original reports

Radioembolization With Chemotherapy for Colorectal Liver Metastases: A Randomized, Open-Label, International, Multicenter, Phase III Trial

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abstract

PURPOSE To study the impact of transarterial Yttrium-90 radioembolization (TARE) in combination with second-line systemic chemotherapy for colorectal liver metastases (CLM).

METHODS In this international, multicenter, open-label phase III trial, patients with CLM who progressed on oxaliplatin- or irinotecan-based first-line therapy were randomly assigned 1:1 to receive second-line chemotherapy with or without TARE. The two primary end points were progression-free survival (PFS) and hepatic PFS (hPFS), assessed by blinded independent central review. Random assignment was performed using a web- or voice-based system stratified by unilobar or bilobar disease, oxaliplatin- or irinotecan-based first-line chemotherapy, and *KRAS* mutation status.

RESULTS Four hundred twenty-eight patients from 95 centers in North America, Europe, and Asia were randomly assigned to chemotherapy with or without TARE; this represents the intention-to-treat population and included 215 patients in the TARE plus chemotherapy group and 213 patients in the chemotherapy alone group. The hazard ratio (HR) for PFS was 0.69 (95% CI, 0.54 to 0.88; 1-sided $P = .0013$), with a median PFS of 8.0 (95% CI, 7.2 to 9.2) and 7.2 (95% CI, 5.7 to 7.6) months, respectively. The HR for hPFS was 0.59 (95% CI, 0.46 to 0.77; 1-sided $P < .0001$), with a median hPFS of 9.1 (95% CI, 7.8 to 9.7) and 7.2 (95% CI, 5.7 to 7.6) months, respectively. Objective response rates were 34.0% (95% CI, 28.0 to 40.5) and 21.1% (95% CI, 16.2 to 27.1; 1-sided $P = .0019$) for the TARE and chemotherapy groups, respectively. Median overall survival was 14.0 (95% CI, 11.8 to 15.5) and 14.4 months (95% CI, 12.8 to 16.4; 1-sided $P = .7229$) with a HR of 1.07 (95% CI, 0.86 to 1.32) for TARE and chemotherapy groups, respectively. Grade 3 adverse events were reported more frequently with TARE (68.4% *v* 49.3%). Both groups received full chemotherapy dose intensity.

CONCLUSION The addition of TARE to systemic therapy for second-line CLM led to longer PFS and hPFS. Further subset analyses are needed to better define the ideal patient population that would benefit from TARE.

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ASSOCIATED CONTENT

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Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

An estimated 60% of patients diagnosed with colorectal cancer (CRC) eventually will demonstrate liver disease as a predominant site of spread.[1,2] Consequently, much of the morbidity and mortality in these patients results from unresectability and progression of liver metastases. Nonsurgical locoregional approaches for colorectal liver metastases (CLM) may offer clinically meaningful benefit beyond systemic therapy alone.[2]

Transarterial radioembolization with Yttrium-90 glass microspheres (TARE) is an arterially based microembolic radiotherapy that delivers micron-sized beta-emitting particles through the hepatic tumor-feeding arteries.[3] By administering radiotherapy using a selective internal approach, radiation delivery to the tumor is optimized and nontarget parenchymal exposure is minimized. While historical use of glass-based TARE has been mainly for hepatocellular carcinoma, there are several uncontrolled studies in CLM.[4,5] In a 531-patient multicenter cohort analysis of CRC, TARE was found to be safe with promising survival outcomes.[6] Although TARE has been investigated in the first-line setting for CLM, there are no prospective data in the second-line setting.[7] Furthermore, the inherent vascularity of hepatic CRC lesions in the arterial (not

CONTEXT

Key Objective

To our knowledge, EPOCH (Evaluating TheraSphere in Patients with metastatic colorectal carcinoma Of the liver who have progressed on first-line Chemotherapy) is the first study to investigate the role of transarterial radioembolization with Yttrium-90 (TARE) when added to standard-of-care second-line chemotherapy for colorectal liver metastases.

Knowledge Generated

The study showed that the addition of TARE to second-line chemotherapy improved overall and hepatic progression-free survival.

Relevance

The addition of TARE to chemotherapy resulted in the delaying of disease progression. Future research on the topic will include subset analyses to better identify ideal patients who might benefit most, as well as dosimetric considerations to optimize the risk-benefit profile in the setting of exposure to TARE.

venous) phase provides a rationale for the investigation in the second-line setting.

We conducted a randomized, open-label, international, multicenter, phase III trial, to investigate the safety and efficacy of adding TARE to standard-of-care second-line chemotherapy in patients with CLM who had progressed on first-line treatment.

METHODS

Study Design and Participants

EPOCH is a randomized phase III clinical trial evaluating TARE in patients with metastatic colorectal carcinoma of the liver who have progressed on first-line chemotherapy. The Protocol (online only) was approved by the Food and Drug Administration (FDA) under an investigational device exemption. Eligibility criteria included age $\geq$ 18 years, unresectable unilobar or bilobar CLM, able to receive second-line irinotecan- or oxaliplatin-based chemotherapy, measurable disease by RECIST 1.1, performance status 0 or 1, bilirubin $\leq$ 1.2 upper limit normal, and albumin $\geq$ 3.0 g/dL. Key exclusion criteria were prior arterial or radiotherapy to the liver, clinically evident ascites, unresolved toxicities from first-line therapy, confirmed extrahepatic metastases, or contraindication to angiography. All efforts were made to distinguish benign extrahepatic lesions, such as reactive lymph nodes or benign lung lesions, from true extrahepatic metastases.

Random Assignment

Patients were randomly assigned 1:1 to receive second-line chemotherapy with or without TARE.[8] Random assignment was web- or voice-based and stratified by unilobar or bilobar disease, oxaliplatin- or irinotecan-based first-line chemotherapy, and *KRAS* mutation status.

Procedures

Patients in the control arm received either irinotecan- or oxaliplatin-based chemotherapy after random assignment per standard of care. Patients assigned to TARE received whole liver (separate right or left lobar injections) or unilobar treatment before second-line chemotherapy; they were permitted one chemotherapy infusion while awaiting planning angiography and dosimetry. In brief, a planning angiogram was performed to assess vascularity, tumor distribution, assessment of lung shunting fraction, and extrahepatic blood supply. Treatment was planned for 120 Gy $\pm$ 10% using single-compartment dosimetry to either one or both lobes in a single setting.[3,9] Glass-based TARE was performed (TheraSphere; Boston Scientific Corporation, Marlborough, MA).

End Points and Outcomes Assessment

The two primary end points were progression-free survival (PFS) and hepatic PFS (hPFS) from the time of random assignment using RECIST 1.1.[10] Secondary end points included overall survival (OS), objective response rate (ORR), and disease control rate (DCR). A blinded independent central review facility performed all imaging reads, which were used to determine PFS, hPFS, ORR, and DCR. Imaging was performed using computed tomography or magnetic resonance imaging at baseline and every 8 weeks thereafter. Adverse event (AE) assessment was performed following National Cancer Institute v3.0 guidelines. While AEs related to chemotherapy administration in both groups were recorded at regular time intervals, there was additional reporting of AEs in the TARE group related to two or more additional procedures (mapping angiography plus Yttrium-90 treatment[s]). Follow-up time was determined using reverse Kaplan-Meier (KM). Safety assessment included patients randomly assigned who received at least one administration of trial treatment.

Statistical Analysis

The study was to be considered positive if at least one of the two primary end points was statistically significant.

Approximately 420 patients were planned for 1:1 random assignment to obtain 344 PFS events. The study was designed to have a $\geq$ 80% power to detect a hazard ratio

(HR) of 0.71 for PFS and 0.65 for hPFS favoring TARE plus chemotherapy over chemotherapy, on the basis of a log-rank test with a 1-sided significance level of .025 over the two primary end points. Further details on the sample size calculation have been reported.[8] The Hochberg procedure was to be used to control type 1 error for the two primary end points at final analysis. Secondary end points were to be tested hierarchically if both the primary end points were significant.

Two interim analyses and a final analysis were planned. The rho family α spending function with a rho parameter of 1.5 was used to construct group sequential boundaries to control type 1 error rate. The first interim analysis was planned after 172 PFS events and occurred after 204 events. The criterion to stop early based on efficacy (1-sided P value of PFS $< .0114$) was not met in this analysis and the study continued. The second interim analysis was planned to occur after 241 PFS events and occurred after 287 events. An additional censoring rule was applied in the second interim analysis at the time of the last imaging assessment before subsequent CRC therapy. The criterion to stop the study early for efficacy (1-sided P value of PFS $< .0131$) was not met in this second interim analysis and the study continued. The final analysis was planned after 344 PFS events; however, because of a higher-than-expected number of patients without events, the statistical analysis plan was amended (after FDA agreement) to perform the final analysis with 330 events, or with a data cutoff of August 31, 2020, whichever came first. The final analysis was based on the cutoff date criterion, when 267 events were observed. For the final analysis, patients with a PFS event were censored at the time of last imaging assessment preceding ≥ 2 missed imaging assessments, at the request of FDA. Considering the α spent in the two interim analyses, the one-sided α remaining at the final analysis was .00248. According to the Hochberg procedure, if the larger of the P values is $\leq .00248$, then both primary end points are statistically significant. However, if the larger of the P values is $> .00248$, then that end point is not statistically significant, and the other primary end point is statistically significant if $P < .00248/2 = .00124$.

Efficacy was assessed in the intention-to-treat (ITT) population. Time-to-event end points of PFS, hPFS, and OS were compared using log-rank test. HR and 95% CI were estimated using a Cox proportional hazards model. KM plots and estimates were obtained. Binary end points of ORR and DCR were compared between groups with the Newcombe-Wilson method. All subgroup analyses were prespecified; there were no post hoc analyses.

Funding and Oversight

Boston Scientific Corporation was the sponsor and provided the device, and collaborated with the steering committee on trial design and execution (collection, analysis, and data interpretation). EPOCH was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. All patients provided informed consent. The Protocol was approved by each institution's review board. An independent data monitoring committee reviewed unmasked safety and trial conduct data every 6 months. The sponsor was blinded to interim analyses. The manuscript was drafted by the first and senior authors, with collaboration and final approval by all authors. All authors vouch for the accuracy of the data. The trial was registered (NCT01483027).

RESULTS

Between May 2012 and August 2020, 428 patients from 95 centers in North America, Europe, and Asia were randomly assigned to chemotherapy with or without TARE; this represents the ITT population. The groups were well balanced (Table 1). Of the 215 patients randomly assigned to the TARE experimental arm, 187 (87%) received TARE, 16 received chemotherapy only, and 12 received no treatment. Of the 213 randomly assigned to the control arm, 191 received second-line chemotherapy and 22 received no therapy (Fig 1; Data Supplement, online only). Median time to TARE was 25 days from random assignment (range, 12-90 days). Median overall follow-up times were 36.0 months (95% CI, 29.6 to 62.2) and 42.3 months (95% CI, 30.0 to 47.8), respectively. Postprogression therapies are summarized in the Data Supplement.

Of the 215 patients assigned to TARE, 176 and 39 exhibited bilobar and unilobar disease, and received TARE before progression, respectively. Of the 176, 133 received same-day bilobar treatment, one received treatment on separate days, 17 received unilobar treatment, and 25 were not treated. Of the 39 unilobar patients, five received bilobar treatment, 29 received unilobar treatment, and five were not treated.

As of the cutoff date, 140 and 127 PFS events were observed in the TARE and chemotherapy groups, respectively. The HR for PFS was 0.69 (95% CI, 0.54 to 0.88; 1-sided $P = .0013$), with a median PFS of 8.0 and 7.2 months, respectively (Table 2, Fig 2). One hundred twenty-nine and 126 hPFS events were observed in the TARE and chemotherapy groups, respectively. The HR for hPFS was 0.59 (95% CI, 0.46 to 0.77; 1-sided $P < .0001$), with a median hPFS of 9.1 (95% CI, 7.8 to 9.7) and 7.2 months (95% CI, 5.7 to 7.6), respectively (Table 2, Fig 3). The HRs for PFS and hPFS, adjusting for the effect of stratification factors, were consistent with the primary analysis results.

The study was declared a success since both primary end points exhibited P values $\leq .00248$. Subsequently, OS, ORR, and DCR were sequentially tested (Table 3). By ITT, median OS was 14.0 (95% CI, 11.8 to 15.5) and 14.4 months (95% CI, 12.8 to 16.4; 1-sided $P = .7229$) (HR 1.07; 95% CI,

TABLE 1. Baseline Characteristics

Characteristic	TARE (n = 215)	Control (n = 213)	Total (N = 428)
Median age, years	63.0	60.0	61.0
Female, No. (%)	80 (37.2)	75 (35.2)	155 (36.2)
Race, No. (%)			
White	164 (76.3)	169 (79.3)	333 (77.8)
African American	9 (4.2)	8 (3.8)	17 (4.0)
Asian	25 (11.6)	17 (8.0)	42 (9.8)
Other	2 (1.0)	1 (0.5)	3 (0.7)
Missing	15 (7.0)	18 (8.5)	33 (7.7)
Region, No. (%)			
North America	63 (29.3)	56 (26.3)	119 (27.8)
Europe	131 (60.9)	145 (68.1)	276 (64.5)
Asia	21 (9.8)	12 (5.6)	33 (7.7)
Performance status, No. (%)			
0	119 (55.3)	133 (62.4)	252 (58.9)
1	95 (44.2)	78 (36.6)	173 (40.4)
Missing	1 (0.5)	2 (0.9)	3 (0.7)
Albumin at baseline, No. (%)			
< Site LLN	28 (13.0)	30 (14.1)	58 (13.6)
≥ Site LLN	182 (84.7)	177 (83.1)	359 (83.9)
Missing	5 (2.3)	6 (2.8)	11 (2.6)
Tumor distribution, No. (%)			
Unilobar	39 (18.1)	40 (18.8)	79 (18.5)
Bilobar	176 (81.9)	173 (81.2)	349 (81.5)
Location of primary at first diagnosis, No. (%)			
Right side	49 (22.8)	61 (28.6)	110 (25.7)
CEA at baseline, ng/mL, No. (%)			
< 35	91 (42.3)	100 (46.9)	191 (44.6)
≥ 35	116 (54.0)	105 (49.3)	221 (51.6)
Missing	8 (3.7)	8 (3.8)	16 (3.7)
Primary tumor in situ, No. (%)			
Yes	83 (38.6)	69 (32.4)	152 (35.5)
Extrahepatic lesions,[a] No. (%)	113 (52.6)	95 (44.6)	208 (48.6)
Extrahepatic disease,[b] No. (%)	147 (68.4)	128 (60.1)	275 (64.3)
KRAS status, No. (%)			
Mutant	100 (46.5)	101 (47.4)	200 (46.7)
Wild-type	115 (53.5)	112 (52.6)	228 (53.3)
Maximum liver lesion size, mm, No. (%)			
< 40	40 (18.6)	41 (19.2)	81 (18.9)
≥ 40	162 (75.3)	142 (66.7)	304 (71.0)
Missing	13 (6.0)	30 (14.1)	43 (10.0)
Liver tumor burden, %, No. (%)			
< 10	124 (57.7)	121 (56.8)	245 (57.2)
≥ 10 to < 25	54 (25.1)	47 (22.1)	101 (23.6)

(continued on following page)

TABLE 1. Baseline Characteristics (continued)

Characteristic	TARE (n = 215)	Control (n = 213)	Total (N = 428)
≥ 25	29 (13.5)	28 (13.1)	57 (13.3)
Missing	8 (3.7)	17 (8.0)	25 (5.8)
No. of lesions, No. (%)			
< 3	25 (11.6)	21 (9.9)	46 (10.7)
3-5	40 (18.6)	38 (17.8)	78 (18.2)
6-10	54 (25.1)	60 (28.2)	114 (26.6)
> 10	88 (40.9)	77 (36.2)	165 (38.6)
Missing	8 (3.7)	17 (8.0)	25 (5.5)
First-line chemotherapy administered, No. (%)			
Irinotecan-based	78 (36.3)	79 (37.1)	157 (36.7)
Oxaliplatin-based	137 (63.7)	134 (62.9)	271 (63.3)
Second-line chemotherapy administered, No. (%)			
Irinotecan-based	130 (60.5)	123 (57.7)	254 (59.3)
Oxaliplatin-based	73 (34.0)	68 (31.9)	140 (32.7)
Time from end of first-line chemotherapy to start of second-line chemotherapy, months, No. (%)			
< 3	94 (43.7)	94 (44.1)	188 (43.9)
≥ 3	102 (47.4)	95 (44.6)	197 (46.0)
Missing	19 (8.8)	24 (11.3)	43 (10.0)
Time from first-line chemotherapy to progression, months, No. (%)			
≥ 6	154 (71.6)	144 (67.6)	298 (69.6)
≥ 10	95 (44.2)	91 (42.7)	186 (43.5)
Missing	7 (3.3)	7 (3.3)	14 (3.3)

Abbreviations: CEA, carcinoembryonic antigen; LLN, lower limit of normal; TARE, transarterial yttrium-90 radioembolization.
[a]Defined as lesions outside the liver such as lung and lymph nodes excluding primary-in-situ.
[b]Defined as lesions outside the liver such as lung and lymph nodes including primary-in-situ.

0.86 to 1.32) for the TARE and chemotherapy groups, respectively (Appendix Fig A1, online only, Data Supplement). ORRs were 34.0% (95% CI, 28.0 to 40.5) and 21.1% (95% CI, 16.2 to 27.1; nominally superior 1-sided $P = .0019$) for the TARE and chemotherapy groups, respectively. DCRs were 79.5% (95% CI, 73.6 to 84.4) and 72.8% (95% CI, 66.4 to 78.3; 1-sided $P = .0626$) for the TARE and chemotherapy groups, respectively. Per-protocol median OS was 15.2 (95% CI, 12.7 to 17.7) and 14.3 months (95% CI, 12.6 to 16.4; 1-sided $P = .3841$; HR 0.96; 95% CI, 0.74 to 1.24) for the TARE and chemotherapy groups, respectively. Forest plots of PFS, hPFS, and OS for prespecified subgroups of interest are provided in the Data Supplement. The PFS benefit of TARE was observed for tumors with *KRAS* mutation (HR 0.57; 95% CI, 0.40 to 0.80), left-side primary tumor (HR 0.65; 95% CI, 0.48 to 0.88), tumor burden 10%-25% (HR 0.43; 95% CI, 0.26 to 0.72), ≤ 3 lesions (HR 0.33; 95% CI, 0.14 to 0.76), addition of biologic agent (HR 0.58; 95% CI, 0.40 to 0.84), and resected primary (HR 0.63; 95% CI, 0.46 to 0.85). The benefit in PFS with the addition of TARE was demonstrated for those with no detectable extrahepatic lesions (HR 0.68; 95% CI, 0.47 to 0.96), as well as those with extrahepatic lesions deemed to be benign findings (HR 0.69; 95% CI, 0.49 to 0.98).

394 patients received at least one study treatment (187 TARE and 207 chemotherapy); these represent the safety analysis cohort. AEs occurring in ≥ 10% are listed in Table 4. There were more grade 3 AEs (68.4%) reported in the TARE group compared with control (49.3%); this may have been influenced by the increased frequency of visits and AE reporting related to TARE procedures. Despite the more frequent reporting of AEs with TARE, exposure to chemotherapy was similar for both groups, with no reduction in dose intensity or ability to receive planned chemotherapy (Data Supplement). TARE-specific grade ≥ 3 AEs included radiation pneumonitis (n = 1), cholecystitis (n = 2), and duodenal ulcer (n = 1). No arterial dissections were reported. There were 12 grade 5 AEs: eight TARE (radiation-induced liver disease, hepatic failure, and portal hypertension at 3, 3, and 5 months, respectively, deemed possibly related; intestinal obstruction, myocardial

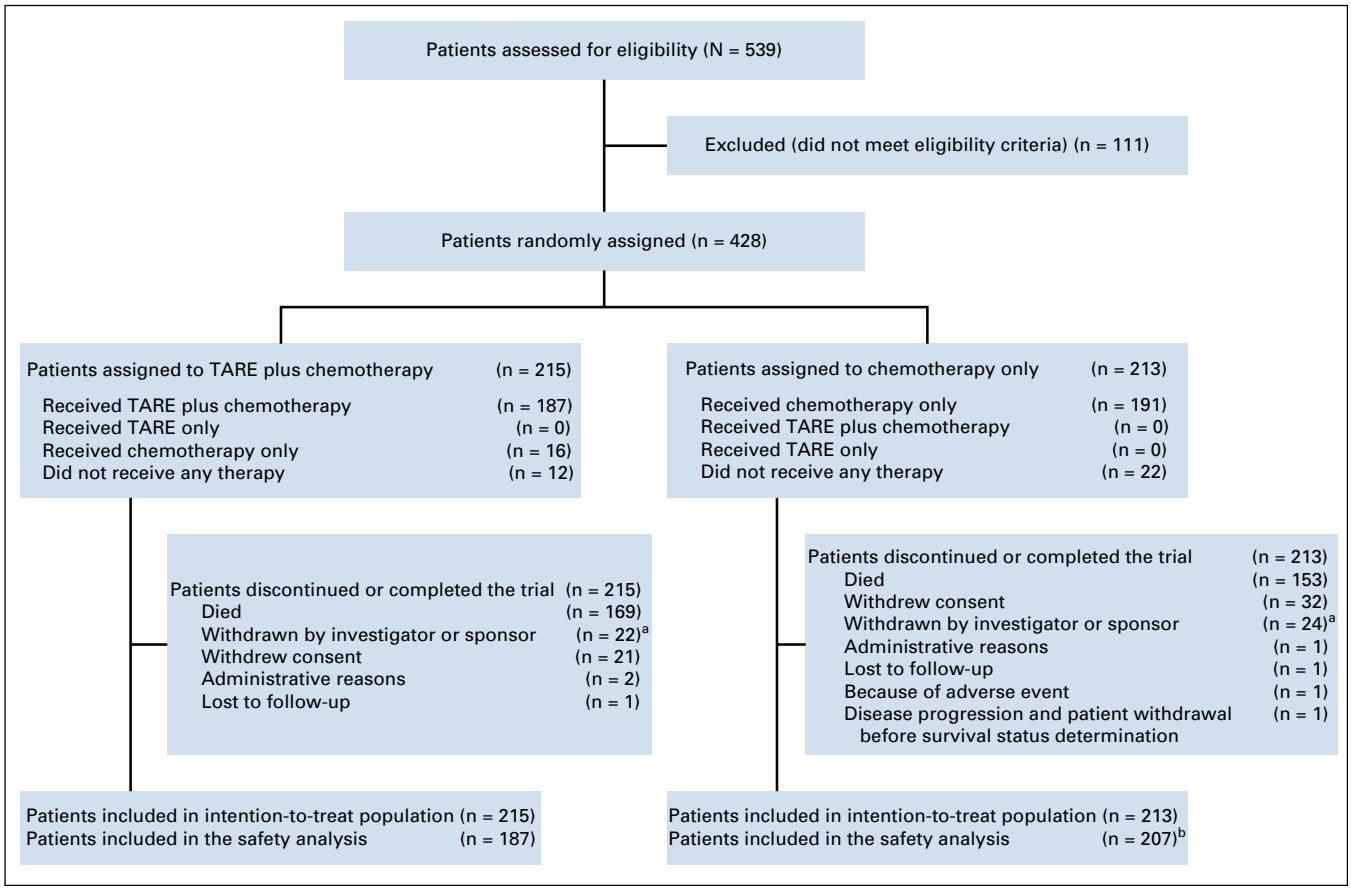

FIG 1. CONSORT diagram showing subject enrollment, treatment allocation, patient disposition, and data analysis. [a]Includes patients on study when study was terminated by sponsor. [b]Includes 16 patients randomly assigned to TARE but who received chemotherapy only. TARE, transarterial yttrium-90 radioembolization.

infarction, pulmonary embolus, and asthenia [n = 2] all deemed unrelated) and four chemotherapy (bowel obstruction, respiratory failure, asthenia deemed unrelated, and pulmonary embolus deemed related). There were no deaths within 30 days of TARE infusion.

DISCUSSION

Over the past decade, the development of TARE for CLM has been based on phase I and uncontrolled phase II studies in the salvage setting, where safety was confirmed and response rates of 20%-40% observed.[11,12] In EPOCH, the primary end points of PFS and hPFS were longer with the addition of TARE to second-line chemotherapy. Moreover, delayed progression was observed for tumors with *KRAS* mutation, left-side primary tumor, hepatic tumor burden of 10%-25%, ≤ 3 lesions, addition of a biologic agent, and resected primary.

In accordance with contemporary thinking on trial design in second-line CLM, the primary end point was PFS.[13] PFS as an end point generates a larger number of events, is not influenced by postprogression treatment, and carries less vulnerability to competing causes of death when compared with OS.[14] With the addition of TARE to chemotherapy, the median PFS was increased from 7.2 to 8.0 months, whereas the median hPFS was increased from 7.2 to 9.1 months. The 2-month benefit in hPFS is comparable to observations made in multiple second-line studies using new agents and strategies.[15-17] In the context of limited available therapies after second line, this is a clinically meaningful benefit, particularly since TARE did not compromise subsequent full-dose, standard-of-care chemotherapy. Meta-analyses have demonstrated that a HR < 0.77 in the first-line setting infers a survival benefit; there are no such data in the second-line setting.[13] This study was not designed or powered for OS, and higher rates of subsequent local therapy including TARE occurred in the control arm; these are confounding factors of OS that limit our ability to draw conclusions. With these caveats, no survival advantage with TARE was demonstrated by ITT or per-protocol.

The understanding and treatment of CRC evolved over the course of this study. Colorectal tumors with *KRAS*, *NRAS*, or *BRAF* mutations, as well as those arising from the right

TABLE 2. Efficacy Analyses

Outcome	TARE (n = 215)	Control (n = 213)
PFS[a]		
Total events, No. (%)	140 (65.1)	127 (59.6)
Median PFS, months (95% CI)	8.0 (7.2 to 9.2)	7.2 (5.7 to 7.6)
PFS rate at 6/12 month (95% CI)	65.2% (58.0 to 71.5)	55.4% (47.2 to 62.8)
	25.8% (18.9 to 33.1)	13.2% (7.5 to 20.5)
HR (95% CI)	0.69 (0.54 to 0.88)	
Superiority log-rank 1-sided *P*	**.0013**	
HPFS[a]		
Total events, No. (%)	129 (60.0)	126 (59.2)
Median HPFS, months (95% CI)	9.1 (7.8 to 9.7)	7.2 (5.7 to 7.6)
HR (95% CI)	0.59 (0.46 to 0.77)	
Superiority log-rank 1-sided *P*	**< .0001**	

NOTE. Bold values are statistically significant.

Abbreviations: HPFS, hepatic progression-free survival; HR, hazard ratio; PD, progressive disease; PFS, progression-free survival; TARE, transarterial yttrium-90 radioembolization.

[a]Patients who received subsequent metastatic colorectal cancer therapy before their last tumor assessment or PD or hepatic PD or death were censored at their last tumor assessment before subsequent metastatic colorectal cancer therapy. Additionally, patients who had PD or hepatic PD or death immediately after ≥ 2 missed visits were censored at their last tumor assessment before the two missed visits.

colon, do not benefit from the addition of epidermal growth factor receptor (EGFR) inhibitors to systemic therapy.[18-20] *BRAF* and *NRAS* status was not assessed in EPOCH. Studies report the incidence of *BRAF* ranging from 10% to 22%, and *NRAS* in 5%-8% of CRCs.[21-23] Forty-seven percent of EPOCH patients had a *KRAS* mutation. In these patients, improvement in PFS appeared to be more pronounced with the addition of TARE, thus providing an option for tumors with an unmet need.

Patients in the TARE arm who received a biologic agent during second-line therapy fared better. While 53% had *KRAS* wild-type tumor, only 17% during first-line and 5% during the second-line received an EGFR inhibitor. The addition of EGFR inhibition for tumors without a *KRAS*, *NRAS*, or *BRAF* mutation may have resulted in better outcomes.[23] Because the HR for PFS in *KRAS* wild-type tumor was 0.79, it is uncertain whether the addition of TARE to chemotherapy and EGFR inhibition would have provided a significant prolongation of PFS.

Right-side colorectal tumors portend a worse overall prognosis as a result of genetic, epigenetic, transcriptomic, and proteomic factors.[24,25] The addition of glass-based TARE to standard chemotherapy in the second-line setting did not yield PFS benefit for metastases arising from a right-side colon tumor. This is in contrast to the findings of FOXFIRE, SIRFLOX, and FOXFIRE-Global, reporting no difference in the OS or PFS with the addition of resin-based TARE to standard chemotherapy in first line.[7,26] However, in the patients with CLM from a right-side primary tumor, the OS was improved with the addition of resin-based TARE, although the HR for progression failed to reach significance.[27] While the discrepancy among the findings in EPOCH and SIRFLOX-FOXFIRE for metastases from right-side colon tumors may be related to different practice patterns, it suggests different optimal timepoints for TARE in the continuum of care for metastases based on left- versus right-side tumors.

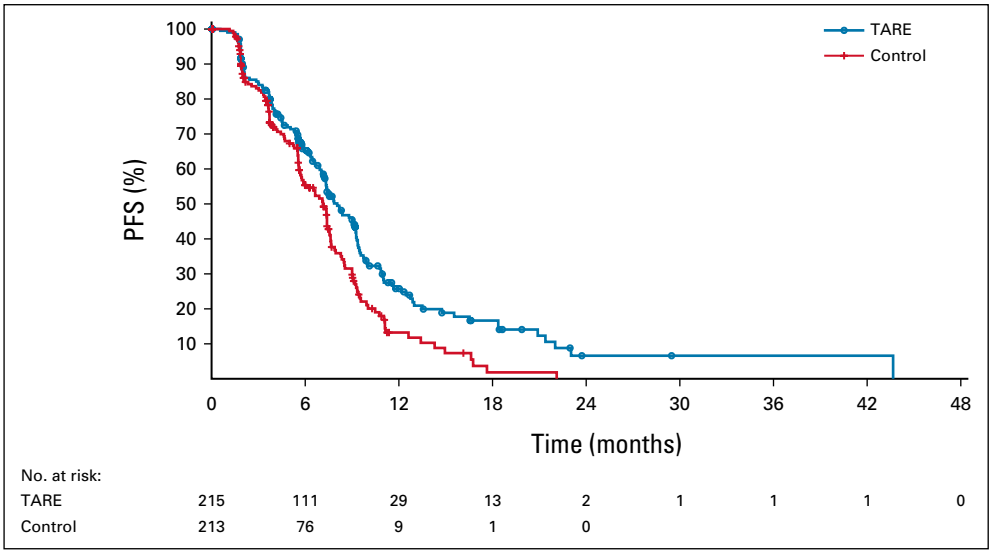

FIG 2. Kaplan-Meier analysis of overall PFS for TARE plus chemotherapy versus chemotherapy in the intention-to-treat population. PFS, progression-free survival; TARE, transarterial yttrium-90 radioembolization.

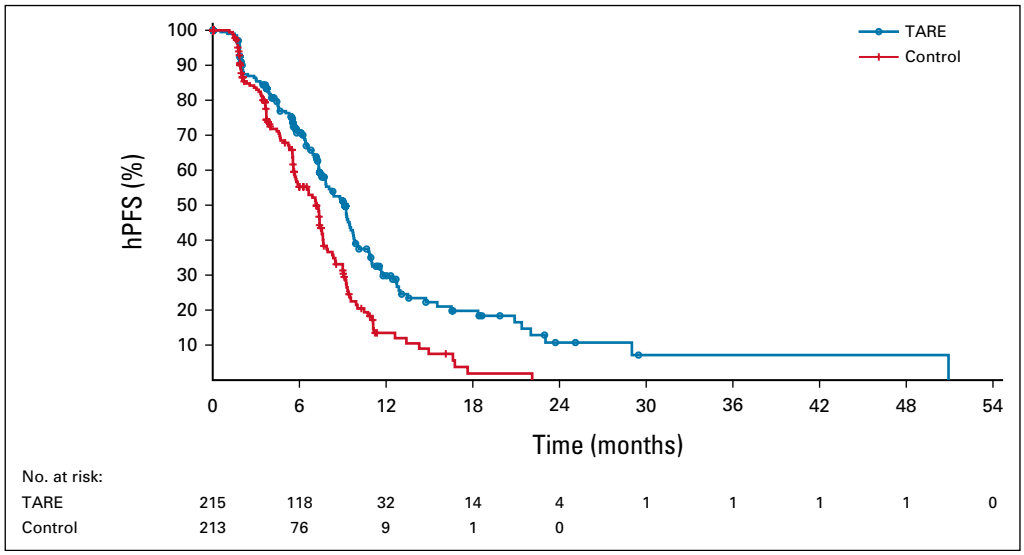

FIG 3. Kaplan-Meier analysis of hPFS for TARE plus chemotherapy versus chemotherapy in the intention-to-treat population. hPFS, hepatic progression-free survival; TARE, transarterial yttrium-90 radioembolization.

The inclusion of patients with extrahepatic disease, even if limited, poses a challenge for any locoregional therapy trial. Furthermore, the resection of asymptomatic primary tumors in the setting of incurable metastatic disease is controversial. A PFS improvement was observed in EPOCH patients with resected primaries. Patients with clinical or pathologic evidence of extrahepatic metastases were excluded. Patients with indeterminate extrahepatic lesions demonstrated a HR for PFS similar to the cohort without indeterminate extrahepatic lesions. Every effort should be made to distinguish patients with benign extrahepatic lesions from those with true metastatic disease; patients in the former group may benefit from a locoregional therapy such as TARE.

There were more grade 3 AEs reported in the TARE arm. Although this observation may have been related to combining radiotherapy with chemotherapy, there were additional visits and AEs recorded periprocedurally with TARE procedures. Despite the more frequent AEs reported,

TABLE 3. ORR and DCR

Outcome	TARE (n = 215)	Control (n = 213)
Best overall response,[a] No. (%)		
CR	2 (0.9)	3 (1.4)
PR	71 (33.0)	42 (19.7)
SD	98 (45.6)	110 (51.6)
PD	27 (12.6)	27 (12.7)
Not evaluable or missing	0/17 (7.9)	1 (0.5)/30 (14.1)
ORR		
CR plus PR, No. (%) (95% CI)	73 (34.0) (28.0 to 40.5)	45 (21.1) (16.2 to 27.1)
Difference (95% CI)	12.8% (4.0 to 21.4)	
Superiority 1-sided *P*	.0019	
DCR		
CR plus PR plus SD, No. (%) (95% CI)	171 (79.5) (73.6 to 84.4)	155 (72.8) (66.4 to 78.3)
Difference (95% CI)	6.8% (–1.6 to 15.1)	
Superiority 1-sided *P*	.0626	

Abbreviations: CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TARE, transarterial yttrium-90 radioembolization.

[a]Best overall response is the best response a patient had following random assignment, but up to and including the first progression or the last postbaseline tumor assessment in the absence of the first progression. Tumor response assessments after the start of subsequent metastatic colorectal cancer therapy are excluded from the analysis of best overall response.

TABLE 4. Treatment-Emergent Adverse Events

	TARE (n = 187)		Control (n = 207)	
Safety Population	**All TEAEs,[a] No. (%) [m]**	**Grade ≥ 3,[a] No. (%) [m]**	**All TEAEs,[a] No. (%) [m]**	**Grade ≥ 3,[a] No. (%) [m]**
Any TEAEs[b]	181 (96.8) [2,789]	128 (68.4) [400]	194 (93.7) [2,555]	102 (49.3) [214]
Fatigue	88 (47.1) [197]	16 (8.6) [18]	93 (44.9) [199]	6 (2.9) [6]
Nausea	84 (44.9) [156]	4 (2.1) [7]	89 (43.0) [173]	1 (0.5) [1]
Diarrhea	59 (31.6) [123]	9 (4.8) [13]	101 (48.8) [212]	9 (4.3) [10]
Neutropenia	59 (31.6) [156]	41 (21.9) [93]	49 (23.7) [91]	28 (13.5) [39]
Constipation	60 (32.1) [81]	—	46 (22.2) [72]	—
Abdominal pain	64 (34.2) [109]	12 (6.4) [13]	37 (17.9) [43]	5 (2.4) [5]
Decreased appetite	44 (23.5) [58]	—	45 (21.7) [60]	—
Vomiting	42 (22.5) [78]	5 (2.7) [8]	34 (16.4) [51]	4 (1.9) [4]
Alopecia	23 (12.3) [27]	—	42 (20.3) [46]	—
Pyrexia	39 (20.9) [55]	—	19 (9.2) [22]	—
Mucosal inflammation	19 (10.2) [39]	—	41 (19.8) [84]	—
Neuropathy peripheral	24 (12.8) [48]	—	34 (16.4) [54]	—
Thrombocytopenia	35 (18.7) [68]	4 (2.1) [6]	18 (8.7) [32]	3 (1.4) [3]
Stomatitis	23 (12.3) [39]	—	32 (15.5) [70]	—
Asthenia	27 (14.4) [75]	7 (3.7) [7]	18 (8.7) [49]	3 (1.4) [4]
Epistaxis	15 (8.0) [20]	—	25 (12.1) [44]	—
Cough	15 (8.0) [16]	—	22 (10.6) [23]	—
Dyspnea	16 (8.6) [16]	—	20 (9.7) [26]	—
Hypertension	19 (10.2) [23]	6 (3.2) [6]	18 (8.7) [42]	7 (3.4) [7]
Anemia	25 (13.4) [37]	13 (7.0) [14]	11 (5.3) [15]	2 (1.0) [2]
Peripheral sensory neuropathy	19 (10.2) [25]	—	17 (8.2) [45]	—
Upper abdominal pain	24 (12.8) [27]	—	8 (3.9) [9]	—
Dyspepsia	23 (12.3) [24]	—	11 (5.3) [18]	—

Abbreviations: m, number of events; TEAE, treatment-emergent adverse event; TARE, transarterial yttrium-90 radioembolization.

[a]Reported are TEAEs that occurred in at least 10% of patients in any group. TEAEs with grade ≥ 3 among these events occurring in ≥ 2% of patients are reported.

[b]Refers to adverse events that were not present at the initiation of chemotherapy or angiogram or worsened in severity following the first dose of chemotherapy or date of angiogram, and occurred up until disease progression by RECIST 1.1, investigator assessment, or 30 days after discontinuation of study therapy, whichever comes first.

exposure to chemotherapy was similar for both groups, with no reduction in dose intensity or ability to receive planned chemotherapy. Previous first-line TARE studies used chemotherapy dose reduction to minimize hepatic toxicity.[7] In EPOCH, patients were able to receive full-dose chemotherapy per standard of care despite the higher rate of reporting hematologic events; these findings were likely because of the combination of radiotherapy-chemotherapy, as well as increased reporting in the periprocedural period. Other studies have investigated radiation dose combined with systemic therapy. One dose-escalation trial using full dose capecitabine did not reach dose-limiting toxicity at 170 Gy.[12] In a contemporary study, a dose-response relationship was observed when using glass-based TARE in CLM.[28] Recent refinements in TARE dosimetry including radiation segmentectomy have translated into higher response rates without added toxicity.[29]

This is the first arterial radiotherapy device to impart a delay of overall progression in a universally systemic disease using level I evidence. It also confirms the ability of interventional therapy trials to achieve uniform technical standardization across international sites, suggesting generalizability of the findings. The trial patient population is reflective of real-life settings, also increasing clinical applicability. Median PFS and hPFS are static, one-time values at the 50% percentile; the HR improvements with TARE of 0.69 and 0.59 reflect the clinical benefit along the entire continuum of the KM curve, translating into a 31% and 41% risk reduction of overall and hepatic progression, respectively. Weaknesses include the dampening of treatment effect by the 13% that did not receive planned TARE, as well as operational challenges of lengthy device trials (8 years) in a rapidly evolving treatment landscape. Postprogression therapies make OS studies in second-line

challenging; future trials will need to adjust for confounding factors of OS. An imbalance in AE reporting was unavoidable, given the additional visits associated with TARE procedures. The use of Choi or mRECIST criteria may have better captured the local radiotherapeutic effect of TARE.[30] Finally, implementation of lobar (rather than bilobar) TARE, enhanced patient selection, and personalized dosimetry will likely improve safety profile and outcomes.

In conclusion, the addition of TARE to systemic therapy improved PFS and hPFS in the second-line setting for CLM, with both groups receiving full-dose intensity second-line chemotherapy. Further studies are needed to identify the optimal second-line patient population that would benefit from TARE.

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DATA SHARING STATEMENT

Boston Scientific may share patient-level data from registered clinical trials with qualified health care practitioners or academic researchers in response to a formal clinical research proposal, and when the request is in the same therapeutic area as the original study. Clinical trial data may be shared when not in conflict with all other applicable regulations, laws, or Boston Scientific policies and/or written agreements. Data may be provided for regulated and approved product 6 months following manuscript publication and after the posting of the study results on clinicaltrials.gov. If made available, data will be accessible for 12-18 months following the end of the trial. There will be limited data availability for trials before January 1, 2018. Boston Scientific will disposition requests consistent with these and other internal company criteria for data sharing. Data sharing requests can be made at: https://www.bostonscientific.com/en-US/data-sharing-requests/data-sharing-request-submission-form.html.

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71:209-249, 2021
2. Uhlig J, Lukovic J, Dawson LA, et al: Locoregional therapies for colorectal cancer liver metastases: Options beyond resection. Am Soc Clin Oncol Ed Book 41: 133-146, 2021
3. Salem R, Thurston KG: Radioembolization with 90Yttrium microspheres: A state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: Technical and methodologic considerations. J Vasc Interv Radiol 17:1251-1278, 2006
4. Mulcahy MF, Lewandowski RJ, Ibrahim SM, et al: Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. Cancer 115:1849-1858, 2009
5. Salem R, Johnson GE, Kim E, et al: Yttrium-90 radioembolization for the treatment of solitary, unresectable hepatocellular carcinoma: The LEGACY study. Hepatology 74:2342-2352, 2021
6. Hickey R, Lewandowski RJ, Prudhomme T, et al: 90Y radioembolization of colorectal hepatic metastases using glass microspheres: Safety and survival outcomes from a 531-patient multicenter study. J Nucl Med 57:665-671, 2016
7. Wasan HS, Gibbs P, Sharma NK, et al: First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): A combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol 18: 1159-1171, 2017
8. Chauhan N, Mulcahy MF, Salem R, et al: TheraSphere yttrium-90 glass microspheres combined with chemotherapy versus chemotherapy alone in second-line treatment of patients with metastatic colorectal carcinoma of the liver: Protocol for the EPOCH phase 3 randomized clinical trial. JMIR Res Protoc 8:e11545, 2019
9. Padia SA, Lewandowski RJ, Johnson GE, et al: Radioembolization of hepatic malignancies: Background, quality improvement guidelines, and future directions. J Vasc Interv Radiol 28:1-15, 2017
10. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009
11. Abbott AM, Kim R, Hoffe SE, et al: Outcomes of therasphere radioembolization for colorectal metastases. Clin Colorectal Cancer 14:146-153, 2015
12. Hickey R, Mulcahy MF, Lewandowski RJ, et al: Chemoradiation of hepatic malignancies: Prospective, phase 1 study of full-dose capecitabine with escalating doses of yttrium-90 radioembolization. Int J Radiat Oncol Biol Phys 88:1025-1031, 2014
13. Buyse M, Burzykowski T, Carroll K, et al: Progression-free survival is a surrogate for survival in advanced colorectal cancer. J Clin Oncol 25:5218-5224, 2007
14. Saad ED, Buyse M: Statistical controversies in clinical research: End points other than overall survival are vital for regulatory approval of anticancer agents. Ann Oncol 27:373-378, 2016
15. Giantonio BJ, Catalano PJ, Meropol NJ, et al: Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 25:1539-1544, 2007
16. Peeters M, Price TJ, Cervantes A, et al: Final results from a randomized phase 3 study of FOLFIRI {+/-} panitumumab for second-line treatment of metastatic colorectal cancer. Ann Oncol 25:107-116, 2014
17. Cremolini C, Antoniotti C, Rossini D, et al: Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): A multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol 21:497-507, 2020
18. Brule SY, Jonker DJ, Karapetis CS, et al: Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. Eur J Cancer 51:1405-1414, 2015
19. Tejpar S, Stintzing S, Ciardiello F, et al: Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: Retrospective analyses of the CRYSTAL and FIRE-3 trials. JAMA Oncol 3:194-201, 2017
20. Venook AP, Niedzwiecki D, Lenz HJ, et al: Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type Advanced or metastatic colorectal cancer: A randomized clinical trial. JAMA 317:2392-2401, 2017
21. Gonsalves WI, Mahoney MR, Sargent DJ, et al: Patient and tumor characteristics and BRAF and KRAS mutations in colon cancer, NCCTG/Alliance N0147. J Natl Cancer Inst 106:dju106, 2014
22. Loree JM, Pereira AAL, Lam M, et al: Classifying colorectal cancer by tumor location rather than sidedness highlights a continuum in mutation profiles and consensus molecular subtypes. Clin Cancer Res 24:1062-1072, 2018
23. Laurent-Puig P, Cayre A, Manceau G, et al: Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer. J Clin Oncol 27:5924-5930, 2009
24. Lee MS, Menter DG, Kopetz S: Right versus left colon cancer biology: Integrating the consensus molecular subtypes. J Natl Compr Canc Netw 15:411-419, 2017
25. Liang L, Zeng JH, Qin XG, et al: Distinguishable prognostic signatures of left- and right-sided colon cancer: A study based on sequencing data. Cell Physiol Biochem 48:475-490, 2018
26. van Hazel GA, Heinemann V, Sharma NK, et al: SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. J Clin Oncol 34:1723-1731, 2016
27. Gibbs P, Heinemann V, Sharma NK, et al: Effect of primary tumor side on survival outcomes in untreated patients with metastatic colorectal cancer when selective internal radiation therapy is added to chemotherapy: Combined analysis of two randomized controlled studies. Clin Colorectal Cancer 17:e617-e629, 2018
28. Alsultan AA, van Roekel C, Barentsz MW, et al: Dose-response and dose-toxicity relationships for yttrium-90 glass radioembolization in patients with colorectal cancer liver metastases. J Nucl Med 62:1616-1623, 2021
29. Padia SA, Johnson GE, Agopian VG, et al: Yttrium-90 radiation segmentectomy for hepatic metastases: A multi-institutional study of safety and efficacy. J Surg Oncol 123:172-178, 2021
30. Dudeck O, Zeile M, Reichardt P, et al: Comparison of RECIST and Choi criteria for computed tomographic response evaluation in patients with advanced gastrointestinal stromal tumor treated with sunitinib. Ann Oncol 22:1828-1833, 2011

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Radioembolization With Chemotherapy for Colorectal Liver Metastases: A Randomized, Open-Label, International, Multicenter, Phase III Trial

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APPENDIX

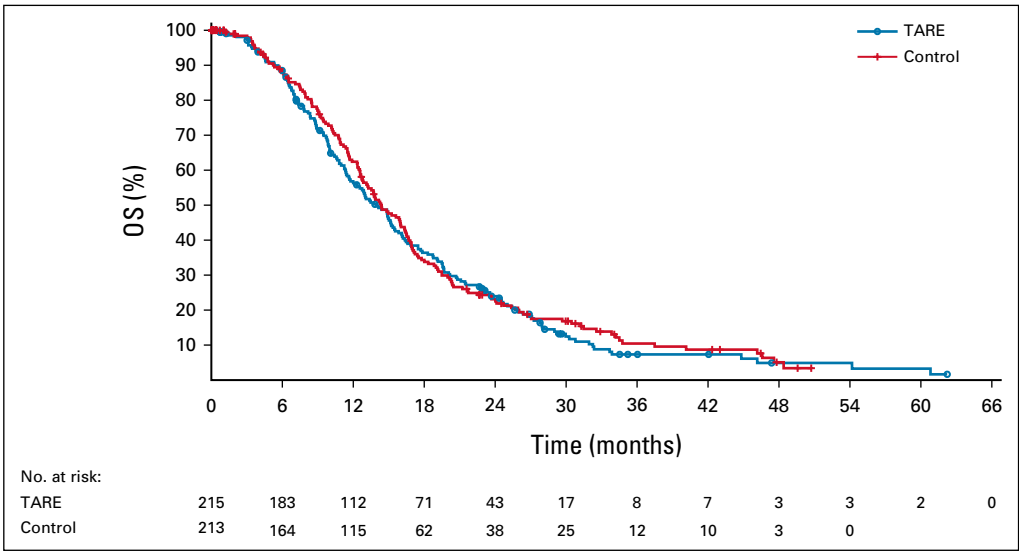

FIG A1. Kaplan-Meier analysis of OS for transarterial yttrium-90 radioembolization plus chemotherapy versus chemotherapy in the intention-to-treat population. OS, overall survival; TARE, transarterial yttrium-90 radioembolization.