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REVIEW

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Light on life: immunoscore immune-checkpoint, a predictor of immunotherapy response

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ABSTRACT

In the last decade, a plethora of immunotherapeutic strategies have been designed to modulate the tumor immune microenvironment. In particular, immune checkpoint (IC) blockade therapies present the most promising advances made in cancer treatment in recent years. In non-small cell lung cancer (NSCLC), biomarkers predicting response to IC treatments are currently lacking. We have recently identified Immunoscore-IC, a powerful biomarker that predicts the efficiency of immune-checkpoint inhibitors (ICIs) in NSCLC patients. Immunoscore-IC is an in vitro diagnostic assay that quantifies densities of PD-L1+, CD8+ cells, and distances between CD8+ and PD-L1+ cells in the tumor microenvironment. Immunoscore-IC can classify responder *vs* non-responder NSCLC patients for ICIs therapy and is revealed as a promising predictive marker of response to anti-PD-1/PD-L1 immunotherapy in these patients. Immunoscore-IC has also shown a significant predictive value, superior to the currently used PD-L1 marker. In colorectal cancer (CRC), the addition of atezolizumab to first-line FOLFOXIRI plus bevacizumab improved progression-free survival (PFS) in patients with previously untreated metastatic CRC. In the AtezoTRIBE trial, Immunoscore-IC emerged as the first biomarker with robust predictive value in stratifying pMMR metastatic CRC patients who critically benefit from checkpoint inhibitors. Thus, Immunoscore-IC could be a universal biomarker to predict response to PD-1/PD-L1 checkpoint inhibitor immunotherapy across multiple cancer indications. Therefore, cancer patient stratification (by Immunoscore-IC), based on the presence of T lymphocytes and PD-L1 potentially provides support for clinicians to guide them through combination cancer treatment decisions.

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Introduction

The immune microenvironment is a key player in cancer development and progression. Landmark advances in immunotherapy have recently shown the potential to harness the immune system to fight cancer. In particular, immune biomarkers of response to checkpoint immunotherapy provide valuable insights into patient responsiveness to treatment.[1]

The immune microenvironment is a complex network that includes a wide variety of immune cells, as well as fibroblasts, cytokines, chemokines, and extracellular matrix proteins. These components highly interact with each other and with tumor cells to modulate cancer growth and progression.[2] In some cases, the immune system recognizes and attacks cancer cells, leading to tumor regression. In other cases, the immune system fails to react to cancer cells, allowing tumors to escape and thus grow unchecked.[3]

T-cell, a type of white blood cell, is a critical component of the immune response to cancer.[4–8] They attack cancer cells by recognizing specific antigens expressed on their surface. Once they encounter these antigens, T-cells become activated; then, they proliferate and migrate to the tumor site. At this location, T-cells either directly kill cancer cells or secrete cytokines that, in turn, recruit other immune cells to attack the tumor.[9–11]

However, cancer cells have evolved various mechanisms to suppress or evade the immune system. These processes are mediated by the downregulation of the expression of antigens or the inhibitory receptors present on T-cells.[1,12] One way by which cancer cells evade the immune system is by overexpressing immune checkpoint (IC) proteins like PD-L1, which interact with T-cell receptors to inhibit their activity. By blocking T-cell activity, cancer cells evade immune surveillance and promote their own growth and survival.

The checkpoint immunotherapy employed in clinical practice consists of monoclonal antibodies that block the interaction between IC proteins and T-cells, thereby releasing the brakes on the immune response to cancer. Immune checkpoint inhibitors (ICI) have shown remarkable potency in treating various types of cancers, including melanoma, lung cancer, bladder cancer, and others.[13] These immunotherapy treatments are effective when employed as mono-immunotherapy. Moreover, they can be combined with other treatment modalities for improved efficacy.[1,14–30]

However, not all patients respond to checkpoint immunotherapy. Thus, identifying biomarkers of response is critical to optimize treatment outcomes. Biomarkers of response to checkpoint immunotherapy can provide valuable information on the likelihood of response to treatment and help guide treatment decisions.[1,31]

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One significant biomarker of response to checkpoint immunotherapy is PD-L1 expression.[32] Tumors that express high levels of PD-L1 are more likely to respond to ICIs, as the inhibition of the PD-L1/PD-1 interaction is likely a critical mechanism of action for these drugs. Nevertheless, PD-L1 expression is not always predictive of response to checkpoint immunotherapy. Multiple other factors like the tumor mutational burden (TMB), microsatellite instability (MSI), and T-cell infiltrates in the tumor microenvironment (TME) also stand as powerful biomarkers of response to IC blockade.[33,34]

TMB refers to the total number of mutations present in the DNA of tumor cells. Tumors with high TMB presumably better respond to checkpoint immunotherapy, as they may produce more neoantigens that can be recognized by T-cells. MSI is due to a defect in the DNA mismatch repair (MMR) system resulting in an accumulation of mutations, in particular frame-shift mutations that are immunogenic. These frameshift peptides can be identified by specific T-cells. As MSI patients generally present natural high cytotoxic T-cell responses,[9–11] they are prone to respond efficiently to immunotherapy approaches.[35] Similarly, the presence of T-cell infiltrates in the TME is thought to be predictive of response, as tumors infiltrated by high density of T-cells are more immunogenic and more likely to respond to IC inhibitors.

A large spectrum of predictive biomarkers of response to checkpoint immunotherapy have been gradually explored. This includes the expression of immune gene signatures or other IC proteins, TIM-3 and LAG-3, that reflect a T-cell exhaustion state that could be reversed by ICIs.[1] CXCL9 and CXCL10 chemoattractants also emerged as predictive markers of response to immunotherapy, since their expression reactivates preexisting intratumoral T cells after IC Blockade.[36–38] CXCL10 expression has also been correlated with better response to ICIs.[39] Additionally, the presence of tumor-infiltrating lymphocytes (TILs), tertiary lymphoid structures (TLS) or the expression of interferon-gamma cytokine, tumor inflammation signature (Tis), Th1 signatures, or Th1 infiltrating cells are promising response biomarkers (Figure 1, Table 1)[1,31,34,40,41]

Immunoscore immune-checkpoint (Immunoscore-IC) in non-small-cell lung cancer (NSCLC)

The survival of cancer patients is significantly associated with Tumor-infiltrating immune cell subpopulations, like cytotoxic T cells. In solid tumors, the immune contexture determines the clinical outcomes and is remarkably associated with immunotherapy responses. Immunoscore (IS) is the first worldwide standardized consensus assay that classifies tumors into cold and hot immune categories, based on the densities of infiltrating CD3+ and CD8+ T-cells. IS has been shown to be clinically useful in predicting the response to chemotherapy in colon cancer patients. Although anti-PD-(L)1 IC therapy has been approved for NSCLC patients, a substantial proportion of patients do not respond to it. Hence, prognosis biomarkers are highly desirable to select appropriate patients for this treatment. PD-L1 expression alone is an imperfect biomarker, and TMB or the combination of TMB and high-PD-L1 expression outperform PD-L1 alone as predictive biomarkers. Additional enrichment of the response in PD-L1+ population may be needed to assess whether PD-L1 is expressed in an adaptive rather than a constitutive manner.

It has been recently shown that the Immunoscore-IC is a potent predictive biomarker of response to anti-PD-1/PD-L1 immunotherapy.[42] Moreover, the positive impact of ICIs therapy is far greater in patients with high Immunoscore-IC, compared to low Immunoscore-IC patients. Immunoscore-IC is a fast and simple standardized assay run on a single FFPE slide, allowing the identification

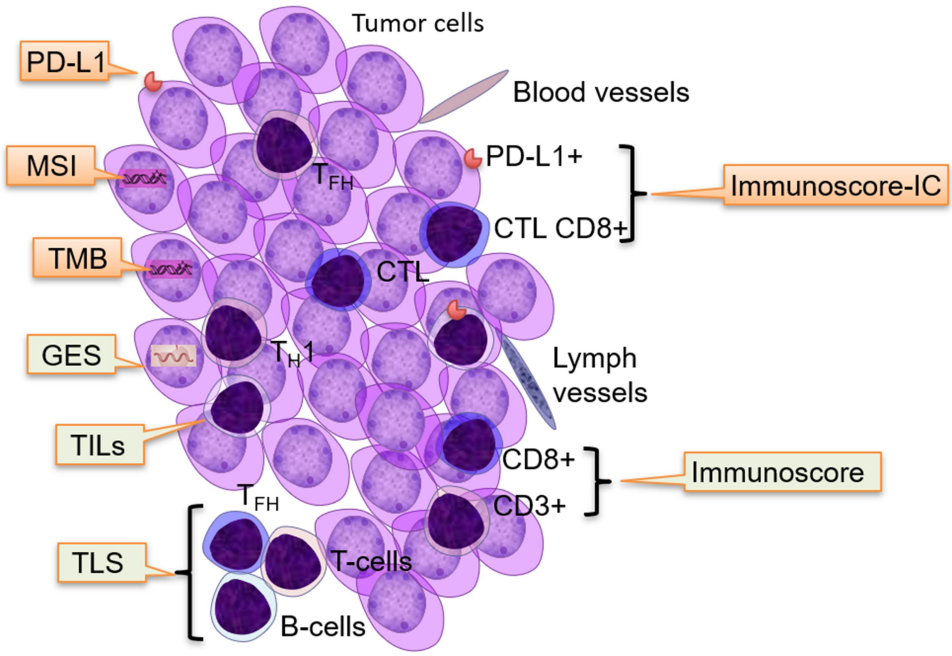

Figure 1. Predictive biomarkers of response and/or survival in patients receiving immune checkpoint immunotherapy. MSI: microsatellite instability, TMB: Tumor mutational burden, GES: gene expression signature, TILs: tumor-infiltrating lymphocytes, TLS: Tertiary lymphoid structures, Immunoscore-IC: digital pathology of CD8+/PD-L1+ cells, Immunoscore: digital pathology of CD3+/CD8+ cells.

Table 1. List of available biomarkers used in immuno-diagnostic assays to predict the response to immunotherapy in cancer patients. For each assay, a description of the technology used, its type, and status are provided. Abbreviations: MSI: Microsatellite instability, PD-L1: Programmed cell Death-Ligand 1, TILs: Tumor Infiltrating lymphocytes, Tis: Tumor infiltration signature, TLS: Tertiary Lymphoid structures, TMB: Tumor mutational burden, IHC: Immunohistochemistry, CDx: Companion Diagnostics, RUO: Research use only.

Assays	technology	Type	Status
MSI	IHC/genomic	Qualitative	CDx approved
TMB	ExomeSeq	Quantitative	CDx approved
PD-L1	IHC	Semi- quantitative	CDx approved
Immunoscore-IC	digital pathology	Quantitative	RUO
Immunoscore	digital pathology	Quantitative	RUO
TILs	IHC	Semi- quantitative	RUO
Tis	Gene expression	Quantitative	RUO
TLS	IHC	Qualitative	RUO
Multiplex IHC	digital pathology	Quantitative	RUO

of responder *vs* non-responder NSCLC patients for ICIs therapy. Immunoscore-IC has a predictive value superior to the currently used PD-L1 solo-staining, which could guide clinicians in the treatment decision-making strategies (Figure 2).

Progression-free survival (PFS) and overall survival (OS) analyses showed that patients treated with ICIs had similar outcomes when only accounting for PD-L1 Tumor Proportion Score (TPS) assessed by pathologists. In contrast, Immunoscore-IC predicted response and significant survival differences for PFS and OS.[42] Using continuous variables of Immunoscore-IC parameters, significant univariate associations with survival were observed for both training and validation cohorts. In the training set ($n = 132$ patients), analyzing Immunoscore-IC in the two-category (High/Low) or three categories (High/Int/Low) allowed the identification of patients with very significantly ($p < 0.0001$) distinct clinical outcome for PFS and OS. In the two-categories Immunoscore-IC, patients with high Immunoscore-IC were long-term survivors of PFS and OS, whereas all (100%) of low Immunoscore-IC patients relapsed within 18 months and died before 30 months following immune checkpoint immunotherapy. In the three-category Immunoscore-IC, strong hazard ratio between high Immunoscore-IC and low Immunoscore-IC was observed with HR = 0.24 and HR = 0.26 for PFS and OS, respectively ($p < 0.0001$).

Similar significant results were observed between Immunoscore-IC and patient's survival in an independent validation cohort of 133 patients, for two- or three-category Immunoscore-IC both for PFS and OS. In the three-category Immunoscore-IC, PFS at 24 months was seen in 0% of the patients with low Immunoscore-IC, in 15% patients with an intermediate Immunoscore-IC and in 31% patients with high Immunoscore-IC. A strong hazard ratio between high Immunoscore-IC and low Immunoscore-IC was also observed with HR = 0.34 and HR = 0.36 for PFS and OS, respectively ($p < 0.005$).[42] Thus, the response and survival following immune checkpoint immunotherapy were far greater for high Immunoscore-IC patients than they were for low Immunoscore-IC patients.

First, Immunoscore-IC is a potent quantitative and predictive assay for response to anti-PD-1/PD-L1 immunotherapy. Second, it identifies responder *vs* non-responder NSCLC patients for ICIs therapy. Third, it was demonstrated as a highly standardized and reproducible assay. Fourth,

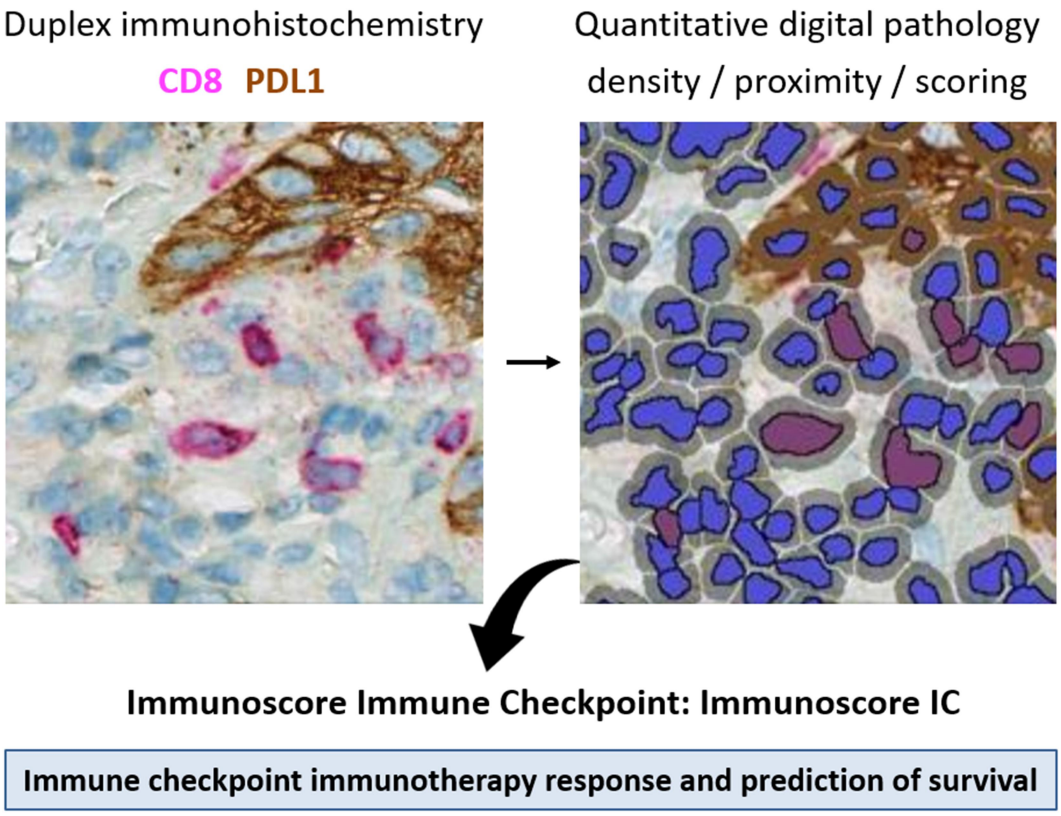

Figure 2. Immunoscore-IC assay. Duplex chromogenic immunohistochemistry on a single FFPE slide. Representative IHC staining of tumors with CD8 and PD-L1 antibodies, before (left) and after (right) digital pathology detection. Immunoscore-IC scores are generated using densities and proximities of CD8 and PD-L1 cells.

Immunoscore-IC has a significant predictive value superior to the currently used PD-L1 solo-staining and therefore could guide clinicians to choose between chemotherapy, ICIs mono-immunotherapy, or combination immunotherapy. However, this study has several limitations, and it is of interest to validate the predictive value of the Immunoscore-IC on larger cohorts of NSCLC patients within randomized clinical trials and other cancer types.[42] Additional efforts are needed to reveal the cell type expressing PDL-1, in addition to the essential implementation of digital slides in clinical practice. Innovative characterization of the TME with a focus on multidimensional, spatially resolved interactions at a cellular level will provide critical mechanistic insights into therapeutic responses. This approach can potentially identify improved biomarkers for patient selection. Whole-slide image scanning and digital pathology (DP) of several markers have paved the way for the development of immune contexture signatures as well as its implementation in hospital-hubs.[43] Besides, pathologists are less reluctant to the idea of using quantitative assessment tools. Furthermore, the employment of DP becomes more common, hence the applications of Immunoscore-IC may become even more prevalent.

In summary, the study shows that Immunoscore-IC is a promising predictive marker of response to anti-PD-1/PD-L1 immunotherapy in NSCLC patients.[42] However, more investigations are needed to validate it on larger cohorts of patients and to standardize the assay's procedures. These findings have raised the critical need for a multidimensional, spatially resolved approach to TME to identify improved biomarkers for patient selection in the era of personalized medicine.

Immunoscore immune-checkpoint in colorectal cancer (CRC)

The AtezoTRIBE study has successfully demonstrated that the addition of atezolizumab to first-line FOLFOXIRI plus bevacizumab may prolong the PFS of patients with metastatic CRC.[44] This trial that included patients with deficient mismatch repair (dMMR) and proficient mismatch repair (pMMR) tumors did not reveal safety concerns for this experimental combination. While outstanding clinical trial results support the use of immunotherapy as an upfront strategy in dMMR metastatic CRC patients, adding chemotherapy to checkpoint inhibitors in the first-line treatment is under evaluation in an ongoing clinical trial.

The study was particularly relevant to the patient subgroups bearing pMMR tumors. Applying the same statistical hypothesis used to calculate the trial sample size, this study would have also met its primary endpoint in this subgroup, thus confirming signals of efficacy of the experimental strategy. Importantly, Immunoscore-IC-high pMMR patients, representing 32% of the population, had a strong and significant PFS benefit when receiving the combination immunotherapy, compared to the standard of care arm.[44]

Multiple negative immunotherapy trials have been performed in CRC; however, these did not consider the preexisting immunity.[45] Disappointing results from previous trials combining atezolizumab and bevacizumab with a fluoropyrimidine in pre-treated patients make the results of the AtezoTRIBE study significant.[46,47] This seems to support the role of a more intensive chemotherapy in a previously untreated setting, which may enhance the antitumor effect of checkpoint inhibitors by increasing tumor immunogenicity.

While recent studies have failed to demonstrate significant PFS by adding nivolumab to first-line FOLFOX plus bevacizumab, both in the intention-to-treat population and in patient subgroup with pMMR tumors, PFS curves suggest that a subgroup of pMMR patients may still achieve prolonged disease control with AtezoTRIBE experimental treatment.[48] This has led us to further investigate the predictors of benefit from the addition of checkpoint inhibitors to first-line therapy in this patient subgroup.

In several biomarker studies, Immunoscore-IC is consistently revealed as a robust marker to predict response and survival, particularly in pMMR patients.[44,49,50] According to the AtezoTRIBE study, both TMB and Immunoscore-IC emerge as promising biomarkers for this purpose, with TMB-high and Immunoscore-IC high tumors being more likely to benefit from the addition of atezolizumab. However, the rarity of pMMR metastatic CRC with >10 mut/Mb makes it difficult to draw conclusions about this small subgroup. The independent impact of Immunoscore-IC and TMB was shown in the multivariable models in the intention-to-treat population. In the pMMR subgroup, the very limited sample size of TMB-high patients makes it controversial to include this feature in a multivariable model. Remarkably, in multivariable analysis, Immunoscore-IC was the best predictor of benefit from the addition of atezolizumab in this subgroup.

In this study analysis ($n = 216$ patients), the Immunoscore-IC pass rate was 100%, disclosing therefore the feasibility of this test.[44] Immunoscore-IC High represented a large proportion (32%) of MSS patients, who display strong and significant survival benefits when receiving combination-immunotherapy (HR = 0.35 [95% CI 0.16–0.73], $P < 0.001$). Kaplan Meier estimates of PFS in the pMMR subgroup (MSS patients) based on Immunoscore-IC revealed prolonged survival only in patients with Immunoscore-IC-High in the combination-immunotherapy arm. The median PFS of Immunoscore IC-low in the standard of care arm or in the combination-immunotherapy arm was up to 12 and 11 months, respectively. The median PFS of Immunoscore IC-high in the standard of care arm was also up to 9 months. In contrast, the median PFS of Immunoscore IC-high in the combination-immunotherapy arm was not reached and is superior to 25 months. A recent report at the ASCO meeting 2023 confirmed these results for overall survival (OS). This demonstrates the predictive value of Immunoscore-IC for response to combination-immunotherapy in first-line pMMR metastatic CRC.[44]

The distribution of tissue biomarkers (MMR, TMB, and Immunoscore-IC) in 119 patients with paired data available revealed that only 7% of them were dMMR (MSI), 13% were TMB-high, with a large overlap since 62% of TMB-high patients were dMMR, and 89% of dMMR patients were also TMB-high (Figure 3). Thus, dMMR and TMB-high represented a minority of metastatic CRC patients, where most of them were Immunoscore-IC-High. Most (93%) metastatic CRC patients were pMMR patients. Among these pMMR patients, only 6% had a TMB-high, whereas Immunoscore-IC-High represented a large group (32%). Among TMB-high patients in the pMMR group, a majority (71%) were also Immunoscore-IC-High. Thus,

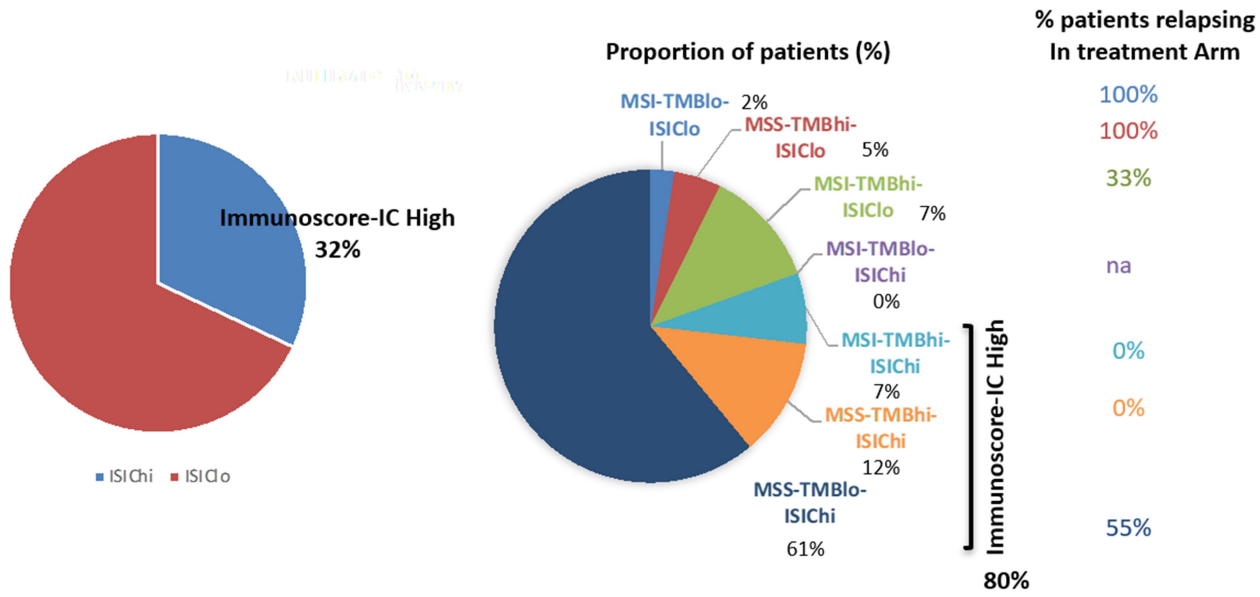

Figure 3. Proportion of immunoscore-IC-High and Immunoscore-IC-Low (left) in metastatic colorectal cancer patients from AtezoTribe trial. Proportion (%) of patients according to MMR, TMB and immunoscore-IC status. Proportion (%) of patients relapsing in the treatment arm for each category (right).

most dMMR (MSI) or TMB-high patients are also Immunoscore-IC-High. Most importantly, 94% of the patients were TMB-low in the pMMR subgroup, and a vast majority (83%) of Immunoscore-IC-High patients in this subgroup were TMB-low. Strikingly and interestingly, in the dMMR (MSI) patients, all patients (100%) without relapse had an Immunoscore-IC-High, whereas all patients (100%) with a relapse had an Immunoscore-IC-Low. Furthermore, in the pMMR (MSS) patients with a TMB-High, all patients (100%) with a relapse had an Immunoscore-IC-Low. Thus, according to biomarkers' distribution, 32% of pMMR patients are Immunoscore-IC-High and could be eligible for this combination immunotherapy treatment.

While the post-hoc nature of the analysis is a limitation of the findings, Immunoscore-IC stands as the first biomarker with potential predictive value in stratifying pMMR metastatic CRC patients who benefit from checkpoint inhibitors. The results are highly consistent from a biological perspective since Immunoscore-IC is a synthetic measure of CD8+ T lymphocyte infiltration, PD-L1+ cell abundance, and the proximity between PD-L1+ and CD8+ cells. The independent predictive impact of Immunoscore-IC on the overall population, shown in the multivariable model including MMR status and TMB, supports the relevance of this tool to evaluate tumor immunogenicity.

In summary, the AtezoTRIBE study demonstrated that the addition of atezolizumab to first-line FOLFOXIRI plus bevacizumab may prolong the PFS of patients with pMMR metastatic CRC, especially in the subgroup with high Immunoscore-IC tumors.[44] PD-L1 expression has been approved as companion diagnostics (CDx) (Table 1) or recommended in multiple indications for patients treated with checkpoint PD-1/PD-L1 immunotherapy, including NSCLC, squamous and non-squamous lung cancer, melanoma, and bladder and gastrointestinal cancers. Furthermore, the good prognostic value of CD8+ T-cells was demonstrated in multiple cancer indications, such as colorectal, breast, gastric, hepatocellular carcinoma, pancreatic cancer, lung, melanoma, ovarian, bladder, head and neck, thyroid, biliary tract, and Merkel cell carcinoma.[2,51,52] Thus, Immunoscore-IC that quantifies both CD8+ and PD-L1+ could be a universal biomarker to predict response to PD-1/PD-L1 checkpoint inhibitor immunotherapy across multiple cancer indications.

Immunoscore immune-checkpoint, a potential universal biomarker for immunotherapy

We previously developed the Immunoscore, a biomarker that allows us to measure the densities of CD3+ and CD8+ lymphocytes in the tumor center and its invasive margin.[53] Based on these immune parameters, Immunoscore classifies tumors into categories, while providing powerful prognostic information on treatment outcomes.[1] In CRC patients, Immunoscore robustly predicts tumor recurrence. It also presents a significant predictive value for patients' response to chemotherapy and radiochemotherapy. Similarly, Immunoscore-IC exhibited high prognostic value and allowed to predict tumor recurrence. However, Immunoscore-IC specifically quantifies the densities of PD-L1+, CD8+ cells, and distances between CD8+ and PD-L1+ cells in the tumor microenvironment. Immunoscore-IC was revealed as a powerful predictive biomarker for the response to combination immunotherapy in metastatic CRC patients and to ICI therapy in NSCLC. Thus, an Immunoscore-IC assay can guide patient selection with high-risk clinical features and highest chances of response to ICI therapy.[42] Immunoscore-IC also presented a predictive value superior to the currently used MSI status or PD-L1 solo-staining,[42] thus it could guide clinicians to choose appropriate treatment for NSCLC[42] and CRC patients.[44]

Herein, we describe four distinct mechanistic subgroups of patients who emerged according to CD8 and PD-L1 categories.[54]

Type I cancers, characterized by PD-L1+ expression and tumor-infiltrating lymphocytes (TILs), are shown to be highly responsive to checkpoint blockade in advanced melanoma.

These tumors potentially benefit from single-agent anti-PD-1/PD-L1 therapy, due to their preexisting intratumor T-cells that can be turned off by PD-L1 engagement. However, the density and location of TILs and their interaction with PD-L1 positive TME need to be considered. In addition, a quantitative assessment of TILs and PD-L1 in biopsies is necessary to derive the desired predictive information. Anti-PD-1 may be substituted or combined with various anti-PD-L1 mAbs to enhance antitumor efficacy. However, their combination may also increase the chances of toxicity, as shown in patients treated with nivolumab who displayed an increased risk of pneumonitis. Other targets like LAG-3, TIGIT, and TIM-3, commonly co-expressed in the TME, in activated and potentially exhausted T-cells, may be tested in type I tumors and other cancer types, where TILs are present but anti-PD-1/PD-L1 are ineffective. Agonizing T and antigen-presenting cell function via costimulatory molecules and toll-like receptors also have great merit in these cancers, enriched with TILs that are potentially functional.

Melanoma patients, with Type II TME lacking detectable immune reactions, have poor prognosis and are unlikely to benefit from single-agent checkpoint blockade. Among combination therapies, anti-CTLA-4 and anti-PD-1 could be effective, as they enhance tumor T-cell infiltration and boost their activity. Recent clinical trials combining these checkpoint inhibitors reported high response rates and improved overall survival in advanced melanoma patients. This highlights the critical importance of combination approaches in increasing antitumor efficiency. Another therapeutic strategy is to induce a Type I IFN response to attract T-cell infiltrates into tumors. Several approaches based on tumor T-cell recruitment, like vaccination or adoptive transfer, might also be useful in the case of tumor-associated antigen expression.

Type III cancers, which express PD-L1 but lack TILs, may not show a response to anti-PD-1 or anti-PD-L1 therapies. In this case, common therapeutic modalities applied on Type II cancers could be in use.

Type III TME is found in only 1% of melanoma patients but may be more common in other cancers, like NSCLC. This occurs when PD-L1 is constitutively expressed in cancer cells through oncogenic signaling. PD-L1 positivity is not the unique reliable predictor of response to anti-PD-1 or anti-PD-L1 therapies, as TILs are also key players for T-cell response to cancer. In this patient group, radiotherapy can be used in combination with anti-PD-1 to induce immunogenic cell death and T-cell responses.

Type IV cancers feature a Type I TME with no obvious adaptive resistance. Targeting non-PD-1/PD-L1 checkpoint receptors, immunosuppressive pathways, and non-T-cell effector strategies are potential effective therapies for these patients. Currently, these approaches remain very preliminary; however, several will likely be introduced into clinical practice in the near future.

Further stratification of these markers (by Immunoscore-IC) was based on the spatial distribution of immune infiltration (immune contexture), distance between CD8+ cells and proximity of PD-L1+ cells to CD8+ T-cells, together with the densities of CD8+ and PDL1+ cells. The advantage of this approach is to generate a continuous score, with the possibility of using the same assay for different cancer types or for immunotherapy treatments. However, one potential limitation could be related to the cut-off of Immunoscore-IC, which may change in function of the tumor type, an aspect that remains to be prospectively determined.

Conclusion

There are multiple challenges facing the development of a biomarker that can guide treatment decisions in cancer patients[55]. Although immune gene signatures have been identified, no pretreatment biomarker has been validated yet. However, a tumor stratification based on the presence of T cells and PD-L1 could provide a starting framework to consider various combination cancer therapy approaches. This stratification will likely require more complex quantitative and special determination techniques to be used as highly predictive tools. The use of imaging technologies can also help determine tumor-infiltrating lymphocytes and the temporal expression of immunosuppressive pathways. New checkpoint blockade pathways that complement PD-1/PD-L1 interactions hold great promise for improving responses in type I tumors displaying adaptive resistance. However, a large fraction of tumors with an immune ignorant phenotype (type II) have a very poor prognosis. Thus, effective vaccination or neoantigens may be required to apply immunotherapy to patients bearing these tumors. Ultimately, a simple rational patient stratification is initially recommended to ensure the economic development of combination therapies that increasingly incorporate immunology.

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Disclosure statement

JG has patents associated with immune prognostic biomarkers and immunotherapies. JG is co-founder of HalioDx Biotech Company, a Veracyte company and has part-time employment at Veracyte. Immunoscore® a registered trademark from the National Institute of Health and Medical Research licensed to Veracyte.

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