Supplementary Information

Methods:

Exclusion criteria: Patients were also excluded if they had received chemotherapy or biologic therapy for ≤ 3 weeks, radiation or small-molecule–targeted therapy for ≤ 2 weeks, or adjuvant chemotherapy for ≤ 6 months before study enrollment. Any patient with a disease or condition that required systemic steroids or immunosuppressive agents was also excluded from the study. Patients with treated brain metastasis were allowed in the study if the disease had been stable for ≥ 1 month at screening, there was no evidence of progression or hemorrhage posttreatment, and there was no requirement for ongoing treatment with corticosteroids.

Hematologic DLTs: Included any thrombocytopenia or neutropenia of grade 4 severity that lasted for more than 7 days. Nonhematologic DLTs included episcleritis, uveitis, or iritis (≥ grade 2); any grade 4 toxicities; and certain grade 3 toxicities (all grade 3 nonhematologic toxicities were considered DLTs except for: nausea, vomiting, or diarrhea controlled within 72 hours; rash in the absence of desquamation or mucosal involvement, which did not require steroids, and resolved to grade 1 by the next dose of pembrolizumab; elevation of alanine aminotransferase or aspartate aminotransferase level for ≤ 3 days with or without steroid use.

Supplemental Table 1. Fatal TEAE(s)

Parameter, n (%)	Eribulin + Pembrolizumab (Total Study Population N = 167)
Any grade 5 TEAEs	15 (9.0)
Malignant neoplasm progression	4 (2.4)
Acute respiratory failure	2 (1.2)
Respiratory failure	2 (1.2)
Cardiac arrest	1 (0.6)
Death	1 (0.6)
Dyspnea	1 (0.6)
Metastasized to central nervous system	1 (0.6)
Metastasized to meninges	1 (0.6)
Multiple organ dysfunction syndrome	1 (0.6)
Pleural effusion	1 (0.6)
Sepsis	1 (0.6)

Adverse event terms were coded using Medical Dictionary for Drug Regulatory Affairs version 22.0 and were graded using Common Terminology Criteria for Adverse Events version 4.03. Patients who experienced different grades for a single preferred term were counted only once per preferred term using the highest severity grade.
Patients may have had ≥1 concurrent fatal TEAE.
TEAE, treatment-emergent adverse event.

Supplemental Table 2. TEAEs of clinical interest for pembrolizumab.

Parameter, n (%)	Eribulin + Pembrolizumab (N = 167)	
	Any Grade	**Grade 3 or 4**
TEAEs of clinical interest	71 (42.5)	20 (12.0)
Hypothyroidism	30 (18.0)	0
Pneumonitis	18 (10.8)	4 (2.4)
Hyperthyroidism	13 (7.8)	0
Infusion related reaction	5 (3.0)	0
Adrenal insufficiency	4 (2.4)	2 (1.2)
Colitis	4 (2.4)	0
Diabetic ketoacidosis	3 (1.8)	3 (1.8)
Rash maculo-papular	3 (1.8)	3 (1.8)
Hypophysitis	2 (1.2)	0
Pancreatitis	2 (1.2)	2 (1.2)
Rash	2 (1.2)	2 (1.2)
Rash generalized	2 (1.2)	2 (1.2)
Type 1 diabetes mellitus	2 (1.2)	2 (1.2)
Colitis microscopic	1 (0.6)	0
Dermatitis bullous	1 (0.6)	0
Drug hypersensitivity	1 (0.6)	0
Exfoliative rash	1 (0.6)	0
Hepatitis	1 (0.6)	1 (0.6)
Nephritis	1 (0.6)	1 (0.6)
Organizing pneumonia	1 (0.6)	0
Pruritus	1 (0.6)	1 (0.6)
Subacute inflammatory demyelinating polyneuropathy	1 (0.6)	1 (0.6)
Uveitis	1 (0.6)	0
Iritis	1 (0.6)	0

Adverse event terms were coded using Medical Dictionary for Drug Regulatory Affairs version 22.0 and were graded using Common Terminology Criteria for Adverse Events version 4.03. Patients who experienced different grades for a single preferred term were counted only once per preferred term using the highest severity grade.
TEAE, treatment-emergent adverse event.

Supplemental Table 3. Efficacy outcomes reported by prior systemic anticancer therapy (Stratum 1, **A**; Stratum 2, **B**) and tumor PD-L1-expression status using a combined positive score cutoff of 1 or 10.

A

Parameter	Eribulin + Pembrolizumab, Stratum 1 (n = 66)			
	n = 60[a]		n = 60[a]	
	PD-L1+	PD-L1−	PD-L1+	PD-L1−
	CPS ≥ 1 (n = 29)	CPS < 1 (n = 31)	CPS ≥ 10 (n = 13)	CPS < 10 (n = 47)
ORR[b,c], n (%) **95% CI**	10 (34.5) 17.9–54.3	5 (16.1) 5.5–33.7	4 (30.8) 9.1–61.4	11 (23.4) 12.3–38.0
CR, n (%)	4 (13.8)	0	2 (15.4)	2 (4.3)
PR, n (%)	6 (20.7)	5 (16.1)	2 (15.4)	9 (19.1)
CBR[d], n (%) **95% CI**	14 (48.3) 29.4–67.5	8 (25.8) 11.9–44.6	6 (46.2) 19.2–74.9	16 (34.0) 20.9–49.3
mDOR[e,f], months **95% CI**	8.3 3.2–NE	15.2 6.5–22.2	NE 4.2–NE	8.1 3.2–22.2
mPFS[e], months **95% CI**	6.1 4.1–10.2	3.5 2.0–4.2	6.1 3.5–14.8	4.1 2.1–5.5
mOS[e], months **95% CI**	21.0 8.3–29.0	15.2 12.8–19.4	21.0 7.6–39.6	17.1 13.3–20.2
mFollow-up, months **95% CI**	38.9 35.3–41.9	39.8 35.7–39.8	38.2 35.3–40.0	39.8 35.7–41.9

[a]Excludes 6 patients for whom PD-L1 status was not available.
[b]ORR = CR + PR; 95% CIs were calculated by Clopper–Pearson method.
[c]ORR does not include 6 patients with unknown PD-L1 status. Among the patients with unknown PD-L1 status in stratum 1 (n= 6), 2/6 patients are responders (CR, n = 1; PR, n = 1).
[d]CBR is defined as the proportion of patients with CR + PR + durable SD (≥ 24 weeks); 95% CIs were calculated by Clopper–Pearson method.
[e]Medians for PFS, OS, and DOR were estimated using the Kaplan–Meier method and their corresponding 95% CIs were calculated using a generalized Brookmeyer and Crowley method.
[f]In patients with a confirmed CR or PR as best overall response.
CI, confidence interval; CBR, clinical benefit rate; CPS, combined positive score; CR, complete response; DOR, duration of response; m, median; NE, not estimable; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease.
Stratum 1: no prior systemic anticancer therapy for metastatic disease.

B

Parameter	Eribulin + Pembrolizumab, Stratum 2 (n = 101)			
	n = 89[a]		n = 89[a]	
	PD-L1+	PD-L1−	PD-L1+	PD-L1−
	CPS ≥ 1 (n = 45)	CPS < 1 (n = 44)	CPS ≥ 10 (n = 21)	CPS < 10 (n = 68)
ORR[b,c], n (%) **95% CI[d]**	11 (24.4) 12.9–39.5	8 (18.2) 8.2–32.7	5 (23.8) 8.2–47.2	14 (20.6) 11.7–32.1
CR, n (%)	2 (4.4)	0	0	2 (2.9)
PR, n (%)	9 (20.0)	8 (18.2)	5 (23.8)	12 (17.6)
CBR[d], n (%) **95% CI**	13 (28.9) 16.4–44.3	13 (29.5) 16.8–45.2	6 (28.6) 11.3–52.2	20 (29.4) 19.0–41.7
mDOR[e,f], months **95% CI**	8.2 5.1–25.1	8.6 3.5–13.2	7.2 5.1–NE	8.3 4.3–25.1
mPFS[e], months **95% CI**	4.1 2.1–4.8	3.9 2.3–6.3	4.2 2.1–6.1	3.9 2.2–4.9
mOS[e], months **95% CI**	14.0 11.0–19.4	15.5 12.4–18.7	19.4 8.2–NE	14.1 11.1–17.5
mFollow-up, months **95% CI**	17.3 15.7–39.4	39.6 15.4–41.8	17.3 11.3–41.6	18.0 15.9–40.9

[a]Excludes 12 patients for whom PD-L1 status was not available.
[b]ORR = CR + PR; 95% CIs were calculated by Clopper–Pearson method.
[c]ORR does not include 12 patients with unknown PD-L1 status. Among the patients with unknown PD-L1 status in stratum 2 (n = 12), 3/12 patients are responders (CR, n = 1; PR, n = 2).
[d]CBR is defined as the proportion of patients with CR + PR + durable SD (≥ 24 weeks); 95% CIs were calculated by Clopper–Pearson method.
[e]Medians for PFS, OS, and DOR were estimated using the Kaplan–Meier method and their corresponding 95% CIs were calculated using a generalized Brookmeyer and Crowley method.
[f]In patients with a confirmed CR or PR as best overall response.
CI, confidence interval; CBR, clinical benefit rate; CPS, combined positive score; CR, complete response; DOR, duration of response; m, median; n, number; NE, not estimable; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease.
Stratum 2: 1–2 prior systemic anticancer therapies for metastatic disease.