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PHASE I STUDIES

Survival outcome and prognostic model of patients with colorectal cancer on phase 1 trials

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Summary

Background Patients with metastatic colorectal cancer (mCRC) who progress on standard therapies may be eligible for phase I trials. To better delineate the risk-benefit ratio, we assessed toxicities, clinical outcomes and prognostic factors. *Methods* Records of mCRC patients on phase I trials at our institution over 18 years were reviewed. Univariable (UVA) and multivariable analyses (MVA) were undertaken and a prognostic model developed. *Results* There were 187 enrollments on 37 phase I trials. Median age was: 59 (29–83) years and number of prior therapies: 3 (0–8). The clinical benefit rate (CBR): response (5.6%) + stable disease, was 43.1%. Median progression free survival (PFS) and overall survival (OS) was 7.7 weeks and 43.7 weeks, respectively. The MVA identified age > 60 years (HR 1.63, $p < 0.004$), albumin<3.5 g/dL (HR 3.69, $p < 0.001$), direct bilirubin>ULN (HR1.69, $p < 0.01$), and WBC ≥ 5.2 k/uL (HR 1.97, $p < 0.001$) as negative prognostic factors. A risk score based on the MVA revealed that patients with a score of 0–1 had an improved OS (58.7 weeks) compared to a score of 2 (49.9 weeks, $p < 0.01$) and 3 (14.1 weeks, $p < 0.001$). *Conclusions* Phase 1 trials may offer similar or better clinical outcome for mCRC patients than standard third line therapies; the prognostic model could assist in selecting appropriate patients.

Keywords Survival · Colorectal cancer · Phase I trials

Introduction

Colorectal cancer (CRC) has the fourth highest incidence in the United States and is the second leading cause of cancer mortality. There were 135,430 new cases and 50,260 deaths for 2017. The median age at diagnosis is 67 years and 21% of patients have distant metastases at the time of diagnosis [1].

Patients with metastatic colorectal cancer (mCRC) have a median overall survival (OS) of 6 months with best supportive care, which increases to 24–30 months with modern cytotoxic drugs (oxaliplatin and irinotecan) and biologic agents targeting the Vascular Endothelial Growth Factor Receptor (VEGFR) and Epidermal Growth Factor Receptor (EGFR) [2–4]. The typical treatment paradigm for managing mCRC patients includes the use of FOLFOX followed by FOLFIRI or vice versa, usually combined with biologic agents such as anti VEGF and anti EGFR drugs. Subsequently, the options of regorafenib or Lonsurf (trifluridine and tipiracil) are available, albeit with limited efficacy. More recently, immunotherapy has evolved as a treatment option for microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) mCRC after progression on fluoropyrimidine, oxaliplatin, and irinotecan [5, 6]. Once patients have progressed on all approved standard therapies, prognosis is poor with very limited treatment options. Patients who maintain a good performance status may benefit from phase I trials.

Phase I clinical trials represent a critical transition point between preclinical data and clinical application in the

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development of antineoplastic drugs. The primary objective in phase 1 trials is to determine the maximum tolerated dose (MTD), pharmacokinetics and pharmacodynamics of the drug. Important secondary endpoints include overall response rate (ORR) and clinical benefit rate (CBR). A review of published phase I trials reveals an ORR of 4.0–10.6% and CBR of 24–53% [7–13]. The selection of patients for phase I trials remains a challenge. Commonly accepted eligibility criteria include a life expectancy >3 months, good performance status, and adequate organ function. Despite screening criteria, up to 15–20% of patients succumb to cancer within the first 90 days of phase 1 trial entry [9, 13, 14]. Prognostic factors for overall survival (OS) should also be considered in the screening process. Current prognostic models include the Royal Marsden Hospital Index (RMI), the Princess Margaret Hospital Index (PMHI), and the MD Anderson Cancer Center (MDACC) model. The RMI identifies low albumin, number of metastatic sites and elevated LDH as negative prognostic factors [7]. The PMHI is comprised of albumin, number of metastatic sites, performance status and the MDACC is comprised of albumin, number of metastatic sites, LDH, performance status and GI tumor type [12, 15]. However, these models are based on retrospective studies of patients with variable cancer diagnoses and are not tumor specific. Furthermore, nationwide in the US, accrual to clinical trials comprises predominantly non-Hispanic White patients, and little is known about outcomes among minorities, including non-Hispanic Black and Hispanic patients. We cater to a unique patient population, consisting of a high proportion of minorities, and also wished to study racial differences in outcome.

Herein, we report the clinical outcome of patients with mCRC who were enrolled on phase 1 trials at our institution from January 1999 to December 2016. Prognostic factors were identified and a prognostic model for mCRC patients entering phase 1 trials is proposed. Finally, the performance of our prognostic model in predicting overall survival was compared to the aforementioned models.

Each individual clinical trial from which data was extracted was approved by the ethics committee of Montefiore Medical Center. All patients entering the study have signed the informed consent document. Each individual trial was performed in accordance with the Declaration of Helsinki.

Methods

Patients

Patients aged 18 years and above with pathologically confirmed diagnosis of mCRC who were enrolled on Phase 1 trials at Montefiore Medical Center/Albert Einstein College of Medicine between January 1999 and December 2016 were included. Institutional review board approved the clinical trials and informed consent was obtained from the patients before enrollment. Patient demographics (including self-reported race), performance status, metastases, prior therapies, baseline hematologic and biochemical laboratory parameters, start and end date of study, response, toxicity, date last seen, date of death, were abstracted from patient records. Each clinical trial was approved by the local ethics committee.

Clinical outcomes

Response was determined by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria v. 1.0–1.1 depending on the date of trial activation. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v. 2.0–4.0 depending on the date of trial activation. Overall survival (OS) was defined as the date on study to death from any cause or last follow-up. Progression free survival (PFS) was defined as the time from enrollment on phase 1 trial to date of progression of disease (PD). Overall response rate (ORR) was defined as complete response (CR) plus partial response (PR). Clinical benefit rate (CBR) was defined as stable disease (SD) plus response.

Statistical considerations

Data were initially analyzed with descriptive statistics. The Kaplan Meier survival function was used to depict the survival experience of the entire cohort, as well as of patient subgroups determined by key variables; differences were tested with the log-rank test. Cox Proportional Hazard (PH) regression analysis was utilized to generate HR for each univariate (UVA) association of mortality risk with key variables. Cox Proportional Hazard (PH) regression multivariable analysis (MVA) was used to build a predictive model of survival for patients with CRC participating in phase I trials. The results of univariate analyses were utilized in the selection of the variables included in the initial model. A p value less than 0.25 was set as the statistical significance-cutoff for inclusion to the regression model. Age, sex and race variables were forced into the model. A manual backward stepwise selection process was followed in model building. The assumption of linearity for continuous and ordinal variables was evaluated with fractional polynomial regression and assessment of post-estimation partial residual plots, as well as the dummy variable method. The PH assumption was tested by analysis of Schoenfeld residuals and assessed graphically with log-log curves. A two-tailed alpha 0.05 level was used to determine statistical significance.

A prognostic scoring system was developed based on the coefficients from the Cox regression model. The Harrel C-statistic was used to compare the performance in survival prediction of the newly developed score to other established scores. Bootstrapping techniques were used to adjust the

estimated model performance for over optimism or overfitting (validate the model). The C-statistic of the final multivariate model, corrected for optimism, was reported.

All statistical analyses were performed with STATA software, version 12.0.

Results

Patient and trial characteristics

From January 1999 to December 2016, there were 187 patient enrollments, with 150 unique patients accrued on 37 distinct phase 1 trials at the Montefiore Medical Center/Albert Einstein College of Medicine. Ninety (48.1%) patients were enrolled on a trial with a cytotoxic regimen, 51 (27.3%) patients on a biologic/targeted regimen, and 46 (24.6%) patients on combined therapy. Twenty-three (15.0%) patients were enrolled in more than one trial. The maximum number of trials that a single patient was enrolled in was five. The median duration on a trial was 51 days (range 3–631 days). The median age of patients was 59 years (range 29–83 years), with a female to male ratio of 1.17 (101 females and 86 males). There was roughly an equal proportion of non-Hispanic White, non-Hispanic Black, and Hispanic patients (32.6%, 31.0%, and 34.2%, respectively). The median number of prior systemic therapy was 3 (range 0–8). Prior therapies included: 5-fluorouracil or capecitabine (95.2%), irinotecan (66.3%), oxaliplatin (60.4%), bevacizumab (37.4%) and cetuximab or panitumumab (23.0%). The Eastern Cooperative Oncology Group (ECOG) was 0–1 in 93.0%, and 2 in 5.9% of patients. The median number of metastatic sites was 3 (range 1–6). Baseline biochemical testing showed an elevated direct bilirubin in 9.1% of patients, albumin <3.5 g/dL in 24.1%, and elevated LDH in 39.0%. Of note, the incidence of elevated bilirubin was higher than expected for phase 1 trials as some trials allowed for and were specifically designed for patients with liver (and/or renal) dysfunction. Baseline hematologic lab values demonstrated a WBC > 10.8 k/uL in 5.9% of patients, hemoglobin <12 g/dL in 65.2%, and platelets >400 k/uL in 7.0%. Baseline patient characteristics are summarized in Table 1.

Table 1 Baseline patient characteristics ($n = 187$)

Characteristic	Median (range)	Number	%
Sex			
Male		86	46.0
Female		101	54.0
Age	59 (29–83)		
≤60 yrs		92	49.2
>60 yrs		95	50.8
Race			
Non-Hispanic White		61	32.6
Non-Hispanic Black		58	31.0
Hispanic		64	34.2
Other		4	2.2
Performance status			
ECOG 0–1		174	93.0
ECOG 2		11	5.9
Not available		2	1.1
Prior chemotherapy	3 (0–8)		
0–2		87	46.5
≥3		97	51.9
Not available		3	1.6
Number of metastatic sites	3 (1–6)		
1–2		86	46.0
≥3		96	51.3
Not available		5	2.7
Creatinine	0.8 (0.3–3.7)		
≤0.8		92	49.2
>0.8		87	46.5
Not available		8	4.3
AST	28 (3–206)		
Normal		138	73.8
Elevated		41	21.9
Not available		8	4.3
ALT	19 (2–158)		
Normal		149	79.7
Elevated		30	16.0
Not available		8	4.3
Total bilirubin	0.5 0.1–27.6)		
Normal		165	88.2
Elevated		14	7.4
Not available		8	4.3
Direct bilirubin	0.1 (0.0–18.4)		
Normal		151	80.7
Elevated		17	9.1
Not available		19	10.2
Albumin	4 (2–5)		
<3.5 g/dL		45	24.1
≥3.5 g/dL		139	74.3
Not available		3	1.6
LDH	278.5 (2–4621)		
Normal		107	57.2
Elevated		73	39.0
Not available		7	3.7
White blood cell count	5.1 (0.5–18.8)		
≤10.8 k/uL		176	94.1
>10.8 k/uL		11	5.9
Hemoglobin	11.2 (6.0–16.2)		
<12 g/dL		122	65.2
≥12 g/dL		65	34.8
Platelet count	218 (16–1231)		
≤400 k/uL		174	93.0
>400 k/uL		13	7.0

Table depicts baseline patient characteristics of the 187 patients who were included in this study

ECOG, Eastern Cooperative Oncololgy Group; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *LDH*, lactate dehydrogenase

Clinical outcome and effect of race

Among the 187 patients, 144 were evaluable for response by the RECIST criteria. Complete response (CR) was seen in 1 patient (0.7%), partial response (PR) in 7 patients (4.9%), stable disease in 54 patients (37.5%), and progressive disease (PD) in 82 patients (56.9%). The overall response rate (ORR) was 5.6%. The clinical benefit rate (CBR) was 43.1%. Treatment response is summarized in Table 2. The median PFS and OS for the entire cohort was 7.7 weeks and 43.7 weeks (wk), respectively. Median OS by type of therapy was biologic (29.9 wk), cytotoxic (45.1 wk), and combined therapy (54.0 wk) and was not statistically different ($p = 0.57$). In terms of racial groups and outcomes, the median OS was

Table 2 Best response

Response	$n = 144$ (%)
Complete Response (CR)	1 (0.7)
Partial Response (PR)	7 (4.9)
Stable Disease (SD)	54 (37.5)
Progressive Disease (PD)	82 (56.9)
Overall Response Rate (ORR)	8 (5.6)
Clinical Benefit Rate (CBR)	62 (43.1)

Table depicts best response for 144 out of 187 patients who were evaluable for response

CR, complete response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease; *ORR*, overall response rate; *CBR*, clinical benefit rate

45.3 wk. in non-Hispanic Whites ($n = 61$), 40.9 wk. in non-Hispanic Black ($n = 58$), and 38.4 wk. among Hispanics ($n = 64$), and 77.9 wk., Asian/other ($n = 4$); with a non-significant p value of 0.78.

Toxicity

One hundred and eighty-four patients were evaluable for adverse events (Appendix, Table A1, online only). Grade 3 and 4 hematologic toxicities were observed in 32 patients (17.3%). Grade 3 and 4 non-hematologic toxicities were observed in 47 patients (25.5%). There was 1 toxicity related death (0.5%). The most common grade 1 and 2 non-hematologic toxicities were fatigue (44.9%) and nausea (46.0%).

Prognostic factors for overall survival

Univariable analysis (UVA) revealed that performance status (ECOG ≥2), number of metastatic sites (>2), LDH > upper limit of normal (ULN), albumin (<3.5 g/dL), direct bilirubin (>ULN), WBC (≥5.2 k/uL), hemoglobin (<13 g/dL in males and < 12 g/dL in females), predicted a shorter overall survival (Table 3). Multivariable analysis (MVA), with forced variables of age, sex, and race, identified age > 60 years (p value = 0.004), albumin <3.5 g/dL (p value<0.001), direct bilirubin >ULN (p value = 0.01), and WBC ≥5.2 k/uL (p value<0.001) as negative prognostic factors (Table 3). Survival was not statistically different by race: non-Hispanic White (HR 1.00), non-Hispanic Black (HR 0.96, $p = 0.83$), Hispanic (HR 1.12, $p = 0.57$), and Asian (HR 1.29, $p = 0.47$).

Montefiore Einstein Cancer center (MECC) prognostic model

Based on the MVA, we derived a prognostic scoring system consisting of 4 variables: age > 60 years (1 point), albumin <3.5 g/dL (2 points), direct bilirubin >ULN (1 point), and WBC ≥5.2 k/uL (1 point). Patients with 0–1 points were categorized as low-risk, 2 points intermediate risk, and 3 points high risk. The median OS of low risk patients was 58.7 weeks, compared to 49.9 weeks for intermediate risk (p value<0.01), and 14.1 weeks for high-risk (p value<0.001) (Table 4, Fig. 1).

To compare the performance of the Montefiore Einstein Cancer Center (MECC) model in predicting overall survival to existing models, we derived the RMI, PMHI, and MDACC scores in our patient population and calculated the Harrell C-statistic (Table 5). Our prognostic model performed similarly in predicting OS compared to existing models with a c-index of 0.64. In addition, the performance of our model was unchanged after adjusting for type of therapy..

Discussion

The primary purpose of phase I trials is to assess toxicities and determine a dose that is considered safe for further development. Other important objectives are to evaluate pharmacokinetics, and pharmacodynamics. Overall responses and potential clinical benefit remain crucial, and yet secondary endpoints. In spite of presenting this information to patients, it has been observed, that from the patients' perspective, their primary objective of consenting and volunteering for a phase I study is to derive some form of clinical benefit, and improve their outcomes. Furthermore, for the general oncologist, once a patient progresses or is intolerant to front and second line therapies, options are limited, and they constantly seek out more options for their patients, including enrolment in novel phase I clinical trials.

Over the past decades, we observed a number of patients with mCRC on phase I trials that appeared to derive prolonged clinical benefit. This prompted us to objectively collate our data and experience and report it. To date, this is the single largest cohort of mCRC patients enrolled on phase 1 trials for which the clinical outcomes and prognostic factors are reported. There were a total of 187 enrollments with 150 unique patients enrolled on 37 phase 1 trials. A prognostic model scoring system, the Montefiore Einstein Cancer Center (MECC) model, is described with the aim of improving the selection of mCRC patients for phase 1 trials.

In our phase 1 trial cohort, the ORR was 5.6% and CBR was 43.1%, with a median OS of 43.7 weeks (10.1 months). These clinical outcomes are superior to those observed with third line therapies for mCRC, such as regorafenib and trifluridine/tipiracil. Based on the CORRECT trial, regorafenib has an ORR of 1.0%, CBR of 41% and median OS of 6.4 mos [16]. In the case of trifluridine/tipiracil, the ORR was 1.6% and CBR is 44%, with a median OS of 7.1 mos [17]. The profile of patients in our cohort is quite similar to these two randomized phase 3 registration studies with a median of 3 prior regimens, and prior exposure to oxalipatin and

Table 3 Univariate and multivariate analysis

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age				
≤60 yrs	1.00		1.00	
>60 yrs	1.20 (0.88–1.65)	0.24	1.63 (1.17–2.29)	**0.004**
Sex				
Female	1.00		1.00	
Male	0.90 (0.66–1.22)	0.5	0.75 (0.54–1.04)	0.09
Race				
Non-Hispanic White	1.00		1.00	
Non-Hispanic Black	0.94 (0.63–1.40)	0.77	0.96 (0.64–1.44)	0.83
Hispanic	1.09 (0.74–1.58)	0.67	1.12 (0.76–1.64)	0.57
Other	0.70 (0.25–1.93)	0.49	1.29 (0.45–3.75)	0.64
ECOG				
0–1	1.00			
≥2	2.65 (1.28–5.48)	**0.01**		
Metastatic sites				
≤2	1.00			
>2	1.40 (1.02–1.91)	**0.04**		
Prior therapies				
≤2	1.00			
>2	1.30 (0.94–1.77)	0.11		
Type of prior therapy				
Biologic	1.00			
Cytotoxic	0.88 (0.61–1.26)	0.48		
Combined	0.79 (0.51–1.23)	0.30		
LDH				
WNL	1.00			
>ULN	1.85 (1.36–2.54)	**<0.001**		
Albumin				
≥3.5 g/dL	1.00		1.00	
<3.5 g/dL	3.11 (2.16–4.48)	**<0.001**	3.69 (2.51–5.42)	**<0.001**
Creatinine				
≤1.5 mg/dL	1.00			
>1.5 mg/dL	1.39 (0.79–2.46)	0.25		
Total bilirubin				
WNL	1.00			
>ULN	1.48 (0.93–2.35)	0.10		
Direct bilirubin				
WNL	1.00		1.00	
>ULN	1.55 (1.06–2.28)	**0.02**	1.69 (1.14–2.52)	**0.01**
AST				
WNL	1.00			
>ULN	1.38 (0.99–1.92)	0.05		
ALT				
WNL	1.00			
>ULN	0.96 (0.69–1.35)	0.84		
WBC count				
<5.2 k/uL	1.00		1.00	
≥5.2 k/uL	1.70 (1.24–2.33)	**0.001**	1.97 (1.42–2.75)	**<0.001**
Hemoglobin				
NL	1.00			
WHO anemia	1.48 (1.01–2.17)	**<0.05**		
Platelet count				
≥150 k/uL	1.00			
<150 k/uL	1.07 (0.75–1.52)	0.7		

Results of univariate and multivariate modeling of all important clinical characteristics. Each row depicts the characteristic, followed by the HR and the associated *p* value for each variable. Multivariate modeling included all univariate variables with $p < 0.25$, and with forcing of age, gender and race. The multivariate model identified the following statistically significant variables: age > 60 years (p value = 0.004), albumin <3.5 g/dL (p value<0.001), direct bilirubin >ULN (p value = 0.01), and WBC ≥5.2 k/uL (p value<0.001)

HR, hazard ratio; *CI*, confidence interval; *ECOG*, Eastern Cooperative Oncology Group; *LDH*, lactate dehydrogenase; *WNL*, within normal limits; *ULN*, upper limit of normal; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *WBC*, white blood cell; *WHO anemia*, World Health Organization definition of anemia (hemoglobin <13 g/dL in males, <12 g/dL in females)

irinotecan. We therefore believe that phase 1 trials offer a potential option for patients with mCRC who progress on first and second-line therapies.

In regard to the type of therapy received on phase 1 trial, we did not observe a statistically significant difference in median OS between cytotoxic vs. biologic vs. combined therapy (i.e.

Table 4 MECC prognostic model

Prognostic factor	Points	Risk group (total points)	Median OS	p value
Albumin<3.5 g/dL	2	Low (0–1)	58.7 wks	
Age > 60 yrs	1	Intermediate (2)	49.9 wks	<0.01
Direct bilirubin >ULN	1	High (≥3)	14.1 wks	<0.001
WBC ≥5.2 k/uL	1			

Table depicts each prognostic variable with a corresponding point-value derived from the coefficient in the cox regression model. Risk group based on total points with corresponding median OS and p value

MECC, Montefiore Einstein Cancer Center; *OS*, overall survival; *WBC*, white blood cell

cytotoxic plus biologic therapy). Combined therapy appeared to provide the longest median OS (54.0 wk), followed by cytotoxic therapy (45.1 wk) and biologic therapy (29.9 wk), however the *p* value did not achieve statistical significance ($p = 0.57$). This is consistent with our knowledge of improved of improved response rate, PFS, and OS with doublet chemotherapy plus targeted agent (anti-EGFR or VEGF) in first line therapy for mCRC vs. chemotherapy alone [18–21]. In addition, single agent biologics in mCRC are typically associated with a lower response rate and median OS when compared to chemotherapy alone and combination therapy [22].

In order to determine and narrow down those patients that will derive clinical benefit from a phase 1 trial, prognostic factors for OS need to be identified. Prognostic models that are specific for tumor type would be most useful for clinical application. For example, the Memorial Sloan Kettering Cancer Center (MSKCC) model for metastatic renal cell carcinoma, which has since been validated by Heng et al., identified the following variables as negative prognostic factors: time from diagnosis to treatment <1 year, Karnofsky performance status <80%, LDH > 1.5 X ULN, corrected serum calcium >ULN, and hemoglobin < lower limit of normal (LLN) [23, 24]. However, the prognostic models derived from phase 1 patient populations, to date, have not been tumor specific and include patients with variable cancer diagnoses. The most commonly identified prognostic variables on their MVA include: LDH, performance status, albumin, and number of metastatic sites [7, 9, 10, 12, 13, 25–30]. The most widely reported prognostic scoring systems are the RMI, PMHI and MDACC. The RMI comprises albumin, number of metastatic sites and LDH [7]. The PMHI includes albumin, number of metastatic sites, performance status, and the MDACC is incorporates albumin, number of metastatic sites, LDH, performance status and GI tumor type [12, 15]. The RMI is the only prognostic model that has been validated in a colorectal cancer patient cohort [31].

In our MVA, we identified age > 60 years, albumin <3.5 g/dL, direct bilirubin >ULN, and WBC ≥5.2 k/uL as negative prognostic factors. While albumin is part of the RMI model, age, direct bilirubin and WBC are unique variables to our model. Increasing age may reflect decreasing functional reserve, and elevated direct bilirubin is a marker of liver dysfunction and possibly more advanced cancer. Interestingly, leukocytosis, is also a prognostic maker in the modified Heng criteria for renal cell cancer, and has been shown to be a poor prognostic marker for several types of malignancies [24, 32–34]. In terms of performance in predicting overall survival, the MECC performed similarly to the RMI, PMHI and MDACC models, with a c-index of 0.64, compared to 0.61, 0.58, and 0.65, respectively. Furthermore, the performance of our model was unchanged after adjusting for type of therapy (i.e. cytotoxic, biologic, combined).

Another unique feature of our cancer center is our commitment to ethnic minorities and our processes that have been put in place to ensure that they have a similar access to clinical trials as the non-Hispanic White patients. This effort has led to the accrual of over 65% of minority patients among the entire cohort (Black 31.0%, Hispanic 34.2%). Importantly, the median OS was similar in non-Hispanic White (45.3 wk), non-Hispanic Blacks (40.9 wk), and Hispanic (38.4 wk) patients, $p = 0.78$. This is the first study to evaluate the outcome of minorities enrolled on phase 1 trials. Black and Hispanics derive similar benefit compared to Caucasian patients and their participation in phase 1 trials is strongly encouraged.

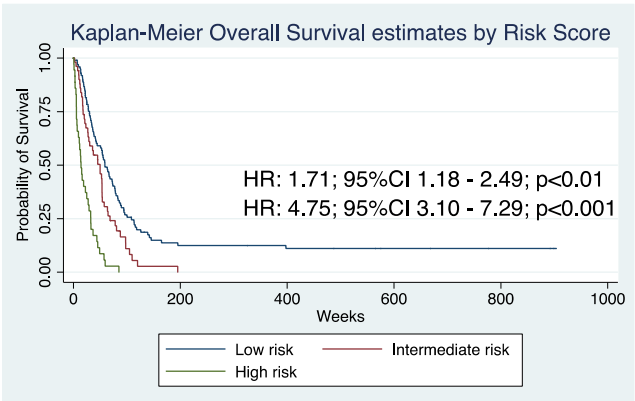

Fig. 1 Kaplan-Meier Curve for OS by Risk Score. Overall survival estimates by risk category: low risk (blue), intermediate risk (red), high risk (green). The HR, 95%CI and respective *p* values are derived from a Cox PH regression analysis of mortality risk by risk score category. Patients in the low risk category had a longer overall survival compared to intermediate risk (HR = 1.71 [95%CI 1.18–2.49], $p < 0.01$) and high risk (HR = 4.75 [95%CI 3.10–7.29], $p < 0.001$) patients

Table 5 Comparative performance of prognostic models

	RMI		PMHI		MDACC		MECC	
		Median OS (wks)		Median OS (wks)		Median OS (wks)		Median OS (wks)
Risk score	0–1	54.1	0–1	55.3	1	63.4	0–1	58.7
	≥2	29.9	≥2	32.1	2	77.1	2	49.9
					3	37.9	3	14.1
					4	28		
					5	11		
C-index(95%CI)	0.61 (0.57–0.66)		0.58 (0.54–0.63)		0.65 (0.61–0.70)		0.64 (0.64–0.68)	

Table comparing the performance of the MECC prognostic model to the RMI, PMHI, and MDACC scoring systems. For each prognostic model, risk score with the corresponding median OS is shown. Harrell C-statistic (c-index) is used to compare the performance of all prognostic models

RMI , Royal Marsden Index; *PMHI*, Princess Margaret Hospital Index; *MDACC*, MD Anderson Cancer Center; *MECC*, Montefiore Einstein Cancer Center; *OS*, overall survival

We recognize that there are certain limitations with this study. For one, mutation status (KRAS, NRAS, and BRAF) was not included in the prognostic analysis as a number of the trials were done prior to the availability of such testing. However, even though it is established that BRAF mutation is a poor prognostic marker, its incidence is of the order of 8–10%, and it is highly unlikely that the distribution of these mutations among the various patient populations will be different enough to impact the overall outcome [35]. Secondly, we recognize that the variables in our prognostic model reflect patient characteristics, which may independently predict overall survival outside of phase 1 trials. However, this is a limitation seen across all phase 1 prognostic models, including the RMI, PMHI, and MDACC models. Despite this, our model may still help identify the subgroup of patients participating in phase I trials that are likely to benefit. Thirdly, the data is from a single institution, which would limit generalizability to other cancer centers with different sponsors with regimens and trials. In addition, the phase 1 trials included in the analysis were over a long period of time and there was heterogeneity in the treatments across different trials. Finally, this study is retrospective and our model would need to be prospectively validated.

In conclusion, patients with mCRC who progress on first and second-line therapy are appropriate candidates for whom the option of phase 1 trials should be presented. With an ORR of 5.6%, CBR of 43.1% and median OS of 10.1 months, the clinical outcome is at least similar to, even if not superior, to third line therapies including, regorafenib and trifluridine/tipiracil. Negative prognostic factors for overall survival include: age > 60, albumin<3.5 g/dL, direct bilirubin>ULN and WBC ≥5.2 k/uL. A risk score based on these parameters showed that patients with a higher score had a significantly shorter OS, than those with a lower score. This may help the clinician in making a decision when faced with a patient with mCRC who has progressed on oxaliplatin and irinotecan and is seeking further therapeutic options, including enrolment to a phase I clinical trial.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval Each individual clinical trial from which data was extracted was approved by the ethics committee of Montefiore Medical Center. Each individual trial was performed in accordance with the 1964 Helsinki declaration and its later amendments.

Informed consent All patients entering the clinical trials have signed the informed consent document.

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