Received: 22 May 2020 Revised: 4 September 2020 Accepted: 30 September 2020
DOI: 10.1002/pds.5148

Effectiveness of adjuvant FOLFOX vs 5FU/LV in adults over age 65 with stage II and III colon cancer using a novel hybrid approach

Jennifer L. Lund[1,2] | Michael A. Webster-Clark[1] | Sharon Peacock Hinton[1] | Shahar Shmuel[1] | Til Stürmer[1,2] | Hanna K. Sanoff[2,3]

[1]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[2]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[3]Division of Hematology/Oncology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Correspondence
Jennifer L. Lund, Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, McGavran-Greenberg Hall, CB #7345, Chapel Hill, NC 27599-7435.
Email: jennifer.lund@unc.edu

Funding information
Patient-Centered Outcomes Research Institute, Grant/Award Number: ME-2017C3-9337

Abstract

Purpose: Estimates of cancer therapy effects can differ in clinical trials and clinical practice, partly due to underrepresentation of certain patient subgroups in trials. We utilize a hybrid approach, combining clinical trial and real-world data, to estimate the comparative effectiveness of two adjuvant chemotherapy regimens for colon cancer.

Methods: We identified patients aged 66 and older enrolled in the Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer. Similar patients were identified in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, initiating adjuvant chemotherapy with either 5-fluorouracil (5FU) alone or in combination with oxaliplatin (FOLFOX). We used logistic regression to estimate the likelihood of trial enrollment as a function of age, sex, and substage. Using inverse odds of sampling weights (IOSW), we compared 5-year mortality in patients randomized to FOLFOX vs 5FU using weighted Cox proportional hazards regression, the Nelson-Aalen estimator for cumulative hazards, and bootstrapping for 95% confidence intervals (CIs).

Results: There were 690 trial participants and 3834 SEER-Medicare patients. The SEER-Medicare population was older and had a higher proportion of stage IIIB and IIIC patients than the trial. After controlling for differences between populations, the IOSW 5-year HR was 1.21 (0.89, 1.65), slightly farther from the null than the trial estimate (HR = 1.14, 95%CI: 0.87, 1.49).

Conclusions: This study supports mounting evidence of little to no incremental reduction in 5-year mortality for FOLFOX vs 5FU in older adults with stage II-III colon cancer, emphasizing the importance of combining clinical trial and real-world data to support such conclusions.

KEYWORDS
aging, cancer, chemotherapy, comparative effectiveness research, pharmacoepidemiology

1 | INTRODUCTION

Randomized controlled trials (RCTs) are the gold standard for establishing the efficacy of cancer therapies and are required for marketing approval. However, RCT enrollment is a complex function of clinical and structural

Presentation: This work was previously presented in abstract form at the 2018 Society for Epidemiologic Research Annual Meeting in Baltimore, MD. All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors, or Methodology Committee.

factors, a physician's views of a patient's fitness and eligibility, and a patient's willingness to enroll and be randomized.[1] As a result, less than 5% of patients participate in cancer clinical trials,[2] and studies have shown that specific groups of patients, including older adults aged 65 years and older, are often underrepresented.[2-12] This underrepresentation can be problematic if treatment efficacy varies across patient subgroups (ie, there is heterogeneity of treatment effects), leading to external validity bias[13] where the treatment effect from an RCT differs from the treatment effect observed in a different population (eg, patients treated following drug approval in clinical practice). Given the increasing interest in the use of real-world data to generate evidence supporting regulatory submissions,[14] new methodologic approaches are needed.

In 2004, the Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) demonstrated superior efficacy of 6-months of adjuvant chemotherapy with oxaliplatin (FOLFOX) vs 6-months of 5-fluorouracil (5FU) alone in reducing recurrence and all-cause mortality in stage III (but not stage II) colon cancer.[15-17] However, long-term trial follow-up,[18-20] pooled trial analyses,[21,22] and observational studies[23,24] have yielded conflicting evidence regarding the benefits of FOLFOX in older adults—a subgroup representing nearly 50% of patients diagnosed with colon cancer annually.[25] In particular, observational studies have been criticized because of their potential for unmeasured confounding, where older adults initiating FOLFOX may be more fit than those initiating 5FU alone in ways not captured in routinely collected data. This type of confounding can artificially exaggerate the observed benefits of FOLFOX compared to 5FU.

In this study, we apply a novel hybrid approach to estimate the effectiveness of FOLFOX vs 5FU on reducing all-cause mortality among adults aged 66 to 75 years old diagnosed with stage II or III colon cancer and treated in clinical practice. This hybrid study approach draws upon data from the MOSAIC trial and real-world data from cancer registries and Medicare enrollment and claims. Using these sources, we reweight the MOSAIC trial data to reflect the characteristics of the real-world Medicare population to answer the question: "What would the results of the MOSAIC trial have been if the trial population had a age, sex, and substage distributions similar to Medicare beneficiaries aged 66-75 with stage II-III colon cancer initiating adjuvant chemotherapy with FOLFOX or 5FU?"

KEY POINTS

- In this study, MOSAIC trial participants were younger and had lower stage disease (ie, less aggressive) than patients treated in clinical practice settings.
- Using a hybrid approach incorporating clinical trial and observational data, we found that adjuvant FOLFOX did not incrementally reduce mortality compared with 5FU alone in adults with stage II and III colon cancer aged 66 to 75 years old.
- Results were similar when the analysis was restricted to patients with stage III disease only.
- With the emerging focus of using real-world data for generating real-world evidence, hybrid study approaches may be used as a potential bridge to understanding differences between treatment effects observed in trial and clinical practice settings.

2 | METHODS

2.1 | Data sources and study populations

For this study, we used information from the phase III MOSAIC trial and the National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER)-Medicare linked database.

2.1.1 | MOSAIC trial

We obtained access to the MOSAIC trial through ClinicalStudy DataRequest.com, a consortium of clinical study data providers.[26] These data are stored and must be analyzed on a third party server maintained by SAS, the Clinical Trial Data Transparency (CTDT) platform. Eligibility criteria for the MOSAIC trial are described in detail elsewhere.[16] Briefly, patients were enrolled from 1998 to 2001 across 146 centers in 20 countries and randomized to receive 6 months of either FOLFOX or 5FU alone. Key eligibility criteria included age 18 to 75 years, resected stage II (T3 or T4, N0, M0) or stage III (any T, N1 or N2, M0) colon carcinoma, Karnofsky performance status (KPS) of ≥60, and adequate organ function.

For all analyses, we restricted the MOSAIC population to adults aged 66 to 75 years to match the real-world population of patients observed in the SEER-Medicare database (detailed below). In sub-analyses, the trial data were restricted to stage III patients.

2.1.2 | Surveillance, epidemiology, and end results (SEER)-Medicare linked database

We accessed data from the National Cancer Institute's SEER program linked with Medicare enrollment and claims data.[27] The SEER data include demographic information, clinical and tumor characteristics, vital status, and cause of death for all individuals diagnosed with cancer residing within one of the SEER regions, covering approximately 35% of the US population. Medicare claims data provide information on specific service dates, diagnoses, procedures, and specific treatments delivered during medical encounters.

To identify a clinically relevant population in SEER-Medicare, using inclusion and exclusion criteria similar to those applied in the MOSAIC trial, we identified individuals who were diagnosed with a first primary cancer of the colon histologically confirmed as AJCC stage II or III at age 66 to 75 years from 2004 to 2011. All individuals had to undergo surgical resection within 90 days of diagnosis (set as

the first day of the diagnosis month), identified using International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9) procedure codes and Healthcare Common Procedural Coding System (HCPCS) codes. In addition, all individuals were required to have at least 12 months of continuous Medicare Parts A and B enrollment prior to the date of diagnosis (set to the first of the month) to assess Medicare claims based indicators of disability status[28] as a proxy for the Karnofsky performance status exclusion criteria. Those with a claims based predicted probability of disability of >11.5% (proxy for ECOG >2) were excluded. Finally, all individuals had to survive and have at least one claim for oxaliplatin or 5-FU within 120 days from surgical resection, identified using HCPCS codes. These patients were then classified as having initiated FOLFOX or 5-FU alone based on their first cycle of therapy. FOLFOX and 5FU were the only approved therapies for the treatment of stage II-III colon cancer during the study period. The time windows used to define treatments were based on clinical guidelines[15] and our prior work.[23,24,29-32]

2.2 | Study design

We implemented a hybrid approach, which is detailed in Figure 1. This approach, developed by Cole and Stuart[33] with recent extensions,[34-36] has been applied to generalize or transport treatment effects observed in RCTs to various target populations of interest, particularly in the setting of HIV[37-41] and cardiovascular diseases.[35,42,43] In this design, the RCT treatment and outcome data serve as the foundation for analysis. However, the RCT data are reweighted or standardized to reflect the distribution of patient characteristics (ie, effect measure modifiers) in the real-world population that potentially modify the effect of treatment. These reweighted RCT data are then reanalyzed to estimate treatment effectiveness relevant to the real-world population setting.

2.3 | Statistical analysis

We first summarized the trial and real-world populations' patient characteristics using descriptive statistics and quantified differences between the two groups using standardized mean differences. Based on the long-term follow-up subgroup analyses reported from the MOSAIC trial[19] and clinical input, we then identified the following patient-level factors captured in both data sources that could potentially modify treatment effects: age measured at MOSAIC randomization or SEER-Medicare treatment initiation (<70 vs 70+ years), sex (male vs female), and substage of disease measured at surgical resection (IIA, IIB, IIIA, IIIB, IIIC).

To transport the MOSAIC treatment effect to the SEER-Medicare target populations, inverse odds of sampling weights (IOSWs)[34] were estimated. IOSWs are typically estimated by first stacking the two study populations (trial and real-world data) and running a logistic regression model to predict the probability of trial enrollment as a function of patient characteristics, $\mathbf{z} = z_1, \ldots, z_k$, that are potential effect measure modifiers [Equation (1)]. This weighting approach is similar to the propensity score, but instead of predicting the probability of treatment, this model predicts the probability of trial enrollment.

$$ln\left[\frac{Pr(trial_i = 1 \mid z)}{Pr(trial_i = 0 \mid z)}\right] = \beta_0 + \beta_1 z_1 + \ldots + \beta_k z_k. \quad (1)$$

Each individual is then assigned a weight, w_i, based on their predicted probability of trial enrollment [Equation (2)]. Notably, all individuals in the real-world data are assigned a weight of 0 as they are not used in subsequent analysis.

$$W_i = \begin{cases} \dfrac{Pr(trial_i = 0 \mid Z_i)}{Pr(trial_i = 1 \mid Z_i)} \times \dfrac{p(trial_i = 1)}{p(trial_i = 0)}, & trial_i = 1 \\ 0, & trial_i = 0 \end{cases}. \quad (2)$$

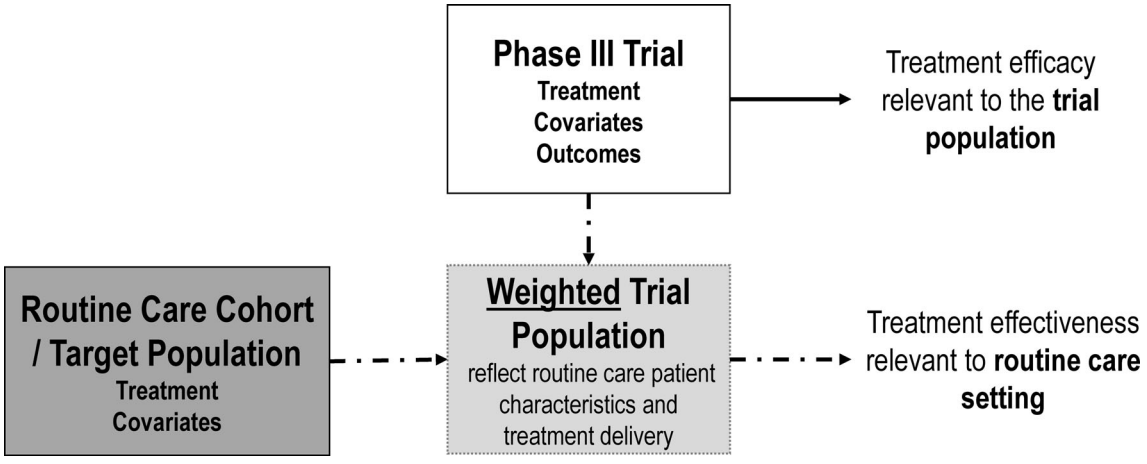

FIGURE 1 Hybrid study approach to estimating treatment effectiveness in routine care settings. this schematic shows the inputs for the hybrid study approach. In a traditional phase III trial, treatment efficacy is estimated in the trial population (solid line). In the hybrid study design applied in this study (dashed lines), we used treatment, covariate, and outcome data from the MOSAIC trial and treatment and covariate data from the SEER-Medicare data to estimate treatment effectiveness in the three different real-world populations of interest

Because neither the individual-level MOSAIC trial data on the Clinical Trial Data Transparency (CTDT) platform nor the individual-level SEER-Medicare data on the UNC secure server could be moved, we had to take a slightly different approach to modeling, similar to that used by Cole and Stuart[33] First, we created a SEER-Medicare target population data table that was jointly stratified by age (66-70 vs 71-75), sex, and substage (all cell sizes >11). These joint distributions were then used to reconstruct a synthetic SEER-Medicare population on the CTDT platform. At that point, the MOSAIC trial and SEER-Medicare synthetic data were concatenated (or stacked on top of each other) to create one combined dataset with one record per MOSAIC participant and one record per SEER-Medicare patient. This dataset contained a flag for whether the individual was in the MOSAIC or SEER-Medicare population, as well as information on age, sex, and substage. An indicator for vital status at 5 years (and days from randomization to death) was included for the MOSAIC trial patients only. A multivariable logistic regression model was then run to estimate IOSW as described above.

We then ran Cox proportional hazards models using the unweighted and IOSW MOSAIC data to estimate hazard ratios (HRs), estimating the effectiveness of FOLFOX vs 5FU alone on 5-year all-cause mortality. In addition, we used the Nelson-Aalen estimator for cumulative hazards, a Kaplan-Meier analogue that uses weighted observations, to estimate unweighted and weighted 5-year risk differences (RD) for all-cause mortality comparing patients randomized to FOLFOX vs 5FU. For both models, 95% confidence intervals (CIs) were estimated by calculating the SD of 1000 bootstrap replicates of both the SEER-Medicare and MOSAIC trial populations. Analyses were run within subgroups of the SEER-Medicare population where greater benefits of FOLFOX vs 5FU were expected: (a) stage III patients only (the Food and Drug Administration approved indication)[44] and (b) all patients initiating FOLFOX (a population identified by oncologists as candidates for more aggressive therapy).

Finally, as the MOSAIC trial did not use block randomization, we observed chance imbalances in the age, sex, and substage distributions between the FOLFOX and 5FU arms in MOSAIC participants aged 66 to 75 years. To mitigate the potential confounding effects of these baseline imbalances, we used propensity scores, including these characteristics, to predict randomization to the FOLFOX arm vs 5FU arm and then estimated inverse probability of treatment weights (IPTW).[45] We then estimated the effect of FOLFOX vs 5FU on all-cause mortality in the unweighted and IPTW MOSAIC populations. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). This study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

3 | RESULTS

3.1 | Study populations

After applying all study inclusion and exclusion criteria, there were 690 MOSAIC participants aged 66 or older, of whom 411 had stage III disease, and 3834 SEER-Medicare patients, of whom 2859 had stage III disease and 2560 initiated FOLFOX (Figure 2). Differences between the overall trial and target populations for the potential effect measure modifiers are shown in Table 1; similar descriptions for the stage III populations are provided in Table S1. Overall, the SEER-Medicare target population was older than the MOSAIC population, with 61% of patients aged 70 to 75 vs only 46% in MOSAIC. Notably, the MOSAIC trial enrolled a higher proportion of stage II patients at 40% compared with the overall SEER-Medicare population at 25%.

3.2 | Five-year events, risk of mortality, and risk differences

Table 2 summarizes the 5-year mortality and risk differences, comparing FOLFOX to 5FU across various target populations. In the MOSAIC population, aged 66 and older, there were 74 deaths in the 5FU arm and 82 deaths in the FOLFOX arm, translating to a 5-year mortality risk of 22.2% and 24.2%, respectively (crude 5-year RD = 2.0%, 95% CI: −4.4%, 6.1%). After controlling for baseline differences between the trial and the real-world population of patients initiating FOLFOX or 5FU in SEER-Medicare, the IOSW 5-year RD was 2.9% (−4.6%, 10.6%). Like the overall estimate, the 5-year RD was similar when the trial and the target populations were restricted to stage III patients only (IOSW RD = 2.8%, 95% CI: −6.3%, 12.4%) and when the target was restricted to patients initiating FOLFOX only (IOSW RD = 2.7%, 95% CI: −6.0%, 11.3%).

3.3 | Five-year mortality hazard ratios

Figure 3 reports the HR estimates and 95% CIs for 5-year mortality, comparing the effectiveness of FOLFOX vs 5FU. In the crude MOSAIC population, the hazard ratio (HR) for 5-year mortality, comparing patients aged 66 and older randomized to FOLFOX vs 5FU, was 1.14 (95% CI: 0.87, 1.49). After IPTW, to account for baseline imbalances, the estimate was largely unchanged (HR: 1.17 [95% CI: 0.89, 1.52]). When we applied the IOSW to account for observed differences between the MOSAIC trial and SEER-Medicare target population with respect to age, sex, and substage, we found the overall HR estimate for 5-year mortality moved slightly farther away from the null value (HR = 1.21 [95% CI: 0.89, 1.65]). HR estimates were similar when we restricted the target population and trial to stage III patients (HR: 1.21 [95% CI: 0.85, 1.71]) and when the target population included those initiating FOLFOX only (HR: 1.19 [95% CI: 0.86, 1.59]).

4 | DISCUSSION

In this study, we demonstrate the application of a hybrid study approach to evaluate the comparative effectiveness of two adjuvant chemotherapy regimens for stage II-III colon cancer. Drawing upon both the phase III MOSAIC trial and SEER-Medicare data, we found

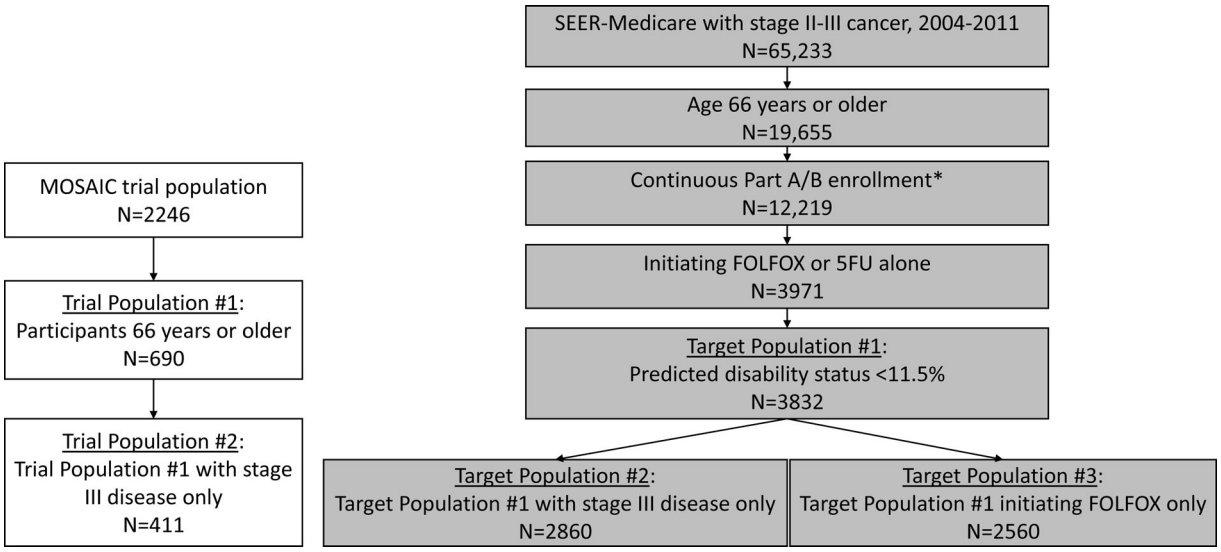

FIGURE 2 Study Inclusion and Exclusion Cascade for the MOSAIC trial and SEER-Medicare Target Populations

TABLE 1 Characteristics of the MOSAIC and SEER-Medicare study populations

	MOSAIC trial population						SEER-Medicare population					
	FOLFOX		5FU		Total		FOLFOX		5FU		Total	
	n = 342	%	n = 348	%	n = 690	%	n = 2560	%	n = 1272	%	n = 3832	%
Age group												
66-69	182	53	193	55	375	54	1088	43	453	36	1541	40
70-75	160	47	155	45	315	46	1472	58	819	64	2291	60
Sex												
Male	169	49	204	59	373	54	1297	51	659	52	1956	51
Female	173	51	144	41	317	46	1261	49	613	48	1874	49
AJCC Substage												
IIA	113	33	119	34	232	34	329	13	439	35	768	20
IIB	24	7	23	7	47	7	114	4	90	7	204	5
IIIA	9	3	13	4	22	3	236	9	103	8	339	9
IIIB	132	39	127	36	259	38	1156	45	455	36	1611	42
IIIC	64	19	66	19	130	19	723	28	185	15	908	24

Abbreviations: AJCC, American Joint Commission on Cancer; FOLFOX, oxaliplatin +5FU; MOSAIC, Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer; SEER, Surveillance, Epidemiology, and End Results program; 5FU, 5-fluorouracil.

that adjuvant FOLFOX does not incrementally reduce mortality compared with 5FU alone in adults with stage II and III colon cancer, aged 66 to 75 years old. We found similar results when restricting investigation to stage III patients only. This analysis adds to the current literature on the effectiveness of FOLFOX vs 5FU in older adult populations by utilizing an approach that leverages the internal validity achieved from randomization in the MOSAIC trial and the external validity generated from reweighting the trial to reflect the characteristics of patients treated in clinical practice.

Following the 2004 Food and Drug Administration approval of FOLFOX for the adjuvant treatment of stage III colon cancer, several trial subgroup analyses compared the efficacy of FOLFOX and 5FU in older adult populations. Analyses based on the MOSAIC trial[17,19] and a pooled analyses of adjuvant chemotherapy trials from the ACCENT database[22] suggested little to no incremental benefit of FOLFOX in older adults—defined as either 65+ years or 70+ years. On the other hand, a more recent pooled analysis[21] of phase III trials comparing 5FU or capecitabine with or without oxaliplatin suggested that FOLFOX/XELOX efficacy in adults ≥70 years was similar, but slightly attenuated when compared with younger adults.

Concurrently, observational studies aimed to evaluate the comparative effectiveness of FOLFOX vs 5FU in older adults treated in clinical practice settings. While these studies are incredibly important for generating evidence of the uses, benefits, and harms of cancer

TABLE 2 Five-year mortality risks and risk differences comparing FOLFOX versus 5FU weighted to specific target populations[a]

Source data	MOSAIC study population	Target population	MOSAIC person-years	MOSAIC deaths	Five-year mortality	Five-year risk difference(95% CI)
RCT only	**Crude Overall MOSAIC**					
	5FU Arm	All MOSAIC participants aged 66–75	1465	74	22.2%	Ref.
	FOLFOX Arm		1478	82	24.2%	2.0% (−4.4%, 6.1%)
RCT only	**Crude Stage III MOSAIC**					
	5FU Arm	All MOSAIC participants aged 66-75 with stage III cancer	836	58	29.1%	Ref.
	FOLFOX Arm		848	60	29.8%	0.7% (−8.2%, 8.5%)
RCT only	**IPTW Overall MOSAIC**					
	5FU Arm	All MOSAIC participants aged 66-75	1470	72.7	21.8%	Ref.
	FOLFOX Arm		1477	82.8	24.4%	2.6% (−3.7%, 8.6%)
RCT only	**IPTW Stage III MOSAIC**					
	5FU Arm	All MOSAIC participants aged 66-75 with stage III cancer	840	57.0	28.6%	Ref.
	FOLFOX Arm		844	61.2	30.3%	1.7% (−7.1%, 10.1%)
RCT + Obs	**IOSW Overall MOSAIC**					
	5FU Arm	Target population #1: All patients initiating FOLFOX or 5FU in SEER-Medicare	1450	81.4	24.2%	Ref.
	FOLFOX Arm		1433	92.3	27.2%	2.9% (−4.6%, 10.6%)
RCT + Obs	**IOSW Stage III MOSAIC**					
	5FU Arm	Target population #2: All patients initiating FOLFOX or 5FU with stage III cancer in SEER-Medicare	838	55.3	27.9%	Ref.
	FOLFOX Arm		831	62.0	30.7%	2.8% (−6.3%, 12.4%)
RCT + Obs	**IOSW Overall MOSAIC**					
	5FU Arm	Target population #3: All patients initiating FOLFOX in SEER-Medicare	1437	88.4	26.2%	Ref.
	FOLFOX Arm		1416	98.4	28.9%	2.7% (−6.0%, 11.3%)

Abbreviations: CI, confidence interval; FOLFOX, oxaliplatin+5-fluorouracil; IOSW, inverse odds of sampling weighting; IPTW, inverse probability of treatment weighting; MOSAIC, Multileft International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer; Obs, Observational data; RCT, randomized clinical trial; 5FU, 5-fluorouracil.

[a]For relevant results, person-years, deaths, mortality risks, and risk differences are weighted using either IPTW or IOSW.

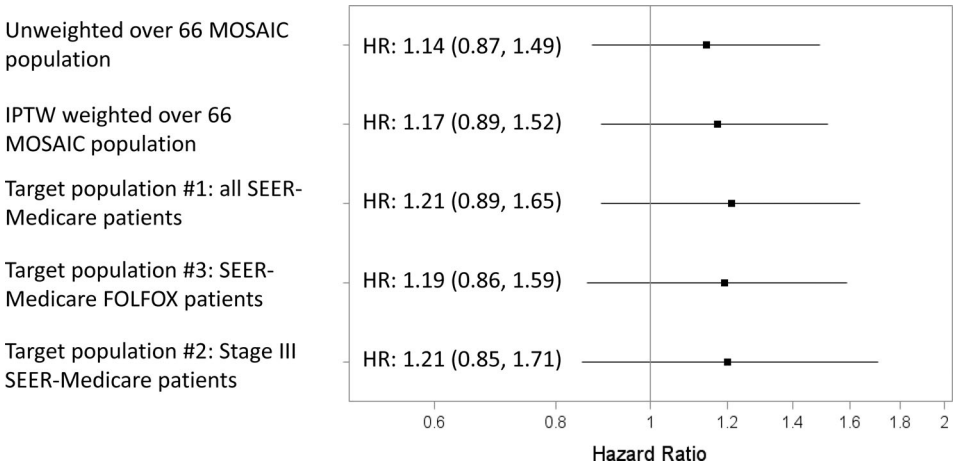

FIGURE 3 Comparison of 5-year mortality hazard ratio estimates comparing FOLFOX vs 5FU weighted to SEER-Medicare target populations

therapies in real-world settings, they face several challenges to their validity. First and foremost, unmeasured confounding is a major concern, given that most of these analyses were conducted within administrative claims datasets, which lack detailed clinical information. In this specific setting, claims data do not directly capture measures of poor underlying health status, which may strongly channel patients away from FOLFOX, a toxic treatment with more side effects. In fact, a recent study[46] showed that several claims based measures of poor

function are associated with both adjuvant chemotherapy choice (5FU vs FOLFOX) and mortality. As a result of this potential for channeling, previous observational studies based on claims data all reported an incremental benefit of FOLFOX compared with 5FU on mortality reduction,[23,24,47,48] although benefits were attenuated among those aged 75+ years.[24]

Substantial variation in the use of FOLFOX exists in clinical practice. Yet overall, our work[31] using the Surveillance, Epidemiology, and End Results (SEER)-Medicare data shows that among older adults (aged 66+ years) with stage II and III colon cancer initiating adjuvant chemotherapy, the proportion initiating adjuvant FOLFOX (vs 5FU alone) increased dramatically from 2004 to 2007, from 15% to 60% in stage II patients and 33% to 73% in stage III patients. Because FOLFOX increases the risk of several adverse events,[16] its continued use among patients with little to no expected benefit could potentially lead to net-harm. As such, the current National Comprehensive Cancer Network colon cancer treatment guidelines caution that "a benefit for the addition of oxaliplatin to 5-FU/LV in patients aged 70 years and older has not been proven in stage II or III colon cancer."[15]

Limitations of the study should be noted. First, our analyses were restricted to patients aged 66 to 75 years to ensure that patients in the SEER-Medicare data could be exchangeable with the MOSAIC trial participants. Thus, our findings do not directly translate to those aged >75 treated in clinical practice; however, it is unlikely that any further benefit of FOLFOX would accrue to this population. Second, our analytic approach only accounts for differences in the distributions of age, sex, and substage between the MOSAIC trial and SEER-Medicare populations. It does not account for other potential effect measure modifiers (eg, body mass index) that were not measured in both the MOSAIC trial and SEER-Medicare populations, and have relations above and beyond those that exist through age, sex, and substage. In addition, treatment effect estimates from this analysis do not consider differences in the delivery of and adherence to adjuvant therapy, again beyond the extent to which they are correlated with age, sex, and substage; such differences could impact treatment effectiveness. The MOSAIC trial reported that over 75% of patients randomized to FOLFOX and 87% of those randomized to 5FU completed all 12 cycles of therapy,[16] whereas this percentage is likely to be lower in clinical practice settings and may also influence both treatment effectiveness and safety. Finally, our transport estimates do not account for higher-level potential differences in patient characteristics in SEER vs non-SEER populations[49,50] or in the Medicare fee-for-service vs Medicare Advantage populations.[51] This may limit their overall generalizability to the broader population of older adults.

This study, utilizing a novel hybrid approach drawing on phase III trial and real-world data, contributes to the weight of evidence indicating no incremental benefit of FOLFOX vs 5FU on reducing 5-year mortality among older adults aged 66 to 75 years with stage II or III colon cancer. In contrast to studies relying solely on observational data, this approach leverages trial randomization to minimize concerns of internal validity related to confounding by underlying health status that can bias observed treatment effects. In the current regulatory climate focused on the use of real-world data for generating real-world evidence, hybrid study approaches may be used as a potential bridge to understanding differences between treatment effects observed in trial and clinical practice settings.

ETHICS STATEMENT

The study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

ACKNOWLEDGEMENTS

We acknowledge Sanofi, the MOSAIC trial sponsor, who made their data available to researchers through the data sharing platform, Clinical Study Data Request (www.clinicalstudydatarequest.com). This work was supported, in part, through a Patient-Centered Outcomes Research Institute (PCORI) Program Award (ME-2017C3-9337) and a developmental award from the Lineberger Comprehensive Cancer Center. All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors, or Methodology Committee. This study also used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology, and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement # U58DP003862-01 awarded to the California Department of Public Health. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred. The authors acknowledge the efforts of the National Cancer Institute; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Jennifer L. Lund https://orcid.org/0000-0002-1108-0689
Michael A. Webster-Clark https://orcid.org/0000-0002-8079-8504
Shahar Shmuel https://orcid.org/0000-0003-1726-1875
Til Stürmer https://orcid.org/0000-0002-9204-7177

REFERENCES

1. Unger JM, Cook E, Tai E, Bleyer A. The role of clinical trial participation in cancer research: barriers, evidence, and strategies. *Am Soc Clin Oncol Educ Book*. 2016;35:185-198.

2. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA*. 2004;291:2720-2726.
3. Ahaghotu C, Tyler R, Sartor O. African American participation in oncology clinical trials–focus on prostate cancer: implications, barriers, and potential solutions. *Clin Genitourin Cancer*. 2016;14: 105-116.
4. Al-Refaie WB, Vickers SM, Zhong W, Parsons H, Rothenberger D, Habermann EB. Cancer trials versus the real world in the United States. *Ann Surg*. 2011;254:438-442; discussion 442-3.
5. Brown DR, Fouad MN, Basen-Engquist K, Tortolero-Luna G. Recruitment and retention of minority women in cancer screening, prevention, and treatment trials. *Ann Epidemiol*. 2000;10:S13-S21.
6. del Carmen MG, Rice LW. Underrepresentation of women in clinical trials: why gynecologic oncologists are worried. *Obstet Gynecol*. 2015; 125:616-619.
7. Hori A, Shibata T, Kami M, et al. Age disparity between a cancer population and participants in clinical trials submitted as a new drug application of anticancer drugs in Japan. *Cancer*. 2007;109:2541-2546.
8. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med*. 1999;341:2061-2067.
9. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol*. 2003;21: 1383-1389.
10. Luo J, Kesselheim AS. Underrepresentation of older adults in cancer trials. *JAMA*. 2014;311:965-966.
11. Mishkin G, Minasian LM, Kohn EC, Noone AM, Temkin SM. The generalizability of NCI-sponsored clinical trials accrual among women with gynecologic malignancies. *Gynecol Oncol*. 2016;143:611-616.
12. Sharrocks K, Spicer J, Camidge DR, Papa S. The impact of socioeconomic status on access to cancer clinical trials. *Br J Cancer*. 2014;111: 1684-1687.
13. Westreich D, Edwards JK, Lesko CR, Cole SR, Stuart EA. Target validity and the hierarchy of study designs. *Am J Epidemiol*. 2019;188: 438-443.
14. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics Guidance for Industry: DRAFT GUIDANCE. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drugs-and-biologics-guidance. Accessed November 12, 2019.
15. NCCN. Clinical practice guidelines in oncology. Colon Cancer (version 4.2019). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed: November 11, 2019.
16. Andre T, Boni C, Mounedji-Boudiaf L, et al; Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med*. 2004;350:2343-2351.
17. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol*. 2009;27:3109-3116.
18. Tournigand C, Andre T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. *J Clin Oncol*. 2012;30:3353-3360.
19. Andre T, de Gramont A, Vernerey D, et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. *J Clin Oncol*. 2015;33: 4176-4187.
20. Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol*. 2011;29: 3768-3774.
21. Haller DG, O'Connell MJ, Cartwright TH, et al. Impact of age and medical comorbidity on adjuvant treatment outcomes for stage III colon cancer: a pooled analysis of individual patient data from four randomized, controlled trials. *Ann Oncol*. 2015;26:715-724.
22. McCleary NJ, Meyerhardt JA, Green E, et al. Impact of age on the efficacy of newer adjuvant therapies in patients with stage II/III colon cancer: findings from the ACCENT database. *J Clin Oncol*. 2013;31: 2600-2606.
23. Sanoff HK, Carpenter WR, Martin CF, et al. Comparative effectiveness of oxaliplatin vs non-oxaliplatin-containing adjuvant chemotherapy for stage III colon cancer. *J Natl Cancer Inst*. 2012;104: 211-227.
24. Sanoff HK, Carpenter WR, Sturmer T, et al. Effect of adjuvant chemotherapy on survival of patients with stage III colon cancer diagnosed after age 75 years. *J Clin Oncol*. 2012;30:2624-2634.
25. American Cancer Society. *Colorectal Cancer Facts & Figures 2017-2019*. Atlanta, GA: American Cancer Society; 2017.
26. Clinical Study Data Request website. https://clinicalstudydatarequest.com. Accessed October 15, 2019.
27. National Cancer Institute. SEER-Medicare: Brief Description of the SEER-Medicare Database. https://healthcaredelivery.cancer.gov/seermedicare/overview/. Accessed June 23, 2018.
28. Davidoff AJ, Zuckerman IH, Pandya N, et al. A novel approach to improve health status measurement in observational claims-based studies of cancer treatment and outcomes. *J Geriatr Oncol*. 2013;4: 157-165.
29. Lund JL, Sturmer T, Harlan LC, et al. Identifying specific chemotherapeutic agents in Medicare data: a validation study. *Med Care*. 2013; 51:e27-e34.
30. Lund JL, Sturmer T, Sanoff HK. Comparative effectiveness of postoperative chemotherapy among older patients with non-metastatic rectal cancer treated with preoperative chemoradiotherapy. *J Geriatr Oncol*. 2016;7:176-186.
31. Lund JL, Sturmer T, Sanoff HK, Brookhart A, Sandler RS, Warren JL. Determinants of adjuvant oxaliplatin receipt among older stage II and III colorectal cancer patients. *Cancer*. 2013;119:2038-2047.
32. Sanoff HK, Carpenter WR, Freburger J, et al. Comparison of adverse events during 5-fluorouracil versus 5-fluorouracil/oxaliplatin adjuvant chemotherapy for stage III colon cancer: a population-based analysis. *Cancer*. 2012;118:4309-4320.
33. Cole SR, Stuart EA. Generalizing evidence from randomized clinical trials to target populations: the ACTG 320 trial. *Am J Epidemiol*. 2010; 172:107-115.
34. Westreich D, Edwards JK, Lesko CR, Stuart E, Cole SR. Transportability of trial results using inverse odds of sampling weights. *Am J Epidemiol*. 2017;186:1010-1014.
35. Dahabreh IJ, Robertson SE, Tchetgen EJ, Stuart EA, Hernán MA. Generalizing causal inferences from individuals in randomized trials to all trial-eligible individuals. *Biometrics*. 2019;75:685-694.
36. Rudolph KE, van der Laan MJ. Robust estimation of encouragement-design intervention effects transported across sites. *J R Stat Soc Series B Stat Methodol*. 2017;79:1509-1525.
37. Bengtson AM, Pence BW, Gaynes BN, et al. Improving depression among HIV-infected adults: transporting the effect of a depression treatment intervention to routine care. *J Acquir Immune Defic Syndr*. 2016;73:482-488.
38. Edwards JK, Cole SR, Hall HI, et al. Virologic suppression and CD4+ cell count recovery after initiation of raltegravir or efavirenz-containing HIV treatment regimens. *AIDS*. 2018;32:261-266.

39. Edwards JK, Cole SR, Lesko CR, et al. An illustration of inverse probability weighting to estimate policy-relevant causal effects. *Am J Epidemiol*. 2016;184:336-344.
40. Lesko CR, Buchanan AL, Westreich D, Edwards JK, Hudgens MG, Cole SR. Generalizing study results: a potential outcomes perspective. *Epidemiology*. 2017;28:553-561.
41. Lesko CR, Cole SR, Hall HI, et al. The effect of antiretroviral therapy on all-cause mortality, generalized to persons diagnosed with HIV in the USA, 2009-11. *Int J Epidemiol*. 2016;45:140-150.
42. Hong JL, Jonsson Funk M, LoCasale R, et al. Generalizing randomized clinical trial results: implementation and challenges related to missing data in the target population. *Am J Epidemiol*. 2017;187(4):817-827.
43. Hong JL, Webster-Clark M, Jonsson Funk M, et al. Comparison of methods to generalize randomized clinical trial results without individual-level data for the target population. *Am J Epidemiol*. 2019; 188:426-437.
44. Drugs@FDA. FDA-Approved Drugs. Oxaliplatin. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021492s016lbl.pdf. Accessed August 20, 2020,
45. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11:550-560.
46. Mayer SE, Tan HJ, Peacock Hinton S, et al. Comparison of medicare claims-based proxy measures of poor function and associations with treatment receipt and mortality in older colon cancer patients. *Med Care*. 2019;57:286-294.
47. Mack CD, Brookhart MA, Glynn RJ, et al. Comparative effectiveness of oxaliplatin versus 5-flourouricil in older adults: an instrumental variable analysis. *Epidemiology*. 2015;26:690-699.
48. Mack CD, Glynn RJ, Brookhart MA, et al. Calendar time-specific propensity scores and comparative effectiveness research for stage III colon cancer chemotherapy. *Pharmacoepidemiol Drug Saf*. 2013;22:810-818.
49. Kuo TM, Mobley LR. How generalizable are the SEER registries to the cancer populations of the USA? *Cancer Causes Control*. 2016;27: 1117-1126.
50. Hankey BF, Ries LA, Edwards BK. The surveillance, epidemiology, and end results program: a national resource. *Cancer Epidemiol Biomarkers Prev*. 1999;8:1117-1121.
51. Enewold L, Parsons H, Zhao L, et al. Updated overview of the SEER-Medicare data: enhanced content and applications. *JNCI Monogr*. 2020;2020:3-13.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Lund JL, Webster-Clark MA, Hinton SP, Shmuel S, Stürmer T, Sanoff HK. Effectiveness of adjuvant FOLFOX vs 5FU/LV in adults over age 65 with stage II and III colon cancer using a novel hybrid approach. *Pharmacoepidemiol Drug Saf*. 2020;29:1579–1587. https://doi.org/10.1002/pds.5148