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The Immunoscore: Colon Cancer and Beyond

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ABSTRACT

Tumors evolve in close interaction with their microenvironment, which encompasses a continual tension between the developing tumor and the host immune system. Clinical trials have shown that appropriate enhancement of a tumor immune response can lead to long-lasting clinical responses and patient benefit. Understanding the contribution of the immune contexture, in addition to the molecular subtype across different tumor indications, is a significant knowledge gap with limited sagacity to drive rational immunotherapy combinations. To better inform clinical studies, we must first strive to understand the multifaceted elements of the tumor-immune interaction, the spatiotemporal interplay of numerous different immune cell types, in conjunction with an understanding of the oncogenic drivers and mutations that may lead to presentation of neoepitopes and could drive changes within the tumor microenvironment. In this review, we discuss the Immunoscore and its probable universal characteristic. The overlay of immune quantification with the molecular segments of disease and how this may benefit identification of patients at high risk of tumor recurrence will be discussed. The Immunoscore may translate to provide a tumor agnostic method to define immune fitness of a given tumor and predict and stratify patients who will benefit from certain therapies (in particular immune therapies) and, ultimately, help save the lives of patients with cancer.

Introduction

Current cancer classification is provided by the American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) and strictly relies on tumor characteristics, such as the extent of the primary tumor (T), the involvement of regional lymph nodes (N), and the presence of distant metastases (M) (TNM staging). Additional tumor cell parameters are utilized as an indication of the intrinsic biology of the tumor and provide an estimation of tumor progression at the time of the surgical resection. Although powerful, the AJCC/UICC-TNM classification fails to provide complete prognostic information. Clinical outcome can vary significantly among patients within the same histologic tumor stage. This approach has stood the test of time for prognostication; however, the TNM-staging system provides incomplete prognostic information beyond the tumor cell and does not provide insights into the immune status of a tumor and therefore may not predict response to a variety of therapeutic modalities (**Fig. 1**).

The Immunoscore Classification of Colorectal Cancer

Increasing evidence demonstrates that the evolution of cancer is strongly dependent on the complex tumor microenvironment (TME) in which it develops. The TME comprises a variety of cellular entities including fibroblasts, endothelial cells, blood vessels, lymph vessels, and cells of the immune system. Adaptive immune cell infiltration was shown to have a prognostic value superior to the classic tumor invasion criteria, including grade, stage, and metastatic status (1, 2). We have previously defined these major survival-associated immune parameters as the "immune contexture" (2, 3), delineated as the type, functional orientation, density, and location of adaptive immune cells within distinct tumor regions (1–5). In addition to the physical components within the tumor, the TME includes several soluble factors such as cytokines, chemokines, and products of cellular metabolism. Tumor progression and patient survival therefore reflect the complex cellular and molecular interactions of the tumor with the immune system of the host (3).

A potential clinical translation of the immune contexture into a prognostic marker in CRC was established and designated the "Immunoscore" (2, 4, 5). The Immunoscore is based on the quantification of lymphocyte populations, in particular CD3 and CD8-positive T cells, both at the tumor center (CT) and at the invasive margin (IM). The Immunoscore provides a scoring system ranging from low immune cell densities found at both the CT and the IM, Immunoscore 0 (I0), to high densities classed as Immunoscore 4 (I4), with increasing score correlating with longer patient survival. Briefly, CD3- and CD8-immunostained formalin-fixed, paraffin-embedded (FFPE) slides are scanned and the two corresponding digital images validated by the operator (**Fig. 2**). Image analysis is performed via a dedicated software (Immunoscore Analyzer, HalioDx): automatic detection of the tissue histologic structure is followed by an operator-guided definition of the tumor (adenocarcinoma), healthy tissue (submucosa, muscularis propria, serosa), and the epithelium (mucosa). The operator also excludes all areas of necrosis, abscess, and artifacts (bubbles folds, torn areas, background) to avoid false positives. The IM, spanning 360 μm into the healthy tissue and 360 μm into the tumor, is calculated automatically by the software. In the presence of multiple FFPE blocks, the one to select for the Immunoscore evaluation is the one containing the IM. If more than one IM-containing FFPE block is available, the one containing the most immune cells (based on low magnification optical evaluation of the corresponding H&E slide) should be selected. Nonetheless, comparison between the most immune-infiltrated block and a random block showed no significant differences in terms of final Immunoscore categories, supporting the robustness of the assay. The whole procedure, including all material, instrumentation, and software, has been validated and approved for use in clinical practice.

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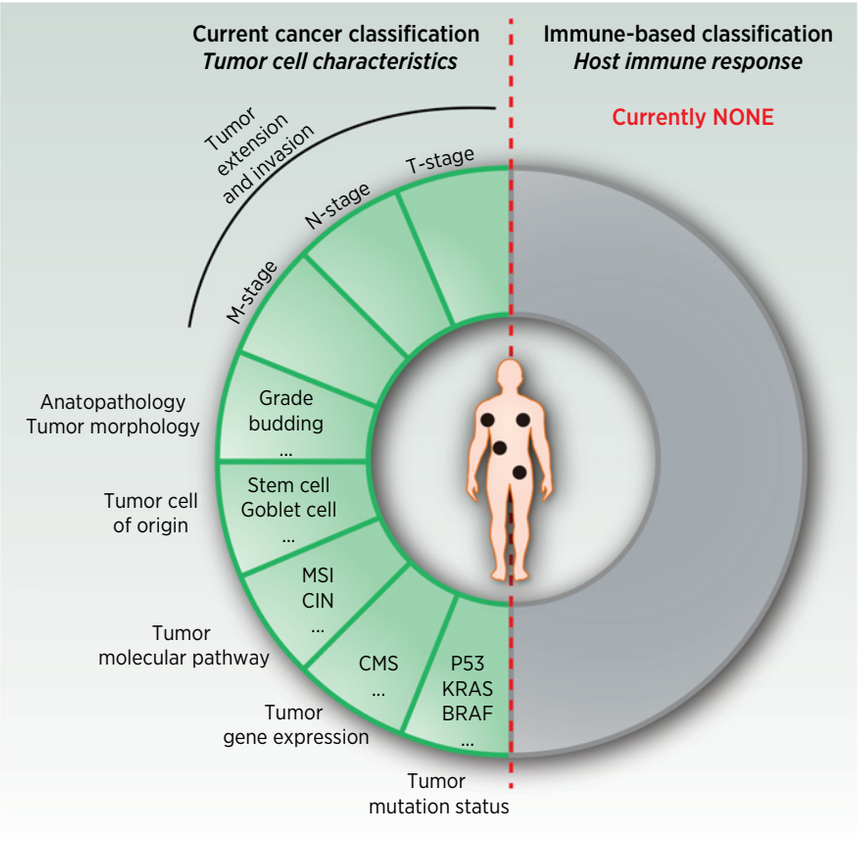

Figure 1.
Pie chart represents current and possible cancer classification approaches. Tumors are currently classified based solely on tumor cell characteristics (left). These include the AJCC/UICC-TNM stratification system, tumor morphology (i.e., grade of differentiation; tumor budding; sidedness; location; venous emboli, lymphatic invasion, perineural invasion–VELIPI), tumor cell of origin, deregulated molecular pathways, specific tumor signatures, and mutational status. Despite the existence of compelling evidence demonstrating the strength of immune-based classifications (such as that provided by the Immunoscore), current cancer classification does not include any immune parameter to date (right). CIN, chromosomal instability; CMS, consensus molecular subtypes; MSI, microsatellite instability.

In terms of prognostic power, the Immunoscore-measured host immune reaction outperformed the gold standard TNM classification for disease-free survival (DFS), disease-specific survival, and overall survival (OS) (6). Such prognostic superiority was shown to be statistically significant for stage I, II, and III CRC, with tumor progression and invasion depending on the immune parameters (6, 7).

As the Immunoscore is a direct measure of T-cell infiltration into tumors, any mechanism directly or indirectly affecting this process will also affect the Immunoscore category. At the core of this mechanism is the presence of "sufficient" tumor immunogenicity (the ability to elicit a T-cell-mediated immune response), which is related to the neoantigen load and most frequently found in microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) patients. Indeed, CRCs associated to Lynch syndrome (characterized by MSI-H) display higher tumor-infiltrating immune cells (including $CD3^+$ and $CD8^+$) (8). In turn, tumor immunogenicity is shaped by the presence of oncogenic driver mutations, which can also affect indirectly the steps leading to the recruitment of effector T cells. Activation of the oncogenic WNT/β-catenin signaling pathway prevented the recruitment of antigen-presenting dendritic cells, which are a source of T-cell-recruiting chemokines CXCL9 and CXCL10 (9). Of note, the presence of a "good" gut microbiota was also shown to stimulate T-cell recruiting chemokines expression by tumor cells (10). The absence of physical barriers impeding T-cell infiltration and the presence of factors that mediate T-cell expansion (such as IL-15 (11)) and that of a functional immune orientation of the immune contexture (5) are among the other key factors positively affecting the Immunoscore. Thus, the Immunoscore-based stratification constitutes a powerful prognostic tool recapitulating the complex interplay among numerous immune and nonimmune factors within the TME. Immunoscore-high patients are likely to share the majority, if not all of these favorable features.

Apart from constituting a prognostic factor at baseline, the Immunoscore could also play a role as a marker to predict the response to biotherapies targeting key immune checkpoints, such as PD-1/PD-L1 or CTLA4 (3, 4, 12, 13).

In an effort to promote the utilization of the Immunoscore in routine clinical settings, a worldwide Immunoscore consortium was initiated, with the support of the Society for Immunotherapy of Cancer (13). The main objectives of this consortium were to demonstrate feasibility, reproducibility, significance, and robustness of Immunoscore in a worldwide study (**Table 1**). The consortium identified a strategy to demonstrate the feasibility and reproducibility of the Immunoscore, validated its major prognostic power and robustness in colon cancer stage I/II/III, and demonstrated the utility of the Immunoscore to predict patients with stage II colon cancer with high risk of recurrence (13). The primary study endpoint was time-to-recurrence for Immunoscore (high/low), which was reached in the three cohorts of patients tested. Secondary endpoints were also validated, such as significance in DFS and OS, significance with Immunoscore classified by three versus five groups, significance in patients with stage II colon cancer, and significance in multivariate analysis, adjusted for Immunoscore, age, gender, T-stage, N-stage, microsatellite instability (MSI), and stratified by city centers.

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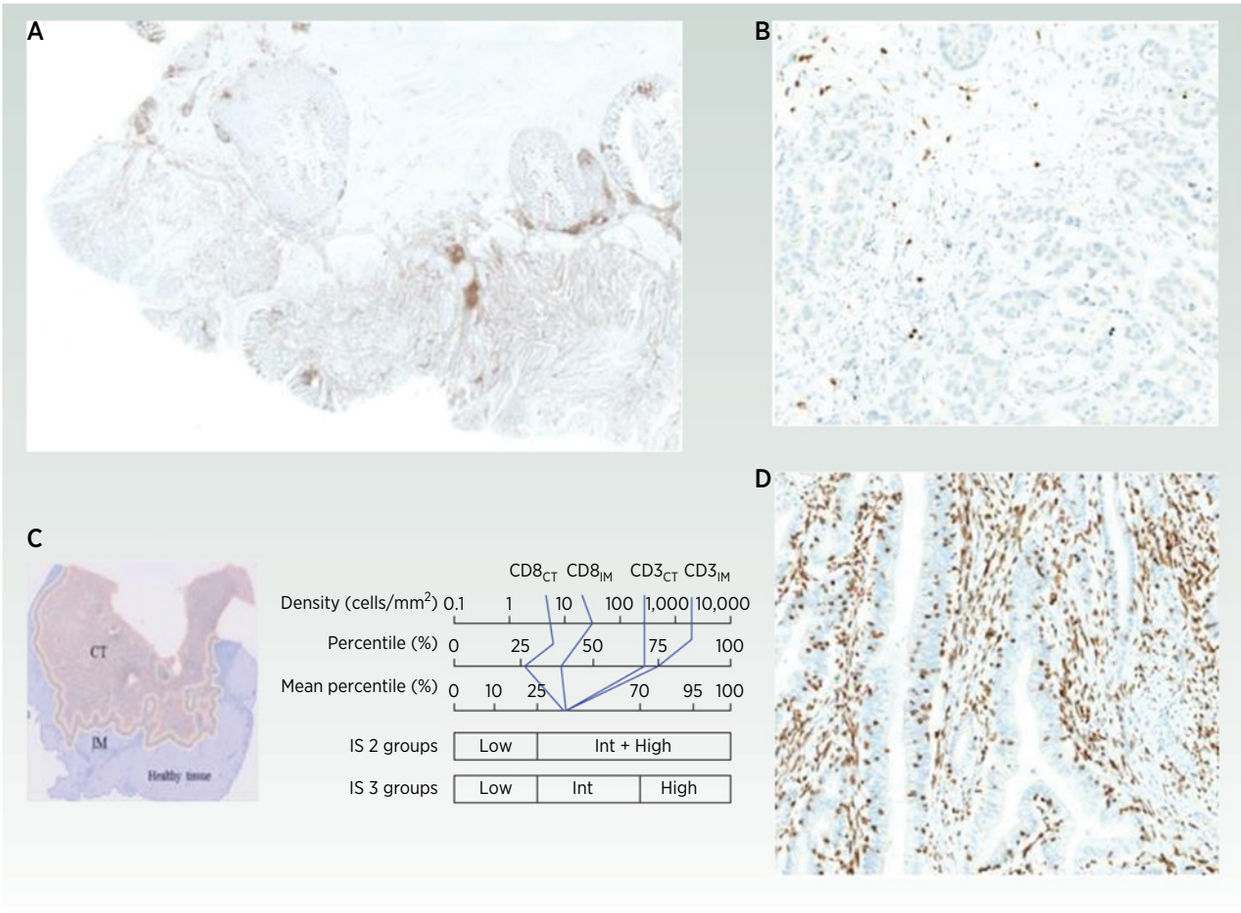

Figure 2.

A, Example of whole-slide CD3 staining. **B,** Example of staining for a low Immunoscore patient. **C,** Digital representation of tissue areas including CT, tumor center; IM, invasive margin; and adjacent excluded healthy tissue. Cell density cutoffs also indicated for CD3 and CD8. (CD3CT, CD8CT, CD3IM, and CD8IM). **D,** Example of staining for a high Immunoscore patient.

Importantly, Immunoscore was demonstrated to have the highest relative contribution to the risk among all clinical parameters, including the AJCC/UICC-TNM staging (**Fig. 3**) (14). The implementation of Immunoscore in clinical settings and the introduction of an "immune" component (I) to the TNM staging (this becoming TNM-I) have been advocated. The immediate advantages of this approach are multiple, including: an improved prognosis of patients with cancer; an improved identification of patients at high risk of tumor recurrence; and a better stratification of patients who will benefit from immunotherapies and specific combination therapies (4, 15).

Translation of the Immunoscore into Additional Indications

For widespread clinical implementation, a good biomarker should possess a series of features including, but not limited to, ease of routine applicability, feasibility, uncomplicatedness, robustness, and reproducibility (a comprehensive list can be found in Table 1). Remarkably, the Immunoscore has been shown to possess all these key characteristics.

The positive impact of tumor-associated cytotoxic and memory T cells on clinical outcome has been largely demonstrated in a plethora of anatomically and cytologically distinct solid tumors (5, 16). These findings encourage us to shift our focus from the classic location- or cytology-based prognosis to an immune-based one. In this scenario, the main characters associated with prolonged survival are the cytotoxic T cells, memory T cells, T_H1 cells, and the newly identified lineage of tissue-resident memory T (T_{RM}) cells (3, 4, 16, 17).

The nowadays recognized role of the immune system in shaping cancer evolution, together with the recent breakthrough provided by cancer immunotherapies, calls for a deep assessment of the immune microenvironment within precancerous lesions. A recent study demonstrated the occurrence of immune activation and immune escape (via the expression of immune checkpoints) at the stages preceding lung squamous cell carcinoma (18). It is tempting to speculate that a similar pattern can be found in other precancerous settings, such as colorectal carcinogenesis. To date, no biomarker or test exists to stratify patients according to their likelihood to develop primary

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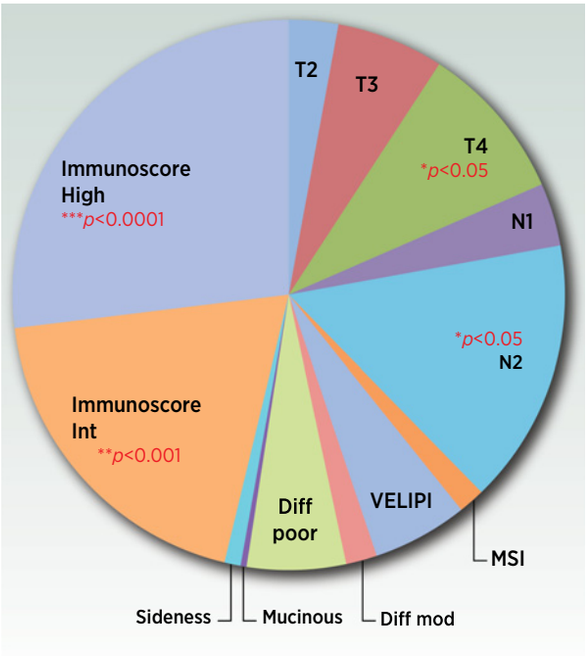

Figure 3.

Pie chart represents the significance (log *P* value) in multivariate analysis for OS. T stage with T1 as reference. N stage with N0 as reference. Differentiation with well differentiated as reference. Immunoscore with Immunoscore low as reference. $^{*}P < 0.05$; $^{**}P < 0.001$; $^{***}P < 0.0001$. Int, intermediate; Mod, moderate.

disease. It would be of tremendous interest to determine whether the Immunoscore or an Immunoscore-like test could predict patients' survival and outcome at the preinvasive stages of carcinogenesis. By stratifying patients at the premalignant stages, this type of evaluation could support the design and implementation of effective therapeutic approaches (such as checkpoint inhibitors) in selected, high-risk subgroups of patients.

The Immunoscore is not without its faults. First, it is a quantitative assay, quantifying the density of specific immune cells (CD3+, CD8+) using digital pathology. A very high number of T cells infiltrate tumors. Indeed, the mean number of CD3+ cells per tumor slide from resected colon cancer is 88,000 cells/slide. Optical tumor-infiltrating lymphocyte (TIL) evaluation from an H&E was compared with the Immunoscore, resulting in 48% discordance and highlighting the fundamental need of digital pathology for correct and reproducible evaluation (14). This would represent the first biomarker requiring digital pathology, which is not yet fully accepted by the pathology community, even though it has demonstrated high performance (14). The Immunoscore requires rigorous pathology and experimental practice for the staining, and deviation from the predefined standardized operating procedure may result in improper quantification of the Immunoscore. To ensure the robustness of this assay, an approved *in vitro* diagnostic Immunoscore assay for clinical use (CE-IVD) has been developed by Hal*i*oDx (19). Furthermore, Immunoscore can be performed in Clinical Laboratory Improvement Amendments–certified laboratories in the United States. In clinical trials, samples are often biopsies from metastases and not resected tumors. Therefore, the IM is rarely available. Thus, an Immunoscore for biopsy (without the need of the IM for quantification) has been developed and compared with the consensus Immunoscore for resected tumors. The Immunoscore on biopsy significantly predicts the prognosis of the patients, even if not as powerful as the Immunoscore incorporating the IM (20). Furthermore, the ROC curves testing the specificity sensitivity, or false-negative false-positive results when evaluating Immunoscore biopsy (without IM) compared with Immunoscore, showed 77% sensitivity and 96% specificity, illustrating the good performance of the evaluation of Immunoscore on biopsy (20).

As the concept of immune control of tumors applies virtually to all solid malignancies, it is plausible to extend the introduction of the Immunoscore as an additional prognostic immune parameter to additional cancer types (4, 12, 13, 21, 22). Of course, this does not exclude the subsequent evaluation and possibly addition of further markers. Recent evidence showed that the presence of infiltrating TIM-3^{+} PD-1^{+} CD8^{+} T cells correlated with poor clinical outcome in renal cell carcinoma (RCC) (23). Of note, RCC is one of the notable exceptions in which T cells bear negative prognostic value (24), possibly due to an exhausted phenotype (23, 25). Therefore, the assessment of additional exhaustion parameters could prove instrumental in fine-tuning the prognostic value of the Immunoscore in seemingly unsuitable cancer types.

As part of an ongoing collaboration between AstraZeneca and INSERM, we are committed to understanding the prognostic significance of the Immunoscore in additional indications, including gastric, NSCLC, SCLC, SCCHN, TNBC, ovarian, and bladder cancer. The value of Immunoscore goes beyond its prognostic utility. Indeed, the Immunoscore might constitute a powerful tool for predicting response to novel therapeutic approaches, including immunotherapy, thereby highlighting its potential utilization as predictive biomarker. This hypothesis will have to be tested in prospective clinical trials.

The terms "hot" and "cold" tumors have been increasingly used to distinguish tumors according to their degree (high and low, respectively) of immune infiltration, but a general consensus on the definition of these categories is lacking. A step forward to a more standardized and univocal definition of these tumors based on the consensus Immunoscore has been proposed, together with the introduction of two intermediate categories (altered-immunosuppressed and altered-excluded) (15, 26). By stratifying these major groups based on T-cell infiltration, the Immunoscore might be used as a tool to identify phenotypes responding to distinct classes of mono- or combinational therapies. Furthermore, understanding how the immune landscape changes in subsets of molecular segments of disease is of great importance.

The Immune Landscape in Human Tumors and Molecular Subtypes

Morphology, mutation status, cell origin, tumor cell gene expression, and molecular pathways are among the tumor cell characteristics used to distinguish the numerous subtypes of CRC. The most common morphology-based classification distinguishes histologic variants (mucinous, signet ring cell, medullary, micropapillary, serrated, cribriform comedo-type, adenosquamous, spindle cell, and undifferentiated). None of these criteria hold a strong prognostic value.

Additional methods to classify cancer are based on mutation analysis including oncogenes, tumor suppressor genes, and metastasis suppressor genes. Cancers can also be classified by molecular pathways: chromosomal instability, MSI, and a CpG island

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Table 1. Consensus Immunoscore characteristics for colorectal cancer classification.

Good biomarker	Immunoscore characteristics	
Feasible	Established pathology techniques, using two regular whole-slide FFPE sections	Yes
Routine	Technique to be performed by pathologist using bright field and precise cell evaluation	Yes
Rapid	Autostainers, scanner, digital pathology reduces the time to perform an Immunoscore	Yes
Robust	Two strong membrane stainings, with no background, allowing the enumeration of individual cells	Yes
Reproducible	Interobservers' variability is removed by the use of digital pathology, taking into account cell location and counts (14)	Yes
Simple	Automatized immunochemistry	Yes
Standardized	Standardized operating procedure, worldwide consensus Immunoscore, approved test for clinical use (CE-IVD)	Yes
Pathology-based	Pathologist expertise to validate cell type, cell location, and cell counts performed by digital pathology	Yes
Powerful	Immunoscore has the highest prognostic value among all known prognostic parameters, including Cox multivariate with TNM classification (1) (7) (14)	Yes
Quantitative	Precise cell density (cell number/surface area)	Yes
Validated	Worldwide consensus Immunoscore study validated the power and reproducibility (14)	Yes
IVD	Approved for *in vitro* diagnostic for clinical use in colon cancer	Yes
FDA	Not yet	No
CLIA	Available within U.S.-certified CLIA laboratories	Yes
Classification (WHO, UICC, AJCC, NCCN)	Not yet	No
Reimbursement	Not yet	No

Note: The first column shows the desired features of a good biomarker (feasible, routine, rapid, robust, reproducible, simple, standardized, pathology-based, powerful, quantitative, validated), which are all satisfied by the consensus Immunoscore (right column).
Abbreviations: AJCC, American Joint Committee on Cancer; CLIA, Clinical Laboratory Improvement Amendments; FDA, Food and Drug Administration; IVD, *in vitro* diagnostic; NCCN, National Comprehensive Cancer Network; UICC, Union Internationale Contre le Cancer; WHO, World Health Organization.

methylator phenotype. Use of whole-genome mRNA expression profiling has, for example, identified similarities between the molecular subtypes of muscle-invasive bladder cancer with the molecular features (e.g., p53) of basal and luminal breast cancers. Recently, transcriptomics analyses identified four consensus molecular subtypes (CMS) of CRC possessing distinct prognostic profiles, including both classical genomic and immune features (27, 28). MSI has utility as a predictive biomarker for response to PD-1/PD-L1 blockade (29, 30), potentially related to the high tumor mutational burden (TMB) and neoantigen generation associated with MSI-high (MSI-H) tumors (31). The increased number of immunogenic peptides found in MSI-H tumors is paralleled by increased TILs, a higher likelihood of immune engagement and increased PD-L1 expression in the tumor (32). The U.S. Food and Drug Administration has since granted accelerated approval to pembrolizumab for patients with MSI-H or dMMR solid tumors (33). High nonsynonymous TMB is also emerging as a potential tumor genomic determinant associated with improved progression-free survival (PFS) and durable clinical benefit, correlating with higher neoantigen load (34, 35). Furthermore, the increased adaptive immunity typically associated with MSI-H and high TMB prevents metastatic dissemination, and very few MSI-H patients (<5%) develop metastases (36). Different alterations in the TME are associated with metastatic invasion. The development of distant metastases is a consequence of the decrease in lymphatic vessels and lymphocyte cytotoxicity; accordingly, the immune phenotype is likely to be a major determinant preventing metastatic spreading (36). These results have important clinical implications and plausibly will affect the outcome of clinical trials testing therapies that enhance T-lymphocyte function (anti-CTLA4, anti-PD1, and anti-PD-L1). Studies support the use of T-cell–based immunotherapy at early-stage disease to prevent metastases and suggest that immune analysis of primary tumors may help predict the presence and development of metastasis. Recently, the analysis of longitudinal data sets of metastases from colorectal cancers revealed how the clonal evolution patterns depend on the immune contexture at the metastatic site (37). Immunoediting and Immunoscore were found to be the best predictors of clinical outcome (37). Hence, these parameters could be employed to stratify tumors and metastases based on their probability of recurrence. In the proposed "parallel immune selection model," persisting and progressing tumor clones were found to be immune-privileged, i.e., unedited or nonimmunogenic (37): these should be the object of therapeutic targeting. Overall, these results strongly suggest that an improved understanding of the processes leading to metastasis could help develop novel treatments for patients with late-stage tumors. In an era of personalized medicine, different immunotherapy strategies are likely to be needed for lymph node and distant metastasis patients, as their immune escape mechanisms are expected to be different.

Adapting Clinical Trials Design for Immunotherapy

Successful applications of immunotherapy are being increasingly reported in several cancer settings; notable examples include Sipuleucel-T for prostate cancer (3, 38), ipilimumab for melanoma (39), and recently, the combination of pembrolizumab plus chemotherapy for NSCLC (40). It seems likely that effective immunoguiding could better direct therapeutic choices at baseline (before therapy) (3, 41, 42). To-date, the performance of any anticancer therapeutic intervention, including that of immunotherapies, is evaluated in terms of clinical outcome, OS, or PFS. The newly revealed key role for the immune system brings along the possibility to monitor therapeutic efficacy much earlier by assessing the immune responses during therapy. Of note, the time required for the activation and successful establishment of immune effector mechanisms results typically in delayed objective clinical responses,

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compared with standard-of-care therapies (39). This delayed time frame is ultimately responsible for tumor "flare" or pseudoprogression. Clinical trial design should incorporate response rates at late, rather than early, time points to avoid the underestimation of the true clinical benefit of immune checkpoint inhibitors. The use of novel surrogate endpoints, such as milestone survival and objective response rate, has also been advocated (43).

The use of novel biomarkers and assays has also become a clear need. In addition to biomarkers and methods directly involving the TME, the assessment of circulating components, whether blood- or bone marrow–associated, or combinations of thereof, seems to constitute promising tools (44–47). In order to successfully demonstrate the correlation between vaccine- or spontaneously induced immune responses and clinical benefit, most studies rely on the use of well-recognized, externally validated and harmonized immune assays (48). However, to date, biomarkers for reliable immunoguiding remain to be established.

Data continue to emerge evaluating the overlap between immune components and response to immunotherapy in clinical trial samples (49). Broadening our understanding around the overlap of molecular segments of disease, with markers that infer sensitivity to immunotherapies, may help better identify those patients who will respond to combinations of immunotherapy with targeted therapies (15). One example is looking at DNA-damaging response inhibitors such as the poly(ADP-ribose) polymerase inhibitor (PARPi), olaparib. Differences in the immune phenotype across the molecular aberrations, such as BRCA1, BRCA2, and mutations in the homologous recombination repair pathway, are known to infer response to PARPi. Such detailed understanding is required to predict to what extent PARP inhibitors may enhance response to immune checkpoint blockade, such as PD-L1 (50–53), or other immunotherapy approaches.

Successes in Immunotherapy: Challenges and Opportunities Ahead

It has been widely accepted that cancer develops as a result of a failure in one or more mechanisms regulating the immune control of key molecular events (54). By tackling one of the main mechanisms of T-cell exhaustion/dysfunction, immune checkpoint inhibitors (ICIs) yield clinical benefit in the cases in which this is the critical step limiting the immune control of the tumor. A multitude of therapeutic antibodies targeting tumor cell surface molecules, growth factors, or cytokine receptors that sustain tumor growth have found their way into the clinic. Many studies have shown that immunotherapies based on the transfer, activation, expansion, or de-blocking of tumor-specific T cells resulted in clinical success (15, 55–58). When achieved, successful responses are often impressive and durable (59), reinforcing our opinion that the systemic and local tumor-specific T-cell response is at the forefront of cancer therapy.

Despite these encouraging results, efficacy of ICIs is not consistent across indications, and the percentage of responders is far from optimal (60). Several mechanisms could be at play underlying these differential clinical activities. Efficacy of ICIs requires a preexisting strong immune infiltrate and generation or rescue of an effective antitumor immune response. Of note, this parallels the prognostic importance of the Immunoscore. In order to increase clinical benefit, these immune-activating strategies may be combined with chemotherapy, radiotherapy, or targeted therapy to reduce tumor load and increase immunogenicity. As the number of combinational possibilities increases, the pressure to provide sound rationale and appropriate biomarker(s) for the choice of immunotherapeutic agents and combinations also increases. Notwithstanding, the heightened flexibility seen in more recent platform and window of opportunity trials, looking for every possible synergistic combinations of known drugs with immunotherapy, even just for a single cancer type, remains unfeasible. Plus, this kind of approach might not be successful, as the immune microenvironment differs between patients within a given tumor type as well as across tumor types (5, 61). It is desirable and highly likely and that the choice of treatment option will take into account not only the tumor type but also the tumor-associated immune parameters.

The immune regulatory networks differ over time and with clinical outcome (21), adding an extra level of complexity to this already heterogeneous landscape. Only the combined evaluation of the spatiotemporal interplay of the different immune cell types, together with an understanding of the oncogenic drivers within the specific malignancy, could dissect the complex dynamics of the tumor-immune interaction during tumor progression. Nonetheless, existing immune-related parameters, such as the consensus Immunoscore, together with tumor drivers' assessment (62), TMB measurement (63), LOH HLA (loss of heterozygosity at the HLA locus) evaluation (64, 65), PD-L1 expression (66), and presence of specific immune gene expression signatures (67, 68) can already be exploited to further advance cancer classification. The fact that the Immunoscore is already available with a consensus detailed protocol (14), and gained CE-IVD approval, makes it an ideal solution to relieve this urgent unmet need for improved patients' stratification. Nowadays, a limit to the widespread use of the Immunoscore is the fact that it is not yet reimbursed by the public health services. A first step in this sense came in January 2019, when the Immunoscore become fully reimbursable by a major private medical insurer in the United Kingdom. The limited percentage of patients displaying clinical responses to the novel immunotherapies, coupled with their high costs, threatens the sustainability of these effective therapeutic strategies (69). By enabling the physicians to make better-informed decisions, diagnostics tests such as the Immunoscore can help tailor medicine to an individual's biology, to the benefit of individual patients (which could be, for instance, spared unnecessary treatments), and the society alike.

Disclosure of Potential Conflicts of Interest

H.K. Angell, J.C. Barrett, and R. Herbst are employees and shareholders of AstraZeneca/MedImmune. H.K. Angell is a consultant/advisory board member for INSERM, Perkin-Elmer, Definiens, and HalioDx. R. Herbst is an unpaid consultant/advisory board member for Definiens SAB. J. Galon is developer of the Immunoscore; reports receiving commercial research grants from MedImmune, AstraZeneca, Janssen, and Imcheck Therapeutics; holds ownership interest (including patents) in HalioDx and INSERM; and is a consultant/advisory board member for Bristol-Myers Squibb, Merck Serono, Illumina, Northwest Biotherapeutics, Actelion, Gilead, Amgen, Merck MSD, CatalYm, Sanofi, and IObiotech. No potential conflicts of interest were disclosed by the other author.

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