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No time to die: the consensus immunoscore for predicting survival and response to chemotherapy of locally advanced colon cancer patients in a multicenter international study

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ABSTRACT

The multicenter international Society for Immunotherapy of Cancer (SITC) study of the consensus Immunoscore demonstrated the prediction of survival and response to chemotherapy in 763 Stage III colon cancer (CC) patients. Similar Immunoscore groups were found in elderly patients, and densities of immune cells and intratumoral T-cell repertoire were not decreasing with age in the tumor microenvironment. In two independent cohorts, Immunoscore significantly predicted time to recurrence (TTR), disease-free survival (DFS), and overall survival (OS), including within high-risk (T4 or N2) and low-risk (T1-3, N1) patients. In stratified Cox multivariable analysis for TTR, DFS, and OS, Immunoscore's association to outcomes was independent of the patient's age, sidedness, gender, T-stage, N-stage, and microsatellite instability status. Furthermore, the relative contribution to the risk test showed that Immunoscore had the highest contribution to survival. Importantly Immunoscore predicted the likelihood of response to chemotherapy. Only patients with a high-Immunoscore significantly benefited from chemotherapy. The prognostic value of Immunoscore was confirmed in two independent phase 3 clinical trials (NCCTG-N0147, n = 559; Prodige-IDEA, n = 1062). Moreover, results from IDEA phase 3 randomized trial revealed the predictive value of Immunoscore for response to adjuvant FOLFOX chemotherapy duration. The latest edition of the WHO Digestive System Tumors classification introduced the immune response as measured by Immunoscore as essential and desirable diagnostic criteria for CC, and Immunoscore was introduced into the 2020 ESMO Clinical Practice Guidelines for CC to refine the prognosis and adjust chemotherapy decision-making process in stages II and III patients. These results highlight the clinical utility of Immunoscore.

Clinical utility of immunoscore in stage III colon cancer

A meta-analysis of the literature including more than 200 published articles for the implication of cytotoxic T-cells and T-cell subpopulations with regard to prognosis of cancer patients (in 20 different cancer types) revealed that cytotoxic CD8 + T-cells were associated with a good prognosis in 97% of the studies.[1] We previously showed that tumor recurrence and overall survival times of patients with colon cancer were mostly dependent on the presence of cytotoxic and memory T cells within specific regions of primary tumors. We performed a clinical study on human colorectal cancer showing that cytotoxic and memory T-cells were predicting the clinical outcome in early Stage (I/II) colorectal cancer patients. We further showed that histopathologic-based prognostic factors of colorectal cancers are associated with the state of the local immune reaction. The assessment of CD8(+) cytotoxic T lymphocytes in combined tumor regions provided an indicator of tumor recurrence beyond that predicted by AJCC/UICC-TNM staging.[2–4] The importance of the patient intratumor natural

adaptive immune reaction for the survival of patients revealed that immune parameters are beyond tumor progression and invasion (TNM classification). This immune response was defined as the "Immunoscore".[1,5–7]

The results of an international Immunoscore consortium on Stage I/II/III colon cancer patients using the first worldwide recognized and standardized consensus assay to quantify the preexisting immunity were published. The results showed that Immunoscore significantly predicted time to recurrence (TTR), disease-free survival (DFS) and overall survival (OS). Secondly, Immunoscore predicted high-risk and low-risk patients in the restricted population of Stage II colon cancer patients. This established the consensus as a robust and powerful stratifier to predict the prognosis of colon cancer patients.[8] Before the inclusion of an immune parameter into the TNM-staging system, to move to a TNM-Immune (TNM-I) classification, it is important to also demonstrate the clinical utility of Immunoscore at each stage of the current staging-system. Thus, the clinical utility of Immunoscore has been reinforced by the recent publications demonstrating the prognosis value of Immunoscore in

Stage III CC patients, and its predictive value in response to chemotherapy.

Recently, the multicenter international Society for Immunotherapy of Cancer (SITC) study of the consensus Immunoscore demonstrated the prediction of survival and response to chemotherapy in Stage III colon cancer.[9] This international study led by the SITC evaluated the pre-defined consensus Immunoscore in 763 patients with AJCC/UICC-TNM Stage III CC from 2 cohorts, a first cohort (Canada/USA) and a second cohort (Europe/Asia). The consensus Immunoscore was evaluated by quantifying the CD3+ and cytotoxic CD8 + T-lymphocyte densities in the tumor and invasive-margin by digital-pathology using pre-defined cut-points and categories. The lowest risk of recurrence was observed in patients with a high-Immunoscore in both cohorts. Immunoscore Low, Intermediate and High had recurrence-free rates at 3 y of 56.9%, 65.9%, and 76.4%, respectively, with a significant hazard-ratio of 0.48 (P= .0003). Significant (all P< .001) association with prolonged TTR, OS and DFS were found for patients having a High-Immunoscore . Immunoscore association to TTR was independent (P = .0003) of patient's gender, T-stage, N-stage, sidedness, and microsatellite instability-status, in Cox multivariable analysis. Significant association of High-Immunoscore with prolonged TTR was also found among MSS patients (P = .0003). Importantly, Immunoscore had the strongest contribution for influencing survival (TTR and OS) as measured with X^2 proportion statistical analysis. Patients with a high-Immunoscore responded to chemotherapy and had prolonged survival compared to patients not receiving chemotherapy. In contrast, Low-Immunoscore patients did not significantly benefit from chemotherapy treatment. Furthermore, the predictive value of

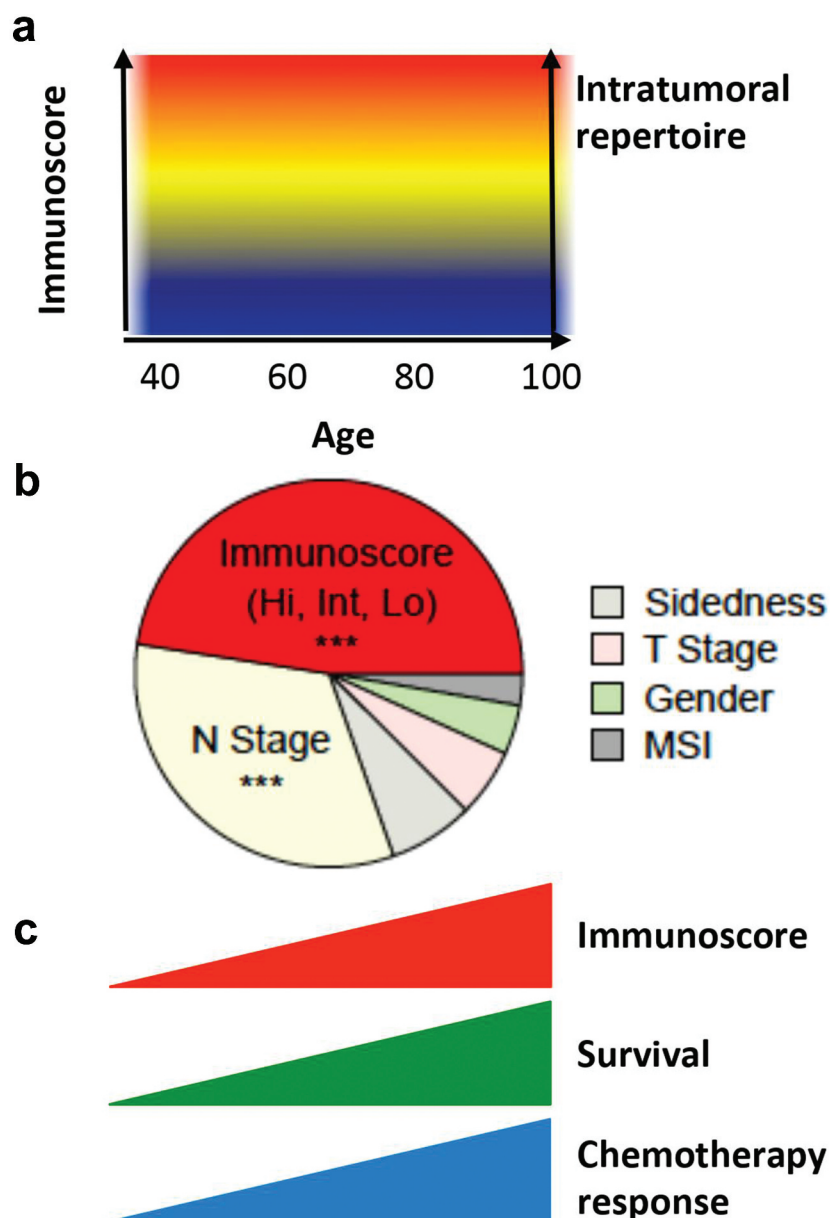Figure 1. Clinical utility of the Immunoscore. (a) Immunoscore and intratumoral T-cell repertoire remain stable with age. (b) Relative contribution of each risk parameter to survival risk for overall survival in Stage III CC using the x2 proportion test for clinical parameters and Immunoscore. (c) Immunoscore is a powerful prognosis marker and a predictive marker of response to chemotherapy for stage III colon cancer patients.

a high-Immunoscore for response to chemotherapy and prolonged survival was found for both low-risk (T1-3, N1) (HR = 0.42, *P*= .001) and high-risk (T4 and/or N2) (HR = 0.5, *P*= .001) patients.

This study demonstrated five key findings.[9]

First, we showed that densities of immune cells and intra-tumoral T-cell repertoire are not decreasing with age. Furthermore, the same proportion of Immunoscore groups is found below 60 y-old and above 85 y-old which is of importance fundamentally and in considering treatment options.

Second, we demonstrated, in two independent cohorts of patients from this international study that Immunoscore significantly predicted time to recurrence (TTR), disease-free survival (DFS) and overall survival (OS) in Stage III patients.

Third, we showed that Immunoscore predicted outcome within the MSS population, and also predicted outcome within high-risk (T4 or N2) and low-risk (T1-3, N1) stage III patients.

Fourth, in stratified Cox multivariable analysis for TTR, DFS and OS, Immunoscore's association to outcomes was independent of the patient's age, sidedness, gender, T-stage, N-stage, and microsatellite instability (MSI) status. Furthermore, the relative contribution to the risk test showed that Immunoscore had the highest contribution to survival in comparison to all other clinical parameters.

Fifth, importantly Immunoscore predicted the likelihood of response to chemotherapy. Indeed, patients who did not receive chemotherapy had similar outcomes as those who received chemotherapy, if they had a low-Immunoscore, and did not significantly benefit from chemotherapy. In contrast, patients with an Intermediate/high-Immunoscore significantly benefited from chemotherapy.

This illustrates the fact that the benefit of chemotherapy may be dependent upon a proper preexisting immunity (Figure 1).

Validation in two randomized phase 3 trials

The results of Immunoscore in Stage III CC patients were confirmed in two independent randomized phase 3 clinical trials. The Immunoscore-N0147 study was conducted in collaboration with clinicians and researchers from the Mayo Clinic.[10] The study included 559 patient samples from the FOLFOX arm of the NCCTG-N0147 trial and used the pre-defined consensus Immunoscore. Immunoscore predicted relapse and death in stage III CC patients treated with a standard adjuvant treatment combining fluoropyrimidine and oxaliplatin in the N0147 trial.[10] Another randomized phase 3 clinical trial (IDEA) in 1062 Stage III CC patients tested the consensus Immunoscore.[11] The two studies were performed, using the pre-defined consensus Immunoscore, had similar significant results regarding the prognostic value of Immunoscore.

The randomized phase 3 clinical trial IDEA aimed to evaluate the non-inferiority of 3 months of chemotherapy (FOLFOX or CAPOX) compared to 6 months. The primary objective of this trial (IDEA) was not met, and it could not be concluded that this non-inferiority was achieved. However, the IDEA study showed that 3 months adjuvant treatment was associated with a significantly lower

incidence and severity of adverse events compared to 6 months. Even if the primary objective of this trial was not met, secondary subgroup analyses were carried out and showed that CAPOX met the criteria for non-inferiority, but not those for FOLFOX. Differences in DFS depending on treatment-duration were modest. Based on these data it was proposed to treat low-risk patients (T1-3N1) with 3 months of chemotherapy. However, this study highlighted the need for additional biomarkers to predict the efficacy of adjuvant chemotherapy in CC patients.

Not only the phase 3 trial IDEA confirmed the prognostic value of Immunoscore but it also confirmed its predictive value in response to chemotherapy.[11] High-Immunoscore patients significantly benefited from 6-month treatment compared to 3month treatment. Conversely, in patients with Low-Immunoscore, no significant benefit of 6-month FOLFOX was observed compared to 3-month treatment. These results were also observed independently of the clinical stage. Both high-risk (T_4 and/or N_2) and low-risk (T_{1-3}, N_1) patients significantly benefited from 6-month FOLFOX when they had a High-Immunoscore, but not when they had a Low-Immunoscore. This validated and further demonstrated the predictive value of Immunoscore in response to chemotherapy. Importantly, clinically low-risk patients (T_{1-3}, N_1) with High-Immunoscore had 91.4% DFS at 3-y when treated with the 6-month FOLFOX, but only 80.8% with the 3-month treatment regimen. Thus, even low-risk (T_{1-3}, N_1) patients with a High-Immunoscore could effectively benefit from 6 months of FOLFOX, thereby changing clinical practice. Unfortunately, patients with Low-Immunoscore (44.6% of Stage III) not only had an increased risk of recurrence but also a lack of benefit from longer duration of chemotherapy treatment. Given the poor outcome in these patients, new therapeutic strategies and clinical trials should be initiated in this population. FOLFOX chemotherapy contains 5-fluorouracil and Oxaliplatin. These components may have a dual impact on the immune system. On one hand, 5-fluorouracil may partially deplete or transiently inactivate inhibitory immune cells, and on the other hand oxaliplatin may increase cytotoxic T-cell infiltration and induce immunogenic cell death (ICD).[12–14] It could be hypothesized that ICD-driven immunity is inefficient in tumors with a weak preexisting immunity such as Low-Immunoscore patients. Thus, it will be important to identify Immunoscore-Low patients to test combination immunotherapies that can prime and expand anti-cancer immunity in this population, in order to prolong their survival.

Conclusions

These results highlight the prognostic value of Immunoscore regardless of the patient's age. It further strengthens the Level of Evidence and clinical utility of Immunoscore in stage III CC patients. The Immunoscore assay has been developed as an *in vitro* diagnostic test (CE-IVD) and is available in FDA CLIA-certified laboratories for routine use. Importantly, in the latest (5th) edition of the WHO Digestive System Tumors classification, was introduced "*the immune response as essential and desirable diagnostic criteria for colorectal cancer,*" and citing the consensus Immunoscore as best clinical evidence in colon

cancer. Furthermore, Immunoscore was introduced into the 2020 ESMO Clinical Practice Guidelines for colon cancer to refine the prognosis and thus adjust the chemotherapy decision-making process in stage II and even in low-risk stage III patients. The results of Immunoscore in the multicenter international SITC study and the recent inclusions into WHO and ESMO guidelines argue for the benefit of implementing the Immunoscore in clinical practice and for its introduction in a new TNM-Immune (TNMI) classification system.

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