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ORIGINAL ARTICLE

Estimating 12-week death probability in patients with refractory metastatic colorectal cancer: the Colon Life nomogram

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Background: Regorafenib and TAS-102 have recently demonstrated statistically significant survival gains in patients with refractory metastatic colorectal cancer (mCRC). Life expectancy ≥12 weeks was an inclusion criterion in registrative trials, and the identification of proper clinical selection tools for the daily use of these drugs in heavily pre-treated patients is needed to improve the cost-benefit ratio. We aimed at building a nomogram able to predict death probability within 12 weeks from the date of assessment of refractory mCRC.

Patients and methods: Four hundred eleven refractory mCRC patients with ECOG performance status (PS) ≤2 receiving regorafenib, TAS-102 or other treatments were used as developing set. Putative prognostic variables were selected using a random forest model and included in a binary logistic model from which the nomogram was developed. The nomogram was externally validated and its performance was evaluated by examining calibration (how close predictions were to the actual outcome) and discriminative ability (Harrell C index) both on developing (internal validation) and validating (external validation) sets.

Results: Four variables were selected and included in the nomogram: PS ($P < 0.0001$), primary tumor resection ($P = 0.027$), LDH value ($P = 0.0001$) and peritoneal involvement ($P = 0.081$). In the developing set, the nomogram discriminative ability was high ($C = 0.778$), and was confirmed in the validating set ($C = 0.778$), where the overall outcome was better as a consequence of the enrichment in patients receiving regorafenib or TAS-102 (46% versus 34%; $P < 0.0001$).

Conclusions: Our nomogram may be a useful tool to predict the probability of death within 12 weeks in patients with refractory mCRC. Based on four easy-to-collect variables, the 'Colon Life' nomogram and free app for smartphones may improve mCRC patients' selection for later-line therapies and assist researchers for the enrollment in clinical trials in this setting.

Key words: nomogram, colorectal cancer, refractory, prognosis, regorafenib, TAS-102

Introduction

In the last years the therapeutic landscape of metastatic colorectal cancer (mCRC) has notably evolved and new agents are now available after failure of previous therapies including fluoropyrimidines, irinotecan and oxaliplatin, antiangiogenic agents (bevacizumab, aflibercept and ramucirumab), and anti-EGFR monoclonal antibodies (cetuximab or panitumumab) for *RAS* wild-type tumors [1]. FDA and EMA have recently approved regorafenib, a multitarget tyrosine kinase inhibitor, and TAS-102, a new oral fluoropyrimidine, based on results of phase III placebo-controlled studies showing significant survival improvements [2–4]. Moreover, targeted treatments for molecularly defined subgroups (such as *BRAF* mutated, HER2-positive, *NTRK*-rearranged, *MGMT*-silenced or MSI-high) demonstrated promising activity in heavily pretreated patients [5–10].

Eligibility criteria in clinical trials in the refractory setting often include life expectancy ≥12 weeks, but physicians often overestimate survival in terminally ill cancer patients [11], and are not assisted by evidence-based tools.

Moreover, the clinical benefit from both regorafenib and TAS-102 is quite limited, and no molecular predictors have been identified, so that a proper clinical selection is currently needed to optimize the cost-effectiveness balance. Nevertheless, the clinical course of refractory disease is hardly predictable and prognostic scores developed in newly diagnosed patients [12,13] cannot be easily translated into the refractory setting.

The availability of new options highlights the clear need for a prognostic tool to be used by clinicians both in their daily practice and for inclusion in clinical trials. The aim of the present work was to build a nomogram for predicting the probability of death within 12 weeks for individual patients with refractory mCRC.

Methods

Study design and patients

The nomogram endpoint was death within 12 weeks from the date of Investigator-assessed refractory disease. The *a priori* chosen putative nomogram predictors were clinical and pathological data retrospectively collected and mostly related to the time of refractory disease, i.e. age, gender, ECOG PS, primary tumor site, primary tumor resection (yes, no), presentation of metastases (metachronous, synchronous), number of metastatic sites (1,2, ≥3), specific sites of metastases (peritoneal, extraregional lymph nodes, liver, lung, bone, brain), laboratory tests (CEA, white blood cells—<10000 versus ≥10000/μl, hemoglobin, platelets—<400 versus ≥400/μl, neutrofils-to-lymphocytes ratio—<5 versus ≥5, sodium, LDH, alkaline phosphatase—<300 versus ≥300), time to refractory disease (defined as the interval between first-line treatment start and date of refractory disease), number of previous treatment lines, mutational status of *KRAS*, *NRAS* and *BRAF* genes.

The nomogram was developed in a set including consecutive mCRC patients with cancer judged as refractory in the period 2006-2015 at 5 Italian Institutions (developing set). Treatment for refractory disease was administered as per Investigators' choice. Main inclusion criteria were: age ≥ 18 years; ECOG performance status (PS) ≤2; histologically confirmed diagnosis of mCRC; imaging-defined progressive disease (PD) during or within 3 months following the last administration of approved standard therapies, including fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab if *(K)RAS* wild type. In addition, those patients who previously experienced unacceptable toxicity warranting treatment discontinuation and unable to receive the same treatment again, were eligible. Only patients with a minimum follow-up of 12 weeks from the date of refractory disease were evaluable.

A different cohort of consecutive mCRC patients with cancer judged as refractory in the period 2010-2016 at 12 Italian Institutions formed the independent external validating set; inclusion criteria were the same as in the developing set. Being the treatment administered in a relatively more recent period of observation, the validating set was therefore enriched with patients treated with advanced lines options, i.e. regorafenib or TAS-102. Since patients with ECOG PS ≥2 were excluded from registration trials of both regorafenib and TAS-102, only patients with ECOG PS 0-1 patients were included in the validating set.

The study was approved by the Institutional Ethics Committee of the Coordinating Center, Fondazione IRCCS Istituto Nazionale dei Tumori (Study Protocol INT 136/14).

Statistical analysis

The analyses were carried out using the SAS® [14] and R software [15]. We considered a statistical test as significant when the corresponding *P* value was <0.05. The comparison of the variable distributions between developing set and validating set was performed using the Kolmogorov–Smirnov test with continuous variables, and the Fisher–Freeman–Halton test [16] with categorical variables. The overall survival was estimated with the Kaplan–Meier method.

To build the nomogram we started from a multivariable random forest (RF) classification model [17] including all the above-mentioned *a priori* chosen putative predictors. An interesting feature of the RF model is that it allows handling many predictor variables and the possibility to quantify the relative importance (RI) of each variable, whereby higher figures indicate stronger prognostic value. Variable selection was performed according to the statistical significance based on RIs calculated by applying a permutation procedure [18].

The selected variables were included in a multivariable binary logistic model that was used to develop the nomogram. The categorical covariates were modeled by using dummy variables, whereas continuous variables by using three-knots restricted cubic splines to obtain flexible fit [19]. Nomogram model performance was evaluated both in the development and validating sets by examining calibration (how close the predictions were to the actual outcome; calibration plots and Hosmer and Lemeshow test were used) [20] and discrimination (Harrell C index [21] together with its 95% bootstrap confidence interval [22]). In external calibration plots, points parallel to the reference line would indicate similar prognostic effect of the nomogram covariates in the development and validation sets.

Results

Developing set

The series originally included 492 consecutive patients. Two patients lost to follow-up before 12 weeks and 79 patients with missing data on the putative prognostic variables were excluded, thus leading to 411 evaluable patients. Patients and disease characteristics are listed in Table 1. Patients' distribution according to treatments chosen at the time of refractory disease is shown in supplementary Figure S1, available at *Annals of Oncology* online. Median overall survival was 5 months (95% Confidence Interval, 95% CI, 5-6 months), with 398 (96.8%) deaths for all causes, 124 of which within 12 weeks (30.2%; 95% exact CI: 25.8-34.9%).

Table 1. Patients and disease characteristics in the developing and in the validating sets

	Developing set		Validating set		*P*
	No.	%	No.	%	
Total	411	100	410	100	
Patient's age (years)					0.113
Median (IQR)	66 (58–72)			65 (55–71)	
Sex					0.522
Male	242	59	251	61	
Female	169	41	159	39	
ECOG performance status					<0.001
0	194	47	210	51	
1	154	38	200	49	
2	63	15	–		
Primary tumor site[a]					0.049
Rectum	127	31	96	23	
Left colon	156	38	179	44	
Right colon	128	31	135	33	
Primary tumor resection					
Yes	348	85	358	87	0.315
No	63	15	52	13	
Presentation of metastases					0.153
Metachronous	119	29	138	34	
Synchronous	292	71	272	66	
Number of metastatic sites					0.089
1	87	21	81	20	
2	172	42	147	36	
≥3	152	37	182	44	
Specific sites of metastases					
Liver	313	76	308	75	0.746
Lung	258	63	254	62	0.829
Extra-regional lymph nodes	157	38	189	46	0.024
Peritoneum	95	23	102	25	0.568
Bone	36	9	29	7	0.438
Brain	10	2	11	3	0.830
CEA (ng/ml)				0.005	
Median (IQR)	42 (7–190)			58 (15–252)	
White blood cells (/μl)					0.459
<10 000	345	84	336	82	
≥10 000	66	16	74	18	
Haemoglobin (g/dl)					0.946
Median (IQR)	12.4 (11.1–13.7)			12.4 (11.2–13.6)	
Platelets (/μl)					0.620
<400	378	92	373	91	
≥400	33	8	37	9	
Neutrophils/lymphocytes ratio					0.742
<5	317	77	312	76	
≥5	94	23	98	24	
Lactate dehydrogenase (U/l)					<0.001
Median (IQR)	271 (191–480)			353 (215–529)	
Alkaline phosphatase (U/l)					<0.001
<300	337	82	319	78	
≥300	66	16	54	13	
Missing value	8	2	37	9	
Sodium (mEq/l)					0.143
Median (IQR)	139 (137–141)		140 (138–141)		
Time to chemorefractoriness (months)					<0.001
Median (IQR)	19 (13–29)		26 (17–40)		
Previous treatment lines					0.314
Median (range)	3 (1–7)		3 (1–9)		

Continued

Table 1. *Continued*

	Developing set		Validating set		*P*
	No.	%	No.	%	
Mutational status[b]					
KRAS wild-type	173	42	133	32	0.001
RAS mutated	167	41	198	49	0.030
BRAF mutated	13	3	17	4	0.127
Missing	58	14	91	22	

[a]Primary tumor site was classified as: right colon (from cecum to splenic flexure); left colon (from splenic flexure to rectum) and rectum (extraperitoneal, i.e. below the peritoneal reflection).
[b]In the developing set, 225 pts had pan-*RAS* tested and 232 had *BRAF* tested and in the validating set 278 pts had pan-*RAS* tested and 241 had *BRAF* tested. *KRAS* (exons 2,3,4), *NRAS* (exons 2,3,4) and *BRAF* (exon 15) were tested with certified methods as per standard practice.
IQR, interquartile range.

Table 2. Results of the multivariable binary logistic model including the nomogram variables

	OR	95% CI	*P*[†]
ECOG performance status			<0.0001
1 versus 0	2.73	1.58–4.70	
2 versus 0	7.82	3.85–15.86	
Primary tumor resection			0.027
No versus yes	2.01	1.08–3.71	
Lactate dehydrogenase (U/l)			0.0001
480 versus 191*	1.64	0.96–2.80	
Peritoneal metastases			0.081
Yes versus no	1.65	0.94–2.88	

*The two values are, respectively, the 3rd and 1st quartiles of the variable distribution.
[†]*P*, two-sided Wald test *P* value.
OR, odds ratio; CI, confidence interval.

ECOG PS, primary tumor resection, LDH and presence/absence of peritoneal metastases were selected according to their significance in the RF model (supplementary Table S1, available at *Annals of Oncology* online) and were included into a multivariable logistic model that was then used to develop the nomogram (Table 2). The nomogram is shown in Figure 1; it predicts the probability that the patient will die of any cause within 12 weeks after the date of refractory disease. The nomogram scoring system, which can be used for a more precise calculation of prediction, is reported in supplementary Table S2, available at *Annals of Oncology* online.

The calibration plot for internal validation is shown in Figure 2A; the observed proportion of deaths was well in agreement with the predicted probability in all the subgroups but the third one from the left (18% predicted probability versus 28% observed proportion). Accordingly, the Hosmer–Lemeshow calibration test was not significant ($P = 0.117$). The Harrell C index was 0.778 (95% CI 0.730-0.824).

Validating set

The series originally included 424 consecutive patients treated in 12 centers between 2010 and 2016. Fourteen patients lost to follow-up before 12 weeks were excluded, thus leading to 410 evaluable patients. The distribution of the patients' and disease characteristics in the validating set are summarized in Table 1; the developing and validating sets did not differ according to all the nomogram variables, except for significantly higher LDH levels ($P = 0.0002$) and absence of ECOG PS 2 patients in the validating set (as explained earlier) (Table 1). Patients' distribution according to treatment received is shown in supplementary Figure S1, available at *Annals of Oncology* online; in the development set the percentage of patients treated with regorafenib or TAS102 was lower than the validation set (34% versus 46%; $P < 0.0001$). Median overall survival was 6 months (95% Confidence Interval, 95% CI, 6-7 months), with 294 patients dead for all causes, 89 of which within 12 weeks (21.7%; 95% exact CI: 17.8-26.0%).

The nomogram discriminative ability on the validating series was quite good, being the Harrell C index as high as 0.778 (95% CI 0.732-0.826). The calibration plot for external validation is shown in Figure 2B; the predicted probability tended to be higher than the observed proportion of deaths within 12 weeks, and this produced a significant result for the Hosmer–Lemeshow calibration test ($P = 0.002$). However, as explained earlier, the validating set was enriched with patients treated with regorafenib or TAS-102 (46% versus 34% in the developing set; supplementary Figure S1, available at *Annals of Oncology* online). The nomogram calibration would improve by excluding patients treated with regorafenib or TAS-102 (supplementary Figure S2, available at *Annals of Oncology* online; *P* value at Hosmer–Lemeshow test = 0.238).

Discussion

The survival of mCRC has been notably improved in the last years as a result of incremental gains more than seismic effects provided by new available agents [23]. Exploiting the continuum of care and exposing patients to all available options allow prolonging as much as possible mCRC patients' survival. At the same

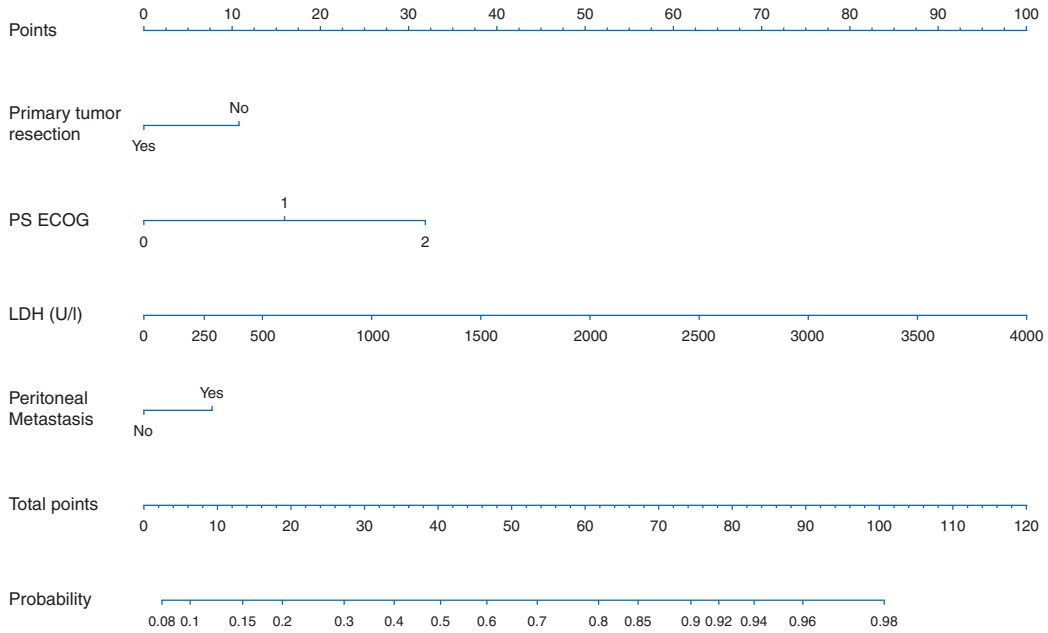

Figure 1. A 12-week death nomogram. The nomogram provides a method to calculate 12-week probability of death after investigator's assessed date of refractory mCRC. To use, locate primary tumor resection (yes, no), draw a line straight up to the 'Points' axis to determine the score associated to primary tumor resection. Repeat for the other three variables: ECOG Performance Status (0, 1 or 2), LDH value and presence of peritoneal metastases (no, yes). Sum the scores and locate the total score on the 'Total Points' axis. Draw a line straight downwards to the 'Probability' axis to obtain the probability.

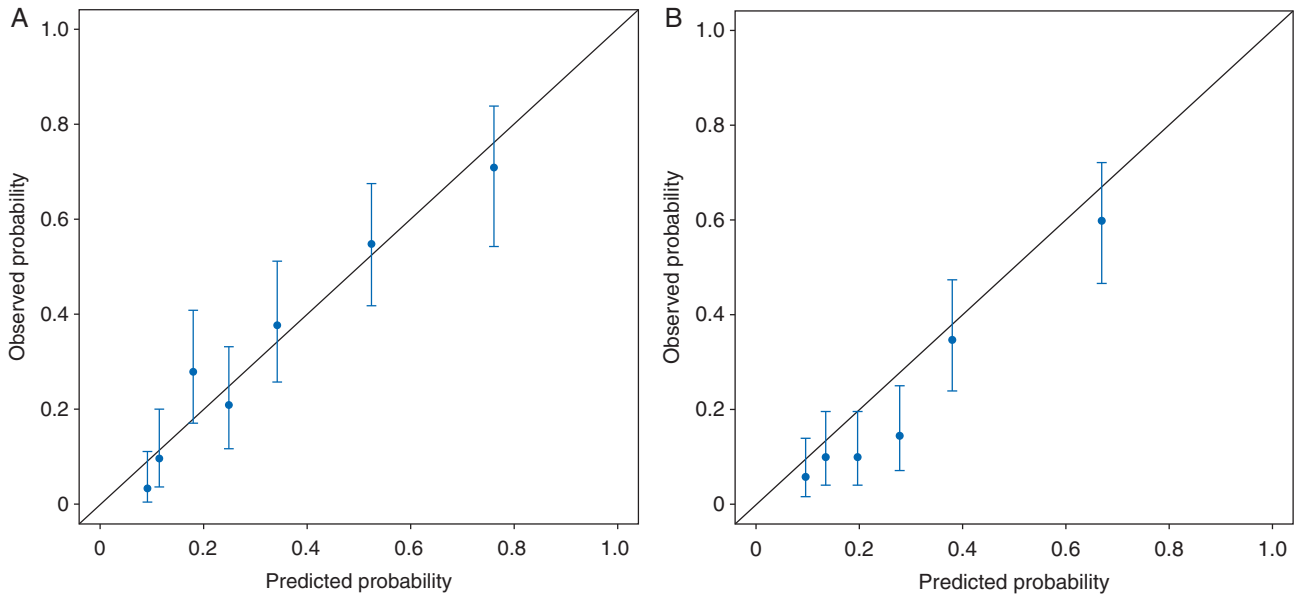

Figure 2. Calibration plots for internal (developing cohort, panel A) and external (validating cohort, panel B) validation of the 12-week death nomogram. The nomogram predicted probabilities were stratified in equally sized subgroups. For each subgroup, the average predicted probability (nomogram-predicted 12-week death; *x* axis) was plotted against the observed proportion of deaths (observed 12-week deaths; *y* axis). 95% CIs of the estimates are indicated with vertical lines. Dashed line indicates the reference line, indicating where an ideal nomogram would lie.

time, later line treatments have an extremely palliative intent, and the relatively small magnitude of benefit should always be balanced with a careful evaluation of costs, in terms of both toxicity profile and financial burden. Molecular biomarkers, able to refine patients' selection, would help optimizing this balance, but are currently lacking and no promising biomarkers may be distinguished on the horizon.

Moreover, all major guidelines recommend to avoid useless and potentially toxic end-of-life treatments [24], so that in the refractory setting a crucial question is whether to administer a

further treatment or not, more than which agent may be preferred in each single patient. This decision is therefore tightly related to patient's life expectancy, that is usually estimated based on patients' age and general conditions. The lack of a prognostic tool able to assist clinicians in this estimation is a clear unmet need. Some tools—such as the Palliative Prognostic Score (PaP Score)—are available in terminally ill cancer patients [25], but mCRC-specific tools are lacking.

To build the nomogram we investigated a number of variables potentially related to life expectancy among clinical and hematological parameters commonly used in daily clinical practice worldwide. In fact, although the nomogram was built in an Italian population, it is transferrable to all other countries in which the same treatment options are available. Even if *BRAF* V600E mutation is associated with poor prognosis, the mutational status was not found to be a significant factor. A clear limitation of the present analysis is that only 232 of 411 patients in the developing set had *BRAF* status assessed. However, the prevalence of *BRAF* mutant patients in the refractory setting is extremely low in the real-life, since these patients often experience very rapid progression to first-line treatments and do not receive all available agents. This is also confirmed by the low percentage of *BRAF* mutant patients reported in the present series (3%).

Four easy-to-collect variables were selected to predict the probability of death within 12 weeks in patients with refractory mCRC. Not surprisingly, ECOG PS was significantly associated with outcome consistently with data in the first-line setting [12, 13]. The choice of including only patients with ECOG PS 0 or 1 in the validating set was based on the exclusion of patients with ECOG PS >1 from phase III randomized trials of regorafenib [2, 3] or TAS-102 versus placebo [4]. Therefore, only limited information is available about the use of these drugs in patients with ECOG PS 2 and the impact of palliative treatments on quality of life near death is highly debated in patients with suboptimal general conditions [26].

The most relevant laboratory test was LDH—which may reflect both disease burden and risk of liver failure. In our study, 10.000/μl was chosen as cut-off value based on previous literature [13] to discriminate patients with or without leukocytosis. This variable was not included in the final nomogram, in contrast with the AIO-60-Day-Mortality score, which identified the highest early death risk in patients with ECOG PS 2 and $\geq$8.000/μl white blood cells [12]. However, this score was developed in first-line, and thus is not transferrable into the refractory setting.

In addition, primary tumor resection is a well-known prognostic factor in first-line [27, 28], even if it may reflect the intrinsic better prognosis of less aggressive disease, thus leading to a relevant bias. However, in the refractory setting, it is more reasonable to hypothesize that local progression of *in situ* primary tumors may cause severe complications and preclude further treatment or even lead to rapid deterioration.

Even if peritoneal metastases are often not evaluable on imaging scans, peritoneal involvement at later stages of disease may be associated with malnutrition, inability to swallow medications, and obstructive symptoms [29]. Unfortunately, information about body mass index, whose prognostic relevance in first-line was evidenced in a recent analysis, was not collected for the present analysis [30].

The nomogram discriminative ability achieved in the developing set, as measured by the Harrell C index, was reproduced in the independent validating set. However, the nomogram slightly overestimated the observed death proportion when applied to validating set patients. Since the global outcome observed in the latter was better than in the developing set (12-week death proportion 21.7% versus 30.2%), and since the nomogram predictions were based on prognostic characteristics of refractory disease (thereby excluding the potential impact on survival of effective later lines options), we hypothesize that the external calibration results may be related to two issues: (i) the significantly higher proportion of patients treated with evidence-based treatments (regorafenib and TAS-102) in the validating set (46% versus 34% in the developing set; $P < 0.0001$), (ii) more recent timeframe of patients in the validating set, with potential availability of more effective treatments in subsequent lines. Actually, external calibration sensibly improved when excluding patients treated with regorafenib or TAS-102 (supplementary Figure S2, available at *Annals of Oncology* online, and Hosmer–Lemeshow test $P = 0.238$). The absence of PS2 patients in the validating set should not influence the external calibration results, as the nomogram is able to generate predictions for PS0 or PS1 patients; however, it prevented us to externally test the predictions on PS2 patients. Nevertheless, we are confident that our predictions would be calibrated also on PS2 patients, because in the external calibration the difference between the observed and predicted mortality was mainly due to the validating set better survival versus the development set and not to a difference in the covariates effect (calibration plot points almost parallel to the reference line). A free app called Colon Life has been developed for smartphones and tablets and is distributed via the official app stores; it allows the user to calculate the 12-week death probability on the basis of a patient's combination of the nomogram covariates.

The predictive ability of our nomogram should be further assessed in prospective trials, as it may represent a useful tool not only to select patients for later lines treatments in the daily clinical practice, but also to assist researchers in a more evidence-based evaluation of patients with refractory mCRC for their inclusion in clinical trials.

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