combined with perioperative pembrolizumab, is standard of care for stage II-III triple-negative breast cancer, but is associated with substantial toxicity, with only a subset of patients benefiting from the added chemo-immunotherapy. The Phase II NeoPACT trial evaluated an anthracycline-free regimen of carboplatin and docetaxel plus pembrolizumab. This study reported a 58% pathologic complete response rate and substantially reduced toxicity.<sup>51</sup> However, as a single-arm Phase II study, NeoPACT does not establish equivalence to the KEYNOTE-522 regimen. The randomized evidence needed to de-escalate with confidence is not yet available, and in its absence a more reliable biomarker of ICI-monotherapy sufficiency is needed to justify removing a component of a proven regimen.

## **Conclusion**

These five gaps reflect a common limitation: PD-L1, TMB-H, and MSI-H/dMMR are static, indirect measures of a dynamic biological process, and for many tumor types, no biomarkers exist at all. The same limitation applies to mechanism selection, re-challenge, and to high-risk populations where standard biomarkers offer little insight into risk-adjusted benefit. Regulatory movement toward functional, direct-measurement approaches has begun.



In July 2026, the American Society of Clinical Oncology (ASCO) clarified that its 2004 and 2011 guidance restricting ex vivo tumor sensitivity testing (based on the technical limitations of that era's assays) is archived, inactive, and should not be used to limit clinical or insurance access to modern functional platforms.<sup>52</sup> ASCO describes modern platforms as including automated high-throughput and 3D culture systems that recapitulate tumor heterogeneity and microenvironment, with feasibility demonstrated

using standard-of-care biopsy formats (core needle biopsy, fine needle aspirates, liquid biopsy). ASCO stopped short of recommending for or against clinical use of these assays, noting a still-maturing evidence base. This clarification underscores the relevance of tools capable of addressing the over 500,000 US patients who fall outside of current ICI eligibility, along with the additional gaps in re-challenge, mechanism selection, and at-risk populations that static biomarkers were not designed to resolve.

## Functional insights into the tumor microenvironment

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