2022 ASCO® ANNUAL MEETING

Panitumumab plus mFOLFOX6 versus Bevacizumab plus mFOLFOX6 as first-line treatment in patients with *RAS* wild-type metastatic colorectal cancer: results from the phase 3 PARADIGM trial

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Introduction

- Adding an anti-EGFR or anti-VEGF antibody to chemotherapy improves overall survival (OS) of patients with unresectable metastatic colorectal cancer (mCRC) up to 30 months.[1,2]
- In comparative trials, post-hoc analyses of *RAS* wild-type (WT) patients show inconclusive results:
  - US CALGB/SWOG 80405: OS was similar for cetuximab and bevacizumab (HR, 0.88; 95% CI, 0.72-1.08)[1]
  - EU FIRE-3: Cetuximab improved OS vs. bevacizumab (HR, 0.70; 95% CI, 0.54-0.90)[3]
- The benefit of an anti-EGFR antibody may be enriched in *RAS* WT patients with primary tumor originating in the left side of the colon and rectum.[4]
- PARADIGM is the first prospective trial to test the superiority of panitumumab vs. bevacizumab plus standard chemotherapy for patients with *RAS* WT and left-sided mCRC.[5,6]

EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; OS, overall survival; mCRC, metastatic colorectal cancer; WT, wild type, HR, hazard ratio; CI, confidence interval.

1. Venook AP, et al. JAMA. 2017;317:2392-2401. 2. Heinemann V, et al. Lancet Oncol. 2014;15:1065-1075. 3. Stintzing S, et al. Lancet Oncol. 2016;17:1426-1434. 4. Arnold D, et al. Ann Oncol. 2017;28:1713-1729.
5. Yoshino T, et al. Clin Colorectal Cancer 2017;16:158-63. 6. Yoshino T, et al. J Clin Oncol 2021; 39 (3 suppl):85.

PARADIGM Trial Design

Phase 3, randomized, open-label, multicenter study (NCT02394795)

Patients with *RAS* WT mCRC

- Unresectable disease
- No previous chemotherapy[a]
- Age: 20–79 years
- ECOG performance status 0–1
- At least 1 evaluable lesion
- Adequate organ function
- Life expectancy ≥ 3 months

N=823

R 1:1

Panitumumab +mFOLFOX6[b]

Bevacizumab +mFOLFOX6[b]

Primary endpoint

- OS: left-sided[c] population; if significant, analyzed in overall population

Secondary endpoints

- PFS, RR, DOR, R0 resection: left-sided[c] and overall populations
- Safety: all treated patients

Exploratory endpoints

- ETS, depth of response, DCR: left-sided[c] and overall populations

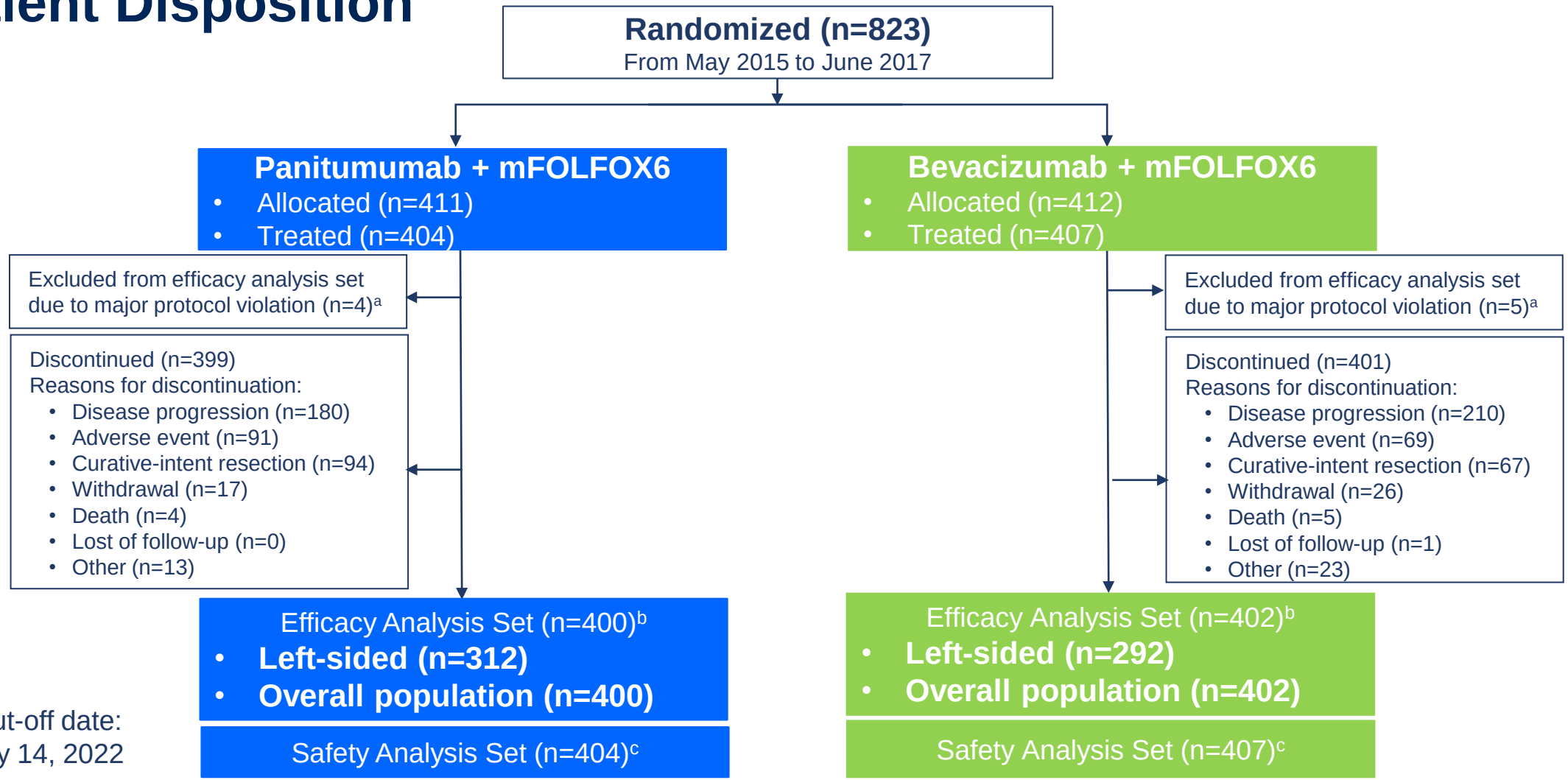
Stratification factors

- Institution
- Age: 20–64 vs 65–79 years
- Liver metastases: present vs absent

DCR, disease control rate; DOR; duration of response; ECOG, Eastern Cooperative Oncology Group; ETS, early tumor shrinkage; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression free survival; RR, response rate; R0, curative resection; WT, wild type.

[a]Adjuvant fluoropyrimidine monotherapy allowed if completed > 6 months before enrollment. [b]Until disease progression, unacceptable toxicity, withdrawal of consent or investigator's judgement or curative intent resection. [c]Primary tumor in descending colon, sigmoid colon, rectosigmoid, and rectum.

Patient Disposition



Data cut-off date:
January 14, 2022

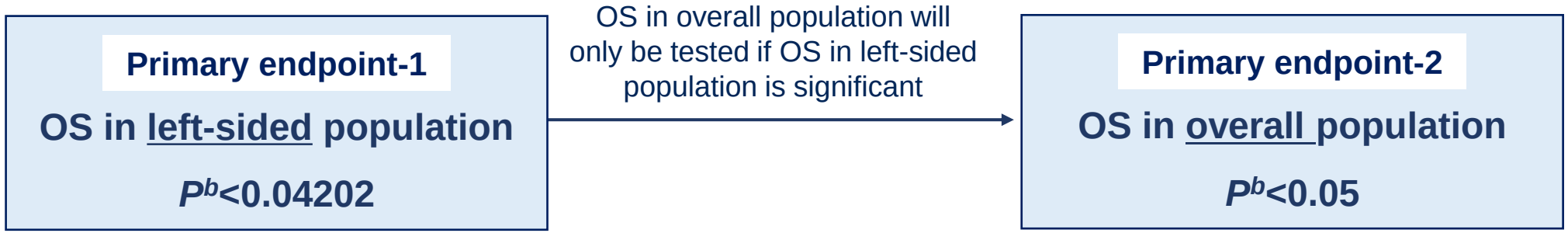
Median follow-up time: 61 months

[a]Panitumumab arm (2 patients [pts] with Stage 3 and 2 pts with previous chemotherapy), Bevacizumab arm (3 pts with Stage 3, one pt with previous chemotherapy and one pt with prostate cancer with rectal invasion). [b]Randomized pts who received at least one dose of study treatment and satisfied the eligibility criteria. [C]Randomized pts who received at least one dose of study treatment.

Statistical Considerations

Final Analysis (protocol version 3[1], July 2020):

- OS as primary endpoint was hierarchically tested in the following order
- All data reported are based on a data base lock of February 10, 2022[a]



- Targeted number of events: 420 events (deaths) in left-sided population
- 80% power to detect HR = 0.74; two-sided significance level of 0.04202 determined on the alpha spending function approach after one interim analysis

[a]Data cut-off date: January 14, 2022. [b]Log-rank test stratified by age (20–64 vs. 65–79 years) and liver metastases (present vs. absent).[2]

Revision History of Statistical analysis Plan

- The initial protocol (version 1, March 2015) had OS as primary endpoint and total sample size of 800 to detect OS HR of 0.76, with 80% power at two-sided significance level of 0.05.[2]
- Protocol revision (version 2, May 2019) changed primary analysis to detect significant difference in OS in overall and left-sided populations, with a two-side type 1 error of 0.025 for each population.[3]

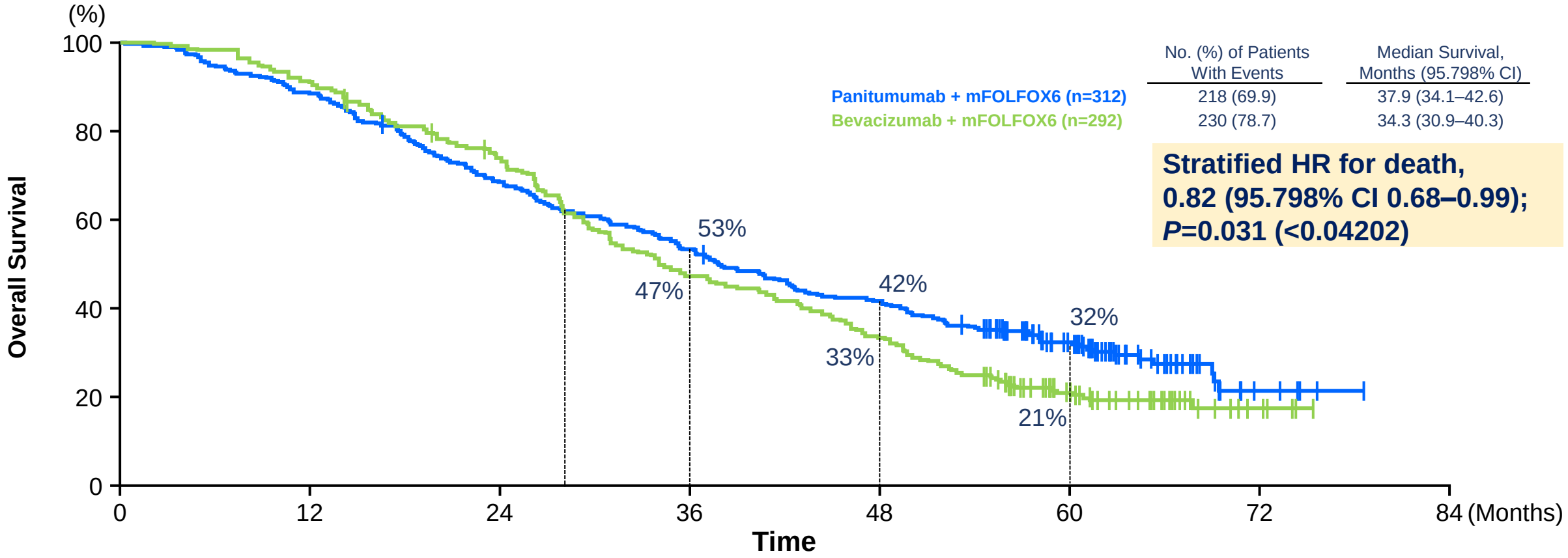
1. Yoshino T, et al. *J Clin Oncol* 2021; 39 (3 suppl):85. 2. Yoshino T, et al. *Clin Colorectal Cancer*. 2017;16(2):158-163. 3. Muro K, et al. *Ann Oncol*. 2019;30(suppl 4):iv10.

Baseline Patient Characteristics

Characteristic	Left-sided Population		Overall Population	
	Panitumumab + mFOLFOX6 (n=312)	Bevacizumab + mFOLFOX6 (n=292)	Panitumumab + mFOLFOX6 (n=400)	Bevacizumab + mFOLFOX6 (n=402)
Age category, n (%)				
20–64 years	138 (44.2)	127 (43.5)	164 (41.0)	168 (41.8)
65–79 years	174 (55.8)	165 (56.5)	236 (59.0)	234 (58.2)
Sex, female, n (%)	104 (33.3)	91 (31.2)	148 (37.0)	134 (33.3)
ECOG performance status, n (%)				
0	261 (83.7)	231 (79.1)	328 (82.0)	319 (79.4)
1	51 (16.3)	61 (20.9)	71 (17.8)	83 (20.6)
Primary tumor location, n (%)[a]				
Left-sided	312 (100.0)	292 (100.0)	312 (78.0)	292 (72.6)
Right-sided	0	0	84 (21.0)	103 (25.6)
Number of metastatic organs, n (%)				
1	155 (49.7)	147 (50.3)	196 (49.0)	194 (48.3)
≥2	157 (50.3)	145 (49.7)	204 (51.0)	208 (51.7)
Metastatic site, n (%)				
Liver	225 (72.1)	206 (70.5)	275 (68.8)	278 (69.2)
Liver as only site of metastasis	90 (28.8)	89 (30.5)	105 (26.3)	113 (28.1)
Prior treatment, n (%)				
Primary tumor resection	185 (59.3)	193 (66.1)	239 (59.8)	272 (67.7)
Radiotherapy	2 (0.6)	2 (0.7)	2 (0.5)	3 (0.7)
Adjuvant chemotherapy[b]	17 (5.4)	16 (5.5)	22 (5.5)	20 (5.0)

[a] 4 patients receiving panitumumab and 7 patients receiving bevacizumab had multiple primary lesions in both the left-sided and right-sided. [b] Adjuvant fluoropyrimidine monotherapy allowed if completed > 6 months before enrollment.

Primary Endpoint-1; Overall Survival in Left-sided Population

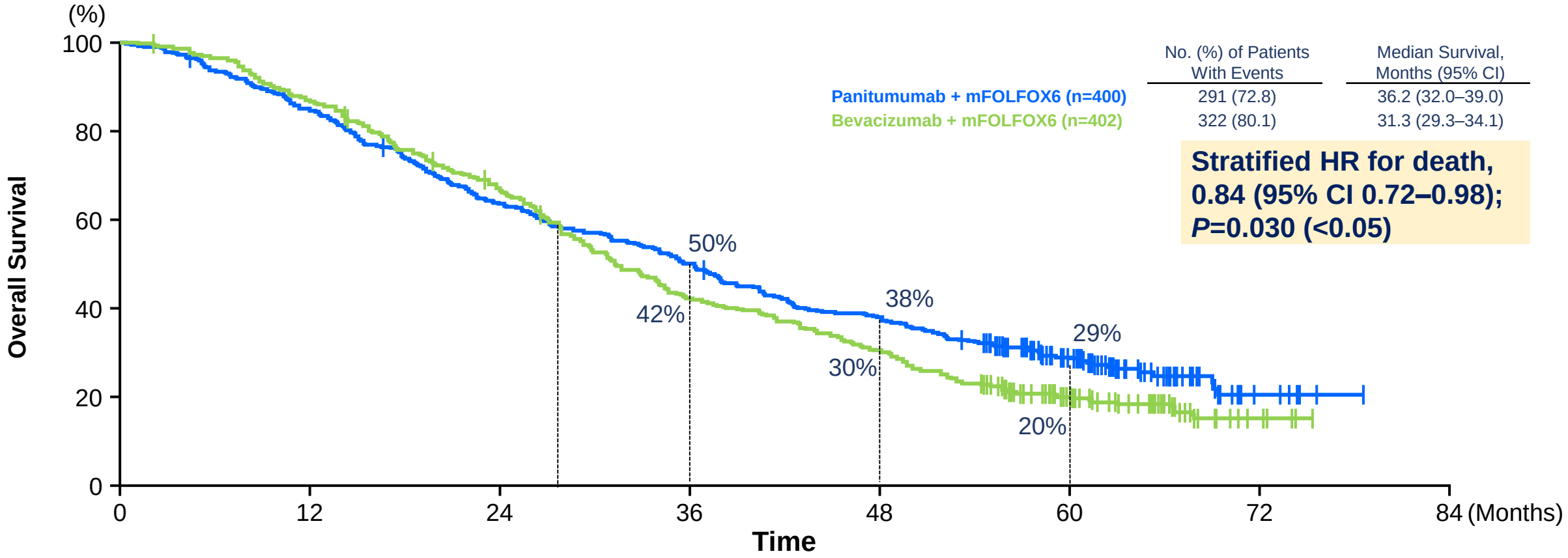


	No. (%) of Patients With Events	Median Survival, Months (95.798% CI)
Panitumumab + mFOLFOX6 (n=312)	218 (69.9)	37.9 (34.1–42.6)
Bevacizumab + mFOLFOX6 (n=292)	230 (78.7)	34.3 (30.9–40.3)

Stratified HR for death, 0.82 (95.798% CI 0.68–0.99); *P*=0.031 (<0.04202)

No. at risk								
Panitumumab	312	276	213	166	129	68	5	0
Bevacizumab	292	266	212	136	96	40	5	0

Primary Endpoint-2; Overall Survival in Overall Population



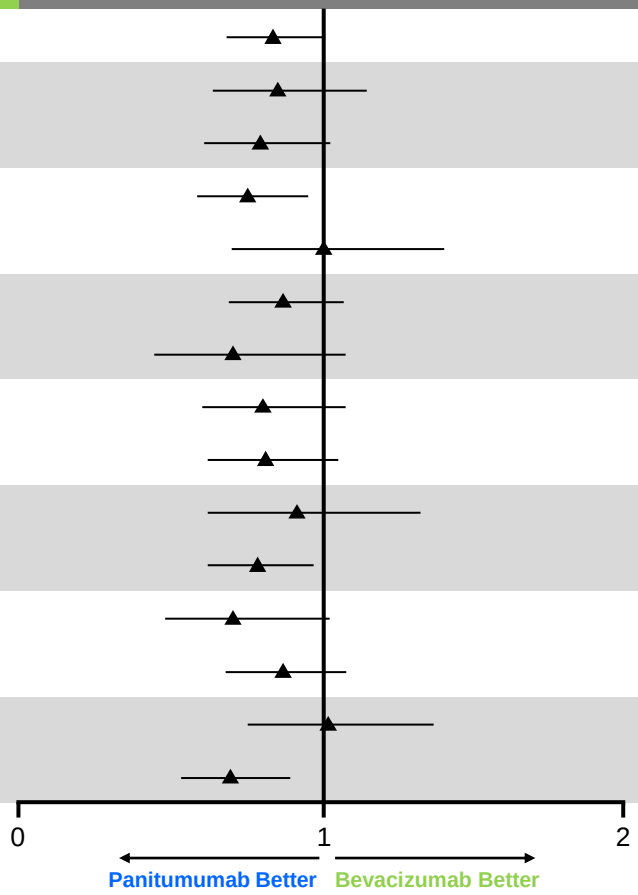
	No. (%) of Patients With Events	Median Survival, Months (95% CI)
Panitumumab + mFOLFOX6 (n=400)	291 (72.8)	36.2 (32.0–39.0)
Bevacizumab + mFOLFOX6 (n=402)	322 (80.1)	31.3 (29.3–34.1)

Stratified HR for death, 0.84 (95% CI 0.72–0.98); *P*=0.030 (<0.05)

No. at risk								
Panitumumab	400	338	253	199	150	80	6	0
Bevacizumab	402	348	265	166	119	54	5	0

Subgroup Analyses of Overall Survival in Left-sided Population

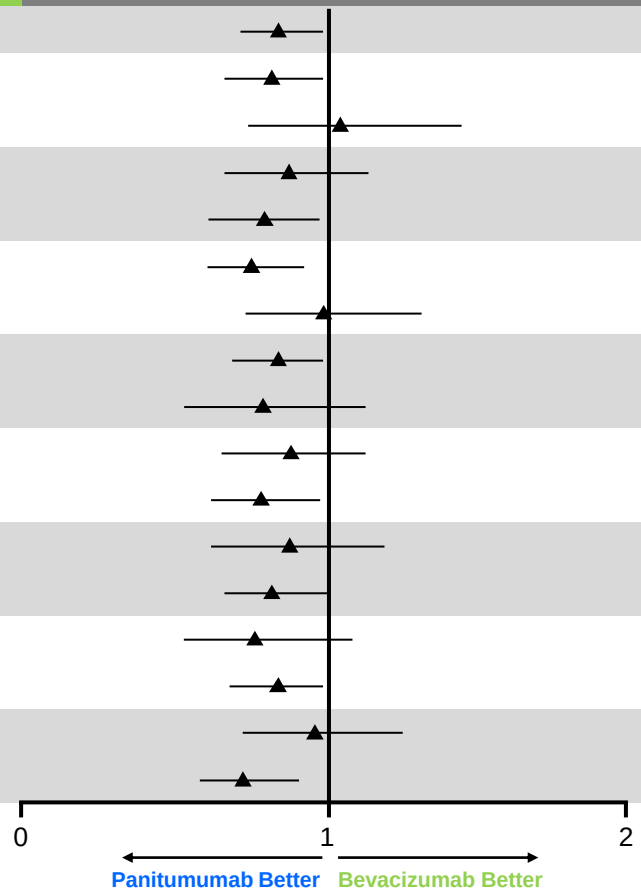
Subgroup		Events/Patients: Panitumumab + mFOLFOX6	Events/Patients: Bevacizumab + mFOFLFOX6	Hazard Ratio (95% CI)
	Overall*	218/312	230/292	0.82 (0.68–0.99)
Age	20-64 yr	95/138	95/127	0.86 (0.65–1.15)
	65-79 yr	123/174	135/165	0.80 (0.63–1.02)
Sex	Male	147/208	164/201	0.76 (0.61–0.95)
	Female	71/104	66/91	1.00 (0.71–1.40)
ECOG PS	0	182/261	179/231	0.87 (0.70–1.07)
	1	36/51	51/61	0.70 (0.46–1.08)
No. of organs with metastasis	0-1	91/155	100/147	0.81 (0.61–1.08)
	≥2	127/157	130/145	0.81 (0.64–1.04)
Liver metastasis	No	56/87	59/86	0.91 (0.63–1.32)
	Yes	162/225	171/206	0.79 (0.63–0.97)
Organs with metastasis	Liver only	52/90	65/89	0.71 (0.49–1.02)
	Other	166/222	165/203	0.87 (0.70–1.07)
Primary tumor resection	No	101/127	81/99	1.02 (0.76–1.37)
	Yes	117/185	149/193	0.69 (0.54–0.89)



*Stratified Hazard Ratio is shown with 95.798% CI.

Subgroup Analyses of Overall Survival in Overall Population

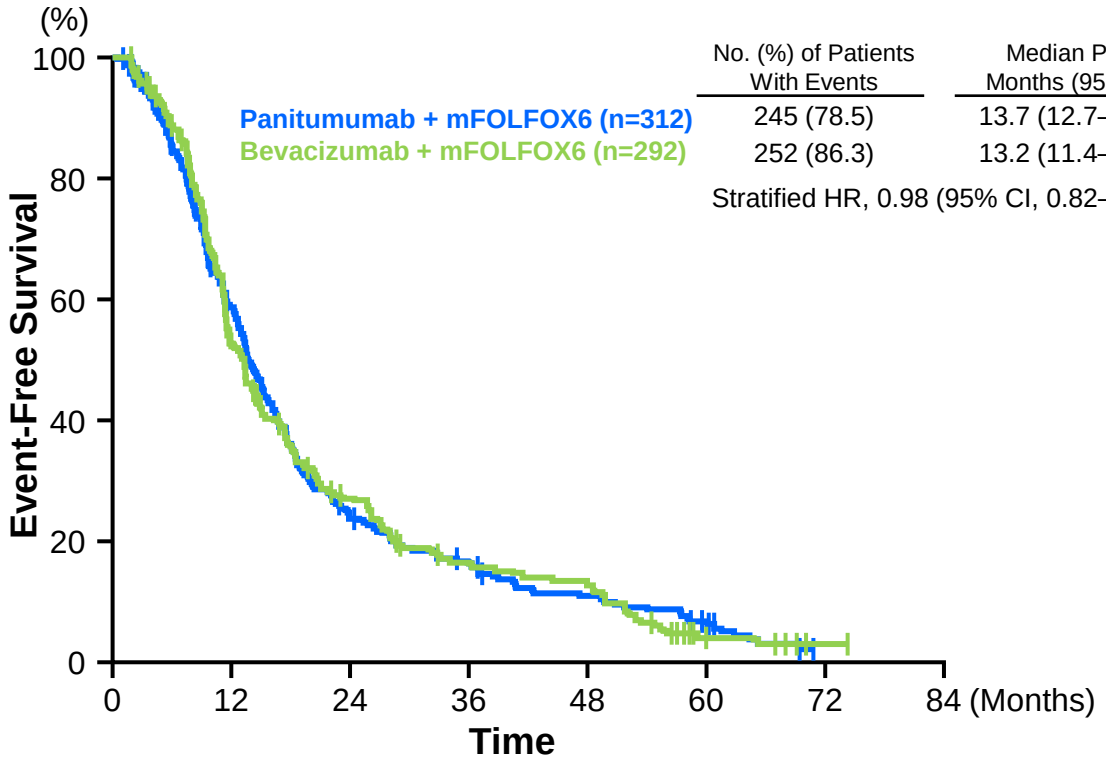
Subgroup		Events/Patients: Panitumumab + mFOLFOX6	Events/Patients: Bevacizumab + mFOFLFOX6	Hazard Ratio (95% CI)
	Overall*	291/400	322/402	0.84 (0.72–0.98)
Primary tumor location	Left-sided	218/312	230/292	0.83 (0.69–1.00)
	Right-sided	71/84	85/103	1.06 (0.77–1.45)
Age	20-64 yr	117/164	129/168	0.89 (0.69–1.14)
	65-79 yr	174/236	193/234	0.81 (0.66–1.00)
Sex	Male	185/252	221/268	0.77 (0.63–0.93)
	Female	106/148	101/134	1.00 (0.76–1.31)
ECOG PS	0	237/328	253/319	0.85 (0.71–1.02)
	1	53/71	69/83	0.79 (0.56–1.14)
No. of organs with metastasis	0-1	123/196	133/194	0.88 (0.69–1.13)
	≥2	168/204	189/208	0.79 (0.64–0.98)
Liver metastasis	No	83/125	89/124	0.88 (0.65–1.19)
	Yes	208/275	233/278	0.83 (0.68–1.00)
Organs with metastasis	Liver only	66/105	83/113	0.78 (0.56–1.08)
	Other	225/295	239/289	0.85 (0.71–1.02)
Primary tumor resection	No	132/161	110/130	0.97 (0.75–1.25)
	Yes	159/239	212/272	0.74 (0.60–0.91)



*Stratified Hazard Ratio is shown with 95% CI.

Progression-free Survival[a]

Left-sided Population

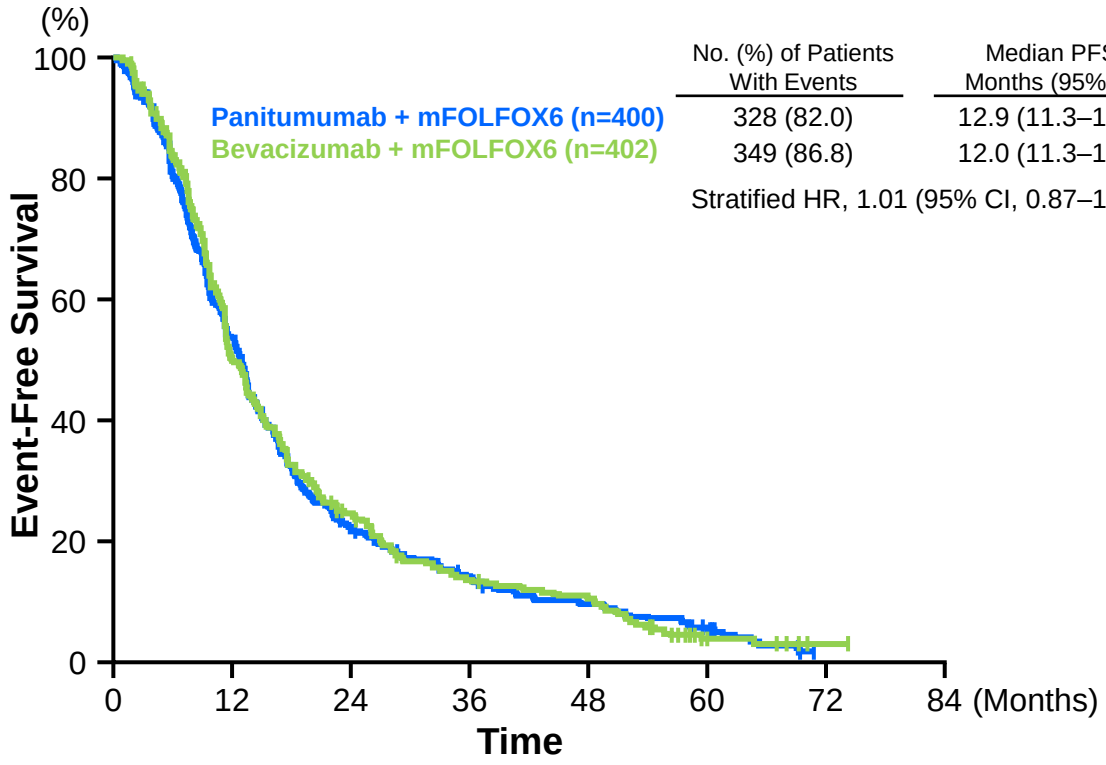


	No. (%) of Patients With Events	Median PFS, Months (95% CI)
Panitumumab + mFOLFOX6 (n=312)	245 (78.5)	13.7 (12.7–15.3)
Bevacizumab + mFOLFOX6 (n=292)	252 (86.3)	13.2 (11.4–14.5)

Stratified HR, 0.98 (95% CI, 0.82–1.17)

No. at risk								
Panitumumab	312	149	59	38	24	13	0	0
Bevacizumab	292	139	67	40	31	5	1	0

Overall Population



	No. (%) of Patients With Events	Median PFS, Months (95% CI)
Panitumumab + mFOLFOX6 (n=400)	328 (82.0)	12.9 (11.3–13.6)
Bevacizumab + mFOLFOX6 (n=402)	349 (86.8)	12.0 (11.3–13.5)

Stratified HR, 1.01 (95% CI, 0.87–1.18)

No. at risk								
Panitumumab	400	179	71	43	28	15	0	0
Bevacizumab	402	182	83	45	35	6	1	0

[a]Patients who underwent curative-intent resection were censored at the last tumor evaluable assessment date before the resection.

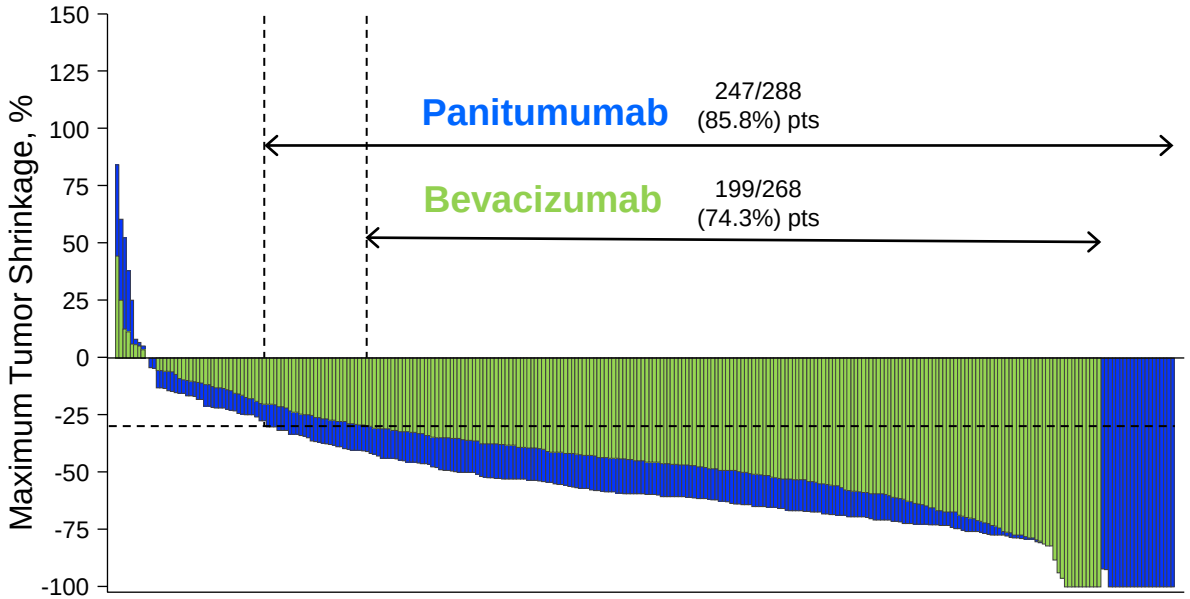
Other Efficacy Outcomes

Parameter	Left-sided Population		Overall Population	
	Panitumumab + mFOLFOX6 (n=308)	Bevacizumab + mFOLFOX6 (n=287)	Panitumumab + mFOLFOX6 (n=394)	Bevacizumab + mFOLFOX6 (n=397)
Response rate, % (95% CI)	80.2 (75.3–84.5)	68.6 (62.9–74.0)	74.9 (70.3–79.1)	67.3 (62.4–71.9)
Difference, % (95% CI)	11.2 (4.4–17.9)		7.7 (1.5–13.8)	
DCR, % (95% CI)	97.4 (94.9–98.9)	96.5 (93.7–98.3)	94.9 (92.3–96.9)	95.5 (92.9–97.3)
Median DOR,[a] months (95% CI)	13.1 (11.1–14.8)	11.2 (9.6–13.1)	11.9 (10.5–13.4)	10.7 (9.5–12.2)
R0 rate,[b] % (95% CI)	18.3 (14.1–23.0)	11.6 (8.2–15.9]	16.5 (13.0–20.5)	10.9 (8.1–17.1)

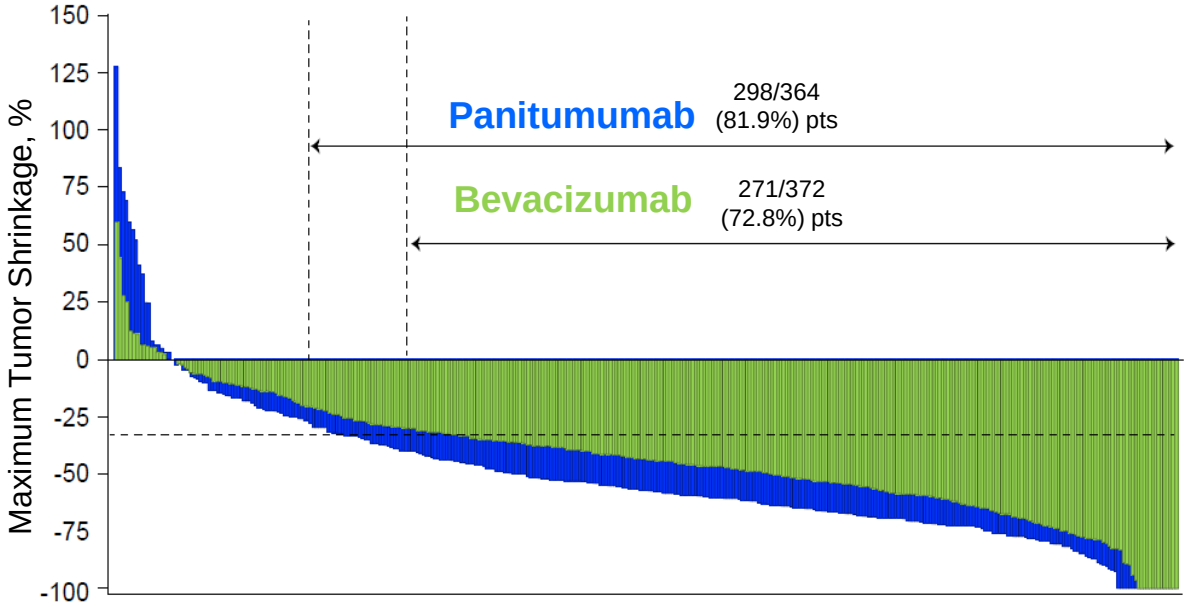
RR, response rate; DCR, disease control rate; DOR, duration of response; R0, curative resection.
[a] DOR was evaluated in patients with complete or partial response.
[b] R0 rate was evaluated in all the patients of efficacy analysis population (left-sided: n=312 for panitumumab and n=292 for bevacizumab; overall: n=400 and 402, respectively).

Other Efficacy Outcome: Depth of Response

Left-Sided Population



Overall Population



Horizontal dotted line at 30% indicates response per RECIST v1.1.

	Left-sided Population		Overall Population	
	Panitumumab + mFOLFOX6 (n=288)	Bevacizumab + mFOLFOX6 (n=268)	Panitumumab + mFOLFOX6 (n=364)	Bevacizumab + mFOLFOX6 (n=372)
Median, %	-59.4	-43.6	-57.3	-43.6

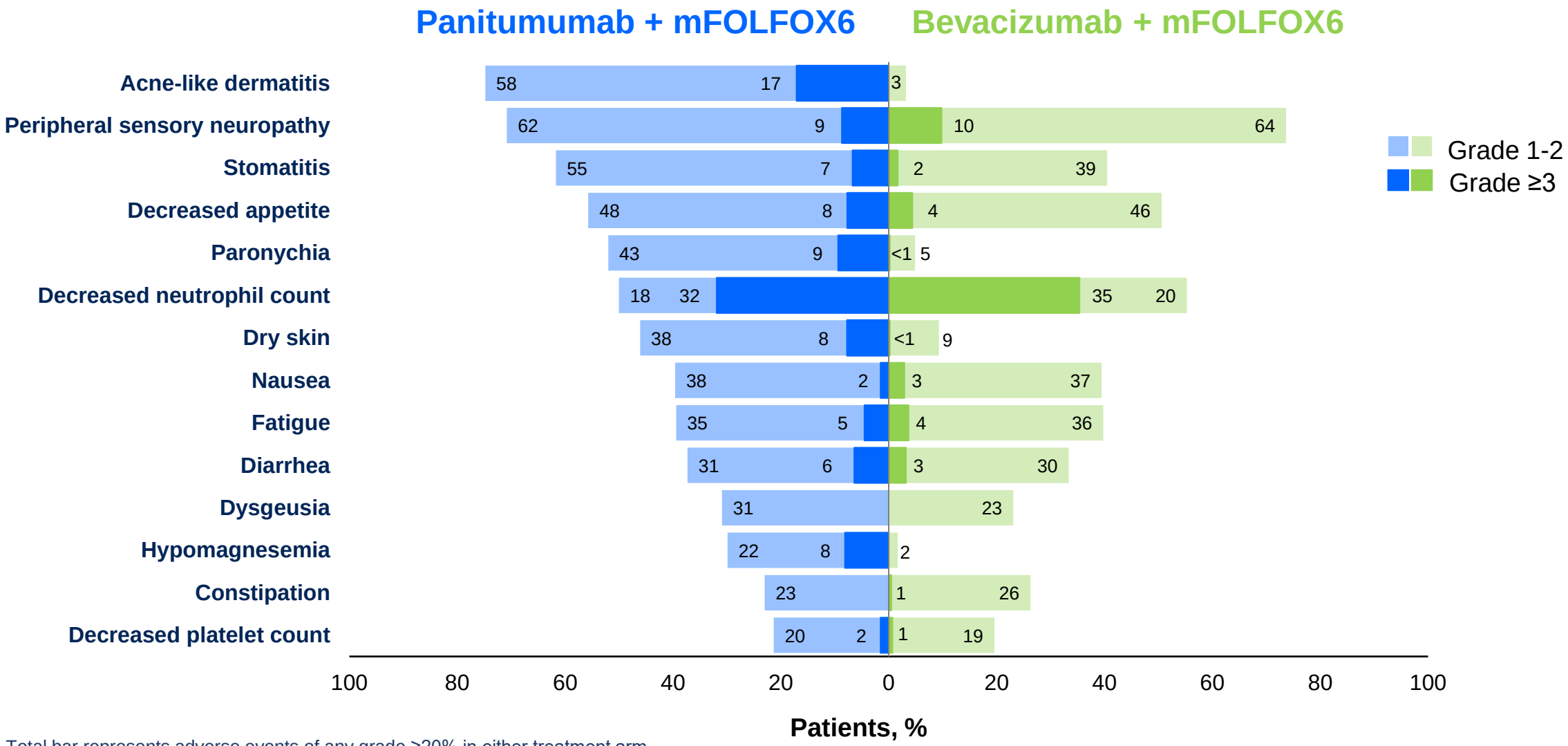
Depth of response was assessed in patients with measurable lesions at baseline.

Summary of Adverse Events

Adverse Event, n (%)	Panitumumab + mFOLFOX6 (n=404)	Bevacizumab + mFOLFOX6 (n=407)
Any adverse event	402 (99.5)	399 (98.0)
Grade ≥3 adverse events	290 (71.8)	264 (64.9)
Serious adverse events related to study treatment	72 (17.8)	44 (10.8)
Adverse events leading to discontinuation of study treatment	96 (23.8)	75 (18.4)

No new safety signals were observed.
Treatment-related deaths:
Panitumumab (n=10), 4 with interstitial lung disease and 1 patient each with lung disorder, pneumonia, pneumonitis, pneumonia and pancytopenia, sepsis and peritonitis, and cerebral hemorrhage
Bevacizumab (n=2), 1 with respiratory failure and 1 was not specified

Adverse Events Reported in ≥ 20% of Patients



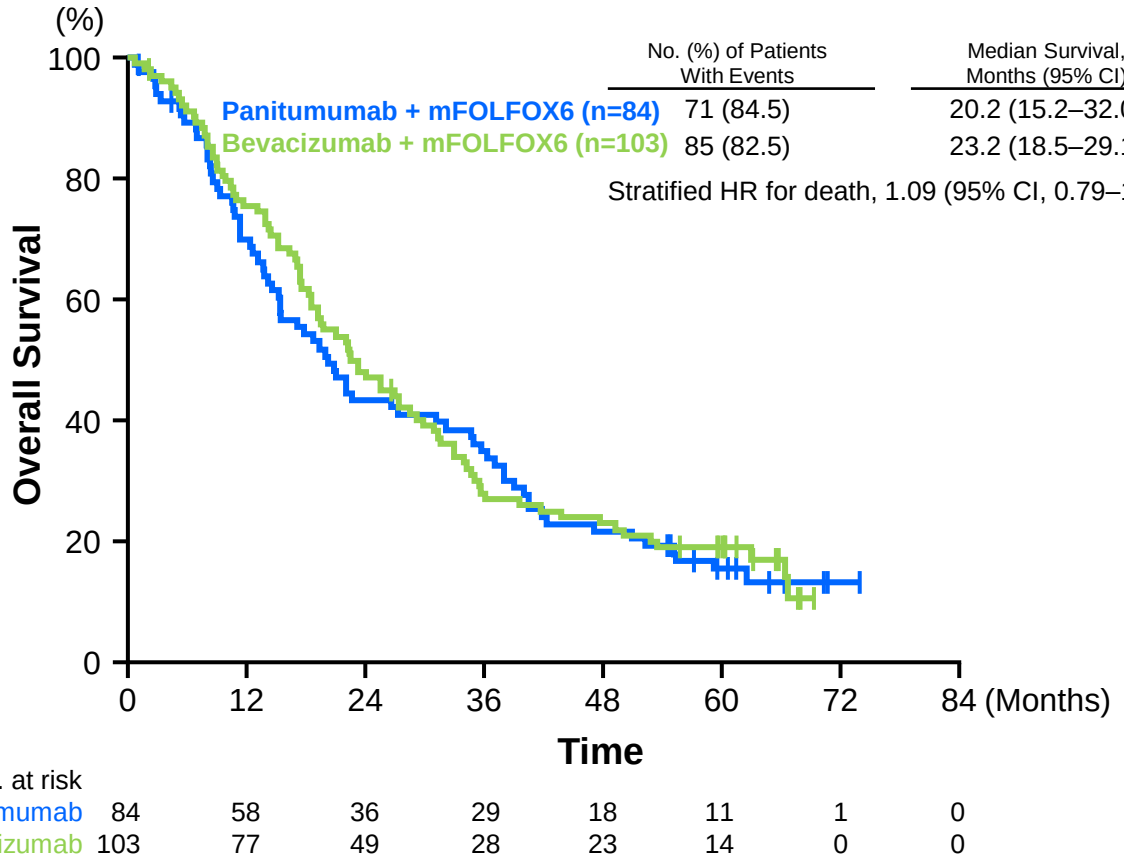
Total bar represents adverse events of any grade ≥20% in either treatment arm.

Subsequent Systemic Treatment

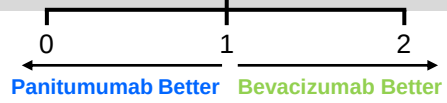
	Left-sided Population		Overall Population	
	Panitumumab + mFOLFOX6 (n=312)	Bevacizumab + mFOLFOX6 (n=292)	Panitumumab + mFOLFOX6 (n=400)	Bevacizumab + mFOLFOX6 (n=402)
Patients receiving subsequent line of therapy, n (%)				
Second-line therapy	**253 (81.1)**	**241 (82.5)**	**321 (80.3)**	**329 (81.8)**
Third-line therapy	**195 (62.5)**	**190 (65.1)**	**242 (60.5)**	**261 (64.9)**
Fourth-line therapy	**130 (41.7)**	**139 (47.6)**	**160 (40.0)**	**185 (46.0)**
Post-study treatment during any lines of therapy				
Cytotoxic Agents				
Fluoropyrimidine	232 (74.4)	222 (76.0)	293 (73.3)	300 (74.6)
Irinotecan	191 (61.2)	190 (65.1)	245 (61.3)	258 (64.2)
Oxaliplatin	81 (26.0)	60 (20.5)	99 (24.8)	77 (19.2)
VEGF inhibitor	**168 (53.8)**	**166 (56.8)**	**224 (56.0)**	**227 (56.5)**
Bevacizumab	139 (44.6)	148 (50.7)	185 (46.3)	192 (47.8)
Ramucirumab	32 (10.3)	26 (8.9)	44 (11.0)	46 (11.4)
Aflibercept	20 (6.4)	13 (4.5)	25 (6.3)	26 (6.5)
EGFR inhibitor	**97 (31.1)**	**160 (54.8)**	**123 (30.8)**	**222 (55.2)**
Panitumumab	82 (26.3)	134 (45.9)	101 (25.3)	183 (45.5)
Cetuximab	17 (5.4)	36 (12.3)	24 (6.0)	49 (12.2)
Trifluridine/tipiracil hydrochloride	69 (22.1)	77 (26.4)	90 (22.5)	95 (23.6)
Regorafenib	25 (8.0)	33 (11.3)	37 (9.3)	44 (10.9)

Anti-PD-1/PD-L1 therapies, ipilimumab, and BRAF/MEK inhibitors were used in a few patients.

OS and Subgroup Analysis in Right-sided Population



Subgroup		Events/Patients: Panitumumab + mFOLFOX6	Events/Patients: Bevacizumab + mFOLFOX6	Hazard Ratio (95% CI)
	Overall*	71/84	85/103	1.09 (0.79-1.51)
Age	20-64 yr	22/26	32/39	1.26 (0.73-2.17)
	65-79 yr	49/58	53/64	0.97 (0.66-1.44)
Sex	Male	37/41	51/61	1.04 (0.68-1.60)
	Female	34/43	34/42	1.08 (0.67-1.74)
ECOG PS	0	54/65	68/82	0.96 (0.67-1.37)
	1	16/18	17/21	1.33 (0.66-2.67)
No. of organs with metastasis	0-1	31/40	30/44	1.27 (0.77-2.10)
	≥2	40/44	55/59	0.94 (0.63-1.42)
Liver metastasis	No	26/35	29/37	0.87 (0.51-1.49)
	Yes	45/49	56/66	1.23 (0.83-1.83)
Organs with metastasis	Liver only	13/14	15/21	1.66 (0.79-3.50)
	Other	58/70	70/82	0.93 (0.66-1.32)
Primary tumor resection	No	30/33	28/30	0.87 (0.51-1.45)
	Yes	41/51	57/73	1.09 (0.73-1.63)



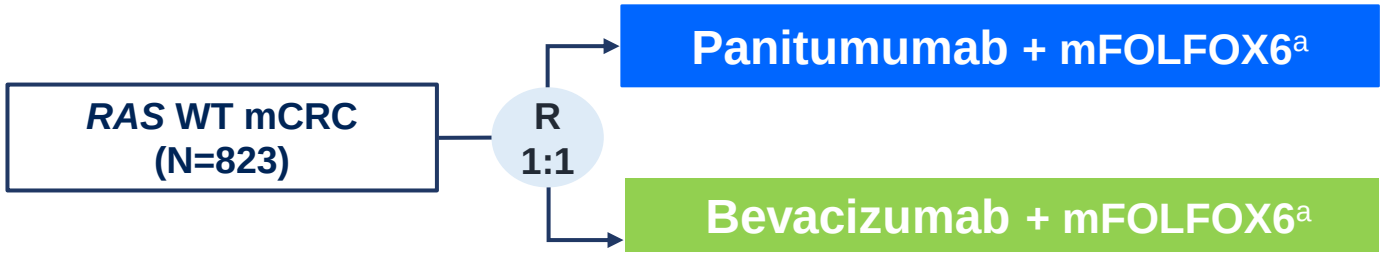
*Stratified Hazard Ratio is shown with 95% CI.

Conclusions

- The phase 3 PARADIGM trial met the primary endpoint, demonstrating the superiority of first-line panitumumab versus bevacizumab in combination with mFOLFOX6 in the left-sided and overall mCRC populations.
  - Left-sided: mOS 37.9 vs. 34.3 months, HR = 0.82 (95.798% CI: 0.68–0.99), *P*=0.031
  - Overall: mOS 36.2 vs. 31.3 months, HR = 0.84 (95% CI: 0.72–0.98), *P*=0.030
  - mOS exceeded 36 months in panitumumab patients, while those in bevacizumab were consistent with previous reports
  - (Exploratory) Right-sided: mOS 20.2 vs. 23.2 months, HR=1.09 (95% CI: 0.79–1.51)
- Although PFS was comparable between two arms, RR and R0 resection rates were higher with panitumumab in the left-sided and overall populations versus bevacizumab.
  - Left-sided: mPFS 13.7 vs. 13.2, RR 80.2 vs. 68.6%, R0 resection rates 18.3 vs. 11.6%
  - Overall: mPFS 12.9 vs. 12.0, RR 74.9 vs. 67.3%, R0 resection rates 16.5 vs. 10.9%
- No new safety signals were observed; both treatments had manageable safety profiles.
- These results support panitumumab + mFOLFOX6 as a first-line therapy for patients with *RAS* WT and left-sided mCRC.

Future Directions: Biomarker Multi-omics Analysis

- A large-scale biomarker analysis is currently underway using plasma and tumor tissue samples collected pre- and post-treatments (NCT02394834).
- Potential biomarkers on outcomes will be reported in upcoming meetings.



Analysis Items

- Tissue and plasma DNA targeted sequencing
- Tissue RNA targeted sequencing
- Signature (MSI, TMB, CMS, IFN, etc.)
- IHC
- Multiplex IF

with Artificial Intelligence

CMS, consensus molecular subtypes; IF, immunofluorescence; IFN, interferon gene signature; IHC, immunohistochemistry; mCRC, metastatic colorectal cancer; MSI, Microsatellite instability; TMB, tumor mutational burden; WT, wild type. [a]Until disease progression, unacceptable toxicity, withdrawal of consent or investigator's judgement or curative intent resection.

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