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Carcinoembryonic antigen kinetics predict response to first-line treatment in metastatic colorectal cancer: Analysis from PRODIGE 9 trial

Delphine Salfati[a,1], Margaux Huot[b,1], Thomas Aparicio[a], Come Lepage[b], Julien Taieb[c], Olivier Bouché[d], Valérie Boige[e], Jean-Marc Phelip[f], Laetitia Dahan[g,h], Jaafar Bennouna[i], Karine Le Malicot[b], Olayide Boussari[b,1], Jean-Marc Gornet[a,1,*]

[a] Assistance Publique – Hôpitaux de Paris, Hôpital Saint Louis, Université de Paris Cité, Paris, France
[b] FFCD, EPICAD INSERM LNC-UMR 1231, University of Burgundy and Franche Comté, Dijon, France
[c] Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Université de Paris, SIRIC CARPEM, Paris, France
[d] Department of Gastroenterology and Digestive Oncology, CHU Reims, Université de Reims Champagne-Ardenne (URCA), Reims, France
[e] Department of Cancer Medicine, Gustave Roussy, Université Paris-Saclay Villejuif, France
[f] Department of Gastroenterology and Digestive Oncology, University Hospital of Saint Etienne, Saint Etienne, France
[g] Cancer Research Center of Marseille, CRCM, Inserm, CNRS, Paoli-Calmettes Institut, Aix-Marseille University, Marseille, France
[h] La Timone Hospital, Marseille, France
[i] Department of Oncology, Foch Hospital, Suresnes, France

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ABSTRACT

Background: To examine the relationship between carcinoembryonic antigen (CEA) kinetics and prognosis in metastatic colorectal cancer (mCRC) patients receiving first-line chemotherapy in the PRODIGE9 trial.
Methods: Associations between monthly CEA measurements within 6 months since baseline and progression-free survival (PFS) were evaluated using a joint-latent class-mixed model. A validation set was used to test our prognosis model. Correlations between CEA trajectories (classes) and baseline characteristics were also investigated.
Results: Three classes were identified. Class 1 had low baseline CEA with small variations. Class 2 had high baseline CEA with a rapid decrease reaching the same CEA level at 6 months as in class 1. Class 3 had high baseline CEA with a transient decrease followed by an increase to reach, at 6 months, the same CEA level as at baseline. Six-month PFS was significantly lower in class 3 than in classes 1 and 2 (57% vs. 91% and 93% respectively; $p<0.01$). Class 3 was significantly associated with ECOG 2 status, a high LDH level and non-resected primary tumor.
Discussion: Variations in CEA kinetics correlate with prognosis in patients receiving first-line chemotherapy for mCRC. We propose here a user-friendly application to classify CEA trajectory.

1. Background

Chemotherapy remains the cornerstone of metastatic colorectal cancer (mCRC) treatment. Multiple treatment options are possible, mainly depending on a patient's characteristics, tumor aggressiveness and molecular status [1,2]. Numerous predictors of outcome, including clinical and biological parameters, have been reported in mCRC patients [3–5]. Serum carcinoembryonic antigen (CEA) is a biomarker of CRC, and is increased at baseline in approximately 80% of patients in the metastatic setting. French clinical practice guidelines recommend the pre-therapeutic measurement of serum CEA levels [2]. In mCRC patients, it has been suggested that baseline CEA levels and decreases in CEA correlate with response rates and survival [6–9]. However, despite their routine use, these data are still controversial, and in clinical practice CEA values are not considered a key tool to guide chemotherapy modalities. CEA kinetics have been poorly investigated but are considered a potential biomarker in mCRC patients [10]. Previous studies assessed CEA kinetics according to the slope from baseline and used a predefined threshold to obtain a binary measurement [11–15]. Moreover, it has been suggested that CEA kinetics could correlate with imaging response [7]. In the present study, we propose an approach that

* Corresponding author at: Gastroenterology Unit, Saint Louis Hospital, AP-HP, Université de Paris, 1 Avenue Claude Vellefaux 75010 Paris, France.
E-mail address: jean-marc.gornet@aphp.fr (J.-M. Gornet).
URL: https://orcid.org/0000-0003-2851-6247 (J.-M. Gornet)
[1] *These authors contributed equally.*

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takes account of all CEA measurements since baseline to predict disease progression. Our objective was then to use CEA kinetics as a prognostic factor for progression-free survival (PFS) and to provide a simple algorithm, based on CEA kinetics, to classify first-line mCRC patients according to the risk of progression or death.

2. Methods

We used individual data from patients randomized in the Fédération Francophone de Cancérologie Digestive (FFCD) phase III trial comparing Bevacizumab maintenance versus no maintenance during chemotherapy-free intervals in first-line mCRC patients [16]. All patients were treated with cytotoxic doublet therapy using 5-FU/Leucovorin/Irinotecan (FOLFIRI) and Bevacizumab every 2 weeks for 6 months. The results of PRODIGE 9 revealed no difference in survival between the two treatment arms.

2.1. Patients' selection

In the PRODIGE 9 trial (Clinical trial number: NCT00952029), CEA measurements were to be recorded at baseline (0–14 days before randomization) and then every 4 weeks during the first sequence of chemotherapy. To capture the non-linear feature of CEA kinetics, we considered for analysis all patients who had at least three CEA measurements in the 3.5 months since baseline. Patients who progressed or died during this 3.5-month period were excluded from the analysis. Data were randomly split into two sets, one to build the statistical model (the learning set), composed of 75% of the patients, and the other, composed of 25% of the patients, for model validation purposes (the validation set).

2.2. The proposed prognostic model

2.2.1. The joint modeling of PFS and CEA longitudinal measurements: motivation and specification

Progression-free survival (PFS) was defined as the time from baseline to the first disease progression or death from any cause. To focus on short follow-up times and to build an early risk discrimination tool, PFS was censored at 6 months for patients alive and progression-free at this time point. Consequently, when building the prognostic model, we only used the CEA measurements available during the 6 months since baseline. For a given patient, repeated CEA measurements were related to survival outcomes since these measurements ended when death or disease progression occurred, and therefore were correlated with the probability of experiencing an event. CEA thus appeared as an endogenous variable [17]. To take account of this feature of the CEA variable in determining its association with the time-to-event outcome, we estimated these two variables simultaneously through a joint model framework. The literature showed that these models were better suited to analyzing such data because they estimated jointly the relative risk of the time-to-event outcome contingent upon the longitudinal outcome [18,19]. Moreover, to take account of repeated CEA measurements for a given patient, the longitudinal part was modeled with a mixed model that captured within-individual variability [20]. We also took advantage of a latent-class mixed model to characterize different groups of patients in terms of CEA trajectories [21,22].

Several models differing by the number of latent classes and covariates (patients' characteristics at baseline) were tested, and the best one, in terms of the Bayesian Information Criterion (reflecting the model's goodness of fit) and entropy (reflecting the model's ability to assign a subject to a latent class without ambiguity), was selected [22,23]. A detailed description of the joint latent class mixed model considered in our work is provided in Supplementary File A.

2.2.2. Subject classification and risk prognosis

For a given patient, posterior probabilities of belonging to latent classes (one per class) were computed. Based on the Maximum A posterior Probability of class-membership rule (MAP rule), each patient was assigned to the latent class to which he/she had the highest posterior probability of belonging to [20,21].

2.2.3. Model validation

A validation set of patients was used to validate the proposed prognostic model. Using the estimated parameters obtained at the learning step, and using CEA measurements until 3.5 months, posterior class-membership probabilities (one per class) were predicted for each subject of the validation set. Then, based on the MAP rule, each subject was assigned to one of the predefined latent classes. For each subject's group obtained from this classification, PFS was estimated and compared, using a log-rank test, with that of the learning set subjects belonging to the same class.

Of note, we used only CEA measurements until 3.5 months to focus on the prognostic ability of the earliest measurements of the marker. To determine whether the subject's classification was sensitive to CEA measurements over 3.5 months, we built a second classification of the validation set subjects based on CEA measurements until 6 months, and then assessed the agreement with the first one using Cohen's kappa [24].

3. Results

3.1. Study population

Among the 488 patients from the intention to treat (ITT) population of the PRODIGE 9 trial, 331 could be considered for analysis. The learning set comprised 248 patients (75%) and data from the remaining 83 patients (25%) were used for the validation step (Fig. 1).

The median CEA level at baseline was 53.65 (Interquartile range (IQR) = 8.08–388.73) in the learning set and 65.95 (IQR = 13.83–331.18) in the validation set. The survival probability at 6 months was 88% (95% CI: 84–92%) and 93% (95% CI: 87–99%) in the learning set and the validation set, respectively.

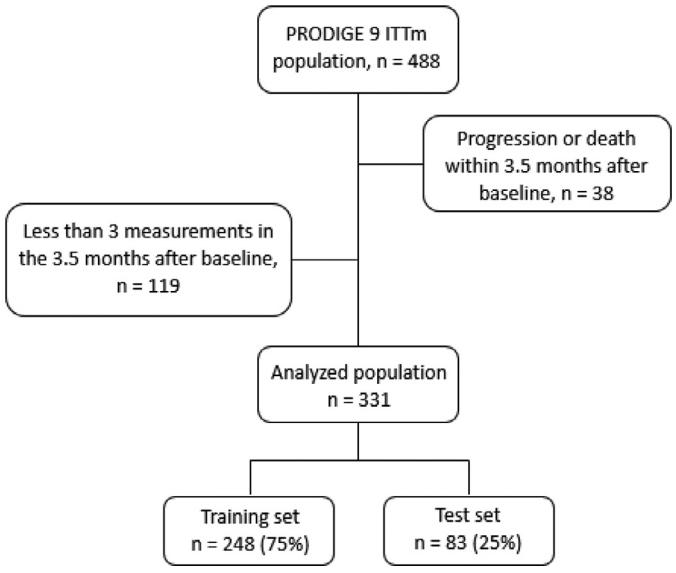

Fig. 1. Flowchart of the whole population of PRODIGE 9 trial.

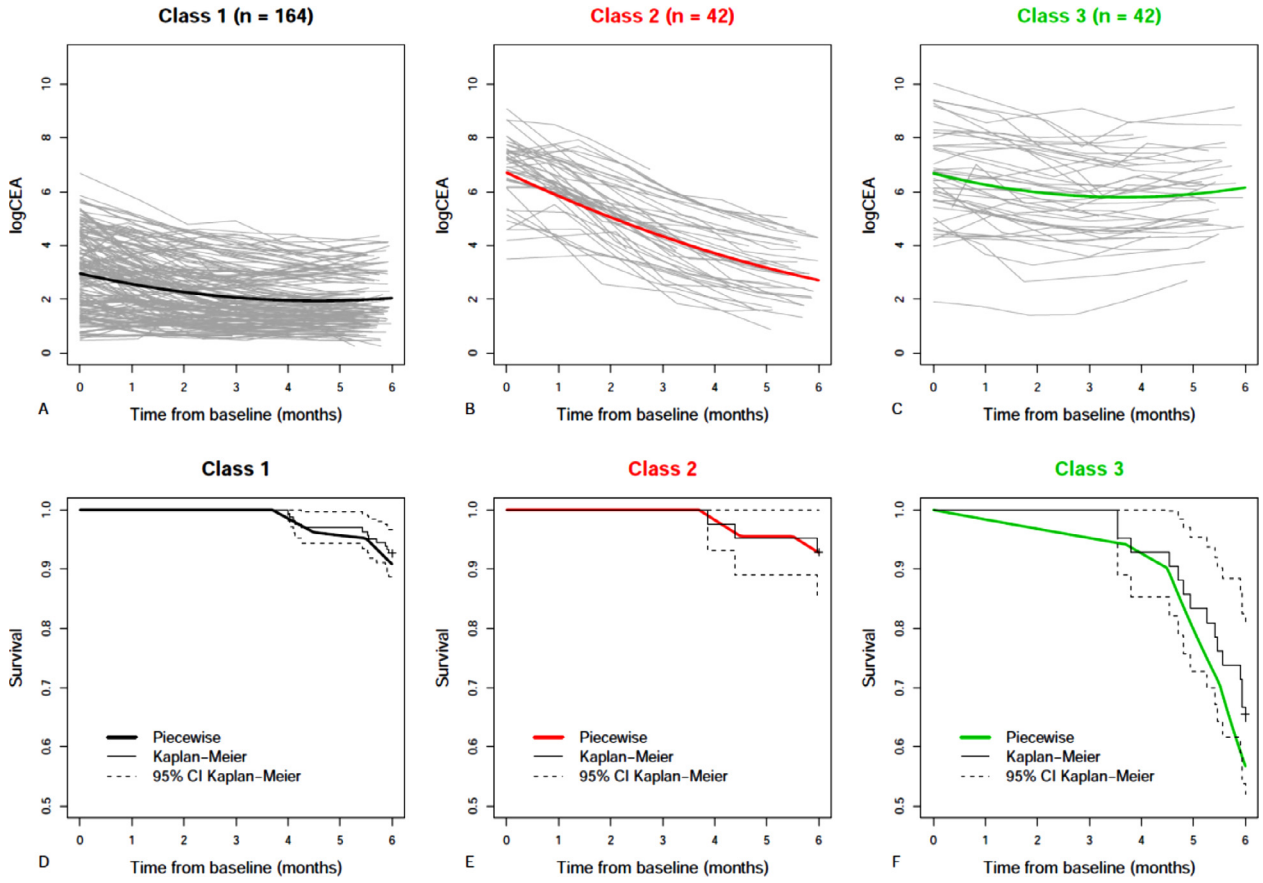

Fig. 2. CEA typical trajectories and PFS curves and their confidence intervals (CI) estimated from the learning set. Top panels (A,B,C) show CEA typical trajectories (thick curves) and observed individual trajectories of CEA (grey curves) in class 1, 2 and 3 respectively. Bottom panels (D,E,F) are the corresponding PFS curves and their CIs in class 1, 2 and 3 respectively.

3.2. CEA kinetics to predict PFS

A joint latent class mixed model with three latent classes was selected, including primary tumor resection as a class-membership predictor and treatment arm as a survival predictor. Based on the MAP rule, the distribution of the 248 patients in the three classes was 164 (class 1), 42 (class 2) and 42 (class 3). We identified from the model estimates three typical shapes of the CEA trajectories (denoted hereafter as 'classes') and correlated each of them with PFS (Fig. 2). Roughly, individual CEA trajectories belonging to the same class were similar not only for their level but also for their shape, reflecting the important role played by the whole CEA kinetic in the classification. Class 1 was characterized by a typical CEA trajectory in which values were low at baseline (around 19) then decreasing slowly during the first 5 months (nadir of 7 reached at 5 months, meaning a 63% decrease from baseline) before increasing slightly to reach 8 at 6 months (a 60% decrease from baseline). PFS among Class 1 trajectory patients was 91% at 6 months. The typical CEA trajectory in class 2 started with a high level at baseline (817), which then dramatically fell throughout the first 6 months to reach a similar level as the typical class 1 trajectory (15, meaning a 98% decrease from baseline). PFS among Class 2 trajectory patients was 93% at 6 months. Class 3 was characterized by a typical CEA trajectory beginning with a high level at baseline (799) followed by a short decrease to reach a nadir of 341 at 3 months (corresponding to a 57% decrease), which is followed by a period of increase until 6 months to reach 475. PFS among Class 3 trajectory patients was 57% at 6 months. The percentages of CAE variations level at baseline, month 3 and month 6 are presented in supplementary file C. Log-rank tests showed significant differences between the survival curve in class 3 and the survival curves in classes 1 and 2 (p-values < 0.01). There was no significant difference between the survival curve in class 1 and class 2 (p-value $= 1$). Of note, for patients with a resected primary tumor, the prior probability of belonging to a given class differed significantly between classes (0.81 [0.74; 0.89], 0.11 [0.04; 0.16], 0.08 [0.03; 0.13] for class 1, 2 and 3, respectively). These probabilities were similar for patients with a non-resected primary tumor (0.45 [0.33; 0.58], 0.28 [0.17; 0.38], 0.27 [0.17; 0.38] for class 1, 2 and 3, respectively). We found no significant treatment-dependent effect on PFS, as reported in the main publication of the PRODIGE 9 trial.

Baseline characteristics in each class are presented in Table 1; most of them, including validated scores predicting survival in mCRC, correlated significantly with the probability of being in one of the 3 classes. Although the impact on PFS is similar in classes 1 and 2, some baseline characteristics are significantly different between the two classes. Class 2 is significantly associated with a lower proportion of male, ECOG Performance status > 0, non-resection of the primary tumor and elevated LDH reflecting a higher tumor burden which is consistent with the high CEA rate.

3.3. Validation

Using the CEA measurements until 3.5 months and the estimates of the proposed model, the posterior probability of belonging to a given class was predicted for the 83 subjects of the validation set. Patients' characteristics are presented in Table 2. This allowed us to assign 55, 15 and 13 subjects, respectively, to

Table 1
Patient baseline characteristics in the 3 classes of the learning set.

Characteristics	All $N = 248$	Class 1 $N = 164$	Class 2 $N = 42$	Class 3 $N = 42$	p-value[#]
Age, median (IQR) years	64 (58–72)	64 (58–73)	65 (61–71)	62 (49–69)	0.08
Sex, N (%)					0.05
Male	161 (64.92)	115 (70.12)	22 (52.38)	24 (57.14)	
Female	87 (35.08)	49 (29.88)	20 (47.62)	18 (42.86)	
Treatment arm, N (%)					0.81
1	132 (53.23)	85 (51.83)	24 (57.14)	23 (54.76)	
2	116 (46.77)	79 (48.17)	18 (42.86)	19 (45.24)	
BMI, median (IQR)	24.69 (22.45–28.07)	24.77 (22.66–28.17)	24.62 (20.54–27.26)	24.27 (22.52–28.28)	0.70
ECOG performance status, N (%)					<0.01
0	128 (51.61)	100 (60.98)	13 (30.95)	15 (35.71)	
1	107 (43.15)	59 (35.98)	27 (64.29)	21 (50)	
2	13 (5.24)	5 (3.05)	2 (4.76)	6 (14.29)	
Primary tumor resected, N (%)					<0.01
Yes	142 (57.26)	116 (70.73)	14 (33.33)	12 (28.57)	
No	106 (42.74)	48 (29.27)	28 (66.67)	30 (71.43)	
Number of metastatic sites, N (%)					0.17
1	94 (37.90)	60 (36.59)	21 (50)	13 (30.95)	
> 1	154 (62.10)	104 (63.41)	21 (50)	29 (69.05)	
CEA at baseline, median (IQR) μg/L	53.65 (8.08–388.73)	17 (4.30–59.30)	1066.5 (520.22–1814.75)	658.4 (285.90–2238)	<0.01
CA 19.9 at baseline, median (IQR) U/mL	81 (10–734)	34 (8–205.25)	771 (120–2624)	828 (78.5–4272.25)	<0.01
LDH at baseline, median (IQR) UI/L	342.0 (220.5–594.5)	291.5 (193.8–429.2)	508.5 (306.2–869.8)	592.0 (292.5–1137.0)	<0.01
Köhne criteria, N (%)					<0.01
Low	90 (36.59)	58 (35.58)	20 (48.78)	12 (28.57)	
Intermediate	117 (47.56)	87 (53.37)	15 (36.59)	15 (35.71)	
High	39 (15.85)	18 (11.04)	6 (14.63)	15 (35.71)	
GERCOR score [22], N (%)					<0.01
Low	31 (13.9)	30 (20.27)	1 (2.78)	0 (0)	
Intermediate	162 (72.65)	110 (74.32)	24 (66.67)	28 (71.79)	
High	30 (13.45)	8 (5.41)	11 (30.56)	11 (28.21)	

[#]comparison between classes
Abbreviations: Eastern Cooperative Oncology Group (ECOG) performance status, CA 19-9 : Carbohydrate antigen 19-9, LDH: Lactate dehydrogenase, BMI : body mass index; GERCOR : Groupe Coopérateur Multidisciplinaire en Oncologie, IQR : Interquartile range (1st – 3rd quartiles).

Table 2
Patient baseline characteristics in the 3 classes of the validation set.

Characteristics	All $n = 83$	Class 1 $n = 55$	Class 2 $n = 15$	Class 3 $n = 13$	p-value[#]
Age, median (IQR) years	65 (57–72)	65 (58–73)	65 (54–71)	66 (59–69)	0.77
Sex, No. (%)					0.04
Male	60 (72.29)	35 (63.64)	14 (93.33)	11 (84.62)	
Female	23 (27.71)	20 (36.36)	1 (6.67)	2 (15.38)	
Treatment arm, N (%)					0.78
1	37 (44.58)	26 (47.27)	6 (40)	5 (38.46)	
2	46 (55.42)	29 (52.73)	9 (60)	8 (61.54)	
BMI, median (IQR)	24.91 (21.89–27.98)	25.46 (21.92–27.71)	24.21 (23.21–28.11)	23.24 (21.45–25.06)	0.56
ECOG performance status, N (%)					0.30
0	42 (50.60)	31 (56.36)	7 (46.67)	4 (30.77)	
1	38 (45.78)	21 (38.18)	8 (53.33)	9 (69.23)	
2	3 (3.61)	3 (5.45)	0 (0)	0 (0)	
Primary tumor resected, N (%)					<0.01
Yes	50 (60.24)	41 (74.55)	4 (26.67)	5 (38.46)	
No	33 (39.76)	14 (25.45)	11 (73.33)	8 (61.54)	
Number of metastatic sites, N (%)					0.14
1	33 (39.76)	25 (45.45)	6 (40)	2 (15.38)	
> 1	50 (60.24)	30 (54.55)	9 (60)	11 (84.62)	
CEA at baseline, median (IQR) μg/L	65.95 (13.83–331.18)	17.40 (6.40–65.95)	541.00 (329.45–1101.00)	1143.50 (408.65–2643.25)	<0.01
CA 19.9 at baseline, median (IQR) U/mL	48 (11–293.50)	29 (10–180)	225 (65.5–490.5)	293 (11–1130)	0.07
LDH at baseline, median (IQR) UI/L	302.0 (204.0–525.5)	243.0 (192.8–430.2)	552.5 (280.5–1278.8)	450.0 (295.0–741.0)	0.01
Köhne criteria, N (%)					0.21
Low	32 (39.02)	24 (43.64)	6 (40.00)	2 (16.67)	
Intermediate	39 (47.56)	25 (45.45)	8 (53.33)	6 (50.00)	
High	11 (13.41)	6 (10.91)	1 (6.67)	4 (33.33)	
GERCOR score, N (%)					0.12
Low	9 (12.68)	9 (18.75)	0 (0)	0 (0)	
Intermediate	51 (71.83)	30 (62.5)	12 (85.71)	9 (100)	
High	11 (15.49)	9 (18.75)	2 (14.29)	0 (0)	

[#]comparison between classes
Abbreviations: Eastern Cooperative Oncology Group (ECOG) performance status, CA 19-9 : Carbohydrate antigen 19-9, LDH: Lactate dehydrogenase, BMI : body mass index; GERCOR : Groupe Coopérateur Multidisciplinaire en Oncologie, IQR : Interquartile range (1st – 3rd quartiles).

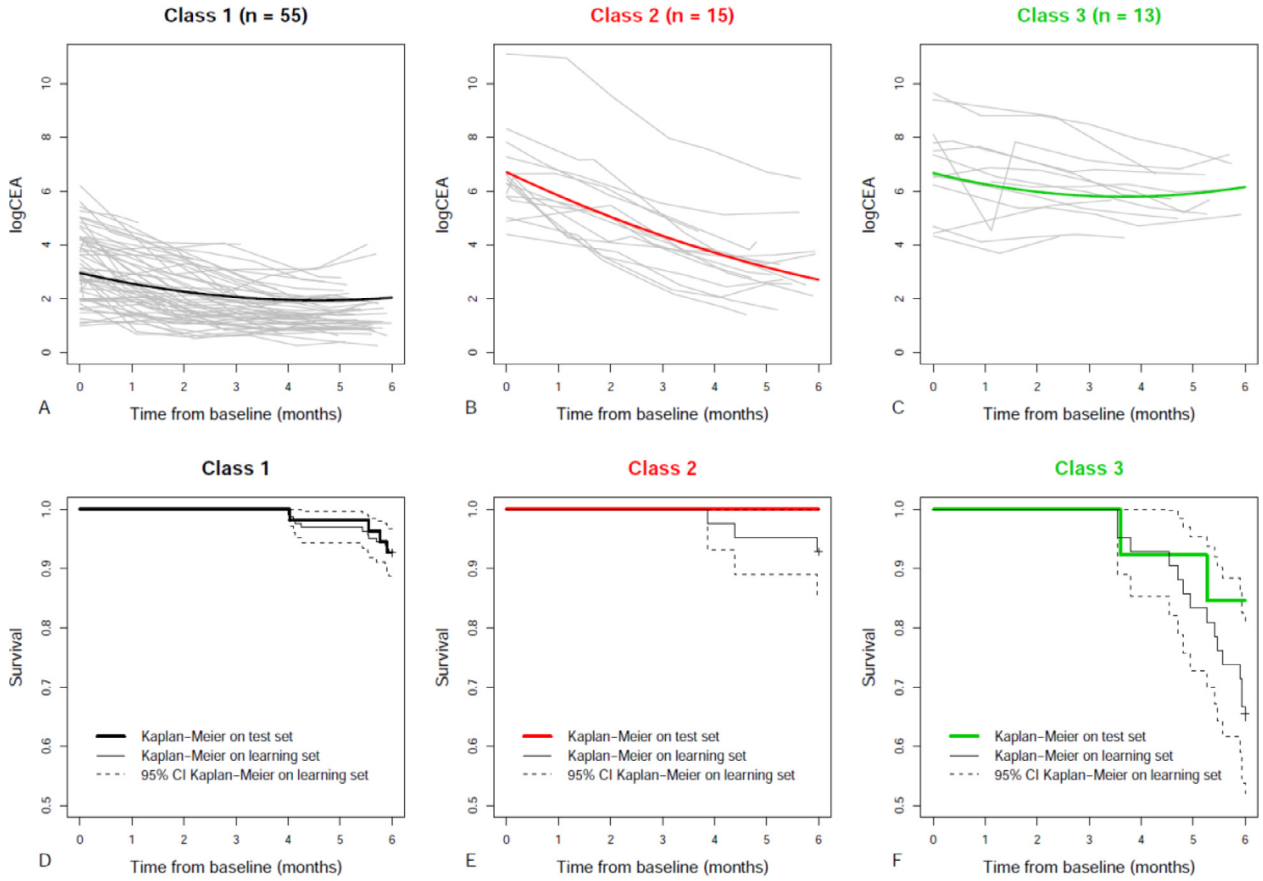

Fig. 3. CEA typical trajectories and PFS curves and their confidence intervals (CI) estimated from the validation set. Top panels (A, B, C) show CEA typical trajectories (thick curves) and observed individual trajectories of CEA (grey curves) in class 1, 2 and 3 respectively. Bottom panels (D, E, F) are the corresponding PFS curves and their CIs in class 1, 2 and 3 respectively.

classes 1, 2 and 3 identified at the learning step. Fig. 3 (panels A, B, C) show that for each class the individual CEA trajectories were in accordance with the estimated typical trajectory obtained at the learning step. Corresponding PFS estimates were plotted in Fig. 3 (panels D, E, F). As at the learning step, 6-month PFS in class 1 and class 2 were similar, and better than in class 3 (93%, 100%, 85%, respectively). For each class, no significant difference was observed between estimated PFS from both the learning and validation sets (log rank test p-values > 0.2). Contrarily to the learning set, the only baseline characteristic significantly associated with Class 2 comparing to Class 1 is non-resection of the primary tumor.

When using CEA measurements until 6 months to predict a subject's posterior probability of belonging to a given class, the derived classification was very close to that obtained previously (Cohen's Kappa = 0.82, see also Contingency Table in Supplementary File B), showing that CEA kinetics until 3.5 months carried enough information to predict the risk of progression or death. Hence, we propose as a user-friendly web application available here, a pragmatic use of the results of our work to support, for instance, therapeutic decision-making.

3.4. Response rate and overall survival according to CEA kinetics

The objective response rates at first and second evaluations were better in classes 1 and 2 of CEA trajectories than in class 3, showing consistency with results on PFS in the three classes (see Table 3). In the learning set, the objective response rates at first and second evaluations were 31% and 47% in Class 1, 42.5% and 62.5% in Class 2, 9.5% and 10.5% in class 3 respectively. In the validation set, the objective response rates at first and second evaluations were 44.4% and 60% in Class 1, 33.3% and 53.8% in Class 2, 23.1% and 33.3% in class 3 respectively.

Overall survivals at 6 months according to the 3 CEA trajectories in the learning and validation sets (Fig. 4) were 99% and 98% in Class 1, 97% and 100% in Class 2 and 88% and 100% in Class 3 respectively.

4. Discussion

We report for the first time a CEA kinetics analysis that identified three different kinetic profiles that correlated with prognosis in mCRC patients treated with first-line FOLFIRI-Bevacizumab. We showed that Class 1 and 2 were associated with a favorable 6-month PFS of over 90%.

The kinetic profile of the Class 2 group has already been associated with a better prognosis in some studies. In a post-hoc analysis of the FIRE 3 trial, comparing FOLFIRI-Cetuximab with F-Bevacizumab in *KRAS* wild-type mCRC, Michl et al. defined CEA response as a decrease in CEA level by at least 75% [25]. In that study, the CEA nadir was defined as the lowest level measured at any time point for each individual compared with the baseline CEA level. They showed that CEA responders had better overall survival only in the sub-group of patients treated with the FOLFIRI-Cetuximab regimen. Although the methodology used in their study was different, our results are consistent in suggesting that patients showing this type of CEA kinetic profile (analogous to class 2 in our work) have a good prognosis. The originality of our approach is to consider all available measurements of CEA (at least three) in the early months to account for the non-linearity of the CEA trajectories in the first months following treatment initiation.

Table 3
Response rate at the first and second evaluations according to CEA kinetic.

Learning set		Class 1 (n = 164)	Class 2 (n = 42)	Class 3 (n = 42)
First assessment	Objective response	50 (31%)	17 (42.5%)	4 (9.5%)
	Non-response	113 (69%)	23 (57.5%)	38 (90.5%)
Second assessment	Objective response	73 (47%)	25 (62.5%)	4 (10.5%)
	Non-response	82 (53%)	15 (37.5%)	34 (89.5%)
Validation set		**Class 1 (n = 55)**	**Class 2 (n = 15)**	**Class 3 (n = 13)**
First assessment	Objective response	24 (44.44%)	5 (33.33%)	3 (23.08%)
	Non-response	30 (55.56%)	10 (66.67%)	10 (76.92%)
Second assessment	Objective response	30 (60%)	7 (53.84%)	4 (33.33%)
	Non-response	20 (40%)	6 (46.16%)	8 (66.67%)

Objective response includes complete and partial response, Non-response includes stable and progressive disease, Percentages are calculated excluding missing data.

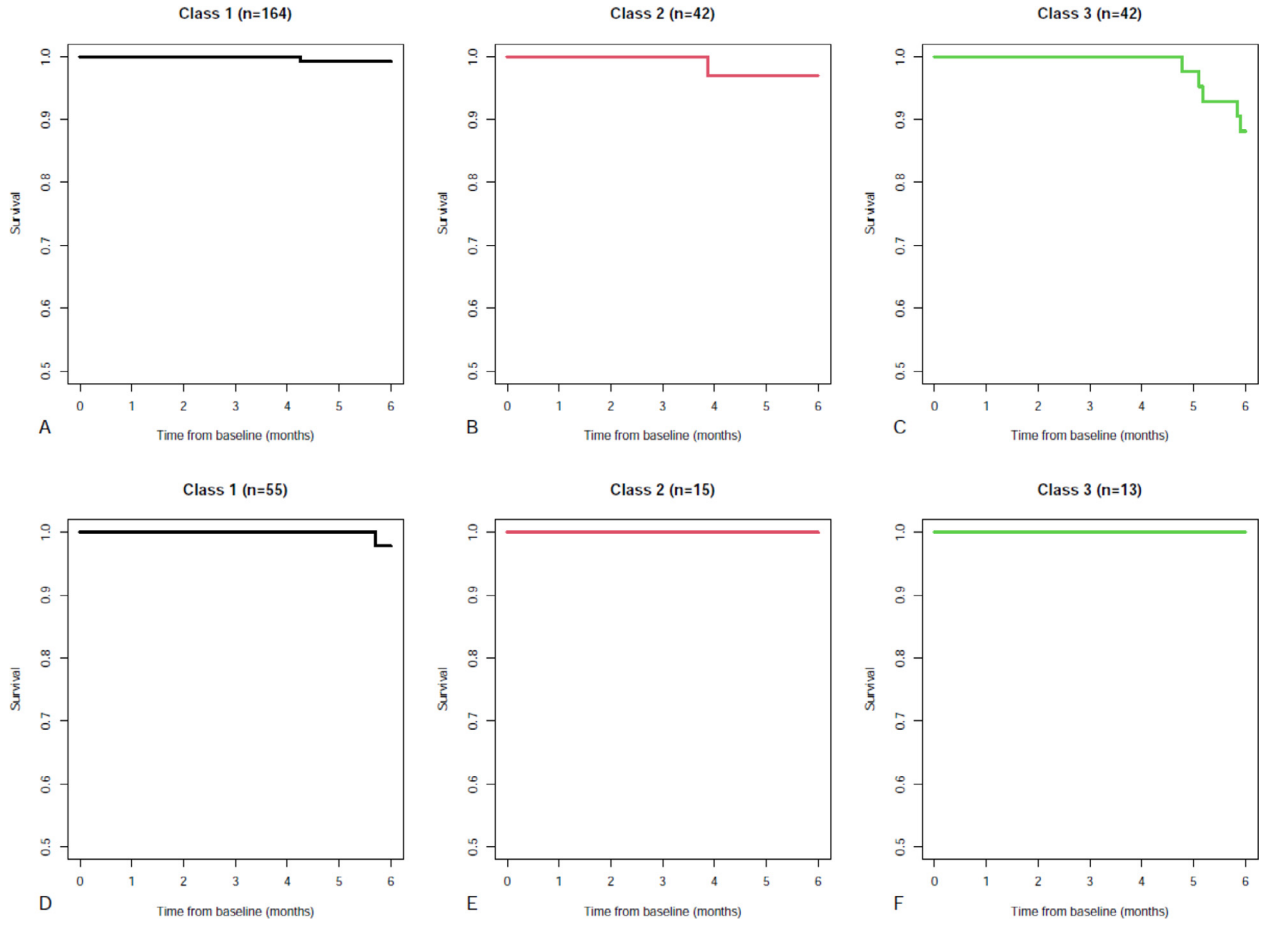

Fig. 4. Overall survival according to classes of CEA trajectories, estimated from the learning set (panels A,B,C) and the validation set (panels D,E,F).

Consequently, we were able to better capture the CEA variations and therefore to better estimate the correlation with the PFS.

There are no robust data in the literature defining a baseline CEA level best associated with a worse prognosis in mCRC. It has been shown that a decrease in CEA level is associated with a better clinical outcome [9]. In the PRODIGE 9 trial, it was reported that increasing CEA at 2 months was an independent factor associated with disease progression during induction chemotherapy [26]. However, the degree of the decrease in CEA level associated with tumor regression and better survival is unknown. The prognosis in Class 1 patients was equivalent to those in Class 2. This kinetic profile has not been previously associated with a good prognosis in the literature. In mCRC, a high baseline CEA level is an independent predictor of a poor prognosis, possibly reflecting tumor burden and a more aggressive biology [27]. However, the threshold for CEA positivity is still debated as it may increase in some non-tumor diseases or in smokers [28,29]. A threshold of $\geq$ 5 ng/ml is usually used. There is no consensus on what constitutes a low CEA level at baseline. It is generally accepted that a CEA level below the laboratory standard or considered 'low' may be associated with a less aggressive disease. However, in the absence of a threshold CEA level clearly associated with a different prognosis, the CEA level at baseline is a criterion that is not used to help in decision making. Our study suggests that in patients with a CEA level considered low by clinicians, repeated measurements can define a subgroup of patients with a good prognosis. Thus, a small change in the CEA slope on early iterative measurements appeared to be a good, inexpensive prognostic marker that may be useful in routine practice. We further reported a subgroup of patients with CEA levels that were high at baseline, but which subsequently de-

creased. These patients may experience a potentially favorable clinical course. Nevertheless, the rapid increase in CEA levels defined a kinetic profile associated with a poor prognosis. This type of kinetic profile has not previously been reported in the literature. In the absence of repeated measurements, this type of kinetic profile cannot be captured by the clinician. Considering the prognostic impact, repeated CEA measurements may be useful in routine practice in decision making in this subgroup of patients.

Interestingly, several baseline patients' characteristics were associated with the kinetic profile of class 3 patients. Thus, female sex, an ECOG performance status of 1 or 2 vs. 0, the absence of primary tumor resection and high LDH levels were significantly associated with this poor prognosis subgroup. These factors have previously been reported as potential factors of a poor prognosis or of severe chemotherapy-induced toxicity. These associations with the class 3 kinetic profile reinforce the hypothesis that this subgroup is of particular interest in current practice, especially given the significant correlation between class 3 and clinico-biological scores validated in the literature [4,5].

We observed that a high baseline CA 19-9 level was also significantly associated with class 3. This assay is frequently used in routine practice although not recommended. CA 19.9 level also seems to be associated with PFS and OS in mCRC [12]. Further studies on baseline CA 19-9 or kinetics could help to better define its potential interest in clinical practice.

Our work suffers from several limitations. First, we cannot extrapolate our results to other chemotherapy regimens than FOLFIRI-Bevacizumab. In addition, although repeated assays were specified in the study, there were missing data, leading to the exclusion of some patients from the analysis, which could lead to a bias in the interpretation of our results. In addition, the design of the Prodige 9 trial did not allow us to establish a kinetic profile beyond the first months of treatment.

Nevertheless, our work has some strengths. Our data were obtained from a prospective randomized trial using a chemotherapy protocol considered a therapeutic standard. The methodology used, including confirmation of our results on a validation set, reinforces the robustness of our work. In addition, we propose a computer tool that allows clinicians to apply our results in everyday practice.

Other biological markers to better define prognosis at baseline have recently emerged, such as the determination of circulating tumor DNA. However, it is a costly technique that is not yet approved in everyday practice. Moreover, its interest in early treatment modification has not been demonstrated in prospective randomized trials. Osumi et al. studied the correlation between cDNA and CEA levels and showed the overall concordance rate between the two levels was 75.5% [30]. This positive correlation suggests that CEA measurement remains an inexpensive alternative to this new technique.

Scheduled imaging, mainly with computed tomography, and CEA testing are usually carried out every 4 to 6 chemotherapy cycles i.e. every 2 to 3 months with the current protocols. Our work suggests that repeated measurements of CEA from baseline may be a cost-effective way to define subgroups of mCRC patients with a different prognosis based on their CEA kinetic profile.

Conflict of interest

DS, MH, KLM and OB have no conflict of interest to declare

TA declared Honoraria from Sanofi, Roche, Amgen, Servier, Pierre Fabre and Astra Zeneca ; Consultancy / Advisory role for Bioven, Pierre Fabre, MSD and Sirtec ; Travel accommodations from Roche.

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Author contributions

D.S, J.M.G, M.H., O.B.: conception and design, data interpretation and paper writing; T.A., K.L.M.: data interpretation and paper review; C.L., J.T., O.B., V.B., J.M.P., L.D., J.B.: provision of study patients and paper review. The final version of the paper has been approved by all authors.

Ethics approval and consent to participate

The study used data from PRODIGE 9 trial. It was done in accordance with the Declaration of Helsinki. PRODIGE 9 trial was approved by the Committee for the Protection of Persons Ile-de France VIII on 12/07/2011. Reminder of regulatory texts currently in force: This trial will be conducted in accordance with the New European Directive 2001/20/EC. Civil liability insurance: An insurance policy was taken out by the sponsor with SHAM under contract number 137681, in accordance with article L 1121-10 of the Public Health Code. Request for CPP and AFSSAPS authorization: This protocol has received approval from the CPP [Comité de Protection des Personnes] (Medical Ethics Committee) Ile-de-France VIII (Boulogne A. Paré) on 12/07/2011. This protocol has been authorised by the AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé) (French Health Products Safety Agency) on 25/07/2011.

Consent for publication

Not applicable.

Data availability

PRODIGE 9 trial (Clinical trial number: NCT00952029) data base. Data supporting this publication are stored at the FFCD Data Center.

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Reporting guidelines

We used REMARK guidelines to write this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.12.018.

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