Avelumab: is it time to get excited?

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1. Introduction

Avelumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody that is designed to specifically bind programmed death-ligand 1 (PD-L1) and block the immune-inhibitory interaction with its cognate receptor, programmed death-1 (PD-1), as well as with B7.1 (CD80) on dendritic cells and other immune cells. Disruption of the PD-1/PD-L1 axis obstructs an important immunosuppressive mechanism within the tumor microenvironment (TME), thereby reinvigorating antitumor T-cell responses. Anti-PD-1/PD-L1 blockade represents a breakthrough for cancer immunotherapy and has led to the approval of several anti-PD-1/PD-L1 agents by the U.S. Food and Drug Administration (FDA) across several cancer subtypes since 2014. Among the currently FDA-approved PD-1/PD-L1 agents, avelumab has unique due to its native crystallizable fragment (Fc) region which has demonstrated, in preclinical and ex vivo studies, augmented tumor killing via antibody-dependent cell-mediated cytotoxicity (ADCC) mediated by interaction between the Fc domain of avelumab and CD16 (FcγRIII) on natural killer (NK) cells [1–3]. If confirmed in vivo, this dual mechanism of action suggests that avelumab has the capacity to engage both innate and adaptive immune responses providing rationale to explore novel immuno-oncology (IO) combination strategies designed to exploit this biology.

2. Avelumab monotherapy: clinical successes and the road to approval

The rapid approval of avelumab was based on accelerated regulatory review as established by the FDA Oncology Center of Excellence, a program created to more rapidly review promising agents for patients with limited treatment options [4,5]. Merkel cell carcinoma (MCC) is a clear beneficiary of this innovative approach to drug development as there were no FDA-approved therapies for MCC prior to avelumab’s approval in March 2017 and metastatic disease is associated with a dismal prognosis. Based on encouraging preliminary data from the phase II JAVELIN Merkel 200 trial (n = 88), avelumab received orphan drug status, as well as breakthrough therapy and fast-track designation for MCC in 2015 [6]. Avelumab was subsequently granted FDA accelerated approval for metastatic MCC given the objective response rate (ORR) of 31.8% coupled with a favorable duration of response (DOR; 92% of responders with ongoing response at 6 s) [7]. This compares favorably to chemotherapy in second-line where response rates are usually 8–20% with median duration being generally less than 3 s. Avelumab may be more effective in the first-line setting with preliminary data presented at ASCO 2017 suggesting an ORR of 56.3% (NCT02155647). This has since been confirmed in a pre-planned interim analysis of 39 patients treated with avelumab in the first-line setting [8]. In this cohort, an ORR of 62.1% [95% CI, 42.3–79.3%] was seen after a median follow-up of 5.1 s (range, 0.3–11.3). Responses appeared durable with 77.8% ongoing at the time of analysis. Accelerated approval based on these nontraditional, yet, clinically meaningful, efficacy endpoints (i.e. ORR, DOR) highlights the novel regulatory approaches that are being adopted to expedite access to transformative immunotherapies for cancer patients [9].

Avelumab is also indicated in the platinum-refractory setting for patients with locally advanced/metastatic urothelial carcinoma (UC) after receiving accelerated approval in May 2017. This indication is supported by promising response rates observed in a phase Ib dose-expansion cohort of UC patients enrolled on the JAVELIN Solid Tumor study [10]. A recent pooled analysis of two avelumab-treated UC expansion cohorts (n = 249) confirmed a durable ORR of 17% and median DOR that was not yet reached at time of analysis. The remarkably high proportion of responders (96%) with ongoing responses at the six-assessment period and an overall survival rate of 53% at 6 s compares favorably with the modest and short-lived responses to chemotherapy in second-line where response rates are usually 8–20% with median duration being generally less than 3 s. This compares favorably to chemotherapy in second-line where response rates are usually 8–20% with median duration being generally less than 3 s. Avelumab may be more effective in the first-line setting with preliminary data presented at ASCO 2017 suggesting an ORR of 56.3% (NCT02155647). This has since been confirmed in a pre-planned interim analysis of 39 patients treated with avelumab in the first-line setting [8]. In this cohort, an ORR of 62.1% [95% CI, 42.3–79.3%] was seen after a median follow-up of 5.1 s (range, 0.3–11.3). Responses appeared durable with 77.8% ongoing at the time of analysis. Accelerated approval based on these nontraditional, yet, clinically meaningful, efficacy endpoints (i.e. ORR, DOR) highlights the novel regulatory approaches that are being adopted to expedite access to transformative immunotherapies for cancer patients [9].

The JAVELIN Solid Tumor investigators initiated a global open-label phase I trial to study avelumab in 12 different cancer subtypes with an enrollment of more than 1700 patients since 2013 [6]. This ‘seamless’ multi-cohort dose-expansion adaptive design has facilitated timely and efficient evaluation of clinical activity, dose-finding, and safety signals with avelumab monotherapy across a broad spectrum of malignancies [4,5]. As these data mature, they may define new indications for avelumab and help inform pivotal phase III studies. Alternatively, in disease settings where there are only modest response rates with monotherapy, avelumab...
might form the therapeutic backbone for combination immunotherapy approaches. The available clinical data (Table 1) suggest that there is heterogeneity of responses to avelumab monotherapy ranging from a disappointing ORR of 3% in treatment-refractory metastatic breast cancer to ~ 56% in first-line MCC. While responses are variable across disease sites, the median time to response (TTR) among responders appears to be relatively rapid (~6–12 weeks). Further, while enrollment in JAVELIN Solid Tumor studies was generally independent of PD-L1 status, expression of PD-L1 (by tumor cells or tumor-infiltrating immune cells) does not consistently predict response to avelumab, and thus its role as a biomarker remains undefined at present.

Treatment with avelumab appears to be well-tolerated with a manageable toxicity profile – current studies suggest that a minority (5–20%) of patients develop serious treatment-related adverse events (Table 1). The most common adverse events reported include fatigue and infusion-related drug reactions. The infusion reactions can be prevented by premedication using an H1 anti-histamine and acetaminophen given 30–60 min prior to infusion. Rarely, these can be higher grade or recurrent despite premedication and treatment may need to be halted. Other serious treatment-related adverse events (TRAEs) have been reported with avelumab, but these have typically been low grade and are easily managed. In the MCC trial, avelumab was associated with no grade 4 TRAEs but five grade 3 TRAEs were reported in 4 of 88 patients (4.5%); these included lymphopenia in two patients, an increase in creatine phosphokinase in one patient, and elevated hepatic transaminases and cholesterol in one patient [7]. In addition, immune-related adverse events occurred in 6 of 88 patients (6.8%), of which thyroid effects were the most common with three cases of hypothyroidism and two cases of hyperthyroidism reported, which were all grade 2 or less. In a study of refractory metastatic UC, the most common TRAEs were fatigue and asthenia in 31.8%, infusion-related reactions in 20.5%, and nausea in 11.4% of the subjects [10]. Grade 3–4 TRAEs were unusual and reported in only three patients (6.8%), which included asthenia, anorexia, and laboratory elevations (AST and creatinine phosphokinase). A similar toxicity profile was reported in patients with platinum-refractory UC where 29% of the patients experienced infusion-related reactions, but these were all grade 1 or 2 and 16% of the patients reported fatigue [11]. Grade 3 or worse TRAEs in this study were observed in 21 of 249 subjects (8%) and the most common events were fatigue in four patients and asthenia, lipase increase, hypophosphatemia, and pneumonitis in two patients. In this trial, there was one treatment-related death due to pneumonitis highlighting the importance of monitoring patients treated with avelumab for immune-related adverse events, which appear to manifest similar to such events in patients treated with PD-1 blockade. As cancer therapy is increasingly appreciated to place considerable socioeconomic burden on cancers patients and society, it will be important to assess quality-of-life metrics, establish the value profile including cost-effectiveness analyses, and evaluate potential financial toxicity associated with avelumab treatment.

3. Maximizing avelumab’s potential through rational combinations

While deep and durable responses are achieved in a subset of patients treated with immune checkpoint blockade (ICB) – most patients fail to respond. In addition to ‘primary refractory’ nonresponders that derive minimal benefit from monotherapy, acquired resistance also develops in a proportion of patients that had initially responded to ICB. As such, strategies to improve response rates and address resistance are needed to extend the benefit of immunotherapy to a greater number of patients and to tumor subtypes that are not traditionally considered to be immunogenic. Clinical investigations exploring various combinations of PD-1/PD-L1 blockade with novel IO agents, cytotoxic therapies, or targeted therapies are gaining traction and challenging the existing standard-of-care across a variety malignancies.

Of interest are avelumab-IO combinations which target distinct aspects of the cancer-immunity cycle to boost immune responses (Table 2). A common theme across several ongoing avelumab-IO combination studies is the concept of inducing inflammation in immunologically ‘cold’ tumors using vaccines (NCT03260023, NCT03050814), radiotherapy (NCT03217747), or adoptive T-cell transfer (NCT02584829). These approaches which amplify the magnitude of T-cell responses and drive T-cell infiltration (and consequently PD-L1 expression) potentially synergize with the on-target action of avelumab within the TME and might be especially valuable for tumors with low baseline immune infiltration. Augmenting ADCC activity is another intriguing avenue by which rational IO combinations with avelumab could improve clinical outcomes. The intact IgG1 Fc domain of avelumab potentiates ADCC via interaction with NK cells – indeed, therapies that augment NK activity, such as IL-15 superagonists, NHS-IL12 immunocytokine conjugates, or engineered NK cells expressing the high-affinity CD16 allele, have demonstrated promise preclinically and are in various phases of clinical testing (NCT03138406, NCT03329248) [12,13].

The practice-changing PACIFIC trial reporting a remarkable progression-free survival benefit with the addition of consolidative durvalumab after definitive chemoradiation in locally advanced non-small cell lung cancer (NSCLC) has ushered in a new era for ICB in the nonmetastatic setting [14]. These data, as well as the recent approval of nivolumab in the adjuvant setting for melanoma, provide a signal that ICB might be more efficacious in patients with lower disease burden and in earlier stages of disease. Supporting this notion, response rates to avelumab in treatment-naive MCC are nearly doubled (ORR; 56.3% vs 31.8%) in comparison to chemo-refractory disease and this trend is also observed with first-line vs heavily pre-treated metastatic NSCLC [7,15]. Accordingly, avelumab is being explored in earlier/lower volume disease settings, including adjuvant treatment for resected/locally advanced MCC (NCT03271372), high-risk triple-negative breast cancer (NCT02926196), as well as first-line maintenance for gastric/gastroesophageal junction cancer (Table 1). Successful integration of avelumab into the localized disease space will require improved understanding of the optimal timing/sequencing with established definitive treatment paradigms and refined patient selection to understand who might benefit from rational IO combinations.
Table 1. Clinical activity with avelumab monotherapy across different malignancies.

| Disease site – ClinicalTrials.gov ID | Study design/patient population | Subgroup analysis | ORR | Median DoR | Median TTR | Median PFS | Median OS | ≥Grade 3 TRAE |
|-------------------------------------|---------------------------------|-------------------|-----|------------|------------|------------|-----------|--------------|
| Merkel cell carcinoma               | JAVELIN Merkel 200 – NCT02155647 | - Metastatic, chemotherapy-refractory Merkel cell carcinoma (n = 88) PD-L1 (+) (TC ≥1%) | 31.8% | 92% (at 6 mo) | Not reached | 2.7 mo | 11.3 mo | 5% |
|                                   |                                 | - Open-label phase II PD-L1 and MCPyV status unselected MCPyV (+) | 34.5% | Not reached | | 40% (at 6 mo) | 69% (at 6 mo) | |
|                                   |                                 | - Metastatic urothelial carcinoma with platinum-refractory disease after ≥1 prior therapy (n = 161) PD-L1 (+) (TC ≥5%) | 17% | 96% (at 6 mo) | Not reached | 11.4 weeks | 6.3 mo | 6.5 mo | 8% |
|                                   |                                 | - Pooled analysis of open-label phase Ib dose-expansion cohorts PD-L1 (−) (TC <5%) | 24% | Not reached | | 11.9 mo | 8.2 mo | |
|                                   |                                 | - PD-L1 status unselected | 13% | Not reached | | 6.1 mo | 6.2 mo | |
|                                   |                                 | - Stage IIIIB/IV progressive or platinum-refractory NSCLC (n = 184) PD-L1 (+) (TC ≥1%) | 12% | 83% (at 6 mo) | Not reached | 12 weeks | 2.9 mo | 8.4 mo | |
|                                   |                                 | - Open-label phase Ib dose-expansion cohort PD-L1 (−) (IC <10%) | 9% | Not reached | | 3.0 mo | 8.9 mo | |
|                                   |                                 | - PD-L1, EGFR, KRAS, ALK status unselected PD-L1 (−) (TC <1%) | 14% | Not reached | | 21% (at 12 mo) | 39% (at 12 mo) | |
|                                   |                                 | - Histologically confirmed LABC/ metastatic breast cancer with refractory or progressive disease on SOC (n = 168, 58 with TNBC) PD-L1 (+) (IC ≥10%) | 4.6 mo | 3% | Not reached | 11.4 weeks | 1.5 mo | 8.1 mo | 13.7% |
|                                   |                                 | - PD-L1 status unselected PD-L1 (−) (IC <10%) | 36% (at 12 mo) | [5.2% TNBC] | | 10.1% (at 6 mo) | 40.3% (at 12 mo) | |
|                                   |                                 | - Recurrent/refractory stage III/IV ovarian cancer with PD within 6 mo of platinum or after subsequent therapy for relapse (n = 124) PD-L1 (+) (TC ≥1%) | 9.7% | 12.3% | | 1.5 mo | 6.8 mo | |
|                                   |                                 | - open-label phase Ib dose-expansion cohort PD-L1 (−) (TC <1%) | 7% (at 6 mo) | [2.6% TNBC] | | 37.4% (at 12 mo) | |
|                                   |                                 | - PD-L1 status unselected | 5.9% | Not reached | | 2.8 mo | 10.8 mo | |
|                                   |                                 | - Advanced gastric or GEJ cancer as first-line maintenance or second-line therapy (n = 151) PD-L1 (+) (TC ≥1%) | 9.0% [M] | 9.7% [2L] | | 3.0 mo [M] | 1.5 mo [2L] | 9.9% |
|                                   |                                 | - Phase Ib expansion; subgroups: switch maintenance [M, n = 89] or as second-line [2L, n = 62] PD-L1 (−) (TC <1%) | 10.0% [M] | 18.2% [2L] | | 4.4 mo [M] | 1.6 mo [2L] | |
|                                   |                                 | - PD-L1 status unselected | 3.1% [M] | 9.1% [2L] | | 2.9 mo [M] | 2.6 mo [2L] | |

(Continued)
4. A pressing need for immuno-oncology biomarkers

The development and validation of reliable biomarkers remains an important and unmet need for IO. Tumor mutational burden, immune contexture of the TME, interferon-γ-related/T-cell-inflamed gene signature, and PD-L1 expression are all candidate biomarkers of interest, but their utility and general applicability are unproven. Interpretation of PD-L1 expression has been particularly challenging given the lack of standardization between assays used for various anti-PD-1/PD-L1 antibodies and somewhat arbitrary definitions to define ‘positivity’ by expression on tumor cells, immune cells, or both. As such, uniform biomarkers are desperately needed to learn from our existing clinical data and to compare efficacy and safety across large data sets of patients treated with different ICB agents. Progress with IO biomarker development will facilitate a personalized approach by helping to determine which subsets of patients might be upfront responders to avelumab monotherapy and those that may require combinations. Importantly, renewed focus in understanding the underlying immunobiology, mechanisms of immune evasion, and resistance to avelumab from clinical biospecimens can help build a platform for individualized combination strategies.

5. Concluding remarks – is it time to get excited about avelumab?

We are in the midst of the cancer immunotherapy revolution. Several therapies targeting the PD-1/PD-L1 axis have now demonstrated clinical efficacy leading to multiple FDA approvals which has generated tremendous excitement but also urgency to best define their optimal application. Whether there is cross-resistance among PD-1- and PD-L1-directed agents is not clear. The ongoing JAVELIN Solid Tumor trials will provide efficacy and

### Table 1. (Continued)

| Disease site – ClinicaTrial.gov ID | Study design/patient population | Subgroup analysis | ORR | Median DoR<sup>a</sup> | Median TTR | Median PFS<sup>b</sup> | Median OS | ≥Grade 3 TRAE |
|-----------------------------------|---------------------------------|-------------------|-----|------------------------|------------|------------------------|-----------|---------------|
| **Gastric and GEJ cancer**        | **JAVELIN JPN – NCT01943461**   | Total population  | 15% | PD-L1 (+) (TC ≥1%)       | 40%        | 3.1 mo                 | 60% (at 3 mo) | 73%           |
|                                   |                                 | PD-L1 (–) (TC <1%) | 7.1 |                        |            | 2.8 mo                 | 32.1% (at 3 mo) |               |
|                                   | Nishina T et al. ASCO 2016. / Clin Oncol 34, 2016 (no. 4_suppl; Abstract 168) | Phase Ib dose expansion JAVELIN in Japanese patients (n = 20) | PD-L1 status unselected | Total population | 15%        | 3.1 mo                 | 60% (at 3 mo) | 73%           |
| **Non-small cell Lung cancer (1L)** | **JAVELIN phase Ib – NCT01772004** | Total population  | 18.7% | PD-L1 (+) (TC ≥1%)       | 20%        | 2.9 mo                 | 9%         |               |
|                                   | Verschraegen CF et al. ASCO 2016. / Clin Oncol 34, 2016 (suppl; Abstract 9036) | 1L avelumab for metastatic/recurrent NSCLC, systemic chemotherapy-naïve for metastatic disease (n = 75 with ≥3 mo FUP) | EGFR-wildtype, ALK rearrangement-negative | PD-L1 status unselected | 18.7% | 2.9 mo                 | 9%         |               |
| **Merkel cell carcinoma (1L)**    | **JAVELIN Merkel 200 – NCT02155647** | Total population  | 62.1% | PD-L1 and MCPyV status unselected | 77.8%      | 20.5%                  | not reached |               |
|                                   | D’Angelo SP et al. JAMA Oncol. 2018 | 1L avelumab for chemotherapy-naïve metastatic Merkel cell carcinoma (n = 39) | Open-label phase II, pre-planned interim analysis | PD-L1 and MCPyV status unselected | 62.1% | 77.8%      | not reached |               |

<sup>a</sup> among responders, proportion of patients with durable response defined as response ≥6 s.
<sup>b</sup> median PFS reported as weeks in primary source are displayed as s for consistency.
<sup>c</sup> median time to response (TTR) not reported, 39% of responders had responded by 6 weeks and 73% of responders had responded by 12 weeks.
<sup>d</sup> median time to response (TTR) not reported, 50% of responders (n = 6) had responded by 6 weeks and 83.3% of responders has responded by 10 weeks.

**Abbreviations:** 1L: first-line; 2L: second-line; AE:DoR: duration of response; FUP: follow-up; GEJ: gastroesophageal junction; IC: tumor-associated immune cells; LABC: locally advanced breast cancer; M: maintenance therapy; MCPyV: Merkel cell polyoma virus; mo: months; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PD: progression of disease; PFS: progression-free survival; SOC: standard-of-care; TC: tumor cell; TNBC: triple-negative breast cancer; TRAE: treatment-related adverse event; TTR: time to response;
Table 2. Select clinical trials evaluating avelumab in combination with other immuno-oncology (IO) agents.

| Avelumab + IO combos (ClinicalTrials.gov ID) | Trial | Patient population | Primary/secondary endpoint | Enrollment status* anticipated completion |
|---------------------------------------------|-------|--------------------|----------------------------|-------------------------------------------|
| **Arm A: avelumab (IV 10 mg/kg)** | **NCT03268057** (opened Oct 2017) | VX15/2503 (anti-Semaphorin 4D/SEMA4D mAb) in combination with avelumab in advanced NSCLC | Phase Ib/II, 3 + 3 dose escalation/dose expansion | 1° EP: number of DLTs per dose level, frequency of AEs |
| | | | Stage III/IV NSCLC with progression on cytotoxic chemotherapy | | Completion date May 2020 |
| | | | VX15/2503 dose escalation 5 mg/kg to 15 mg/kg, biweekly dosing cycle | | |
| | | | Biweekly IV avelumab (10 mg/kg) | | |
| **Arm B: avelumab + OX40 agonist [PF-04518600]** | **NCT03260023** (opened Sept 2017) | Combination of TG4001 and Avelumab in HPV-16 + oropharyngeal HNSCC | Phase Ib/II, 3 + 3 dose escalation/dose expansion | 1° EP: DLTs, AEs/ORR [phase II] |
| | | | Recurrent/unresectable or metastatic HPV-16+ cancer, prior platinum required (< 2 prior systemic therapies) | | Currently recruiting (n = 52) |
| | | | Phase II expansion cohort of oropharyngeal HNSCC | | Completion date May 2021 |
| | | | TG4001 (MVA-HPV-IL2) is a modified vaccinia virus Ankara vector encoding HPV-16 E6/E7 antigens and IL-2 adjuvant | | |
| **Arm C: avelumab + anti-4-1BB/utomilumab (IV 100 mg q4wks)** | **NCT02994953** (opened Jan 2017) | Avelumab in combination with NHS-IL12 (M9241) in solid tumors | Phase Ib, dose-finding | 1° EP: treatment-related, DLTs and best overall response |
| | | | Recurrent/unresectable or metastatic solid tumors; part B will enroll post-platinum UC, 1st line mNSCLC, recurrent/refractory CRC (MSS only), RCC after immune checkpoint failure | | Currently recruiting (n = 170) |
| | | | NHS-IL12 SC injection day 1 each cycle (ly) and biweekly IV avelumab (days 1 and 15) | | Completion date Apr 2019 |
| **Arm D: avelumab + anti-4-1BB + RT (6 Gy × 10)** | **NCT02584829** (opened Nov 2015) | Avelumab in combination with MHC upregulation (intratumoral IFNβ or RT) ± adoptive transfer of MCPyV TAg-specific CD8+ T-cells in metastatic Merkel Cell Carcinoma | Phase I/II, metastatic Merkel Cell Carcinoma | 1° EP: time to new metastasis (response), AEs |
| | | | MHC upregulation: localized RT or intratumoral IFNβ, delivered 7–10 days after first dose of avelumab (IV biweekly up to 1 year) | | Currently recruiting (n = 20) |
| | | | Adoptive T-cell transfer: two infusions of MCPyV TAg-specific polyclonal autologous CD8+ T-cells, delivered 2–5 days after avelumab | | Completion date Jul 2019 |
| **Arm E: avelumab + OX40 agonist (PF-04518600) ± RT (1.8 Gy × 25)** | **NCT03217747** (opened Aug 2017) | Avelumab in combination with other anti-cancer therapies in advanced malignancies | Phase I/II, avelumab combined with checkpoint agonists ± RT or cisplatin/RT of limited/locally advanced/metastatic solid tumors | 1° EP: MTD, AEs, changes in CD8 expression before/after treatment – correlated clinical benefit with response |
| | | | Arm A: avelumab (IV 10 mg/kg q2wks) + anti-4-1BB/utomilumab (IV 100 mg q4wks) | | Currently recruiting (n = 188) |
| | | | Arm B: avelumab + OX40 agonist (PF-04518600) (IV 0.3 mg/kg q2wks) | | Completion date Aug 2022 |
| | | | Arm C: avelumab + anti-4-1BB + OX40 agonist (IV 0.1 mg/kg q2wks) | | |
| | | | Arm D: avelumab + anti-4-1BB + RT (6 Gy × 10) | | |
| | | | Arm E: avelumab + OX40 agonist + RT (6 Gy × 10) | | |
| | | | Arm F: avelumab + anti-4-1BB + OX40 agonist + RT (6 Gy × 10) | | |
| | | | Arm G: avelumab + cisplatin (IV 40 mg/m²)/RT (1.8 Gy × 25) | | |
| **Arm F: avelumab + anti-4-1BB + OX40 agonist** | **NCT02554812** (opened Nov 2015) | Avelumab in combination with other cancer immunotherapies in advanced malignancies (JAVELIN Medley) | Phase Ib/II – locally advanced/metastatic solid tumors with progression on SOC or without treatment options; NSCLC, melanoma, HNSCC, TNBC, CRC, gastric cancer, ovarian cancer, UC | 1° EP: DLTs for combination therapy, objective response |
| | | | Cohort A: avelumab + anti-4-1BB/utomilumab | | Currently recruiting (n = 560) |
| | | | Cohort B: avelumab + OX40 agonist (PF-04518600) | | Completion date Feb 2020 |
| | | | Cohort C: avelumab + anti-M-CSF (PD-0360324) | | |
| | | | Cohort D: avelumab + anti-4-1BB + OX40 agonist | | |

(Continued)
Avelumab + IO combos (ClinicalTrials.gov ID) | Trial | Patient population phase/design | Primary/secondary endpoint immunologic correlates | Enrolment statusa/ anticipated completion
---|---|---|---|---
**NCT03050814** (opened Apr 2017) | Ad-CEA vaccine and Avelumab in previously untreated mCRC | • Randomized phase II, mCRC-MSS [lacking mismatch repair deficiency] | • 1° EP: PFS at 18 mo | Currently recruiting (n = 81) / Completion date Aug 2021
Arm A: SOC = FOLFOX + bevacizumab | • Arm A: SOC = FOLFOX + bevacizumab followed by bevacizumab + capecitabine maintenance | • 2° EP: AE, ORR, mOS | | 
Arm B: SOC + avelumab + Ad-CEA vaccine (SC injection) + SOC | • Arm B: SOC + avelumab + Ad-CEA vaccine (SC injection) + SOC | • Genomic/proteomic profiling and quantitative immunologic analysis | | 
Arm C: SOC + yeast-vaccine expressing mutant Ras (S. cerevisiae) | • Arm C: avelumab + utomilumab + rituximab | • ALT-803, IL-15 superagonist or chemotherapy in refractory/refractory DLBCL (JAVELIN DLBCL) | | 
• Ad-CEA, adenovirus-based CEA-targeting vaccine | • Arm B: avelumab + utomilumab + azacitidine | • Phase Ib/II, relapsed/refractory DLBCL, ≤4 prior lines of rituximab-containing multi-agent chemotherapy or ASCT failure/ineligible. | • 1° EP: DLT, ORR (phase Ib); PFS [phase III] | Currently recruiting (n = 304) / Completion date May 2021
• Arm C: avelumab + rituximab + bendamustine | • Arm D selected based on phase Ib arm A – C, will enter phase III randomization vs SOC (arm E) | • phase III: Arm D vs Arm E (rituximab/bendamustine or rituximab/gemcitabine/oxaliplatin) | • 2° EP: DoR, TTR, PFS, OS, minimal residual disease [phase Ib]: OS, PFS, ORR, TTR, DoR, DCR [phase III] | | 
• phase II: CR during induction phase will enter maintenance phase | • Combination: ALT-803, ETBX-011, GI-4000, aNK, avelumab, multi-agent chemo | • Combination regimens of immunotherapy, epigenetic modulator and CD20-antagonist or chemotherapy in refractory/refractory DLBCL (JAVELIN DLBCL) | • PD-L1 expression levels on tumor cells and TIL at baseline | | 
**NCT02951156** (opened Dec 2016) | Combination immunotherapy with aNK in pancreatic cancer with progression on/after SOC | • Phase Ib/II, pancreatic cancer patients with PD after prior SOC chemotherapy | • 1° EP: treatment-related AEs [phase Ib]; ORR by RECIST and irRC [phase II] | Currently recruiting (n = 80) / Completion date Dec 2018
Arm A: SOC (arm E) | • Arm A: SOC + avelumab + multi-agent chemo + anti-VEGFR2 mAbs | • Avelumab has demonstrated clinical relevant ADCC, avelumab may hold a distinct advantage over other FDA-approved agents in this class given the potential for both innate and adaptive immune activation via ADCC and PD-L1 targeting, respectively. This consideration may be particularly important for combination therapies involving avelumab; however, progress in biomarker development and patient selection will be needed to fully realize the potential of avelumab. Avelumab has demonstrated therapeutic responses across different tumors with an | | 
Arm B: SOC + avelumab + multi-agent chemo | • Avelumab + ALT-803, GI-4000, aNK, avelumab, multi-agent chemo, SBRT | | | 
Arm C: SOC + avelumab + multi-agent chemo + anti-VEGFR2 mAbs | • Vaccines: ETBX-011 (CEA-targeting vaccine), GI-4000 (recombinant S. cerevisiae yeast-vaccine expressing mutant Ras proteins) | • ALT-803, IL-15 superagonist, aNK, activated NK cells engineered to not express killer inhibitory receptors (KIR) | | 
**NCT02938406** (opened Dec 2017) | Combination immunotherapy with haNK in pancreatic cancer with progression on/after SOC | • Phase Ib/II, pancreatic cancer patients with PD after prior SOC chemotherapy | • 1° EP: treatment-related AEs [phase Ib]; ORR by RECIST and irRC [phase II] | Currently recruiting (n = 80) / Completion date Dec 2019
Arm A: SOC (arm E) | • Arm A: avelumab, high-affinity NK cells expressing mutant Ras proteins | • Avelumab in combination with haNK in pancreatic cancer with progression on/after SOC | • 2° EP: ORR/DFS by RECIST/irRECIST, OS, DoR, DCR [phase Ib]; DFS/OS, DoR, DCR, patient-reported outcomes, treatment-related AEs | | 
Arm B: SOC + avelumab | • ALT-803, IL-15 superagonist, haNK, modified NK cells to express high-affinity CD16 to potentiate ADCC | • Phase Ib II, Simon 2-stage design; those with CR during induction phase will enter maintenance phase | • 2° EP: ORR, DFS by RECIST/irRECIST, OS, DoR, DCR [phase Ib]; PFS/OS, DoR, DCR, patient-reported outcomes | | 
Arm C: SOC + avelumab + agent B | • Vaccines: ETBX-011 (CEA-targeting vaccine), GI-4000 (Ras-mutant targeting vaccine), GI-4000 (recombinant S. cerevisiae yeast-vaccine) | • ALT-803, IL-15 superagonist, haNK, modified NK cells to express high-affinity CD16 to potentiate ADCC | | 
Arm D: SOC + avelumab + agent B | • ALT-803, IL-15 superagonist, haNK, modified NK cells to express high-affinity CD16 to potentiate ADCC | • ALT-803, IL-15 superagonist, haNK, modified NK cells to express high-affinity CD16 to potentiate ADCC | | 
Arm E: SOC | • ALT-803, IL-15 superagonist, haNK, modified NK cells to express high-affinity CD16 to potentiate ADCC | | | 

*a Study recruitment status as of December 1st, 2017 per ClinicalTrials.gov.

1° EP: primary endpoint; 2° EP: secondary endpoint; ADCC: antibody dependent cell-mediated cytotoxicity; AEs: adverse events; aNK: activated natural killer cells; ASCT: autologous stem cell transplant; CR: complete response; CRC: colorectal carcinoma; DCR: disease control rate; DLBCL: diffuse large B-cell lymphoma; DLT: dose-limiting toxicity; DoR: duration of response; haNK: high-affinity natural killer cells; HNSCC: squamous cell carcinoma of the head & neck; ID: intradermal; IFN: interferon; IO: Immuno-oncology; irRC: immune-related RECIST; IV: intravenous; mAb: monoclonal antibody; MCPyV Tag: Merkel cell polyoma virus T antigen; mCRC: metastatic colorectal cancer; M-CSF: macrophage-colony stimulating factor; mNSCLC: metastatic NSCLC; MSS: mismatch repair-proficient; RECIST: response evaluation criteria in solid tumors; MTD: maximum tolerated dose; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PD: progression of disease; PFS: progression-free survival; PFS: progression-free survival; RCC: renal cell carcinoma; RT: radiation therapy; SBRT: stereotactic body radiation therapy; SC: subcutaneous; SOC: standard-of-care; TIL: tumor infiltrating lymphocytes; TNBC: triple negative breast cancer; TTR: time to tumor response; UC: urothelial carcinoma.
acceptable safety profile. Thus, we are excited about this agent and eagerly look forward to results from ongoing clinical trials and biomarker investigations.

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**Declaration of interest**

H Kaufman is an employee of Replimune Inc. and has served on advisory boards for Merck KGaA/EMD Serono. J Gulley has served on advisory boards for EMD Serono, although participated in this project as part of his official duties for the U.S. federal government and received no compensation from EMD Serono. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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