Characteristics of Patients and Prognostic Factors Across Treatment Lines in Metastatic Colorectal Cancer: An Analysis From the Aide et Recherche en Cancérologie Digestive Database

Jean-Baptiste Bachet, MD[1]; Aimery de Gramont, MD[2,3]; Morteza Raeisi, PhD[4]; Manel Rakez, PhD[4]; Richard M. Goldberg, MD[5]; Niall C. Tebbutt, MD, PhD[6]; Eric Van Cutsem, MD, PhD[7]; Daniel G. Haller, MD[8]; J. Randolph Hecht, MD[9]; Robert J. Mayer, MD[10]; Stuart M. Lichtman, MD[11]; Al B. Benson, MD[12]; Alberto F. Sobrero, MD[13]; Josep Tabernero, MD[14]; Richard Adams, MD[15]; John R. Zalcberg, MD[16]; Axel Grothey, MD[17]; Takayuki Yoshino, MD, PhD[18]; Thierry André, MD[3,19]; Qian Shi, PhD[20]; and Benoist Chibaudel, MD[2]

DOI https://doi.org/10.1200/JCO-24-01968

ABSTRACT

PURPOSE Several lines of treatment can be used sequentially in patients with metastatic colorectal cancer. We investigated the evolution of patient/tumor characteristics and their prognostic impact across treatment lines to develop an overall prognostic score (OPS).

PATIENTS AND METHODS Individual patient data from 48 randomized trials were analyzed. The end point was overall survival (from random assignment to death). Missing data were imputed. The complete data set was then separated into construction (80%) and validation sets (20%). The Cox's model was used to define risk groups for survival using the OPS. The discrimination capability was assessed in each treatment-line via bootstrapping to obtain optimism-corrected calibration and discrimination C-indices. Internal validation was done in the validation set.

RESULTS A total of 37,560 patients (26,974 in first-line [1L], 7,693 in second-line [2L], and 2,893 in third-line [3L]) were analyzed. Some clinical, biological, and molecular characteristics of patients/tumors included in therapeutic trials evolve over the lines. Seven independent prognostic variables were retained in the final multivariate model common to all lines: Eastern Cooperative Oncology Group performance status, hemoglobin, platelet count, WBC/absolute neutrophil count ratio, lactate dehydrogenase, alkaline phosphatase, and the number of metastatic sites. The OPS was used to define four patient subgroups with significantly different prognoses in 1L, 2L, and 3L, separately, with adequate C-indices: 0.65, 0.66, and 0.69 in the construction set and 0.65, 0.66, and 0.68 in the validation set, respectively. The OPS was not predictive, with 3L drugs (*v* placebo) or subsequent line (2L/1L or 3L/2L) extending survival in all prognostic groups.

CONCLUSION The same prognostic model using practical variables can be used before all treatment lines. The OPS could better stratify patients in future clinical trials and help to therapeutic decision in routine practice.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Accepted March 14, 2025
Published May 5, 2025

J Clin Oncol 43:2094-2106
© 2025 by American Society of Clinical Oncology

View Online Article

Creative Commons Attribution Non-Commercial No Derivatives 4.0 License

INTRODUCTION

The overall survival (OS) of patients with metastatic colorectal cancer (mCRC) has steadily increased over the past 20 years, reaching more than 30 months in first-line (1L) phase III studies.[1-3]

In 1L, there are multiple therapeutic options with cytotoxic agents, targeted therapies (anti-EGFR antibodies in molecularly selected patients and antiangiogenic agents), and immune checkpoint inhibitors for deficient mismatch repair (dMMR)/microsatellite instability (MSI) phenotype tumors.[4-9] In second-line (2L), a combination of cytotoxic and antiangiogenic agents is the standard,[7,10] with the exception of the combination encorafenib plus cetuximab in mutated *BRAF*/V600E tumor subgroup.[11] Finally, in advanced lines, trifluridine/tipiracil and regorafenib were the two therapeutic options before the results of the SUNLIGHT and

CONTEXT

Key Objective
To define a prognostic score that can be used before each line of chemotherapy.

Knowledge Generated
Treatment guidelines for patients with metastatic colorectal cancer (mCRC) are formulated according to successive lines of treatment. However, the prognosis of patients is very heterogeneous, and between 30% and 50% of the patients are not eligible to a subsequent line.

Relevance *(E.M. O'Reilly)*
The overall prognostic score model, derived from clinical and biologic factors from a very large data set, provides prognostic insights for patients with mCRC. In the future, such modeling approaches may inform specific treatment assignments.*

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

FRESCO2 trials positioned a combination of trifluridine/tipiracil plus bevacizumab and fruquintinib as new therapeutic options in third-line (3L) and fourth-line, respectively.[12-15] These data have been fully integrated into oncology guidelines in which therapeutic options are described according to successive therapeutic lines.[3,16]

In population-based studies, almost one in two patients do not receive a subsequent therapeutic line with 2L and 3L treatment rates of 50%-60% and 20%-30%, respectively.[17,18] These results highlight that multiline treatment strategies are not feasible for all patients and that patients included in late-line clinical trials were highly selected. In routine practice, physicians often overestimate survival of patients with cancer, and the benefit/risk ratio of a subsequent line is not easy to estimate.[19,20] Several prognostic scores have been proposed in patients with mCRC, in 1L as well as in late-line.[21-24] However, treatment options and clinical practice have evolved since the time that these prognostic scores were developed.

In this analysis, using pooled individual patient data from randomized clinical trials in the Aide et Recherche en Cancérologie Digestive (ARCAD) database of patients with mCRC, we aim to investigate the different features of patients included in first, 2L, and 3L treatments, and develop an overall prognostic score (OPS). To be easily used in routine practice, this OPS had to include the same variables, whatever the line, and to be prognostic before the beginning of each therapeutic line.

PATIENTS AND METHODS

Trial and Patient Selection

Individual patient data from 48 randomized clinical trials across treatment lines of mCRC were analyzed to construct and independently validate a prognostic score model for OS. Detailed information on trials and treatment arms included are provided in the Data Supplement (Table S1, online only). Eligible variables had to be available in all lines with a missing data percentage ≤65% in 1L trials, 35% in 2L trials, and 20% in 3L trials. Candidate variables were sex (men, women), age (<75, ≥75 years), BMI (<30, ≥30 kg/m^2), Eastern Cooperative Oncology Group (ECOG) performance status (PS; 0, 1, ≥2), bilirubin (<1.17, ≥1.17 mg/dL), hemoglobin (HGB; <12, ≥12 g/dL), platelet (PLT) count (<400, ≥400 10^9/L), WBC count (<10, ≥10 10^9/L), absolute neutrophil count (ANC; <4, ≥4 10^9/L), lactate dehydrogenase (LDH; <1 UNL, ≥1 UNL), alkaline phosphatase (ALP; <1 UNL, 1-3 UNL, ≥3 UNL), *KRAS* status (mutated *v* wild-type [WT]), primary tumor location (colon, rectum, both, where both refers to cases with synchronous primary tumors in both the colon and rectum), number of metastatic sites (0-1, ≥2), and lung (absence, presence) and liver metastases (absence, presence); derived WBCs-to-ANCs ratio (WBC/ANC; <1.45, ≥1.45) was also selected as a variable because of the partial redundancy between the two variables (WBC and ANC) and a better prognostic value of it independently of the other two variables taken independently.[25] For laboratory parameters, the upper limit of the normal range was initially used as the cutoff. The WBC/ANC ratio cutoff was determined using a method to optimize differentiation of patient groups with distinct survival outcomes, maximizing its prognostic value. All the clinical and laboratory parameters were measured at the time of enrollment in the clinical trials.

Statistical Analyses

The end point was OS, which was defined as the time from random assignment to death from any cause. The continuous variables were described using the median (IQR) and were compared using Wilcoxon rank sum test or Kruskal-Wallis test. The categorical variables were described using frequencies and were compared across treatment lines using

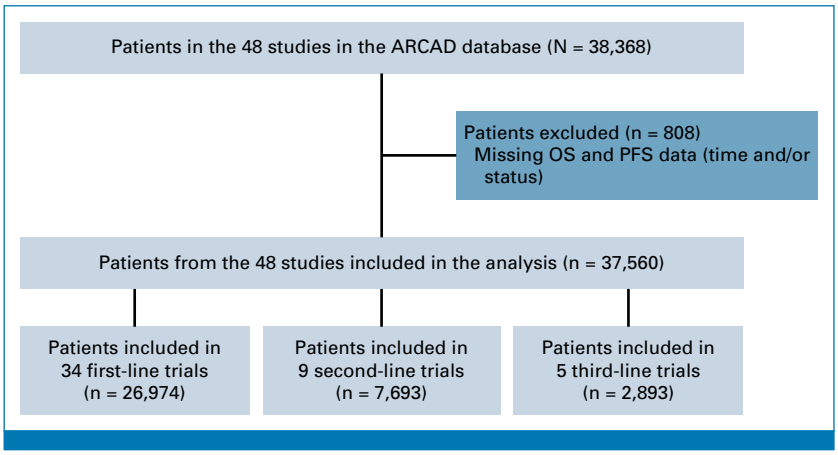

FIG 1. Flow diagram of the population study. ARCAD, Aide et Recherche en Cancérologie Digestive; OS, overall survival; PFS, progression-free survival.

Fisher's exact test and χ^2 test. To account for missing data in the candidate variables, multiple imputations technique using the chained equations methods was employed separately within each treatment line.[26] The complete data set was then randomly selected and separated into construction (n = 30,050; 80%) and validation sets (n = 7,510; 20%) to construct and validate the OPS model for survival. To construct the OPS model, first, univariate and multivariate analyses, on the construction data set, of candidate factors were performed separately in 2L and 3L to identify common prognostic factors. Univariate Cox models stratified by treatment arm within each study estimated the hazard ratio (HR) and 95% CI for factors associated with OS. Because of the large sample size, variables significantly associated with OS in univariate analysis, particularly those with a strong impact, were included in the multivariate model. The final multivariate Cox model included all variables with $P < .05$ and HR ≥1.30 from the univariate model. Statistically significant prognostic factors from the multivariate Cox model were selected using backward elimination procedure. The OPS model was developed using the final multivariate Cox regression model coefficients. For each patient i, an individual raw prognostic score was calculated as the sum of the corresponding coefficients of the p prognostic factors included in the final model. For example, with a binary variable X_p, the individual score was set to 1 if the individual observed value was in the reference category and $\exp(\beta_p)$ otherwise (individual observed value ≠ reference class).[27] This approach ensured each patient received a raw prognostic score reflecting their individual risk profile. The raw scores were then normalized to a range of 0-5 using linear scaling to ensure patient comparability. To classify patients into four prognostic groups, cutoffs for the normalized scores were determined using a standardized approach on the basis of Cox's[28] optimal cutoff method. These groups represent increasing risk levels, with higher scores indicating a poorer prognosis. The derivation of the cutoffs and detailed calculation steps are provided in the Data Supplement.

To ensure the model's applicability across different lines of treatment, it was also applied to the 1L trials. The discrimination capability was assessed in each treatment line via bootstrapping to obtain optimism-corrected calibration and discrimination C-indices.[29,30] Internal validation was performed on the validation set. The predictive accuracy of the OPS model was examined and compared with the GERCOR scoring system by calculating Harrell's C-index, and the statistical significance was assessed using DeLong's test. Analyses were conducted with R software (version 3.5.2), with all statistical tests being two-sided and considered statistically significant when $P < .05$. All CIs are 95%.

RESULTS

Population Study

A total of 37,560 patients (26,974 in 1L, 7,693 patients in 2L, and 2,893 patients in 3L) were analyzed (Fig 1). The following patient/tumor characteristics increased continuously over treatment lines: ≥two metastatic sites, lung metastases, lymph node metastases, *KRAS* mutation, and elevated ALP; *BRAF* mutation decreased. In 1L versus 3L trials, 70% versus 89% of patients had primary tumor resection, and 10% versus 80% had at least one metastasectomy (Table 1).

Imputation

Imputation results were satisfactory overall in all treatment lines, with a difference after and before imputation lower than 5% at the exception of a slightly higher difference for lung metastases in 1L and 2L scenarios (Δ = 5.40% and 5.86%, respectively; Data Supplement, Table S2).

OPS Model

After univariate then multivariate analyses in 2L and 3L on the construction data set, the common multivariate model

TABLE 1. Patient Characteristics Across Treatment Lines

Variable	First-Line (n = 26,974), No. (%)	Second-Line (n = 7,693), No. (%)	Third-Line (n = 2,893), No. (%)	*P*
Sex				.240
Female	10,371 (38.47)	3,026 (39.33)	1,091 (37.71)	
Male	16,585 (61.53)	4,667 (60.67)	1,802 (62.29)	
Missing	18 (0.07)	—	—	
Age, years				.008
<75	24,528 (90.96)	7,073 (91.96)	2,660 (91.95)	
≥75	2,439 (9.04)	618 (8.04)	233 (8.05)	
Missing	7 (0.03)	2 (0.03)	—	
ECOG PS				<.001
0	14,553 (54.46)	3,661 (50.97)	1,387 (47.94)	
1	11,169 (41.80)	3,218 (44.80)	1,301 (44.97)	
≥2	1,000 (3.74)	304 (4.23)	205 (7.09)	
Missing	252 (0.93)	510 (6.63)	—	
BMI, kg/m^2				.044
<30	20,690 (80.97)	5,161 (80.89)	2,000 (83.02)	
≥30	4,862 (19.03)	1,219 (19.11)	409 (16.98)	
Missing	1,422 (5.27)	1,313 (17.07)	484 (16.73)	
Albumin, g/L				.990
<30	493 (4.78)	241 (4.84)	105 (4.77)	
≥30	9,821 (95.22)	4,740 (95.16)	2,097 (95.23)	
Missing	16,660 (61.76)	2,712 (35.25)	691 (23.89)	
Bilirubin, mg/dL				<.001
<1.17	21,843 (91.68)	4,757 (77.44)	2,579 (90.59)	
≥1.17	1,982 (8.32)	1,386 (22.56)	268 (9.41)	
Missing	3,149 (11.67)	1,550 (20.15)	46 (1.59)	
HGB, g/dL				<.001
<12	7,589 (39.79)	2,035 (35.52)	1,163 (40.78)	
≥12	11,482 (60.21)	3,694 (64.48)	1,689 (59.22)	
Missing	7,903 (29.30)	1,964 (25.53)	41 (1.42)	
PLTs, 10^9				<.001
<400	18,297 (75.45)	5,378 (92.52)	2,573 (90.25)	
≥400	5,953 (24.55)	464 (7.48)	278 (9.75)	
Missing	2,724 (10.10)	1,491 (19.38)	42 (1.45)	
WBC, 10^9				<.001
<10	17,347 (77.55)	5,129 (86.49)	2,299 (80.58)	
≥10	5,023 (22.45)	801 (13.51)	554 (19.42)	
Missing	4,604 (17.07)	1,763 (22.92)	40 (1.38)	
ANC, 10^9				<.001
<4	5,017 (25.23)	2,303 (37.85)	734 (26.94)	
≥4	14,869 (74.77)	3,781 (62.15)	1,991 (73.06)	
Missing	7,088 (26.28)	1,609 (20.92)	168 (5.81)	
LDH, U/L				<.001
<1 UNL	4,112 (51.58)	2,441 (49.79)	734 (32.39)	
≥1 UNL	3,860 (48.42)	2,462 (50.21)	1,532 (67.61)	
Missing	19,002 (70.45)	2,790 (36.27)	627 (21.67)	
ALP, U/L				<.001
<1 UNL	4,441 (53.87)	2,840 (47.88)	1,098 (38.66)	
1-3 UNL	2,984 (36.20)	2,513 (42.36)	1,374 (48.38)	
≥3 UNL	819 (9.93)	579 (9.76)	368 (12.96)	

(continued on following page)

TABLE 1. Patient Characteristics Across Treatment Lines (continued)

Variable	First-Line (n = 26,974), No. (%)	Second-Line (n = 7,693), No. (%)	Third-Line (n = 2,893), No. (%)	*P*
Missing	18,730 (69.44)	1,761 (22.89)	53 (1.83)	
CEA, ng/mL				<.001
Median (Q1-Q3)	42 (9-229.2)	42.9 (9.2-203)	160.6 (31.75-661)	
Missing	13,204 (48.95)	3,572 (46.43)	2,293 (79.26)	
CEA, UNL				<.001
Median (Q1-Q3)	4.99 (3-5)	5 (4.99-5)	3 (3-3)	
Missing	22,096 (81.92)	4,296 (55.84)	2,307 (79.74)	
KRAS				<.001
WT	6,769 (63.59)	1,708 (53.41)	1,165 (49.57)	
MT	3,876 (36.41)	1,490 (46.59)	1,185 (50.43)	
Missing	16,329 (60.54)	4,495 (58.43)	543 (18.77)	
BRAF				<.001
WT	6,489 (90.69)	621 (92.00)	835 (94.67)	
MT	666 (9.31)	54 (8.00)	47 (5.33)	
Missing	19,819 (77.18)	7,018 (91.23)	2,011 (69.51)	
RAS				—
WT	2,838 (54.96)	—	—	
MT	2,326 (45.04)	—	—	
Missing	21,810 (80.86)	7,693 (100)	2,893 (100)	
Primary tumor site				<.001
Colon only	13,387 (69.08)	3,420 (65.96)	1,846 (63.92)	
Rectum only	5,700 (29.41)	1,704 (32.86)	891 (30.85)	
Both	293 (1.51)	61 (1.18)	151 (5.23)	
Missing	7,594 (28.15)	2,508 (32.6)	5 (0.17)	
Primary tumor sidedness				—
Left	11,435 (77.36)	1,707 (100)	1,207 (89.47)	
Right	3,346 (37.69)	—	142 (10.53)	
Missing	12,193 (45.20)	5,989 (77.85)	1,544 (53.37)	
Number of metastatic sites				<.001
0-1	11,495 (43.20)	2,136 (27.87)	512 (17.88)	
≥2	15,111 (56.80)	5,528 (72.13)	2,351 (82.12)	
Missing	368 (1.36)	29 (0.38)	30 (1.04)	
Lung metastases				<.001
Absent	9,906 (49.78)	1,359 (25.53)	201 (8.93)	
Present	9,993 (50.22)	3,964 (74.47)	2,050 (91.07)	
Missing	7,075 (26.23)	2,370 (30.81)	642 (22.19)	
Liver metastases				<.001
Absent	3,723 (15.11)	1,364 (18.87)	107 (4.57)	
Present	20,921 (84.89)	5,864 (81.13)	2,234 (95.43)	
Missing	2,330 (8.64)	465 (6.04)	552 (19.08)	
Lymph node metastases				<.001
Absent	8,563 (49.47)	1,773 (38.51)	308 (20.49)	
Present	8,745 (50.53)	2,831 (61.49)	1,195 (79.51)	
Missing	9,666 (35.83)	3,089 (40.15)	1,390 (48.05)	
Peritoneum metastases				<.001
Absent	11,610 (84.19)	689 (46.27)	456 (56.44)	
Present	2,181 (15.81)	800 (53.73)	352 (43.56)	
Missing	13,183 (48.87)	6,204 (80.64)	2,085 (72.07)	
Disease status				<.001

(continued on following page)

TABLE 1. Patient Characteristics Across Treatment Lines (continued)

Variable	First-Line (n = 26,974), No. (%)	Second-Line (n = 7,693), No. (%)	Third-Line (n = 2,893), No. (%)	*P*
Synchronous	5,241 (65.58)	1,493 (58.41)	151 (18.69)	
Early metachronous	2,751 (34.42)	1,063 (41.59)	744 (81.31)	
Missing	18,982 (70.37)	5,137 (66.77)	1,998 (69.06)	
Primary tumor resection				<.001
No	2,885 (29.67)	24 (13.11)	87 (11.45)	
Yes	6,840 (70.33)	159 (86.89)	673 (88.55)	
Missing	17,249	7,510	2,133	
Metastasis surgery				<.001
No	8,922 (90.39)	2,230 (76.79)	315 (20.31)	
Yes	949 (9.61)	674 (23.21)	1,236 (79.69)	
Missing	17,103	4,789	1,352	

Abbreviations: ALP, alkaline phosphatase; ANC, absolute neutrophil count; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; HGB, hemoglobin; LDH, lactate dehydrogenase; MT, mutated; PLTs, platelets; PS, performance status; UNL, upper normal limit; WT, wild-type.

included seven variables of ECOG PS, HGB, PLT, WBC/ANC ratio, LDH, ALP, and number of metastatic sites (Data Supplement, Tables S3 and S4). The weighted prognostic factors across lines are reported in the Data Supplement (Tables S5-S7). Patients' scores were then grouped into four prognostic categories that were determined using the optimal cutoff point in the Cox method (Data Supplement, Tables S8-S10).

The OPS allowed us to define four patients' groups with significantly different prognoses in 2L and 3L with adequate C-index of 0.66 and 0.69 in the construction set and of 0.66 and 0.68 in the validation set, respectively (Figs 2 and 3). The OPS model in 1L outcomes were C-index of 0.65 in the construction set and 0.65 in the validation set (Fig 4).

The patient characteristics across the four prognostic subgroups within each treatment line are presented in the Data Supplement (Table S11). An increasing percentage of poor prognostic factors (liver metastases, multiple metastatic sites, and PS 2+) was observed from class 1 (low-risk) to class 4 (high-risk), but the percentage of *KRAS*/*BRAF* mutations was relatively similar in the different class groups. Approximately 40% of patients were classified as class 1 across all treatment lines (Data Supplement, Table S12).

Sensitively and Exploratory Analyses

In a sensitively analysis, the same common multivariate model was selected (seven variables) with the OPS model still valid when excluding patients with PS 2+ (Data Supplement, Table S12). In exploratory analyses, the relevance of the OS prognostic score was evaluated in different subgroups for which the missing data percentage was too high: in patients with *RAS*/*BRAF* WT tumor (n = 5,119), with *RAS* (n = 14,952) or *BRAF* (n = 767) mutated tumor, and in patients with left-sided primary tumors (n = 14,349), with synchronous (n = 6,885) or early metachronous (<6 months; n = 4,558) mCRC. In all these subgroups, the OPS was validated (Data Supplement, Figs S1-S6).

Predictive Performance of Prognostic Score Model

First, prediction of treatment effect according to prognostic groups was evaluated in heavily pretreated patients (≥3L). In two phase III trials, patients were randomly assigned to receive either placebo (PBO, n = 521) or an oral drug (regorafenib or TAS-102, n = 1,039). The treatment effect versus placebo was similar in all prognostic subgroups (Fig 5A).

Second, a total of 15,886 patients for whom information on the administration of a subsequent treatment-line was provided were selected to evaluate the discrimination and the predictive value of the four-class prognostic score (Data Supplement, Figs S7 and S8). Receiving subsequent lines (2L/1L or 3L/2L) improved the prognosis in all subgroups (Figs 5B and 5C).

GERCOR Score Model

By applying the GERCOR score model to the construction and validation sets in 1L, C-indices of 0.62 and 0.61, respectively, were obtained (Data Supplement, Fig S9). The GERCOR score model in the construction set yielded a median OS of 13.3 months (95% CI, 13.0 to 13.6) versus 9.8 months (95% CI, 9.4 to 10.3) with the OPS in the high-risk class. A DeLong's test comparison of the C-indices revealed a statistically significant difference ($P < .001$); the difference in C-indices (GERCOR minus OPS) had a 95% CI ranging from −0.0253 to −0.0136.

DISCUSSION

At the time of analysis, the ARCAD CRC database had included 37,560 patients with mCRC enrolled into 48

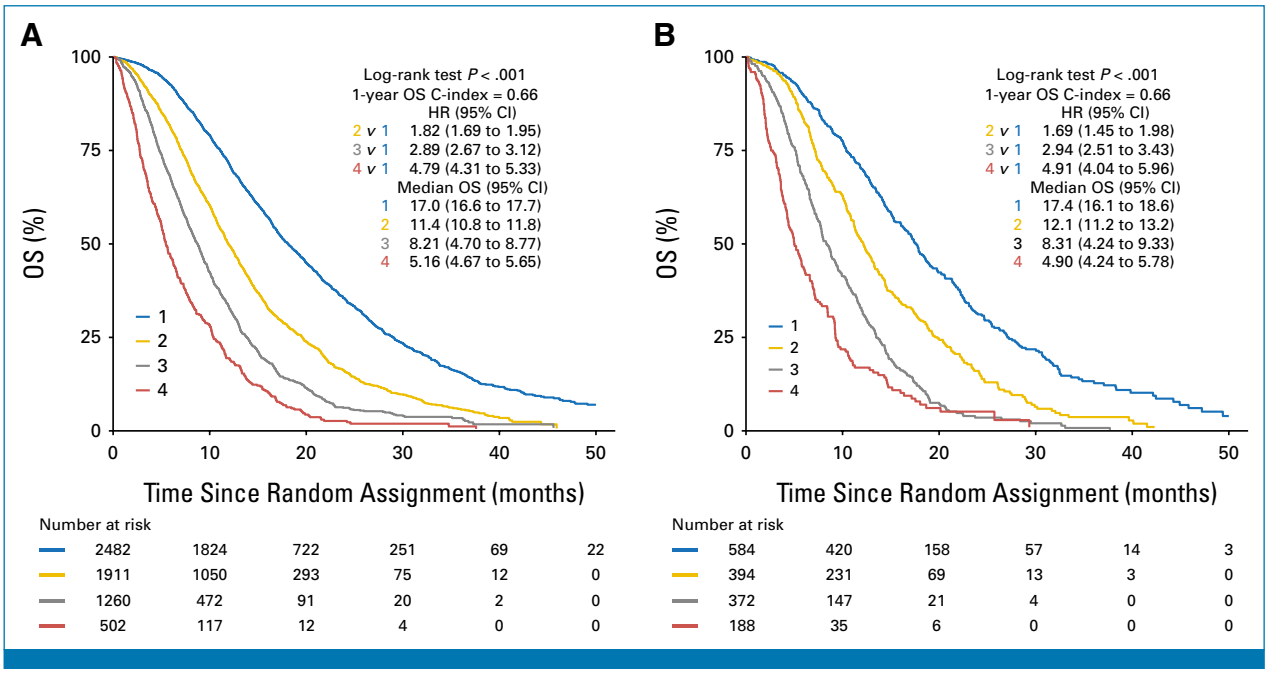

FIG 2. OS curves according to four risk classes of the prognostic model in 2L treatment of patients with mCRC from (A) construction set and (B) validation set. 2L, second-line; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival.

randomized clinical trials across different treatment lines. This large database allowed us to highlight the different features of patients included according to treatment line, then to construct and independently validate an OPS model for OS.

If some general characteristics (sex, age, BMI, primary tumor site, and albumin level) were relatively similar, whatever the treatment line, some others increased continuously over treatment line (number of metastatic sites, lung metastases, lymph nodes metastases, ALP level, and LDH level).

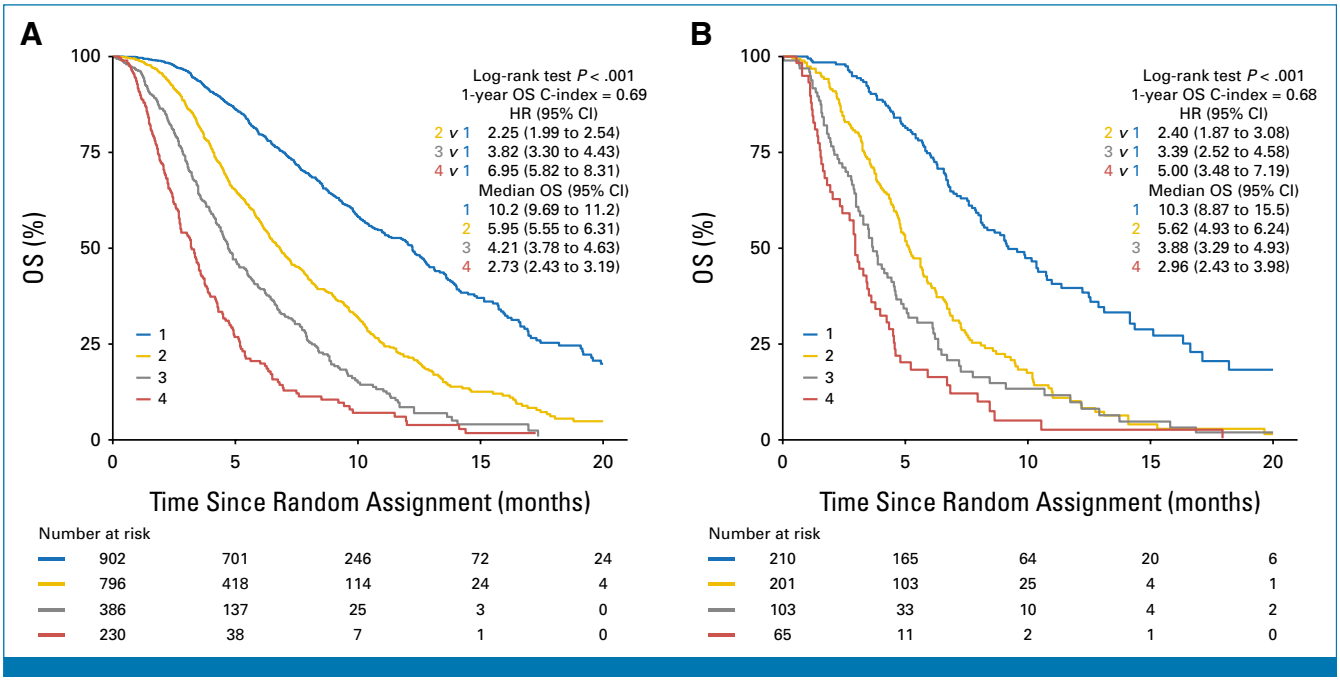

FIG 3. OS curves according to four risk classes of the prognostic model in 3L treatment of patients with mCRC from (A) construction set and (B) validation set. 3L, third-line; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival.

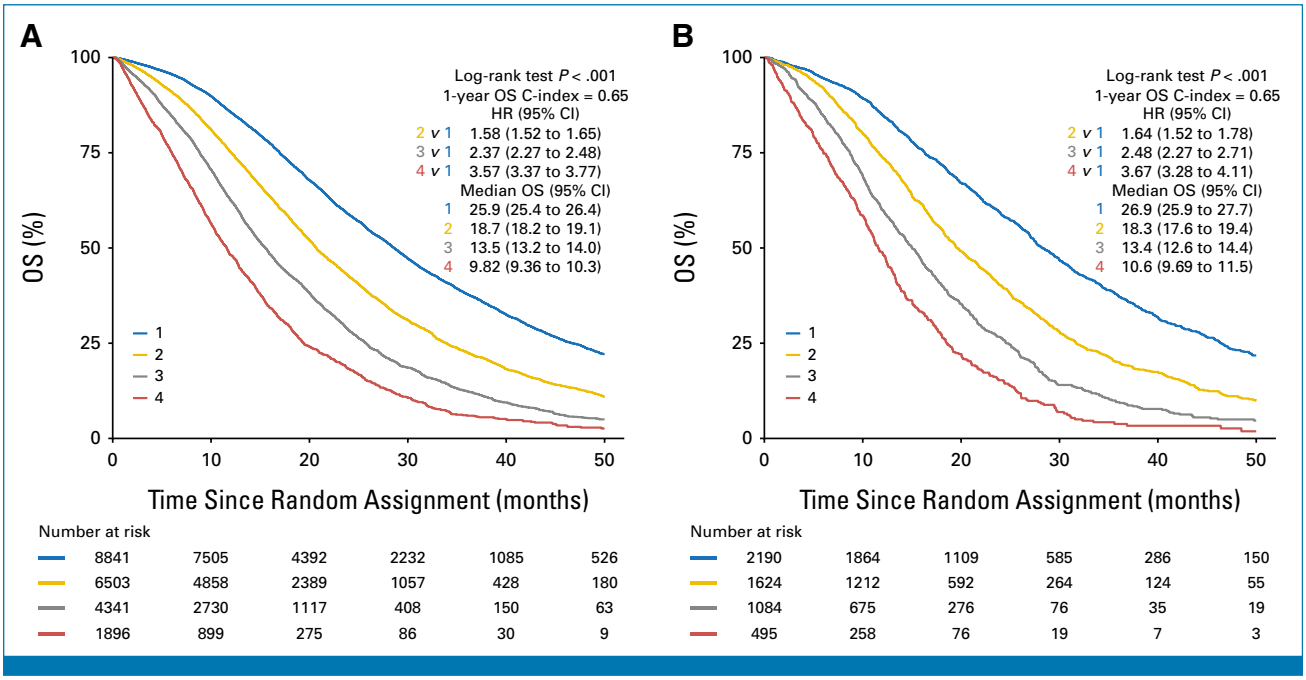

FIG 4. OS curves according to four risk classes of the prognostic model in 1L treatment of patients with mCRC from (A) construction set and (B) validation set. 1L, first-line; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival.

Interestingly, the rates of high PLT, WBC, and ANC levels were significantly higher in 1L compared with 2L and 3L (*P* values of <.001 for both 1L *v* 2L and 1L *v* 3L for PLT and WBC, and *P* values of <.001 for 1L *v* 2L and .029 for 1L *v* 3L for ANC). On the one hand, these differences may reflect progressive myelosuppression due to cytotoxic chemotherapy in later lines of therapy but, on the other hand, could also highlight a selection effect under treatment of the patients with a less aggressive biology. Considering the theragnostic molecular subgroups, the rate of *KRAS* mutation increased (37%, 47%, and 51%) continuously while the rate of *BRAF* mutation decreased (9%, 7%, and 5%). The lower rate of *KRAS* mutation in 1L could be explained by the fact that two trials were limited to *KRAS* WT mCRC. The decreased rate of *BRAF* mutation is probably because of the worse prognosis of *BRAF*-mutated mCRC. In comparison with 1L, patients included in 3L trials appeared highly selected with most patients manifesting early metachronous (<6 months) mCRC (31% *v* 78%), a history of primary tumor resection (70% *v* 89%), or metastases resection (10% *v* 80%). These results illustrated the selection process occurring across treatment lines.[17,18]

We constructed an OPS from prognostic variables common to all lines of treatment, allowing us to define four independent prognostic subgroups of patients. The best prognostic subgroup was the most frequent (from 36% to 41% according to construction or validation set and treatment line) and was associated with OS >25 months in 1L, >16 months in 2L, and >10 months in 3L. The worse prognostic subgroup was the smallest (from 8% to 12%) and was associated with OS of about 10 months in 1L, 5 months in 2L, and <3 months in 3L. Two intermediate subgroups were defined: one representing 26%-35% of patients with OS of 18, 11, and >5 months, and another comprising 17%-24% of patients with OS of 14, 8, and 4 months in 1L, 2L, and 3L, respectively. The OPS had good Harrell's C-index, whatever the treatment line, ranging from 0.65 to 0.69.

The variables included in this score have all been previously reported as prognostic. The ECOG PS was included in all the prognostic scores.[21-24] The number of metastatic sites in 1L is included in the Köhne score and the ARCAD nomogram, and was a prognostic factor in the GERCOR study.[21-23] The number of metastatic sites was also an independent prognostic factor in the RECOURSE trial.[31] Among the biological variables, WBC level was included in the Köhne score and ARCAD nomogram, LDH level in the GERCOR score and Colon Life nomogram, ALP level in the Köhne score, and HGB, ANC, and PLT levels in the ARCAD nomogram. Among these variables, PS reflects the patient's general conditions and symptoms related to the disease. Its prognostic value is highly validated, and PS is a stratification factor in most clinical trials. The number of metastatic sites, the LDH and ALP levels are associated with tumor burden, and elevated LDH and ALP levels are associated with liver involvement. Finally, HGB level, PLT level, and WBC/ANC ratio reflect systemic inflammation that is associated with cancer development and progression. The secretion of pro-inflammatory and angiogenesis factors by the tumor microenvironment is implicated in tumor development, metastatic spread, and immune evasion.[32,33] High platelet

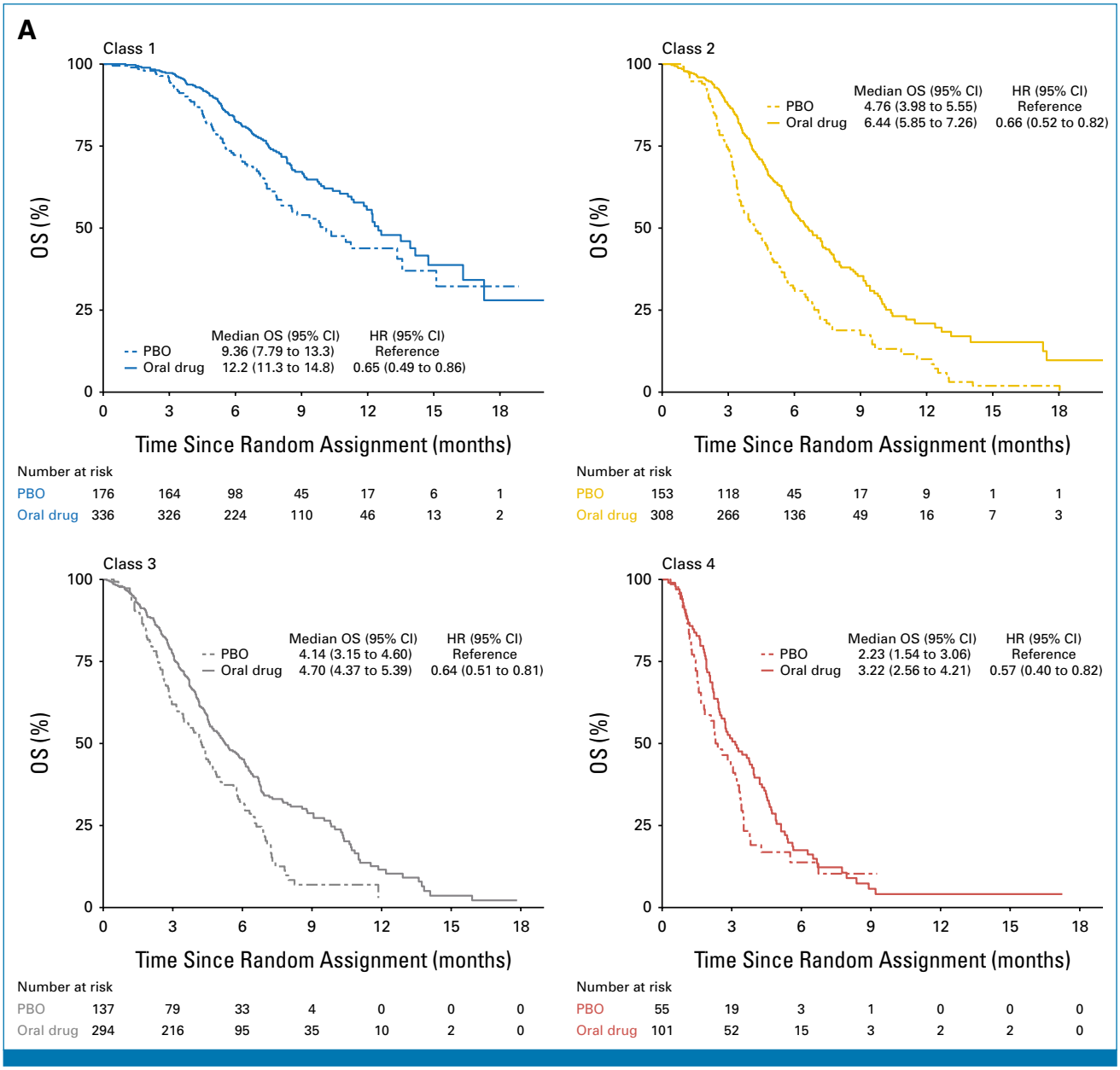

FIG 5. Assessment of the predictive value of the OPS: (A) Assessment of the association between the OPS and the treatment effect of the oral drugs (regorafenib or TAS-102) versus placebo in highly pretreated patients (≥3L) included in CORRECT (N = 760) and RECOURSE (N = 800) studies with HR (95% CI). Assessment of the association between the OPS and the presence of a subsequent line (B) on the subset of 1L (impact 2L) and (C) on the subset of 2L (impact 3L) reported by median OS (95% CI) with comparison of HR (95% CI) of presence versus absence of a subsequent line. 1L, first-line; 2L, second-line; 3L, third-line; HR, hazard ratio; OPS, overall prognostic score; OS, overall survival; PBO, placebo. (continued on following page)

and neutrophils levels have been reported as poor prognostic factors.[33,34] Conversely, because they are the primary drivers of anticancer immunity, low lymphocyte levels are associated with worse outcome.[33]

The ANC was the only component of the WBC count available in the ARCAD database. Thus, we decided to include the WBC/ANC ratio in our analyses to indirectly estimate the proportion of lymphocytes and monocytes. However, the neutrophil-to-lymphocyte ratio (NLR) and, more recently, the pan-immune-inflammation value (PIV= [neutrophil count × PLT × monocyte count]/lymphocyte count) have been reported as being prognostic in patients with mCRC.[35,36] PIV appeared to be the most complete index, superior to NLR, and could theoretically refine the information provided by the WBC/ANC ratio.[36]

KRAS mutation was significantly associated with OS in univariate analyses, but was not included in the multivariate model (HR <1.30). In exploratory analyses, we forced the inclusion of *KRAS* status as an additional variable in the OPS (data not shown). No improvements were

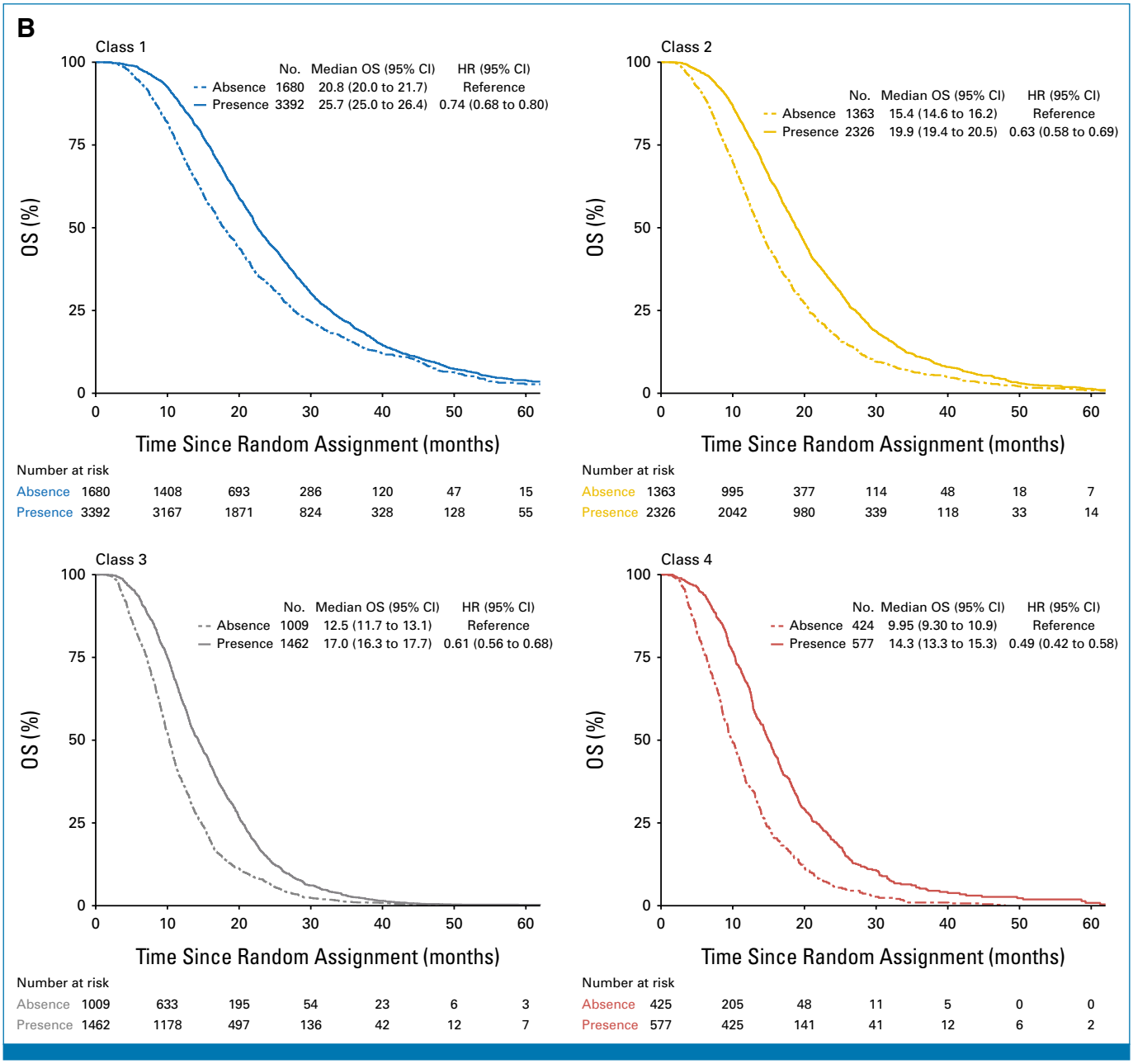

FIG 5. (Continued).

seen in the validation set or other treatment lines at the exception of a minor increase in the 1-year C-index for the 3L construction set. This suggests that although *KRAS* mutations are an important prognostic factor, their impact may be more modest relative to other variables. Further studies are warranted to explore its role in later treatment lines.

Because of missing data and the rules defined, some validated prognostic factors were not included in analyses: peritoneal carcinomatosis, primary tumor sidedness, synchronous/metachronous mCRC, *RAS*/*BRAF* status, or carcinoembryonic antigen level. To avoid potential bias, we conducted several exploratory analyses to investigate the OPS in specific subgroups, ensuring that the robustness of the OPS model was maintained.

No predictive value of OPS was observed. In 3L trials, HRs of treatment effect were comparable in the different subgroups defined by the OPS leading to an absolute benefit on OS highly correlated with the assigned prognostic subgroup. For example, the median OS benefit of a 3L treatment is of about 3 months in the best OPS subgroup (from 9.4 to 12.2 months) but is limited to 1 month in the worst OPS subgroup (from 2.3 to 3.2 months; Fig 5A). Thus, the prognostic information given by the OPS, the safety profile, and the potential efficacy of the available treatments at a specific time of multiline strategy can help to better evaluate the benefit/risk ratio of

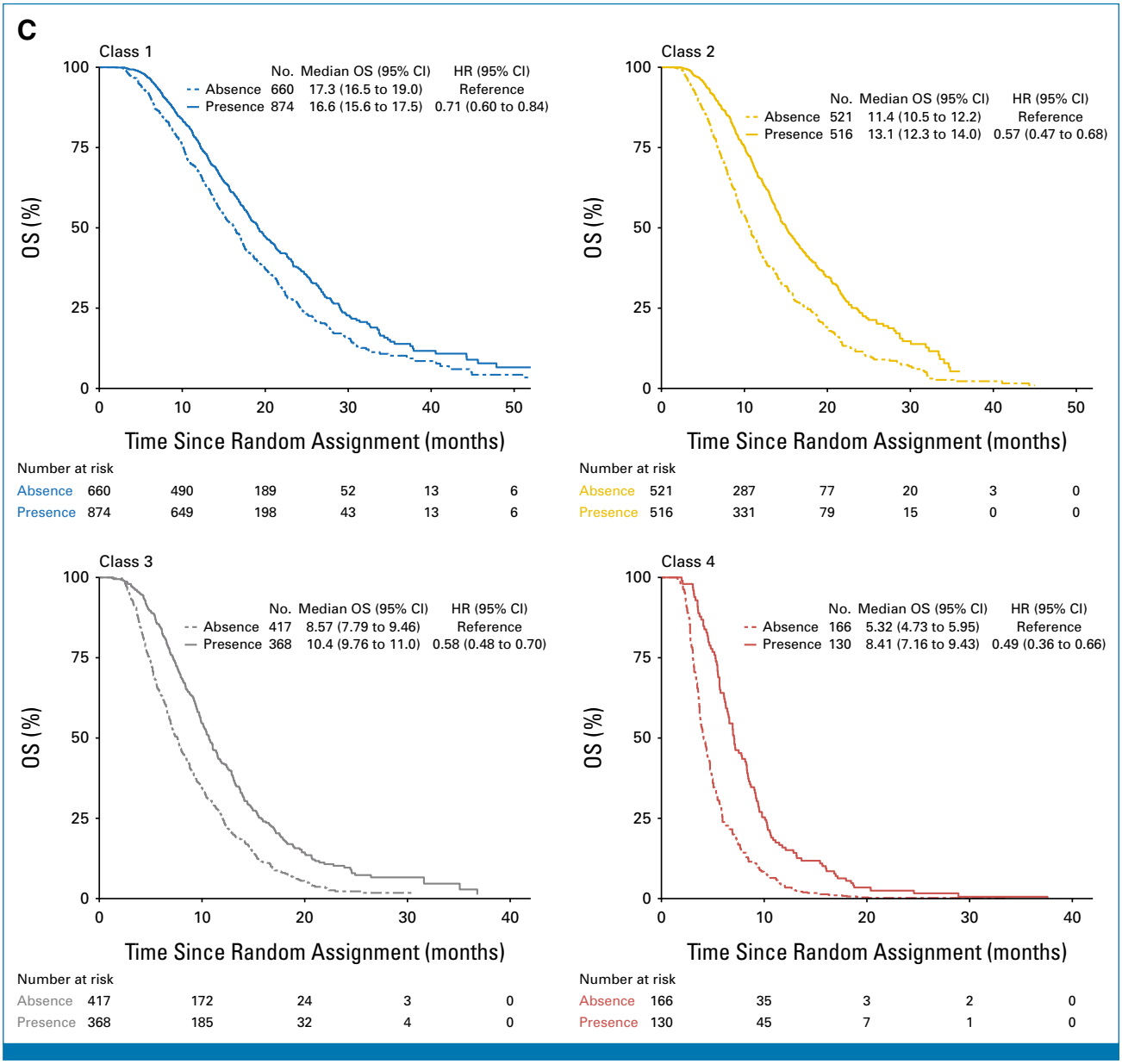

FIG 5. (Continued).

remaining therapeutic options. Such information can help both the physician and the patient to make choices according to patients' life expectancy, symptoms, and general condition. In addition, the OPS could also allow to better stratify patients in clinical trials, particularly in later-line trials to define synthetic control arm,[37] or to evaluate new treatments in subgroups with worse prognostic factors.

The OPS model was developed to address limitations of earlier prognostic models that were primarily designed for 1L treatment.[21–23] In our analysis, the GERCOR score yielded a C-index lower than the OPS model. In comparison with ARCAD nomogram, the C-index was relatively lower (0.65 *v* 0.68) but the number of included variables is also limited (7 *v* 17). The aim of the OPS was to develop a prognostic score easy to calculate, and validated before each therapeutic line; thus, the OPS is complementary of the ARCADE nomogram and noncompetitive. The interest to use one or the other could be decided according to the discretion of each physician. Moreover, developments of new targeted therapies lead to designing clinical trials in specific molecular subgroups (*BRAF*, dMMR/MSI, *KRAS* G12C...), partially impacting the interest to add these molecular variables in a prognostic score.

The OPS provides consistent prognostic assessment across multiple lines, accommodating changes in patient and tumor characteristics throughout treatment. The 80:20

split was chosen to maximize training data, ensuring reliable coefficients and high confidence in the model's real-world application. We also analyzed a 70:30 split (data not shown) that showed stability of prognostic factors and comparable performance metrics (C-index values and median OS). To facilitate its use, we plan to develop a web progressive application called Score Prognostic in Oncology Digestive that can be used on smartphones, tablets, or computers (ARCAD Foundation[38]—session for professionals Healthcare).

One of the strengths of this study is that it includes 48 randomized studies conducted over a period of 20 years, across all available lines. The number of trials and the different regimens studied are a guarantee of relatively significant heterogeneity in the profile of the patients included. However, the model is derived from patients eligible for clinical trials, which may not fully represent the broader population of patients treated in clinical practice. The evolving characteristics of patients in later treatment lines emphasize the potential discrepancies between trial populations and real-world cohorts. Consequently, although our findings are informative, further validation in real-world settings is essential to ensure the model's applicability across diverse patient groups.

Another limitation of this work is the number of prognostic factors assessed in analyses. As discussed above, some validated prognostic factors were missing and some new promising biomarkers such as the PIV or circulating tumor DNA were not available.[36,39]

In conclusion, we have shown that patient and tumor characteristics may vary across treatment lines in a selected population coming from randomized trials. The same prognostic model using practical clinical and biological variables can be used in all treatment lines.

AFFILIATIONS

[1]Hepato-gastroenterology and Digestive Oncology Department, Pitié Salpêtrière Hospital, APHP, Sorbonne Université, Paris, France
[2]Department of Medical Oncology, Franco-British Hospital, Fondation Cognacq-Jay, Cancérologie Paris Ouest, Levallois-Perret, France
[3]ARCAD Foundation, Paris, France
[4]Statistical Unit, ARCAD Foundation, Paris, France
[5]Department of Medicine, West Virginia University Cancer Institute, Morgantown, WV
[6]Department of Medical Oncology, Olivia Newton-John Cancer, Wellness and Research Centre, Austin Health, Heidelberg, VIC, Australia
[7]Digestive Oncology, University Hospitals Leuven and KU Leuven, Leuven, Belgium
[8]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA
[9]UCLA Jonsson Comprehensive Cancer Center, Santa Monica, CA
[10]Dana-Farber Cancer Institute, Boston, MA
[11]Wilmot Cancer Institute Geriatric Oncology Research Group, University of Rochester, Rochester, NY
[12]Division of Hematology/Oncology, Northwestern University's Feinberg School of Medicine, Chicago, IL
[13]Department of Medical Oncology, Ospedale San Martino, Genoa, Italy
[14]Vall d'Hebron Hospital Campus and Vall d'Hebron Institute of Oncology (VHIO), IOB-Quiron, Barcelona, Spain
[15]Cardiff University and Velindre Cancer Centre, Cardiff, United Kingdom
[16]Department of Medical Oncology, Monash University School of Public Health and Preventive Medicine, Alfred Health, Melbourne, VIC, Australia
[17]West Cancer Center, Germantown, TN
[18]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan
[19]Department of Medical Oncology, Saint Antoine Hospital, APHP, Sorbonne Université, Paris, France
[20]Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN

CORRESPONDING AUTHOR

Jean-Baptiste Bachet, MD; e-mail: jean-baptiste.bachet@aphp.fr.

PRIOR PRESENTATION

Presented in part at the ASCO meeting, Chicago, IL, June 4, 2021 (abstr 3575).

SUPPORT

Supported by the ARCAD foundation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-24-01968.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-24-01968.

AUTHOR CONTRIBUTIONS

Conception and design: Jean-Baptiste Bachet, Aimery de Gramont, Morteza Raeisi, Manel Rakez, Richard M. Goldberg, Josep Tabernero, Richard Adams, John R. Zalcberg, Axel Grothey, Takayuki Yoshino, Qian Shi, Benoist Chibaudel
Administrative support: Thierry André, Qian Shi
Provision of study materials or patients: Jean-Baptiste Bachet, Aimery de Gramont, Richard M. Goldberg, Niall C. Tebbutt, Eric Van Cutsem, Daniel G. Haller, J. Randolph Hecht, Robert J. Mayer, Alberto F. Sobrero, Josep Tabernero, Thierry André, Qian Shi
Collection and assembly of data: Aimery de Gramont, Richard M. Goldberg, Niall C. Tebbutt, Eric Van Cutsem, Daniel G. Haller, J. Randolph Hecht, Robert J. Mayer, Stuart M. Lichtman, Alberto F. Sobrero, Richard Adams, Axel Grothey, Takayuki Yoshino, Thierry André, Qian Shi
Data analysis and interpretation: Jean-Baptiste Bachet, Aimery de Gramont, Morteza Raeisi, Manel Rakez, Richard M. Goldberg, Niall C. Tebbutt, Eric Van Cutsem, J. Randolph Hecht, Al B. Benson, Alberto F.

Sobrero, Josep Tabernero, Richard Adams, John R. Zalcberg, Axel Grothey, Takayuki Yoshino, Qian Shi, Benoist Chibaudel
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The web progressive application Score Prognostic in Oncology Digestive was developed by ARCAD and Rachel Py Tse.

REFERENCES

1. Watanabe J, Muro K, Shitara K, et al: Panitumumab vs bevacizumab added to standard first-line chemotherapy and overall survival among patients with RAS wild-type, left-sided metastatic colorectal cancer: A randomized clinical trial. JAMA 329:1271-1282, 2023
2. Cremolini C, Antoniotti C, Stein A, et al: Individual patient data meta-analysis of FOLFOXIRI plus bevacizumab versus doublets plus bevacizumab as initial therapy of unresectable metastatic colorectal cancer. J Clin Oncol 38:3314-3324, 2020
3. Cervantes A, Adam R, Roselló S, et al: Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 34:10-32, 2023
4. Hurwitz H, Fehrenbacher L, Novotny W, et al: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350:2335-2342, 2004
5. Van Cutsem E, Köhne CH, Hitre E, et al: Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 360:1408-1417, 2009
6. Douillard JY, Oliner KS, Siena S, et al: Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 369:1023-1034, 2013
7. Van Cutsem E, Tabernero J, Lakomy R, et al: Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol 30:3499-3506, 2012
8. Tabernero J, Yoshino T, Cohn AL, et al: Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): A randomised, double-blind, multicentre, phase 3 study. Lancet Oncol 16:499-508, 2015
9. André T, Shiu KK, Kim TW, et al: Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med 383:2207-2218, 2020
10. Bennouna J, Sastre J, Arnold D, et al: Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): A randomised phase 3 trial. Lancet Oncol 14:29-37, 2013
11. Tabernero J, Grothey A, Van Cutsem E, et al: Encorafenib plus cetuximab as a new standard of care for previously treated BRAF V600E-mutant metastatic colorectal cancer: Updated survival results and subgroup analyses from the BEACON study. J Clin Oncol 39:273-284, 2021
12. Mayer RJ, Van Cutsem E, Falcone A, et al: Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 372:1909-1919, 2015
13. Grothey A, Van Cutsem E, Sobrero A, et al: Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 381:303-312, 2013
14. Prager GW, Taieb J, Fakih M, et al: Trifluridine-tipiracil and bevacizumab in refractory metastatic colorectal cancer. N Engl J Med 388:1657-1667, 2023
15. Dasari A, Lonardi S, Garcia-Carbonero R, et al: Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): An international, multicentre, randomised, double-blind, phase 3 study. Lancet 402:41-53, 2023
16. Benson AB, Venook AP, Al-Hawary MM, et al: Colon cancer, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 19:329-359, 2021
17. Abrams TA, Meyer G, Schrag D, et al: Chemotherapy usage patterns in a US-wide cohort of patients with metastatic colorectal cancer. J Natl Cancer Inst 106:djt371, 2014
18. Mas L, Bachet JB, Jooste V, et al: Chemotherapy of metastatic colon cancer in France: A population-based study. Dig Liver Dis 53:1334-1342, 2021
19. Glare P, Virik K, Jones M, et al: A systematic review of physicians' survival predictions in terminally ill cancer patients. BMJ 327:195-198, 2003
20. Cheon S, Agarwal A, Popovic M, et al: The accuracy of clinicians' predictions of survival in advanced cancer: A review. Ann Palliat Med 5:22-29, 2016
21. Köhne CH, Cunningham D, Di Costanzo F, et al: Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: Results of a multivariate analysis of 3825 patients. Ann Oncol 13:308-317, 2002
22. Chibaudel B, Bonnetain F, Tournigand C, et al: Simplified prognostic model in patients with oxaliplatin-based or irinotecan-based first-line chemotherapy for metastatic colorectal cancer: A GERCOR study. Oncologist 16:1228-1238, 2011
23. Sjoquist KM, Renfro LA, Simes RJ, et al: Personalizing survival predictions in advanced colorectal cancer: The ARCAD nomogram project. J Natl Cancer Inst 110:638-648, 2018
24. Pietrantonio F, Miceli R, Rimassa L, et al: Estimating 12-week death probability in patients with refractory metastatic colorectal cancer: The Colon Life nomogram. Ann Oncol 28:555-561, 2017
25. Walsh SR, Cook EJ, Goulder F, et al: Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol 91:181-184, 2005
26. van Buuren S, Groothuis-Oudshoorn K: mice: Multivariate imputation by chained equations in *R*. J Stat Softw 45:1-67, 2011
27. Hasford J, Pfirrmann M, Hehlmann R, et al: A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst 90:850-858, 1998
28. Cox DR: Note on grouping. J Am Stat Assoc 52:543-547, 1957
29. Harrell FE Jr, Lee KL, Mark DB: Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15:361-387, 1996
30. Steyerberg EW, Vickers AJ, Cook NR, et al: Assessing the performance of prediction models: A framework for traditional and novel measures. Epidemiology 21:128-138, 2010
31. Tabernero J, Argiles G, Sobrero AF, et al: Effect of trifluridine/tipiracil in patients treated in RECOURSE by prognostic factors at baseline: An exploratory analysis. ESMO Open 5:e000752, 2020
32. Schmitt M, Greten FR: The inflammatory pathogenesis of colorectal cancer. Nat Rev Immunol 21:653-667, 2021
33. Guven DC, Sahin TK, Erul E, et al: The association between the pan-immune-inflammation value and cancer prognosis: A systematic review and meta-analysis. Cancers (Basel) 14:2675, 2022
34. Xiong S, Dong L, Cheng L: Neutrophils in cancer carcinogenesis and metastasis. J Hematol Oncol 14:173, 2021
35. Papakonstantinou M, Fiflis S, Christodoulidis G, et al: Neutrophil-to-lymphocyte ratio as a prognostic factor for survival in patients with colorectal liver metastases: A systematic review. World J Clin Oncol 13:822-834, 2022
36. Fucà G, Guarini V, Antoniotti C, et al: The pan-immune-inflammation value is a new prognostic biomarker in metastatic colorectal cancer: Results from a pooled-analysis of the Valentino and TRIBE first-line trials. Br J Cancer 123:403-409, 2020
37. Cohen R, Raeisi M, Chibaudel B, et al: Efficacy of immune checkpoint inhibitors for metastatic colorectal cancer with microsatellite instability in second or latter line using synthetic control arms: A non-randomised evaluation. Eur J Cancer 199:113537, 2024
38. Fondation A.R.C.A.D.: www.fondationarcad.org
39. Bachet JB, Laurent-Puig P, Meurisse A, et al: Circulating tumour DNA at baseline for individualised prognostication in patients with chemotherapy-naïve metastatic colorectal cancer. An AGEO prospective study. Eur J Cancer 189:112934, 2023

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Characteristics of Patients and Prognostic Factors Across Treatment Lines in Metastatic Colorectal Cancer: An Analysis From the Aide et Recherche en Cancérologie Digestive Database

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Jean-Baptiste Bachet
Honoraria: Amgen, Bayer, Merck Serono, Servier, AstraZeneca, Pierre Fabre, Viatris, MSD Oncology, Takeda
Consulting or Advisory Role: Amgen, Bayer, Merck Serono, Servier, Acobiom, GlaxoSmithKline, BMS, MSD, Incyte, AbbVie, Takeda
Travel, Accommodations, Expenses: Merck Serono, Amgen, Roche, Servier, Sanofi

Richard M. Goldberg
Stock and Other Ownership Interests: Advanced Chemotherapy Technologies, Quest Diagnostics, Compass Therapeutics
Consulting or Advisory Role: Taiho Pharmaceutical, AstraZeneca, Bayer, G1 Therapeutics, Compass Therapeutics, UpToDate, Eisai/H3 Biomedicine, Sorrento Therapeutics, IQVIA, Merck, AbbVie, Valar Labs, Takeda, RIN Institute, GeneCentric, Inspira, Focal Medical, Inc, Agenus, Innovative Cellular Therapeutics Co, Modulation Therapeutics, Haystack Oncology
Expert Testimony: Taiho Pharmaceutical, Johns Hopkins Hospital

Niall C. Tebbutt
Honoraria: Bristol Myers Squibb, AstraZeneca, Merck, BeiGene, Takeda, Astellas Pharma
Consulting or Advisory Role: Bristol Myers Squibb, AstraZeneca, Merck, BeiGene, Takeda, Astellas Pharma
Expert Testimony: Astellas Pharma

Eric Van Cutsem
Consulting or Advisory Role: Bayer, Lilly, Servier, Bristol Myers Squibb, Merck Sharp & Dohme, Merck KGaA, Novartis, AstraZeneca, Daiichi Sankyo, Pierre Fabre, Taiho Pharmaceutical, Astellas Pharma, GlaxoSmithKline, Nordic Group, Pfizer, Takeda, ALX Oncology, AbbVie, BeiGene, Boehringer Ingelheim, Mirati Therapeutics, Seagen, Ipsen, Agenus, Amgen, Arcus Biosciences, BioNTech SE, Debiopharm Group, ElmediX, Eisai, Simcere, Bexon Clinical Consulting, Cantargia AB, Fosum, Galapagos NV, ITeos Therapeutics, Microbial Machines, Novocure, Sanofi, Trishula Therapeutics

J. Randolph Hecht
Stock and Other Ownership Interests: Rafael Pharmaceuticals, Actym Therapeutics, Trumvira
Consulting or Advisory Role: Astellas Pharma, BeiGene, Taiho Pharmaceutical, Galvanize Therapeutics, Bristol Myers Squibb/Medarex, MBQ Pharma, Xilio Therapeutics, Agenus, Revolution Medicines
Research Funding: Amgen (Inst), Merck (Inst), Gritstone Bio (Inst), Bold Therapeutics (Inst), Tizona Therapeutics, Inc (Inst), A2 Biotherapeutics (Inst), Gilead Sciences (Inst), Exelixis (Inst), NGM Biopharmaceuticals (Inst), Camurus (Inst), CG Pharmaceuticals (Inst), Crinetics Pharmaceuticals (Inst), Lyell Immunopharma (Inst), Mirati Therapeutics (Inst), Xilio Therapeutics (Inst), Revolution Medicines (Inst), Regeneron (Inst), Agenus (Inst), Neogene Therapeutics (Inst), Affini-T Therapeutics (Inst), Janssen Oncology (Inst), Seagen (Inst), Cardiff Oncology (Inst)

Stuart M. Lichtman
Consulting or Advisory Role: Magellan Health

Al B. Benson
Consulting or Advisory Role: Merck Sharp & Dohme, Array BioPharma, Bristol Myers Squibb, Samsung Bioepis, Pfizer, HalioDx, AbbVie, Janssen Oncology, Natera, Apexigen, Artemida Pharma, Xencor, Therabionic, Mirati Therapeutics, Boston Scientific, Hutchmed, Bristol Myers Squibb Foundation, GlaxoSmithKline, Amgen Astellas BioPharma, Boehringer Ingelheim, Novartis/Pfizer
Research Funding: Infinity Pharmaceuticals (Inst), Merck Sharp & Dohme (Inst), Taiho Pharmaceutical (Inst), Bristol Myers Squibb (Inst), Celgene (Inst), Rafael Pharmaceuticals (Inst), MedImmune (Inst), Xencor (Inst), Astellas Pharma (Inst), Amgen (Inst), SynCoreBio (Inst), Elevar Therapeutics (Inst), Tyme Inc (Inst), ST Pharm (Inst), ITM Solucin (Inst)

Alberto F. Sobrero
Consulting or Advisory Role: Servier, Amgen, Bayer, BMS, MSD Oncology, GlaxoSmithKline
Speakers' Bureau: Bayer, Amgen, AstraZeneca, Bristol Myers Squibb
Travel, Accommodations, Expenses: Bayer

Josep Tabernero
Stock and Other Ownership Interests: Oniria Therapeutics, Alentis Therapeutics, 1TRIALSP, Pangaea Oncology
Consulting or Advisory Role: Boehringer Ingelheim, Lilly, MSD, Novartis, Taiho Pharmaceutical, Peptomyc, Chugai Pharma, Pfizer, AstraZeneca, Genentech, Menarini, Servier, F. Hoffmann LaRoche, Pierre Fabre, Daiichi Sankyo, Merus, Scandion Oncology, Sotio, Scorpion Therapeutics, Tolremo, Takeda Pharmaceuticals International AG, Alentis Therapeutics, Quantro Therapeutics, Accent Therapeutics, Ono Pharmaceutical, Bristol Myers Squibb, Cartography Biosciences

Richard Adams
Honoraria: Servier, Amgen, AstraZeneca, Bayer, Takeda, Teysuno
Consulting or Advisory Role: Merck Serono, Amgen, Servier, Bayer
Speakers' Bureau: Merck Serono, Amgen, Bayer, Servier, Seagen
Research Funding: AstraZeneca (Inst), Merck Sharp & Dohme (Inst)
Travel, Accommodations, Expenses: Servier, Amgen, AstraZeneca

John R. Zalcberg
Leadership: Icon Group, Lipotek, Praxis Therapeutics
Stock and Other Ownership Interests: Biomarin, Opthea, Amarin Corporation, Frequency Therapeutics, Gilead Sciences, UniQure, Orphazyme, Moderna Therapeutics, Novavax, CSL Limited, Korro
Consulting or Advisory Role: Merck Sharp & Dohme, Deciphera, Revolution Medicine, FivePHusion, Genor BioPharma, 1Globe Health

Institute, Alloplex Biotherapeutics Inc, Oncology Republic, Duo Oncology, Taiho Oncology, Takeda, Avance Clinical, BioNTech SE, BioIntelect
Research Funding: Bristol Myers Squibb (Inst), AstraZeneca (Inst), Pfizer (Inst), IQVIA (Inst), Mylan (Inst), Ipsen (Inst), Eisai (Inst), Medtronic (Inst), MSD Oncology (Inst), Servier (Inst), Astellas Pharma (Inst), Taiho Oncology (Inst)
Travel, Accommodations, Expenses: MSD Oncology, ICON Group, Praxis Therapeutics

Axel Grothey
Honoraria: Total Health Conferencing, Cardinal Health
Consulting or Advisory Role: Bristol Myers Squibb (Inst), Lilly (Inst), Amgen (Inst), Daiichi Sankyo (Inst), OBI Pharma, Caris Life Sciences (Inst), Guardant Health (Inst), Natera (Inst), Replimune (Inst)
Research Funding: Eisai (Inst), Lilly (Inst), Daiichi Sankyo (Inst), Replimune (Inst), Natera (Inst), Caris Life Sciences (Inst), Guardant Health (Inst)
Travel, Accommodations, Expenses: Cardinal Health, Total Health Conferencing

Takayuki Yoshino
Honoraria: Chugai Pharma, MSD K.K, Takeda, Merck
Consulting or Advisory Role: Sumitomo Corp
Research Funding: MSD (Inst), Daiichi Sankyo Company, Limited (Inst), Ono Pharmaceutical (Inst), Taiho Pharmaceutical (Inst), Amgen (Inst), Sanofi (Inst), Pfizer (Inst), Sysmex (Inst), Chugai Pharma (Inst), Eisai (Inst), Molecular Health (Inst), Roche (Inst), FALCO Biosystems Ltd (Inst), Merus (Inst), Bristol Myers Squibb Japan (Inst), Medical & Biological Laboratories Co, Ltd (Inst), Takeda (Inst)

Thierry André
Honoraria: Bristol Myers Squibb, Servier, Merck, Merck Serono, Sanofi, Seagen
Consulting or Advisory Role: Bristol Myers Squibb, MSD Oncology, Servier, GlaxoSmithKline, Seagen, Nordic Bioscience, Aptitude Health, Gilead Sciences, Pfizer, Takeda, AbbVie, Nimbus Therapeutics
Travel, Accommodations, Expenses: MSD Oncology, Bristol Myers Squibb, Takeda
Other Relationship: Inspirna
(OPTIONAL) Uncompensated Relationships: ARCAD Foundation, Adjuvant Colon Cancer End Points (ACCENT) Collaborative Group

Qian Shi
Honoraria: Chugai Pharma
Consulting or Advisory Role: Yiviva, Regeneron, Hoosier Cancer Research Network, Kronos Bio, Mirati Therapeutics
Research Funding: Celgene (Inst), Roche/Genentech (Inst), Janssen (Inst), BMS (Inst), Novartis (Inst), Regeneron (Inst)

Benoist Chibaudel
Honoraria: Amgen, Roche, Sanofi, Merck KGaA, BMS GmbH & Co KG, SeqOne Genomics, Pierre Fabre
Consulting or Advisory Role: Bayer, MSD, BMS GmbH & Co KG, Sanofi, Roche
Travel, Accommodations, Expenses: Daiichi Sankyo/AstraZeneca, Pierre Fabre

No other potential conflicts of interest were reported.

© 2025 by American Society of Clinical Oncology