Supplementary Appendix

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

Supplement to: Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015-26. DOI: 10.1056/NEJMoa1613683

Supplementary Appendix: Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. Bellmunt J et al.

Table of Contents

List of Investigators

Country	Site Name	Principal Investigator	No. Patients Enrolled
Australia	Crown Princess Mary Cancer Centre Westmead	Howard Gurney	10
	Princess Alexandra Hospital	Elizabeth McCaffrey	1
	Tasman Oncology Research Pty Ltd	Andrew Hill	2
Austria	AKH der Stadt Wien - Medizinische Universitaetskliniken	Shahrokh Shariat	3
	Krankenhaus der Barmherzigen Schwestern	Wolfgang Loidl	2
	Landeskrankenhaus Innsbruck – Medizinische Universitatskliniken	Renate Pichler	4
	LKH Univ Klinikum Graz	Hellmut Samonigg	2
Belgium	CHU Sart Tilman-Service d'Oncologie Médicale	Brieuc Sautois	4
	UCL Saint-Luc - Oncologie Medicale	Jean-Pascal Machiels	9
Canada	CHUQ - Pavillon Hotel Dieu	Yves Fradet	13
	Nova Scotia Cancer Centre	Robyn Macfarlane	7
Chile	Centro de Cancer Nuestra Senora de la Esperanza	Cesar Sanchez	5
	Centro Oncologico Antofagasta	Luis Matamala	3
Denmark	Aalborg University Hospital	Mette Kempel	4

	Aarhus University Hospital	Mads Agerbaek	5
	Herlev Hospital	Lisa Sengelov	5
	Rigshospitalet	Helle Pappot	5
France	APH Paris, Hopital Saint Louis	Stephane Culine	8
	Centre Georges Francois Leclerc	Sylvie Zanetta	6
	Centre Leon-Berard	Aude Flechon	3
	Hopital Cochin	Jerome Alexandre	5
	Hopital European Georges Pompidou	Stephane Oudard	3
Germany	Johannes Gutenberg Universitat Mainz	Andreas Neisius	6
	Medizinische Hochschule Hannover	Axel Merseburger	1
	Universitaetsklinikum Muenster	Martin Boegemann	3
	Universitaetsklinikum Schleswig-Holstein	Axel Merseburger	1
Hungary	Orszagos Onkologiai Intezet	Lajos Geczi	6
	Pecsi Tudomanyegyetem	Laszlo Mangel	1
	Semmelweis Egyetem	Peter Nyirady	2
	Somogy Megyei Kaposi Mor Oktatokorhaz	Agnes Ruzsa	2
	Uzsoki Utcai Korhaz	Laszlo Landherr	4
Ireland	Adelaide and Meath Hospital of Dublin	Sean McDermott	4
Israel	Assaf Harofeh MC	Avishay Sella	5
	Hadassah Ein Karem [Jerusalem, Israel]	Stephen Frank	5
	Meir Medical Center	Daniel Keizman	8

	Sheba Medical Center - Oncology Division	Raanan Berger	6
	Soroka Medical Center	Keren Rouvinov	4
	Rabin Medical Center	Eli Rosenbaum	5
	Rambam Medical Center	Avivit Peer	7
Italy	San Camillo and Forlanini Hospitals	Cora Sternberg	8
	Azienda Ospedaliera S. Maria degli Angeli	Giovanni Lo Re	5
	Azienda Policlinico Romano Umberto I	Enrico Cortesi	4
	Istituto Nazionale Per Lo Studio E La Cura Dei Tumori	Rosa Tambaro	7
	Fondazione IRCCS Istituto Nazionale dei Tumori, Milano	Andrea Necchi	11
	Ospedale San Vincenzo di Taormina	Francesco Ferrau	1
Japan	Chiba Cancer Center	Satoshi Fukasawa	3
	Harasanshin Hospital	Akito Yamaguchi	1
	Iwate Medical University Hospital	Wataru Obara	1
	Jichi Medical University Hospital	Tatsuya Takayama	2
	Kagoshima University Medical and Dental Hospital	Hideki Enokida	3
	Kansai Medical University Hirakata Hospital	Hidefumi Kinoshita	2
	Keio University Hospital	Mototsugu Oya	2

	Kyushu University Hospital	Akira Yokomizo	2
	Medical Hospital, Tokyo Medical And Dental University	Minato Yokoyama	3
	Nagoya University Hospital	Naoto Sassa	4
	Nara Medical University Hospital	Kiyohide Fujimoto	4
	Niigata Cancer Center Hospital	Toshihiro Saito	2
	Osaka Medical Center for Cancer and Cardiovascular Diseases	Kazuo Nishimura	4
	Osaka Medical College Hospital	Teruo Inamoto	2
	Saitama Medical University International Medical Center	Masafumi Oyama	2
	Sapporo Medical University Hospital	Hiroshi Kitamura	2
	Tokushima University Hospital	Hiroomi Kanayama	2
	University of Tsukuba Hospital	Hiroyuki Nishiyama	3
	Yamagata University Hospital	Tomoyuki Kato	2
	Yamaguchi University Hospital	Yoshiaki Yamamoto	6
Netherlands	Erasmus MC	Ronald De Wit	12
	Medisch Centrum Alkmaar	M. P. Hendriks	7
	Radboud University	Winald Gerritsen	10
New Zealand	Auckland City Hospital	Fritha Hanning	2
	Canterbury Regional Cancer & Blood Service	David Gibbs	2
Norway	Haukeland Universitetssykehus, Klinisk	Svein Helle	2

	forskningspost voksne		
	Oslo Universitetssykehus Radiumhospitalet	Gunnar Tafjord	4
Peru	Instituto Nacional de Enfermedades Neoplasicas	Silvia Neciosup de D.	2
Poland	Centrum Onkologii-Instytut im. Marii Sklodowskiej-Curie	Tomasz Demkow	3
Portugal	Centro Hospitalar Lisboa Norte EPE - Hospital de Santa Maria	Antonio Quintela	3
	Fundacao Champalimaud	Nuno Vau	1
Puerto Rico	Fundacion de Investigacion de Diego	Deana Hallman-Navarro	1
Romania	Centrul de Oncologie Sf. Nectarie SRL	Michael Schenker	4
	Institutul Oncologic Bucuresti Prof. Dr. Alex. Trestioreanu	Dana Stanculeanu	1
Singapore	National Cancer Centre Singapore	Ravindran Kanesvaran	7
South Korea	Asan Medical Center	Jae Lyun Lee	13
	Seoul National University Hospital	Bhumsuk Keam	8
	Severance Hospital, Yonsei University Health System	Sun Young Rha	10
Spain	Hospital Gregorio Maranon	Jose Arranz	5
	Hospital 12 de Octubre	Daniel Castellano	6

		Gauna	
	Hospital Universitario La Paz	Enrique Espinosa	2
	Hospital Universitario Marques de Valdecilla	Marta Lopez Brea	6
	Hospital Universitario San Carlos	Javier Puente	4
	Instituto Valenciano de Oncologia (IVO)	Miguel Climent Duran	12
Sweden	Akademiska Sjukhuset	Anna Laurell	3
Taiwan	Chang Gung Memorial Hospital, Kaohsiung Branch	Po-Hui Chiang	6
	China Medical University Hospital	Hsi-Chin Wu	2
	National Cheng Kung University Hospital	Wu-Chou Su	6
	National Taiwan University Hospital	Chia-Chi Lin	5
	Taipei Veterans General Hospital	Yen-Hwa Chang	4
Turkey	Bezmialem Vakif University	Mahmut Gumus	3
	Erciyes Uni. Tip Fakultesi	Halit Karaca	3
	Istanbul Uni. Cerrahpasa Tip Fakultesi	Zeynep Turna	5
	Pamukkale Unv. Tip Fak.	Arzu Yaren	2
United Kingdom	Belfast City Hospital	Darren Mitchell	2
	The Royal Marsden NHS Foundation Trust	Vincent Khoo	2
United States	Beth Israel Deaconess Medical Center	Glenn Bubley	1

	Cleveland Clinic	Petros Grivas	5
	Comprehensive Cancer Centers of Nevada	Nicholas Vogelzang	12
	Dana Farber Cancer Institute	Joaquim Bellmunt	5
	Mount Sinai Medical Center	Matthew Galsky	1
	New York University Langone Medical Center	Arjun Balar	4
	Shands Hospital - University of Florida	Long Dang	3
	Sidney Kimmel Center for Prostate and Urologic Cancers	Dean Bajorin	2
	Smilow Cancer Hospital at Yale New Haven	Daniel Petrylak	11
	UCLA Medical Center Hematology Oncology	Alexandra Drakaki	4
	UCSF Helen Diller Family Comprehensive Cancer Center	Lawrence Fong	12
	USC Norris Comprehensive Cancer Center and Hospital	David Quinn	9
	University Hospitals Case Medical Center	Christopher Hoimes	4
	University of California San Diego Moores Cancer Center	James Randall	1
	University of Chicago Medical Center	Peter O'Donnell	5

	University of North Carolina - Cancer Hospital	Matthew Milowsky	1
	University of Pennsylvania	David Vaughn	17
	University of Rochester Medical Center	Elizabeth Guancial	5
	West Clinic	Bradley Somer	3

Data Monitoring Committee

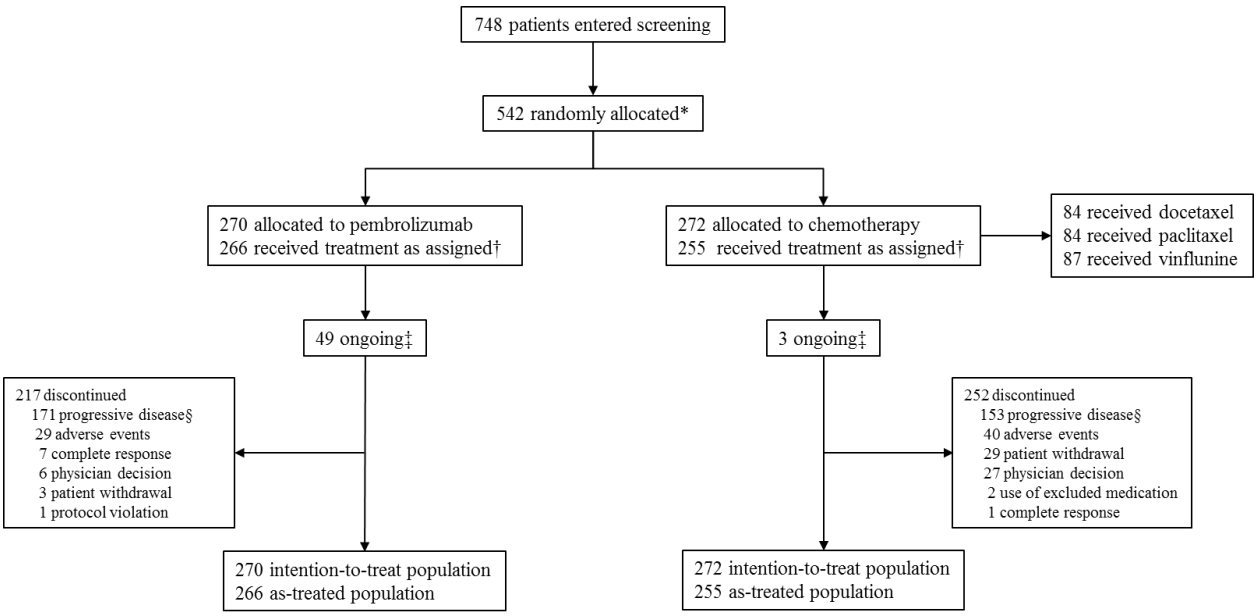
James J. Dignam, PhD: University of Chicago, Chicago, IL, USA

Mario A. Eisenberger, MD: Sidney Kimmel Cancer Center at Johns Hopkins, Baltimore, MD, USA

Phillip W. Kantoff, MD: Memorial Sloan Kettering Cancer Center, New York, NY, USA

Timothy M. Kuzel, MD: Rush University Medical Center, Chicago, IL, USA

Figure S1. Patient Disposition and Treatment in the Intention-to-Treat Population.



*Reasons for screen failure were inadequate performance status (n=56), inadequate organ function (n=42), lack of written, informed consent (n=27), lack of tissue for biomarker analysis (n=23), lack of measurable disease based on Response Evaluation Criteria in Solid Tumors, version 1.1 (n=19), lack of progression on or recurrence after platinum-containing chemotherapy (n=18), prohibited concomitant condition (n=20), central nervous system metastases (n=10), receipt of >2 prior lines of systemic chemotherapy (n=9), lack of histologically or cytological confirmed, transitional cell or transitional cell predominant disease (n=8), additional metastases requiring active treatment (n=8), active infection requiring systemic therapy (n=7), age <18 years (n=6), inadequate contraception (n=6), diagnosis of immunodeficiency or receiving systemic corticosteroid therapy or other immunosuppressive therapy (n=6), received most recent anticancer therapy within the prohibited window or did not recover from all adverse events caused by a previously administered therapy (n=6), active cardiac disease (n=6), evidence of interstitial lung disease or active noninfectious pneumonitis (n=5), active hepatitis B or C infection (n=5), or other (n=37). Subjects may have failed screening for >1 reason.

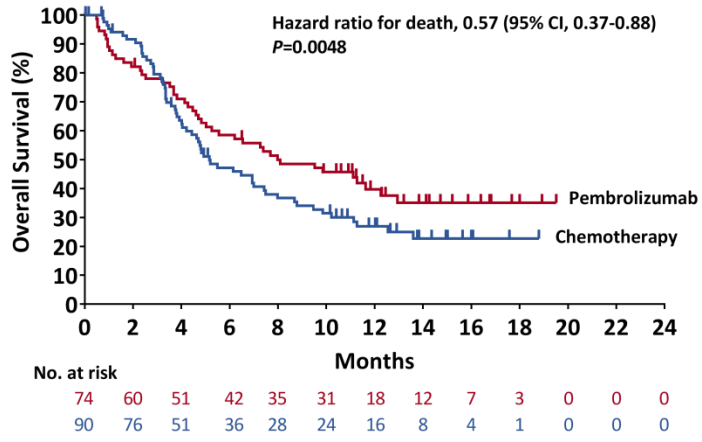
†Reasons for not receiving study treatment were randomization in error based on failure to meet all eligibility criteria (n=2) and fatal adverse events (n=2) in the pembrolizumab group and withdrawal of consent after randomization (n=15), worsening physical condition (n=1), and a decrease in platelet count that precluded treatment (n=1) in the chemotherapy group.

‡Patients without a completed study medication discontinuation form.

§Includes patients with radiologic and clinical disease progression.

Figure S2. Overall (Panel A) and Progression-Free (Panel B) Survival in the PD-L1 Combined Positive Score ≥10% Intention-to-Treat Population. Shown are Kaplan-Meier estimates of overall and progression-free survival according to treatment group. Tick marks represent patients censored at the last time they were known to be alive (A) or alive and without disease progression assessed per RECIST v1.1 by blinded, independent central radiologic review (B). The intention-to-treat population includes all patients who were randomly assigned to study treatment. PD-L1 combined positive score (CPS) was defined as the percentage of tumor and infiltrating immune cells with PD-L1 expression out of the total number of tumor cells. The one-sided superiority thresholds for pembrolizumab were P=0.0065 for overall survival and P=0.0029 for progression-free survival.

(A)



(B)

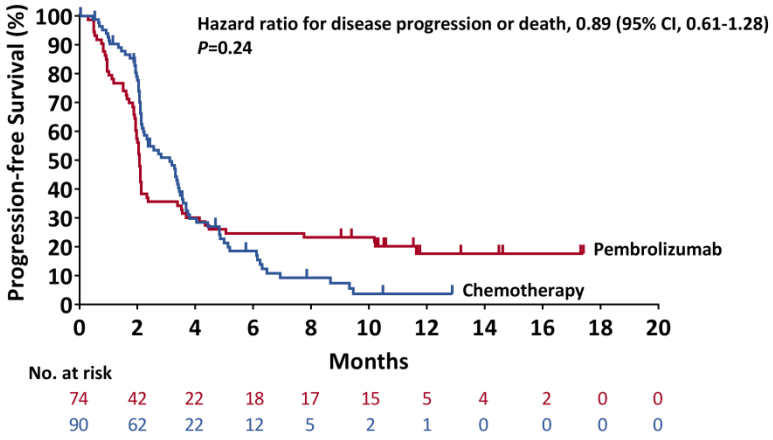
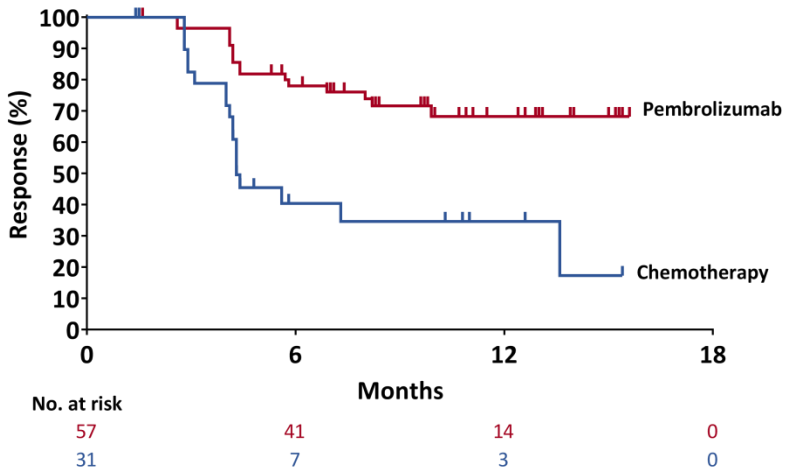

Hazard ratio for disease progression or death, 0.89 (95% CI, 0.61-1.28)
P=0.24
Progression-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20
Months
Pembrolizumab
Chemotherapy
No. at risk
74 42 22 18 17 15 5 4 2 0 0
90 62 22 12 5 2 1 0 0 0 0

Figure S3. Duration of Response in Patients With an Objective Response In the Total (Panel A) and PD-L1 Combined Positive Score ≥10% Populations. Shown are Kaplan-Meier estimates of duration of response according to treatment group. Tick marks represent patients censored at the last time they were known to be radiologic disease progression assessed per Response Evaluation Criteria in Solid Tumors, version 1.1, by blinded, independent, central radiology review. PD-L1 combined positive score (CPS) was defined as the percentage of tumor and infiltrating immune cells with PD-L1 expression out of the total number of tumor cells.

(A)



(B)

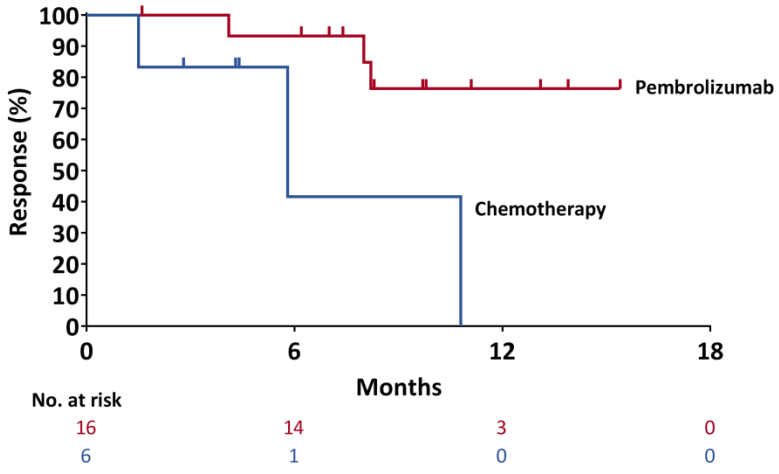


Table S1. One-Sided Superiority Thresholds for Pembrolizumab in the Intention-To-Treat Population at the Second Interim Analysis.*

	Before Alpha Roll Over	**After Alpha Roll Over**
Overall survival, total population	P=0.0068	P=0.0123
Progression-free survival, total population	P=0.0007	P=0.0151
Overall survival, CPS ≥10% population	P=0.0065	P=0.0065
Progression-free survival, CPS ≥10% population	P=0.0029	P=0.0029
Objective response rate, total population	—	P=0.0170

*The intention-to-treat population includes all patients who were randomly allocated to treatment. Response was assessed per Response Evaluation Criteria in Solid Tumors, version 1.1, by blinded, independent, central radiology review. PD-L1 combined positive score (CPS) was defined as the percentage of tumor and infiltrating immune cells with PD-L1 expression out of the total number of tumor cells. Full details of the statistical analysis plan are found in the study protocol.

Table S2. Baseline Demographics and Disease Characteristics in the Intention-to-Treat Population.*

	Pembrolizumab Group (N=270)	**Chemotherapy Group (N=272)**
Age		
Median (range), yr	67.0 (29-88)	65.0 (26-84)
≥65 yr, no. (%)	165 (61.1)	147 (54.0)
Male sex, no. (%)	200 (74.1)	202 (74.3)
ECOG performance status,† no. (%)		
0	119 (44.1)	106 (39.0)
1	143 (53.0)	158 (58.1)
2	2 (0.7)	4 (1.5)
Smoking status,‡ no. (%)		
Current	29 (10.7)	38 (14.0)
Former	136 (50.4)	148 (54.4)
Never	104 (38.5)	83 (30.5)
Histology,§ no. (%)		
Pure transitional cell	186 (68.9)	197 (72.4)
Predominantly transitional cell	82 (30.4)	73 (26.8)
PD-L1 CPS,‖ no. (%)		
<10%	186 (68.9)	176 (64.7)
≥10%	74 (27.4)	90 (33.1)
Site of primary tumor,¶ no. (%)		

Upper tract (renal pelvis or ureter)	38 (14.1)	37 (13.6)
Lower tract (bladder or urethra)	232 (85.9)	234 (86.0)
Visceral disease, no. (%)	240 (88.9)	233 (85.7)
Liver metastases	91 (33.7)	95 (34.9)
Hemoglobin level,** no. (%)		
<10 g/dL (<100 g/L)	43 (15.9)	44 (16.2)
≥10 g/dL (≥100 g/L)	219 (81.1)	223 (82.0)
No. of risk factors,†† no. (%)		
0	54 (20.0)	44 (16.2)
1	96 (35.6)	97 (35.7)
2	66 (24.4)	80 (29.4)
3-4	45 (16.7)	45 (16.5)
Setting of most recent prior therapy,‡‡ no. (%)		
Neoadjuvant or adjuvant	31 (11.5)	53 (19.5)
First line	183 (67.8)	157 (57.7)
Second line	55 (20.4)	60 (22.1)
Time since completion or discontinuation of most recent prior therapy,§§ no. (%)		
<3 months	103 (38.1)	104 (38.2)
≥3 months	166 (61.5)	167 (61.4)
Prior platinum,§§ no. (%)		
Cisplatin	198 (73.3)	213 (78.3)
Carboplatin	70 (25.9)	56 (20.6)

Oxaliplatin or nedaplatin	1 (0.4)	2 (0.7)
Prior cystectomy or nephroureterectomy, no. (%)	61 (22.6)	51 (18.8)
Prior Bacillus Calmette–Guérin therapy, no. (%)	32 (11.9)	22 (8.1)

*The intention-to-treat population includes all patients who were randomly allocated to treatment. There were no significant difference between treatment groups.

†Eastern Cooperative Oncology Group (ECOG) performance status ranges from 0 to 5, with 0 indicating no symptoms and higher score indicating increasing disability. Six (2.2%) patients in the pembrolizumab group and 4 (1.5%) patients in the chemotherapy group had a missing ECOG performance status.

‡Smoking status was missing for 1 (0.4%) patient in the pembrolizumab group and 3 (1.1%) patients in the chemotherapy group.

§One (0.7%) patient in the pembrolizumab group had clear cell adenocarcinoma, and 1 (0.7%) patient had unknown histology. Two (0.7%) patients in the chemotherapy group had missing histology.

‖PD-L1 combined positive score (CPS) was defined as the percentage of tumor and infiltrating immune cells with PD-L1 expression out of the total number of tumor cells. PD-L1 CPS was not evaluable for 10 (3.7%) patients in the pembrolizumab group and 6 (2.2%) in the chemotherapy group.

¶Primary tumor site was missing for 1 (0.4%) patient in the chemotherapy group.

**Baseline hemoglobin level was missing for 8 (3.0%) patients in the pembrolizumab group and 5 (1.8%) patients in the chemotherapy group.

††Risk factors include the Bellmunt risk factors of ECOG performance status >0, hemoglobin level <10 g/dL (<100 g/L), and presence of liver metastases[1] plus time since completion or discontinuation of <3 months.[2] The number of risk factors was unknown for 9 (3.3%) patients in the pembrolizumab group and 6 (2.2%) patients in the chemotherapy group.

‡‡The setting of the most recent prior therapy was the third line for 1 (0.4%) patient in the chemotherapy group and was missing for 1 (0.4%) patient each in the pembrolizumab and chemotherapy groups.

§§The time since completion or discontinuation of most recent prior therapy and the specific prior platinum were missing for 1 (0.4%) patient in each treatment group.

Table S3. Baseline Demographics and Disease Characteristics in the PD-L1 Combined Positive Score ≥10% Intention-to-Treat Population.*

	Pembrolizumab Group (N=74)	**Chemotherapy Group (N=90)**
Age, yr, median (range)	66.0 (43-88)	63.0 (38-83)
Male sex, no. (%)	54 (73.0)	60 (66.7)
ECOG performance status,† no. (%)		
0	32 (43.2)	33 (36.7)
1	40 (54.1)	55 (66.1)
2	1 (1.4)	2 (2.2)
Smoking status, no. (%)		
Current	8 (10.8)	15 (16.7)
Former	27 (36.5)	45 (50.0)
Never	39 (52.7)	30 (33.3)
Histology,‡ no. (%)		
Pure transitional cell	40 (54.1)	59 (65.6)
Predominantly transitional cell	33 (44.6)	3 (34.4)
Site of primary tumor, no. (%)		
Upper tract	13 (17.6)	12 (13.3)
Lower tract	61 (82.4)	78 (86.7)
Visceral disease, no. (%)	63 (85.1)	75 (83.3)
Liver metastases	28 (37.8)	29 (32.2)
Hemoglobin level,§ no. (%)		

<10 g/dL (<100 g/L)	18 (24.3)	13 (14.4)
≥10 g/dL (≥100 g/L)	53 (71.6)	77 (85.6)
No. of risk factors,‖ no. (%)		
0	13 (17.6)	16 (17.8)
1	20 (27.0)	33 (36.7)
2	15 (20.3)	22 (24.4)
3-4	23 (31.1)	19 (21.1)
Setting of most recent prior therapy,¶ no. (%)		
Neoadjuvant or adjuvant	11 (14.9)	21 (23.3)
First line	43 (58.1)	47 (52.2)
Second line	19 (25.7)	22 (24.4)
Time since completion or discontinuation of most recent prior therapy,** no. (%)		
<3 months	42 (56.8)	38 (42.2)
≥3 months	31 (41.9)	52 (57.8)
Prior platinum,** no. (%)		
Cisplatin	59 (79.7)	70 (77.8)
Carboplatin	14 (18.9)	19 (21.1)
Nedaplatin	0	1 (1.1)
Prior cystectomy or nephroureterectomy, no. (%)	12 (16.2)	17 (18.9)
Prior Bacillus Calmette–Guérin therapy, no. (%)	2 (2.7)	9 (10.0)

*The intention-to-treat population includes all patients who were randomly allocated to treatment. PD-L1 combined positive score (CPS) was defined as the percentage of tumor and infiltrating immune cells with PD-L1 expression out of the total number of tumor cells.

†Eastern Cooperative Oncology Group (ECOG) performance status ranges from 0 to 5, with 0 indicating no symptoms and higher score indicating increasing disability. 1 (1.4%) patient in the pembrolizumab group had a missing ECOG performance status.

‡One (1.4%) patient in the pembrolizumab group had unknown histology.

§Baseline hemoglobin level was missing for 3 (4.1%) patients in the pembrolizumab group.

‖Risk factors include the Bellmunt risk factors of ECOG performance status >0, hemoglobin level <10 g/dL (<100 g/L), and presence of liver metastases[1] plus time since completion or discontinuation of <3 months.[2] The number of risk factors was unknown for 3 (4.1%) patients in the pembrolizumab group.

¶The setting of the most recent prior therapy was missing for 1 (1.4%) patient in the pembrolizumab group.

**The time since completion or discontinuation of most recent prior therapy and the specific prior platinum were missing for 1 (1.4%) patient in the pembrolizumab group.

Table S4. Summary of Response in the Total and PD-L1 Combined Positive Score Intention-to-Treat Populations.*

Variable	Total Population		CPS ≥10% Population	
	Pembrolizumab Group (N=270)	Chemotherapy Group (N=272)	Pembrolizumab Group (N=74)	Chemotherapy Group (N=90)
Objective response†				
No. of patients	57	31	16	6
% (95% CI)	21.1 (16.4 to 26.5)	11.4 (7.9 to 15.8)	21.6 (12.9 to 32.7)	6.7 (2.5 to 13.9)
Time to response,‡ months				
Median (range)	2.1 (1.4 to 6.3)	2.1 (1.7 to 4.9)	2.1 (1.4 to 5.3)	2.1 (1.9 to 2.2)
Duration of response,‡§ months				
Median (range)	NR (1.6+ to 15.6+)	4.3 (1.4+ to 15.4+)	NR (1.6+ to 15.4+)	4.4 (1.5+ to 10.8+)
Response ≥6 months	41 (78)	7 (40)	14 (93)	1 (40)
Response ≥12 months	14 (68)	3 (35)	3 (76)	0
Best overall response, no. (%)				
Complete response	19 (7.0)	9 (3.3)	5 (6.8)	2 (2.2)

Partial response	38 (14.1)	22 (8.1)	11 (14.9)	4 (4.4)
Stable disease	47 (17.4)	91 (33.5)	9 (12.2)	35 (35.6)
Progressive disease	131 (48.5)	90 (33.1)	37 (50.0)	38 (31.1)
Nonevaluable or no assessment	35 (13.0)	60 (22.1)	12 (16.2)	24 (26.7)

*The intention-treat population includes all patients who were randomly allocated to treatment. PD-L1 combined positive score (CPS) was defined as the percentage of tumor and infiltrating immune cells with PD-L1 expression out of the total number of tumor cells. Response was assessed by Response Evaluation Criteria in Solid Tumors, version 1.1, but blinded, independent, central radiology review.

†Objective response included patients with confirmed complete or partial response. The estimated difference between the pembrolizumab and chemotherapy groups, assessed using the stratified Miettinen and Nurminen's method, was 9.6 percentage points (95% CI, 3.5 to 15.9) (P=0.0011) in the total population and 19.3 percentage points (95% CI, 8.6-31.7) in the CPS ≥10% population. The one-sided superiority threshold for pembrolizumab in the total population was P=0.0170. No alpha was allocated to the comparison of response rate in the CPS ≥10% population.

‡Time to and duration of response were assessed in patients who experienced an objective response.

§Duration of response was calculated using the Kaplan-Meier method. Plus signs in the ranges indicate that the response was ongoing at the time of data cutoff.

Table S5. Adverse Events, Regardless of Attribution to Treatment by the Investigator, With Incidence of At Least 5% in the As-Treated Population.*

Adverse Event, no. (%)	Pembrolizumab Group (N=266)		Chemotherapy Group (N=255)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
Any	248 (93.2)	139 (52.3)	250 (98.0)	160 (62.7)
Led to discontinuation	22 (8.3)	18 (6.8)	32 (12.5)	20 (7.8)
Led to death	13 (3.9)	13 (3.9)	8 (3.1)	8 (3.1)
Individual events†				
Blood and lymphatic system disorders	53 (19.9)	25 (9.4)	130 (51.0)	76 (29.8)
Anemia	46 (17.3)	22 (8.3)	91 (35.7)	31 (12.2)
Febrile neutropenia	0	0	19 (7.5)	19 (7.5)
Neutropenia	0	0	43 (16.9)	37 (14.5)
Cardiac disorders	15 (5.6)	3 (1.1)	16 (6.3)	4 (1.6)
Endocrine disorders	28 (10.5)	3 (1.1)	4 (1.6)	0
Hypothyroidism	17 (6.4)	0	3 (1.2)	0
Eye disorders	20 (7.5)	2 (0.8)	17 (6.7)	0

Gastrointestinal disorders	150 (56.4)	20 (7.5)	174 (68.2)	41 (16.1)
Abdominal pain	34 (12.8)	3 (1.1)	34 (13.3)	7 (2.7)
Abdominal pain upper	9 (3.4)	0	14 (5.5)	1 (0.4)
Constipation	50 (18.8)	3 (1.1)	81 (31.8)	8 (3.1)
Diarrhea	43 (16.2)	4 (1.5)	48 (18.8)	4 (1.6)
Nausea	55 (20.7)	3 (1.1)	73 (28.6)	4 (1.6)
Stomatitis	6 (2.3)	1 (0.4)	22 (8.6)	1 (0.4)
Vomiting	39 (14.7)	1 (0.4)	34 (13.3)	1 (0.4)
General disorders and administration site conditions	153 (57.5)	21 (7.9)	184 (72.2)	38 (14.9)
Asthenia	30 (11.3)	2 (0.8)	53 (20.8)	13 (5.1)
Fatigue	69 (25.9)	10 (3.8)	86 (33.7)	15 (5.9)
Mucosal inflammation	5 (1.9)	1 (0.4)	20 (7.8)	4 (1.6)
Peripheral edema	26 (9.8)	0	40 (15.7)	2 (0.8)
Pyrexia	36 (13.5)	2 (0.8)	33 (12.9)	3 (1.2)
Infections and infestations	105 (39.5)	36 (13.5)	94 (36.9)	29 (11.4)

Nasopharyngitis	14 (5.3)	0	4 (1.6)	0
Urinary tract infection	39 (14.7)	13 (4.9)	34 (13.3)	11 (4.3)
Injury, poisoning and procedural complications	25 (9.4)	6 (2.3)	24 (9.4)	4 (1.6)
Investigations	77 (28.9)	22 (8.3)	89 (34.9)	42 (16.5)
ALT increased	14 (5.3)	3 (1.1)	4 (1.6)	0
AST increased	14 (5.3)	6 (2.3)	3 (1.2)	0
Blood creatinine increased	13 (4.9)	2 (0.8)	15 (5.9)	1 (0.4)
Neutrophil count decreased	1 (0.4)	1 (0.4)	38 (14.9)	32 (12.5)
Weight decreased	24 (9.0)	2 (0.8)	21 (8.2)	0
White blood cell count decreased	1 (0.4)	1 (0.4)	20 (7.8)	14 (5.5)
Metabolism and nutrition disorders	101 (38.0)	31 (11.7)	97 (38.0)	28 (11.0)
Decreased appetite	56 (21.1)	10 (3.8)	53 (20.8)	3 (1.2)
Hyponatremia	15 (5.6)	5 (1.9)	18 (7.1)	8 (3.1)
Musculoskeletal	113 (42.5)	14 (5.3)	95 (37.3)	10 (3.9)

and connective tissue disorders				
Arthralgia	24 (9.0)	0	30 (11.8)	3 (1.2)
Back pain	37 (13.9)	2 (0.8)	21 (8.2)	1 (0.4)
Myalgia	14 (5.3)	1 (0.4)	17 (6.7)	0
Pain in extremity	21 (7.9)	0	28 (11.0)	3 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	18 (6.8)	11 (4.1)	12 (4.7)	5 (2.0)
Nervous system disorders	58 (21.8)	5 (1.9)	105 (41.2)	17 (6.7)
Dizziness	15 (5.6)	0	19 (7.5)	1 (0.4)
Dysgeusia	7 (2.6)	0	18 (7.1)	0
Headache	13 (4.9)	1 (0.4)	13 (5.1)	0
Neuropathy peripheral	1 (0.4)	0	31 (12.2)	2 (0.8)
Peripheral sensory neuropathy	2 (0.8)	0	28 (11.0)	5 (2.0)
Psychiatric	38 (14.3)	1 (0.4)	43 (16.9)	2 (0.8)

disorders				
Insomnia	16 (6.0)	1 (0.4)	19 (7.5)	0
Renal and urinary disorders	72 (27.1)	27 (10.2)	45 (17.6)	10 (3.9)
Acute kidney injury	15 (5.6)	7 (2.6)	7 (2.7)	3 (1.2)
Hematuria	30 (11.3)	6 (2.3)	20 (7.8)	4 (1.6)
Reproductive system and breast disorders	18 (6.8)	2 (0.8)	8 (3.1)	2 (0.8)
Respiratory, thoracic and mediastinal disorders	91 (34.2)	15 (5.6)	75 (29.4)	9 (3.5)
Cough	38 (14.3)	1 (0.4)	18 (7.1)	0
Dyspnea	33 (12.4)	5 (1.9)	23 (9.0)	3 (1.2)
Skin and subcutaneous tissue disorders	114 (42.9)	1 (0.4)	127 (49.8)	6 (2.4)
Alopecia	2 (0.8)	0	99 (38.8)	3 (1.2)
Dry skin	14 (5.3)	0	9 (3.5)	0
Pruritus	62 (23.3)	0	14 (5.5)	1 (0.4)
Rash	29 (10.9)	1 (0.4)	16 (6.3)	0

Vascular disorders	39 (14.7)	11 (4.1)	32 (12.5)	4 (1.6)

*The as-treated population includes all patients who received at least one dose of study treatment.

†Events are listed alphabetically by system organ class.

References

1. Bellmunt J, Choueiri TK, Fougeray R, et al. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. J Clin Oncol 2010;28:1850-5.

2. Sonpavde G, Pond GR, Fougeray R, et al. Time from prior chemotherapy enhances prognostic risk grouping in the second-line setting of advanced urothelial carcinoma: a retrospective analysis of pooled, prospective phase 2 trials. Eur Urol 2013;63:717-23.