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Article

Metastatic Colorectal Cancer Outcomes by Age Among ARCAD First- and Second-Line Clinical Trials

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Abstract

Background: We evaluated the time to progression (TTP) and survival outcomes of second-line therapy for metastatic colorectal cancer among adults aged 70 years and older compared with younger adults following progression on first-line clinical trials. **Methods:** Associations between clinical and disease characteristics, time to initial progression, and rate of receipt of second-line therapy were evaluated. TTP and overall survival (OS) were compared between older and younger adults in first- and second-line trials by Cox regression, adjusting for age, sex, Eastern Cooperative Oncology Group Performance Status, number of metastatic sites and presence of metastasis in the lung, liver, or peritoneum. All statistical tests were 2-sided. **Results:** Older adults comprised 16.4% of patients on first-line trials (870 total older adults aged >70 years; 4419 total younger adults aged ≤70 years, on first-line trials). Older adults and those with Eastern Cooperative Oncology Group Performance Status >0 were less likely to receive second-line therapy than younger adults. Odds of receiving second-line therapy decreased by 11% for each additional decade of life in multivariable analysis (odds ratio = 1.11, 95% confidence interval = 1.02 to 1.21, $P = .01$). Older and younger adults enrolled in second-line trials experienced similar median TTP and median OS (median TTP = 5.1 vs 5.2 months, respectively; median OS = 11.6 vs 12.4 months, respectively). **Conclusions:** Older adults were less likely to receive second-line therapy for metastatic colorectal cancer, though we did not observe a statistical difference in

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survival outcomes vs younger adults following second-line therapy. Further study should examine factors affecting decisions to treat older adults with second-line therapy. Inclusion of geriatric assessment may provide better criteria regarding the risks and benefits of second-line therapy.

The increasing prevalence of older adults with cancer in the United States—dubbed the "Silver Tsunami"—accompanies an increase in prevalence of cancer by age in the US population from 216 million in 1975 to an estimated 380 million by 2040 (1). This trend is exemplified in colorectal cancer (CRC), where the highest rates of new cases and deaths occur among adults aged 75-84 years (2). Given that the median age at diagnosis of CRC is between age 69 and 70 years, 70 years is often referenced in the literature as the appropriate age threshold for studying CRC in older adults. Although there has been a modest downward shift in the age at diagnosis in CRC [with incidence expected to increase among those aged <50 years (3-5)], the prevalence of disease remains highest among older adults. According to the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results Program database, adults aged 65-74 years and 75+ years with CRC make up 1.26% and 2.78% of the US population, respectively, compared with 0.37% of adults aged 40-64 years (2017 age at prevalence estimate). Because older adults are more likely to be diagnosed with metastatic CRC (mCRC), have a higher prevalence of disease (2), and constitute a substantial proportion of the US population, the need to determine best practices for treatment of older adults diagnosed with mCRC based on clinical trials is imperative.

Prior studies evaluating survival outcomes in older adults enrolled in first-line treatment clinical trials for mCRC found no statistically significant difference in overall survival (OS) among older and younger adults in individual trials and pooled trials (6-9). In those studies, the median OS of older adults ranged from 11 to 20 months, with median progression-free survival (PFS) of 5.5 to 9 months. Taken together, the evidence suggests a reasonable survival advantage from initial palliative chemotherapy for older adults meeting enrollment criteria, including being considered fit enough to participate in a therapeutic clinical trial. However, although there are data from individual trials, there are no known data that pool outcomes across trials, inclusive of standard second-line regimens, to aid in discerning the survival benefit for continuing palliative chemotherapy in older adults beyond first progression. Such data could inform patient and physician choices in this setting. The Aide et Recherche en CAncerologie Digestive (ARCAD) is a clinical database of 48 mCRC therapeutic clinical trials that pools individual patient, disease, treatment, and outcome data of 40 016 participants. ARCAD is an international collaborative effort founded as a standing resource to accelerate understanding of mCRC, increase the efficiency of industry-sponsored clinical trials, and improve the efficacy of clinical treatment for patients. Similar pooled analyses of individual data have contributed to our understanding of treatment outcomes for older adults (10) and have been employed by both National Comprehensive Cancer Network (11,12) and European Society for Medical Oncology (13) expert panels to construct recommendations regarding care for this growing subset of patients. Given the current gap in evidence regarding second-line treatment for older adults diagnosed with mCRC, we sought to determine the survival outcomes for older adults participating in first-line trials for mCRC, rate of enrollment on second-line trials, and survival outcomes.

Methods

First-Line Trials

The outcome for first-line trials is time to progression 1 (TTP1), defined as the time from date of random assignment to the date of first disease progression (in which death is censored). For second-line trials, the time to progression 2 (TTP2) outcome is defined as the time from date of random assignment to second-line treatment to the date of first disease progression on second-line treatment. The populations included in first- and second-line trials were unique and did not overlap. We examined OS from initiation of second-line treatment. In sequential trials, this was defined as the time to death since study enrollment. In nonsequential trials, this was defined as time to death since first-line trial enrollment. We also examined age at enrollment using the age threshold of 70 years or younger to indicate younger adults and age older than 70 years to indicate older adults, as per prior analyses (10,14,15). We surveyed a number of clinical trials in the ARCAD database that enrolled participants with mCRC. For first-line trials, we selected those trials that only specified first-line therapy (as opposed to specifying sequential lines of therapy) and that collected data on TTP for subsequent lines of treatment. All studies with subsequent treatment data available were included for analysis. Study and enrollment characteristics for each trial can be found in Table 1. Ten ARCAD trials were included in first-line analysis with available data for subsequent therapy: OPUS, N9741, NO16966, HORIZON III, HORIZON II, HORG 99.30, FOCUS, FIRE II (CIOX), CRYSTAL, and AGITG (MAX) (Figure 1).

Second-Line Trials

Both sequential and nonsequential trials were included in analyses of second-line trials. Sequential trials were defined as second-line trials with predetermined first-line treatment, and nonsequential trials were defined as second-line trials with enrollment not dependent on the regimen and results of a previous trial. By this definition, sequential trial patients were newly diagnosed, and the study protocol had already been defined for first- and second-line treatment. Analyses utilized Cox regressions to adjust for age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS), number of metastatic sites, and the presence or absence of metastasis in the lung, liver, or peritoneum. Trials included in this analysis reflect outcomes of patients enrolled in first-line trials who subsequently enrolled in any of the following 10 second-line ARCAD sequential trials: AMGEN C181, BEBYP, CAIRO3, E3200, EPIC, N016967, N9841, RAISE, TML, or VELOUR (Figure 1). Study and enrollment characteristics for each second-line trial can also be found in Table 1. Pooled analysis did not capture the absolute number of individuals enrolled in first-line trials who subsequently enrolled in second-line trials within the ARCAD database; first- and second-line participants reflected in this analysis represent mutually exclusive populations.

All analyses were performed with approval from the local institutional review board in accordance with the precepts of the Helsinki Declaration.

Table 1. Study and enrollment characteristics of ARCAD first- and second-line mCRC clinical trials

Study	Regimen	Key eligibility	Total accrual (No.)	Age[a], No. (%)		Sex, No. (%)		ECOG PS, No. (%)		Metastatic sites[a], No. (%)	
				<70 y	≥70 y	Female	Male	0	>0	<2	≥2
First-line											
AGITG (MAX)	C v C + B vs C + B + M	ECOG performance status ≤2 No prior chemotherapy except adjuvant ≥6 mo before relapse No major surgical procedure within 28 d	471	284 (60.3)	187 (39.7)	176 (37.4)	295 (62.6)	263 (55.8)	208 (44.2)	110 (23.4)	361 (76.7)
CRYSTAL	FOLFIRI vs FOLFIRI + C	Immunohistochemical evidence of tumor EGFR expression ECOG performance status ≤2 No previous exposure to anti-EGFR therapy or irinotecan-based chemotherapy No prior chemotherapy No adjuvant chemotherapy ≤6 mo trial No radiotherapy, surgery (except diagnostic biopsy), or any investigational drug within 30 d before trial	1217	987 (81.2)	230 (18.8)	484 (39.6)	737 (60.4)	659 (53.0)	562 (46.0)	Not available	
FIRE II (CIOX)	C + CAPIRI vs C + CAPOX	Age 18-75 years Karnofsky performance status ≥70% Immunohistochemical evidence of tumor EGFR expression No radiotherapy, surgery 4 wk before trial No prior treatment with topoisomerase-1 inhibitors or anti-EGFR agents, cytotoxic treatment for CRC (except adjuvant chemotherapy ≥6 mo before trial)	177	150 (84.7)	27 (15.3)	51 (28.8)	126 (71.2)	123 (69.5)	54 (30.5)	76 (42.9)	101 (57.1)

(continued)

Table 1. (continued)

Study	Regimen	Key eligibility	Total accrual (No.)	Age[a], No. (%)		Sex, No. (%)		ECOG PS, No. (%)		Metastatic sites[a], No. (%)	
				<70 y	≥70 y	Female	Male	0	>0	<2	≥2
FOCUS	FU ± Ir vs FU ± IrFU/OxFU vs IrFU/OxFU	WHO performance status ≤2 No previous chemotherapy for metastatic disease	2135	1623 (75.8)	512 (24.2)	668 (31.5)	1450 (68.5)	877 (41.4)	1241 (58.6)	901 (42.5)	1171 (55.3)
HORG 99.30	FOLFIRI vs FOLFOXIRI	5-FU-based chemotherapy naïve or ≥6 mo after adjuvant therapy ECOG performance status ≤2 No prior irradiation affecting more than >30% of active bone marrow	285	194 (67.8)	91 (32.2)	122 (43.1)	161 (56.9)	151 (53.4)	132 (46.6)	117 (41.3)	166 (58.7)
HORIZON II	FOLFOX4/mFOLFOX6/CAPOX + Ce 30 mg/d vs FOLFOX4/mFOLFOX6/CAPOX + Ce 20 mg/d vs FOLFOX4/mFOLFOX6/CAPOX + placebo	WHO performance status ≤1 No prior systemic therapy for mCRC No adjuvant or neoadjuvant therapy with oxaliplatin or FU within 12 mo or 6 mo of trial No prior anti-VEGF or anti-VEGF receptor therapy with monoclonal antibodies or small-molecule inhibitors	1076	919 (85.4)	157 (14.6)	442 (41.1)	634 (58.9)	624 (57.0)	452 (42.0)	519 (48.2)	553 (51.4)
HORIZON III	Phase II: B + Ce 20 mg/d + mFOLFOX6 vs B + Ce 30 mg/d + mFOLFOX6 vs B + placebo + mFOLFOX6 Phase III: mFOLFOX6 + Ce 20 mg/d vs mFOLFOX6 + placebo	WHO performance status ≤1 No prior systemic therapy for mCRC No adjuvant or neoadjuvant therapy with oxaliplatin or FU within 12 mo or 6 mo of trial, respectively No CTC grade >2 from previous anticancer therapy (except hematologic toxicity and alopecia) No prior anti-VEGF or anti-VEGF receptor therapy with monoclonal antibodies or small-molecule inhibitors	1614	1360 (84.1)	254 (15.9)	663 (41.4)	938 (58.6)	910 (56.8)	691 (43.2)	731 (45.7)	858 (53.6)

(continued)

Table 1. (continued)

Study	Regimen	Key eligibility	Total accrual (No.)	Age[a], No. (%)		Sex, No. (%)		ECOG PS, No. (%)		Metastatic sites[a], No. (%)	
				<70 y	≥70 y	Female	Male	0	>0	<2	≥2
N016966	XELOX + B vs XELOX + Placebo	ECOG performance status ≤1 No prior systemic therapy for mCRC No prior treatment with oxaliplatin or bevacizumab No radiotherapy or surgery (except diagnostic biopsy) for mCRC within 4 weeks before trial	1400	999 (80.3)	401 (19.7)	827 (40.7)	1207 (59.3)	1146 (56.3)	888 (43.7)	831 (40.9)	1203 (59.1)
N9741	IFL vs FOLFOX vs IROX	ECOG performance status ≤2 No adjuvant fluorouracil in previous 12 mo No prior treatment for advanced disease No prior radiation to ≥15% of bone marrow	795	474 (77.3)	321 (22.7)	556 (39.3)	860 (60.7)	637 (44.0)	779 (55.0)	716 (50.6)	700 (49.4)
OPUS	FOLFOX4 vs FOLFOX4 + Ce	EGFR-expressing mCRC ECOG performance status ≤2 No previous exposure to EGFR-targeted therapy or previous chemotherapy (except adjuvant treatment) for mCRC	344	274 (79.7)	70 (20.3)	160 (46.5)	184 (53.5)	143 (41.6)	201 (58.4)	154 (44.8)	189 (54.9)
Second-line											
AMGEN C181	FOLFIRI vs FOLFIRI + P	ECOG performance status ≤2 Only 1 prior chemotherapy regimen for mCRC consisting of first-line fluoropyrimidine-based therapy No prior irinotecan or anti-EGFR therapy No systemic chemotherapy, hormonal therapy, approved proteins/antibodies, or experimental agent or therapy within 30 d No radiotherapy within 14 d No major surgery ≤28 d	1186	928 (78.2)	258 (21.8)	464 (39.1)	722 (60.9)	574 (48.4)	612 (51.6)	Not available	

(continued)

Table 1. (continued)

Study	Regimen	Key eligibility	Total accrual (No.)	Age[a], No. (%)		Sex, No. (%)		ECOG PS, No. (%)		Metastatic sites[a], No. (%)	
				<70 y	≥70 y	Female	Male	0	>0	<2	≥2
BEBYP	mFOLFOX6/ FOLFIRI vs mFOLFOX/ FOLFIRI + B	Aged 18-75 y ECOG performance status ≤2 No radiotherapy within 6 wk No surgery with 4 wk After or during fist-line therapy with fluoropyrimidine, FOLFIRI or FOLFOX plus bevacizumab or >3 mo after last dose of FOLFOXIRI plus bevacizumab	185	121 (65.2)	64 (34.8)	63 (34.2)	121 (65.8)	150 (81.5)	34 (18.5)	44 (23.9)	140 (76.1)
CAIRO3	CAPOX-B → control vs C + B	Stable disease, partial response, or complete responses as defined by RECIST after 6 cycles of induction treatment with CAPOX-B (capecitabine 1000 mg/m^2 orally 2×/d on days 1-14, oxaliplatin 130 mg/m^2 IV on day 1, and bevacizumab 7.5 mg/kg IV on day 1) WHO performance status ≤1	558	421 (75.4)	137 (24.6)	196 (35.2)	361 (64.8)	345 (61.9)	212 (38.1)	238 (42.7)	305 (54.8)
E3200	FOLFOX vs B vs FOLFOX + B	Prior chemotherapy with irinotecan and a fluoropyrimidine required No prior chemotherapy with oxaliplatin or bevacizumab No major surgery within 28 d No radiotherapy within 14 d	829	644 (77.4)	185 (22.6)	326 (39.8)	494 (60.2)	407 (49.6)	413 (50.4)	251 (30.6)	569 (69.4)
EPIC	Ir vs Ir + Cx	Failure (disease progression/discontinuation due to toxicity) within 6 mo of the last-dose of first line fluoropyrimidine and oxaliplatin treatment for metastatic disease No previous irinotecan or anti-EGFR therapies	1289	989 (76.9)	300 (23.1)	482 (37.1)	816 (62.9)	664 (51.2)	634 (48.8)	Not available	

(continued)

Table 1. (continued)

Study	Regimen	Key eligibility	Total accrual (No.)	Age[a], No. (%)		Sex, No. (%)		ECOG PS, No. (%)		Metastatic sites[a], No. (%)	
				<70 y	≥70 y	Female	Male	0	>0	<2	≥2
N016967	XELOX vs FOLFOX4	ECOG performance status ≤2 Progression within 6 mo after first-line chemotherapy for metastatic disease with irinotecan-based regiment No chemotherapy within 3 wk Prior radiotherapy allowed except for target lesions (unless progression was documented) and except for therapy completed within 4 wk of randomization	627	507 (80.9)	120 (19.1)	242 (38.6)	385 (61.4)	295 (47.1)	332 (52.9)	208 (33.2)	419 (66.8)
N9841	Ir vs FOLFOX4	ECOG performance status ≤2 Progressive disease after 1 prior FU-based chemotherapy regimen or failure during or within 6 mo of finishing FU-based adjuvant therapy No more than 1 prior chemotherapy regimen No previous irinotecan or other camptothecin derivative No previous therapy with oxaliplatin	491	367 (74.7)	124 (25.3)	204 (41.6)	287 (58.4)	0 (0)	491 (100)	225 (45.8)	262 (53.4)
RAISE	R → FOLFIRI vs placebo → FOLFIRI	Known KRAS exon 2 mutation status (mutant or wild-type) ECOG performance status <2 Disease progression during or within 6 mo of finishing first-line combination therapy with bevacizumab, oxaliplatin, and a	1072	847 (79.0)	225 (21.0)	457 (42.6)	615 (57.4)	522 (48.7)	550 (51.3)	364 (33.0)	702 (65.5)

(continued)

Table 1. (continued)

Study	Regimen	Key eligibility	Total accrual (No.)	Age[a], No. (%)		Sex, No. (%)		ECOG PS, No. (%)		Metastatic sites[a], No. (%)	
				<70 y	≥70 y	Female	Male	0	>0	<2	≥2
		fluoropyrimidine for metastatic disease, and had received at least 1 cycle of the triplet therapy No bevacizumab with 28 d or chemotherapy within 21 d									
TML	F/C + Ir/Ox vs F/C + Ir/Ox + B	ECOG performance status ≤2 At least 3 mo prior treatment with standard first line chemotherapy with bevacizumab	820	640 (78.0)	180 (22.0)	294 (35.9)	526 (64.1)	357 (43.5)	463 (56.5)	Not available	
VELOUR	FOLFIRI + placebo vs FOLIRI + Af	ECOG performance status <2 Documented progression while on or with 6 months of completion of a single prior oxaliplatin-based adjuvant therapy No prior irinotecan No prior radiotherapy, chemotherapy, or major surgery within 28 days No participation in another clinical trial with an investigational drug within 30 d	1226	1002 (81.7)	224 (18.3)	508 (41.4)	718 (58.6)	702 (57.3)	524 (42.7)	Not available	

[a]Number/percent missing not included in this table. Af = aflibercept; ARCAD = Aide et Recherche en CAncerologie Digestive; B = bevacizumab; C = capecitabine; CAPIRI = irinotecan, capecitabine; CAPOX = oxaliplatin, capecitabine; Ce = cediranib; Cx = cetuximab; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; F = flourouracil; FOLFIRI = irinotecan, levofolinate, fluorouracil; FOLFOXIRI = irinotecan, levofolinate, fluorouracil, oxaliplatin; FU = levofolinate, fluorouracil, dexamethasone; IFL = irinotecan, fluorouracil; Ir = irinotecan; IrFU = irinotecan, levofolinate, fluorouracil, dexamathasone; IROX = oxaliplatin, irinotecan; KRAS exon 2 mutation = molecular genetic abnormality indicating the presence of a mutation in exon 2 of the KRAS gene; M = mitomycin; mCRC = metastatic colorectal cancer; Ox = Oxaliplatin; OxFU = oxaliplatin, levofolinate, fluorouracil, dexamethasone; P = panitumumab; R = ramucirumab; VEGF = vascular endothelial growth factor; XELOX = oxaliplatin, capecitabine.

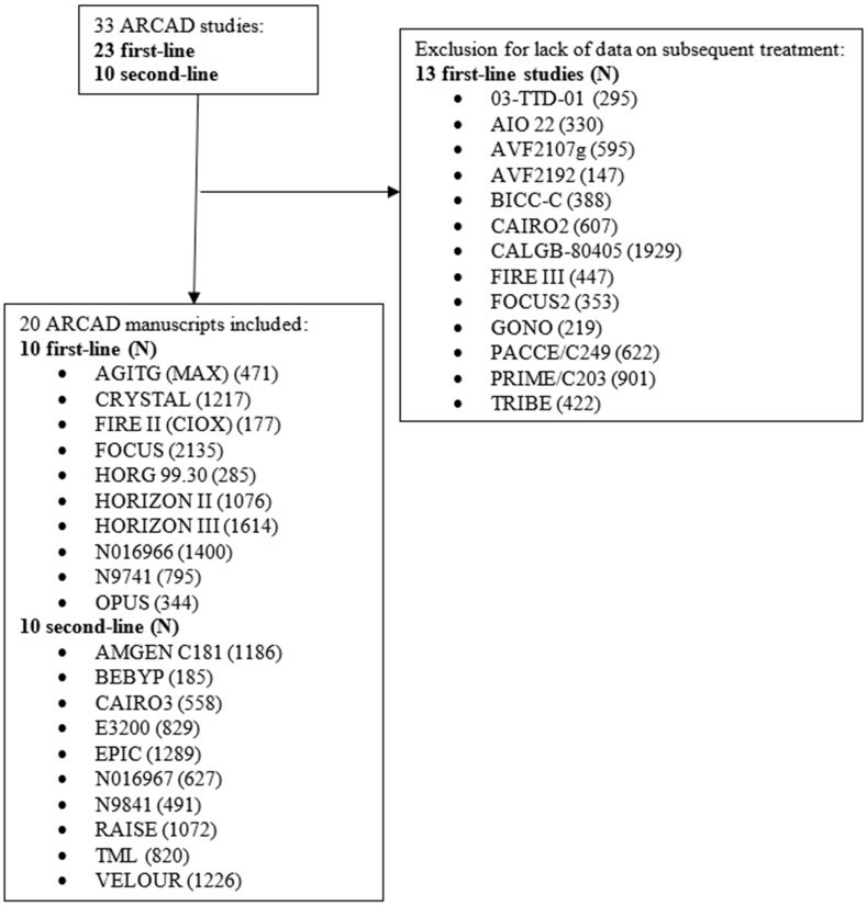

Figure 1. Consort diagram.

Statistical Analysis

The distributions of time-to-event endpoints were compared by Cox regression models adjusting for covariates. The binary endpoints were compared by log rank test. All statistical tests were 2-sided, and a *P* value of less than .05 was considered statistically significant.

Results

First-Line Trials

A total of 5289 participants were evaluable for 10 first-line nonsequential studies (Table 1). Older adults comprised 16.4% of patients on first-line trials (870 total older adults aged >70 years; 4419 younger adults aged ≤70 years in first-line trials). Participants in first-line trials were more often younger adults (83.6% were aged ≤70 years), male (62.4%), ECOG PS 0 (55.5%), and had at least 2 metastatic sites (61.8%). In univariate analysis of nonsequential trials of participants with TTP1 failure, older adults and an ECOG PS of at least 1 had statistically significantly lower odds of receiving subsequent treatment (older adults: odds ratio [OR] = 1.24, 95% confidence interval [CI] = 1.01 to 1.53; ECOG PS ≥1: OR = 1.70, 95% CI = 1.44 to 2.02). We observed that a 10-year increase in age was associated with 12% increased odds of no subsequent treatment (OR for age per 10 years = 1.12, 95% CI = 1.04 to 1.21, *P* = .004).

In a multivariable model, relative to PS = 0, a patient who was ECOG PS of at least 1 had a statistically significantly increased odds of no subsequent treatment (ECOG PS = 1: HR = 1.55, 95% CI = 1.30 to 1.84; ECOG PS >1: HR = 4.07, 95% CI = 2.85 to 5.82) (Table 2).

In both univariate and multivariable analysis, loss of each additional month from treatment to TTP1 was statistically significantly associated with shorter OS (HR = 0.95, 95% CI = 0.95 to 0.96, *P* < .001; and HR = 0.96, 95% CI = 0.95 to 0.96, *P* < .001) (Figure 2, A). In a univariate model examining age per 10 years, replacing the age category of younger than 70 years or 70 years and older, each additional decade of age was statistically significantly associated with OS (HR = 1.11, 95% CI = 1.02 to 1.21, *P* = .01).

Second-Line Trials

A total of 7921 participants were evaluable for TTP2 in the 10 second-line sequential and nonsequential studies (Table 1). Older and younger adults enrolled in second-line trials experienced similar median TTP and median OS (median TTP = 5.1 vs 5.2 months, respectively; median OS = 11.6 vs 12.4 months, respectively). Participants in second-line trials were often younger (≤70 years) adults (78.3%), male (61.1%), ECOG PS 0 (52.7%), and had at least 2 metastatic sites (74.3%). In multivariable analysis, ECOG PS of at least 1, presence of liver metastasis, and number of metastatic sites of at least 2 were statistically significantly associated with shorter TTP2 and OS (Table 2). Median follow-up for

Table 2. Odds of no subsequent treatment following participation in first-line trials and survival following participation in second-line trials

Characteristic	First-line therapy Odds of no subsequent treatment (n = 5289 [5121 evaluable])			Second-line therapy Time to progression (n = 7921 [7408 evaluable])		Second-line therapy Overall survival (n = 8280 [7764 evaluable])	
	No. (%)	OR (95% CI)	P[b]	HR (95% CI)	P[b]	HR (95% CI)	P[b]
Age at enrollment, per 10 y	59.9 (10.7)[a]	1.11 (1.02 to 1.21)	.01	0.97 (0.94 to 0.99)	.005	0.99 (0.97 to 1.02)	.62
Age category							
≤70 y	3889 (88.0)	–	–	–	–	–	–
>70 y	744 (85.5)	–	–	–	–	–	–
Sex							
Female	1753 (88.2)	Referent					
Male	2880 (87.2)	1.15 (0.96 to 1.38)	.12	0.98 (0.94 to 1.04)	.54	0.97 (0.92 to 1.02)	.20
ECOG PS							
0	2566 (90.4)	Referent	<.001		<.001		<.001
1	1815 (85.8)	1.55 (1.30 to 1.84)		1.22 (1.16 to 1.28)		1.51 (1.43 to 1.59)	
>1	115 (69.7)	4.07 (2.85 to 5.82)		1.59 (1.38 to 1.83)		3.54 (3.13 to 4.02)	
Metastasis							
Lung	1562 (87.4)	1.03 (0.86 to 1.23)	.76	1.10 (1.04 to 1.18)	.003	1.08 (1.01 to 1.16)	.02
Liver	3421 (88.0)	0.90 (0.75 to 1.09)	.29	1.36 (1.28 to 1.45)	<.001	1.62 (1.52 to 1.74)	<.001
Peritoneum	407 (88.1)	0.92 (0.68 to 1.24)	.57	1.27 (1.03 to 1.57)	.03	1.42 (1.15 to 1.75)	.001

[a]Values are mean (SD). CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = hazard ratio; OR = odds ratio.
[b]P values were calculated using a 2-sided Log rank test.

TTP2 for both sequential and nonsequential trials was 13.7 months. Regarding patient age, univariate analysis showed that each subsequent decade was associated with slightly reduced risk of TTP2 (HR = 0.98, 95% CI = 0.95 to 1.00), indicating similar TTP regardless of increasing age. Further, in univariate analysis, there was no statistically significant difference in TTP2 during second-line clinical trials for older adults and younger adults (HR = 1.00, 95% CI = 0.94 to 1.06, P = .97) (Figure 2, B).

A total of 8280 participants were evaluable for OS in the 10 second-line sequential and nonsequential studies (Table 1). Unique participants in second-line trials were more likely to be younger (≤70 years) adults (78.0%), male (60.9%), ECOG PS 0 (51.7%), and have at least 2 metastatic sites (74.3%). Median follow-up for OS for both sequential and nonsequential trials was 30.4 months.

Median OS was 12.4 and 12.3 months for older adults and younger adults, respectively. In multivariable analysis, ECOG PS of at least 1, presence of liver metastasis, peritoneal metastases, and 2 or more metastatic sites were statistically significant associated with shorter OS (Table 2). Statistically significantly shorter OS was observed for ECOG PS of at least 1 and liver and/or peritoneal metastases in multivariable analysis, with lung metastases emerging as another statistically significant risk factor for shorter OS. Unlike analysis for TTP1 for first-line trials and TTP2 for second-line trials, cohorts separated by each additional decade of age did not show any statistically significant association by cohort with OS (P = .62) (Figure 2). There was no statistically significant difference in OS during second-line clinical trials for older adults and younger adults (OS: HR = 1.05, 95% CI = 0.99 to 1.12, P = .11) (Figure 2, C).

Discussion

Older adults remain underrepresented as a proportion of the population of patients with mCRC in clinical trials of both first- and second-line treatments. Despite the fact that older adults are more likely to develop CRC, analysis of the ARCAD database clearly shows that there are statistically significantly fewer older adults enrolled in both first-line and second-line clinical trials. Beyond this, our data show that the chance of receiving second-line therapy decreased by 11% for each additional decade of life in multivariable analysis (P = .01). The a priori age threshold of older than 70 years did not predict progression or OS on first- or second-line trials.

Despite the fact that fewer older adults participated in first- and second-line clinical trials, older adults with CRC had similar outcomes to younger adults enrolled in CRC clinical trials. On both first-line and second-line trials, there was no difference in TTP or OS between older and younger adults with CRC.

Prior studies have established similar survival rates among older adults and younger adults in the palliative treatment setting. Folprecht and colleagues noted a similar median overall survival of 11 months and slightly better median PFS of 5.5 months in pooled analysis of 22 trials of fluorouracil for older adults vs younger adults (median OS = 10.8 vs 11.3 months, P value not statistically significant; median PFS 5.5 vs 5.3 months, P = .01 for older adults aged ≥70 years vs younger adults aged <70 years) (16). Similar survival was also noted in studies of oxaliplatin-based (17-19) and irinotecan-based (20) regimens. Studies of regimens that included targeted therapies have not included specific age analyses (21-27). Age-specific analyses of immunotherapy trials are forthcoming but not applicable to the current analysis, which lacked studies including immunotherapy for mCRC (28).

Understanding treatment patterns for older adults beyond first-line therapy provides useful insights into the dissemination and uptake of treatment recommendations. On the whole, older adults are less likely to be referred for oncology subspecialty care and, when referred, have lower rates of both routine- and clinical trial-based therapy for advanced disease (29,30). We have now established similarly low rates of enrollment in clinical trials beyond first-line therapy. Several factors may explain this difference in clinical trial enrollment by age, including patient preference, provider bias, presence of limiting concurrent

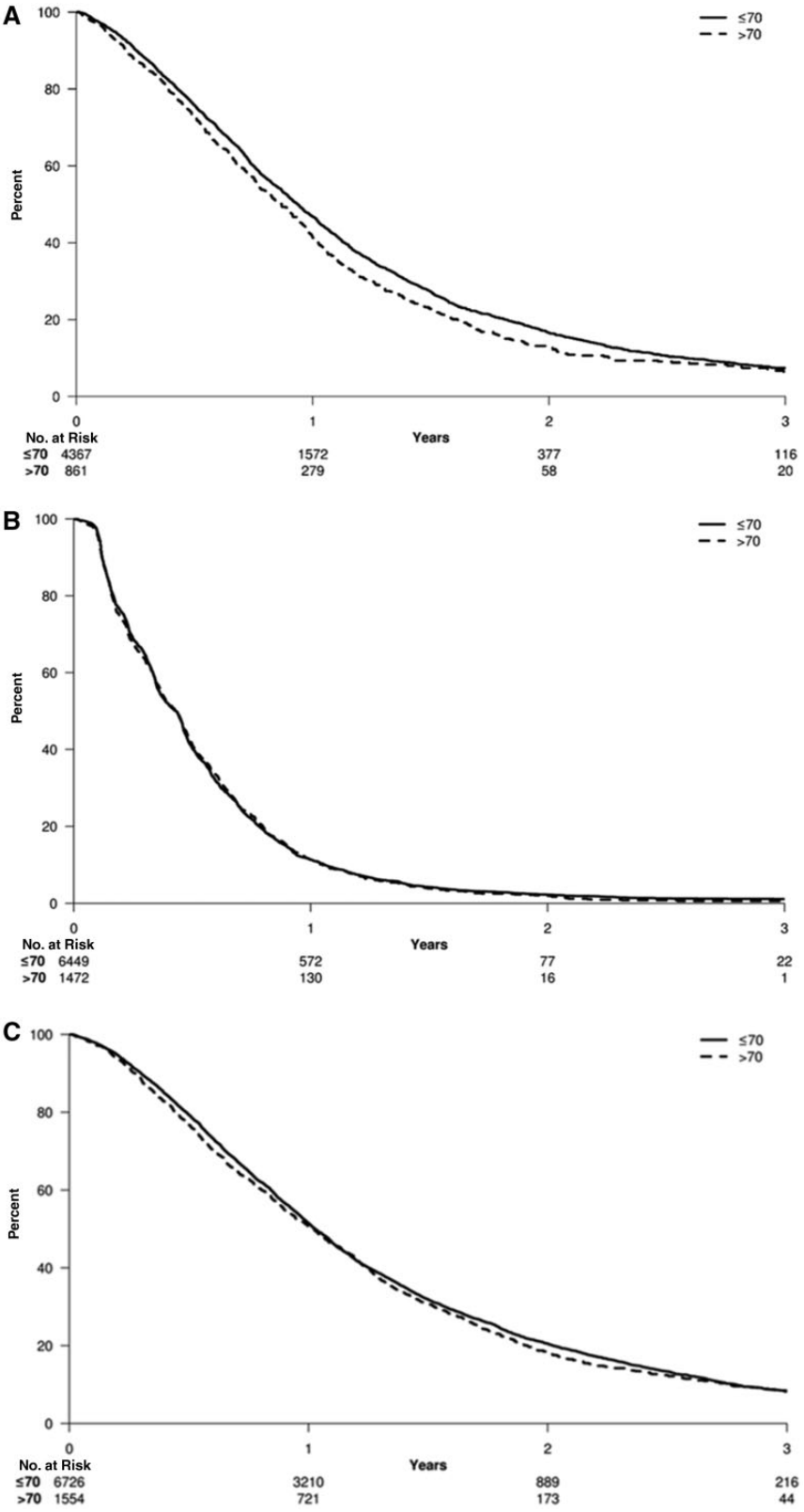

Figure 2. Time to progression and overall survival (OS) analyses for first- and second-line clinical trials in older adults vs younger adults. Kaplan-Meier curves are shown for (A) first-line OS (hazard ratio [HR] = 1.11, 95% confidence interval [CI] = 1.02 to 1.21, $P = .01$), (B) second-line time to progression 2 [TTP2] (HR = 1.00, 95% CI = 0.94 to 1.06, $P = .97$), and (C) second-line OS (HR = 1.05, 95% CI = 0.99 to 1.12, $P = .11$). *P* values were calculated using a 2-sided Log rank test.

medical conditions (frequently leading to reduced eligibility for trials), or difficulties in access to treatment (31-33). Understanding that TTP2 is comparable regardless of age, we must question whether the observed differences in trial enrollment rates are (1) comparable with the proportion of older adults receiving standard therapy outside of clinical trials, and (2) whether this difference is due to objective selection criteria.

Knowing that standards for cancer care emerge from results of clinical trials, it is imperative that we enable generalization of findings in both structure and execution of clinical trials for patients with mCRC. How can we increase cancer care parity for older adults? In addition to increasing enrollment in first-line trials, we also need to design studies such that we can learn as much as possible about the outcomes of older adults. Previous work has demonstrated that validated measures of frailty are an important metric in assessing the benefit of a therapeutic intervention in the elderly population. The Geriatric Assessment has been successfully embedded within cooperative group clinical trials (34), and the Cancer in Aging Research Group Toxicity Score can identify subsets of older adults at higher risk of symptomatic adverse events or death (35). Clinical trial endpoints should include those outcomes that mirror the values and preferences of older adults (33,36,37). Specifically, measures of quality of survival rather than TTP or OS may provide insights into preservation or recovery of function, active life expectancy, and disability-free survival. Increased inclusion of patient-reported outcomes is encouraged by the US Food and Drug Administration to enhance the drug approval process with the added insight of the patient experience (38). This is supported by the subsequent NCI development, validation, and improved survival outcome measures associated with systematic documentation of patient-reported outcomes in clinical trials and routine care (39-41).

Secondly, we must expand clinical trial methodology to include key patient characteristics pertinent to older adults. Specific recommendations have been published in detail elsewhere and are summarized here (42,43). ARCAD investigators have previously called for standardization of baseline characteristics to report in Phase 3 trials investigating systemic treatment of mCRC. Among recommendations for standard inclusion of demographic, cancer characteristics (stage, differentiation, metastases, potential for resection, etc), and laboratory values, recommendations include consideration of comorbidity or evaluation of frailty defined as the accumulation of biologic deficits or disability associated with reduced quality and duration of life (44).

Although the strength of this trial is that it evaluated outcomes from 20 trials and 13 149 patients, the current analysis included only patients enrolled in clinical trials and as such is limited by lack of data regarding the toxicity among older and younger adults, concurrent medical conditions, dose modifications, genomic data, sidedness, patient and family preferences, provider bias, or comparison of patient characteristics among those patients not referred to an oncology subspecialist and those who were referred but either were not offered or chose not to enroll in these clinical trials. Adverse event data were not collected consistently across all studies to permit robust comparison by age. It is unclear whether the addition of that data would statistically significantly affect PFS and OS, although death from other conditions certainly contributes to observed OS outcomes.

This ARCAD analysis provides the largest analysis to date evaluating enrollment and survival outcomes of older adults accrued to pivotal second-line mCRC clinical trials, providing insights into factors associated with enrollment and outcome disparities by age. Age should be considered less of an enrollment criterion for clinical trials. Although the age threshold selected aligns with prior published studies, the examination of cohorts of patients with increasing age by decade likely reflects the competing risk of older adult death from noncancer causes. The analyses are limited by rates of enrollment for older adults in individual studies with limited accrual of the oldest subsets of older adults, for example, those aged 80 years or older. Yet, the findings support consideration of enrollment of older adults in second-line trials to understand how the treatments under study and treatment dose intensity influence their PFS and OS. Further prospective studies are needed to understand the impact of concurrent medical conditions, polypharmacy, and sociodemographic factors beyond age on clinical trial offerings by providers and on preferences of patients. Further consideration should be given to the intersection of age with these factors and inclusion of objective assessment of fitness for clinical trials to enhance offerings for older adults.

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Data Availability

The data sharing of individual patient data from each participating trial will be subject to the policy and procedures of the institutions and groups who conducted the original study. Please contact Nadine Jackson McCleary, MD MPH at 450 Brookline Ave, Boston, MA 02215. Email address: nj_mccleary@dfci.harvard.edu.

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