HHS Public Access

Author manuscript

Int Ophthalmol Clin. Author manuscript; available in PMC 2021 April 01.

Published in final edited form as:

Int Ophthalmol Clin. 2020 ; 60(2): 91–102. doi:10.1097/IIO.0000000000000306.

Avelumab as an Emerging Therapy for Eyelid and Periocular Merkel Cell Carcinoma

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Abstract

Merkel cell carcinoma (MCC) is a highly aggressive cutaneous malignancy, with a high metastasis rate and a significant proportion of cases affecting the eyelid or periocular region. Current treatments for periocular MCC include wide local excision (WLE) with or without adjuvant radiotherapy and can result in profound morbidity and visual deficit. Metastatic disease has been traditionally treated with chemotherapy, though durable responses are typically poor and toxicity is high. Avelumab (Bavencio®, Merck KgaA, Darmstadt, Germany and Pfizer Inc., New York, NY, USA), the first FDA-approved human anti-programmed death-ligand 1 (PD-L1) antibody for the treatment of metastatic MCC (mMCC), has demonstrated safety and efficacy as first-line treatment and in chemotherapy-refractory cases. This review summarizes pivotal clinical trial data for avelumab in the treatment of mMCC, including efficacy, safety and tolerability, and describes the efficacy of two other immune checkpoint inhibitors, pembrolizumab (Keytruda®, Merck & Co., Inc., Kenilworth, NJ, USA) and nivolumab (Opdivo®, Bristol-Myers Squibb, New York, NY, USA and Ono Pharmaceuticals, Trenton, NJ, USA) for the treatment of advanced MCC. Our purpose is to provide the rationale to further investigate avelumab as a potential therapy for advanced or metastatic eyelid and periocular MCC.

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare, highly aggressive skin cancer of both epithelial and neuroendocrine origin.[1] Most commonly affecting Caucasians after the sixth decade, it affects men twice as frequently as women.[2] The estimated annual incidence of MCC in 2006 was 0.6 per 100,000 persons yet studies suggest a rising incidence in the US.[2–5] Typically, MCC presents with local disease, but regional lymph node and distant metastasis may be present in up to 30% of new cases and overall mortality rates range from 25–32%.[5]

Risk factors for MCC include immunosuppression – particularly in individuals with chronic lymphocytic leukemia, human immunodeficiency virus infection, and in solid-organ transplant recipients – as well as exposure to ultraviolet light and the Merkel cell polyoma virus (MCPyV).[6] MCC is considered an immunogenic cancer due to its increased prevalence and worse prognosis in immunosuppressed persons. [7] Additionally, evidence indicates that

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approximately 50% of MCC express PD-1 on tumor-infiltrating lymphocytes and express PD-L1 on tumor cells or infiltrating macrophages.[8]

Approximately 2.5–10% of MCC occur on the eyelid or periocular region,[9,10] and represent 5–20% of all head and neck MCC.[11–15] Wide local excision (WLE) with or without adjuvant radiotherapy has been a mainstay of treatment. Other therapeutic modalities include Mohs micrographic surgery, exenteration, or WLE with neoadjuvant chemotherapy.[16,17] Delayed diagnosis can result in in significant morbidity – including blindness, loss of the eye, and cosmetic deformity – and mortality. Until recently, metastatic MCC (mMCC) has been managed with conventional chemotherapies. Durable responses to chemotherapy are uncommon, however, with a median progression-free survival of only 3 months.[18,19]

The advent of immunotherapy has heralded new and promising treatment paradigms for the management of advanced and mMCC. In 2017, avelumab (Bavencio®, Merck KgaA, Darmstadt, Germany and Pfizer Inc., New York, NY, USA), a human anti-programmed death-ligand 1 (PD-L1) antibody, was the first FDA-approved drug as an alternative to chemotherapy for the treatment of mMCC.[20–22] Pembrolizumab (Keytruda®, Merck & Co., Inc., Kenilworth, NJ, USA), an IgG1 anti-programmed cell death protein 1 (PD-1) monoclonal antibody, was then approved for treatment of advanced MCC in 2018.[23]

Clinical trials with pembrolizumab and avelumab, both immune checkpoint inhibitors (ICIs), have demonstrated safety and efficacy for the treatment of advanced MCC and mMCC respectively. Avelumab, in particular, has demonstrated encouraging results for both primary treatment as well as in chemotherapy-refractory disease. Though no clinical trials have specifically assessed the use of ICIs for primary or metastatic periocular MCC, previous studies provide a strong rationale to further investigate avelumab as a therapeutic option for advanced eyelid and periocular MCC.

PHARMACOLOGY

Mechanism of Action

Avelumab's antitumor activity may be achieved through a dual mechanism of action. First, it is a human IgG1 monoclonal antibody that binds to and inhibits PD-L1 on tumor cells which prevents PD-L1 from binding to thePD-1 receptor on T cells.[24] PD-1 is a surface expressed T cell protein that acts as an immune checkpoint inhibitor upon interaction with PD-L1, a protein found on normal and tumor cells. Tumor cells and tumor infiltrating lymphocytes often show upregulation of PD-1 and PD-L1 thereby promoting tumor immune subversion. Blocking this interaction with PD-1 antibodies prevents tumor immuno-evasion and promotes T-cell mediated destruction of tumor cells.[25] The drug's mean target occupancy of PD-L1 on CD3+ T-cells has been demonstrated to be 93% two weeks after a dose of 10 mg/kg in individuals with solid tumors.[26] Second, avelumab bears a crystallizable fragment (Fc) IgG1 region that targets the Fc-γ receptor on natural killer (Nk) cells and is believed to enable antibody-dependent cell-mediated cytotoxicity (ADCC) by these cells.[27,28] No evidence has thus far demonstrated that ADCC contributes to the clinical activity of avelumab, nonetheless, this engagement of both the adaptive and innate immune system is believed to enable a robust antitumor response.

Pharmacokinetics

Avelumab is administered by intravenous (IV) infusion, with maximum concentrations achieved by one hour.[26] A dose of 10 mg/kg IV once every two weeks has been established through developmental investigations based on pharmacokinetic, target occupancy, and immunological analysis.[26] With repeated dosing at 2-week intervals, steady-state concentrations are reached after approximately 4–6 weeks.[26,29,30] An acceptable toxicity profile of up to 20 mg/kg was established in clinical trials.[26]

The degradation of avelumab is believed to be carried out by the same proteolytic mechanisms by which native IgG is catabolized.[30,31] Infusion of 10 mg/kg yields a terminal elimination half-life of 6.1 days, and systemic clearance of 0.59 liters/day.[29,30] Clearance does not appear to significantly differ on the basis of age, gender, PD-L1 status, mild-moderate hepatic impairment, or renal impairment. [29,30]

EFFICACY TRIALS

To date, there has been one pivotal clinical trial assessing avelumab for the treatment of mMCC (Table 1). No clinical trials to date have specifically assessed the use of avelumab for cases with primary or metastatic eyelid or periocular MCC. Adverse events data are addressed in *Safety and Tolerability*.

JAVELIN Merkel 200 Trial[32–36]

JAVELIN Merkel 200 is a pivotal phase 2, prospective, multicenter, open-label, single-arm trial of avelumab in individuals with mMCC. The trial comprises two cohorts: individuals with disease refractory to chemotherapy (*Part A*), and patients with no prior systemic therapy for mMCC (*Part B*).

JAVELIN Merkel 200 Part A: Second-Line (or Later) Treatment—Eighty-eight immunocompetent adults (mean: 72.5 years) with refractory mMCC were followed for a median of 10.4 months.[32] Primary cutaneous tumors were identified in 76% of participants, though the location of these primary tumors were not reported. Patients were treated with 10 mg/kg of IV avelumab every 2 weeks with a median of 7 doses, and a median treatment duration of 17 weeks.

Overall, the objective response rate (ORR) was 31.8%. Most responses (82%) were observed as early as the first post-treatment assessment (week 7). Almost a third (29%) of patients demonstrated a durable response of at least 6 months. Median progression-free survival (PFS) was 2.7 months, and median overall survival (OS) was 11.3 months. A subsequent analysis determined that early objective response to avelumab is of clinical importance, noting that subjects with objective response by weeks 7–13 had significantly longer overall survival (OS) compared to patients with early nonresponse.[33] The proportion of responders with at least 1 year response duration was similar irrespective of MCPyV or PD-L1 status. However, higher ORRs were noted in subjects who had received fewer lines of prior chemotherapy, as well as those with lower disease burden and those with PD-L1 positive tumors. The investigators surmise that these subjects may be more likely to be immunocompetent and therefore demonstrate more robust response to immunotherapy.[34]

Expanded data from patients with ≥2 y of follow-up (median 29.2 months) demonstrated an ORR of 33%.[35,36] Complete response was observed in 11.4% of patients. PFS rate at 1 year, 18 months, and 2 years were stable at 29%, 29%, and 26%, respectively. Median OS was 12.6 months, with a 2-year OS rate of 36%.

JAVELIN Merkel 200 Part B: First-Line Treatment[37]—Part B assessed the efficacy and safety of avelumab as a first-line treatment in 39 patients (median age, 75 years) with mMCC.[37] The primary end point was durable response with at least 6 months duration and secondary endpoints included best overall response, duration of response, PFS, and safety.

Median treatment duration was 12 weeks (range, 2.0–49.9), with median follow-up of 5.1 months (range, 0.3–11.3). PFS at 3 months was 67%, with a median PFS of 9.1 months (range, 1.9-not estimable). Disease progression was observed in 17.9% of subjects, with two deaths noted (5.1%).

SAFETY AND TOLERABILITY

The avelumab clinical trials data have demonstrated an overall acceptable safety and tolerability profile. Unless otherwise specified, safety profiles discussed herein are derived from pooled data from a total of 1738 subjects from Part A of the JAVELIN Merkel 200 study and the entirety of the phase 1 JAVELIN Solid Tumor study,[24] which evaluated the safety of avelumab in the treatment of metastatic or locally advanced solid tumors (n = 88 and n=1650, respectively).[38] Overall incidence of treatment-related adverse events (TRAEs) of any grade was 67.0%. However, incidence of grade 3 or greater TRAEs was only 10.2%, the most common of which were fatigue (1%), elevated serum lipase (1%), infusion-related reactions (IRRs, 0.6%), and elevated serum gamma-glutamyl transferase (0.6%). Permanent discontinuation of the drug resulting from TRAEs was uncommon, occurring in 6.2% of patients. This safety profile is similar to safety data reported for first-line pembrolizumab for advanced MCC.[39]. Additionally, this safety profile is similar to 127 subjects with mMCC (88 subjects in JAVELIN Merkel 200 Part A, 39 in Part B; Table 2) treated with avelumab.

Infusion-Related Reactions

IRR such as pyrexia, hypersensitivity, or dyspnea of any grade occurred in 25.3% of patients, most commonly at the time of first infusion. Two percent of patients required treatment discontinuation due to IRRs. As such, premedication with acetaminophen and diphenhydramine is recommended before administration of the first four doses.[29,30,40] Grade 1 and 2 IRRs warrant slowing or interruption of the infusion, and treatment should be permanently discontinued in cases of grade 3 and 4 IRRs.

Immune-Related Adverse Events

ICIs have been associated with immune-related adverse events (IRAEs).[41] Overall incidence of IRAEs with avelumab was 14.2%. Grade 3 or greater IRAEs were experienced by 2.2% of subjects, most commonly thyroid disorder (5.6%) and rash (5.2%).[30] IRAE were considered serious in 2.5% of patients. Treatment with a systemic corticosteroid was required in 44.1% of IRAEs. Life-threatening immune events, though rare, have been

described with avelumab, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, myocarditis, myositis, and Guillain-Barré Syndrome.[29,30]

Death Associated with Avelumab

TRAEs were considered to be the primary cause of death in 0.2% of patients treated with avelumab. These cases included (1) autoimmune hepatitis, ascites, and peritoneal metastases in an individual with gastric cancer, (2) liver metastases and acute liver failure in a patient with metastatic breast cancer, (3) respiratory distress in another individual with metastatic breast cancer, and (4) treatment-related pneumonitis in a subject with urothelial carcinoma. Of note, none of the treatment fatalities occurred in patients with mMCC.

Ocular and Periocular Adverse Events

Ocular side effects of ICIs are typically less common than systemic adverse events (AEs), and most frequently include dry eye (1–24%) and uveitis (1%).[42] Warner et al. report new onset dry eye in four of eight patients treated with avelumab for visceral neoplasms.[43] One of these four patients experienced severe dry eye while the other 3 were reported as mild dry eye. Uveitis has not been reported in association with avelumab therapy to date, though it is a known immune-related adverse event that can occur with other PD-1/PD-L1 checkpoint inhibitors.[42,44] The only periocular AE reported in avelumab treated mMCC patients was an unspecified grade 3 eyelid function disorder classified as a treatment-emergent adverse event.[32]

PATIENT-CENTERED PERSPECTIVES

The psychological implications of the management of patients with a rare, aggressive, and potentially disfiguring or life-threatening disease such as MCC is clinically significant. Controlling for physical symptomatology, patients with advanced malignancies appear to experience less psychological morbidity when treated with immunotherapy as compared to chemotherapy.[45] Similarly chemorefractive mMCC patients treated with avelumab reported a clinically-relevant improvement in health-related quality of life, and a perceived comparatively better experience with avelumab than chemotherapy.[46,50] These relatively better psychological experiences may derive from lower toxicity, disease-related morbidity, and improved functional and survival outcomes with avelumab.

OTHER IMMUNE CHECKPOINT INHIBITORS FOR ADVANCED MCC

In addition to avelumab, two other ICIs – pembrolizumab and nivolumab (Opdivo®, Bristol-Myers Squibb, New York, NY, USA and Ono Pharmaceuticals, Trenton, NJ, USA) – have been explored in clinical trials as treatment for advanced MCC.

Pembrolizumab, an anti-PD-1 antibody, was FDA approved for adult and pediatric patients with mMCC or recurrent locoregional disease. In a non-controlled phase 2 trial of 26 individuals (median age, 68 years) with advanced MCC, first-line pembrolizumab demonstrated an ORR of 56%.[36] A higher response rate was noted in MCPyV-positive compared to MCPyV-negative tumors (62% versus 44%, respectively). TRAEs, most commonly fatigue and laboratory abnormalities, were observed in 77% of individuals. Grade

3 or 4 adverse events occurred in 15% of individuals, and these were managed by discontinuation of pembrolizumab and initiation of corticosteroid therapy when appropriate. Additionally, pembrolizumab has been reported in the treatment of a metastatic MCC to the orbit with a dramatic response to combined pembrolizumab and XRT.[51]

Nivolumab, an anti-PD-1 pathway inhibitor, has also shown durable responses in advanced MCC.[52–54] Preliminary analyses from a non-comparative, open-label, phase 1/2 trial of 25 patients with advanced MCC (median follow up, 51 weeks) demonstrated an ORR of 64%. The neoadjuvant use of nivolumab has also been reported effective in advanced MCC. Topalian et al.,[54] report substantial pathologic and radiologic tumor regression after a 4-week course prior to surgery.

In 2018, the National Comprehensive Cancer Network listed avelumab, pembrolizumab, and nivolumab as preferred first-line therapies for metastatic or unresectable MCC.[55] To date, no direct comparisons of the efficacy and safety of avelumab, pembrolizumab, or nivolumab for the treatment of advanced MCC have been reported though efficacy data and safety profiles appear similar.

CONCLUSIONS

Avelumab is approved for the treatment of mMCC and represents a promising immunotherapeutic agent for the treatment of advanced MCC. Studies have shown significantly longer response duration, with some responses continuing at up to 2 years, when compared to standard chemotherapy. The clinical activity of avelumab does not appear to substantially differ based on tumor PD-L1 or MCPyV status, though additional studies are needed. Improved health-related quality of life and enhanced psychological outcomes compared to those experienced with chemotherapy may add to avelumab's perceived benefits.

Pembrolizumab[39,,56] and nivolumab[52–54] have demonstrated efficacy in the treatment of advanced MCC though no reported cases specifically assess their use for advanced eyelid or periocular lesions. While no clinical trials to date have studied avelumab for advanced MCC or periocular MCC, the efficacy and safety of trials on avelumab for mMCC and pembrolizumab for advanced MCC provide rationale for the use of avelumab for the treatment of advanced or metastatic periocular MCC. Further investigation of the efficacy, safety and tolerability of avelumab for use in metastatic cases with eyelid or periocular involvement or for primary advanced eyelid and orbital lesions is warranted.

Acknowledgments

Sources of Support: This work was supported in part by: NIH Center Core Grant P30EY026877; Research to Prevent Blindness Unrestricted Grant, Inc, New York. The sponsor or funding organization had no role in the writing of this manuscript.

Abbreviations:

ADCC	antibody-dependent cell-mediated cytotoxicity

AE	adverse event
CI	confidence interval
Fc	crystallizable fragment
ICI	immune-checkpoint inhibitor
FDA	Food and Drug Administration
IgG1	immunoglobulin G1
IRAE	immune-related adverse event
IRR	infusion-related reaction
MCC	Merkel cell carcinoma
mMCC	metastatic Merkel cell carcinoma
MCPyV	Merkel cell polyoma virus
Nk	Natural killer
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
TRAE	treatment-related adverse event
WLE	wide local excision

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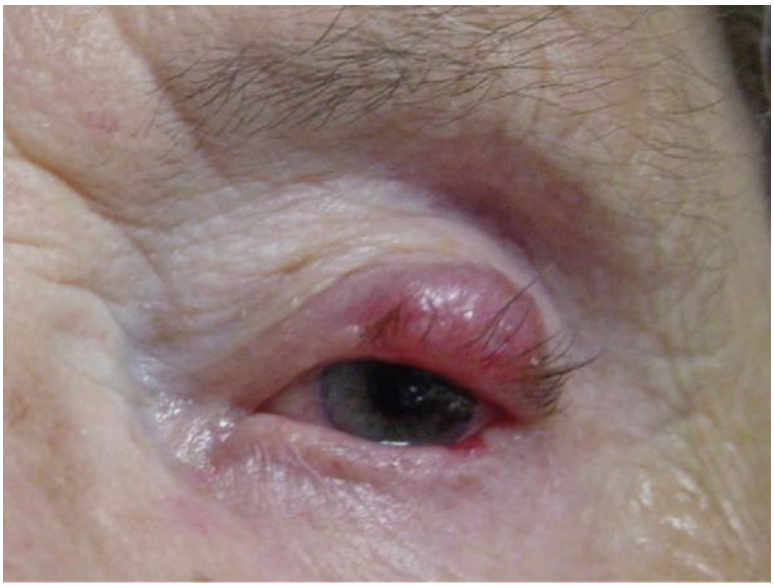

Figure 1. Merkel cell carcinoma of the upper eyelid.

The mass often presents as a violaceous nodule that can masquerade as a chalazion, cyst, or basal cell carcinoma. The large lesion depicted here has induced a mechanical ptosis. Reproduced, with permission, from DermNet New Zealand (www.dermnetnz.org), following licensing requirements from Creative Commons Attribution-NonCommercial-NoDerivs 3.0, New Zealand (https://creativecommons.org/licenses/by-nc-nd/3.0/nz/legalcode).

Table 1.

JAVELIN Merkel 200 trial data of avelumab for the treatment of mMCC. The trial comprises two cohorts: individuals with disease refractory to chemotherapy (*Part A*), and patients with no prior systemic therapy for mMCC (*Part B*).

Trial	Design	Subjects	Dosage	Median Treatment Duration	Selected Outcomes
Phase II					
JAVELIN Merkel 200, Part A(Second-line or later therapy)	Multicenter, international,open-label,single-arm	88	10 mg/kg	3.9 m[†]	Confirmed ORR: 33.0%[†] Complete response: 11.4%[†] 2-year PFS: 26%[†] 2-year OS: 36%[†] Median OS: 12.6 m[†] Clinical activity independent of PD-L1 or MCPyV status[†]
JAVELIN Merkel 200, Part B(First-line therapy)	Multicenter, international,open-label,single-arm, pre-planned interim analysis	39	10 mg/kg	12 w	Confirmed ORR: 62.1%[‡] Complete response: 13.8%%[‡] 3-month PFS: 67%[a] Median PFS: 9.1 m[a]

Dosing of avelumab in both parts of this trial was by intravenous infusion every two weeks.

[*] Number of subjects in the dose escalation cohort, 18 of whom were included in dose-limiting toxicity analysis set. 53 were then included in the dose-escalation safety analysis set, who were then combined with 33 patients from the dose-expansion part of the same trial to comprise 86 patients assess for pharmacokinetic parameters.

[†] From expanded data from this cohort in patients with ≥ 2 years follow up

[‡] In subset of 29 patients with at least 3 months follow up

[a] Of cohort of all 39 treated patients

mMCC, metastatic Merkel cell carcinoma; Mg, milligrams; kg, kilograms; w, weeks; m, months; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; PD-L1, programmed death-ligand 1; MCPyV, Merkel cell polyoma virus

Table 2.

Treatment-related adverse events (TRAEs) in patients with metastatic Merkel cell carcinoma treated with avelumab, as reported in Part A and Part B of the JAVELIN Merkel 200 Trial

	Part A	Part B	Pooled Total
Number of subjects receiving at least one dose of avelumab	88	39	127
TRAEs[*], N(%)			
Any TRAE	62 (70.0)	28 (71.8)	90 (70.9)
Fatigue	21 (24.0)	9 (23.1)	30 (23.6)
Infusion-related reaction	15 (17.0)	9 (23.1)	24 (18.9)
Rash[†,a]	11 (12.5)	2 (5.1)	13 (10.2)
Nausea	8 (9.1)	2 (5.1)	10 (7.9)
Asthenia	7 (8.0)	3 (7.7)	10 (7.9)
Diarrhea	8 (9.1)	2 (5.1)	10 (7.9)
ALT increase	3 (3.4)	3 (7.7)	6 (4.7)
Arthralgia	4 (4.5)	2 (5.1)	6 (4.7)
Pruritus[a]	4 (4.5)	2 (5.1)	6 (4.7)
Chills	3 (3.4)	2 (5.1)	5 (3.9)
Decreased appetite	5 (5.7)	0 (0.0)	5 (3.9)
Blood CPK increase	2 (2.3)	2 (5.1)	4 (3.1)
AST increase	3 (3.4)	1 (2.6)	4 (3.1)
Dry mouth	2 (2.3)	2 (5.1)	4 (3.1)
Dyspnea	2 (2.3)	2 (5.1)	4 (3.1)
Pyrexia	2 (2.3)	2 (5.1)	4 (3.1)
Dizziness	3 (3.4)	0 (0.0)	3 (2.4)
Dry skin	2 (2.3)	0 (0.0)	2 (1.6)
Dysgeusia	2 (2.3)	0 (0.0)	2 (1.6)
Headache	2 (2.3)	0 (0.0)	2 (1.6)
Influenza-like illness	2 (2.3)	0 (0.0)	2 (1.6)
Palpitations	2 (2.3)	0 (0.0)	2 (1.6)
Lymphopenia	2 (2.3)	0 (0.0)	2 (1.6)
Vomiting	2 (2.3)	0 (0.0)	2 (1.6)
Decreased weight	0 (0.0)	2 (5.1)	2 (1.6)
Eosinophilia	0 (0.0)	2 (5.1)	2 (1.6)
Autoimmune nephritis	0 (0.0)	1 (2.6)	1 (0.8)
Cholangitis	0 (0.0)	1 (2.6)	1 (0.8)
Gait disturbance	0 (0.0)	1 (2.6)	1 (0.8)
Paraneoplastic encephalomyelitis	0 (0.0)	1 (2.6)	1 (0.8)
Paraneoplastic syndrome	0 (0.0)	1 (2.6)	1 (0.8)
Polyneuropathy	0 (0.0)	1 (2.6)	1 (0.8)
Troponin increase	0 (0.0)	1 (2.6)	1 (0.8)
Blood cholesterol increased	1 (1.1)	0 (0.0)	1 (0.8)

	Part A	Part B	Pooled Total
TRAEs leading to discontinuation of therapy	2 (2.3)	6 (15.4)	8 (6.3)

[*] Includes adverse events of any grade

[†] Includes both non-specified rash and maculopapular rash

[a] One case of pruritus and two cases of maculopapular rash were additionally classified as immune-related adverse events in Part B.

ALT, alanine aminotransferase; CPK, creatine phosphokinase; AST aspartate aminotransferase.