ARC-9: A Randomized Study to Evaluate Etrumadenant Based Treatment Combinations in Previously Treated Metastatic Colorectal Cancer

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PRESENTED BY: Zev A. Wainberg, MD

Key Takeaways

- ARC-9 is the first randomized, phase 2, proof-of-concept study that showed that etrumadenant + zimberelimab + mFOLFOX-6 + bevacizumab (EZFB) significantly improves progression-free survival (PFS) and overall survival (OS) compared with standard of care in microsatellite-stable third line (3L) metastatic colorectal cancer (mCRC)
  - Longest OS reported for a randomized clinical trial in 3L mCRC
  - Meaningful improvement shown across all subgroups, including 20-month median OS in patients with liver metastasis
- Safety was consistent with toxicity profiles of individual study drugs and manageable with no safety-related deaths
- These data demonstrate that EZFB is a promising regimen in mCRC and add to the growing body of evidence supporting the adenosine pathway as an effective therapeutic target across multiple tumor types, warranting future studies

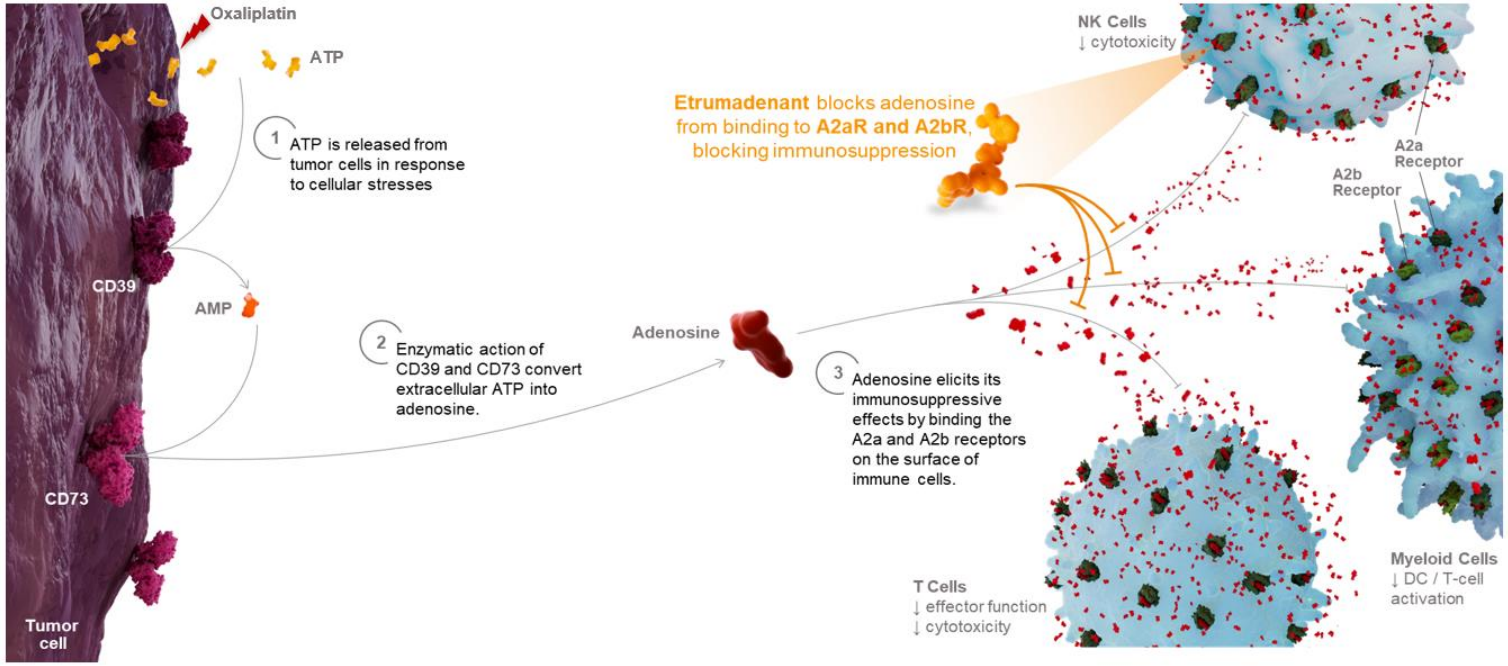
Background

- CRC is the second leading cause of cancer deaths worldwide, with a median OS of only 6-11 months after progressing on FOLFOX and FOLFIRI[1-3]
- FOLFOX rechallenge is frequently used in the management of mCRC; data from global prospective studies are lacking in the 3L treatment setting[4]
- ARC-3: Phase 1/1b dose escalation and expansion study of etrumadenant (etruma) + mFOLFOX-6 in mCRC[5]
  - In ≥3L patients, median PFS of 4.2 months and median OS of 13.6 months were achieved
  - No additive toxicity was observed with safety profile consistent with previous findings
- Promising OS signal observed in ARC-3 established the rationale for etruma-based combinations in previously treated mCRC (ARC-9)
- Zimberelimab (zim) is an anti–PD-1 antibody that has been evaluated in more than 1000 patients with a manageable safety profile[6-10] and is currently being studied in multiple phase 3 randomized clinical trials

1. Cancer.Net. Colorectal Cancer: Statistics. https://www.cancer.net/cancer-types/colorectal-cancer/statistics 2.Tournigand C, et al. *J Clin Oncol*. 2004;22(2):229-37. 3. Neugut AI, et al. *Clin Colorectal Cancer*. 2019;18(2):133-140.
4. Mauri G, et al. *Cancer Treat Rev*. 2020;91:102112. 5. Cecchini M, et al. *Cancer Res*. 2021;81(suppl 13):CT129. 6. Johnson M, et al. *J Clin Oncol*. 2022;40(suppl 36):397600. 7. Subudhi SK, et al. *J Clin Oncol*. 2021;39(suppl 15):5039.
8. Spira A, et al. *Annal Oncol*. 2020;31(suppl 4):S754-S840. 9. Wainberg, ZA, et al. *J Clin Oncol*. 2024;42(suppl 3):665. 10. Arcus Biosciences. Clinical Pipeline. Accessed May 22, 2024. https://arcusbio.com/our-science/pipeline/

Immunosuppression by Adenosine Is Mediated by $A_{2a}R$ and $A_{2b}R$ Within the Tumor Microenvironment

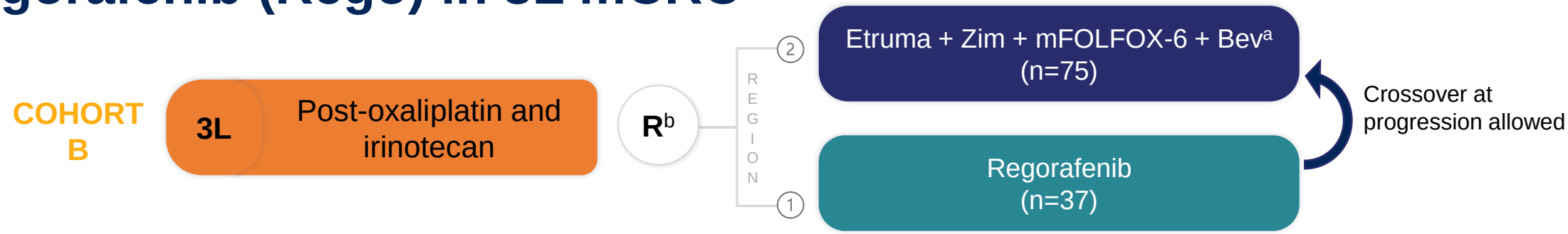
- In multiple analyses of human tumors, CRC has been shown to have some of the highest tumor expression levels of CD73, the main source of extracellular adenosine[1,2]
- Etruma has previously been evaluated in multiple clinical trials of solid tumor indications including colorectal, prostate, and non-small cell lung cancer, showing promising clinical activity when combined with chemo/immunotherapy[3-6]



ATP, adenosine triphosphate; NK, natural killer.

1. Bach N, et al. *Int J Mol Sci*. 2023;24(14):11759. 2. Saigi M, et al. *Cancers*. 2023;15(23):5706. 3. Johnson M, et al. *J Clin Oncol*. 2022;40(36_suppl):397600. 4. Subudhi SK, et al. *J Clin Oncol*. 2021;39(15_suppl):5039. 5. Cecchini M, et al. *Cancer Res*. 2021;81(suppl 13): CT129. 6. Spira A, et al. *Annal Oncol*. 2020;31(suppl 4):S754-S840.

ARC-9 Cohort B: Etruma + Zim + mFOLFOX-6 + Bev[a] (EZFB) vs Regorafenib (Rego) in 3L mCRC



Sample size of approximately 105 participants was estimated in a 2:1 ratio randomization to detect an improvement of HR of 0.5 in PFS using a log-rank test in order to achieve 80% power at a two-sided significance level of 0.05

Key inclusion criteria	• Histologically confirmed unresectable mCRC
	• Measurable disease per RECIST v1.1
	• ECOG PS of 0 or 1
	• Disease progression **on or after** treatment with oxaliplatin and irinotecan containing chemotherapy in combination with anti-VEGF(R) or anti-EGFR
	  • **≤ 2 prior lines** of treatment in the metastatic setting
	  • Re-introduction of an initially successful induction regimen, per investigator judgement, not counted as one additional line of treatment
	  • **Metastatic setting:** could not have progressed ≤2 months of last dose of oxaliplatin
	  • **Adjuvant setting:** will count as line of treatment if progressed ≤6 months of last dose
	  • Patients treated with FOLFIRINOX meet this eligibility criteria if they did not progress ≤2 months of last dose of oxaliplatin

Key exclusion criteria	• Prior treatment with immune checkpoint blockade therapies • Mutation in the *BRAF* oncogene; patients with unknown *BRAF* status will be required to undergo testing at a local laboratory and provide results at screening

Primary Endpoints
PFS (Investigator assessed)

Key Secondary Endpoints
OS
ORR (Investigator assessed)
Safety

3L, third line; bev, bevacizumab; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; etruma, etrumadenant; mCRC, metastatic CRC; ORR, objective response rate; OS, overall survival; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; zim, zimberelimab.
[a] bev will be included for all patients in whom it is not contraindicated. [b] Patients were randomized 2:1 to EZFB: E (150 mg orally [PO] once daily [QD]) + Z (240 mg intravenous [IV] once every 2 weeks [Q2W]) + mFOLFOX-6 + bev (5 mg/kg IV Q2W), or rego (160 mg PO QD [days 1-21 every 4 weeks]).

Baseline Demographics & Disease Characteristics

	EZFB (N=75)	Rego (N=37)	Total (N=112)
Median age, y	58.0	60.0	59.0
Female, n (%)	22 (29)	15 (41)	37 (33)
ECOG PS, 0/1, %	40 / 60	49 / 51	43 / 57
Overall TNM stage at initial diagnosis, n (%)			
Stage IV	56 (75)	29 (78)	85 (76)
Primary diagnosis, n (%)			
Colon	56 (75)	27 (73)	83 (74)
Rectal	19 (25)	10 (27)	29 (26)
Primary tumor location, n (%)			
Left	53 (71)	23 (62)[a]	76 (68)[a]
Metastatic site, n (%)			
Liver	53 (71)	29 (78)	82 (73)
Peritoneal	18 (24)	9 (24)	27 (24)
Lung only	4 (5)	2 (5)	6 (5)
Microsatellite,[b] n (%)			
Stable (MSS or MSI-L)	61 (81)	30 (81)	91 (81)
Unstable (MSI-H)	1 (1)	0	1 (1)
KRAS,[c] n (%)			
Mutant	38 (51)	20 (54)	58 (52)
Wild-Type	27 (36)	11 (30)	38 (34)
Missing	10 (13)	6 (16)	16 (14)

Date cutoff date: November 13, 2023.
Efficacy-evaluable population; defined as all participants who were enrolled and randomized.
ECOG PS, Eastern Cooperative Oncology Group performance status; EZFB, etrumadenant + zimberelimab + mFOLFOX-6 + bevacizumab; MS, microsatellite; MSS, MS stable; MSI-H, MS instability-high; MSI-L, MS instability-low; rego, regorafenib.
[a] Unknown n=2; [b] Microsatellite status based on PCR. [c] KRAS based on NGS; Indeterminate, n=1 EZFB.

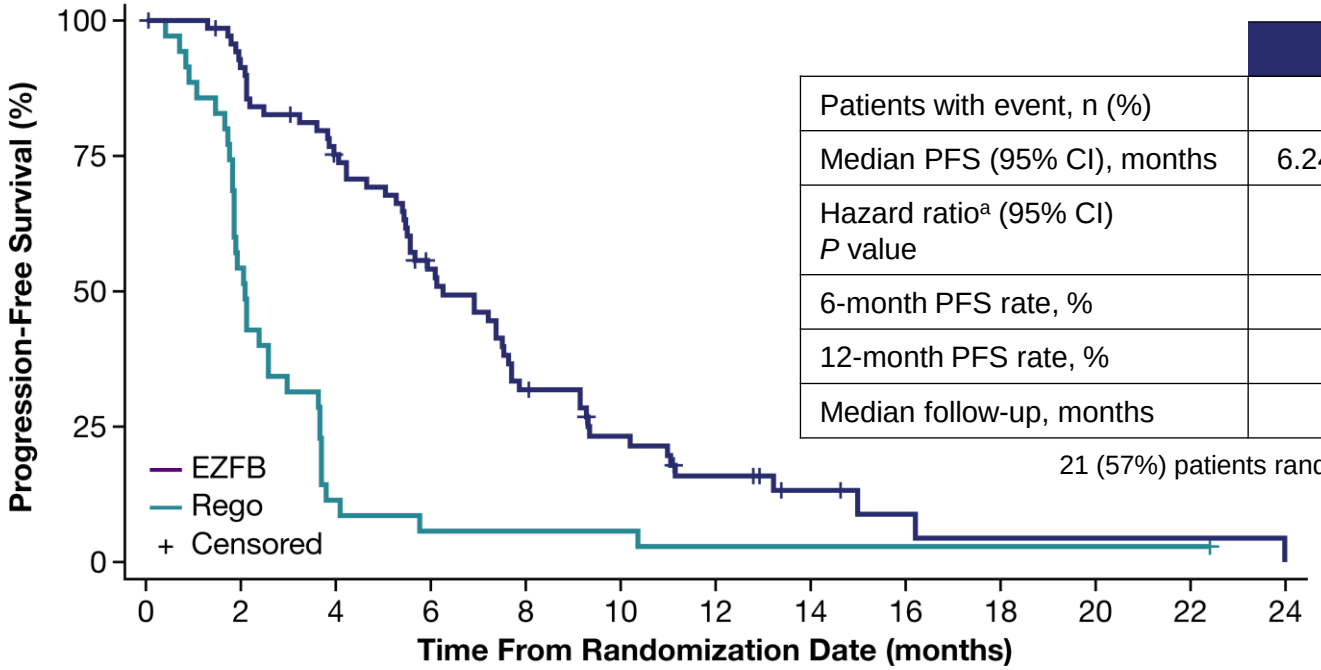
Prior Treatment History

	EZFB (N=75)	Rego (N=37)	Total (N=112)
Prior irinotecan, n (%)	73 (97)	37 (100)	110 (98)[d]
Prior oxaliplatin,[a] n (%)	74 (99)	36 (97)	110 (98)[e]
Metastatic 1L 2L+	63 (84) 53 (71) 15 (20)	31 (84) 27 (73) 7 (19)	94 (84) 80 (71) 22 (20)
Adjuvant/neo adjuvant	10 (13)	5 (14)	15 (13)
Locally advanced	4 (5)	2 (5)	6 (5)
Prior Anti-VEGF(R),[b] n (%)	64 (85)	36 (97)	100 (89)
Prior Anti-EGFR, n (%)	27 (36)	11 (30)	38 (34)
Prior anticancer surgery,[c] n (%)	52 (69)	21 (57)	73 (65)
Time from first oxaliplatin dose date to progression/discontinuation date of the last prior oxaliplatin-containing regimen, n (%)	74 (99)	36 (97)	110 (98)
Median, months	9.0	9.8	9.2

Date cutoff date: November 13, 2023.
1L, first line; 2L+, second line or greater; EZFB, etrumadenant + zimberelimab + mFOLFOX-6 + bevacizumab; rego, regorafenib.
[a] A patient could be counted more than once if they had prior oxaliplatin in multiple settings. [b] Includes bevacizumab, ramucirumab, and aflibercept regardless of treatment setting. [c] includes primary resection as well as metastasectomy. If a patient had both prior anticancer surgery and prior non-surgical anticancer procedure done, that patient is counted in each respective category. [d] EDC was subsequently updated after the data cutoff of 13 Nov 2023 showing these 2 patients had received prior irinotecan per the eligibility criteria. [e] EDC was subsequently updated after the data cutoff of 13 Nov 2023 showing these 2 patients had received prior oxaliplatin per the eligibility criteria .

Primary Endpoint: Investigator-Assessed Progression-Free Survival (Efficacy Evaluable Population)

- EZFB demonstrated statistically significant improvement in PFS vs rego



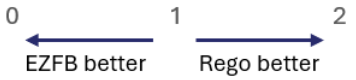
	EZFB	Rego
Patients with event, n (%)	58 (77)	34 (92)
Median PFS (95% CI), months	6.24 (5.49, 7.52)	2.07 (1.84, 2.96)
Hazard ratio[a] (95% CI) *P* value	0.27 (0.17, 0.43) <0.001	
6-month PFS rate, %	54	6
12-month PFS rate, %	16	3
Median follow-up, months	20.4	

21 (57%) patients randomized to rego crossed over to EZFB

Date cutoff date: November 13, 2023.
PFS is defined as the first occurrence of progressive disease per RECIST v1.1 or death, whichever occurs first. Patients without documented disease progression at the time of analysis were censored on the date of their last adequate tumor assessment. If no tumor assessment was performed after the start of study treatment, PFS will be censored on the date of first dose of study treatment with duration of 1 day.
EZFB, etrumadenant + zimberelimab + mFOLFOX-6 + bevacizumab; PFS, progression-free survival; rego, regorafenib.
[a] Hazard ratio and 95% CIs are based on stratified (geographic region) Cox model. Study was not designed as a powered study to control for alpha in multiplicity testing.

PFS Was Consistently Longer in EZFB Arm vs Rego Arm in All Subgroups Analyzed

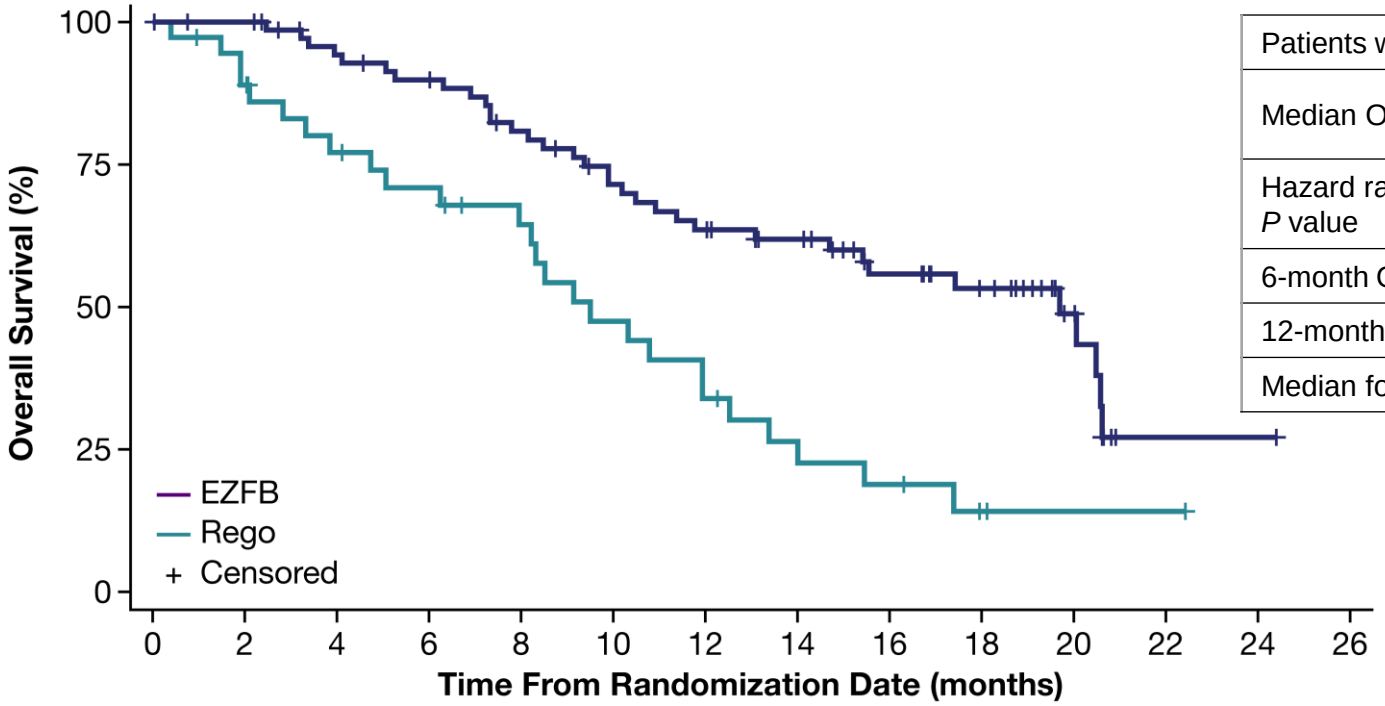
		EZFB #event/N (%); median PFS	Rego #event/N (%); median PFS	HR (95%CI)
	Overall	58/75 (77%); 6.2	34/37 (92%); 2.1	0.27 (0.17, 0.43)
Region	EU + South Korea	41/49 (84%); 6.9	22/23 (96%); 2	0.25 (0.14, 0.45)
	US	17/26 (65%); 6.1	12/14 (86%); 2.5	0.31 (0.14, 0.67)
Baseline ECOG PS	D	20/30 (67%); 7.6	16/18 (89%); 2.1	0.28 (0.14, 0.56)
	1	38/45 (84%); 5.5	18/19 (95%); 2	0.18 (0.09, 0.38)
Baseline liver metastasis	Yes	45/53 (85%); 5.7	28/29 (97%); 2	0.19 (0.1, 0.35)
	No	13/22 (59%); 10.2	6/8 (75%); 2.6	0.4 (0.14, 1.16)
Primary diagnosis	Colon	45/56 (80%); 5.9	25/27 (93%); 2	0.26 (0.15, 0.44)
	Rectal	13/19 (68%); 7.9	9/10 (90%); 3.6	0.03 (0, 0.3)
Primary tumor location	Left	40/53 (75%); 7.4	21/23 (91%); 2.2	0.29 (0.16, 0.51)
	Right	18/22 (82%); 5	11/12 (92%); 2.1	0.3 (0.12, 0.74)
Prior oxaliplatin under metastatic setting	Yes	49/63 (78%); 6.9	30/31 (97%); 2.1	0.16 (0.09, 0.28)
	No	9/12 (75%); 5.5	4/6 (67%); 3.7	0.69 (0.2, 2.37)
Time from first prior oxaliplatin dose under metastatic setting to progression or end of regimen in 1L	≥9 months	20/25 (80%); 7.5	17/17 (100%); 2.1	0.18 (0.08, 0.42)
	<9 months	24/28 (86%); 5.6	9/10 (90%); 2	0.12 (0.04, 0.36)
Prior bevacizumab under metastatic setting	Yes	43/56 (77%); 6.1	30/33 (91%); 2.1	0.32 (0.19, 0.52)
	No	15/19 (79%); 7.7	4/4 (100%); 2.1	0.03 (0, 0.27)



Date cutoff date: November 13, 2023.
1L, first line; ECOG PS, Eastern Cooperative Oncology Group performance status; EZFB, etrumadenant + zimberelimab + mFOLFOX-6 + bevacizumab; PFS, progression-free survival; rego, regorafenib.

Overall Survival (Efficacy Evaluable Population)

- EZFB demonstrated significant improvement in OS vs rego



Number of patients at risk

EZFB	75	73	65	61	53	45	40	35	26	20	10	1	1
Rego	37	32	26	23	19	14	10	6	5	2	1	1	0

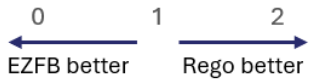
	EZFB	Rego
Patients with event, n (%)	34 (45)	26 (70)
Median OS (95% CI), months	19.68 (14.69, 20.60)	9.49 (7.95, 12.52)
Hazard ratio[a] (95% CI) *P* value	0.37 (0.22, 0.63) <0.001	
6-month OS rate, %	90	71
12-month OS rate, %	64	34
Median follow-up, months	20.4	

21 (57%) patients randomized to rego crossed over to EZFB

Date cutoff date: November 13, 2023.
OS is defined as time (months) from randomization until death from any cause. Patients who did not die while on study are censored at the last known date they were alive.
EZFB, etrumadenant + zimberelimab + mFOLFOX-6 + bevacizumab; OS, overall survival; rego, regorafenib.
[a] Hazard ratio and 95% CIs are based on stratified (geographic region) Cox model. Study was not designed as a powered study to control for alpha in multiplicity testing.

OS Was Consistently Longer in EZFB Arm vs Rego Arm in All Subgroups Analyzed

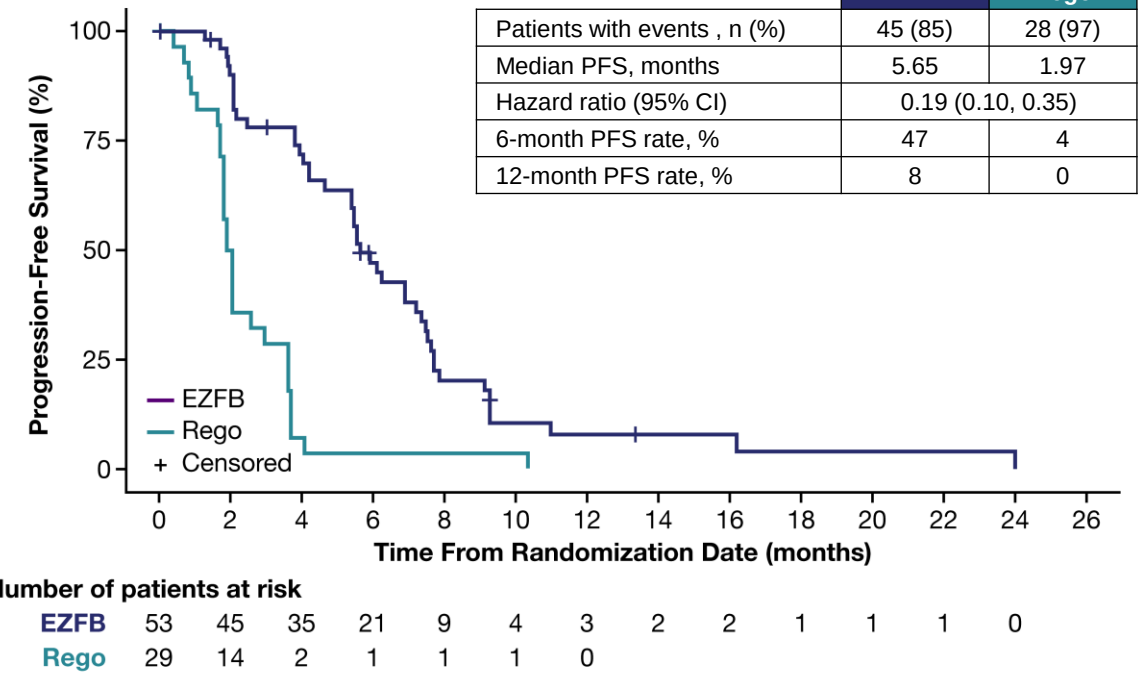
		EZFB #event/N (%); median OS	Rego #event/N (%); median OS	HR (95%CI)
	Overall	34/75 (45%); 19.7	26/37 (70%); 9.5	0.37 (0.22, 0.63)
Region	EU + South Korea	22/49 (45%); 20	17/23 (74%); 10.8	0.44 (0.23, 0.84)
	US	12/26 (46%); 19.7	9/14 (64%); 8.2	0.25 (0.1, 0.65)
Baseline ECOG PS	0	11/30 (37%); 20.5	11/18 (61%); 12.5	0.26 (0.1, 0.65)
	1	23/45 (51%); 10.9	15/19 (79%); 6.2	0.34 (0.17, 0.68)
Baseline liver metastasis	Yes	27/53 (51%); 19.7	22/29 (76%); 9.1	0.36 (0.2, 0.66)
	No	7/22 (32%); NA	4/8 (50%); 17.4	0.66 (0.19, 2.35)
Primary diagnosis	Colon	27/56 (48%); 19.7	20/27 (74%); 8.2	0.34 (0.18, 0.64)
	Rectal	7/19 (37%); 20	6/10 (60%); 11.9	0.26 (0.07, 0.98)
Primary tumor location	Left	23/53 (43%); 20	17/23 (74%); 9.5	0.33 (0.17, 0.63)
	Right	11/22 (50%); 11.8	8/12 (67%); 12.5	0.49 (0.18, 1.34)
Prior oxaliplatin under metastatic setting	Yes	28/63 (44%); 19.7	23/31 (74%); 10.3	0.33 (0.19, 0.6)
	No	6/12 (50%); 11.8	3/6 (50%); 8.5	0.33 (0.07, 1.53)
Time from first prior oxaliplatin dose under metastatic setting to progression or end of regimen in 1L	≥9 months	13/25 (52%); 19.7	14/17 (82%); 9.5	0.23 (0.1, 0.57)
	<9 months	12/28 (43%); 20.6	7/10 (70%); 8.3	0.42 (0.16, 1.13)
Prior bevacizumab under metastatic setting	Yes	25/56 (45%); 19.7	22/33 (67%); 10.3	0.41 (0.22, 0.75)
	No	9/19 (47%); 20	4/4 (100%); 8.4	0.16 (0.04, 0.61)



Date cutoff date: November 13, 2023.
1L, first line; ECOG PS, Eastern Cooperative Oncology Group performance status; EZFB, etrumadenant + zimberelimab + mFOLFOX-6 + bevacizumab; OS, overall survival; rego, regorafenib.

Progression-Free Survival and Overall Survival in Patients With Baseline Liver Metastasis

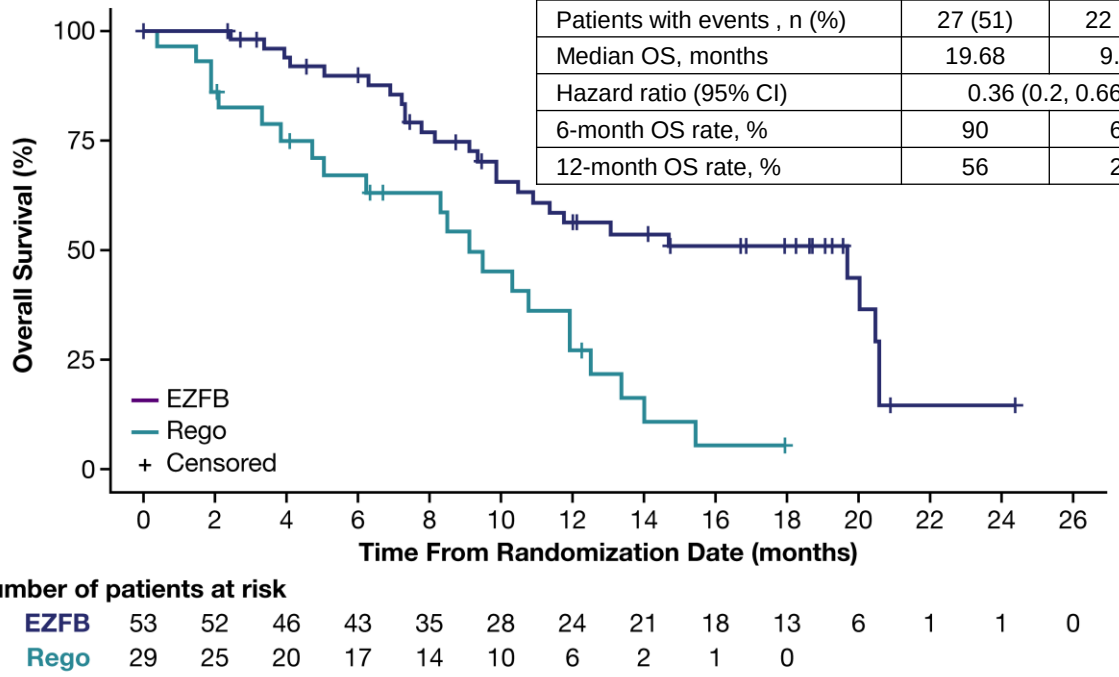
- 5.7 month median PFS for EZFB in patients with liver metastasis
- 20 month median OS for EZFB in patients with liver metastasis



	EZFB	Rego
Patients with events , n (%)	45 (85)	28 (97)
Median PFS, months	5.65	1.97
Hazard ratio (95% CI)	0.19 (0.10, 0.35)	
6-month PFS rate, %	47	4
12-month PFS rate, %	8	0

Number of patients at risk

EZFB	53	45	35	21	9	4	3	2	2	1	1	1	0
Rego	29	14	2	1	1	1	0						



	EZFB	Rego
Patients with events , n (%)	27 (51)	22 (76)
Median OS, months	19.68	9.13
Hazard ratio (95% CI)	0.36 (0.2, 0.66)	
6-month OS rate, %	90	67
12-month OS rate, %	56	27

Number of patients at risk

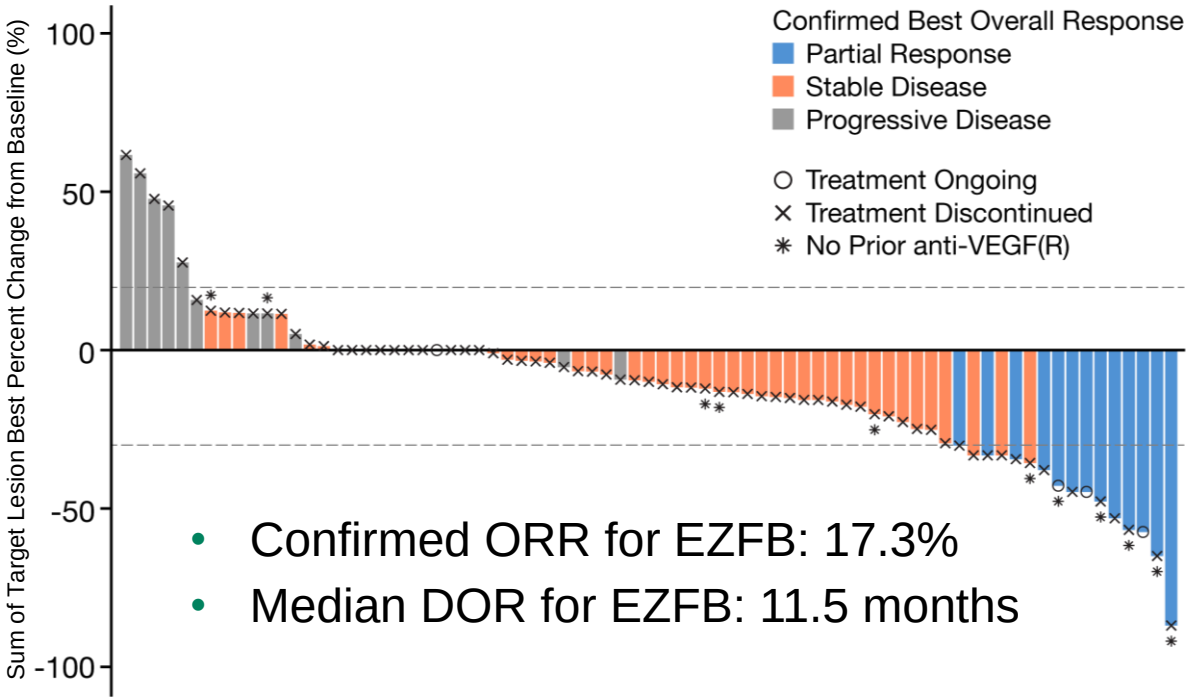
EZFB	53	52	46	43	35	28	24	21	18	13	6	1	1	0
Rego	29	25	20	17	14	10	6	2	1	0				

Date cutoff date: November 13, 2023.
PFS is defined as the first occurrence of progressive disease per RECIST v1.1 or death, whichever occurs first. Patients without documented disease progression at the time of analysis were censored on the date of their last adequate tumor assessment. If no tumor assessment was performed after the start of study treatment, PFS will be censored on the date of first dose of study treatment with duration of 1 day. OS is defined as time (months) from randomization until death from any cause. Patients who did not die while on study are censored at the last known date they were alive.
EZFB, etrumadenant + zimberelimab + mFOLFOX-6 + bevacizumab; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; rego, regorafenib.

PRESENTED BY: Zev A. Wainberg, MD

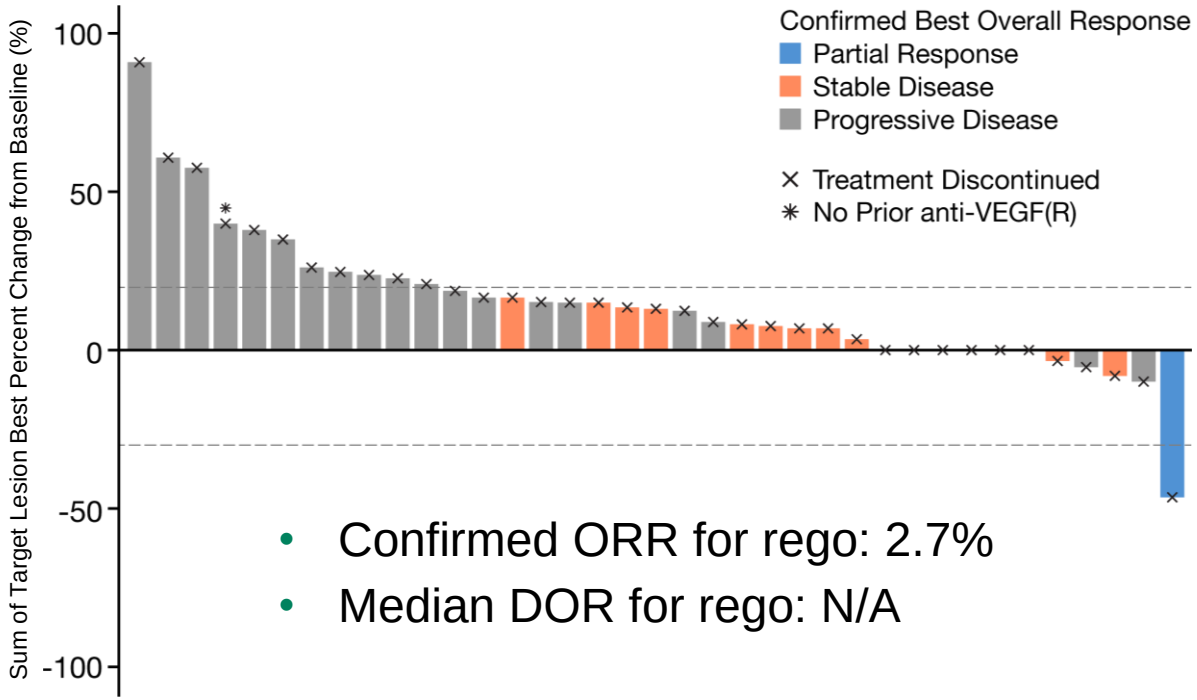
Investigator-Assessed Objective Response Rate (Efficacy Evaluable Population)

EZFB



- Confirmed ORR for EZFB: 17.3%
- Median DOR for EZFB: 11.5 months

REGO



- Confirmed ORR for rego: 2.7%
- Median DOR for rego: N/A

Date cutoff date: November 13, 2023.
DOR was defined as the time from first documentation of confirmed disease response (CR or PR) until first documentation of progressive disease per RECIST v1.1.
DOR, duration of response; EZFB, etrumadenant + zimberelimab + mFOLFOX-6 + bevacizumab; N/A, not applicable; ORR, objective response rate; rego, regorafenib.

Safety Summary

- EZFB had an acceptable safety profile, consistent with known toxicity profile of mFOLFOX-6/bev in combination with anti–PD-1

n (%)	EZFB (N=74)	Rego (N=35)
Median treatment duration, weeks	26	7
Any TEAEs	73 (99)	31 (89)
Serious TEAEs	37 (50)	9 (26)
Grade ≥3 TEAEs	61 (82)	17 (49)
Any TEAEs leading to discontinuation of study drug Leading to oxaliplatin discontinuation[a]	44 (59) 39 (53)[a]	7 (20) -
Any TEAE leading to discontinuation of all study drugs	4 (5)	6 (17)
Any TEAEs leading to death	0	0
Any TEAEs that are immune-mediated reactions (per sponsor)[b]	12 (16)	2 (6)
Grade ≥3 event	4 (5)	0

Date cutoff date: November 13, 2023.
Safety-evaluable population includes all enrolled patients who received any amount of any study treatment. TEAEs are any AEs that start on or after the study treatment start date/time and within 90 days of the last dose date for all zim arms (30 days for non-zim arms), excluding any AEs occurring after initiation of new anti-cancer therapy. Treatment related corresponds to any adverse event marked as related to etruma or zim or mFOLFOX-6 or bev or rego on the case report form.
AE, adverse event; bev, bevacizumab; etruma, etrumadenant; EZFB, etruma + zimberelimab + mFOLFOX-6 + bev; rego, regorafenib; TEAE, treatment-emergent AE; zim, zimberelimab.
[a] AEs leading to oxaliplatin discontinuation included: neuropathy, neutropenia, thrombocytopenia, and infusion reactions. [b] Immune-mediated reactions programmatically identified via sponsor-defined preferred terms.

Treatment-Emergent and Immune-Mediated Adverse Events

Most Common Grade ≥3 TEAEs Occurring in ≥5%

n (%)	EZFB (N=74)	Rego (N=35)
Grade ≥3 TEAEs	61 (82)	17 (49)
Neutropenia[a]	35 (47)	0
Nausea	8 (11)	0
Bilirubin increased	7 (9)	2 (6)
Diarrhea	6 (8)	0
Hypersensitivity[a]	6 (8)	0
WBC count decreased	6 (8)	0
Anemia	5 (7)	1 (3)
Neuropathy[a]	5 (7)	0
Vomiting	5 (7)	0
Abdominal pain	4 (5)	1 (3)
Thrombocytopenia[a]	4 (5)	1 (3)

Immune-Mediated AEs[b]

n (%)	EZFB (N=74)	Rego (N=35)
Any grade immune-mediated AE (per sponsor)[b]	12 (16)	2 (6)
Grade ≥3 event[c]	4 (5)	0
Hypothyroidism, any grade	4 (5)	2 (6)
Adrenal insufficiency, any grade	2 (3)	0
Pneumonitis, any grade Grade ≥3	2 (3) 0	0 0
Grade ≥3 skin reaction Pruritus Maculopapular rash	2 (3) 1 (1) 1 (1)	0
Hemolytic anemia Grade 3	2 (3) 2 (3)	0
Hemophagocytic lymphohistiocytosis, any grade	0	1 (3)
Hyperthyroidism, any grade	1 (1)	0

Date cutoff date: November 13, 2023.
TEAEs are any AEs that start on or after the study treatment start date/time and within 90 days of the last dose date for all zim arms (30 days for non-zim arms), excluding any AEs occurring after initiation of new anti-cancer therapy. AE reported terms were coded using the MedDRA version 24.0. Preferred terms are listed unless otherwise noted.
[a] Indicates grouped term. [b] Immune-mediated reactions programmatically identified via sponsor-defined preferred terms. [c] There were no grade 5 immune-mediated AEs .
AE, adverse event; EZFB, etrumadenant + zimberelimab + mFOLFOX-6 + bevacizumab; MedDRA, Medical Dictionary for Regulatory Activities; rego, regorafenib; TEAE, treatment-emergent AE; WBC, white blood cell; zim, zimberelimab.

Conclusions

- This is the first randomized, phase 2, proof-of-concept study showing EZFB significantly improves PFS and OS compared with standard-of-care in microsatellite-stable 3L mCRC
  - Longest OS reported for a randomized clinical trial in 3L mCRC
  - Meaningful improvement shown across all subgroups, including 20-month median OS in patients with liver metastasis
- Safety was consistent with the individual study drugs and manageable with no treatment related deaths
- These data demonstrate the therapeutic potential of etruma in CRC and supports further development of EZFB as a regimen in CRC

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