Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Additional Inclusion and Exclusion Criteria

Inclusion criteria: Measurable disease, Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1, life expectancy ≥3 months, and adequate organ function. Prior therapies such as ramucirumab, aflibercept, regorafenib, and trifluridine-tipiracil were permitted but not required.

Exclusion criteria: Chemotherapy, biologic anticancer therapy, investigational agent, or central field radiation therapy ≤28 days before randomization (local or stereotactic radiation ≤14 days before randomization); history of allergic reactions to therapeutic antibodies; known dihydropyrimidine dehydrogenase deficiency; known untreated central nervous system metastases; significant cardiac risk factors; recent surgeries, procedures, or endoluminal stents; and history of inflammatory disorders, autoimmune disorders, immunosuppression, immunodeficiency, or infectious conditions.

eMethods 2. Criteria for Bevacizumab and Atezolizumab Interruption and Discontinuation

Infusion of bevacizumab was interrupted if an infusion-related reaction was suspected. Bevacizumab dosing was temporarily suspended if patients experienced a serious adverse event (AE) or a grade 3/4 nonserious AE assessed by the investigator as related to bevacizumab. If the AE resolved to grade ≤1, bevacizumab could be restarted at the same dose level. If bevacizumab was delayed due to toxicity for >42 days after the next dose should have been given, patients permanently discontinued bevacizumab treatment. Atezolizumab treatment was interrupted if patients experienced any of the following: grade 2 pulmonary AEs, including pneumonitis; grade 2 total bilirubin, alanine aminotransferase (ALT), or aspartate aminotransferase (AST) increase; grade 2 ocular AEs, infusion-related reaction, or immune-related neuropathy; grade 2/3 diarrhea, colitis, or immune-related pancreatitis; grade 3 dermatologic AE; grade 3/4 hyperglycemia or amylase/lipase elevation; symptomatic hypothyroidism or hyperthyroidism; and grade 2–4 symptomatic adrenal insufficiency. If these AEs were not resolved to grade ≤1 within 12 weeks, atezolizumab treatment was permanently discontinued. Other criteria for atezolizumab discontinuation were: any-grade myasthenia gravis or Guillain-Barré syndrome; any-grade immune-related meningoencephalitis; grade 3/4 pulmonary AEs; grade 3/4 total bilirubin, ALT, or AST increase (>3× upper limit of normal); grade 3/4 ocular AEs, infusion-related reaction, or immune-related neuropathy; and grade 4 diarrhea, colitis, immune-related pancreatitis, or dermatologic AEs. Patients received full supportive care, including blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions.

eTable 1. Dosing Information for Atezolizumab[a] and Placebo

	Investigational Arm (Capecitabine + Bevacizumab + Atezolizumab) (n=81[b])	Placebo Arm (Capecitabine + Bevacizumab + Placebo) (n=46)	Total (N=127)
Treatment duration (days)			
N	81	46	127
Mean (SD)	160.5 (149.7)	146.7 (144.4)	155.5 (147.4)
Median	125.0	90.5	120.0
Q1, Q3	55.0, 188.0	55.0, 186.0	55.0, 188.0
Range	(0.0–874.0)	(0.0–721.0)	(0.0–874.0)
Percentage of targeted dose			
N	81	46	127
Mean (SD)	96.5 (13.1)	96.2 (9.9)	96.4 (12.0)
Median	100.0	100.0	100.0
Q1, Q3	100.0, 100.0	100.0, 100.0	100.0, 100.0
Range	(33.3–100.0)	(66.7–100.0)	(33.3–100.0)
At least 1 dose delay, n (%)			
No	56 (69.1%)	32 (69.6%)	88 (69.3%)
Yes	25 (30.9%)	14 (30.4%)	39 (30.7%)
No. of dose delays			
N	25	14	39
Mean (SD)	2.0 (1.5)	1.6 (0.8)	1.8 (1.3)
Median	2.0	1.0	1.0
Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0
Range	(1.0–6.0)	(1.0–3.0)	(1.0–6.0)
At least 1 dose omission, n (%)			
No	75 (92.6%)	39 (84.8%)	114 (89.8%)
Yes	6 (7.4%)	7 (15.2%)	13 (10.2%)
No. of dose omissions			
N	6	7	13
Mean (SD)	1.7 (1.2)	1.4 (0.8)	1.5 (1.0)
Median	1.0	1.0	1.0
Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0
Range	(1.0–4.0)	(1.0–3.0)	(1.0–4.0)

[a]No reduction of the atezolizumab dose was allowed per protocol. [b]One patient never began protocol treatment.
Q, quartile; SD, standard deviation.

eTable 2. Dosing Information for Bevacizumab[a]

	Investigational Arm (Capecitabine + Bevacizumab + Atezolizumab) (n=81[b])	Placebo Arm (Capecitabine + Bevacizumab + Placebo) (n=46)	Total (N=127)
Treatment duration (days)			
N	81	46	127
Mean (SD)	160.5 (149.7)	146.7 (144.4)	155.5 (147.4)
Median	125.0	90.5	120.0
Q1, Q3	55.0, 188.0	55.0, 186.0	55.0, 188.0
Range	(0.0–874.0)	(0.0–721.0)	(0.0–874.0)
Percentage of targeted dose			
N	81	46	127
Mean (SD)	96.8 (10.3)	97.7 (9.2)	97.1 (9.9)
Median	100.0	100.2	100.0
Q1, Q3	97.9, 100.5	99.3, 101.7	99.1, 101.0
Range	(49.4–104.9)	(65.5–104.8)	(49.4–104.9)
At least 1 dose delay, n (%)			
No	56 (69.1%)	29 (63.0%)	85 (66.9%)
Yes	25 (30.9%)	17 (37.0%)	42 (33.1%)
No. of dose delays			
N	25	17	42
Mean (SD)	1.8 (1.3)	1.6 (0.8)	1.7 (1.1)
Median	1.0	1.0	1.0
Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0
Range	(1.0–5.0)	(1.0–3.0)	(1.0–5.0)
At least 1 dose omission, n (%)			
No	68 (84.0%)	40 (87.0%)	108 (85.0%)
Yes	13 (16.0%)	6 (13.0%)	19 (15.0%)
No. of dose omissions			
N	13	6	19
Mean (SD)	1.8 (1.3)	2.7 (3.6)	2.1 (2.2)
Median	1.0	1.0	1.0
Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0
Range	(1.0–5.0)	(1.0–10.0)	(1.0–10.0)

[a]No reduction of the bevacizumab dose was allowed per protocol. [b]One patient never began protocol treatment.
Q, quartile; SD, standard deviation.

eTable 3. Dosing Information for Capecitabine

	Investigational Arm (Capecitabine + Bevacizumab + Atezolizumab) (n=81[a])	Placebo Arm (Capecitabine + Bevacizumab + Placebo) (n=46)	Total (N=127)
Treatment duration (days)			
N	81	46	127
Mean (SD)	160.5 (149.7)	146.7 (144.4)	155.5 (147.4)
Median	125.0	90.5	120.0
Q1, Q3	55.0, 188.0	55.0, 186.0	55.0, 188.0
Range	(0.0–874.0)	(0.0–721.0)	(0.0–874.0)
Percentage of targeted dose			
N	81	46	127
Mean (SD)	79.3 (24.1)	85.9 (18.7)	81.7 (22.4)
Median	88.6	89.6	88.8
Q1, Q3	69.8, 94.9	82.6, 97.9	73.0, 95.9
Range	(0.0–106.3)	(0.0–107.8)	(0.0–107.8)
At least 1 dose delay, n (%)			
No	47 (58.0%)	26 (56.5%)	73 (57.5%)
Yes	34 (42.0%)	20 (43.5%)	54 (42.5%)
No. of dose delays			
N	34	20	54
Mean (SD)	1.9 (1.4)	1.6 (1.2)	1.8 (1.3)
Median	1.0	1.0	1.0
Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0
Range	(1.0–6.0)	(1.0–6.0)	(1.0–6.0)
At least 1 dose omission, n (%)			
No	31 (38.3%)	20 (43.5%)	51 (40.2%)
Yes	50 (61.7%)	26 (56.5%)	76 (59.8%)
No. of dose omissions			
N	50	26	76
Mean (SD)	2.5 (1.8)	2.9 (2.6)	2.6 (2.1)
Median	2.0	2.0	2.0
Q1, Q3	1.0, 4.0	1.0, 3.0	1.0, 3.5
Range	(1.0–10.0)	(1.0–12.0)	(1.0–12.0)
At least 1 dose reduction, n (%)			
Missing	2	1	3
No	46 (58.2%)	28 (62.2%)	74 (59.7%)
Yes	33 (41.8%)	17 (37.8%)	50 (40.3%)
No. of dose reductions			
N	33	17	50
Mean (SD)	1.5 (0.9)	1.2 (0.6)	1.4 (0.8)
Median	1.0	1.0	1.0
Q1, Q3	1.0, 2.0	1.0, 1.0	1.0, 2.0
Range	(1.0–5.0)	(1.0–3.0)	(1.0–5.0)

[a]One patient never began protocol treatment.
Q, quartile; SD, standard deviation.

eTable 4. *BRAF* Variation Status of Primary Analysis Population

	MSI Status				
	Missing (n=5)	**MSI-H or dMMR (n=13)**	**MSS/pMMR (n=110)**	**Total (N=128)**	***P* Value**
***BRAF* status, n (%)**					.2329[a]
Missing	1	0	11	11	
Mutant	0	2 (15.4)	6 (6.1)	8 (7.1)	
Wild-type	4	11 (84.6)	93 (93.9)	104 (92.9)	

[a]Fisher exact.
dMMR, deficient mismatch repair, MSI-H, microsatellite instability high; MSS, microsatellite stable; pMMR, proficient mismatch repair.

eTable 5. Sites of Metastatic Disease (mITT)

Site, n (%)	Investigational Arm (Capecitabine + Bevacizumab + Atezolizumab) (n=82)	Placebo Arm (Capecitabine + Bevacizumab + Placebo) (n=46)	Total (N=128)	*P* Value[a]
Abdominal wall				.3079
Yes	10 (12.2)	3 (6.5)	13 (10.2)	
No	72 (87.8)	43 (93.5)	115 (89.8)	
Bone				.0079
Yes	6 (7.3)	11 (23.9)	17 (13.3)	
No	76 (92.7)	35 (76.1)	111 (86.7)	
Brain				
No	82 (100)	46 (100)	128 (100)	
Liver				.4053
Yes	69 (84.1)	36 (78.3)	105 (82.0)	
No	13 (15.9)	10 (21.7)	23 (18.0)	
Lung				.5234
Yes	60 (73.2)	36 (78.3)	96 (75.0)	
No	22 (26.8)	10 (21.7)	32 (25.0)	
Lymph nodes				.1041
Yes	57 (69.5)	38 (82.6)	95 (74.2)	
No	25 (30.5)	8 (17.4)	33 (25.8)	
Pelvis				.8986
Yes	15 (18.3)	8 (17.4)	23 (18.0)	
No	67 (81.7)	38 (82.6)	105 (82.0)	
Peritoneum				.6238
Yes	21 (25.6)	10 (21.7)	31 (24.2)	
No	61 (74.4)	36 (78.3)	97 (75.8)	
Other				.8230
Yes	10 (12.2)	5 (10.9)	15 (11.7)	
No	72 (87.8%)	41 (89.1%)	113 (88.3)	

[a]Chi-square.
mITT, modified intent-to-treat.

eTable 6. Response Rates in the Investigational Arm by Sites of Metastatic Disease

Site	Nonresponder (n=75)	Responder (n=7)	Total (N=82)	*P* Value[a]
Abdominal wall				.3025
Yes	10 (100.0)	0 (0.0)	10 (12.2)	
No	65 (90.3%)	7 (9.7%)	72 (87.8%)	
Bone				.4591
Yes	5 (83.3)	1 (16.7)	6 (7.3)	
No	70 (92.1)	6 (7.9)	76 (92.7)	
Brain				
No	75 (91.5)	7 (8.5)	82 (100.0)	
Liver				.0408
Yes	65 (94.2)	4 (5.8)	69 (84.1)	
No	10 (76.9)	3 (23.1)	13 (15.9)	
Lung				.9134
Yes	55 (91.7)	5 (8.3)	60 (73.2)	
No	20 (90.9)	2 (9.1)	22 (26.8)	
Lymph nodes				.3302
Yes	51 (89.5)	6 (10.5)	57 (69.5)	
No	24 (96.0)	1 (4.0)	25 (30.5)	
Pelvis				.7743
Yes	14 (93.3)	1 (6.7)	15 (18.3)	
No	61 (91.0)	6 (9.0)	67 (81.7)	
Peritoneum				.0456
Yes	17 (81.0)	4 (19.0)	21 (25.6)	
No	58 (95.1)	3 (4.9)	61 (74.4)	
Other				.3025
Yes	10 (100.0%)	0 (0.0%)	10 (12.2%)	
No	65 (90.3%)	7 (9.7%)	72 (87.8%)	

[a]Chi-square.

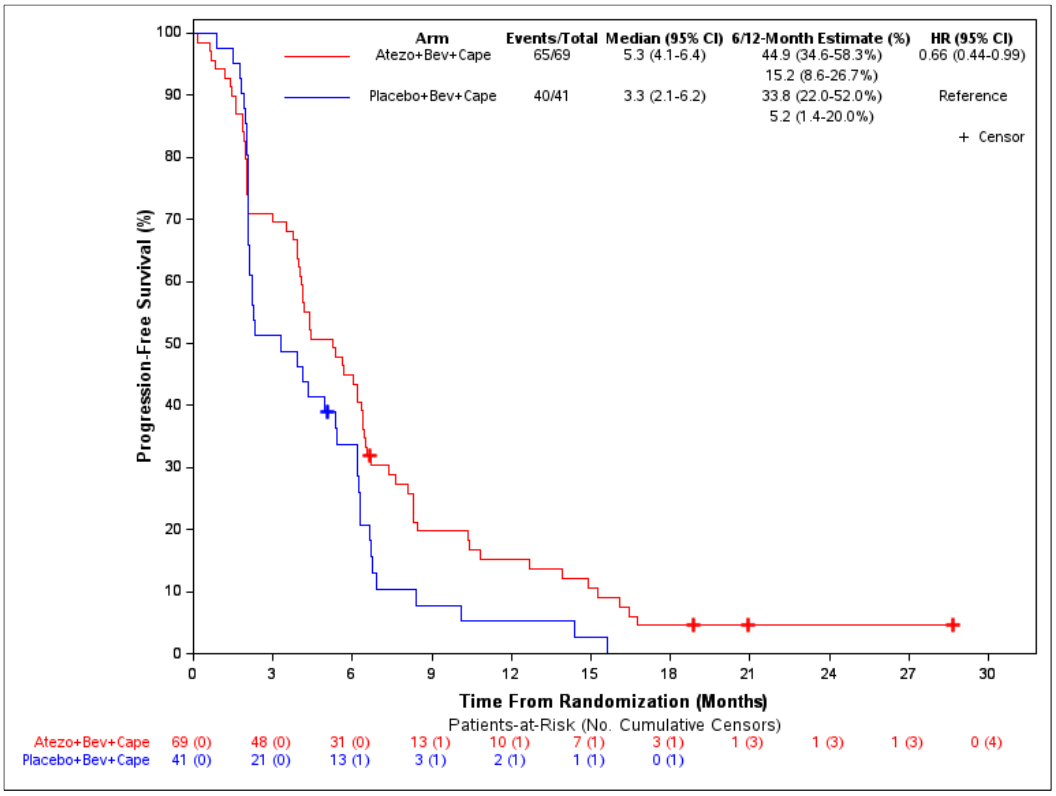
eTable 7. Immune-Related Adverse Events Grade 3 or Higher Considered at Least Possibly Related to Treatment

irAE	Toxicity	Investigational Arm (Capecitabine + Bevacizumab + Atezolizumab) (N=86)	Placebo Arm (Capecitabine + Bevacizumab + Placebo) (N=46)	Total (N=132)
Any irAE	Any irAE	12 (14.0%)	6 (13.0%)	18 (13.6%)
Colitis	Colitis	1 (1.2%)	0 (0.0%)	1 (0.8%)
	Diarrhea	6 (7.0%)	2 (4.3%)	8 (6.1%)
Dermatitis	Rash maculo-papular	0 (0.0%)	1 (2.2%)	1 (0.8%)
Endocrinopathies	Hyperglycemia	0 (0.0%)	1 (2.2%)	1 (0.8%)
Hepatitis	Alanine aminotransferase increased	1 (1.2%)	0 (0.0%)	1 (0.8%)
	Alkaline phosphatase increased	1 (1.2%)	0 (0.0%)	1 (0.8%)
	Aspartate aminotransferase increased	2 (2.3%)	0 (0.0%)	2 (1.5%)
	Blood bilirubin increased	1 (1.2%)	0 (0.0%)	1 (0.8%)
Myocarditis	Myocarditis	1 (1.2%)	0 (0.0%)	1 (0.8%)
Myositis	Generalized muscle weakness	1 (1.2%)	1 (2.2%)	2 (1.5%)
Nephritis	Hematuria	0 (0.0%)	1 (2.2%)	1 (0.8%)
Other rheumatological	Arthralgia	1 (1.2%)	1 (2.2%)	2 (1.5%)
Pneumonitis	Dyspnea	1 (1.2%)	0 (0.0%)	1 (0.8%)
Rhabdomylosis	Acute kidney injury	0 (0.0%)	1 (2.2%)	1 (0.8%)

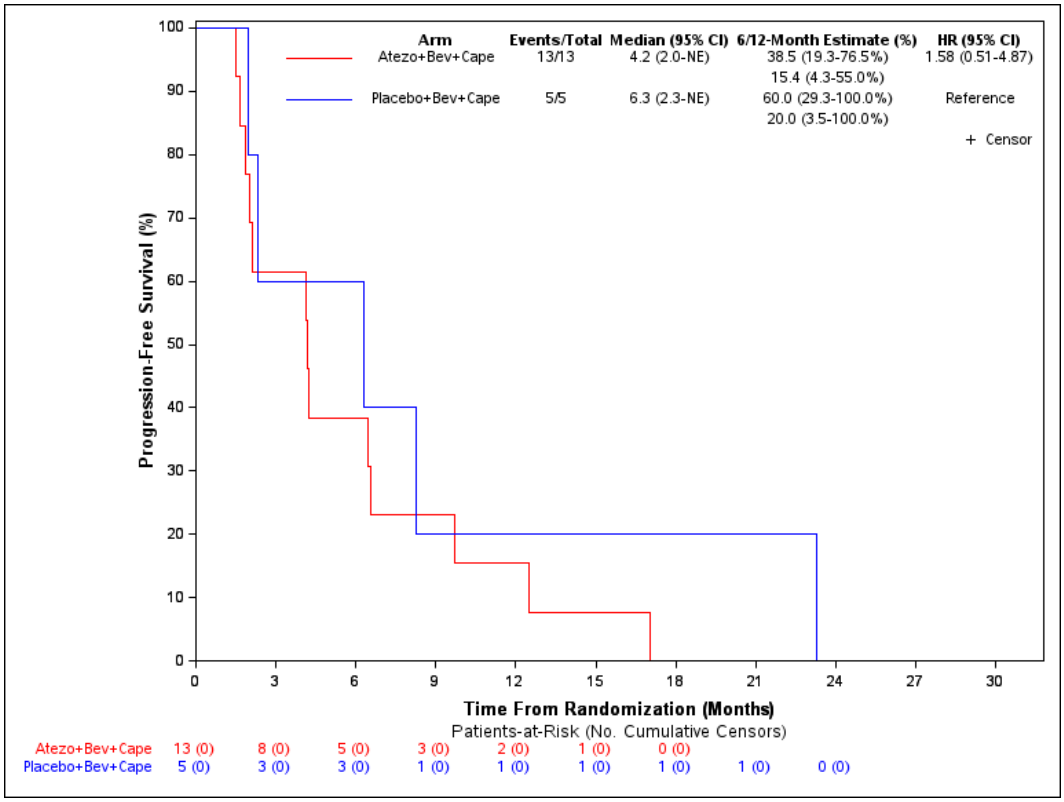
Number (percentage) of patients who experienced each adverse event code are reported.ALT, alanine aminotransferase; AST, aspartate aminotransferase.

eFigure 1. PFS of Atezolizumab vs Placebo by MSS Status

A. MSS patients



B. MSI-H or MSI status unknown



eFigure 2. Sensitivity Analysis of PFS