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

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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

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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

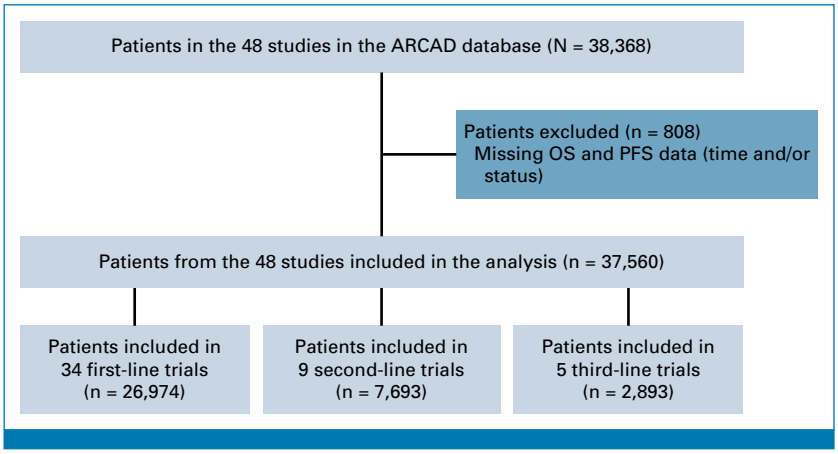

FIG 1. Flow diagram of the population study. ARCAD, Aide et Recherche en Cancérologie Digestive; OS, overall survival; PFS, progression-free survival.

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

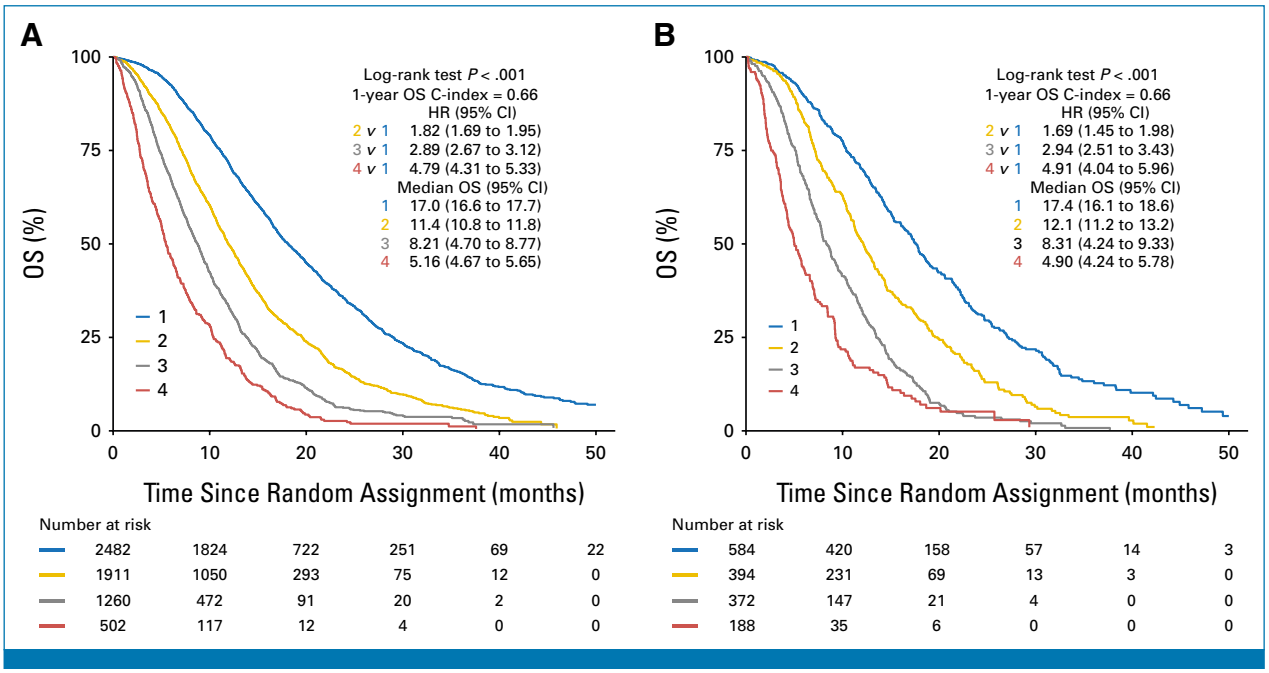

FIG 2. OS curves according to four risk classes of the prognostic model in 2L treatment of patients with mCRC from (A) construction set and (B) validation set. 2L, second-line; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival.

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).

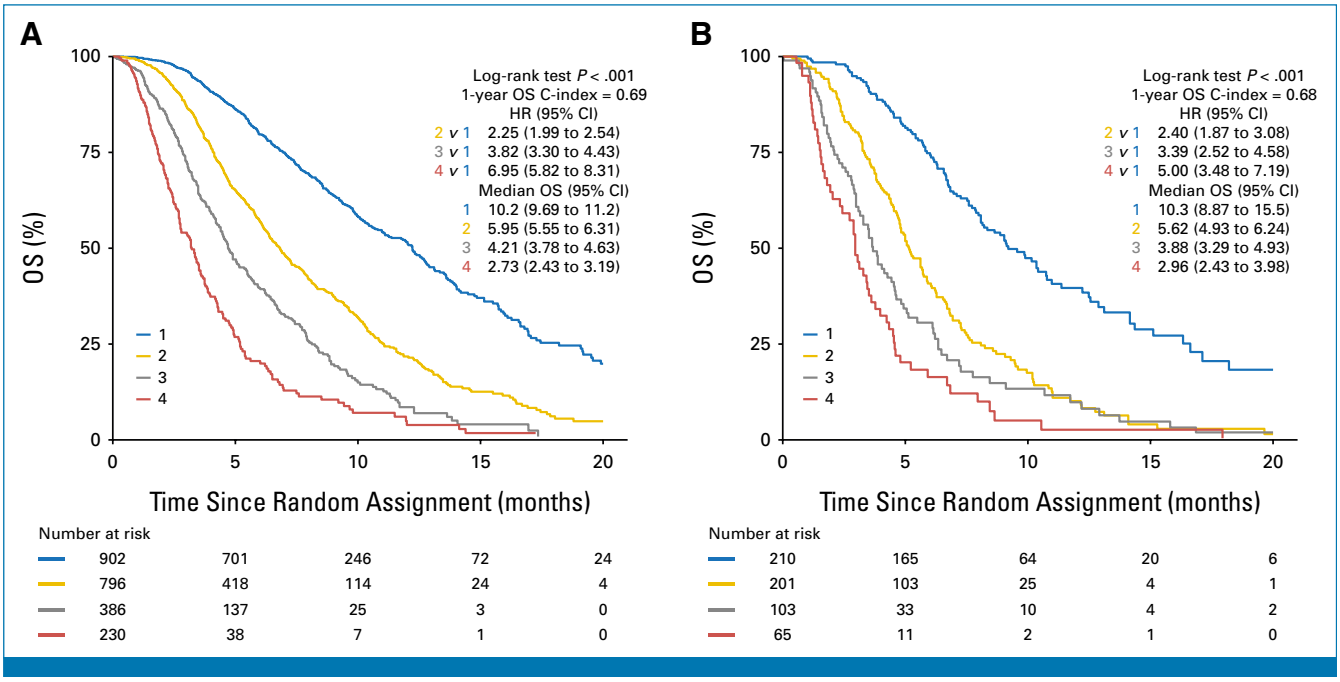

FIG 3. OS curves according to four risk classes of the prognostic model in 3L treatment of patients with mCRC from (A) construction set and (B) validation set. 3L, third-line; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival.

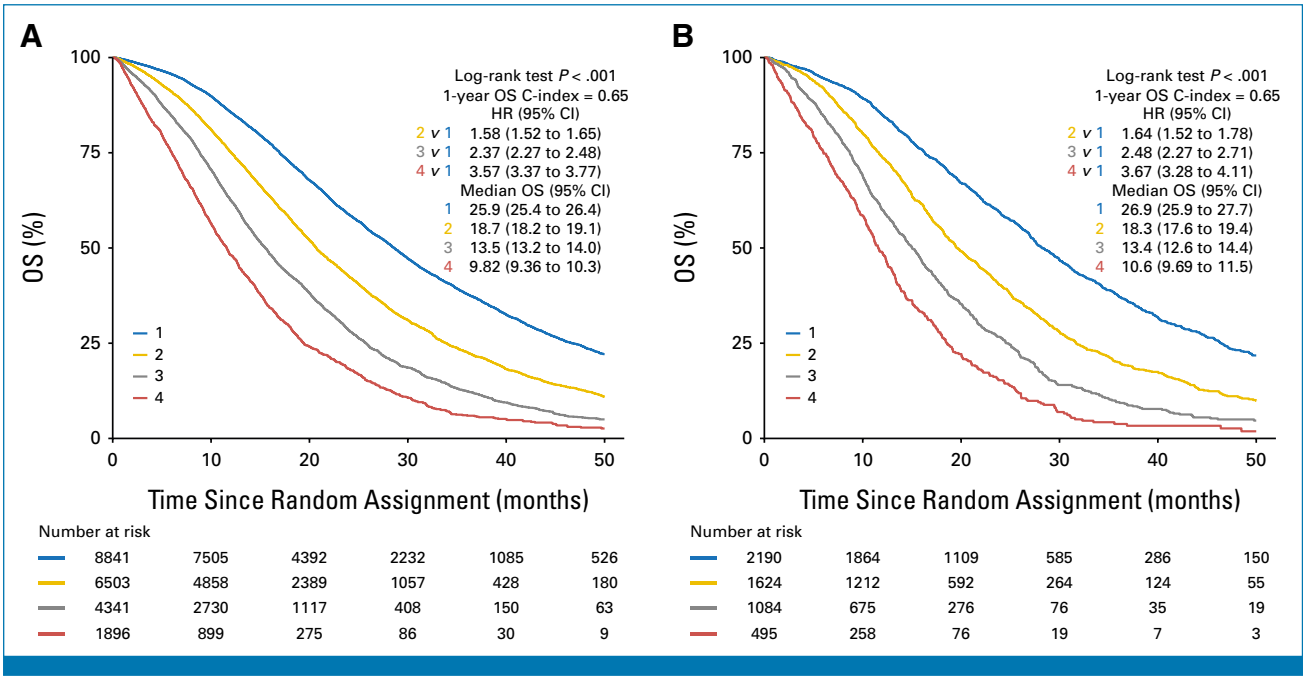

FIG 4. OS curves according to four risk classes of the prognostic model in 1L treatment of patients with mCRC from (A) construction set and (B) validation set. 1L, first-line; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival.

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

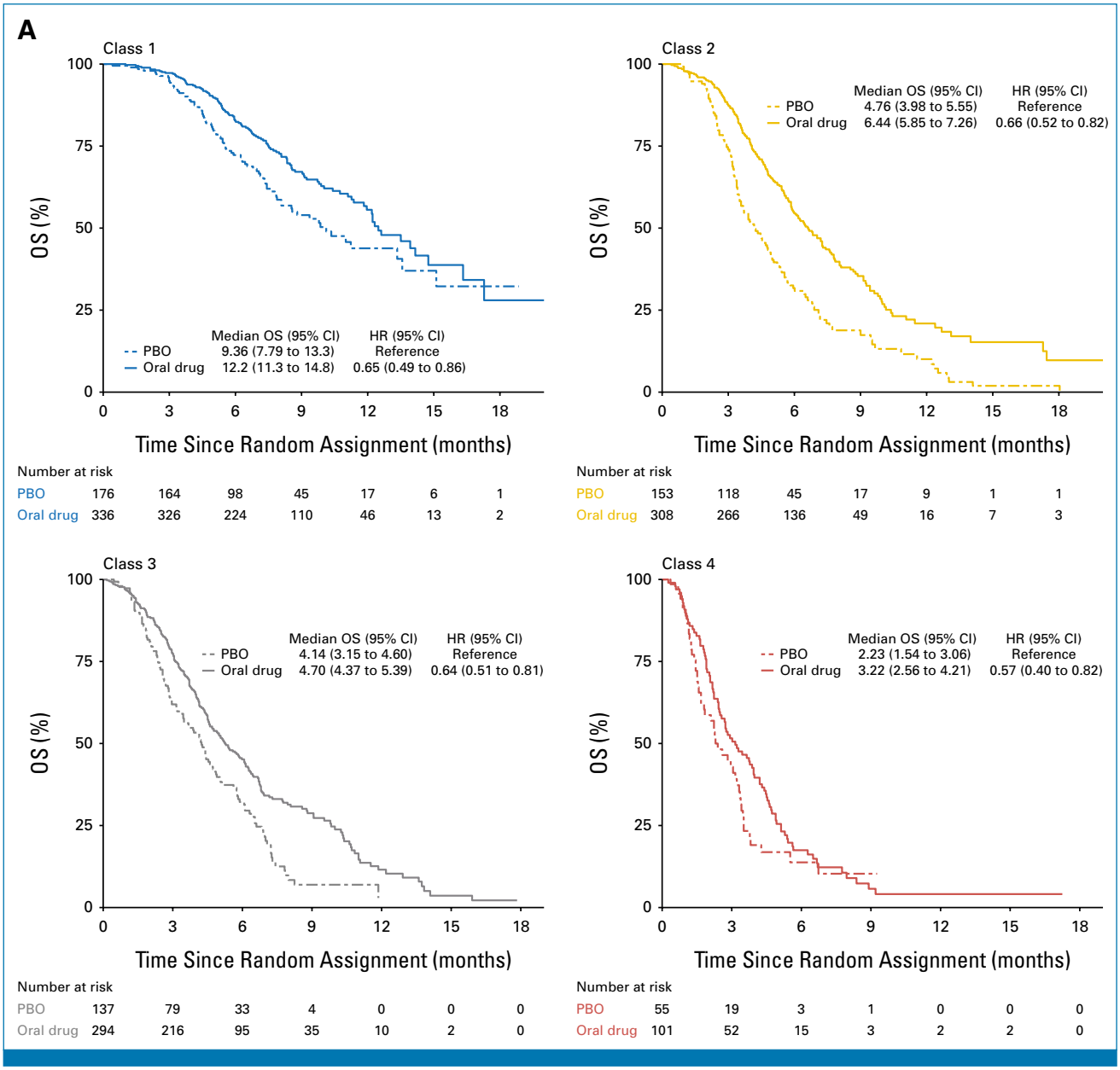

FIG 5. Assessment of the predictive value of the OPS: (A) Assessment of the association between the OPS and the treatment effect of the oral drugs (regorafenib or TAS-102) versus placebo in highly pretreated patients (≥3L) included in CORRECT (N = 760) and RECOURSE (N = 800) studies with HR (95% CI). 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

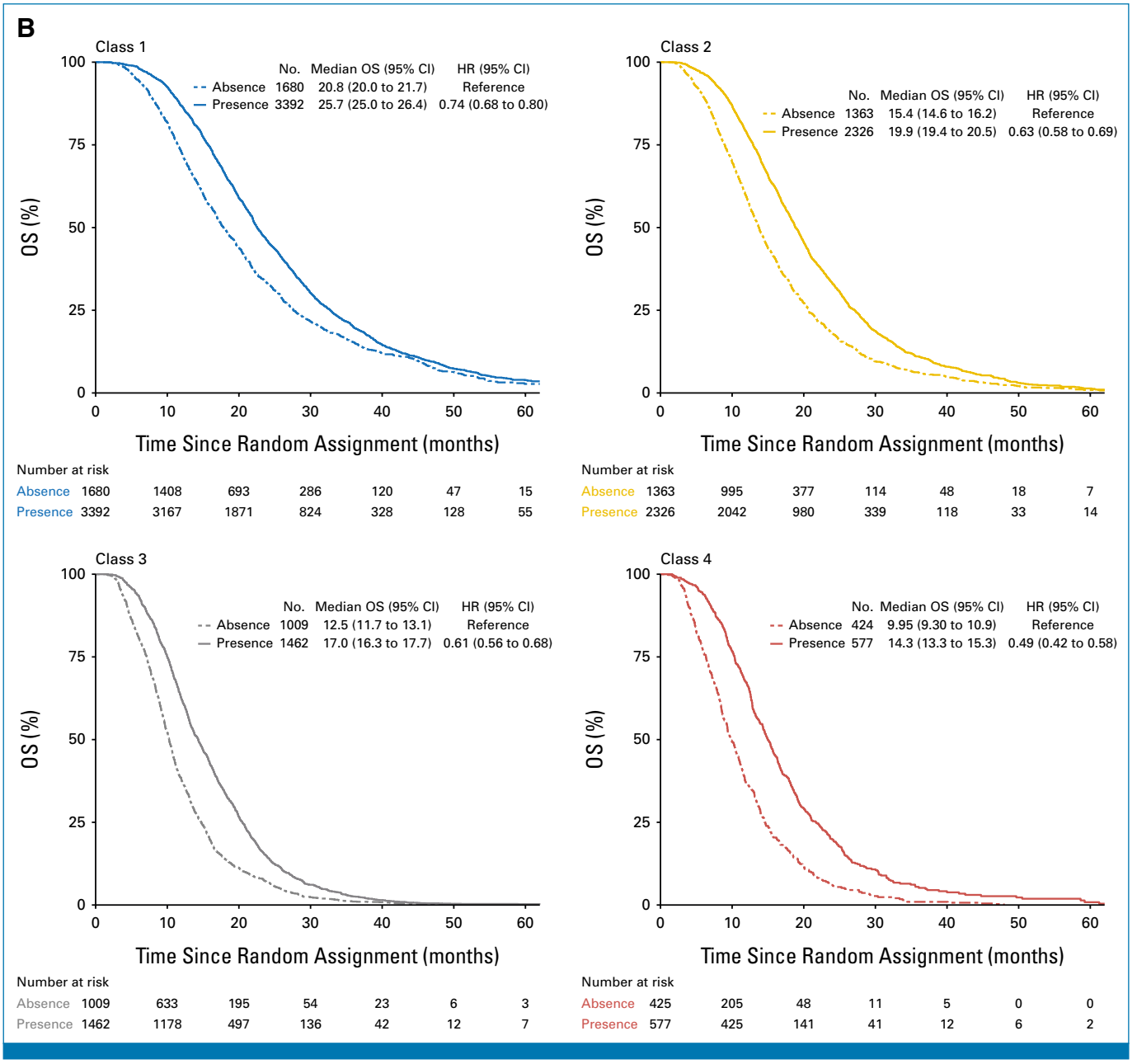

FIG 5. (Continued).

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

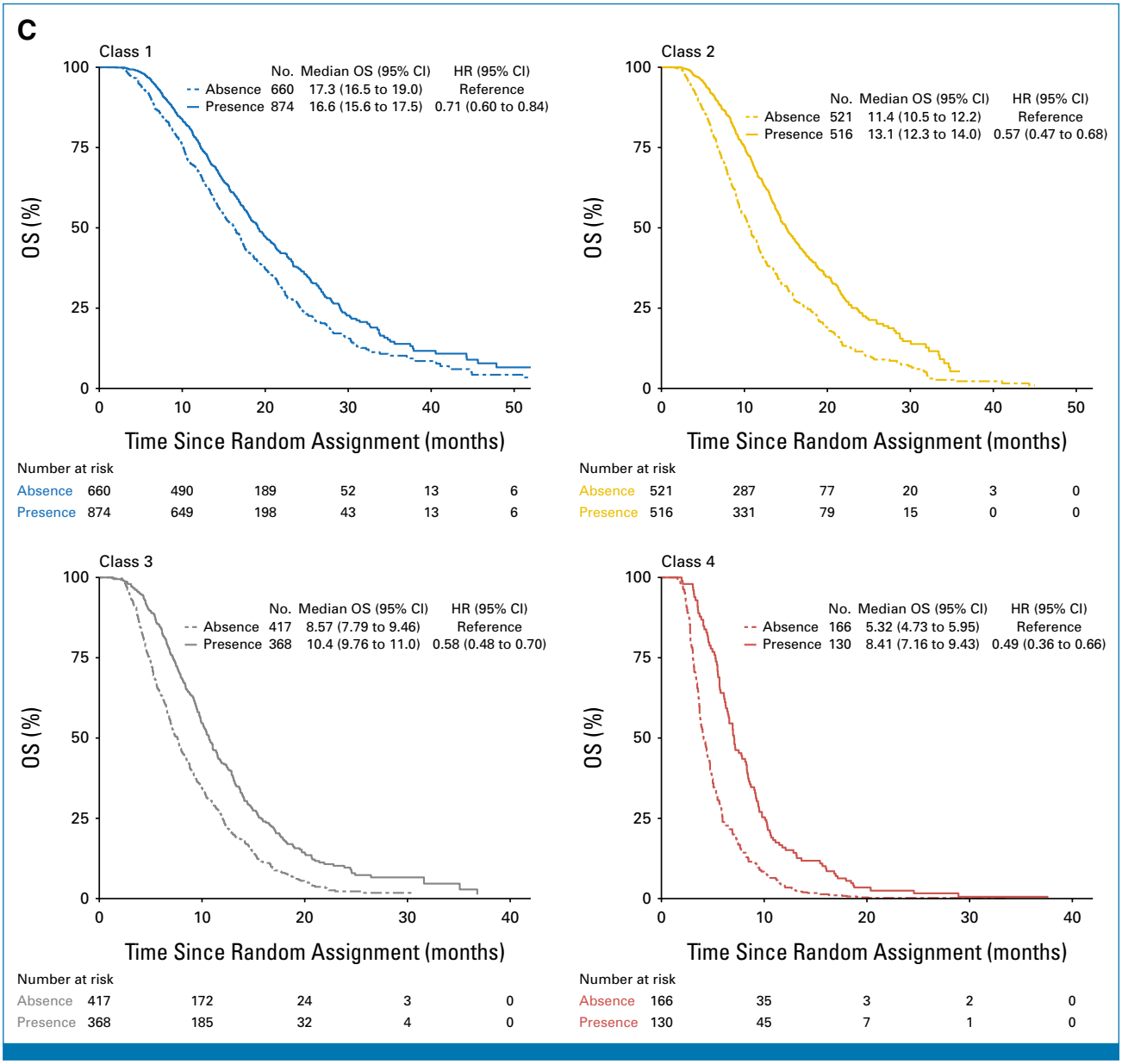

FIG 5. (Continued).

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.

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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

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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

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Research Funding: Celgene (Inst), Roche/Genentech (Inst), Janssen (Inst), BMS (Inst), Novartis (Inst), Regeneron (Inst)

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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.