Supplementary Online Content

Gridelli C, de Castro Carpeno J, Dingemans A-MC, et al. Bevacizumab plus standard-of-care treatment beyond disease progression in patients with advanced non–small cell lung cancer: the AvaALL randomized clinical trial. *JAMA Oncol*. Published online August 30, 2018. doi:10.1001/jamaoncol.2018.3486

eTable 1. Baseline Characteristics and Disease History of the ITT Population

eTable 2. Patients Exposed to Bevacizumab in Both Treatment Arms (Safety Population)

eTable 3. Grade 3 or 4 Adverse Events (Preferred Term Occurring in ≥10% of Patients with Grade 1 or 2 Events in Any Treatment Arm; Safety Population)

eTable 4. Treatment-Emergent Grade 5 Adverse Events by Body System and Preferred Term (Safety Population)

eTable 5. Cause of Death

eFigure 1. Timeline of Progressive Disease and Study Endpoints

eFigure 2. Forest Plot of OS by Subgroups

eFigure 3. PFS: (A) Kaplan-Meier Plot of PFS2 in the ITT Population; (B) Forest Plot of PFS2 by Subgroups

eFigure 4. PFS3 in the ITT Population

eFigure 5. TTP2 in the ITT Population

eFigure 6. TTP3 in the ITT Population

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

eTable 1. Baseline Characteristics and Disease History of the ITT Population

	Bevacizumab Plus SOC (n = 245)	SOC Alone (n = 240)
Median age, years (range)	63.0 (26–84)	63.0 (35–82)
Gender, no. (%)		
Male	155 (63.3)	138 (57.5)
Female	90 (36.7)	102 (42.5)
Ethnicity, no. (%)		
Asian	29 (11.8)	25 (10.4)
Non-Asian	216 (88.2)	215 (89.6)
Smoking status, no. (%)		
Current	89 (36.3)	88 (36.7)
Former	120 (49.0)	117 (48.8)
Never	36 (14.7)	35 (14.6)
ECOG PS at baseline, no. (%)		
0	87 (35.5)	94 (39.2)
1	142 (58.0)	138 (57.5)
2	11 (4.5)	3 (1.3)
Missing	5 (2.0)	5 (2.1)
Disease stage at initial diagnosis, no. (%)		
1	4 (1.6)	5 (2.1)
2	7 (2.9)	9 (3.8)
3A	16 (6.5)	14 (5.8)
3B	14 (5.7)	7 (2.9)

4	204 (83.3)	205 (85.4)
Median time since initial diagnosis, months (range)	10.5 (3–88)	10.3 (3–78)
Disease stage at start of first-line therapy, no. (%)		
3A	8 (3.3)	4 (1.7)
3B	12 (4.9)	7 (2.9)
4	225 (91.8)	229 (95.4)
Median time from start of first-line therapy, months (range)	8.6 (1–28)	8.1 (3–44)
Current stage of disease, no. (%)		
3A	3 (1.2)	0
3B	14 (5.7)	5 (2.1)
4	228 (93.1)	235 (97.9)
Histology, no. (%)		
Adenocarcinoma	227 (92.7)	226 (94.2)
Large cell carcinoma	6 (2.4)	6 (2.5)
Bronchioloalveolar carcinoma/ adenocarcinoma in situ	3 (1.2)	2 (0.8)
Other	9 (3.7)	6 (2.5)
Centrally located tumor at start of first-line therapy, no. (%)		
Yes	77 (31.4)	90 (37.5)
No	168 (68.6)	150 (62.5)

Cavitated tumor at start of first-line therapy, no. (%)		
Yes	19 (7.8)	12 (5.0)
No	225 (91.8)	228 (95.0)
Not done	1 (0.4)	0
EGFR status assessment, no. (%)		
Yes	165 (67.3)	168 (70.0)
Positive (*EGFR* activating) mutation)	1 (0.4)	1 (0.4)
Negative (*EGFR* wild type)	160 (65.3)	161 (67.1)
Not evaluable	4 (1.6)	6 (2.5)
No	80 (32.7)	72 (30.0)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; ITT, intent to treat; SD, standard deviation; SOC, standard of care.

eTable 2. Patients Exposed to Bevacizumab in Both Treatment Arms (Safety Population)

	Bevacizumab Plus SOC (n = 240)	SOC Alone (n = 235)
Mean number of cycles of bevacizumab, no. (SD)	11.9 (9.8)	1.0 (0)
Median treatment duration with bevacizumab, months (range)	6.4 (0.03–40.0)	0.03 (0.03–0.03)
Starting daily dose of bevacizumab, no. (%)		
7.5 mg/kg	116 (48.3)	0
15 mg/kg	124 (51.7)	0
Mean cumulative dose of bevacizumab, mg (SD)	8,826.2 (7,899.2)	455.3 (395.6)
Patients with at least one bevacizumab treatment interruption, no. (%)	17 (7.1)	0

Abbreviations: SD, standard deviation; SOC, standard of care.

eTable 3. Grade 3 or 4 Adverse Events (Preferred Term Occurring in ≥10% of Patients With Grade 1 or 2 Events in Any Treatment Arm; Safety Population)

System Organ Class and Preferred Term, no. (%)	Bevacizumab Plus SOC (n = 243)	SOC Alone (n = 232)
Any AE	186 (76.5)	140 (60.3)
General disorders and administrative site conditions	47 (19.3)	32 (13.8)
Fatigue	12 (4.9)	14 (6.0)
Asthenia	16 (6.6)	12 (5.2)
Gastrointestinal disorders	33 (13.6)	20 (8.6)
Diarrhea	11 (4.5)	6 (2.6)
Nausea	6 (2.5)	4 (1.7)
Constipation	0	1 (0.4)
Vomiting	5 (2.1)	3 (1.3)
Respiratory, thoracic, and mediastinal disorders	36 (14.8)	33 (14.2)
Dyspnea	10 (4.1)	13 (5.6)
Epistaxis	0	1 (0.4)
Blood and lymphatic system disorders	74 (30.5)	50 (21.6)
Anemia	18 (7.4)	20 (8.6)
Skin and subcutaneous tissue disorders	17 (7.0)	6 (2.6)
Alopecia	0	0
Metabolism and nutritional disorders	28 (11.5)	14 (6.0)
Decreased appetite	12 (4.9)	3 (1.3)

Renal and urinary disorders	7 (2.9)	2 (0.9)
Proteinuria	3 (1.2)	1 (0.4)

Abbreviations: AE, adverse event; SOC, standard of care.

eTable 4. Treatment-Emergent Grade 5 Adverse Events by Body System and Preferred Term (Safety Population)

System Organ Class and Preferred Term	Bevacizumab Plus SOC (n = 243)	SOC Alone (n = 232)
Any treatment-emergent grade 5 AE, no. (%)	16 (6.6)	12 (5.2)
General disorders and administrative site conditions	4 (1.6)	2 (0.9)
Fatigue	1 (0.4)	0
Death	1 (0.4)	2 (0.9)
Decreased PS	1 (0.4)	0
Sudden death	1 (0.4)	0
Gastrointestinal disorders	2 (0.8)	0
Large intestine perforation	1 (0.4)	0
Intestinal perforation	1 (0.4)	0
Respiratory, thoracic, and mediastinal disorders	2 (0.8)	1 (0.4)
Respiratory failure	1 (0.4)	0
Aspiration	1 (0.4)	0
Pulmonary embolism	0	1 (0.4)
Infections and infestations	5 (2.1)	9 (3.9)
Pneumonia	2 (0.8)	8 (3.4)
Lung infection	1 (0.4)	1 (0.4)
Respiratory tract infection	1 (0.4)	0
Bronchopulmonary aspergillosis	1 (0.4)	0

Nervous system disorders	1 (0.4)	0
Cerebral infarction	1 (0.4)	0
Renal and urinary disorders	1 (0.4)	0
Nephrotic syndrome	1 (0.4)	0
Cardiac disorders	1 (0.4)	0
Myocardial ischemia	1 (0.4)	0

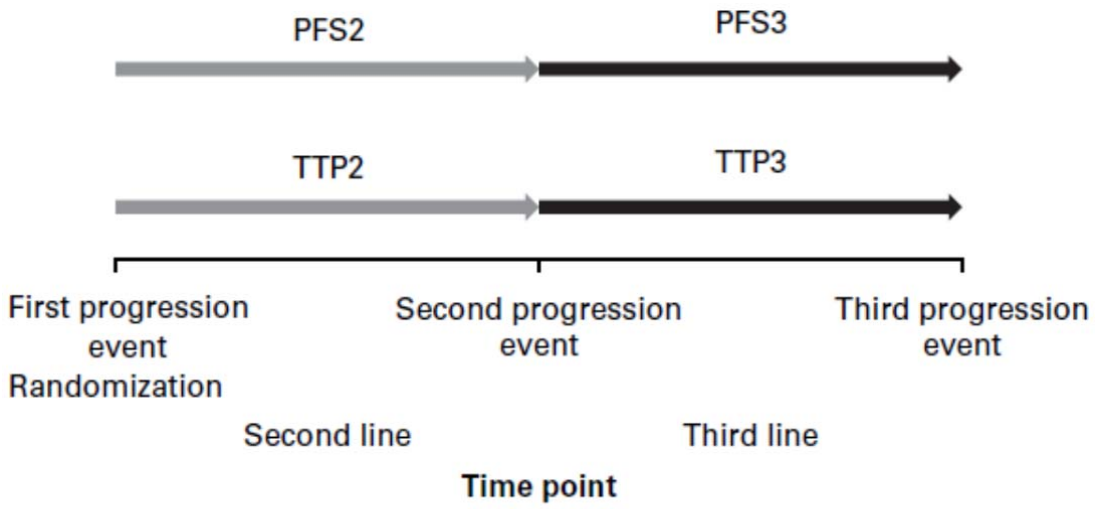
Abbreviations: AE, adverse event; PS, performance status; SOC, standard of care.

eTable 5. Cause of Death

	Bevacizumab Plus SOC (n = 245)	SOC Alone (n = 240)
Patients who died, no. (%)	194 (79.2)	193 (80.4)
Primary reason for death, no. (%)		
Disease progression	173 (70.6)	172 (71.7)
AE	16 (6.5)	10 (4.2)
Other	5 (2.0)	11 (4.6)

Abbreviations: AE, adverse event; SOC, standard of care.

eFigure 1. Timeline of Progressive Disease and Study Endpoints

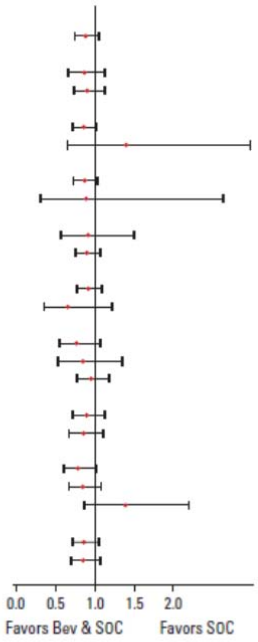


PFS was defined as time from randomization until progression or death; TTP was defined as time from randomization until objective tumor progression.

Abbreviations: PFS, progression-free survival; PFS2, time from randomization at first to second progression; PFS3, time from second to third progression; TTP, time to progression; TTP2, TTP from randomization at first to second progression; TTP3, TTP from second to third progression.

eFigure 2. Forest Plot of OS by Subgroups (Hazard Ratio Not Stratified)

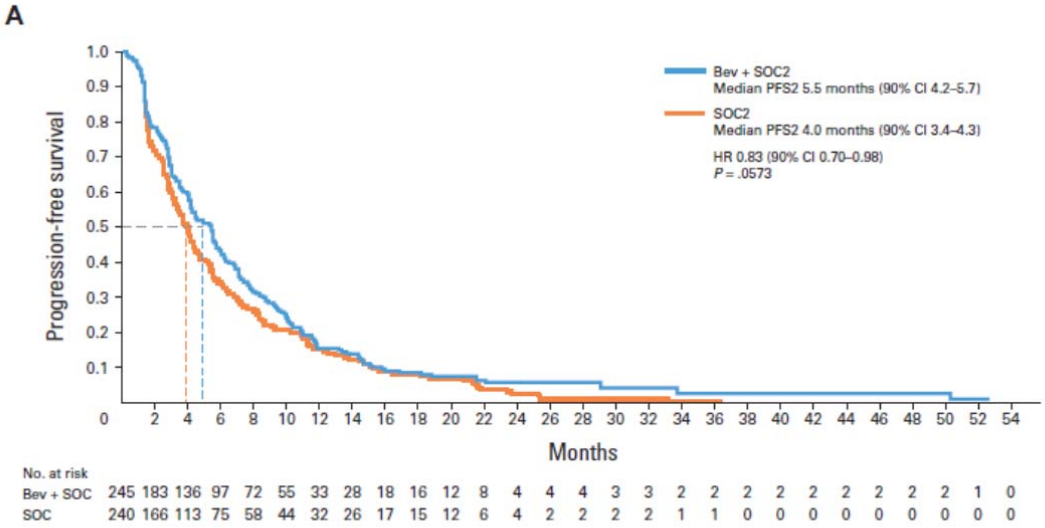
Subgroup	Total N	Bevacizumab + SOC N (Events)	Bevacizumab + SOC Median (90%CI)	SOC Alone N (Events)	SOC Alone Median (90%CI)	HR (90%)
All subjects						
All subjects	485	245 (194)	11.86 (10.22–13.67)	240 (193)	10.22 (8.61–11.93)	0.84 (0.71–1.00)
Gender						
Female	192	90 (71)	13.67 (9.59–16.85)	102 (80)	9.89 (6.90–11.93)	0.86 (0.65–1.12)
Male	293	155 (123)	11.20 (9.43–12.94)	138 (113)	11.30 (8.25–13.44)	0.90 (0.73–1.12)
Age categories						
≤ 75	461	231 (182)	11.79 (10.58–13.77)	230 (185)	9.99 (8.61–11.76)	0.85 (0.72–1.01)
> 75	24	14 (12)	9.20 (4.04–21.45)	10 (8)	13.93 (5.72–35.02)	1.40 (0.65–3.03)
Baseline ECOG score						
0–1	461	229 (179)	12.55 (11.01–14.69)	232 (185)	10.84 (9.00–12.48)	0.86 (0.73–1.02)
2	14	11 (11)	7.75 (3.32–9.46)	3 (3)	1.68 (1.51–23.79)	0.88 (0.29–2.69)
Race						
Asian	54	29 (24)	20.90 (17.08–28.68)	25 (21)	19.81 (7.26–26.02)	0.91 (0.55–1.51)
Non-Asian	431	216 (170)	10.97 (9.13–12.29)	215 (172)	9.89 (8.25–11.63)	0.89 (0.75–1.07)
Histology						
Adenocarcinoma	453	227 (179)	11.86 (10.64–13.77)	226 (180)	10.22 (8.61–12.48)	0.91 (0.76–1.08)
Other	32	18 (15)	9.30 (6.74–26.51)	14 (13)	10.55 (3.38–13.08)	0.64 (0.34–1.22)
Type of planned second-line SOC treatment						
Docetaxel	129	65 (47)	16.36 (12.94–19.22)	64 (50)	14.00 (8.71–16.82)	0.76 (0.54–1.07)
Erlotinib	65	34 (26)	13.67 (8.34–17.94)	31 (25)	10.84 (7.16–14.92)	0.84 (0.53–1.34)
Pemetrexed	291	146 (121)	10.05 (8.54–11.86)	145 (118)	9.43 (7.56–11.63)	0.95 (0.76–1.17)
Number of cycles of bevacizumab maintenance						
≤ 6	270	138 (111)	9.46 (8.08–11.79)	132 (110)	8.71 (6.77–10.22)	0.89 (0.72–1.11)
> 6	215	107 (83)	16.46 (11.86–20.07)	108 (83)	13.44 (10.41–16.39)	0.85 (0.66–1.10)
Smoking status						
Current smoker	178	90 (75)	9.53 (8.54–11.37)	88 (78)	7.95 (6.01–9.99)	0.78 (0.60–1.02)
Former smoker	236	119 (92)	13.57 (10.68–17.31)	117 (91)	10.41 (8.61–12.48)	0.84 (0.66–1.07)
Never smoker	71	36 (27)	14.69 (10.64–20.07)	35 (24)	18.23 (14.00–31.41)	1.39 (0.87–2.22)
Bevacizumab dose						
7.5 mg/kg q3w	117*	117 (90)	11.4 (9.5–14.7)	240 (193)	10.2 (8.6–11.9)	0.86 (0.69–1.07)
15 mg/kg q3w	128*	128 (104)	12.6 (9.7–14.4)	240 (193)	10.2 (8.6–11.9)	0.84 (0.68–1.04)



*Includes patients randomized to bevacizumab, therefore not summing up to the Total N.

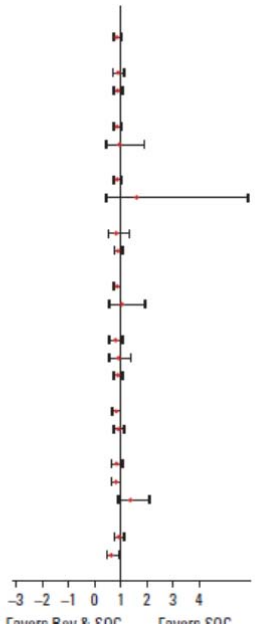
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; q3w, every 3 weeks; SOC, standard of care.

eFigure 3. PFS: (A) Kaplan-Meier Plot of PFS2 in the ITT Population; (B) Forest Plot of PFS2 by Subgroups



B

Subgroup	Total N	Bevacizumab + SOC N (Events)	Bevacizumab + SOC Median (90%CI)	SOC Alone N (Events)	SOC Alone Median (90%CI)	HR (90%)
All subjects						
All subjects	485	245 (212)	5.45 (4.21–5.68)	240 (217)	3.98 (3.38–4.30)	0.83 (0.70–0.98)
Gender						
Female	192	90 (78)	5.36 (4.11–6.18)	102 (92)	3.68 (2.89–4.50)	0.90 (0.69–1.16)
Male	293	155 (134)	5.45 (4.04–5.75)	138 (125)	4.04 (3.25–4.86)	0.83 (0.68–1.02)
Age categories						
≤ 75	461	231 (201)	5.45 (4.21–5.68)	230 (210)	3.91 (3.29–4.30)	0.84 (0.71–0.99)
> 75	24	14 (11)	6.09 (1.48–11.01)	10 (7)	6.18 (1.64–14.72)	1.15 (0.51–2.62)
Baseline ECOG score						
0–1	461	229 (201)	5.45 (4.21–5.91)	232 (209)	4.01 (3.45–4.40)	0.85 (0.72–1.00)
2	14	11 (10)	4.94 (1.38–7.75)	3 (3)	1.38 (1.28–23.79)	1.46 (0.40–5.43)
Race						
Asian	54	29 (26)	7.95 (6.01–11.53)	25 (24)	4.44 (3.12–7.10)	0.82 (0.51–1.31)
Non-Asian	431	216 (186)	4.53 (4.11–5.52)	215 (193)	3.75 (3.25–4.21)	0.86 (0.73–1.02)
Histology						
Adenocarcinoma	453	227 (194)	5.45 (4.24–5.75)	226 (204)	4.01 (3.35–4.37)	0.83 (0.71–0.98)
Other	32	18 (18)	3.56 (1.74–6.74)	14 (13)	3.38 (1.54–5.42)	1.03 (0.56–1.92)
Type of planned second-line SOC treatment						
Docetaxel	129	65 (55)	5.98 (5.52–7.10)	64 (57)	4.40 (3.42–6.47)	0.77 (0.57–1.06)
Erlotinib	65	34 (28)	3.55 (2.96–4.86)	31 (28)	2.07 (1.54–3.75)	0.85 (0.54–1.34)
Pemetrexed	291	146 (129)	4.93 (4.01–6.01)	145 (132)	4.01 (3.25–4.40)	0.86 (0.70–1.06)
Number of cycles of bevacizumab maintenance						
≤ 6	270	138 (116)	4.11 (3.25–5.45)	132 (122)	3.15 (2.60–3.52)	0.77 (0.62–0.95)
> 6	215	107 (96)	6.01 (5.45–7.16)	108 (95)	5.42 (4.40–6.67)	0.92 (0.73–1.17)
Smoking status						
Current smoker	178	90 (81)	4.86 (3.48–5.75)	88 (82)	3.17 (2.07–3.98)	0.82 (0.63–1.06)
Former smoker	236	119 (102)	5.52 (4.17–6.18)	117 (106)	4.04 (3.29–4.70)	0.76 (0.61–0.96)
Never smoker	71	36 (29)	6.31 (2.96–9.92)	35 (29)	6.93 (4.17–12.22)	1.34 (0.86–2.09)
Bevacizumab dose						
7.5 mg/kg q3w	117*	117 (105)	4.4 (3.7–5.5)	240 (217)	4.0 (3.4–4.3)	0.92 (0.75–1.14)
15 mg/kg q3w	128*	128 (107)	6.0 (4.2–6.9)	240 (217)	4.0 (3.4–4.3)	0.77 (0.63–0.95)



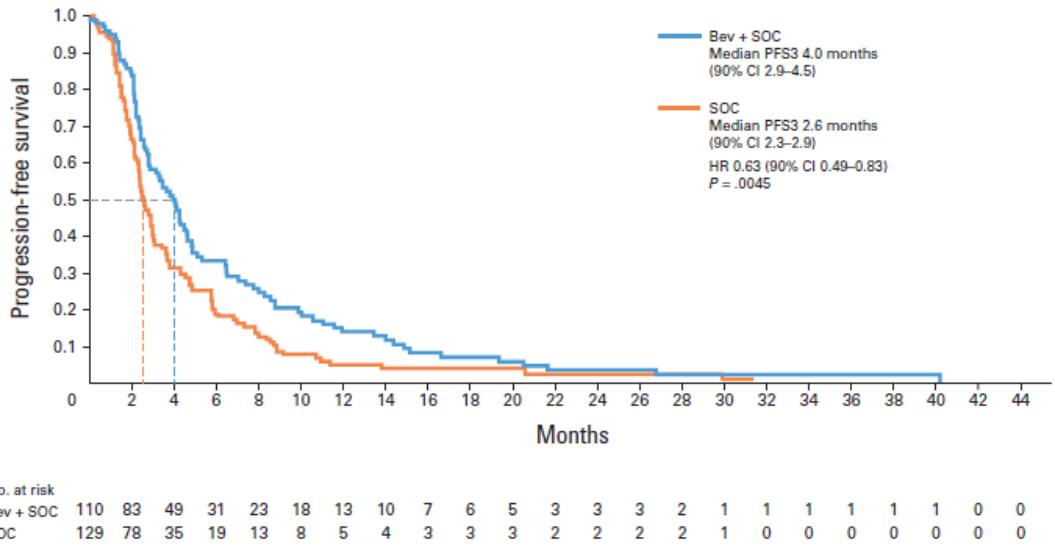
*Includes patients randomized to bevacizumab, therefore not summing up to the Total N.

Abbreviations: Bev, bevacizumab; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent to treat; PFS2,

progression-free survival from first to second progression; q3w, every 3 weeks; SOC, standard of care.

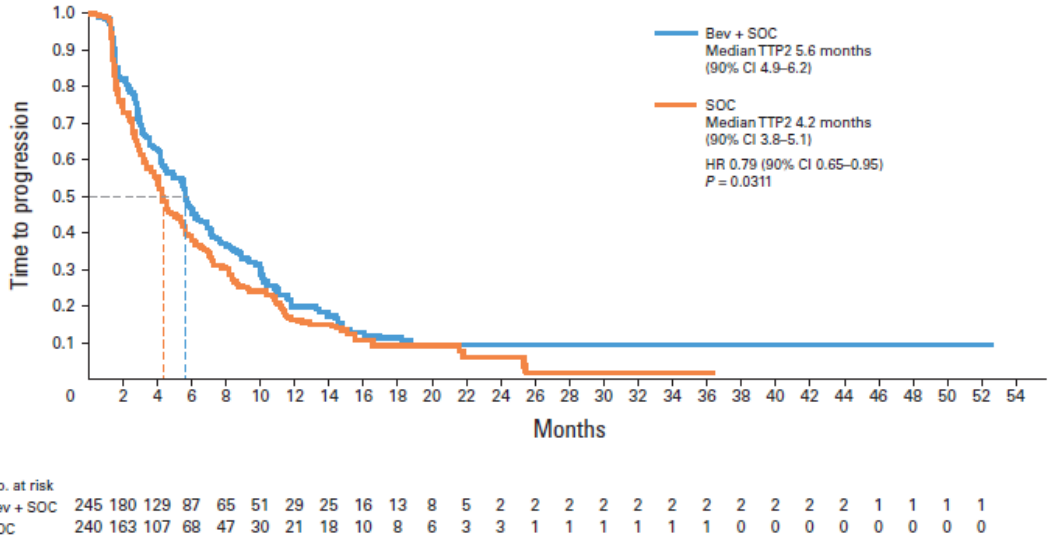
HR for the ITT population is stratified; HR for the subgroups is not stratified.

eFigure 4. PFS3 in the ITT Population



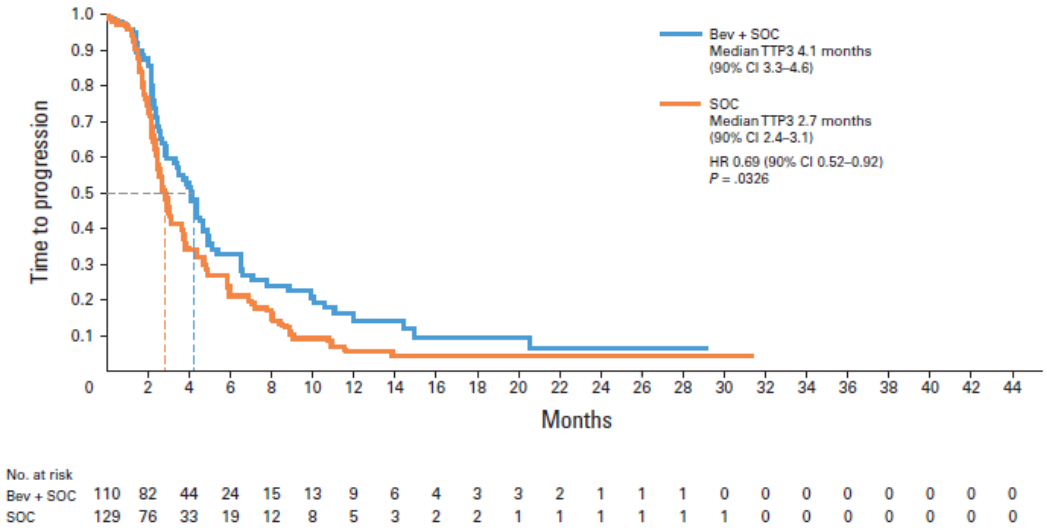
Abbreviations: Bev, bevacizumab; CI, confidence interval; HR, hazard ratio; ITT, intent to treat; PFS3, progression-free survival from second to third progression; SOC, standard of care.

eFigure 5. TTP2 in the ITT Population



Abbreviations: Bev, bevacizumab; CI, confidence interval; HR, hazard ratio; ITT, intent to treat; SOC, standard of care; TTP2, time to progression from randomization at first to second progression.

eFigure 6. TTP3 in the ITT Population



Abbreviations: Bev, bevacizumab; CI, confidence interval; HR, hazard ratio; ITT, intent to treat; SOC, standard of care; TTP3, time to progression from second to third progression.