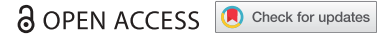




PRODUCT REVIEW



## Product review: avelumab, an anti-PD-L1 antibody

Julie M. Collins  and James L. Gulley 

Medical Oncology Service, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

### ABSTRACT

Although immunotherapies have been employed for many decades, immune checkpoint inhibitors have only recently entered the oncologic landscape. Avelumab is a fully human monoclonal antibody that blocks the interaction between PD-L1 on tumor cells and PD-1 on T cells, thereby inhibiting immunosuppression in the tumor microenvironment and reducing tumor growth. Most early clinical trials of avelumab as monotherapy and in combination regimens were part of the international JAVELIN clinical trial program, which included more than 7000 patients in more than 30 trials with at least 15 tumor types. Avelumab has been approved by the U.S. FDA for the treatment of metastatic Merkel cell carcinoma and metastatic urothelial carcinoma that has progressed during or following treatment with a platinum-based regimen. Its acceptable safety profile and ability to induce durable responses in otherwise deadly tumors provide the rationale for its use in other tumor types and in combination with other therapies.

### ARTICLE HISTORY

Received 6 September 2018  
Revised 5 November 2018  
Accepted 17 November 2018

### KEYWORDS

avelumab; monoclonal antibody; anti-PD-L1; immune checkpoint inhibitor; immunotherapy; MSB0010718C; Merkel cell carcinoma; urothelial carcinoma

### Introduction

Cancer immunotherapy began over 100 years ago when Dr. William Coley began injecting sarcoma patients with streptococcal organisms called “Coley’s toxins” to try to shrink their tumors.<sup>1,2</sup> Since that time there have been significant advances in oncology and immunotherapy, but our understanding of the immune system and its role in cancer development and treatment continues to evolve. Recently, immune checkpoint inhibitors (ICIs), agents targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 have become the predominant immunotherapies for a variety of cancers. The immune inhibitory function of the PD-1/PD-L1 axis has often been described in cancer research,<sup>3,4</sup> and its blockade has been shown to reactivate T cell effector function and reduce or eliminate immunosuppressive signals in the tumor microenvironment (TME) (Figure 1).<sup>5</sup> The tolerability and acceptable toxicity profile of ICIs, especially PD-1 and PD-L1 inhibitors, in conjunction with their ability to induce durable responses in some cancers, have made their use feasible for a wide variety of patients.<sup>6,7</sup> Avelumab is an intravenously (i.v.) administered fully human IgG1 monoclonal antibody (mAb) that blocks the interaction of PD-L1 with its receptors PD-1 and B7.1 on T cells and antigen-presenting cells. It is currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic Merkel cell carcinoma (mMCC) and locally advanced or metastatic urothelial carcinoma (mUC), but many other studies of avelumab as monotherapy and in combination therapies are underway.

### Background

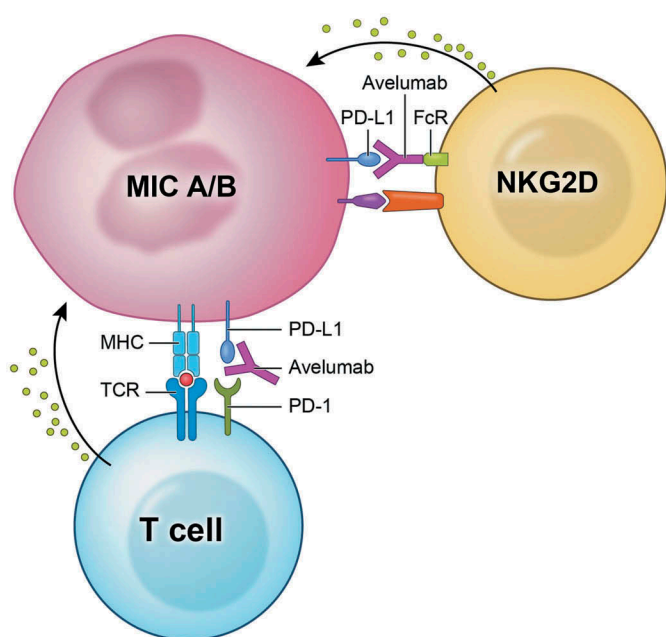
Avelumab, previously known as MSB0010718C, was developed by Merck KGaA, Darmstadt, Germany. Avelumab has been shown to engage both adaptive and innate immune functions.<sup>8</sup> Although many mAbs designed to interfere with the PD-1/PD-L1 pathway are approved, avelumab is unique in that it can mediate antibody-dependent cell-mediated cytotoxicity (ADCC) by retaining a native Fc-region.<sup>5,9</sup> ADCC is a demonstrated mechanism of action for several approved anticancer mAbs, including necitumumab, pertuzumab, cetuximab, rituximab, and trastuzumab.<sup>10–12</sup> Although there was theoretical concern that avelumab may induce lysis of activated immune cells, given that PD-L1 expression may be present on these cells, both preclinical models and clinical studies have shown little or no increase in avelumab-mediated lysis of PD-L1<sup>+</sup> immune cells,<sup>8,9</sup> likely due to the lower density of PD-L1 on immune cells compared to tumor cells.

Among all ICIs, avelumab had the shortest clinical development time, being approved only 52 months after investigational new drug submission.<sup>13</sup> Avelumab was granted accelerated approval by the FDA for the treatment of a) adult and pediatric patients 12 years and older with mMCC and b) patients with locally advanced UC or mUC who have disease progression during or following platinum-containing chemotherapy, or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. These approvals are based on tumor response rate and duration of response (DOR) in adult patients, and both are irrespective of tumor PD-L1 expression levels. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

**CONTACT** James L. Gulley  [gulleyj@mail.nih.gov](mailto:gulleyj@mail.nih.gov)

This work was authored as part of the Contributor’s official duties as an Employee of the United States Government and is therefore a work of the United States Government. In accordance with 17 USC. 105, no copyright protection is available for such works under US Law.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.



**Figure 1.** Avelumab's dual mechanism of action.

Avelumab is an IgG1 monoclonal antibody with a dual mechanism of action. It can inhibit the interaction between PD-L1 and PD-1 and mediate ADCC through retention of its native FcR. Immunosuppressive signals in the TME are decreased via blockade of PD-1/PD-L1 interaction leading to the reinvigoration of effector T cells and antitumor activity. Avelumab is unique among approved ICIs because it is also able to enhance NK cell-mediated ADCC. NK cells are able to bind to and directly kill tumor cells. Avelumab is able to enhance killing of tumor cells by both decreasing immunosuppression in the TME and directly targeting cancer cells via ADCC.

Abbreviations: antibody-dependent cell-mediated cytotoxicity (ADCC); crystallizable fragment region (FcR); immunoglobulin G1 (IgG1); immune checkpoint inhibitor (ICI); major histocompatibility complex (MHC); MHC class I chain-related peptide protein A/B (MIC A/B); natural killer (NK); natural killer group 2D (NKG2D); programmed death 1 (PD-1); programmed-death ligand 1 (PD-L1); T cell receptor (TCR); tumor microenvironment (TME)

Avelumab is being further developed in global partnerships and there are currently more than 80 actively recruiting clinical trials including avelumab (Tables 1 and 2) (as of August 7, 2018; see [clinicaltrials.gov](http://clinicaltrials.gov)). In November 2014, Merck KGaA and Pfizer entered into a global agreement to jointly develop and commercialize avelumab. The majority of early clinical trials of avelumab, both as monotherapy and in combination, were part of the international JAVELIN clinical trial program, which included more than 7000 patients in more than 30 trials with at least 15 different tumor types. Many other partnerships have also been secured to test avelumab in combination with a variety of other therapies in many tumor types.

### Preclinical studies

*In vitro* studies of avelumab have produced several key findings: 1) avelumab can lyse a range of human tumor cells in the presence of peripheral blood mononuclear cells (PBMCs) or natural killer (NK) cells; 2) NK cells are potent effectors for avelumab; 3) levels of avelumab-mediated ADCC lysis of tumor cells are similar using purified NK cells from either healthy donors or patients with cancer; and perhaps most importantly, 4) levels of avelumab-

mediated lysis are very low when whole PBMCs are used as targets.<sup>9,14</sup> These findings, especially avelumab's ability to mediate ADCC, differentiate it from other approved ICIs. Other approved ICIs are either of the IgG4 isotype, which does not mediate ADCC, or the IgG1 isotype but specifically engineered not to induce ADCC. *In vitro* studies of avelumab on human tumor cells have shown that there is a trend toward increased sensitivity to ADCC with increased PD-L1 expression and PD-L1 cell surface density as measured by mean fluorescence intensity.<sup>9</sup> Although NK cells are robust effectors of avelumab-mediated ADCC,<sup>9</sup> this cannot be studied in murine models as avelumab does not mediate ADCC in mice and depletion of NK cells in murine models had little effect on avelumab anti-tumor activity whereas efficacy was highly dependent on CD4 and CD8T cell populations.<sup>14</sup>

### Avelumab administration

Avelumab is a colorless to slightly yellow solution. The recommended dose of avelumab is 10 mg/kg as an i.v. infusion over 60 minutes every 2 weeks. Although avelumab's toxicity profile is generally similar to other ICIs, approximately 20% of patients in phase I studies had infusion-related reactions to avelumab, compared with only 1%–2% of patients receiving other ICIs.<sup>8,15,16</sup> This difference is likely due to the definition of infusion-related reaction used in the JAVELIN analyses, which included an aggregate of drug hypersensitivity or hypersensitivity reactions that occurred on the day of or the day after infusion as well as signs and symptoms of infusion-related reaction on the day of infusion, which is a more extensive definition than used in many other ICI trials. Despite this broad definition, the incidence of grade  $\geq 3$  infusion-related reactions (0.6%) was similar to that in ICI trials that used limited or single-term definitions of infusion-related reaction.<sup>17–19</sup> Most avelumab infusion reactions were grade 1 or 2, occurred with the first or second infusion, did not require treatment discontinuation, and responded to straightforward management.<sup>16,19,20</sup> Premedication with acetaminophen and an antihistamine is required prior to the first 4 doses of avelumab, and then as needed based upon clinical judgement.<sup>21</sup> The optimal duration of treatment with avelumab remains unclear; most clinical trials continued treatment until disease progression or unacceptable toxicity.

### Biomarkers of avelumab activity

Identifying much-needed predictive biomarkers for ICI treatment is a topic of intense debate and research. The most obvious choice is PD-L1 expression on tumor cells, but this has not proven to be straightforward. Tumor PD-L1 expression was assessed in the JAVELIN trials. *Post-hoc* subgroup analyses showed similar activity of avelumab independently of tumor pathology, number of previous lines of therapy, or smoking status, and a prespecified analysis showed that activity was similar irrespective of PD-L1 expression on tumor cells or immune cells. Several different cutoff points of PD-L1 positivity were used: 1%, 5%, or 25% for tumor cells and

**Table 1.** Actively recruiting avelumab monotherapy trials, clinicaltrials.gov (accessed August 7, 2018).

Avelumab Monotherapy Trials					
ClinicalTrials.gov Identifier	Phase	Disease	Sample Size	1° Endpoint	Country
NCT03403777	II	R/R germ cell tumors	43	12-week PFS	Slovakia
NCT03352934	II	A/M high-grade NEC, ≥ 1st line	60	DCR at > 16 weeks	Germany
NCT03389126	II	Advanced HCC after sorafenib	30	RR	Republic of Korea
NCT03150706	II	MSI-H or POLE mutated M CRC, ≥ 2nd line	33	RR	Republic of Korea
NCT03006848	II	R/R osteosarcoma	40	RR, PFS	US
NCT03135769	II	Chemotherapy-resistant GTN	29	Normalization of hCG	France
NCT03000179	I	A/M small intestine adenocarcinoma, ≥ 2nd line	25	Safety; RR	US
NCT03076554	II	R/R thymoma or thymic carcinoma	24	Safety; RR	US
NCT02926196	III	TNBC, adjuvant after chemotherapy, surgery ± RT	335	DFS; DFS in PD-L1 <sup>+</sup>	Italy
NCT03523390	I	A/M solid tumors	21	Safety in Chinese patients	China
NCT02912572	II	R/M endometrial cancer	70	PFS > 6 months	US
NCT03147404	II	Grade 3 M gastro-pancreatic NEC, 2nd line after cisplatin/etoposide	30	BOR ≤ 12 months	Republic of Korea
NCT03278405	I/II	A/M grade 3 NEC	10	RR	Canada
NCT03046953	II	R/R T-cell lymphoma	35	BOR	UK
NCT03451825	I/II	Pediatric advanced solid tumors and lymphoma	148	Safety; BOR	Multinational
NCT03491345	II	Advanced solid tumors, PD-L1 <sup>+</sup> , EBV <sup>+</sup> , MSI-H, POLE mutation, or POLD1 mutation	60	RR	Republic of Korea
NCT03271372	III	Stage III or IIIB MCC	100	RFS	US
NCT02603432	III	LA or M UC, maintenance therapy	688	OS	Multinational
NCT03179410	II	Neuroendocrine prostate cancer	18	RR	US

Abbreviations: advanced/metastatic (A/M); best overall response (BOR); colorectal cancer (CRC); disease control rate (DCR); Epstein-Barr virus (EBV); *gene* polymerase delta 1 (POLD1); gestational trophoblastic neoplasias (GTN); hepatocellular carcinoma (HCC); human chorionic gonadotropin (hCG); locally advanced (LA); Merkel cell carcinoma (MCC); metastatic (M); microsatellite instability high (MSI-H); neuroendocrine carcinoma (NEC); polymerase epsilon (POLE); programmed death-ligand 1 (PD-L1); progression-free survival (PFS); radiation therapy (RT); recurrent or metastatic (R/M); relapsed or refractory (R/R); response rate (RR); triple negative breast cancer (TNBC); urothelial carcinoma (UC)

10% for immune cells.<sup>8</sup> Testing was done via immunohistochemistry (IHC) using a proprietary assay (Dako, Carpinteria, CA) based on an anti-PD-L1 antibody clone (73-10) licensed from Merck KGaA. In non-small cell lung cancer (NSCLC), metastatic breast cancer, and mUC there was a potential trend toward greater activity in patients with PD-L1-expressing tumors, but responses were also seen in PD-L1<sup>-</sup> tumors.<sup>15,16,22</sup> The use of PD-L1 as a predictive biomarker remains controversial given the lack of standardization among PD-L1 antibodies and detection assays, various PD-L1 expression cutoffs, and non-standardized test designs that make comparisons between trials difficult,<sup>23,24</sup> as discussed in detail elsewhere.<sup>25</sup> In addition, the unpredictability of responses to ICI therapies may be due in part to the heterogeneity and dynamics of PD-L1 expression by tumor cells and immune cells.<sup>26,27</sup> Recent reports indicate that PD-L1 expressed by both tumor cells and non-tumor host cells contributes to the efficacy of PD-1/PD-L1 checkpoint blockade therapies in pre-clinical models.<sup>28,29</sup>

A variety of disease-specific biomarkers have been evaluated in JAVELIN studies, such as EGFR mutation and ALK rearrangement status in NSCLC, BRCA mutation status in ovarian cancer, HER2/ER/PR status in metastatic breast cancer, and Merkel cell polyomavirus (MCPyV) status in MCC.<sup>16,20,22,30</sup> To date, no disease-related parameters have been found to predict response to avelumab.

Tumor mutational burden (TMB), high microsatellite instability (MSI-H), mismatch-repair deficiency (dMMR), and HLA diversity are being evaluated as potential biomarkers, and although patients with high TMB, MSI-H, or dMMR have been shown to have a greater response to ICIs, these are not perfect biomarkers. Patients without these alterations have

been known to have responses to ICIs, and not all patients with high TMB, MSI-H, or dMMR respond to ICIs.<sup>31,32</sup> Some cancer subtypes, such as MCPyV<sup>-</sup> MCC, have a better-than-expected response to ICIs, whereas others such as MMR-proficient colorectal cancer have a worse-than-predicted response based on TMB,<sup>32,33</sup> indicating that responsiveness is multifactorial.

Additional investigations of predictive biomarkers for avelumab such as molecular subtyping, tumor-infiltrating lymphocytes (TILs) in the TME, and gene-expression signatures are ongoing.

### Clinical studies

Over 30 JAVELIN trials involving more than 15 different tumor types have been initiated under the global strategic alliance between Merck and Pfizer. In the phase Ia portion of the JAVELIN Solid Tumor study, avelumab was safely administered by i.v. infusion every 2 weeks and had a predictable pharmacokinetic profile at doses up to 20 mg/kg; the 10 mg/kg dose was selected for further study in phase Ib dose-expansion cohorts enrolling a range of tumor types.<sup>8</sup> Unless otherwise noted, avelumab was given at a dose of 10 mg/kg i.v. every 2 weeks.

### Pharmacokinetics

Toxicology studies in cynomolgus monkeys determined a starting dose of 1 mg/kg for avelumab dose-escalation trials in humans.<sup>8</sup> This starting dose level was further supported by preliminary pharmacokinetic data showing that this dose level produced serum concentrations associated with pharmacological activity (i.e., target occupancy and T-cell activation). The

Table 2. Actively recruiting avelumab combination therapy trials, clinicaltrials.gov (accessed August 7, 2018).

Avelumab Combination Trials						
ClinicalTrials.gov Identifier	Phase	Disease	Sample Size	1° Endpoint	Avelumab + other intervention	Country
NCT03288350	II	Resectable LA E/GC, neoadjuvant	55	pCR	Docetaxel, cis, 5-FU	Canada
NCT03512834	II	Unresectable angiosarcoma, 1st line	32	RR	Paclitaxel	Republic of Korea
NCT03047473	II	Treatment-naïve GBM	30	Safety	Temozolomide, RT	Canada
NCT03502681	I	Cis-ineligible M UC	24	Safety; RR	Eribulin	US
NCT03152565	I/II	M1 MSS CRC	33	MTD; PFS	Autologous DC vaccine	US
NCT03244176	I/II	Stage II, III, IV DLBCL, 1st line	28	Immune-related toxicity	RCHOP	Spain
NCT03050554	I/II	Early stage NSCLC, definitive therapy	56	Safety; RFS	SBRT	Australia
NCT03472560	II	Cis-ineligible A/M NSCLC or UC	39	RR	Axitinib	US
NCT03357757	II	Viral-associated cancers	80	RR	Valproic acid	Canada
NCT03409458	I/II	Advanced solid tumors	52	RD of PT-112 in combination with avelumab	PT-112	US
NCT02968940	II	IDH-mutant GBM	43	Safety; PFS	RT	US
NCT03317496	I/II	LA or M NSCLC or UC	80	Safety; RR	Pemetrexed, carbo (NSCLC) or gem, cis (UC)	Multinational
NCT03395873	I	AML, intensive chemotherapy-ineligible, 1st line	15	Safety	Dectabine	US
NCT03399552	I/II	Malignant mesothelioma, ≥ 2nd line after platinum/pemetrexed	36	RR	SBRT	US
NCT03267836	I	Recurrent RT-refractory meningioma	12	Immunogenicity (changes in TILs)	Proton therapy prior to surgery	US
NCT03268057	I/II	Advanced NSCLC	40	Safety	VX15/2503	US
NCT03481920	I	Pancreatic cancer, ≥ 2nd line	24	Safety; RR	PEGPH20	Spain
NCT02953561	I/II	R/R AML	58	MTD	Azactidine	US
NCT03341845	II	Resectable clear-cell RCC	40	PR	Axitinib	Netherlands
NCT03494322	II	R/M HNSCC	130	Safety; DCR at 24 weeks	Avelumab + cetuximab vs. avelumab monotherapy	UK
NCT03270176	I	Advanced solid tumors, A/M NSCLC after platinum	61	MTD; RR	Second mitochondrial activator of caspase mimetic	Canada
NCT03390595	II	Cis-ineligible unresectable or M UC	80	RR	Avelumab + carbo, gemc vs. carbo, gemc	Spain
NCT03330405	I/II	Advanced solid tumors	316	DLT; RR	Talazoparib	Multinational
NCT03324282	II	LA or M UC; 1st line	90	Safety; RR	Avelumab + cis, gem vs. cis, gem	France
NCT03565991	II	LA or M solid tumors with defects in BRCA or ATM genes	200	RR	Talazoparib	US
NCT03341806	I	Recurrent GBM	30	DLT; RR	Laser interstitial thermal therapy	US
NCT03074318	I/II	Advanced leiomyosarcoma and liposarcoma	28	Safety	Trabectedin	US
NCT03475953	I/II	Advanced digestive solid tumors	212	RP2D; RR	Regorafenib	France
NCT03260023	I/II	Advanced HPV16+ cancers and HNSCC	52	Safety	TG4001	France
NCT02943317	I	Platinum-resistant ovarian cancer	98	Safety; BOR	Avelumab + defactinib vs. avelumab monotherapy	US
NCT03291314	II	Recurrent GBM	52	PFS at 6 months	Axitinib	Belgium
NCT02994953	I	Advanced solid tumors	185	Safety; BOR	NHS-IL-12	US
NCT02952586	III	LA HNSCC, 1st line	640	PFS	Avelumab + cis, IMRT vs. cis, IMRT	Multinational
NCT03158883	I	M NSCLC, previous anti-PD-1	26	RR	SBRT	US
NCT03289533	I	Advanced HCC, 1st line	20	Safety	Axitinib	Japan
NCT03258398	II	R/R MSS CRC	70	Safety; RR at 8–16 weeks	Avelumab + eFT508 vs. eFT508 monotherapy	US
NCT02554812	II	LA or M solid tumors	560	Safety; RR	Utomilumab, PF-05082566, PD 0360324	Multinational
NCT03558139	I	Advanced solid tumors and platinum-resistant ovarian cancer	32	Safety; RR	Hu5F9-G4	US
NCT03174405	II	M CRC, 1st line	43	PFS	Cetuximab, FOLFOX	Germany
NCT02938273	I	Cis-ineligible LA HNSCC	10	Safety	Cetuximab, RT	Netherlands
NCT02923466	I/II	Advanced solid tumors	93	MTD	Avelumab + intratumoral vesicular stomatitis virus vs. virus monotherapy	US
NCT02584829	I/II	M MCC	20	Safety; time to new metastasis	RT or intratumoral IFN-β injection ± MCPyV T antigen-specific CD8+ T cells	US
NCT03490292	I/II	Stage II or III resectable esophageal cancer, M sarcomatoid RCC	24	Safety; pCR	Carbo, paclitaxel, RT	US
NCT03483883	I	M sarcomatoid RCC	24	Safety	Gemcitabine	US
NCT03440567	I	R/R DLBCL or MCL	39	Safety; MTD	Avelumab + utomilumab, RICE (DLBCL) or avelumab + rituximab, ibrutinib (MCL)	US

(Continued)

Table 2. (Continued).

Avelumab Combination Trials						
ClinicalTrials.gov Identifier	Phase	Disease	Sample Size	1° Endpoint	Avelumab + other intervention	Country
NCT02576574	III	Recurrent or stage IV PD-L1 + NSCLC, 1st line	1131	PFS; OS	Avelumab vs. platinum-containing chemotherapy	Multinational
NCT03217747	I/II	Advanced solid tumors	188	Safety; CD8 <sup>+</sup> immune biomarkers	Utomilumab, PF-04518600, RT, cis	US
NCT03414658	II	Advanced HER2 <sup>+</sup> breast cancer	100	PFS	Trastuzumab, vinorelbine, utomilumab	US
NCT02999087	III	LA HNSCC	688	PFS	Avelumab + cetuximab, IMRT	France
NCT03312114	II	R/R ovarian cancer	29	RR	RT	US
NCT03147287	II	Advanced HR <sup>+</sup> , HER2 <sup>-</sup> breast cancer, previous CDK 4/6 inhibitor	220	PFS	Avelumab + fulvestrant, palbociclib vs. fulvestrant, palbociclib	US
NCT02951156	III	R/R DLBCL	304	Safety; RR	Avelumab + utomilumab, rituximab, azacitidine, bendamustine vs. rituximab, bendamustine vs. rituximab, gemcitabine, oxaliplatin	Multinational
NCT03050814	II	M CRC, 1st line	81	PFS	Avelumab + Ad-CEA vaccine, SOC vs. SOC	US
NCT03344172	II	Resectable pancreatic cancer	120	Histopathologic response	Avelumab + gem, nab-paclitaxel, hydroxychloroquine vs. gem, nab-paclitaxel, hydroxychloroquine	US
NCT03386929	I/II	A/M NSCLC without targetable mutations	130	Safety; RR; DOR; PFS; OS	Axitinib, palbociclib	Multinational
NCT03390296	II	AML	138	Safety; CR	PF-04518600, utomilumab, azacitidine, glasdegib	US
NCT03399071	II	Resectable E/GC	40	pCR	FLOT	UK
NCT02767063	I/II	CML on TKI > 2 years with complete cytogenetic response	100	Deep molecular response	Avelumab + TKI vs. TKI, pioglitazone	France
NCT02222922	I	Advanced solid tumors	190	Safety	Avelumab + PF-06647020 vs. PF-06647020	US, Spain
NCT03387098	I/II	Progressive pancreatic cancer after SOC	173	Safety; RR	NANT pancreatic cancer vaccine, haNK cells; metronomic combination therapy	US
NCT03387085	I/II	Progressive TNBC after SOC	79	Safety; RR	NANT TNBC vaccine, haNK cells; metronomic combination therapy	US
NCT03387111	I/II	Progressive SCC after SOC	65	Safety; RR	NANT SCC vaccine, haNK cells; metronomic combination therapy	US
NCT03563157	I/II	Previously treated M CRC	332	Safety; PFS; RR	NANT CRC vaccine, haNK cells; metronomic combination therapy	US

Abbreviations: 5-fluorouracil (5-FU); 5-fluorouracil, oxaliplatin (FOLFOX); acute myeloid leukemia (AML); advanced or metastatic (A/M); ataxia telangiectasia mutated (ATM); best overall response (BOR); breast cancer gene (BRCA); carboplatin (carbo); cisplatin (cis); chronic myeloid leukemia (CML); colorectal cancer (CRC); complete response (CR); cyclin-dependent kinase 4/6 (CDK 4/6); dendritic cell (DC); diffuse large B-cell lymphoma (DLBCL); disease control rate (DCR); dose-limiting toxicity (DLT); duration of response (DOR); esophageal/gastric carcinoma (E/GC); folinic acid, oxaliplatin, docetaxel, fluorouracil (FLOT); gemcitabine (gem); glioblastoma multiforme (GBM); head and neck squamous cell carcinoma (HNSCC); hepatocellular carcinoma (HCC); high-affinity natural killer (haNK); hormone receptor (HR); human epidermal growth factor receptor 2 (HER2); human papilloma virus (HPV); intensity-modulated radiation therapy (IMRT); interferon beta (IFN-β); isotretinoin (ISOT); isocitrate dehydrogenase (IDH); locally advanced (LA); mantle cell lymphoma (MCL); maximum tolerated dose (MTD); Merkel cell carcinoma (MCC); Merkel cell polyomavirus (MCPyV); metastatic (M); microsatellite stable (MSS); non-small cell lung cancer (NSCLC); overall survival (OS); partial response (PR); pathologic complete response (pCR); programmed cell death 1 (PD-1); progression-free survival (PFS); radiation therapy (RT); recommended dose (RD); recommended phase II dose (RP2D); relapsed or refractory (R/R); relapse-free survival (RFS); renal cell carcinoma (RCC); response rate (RR); rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (RCHOP); rituximab, ifosfamide, carboplatin, etoposide (RICE); squamous cell carcinoma (SCC); standard of care (SOC); stereotactic body radiation therapy (SBRT); tumor-infiltrating lymphocytes (TILs); tyrosine kinase inhibitor (TKI); United States (US); United Kingdom (UK); urothelial carcinoma (UC)

pharmacokinetics of avelumab were studied in 1629 patients who received i.v. doses of 1–20 mg/kg every 2 weeks. The data showed that the exposure of avelumab increased dose-proportionately in the range of 10–20 mg/kg i.v. every 2 weeks. Steady-state concentrations of avelumab were reached after approximately 4–6 weeks (2–3 cycles) of repeated dosing.<sup>21</sup> Avelumab undergoes proteolytic degradation as the primary mechanism of elimination. Avelumab has a half-life of approximately 6 days, which is significantly shorter than other ICIs, and achieves 90% target occupancy with 10 mg/kg every 2 weeks.<sup>8</sup> Neither age, gender, race, PD-L1 expression status, tumor burden, renal impairment (mild, moderate, or severe), or hepatic impairment (mild or moderate) has any clinically meaningful effect on avelumab clearance. Body weight had a positive correlation with the total systemic clearance of avelumab based on population pharmacokinetic analyses.<sup>21</sup>

### **Phase I: avelumab as monotherapy**

The first-in-human trial of avelumab, JAVELIN Solid Tumor (NCT01772004), began in January 2013. The entire dose escalation portion of the study was conducted at the NIH Clinical Center in Bethesda, MD. The study has since evolved far beyond its original scope using a seamless approach<sup>34</sup> with multiple expansion cohorts.<sup>35</sup> In all cohorts, patients have been enrolled irrespective of PD-L1 expression status.

The phase Ia portion of JAVELIN Solid Tumor is an open-label, single-center, 3 + 3 multicohort, dose-escalation trial of avelumab in metastatic or locally advanced, previously treated solid tumors (n = 53; 4 at 1 mg/kg, 13 at 3 mg/kg, 15 at 10 mg/kg, and 21 at 20 mg/kg). The study established the safety and pharmacokinetics of avelumab and assessed biological correlates for future development. Eighteen patients were analyzed for dose-limiting toxicities (DLTs): 3 at 1 mg/kg, 3 at 3 mg/kg, 6 at 10 mg/kg, and 6 at 20 mg/kg. Only one DLT occurred, at the 20 mg/kg dose. Similar to trials of other ICIs, a maximum tolerated dose was not reached.<sup>8</sup>

Across all dose levels, common treatment-related adverse events (TRAEs) of any grade occurred in ≥ 10% of patients, included fatigue (n = 21; 40%), influenza-like symptoms (n = 11; 21%), fever (n = 8; 15%), and chills (n = 6; 11%).<sup>8</sup> Grade 3–4 TRAEs occurred in only 9 patients (17%). Potential immune-related adverse events (irAEs) occurred in 5 patients and included hypothyroidism, myositis, and unspecified autoimmune disorder. No treatment-related deaths occurred. There was some evidence of clinical activity in various solid tumors, with partial responses (PRs) in 4 patients (8%); 30 additional patients (57%) had stable disease (SD). Avelumab did not have a substantial effect on absolute lymphocyte count or multiple immune cell subsets, including PD-L1-expressing immune cells.<sup>5,8,36</sup> This is important because, despite avelumab's ability to mediate ADCC, it does not seem to have a detrimental effect on PD-L1-expressing immune cells.<sup>5</sup>

Avelumab was well tolerated as a single agent, with a safety profile similar to other anti-PD-1/PD-L1 agents.<sup>37–39</sup> Based on pharmacokinetics, target occupancy, and immunological analysis from the JAVELIN Solid Tumor dose-escalation trial,

avelumab 10 mg/kg i.v. every 2 weeks was chosen as the dose for ongoing development.<sup>8</sup>

A contemporaneous JAVELIN Solid Tumor trial opened in Japan (NCT01943461). It included a dose-escalation cohort (3 mg/kg, 10 mg/kg, and 20 mg/kg) in patients with advanced tumors and a dose-expansion cohort in patients with gastric cancer (10 mg/kg). Among the 17 patients treated in the dose-escalation cohort, the drug was well-tolerated and there were no DLTs. Two patients had a PR and 5 had SD for > 3 months. Pharmacokinetics were similar to those in JAVELIN Solid Tumor.<sup>40</sup> In the gastric cancer dose-expansion cohort, 20 patients with advanced gastric cancer (GC) or gastroesophageal junction (GEJ) adenocarcinoma were treated with i.v. avelumab 10 mg/kg every 2 weeks. Avelumab was well-tolerated and the objective response rate (ORR) was 15% with 3 PRs.<sup>41</sup>

### **Avelumab monotherapy for Merkel cell carcinoma**

MCC is a rare, aggressive, neuroendocrine skin cancer with poor survival outcomes in metastatic disease. Tumorigenesis is predominantly linked to MCPyV and ultraviolet radiation-induced mutation. MCPyV is present in about 80% of MCC tumors.<sup>42</sup> In the U.S., incidence of MCC is 0.79 cases/100,000 people/year.<sup>43</sup> In advanced MCC, responses to chemotherapy are typically not durable. With chemotherapy, the 5-year overall survival (OS) rate for mMCC is 0%–18%, based on retrospective analyses.<sup>20,44–47</sup> JAVELIN Merkel 200 (NCT02155647), the first phase II study of avelumab, was a single-arm, multicenter, international, prospective, open-label trial. The trial evaluated avelumab in 2 cohorts of patients with mMCC: chemotherapy-refractory mMCC (part A) and untreated mMCC (part B). Based on the results of JAVELIN Merkel 200 part A, on November 4, 2015 avelumab was granted FDA breakthrough therapy designation for the treatment of patients with mMCC who progressed after at least one previous chemotherapy regimen. Less than 2 years later, on March 23, 2017, avelumab was granted accelerated FDA approval for adult and pediatric patients (12 years or older) with mMCC, regardless of previous chemotherapy.

#### **JAVELIN Merkel 200 part A**

In part A of JAVELIN Merkel 200, 88 patients with stage IV chemotherapy-refractory MCC were treated with avelumab.<sup>20,48</sup> Patients were unselected for MCPyV and were followed for ≥ 12 months. The primary endpoint was ORR, which was 33.0% (95% CI, 23.3%–43.8%; CR 11.4%). Responses were durable, with approximately 74% lasting ≥ 1 year. Median DOR was not yet reached at the time of study publication (95% CI, 18.0 months–not estimable), and 1-year progression-free survival (PFS) and OS were 30% (95% CI, 21%–41%) and 52% (95% CI, 41%–62%), respectively. Median OS was 12.9 months (95% CI, 7.5–not estimable). Subgroup analyses suggested a higher probability of response in patients receiving fewer prior lines of systemic therapy, with a lower baseline disease burden, and with PD-L1<sup>+</sup> tumors. However, durable responses were achieved irrespective of PD-L1 expression or MCPyV status. Ultraviolet-induced mutational burden likely underlies the response of

virus-negative MCC to anti-PD-L1 therapy whereas viral-driven cancers are immunogenic because they express foreign viral antigens that are recognized by host T cells.<sup>49,50</sup> In further analyses, ORR was associated with a 94% risk reduction of death (hazard ratio: 0.064; 95% CI, 0.022–0.181) at 18 months after treatment initiation.<sup>51</sup> Avelumab therapy for previously treated mMCC demonstrated a clinically relevant and high survival impact.

The results of JAVELIN Merkel 200 far exceeded historical results from chemotherapy trials. In a retrospective study of 62 patients with mMCC, median PFS was 3 months and median OS was 9.5 months from start of chemotherapy.<sup>52</sup> Even among responding patients (n = 34), median PFS was only 5.6 months and median DOR was 2.8 months. Thirty of the 62 patients received second-line chemotherapy, with an ORR of only 23% (1 CR, 6 PRs), median PFS of 2 months, and median DOR of 3.4 months.

Avelumab monotherapy was well tolerated, with only 5 grade 3 TRAEs in 4 patients (5%), no grade 4 TRAEs or treatment-related deaths, and serious TRAEs in 5 patients (6%).<sup>20</sup> Additionally, nonprogression of mMCC during treatment with avelumab has been shown to be associated with improvement in quality of life.<sup>53</sup>

A similar cohort of patients with chemotherapy-refractory mMCC was treated with avelumab in a global expanded access program (NCT03089658).<sup>54</sup> Unlike the JAVELIN Merkel 200 participants, patients in this study could have Eastern Cooperative Oncology Group performance status of 2, treated brain metastases, or immunosuppressive conditions. The majority of patients were from France, Italy, and Australia. Among 131 evaluable patients, the ORR was 51.1%, including CR in 22.1% (n = 29), PR in 29.0% (n = 38, including one patient with HIV), and SD in 19.1% (n = 25). Durable responses were observed in both immunocompetent and immunosuppressed patients. In a real-world setting, avelumab demonstrated safety and efficacy consistent with JAVELIN Merkel 200.

The encouraging findings of JAVELIN Merkel 200 part A provided impetus and rationale to evaluate avelumab in the first-line setting in patients with mMCC.

### **JAVELIN Merkel 200 part b**

JAVELIN Merkel 200 part B evaluated avelumab monotherapy using similar inclusion/exclusion criteria, except that patients had to have untreated mMCC.<sup>55</sup> The primary endpoint was durable response, defined as an objective response with a duration of  $\geq 6$  months. Secondary endpoints included best overall response, DOR, PFS, safety, and tolerability. As of a pre-specified interim analysis on March 24, 2017, 39 patients had been enrolled, with a median follow-up of 5.1 months (range, 0.3–11.3 months). As in part A, no treatment-related deaths or grade 4 AEs occurred. Efficacy was assessed in 29 patients with  $\geq 3$  months of follow-up; PFS was 9.1 months, and the ORR was 62.1% (95% CI, 42.3%–79.3%), with 14/18 responses (77.8%) ongoing at the time of analysis. In responding patients, the estimated proportion with DOR of  $\geq 6$  months was 83% (95% CI, 46%–96%). Avelumab in the first-line setting for mMCC once again outperformed chemotherapy based on contemporary data.<sup>52,56</sup> The results of

JAVELIN Merkel 200 part B corroborate evidence from part A that patients treated with fewer prior lines of therapy experienced more favorable outcomes with avelumab.<sup>20,55</sup> Further results from this trial, such as overall durable response, are awaited.

The ORR with avelumab in first-line treatment of advanced MCC was similar to that seen with pembrolizumab,<sup>57</sup> though pembrolizumab is not currently FDA-approved for this indication. The results of JAVELIN Merkel 200 part B further supported the FDA approval of avelumab as a standard-of-care treatment for mMCC. ICIs are now recommended over chemotherapy for mMCC unless there is a contraindication to immunotherapy.<sup>58</sup>

Adjuvant cytotoxic chemotherapy is not associated with OS benefit in patients with node-positive MCC,<sup>46,59</sup> but these patients are at high risk for relapse despite surgery and radiation therapy (RT),<sup>46</sup> and there is an urgent need for effective adjuvant systemic therapy. The ADAM trial (NCT03271372) is an ongoing multicenter, randomized, double-blind, placebo-controlled, phase III trial of adjuvant avelumab in MCC patients with nodal metastases treated definitively with surgery (with or without adjuvant RT).<sup>60</sup> One hundred patients will be randomized 1:1 to receive either avelumab or placebo for 2 years. The primary endpoint is relapse-free survival; secondary endpoints include OS, disease-specific survival, distant metastasis-free survival, and safety and tolerability.

### **Avelumab monotherapy for urothelial carcinoma**

Urothelial (transitional cell) carcinomas are the most common histologic subtype of bladder cancer in the United States and Europe, but may develop anywhere transitional epithelium is present, from the renal pelvis to the ureter and proximal two thirds of the urethra. PD-L1 is commonly expressed on UC cells and has been associated with higher tumor grade and stage and shorter OS in bladder cancers.<sup>61,62</sup> On May 9, 2017 avelumab was granted accelerated approval for the treatment of locally advanced or mUC that has progressed during or after platinum-based chemotherapy or that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy, regardless of PD-L1 expression levels,<sup>63</sup> based on results of a pooled analysis from the JAVELIN Solid Tumor trial.

The phase Ib multicenter, expansion cohort of the JAVELIN Solid Tumor trial evaluated 45 patients with refractory advanced/mUC that had progressed after  $\geq 1$  previous platinum-based chemotherapy.<sup>15</sup> Median follow-up was 16.5 months (interquartile range, 15.8–16.7 months). The median DOR was not reached (95% CI, 12.1 weeks–not estimable) as of data analysis on March 19, 2016, and responses were ongoing in 6 patients (75% of responding patients). The confirmed ORR was 18.2% (95% CI, 8.2%–32.7%; 5 CRs and 3 PRs). Fifteen patients (34.1%) had SD as best response. The median PFS was 11.6 weeks (95% CI, 6.1–17.4 weeks) and the median OS was 13.7 months (95% CI, 8.5 months–not estimable), with a 12-month OS rate of 54.3% (95% CI, 37.9%–68.1%). Thirty-seven patients were evaluable for PD-L1 expression.

Responses occurred regardless of PD-L1 positivity, which was defined as  $\geq 5\%$  staining by IHC on tumor cells, but there was a trend toward higher response rates and longer PFS and OS in patients with PD-L1<sup>+</sup> tumors. Thirteen patients (29.5%) had PD-L1<sup>+</sup> tumors and 7/8 responding patients had PD-L1<sup>+</sup> tumors. The confirmed ORR was 53.8% in PD-L1<sup>+</sup> tumors (7/13) and 4.2% in PD-L1<sup>-</sup> tumors (1/24). Disease responses and survival in this study were similar if not better than second-line chemotherapy agents such as vinflunine and pemetrexed,<sup>64,65</sup> and DOR was highly encouraging.

The safety profile was similar to other JAVELIN Solid Tumor cohorts. The most frequent TRAEs of any grade were fatigue/asthenia (31.8%), infusion-related reaction (20.5%), and nausea (11.4%).<sup>15</sup> Grades 3–4 TRAEs only occurred in 3 patients (6.8%) and included asthenia, AST elevation, creatine phosphokinase elevation, and decreased appetite. Nine patients (20.5%) had a TRAE of any grade that was potentially immune-related, most commonly hypothyroidism ( $n = 3$ ). There were no treatment-related deaths. On the basis of the promising clinical activity seen in this cohort of the JAVELIN Solid Tumor trial, an additional expansion cohort of approximately 200 patients was enrolled to further characterize the efficacy and safety of avelumab in refractory advanced UC.

Pooled data from 249 patients with refractory advanced mUC from the 2 expansion cohorts were evaluated in a planned interim analysis.<sup>66–68</sup> All patients were followed for  $\geq 6$  months (median of 13.6 months) as of data cutoff on September 2016.<sup>68</sup> The ORR was 17.3%, with 11 (4.4%) CRs, which is similar to other ICIs in this setting.<sup>38,69–71</sup> Response was ongoing in 34 of 43 patients (79.1%) and median DOR was 20.1 months (95% CI, 9.7–20.1). DOR with avelumab compared very favorably to that of historical second-line chemotherapy, which is about 5–7 months.<sup>64,65</sup> The median PFS was 1.6 months (95% CI, 1.4–2.7) and median OS was 8.2 months (95% CI, 6.3–10.8). The most frequent TRAEs were infusion-related reaction in 23.3% of patients and fatigue in 17.3%. Twenty-six patients (10.4%) had a  $\geq$  grade 3 TRAE, most commonly fatigue (1.6%), elevated lipase (1.6%), and pneumonitis (1.2%). Thirty-four patients (14%) had irAEs, mostly rash and hypothyroidism.<sup>67</sup> One patient developed treatment-related pneumonitis resulting in death.

PD-L1 positivity, defined as  $\geq 5\%$  staining by IHC in tumor cells, was found in 33% of patients.<sup>67</sup> Responses occurred regardless of PD-L1 positivity, but there was a trend toward higher response rates and longer PFS and OS in patients with PD-L1<sup>+</sup> tumors. In PD-L1<sup>+</sup> ( $\geq 5\%$  tumor cell staining) and PD-L1<sup>-</sup> patients the ORR was 25.6% and 13.7%, respectively.<sup>68</sup> An association between increased mutational load and improved outcome has been reported with other anti-PD-1/PD-L1 inhibitors.<sup>38,69,72,73</sup> However, an exploratory *post-hoc* analysis of 29 samples from JAVELIN Solid Tumor did not reach statistical significance ( $p = 0.076$ , Wilcoxon rank sum test), possibly due to small sample size.<sup>67</sup> Assessment of antitumor response associated with mutational burden and PD-L1 expression as a combined measure could provide further insights into the possible predictive role of these biomarkers.

Avelumab is now being evaluated in the first-line setting in both metastatic and non-metastatic UC. The AURA trial (EudraCT Number 2017–002758-35) is evaluating avelumab as neoadjuvant therapy in patients with non-metastatic muscle-invasive UC who are candidates for neoadjuvant chemotherapy followed by surgery.<sup>74</sup> Cisplatin-eligible patients will all receive avelumab plus methotrexate-vinblastine-adriamycin-cisplatin or cisplatin-gemcitabine, while cisplatin-ineligible patients will receive paclitaxel-gemcitabine plus avelumab or avelumab alone. The primary objective is to determine the pathologic CR rate and to assess the toxicity profile. Based on the clinical activity of avelumab monotherapy in cisplatin-ineligible patients in the JAVELIN Solid Tumor trial,<sup>67</sup> avelumab will be evaluated as first-line therapy in metastatic cisplatin-ineligible patients in a phase II randomized, multicenter trial (NCT03390595).<sup>75</sup> Patients will be randomized to avelumab plus carboplatin-gemcitabine vs. carboplatin-gemcitabine alone. A large cohort of patients will potentially be eligible for this trial, as approximately 50% of patients are ineligible for cisplatin due to poor performance status or comorbidities. Carboplatin-based combinations are an alternative, but they are associated with inferior survival. Patients will receive 2 cycles of induction avelumab prior to combination carboplatin-gemcitabine plus avelumab for 6 cycles followed by avelumab maintenance, compared to carboplatin-gemcitabine alone. The phase III multicenter, randomized JAVELIN Bladder 100 trial (NCT02603432) is evaluating avelumab plus best supportive care vs. best supportive care alone in the first-line setting as a maintenance treatment in approximately 670 patients with advanced urothelial carcinoma who did not progress after platinum-containing therapy.<sup>76</sup> Both PD-L1<sup>+</sup> and PD-L1<sup>-</sup> patients are eligible and the primary endpoint is OS.

### **Avelumab monotherapy for non-small cell lung cancer**

The field of treatment for metastatic NSCLC is crowded with recent approvals of anti-PD-1/PD-L1 therapies. Several ICIs alone or in combination with chemotherapy are FDA-approved for the treatment of metastatic NSCLC in first-line and later settings. Avelumab was tested in 184 patients with advanced (stage IIIB or IV) platinum-treated NSCLC in one of the earliest JAVELIN Solid Tumor expansion cohort trials.<sup>16,77</sup> Patients were unselected for EGFR or KRAS mutation or ALK translocation status. Median follow-up was 33.9 months (range, 31.0–40.7 months). The most common TRAEs were fatigue (25%), infusion-related reaction (21%), and nausea (13%). Grade  $\geq 3$  TRAEs occurred in 13% of patients, infusion-related reactions and increased lipase levels being the most common. Treatment-related irAEs occurred in 22 patients (12%), the most common being hypothyroidism (6%), adrenal insufficiency (1%), and radiation pneumonitis (1%). Four patients (2%) had a grade  $\geq 3$  treatment-related irAE (one each: radiation pneumonitis, autoimmune neutropenia, pneumonitis, and systemic inflammatory response syndrome). Although one death was initially attributed to radiation pneumonitis, upon further review the death was attributed to disease progression, and no other treatment-related deaths were reported. ORR was 14.1% (95% CI, 9.4–20.0), and median DOR



was 17.5 months (95% CI, 6.9–21.4). Overall, approximately 50% of patients achieved CR, PR, or SD. PD-L1 positivity was defined as > 1% staining by IHC of tumor cells. PD-L1 expression was evaluable in 142 patients; 122 were PD-L1<sup>+</sup> and 20 were PD-L1<sup>-</sup>. There were trends toward increased ORR, PFS, and OS with PD-L1 positivity. Avelumab showed an acceptable safety profile, but OS was only 8.4 months, which is slightly inferior to OS rates in phase III studies of nivolumab, atezolizumab, and pembrolizumab (10.4–13.8 months).<sup>78–80</sup> Preliminary analysis of NSCLC patients from the JAVELIN Solid Tumor trial showed a trend toward higher ORR with increasing avelumab trough concentrations and higher levels of PD-L1 expression. This analysis may provide rationale for studies of more intensive avelumab dosing regimens, such as 10 mg/kg i.v. weekly or 20 mg/kg i.v. every 2 weeks to assess further clinical benefit.<sup>81</sup>

There are several possible reasons for the lackluster results achieved by avelumab in NSCLC. In the JAVELIN Solid Tumor expansion cohort, a third of patients were heavily pretreated, having received  $\geq 2$  previous chemotherapy regimens, compared to randomized trials of nivolumab and pembrolizumab that enrolled patients who had only 1 or 2 previous lines of treatment.<sup>79,82</sup> The JAVELIN Solid Tumor trial recruited patients regardless of PD-L1 expression or the presence of driver mutations, such as EGFR or ALK, which are regarded as less sensitive to immunotherapy than tumors without these mutations. Interestingly, the phase III JAVELIN Lung 200 trial (NCT02395172), which enrolled advanced NSCLC patients who progressed after previous platinum-doublet therapy, failed to meet its primary endpoint of improved OS compared to docetaxel, leaving more questions in its wake.<sup>83</sup> Results may have been confounded by a high crossover rate. Improvements in OS were observed in populations with moderate-to-high ( $\geq 50\%$ ) and high ( $\geq 80\%$ ) PD-L1 expression. Another phase III trial is currently underway to evaluate avelumab in PD-L1<sup>+</sup> advanced NSCLC in the first-line setting (NCT02576574), which may help to answer some lingering questions.

The phase Ib/II JAVELIN Lung 101 trial (NCT02584634) combined avelumab with the ALK tyrosine kinase inhibitor crizotinib and the third-generation ALK inhibitor lorlatinib, in both ALK<sup>+</sup> and ALK<sup>-</sup> previously treated advanced NSCLC.<sup>84</sup> Patients with ALK<sup>-</sup> NSCLC received avelumab plus crizotinib 250 mg p.o. BID, while patients with ALK<sup>+</sup> NSCLC received avelumab plus lorlatinib 100 mg daily. At data cutoff on Oct 27, 2017, 12 ALK<sup>-</sup> patients and 28 ALK<sup>+</sup> patients had been treated, but median follow-up was not specified. DLTs occurred in 41.7% of ALK<sup>-</sup> patients, which included increases in ALT and AST, febrile neutropenia, hepatitis, QT prolongation, and rash. No DLTs occurred in ALK<sup>+</sup> patients. The ORR in ALK<sup>-</sup> patients was 16.7% (95% CI, 2.1–48.4; PR in 2 patients), and 46.4% of ALK<sup>+</sup> patients (95% CI, 27.5–66.1; CR in 1 and PR in 12 patients). Avelumab plus lorlatinib showed an acceptable safety profile and promising antitumor activity in patients with ALK<sup>+</sup> advanced NSCLC and will be further evaluated in treatment-naïve patients in a phase II trial.

### **Avelumab monotherapy for melanoma**

An expansion cohort of the JAVELIN Solid Tumor trial evaluated avelumab in patients with previously treated

unresectable stage IIIC or IV melanoma.<sup>85</sup> As of the data cutoff on December 31, 2016, 51 patients had been followed for a median of 24.2 months (range, 16.1–31.5 months). The majority of primary tumors were cutaneous (54.9%) and ocular (31.4%). Patients had received a median of 2 prior lines of therapy for advanced disease (range, 0–4 lines), including ipilimumab in 51% of patients. Median DOR was not estimable (95% CI, 2.6 months–not estimable). ORR was 21.6% (95% CI, 11.3–35.3) overall, 28.6% (95% CI, 13.2–48.7) in patients with cutaneous melanoma, and 0% in patients with ocular melanoma. The overall ORR of this study compares favorably to ORRs in previous studies of ICIs in which patients were less heavily pre-treated and ocular melanoma was excluded; ORRs were approximately 33% with pembrolizumab, 12% with ipilimumab, and 40% with the combination of ipilimumab plus nivolumab in otherwise similar patient populations.<sup>7,86</sup> The DOR with ICIs is superior to that of chemotherapy agents such as dacarbazine, which only yields an ORR of < 10%.<sup>87,88</sup> Responses were only seen in patients with PD-L1<sup>+</sup> tumors.<sup>85</sup> In patients who received prior ipilimumab (n = 26), the ORR was 30.8% (95% CI, 14.3–51.8), which is similar to nivolumab and slightly better than pembrolizumab following progression on ipilimumab.<sup>89,90</sup> The toxicity profile was similar to other JAVELIN Solid Tumor trial cohorts. Thirty-nine patients (76.5%) had a TRAE, most commonly infusion-related reaction (25.5%), fatigue (17.6%), and chills (11.8%).<sup>85</sup> Only 4 patients (7.8%) had a grade  $\geq 3$  TRAE; there were no treatment-related deaths. Avelumab produced durable responses, promising survival outcomes, and an acceptable safety profile in patients with previously treated metastatic melanoma, but this is already a field crowded with ICI approvals.

### **Avelumab in combination for renal cell carcinoma**

Antiangiogenic agents such as tyrosine kinase inhibitors are being studied in combination with ICIs in renal cell carcinoma (RCC), based on the rationale that VEGF inhibition has an effect on tumor growth, reduces immunosuppression in the TME, and promotes T cell trafficking to the tumor.<sup>91,92</sup> JAVELIN Renal 100 (NCT02493751) is an ongoing open-label, multicenter (U.S., U.K., and Japan), dose-finding and dose-expansion, phase Ib study of avelumab plus axitinib as first-line therapy in patients with advanced clear-cell RCC following primary tumor resection.<sup>93</sup> Patients enrolled in the dose-finding phase received 5 mg of axitinib p.o. twice daily for 7 days, followed by combination therapy with avelumab plus continuation of axitinib. Based on pharmacokinetic data, 10 additional patients were enrolled in the dose-expansion phase and started taking the combination therapy directly. The primary endpoint was DLT in the first 4 weeks (2 cycles) of treatment with avelumab plus axitinib. Safety and antitumor activity analyses were done in all patients who received  $\geq 1$  dose of avelumab or axitinib. Six patients were enrolled in the dose-finding phase and 49 in the dose-expansion phase of the study. One DLT of grade 3 proteinuria due to axitinib was reported among the initial 6 patients. Grade  $\geq 3$  TRAEs were seen in 58% of patients,

the most frequent being hypertension (29%) and increased concentrations of alanine aminotransferase, amylase, and lipase, and palmar-plantar erythrodysesthesia syndrome (7% each). One patient (2%) died due to treatment-related autoimmune myocarditis. The toxicity profile of irAEs in this trial, including the episode of autoimmune myocarditis, is consistent with those reported for other anti-PD-1/PD-L1 mAbs.<sup>94,95</sup> At the data cutoff date of April 13, 2017, the median DOR was not yet reached. The ORR for the 55 patients enrolled was 58% (95% CI, 44–71), which was higher than that seen with axitinib alone<sup>96</sup> and was consistent with response data from other phase I/II studies of anti-PD-1/PD-L1 antibodies combined with angiogenesis inhibitors in first-line treatment of advanced RCC.<sup>97,98</sup> In the JAVELIN Renal 100 study, an assessment of PD-L1 expression on tumor and immune cells found a correlation between intratumor PD-L1 expression ( $\geq 1\%$  staining of tumor cells by IHC) and the likelihood of achieving an objective response after receiving avelumab plus axitinib.<sup>93</sup> The safety profile of the combination of avelumab plus axitinib in treatment-naïve patients with advanced RCC was manageable and consistent with that of each drug alone. The preliminary data on antitumor activity are encouraging. Based on these promising results, the phase III JAVELIN Renal 101 trial is assessing avelumab plus axitinib compared with sunitinib monotherapy as first-line treatment of advanced RCC (NCT02684006). The primary objectives are to demonstrate the superiority of avelumab plus axitinib vs. sunitinib in prolonging PFS and OS. Results have not yet been reported.

### **Avelumab monotherapy for gastric cancer**

In a JAVELIN Solid Tumor trial expansion cohort, patients with advanced GC/GEJC were treated with avelumab as first-line maintenance or second-line therapy.<sup>99,100</sup> As of data cutoff on September 30, 2017, 90 patients in the first-line maintenance subgroup and 60 patients in the second-line subgroup had been followed for a median of 36 months (range, 27–42 months) and 33.7 months (range, 25–42 months), respectively.<sup>100</sup> TRAEs of any grade occurred in 56.7% of patients, the most common being infusion-related reactions (12.7%) and fatigue (10.0%). Grade  $\geq 3$  TRAEs were reported in 8.7% of patients and were similar to those seen in other cohorts. There was one treatment-related death from hepatic failure/autoimmune hepatitis. irAEs occurred in 15.3% of patients, but only 2.0% were grade  $\geq 3$ . The ORR was 6.7% (95% CI, 2.5–13.9) in the maintenance setting including CRs in 2.2%. In the second-line setting, the ORR was 6.7% (95% CI, 1.8–16.2). In the maintenance setting the median PFS was 2.8 months (95% CI, 2.3–4.1) and the median duration of response was 21.4 months (95% CI, 4.0–not estimable). The median PFS in the second-line setting was 1.4 months (95% CI, 1.3–1.5). In the maintenance subgroup, the median OS was 11.1 months (95% CI, 8.9–13.7) from the start of avelumab therapy and 18.7 months (95% CI, 15.4–20.6) when measured from the start of chemotherapy. In the second-line setting the median OS was 6.8 months (95% CI, 5.4–9.5). There was a trend toward higher ORR with PD-L1 positivity in both settings, though PFS did not positively correlate in the second-line setting.<sup>99</sup> Interestingly, a patient who experienced marked clinical improvement with avelumab had a tumor

strongly positive for Epstein-Barr virus. Such tumors are known to be microsatellite stable, indicating that response to ICIs in GC/GEJC may be driven by multiple mechanisms.<sup>101</sup>

Although clinical activity was limited, results of this trial led to the development of 2 phase III trials of avelumab in metastatic GC/GEJC in third-line and maintenance settings. The phase III JAVELIN Gastric 300 trial (NCT02625623) enrolled 371 patients in a multicenter, randomized trial investigating avelumab plus best supportive care vs. physician's choice of protocol-specified chemotherapy (paclitaxel or irinotecan monotherapy) plus best supportive care as a third-line therapy for unresectable, recurrent, or metastatic GC/GEJC that had progressed following 2 prior therapeutic regimens. Although the safety profile of avelumab was consistent with previous studies, the trial failed to meet its primary endpoint of superior OS for avelumab monotherapy over physician's choice of chemotherapy.<sup>102</sup> JAVELIN Gastric 100 (NCT02625610) is evaluating OS with avelumab maintenance therapy vs. continuation of first-line chemotherapy in advanced GC/GEJC that has not progressed after 12 weeks of first-line

### **Avelumab for ovarian cancer**

Ovarian, fallopian tube, and primary peritoneal cancers are collectively known as epithelial ovarian cancer (EOC). The majority of patients relapse and die from their disease despite response to first-line therapy.<sup>103</sup> Effective treatment remains an urgent need as there are currently no approved ICIs despite multiple phase I trials. It was recently shown that in ovarian cancer, PD-L1 is primarily expressed on tumor-associated macrophages rather than on tumor cells, and in high-grade serous carcinoma of the ovary, there is a strong positive association between PD-L1 expression and the presence of multiple TIL subsets, resulting in an immunological stalemate known as adaptive resistance.<sup>104</sup> Despite PD-L1 being a negative regulator of T-cell activation, in high-grade ovarian cancer, PD-L1 is associated with a favorable prognosis, suggesting that it may be possible to overcome the immunosuppressive effects of PD-L1 expression. In a phase Ib expansion cohort of JAVELIN Solid Tumor, 124 patients with previously treated, recurrent, or refractory advanced EOC were treated with avelumab.<sup>30</sup> Patients were heavily pretreated with a median of 4 lines (range, 1–13 lines) of prior therapy. TRAEs occurred in 66.1% of patients, most commonly grade 1 or 2 fatigue (13.7%), infusion-related reaction (12.1%), and diarrhea (11.3%). Grade 3 and 4 TRAEs only occurred in 6.5% of patients, and there were no treatment-related deaths. ORR was 9.7% (95% CI, 5.1–16.3) based on 12 PRs. SD was observed in 44.4% and the disease control rate was 54%. Median PFS was 11.3 weeks (95% CI, 6.1–12.0) and median OS was 10.8 months (95% CI, 7.0–16.1). PD-L1 expression was evaluable in 59.7% of patients. Using a  $\geq 1\%$  tumor cell staining cutoff by IHC, 77% of patients were PD-L1<sup>+</sup>, with an ORR of 12.3% (95% CI, 5.1–23.7) vs. 5.9% in PD-L1<sup>-</sup> patients (95% CI, 0.1–28.7). ORR was 16% in patients with wild-type BRCA whereas no responses were seen in patients with BRCA-mutated tumors, but only 34 tumors were analyzed. Change in CA-125 levels correlated with

response in only about 10% of patients. Although the ORR was relatively low, avelumab was well tolerated and some patients did achieve a durable response in an otherwise deadly disease, which has paved the way for phase III trials that will attempt to overcome adaptive resistance through combinations of avelumab and chemotherapy.

Some chemotherapy agents exhibit immunogenic potential and can increase tumor responsiveness to ICIs.<sup>105,106</sup> In mouse models, treatment with liposomal doxorubicin in combination with an anti-PD-L1 antibody decreased the percentage of regulatory T cells and increased the percentage of CD8<sup>+</sup> T cells among TILs compared with either agent as monotherapy. These effects were associated with an increased rate of CRs and improved survival,<sup>107</sup> providing the rationale for combining avelumab with chemotherapy agents.<sup>107</sup> Two phase III trials of avelumab plus chemotherapy have been fully recruited and results will provide important information on treatment sequencing with an ICI in EOC.

JAVELIN Ovarian 200 (NCT02580058) is the first randomized phase III trial of an ICI in EOC.<sup>108</sup> This 3-arm trial is comparing avelumab alone or in combination with pegylated liposomal doxorubicin vs. pegylated liposomal doxorubicin alone in patients with platinum-resistant/refractory recurrent EOC. OS and PFS are primary endpoints. JAVELIN Ovarian 100 (NCT02718417) is a phase III trial of avelumab in combination with and/or following carboplatin and paclitaxel chemotherapy in previously untreated patients with EOC. This is also a 3-arm trial and will compare avelumab in combination with platinum-based chemotherapy followed by avelumab maintenance, avelumab given only as maintenance after platinum-based chemotherapy, or platinum-based chemotherapy alone. The primary endpoint is PFS.

### **Avelumab as monotherapy for breast cancer**

As in ovarian cancer, high TILs have been shown to be predictive of response to chemotherapy, prognostic in triple-negative breast cancer (TNBC), and predictive of response to treatment with trastuzumab in HER2<sup>+</sup> breast cancer.<sup>109,110</sup> High TIL levels are associated with increased PD-L1 expression in tumors, and PD-L1<sup>+</sup> tumors with high TILs have better outcomes.<sup>110-112</sup> Preclinical and early-phase studies have suggested that ICIs may have clinical activity in breast cancer, particularly in TNBC.<sup>113-116</sup> In a phase I dose-expansion cohort of the JAVELIN Solid Tumor trial, avelumab was tested in 168 patients with metastatic breast cancer refractory to or progressing after standard-of-care therapy.<sup>22</sup> 15.5% of patients had HER2<sup>+</sup> disease (irrespective of ER and PR status), 42.9% had hormone receptor-positive (HR<sup>+</sup>)/HER2<sup>-</sup> disease, and 34.5% had TNBC. Patients had received a median of 3 prior therapies for metastatic disease. Median follow-up was 10 months (range, 6.0–15.2 months). TRAEs occurred in 68.5% of patients, most commonly fatigue (19.0%), infusion-related reaction (14.3%), and nausea (13.1%). Grade  $\geq$  3 TRAEs occurred in 13.7% of patients, including 2 (1.2%) treatment-related deaths, which included a patient who developed autoimmune hepatitis in the setting of progressive liver metastases who died of acute liver failure, and a patient with diffuse visceral metastases (including

lungs) and history of respiratory disorders (cough, dyspnea, and pneumonia) who died of respiratory distress, which was not characterized as pneumonitis. The overall ORR was disappointingly low at 3% (1 CR and 4 PRs) and only 5.2% in patients with TNBC. Within the TNBC subgroup, 15 patients (25.9%) had SD and the disease control rate was 31.0%. Of the 47 patients who achieved either CR, PR, or SD, 14 (29.8%) remained progression-free for  $\geq$  24 weeks. The median DOR was not reached as of data cutoff on February 27, 2015. Tumor specimens were evaluable for PD-L1 expression in 136 patients. Based on a threshold of  $\geq$  1% tumor-cell staining by IHC, 85 had PD-L1<sup>+</sup> tumors, but no efficacy trends were seen based on PD-L1 expression in tumor cells. Using a  $\geq$  10% threshold for PD-L1 expression in TILs, 12/136 evaluable patients (8.8%) had PD-L1<sup>+</sup> tumors. A trend toward higher ORR was seen in patients with PD-L1<sup>+</sup> vs. PD-L1<sup>-</sup> TILs in the overall population (16.7% vs. 1.6%) and in the TNBC subgroup (22.2% vs. 2.6%). The ORR in TNBC with PD-L1<sup>+</sup> TILs is comparable to the response rate of 18.5% and 13% reported for patients with PD-L1<sup>+</sup> TNBC treated with pembrolizumab and atezolizumab, respectively.<sup>113,114</sup> Unlike in the pembrolizumab and atezolizumab trials, PD-L1 expression was evaluated in tumor cells and TILs in the JAVELIN Solid Tumor cohort, and although the number of specimens analyzed was small, this supports the need to evaluate expression of PD-L1 on tumor cells and TILs to better understand their roles in response to ICIs. Avelumab showed an acceptable safety profile and clinical activity, including durable responses in a subset of patients, and is now being evaluated in combination trials.

Several ongoing studies are evaluating avelumab in conjunction with other therapies in several subtypes of metastatic breast cancer. JAVELIN Medley (NCT02554812), which includes a TNBC cohort, is a phase Ib/II study assessing avelumab in combination with novel immunotherapies. And the PACE study is a 3-arm multicenter, randomized phase II study of fulvestrant vs. palbociclib plus fulvestrant with and without avelumab for CDK4/6 inhibitor pretreated HR<sup>+</sup>/HER2<sup>-</sup> metastatic breast cancer.<sup>117</sup>

### **Avelumab for glioblastoma**

An ongoing phase II trial is investigating avelumab plus axitinib, a selective VEGFR inhibitor, in patients with recurrent glioblastoma (NCT03291314).<sup>118</sup> Patients without baseline corticosteroid use receive axitinib 5 mg p.o. BID plus avelumab (Cohort A), while patients with baseline corticosteroid use receive axitinib monotherapy with the option to add avelumab after 6 weeks if the corticosteroid dose can be tapered to  $<$  10 mg prednisolone (Cohort B). As of January 2018, 32 patients, evenly distributed between cohorts, initiated study treatment. All patients had failed prior RT and temozolomide. In Cohort B, 7 patients (44%) initiated treatment with avelumab after 6 weeks of axitinib monotherapy. Treatment with axitinib plus avelumab was ongoing in 10 patients across both cohorts. As of data cutoff, the median treatment duration was 8 weeks (range, 4–30 weeks). TRAEs occurred in all patients; 7 patients (30%) experienced a grade 3 TRAE. There were no grade 4 or 5 AEs and no one

discontinued treatment due to AEs. The safety profile of avelumab plus axitinib appears manageable in patients with recurrent glioblastoma. This clinical trial is being continued to evaluate efficacy.

### **Avelumab monotherapy for mesothelioma**

Malignant mesothelioma has a poor prognosis, and there are currently no approved second-line therapies. Even with first-line chemotherapy with pemetrexed plus cisplatin, OS is just 12 months.<sup>119</sup> In a JAVELIN Solid Tumor expansion cohort study, patients with unresectable pleural or peritoneal mesothelioma whose disease had progressed after platinum and pemetrexed therapy received avelumab.<sup>120</sup> As of December 31, 2016, 53 patients were treated with avelumab and followed for a median of 24.8 months (range, 16.8–27.8 months). Patients had received a median of 2 prior lines of therapy (range, 1–8 lines). TRAEs occurred in 81.1% of patients, most commonly infusion-related reaction (35.8%), chills (15.1%), fatigue (15.1%), and pyrexia (11.3%). No treatment-related deaths occurred. ORR was 9.4% (95% CI, 3.1–20.7; CR in 1.9%, PR in 7.5%) and 49.1% of patients achieved SD. In evaluable patients with PD-L1<sup>+</sup> tumors (n = 16) and PD-L1<sup>-</sup> tumors (n = 27) ( $\geq 5\%$  tumor-cell staining cutoff by IHC), ORR was 18.8% (95% CI, 4.0–45.6) and 7.4% (95% CI, 0.9–24.3), respectively. Median DOR was 15.2 months (95% CI, 11.1–not estimable), which compared favorably to a phase Ib study of pembrolizumab in PD-L1-selected pleural mesothelioma patients who had a median DOR of 12 months.<sup>121</sup> Despite PD-L1 positivity being historically associated with a worse prognosis in mesothelioma (median OS 4.8–5 months vs. 14.5–16.3 months),<sup>122,123</sup> the PD-L1<sup>+</sup> population treated with pembrolizumab achieved an OS of 18 months (95% CI, 9.4–not reached), whereas median OS was 10.9 months (95% CI, 7.5–21.0) with avelumab.<sup>120</sup> Compared to historical studies of non-approved second-line chemotherapy agents with a median OS of 5.7–10.9 months,<sup>124–127</sup> both avelumab and pembrolizumab fare well. Overall, avelumab showed an acceptable safety profile and clinical activity in patients with previously treated mesothelioma.

### **Avelumab for head and neck squamous cell carcinoma**

Preliminary results from a phase Ib trial of RT with concurrent avelumab and cetuximab as primary treatment in patients with locally advanced head and neck squamous cell carcinoma who are ineligible for cisplatin treatment suggest that avelumab can be safely administered with concurrent cetuximab and RT (NCT02938273).<sup>128</sup> At time of data analysis for an online abstract presented at the 2018 American Society of Clinical Oncology Annual Meeting, 6 out of a planned 10 patients had been treated with RT (5 times a week, total dose  $35 \times 2$  Gy) concurrent with cetuximab (loading dose  $400 \text{ mg/m}^2$  in week - 1,  $250 \text{ mg/m}^2$  in weeks 1–7) and avelumab ( $10 \text{ mg/kg}$  every 2 weeks concurrent with RT plus 4 months maintenance). Four patients completed the prescribed treatment; 2 were still continuing maintenance therapy. Median follow-up was 5.7 months (range, 3.7–7.4 months). One patient experienced an avelumab-induced

grade 3 pneumonitis 3 weeks post-RT and discontinued avelumab after 4 cycles. The pneumonitis resolved after 4 days with  $1 \text{ mg/kg}$  prednisone. All patients were in CR 2 weeks after completion of RT and 2 weeks after completion of maintenance therapy.

A phase III trial randomized patients with locally advanced head and neck squamous cell carcinoma to receive avelumab-cetuximab-RT vs. standard of care.<sup>129</sup> All patients in 2 cohorts were treated with intensity-modulated radiation therapy (IMRT) for a total dose of 70 Gy in 33 fractions. Cohort 1 included patients deemed fit to receive high-dose cisplatin  $100 \text{ mg/m}^2$  every 3 weeks. Cohort 2, made up of patients unfit to receive cisplatin, instead received cetuximab  $400 \text{ mg/m}^2$  on day - 7 and  $250 \text{ mg/m}^2$  weekly. In both cohorts, patients in the experimental arms received IMRT concomitant with cetuximab (same as in standard-of-care arms) and avelumab (on day - 7 and every 2 weeks) followed by avelumab every 2 weeks for 12 months. As of data cutoff in December 2017, 29 patients had been randomized. All patients completed IMRT. Six of the 14 patients in experimental arms did not receive the entire systemic regimen, but all received  $\geq 3$  doses of cetuximab and  $\geq 2$  doses of avelumab. Three patients (21.4%) developed a grade 4 AE (dermatitis, lymphopenia, or mucositis).

### **Avelumab for colorectal cancer**

The German phase II AVETUX trial is an ongoing single-arm trial of avelumab and cetuximab in combination with FOLFOX in patients with previously untreated RAS/BRAF wild-type metastatic colorectal cancer (NCT03174405).<sup>130</sup> Avelumab treatment begins on day 1 of cycle 2. The primary endpoint is the rate of PFS at 12 months. A safety analysis was planned after the 15th patient had been followed for 2 months. As of February 1, 2018, 24/43 patients had been treated, with a median follow-up of 3.2 months. Grade 3 and 4 AEs occurred in 9 patients, but only 1 grade 3 AE was related to avelumab. Interestingly, 2 patients with high TIL counts developed uncomplicated fever the day after the first avelumab infusion. An interim safety analysis supported the feasibility of this regimen as first-line treatment for metastatic colorectal cancer.

### **Commercial/safety issues**

Avelumab has been shown to be well tolerated and, except for more frequent infusion reactions, its safety profile is similar to other ICIs.<sup>20,37,39</sup> Across tumor types, infusion-related reactions have generally been low-grade, have occurred only after the first or second infusion, and have rarely resulted in discontinuation.<sup>35</sup> Among 1738 patients in the phase I JAVELIN Solid Tumor and phase II JAVELIN Merkel 200 clinical trials, a minority of patients experienced grade  $\geq 3$  TRAEs or irAEs (Table 3), and discontinuation was uncommon.<sup>19</sup> Grade  $\geq 3$  TRAEs occurred in 10.2% of patients, most commonly fatigue (1.0%) and infusion-related reaction (0.6%). TRAEs resulted in discontinuation in 6.2% and death in 0.2%. Grade  $\geq 3$  irAEs occurred in 39 patients (2.2%) and resulted in discontinuation in 34 patients (2.0%).

Avelumab is just one of many ICI options, but it remains the only FDA-approved treatment for mMCC. For mUC that has

**Table 3.** TRAEs and irAEs in a pooled analysis of data from the JAVELIN solid tumor and JAVELIN Merkel 200 clinical trials.

TRAEs	N = 1738 Number (%)	
	Any Grade	≥ Grade 3
Any TRAE	1164 (67.0)	177 (10.2)
Fatigue	307 (17.7)	17 (1.0)
Infusion-related reaction	295 (17.0)	10 (0.6)
Nausea	150 (8.6)	2 (0.1)
Diarrhea	123 (7.1)	5 (0.3)
Chills	116 (6.7)	0
Pyrexia	106 (6.1)	0
Decreased appetite	90 (5.2)	3 (0.2)
Hypothyroidism	87 (5.0)	3 (0.2)
AST increased	38 (2.2)	8 (0.5)
Lipase increased	25 (1.4)	17 (1.0)
GGT increased	17 (1.0)	10 (0.6)

irAE	N = 1738 Number (%)			
	Any Grade	Grade 3	Grade 4	Grade 5
Any irAE	247 (14.2)	32 (1.8)	4 (0.2)	3 (0.2)
Rash	90 (5.2)	1 (0.1)	0	0
Colitis	26 (1.5)	7 (0.4)	0	0
Pneumonitis	21 (1.2)	5 (0.3)	1 (0.1)	1 (0.1)
Hepatitis	16 (0.9)	11 (0.6)	0	2 (0.1)
Endocrinopathies	106 (6.1)	6 (0.3)	0	0
Thyroid disorders	98 (5.6)	3 (0.2)	0	0
Adrenal insufficiency	8 (0.5)	1 (0.1)	0	0
Type I diabetes mellitus	2 (0.1)	2 (0.1)	0	0
All other irAEs	19 (1.1)	5 (0.3)	3 (0.2)	0
Blood CPK increased	5 (0.3)	1 (0.1)	2 (0.1)	0
Myositis	5 (0.3)	1 (0.1)	1 (0.1)	0
Psoriasis	5 (0.3)	1 (0.1)	0	0
Guillain-Barré syndrome	1 (0.1)	1 (0.1)	0	0
Systemic inflammatory response syndrome	1 (0.1)	1 (0.1)	0	0

Safety data from a pooled analysis of 1738 patients in the phase I JAVELIN Solid Tumor and phase II JAVELIN Merkel 200 clinical trials. TRAEs of any grade occurring in ≥ 5% of patients or TRAEs of grade ≥ 3 in ≥ 0.5% of patients are shown. Categories with an incidence of irAEs of grade ≥ 3 are shown. Events were graded according to the Common Terminology Criteria for Adverse Events (version 4.0). The investigator considered TRAEs to be the primary cause of death in 4 patients (0.2%). Table adapted from Kelly et al. *Cancer*. 2018.

Abbreviations: aspartate aminotransferase (AST); creatinine phosphokinase (CPK); gamma-glutamyl transferase (GGT); immune-related adverse event (irAE); treatment-related adverse event (TRAE)

progressed during or following platinum-containing chemotherapy, avelumab competes with durvalumab, nivolumab, atezolizumab, and pembrolizumab.

## Conclusion/expert opinion

Many trials are underway evaluating avelumab as a single agent, in immunotherapy combinations, and in other combinations including chemotherapy and RT in both solid and hematological malignancies. Clinical trials combining avelumab with agents that further augment ADCC or NK cell activity, such as IL-12 and IL-15, are of special interest because if successful this strategy may set avelumab apart from other ICIs in terms of mechanism of action and efficacy. Avelumab is also being tested in a variety of clinical settings, including neoadjuvant and first-line settings. Although response rates have been modest, they are similar to other PD-L1 and PD-1 targeted antibodies, responses are generally durable, and treatment is well tolerated. More work needs to be done to explore ways to augment the TME to turn a “cold” tumor “hot.” If this can be accomplished, the use of ICIs will be expanded to a larger population, having converted non-responders to responders. There is also a need for standardized testing for PD-L1 expression. Efforts to achieve this are underway, including the Blueprint PD-L1 IHC comparison project, which is evaluating 5 independently developed commercial PD-L1 IHC assays,<sup>131,132</sup>

but it will take time for the scientific community to reach consensus. Studies are currently underway analyzing killer cell immunoglobulin-like receptors (KIR), which are regulatory receptors expressed on NK cells. If there is a correlation between KIR genotype and outcome it would suggest that ADCC may be a clinically relevant mechanism of action (in addition to blocking the PD-1/PD-L1 axis) and could potentially be a predictor for response to avelumab. Avelumab’s acceptable safety profile, unique capacity to enhance ADCC, and ability to induce durable responses in a variety of tumor types provide rationale for continuing to evaluate its efficacy as a single agent and in combination with other therapies.

## Disclosure of potential conflicts of interest

The NCI has a cooperative research and development agreement (CRADA) with EMD Serono that includes resources for preclinical and clinical studies. James Gulley serves as the PI for several EMD Serono clinical trials and is the Co-PI of the CRADA with EMD Serono. James Gulley and Julie Collins receive no money from EMD Serono.

## ORCID

Julie M. Collins  <http://orcid.org/0000-0001-5702-4693>  
James L. Gulley  <http://orcid.org/0000-0002-6569-2912>

## References

- Coley WB II. Contribution to the knowledge of Sarcoma. *Ann Surg.* 14;1891:199–220.
- McCarthy EF. The toxins of William B. Coley and the treatment of bone and soft-tissue sarcomas. *Iowa Orthop J.* 26;2006:154–158.
- Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, Nakamura S, Enomoto K, Yagita H, Azuma M, et al. 2007. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. *Clin Cancer Res.* 13:2151–2157. doi:10.1158/1078-0432.CCR-06-2746.
- Ahmadzadeh M, Johnson LA, Heemskerk B, Wunderlich JR, Dudley ME, White DE, Rosenberg SA. 2009. Tumor antigen-specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. *Blood.* 114:1537–1544. doi:10.1182/blood-2008-12-195792.
- Grenga I, Donahue RN, Lepone LM, Richards J, Schlom J. 2016. A fully human IgG1 anti-PD-L1 MAb in an in vitro assay enhances antigen-specific T-cell responses. *Clin Transl Immunol.* 5:e83. doi:10.1038/cti.2016.27.
- Larkin J, Hodi FS, Wolchok JD. 2015. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med.* 373:1270–1271. doi:10.1056/NEJMc1509660.
- Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, et al. 2015. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med.* 372:2521–2532. doi:10.1056/NEJMoa1503093.
- Heery CR, O'Sullivan-Coyne G, Madan RA, Cordes L, Rajan A, Rauckhorst M, Lamping E, Oyelakin I, Marté JL, Lepone LM, et al. 2017. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. *Lancet Oncol.* 18:587–598. doi:10.1016/S1470-2045(17)30239-5.
- Boyerinas B, Jochems C, Fantini M, Heery CR, Gulley JL, Tsang KY, Schlom J. 2015. Antibody-dependent cellular cytotoxicity activity of a novel anti-pd-l1 antibody avelumab (MSB0010718C) on human tumor cells. *Cancer Immunol Res.* 3:1148–1157. doi:10.1158/2326-6066.CIR-15-0059.
- Scheuer W, Friess T, Burtcher H, Bossenmaier B, Endl J, Hasmann M. 2009. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models. *Cancer Res.* 69:9330–9336. doi:10.1158/0008-5472.CAN-08-4597.
- Weiner LM, Surana R, Wang S. 2010. Monoclonal antibodies: versatile platforms for cancer immunotherapy. *Nat Rev Immunol.* 10:317–327. doi:10.1038/nri2744.
- Greillier L, Tomasini P, Barlesi F. 2015. Necitumumab for non-small cell lung cancer. *Expert Opin Biol Ther.* 15:1231–1239. doi:10.1517/14712598.2015.1055243.
- Jardim DL, de Melo Gagliato D, Giles FJ, Kurzrock R. 2018. Analysis of drug development paradigms for immune checkpoint inhibitors. *Clin Cancer Res.* 24:1785–1794. doi:10.1158/1078-0432.CCR-17-1970.
- Vandever AJ, Fallon JK, Tighe R, Sabzevari H, Schlom J, Greiner JW. 2016. Systemic immunotherapy of non-muscle invasive mouse bladder cancer with avelumab, an anti-PD-L1 immune checkpoint inhibitor. *Cancer Immunol Res.* 4:452–462. doi:10.1158/2326-6066.CIR-15-0176.
- Apolo AB, Infante JR, Balmanoukian A, Patel MR, Wang D, Kelly K, Mega AE, Britten CD, Ravaud A, Mita AC, et al. 2017. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter, phase Ib study. *J Clin Oncol.* 35:2117–2124. doi:10.1200/JCO.2016.71.6795.
- Gulley JL, Rajan A, Spigel DR, Iannotti N, Chandler J, Wong DJL, Leach J, Edenfield WJ, Wang D, Grote HJ, et al. 2017. Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial. *Lancet Oncol.* 18:599–610. doi:10.1016/S1470-2045(17)30240-1.
- Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, et al. 2015. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med.* 372:2018–2028. doi:10.1056/NEJMoa1501824.
- Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, et al. 2012. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med.* 366:2443–2454. doi:10.1056/NEJMoa1200690.
- Kelly K, Infante JR, Taylor MH, Patel MR, Wong DJ, Iannotti N, Mehnert JM, Loos AH, Koch H, Speit I, et al. 2018. Safety profile of avelumab in patients with advanced solid tumors: A pooled analysis of data from the phase 1 JAVELIN solid tumor and phase 2 JAVELIN Merkel 200 clinical trials. *Cancer.* 124:2010–2017. doi:10.1002/cncr.31293.
- Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, Shih KC, Lebbé C, Linette GP, Milella M, et al. 2016. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol.* 17:1374–1385. doi:10.1016/S1470-2045(16)30364-3.
- BAVENCIO Prescribing Information. U.S. Food and Drug Administration, 2017.
- Dirix LY, Takacs I, Jerusalem G, Nikolinakos P, Arkenau HT, Forero-Torres A, Boccia R, Lippman ME, Somer R, Smakal M, et al. 2018. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. *Breast Cancer Res Treat.* 167:671–686. doi:10.1007/s10549-017-4537-5.
- Patel SP, Kurzrock R. 2015. PD-L1 expression as a predictive biomarker in cancer immunotherapy. *Mol Cancer Ther.* 14:847–856. doi:10.1158/1535-7163.MCT-14-0983.
- Wang X, Teng F, Kong L, Yu J. 2016. PD-L1 expression in human cancers and its association with clinical outcomes. *Onco Targets Ther.* 9:5023–5039. doi:10.2147/OTT.S105862.
- Udall M, Rizzo M, Kenny J, Doherty J, Dahm S, Robbins P, Faulkner E. PD-L1 diagnostic tests: a systematic literature review of scoring algorithms and test-validation metrics. *Diagn Pathol.* 2018;13:12. doi:10.1186/s13000-018-0727-7.
- Mansfield AS, Aubry MC, Moser JC, Harrington SM, Dronca RS, Park SS, Dong H. 2016. Temporal and spatial discordance of programmed cell death-ligand 1 expression and lymphocyte tumor infiltration between paired primary lesions and brain metastases in lung cancer. *Ann Oncol.* 27:1953–1958. doi:10.1093/annonc/mdw289.
- Mansfield AS, Murphy SJ, Peikert T, Yi ES, Vasmataz G, Wigle DA, Aubry MC. 2016. Heterogeneity of programmed cell death ligand 1 expression in multifocal lung cancer. *Clin Cancer Res.* 22:2177–2182. doi:10.1158/1078-0432.CCR-15-2246.
- Juneja VR, McGuire KA, Manguso RT, LaFleur MW, Collins N, Haining WN, Freeman GJ, Sharpe AH. 2017. PD-L1 on tumor cells is sufficient for immune evasion in immunogenic tumors and inhibits CD8 T cell cytotoxicity. *J Exp Med.* 214:895–904. doi:10.1084/jem.20160801.
- Lau J, Cheung J, Navarro A, Lianoglou S, Haley B, Totpal K, Sanders L, Koeppen H, Caplazi P, McBride J, et al. 2017. Tumour and host cell PD-L1 is required to mediate suppression of anti-tumour immunity in mice. *Nat Commun.* 8:14572. doi:10.1038/ncomms14572.
- Disis ML, Patel MR, Pant S, Hamilton E, Lockhart A, Kelly K, Beck JT, Gordon MS, Weiss GJ, Taylor MH, et al. Avelumab (MSB0010718C; anti-PD-L1) in patients with recurrent/refractory ovarian cancer from the JAVELIN solid Tumor phase Ib trial: safety and clinical activity. *J Clin Oncol.* 2016;34(suppl15):abstr5533. doi:10.1200/JCO.2016.34.15\_suppl.5533.
- Lemery S, Keegan P, Pazdur R. 2017. First FDA approval agnostic of cancer site - When a biomarker defines the indication. *N Engl J Med.* 377:1409–1412. doi:10.1056/NEJMp1709968.
- Yarchoan M, Johnson BA 3rd, Lutz ER, Laheru DA, Jaffee EM. 2017. Targeting neoantigens to augment antitumour immunity. *Nat Rev Cancer.* 17:569. doi:10.1038/nrc.2017.74.

33. Yarchoan M, Hopkins A, Jaffee EM. 2017. Tumor mutational burden and response rate to PD-1 inhibition. *N Engl J Med.* 377:2500–2501. doi:10.1056/NEJMc1713444.
34. Prowell TM, Theoret MR, Pazdur R. 2016. Seamless oncology-drug development. *N Engl J Med.* 374:2001–2003. doi:10.1056/NEJMp1603747.
35. Kelly K, Heery CR, Patel MR, Infante JR, Iannotti N, Leach J, Wang D, Chandler JC, Arkenau H-T, Taylor MH, et al. Avelumab (MSB0010718C; anti-PD-L1) in patients with advanced cancer: safety data from 1300 patients enrolled in the phase Ib JAVELIN Solid Tumor trial. *J Clin Oncol.* 2016;34(suppl15):abstr3055. doi:10.1200/JCO.2016.34.15\_suppl.3055.
36. Donahue RN, Lepone LM, Grenga I, Jochems C, Fantini M, Madan RA, Heery CR, Gulley JL, Schlom J. 2017. Analyses of the peripheral immunome following multiple administrations of avelumab, a human IgG1 anti-PD-L1 monoclonal antibody. *J Immunother Cancer.* 5:20. doi:10.1186/s40425-017-0220-y.
37. Weber JS, Yang JC, Atkins MB, Disis ML. 2015. Toxicities of immunotherapy for the practitioner. *J Clin Oncol.* 33:2092–2099. doi:10.1200/JCO.2014.60.0379.
38. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, Dawson N, O'Donnell PH, Balmanoukian A, Loriot Y, et al. 2016. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet.* 387:1909–1920. doi:10.1016/S0140-6736(16)00561-4.
39. Pillai RN, Behera M, Owonikoko TK, Kamphorst AO, Pakkala S, Belani CP, Khuri FR, Ahmed R, Ramalingam SS. 2018. Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer: A systematic analysis of the literature. *Cancer.* 124:271–277. doi:10.1002/cncr.31043.
40. Shitara K, Yamada Y, Yoh K, Naito Y, Iwasa S, Yamamoto N, von Heydebreck A, Achiwa H, Doi T. 2015. Phase I, open-label, multi-ascending dose trial of avelumab (MSB0010718C), an anti-PD-L1 monoclonal antibody, in Japanese patients with advanced solid tumors. *J Clin Oncol.* 33(suppl15):abstr 3023.
41. Hironaka S, Shitara K, Iwasa S, Nishina T, Muro K, Esaki T, Satoh T, Hara H, Machida N, von Heydebreck A, Shimizu A, Doi T. OZ-10-4 Avelumab (MSB0010718C; anti-PD-L1), in Japanese patients with advanced gastric cancer: results from phase Ib trial. *Ann Oncol.* 2016;27(suppl7):abstrmdw521.047. doi:10.1093/annonc/mdw141.
42. Feng H, Shuda M, Chang Y, Moore PS. 2008. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science.* 319:1096–1100. doi:10.1126/science.1152586.
43. Fitzgerald TL, Dennis S, Kachare SD, Vohra NA, Wong JH, Zervos EE. dramatic increase in the incidence and mortality from Merkel cell Carcinoma in the United States. *Am Surg.* 81:2015:802–806.
44. Voog E, Biron P, Martin JP, Blay JY. Chemotherapy for patients with locally advanced or metastatic Merkel cell carcinoma. *Cancer.* 85:1999:2589–2595.
45. Tai PT, Yu E, Winquist E, Hammond A, Stitt L, Tonita J, Gilchrist J. 2000. Chemotherapy in neuroendocrine/Merkel cell carcinoma of the skin: case series and review of 204 cases. *J Clin Oncol.* 18:2493–2499. doi:10.1200/JCO.2000.18.12.2493.
46. Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. 2005. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol.* 23:2300–2309. doi:10.1200/JCO.2005.02.329.
47. Santamaria-Barria JA, Boland GM, Yeap BY, Nardi V, Dias-Santagata D, Cusack JC Jr. 2013. Merkel cell carcinoma: 30-year experience from a single institution. *Ann Surg Oncol.* 20:1365–1373. doi:10.1245/s10434-012-2779-3.
48. Kaufman HL, Russell JS, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, Shih KC, Lebbé C, Milella M, Brownell I, et al. 2018. Updated efficacy of avelumab in patients with previously treated metastatic Merkel cell carcinoma after >=1 year of follow-up: JAVELIN Merkel 200, a phase 2 clinical trial. *J Immunother Cancer.* 6:7. doi:10.1186/s40425-017-0310-x.
49. Lyngaa R, Pedersen NW, Schrama D, Thruue CA, Ibrani D, Met O, Thor Straten P, Nghiem P, Becker JC, Hadrup SR. 2014. T-cell responses to oncogenic merkel cell polyomavirus proteins distinguish patients with merkel cell carcinoma from healthy donors. *Clin Cancer Res.* 20:1768–1778. doi:10.1158/1078-0432.CCR-13-2697.
50. Goh G, Walradt T, Markarov V, Blom A, Riaz N, Doumani R, Stafstrom K, Moshiri A, Yelistratova L, Levinsohn J, et al. 2016. Mutational landscape of MCPyV-positive and MCPyV-negative Merkel cell carcinomas with implications for immunotherapy. *Oncotarget.* 7:3403–3415. doi:10.18632/oncotarget.6494.
51. D'Angelo SP, Hunger M, Schlichting M, Hennessy MG, Bharmal M. 2018. Association between objective responses (OR) and overall survival (OS) in patients (pts) with metastatic Merkel cell carcinoma (mMCC) treated with avelumab. *J Clin Oncol.* 36:193. doi:10.1200/JCO.2018.36.5\_suppl.193.
52. Iyer JG, Blom A, Doumani R, Lewis C, Tarabdar ES, Anderson A, Ma C, Bestick A, Parvathaneni U, Bhatia S, et al. 2016. Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma. *Cancer Med.* 5:2294–2301. doi:10.1002/cam4.815.
53. Kaufman HL, Hunger M, Hennessy M, Schlichting M, Bharmal M. 2018. Nonprogression with avelumab treatment associated with gains in quality of life in metastatic Merkel cell carcinoma. *Future Oncol.* 14:255–266. doi:10.2217/fon-2017-0470.
54. Walker J, Kasturi V, Lebbe C, Sandhu S, Grignani G, Hennessy M, Hildemann S, Reed J, Hariharan S. Second-line avelumab treatment of patients (pts) with metastatic Merkel cell carcinoma (mMCC): experience from a global expanded access program (EAP). *J Clin Oncol.* 2018;36(suppl15):abstr9537. doi:10.1200/JCO.2018.36.15\_suppl.9537.
55. D'Angelo SP, Russell J, Lebbe C, Chmielowski B, Gambichler T, Grob JJ, Kiecker F, Rabinowits G, Terheyden P, Zwiener I, et al. 2018. Efficacy and safety of first-line avelumab treatment in patients with stage IV metastatic Merkel cell Carcinoma: A preplanned interim analysis of a clinical trial. *JAMA oncol.* 4: e180077. doi:10.1001/jamaoncol.2018.0077.
56. Cowey CL, Mahnke L, Espirito J, Helwig C, Oksen D, Bharmal M. 2017. Real-world treatment outcomes in patients with metastatic Merkel cell carcinoma treated with chemotherapy in the USA. *Future Oncol.* 13:1699–1710. doi:10.2217/fon-2017-0187.
57. Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, Annamalai L, Berry S, Chartash EK, Daud A, Fling SP, et al. 2016. PD-1 Blockade with pembrolizumab in advanced Merkel-cell Carcinoma. *N Engl J Med.* 374:2542–2552. doi:10.1056/NEJMoa1603702.
58. NCCN. 2018. Clinical practice guidelines in oncology: Merkel cell Carcinoma, v.1. National Compr Cancer Netw. 16(6):742–774.
59. Poulsen MG, Rischin D, Porter I, Walpole E, Harvey J, Hamilton C, Keller J, Tripcony L. 2006. Does chemotherapy improve survival in high-risk stage I and II Merkel cell carcinoma of the skin? *Int J Radiat Oncol Biol Phys.* 64:114–119. doi:10.1016/j.ijrobp.2005.04.042.
60. Bhatia S, Brohl A, Brownell I, Chandra S, Dakhil S, Ernstoff M, Fecher LA, Gooley T, Hanna GJ, Hibbert R, et al. ADAM trial: A multicenter, randomized, double-blinded, placebo-controlled, phase 3 trial of adjuvant avelumab (anti-PD-L1 antibody) in Merkel cell carcinoma patients with clinically detected lymph node metastases; NCT03271372. *J Clin Oncol.* 2018;36(suppl): abstrTPS9605. doi:10.1200/JCO.2018.36.15\_suppl.TPS9605.
61. Nakanishi J, Wada Y, Matsumoto K, Azuma M, Kikuchi K, Ueda S. 2007. Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. *Cancer Immunol Immunother.* 56:1173–1182. doi:10.1007/s00262-006-0266-z.
62. Boorjian SA, Sheinin Y, Crispen PL, Farmer SA, Lohse CM, Kuntz SM, Leibovich BC, Kwon ED, Frank I. 2008. T-cell coregulatory molecule expression in urothelial cell carcinoma:

- clinicopathologic correlations and association with survival. *Clin Cancer Res.* 14:4800–4808. doi:10.1158/1078-0432.CCR-08-0731.
63. Spiess PE, Agarwal N, Bangs R, Boorjian SA, Buyyounouski MK, Clark PE, Downs TM, Efstathiou JA, Flaig TW, Friedlander T, et al. 2017. Bladder cancer, version 5.2017, NCCN clinical practice guidelines in oncology. *J National Compr Cancer Netw.* 15:1240–1267. doi:10.6004/jnccn.2017.0156.
  64. Sweeney CJ, Roth BJ, Kabbinavar FF, Vaughn DJ, Arning M, Curiel RE, Obasaju CK, Wang Y, Nicol SJ, Kaufman DS. 2006. Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. *J Clin Oncol.* 24:3451–3457. doi:10.1200/JCO.2005.03.6699.
  65. Bellmunt J, Theodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, Caty A, Carles J, Jagiello-Gruszfeld A, Karyakin O, et al. 2009. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol.* 27:4454–4461. doi:10.1200/JCO.2008.20.5534.
  66. Apolo AB, Ellerton J, Infante JR, Agrawal M, Gordon M, Aljumaily R, Britten CD, Dirix LY, Lee K-W, Taylor MH, et al. Updated efficacy and safety of avelumab in metastatic urothelial carcinoma (mUC): pooled analysis from 2 cohorts of the phase 1b Javelin solid tumor study. *J Clin Oncol.* 2017;35(suppl15): abstr4528. doi:10.1200/JCO.2017.35.15\_suppl.4528.
  67. Patel MR, Ellerton J, Infante JR, Agrawal M, Gordon M, Aljumaily R, Britten CD, Dirix L, Lee K-W, Taylor M, et al. 2018. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. *Lancet Oncol.* 19:51–64. doi:10.1016/S1470-2045(17)30900-2.
  68. Apolo AB, Ellerton J, Infante JR, Agrawal M, Gordon MS, Aljumaily R, Britten CD, Dirix L, Lee K-W, Taylor MH, et al. 2017. Avelumab treatment of metastatic urothelial carcinoma (mUC) in the phase 1b JAVELIN solid Tumor study: updated analysis with ≥6 months of follow-up in all patients. *Ann Oncol.* 28:mdx371.010-mdx371.010. doi:10.1093/annonc/mdx371.010.
  69. Sharma P, Callahan MK, Bono P, Kim J, Spiliopoulou P, Calvo E, Pillai RN, Ott PA, de Braud F, Morse M, et al. 2016. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. *Lancet Oncol.* 17:1590–1598. doi:10.1016/S1470-2045(16)30496-X.
  70. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, Vogelzang NJ, Climent MA, Petrylak DP, Choueiri TK, et al. 2017. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med.* 376:1015–1026. doi:10.1056/NEJMoa1613683.
  71. Powles T, O'Donnell PH, Massard C, Arkenau HT, Friedlander TW, Hoimes CJ, Lee JL, Ong M, Sridhar SS, Vogelzang NJ, et al. 2017. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. *JAMA oncol.* 3: e172411. doi:10.1001/jamaoncol.2017.2411.
  72. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, Loriot Y, Necchi A, Hoffman-Censits J, Perez-Gracia JL, et al. 2017. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet.* 389:67–76. doi:10.1016/S0140-6736(16)32455-2.
  73. Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J, Plimack ER, Vaena D, Grimm G, Bracarda S, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol.* 2017;18:312–322.
  74. Chanza N, Roumeguere T, Sideris S, Gil T, Peltier A, Awada A. Avelumab as neoadjuvant therapy in subjects with muscle-invasive urothelial carcinoma (AURA trial). *J Clin Oncol.* 2018;36(suppl6):abstrTPS535. doi:10.1200/JCO.2018.36.6\_suppl.TPS535.
  75. Vida A, Mellado B, Muro X, Taus A, Barrera R, Maroto P, Bonfill T, Domenech M, Pinto A, Perez Valderrama B, et al. Phase II randomized study of first line avelumab with carboplatin-gemcitabine versus carboplatin-gemcitabine alone in patients with metastatic urothelial carcinoma ineligible for cisplatin-based therapy. *J Clin Oncol.* 2018;36(suppl15):abstrTPS4591. doi:10.1200/JCO.2018.36.15\_suppl.TPS4591.
  76. Powles T, Grivas P, Aragon-Ching JB, Faroun Y, Kessler ER, Tomita Y, Chakrabarti D, Laliberte RJ, Shnaidman M, Petrylak D. 2016. A multicentre, international, randomised, open-label phase 3 trial of avelumab + best supportive care (BSC) vs BSC alone as maintenance therapy after first-line platinum-based chemotherapy in patients with advanced urothelial cancer (JAVELIN bladder 100). *Ann Oncol.* 27:842TiP-TiP. doi:10.1093/annonc/mdw373.69.
  77. Rajan A, Gulley JL, Spigel DR, Iannotti N, Chandler J, Wong DJ, Leach JW, Edenfield WJ, Wang D, Redfern CH, et al. Avelumab (anti-PD-L1) in patients with platinum-treated advanced NSCLC: 2.5-year follow-up from the JAVELIN Solid Tumor trial. *J Clin Oncol.* 2018;36(suppl15):abstr9090. doi:10.1200/JCO.2018.36.15\_suppl.9090.
  78. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, et al. 2015. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med.* 373:1627–1639. doi:10.1056/NEJMoa1507643.
  79. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, Molina J, Kim J-H, Arvis CD, Ahn M-J, et al. 2016. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet.* 387:1540–1550. doi:10.1016/S0140-6736(15)01281-7.
  80. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM, Hida T, Kowalski DM, Dols MC, et al. 2017. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet.* 389:255–265. doi:10.1016/S0140-6736(16)32517-X.
  81. Gulley JL, Spigel DR, Kelly K, Aisner J, Chand V, Koenig A, Dolgos H, Wang S, Verschraegen CF. Exposure-response and PD-L1 expression analysis of second-line avelumab in patients with advanced NSCLC: data from the JAVELIN Solid Tumor trial. *J Clin Oncol.* 2017;35(suppl15):abstr9086. doi:10.1200/JCO.2017.35.15\_suppl.9086.
  82. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, et al. 2015. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med.* 373:123–135. doi:10.1056/NEJMoa1504627.
  83. Merck KGAA, Darmstadt, Germany, and Pfizer provide update on phase III JAVELIN lung 200 trial of avelumab monotherapy in previously treated patients with advanced non-small cell lung cancer. Pfizer Feb 15, 2018. Available at: <https://www.prnewswire.com/news-releases/merck-kgaa-darmstadt-germany-and-pfizer-provide-update-on-phase-iii-javelin-lung-200-trial-of-avelumab-mono-therapy-in-previously-treated-patients-with-advanced-non-small-cell-lung-cancer-674160433.html>
  84. Shaw A, Lee S, Ramalingam SS, Bauer T, Boyer M, Costa E, Felip E, Han J-Y, Hida T, Hughes BGM, et al. Avelumab (anti-PD-L1) in combination with crizotinib or lorlatinib in patients with previously treated advanced NSCLC: phase 1b results from JAVELIN lung 101. *J Clin Oncol.* 2018;36(suppl15):abstr9008. doi:10.1200/JCO.2018.36.15\_suppl.9008.
  85. Keilholz U, Mehnert JM, Bauer S, Bourgeois H, Patel MR, Gravenor D, Nemunaitis JJ, Taylor MH, Wyrwicz L, Lee K-W, et al. Avelumab in patients with previously treated metastatic melanoma: phase 1b results from the JAVELIN Solid Tumor trial. *J Clin Oncol.* 2018;36(suppl5):abstr191. doi:10.1200/JCO.2018.36.5\_suppl.191.



86. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, Segal NH, Ariyan CE, Gordon R-A, Reed K, et al. 2013. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med.* 369:122–133. doi:10.1056/NEJMoa1302369.
87. Avril MF, Aamdal S, Grob JJ, Hauschild A, Mohr P, Bonerandi JJ, Weichenthal M, Neuber K, Bieber T, Gilde K, et al. 2004. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. *J Clin Oncol.* 22:1118–1125. doi:10.1200/JCO.2004.04.165.
88. Bedikian AY, Millward M, Pehamberger H, Conry R, Gore M, Trefzer U, Pavlick AC, DeConti R, Hersh EM, Hersey P, et al. 2006. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the oblimersen melanoma study group. *J Clin Oncol.* 24:4738–4745. doi:10.1200/JCO.2006.06.0483.
89. Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, Weber JS, Joshua AM, Hwu W-J, Gangadhar TC, et al. 2014. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase I trial. *Lancet.* 384:1109–1117. doi:10.1016/S0140-6736(14)60958-2.
90. Hazarika M, Chuk MK, Theoret MR, Mushti S, He K, Weis SL, Putman AH, Helms WS, Cao X, Li H, et al. 2017. U.S. FDA approval summary: nivolumab for treatment of unresectable or metastatic melanoma following progression on ipilimumab. *Clin Cancer Res.* 23:3484–3488. doi:10.1158/1078-0432.CCR-16-0712.
91. Kandalafi LE, Motz GT, Busch J, Coukos G. 2011. Angiogenesis and the tumor vasculature as antitumor immune modulators: the role of vascular endothelial growth factor and endothelin. *Curr Top Microbiol Immunol.* 344:129–148. doi:10.1007/82\_2010\_95.
92. Tartour E, Pere H, Maillere B, Terme M, Merillon N, Taieb J, Sandoval F, Quintin-Colonna F, Lacerda K, Karadimou A, et al. 2011. Angiogenesis and immunity: a bidirectional link potentially relevant for the monitoring of antiangiogenic therapy and the development of novel therapeutic combination with immunotherapy. *Cancer Metastasis Rev.* 30:83–95. doi:10.1007/s10555-011-9281-4.
93. Choueiri TK, Larkin J, Oya M, Thistlethwaite F, Martignoni M, Nathan P, Powles T, McDermott D, Robbins PB, Chism DD, et al. 2018. Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): an open-label, dose-finding and dose-expansion, phase 1b trial. *Lancet Oncol.* 19:451–460. doi:10.1016/S1470-2045(18)30107-4.
94. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, Hicks M, Puzanov I, Alexander MR, Bloomer TL, et al. 2016. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med.* 375:1749–1755. doi:10.1056/NEJMoa1609214.
95. Choueiri TK, Motzer RJ. 2017. Systemic therapy for metastatic renal-cell Carcinoma. *N Engl J Med.* 376:354–366. doi:10.1056/NEJMra1601333.
96. Hutson TE, Lesovoy V, Al-Shukri S, Stus VP, Lipatov ON, Bair AH, Rosbrook B, Chen C, Kim S, Vogelzang NJ. 2013. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. *Lancet Oncol.* 14:1287–1294. doi:10.1016/S1470-2045(13)70465-0.
97. Atkins MB, Plimack ER, Puzanov I, Fishman MN, McDermott DF, Cho DC, Vaishampayan U, George S, Olencki TE, Tarazi JC, et al. 2018. Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial. *Lancet Oncol.* 19:405–415. doi:10.1016/S1470-2045(18)30081-0.
98. McDermott DF, Huseni MA, Atkins MB, Motzer RJ, Rini BI, Escudier B, Fong L, Joseph RW, Pal SK, Reeves JA, et al. 2018. Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. *Nat Med.* 24:749–757. doi:10.1038/s41591-018-0053-3.
99. Chung H, Arkenau HT, Wyrwicz L, Oh D, Lee K, Infante JR, Lee SS, Lee J, Keilholz U, Mita AC, et al. Avelumab (MSB0010718C; anti-PD-L1) in patients with advanced gastric or gastroesophageal junction cancer from JAVELIN solid tumor phase Ib trial: analysis of safety and clinical activity. *J Clin Oncol.* 2016;34(suppl15):abstr4009. doi:10.1200/JCO.2016.34.15\_suppl.4009.
100. Chung HC, Arkenau H-T, Lee J, Rha SY, Oh D-Y, Wyrwicz L, Kang Y-K, Lee K-W, Bauer TM, Lee SS, et al. 2018. Abstract CT111: avelumab (anti-PD-L1) as first-line maintenance (1L mn) or second-line (2L) therapy in patients with advanced gastric or gastroesophageal junction cancer (GC/GEJC): updated phase Ib results from the JAVELIN Solid Tumor trial. *Cancer Res.* 78:CT111–CT. doi:10.1158/1538-7445.AM2018-CT111.
101. Panda A, Mehnert JM, Hirshfield KM, Riedlinger G, Damare S, Saunders T, Kane M, Sokol L, Stein MN, Poplin E, et al. 2018. Immune activation and benefit from avelumab in EBV-positive gastric cancer. *J Natl Cancer Inst.* 110:316–320. doi:10.1093/jnci/djx213.
102. Merck KGAA, Darmstadt, Germany, and Pfizer provide update on phase III JAVELIN gastric 300 study in patients with pre-treated advanced gastric cancer. Pfizer Nov 28, 2017. Available at: <https://www.prnewswire.com/news-releases/merck-kgaa-darmstadt-germany-and-pfizer-provide-update-on-phase-iii-javelin-gastric-300-study-in-patients-with-pre-treated-advanced-gastric-cancer-660495003.html>
103. Ozols RF. 2006. Systemic therapy for ovarian cancer: current status and new treatments. *Semin Oncol.* 33:S3–11. doi:10.1053/j.seminoncol.2006.03.011.
104. Webb JR, Milne K, Kroeger DR, Nelson BH. 2016. PD-L1 expression is associated with tumor-infiltrating T cells and favorable prognosis in high-grade serous ovarian cancer. *Gynecol Oncol.* 141:293–302. doi:10.1016/j.ygyno.2016.03.008.
105. Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G. 2013. Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. *Immunity.* 39:74–88. doi:10.1016/j.immuni.2013.06.014.
106. Pfirschke C, Engblom C, Rickelt S, Cortez-Retamozo V, Garris C, Pucci F, Yamazaki T, Poirier-Colame V, Newton A, Redouane Y, et al. 2016. Immunogenic chemotherapy sensitizes tumors to checkpoint blockade therapy. *Immunity.* 44:343–354. doi:10.1016/j.immuni.2015.11.024.
107. Rios-Doria J, Durham N, Wetzel L, Rothstein R, Chesebrough J, Holowecyj N, Zhao W, Leow CC, Hollingsworth R. 2015. Doxil synergizes with cancer immunotherapies to enhance antitumor responses in syngeneic mouse models. *Neoplasia.* 17:661–670. doi:10.1016/j.neo.2015.08.004.
108. Pujade-Lauraine E, Fujiwara K, Dychter SS, Devgan G, Monk BJ. Avelumab (anti-PD-L1) in platinum-resistant/refractory ovarian cancer: JAVELIN Ovarian 200 Phase III study design. *Future Oncol.* 2018Mar27. Epub ahead of print. doi: 10.2217/fon-2018-0070.
109. Loi S, Michiels S, Salgado R, Sirtaine N, Jose V, Fumagalli D, Kellokumpu-Lehtinen P-L, Bono P, Kataja V, Desmedt C, et al. 2014. Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. *Ann Oncol.* 25:1544–1550. doi:10.1093/annonc/mdu112.
110. Wimberly H, Brown JR, Schalper K, Haack H, Silver MR, Nixon C, Bossuyt V, Puztai L, Lannin DR, Rimm DL. 2015. PD-L1 expression correlates with tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy in breast cancer. *Cancer Immunol Res.* 3:326–332. doi:10.1158/2326-6066.CIR-14-0133.
111. Schalper KA, Velcheti V, Carvajal D, Wimberly H, Brown J, Puztai L, Rimm DL. 2014. In situ tumor PD-L1 mRNA expression is associated with increased TILs and better outcome in breast carcinomas. *Clin Cancer Res.* 20:2773–2782. doi:10.1158/1078-0432.CCR-13-2702.

112. Cimino-Mathews A, Thompson E, Taube JM, Ye X, Lu Y, Meeker A, Xu H, Sharma R, Lecksel K, Cornish TC, et al. 2016. PD-L1 (B7-H1) expression and the immune tumor microenvironment in primary and metastatic breast carcinomas. *Hum Pathol*. 47:52–63. doi:10.1016/j.humpath.2015.09.003.
113. Nanda R, Chow LQ, Dees EC, Berger R, Gupta S, Geva R, Puztai L, Pathiraja K, Aktan G, Cheng JD, et al. 2016. Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 study. *J Clin Oncol*. 34:2460–2467. doi:10.1200/JCO.2015.64.8931.
114. Schmid P, Cruz C, Braiteh F, Eder J, Tolaney S, Kuter I, Nanda R, Chung C, Cassier P, Delord J-P, et al. Abstract 2986: atezolizumab in metastatic TNBC (mTNBC): long-term clinical outcomes and biomarker analyses. *Cancer Res*. 2017;77(suppl13):abstr2986. doi:10.1158/1538-7445.AM2017-2986.
115. Knudson KM, Hicks KC, Luo X, Chen JQ, Schlom J, Gameiro SR. 2018. M7824, a novel bifunctional anti-PD-L1/TGFbeta Trap fusion protein, promotes anti-tumor efficacy as monotherapy and in combination with vaccine. *Oncoimmunology*. 7:e1426519. doi:10.1080/2162402X.2018.1490854.
116. Ravi R, Noonan KA, Pham V, Bedi R, Zhavoronkov A, Ozerov IV, Makarev E, Artemov A, Wysocki PT, Mehra R, et al. 2018. Bifunctional immune checkpoint-targeted antibody-ligand traps that simultaneously disable TGFbeta enhance the efficacy of cancer immunotherapy. *Nat Commun*. 9:741. doi:10.1038/s41467-017-02696-6.
117. Mayer E, Wander S, Regan M, DeMichele A, Forero A, Rimawi MF, Ma CX, Anders CK, Huang Bartlett C, Koehler M, et al. 2018. Abstract OT3-05-11: palbociclib after CDK inhibitor and endocrine therapy (PACE): A randomized phase II study of fulvestrant versus palbociclib plus fulvestrant, with and without avelumab, for CDK inhibitor pre-treated HR+/HER2- metastatic breast cancer. *Cancer Res*. 78(suppl4):abstrOT3-05-11.
118. Salama L, Duerinck J, Four S, Awada G, Fischbuch L, Cremer J, Rogiers A, Neyns B. Safety of axitinib plus avelumab in patients with recurrent glioblastoma. *J Clin Oncol*. 2018;36(suppl15):abstr14082. doi:10.1200/JCO.2018.36.15\_suppl.e14082.
119. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeier U, Boyer M, Emri S, Manegold C, et al. 2003. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol*. 21:2636–2644. doi:10.1200/JCO.2003.11.136.
120. Hassan R, Thomas A, Nemunaitis J, Patel MR, Bennouna J, Chen F, Delord J-P, Dowlati A, Taylor MH, Powderly JD, et al. Avelumab in patients with previously treated mesothelioma: updated phase 1b results from the JAVELIN Solid Tumor trial. *J Clin Oncol*. 2018;36(suppl5):abstr166. doi:10.1200/JCO.2018.36.5\_suppl.166.
121. Alley EW, Lopez J, Santoro A, Morosky A, Saraf S, Piperdi B, van Brummelen E. 2017. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. *Lancet Oncol*. 18:623–630. doi:10.1016/S1470-2045(17)30169-9.
122. Mansfield AS, Roden AC, Peikert T, Sheinin YM, Harrington SM, Krco CJ, Dong H, Kwon ED. 2014. B7-H1 expression in malignant pleural mesothelioma is associated with sarcomatoid histology and poor prognosis. *J Thorac Oncol*. 9:1036–1040. doi:10.1097/JTO.0000000000000177.
123. Cedrés S, Ponce-Aix S, Zugazagoitia J, Sansano I, Enguita A, Navarro-Mendivil A, Martinez-Marti A, Martinez P, Felip E, Gangopadhyay N. 2015. Analysis of expression of programmed cell death 1 ligand 1 (PD-L1) in malignant pleural mesothelioma (MPM). *PLoS ONE*. 10:e0121071. doi:10.1371/journal.pone.0121071.
124. Okuno SH, Delaune R, Sloan JA, Foster NR, Maurer MJ, Aubry MC, Rowland KM, Soori GS, Nikcevic DA, Kardinal CG, et al. 2008. A phase 2 study of gemcitabine and epirubicin for the treatment of pleural mesothelioma: a north central cancer treatment study, N0021. *Cancer*. 112:1772–1779. doi:10.1002/cncr.23313.
125. Zucali PA, Ceresoli GL, Garassino I, De Vincenzo F, Cavina R, Campagnoli E, Cappuzzo F, Salamina S, Soto Parra HJ, Santoro A. 2008. Gemcitabine and vinorelbine in pemetrexed-pretreated patients with malignant pleural mesothelioma. *Cancer*. 112:1555–1561. doi:10.1002/cncr.23337.
126. Stebbing J, Powles T, McPherson K, Shamash J, Wells P, Sheaff MT, Slater S, Rudd RM, Fennell D, Steele JPC. 2009. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung Cancer*. 63:94–97. doi:10.1016/j.lungcan.2008.04.001.
127. Ceresoli GL, Zucali PA, De Vincenzo F, Gianoncelli L, Simonelli M, Lorenzi E, Ripa C, Giordano L, Santoro A. 2011. Retreatment with pemetrexed-based chemotherapy in patients with malignant pleural mesothelioma. *Lung Cancer*. 72:73–77. doi:10.1016/j.lungcan.2010.12.004.
128. Elbers J, Zuur C, Tesselar M, Lange C, Al-Mamgani A, Boer J. Radiotherapy with concurrent avelumab and cetuximab as primary treatment in patients with locally advanced squamous cell carcinoma of the head and neck: A phase-IB feasibility trial in patients unfit for cisplatin (NCT02938273). *J Clin Oncol*. 2018;36(suppl15):abstr18019. doi:10.1200/JCO.2018.36.15\_suppl.e18019.
129. Tao Y, Auferin A, Sun X, Sire C, Martin L, Bera G, Coutte A, Miroir J, Lafond C, Colin-Bataillou N, et al. Avelumab-cetuximab radiotherapy (RT) versus standards of care (SoC) in locally advanced squamous cell carcinoma of the head and neck (SCCHN): safety phase of the randomized trial GORTEC 2017-01 (REACH). *J Clin Oncol*. 2018;36(suppl15):abstr6076. doi:10.1200/JCO.2018.36.15\_suppl.6076.
130. Stein A, Binder M, Al-Batran S, Hinke A, Waberer L, Goekkurt E, Meyer T, Statovci D, Depenbusch R, Riera-Knorrenschild J, et al. Avelumab and cetuximab in combination with FOLFOX in patients with previously untreated metastatic colorectal cancer (MCRC): results of the safety run-in phase of the phase II AVETUX trial (AIO-KRK-0216). *J Clin Oncol*. 2018;36(suppl15):abstr3561. doi:10.1200/JCO.2018.36.15\_suppl.3561.
131. Tsao MS, Kerr KM, Kockx M, Beasley MB, Borczuk AC, Botling J, Bubendorf L, Chirieac L, Chen G, Chou T-Y, et al. PD-L1 immunohistochemistry comparability study in real-life clinical samples: results of Blueprint phase 2 project. *J Thorac Oncol*. 2018May22; Epub ahead of print. 13:1302–1311. doi: 10.1016/j.jtho.2018.05.013.
132. Hirsch FR, McElhinny A, Stanforth D, Ranger-Moore J, Jansson M, Kulangara K, Richardson W, Towne P, Hanks D, Vennapusa B, et al. 2017. PD-L1 Immunohistochemistry assays for lung cancer: results from phase 1 of the blueprint PD-L1 IHC assay comparison project. *J Thorac Oncol*. 12:208–222. doi:10.1016/j.jtho.2016.11.2228.