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Prognostic Models From Transcriptomic Signatures of the Tumor Microenvironment and Cell Cycle in Stage III Colon Cancer From PETACC-8 and IDEA-France Trials

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ABSTRACT

PURPOSE The objective of this work was to establish prognostic models in stage III colon cancer (CC) on the basis of transcriptomic signatures of the tumor microenvironment (TME) and cell cycle from the PETACC-8 (training set) and IDEA-France (validation set) trials.

PATIENTS AND METHODS 3'RNA sequencing was performed in 1,733 patients from the PETACC-8 trial and 1,248 patients from the IDEA-France trial. Four transcriptomic signatures were analyzed: T-cell and macrophage M2 signatures, the expression of CXCL13, and a score on the basis of the Oncotype DX CC Recurrence Score using the same formula from the stromal score and the cell cycle score. The Immune Proliferative Stromal (IPS) score was defined as the number of dichotomized signatures that fall under the category of a dismal prognosis (from 0 to 4). Time to recurrence (TTR) was defined as the time from the date of random assignment to local and/or metastatic relapse and/or death because of CC, whichever occurs first.

RESULTS High Oncotype-like and M2 scores and low CXCL13 expression and T-cell score were associated with a shorter TTR. A multivariable model including these signatures and all known prognostic factors applied to the IDEA-France cohort by obtaining a value of this model for each patient showed TTR significantly different depending on the quartile of this value and a 3-year rate of patients without recurrence ranging from 56% for the lowest quartile to 89% for the highest quartile ($P < .0001$). The IPS score was significantly associated with TTR in multivariable analysis.

CONCLUSION Using transcriptomic data of patients with stage III CC from two large-scale adjuvant trials, a prognostic model on the basis of signatures of the TME and the cell cycle provides important information in addition to known prognostic factors for patient stratification on risk of recurrence.

ACCOMPANYING CONTENT

 [Data Sharing Statement](#)
 [Data Supplement](#)

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INTRODUCTION

Colon cancer (CC) is highly heterogeneous, particularly in terms of molecular profiles, which can have a prognostic and predictive impact on the treatment efficacy. In stage III CC, no biomarker is used in current clinical practice to guide therapeutic management, particularly on the decision of adjuvant chemotherapy. Only T and N stage and high-risk factors in stage II CC currently guide the treatment after cancer surgery.^{1,2} However, there are various prognostic biomarkers described, such as molecular

factors (deficient mismatch repair [dMMR]/microsatellite instability status,³ RAS and BRAF mutations⁴), pathologic data as Immunoscore,⁵ and transcriptomic classifications as the four consensus molecular subtypes (CMSs)^{6,7} or supervised gene expression signatures developed in localized CC to predict the risk of recurrence.⁸⁻¹²

The Immunoscore, evaluating the densities of CD3⁺ and cytotoxic CD8⁺ T cells in the tumor and invasive margin by digital pathology, is a well-established robust prognostic factor in localized CC.⁵

CONTEXT

Key Objective

The objective of this work was to establish prognostic models in stage III colon cancer (CC) on the basis of transcriptomic signatures of the tumor microenvironment (T cells, B cells, stroma, macrophage M2) and cell cycle from the PETACC-8 (training set) and IDEA-France trials (validation set).

Knowledge Generated

Two prognostic models including these signatures and known prognostic factors have been validated in the two independent cohorts for patient stratification on risk of recurrence in stage III CC. Our findings also suggest that combining transcriptomic signatures with circulating tumor DNA (ctDNA) results provides a more accurate prediction of relapse compared with ctDNA alone.

Relevance (E.M. O'Reilly)

The authors evaluate models to improve prognostic stratification in early-stage CC by incorporating features of the tumor immune microenvironment and genomic signatures in addition to clinical features. Prospective validation will be needed to define clinical utility.*

*Relevance section written by JCO Associate Editor Eileen M. O'Reilly, MD.

Oncotype DX CC Recurrence Score (RS) is one of the most described and validated supervised signatures predictive of recurrence in localized CC, on the basis of the expression of three genes related to stroma (*BGN*, *FAP*, and *INHBA*), three genes related to cell cycle (*KI-67*, *C-MYC*, and *MYBL2*) and *GADD45B*.^{8,13}

Furthermore, many recent studies have shown that genomic signatures of the tumor microenvironment (TME) could further refine this stratification in various cancers.¹⁴ In particular, the expression of *CXCL13*, a B-cell-attracting chemokine, correlates with the infiltration of B cells and the presence of mature tertiary lymphoid structures (TLS),^{15,16} which seems to be a marker of good prognosis in localized CC.¹⁷ M2 macrophages, one of the two phenotypes of tumor-associated macrophages (TAMs), play an immunosuppressive and tumor growth role and seem to be associated with a poorer prognosis, as in CC.¹⁸

The development of 3'RNA seq from paraffin-embedded tissues at a reasonable cost in the near future opens new avenues for elaborating comprehensive profiling of stromal and immunologic features of the tumors in a large series of patients. We applied this approach to evaluate the added value of transcriptomic signatures of the TME and cell cycle for the prediction of the risk of recurrence in patients with stage III CC from PETACC8 trial¹⁹ (training set) and IDEA-France trial (validation set).²⁰

PATIENTS AND METHODS

Patients

PETACC-8 is a phase III randomized trial comparing infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) 4

with FOLFOX4 + cetuximab in 2,550 patients, after curative resection of stage III CC.¹⁹

IDEA-France is a phase III randomized trial comparing 3 months with 6 months of modified sixth version of FOLFOX (mFOLFOX6) or capecitabine and oxaliplatin in 2010 patients, after curative resection of stage III CC.²⁰

Among these patients, 2,043 and 1,693 patients have simultaneously signed informed consent forms for the trial and the translational research study, respectively. Microsatellite instability, *KRAS*, *NRAS*, and *BRAF* status were reported previously in PETACC-8 trial,⁴ and the assessment methods were the same as in the IDEA-France trial.

3'RNA Sequencing and Bioinformatics Analyses

Tumor RNA was extracted from macrodissected formalin-fixed, paraffin-embedded (FFPE) tissue sections using the QIAsymphony RNA kit (Qiagen) in PETACC-8 trial and from macrodissected FFPE punch biopsy using the RNeasy FFPE kit (Qiagen) in IDEA-France trial. The PolyA-RNA sequencing (RNAseq) library preparation protocols were performed using 400 ng of template RNA and the QuantSeq 3'mRNA-Seq Kit FWD for Illumina (Lexogen, Vienna, Austria) according to the manufacturer's instructions. Libraries were sequenced on NovaSeq6000 (Illumina, San Diego, CA).

The workflow of the bioinformatic analyses is summarized in the Data Supplement (Method S1, online only).

Intratumor CMS heterogeneity was reported previously in PETACC-8 trial on the basis of targeted transcriptome data.⁷ We developed a single-sample centroid-based classifier of

the 16 possible combinations of a major CMS and a minor CMS in both PETACC8 and IDEA RNA-seq series (Data Supplement, Method S2). The combinations of CMS with dismal prognosis are CMS1_3, CMS1_4, CMS3_4, and CMS4_1.⁷

Transcriptomic Signatures and Scores

We selected four prognostic transcriptomic signatures from the literature, from which we derived four corresponding continuous scores, which were assessed for each sample:

1. A CXCL13 score, defined as the gene expression of CXCL13
2. An Oncotype-like score, derived from the Oncotype DX CC RS,⁸ on the basis of a stromal score and a cell cycle score using the formula: Oncotype-like score = $44 \times [(0.15 \times \text{stromal score} - 0.30 \times \text{cell cycle score} + 0.15 \times \text{gene expression of GADD45B}] + 0.82$
3. Macrophage M2 and T-cell scores^{14,21} were calculated using the gsva method from the GSVA R package.²²

Simple and Extended Prognostic Models

From the training cohort PETACC-8, we defined two prognostic models for time to recurrence (TTR), using the *coxph* function of the survival R package. The first one, named the Simple Prognostic Model, included only the four aforementioned scores as continuous variables. The second one, named the Extended Prognostic Model, included these four continuous scores and all prognostic clinicopathologic variables derived from our previous publication⁷ (Eastern Cooperative Oncology Group-WHO performance status, bowel obstruction and/or perforation, pT stage, pN stage, histologic grade, RAS and BRAF mutation status, MMR status, and intratumoral CMS heterogeneity). Both the Simple and Extended Prognostic Models yield a continuous value when applied to a given sample. We applied these two models (trained on the PETACC-8 cohort) on the samples of the IDEA-France validation cohort, thus obtaining sample-level continuous values for each of these two models. Then, we divided each cohort into quartiles on the basis of the related values of these two models.

Immune Proliferative Stromal Score

The four scores were dichotomized into high and low subgroups. For each score, the optimal cutpoint value was determined for the PETACC-8 training cohort to predict TTR, using the *surv_cutpoint* function from R package *survminer*. Then, we defined a score named Immune Proliferative Stromal (IPS) score corresponding to the number of deleterious signatures (high or low depending on the signatures), ranging from 0 to 4.

Circulating Tumor DNA in the IDEA-France Cohort

In the IDEA-France trial, plasma samples were collected from patients postsurgery and before the start of

chemotherapy. Retrospective analysis was conducted on plasma samples using a clinically validated, personalized, tumor-informed 16-plex polymerase chain reaction next-generation sequencing (NGS) assay for detecting molecular residual disease (Natera, Inc, San Carlos, CA; Data Supplement, Method S3).

Statistical Analyses

The median values of each score (CXCL13, Oncotype-like, Macrophage M2, T-cell) were compared according to patients' characteristics using the Wilcoxon rank-sum test.

TTR was defined according to DATECAN definition as the time from the date of random assignment to local and/or metastatic relapse and/or death because of CC, whichever occurs first.²³

RESULTS

Patient Characteristics

In the two cohorts of patients, tumor samples suitable for RNA extraction were available from 1,809 patients in the PETACC-8 trial and 1,410 patients in the IDEA-France trial. Interpretable 3'RNAseq data were obtained for 1,733 (95.8%) and 1,248 (88.5%) patients from each trial, respectively (Fig 1). All samples with interpretable 3'RNAseq data had more than 10,000 genes detected. The subset of patients with available 3'RNAseq data closely resembled those who had given informed consent for translational research but from whom 3'RNAseq data could not be acquired (Data Supplement, Table S1). The Oncotype-like and macrophage M2 scores were notably higher in patients exhibiting bowel obstruction and/or perforation, pT4 stage, pN2 stage, G3-4 grade, and BRAF mutation. CXCL13 expression and T-cell score were significantly higher in patients with G3-4 grade, dMMR, RAS wild-type, and BRAF-mutated tumors in the two cohorts (Table 1).

Simple and Extended Prognostic Models

In the PETACC-8 training cohort, the CXCL13, macrophage M2, T-cell, and Oncotype-like scores were each predictive of TTR as isolated covariates (Table 2). Within the Simple Prognostic Model, these signatures demonstrated additional prognostic value in relation to each other (Table 2). Figures 2A and 2B illustrates the TTR on the basis of the quartiles of the Simple Prognostic Model values in PETACC-8 and IDEA-France patients.

Next, we built the Extended Prognostic Model with a C-index of 0.727. The Variance Inflation Factors of the variables included were always <two in the PETACC-8 cohort (Data Supplement, Tables S2 and S3). In the two cohorts, TTR was significantly different according to the quartile of the Extended Prognostic Model values with the best 3-year TTR rate in patients belonging to the first quartile (94%; 95% CI,

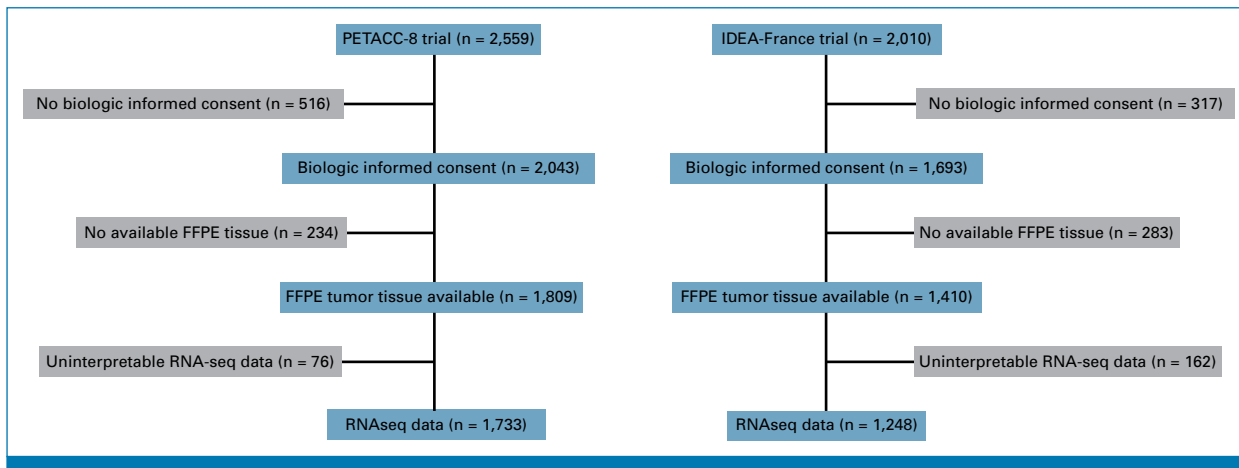


FIG 1. Trial flow diagrams. FFPE, formalin-fixed, paraffin-embedded; RNAseq, RNA sequencing.

92 to 97 and 89%; 95% CI, 85 to 93 in PETACC-8 and IDEA-France cohorts, respectively) and the lowest 3-year TTR rate in patients belonging to the fourth quartile (53%; 95% CI, 48 to 58 and 56%; 95% CI, 50 to 63, respectively; Fig 2). The performance of this model was enhanced compared with models including only well-established prognostic clinicopathologic and molecular factors with a progressive increase in the C-index from 0.672 for the models including only pT and pN variables to 0.727 for the Extended Prognostic Model in the PETACC-8 cohort (Data Supplement, Table S4).

When considering the clinical risk group (low-risk group defined as T1-T3 and N1 and high-risk group defined as T4 and/or N2), we chose to aggregate the patients according to the distribution of quartiles of the Extended Prognostic Model in each clinical risk group to ensure adequate sample sizes in each subgroup (Data Supplement, Fig S1). In the subgroup of patients with a clinical low-risk tumor, TTR was significantly shorter in patients belonging to the third or fourth quartile of the Extended Prognostic Model value compared with those belonging to the first quartile in both the PETACC-8 cohort (3-year TTR rate: 79%; 95% CI, 72 to 87 v 95%; 95% CI, 93 to 98; hazard ratio [HR], 5.22 [95% CI, 3.10 to 8.78]; $P < .001$) and the IDEA-France cohort (3-year TTR rate: 76%; 95% CI, 69 to 84 v 89%; 95% CI, 85 to 93; HR, 2.12; 95% CI, 1.30 to 3.44; $P = .002$). In the subgroup of patients with a clinical high-risk tumor, TTR was significantly shorter in patients belonging to the fourth quartile compared with those belonging to the first or second quartile in the PETACC-8 cohort (3-year TTR rate: 53%; 95% CI, 48 to 59 v 84%; 95% CI, 76 to 92; HR, 3.32 [95% CI, 2.04 to 5.39]; $P < .001$) and the IDEA-France cohort (3-year TTR rate: 54%; 95% CI, 48 to 62 v 83%; 95% CI, 72 to 95; HR, 3.81 [95% CI, 1.77 to 8.19]; $P < .001$; Data Supplement, Fig S2).

We subsequently assessed the impact of chemotherapy duration (either 3 or 6 months) within the IDEA-France cohort. Patients from the IDEA-France study were categorized into low-, intermediate-, and high-risk groups on the

basis of both the Extended Prognostic Model value and clinical classification (Data Supplement, Table S5). Notably, only patients categorized into the intermediate- and high-risk groups exhibited benefit from a 6-month treatment duration (Data Supplement, Fig S3).

IPS Score

The optimal cutpoint values for defining high and low subgroups for each score defined in the PETACC-8 training set are shown in the Data Supplement (Table S6). High Oncotype-like score, high Macrophage M2 score, low CXCL13 expression, and low T-cell score were associated with a significantly shorter TTR in the two cohorts (Data Supplement, Table S7).

As an isolated covariate, the higher the IPS score, the shorter the TTR, with the 3-year TTR rate ranging from 57% (95% CI, 48 to 69) and 61% (95% CI, 52 to 72) in patients with IPS score 4 in PETACC-8 and IDEA-France cohorts, respectively, to 93% (95% CI, 90 to 97) and 90% (95% CI, 84 to 96), respectively, in patients with IPS score 0 (Fig 3).

In multivariable analyses, the IPS score was significantly associated with TTR with an HR increasing with the IPS score, in addition to pT and pN stage, intratumoral CMS heterogeneity, and treatment duration (only in the IDEA-France cohort) in the two cohorts, with C-indexes of 0.71 and 0.68 in the PETACC-8 and IDEA-France cohorts, respectively (Table 3). The variable IPS score explained 31% of the variance of this multivariable model, in the second position after the pN stage, which explained 38% of the variance in the PETACC-8 cohort (Data Supplement, Fig S4).

IPS Score and Postoperative Circulating Tumor DNA in the IDEA-France Trial

The postoperative circulating tumor DNA (ctDNA) results were available for 422 patients (33.8%) in the IDEA-France

TABLE 1. Median Values of the Four Scores According to Patient Characteristics in the PETACC-8 Cohort

Variable	Age				Sex			
	No.	≤70 Years (n = 1,554), Median (IQR)	>70 Years (n = 179), Median (IQR)	P ^a	No.	Female (n = 746), Median (IQR)	Male (n = 987), Median (IQR)	P ^a
Oncotype-like	1,733	36 (26-46)	34 (24-45)	.2	1,733	36 (26-46)	35 (26-46)	>.9
Macrophage M2	1,733	-0.01 (-0.31 to 0.29)	-0.08 (-0.33 to 0.15)	.069	1,733	-0.01 (-0.30 to 0.30)	-0.03 (-0.32 to 0.27)	.2
CXCL13	1,733	4.14 (2.27-5.31)	4.29 (1.95-5.17)	.8	1,733	4.12 (1.80-5.34)	4.19 (2.41-5.28)	.6
T-cell	1,733	-0.03 (-0.49 to 0.46)	-0.07 (-0.48 to 0.47)	.9	1,733	-0.04 (-0.49 to 0.45)	-0.03 (-0.49 to 0.46)	.8
Variable	ECOG-WHO PS				Obstruction or Perforation			
	No.	0 (n = 1,364), Median (IQR)	1-2 (n = 307), Median (IQR)	P ^a	No.	No (n = 1,399), Median (IQR)	Yes (n = 334), Median (IQR)	P ^a
Oncotype-like	1,671	35 (26-46)	36 (27-47)	.5	1,733	35 (25-45)	39 (30-52)	<.001
Macrophage M2	1,671	-0.02 (-0.31 to 0.28)	-0.06 (-0.34 to 0.27)	.6	1,733	-0.04 (-0.34 to 0.26)	0.06 (-0.20 to 0.38)	<.001
CXCL13	1,671	4.15 (2.22-5.31)	4.11 (2.10-5.24)	.4	1,733	4.16 (2.45-5.33)	4.02 (1.29-5.18)	.091
T-cell	1,671	-0.03 (-0.48 to 0.47)	-0.04 (-0.53 to 0.42)	.2	1,733	-0.04 (-0.49 to 0.46)	-0.03 (-0.47 to 0.46)	.8
Variable	pT Stage				pN Stage			
	No.	pT1-3 (n = 1,365), Median (IQR)	pT4 (n = 367), Median (IQR)	P ^a	No.	pN1 (n = 1,087), Median (IQR)	pN2 (n = 646), Median (IQR)	P ^a
Oncotype-like	1,732	34 (25-45)	40 (31-51)	<.001*	1,733	34 (24-46)	37 (29-47)	<.001
Macrophage M2	1,732	-0.05 (-0.34 to 0.27)	0.06 (-0.21 to 0.34)	<.001*	1,733	-0.05 (-0.36 to 0.27)	0.03 (-0.25 to 0.30)	.001
CXCL13	1,732	4.17 (2.34-5.31)	4.11 (1.98-5.26)	.8	1,733	4.13 (2.17-5.30)	4.18 (2.35-5.31)	.6
T-cell	1,732	-0.04 (-0.49 to 0.46)	-0.01 (-0.50 to 0.44)	>.9	1,733	-0.03 (-0.49 to 0.45)	-0.04 (-0.49 to 0.48)	>.9
Variable	Histologic Grade				MMR Status			
	No.	G1-2 (n = 1,390), Median (IQR)	G3-4 (n = 323), Median (IQR)	P ^a	No.	dMMR (n = 171), Median (IQR)	pMMR (n = 1,528), Median (IQR)	P ^a
Oncotype-like	1,713	35 (26-45)	39 (28-49)	<.001*	1,699	38 (28-47)	35 (26-46)	.092
Macrophage M2	1,713	-0.03 (-0.33 to 0.26)	0.06 (-0.25 to 0.36)	.002*	1,699	0.13 (-0.12 to 0.41)	-0.04 (-0.34 to 0.27)	<.001
CXCL13	1,713	4.10 (2.03-5.20)	4.64 (2.93-5.77)	<.001*	1,699	5.64 (4.75-6.69)	3.96 (1.70-5.13)	<.001
T-cell	1,713	-0.05 (-0.50 to 0.44)	0.10 (-0.41 to 0.57)	.005*	1,699	0.40 (-0.13 to 0.71)	-0.09 (-0.52 to 0.43)	<.001
Variable	RAS Mutation Status				BRAF Mutation Status			
	No.	WT (n = 820), Median (IQR)	MT (n = 775), Median (IQR)	P ^a	No.	WT (n = 1,471), Median (IQR)	MT (n = 184), Median (IQR)	P ^a
Oncotype-like	1,595	34 (24-45)	36 (28-47)	<.001*	1,655	35 (26-45)	41 (31-52)	<.001
Macrophage M2	1,595	-0.04 (-0.32 to 0.25)	-0.01 (-0.31 to 0.30)	.3	1,655	-0.05 (-0.33 to 0.25)	0.16 (-0.14 to 0.43)	<.001
CXCL13	1,595	4.21 (2.57-5.34)	3.96 (1.61-5.16)	.007*	1,655	4.05 (2.02-5.22)	4.77 (3.64-5.87)	<.001
T-cell	1,595	0.05 (-0.45 to 0.52)	-0.13 (-0.53 to 0.40)	<.001*	1,655	-0.08 (-0.51 to 0.44)	0.28 (-0.21 to 0.66)	<.001
Variable	CMS							
	No.	CMS1 (n = 309), Median (IQR)	CMS2 (n = 635), Median (IQR)	CMS3 (n = 362), Median (IQR)	CMS4 (n = 412), Median (IQR)	P ^a		
Oncotype-like	1,718	40 (31-48)	28 (20-34)	33 (25-41)	50 (42-58)	<.001		
Macrophage M2	1,718	0.21 (-0.04 to 0.42)	-0.21 (-0.44 to 0.02)	-0.19 (-0.44 to 0.06)	0.28 (0.06 to 0.47)	<.001		

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TABLE 1. Median Values of the Four Scores According to Patient Characteristics in the PETACC-8 Cohort (continued)

Variable	No.	CMS				P ^a
		CMS1 (n = 309), Median (IQR)	CMS2 (n = 635), Median (IQR)	CMS3 (n = 362), Median (IQR)	CMS4 (n = 412), Median (IQR)	
CXCL13	1,718	5.31 (4.22-6.38)	3.74 (0.93-4.92)	3.87 (1.31-4.94)	4.23 (2.19-5.40)	<.001
T-cell	1,718	0.34 (-0.22 to 0.70)	-0.26 (-0.61 to 0.27)	-0.11 (-0.47 to 0.38)	0.10 (-0.37 to 0.50)	<.001

NOTE. Bold indicates $P < .05$.

Abbreviations: CMS, consensus molecular subtype; dMMR, deficient mismatch repair; ECOG, Eastern Cooperative Oncology Group; MMR, mismatch repair; MT, mutated; pMMR, proficient mismatch repair; PS, performance status; WT, wild-type.

^aWilcoxon rank-sum test.

cohort. In the subgroup of patients with positive ctDNA, the 3-year TTR rate was 49% (95% CI, 37 to 65) and 20% (95% CI, 8.3 to 48) in patients with IPS scores 0-2 and 3-4, respectively, and in the subgroup of patients with negative ctDNA, the 3-year TTR rate was 86% (95% CI, 82 to 91) and 76% (95% CI, 68 to 86), respectively (Fig 4). In a multivariable model, IPS scores of 3-4 and ctDNA positivity were still associated with a shorter TTR (HR, 2.32 [95% CI, 1.56 to 3.45]; $P < .001$ and HR, 4.85 [95% CI, 3.22 to 7.32]; $P < .001$, respectively), in addition to T and N stage and chemotherapy duration, with a C-index of 0.75 (Data Supplement, Table S8).

DISCUSSION

From 3'RNAseq data of two large, randomized phase III trials solely composed of patients with stage III CC, these two prognostic models and the IPS score on the basis of four transcriptomic signatures reflecting the TME and cell cycle allowed a good stratification of patients on the risk of recurrence, in addition to well-established prognostic factors.

Overexpressed signatures reflecting T-cell and B-cell/TLS infiltration and cell cycle were associated with a good prognosis, whereas overexpressed signatures reflecting stroma and M2 macrophage infiltration were associated with poorer prognosis in our two independent cohorts of patients.

The Simple and Extended Prognostic Models and the IPS score represent different ways of showing the significant

prognostic value of the combination of these four signatures reflecting different compartments of the TME. The implementation of these four transcriptomic signatures to the known prognostic clinicopathologic and molecular variables in the Extended Prognostic Model improved the performance of the latter for predicting the risk of recurrence. The higher the IPS score, the shorter the TTR, demonstrating an additive effect of these signatures. Interestingly, the weight of the IPS score variable in the explanation of the variance of the TTR model was significant, just after the pN stage but before the pT stage and the pejorative combinations of CMS.

In current clinical practice, the duration of adjuvant chemotherapy is based on clinical risk groups, but using results from this study on transcriptomic classification, patients with clinical high-risk tumors (T4 and/or N2) with a low risk of recurrence could be identified, perhaps because of better effectiveness of adjuvant chemotherapy when the TME is favorable, and conversely the low-risk patients (T1-3 N1) with a high risk of recurrence if the TME is not favorable. Thus, in the IDEA-France cohort comparing 3 months with 6 months of adjuvant chemotherapy, we established a new classification into three groups, on the basis of the clinical risk group and the quartile of the Extended Prognostic Model. We were able to identify the groups that benefited from the extension of chemotherapy duration to 6 months: the intermediate-risk and high-risk groups. It should be noted that 90% of patients in the IDEA-France trial were treated with the FOLFOX regimen, with superiority of FOLFOX 6 months over FOLFOX 3 months in the overall analysis set.²⁰

TABLE 2. Univariable and Multivariable Analyses of the Four Scores in PETACC8 Patients

Variable	Univariable Analysis		Multivariable Model = Simplified Prognostic Model	
	HR (95% CI)	P	HR (95% CI)	P
Oncotype-like	1.02 (1.01 to 1.03)	<.001	1.02 (1.01 to 1.02)	<.001
CXCL13	0.90 (0.87 to 0.94)	<.001	0.92 (0.88 to 0.96)	<.001
T-cell	0.72 (0.60 to 0.86)	<.001	0.71 (0.58 to 0.87)	<.001
Macrophage M2	1.77 (1.37 to 2.29)	<.001	1.49 (1.09 to 2.03)	.012

NOTE. C-index = 0.633 and No. of events = 461.

Abbreviation: HR, hazard ratio.

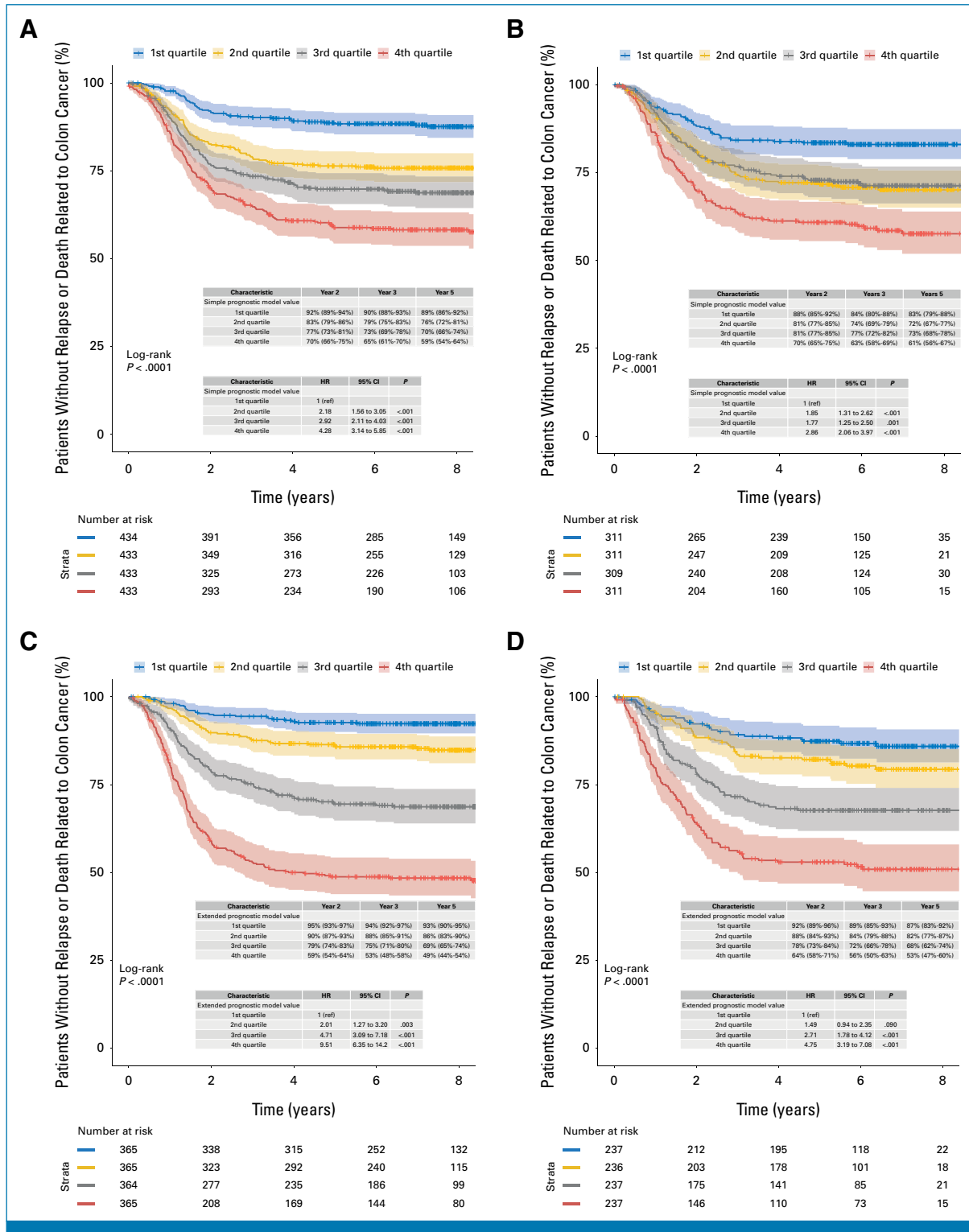


FIG 2. Kaplan-Meier curves for TTR according to the quartile of the simple/extended prognostic model value in PETACC-8 and IDEA-France cohorts. (A) TTR according to the quartile of Simple Prognostic Model value in the PETACC-8 cohort. (B) TTR according to the quartile of Simple Prognostic Model value in the IDEA-France cohort. (C) TTR according to the quartile of the Extended Prognostic Model value in the PETACC-8 cohort. (D) TTR according to the quartile of the Extended Prognostic Model value in the IDEA-France cohort. HR, hazard ratio; ref, reference; TTR, time to recurrence.

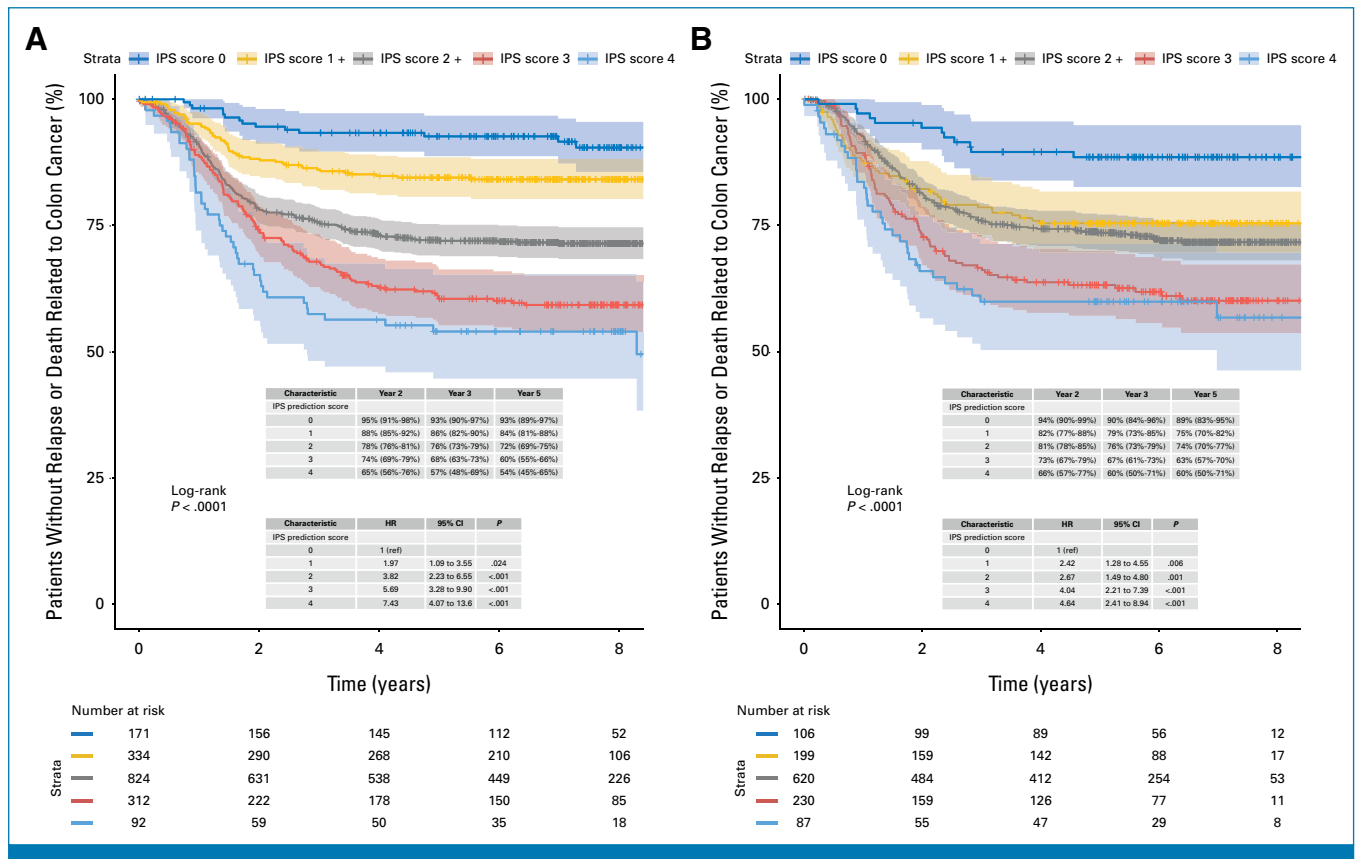


FIG 3. Kaplan-Meier curves for TTR according to IPS score in PETACC-8 and IDEA-France cohorts. (A) TTR according to IPS score in the PETACC-8 cohort. (B) TTR according to IPS score in the IDEA-France cohort. HR, hazard ratio; IPS, Immune Proliferative Stromal; ref, reference; TTR, time to recurrence.

In addition, in patients from the IDEA-France cohort for whom the postoperative ctDNA result with a tumor-informed approach was available, this transcriptomic classification of the TME allowed identification of patients with ctDNA negativity having a high 3-year recurrence rate of 24% in the case of a high IPS score (compared with 14% in those with a low IPS score). Conversely, in patients with ctDNA positivity, the classification identified those with a 3-year recurrence risk of only 51% in the case of a low IPS score (compared with 80% in those with a high IPS score), demonstrating the added value of this classification for patient stratification regarding recurrence risk, in addition to the ctDNA test.

The prognostic value of T-cell infiltration has been demonstrated in many studies, in particular, with the Immunoscore in localized CC.^{5,24} We decided not to include the results of the Immunoscore available for a subgroup of patients from the IDEA-France cohort²⁴ because these were not available for the entire PETACC-8 cohort and only concerned a subset of patients from the IDEA-France cohort. In addition, the analysis of T-cell infiltration using the same method as those of other TME cells, using 3'RNAseq, seemed to be more suitable for a potential use in future clinical

practice. The infiltration of B cells, mediators of adaptive antitumor immunity, especially into mature TLS, is also associated with a better prognosis in localized CC.^{17,25} The prognostic role of TAMs is complex, with a different prognostic impact depending on their types and locations, with M2-polarized TAM, harboring pro-oncogenic functions and associated with the worse prognosis. The study by Herrera et al¹⁸ showed that in 289 patients with CC, high expressions of markers of cancer-associated fibroblasts and macrophages M2 were associated with poor clinical outcomes and that the combination of the two entities improved the prediction prognosis. The intratumoral stroma, in general, also has a prognostic impact, particularly the stroma/tumor cells ratio, as demonstrated in a post hoc analysis of the VICTOR trial in stage II-III CRC.²⁶

Interestingly, the positive prognostic impact of the Oncotype-like cell cycle score in our two cohorts of patients is consistent with literature findings, such as the high expression of KI67 associated with a favorable prognosis,²⁷⁻²⁹ contrary to other tumor types. The study by Anjomshoa et al³⁰ defined a cellular proliferation signature in CRC, showing an increased risk of recurrence in patients with this underexpressed signature across two independent patient cohorts.

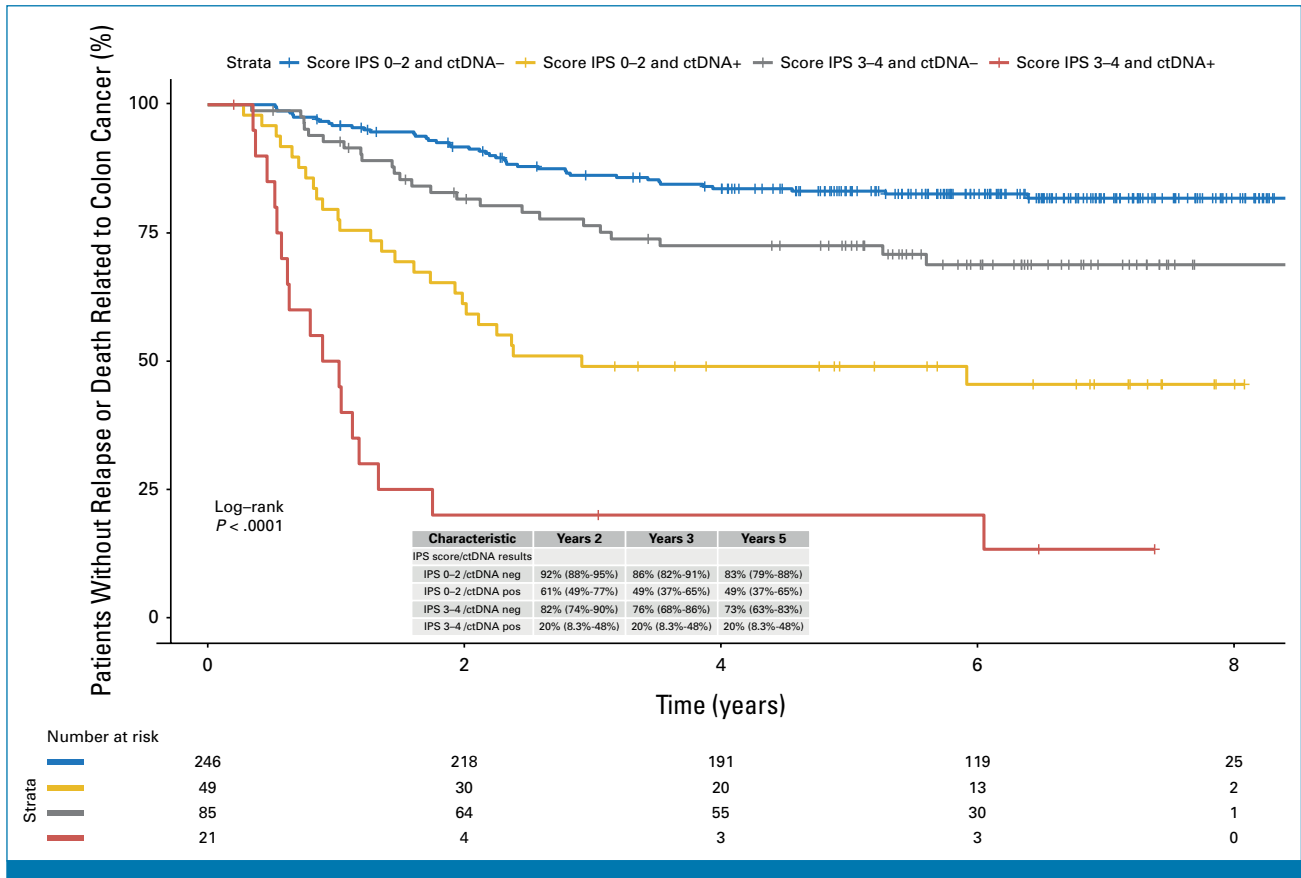


FIG 4. Kaplan-Meier curves for TTR according to IPS score and ctDNA in the IDEA-France cohort. ctDNA, circulating tumor DNA; IPS, Immune Proliferative Stromal; TTR, time to recurrence.

Several hypotheses can be proposed regarding the positive prognostic impact of the proliferating colorectal tumors: the accumulation of genetic events leading to a decrease in cancer cell survival capacity, the induction of a more significant and effective immune response, the reduction in the proportion of slow-dividing cancer stem cells, and the decrease in the epithelial-mesenchymal transition process of cancer cells. Interestingly, among patients with a postoperative positive ctDNA, those with a low IPS score indicating cycling tumors might have a favorable prognosis as adjuvant FOLFOX chemotherapy in this scenario could be particularly effective. Conversely, those with a high IPS score, indicating noncycling tumors, have a poor prognosis, maybe due to the lesser benefit of this chemotherapy in enabling ctDNA clearance.

The strengths of this work lie in the analysis of two distinct sets of clinical trial participants with comprehensive clinical and pathologic annotations. Each set is both large and homogeneous as they come from phase III prospective trials. The two models and the IPS score were built and defined from the training PETACC-8 cohort and were then applied and validated on the independent IDEA-France cohort, demonstrating their prognostic value. Our results are obtained from a single method: bulk 3'RNA seq, easily

performed on FFPE tissue (slides in PETACC-8 and punch biopsies in IDEA-France) and probably at reasonable cost in a near future. Other validated biomarkers, such as Immunoscore or Oncotype DX CC RS, incur higher costs, and this unique 3' RNA-seq method enables the aggregation of this information to mitigate expenses.

Our study also has several limitations including the absence of a matched cohort without adjuvant chemotherapy, making it impossible to conclude on the predictive value of the efficacy of chemotherapy but only on the global prognostic value. In addition, RNAseq is not validated in current clinical practice, and we did not integrate ctDNA data for the majority of patients.

To date, one of the most promising and studied biomarkers is the assessment of minimal residual disease postoperatively using ctDNA detection.^{31,32}

To conclude, these transcriptomic signatures related to the infiltration of T cells, B cells, TLS, macrophages M2, stroma, and cell cycle provide important information in addition to known prognostic factors for patient stratification on risk of recurrence. Beyond T and N stages for the decision of adjuvant chemotherapy in stage III CC, the combination of

TABLE 3. Multivariable Models for TTR Including IPS Score in PETACC-8 and IDEA-France Cohorts

Characteristic	PETACC8 Cohort		IDEA-France Cohort	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
IPS score				
0	—		—	
1	1.82 (1.01 to 3.29)	.047	2.44 (1.29 to 4.60)	.006
2	3.57 (2.08 to 6.13)	<.001	2.71 (1.50 to 4.87)	<.001
3	4.67 (2.68 to 8.14)	<.001	4.08 (2.22 to 7.49)	<.001
4	5.58 (3.04 to 10.3)	<.001	4.80 (2.47 to 9.33)	<.001
pT				
pT1-3	—		—	
pT4	1.98 (1.63 to 2.41)	<.001	1.56 (1.23 to 1.98)	<.001
pN				
pN1	—		—	
pN2	2.29 (1.90 to 2.76)	<.001	2.57 (2.07 to 3.19)	<.001
Pejorative combinations of CMS				
Good	—		—	
Bad	1.50 (1.22 to 1.85)	<.001	1.08 (0.82 to 1.41)	.6
Chemotherapy duration				
6 months	—		—	
3 months	—		1.53 (1.23 to 1.89)	<.001

Abbreviations: CMS, consensus molecular subtype; HR, hazard ratio; IPS, Immune Proliferative Stromal; TTR, time to recurrence.

these different variables could be exploited in the future for personalized care (de-escalation, intensification) or as stratification factors in future adjuvant therapeutic trials.

Integrating this characterization of TME through transcriptome analysis, the genetic profiling of tumor cell DNA (via NGS), and the use of liquid biopsy, as a multiomic approach, thus appears to be an interesting and promising

avenue for better stratifying patients on the basis of recurrence risk to personalize our adjuvant treatment although RNA sequencing normalization, analysis, and interpretation can be more complex for clinicians compared with DNA-based variant calling tests.

This concept needs to be prospectively validated in a dedicated therapeutic trial.

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CLINICAL TRIAL INFORMATION

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DATA SHARING STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Prognostic Models From Transcriptomic Signatures of the Tumor Microenvironment and Cell Cycle in Stage III Colon Cancer From PETACC-8 and IDEA-France Trials**

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