Immunoscore provides prognostic information in low (T3N1) and high (T4 or N2) risk subsets of stage III colon carcinoma patients treated with adjuvant FOLFOX in a phase III trial [NCCTG N0147 (Alliance)

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Background

Immunoscore is based on CD3+ and CD8+ T-cell density and location in primary CRCs where it provides prognostic information, including stage III tumors in the NCCTG N0147 adjuvant trial. Recently, a consensus interpretation of the IDEA study results recommended that T and N risk groups . [low (T1-3N1) and high (T4 or N2)] be used to guide decision-making for the duration of adjuvant FOLFOX or CapeOx chemotherapy. However, immune biomarkers may provide further risk stratification within these risk groups.

Objectives

To determine if the immunoscore can prognostically stratify stage III CC pts (N= 600) within predefined low (T1-3N1) and high (T4 or N2) risk groups from the FOLFOX arm of the NCCTG N0147 phase III trial.

Methods

PATIENTS: Stage III CC pts (N=600) randomly selected from FOLFOX alone arm in a phase III adjuvant trial of FOLFOX +/- cetuximab (NCT00079274).

Patients (pts) were grouped into low (T1-3,N1) and high (T4 or N2) risk subsets given proposed use in guiding duration of adjuvant FOLFOX per the IDEA trial (Shi Q, et al, ASCO 2017)

IMMUNE MARKERS: Immunostaining densities of CD3+ and CD8+ T-cells (known collectively as immunoscore), and CD20+ B-cells, was determined in core tumor (CT) and invasive margin (IM), and then quantified by image analysis software. Immunoscore was calculated using a computer algorithm [(developed on cohort of stage II and III pts., Galon J, et al JCO 34, 2016 (abstr 3500)], categorized into 4 levels (0-4), and dichotomized into pre-determined low (0 and 1) and high (2,3,4) immunoscore groups.

Statistics

Primary outcome: Disease-free survival (DFS). Associations evaluated by Kaplan-Meier curves and multivariable Cox models adjusting for age, T/N stage, sidedness, *KRAS/BRAF*, and DNA mismatch repair (MMR) status.

Table 1. Immunoscore vs clinicopathological variables

	High (2-4) (N=232)	Low (0-1) (N=310)	Total (N=542)	p value
Age				0.1511
Median	60.0	58.0	59.0	
Range	(26.0-83.0)	(21.0-81.0)	(21.0-83.0)	
Sex, n (%)				0.2438
Female	121 (45.3%)	146 (54.7%)	267 (49.3%)	
Male	111 (40.4%)	164 (59.6%)	275 (50.7%)	
T Stage				0.0012
T_1 or T_2	45 (62.5%)	27 (37.5%)	72 (13.3%)	
T_3	165 (40.2%)	245 (59.8%)	410 (75.6%)	
T_4	22 (36.7%)	38 (63.3%)	60 (11.1%)	
N Stage				0.1239
1-3	144 (45.6%)	172 (54.4%)	316 (58.3%)	
≥ 4	88 (38.9%)	138 (61.1%)	226 (41.7%)	
Histology				0.1303
High	68 (48.2%)	73 (51.8%)	141 (26.0%)	
Low	164 (40.9%)	237 (59.1%)	401 (74.0%)	
Tumor Site[3]				0.0034
Right	124 (49.4%)	127 (50.6%)	251 (46.8%)	
Left	105 (36.8%)	180 (63.2%)	285 (53.2%)	
BRAF/ KRAS[4]				0.3730
WT/ WT	113 (40.1%)	169 (59.9%)	282 (53.8%)	
MUT/ WT	76 (45.0%)	93 (55.0%)	169 (32.3%)	
WT/ MUT	35 (47.9%)	38 (52.1%)	73 (13.9%)	
MMR[2]				0.0003
pMMR	192 (39.8%)	290 (60.2%)	482 (89.8%)	
dMMR	36 (65.5%)	19 (34.5%)	55 (10.2%)	

Table 2. Individual marker vs DFS

	Adjusted[1] Hazard Ratio (95% CI)	P-value
Individual Markers (Density values)[2]		
$CD3^+$ CT	0.89 (0.81, 0.98)	0.0057
$CD3^+$ IM	0.90 (0.84, 0.96)	0.0005
$CD8^+$ CT	0.79 (0.64, 0.98)	0.0061
$CD8^+$ IM	0.80 (0.69, 0.94)	0.0025
$CD20^+$ CT	0.92 (0.73, 1.16)	0.4209
$CD20^+$ IM	0.93 (0.84, 1.02)	0.0806
Continuous Immunoscore (Percentile values)		
steps of 2.5%	0.88 (0.82, 0.95)	0.0006
steps of 5%	0.89 (0.82, 0.95)	0.0006

Table 3. Multivariable model for DFS

Characteristics	Adjusted HR_{adj} (95%CI)	P-value
Immunoscore (high vs low)	0.59 (0.43, 0.82)	0.0013
Age (5-year increase)	1.00 (0.93, 1.07)	0.8967
T stage		0.0003
T_1 or T_2	REF	
T_3	2.32 (1.24, 4.33)	
T_4	3.88 (1.92, 7.81)	
N stage (N_2 vs N_1)	1.99 (1.46, 2.72)	<.0001
Site (Right vs Left)	1.44 (1.05, 1.99)	0.0250
BRAF/ KRAS		0.0056
WT/ WT	REF	
KRAS MUT	1.74 (1.24, 2.44)	
BRAF MUT	1.34 (0.84, 2.14)	
MMR (dMMR vs pMMR)	0.77 (0.43, 1.39)	0.3823

Results

Fig. 1. Stratification of DFS by Immunoscore in All Patients

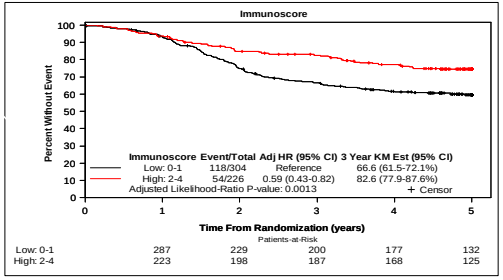


Fig. 2. Stratification of DFS by Immunoscore in pMMR Patients

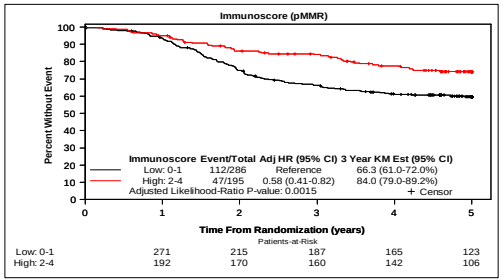


Fig. 3. Stratification of DFS by Immunoscore in T1-3N1 Subset

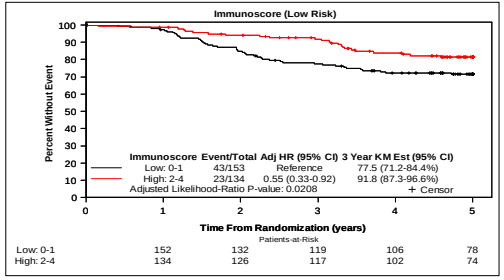
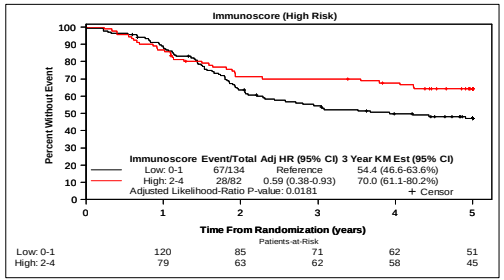


Fig. 3. Stratification of DFS by Immunoscore in T4 or N2 Subset



Key Findings

- Tumors with high vs low immunoscore were significantly associated with $T_{1/2,}$ right-sided location, and deficient MMR.
- Individual immune markers, except $CD20^+$, were each significantly associated with longer DFS, with $CD3^+$ IM being strongest.
- Using a prior Immunoscore risk dichotomization, higher scores were associated with significantly better DFS ($HR_{Adj.}$=0.59, 95% CI, 0.43-0.82, $p_{Adj.}$= 0.0013).
- Results for Immunoscore remained very similar after excluding dMMR pts
- High vs low immunoscore was significantly associated with better 3-year DFS rates of 91% vs 77% among $T_{1-3}N_1$ pts, and 68% vs 54% among T_4 or N_2 pts.
- DFS rate of 91% in high immunoscore T_{1-3}, N_1 pts is similar to the 87% and 84.7% 3-year DFS rates reported for FOLFOX-treated stage II pts in MOSAIC or NSABP C-08 adjuvant trials, respectively.

Conclusions

- Immunoscore is prognostic in stage III colon cancer pts and provides validation in a phase III clinical trial cohort.
- Immunoscore is strongly prognostic within low and high risk T and N subsets defined in the IDEA study.
- These data underscore limitations of T and N staging, and demonstrate the ability of immune biomarkers to further refine prognostication.