Industry corner: perspectives and controversies

Avelumab: clinical trial innovation and collaboration to advance anti-PD-L1 immunotherapy

Cancer development and progression are characterised by evasion of immune responses, including tumour escape mediated through immune checkpoint pathways [1–4]. Programmed death ligand-1 (PD-L1) is a suppressive immune checkpoint ligand that binds two receptors expressed on T cells—programmed death-1 (PD-1) and B7.1 (CD80)—to inhibit T-cell activation, proliferation, and cytotoxicity [5–9]. PD-L1 expression can be upregulated on various immune cells, including antigen-presenting cells (APCs), as a physiological mechanism for regulating immune responses and suppressing T-cell activity [10]. A second checkpoint pathway ligand for PD-1, PD-L2, is expressed on various immune cells and may play a role in immune homeostasis [11, 12]. By overexpressing PD-L1, cancer cells exploit the PD-1/PD-L1 pathway to promote an immunosuppressive environment and allow tumour growth [5, 13]. Blocking PD-L1 inhibitory signals can restore T-cell antitumour activity and thus represents a key therapeutic strategy [13, 14]. Five checkpoint inhibitors are currently approved by the US Food and Drug Administration (FDA) for the treatment of cancer, including an anti-CTLA-4 antibody (ipilimumab), anti-PD-1 antibodies (pembrolizumab and nivolumab), and anti-PD-L1 antibodies (atezolizumab and avelumab).

Avelumab (MSB0010718C) is a human immunoglobulin G1 (IgG1) anti-PD-L1 monoclonal antibody [15] with the potential to utilise both adaptive and innate immune mechanisms to destroy cancer cells [5, 15, 16]. Its ability to induce innate immune mechanisms against cancer cells, shown in preclinical studies [17], makes avelumab unique among anti-PD-L1 or anti-PD-1 antibodies approved or in advanced clinical development. Avelumab is being evaluated in the international JAVELIN clinical trial programme across more than 16 different tumour types, both as monotherapy and in combination [17]. This programme is sponsored by an alliance between two global companies, Merck KGaA, Darmstadt, Germany, and Pfizer, Inc., New York, NY. Evidence of promising antitumour activity and manageable adverse events has been demonstrated for multiple advanced malignancies [18–24], leading to accelerated approval of avelumab by the US FDA in March 2017 for the treatment of metastatic Merkel cell carcinoma [25]. Here, we provide an overview of avelumab's development from discovery to registrational studies in multiple tumour types.

Discovery and mechanism of action

Avelumab was developed within Merck laboratories in 2006 based on a strategic vision for cancer immunotherapy as a pillar of the Merck oncology research and development programme. Preclinical studies of avelumab commenced in 2009, with more formal preclinical development starting in 2011 as part of Merck's translational innovation platform in immuno-oncology (Figure 1).

Avelumab is thought to specifically bind to PD-L1, preventing the interaction between PD-L1 and the inhibitory T-cell receptor PD-1. PD-L1 blockade removes the suppression of T-cell activity, resulting in T-cell-mediated, adaptive antitumour immune responses, which can be measured by the effect of avelumab on interferon-γ release [26]. In addition, avelumab inhibits the interaction of PD-L1 with a second inhibitory receptor, B7.1, which may be expressed on APCs and T cells [9]. Thus, avelumab may also potentiate T-cell reactivation and cytokine production by inhibiting the interaction with PD-1 and B7.1 on T cells with PD-L1 on APCs in the tumour microenvironment or lymph node [27]. Avelumab does not disrupt the interaction between PD-L1 and PD-L2, thereby allowing continuity of PD-L2-mediated homeostasis [12]. Unlike other anti-PD-L1 or anti-PD-1 antibodies, avelumab has a wild-type IgG1 crystallizable fragment (Fc) region, which enables avelumab to engage with Fc-γ receptors on natural killer cells and induce tumour-directed antibody-dependent cell-mediated cytotoxicity (ADCC) *in vitro* [16, 28]. ADCC is a demonstrated mechanism of action for several approved anticancer monoclonal antibodies, including cetuximab, rituximab, and trastuzumab [29]. Anti-PD-1 IgG4 antibodies (e.g. nivolumab or pembrolizumab) and engineered anti-PD-L1 IgG1 antibodies (e.g. atezolizumab or durvalumab) have been developed to minimise or disable ADCC, based on a theoretical potential for ADCC to deplete activated T cells [30–32]. Importantly, preclinical and clinical studies showed minimal changes in immune cell subsets with avelumab treatment [26, 33]. PD-L1 blockade with avelumab therefore has the potential to both enhance tumour-specific effector T cell activity and induce ADCC-mediated lysis of tumour cells, representing a potential unique dual mechanism of action compared with other anti-PD-1/PD-L1 antibodies (Figure 2).

From first human studies to breakthrough status

The first-in-human trial of avelumab, which began in January 2013, has been carried out in partnership with the US National Cancer Institute. This phase 1 study, JAVELIN Solid Tumor (NCT01772004), evolved in size and scope to become a large dose-escalation and multicohort dose-expansion trial [15, 17] and is described in detail in the next section. In parallel, the JAVELIN Solid Tumor JPN (NCT01943461) trial, which included a dose-escalation cohort in patients with advanced

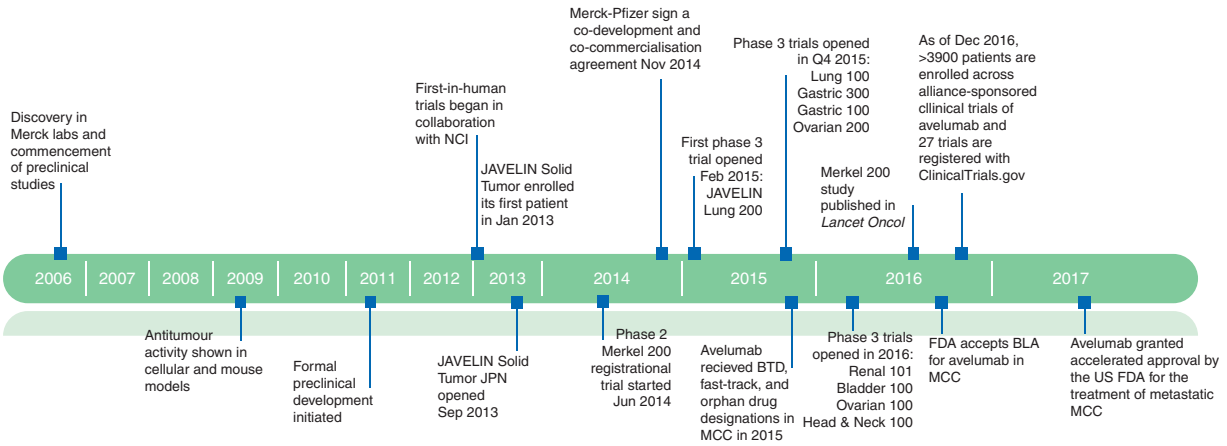

Figure 1. Avelumab timeline from discovery to Merck–Pfizer Alliance, breakthrough status, and phase 3 development. BLA, Biologics License Application; BTD, breakthrough therapy designation; FDA, US Food and Drug Administration; MCC, Merkel cell carcinoma; NCI, US National Cancer Institute.

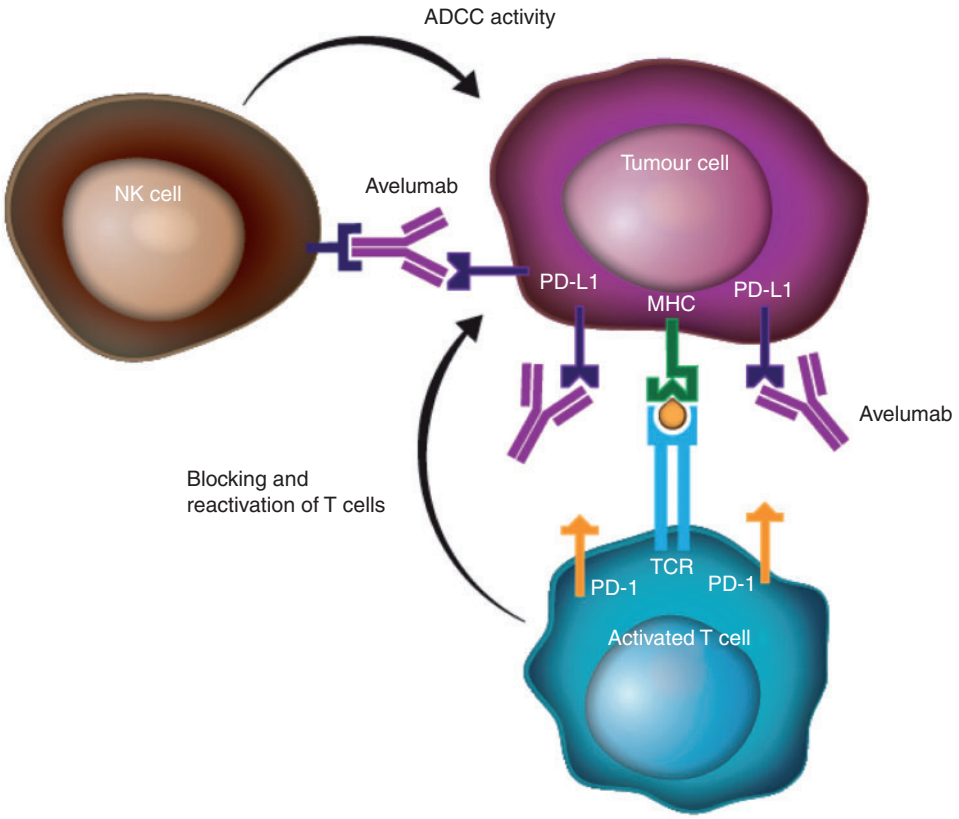

Figure 2. Avelumab's dual mechanism of action. Avelumab is a human IgG1 monoclonal antibody that specifically binds to PD-L1, preventing the interaction between PD-L1 and the inhibitory T-cell receptor, PD-1. PD-L1 blockade removes the suppression of T-cell activity, resulting in T-cell-mediated, adaptive antitumour immune responses. In addition, avelumab has a wild-type IgG1 Fc region that may enable NK cell-mediated ADCC. Avelumab therefore has the potential to utilise both adaptive and innate immune mechanisms to destroy cancer cells. ADCC, antibody-dependent cell-mediated cytotoxicity; Fc, crystallisable fragment; IgG1, immunoglobulin G1; MHC, major histocompatibility complex; NK, natural killer; PD-1, programmed death-1; PD-L1, programmed death ligand-1; TCR, T-cell receptor.

tumours and a dose-expansion cohort in gastric cancer, was opened in Japan in September 2013 [17, 34].

The first phase 2 study of avelumab, JAVELIN Merkel 200 (NCT02155647), was launched in July 2014 and enrolled patients with Merkel cell carcinoma (MCC) progressed after chemotherapy. MCC is a rare, aggressive, and highly immunogenic skin cancer [35–38]. Patients with advanced-stage MCC have a 5-year overall survival rate ranging from 0% to 18% [39, 40] and a

mortality rate higher than that seen in patients with melanoma [41]. Patients with advanced MCC are typically treated with chemotherapy; however, there is no established standard of care [42, 43] and responses are seldom durable [44]. In 2015, preliminary efficacy and safety data from JAVELIN Merkel 200 led to avelumab receiving breakthrough, fast-track, and orphan-drug designations from the FDA and a positive opinion for orphan-drug status from the European Medicines Agency. Recently published data from the primary analysis of JAVELIN Merkel 200 showed that patients with distant metastatic MCC treated with avelumab ($n = 88$) had an objective response rate of 31.8% [95.9% CI (exact repeated), 21.9–43.1], including 9.1% achieving complete remission, with responses ongoing in 82% of responders at the time of analysis [6-month durable response rate of 29% (95% CI, 20–39)] and a 6-month progression-free survival (PFS) rate of 40% (95% CI, 29–50), demonstrating the efficacy of avelumab in this aggressive disease [24]and leading to FDA approval of avelumab in this indication [25].

Focus on JAVELIN Solid Tumor

JAVELIN Solid Tumor is an international, multicohort, open-label, single-arm, multiple-ascending-dose phase 1 study that is one of the largest phase 1 studies carried out to date (>1700 patients enrolled) [46]. This study has evolved beyond its initial design to comprise a dose-escalation part, plus 4 primary expansion cohorts, 8 secondary expansion cohorts, and 4 efficacy expansion cohorts in 12 tumour types (Figure 3) [17, 46]. Its primary objectives are twofold: (i) assess the safety and tolerability and determine the maximum tolerated dose (MTD) of avelumab in patients with metastatic or locally advanced solid tumours; and (ii) evaluate best overall response (BOR) according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 [47] in efficacy expansion cohorts. Secondary and exploratory objectives include assessment of BOR and PFS by RECIST v1.1, overall survival (OS), and clinical activity by modified immune-related response criteria (irRC) [48]; characterization of pharmacokinetics (PK), target occupancy, and immunogenicity; and evaluation of PD-L1 expression and other potential biomarkers. In all cohorts, patients have been enrolled irrespective of PD-L1 expression status.

The dose-escalation part of the trial used a 3 + 3 design, which established the dose level (10 mg/kg) and administration schedule (Q2W) for further studies based on observed safety, PK, and pharmacodynamics data. Of 53 patients enrolled in the dose-escalation part who received avelumab doses of 1–20 mg/kg Q2W, one dose-limiting toxicity occurred at 20 mg/kg in a patient with thymic cancer, and the MTD was not reached. Avelumab exhibited a linear PK profile over the investigational dose range, with maximum plasma concentrations reached within 1 h from the end of infusion and a half-life of ~4 days seen

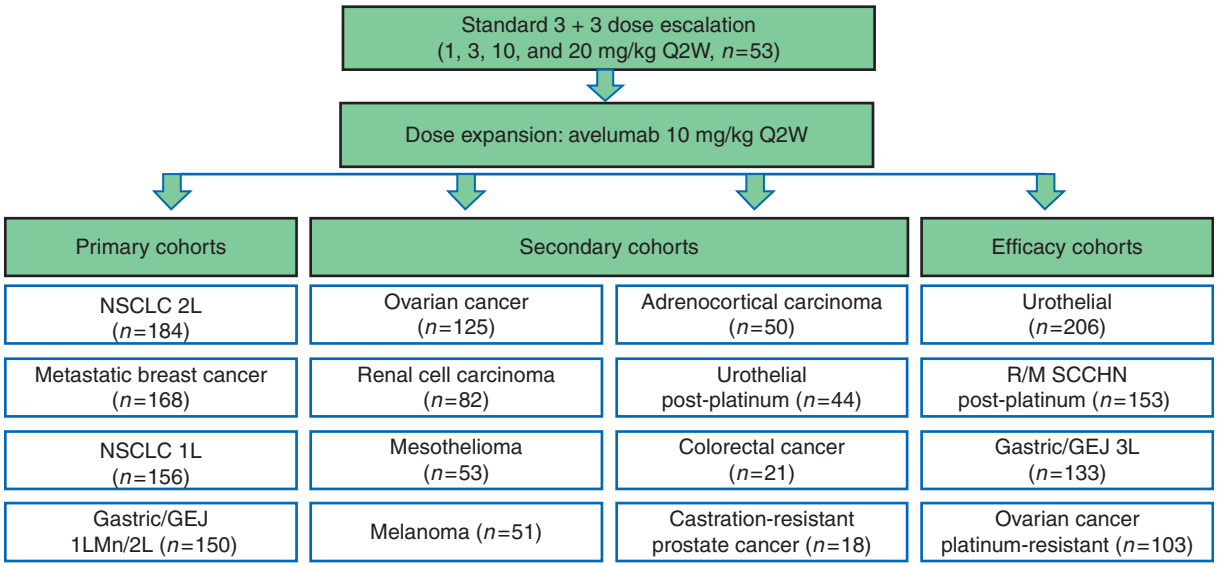

Figure 3. Study design for JAVELIN Solid Tumor: an international, phase 1, multicohort dose-escalation and dose-expansion trial (number of patients enrolled as of December 2016 is shown). The dose-escalation part tested four dose levels of avelumab administered as a 1-hour intravenous infusion Q2W using a standard 3 + 3 design. The 10-mg/kg dose level was selected for the dose-expansion part. The four primary dose-expansion cohorts enrolled patients with 2L NSCLC (post-platinum doublet), 1L NSCLC (previously untreated metastatic or recurrent), gastric or GEJ adenocarcinoma (previously treated with chemotherapy with or without progression for 1L Mn or 2L treatment), and metastatic breast cancer (refractory to or progressive after standard-of-care therapy). Efficacy cohorts comprise patients with urothelial carcinoma (progressed after ?1 line of platinum-based therapy or platinum ineligible), R/M SCCHN (progressed after ?1 line of platinum-based therapy or platinum ineligible), gastric or GEJ adenocarcinoma (progressing after treatment with a 1L chemotherapy combination and a 2L ramucirumab regimen), and ovarian cancer (platinum resistant and previously treated with liposomal doxorubicin). Eligible patients for the eight secondary cohorts and additional details for the primary and efficacy cohorts are listed in Table 1. 1L, first line; 2L, second line; 3L, third line; GEJ, gastro-oesophageal junction; Mn, maintenance; NSCLC, non-small-cell lung cancer; Q2W, every 2 weeks; R/M, recurrent/metastatic, SCCHN, squamous cell carcinoma of the head and neck.

Table 1. Key eligibility criteria for the JAVELIN Solid Tumor phase 1 trial

Inclusion criteria	Exclusion criteria
• Age ≥18 years • Histologically or cytologically confirmed locally advanced or metastatic advanced solid tumour • Biopsy material required (archival tissue acceptable if patient could not provide fresh or recent biopsy) • ECOG performance status score of 0–1 at study entry • Estimated life expectancy ≥3 months • Measurable lesion by RECIST v1.1 (except castration-resistant prostate cancer or metastatic breast cancer) • Adequate haematologic, hepatic, and renal function • Signed written informed consent ***Primary expansion cohorts (planned enrolment)*** **NSCLC second line (*n*=150)** • Stage IIIB or stage IV NSCLC progressed after one line of platinum-containing doublet chemotherapy **NSCLC first line (*n*=150)** • Stage IV or recurrent NSCLC • No activating EGFR mutation or ALK rearrangement • No prior treatment of metastatic or recurrent disease **Gastric and GEJ adenocarcinoma (*n*=150)** • Unresectable locally advanced or metastatic adenocarcinoma of the stomach or GEJ, treated with first-line chemotherapy combination with or without disease progression • No prior trastuzumab treatment (HER2-positive status allowed) **Breast cancer (*n*=150)** • Locally advanced or metastatic breast cancer refractory to or progressive after standard-of-care therapy • ≤3 prior lines of therapy for metastatic disease • Prior taxane and anthracycline treatment, unless contraindicated ***Secondary expansion cohorts (planned enrolment)*** **Ovarian cancer (*n*=120)** • Recurrent or refractory, stage III-IV epithelial ovarian, fallopian tube, or peritoneal cancer progressed following adjuvant therapy or therapy for metastatic disease **Renal cell carcinoma (*n*=20) with first-line expansion (*n*=60)** • Metastatic RCC with a clear-cell component **Adrenocortical carcinoma (*n*=50)** • Metastatic ACC • ≥1 line of systemic therapy for metastatic disease (≥1 must be platinum based) • Patients receiving mitotane at enrolment were permitted to receive ongoing mitotane on study **Mesothelioma (*n*=50)** • Mesothelioma with unresectable disease progressed after either a platinum–pemetrexed-containing regimen or a platinum-containing regimen followed by pemetrexed after disease progression **Melanoma (*n*=50)** • Stage IIIc or IV unresectable melanoma progressed after ≥1 prior standard therapy for metastatic disease **Urothelial carcinoma (*n*=50)** • Locally advanced or metastatic transitional cell carcinoma of the urothelium • Either ineligible for cisplatin-based chemotherapy *or* progressed after ≥1 platinum-containing regimen	• Concurrent treatment with an anticancer treatment or other non-permitted drug • Prior therapy with any drug targeting T-cell coregulatory proteins (patients with metastatic melanoma who had received prior treatment with an anti-CTLA-4 antibody were allowed) • Concurrent systemic therapy with corticosteroids or other immunosuppressive agents or use of any investigational drug within 28 days before starting trial drug; short-term administration of systemic steroids (for allergic reactions or management of immune-mediated adverse events) while on study is allowed • Active or history of central nervous metastases • Previous malignant disease (other than primary malignancy) within the last 5 years, except basal or squamous cell carcinoma of the skin or cervical carcinoma *in situ* • Prior organ transplantation, including allogenic stem-cell transplantation • Known history or testing positive for HIV/AIDS, HBV, or HCV (including acute and chronic infection) • Active or history of any autoimmune disease or immune deficiencies (patients with type 1 diabetes, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment were eligible) • Known monoclonal antibody hypersensitivity, history of anaphylaxis, or uncontrolled asthma • Persisting toxicity related to prior therapy that was grade >1 according to NCI CTCAE v4.0; grade ≤2 sensory neuropathy was allowed • Clinically significant cardiovascular disease, or other diseases that in the investigator's opinion may influence the patient's tolerance of trial treatment

Continued

Table 1. *Continued*

Inclusion criteria	Exclusion criteria
Castration-resistant prostate cancer (*n*=20) • Asymptomatic metastatic CRPC or minimally symptomatic with objective evidence of disease with stable, ongoing adequate testosterone suppression • Additional androgen blockade or treatment with an antiandrogen receptor was permitted **Colorectal cancer (*n*=20)** • Recurrent or refractory metastatic CRC progressed after therapy containing oxaliplatin/fluoropyrimidine and/or irinotecan/fluoropyrimidine and, if eligible, cetuximab and bevacizumab ***Efficacy expansion cohorts (planned enrolment)*** **Urothelial carcinoma (*n*=200)** • Locally advanced or metastatic transitional cell carcinoma of the urothelium • Either ineligible for cisplatin-based chemotherapy *or* progressed after treatment with ≥1 platinum-containing regimen **Head and neck cancer (*n*=150)** • Recurrent or metastatic SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx progressed or recurrent within 6 months of the last dose of platinum-based chemotherapy given in the adjuvant, primary, recurrent, or metastatic setting, *or* platinum ineligible **Gastric and GEJ adenocarcinoma (*n*=150)** • Unresectable locally advanced or metastatic adenocarcinoma of the stomach or GEJ progressed after two lines of chemotherapy, including a ramucirumab-containing regimen in the second-line setting **Ovarian cancer, platinum resistant (*n*=100)** • Confirmed, platinum-resistant (progression within 6 months of platinum-based therapy), stage III and IV epithelial ovarian, fallopian tube, or peritoneal cancer • ≥1 line of prior platinum-based chemotherapy regimen and prior liposomal doxorubicin (monotherapy or combination)	

Target enrolment in expansion cohorts is shown.
ACC, adrenocortical carcinoma; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; GEJ, gastro-oesophageal junction; HBV, hepatitis B virus; HCV, hepatitis C virus; HER2, human epidermal growth factor 2; HIV, human immunodeficiency virus; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria In Solid Tumors; SCCHN, squamous cell carcinoma of the head and neck.

at the highest doses [15]. Analysis of patient samples showed that avelumab 10 mg/kg treatment resulted in >90% target occupancy at the end of the 2-week dosing interval [15].

Following the dose-escalation part, 16 expansion cohorts were opened through stepwise protocol amendments and based on preliminary data analyses (Figure 3; Table 1). Tumour types were selected based on high unmet need, evidence of PD-L1 overexpression, and evidence for susceptibility to cancer immunotherapy, including in the JAVELIN Solid Tumor trial itself. In selected cohorts, planned enrolment was increased to further characterise clinical activity. The size of the four primary cohorts ($n = 150$) was chosen to explore the safety and efficacy of avelumab in specific indications, including subgroups defined by PD-L1 expression. The 4 efficacy cohorts included a primary endpoint of BOR adjudicated by blinded independent review.

Available safety data indicate that avelumab is well tolerated and has a safety profile that is broadly consistent with other immune checkpoint inhibitors [24, 46, 49, 50]. Incidences of grade ≥3 treatment-related adverse events, grade ≥3 immune-related and treatment-related adverse events, and discontinuations related to avelumab have been relatively low (9.5%, 1.5%, and 6.1%, respectively; $n = 1300$) [46]. Following early observations of infusion-related reactions, subsequent cases were assessed as an adverse event of special interest, and a mandatory premedication regimen of paracetamol (acetaminophen) and diphenhydramine was implemented. Across tumour types, infusion-related reactions with avelumab have generally been low grade, occurred after the first or second infusion, and rarely led to discontinuation [46].

Table 2. Ongoing sponsored or collaborative clinical trials of avelumab

ClinicalTrials.gov Identifier	Short title	Phase	Disease	Intervention	Start date
NCT01772004	JAVELIN Solid Tumor	Phase 1	Advanced solid tumours	Monotherapy (dose escalation and expansion)	January 2013
NCT01943461	JAVELIN Solid Tumor JPN	Phase 1	Advanced solid tumours	Monotherapy (dose escalation and expansion)	September 2013
NCT02155647	JAVELIN Merkel 200	Phase 2	Metastatic Merkel cell carcinoma	Monotherapy	January 2014
NCT02395172	JAVELIN Lung 200	Phase 3	NSCLC second line	Monotherapy versus docetaxel	March 2015
NCT02576574	JAVELIN Lung 100	Phase 3	NSCLC first line (PD-L1+ tumours)	Monotherapy versus platinum doublet	October 2015
NCT02493751	JAVELIN Renal 100	Phase 1	Renal cell carcinoma first line	Combination with axitinib (dose finding and expansion)	October 2015
NCT02554812	JAVELIN Medley	Phase 1b/2	Advanced solid tumours	Combination with other cancer immunotherapies (dose finding and expansion)	November 2015
NCT02584829	—	Phase 1/2	Metastatic Merkel cell carcinoma	Localised radiation therapy or recombinant interferon-β and avelumab±cellular adoptive immunotherapy	November 2015
NCT02584634	JAVELIN Lung 101	Phase 1/2	NSCLC first line	Combination with crizotinib or PF06463922 (lorlatinib)	December 2015
NCT02625623	JAVELIN Gastric 300	Phase 3	Gastric or gastro-oesophageal junction adenocarcinoma third line	Monotherapy avelumab+BSC versus paclitaxel or irinotecan+BSC or BSC alone	December 2015
NCT02625610	JAVELIN Gastric 100	Phase 3	Gastric or gastro-oesophageal junction adenocarcinoma first line—switch maintenance	Maintenance avelumab monotherapy versus continuation of chemotherapy following chemotherapy induction	December 2015
NCT02580058	JAVELIN Ovarian 200	Phase 3	Ovarian cancer second line (platinum-resistant or refractory cancer)	Monotherapy versus combination with PLG versus PLG alone	December 2015
NCT02603419	JAVELIN Hodgkins	Phase 1	Hodgkin lymphoma second line	Monotherapy (dose finding)	March 2016
NCT02684006	JAVELIN Renal 101	Phase 3	Renal cell carcinoma first line	Combination with axitinib versus sunitinib	March 2016
NCT02603432	JAVELIN Bladder 100	Phase 3	Urothelial carcinoma first line	Maintenance combination with BSC versus BSC alone	April 2016
NCT02718417	JAVELIN Ovarian 100	Phase 3	Ovarian cancer first line	Combination with and/or following chemotherapy	May 2016
NCT02938273	—	Phase 1	LA SCCHN first line	Bioimmunoradiotherapy (avelumab+ cetuximab+ radiotherapy)	October 2016
NCT02943317	—	Phase 1	Recurrent or resistant epithelial ovarian cancer	Combination with defactinib	October 2016
NCT02915523	—	Phase 1b/2	Epithelial ovarian cancer	Monotherapy versus combination with entinostat	October 2016
NCT02912572	—	Phase 2	MSS, MSI-H, and POLE-mutated recurrent or persistent endometrial cancer	Monotherapy	October 2016
NCT02875613	—	Phase 2	R/M nasopharyngeal cancer	Monotherapy	October 2016
NCT02952586	JAVELIN Head and Neck 100	Phase 3	LA SCCHN first line	Combination with SoC CRT versus SoC CRT	November 2016
NCT02951156	JAVELIN DLBCL	Phase 1b followed by phase 3	Refractory/relapsed DLBCL	Combination with regimens that include an immune agonist, epigenetic modulator, CD20 antagonist, and/or conventional chemotherapy	December 2016

Continued

Table 2. *Continued*

ClinicalTrials.gov Identifier	Short title	Phase	Disease	Intervention	Start date
NCT02953561	—	Phase 1/2	Refractory/relapsedacute myeloid leukaemia	Combination with 5-azacytidine	January 2017
NCT02968940	—	Phase 2	IDH-mutant glioblastoma	Combination with hypofractionated radiation therapy	January 2017

Source: ClinicalTrials.gov (13 December 2016, last date accessed).
BSC, best supportive care; DLBCL, diffuse large B-cell lymphoma; IDH, isocitrate dehydrogenase; LA, locally advanced; MSI-H, microsatellite-instability-high; MSS, microsatellite-stable; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand-1; PLG, pegylated liposomal doxorubicin; POLE, DNA polymerase ϵ; R/M, recurrent/metastatic; SCCHN, squamous cell carcinoma of the head and neck; SoC CRT, standard-of-care chemoradiotherapy.

Initial efficacy results showed that avelumab is associated with early responses (within 6 weeks) and durable responses across a range of tumour types, including non-small-cell lung cancer (NSCLC), mesothelioma, urothelial carcinoma, gastric cancer, ovarian cancer, metastatic breast cancer, renal cell carcinoma, adrenocortical carcinoma, and Merkel cell carcinoma [18–24]. Additional cohorts of patients with urothelial, ovarian, or gastric cancer were opened following preliminary efficacy seen in those tumour types, adding to the robustness of data obtained from the JAVELIN Solid Tumor trial to inform phase 3 development.

Biomarker studies

JAVELIN Solid Tumor and other clinical trials of avelumab have evaluated disease-specific biomarkers and prognostic factors in relation to efficacy endpoints. Subgroup assessments include efficacy based on key baseline patient and disease characteristics 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 MCPyV status in MCC [18, 19, 21, 22, 24].

Tumour PD-L1 expression has been examined as a specified secondary endpoint during avelumab studies. Testing has been carried out by immunohistochemistry using a proprietary assay (Dako, Carpinteria, CA) based on an anti-PD-L1 antibody clone (73-10) under license of Merck KGaA. Although potential differences in efficacy based on PD-L1 expression have been seen in some tumour types, durable efficacy has also been seen in PD-L1–negative subgroups. In patients with Merkel cell carcinoma, responses were seen regardless of PD-L1 expression status and MCPyV status [24]. Data from several cohorts of the JAVELIN Solid Tumor trial did not identify any disease-related parameter associated with response to avelumab, although a potential trend for greater activity in patients with PD-L1+ tumours was observed in NSCLC and metastatic urothelial carcinoma [18, 19]. However, available data remain inconclusive, and studies are ongoing to further investigate the potential role of PD-L1 as a predictive biomarker for avelumab clinical activity.

Merck and Pfizer alliance: from monotherapy to combination trials

The global strategic alliance between Merck and Pfizer was announced on 17 November 2014, with the aim of advancing the development of avelumab and anti-PD-L1 immunotherapy, and bringing together a combined pipeline and correlative research activities. In addition to the first three trials of avelumab described above, five further phase 1/2 trials and eight phase 3 trials have been initiated by the alliance and collaborators (Table 2). The phase 3 programme includes study designs distinct from trials of other immune checkpoint inhibitors, including assessment of avelumab as maintenance therapy after first-line chemotherapy for urothelial, ovarian, or gastric cancer, and in combination with standard therapy for ovarian cancer or renal cell carcinoma.

The success of the JAVELIN Solid Tumor trial encouraged the initiation of a similar dose-finding and expansion study of avelumab-based combination therapy. JAVELIN Medley (NCT02554812) is a phase 1b/2 trial of avelumab in combination with other cancer immunotherapies [18]. Currently active cohorts receive avelumab with anti-4-1BB agonist antibody (utomilumab; PF-05082566), anti-OX40 antibody (PF-04518600), or anti-macrophage colony-stimulating factor antibody (PD-0360324), or a triplet regimen (avelumab/anti-4-1BB/anti-OX-40; Table 2). Expansion cohorts will be opened based on promising early data. The alliance has also entered into partnerships with Debiopharm, Verastem, Transgene, Vaccinex, and Syntax to study other avelumab-based combinations, and Merck is studying avelumab in combination with NHS-IL12 (NCT02994953). The Merck–Pfizer Alliance will continue in its aim to advance immunotherapy and to fulfil unmet clinical needs for patients with some of the most intractable types of advanced cancers.

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KC and VKC are employees of EMD Serono, Inc. VKC holds stock in Bristol-Myers Squibb. DSAN is an employee of Pfizer, Inc., and holds stock in Pfizer, Inc., Peloton Therapeutics, Bristol-Myers Squibb, Amgen, Array BioPharma, Exelixis, GlaxoSmithKline, and Merck.

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