Title

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Clinical Trial Results

A Phase II, Randomized, Double-Blind, Placebo-Controlled Study of Simtuzumab in Combination with FOLFIRI for the Second-Line Treatment of Metastatic *KRAS* Mutant Colorectal Adenocarcinoma

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Trial Information

- **ClinicalTrials.gov Identifier**: NCT01479465
- **Sponsor(s)**: Gilead Sciences, Inc., Foster City, California, USA
- **Principal Investigator**: J. Randolph Hecht
- **IRB Approved**: Yes

Lessons Learned

- The safety profile in the patient groups who received FOLFIRI and simtuzumab did not differ from that in the FOLFIRI and placebo group.
- The addition of simtuzumab to chemotherapy with FOLFIRI does not improve clinical outcomes in patients with metastatic *KRAS* mutant colorectal carcinoma.

Abstract

Background. Simtuzumab, a humanized IgG4 monoclonal antibody to lysyl oxidase-like 2 (LOXL2), blocks desmoplastic reaction in colorectal carcinoma (CRC) cells in vitro.

Methods. Patients with metastatic Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutant CRC were randomized to receive second-line 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) with either 200 or 700 mg simtuzumab or placebo every 2 weeks in cycles of 28 days. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and safety were assessed.

Results. In total, 249 patients were randomized and treated with FOLFIRI/simtuzumab 700 mg ($n = 84$), FOLFIRI/simtuzumab 200 mg ($n = 85$), and FOLFIRI/placebo ($n = 80$). After a median follow-up of 5.1, 3.8, and 5.5 months, respectively, median PFS for each of the respective treatment groups was 5.5 months (adjusted HR [95% CI], p value versus placebo; 1.32 [0.92, 1.89]; $p = .10$), 5.4 months (1.45 [1.01, 2.06]; $p = .04$), and 5.8 months. Median OS was 11.4 months (1.23 [0.80, 1.91]; $p = .25$), 10.5 months (1.50 [0.98, 2.30]; $p = .06$), and 16.3 months, respectively. ORR was 11.9%, 5.9%, and 10%, respectively. Simtuzumab was tolerable in metastatic *KRAS* mutant CRC patients.

Conclusion. The addition of simtuzumab to FOLFIRI did not improve clinical outcomes in patients with metastatic *KRAS* mutant CRC. ***The Oncologist*** 2017;22:243–e23

Discussion

Stroma in the tumor environment is associated with higher numbers of activated fibroblasts, which contribute to the desmoplastic reaction. Tumor-associated activated fibroblasts secrete oncogenic growth factors, produce extracellular matrix (ECM), and promote epithelial cell transformation. Lysyl oxidase-like 2 (LOXL2), an extracellular matrix enzyme that remodels ECM, is thought to contribute to the maintenance of the pathologic stromal microenvironment in cancer and fibrotic diseases and to promote tumor angiogenesis and metastatic progression. LOXL2 is expressed in desmoplastic tumors, including CRC, with no expression in the adjacent nonneoplastic areas. Simtuzumab, a humanized IgG4 monoclonal antibody to LOXL2, inhibits its enzymatic activity.

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Table 1. The efficacy endpoints (FAS analysis set)

Endpoint	Simtuzumab 700 mg/FOLFIRI $n = 84$	Simtuzumab 200 mg/FOLFIRI $n = 85$	Placebo/FOLFIRI $n = 80$
PFS[a]			
KM estimate, months, median (95% CI)	5.5 (4.0, 7.1)	5.4 (3.4, 5.6)	5.8 (4.9, 9.0)
Adjusted HR versus placebo (95% CI)	1.32 (0.92, 1.89)	1.45 (1.01, 2.06)	—
p value versus placebo[b]	.1042	.0395	—
OS			
KM estimate, months, median (95% CI)	11.4 (9.7, 15.6)	10.5 (9.2, 12.6)	16.3 (12.0, 19.5)
Adjusted HR versus placebo (95% CI)	1.23 (0.80, 1.91)	1.50 (0.98, 2.30)	—
p value versus placebo[b]	.2451	.0607	—
ORR[a]			
CR + PR, *n* (%)	10 (11.9)	5 (5.9)	8 (10.0)
Difference in ORR from placebo (95% CI), %	2.0 (−8.1, 11.9)	−4.1 (−13.3, 4.6)	—
p value versus placebo[c]	.6904	.3311	—

[a]Stratified primary analysis per investigator assessment. The results per Independent Review Committee were similar to those obtained by investigator assessment. [b]*p* values based on stratified two-sided log-rank test. [c]*p* values based on Cochran–Mantel–Haenszel test adjusted for stratification factors. Abbreviations: CI, confidence interval; CR, complete response; FAS, full analysis set (all patients randomized and treated with ≥1 dose of study drug); HR, hazard ratio; KM, Kaplan–Meier; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

In preclinical studies with antibody precursors to simtuzumab, inhibition of LOXL2 expression reduced the number of activated fibroblasts, decreased ECM deposition, inhibited angiogenesis, and prevented tumor cell invasion and metastases. In a phase I study in patients with advanced solid tumors, simtuzumab reduced the size of several tumors in some patients.

We assessed the additive efficacy of simtuzumab in a multicenter, randomized, double-blind, placebo-controlled, phase II study of simtuzumab or placebo in combination with FOLFIRI as a second-line therapy in patients with metastatic *KRAS*-mutant adenocarcinoma of the colon or rectum not amenable to complete surgical resection, who previously failed fluoropyrimidine and oxaliplatin therapy (ClinicalTrials.gov #NCT01479465). Eligible patients had metastatic disease; Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2; adequate bone marrow, hepatic, and renal function; and estimated life expectancy >3 months. Patients were randomized 1:1:1 to receive intravenous FOLFIRI in combination with 700 mg simtuzumab, 200 mg simtuzumab, or placebo every 2 weeks in cycles of 28 days until disease progression or unacceptable toxicity; randomization was stratified by ECOG PS 0 versus >0. From December 2011 to March 2014, 255 patients were enrolled and 249 patients received at least 1 cycle of study drug, with a median number of 6 cycles. Overall, 231 (90.6%) patients discontinued study drug, mainly due to disease progression (185 [72.5%]) and adverse events (12 [4.7%]). The majority of patients were male (128/249, 51.4%) and white (212/249, 85.1%), with a mean (range) age of 60.5 (22.0–85.0) years and a mean 20.3 months from diagnosis. A sequential stepwise hypothesis and a Hochberg testing procedure were used to compare between the two simtuzumab dosing groups versus placebo for PFS, OS, and ORR. The efficacy analyses failed to demonstrate improvement in clinical endpoints upon the addition of simtuzumab to FOLFIRI chemotherapy (Table 1). Results from additional sensitivity analyses were consistent with the primary analyses. The safety profile in the patient groups who received FOLFIRI and simtuzumab did not differ from that in the FOLFIRI and placebo group. Among seven adverse events that led to death, a case of febrile neutropenia was deemed related to treatment with FOLFIRI.

Trial Information	
Disease	Colorectal cancer
Stage of disease/treatment	Metastatic/Advanced
Prior therapy	First-line oxaliplatin- and fluoropyrimidine-containing regimen
Type of study - 1	Phase II
Type of study - 2	Randomized
ORR	Difference in ORR from placebo, stratified (primary) analysis was 2.0% for the simtuzumab 700 mg arm (p = .69), and −4.1% for the simtuzumab 200 mg arm (p = .33).
PFS	The median PFS was 5.5 months, (HR 1.32, 0.92, 1.89; p = .10) in the 700 mg simtuzumab arm, 5.4 months (HR 1.45, 1.01, 2.06, p = .04) in the 200 mg simtuzumab arm, and 5.8 month in the control arm

Primary endpoint	Progression-free survival
Secondary endpoint	Overall response rate
Secondary endpoint	Overall survival
Secondary endpoint	Safety

Additional details of endpoints or study design

Patients had to have measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1, defined with all of following criteria: (a) lesions accurately measured in at least one dimension, (b) longest diameter in the plane of measurement was recorded, and (c) minimum size of 10 mm if computed tomography slice thickness $\leq$5 mm; if thickness was $>$5 mm, then the minimum size of measurable lesions was twice the slice thickness. Patients were excluded if they had more than one prior chemotherapy regimen for stage IV/metastatic colorectal cancer; underwent an experimental medical treatment within 30 days prior to study entry; received an antitumor therapy (chemotherapy, antibody therapy, molecular targeted therapy, retinoid therapy, hormonal therapy) within 21 days prior to randomization; or had cerebral metastases, uncontrolled hypertension, coronary heart disease, liver disease, or uncontrolled infection. Treatments were administered on day 1 and 15 of each 28-day cycle. Simtuzumab or placebo was given by IV infusion over 30 minutes. FOLFIRI consisted of 200 mg/m^2 leucovorin or 400 mg/m^2 dl-leucovorin administered as a 2-hour infusion; 180 mg/m^2 irinotecan given as a 90-minute infusion in 500 mL dextrose 5% via a Y-connector; and 400 mg/m^2 fluorouracil bolus followed by a 46-hour infusion of 2,400 mg/m^2 fluorouracil. Efficacy was analyzed in all randomized patients who received at least one dose of study drug (full analysis set [FAS]) based on investigator assessment. Safety analysis set included patients in the FAS population grouped for analyses with treatment assignments designated according to the actual study drug received. Safety assessments included the incidence of adverse events (AEs), infusion site reactions, and clinically relevant changes in laboratory values and vital signs. AEs were coded according to MedDRA version 17.1 and graded per National Cancer Institute Common Toxicity Criteria (CTCAE version 4.03). Overall response rate (ORR) was assessed by the investigator per RECIST v1.1 as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The difference in PFS and OS from placebo was assessed using Kaplan–Meier methods and the stratified log-rank test, adjusted for the stratification factor ECOG 0 or $>$0 at randomization. Cochran–Mantel–Haenszel test was used for calculating difference in ORR from placebo. A sequential stepwise hypothesis and a Hochberg testing procedure were used to compare between simtuzumab dosing groups versus placebo for PFS, OS, and ORR, per investigator assessment. A number of sensitivity analyses for PFS, OS, and ORR were also performed to confirm the results of primary analyses. A total of 185 PFS events had to be observed in this study to detect a hazard ratio of 0.6 with approximately 90% power at a two-sided 0.05 significance level based on Hochberg procedure to claim that at least one of the simtuzumab treatment groups improved PFS significantly compared with placebo. The estimated sample size was 255 patients.

Investigator's analysis	Level of activity did not meet planned endpoint.

Drug Information Control Arm	
Drug 1	
Generic/Working name	Folinic acid (leucovorin)
Drug type	Small molecule
Drug class	Antimetabolite
Dose	200 mg/m^2
Route	IV over 2 hours
Schedule of administration	Day 1 and 15 of each 28-day cycle
Drug 2	
Generic/working name	5-FU
Drug type	Small molecule
Drug class	Antimetabolite
Dose	2,400 mg/m^2 (bolus 400 mg/m^2)
Route	Continuous intravenous infusion (CIV) over 46 hours
Schedule of administration	Day 1 and 15 of each 28-day cycle
Drug 3	
Generic/working name	Irinotecan
Drug type	Small molecule
Drug class	Inhibitor of topoisomerase I
Dose	180 mg/m^2
Route	IV over 1.5 hours
Schedule of administration	Day 1 and 15 of each 28-day cycle

Drug Information Experimental Arm A: Simtuzumab 200 mg	
Drug 1	
Generic/working name	Simtuzumab (GS-6624)
Company name	Gilead Sciences, Inc.
Drug type	Antibody
Drug class	Inhibitor of lysyl oxidase-like 2 enzyme
Dose	200 mg per flat dose
Route	IV
Schedule of administration	Day 1 and 15 of each 28-day cycle
Drug 2	
Generic/working name	Leucovorin
Drug type	Small molecule
Drug class	Antimetabolite
Dose	200 mg/m^2
Route	IV over 2 hours
Schedule of administration	Day 1 and 15 of each 28-day cycle
Drug 3	
Generic/working name	5-FU
Drug type	Small molecule
Drug class	Antimetabolite
Dose	2,400 mg/m^2 (bolus 400 mg/m^2)
Route	Continuous intravenous infusion (CIV) over 46 hours
Schedule of administration	Day 1 and 15 of each 28-day cycle
Drug 4	
Generic/working name	Irinotecan
Drug type	Small molecule
Drug class	Inhibitor of topoisomerase I
Dose	180 mg/m^2
Route	IV over 1.5 hours
Schedule of administration	Day 1 and 15 of each 28-day cycle

Drug Information Experimental Arm B: Simtuzumab 700 mg	
Drug 1	
Generic/working name	Simtuzumab (GS-6624)
Company name	Gilead Sciences, Inc.
Drug type	Antibody
Drug class	Inhibitor of lysyl oxidase-like 2 enzyme
Dose	700 mg per flat dose
Route	IV
Schedule of administration	Day 1 and 15 of each 28-day cycle
Drug 2	
Generic/working name	Leucovorin
Drug type	Small molecule
Drug class	Antimetabolite
Dose	200 mg/m^2
Route	IV over 2 hours
Schedule of administration	Day 1 and 15 of each 28-day cycle

Drug 3	
Generic/working name	5-FU
Drug type	Small molecule
Drug class	Antimetabolite
Dose	2,400 mg/m^2 (bolus 400 mg/m^2)
Route	Continuous intravenous infusion (CIV) over 46 hours
Schedule of administration	Day 1 and 15 of each 28-day cycle
Drug 4	
Generic/working name	Irinotecan
Drug type	Small molecule
Drug class	Inhibitor of topoisomerase I
Dose	180 mg/m^2
Route	IV over 1.5 hours
Schedule of administration	Day 1 and 15 of each 28-day cycle

Patient Characteristics	
Number of patients, male	128
Number of patients, female	121
Stage	Advanced, metastatic, stage IV
Age	Median (range), years: 700 mg simtuzumab, 61 (22–78); 200 mg simtuzumab, 64 (31–83); placebo, 60.5 (32–85)
Number of prior systemic therapies	1, first-line oxaliplatin- and fluoropyrimidine-containing regimen
Performance status: ECOG	0 — 118
	1 — 126
	2 — 5

Primary Assessment Method	
Control Arm:	
Number of patients enrolled	84
Number of patients evaluable for toxicity	80
Number of patients evaluated for efficacy	80
Response assessment CR	n = 0 (0%)
Response assessment PR	n = 8 (10%)
Response assessment SD	n = 53 (66%)
Response assessment PD	n = 17 (21%)
Response assessment OTHER	n = 2 (3%)
(Median) duration assessments PFS	5.8 months, CI: 4.9–9.0
(Median) duration assessments OS	16.3 months, CI: 12.0–19.5
Experimental Arm A: Simtuzumab 200 mg	
Number of patients enrolled	86
Number of patients evaluable for toxicity	85
Number of patients evaluated for efficacy	85
Response assessment CR	n = 0 (0%)
Response assessment PR	n = 5 (6%)
Response assessment SD	n = 50 (59%)
Response assessment PD	n = 23 (27%)
Response assessment OTHER	n = 7 (8%)

(Median) duration assessments PFS	5.4 months, CI: 3.4–5.6
(Median) duration assessments OS	10.5 months, CI: 9.2–12.6
Experimental Arm B: Simtuzumab 700 mg	
Number of patients enrolled	85
Number of patients evaluable for toxicity	84
Number of patients evaluated for efficacy	84
Response assessment CR	n = 0 (0%)
Response assessment PR	n = 10 (12%)
Response assessment SD	n = 49 (58%)
Response assessment PD	n = 23 (27%)
Response assessment OTHER	n = 2 (2%)
(Median) duration assessments PFS	5.5 months, CI: 4.0–7.1
(Median) duration assessments OS	11.4 months, CI: 9.7–15.6

Adverse Events Control Arm

All Dose Levels, All Cycles

Name	*NC/NA	1	2	3	4	5	All Grades
Diarrhea	45%	28%	18%	9%	0%	0%	55%
Nausea	54%	21%	21%	4%	0%	0%	46%
Fatigue	57%	21%	15%	6%	0%	0%	43%
Neutropenia	58%	6%	11%	20%	5%	0%	42%
Vomiting	70%	21%	6%	3%	0%	0%	30%
Decreased appetite	74%	16%	9%	1%	0%	0%	26%
Alopecia	74%	20%	6%	0%	0%	0%	26%
Anemia	76%	10%	8%	6%	0%	0%	24%
Abdominal pain	76%	9%	10%	5%	0%	0%	24%
Stomatitis	79%	9%	8%	5%	0%	0%	21%
Constipation	79%	11%	10%	0%	0%	0%	21%
Asthenia	85%	10%	5%	0%	0%	0%	15%
Pyrexia	87%	9%	4%	0%	0%	0%	13%
Mucosal inflammation	87%	4%	8%	1%	0%	0%	13%
Epistaxis	87%	13%	0%	0%	0%	0%	13%
Leukopenia	88%	3%	6%	3%	0%	0%	12%
Cough	88%	11%	1%	0%	0%	0%	12%
Dyspnea	88%	11%	1%	0%	0%	0%	12%
Insomnia	89%	8%	3%	0%	0%	0%	11%
Hypokalemia	90%	5%	1%	4%	0%	0%	10%

*NC/NA No change from baseline/no adverse event
Adverse events that occurred in ≥10% of patients. *n* = 80, safety analysis set. Clinical and laboratory adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 and graded using the National Cancer Institute Common Toxicity Criteria (CTCAE version 4.03).

Serious Adverse Events Control Arm

Name	Grade	Attribution
Febrile neutropenia	4	Probable
Dehydration	2	Probable
Dehydration	3	Probable
Vomiting	2	Probable
Nausea	2	Probable
Nausea	3	Probable
Diarrhea	3	Probable
Abdominal pain	3	Probable

Enteritis	3	Probable
Gastroenteritis	3	Probable

SAEs deemed related to simtuzumab/placebo. As this was a double-blind study, the SAEs considered related to simtuzumab were recorded for both treatment arms. SAEs related to FOLFIRI were not collected. $n = 80$, safety analysis set.

Adverse Events Both Experimental Arms

All Dose Levels, All Cycles

Name	*NC/NA	1	2	3	4	5	All Grades
Neutropenia	51%	4%	15%	20%	10%	0%	49%
Fatigue	52%	22%	20%	6%	0%	0%	48%
Nausea	52%	27%	21%	0%	0%	0%	48%
Diarrhea	54%	29%	11%	6%	0%	0%	46%
Anemia	74%	9%	13%	4%	0%	0%	26%
Vomiting	74%	18%	7%	1%	0%	0%	26%
Alopecia	75%	16%	9%	0%	0%	0%	25%
Abdominal pain	77%	8%	13%	2%	0%	0%	23%
Constipation	77%	15%	8%	0%	0%	0%	23%
Decreased appetite	80%	10%	8%	2%	0%	0%	20%
Leukopenia	86%	4%	5%	6%	1%	0%	16%
Edema, peripheral	85%	10%	4%	1%	0%	0%	15%
Asthenia	85%	5%	8%	2%	0%	0%	15%
Cough	86%	13%	1%	0%	0%	0%	14%
Stomatitis	86%	8%	5%	1%	0%	0%	14%
Mucosal inflammation	87%	7%	5%	1%	0%	0%	13%
Pyrexia	87%	11%	2%	0%	0%	0%	13%
Dizziness	87%	12%	1%	0%	0%	0%	13%
Dyspnea	88%	8%	4%	0%	0%	0%	12%
Thrombocytopenia	88%	11%	1%	0%	0%	0%	12%
Back pain	89%	6%	3%	2%	0%	0%	11%
Hypokalemia	90%	5%	1%	4%	0%	0%	10%

*NC/NA No change from baseline/no adverse event
Adverse events that occurred in $\geq$10% of patients. $n = 169$, safety analysis set. Clinical and laboratory adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 and graded using the National Cancer Institute Common Toxicity Criteria (CTCAE version 4.03).

Serious Adverse Events Experimental Arm

Name	Grade	Attribution
Sepsis	4	Probable
Urosepsis	4	Probable
Febrile neutropenia	3	Probable
Febrile neutropenia	4	Probable
Thrombocytopenia	4	Probable
Diverticulitis	3	Probable
Lung infection	2	Probable
Lower respiratory tract inflammation	4	Probable
Pneumothorax	4	Probable
Diarrhea	3	Probable
Delirium	4	Probable
Confusional state	4	Probable

SAEs deemed related to simtuzumab. SAEs related to FOLFIRI were not collected. $n = 169$, safety analysis set.

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics/Pharmacodynamics	Not Collected
Investigator's Assessment	Level of activity did not meet planned endpoint

Colorectal cancer (CRC) accounts for 9.7% of all incident cancers worldwide and is the fourth leading cause of cancer mortality [1]. One of the frequent genetic mutations in CRC is in the *KRAS* gene in the chromosomal instability pathway [2]. *KRAS* mutation-positive patients do not respond to anti-epidermal growth factor receptor antibody therapy [3] and have poorer survival than patients with the *KRAS* wild-type gene [4]. The currently available therapies for advanced *KRAS*-mutated CRC include chemotherapy alone or in combination with antiangiogenic antibodies such as bevacizumab, aflibercept, or ramucirumab [5]. New therapies are urgently needed for this patient population.

Activated stroma in the tumor environment is associated with higher numbers of activated fibroblasts, which contribute to the desmoplastic reaction [6, 7]. Tumor-associated activated fibroblasts secrete oncogenic growth factors, produce extracellular matrix (ECM), and promote epithelial cell transformation [7, 8]. Lysyl oxidase-like 2 (LOXL2), an enzyme that remodels the ECM, contributes to the maintenance of the pathologic stromal microenvironment in cancer and fibrotic diseases [9] and promotes tumor angiogenesis [10] and metastatic progression [11]. LOXL2 is expressed in desmoplastic tumors, including CRC, with no expression in the adjacent nonneoplastic areas [8, 12].

Simtuzumab, a humanized IgG4 monoclonal antibody against LOXL2, inhibits its enzymatic activity [13]. In preclinical studies with antibody precursors to simtuzumab, inhibition of LOXL2 expression reduced numbers of activated fibroblasts, decreased ECM deposition [9], inhibited angiogenesis [14], and prevented tumor cell invasion and metastases [15]. Of note, in preclinical models, simtuzumab had better efficacy in *KRAS* mutant cell lines (Gilead Sciences, Inc., data on file). In a phase I study in patients with advanced solid tumors, single agent simtuzumab reduced the size of several tumors in select patients [16].

In a multicenter, randomized, double-blind, placebo-controlled phase II study, we evaluated the efficacy of simtuzumab or placebo in combination with FOLFIRI as a second-line therapy in patients with metastatic *KRAS*-mutant CRC who progressed following oxaliplatin- and fluoropyrimidine-containing first-line therapy (ClinicalTrials.gov #NCT01479465).

The key endpoints included progression-free survival (PFS), overall survival (OS), objective response rate (ORR) per RECIST v1.1, and safety. Enrolled patients had stage IV disease; ECOG PS $\leq$2; adequate bone marrow, hepatic, and renal function; and estimated life expectancy $>$3 months. Patients were randomized 1:1:1 to receive intravenous FOLFIRI in combination with simtuzumab or placebo until disease progression or unacceptable toxicity; randomization was stratified by Eastern Cooperative Oncology Group performance status (ECOG PS) 0 vs $>$0. Patients were scheduled for 2 visits per cycle and a computed tomography (CT) or magnetic resonance imaging (MRI) scan every 8 weeks.

From December 2011 to March 2014, 255 patients were randomized, 249 patients received at least one 28-day cycle of study drug (full analysis set [FAS]), and 233 (94%) patients received $\geq$2 cycles, with a median number of 6 cycles. The majority of enrolled patients were male (128/249, 51.4%) and white (212/249, 85.1%), with a mean (range) age of 60.5 (22.0–85.0) years (Table 2). The mean (SD) time since first diagnosis of colorectal cancer was 20.3 (20.31) months. In total, 42% of patients had 3 or more target lesions at baseline. The most common target lesion sites included liver (73%), lung (45%), and lymph nodes (16%) (Table 2).

Overall, 231 (90.6%) patients had discontinued study, mainly due to disease progression (185 [72.5%]) and adverse events (12 [4.7%]). A sequential stepwise hypothesis and a Hochberg testing procedure were used to compare between the two simtuzumab dosing groups versus placebo for PFS, OS, and ORR. A number of sensitivity analyses were also conducted for PFS, OS, and ORR to confirm the results of the primary analyses. The study failed to reach any of the prespecified efficacy endpoints. Median PFS for FOLFIRI/simtuzumab 700 mg, FOLFIRI/simtuzumab 200 mg, and FOLFIRI/placebo was 5.5 months (adjusted hazard ratios [HRs] with 95% confidence interval [CIs] for the stratified primary analysis, *p* value versus placebo; 1.32 [0.92, 1.89]; $p = .10$), 5.4 months (1.45 [1.01, 2.06] $p = .04$), and 5.8 months, respectively (Fig. 1), after a median follow-up of 5.1, 3.8, and 5.5 months, respectively. Median OS for the FOLFIRI/simtuzumab 700 mg, FOLFIRI/simtuzumab 200 mg, and FOLFIRI/placebo was 11.4 months (adjusted HR, [95% CIs] for the stratified OS primary analysis, *p* value versus placebo; 1.23 [0.80, 1.91]; $p = .25$), 10.5 months (1.50 [0.98, 2.30]; $p = .06$), and 16.3 months, respectively (Fig. 2). The adjusted HRs for PFS and OS for the simtuzumab arms compared with placebo were all greater than 1. The ORRs in FOLFIRI/simtuzumab 700 mg, FOLFIRI/simtuzumab 200 mg, and FOLFIRI/placebo were 11.9%, 5.9%, and 10.0%, respectively. The difference (95% CI) in ORR for patients treated with 700 mg FOLFIRI plus simtuzumab versus patients treated with FOLFIRI plus placebo was 2.0% ($-$8.1, 11.9; $p = .69$) and $-$4.1% ($-$13.3, 4.6; $p = .33$) for patients treated with 200 mg FOLFIRI plus simtuzumab compared with FOLFIRI plus placebo. Results from sensitivity analyses were consistent with the primary analyses.

The safety profile in the patient groups who received FOLFIRI combined with simtuzumab was not different from patients who received FOLFIRI with placebo. The most common adverse events (AEs) deemed by the investigator to be related to study treatment were fatigue, diarrhea, nausea and neutropenia. AEs greater than or equal to grade 3 were reported in 59.5% in the FOLFIRI/simtuzumab 700 mg group, 67.1% in the FOLFIRI/simtuzumab 200 mg group, and 61.3% in the FOLFIRI/placebo group. Seven AEs leading to death occurred during this study; one case of febrile neutropenia was deemed related to FOLFIRI treatment. None of the deaths on study were considered related to simtuzumab.

In conclusion, the addition of simtuzumab to FOLFIRI did not improve PFS, OS, or ORR in patients with metastatic *KRAS* mutant CRC.

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Figures and Tables

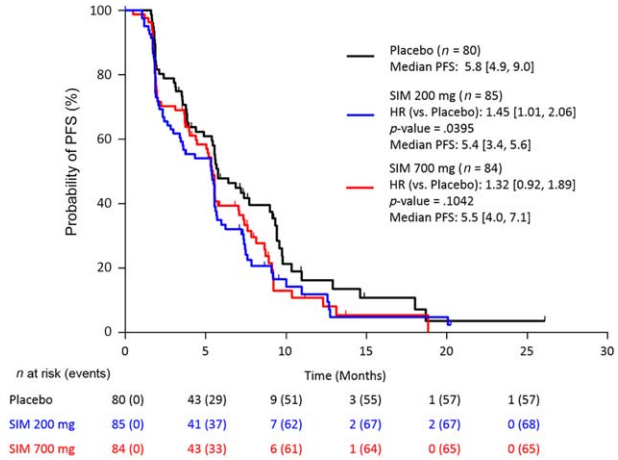

Figure 1. Stratified Kaplan–Meier plot of progression-free survival by investigator assessment (FAS population).

Abbreviations: CI, confidence interval; FAS, full analysis set (all patients randomized and treated with ≥1 dose of study drug); HR, hazard ratio (numbers in brackets are 95% CIs); PFS, progression-free survival; SIM, simtuzumab.

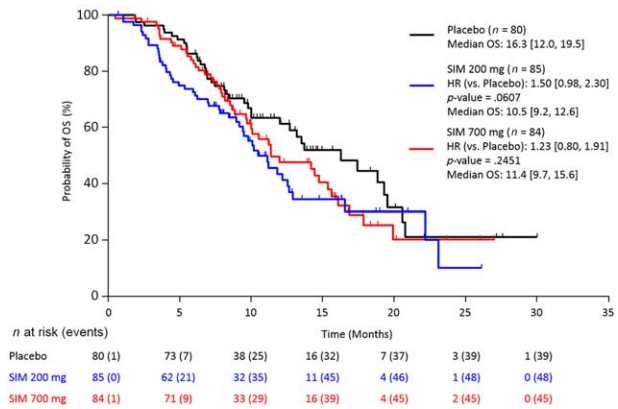

Figure 2. Stratified Kaplan–Meier plot of overall survival (FAS population).

Abbreviations: CI, confidence interval; FAS, full analysis set (all patients randomized and treated with ≥1 dose of study drug); HR, hazard ratio (numbers in brackets are 95% CIs); OS, overall survival; SIM, simtuzumab.

Table 2. Demographic and baseline characteristics (FAS analysis set)

Characteristic	Simtuzumab 700 mg/ FOLFIRI *n* = 84	Simtuzumab 200 mg/ FOLFIRI *n* = 85	Placebo/FOLFIRI *n* = 80
Mean age in years (range)	60.1 (22.0–78.0)	62.6 (31.0–83.0)	58.8 (32.0–85.0)
ECOG performance status, *n* (%)			
0	35 (41.7)	40 (47.1)	43 (53.8)
1	48 (57.1)	42 (49.4)	36 (45.0)
2	1 (1.2)	3 (3.5)	1 (1.3)
Mean time since first diagnosis of colorectal cancer in months (SD)	20.7 (24.72)	20.5 (17.53)	19.6 (17.87)
Patients with prior chemoimmunotherapy, *n* (%)	84 (100)	85 (100)	80 (100)
Patients with prior radiotherapy related to current disease, *n* (%)	13 (15.5)	17 (20.0)	16 (20.0)
No. of target lesions at baseline, *n* (%)			
1	12 (14.3)	11 (12.9)	14 (17.5)
2	31 (36.9)	35 (41.2)	39 (48.8)
3	20 (23.8)	18 (21.2)	16 (20.0)
4	12 (14.3)	15 (17.6)	9 (11.3)
5	8 (9.5)	5 (5.9)	2 (2.5)
Lesion site, *n* (%)			
Liver	59 (70.2)	64 (75.3)	58 (72.5)
Lung	42 (50.0)	37 (43.5)	34 (42.5)
Lymph nodes (shortest diameter)	14 (16.7)	15 (17.6)	11 (13.8)
Mean tumor sum of diameter at baseline per investigator in millimeters (SD)	90.3 (57.38)	87.9 (58.04)	77.2 (52.54)
Mean tumor sum of diameter at baseline per IRR in millimeters (SD)	89.7 (50.93)	91.1 (50.67)	82.8 (61.45)
Mean tumor marker CEA in μg/L (SD)	264.7 (861.88)	462.8 (1325.24)	320.3 (970.59)

Abbreviations: CEA, carcinoembryonic antigen; FAS, full analysis set (all patients randomized and treated with ≥1 dose of study drug); IRR, Independent Radiology Review; SD, standard deviation.