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

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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. 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, 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). 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 them use feasible for a wide variety of patients. 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. 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. ADCC is a demonstrated mechanism of action for several approved anticancer mAbs, including necitumumab, pertuzumab, cetuximab, rituximab, and trastuzumab. 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+ immune cells, 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. 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.
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). 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. 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. Although NK cells are robust effectors of avelumab-mediated ADCC, 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 antitumor activity whereas efficacy was highly dependent on CD4 and CD8T cell populations.

**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. 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 ≥ 3 infusion-related reactions (0.6%) was similar to that in ICI trials that used limited or single-term definitions of infusion-related reaction. 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. Premedication with acetaminophen and an antihistamine is required prior to the first 4 doses of avelumab, and then as needed based upon clinical judgement. 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
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 tumors.\(^\text{15,16,22}\) 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,\(^\text{23,24}\) as discussed in detail elsewhere.\(^\text{25}\) 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.\(^\text{26,27}\) 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 preclinical models.\(^\text{28,29}\)

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.\(^\text{16,20,22,30}\) To date, no disease-related parameters have been found to predict response to avelumab.\(^\text{8}\)

Tumor mutational burden (TMB), high microsatellite instability (MSI-H), mismatch-repair defect (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.\(^\text{31,32}\) Some cancer subtypes, such as MCPyV\(^\text{+}\) 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,\(^\text{32,33}\) 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.\(^\text{8}\) 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.\(^\text{8}\) 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).
| 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-naive GBM | 30 | Safety | Temozolomide, RT | Spain |
| NCT03502681                  | I/II  | M/ MSS CRC | 33 | MTD, PFS | Autologous DC vaccine | Australia |
| NCT03152565                  | I/II  | Stage II, III, IV DLBCL, 1st line | 28 | Immune-related toxicity | RCHOP | Netherlands |
| NCT03050554                  | II    | Early stage NSCLC, definitive therapy | 56 | Safety; DFS | SBRT | US |
| NCT03472560                  | II    | Gis-ineligible A/M NSCLC or UC | 80 | RR | Axitinib | US |
| NCT03375775                  | II    | Viral-associated cancers | 39 | 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; DFS | RT | US |
| NCT03317496                  | I/II  | LA or M NSCLC or UC | 80 | Safety; RR | Pemetrexed, carbo (NSCLC) or gem, cis (UC) | Multinational |
| NCT03395873                  | I/II  | AML, intensive chemotherapy-ineligible, 1st line | 15 | Safety | Decitabine | 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 | Azacitidine | US |
| NCT03434185                  | I      | Resectable clear-cell RCC | 40 | PR | Axitinib | Netherlands |
| NCT03494322                  | II     | R/M HNSCC | 130 | Safety; DFS at 24 weeks | Avelumab + cetuximab vs. avelumab monotherapy | US |
| NCT03270176                  | I      | Advanced solid tumors, A/M NSCLC after platinum | 61 | MTD; RR | Second mitochondrial activator of caspase mimetic | Canada |
| NCT03390595                  | II     | Gis-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 |
| NCT03324082                  | I/II   | LA or M UC, 1st line | 90 | Safety; RR | Avelumab + cis, gem vs. cis, gem | France |
| NCT03565991                  | I/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-IIL-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 |
| NCT03253898                  | I/II   | LA or M solid tumors | 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/II   | 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 | 24 | Safety; pCR | Carbo, paclitaxel, RT | US |
| NCT03483883                  | I      | M sarcomatoid RCC | 24 | Safety | Gemcitabine | US |
| NCT03440567                  | I/II   | R/R DLBCL or MCL | 39 | Safety; MTD | Avelumab + utomilumab, RICE (DLBCL) or avelumab + rituximab, ibrutinib (MCL) | US |
| 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/I   | Advanced solid tumors | 188         | Safety; CDB+ immune biomarkers | Utomilumab, PF-04518600, RT, cis | US |
| NCT03414658                | II    | Advanced HER2+ breast cancer | 100        | PFS         | Trastuzumab, vinorelbine, utomilumab | US2 |
| NCT02999087                | III   | LA HNSCC | 688        | PFS         | Avelumab + cetuximab, IMRT vs. cetuximab, IMRT | France |
| NCT03121114                | II    | R/R ovarian cancer | 29         | RR          | RT                          | US |
| NCT03147287                | II    | Advanced HR+, HER2+ breast cancer, previous CDK 4/6 inhibitor | 220        | PFS         | Avelumab + fulvestrant, palbociclib vs. fulvestrant vs. fulvestrant, palbociclib | US |
| NCT02951156                | III   | R/R DLBCL | 304        | Safety; RR  | Avelumab + utomilumab, rituximab, azacitadine, 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/I   | A/M NSCLC without targetable mutations | 130        | Safety; RR; DOR; PFS; OS | Axitinib, palbociclib | Multinational |
| NCT03390296                | I     | AML     | 138        | Safety; CR  | PF-04518600, utomilumab, azacitadine, glasdegib | US |
| NCT03390671                | I/I   | Resectable E/GC | 40         | pCR         | FLOT                        | UK |
| NCT02767063                | I/I   | CML on TKI > 2 years with complete cytogenetic response | 100        | Deep molecular response | Avelumab + TYK vs. TYK vs. TYK, pioglitazone | France |
| NCT02222922                | I     | Advanced solid tumors | 190        | Safety      | Avelumab + PF-06647020 vs. PF-06647020 | US, Spain |
| NCT03387098                | I/I   | Progressive pancreatic cancer after SOC | 173        | Safety; RR  | NANT pancreatic cancer vaccine, hANK cells, metronomic combination therapy | US |
| NCT03387085                | I/I   | Progressive TNBC after SOC | 79         | Safety; RR  | NANT TNBC vaccine, hANK cells, metronomic combination therapy | US |
| NCT03387111                | I/I   | Progressive SCC after SOC | 65         | Safety; RR  | NANT SCC vaccine, hANK cells, metronomic combination therapy | US |
| NCT03563157                | I/I   | 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); diffuse large B-cell lymphoma (DLBCL); disease control rate (DCR); dose-limiting toxicity (DLT); duration of response (DOR); esophageal/gastric carcinoma (E/GC); folic 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); 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. 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. 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.

**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 with multiple expansion cohorts. 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.

Across all dose levels, common treatment-related adverse events (TRAEs) of any grade occurred in ≥ 10% of patients, including fatigue (n = 21; 40%), influenza-like symptoms (n = 11; 21%), fever (n = 8; 15%), and chills (n = 6; 11%). 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. 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.

Avelumab was well tolerated as a single agent, with a safety profile similar to other anti-PD-1/PD-L1 agents. 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.

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. 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.

**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. In the U.S., incidence of MCC is 0.79 cases/100,000 people/year. 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. 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 mMCC were treated with avelumab. Patients were unscreened 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+ 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.\textsuperscript{55} 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.\textsuperscript{51} 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.\textsuperscript{52} 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%).\textsuperscript{20} Additionally, nonprogression of mMCC during treatment with avelumab has been shown to be associated with improvement in quality of life.\textsuperscript{53}

A similar cohort of patients with chemotherapy-refractory mMCC was treated with avelumab in a global expanded access program (NCT03089658).\textsuperscript{54} 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.\textsuperscript{55} The primary endpoint was durable response, defined as an objective response with a duration of ≥ 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 AE occurred. Efficacy was assessed in 29 patients with ≥ 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 ≥ 6 months was 83% (95% CI, 46%–96%). Avelumab in the first-line setting for mMCC once again outperformed chemotherapy based on contemporary data.\textsuperscript{52,56} 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.\textsuperscript{20,55} 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,\textsuperscript{57} 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.\textsuperscript{58}

Adjuvant cytotoxic chemotherapy is not associated with OS benefit in patients with node-positive MCC,\textsuperscript{46,59} but these patients are at high risk for relapse despite surgery and radiation therapy (RT).\textsuperscript{46} 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).\textsuperscript{50} 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 in urothelial tumors, and there is a strong immunogenic response against antigens that are recognized by host T cells.\textsuperscript{50}–\textsuperscript{52}–\textsuperscript{54}–\textsuperscript{56} Avelumab in patients with urothelial tumors has shown an OS of 51% (95% CI, 37%–65%) at 2 years, 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 ≥ 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+ tumors. Thirteen patients (29.5%) had PD-L1+ tumors and 7/8 responding patients had PD-L1+ tumors. The confirmed ORR was 53.8% in PD-L1+ tumors (7/13) and 4.2% in PD-L1- 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,54,65 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%).15 Grades 3–4 TRAEs only occurred in 3 patients (6.8%) and included asthenia, AST elevation, creatine phosphokinase elevation, and decreased appetite. Nine patients (20.3%) 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.66–68 All patients were followed for ≥ 6 months (median of 13.6 months) as of data cutoff on September 2016.68 The ORR was 17.3%, with 11 (4.4%) CRs, which is similar to other ICIs in this setting.38,69–71 Response was ongoing in 34 of 43 patients (79.1%) and median DOR was 20.1 months (95% CI, 9.7–70.0). DOR with avelumab compared very favorably to that of historical second-line chemotherapy, which is about 5–7 months.64,65 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 ≥ 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.67 One patient developed treatment-related pneumonitis resulting in death.

PD-L1 positivity, defined as ≥ 5% staining by IHC in tumor cells, was found in 33% of patients.67 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+ tumors. In PD-L1+ (≥ 5% tumor cell staining) and PD-L1- patients the ORR was 25.6% and 13.7%, respectively.68 An association between increased mutational load and improved outcome has been reported with other anti-PD-1/PD-L1 inhibitors.38,69,72,73 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.67 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.74 Cisplatin-eligible patients will all receive avelumab plus methotrexate-vinblastine-adracycin-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,67 avelumab will be evaluated as first-line therapy in metastatic cisplatin-ineligible patients in a phase II randomized, multicenter trial (NCT03390595).75 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.76 Both PD-L1+ and PD-L1 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.16,77 Patients were unsolicited 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 ≥ 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 ≥ 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+ and 20 were PD-L1−. 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). Preclinical 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. 

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 ≥ 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. 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. Results may have been confounded by a high crossover rate. Improvements in OS were observed in populations with moderate-to-high (≥ 50%) and high (≥ 80%) PD-L1 expression. Another phase III trial is currently underway to evaluate avelumab in PD-L1+ 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+ and ALK− previously treated advanced NSCLC. Patients with ALK+ NSCLC received avelumab plus crizotinib 250 mg p.o. BID, while patients with ALK− NSCLC received avelumab plus lorlatinib 100 mg daily. At data cutoff on Oct 27, 2017, 12 ALK− patients and 28 ALK+ patients had been treated, but median follow-up was not specified. DLTs occurred in 41.7% of ALK− patients, which included increases in ALT and AST, febrile neutropenia, hepatitis, QT prolongation, and rash. No DLTs occurred in ALK+ patients. The ORR in ALK− patients was 16.7% (95% CI, 2.1–48.4; PR in 2 patients), and 46.4% of ALK+ 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+ advanced NSCLC and will be further evaluated in treatment-naive 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. 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. The DOR with ICIs is superior to that of chemotherapy agents such as dacarbazine, which only yields an ORR of < 10%, Responses were only seen in patients with PD-L1+ tumors. 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. 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%). Only 4 patients (7.8%) had a grade ≥ 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. 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. 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 ≥ 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 ≥ 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. 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 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. In the JAVELIN Renal 101 study, an assessment of PD-L1 expression on tumor and immune cells found a correlation between intratumor PD-L1 expression (≥1% staining of tumor cells by IHC) and the likelihood of achieving an objective response after receiving avelumab plus axitinib. 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. 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. 100 TRAEs of any grade occurred in 56.7% of patients, the most common being infusion-related reactions (12.7%) and fatigue (10.0%). Grade ≥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 ≥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. 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.101

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.102 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.103 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.104 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 IIb expansion cohort of JAVELIN Solid Tumor, 124 patients with previously treated, recurrent, or refractory advanced EOC were treated with avelumab.105 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 ≥1% tumor cell staining cutoff by IHC, 77% of patients were PD-L1+, with an ORR of 12.3% (95% CI, 5.1–23.7) vs. 5.9% in PD-L1+ 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. 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+ T cells among TILs compared with either agent as monotherapy. These effects were associated with an increased rate of CRs and improved survival, providing the rationale for combining avelumab with chemotherapy agents. 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. 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 patients with platinum-resistant/refractory recurrent 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+ breast cancer. High TIL levels are associated with increased PD-L1 expression in tumor cells and TILs in the JAVELIN Solid Tumor trial, 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+/HER2- metastatic breast cancer.

**Avelumab for glioblastoma**

An ongoing phase II trial is investigating avelumab plus axitinib, a selective VEGFR inhibitor, in patients with recurrent glioblastoma (NCT03291314). 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 extended 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.119 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.120 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+ tumors (n = 16) and PD-L1- tumors (n = 27) (≥ 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 a had a median DOR of 12 months.121 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),122,123 the PD-L1+ 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.120 Compared to historical studies of non-approved second-line chemotherapy agents with a median OS of 5.7–10.9 months,124,127 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).128 At time of data analysis, an interim safety analysis 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 × 2 Gy) concurrent with cetuximab (loading dose 400 mg/m² in week 1, 250 mg/m² in weeks 1–7) and avelumab (10 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 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.129 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 mg/m² every 3 weeks. Cohort 2, made up of patients unfit to receive cisplatin, instead received cetuximab 400 mg/m² on day –7 and 250 mg/m² 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 ≥ 3 doses of cetuximab and ≥ 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).130 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.20,37,39 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.35 Among 1738 patients in the phase I JAVELIN Solid Tumor and phase II JAVELIN Merkel 200 clinical trials, a minority of patients experienced grade ≥ 3 TRAEs or irAEs (Table 3), and discontinuation was uncommon.19 Grade ≥ 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 ≥ 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                                      | 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)    |
| Hypothyroid                                | 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                                        | 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       |
| Collitis                                    | 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 1 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,

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.

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