Table 1. Patients' characteristics			
	Qualitative ≤1+ proteinuria (n=535)	Qualitative ≥2+ proteinuria (n=199)	P
Age (y), mean (range)	64 (19–92)	65 (20–90)	0.15
Male, n (%)	261 (48.8)	96 (48.2)	0.962
Body weight (kg), mean (range)	60.7 (36.2–99.9)	61.4 (32.8–99.9)	0.47
Primary site, n (%)			
Colorectal cancer	220 (41.1)	64 (32.2)	0.03
Lung cancer	157 (29.3)	74 (37.2)	0.05
Glioma	80 (15.0)	34 (17.1)	0.55
Ovarian cancer	36 (6.7)	16 (8.0)	0.52
Breast caner	23 (4.3)	7 (3.5)	0.83
Cervical cancer	14 (2.6)	2 (1.0)	0.26
Cancer of unknown primary	3 (0.6)	2 (1.0)	0.62
Other	2 (0.4)	0 (0.0)	1
Medical history, n (%)			
Hypertension	103 (19.3)	44 (22.1)	0.449
Diabetes mellitus	48 (9.0)	28 (14.1)	0.06
Dyslipidemia	85 (15.9)	28 (14.1)	0.623
Smoking history			0.020
Yes	262 (49.0)	78 (39.2)	
No	272 (51.0)	121 (60.8)	
eGFR at the initial treatment, mL/min/1.73 m^2			0.103
>60	459 (85.7)	157 (78.9)	
45–59	63 (11.8)	32 (16.1)	
30–44	13 (2.4)	10 (5.0)	
BUN, mg/dl	14.0 ± 4.6	14.5 ± 4.9	0.169
Alb, mg/dl	3.8 ± 0.5	3.8 ± 0.5	0.678
The data were assessed using the chi-squared test or Fisher's exact test, as appropriate eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; Alb, albumin			

Table 2. The details of patients with renal dysfunction

	Age	Sex	Cancer	Proteinuria grade	eGFR decline (%)	Cause of renal dysfunction	Reason for BV discontinuation	Dose (mg/kg)	Total BV
Reversible eGFR decline									
	57	F	Colorectal	2+	88.5	Post-renal	Progressive disease	7.5	73
	64	M	Glioma	+-	86.1	DIC	Progressive disease	10	8
	56	M	Colorectal	2+	77.2	Septic AKI	GI perforation	7.5	8
	72	F	Colorectal	2+	76.9	Pre-renal	Progressive disease	5	26
	74	M	Colorectal	-	71.4	Pre-renal	GI bleeding	7.5	6
	70	F	Colorectal	+-	69.9	Pre-renal	Dehydration	7.5	1
	57	M	Colorectal	2+	68.6	Post-renal	Progressive disease	7.5	3
	43	M	Glioma	+-	67.8	Not applicable [a]	Progressive disease	10	13
	56	M	Colorectal	+-	65.6	Terminal	Progressive disease	7.5	13
	73	F	Lung	1+	64.3	Pre-renal	Progressive disease	15	17
	69	M	Colorectal	3+	63.5	Pre-renal	Progressive disease	7.5	55
	66	F	Colorectal	3+	62.0	Pre-renal	Encephalopathy	5	50
	58	M	Colorectal	-	61.5	Pre-renal	Pulmonary embolism	5	13
	78	M	Colorectal	1+	60.4	Post-renal	Progressive disease	5	8
	65	F	Breast	2+	57.5	Prerenal	Progressive disease	10	50
Irreversible eGFR decline									
Case 1*	67	M	Lung	3+	76.6	DM, BV	Proteinuria	15	17
Case 2*	63	M	Colorectal	3+	70.6	BV	Nephrotic syndrome	5	70
	66	F	Cervical	+-	66.1	CDDP, ARB	Finished treatment [b]	7.5	10
	66	M	Lung	2+	65.9	LVFX	AKI	15	1
	71	M	Colorectal	1+	65.8	Terminal	Pulmonary embolism	5	1
	41	F	Lung	-	65.6	Terminal	Sepsis	15	7
Case 3*	62	F	Colorectal	3+	62.0	BV	Renal dysfunction	7.5	48
	57	F	Lung	2+	59.5	ALK inhibitor	Progressive disease	15	13
Case 4*	57	F	Lung	2+	57.9	PEM, BV	Nephrotic syndrome	15	21
	44	F	Cervical	1+	57.7	CDDP, diuretic, ARB	Progressive disease	15	7

BV, bevacizumab; DIC, disseminated intravascular coagulation; AKI, acute kidney injury; GI, gastrointestinal; DM, Diabetes mellitus; CDDP, cisplatin; ARB, angiotensin receptor blocker; LVFX, levofloxacin; ALK, anaplastic lymphoma kinase; PEM, pemetrexed

* Proteinuria in these four patients, labeled as Cases 1–4, was likely related to BV. See the text for details.

[a] This patient had a large change in the eGFR because of a high initial eGFR level, which did not represent renal dysfunction.

[b] The scheduled maintenance therapy was completed.

Supplemental Table 1. Frequency of other bevacizumab-associated adverse events			
	Qualitative ≤1+ proteinuria (n=535)	Qualitative ≥2+ proteinuria (n=199)	P
Adverse Events, n (%)			
Cardiovascular events	4 (0.7)	2 (1.0)	0.664
Venous thromboembolic events	15 (2.8)	1 (0.5)	0.083
Cerebrovascular complications	8 (1.5)	5 (2.5)	0.354
Hemorrhage	7 (1.3)	3 (1.5)	0.736
Gastrointestinal perforation	2 (0.4)	1 (0.5)	1.0
Other	2 (0.4)	1 (0.5)	1.0
Fisher's exact test was used to analyze the differences in the frequencies of renal dysfunction and other adverse events among patients with varying grades of proteinuria.			

Supplemental Table 2. Details in patients with pre-existing proteinuria

Case	Age	Sex	Disease	Background	DM	Total BV	Dose modification	Reason for discontinuing BV	Cre initial→last	Alb initial→last	Edema
1	51	F	Colorectal	Ureteral stent	-	37	-	Ongoing	0.60→0.96	3.7→4.0	-
2	62	M	Colorectal	Diabetic nephropathy	+	12	-	Proteinuria	0.5→0.6	3.4→3.1	-
3	22	M	Colorectal	Ureteral stent	-	11	-	Progressive disease	0.94→0.74	4.5→3.7	-
4	50	M	Colorectal	HD(diabetic nephropathy)	+	10	-	Alveolar bleeding	7.2→7.2	3.9→3.2	-
5	65	M	Lung	unknown	-	9	-	Hypertension	1.33→1.05	4→3.7	-
6	50	F	Cervical	Ureteral stent	-	8	-	Ongoing	0.74→1.20	3.1→3.8	-
7	48	M	Glioma	Unknown	+	8	-	Poor PS	0.89→0.84	3.8→3.6	-
8	73	M	Colorectal	Diabetic nephropathy	+	7	-	Treatment for GIST	1.5→1.8	2.5→3.2	-
9	71	F	Lung	HD (IgA nephropathy)	-	3	-	Pneumoniae	4.87→5.12	3.5→3.4	-
10	78	F	Lung	Diabetic nephropathy	+	3	-	Proteinuria	0.7→1.0	2.9→3.0	-
11	45	F	Colorectal	Ureteral stent	-	1	-	FN, progressive disease	1.0→0.8	3.3→3.3	-
12	64	M	Colorectal	Bladder invasion*	-	37 (5)*	-	Progressive disease	0.8→0.85	3.7→3.5	-
13	81	M	Colorectal	Diabetic nephropathy	+	2	-	Diarrhea	1.06→1.08	2.6→2.9	-
14	68	M	Lung	Unknown	-	2	-	Proteinuria	0.8→0.9	3.4→3.2	-
15	63	F	Ovarian	Invading urinary tract	-	5	-	PR changed to PARPi	0.63→0.62	3.7→4.3	-
16	72	M	Lung	Unknown	-	3	-	Progressive disease	1.03→0.89	2.5→2.8	-
17	55	M	Colorectal	Unknown	-	3	-	Preparation for surgery	0.95→0.92	4.6→4.4	-
18	73	M	Colorectal	After nephrectomy	-	1	-	Diarrhea	1.38→1.41	3.3→3.3	-
19	66	M	Colorectal	Diabetic nephropathy	+	7	-	Progressive disease	0.8→0.72	3.4→2.6	-
20	36	F	Ovarian	Unknown	-	1	-	Neutropenia	0.47→0.38	3.7→3.7	-

DM, diabetes mellitus; BV, bevacizumab; Cre, creatinine; Alb, albumin; HD, hemodialysis; IgA, immunoglobulin A; PS, performance status; GIST, gastrointestinal stromal tumor; FN, febrile neutropenia; PR, partial response; PARPi, poly ADP-ribose polymerase inhibitor

* This patient had colorectal cancer with bladder invasion. After 5-cycle BV chemotherapy, he received a total cystectomy.