Supplementary appendix

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Appendix tables

Table S1. Investigator sites

Site number	Principal investigator	Site/Institution	Patients treated (N=249)
141	Patel, Manish	Florida Cancer Specialists	13
102	Infante, Jeffrey	SCRI - Tennessee Oncology	10
169	Ellerton, John	Southern Nevada Cancer Research Foundation	9
120	Gordon, Michael	Pinnacle Oncology Hematology	8
124	Agrawal, Manish	Maryland Oncology Hematology, P.A.	7
193	Taylor, Matthew	Oregon Health & Science University	6
221	Dirix, Luc	GZA Ziekenhuizen - Campus Sint-Augustinus	6
112	Aljumaily, Raid	Oklahoma University Medical Center	6
904	Lee, Keun-wook	Seoul National University Bundang Hospital	6
165	Britten, Carolyn	Medical University of South Carolina	6
402	Delord, Jean-Pierre	Institut Claudius Regaud-Oncopole	5
223	Schoffski, Patrick	UZ Leuven	5
202	Verschraegen, Claire	University of Vermont Medical Center	5
406	Kotecki, Nuria	Centre Oscar Lambret	5
167	Wang, Ding	Henry Ford Medical Center	5
176	Belani, Chandra	Penn State Univ. Milton S. Hershey Medical Center	5
225	Forget, Frédéric	Centre Hospitalier de l'Ardenne	4
107	Kelly, Karen	University of California Davis Health System	4
407	Isambert, Nicolas	Centre Georges François Leclerc	4
156	Kochuparambil, Samith	Virginia Piper Cancer Institute	4
209	Hamid, Omid	The Angeles Clinic and Research Institute - West LA	4
159	Safran, Howard	Rhode Island Hospital	4
405	Ravaud, Alain	Groupe Hospitalier Saint André - Hôpital Saint André	4
171	Peguero, Julio	Oncology Consultants, P.A.	4
805	Arkenau, Hendrik-Tobias	Sarah Cannon Research Institute UK	4
101	Gulley, James	National Cancer Institute	4
152	Powderly, John	Carolina BioOncology Institute, LLC	4
222	Jerusalem, Guy	CHU Sart Tilman	3
502	Folprecht, Gunnar	Universitaetsklinikum Carl Gustav Carus TU Dresden	3
145	Khleif, Samir	Augusta University	3
179	Frank, Richard	Whittingham Cancer Center	3
139	Lenz, Heinz	Keck School of Medicine of USC	3
184	Vaishampayan, Ulka	Karmanos Cancer Institute	3
166	Wong, Deborah	UCLA Department of Medicine	3
135	Morris, John	UC Health Clinical Trials Office	3
404	Le Tourneau, Christophe	Institut Curie - Centre de Lutte Contre le Cancer (CLCC) de Paris	3
204	Mehnert, Janice	Rutgers Cancer Institute of New Jersey	3
157	Assikis, Vasileios	Peachtree Hematology-Oncology Consultants, P.C.	3
117	Redfern, Charles	Sharp Memorial Hospital	3
172	MacVicar, Gary	Illinois Cancer Care, P.C.	3
164	Neidhart, Jeffrey	San Juan Oncology Associates	2
412	Lesimple, Thierry	CRLCC Eugene Marquis	2
108	Smith, Pamela	Billings Clinic Cancer Center	2
149	Villa, Luis	AMPM Research Clinic	2
161	Lee, Carrie	University of North Carolina at Chapel Hill	2
908	Kim, Yeul Hong	Korea University Anam Hospital	2
148	Boccia, Ralph	RCCA MD LLC	2
303	Smakal, Martin	Nemocnice Rudolfa a Stefanie Benesov, a.s.	2
411	Borel, Christian	Centre Paul Strauss	2
308	Zemanova, Milada	Vseobecna fakultni nemocnice V Praze	2
501	Keilholz, Ulrich	Charite Universitaetsmedizin Berlin - Campus Benjamin Franklin	2
906	Chung, Hyun Cheol	Severance Hospital, Yonsei University	2

506	Claus, Rainer	Universitaetsklinikum Freiburg	2
208	Chandler, Jason	The West Clinic	2
180	Gelmann, Edward	Columbia University College of Phys & Surgeons	2
118	Zarwan, Corrine	Lahey Clinic Inc.	2
116	Chaves, Jorge	Northwest Medical Specialties, PLLC	2
207	Segota, Zdenka	Holy Cross Hospital	2
186	Mita, Alain	Cedars-Sinai Medical Center	2
188	Nemunaitis, John	Mary Crowley Cancer Research Centers	1
213	Dreisbach, Luke	Desert Hematology Oncology Medical Group, Inc.	1
155	Gurtler, Jayne	Metairie Oncologist, LLC	1
306	Prausova, Jana	Fakultni nemocnice v Motole	1
162	Edenfield, William	Greenville Hospital System University Medical Center (ITOR)	1
307	Melichar, Bohuslav	Fakultni nemocnice Olomouc	1
224	Rolfo, Christian	UZ Antwerpen	1
199	Rubenstein, Stephen	Franciscan St. Francis Health Cancer Center	1
198	Papish, Steven	Morristown Medical Center	1
173	Lee, Wes	St Joseph Heritage Healthcare	1
218	Nimeiri, Halla	Robert H. Lurie Comprehensive Cancer Center of Northwestern University	1
113	Goel, Sanjay	Montefiore Medical Center	1
187	Nakka, Sushma	Lakeland Regional Cancer Center	1
119	Freilich, Bradley	Kansas City Research Institute, LLC	1
902	Lee, Jeeyun	Samsung Medical Center	1
115	Beck, Joseph	Highlands Oncology Group	1
905	Roh, Sang-Young	The Catholic University of Korea, Seoul St. Mary's Hospital	1
122	Iannotti, Nicholas	Hematology - Oncology Associates of Treasure Coast	1
301	Obermannova, Radka	Masarykuv onkologicky ustav	1
408	Bourgeois, Hugues	Clinique Victor Hugo - Centre Jean Bernard	1
210	McClay, Edward	California Cancer Associates for Research & Excellence, Inc.	1

Table S2: Eligibility Criteria for Trial Enrolment

Inclusion criteria	Exclusion criteria

• Signed and written informed consent
• Age ≥18 years with estimated life expectancy ≥3 months
• Histologically confirmed locally advanced or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, urethra)
• Eligible patients must have either:
  ○ Progressed after treatment with ≥1 platinum-containing regimen (i.e., platinum plus another agent such as gemcitabine, methotrexate, vinblastine, doxorubicin) for inoperable locally advanced or metastatic urothelial carcinoma or disease recurrence, *or*
  ○ Been ineligible for cisplatin-based chemotherapy, with ineligibility to a platinum salt defined by any impaired renal function, a hearing loss of 25 decibels at two contiguous frequencies, or grade ≥ 2 peripheral neuropathy
• Biopsy material was required (archival tissue was acceptable if patient could not provide fresh or recent biopsy)
• ECOG PS of 0 to 1 at study entry
• ≥1 unidimensional measurable lesion by RECIST v 1.1
• Adequate haematologic function defined by white blood cell count ≥3 × 10^9/L with absolute neutrophil count ≥1.5 × 10^9/L, lymphocyte count ≥ 0.5 × 10^9/L, platelet count ≥100 × 10^9/L, and haemoglobin ≥9 g/dL (may have been transfused)
• Adequate hepatic function defined by a total bilirubin level ≤1.5 × ULN, an AST level ≤2.5 × ULN, and an ALT level ≤2.5 × ULN or, for patients with documented metastatic disease to the liver, AST and ALT levels ≤5 × ULN
• Adequate renal function defined by an estimated creatinine clearance > 50 mL/min according to the Cockcroft-Gault formula
• Use of highly effective contraception
	• Concurrent treatment with an anticancer treatment (within 28 days) or other non-permitted drug
	• Prior therapy with any drug targeting T–cell coregulatory proteins
	• Concurrent systemic therapy with corticosteroids or other immunosuppressive agents, or use of any investigational drug within 28 days before starting trial drug; short-term administration of systemic steroids (steroids with no or minimal systemic effect were allowed); any prior surgery for any reason within 4 weeks or if the patient had not fully recovered within 4 weeks
	• Previous malignant disease (other than urothelial carcinoma) within the last 5 years, with the exclusion of basal or squamous cell carcinoma of the skin or cervical carcinoma in situ
	• Rapidly progressive disease (eg, tumour lysis syndrome)
	• Active or history of central nervous metastasis
	• Known history of testing positive for HIV/AIDS, HBV, or HCV (including acute and chronic infection)
	• Known monoclonal antibody hypersensitivity, history of anaphylaxis, or uncontrolled asthma
	• Persisting toxicity related to prior therapy that was grade >1 according to NCI-CTCAE v4.0 (grade ≤2 sensory neuropathy was acceptable)
	• Prior organ transplantation, including allogeneic stem-cell transplantation
	• Active or history of any autoimmune disease or immune-deficiencies (patients with type 1 diabetes, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment were eligible)
	• Pregnancy or lactation
	• Known alcohol or drug use
	• Clinically significant cardiovascular disease
	• All other significant diseases that, in the investigator's opinion, may have influenced the patient's tolerance of trial treatment
	• Legal incapacity or limited legal capacity, including any psychiatric condition that would prohibit the understanding or rendering of informed consent
	• Vaccination within 4 weeks of the first dose of avelumab and while on study except for administration of inactivated vaccines (eg, inactivated influenza vaccines)

ALT=alanine aminotransferase. AST=aspartate aminotransferase. ECOG PS=Eastern Cooperative Oncology Group performance status. HBV=hepatitis B virus. HCV=hepatitis C virus. HIV=human immunodeficiency virus. NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events. RECIST=Response Evaluation Criteria In Solid Tumors. ULN=upper limit of normal.

Table S3: Reasons for Avelumab Treatment Discontinuation or Delay

Permanent treatment discontinuation

- Any grade 4 adverse events required treatment discontinuation except for single laboratory values out of normal range that were unrelated to trial treatment per investigator, did not have clinical correlates, and resolved within 7 days with adequate medical intervention
- Any grade 3 adverse events required treatment discontinuation, other than the following:
    - Transient (≤6 hours) grade 3 flu-like symptoms or fever controlled with medical intervention
    - Transient (≤24 hours) grade 3 fatigue, local reactions, headache, nausea, or emesis resolving to grade ≤1
    - Single laboratory values out of normal range (excluding grade ≥3 liver function test increase) that were unrelated to trial treatment per investigator, had no clinical correlates, and resolved to grade ≤1 within 7 days with adequate medical management
    - Tumour flare event (eg. local pain, irritation, or rash) localised at sites of known or suspected tumour
    - Any grade ≥3 drug-related amylase or lipase abnormality that was not associated with symptoms or clinical manifestations of pancreatitis that did not require dose delay
    - Increased ECOG PS ≥3 (did not resolve to ≤2 by cycle day 14 of the following cycle); infusion was not given on the following cycle if the ECOG PS was ≥3 on the day of study drug administration

Management of grade 2 adverse events

- Treatment was continued if a grade 2 adverse event resolved to grade ≤1 by the last day of the current cycle
- If there was no resolution of a grade 2 adverse event by the last day of the current cycle, infusions were not given the following cycle.
    - If at the end of the following cycle, the event had not resolved to grade 1, the patient permanently discontinued treatment (excluding hormone insufficiencies managed by replacement therapy; for these hormone insufficiencies, up to two subsequent doses were omitted)
- Treatment with avelumab was permanently discontinued following the second occurrence of the same grade 2 adverse event (excluding hormone insufficiencies that were managed by replacement therapy) in the same patient
- Infusion-related reactions, hypersensitivity reactions (grades 1–4), and tumour lysis syndrome were handled based on protocol guidelines

ECOG PS=Eastern Cooperative Oncology Group performance status.

Table S4: Additional Patient Demographics and Disease Characteristics

Characteristics	N=249
Prior surgery	237 (95%)
Prior radiotherapy	76 (31%)
Prior drug therapy	243 (98%)
Number of prior anticancer therapies in any setting	
1	81 (33%)
2	80 (32%)
≥3	82 (33%)
Unknown	6 (2%)
Median	2·0 (1–3)
Prior platinum regimen	
Cisplatin-based	159 (64%)
Carboplatin-based	129 (52%)
Type of prior anticancer therapy	
Chemotherapy	243 (98%)
Hormonal therapy	2 (1%)
Antibody therapy	3 (1%)
Kinase inhibitor	2 (1%)
Vaccines	5 (2%)
Other	24 (10%)
Intent of any prior therapy	
Neoadjuvant	34 (14%)
Adjuvant	51 (21%)
Metastatic	221 (89%)
Locally advanced	37 (15%)

Data are median (interquartile range), and n (%).

Table S5: Prior Anticancer Therapies

Patients receiving prior anticancer therapy	N=249
Gemcitabine	159 (64%)
Cisplatin	153 (61%)
Carboplatin	122 (49%)
Paclitaxel	64 (26%)
Gemcitabine hydrochloride	59 (24%)
Methotrexate	44 (18%)
Vinblastine	39 (16%)
Doxorubicin	38 (15%)
Bacillus Calmette-Guérin vaccine	36 (15%)
Docetaxel	22 (9%)
Mitomycin	19 (8%)
Investigational drug	12 (5%)
Pemetrexed	10 (4%)
Pemetrexed disodium	10 (4%)
Vinblastine sulfate	7 (3%)
Vinflunine	6 (2%)
Carboplatin with gemcitabine	5 (2%)
Combinations of antineoplastic agents	5 (2%)
Bevacizumab	4 (2%)
Etoposide	4 (2%)
Vinorelbine	4 (2%)
Antineoplastic agents	3 (1%)
Cabozantinib	3 (1%)
Capecitabine	3 (1%)
Cisplatin with gemcitabine	3 (1%)
Cisplatin with gemcitabine hydrochloride	3 (1%)
Doxorubicin hydrochloride	3 (1%)
Fluorouracil	3 (1%)
Ifosfamide	3 (1%)
Paclitaxel albumin	3 (1%)
Azacitidine	2 (1%)
Carboplatin with paclitaxel	2 (1%)
Everolimus	2 (1%)
Valrubicin	2 (1%)
Amrubicin	1 (<1%)
Epirubicin	1 (<1%)
Epirubicin hydrochloride	1 (<1%)
Eribulin	1 (<1%)
FOLFOX	1 (<1%)
Idarubicin hydrochloride	1 (<1%)
Irinotecan	1 (<1%)

Lapatinib	1 (<1%)
Pazopanib	1 (<1%)
Pertuzumab	1 (<1%)
Pyrimidine analogues	1 (<1%)
Ramucirumab	1 (<1%)
Sorafenib	1 (<1%)
Thiotepa	1 (<1%)
Topotecan hydrochloride	1 (<1%)
Trastuzumab	1 (<1%)
Vincristine	1 (<1%)
Vinflunine ditartrate	1 (<1%)

Data are n (%). FOLFOX=fluorouracil, leucovorin, oxaliplatin.

Table S6: Overall summary of safety

Patients with AEs	**N=249**
Any AE	244 (98%)
Any treatment-related AE	166 (67%)
Any grade ≥3 AE	154 (62%)
Any treatment-related grade ≥3 AE	21 (8%)
Any serious AE	117 (47%)
Any treatment-related serious AE	19 (8%)
Any AE leading to permanent treatment discontinuation	40 (16%)
Any treatment-related AE leading to permanent treatment discontinuation	14 (6%)
Any AE leading to death	46 (19%)
Any treatment-related AE leading to death	1 (<1%)
Any immune-mediated AE	34 (14%)
Any treatment-related immune-mediated AE	29 (12%)

Data are n (%) or % (95% CI). AE=adverse event.