

Phase I clinical trial evaluating the safety and efficacy of ADP-A2M10 SPEAR T cells in patients with MAGE-A10⁺ advanced non-small cell lung cancer

George R Blumenschein,¹ Siddhartha Devarakonda,² Melissa Johnson,³ Victor Moreno,⁴ Justin Gainor,⁵ Martin J Edelman,⁶ John V Heymach,¹ Ramaswamy Govindan,² Carlos Bachier,⁷ Bernard Doger de Spéville,⁴ Matthew J Frigault,⁸ Anthony J Olszanski,⁶ Vincent K Lam,⁹ Natalie Hyland,¹⁰ Jean-Marc Navenot,¹¹ Svetlana Fayngerts,¹¹ Zohar Wolchinsky,¹⁰ Robyn Broad,¹⁰ Dzmitry Batrakou,¹⁰ Melissa M Pentony,¹⁰ Joseph P Sanderson,¹⁰ Andrew Gerry,¹⁰ Diane Marks,¹¹ Jane Bai,¹¹ Tom Holdich,¹⁰ Elliot Norry,¹¹ Paula M Fracasso ¹¹

To cite: Blumenschein GR, Devarakonda S, Johnson M, *et al.* Phase I clinical trial evaluating the safety and efficacy of ADP-A2M10 SPEAR T cells in patients with MAGE-A10⁺ advanced non-small cell lung cancer. *Journal for ImmunoTherapy of Cancer* 2022;**10**:e003581. doi:10.1136/jitc-2021-003581

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/jitc-2021-003581>).

Accepted 27 October 2021



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr George R Blumenschein; gblumens@mdanderson.org

ABSTRACT

Background ADP-A2M10 specific peptide enhanced affinity receptor (SPEAR) T cells (ADP-A2M10) are genetically engineered autologous T cells that express a high-affinity melanoma-associated antigen A10 (MAGE-A10)-specific T-cell receptor (TCR) targeting MAGE-A10⁺ tumors in the context of human leukocyte antigen (HLA)-A*02. ADP-0022-003 was a phase I dose-escalation trial that aimed to evaluate the safety and antitumor activity of ADP-A2M10 in non-small cell lung cancer (NSCLC) (NCT02592577).

Methods Eligible patients were HLA-A*02 positive with advanced NSCLC expressing MAGE-A10. Patients underwent apheresis; T cells were isolated, transduced with a lentiviral vector containing the TCR targeting MAGE-A10, and expanded. Patients underwent lymphodepletion with varying doses/schedules of fludarabine and cyclophosphamide prior to receiving ADP-A2M10. ADP-A2M10 were administered at 0.08–0.12×10⁹ (dose group 1), 0.5–1.2×10⁹ (dose group 2), and 1.2–15×10⁹ (dose group 3/expansion) transduced cells.

Results Eleven patients (male, n=6; female, n=5) with NSCLC (adenocarcinoma, n=8; squamous cell carcinoma, n=3) were treated. Five, three, and three patients received cells in dose group 1, dose group 2, and dose group 3/expansion, respectively. The most frequently reported grade ≥3 adverse events were lymphopenia (n=11), leukopenia (n=10), neutropenia (n=8), anemia (n=6), thrombocytopenia (n=5), and hyponatremia (n=5). Three patients presented with cytokine release syndrome (grades 1, 2, and 4, respectively). One patient received the highest dose of lymphodepletion (fludarabine 30 mg/m² on days –5 to –2 and cyclophosphamide 1800 mg/m² on days –5 to –4) prior to a second infusion of ADP-A2M10 and had a partial response, subsequently complicated by aplastic anemia and death. Responses included: partial response (after second infusion; one patient), stable disease (four patients), clinical or radiographic progressive disease (five

patients), and not evaluable (one patient). ADP-A2M10 were detectable in peripheral blood and in tumor tissue. Peak persistence was higher in patients who received higher doses of ADP-A2M10.

Conclusions ADP-A2M10 demonstrated an acceptable safety profile and no evidence of toxicity related to off-target binding or alloreactivity. There was persistence of ADP-A2M10 in peripheral blood as well as ADP-A2M10 trafficking into the tumor. Given the discovery that MAGE-A10 and MAGE-A4 expression frequently overlap, this clinical program closed as trials with SPEAR T cells targeting MAGE-A4 are ongoing.

INTRODUCTION

Lung cancer is the most commonly diagnosed cancer and leading cause of cancer deaths worldwide.¹ Non-small cell lung cancer (NSCLC) accounts for 84% of lung cancers.² Targeted therapies are the treatment of choice for patients with newly diagnosed stage IV, relapsed, or recurrent disease with specific actionable molecular markers.³ Following failure of these therapies or for those without specific oncogenic drivers, first-line treatment is usually platinum-based doublet chemotherapy in combination with a programmed cell death-ligand 1 (PD-L1) or a programmed cell death 1 (PD-1) inhibitor depending on tumor PD-L1 expression status.³ The combination of a PD-1 inhibitor and a cytotoxic T lymphocyte antigen-4 inhibitor, with or without chemotherapy, is also appropriate. After progression on first-line therapy, alternative chemotherapy or, if not already utilized, PD-1/PD-L1 inhibitors are

administered. However, outcomes associated with treatments administered beyond first-line therapy are often limited, and there continues to be a significant unmet medical need for more effective therapies for patients with advanced NSCLC.

Adoptive cell therapy is a cancer immunotherapy approach that uses a patient's own T lymphocytes, which may be genetically modified to recognize specific cancer antigens, expanded *in vitro*, and reinfused into the patient to stimulate and expand antigen-specific T-cell immunity. Primarily with the use of chimeric antigen receptor T cells, tumor-infiltrating lymphocytes, or T-cell receptor (TCR) T cells, responses have been demonstrated in several malignancies, paving the way for the approval of several chimeric antigen receptor T-cell therapies in hematologic malignancies.^{4–8} Tumor-infiltrating lymphocyte therapy has shown activity in several solid tumors.⁹ For engineered T-cell therapy to be successful in the treatment of solid tumors, as has been recently demonstrated in human papillomavirus-associated epithelial cancers,¹⁰ the selection of a target antigen specific to the tumor together with effective tumor trafficking, tumor infiltration, and cellular persistence by the T-cell therapy are required.

Cancer/testis antigens (CTAs) are an example of tumor-specific antigens typically restricted to male germ cells in adults. CTAs are overexpressed in various cancers and have been a target for TCR therapy.^{11–16} Melanoma-associated antigen A10 (MAGE-A10) is a cancer/testis protein associated with many cancers.^{17–23} MAGE-A10 expression has been described in varying frequencies in NSCLC.^{17 18 22 23} MAGE-A10 expression by protein using immunohistochemistry (IHC)^{17 18} or by RNA using reverse transcription PCR^{22 23} has been reported to be from 4.5% to 25% for adenocarcinoma (AC) and from 33.84% to 50% for squamous cell carcinoma (SCC). In those tumors which were considered positive for MAGE-A10, Schultz-Thater *et al* reported the % positive cells in the tumors were 56.1% and 65.3% in AC and squamous cell histologies, respectively.¹⁸

ADP-A2M10 specific peptide enhanced affinity receptor (SPEAR) T cells (ADP-A2M10) are genetically engineered autologous T cells that incorporate an affinity-enhanced TCR capable of recognizing a complex consisting of human leukocyte antigen (HLA)-A*02:01 or A*02:06 and the GLYDGM EHL peptide derived from the MAGE-A10 CTAs.²⁴ This phase I trial (ADP-0022-003; NCT02592577; EudraCT: 2016-002518-28) assessed the safety of ADP-A2M10 in a dose-escalation trial with an expansion group for patients with advanced NSCLC.

METHODS

Patient eligibility and trial design

This multicenter, open-label, dose-escalation trial included HLA-A*02:01- and/or HLA-A*02:06-positive (*) patients with MAGE-A10-expressing NSCLC (ADP-0022-003 protocol; online supplemental file 2). Patients

were between 18 and 75 years of age with a diagnosis of histologically or cytologically confirmed advanced NSCLC (stage IIIB or IV) or recurrent disease and had received at least one line of prior therapy. Patients with known *EGFR* mutations or *ALK* or *ROS1* gene rearrangements received at least one prior EGFR or ALK or ROS1 tyrosine kinase inhibitor where indicated. Methods for HLA and MAGE-A10 testing are described in the online supplemental methods. Biopsies were given both a MAGE-A10 P-score and H-score. The P-score was the MAGE-A10 IHC positivity determined by a pathologist on the basis of both percentage of positive tumor cells and intensity of expression. The H-score was derived from the P-score by $1 \times (\% \text{ of } 1^+ \text{ cells}) + 2 \times (\% \text{ of } 2^+ \text{ cells}) + 3 \times (\% \text{ of } 3^+ \text{ cells})$. Patients had an Eastern Cooperative Oncology Group performance status of 0 or 1, adequate organ function, pulmonary function with mechanical parameters $\geq 40\%$ predicted (forced expiratory volume in 1 s, forced vital capacity, total lung capacity, diffusing capacity of the lungs for carbon monoxide), left ventricular ejection fraction $\geq 50\%$, and measurable disease by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST V.1.1) before lymphodepletion (not required before leukapheresis).²⁵

Eligible patients underwent leukapheresis for collection of CD3⁺ T cells for ADP-A2M10 manufacture (online supplemental methods). Bridging therapy was permissible prior to lymphodepleting chemotherapy with cyclophosphamide and fludarabine followed by infusion of ADP-A2M10 (table 1). Prior to the administration of lymphodepleting chemotherapy, all eligibility criteria were reconfirmed, and a baseline tumor assessment was obtained. Patients were eligible for a second infusion if they had a documented confirmed response (partial response (PR) or complete response) or clinical benefit ≥ 4 weeks after the first T-cell infusion.

The ADP-A2M10 dose-escalation scheme and lymphodepletion regimen are presented in table 1. The lymphodepletion regimen varied by dose group with a cyclophosphamide dose of 600 or 1800 mg/m²/day administered over 3 or 2 days, respectively, with or without fludarabine 30 mg/m²/day administered over 3 or 4 days (table 1). There were intervals of 21 days (dose group 1) and 7 days (dose groups 2, 3, and expansion group) between dosing each patient in dose groups 1–3, and among the first three patients who received transduced cells at $>6 \times 10^9$ in the expansion group only. The interventional phase lasted until progressive disease (PD), death, or withdrawal, after which patients with PD were rolled over into long-term follow-up for up to 15 years postinfusion.

Tumor biopsies were required at screening and optional at baseline and after T-cell infusion. Screening biopsies were performed using either archival tumor samples or fresh samples required for eligibility. Baseline and post-infusion biopsy samples were collected anytime from 2 months to 1 week prior to lymphodepletion and from 3 to 8 weeks after infusion, respectively.

Table 1 Dose groups—lymphodepletion and cell doses

Dose group	Lymphodepleting chemotherapy	Transduced ADP-A2M10 (range)	Patient ID
1	Cyclophosphamide 1800 mg/m ² /day on days -7 and -6	0.1×10 ⁹ (0.08×10 ⁹ –0.12×10 ⁹)	1–5
2	Cyclophosphamide 600 mg/m ² /day and fludarabine 30 mg/m ² /day on days -7, -6, and -5	1.0×10 ⁹ (0.5×10 ⁹ –1.2×10 ⁹)	6–8
3	Cyclophosphamide 600 mg/m ² /day on days -7, -6, and -5, and fludarabine 30 mg/m ² /day on days -7, -6, -5, and -4	5.0×10 ⁹ (1.2×10 ⁹ –6×10 ⁹)	9–10
Expansion group	Cyclophosphamide 1800 mg/m ² /day on days -3 and -2, and fludarabine 30 mg/m ² /day on days -5, -4, -3, and -2	5.0×10 ⁹ (1.2×10 ⁹ –15×10 ⁹)	9*
	Cyclophosphamide 600 mg/m ² /day on days -7, -6, and -5, and fludarabine 30 mg/m ² /day on days -7, -6, -5, and -4	5.0×10 ⁹ (1.2×10 ⁹ –15×10 ⁹)	11

*One patient (patient 9) received a second infusion at this schedule of cyclophosphamide and fludarabine and ADP-A2M10. ID, identifier.

Assessment of toxicities and response

Safety and tolerability were conducted at each study visit as follows: baseline, days -7 to -4, days 1 to 5, 8, 10, 12; weeks 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24; every 3 months until year 2; then every 6 months after year 2 or until disease progression, and at completion. Adverse events (AEs) of special interest were cytokine release syndrome (CRS), prolonged cytopenia, neurotoxicity, and graft-versus-host disease. AEs were graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) V.4.0, with two exceptions. CRS was graded as described in Lee *et al.*²⁶ In addition, prolonged cytopenias were graded in accordance with CTCAE V.5.0 as grade ≥ 3 neutropenia, anemia, or thrombocytopenia persisting for ≥ 4 weeks from ADP-A2M10 treatment.

A dose-limiting toxicity (DLT) was defined as a grade ≥ 3 AE within the first 30 days after administration of ADP-A2M10 regardless of the investigator's assessment of the relationship to ADP-A2M10. In evaluating potential DLTs, grade 3 or 4 CRS resolving to grade ≤ 2 within 7 days, and toxicities of any grade considered attributable to the underlying malignancy, lymphodepletion chemotherapy, or otherwise clearly unrelated to the ADP-A2M10, were deemed not a DLT by the Safety Review Committee.

Patients will be followed for 15 years after treatment with genetically modified T cells, according to the US Food and Drug Administration and European Medicines Agency guidance,^{27–29} for gene therapy-related delayed AEs, replication-competent lentivirus testing (quantitative PCR (qPCR) for the vesicular stomatitis virus-G DNA sequence), and, if necessary, insertional oncogenesis (online supplemental methods).

Efficacy was evaluated using RECIST V.1.1 criteria at the following study visits: baseline (within 7 days of lymphodepleting chemotherapy), weeks 4, 8, 12, and 24; every 3 months until year 2; then every 6 months from year 2 or until disease progression; and at completion.

Translational studies

Translational studies included the assessment of ADP-A2M10 persistence in peripheral blood and bone marrow, serum cytokine levels during CRS events, ADP-A2M10 in postinfusion tumor samples, PD-L1, CD3, major histocompatibility complex I (MHCI) expression, and HLA-A*02:01 loss of heterozygosity (LOH) in preinfusion and postinfusion tumor samples, transcriptomic analyses for antigen-processing machinery (APM), CD3⁺ T cells, CD8⁺ T cells, and T-cell exhaustion in preinfusion tumor samples.

Persistence of transduced ADP-A2M10 was assessed at BioAgilytix (Boston, Massachusetts, USA) by measuring the number of copies of integrated lentiviral vectors (Psi element sequence) per microgram of genomic DNA from peripheral blood and, when applicable, in bone marrow mononuclear cells (BMMC) by qPCR at the following time points: baseline; days 2, 4, and 8; weeks 2, 4, 8, 12, and 24; and every 3 months until year 2.

Levels of serum cytokines including interferon gamma (IFN γ), interleukin (IL)-6, IL-8, and IL-10 were collected at baseline, days 1–5 and 8, weeks 2, 3, 4, 6, 12, and 24, and every 3 months, and were evaluated as previously described.¹⁶

RNA in situ hybridization (RNAish) for ADP-A2M10 TCR was performed on the Ventana Discovery Ultra automation platform (Roche Diagnostics; Indianapolis, Indiana, USA) using the RNAscope 2.5 LS Red kit (Advanced Cell Diagnostics; Newark, California, USA) and RNAscope probes specific to ADP-A2M10 TCR (Advanced Cell Diagnostics) according to the manufacturer's instructions. RNAish assay was followed by CD3 chromogenic precipitate IHC (anti-CD3 (2GV6), rabbit monoclonal primary antibody; Roche Diagnostics, Indianapolis, Indiana, USA) using the DISCOVERY Teal HRP detection kit (Roche Diagnostics) (online supplemental methods).

CD3, MHCI, and PD-L1 expression was assessed by IHC at a CLIA-certified and Belgian Accreditation

Organization and College of American Pathologists-accredited laboratory (CellCarta, Antwerp, Belgium) as previously described.¹⁴ Antibody clones are described in the online supplemental methods.

HLA-A*0201 LOH assessment was performed using whole exome sequencing data generated from tumor and matched normal samples as described in the online supplemental methods. Transcriptomic analyses were performed at CellCarta (Antwerp, Belgium) as previously reported,¹⁶ with modifications described in the online supplemental methods. The following gene signatures were used for analyses: APM,³⁰ CD3⁺ T cells, CD8⁺ T cells³¹ (NanoString Technologies; Seattle, Washington, USA), and T-cell exhaustion.³²

Statistical considerations

The primary objective was evaluation of the safety and tolerability of ADP-A2M10. Secondary objectives included antitumor activity according to RECIST V.1.1 and the evaluation of potential gene therapy-related delayed AEs. Exploratory objectives were to assess persistence of transduced ADP-A2M10 in peripheral blood and their trafficking into tumor tissue, the production of cytokines postinfusion, and the characteristics of the tumor and tumor microenvironment in preinfusion and postinfusion tumor samples.

Progression-free survival (PFS), overall survival (OS), and duration of stable disease (DoSD) were summarized and graphically displayed using the Kaplan-Meier method to estimate the 25th, 50th (median), and 75th percentiles with corresponding 95% CIs. The intention-to-treat (ITT) population for analysis was defined as all eligible patients who were enrolled in the trial. The modified ITT (mITT) population includes all patients in the ITT population who received at least one ADP-A2M10 infusion. The mITT population was the primary population for the safety and efficacy analysis.

RESULTS

Patient characteristics

From July 2017 to December 2019, 11 patients underwent lymphodepletion and were treated with ADP-A2M10 (online supplemental results and table 1). One patient received a second ADP-A2M10 infusion. Patients 1–5, 6–8, 9–10, and 11 were treated in dose groups 1, 2, 3, and the expansion group, respectively (table 1). Demographic and baseline characteristics are detailed in table 2. The median (range) age of treated patients was 61 (46–72) years, race and ethnicity were white and not Hispanic/Latino, respectively. The histology of the NSCLC was AC (eight patients) and SCC (three patients). HLA and MAGE-A10 expression and ADP-A2M10 cell dose are as described. All 11 treated patients had at least one prior systemic therapy (median: 3; range: 1–6). All patients reported prior chemotherapy, nine reported prior immunotherapy, three reported prior targeted therapy, and seven reported prior radiotherapy.

Treatment and AEs

Of the 11 treated patients, all received transduced ADP-A2M10 doses between 0.1 and 6.77×10^9 transduced T cells (table 2). Several lymphodepletion regimens were used (table 1). On the basis of response, duration of response, and achieving optimal postinfusion peak expansion, a higher-dose lymphodepletion consisting of cyclophosphamide 1800 mg/m²/day for 2 days in combination with fludarabine 30 mg/m²/day for 4 days was initially administered in the expansion group (table 1).¹⁶

In dose group 1, there was a protocol-defined DLT of grade 4 CRS (detailed below) in patient 1, who received 0.1×10^9 ($\pm 20\%$) transduced cells. This resulted in the expansion of dose group 1 with four additional patients who did not have a further DLT. Given that three patients were also treated at this same ADP-A2M10 dose level in ADP-0022-004 (NCT02989064) without a DLT, the Safety Review Committee agreed that dose escalation could proceed. Similarly, based on data from ADP-0022-004 (NCT02989064), the Safety Review Committee also endorsed progression from group 3 to the expansion group after only 2 patients were treated in group 3. There were no additional DLTs in dose groups 2, 3, and expansion group. There were no apparent differences in AE grades across all dose groups and the expansion group of ADP-A2M10 after the first infusion.

All 11 treated patients experienced at least one AE. AEs of grade ≥ 3 occurring in $\geq 20\%$ of patients are shown in table 3. Ten patients (91%) had AEs of grade 3 or 4, and two patients (18%) had a grade 5 AE (unrelated to treatment and consisting of pneumonia and disease progression, respectively) following their first dose (table 3). The most common grade 3 or 4 AEs reported were lymphopenia/lymphocyte count decreased, leukopenia/white blood cell count decreased, anemia/red blood cell count decreased, neutropenia/neutrophil count decreased, thrombocytopenia/platelet count decreased, and hyponatremia.

Eight patients had AEs definitely, probably, or possibly related to ADP-A2M10 therapy alone (online supplemental table 2). The most common related AEs were cytopenias. There were no grade 5-related AEs following the first infusion; however, one patient who was initially treated in dose group 3 had a grade 5-related AE following the second infusion (further described below). Three patients had serious AEs that were considered related to the first infusion of ADP-A2M10 by the investigators, including patients 1 and 8 with grades 4 and 1 CRS, respectively, and patient 6 with grade 2 hemoptysis and a prior history of tracheal stenting due to an endobronchial tumor.

One patient (patient 9), with SCC of the lung previously treated with carboplatin and paclitaxel, had stable disease (SD) after the first treatment with ADP-A2M10 in group 3. Having completed accrual safely in dose group 3, this patient was offered a second treatment in the expansion group. As noted above, the second, higher-dose lymphodepletion regimen consisted of

Table 2 HLA and MAGE-A10 expression, ADP-A2M10 dose and response in individual patients (ITT population) with NSCLC of various histologies at screening

Patient ID	Age, years Sex	Tumor histology	HLA-A, allele 1/ allele 2	MAGE-A10 P-score,* % score <1 ⁺ , 1 ⁺ , 2 ⁺ , 3 ⁺	MAGE-A10 H-score†	Actual ADP-A2M10 dose, cells×10 ⁹	Response (DoSD‡)
1	48 F	AC	01:01/02:01	70, 20, 10, 0	40	0.1	PD
2	72 M	AC	01:01/02:01	80, 0, 0, 20	60	0.1	cPD
3	46 M	AC	02:01/23:01	85, 5, 5, 5	30	0.1	cPD
4	60 M	AC	02:01/02:01	0, 10, 30, 60	250	0.1	PD
5	61 F	SCC	02:01/23:01	20, 20, 30, 30	170	0.1	cPD
6	53 F	AC	02:01/03:01	50, 20, 20, 10	90	1.2	NE
7	69 F	SCC	02:01/30:04	10, 30, 50, 10	160	1.2	SD (58 days)
8	69 M	AC	01:01/02:01	50, 45, 0, 5	60	0.67	SD (89 days)
9§	65 M	SCC	02:01/23:01	0, 5, 5, 90	285	6.01 5.23§	SD→PR§ SD (170 days) PR (32 days)
10	63 M	AC	02:01/24:AUJRX	75, 0, 0, 25	75	5.19	SD (52 days)
11	59 F	AC	02:01/68:01	40, 20, 10, 30	130	6.77	SD (61 days)

*P-score was IHC positivity determined by a pathologist on the basis of both percentage of positive tumor cells and intensity of expression.

†H-score was derived from the P-score by $1 \times (\% \text{ of } 1^+ \text{ cells}) + 2 \times (\% \text{ of } 2^+ \text{ cells}) + 3 \times (\% \text{ of } 3^+ \text{ cells})$.

‡DoSD was only analyzed in patients with SD.

§Patient 9 had a second ADP-A2M10 infusion after SD was demonstrated following the first infusion (see text for details).

AC, adenocarcinoma; cPD, clinical PD; DoSD, duration of SD; F, female; HLA, human leukocyte antigen; H-score, histoscore; ID, identifier; IHC, immunohistochemistry; ITT, intention-to-treat; M, male; MAGE-A10, melanoma-associated antigen A10; NE, not evaluable; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; P-score, percent score; SCC, squamous cell carcinoma; SD, stable disease.

cyclophosphamide 1800 mg/m²/day for 2 days and fludarabine 30 mg/m²/day for 4 days. The patient received ADP-A2M10 5.2×10⁹ 113 days (week 16) after their first infusion of ADP-A2M10. Following the second infusion, the patient experienced erythroderma, aplastic anemia, and infection due to prolonged pancytopenia. The patient underwent haploidentical stem cell transplant using CD34⁺ cells and died on day 211 (week 30) following the first infusion (day 98 after the second infusion) of ADP-A2M10 as a result of bone marrow aplasia, sepsis, and acute respiratory distress syndrome. Following this event, lymphodepletion reverted to the group 3 regimen for future patients with a lower dose of cyclophosphamide (600 mg/m² per day for 3 days) administered with fludarabine.

Of the 11 patients treated, four entered long-term follow-up and all have died due to PD. No AEs related to gene-modified cell therapy were reported, all samples tested for molecular replication-competent lentivirus

were negative, and no patients met the criteria for insertional oncogenesis analysis.

AEs of special interest

CRS was reported in three of the 11 treated patients following the first ADP-A2M10 infusion with severity of grades 1, 2, and 4. The time to occurrence of CRS and time to maximum-grade CRS in these three patients was 2 days following the infusion of ADP-A2M10. Patient 2 had symptoms of nausea, vomiting, and tachycardia. Although resolution of CRS was not reported by the investigator, the patient did not receive treatment. In patient 1, symptoms of fever, nausea, vomiting, rash, confusion, hypotension, and hypoxia resolved after treatment with tocilizumab, fluids, mechanical ventilation, and antibiotics. Though these symptoms resolved, the patient died due to PD 9 days following ADP-A2M10 infusion. Patient 8 with symptoms of fever, chills, nausea, vomiting, and hypotension received treatment with fluids, dexamethasone

Table 3 AEs in $\geq 20\%$ of patients by grade following first infusion: mITT population

Preferred term	No of patients with AEs (N=11)			
	Any grade	Grade 3	Grade 4	Grade 5
Patients with any AEs	11	10	10	2*
Lymphopenia /lymphocyte count decreased	11	1	10	0
Leukopenia/WBC count decreased	10	0	10	0
Anemia/RBC count decreased	9	6	0	0
Neutropenia/neutrophil count decreased	9	0	8	0
Nausea	7	1	0	0
Pyrexia	6	0	0	0
Constipation	5	0	0	0
Hyponatremia	5	5	0	0
Edema peripheral	5	0	0	0
Thrombocytopenia /platelet count decreased	5	3	2	0
Chills	4	0	0	0
Decreased appetite	4	0	0	0
Fatigue	4	1	0	0
Pneumonia	4	1	0	1
Alopecia	3	0	0	0
CRS	3	0	1	0
Diarrhea	3	0	0	0
Pancytopenia	3	1	2	0
Sinus tachycardia/ tachycardia	3	0	0	0

*There were two grade 5 events: one each of pneumonia and disease progression; neither was considered related to treatment.
AE, adverse event; CRS, cytokine release syndrome; mITT, modified intention-to-treat; RBC, red blood cell; WBC, white blood cell.

and antibiotics, which resolved symptoms. The transient increase in CRS-associated serum cytokines, such as IFN γ , IL-6, IL-8, and IL-10, was observed after ADP-A2M10 infusion in all patients (online supplemental figure 1). Notably, patient 1 with grade 4 CRS had relatively high levels of IL-6 and IL-8, and patient 2 with grade 1 CRS had relatively high levels of IL-8. However, there was no marked difference in levels of these cytokines between those who had CRS and those who did not (online supplemental figure 1), although the small number of patients limits the conclusions that can be drawn.

No patients experienced prolonged cytopenia following their first infusion with ADP-A2M10. However, patient 9 experienced prolonged pancytopenia and aplastic anemia following the second infusion of ADP-A2M10 at the highest lymphodepletion regimen as described above. To evaluate the possible role of ADP-A2M10 in the development of aplastic anemia in patient 9, persistence of ADP-A2M10 in the patient's bone marrow and peripheral blood was evaluated by qPCR (figure 1A). Although ADP-A2M10 were detected in the BMBC, no evidence of

enrichment of ADP-A2M10 in the marrow was observed (figure 1A, online supplemental results).

Two patients (patients 1 and 9) had neurotoxicity that was possibly related to ADP-A2M10: grade 2 delirium and grade 1 lightheadedness, respectively. Patient 1 developed grade 2 delirium on the day of ADP-A2M10 infusion and was noted to have grade 4 CRS on day 2 (see details above). Patient 9 developed grade 1 lightheadedness while in the expansion group, 16 days following a second infusion of ADP-A2M10. Both patients had resolution of symptoms. There were no graft-versus-host disease events reported.

Response data

Seven of the 11 treated patients were evaluable for response by RECIST V.1.1 (table 2). Of the seven evaluable patients after the first infusion, five had SD, and two had PD as their best overall response. Of the remaining four patients, three had clinical PD by investigator assessment, and one was not evaluable because the patient did not have post-baseline assessments (table 2). Of the patients with SD, two were in dose group 2, two were in dose group 3, and one was in the expansion group. Patient 9 had a 25% tumor reduction by RECIST V.1.1 after the first infusion and underwent a second ADP-A2M10 infusion. Eight weeks after the second infusion, this patient achieved a PR (later confirmed) when compared against the baseline measurement taken prior to the first infusion (figure 1A,B).

The median PFS, OS, and DoSD were obtained for all patients after the first infusion. The median (range) PFS was 58 (1–89) days, with median (range) PFS for dose group 3 and the expansion group at 61 (52–88) days. The median (range) OS was 132 (10–458) days, with median (range) OS for dose group 3 and the expansion group at 211 (132–458) days. The median (range) overall DoSD was 61 (52–89) days.

Translational data

The kinetics of persistence of transduced ADP-A2M10 varied among patients; however, the persistence of transduced cells was observed in all patients throughout the follow-up period and up to 12 months postinfusion (figure 2A). On average, peak persistence was higher in patients from dose group 3 and the expansion group compared with patients from dose groups 1 and 2 (online supplemental table 3). Time to peak persistence was comparable between patients across the groups. Peak persistence trended higher in patients with SD; however, the small sample size limits the ability to draw conclusions. ADP-A2M10 infiltration was evaluated in four biopsies taken within 8 weeks after infusion. ADP-A2M10 was detected in the tumor tissue of a patient with SCC from dose group 1 and a patient with AC from dose group 3 (figure 2B,C). ADP-A2M10 infiltration was not observed in the tumor tissue of a patient with AC from dose group 2 and a patient with SCC from dose group 3 (figure 2C).

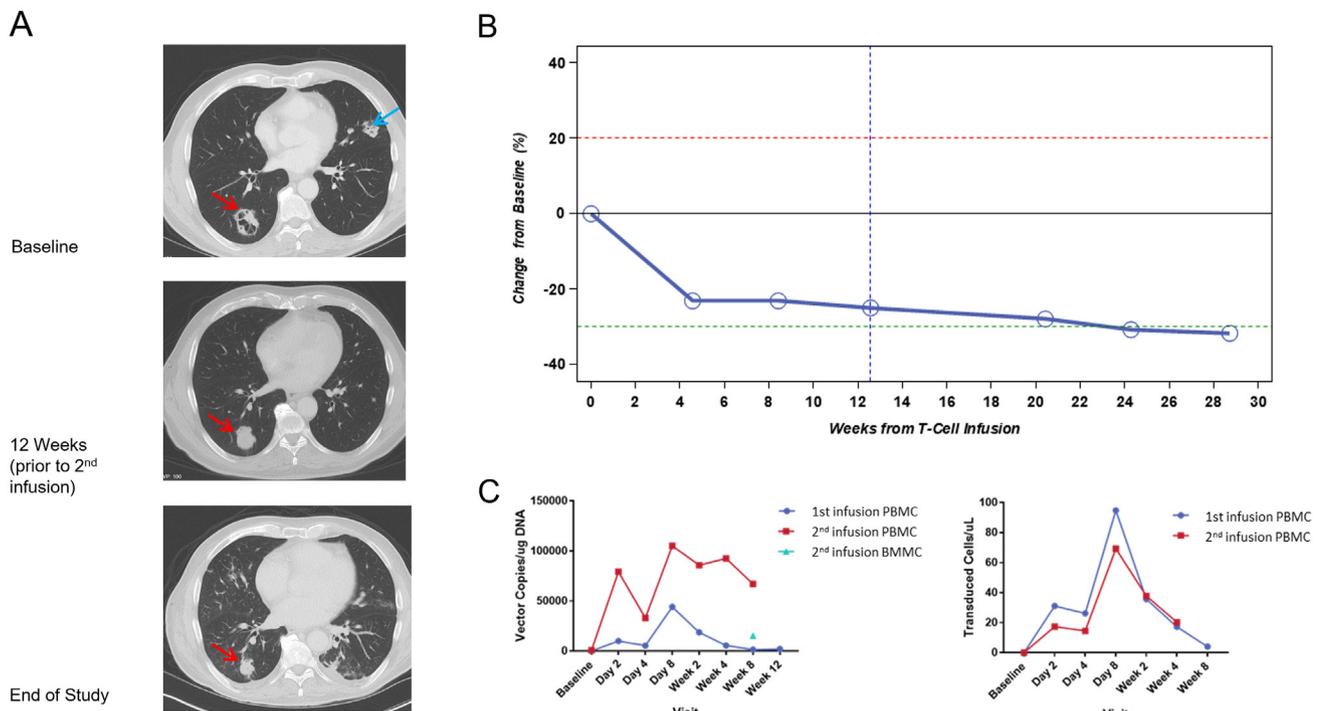


Figure 1 Patient 9: Response to treatment and persistence of ADP-A2M10. (A) CT scans of the RLL (red arrow) and LUL lung masses (blue arrow) at baseline (prior to the first infusion of ADP-A2M10, during week 12 (3 weeks prior to the second infusion of ADP-A2M10), and at the end of study (~28 and ~13 weeks from the first and second ADP-A2M10 infusions, respectively). (B) Graphical representation of the response by RECIST V.1.1. The patient's baseline response for the second infusion used the week 12 tumor assessment from the first infusion of ADP-A2M10, as target and non-target lesions were the same as the first infusion. Percentage change in the sum of diameters is calculated on the basis of the baseline measurement from the first infusion. The blue dotted line signifies the baseline for the second infusion. (C) Persistence assessed as vector copies/microgram DNA (left panel) and as ADP-A2M10/microliter (right panel) for samples where absolute cell count data were available. BMMC, bone marrow mononuclear cells; LUL, left upper lobe; PBMC, peripheral blood mononuclear cells; RLL, right lower lobe.

To better understand the potential basis for the limited clinical benefit of ADP-A2M10 therapy, different characteristics of patients' tumor tissue were evaluated. The preinfusion levels of MAGE-A10 and MHC1 proteins in tumor cells were highly variable across patients (figure 3A,B, online supplemental figure 2A, and online supplemental results). Preinfusion MAGE-A10 levels were higher in patients with SCC compared with patients with AC (figure 3C and online supplemental figure 2B). In contrast, preinfusion MHC1 levels were lower in patients with SCC compared with patients with AC (figure 3C). HLA-A*0201 LOH was detected in two of four samples examined in the study (online supplemental figure 2C). Marked variability across patients was also observed in preinfusion levels of CD3 and PD-L1 protein expression, and in preinfusion levels of CD3⁺ T-cell, CD8⁺ T-cell, T-cell exhaustion, and APM (in tumor and stromal cells) gene expression (online supplemental figures 3, 4, and 5). Preinfusion levels of PD-L1 protein expression were low (tumor proportion score <1) in four of nine preinfusion tumor samples (online supplemental figure 3B). There was no correlation noted between PD-L1 expression and CD3⁺ T-cell infiltration (online supplemental figures 3C, 4B). Owing to the small number of postinfusion samples available, it is difficult to draw any conclusion about

effects of ADP-A2M10 infusion on MAGE-A10, MHC1, CD3, and PD-L1 levels (figure 3A,B and online supplemental figures 3A,B, 4A). Taken together, the data obtained on the patients' tumors were limited and insufficient to conclude that one of the characteristics influenced the limited clinical benefit observed with ADP-A2M10 therapy.

DISCUSSION

ADP-0022-003 is a single-arm, open-label phase I dose-escalation trial to assess ADP-A2M10 in advanced NSCLC. Eleven patients were treated with lymphodepletion chemotherapy followed by ADP-A2M10 administered to a target dose of 5×10^9 transduced T cells. There was only one DLT (grade 4 CRS) in the first patient treated, resulting in an expansion of dose group 1. Cytopenias were the most common AEs reported. Treatment-related AEs of special interest following the first infusion of ADP-A2M10 were observed in two patients with CRS alone (grades 1 and 2), and in one patient with CRS (grade 4) with neurotoxicity (grade 2 delirium). Following a second infusion with a higher lymphodepletion regimen, one patient developed prolonged pancytopenia with complications and subsequent death.

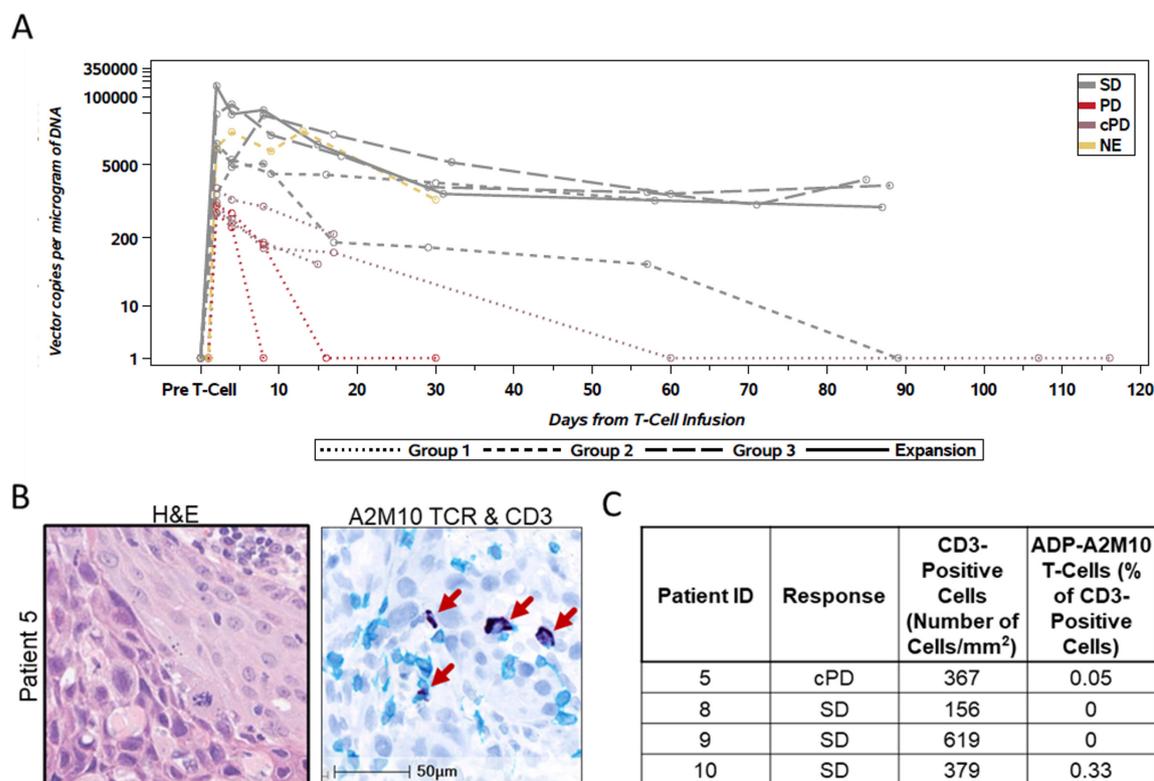


Figure 2 ADP-A2M10 was detected in peripheral blood and tumor tissue after the first infusion. (A) Persistence of ADP-A2M10 was measured by quantitative PCR of the Psi element sequence in genomic DNA extracted from peripheral blood mononuclear cells. Dotted, dashed, broken, and solid lines indicate dose group ($0.08\text{--}0.12 \times 10^9$, group 1; $0.5\text{--}1.2 \times 10^9$, group 2; and $1.2\text{--}15 \times 10^9$, dose group 3/expansion). In addition, data points are colored by response based on RECIST V.1.1 except for three patients who had clinical progression by investigator assessment. (B) Representative field of (left) H&E stain and (right) CD3 IHC/ADP-A2M10 TCR RNAish duplex stain performed for the detection of CD3⁺ and/or ADP-A2M10 TCR⁺ cells in the tumor tissue of patient 5 collected within 8 weeks after infusion. In the right image, CD3⁺ cells are shown in teal, ADP-A2M10 TCR⁺ cells are shown in dark blue, and nuclei are shown in light blue (hematoxylin stain). (C) Result table for CD3 IHC/RNAish duplex assays reporting the detection of ADP-A2M10 in two of four postinfusion tumor samples. cPD, clinical PD; IHC, immunohistochemistry; NE, not evaluable; PD, progressive disease; RECIST V.1.1, Response Evaluation Criteria in Solid Tumors V.1.1; RNAish, RNA in situ hybridization; SD, stable disease; TCR, T-cell receptor.

There were several lymphodepletion regimens used in this protocol. ADP-A2M10 with a lymphodepleting chemotherapy consisting of intravenous cyclophosphamide $600 \text{ mg/m}^2/\text{day}$ for 3 days and intravenous fludarabine $30 \text{ mg/m}^2/\text{day}$ for 3 or 4 days was associated with an acceptable safety profile. However, on the basis of clinical data that indicated that higher-dose lymphodepletion may be needed to achieve optimal postinfusion peak expansion and durable responses in HLA-A2⁺ patients with synovial sarcoma treated with New York Esophageal Antigen-1 (NY-ESO-1)^{e259T} (NCT01343043³³), a lymphodepletion regimen including a higher dose of cyclophosphamide $1800 \text{ mg/m}^2/\text{day}$ for 2 days with fludarabine $30 \text{ mg/m}^2/\text{day}$ for 4 days was also administered to one patient in the expansion group. This patient received this regimen prior to a second ADP-A2M10 infusion, after which the patient developed prolonged pancytopenia and died from treatment-related aplastic anemia, sepsis, and acute respiratory distress syndrome. The following patient (patient 11) was treated with the lower lymphodepletion regimen used in dose group 3.

There are reported cases of prolonged cytopenias with lymphodepletion regimens administered prior to adoptive T-cell therapy.^{34 35} Aplastic anemia has been observed after high-dose lymphodepletion similar to that employed in the patient treated in this trial.^{12 33 36 37} In addition, cyclophosphamide and fludarabine have either bone marrow failure or aplasia, respectively, listed as warnings/precautions in their prescribing information.^{38 39} We examined the possible role of ADP-A2M10 in the development of aplastic anemia in patient 9. Transduced ADP-A2M10 were detected by qPCR for the Psi vector element in genomic DNA extracted from the BMCM of patient 9, but no evidence of bone marrow enrichment of ADP-A2M10 was observed compared with levels in peripheral blood. Patient-derived bone marrow was of insufficient quality to assess antigen expression or perform T-cell activation analysis, but evaluation of CD34⁺ BMCM from 12 healthy donors and hematopoietic precursors sorted by IHC and RNAseq found no evidence of MAGE-A10 expression (data not shown). In addition, ADP-A2M10 did not display in vitro functional responses (as

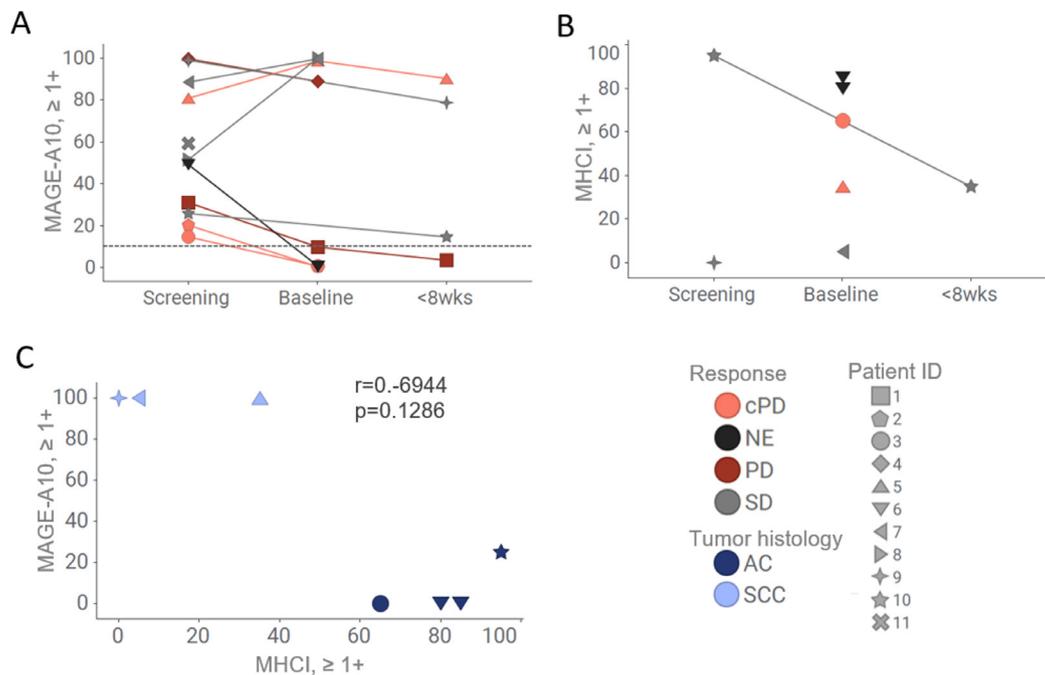


Figure 3 Variability of MAGE-A10 and MHC1 expression in tumor cells across the trial patients. Preinfusion biopsies (screening and baseline) (A–C) and postinfusion biopsies collected within 8 weeks after the first infusion of ADP-A2M10 (A, B) were used for MAGE-A10 expression and MHC1 expression evaluation. (A, C) MAGE-A10 expression was assessed by MAGE-A10 IHC and plotted as percentage of tumor cells with 1⁺, 2⁺, and 3⁺ intensities. (A) Horizontal lines designate the cut-off of 10% of tumor with ≥1⁺ intensity of staining. (B, C) MHC1 expression was assessed using MHC1 IHC assay and plotted as percentage of tumor cells with 1⁺, 2⁺, and 3⁺ intensities. Data points are colored by response (A, B) or by tumor histology (C). Patient IDs are indicated by shape. AC, adenocarcinoma; cPD, clinical PD; ID, identifier; IHC, immunohistochemistry; MAGE-A10, melanoma-associated antigen A10; MHC1, major histocompatibility complex I; NE, not evaluable; PD, progressive disease; SCC, squamous cell carcinoma; SD, stable disease; wks, weeks.

determined by IFN γ release) to any of the HLA-A2⁺ CD34⁺ BMDC derived from four healthy donors (data not shown). Taken together, the data suggest that a causal relationship between ADP-A2M10 and the pancytopenia/aplastic anemia observed in this patient was unlikely, and that these AEs were more likely due to the lymphodepletion regimen.

In this trial, a PR was only seen in one patient after a second infusion and SD was noted in four patients. There are many factors that may contribute to the efficacy of autologous TCR-engineered T-cell products, such as antigen expression, T-cell dose, TCR expression levels, tumor trafficking and persistence in peripheral blood, and pre-existing and acquired immunosuppression.^{4,7,8} High expression of NY-ESO-1 or MAGE-A4 antigen as designated by histoscore (H-score) has been associated with responses in patients with synovial sarcoma.^{11,16} In this trial, though the MAGE-A10 H-score of the patient with a PR was high, there were no obvious differences in MAGE-A10 expression in patients with SD or PD. It is possible that this may be related to the interlesional and intralesional tumor heterogeneity of MAGE-A10 expression,⁴⁰ and that although antigen expression may be required, it alone is not sufficient to result in response. Cell dose has also been reported to be important for antitumor responses. Antitumor responses have more often been observed in patients who received NY-ESO-1

transduced cell doses of $\geq 1 \times 10^{9.14}$ and doses of $\geq 5 \times 10^9$ afamitresgene autoleucel (ADP-A2M4).¹¹ In this trial, three patients received a dose of $\geq 5 \times 10^9$ ADP-A2M10. Interestingly, PR and SD were demonstrated in these patients. Peak persistence trended higher in patients from dose group 3 and the expansion group, and in those with SD after the first infusion. Although the small number of patients treated in this trial limits the ability to draw any firm conclusions, there appears to be a trend toward a higher ADP-A2M10 dose, persistence, and disease control. Moreover, intratumoral immunosuppression may limit the efficacy of ADP-A2M10 therapy. The development of next-generation SPEAR T cells coexpressing additional immunoregulatory molecules, such as CD8 α or IL-7/CCL19 and novel combinations of SPEAR T cells with checkpoint inhibitors, may increase antitumor activity by overcoming immunosuppression and improving clinical responses in patients with epithelial cancers.^{13,41}

In conclusion, ADP-A2M10 has shown an expected safety profile and no off-target binding or alloreactivity. However, enrolment was challenging owing to the low frequency of MAGE-A10 positivity in HLA-eligible patients with NSCLC, especially in those with AC. While this trial was in progress, ADP-0044-001 (NCT03132922) began treating patients with afamitresgene autoleucel, targeting the MAGE-A4 antigen, and responses were seen in patients with NSCLC, head and

neck cancer, and synovial sarcoma.¹² Given the finding that MAGE-A10 expression frequently overlapped with MAGE-A4 expression in many tumors (Adaptimmune internal data), the ADP-A2M10 clinical program closed and several trials targeting MAGE-A4, including a registrational trial in sarcoma, are ongoing (NCT03132922, NCT04044768, and NCT04044859). Finally, the coexpression of both MAGE-A4 and MAGE-A10 in some tumors suggests that targeting multiple antigens, as has recently been done in lymphoma,⁴² may further represent a path toward overcoming local tolerance and inhibitory mechanisms.

Author affiliations

¹Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

²Medical Oncology, Washington University School of Medicine, St Louis, Missouri, USA

³Lung Cancer Research and Drug Development, Sarah Cannon Research Institute at Tennessee Oncology, Nashville, Tennessee, USA

⁴START Madrid-FJD, Fundación Jiménez Díaz University Hospital, Madrid, Spain

⁵Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA

⁶Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA

⁷Hematology, Sarah Cannon Center for Blood Cancer at TriStar Centennial, Nashville, Tennessee, USA

⁸Bone Marrow Transplant & Cellular Therapy, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

⁹Oncology, Johns Hopkins School of Medicine, Baltimore, Maryland, USA

¹⁰Adaptimmune, Milton Park, Abingdon, Oxfordshire, UK

¹¹Adaptimmune, Philadelphia, Pennsylvania, USA

Twitter Victor Moreno @VicMorenoGarcia and Matthew J Frigault @MJFzeta

Acknowledgements We wish to thank the patients and their families for their participation, and the nurses, study coordinators, and data managers at the centers for caring for the patients in this trial. In addition, we thank Steve Dawe, Susan Howard, Olga Ochkur, and Marina Guarisma for project and trial management support; and Paul Noto, Cheryl McAlpine, Ruoxi Wang, and Joana Senra for translational work (all of Adaptimmune). Data from this manuscript were presented at the Society of Immunotherapy of Cancer 2020 Meeting; November 11–14, 2020; *J Immunother Cancer* 2020;8(Suppl 3):A169–70; DOI: 10.1136/jitc-2020-SITC2020.0278.

Contributors AG: Contributed to the conception of the work and interpretation of data, as well as critical review/revision and approval of the work. He also agreed to be accountable for all aspects of the work. AJO: Interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. BDdS: Acquisition of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CB: The conception or design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. DB: Performed bioinformatic analysis of the translational data; contributed to writing of the manuscript; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. DM: The conception or design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. EN: Conception or design, interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to

be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. GRB: The conception or design, acquisition, analysis, and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JB: The interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JG: Interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. J-MN: The acquisition, analysis, and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JPS: The conception or design of the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JVH: The conception or design, acquisition, analysis, and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MJ: The acquisition, analysis, and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MJF: The conception or design of the work, the acquisition, analysis, and interpretation of data for the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MMP: Performed bioinformatic analysis of the translational data; contributed to writing of the manuscript; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. NH: Coordinated and oversaw the management of the study including acquisition of data, also reviewed and approved the manuscript. PMF: Provided clinical or scientific input into the study design and protocol, monitored and analyzed data, writing, review, and revision of the manuscript, and approval of the final submission. PMF also accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. RB: Designed and carried out the translational experiments; contributed to writing of the manuscript; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. RG: The acquisition, analysis of data for the work; revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SD: Helped in acquisition of data for this trial by serving as the treating physician. SD critically reviewed the draft and approved the final version; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SF: Designed the translational studies, contributed to the trial design, and wrote the manuscript; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. TH: Designed the study and wrote the original protocol. TH then led the MAGE-A10 project and had clinical responsibility

for this study from ~July 2017 through to early 2019 and was involved in the ongoing review of patients and the emerging safety and efficacy data. VKL: The acquisition and analysis of data for the work; drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. VM: The conception or design, acquisition, analysis, and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. ZW: Designed and carried out the translational experiments; contributed to writing of the manuscript; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding Adaptimmune wholly funded this work and contributed to study design, analysis, and interpretation of the data. Editorial and writing support for this manuscript was provided by Excel Scientific Solutions (Envision Pharma Group), which was contracted and compensated by Adaptimmune for these services.

Competing interests AG holds stock options in Adaptimmune. AJO has received research contracts from Alkermes, Antegene, Astellas, Checkmate, Gan & Lee, GlycoNex, InstilBio, Intensity, Istari, Kadmon, Kartos, Neolmmune, NGM, OncoSec, Soud Bio, SpringBank, Takeda; has received payment for advisory board roles from Merck, BMS, Pfizer, Takeda, Sanofi, Eisai. DB, DM, EN, JB, J-MN, JPS, MMP, NH, RB, SF are or were employees of Adaptimmune at the time of the study. GRB has received grants/contracts from Amgen, Bayer, Adaptimmune, Elelxis, Daiichi Sankyo, GlaxoSmithKline, Immatics, Immunocore, Incyte, Kite Pharma, Macrogenics, Torque, AstraZeneca, Bristol-Myers Squibb, Celgene, Genentech, MedImmune, Merck, Novartis, Roche, Xcovery, Tmunity Therapeutics, Regeneron, Beigene, Repertoire Immune Medicines, Verastem; consulting fees from Abbvie, Adicet, Amgen, Ariad, Bayer, Clovis Oncology, AstraZeneca, Bristol-Myers Squibb, Celgene, Daiichi Sankyo, Instil Bio, Genentech, Gilead, Lilly, Janssen, MedImmune, Merck, Novartis, Roche, Tyme Oncology, Xcovery, Virogin Biotech, Maverick Therapeutics; has participated on a Data Safety Monitoring Board or Advisory Board for Virogen Biotech, Maverick Therapeutics; holds stock or stock options in Virogin Biotech; and has other financial or non-financial interests in Johnson & Johnson/Janssen (immediate family member employed). JG has been a compensated consultant or received honoraria from Bristol-Myers Squibb, Genentech, Ariad/Takeda, Loxo, Pfizer, Incyte, Novartis, Merck, Agios, Amgen, Jounce, Karyopharm, GlydeBio, Mirati, AstraZeneca, Regeneron, Oncorus, Helsinn, Array, and Clovis Oncology; has been an employee (immediate family member) with equity in Ironwood Pharmaceuticals; has received research funding from Novartis, Genentech/Roche, and Ariad/Takeda; has received institutional research support from Tesaro, Moderna, Blueprint, Scholar Rock, BMS, Array, Adaptimmune, Novartis, Genentech/Roche, Alexo and Merck. JVH has received grants/contracts from AstraZeneca, GlaxoSmithKline and Spectrum; holds royalty/licenses in Spectrum; has received consulting fees from AstraZeneca, Boehringer-Ingelheim, Catalyt, Genentech, GlaxoSmithKline, Guardant Health, Foundation medicine, Hengrui Therapeutics, Eli Lilly, Novartis, Spectrum, EMD Serono, Sanofi, Takeda, Mirati Therapeutics, BMS, BrightPath Biotherapeutics, Janssen Global Services, Nexus Health Systems, EMD Serono, Pneuma Respiratory, Kairos Venture Investments, Roche, Leads Biolabs, RefleXion; has received honoraria from Medlinker, Peerview, Nexus Health Medicine, Targeted Oncology, MJH Events; has received support for attending meetings from IASLC Targeted Therapies, IASLC World Conference on Lung Cancer; has been in a leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid for Mechanisms of Cancer Therapeutics-1 (MCT1) (Study Section – Chair). MJ has received research funding from AbbVie, Acerta, Adaptimmune, Apexigen, Array BioPharma, AstraZeneca, Atreca, BeiGene, Boehringer Ingelheim, Checkpoint Therapeutics, Corvus Pharmaceuticals, CytomX, Daiichi Sankyo, Dynavax, Lilly, EMD Serono, Genentech/Roche, Genmab, Genocoea Biosciences, GlaxoSmithKline, Gritstone Oncology, Guardant Health, Hengrui Therapeutics, Immunocore, Incyte, Janssen, Jounce Therapeutics, Kadmon Pharmaceuticals, Loxo Oncology, Lycera, Merck, Mirati Therapeutics, Neovia Oncology, Novartis, OncoMed Pharmaceuticals, Pfizer, Regeneron Pharmaceuticals, Sanofi, Seven and Eight Biopharmaceuticals, Shattuck Labs, Stem CentRx, Syndax Pharmaceuticals, Takeda Pharmaceuticals, Tarveda, University of Michigan, WindMIL, TCR2 Therapeutics, Arcus Biosciences, Ribon Therapeutics, Amgen; has held a consulting/advisory role (spouse) for Astellas, Otsuka Pharmaceuticals; has held a consulting/advisory role (self) for AbbVie, Achilles Therapeutics, AstraZeneca, Atreca, Boehringer Ingelheim, Calithera Biosciences, Genentech, GlaxoSmithKline, Gritstone Oncology, Guardant Health,

Incyte, Janssen, Lilly, Loxo Oncology, Merck, Mirati Therapeutics, Novartis, Pfizer, Ribon Therapeutics, Sanofi, Association of Community Cancer Center; has received food/beverage/travel expenses from Abbvie, Astellas, AstraZeneca, Boehringer Ingelheim, Clovis, Daiichi Sankyo, EMD Serono, Bristol Myers Squibb, Exelixis, Genentech/Roche, Incyte, Merck, Pfizer, Sysmex Inostics, Vapotherm, Janssen, Lilly, Novartis, Sanofi. MJE has received research funding from GlaxoSmithKline, Mersana, Amgen, Windmil, Nektar, Apexigen, Adaptimmune; has received consulting fees from Kanaph, Flame; has received honoraria from Sanofi; has been a member of DSMB for AstraZeneca, Seattle Genetics, GlaxoSmithKline, Takeda; has been a consultant/on an advisory board for Windmil, Regeneron, Syndax; has been the Chair, Scientific Advisory board for Lung Cancer Foundation of America; has been the Deputy Editor of 'Lung Cancer'; has received stock options from Biomarker strategies; Creaty Biotech. MJF has been a consultant for Arcellx, BMS, Novartis, Kite, Iovance. PMF is an employee of Adaptimmune; holds stock in Adaptimmune and Bristol-Myers Squibb; has received compensation for travel and congress meetings. RG has received consulting fees from BMS, Abbvie, Geneplus; has participated on a Data Safety Monitoring Board or Advisory Board for Roche Genentech. SD has been a consultant for Jacobio pharmaceuticals (without financial compensation). TH was an employee of Adaptimmune at the time of the study; has been a consultant for Adaptimmune. VKL has been in a consulting or advisory role for Takeda, Bristol-Myers Squibb, Seattle Genetics; has received research funding from GlaxoSmithKline, Bristol-Myers Squibb, Guardant Health, Takeda. VM has received consulting fees from Roche, Bayer, Pieris, BMS, Janssen and Basilea. BDdS, CB, ZW have nothing to declare.

Patient consent for publication Not applicable.

Ethics approval The protocol and amendments were approved by the institutional review board or ethics committee at each participating site, and the trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All patients provided written informed consent prior to enrolment as per institutional guidelines.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplemental information. The raw data sets generated, used, and analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID ID

Paula M Fracasso <http://orcid.org/0000-0003-1211-3304>

REFERENCES

- 1 Bray F, Ferlay J, Soerjomataram I, *et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.
- 2 US National Institute of Health. WHO/IASLC histologic classification of NSCLC. Available: https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#link/_361_toc [Accessed Apr 2021].
- 3 US National Institute of Health. Non-small cell lung cancer treatment (PDQ®). Available: <https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq> [Accessed Apr 2021].
- 4 Weber EW, Maus MV, Mackall CL. The emerging landscape of immune cell therapies. *Cell* 2020;181:46–62.
- 5 Klebanoff CA, Rosenberg SA, Restifo NP. Prospects for gene-engineered T cell immunotherapy for solid cancers. *Nat Med* 2016;22:26–36.

- 6 Kalos M, June CH. Adoptive T cell transfer for cancer immunotherapy in the era of synthetic biology. *Immunity* 2013;39:49–60.
- 7 Grimes JM, Carvajal RD, Muranski P. Cellular therapy for the treatment of solid tumors. *Transfus Apher Sci* 2021;60:103056.
- 8 Jones HF, Molvi Z, Klatt MG, et al. Empirical and rational design of T cell receptor-based immunotherapies. *Front Immunol* 2020;11:585385.
- 9 Rohaan MW, van den Berg JH, Kvistborg P, et al. Adoptive transfer of tumor-infiltrating lymphocytes in melanoma: a viable treatment option. *J Immunother Cancer* 2018;6:102.
- 10 Nagarsheth NB, Norberg SM, Sinkoe AL, et al. TCR-engineered T cells targeting E7 for patients with metastatic HPV-associated epithelial cancers. *Nat Med* 2021;27:419–25.
- 11 Van Tine BA, Hong DS, Johnson ML, et al. Durable responses in patients with synovial sarcoma in the phase I trial of ADP-A2M4 (MAGE-A4). *Connective Tissue Oncology Society* 2020 https://www.ctos.org/Portals/0/PDF/2020%20CTOS%20Prelim%20Program_FINAL.pdf
- 12 Hong DS, Van Tine BA, Olszanski AJ, et al. Phase I dose escalation and expansion trial to assess the safety and efficacy of ADP-A2M4 spear T cells in advanced solid tumors. *JCO* 2020;38:102.
- 13 Hong D, Clarke J, Johanns T, et al. Initial safety, efficacy, and product attributes from the SURPASS trial with ADP-A2M4CD8, a SPEAR T-cell therapy incorporating an affinity optimized TCR targeting MAGE-A4 and a CD8 α co-receptor. *J Immunother Cancer* 2020;8(Suppl 3):A231.
- 14 D'Angelo SP, Melchiori L, Merchant MS, et al. Antitumor activity associated with prolonged persistence of adoptively transferred NY-ESO-1^{ct259}T cells in synovial sarcoma. *Cancer Discov* 2018;8:944–57.
- 15 Robbins PF, Kassim SH, Tran TLN, et al. A pilot trial using lymphocytes genetically engineered with an NY-ESO-1-reactive T-cell receptor: long-term follow-up and correlates with response. *Clin Cancer Res* 2015;21:1019–27.
- 16 Ramachandran I, Lowther DE, Dryer-Minnerly R, et al. Systemic and local immunity following adoptive transfer of NY-ESO-1 SPEAR T cells in synovial sarcoma. *J Immunother Cancer* 2019;7:276.
- 17 Su C, Xu Y, Li X, et al. Predictive and prognostic effect of CD133 and cancer-testis antigens in stage Ib-IIIa non-small cell lung cancer. *Int J Clin Exp Pathol* 2015;8:5509–18.
- 18 Schultz-Thater E, Piscuoglio S, Iezzi G, et al. MAGE-A10 is a nuclear protein frequently expressed in high percentages of tumor cells in lung, skin and urothelial malignancies. *Int J Cancer* 2011;129:1137–48.
- 19 Mengus C, Schultz-Thater E, Coulot J, et al. MAGE-A10 cancer/testis antigen is highly expressed in high-grade non-muscle-invasive bladder carcinomas. *Int J Cancer* 2013;132:2459–63.
- 20 Lin J, Lin L, Thomas DG, et al. Melanoma-associated antigens in esophageal adenocarcinoma: identification of novel MAGE-A10 splice variants. *Clin Cancer Res* 2004;10:5708–16.
- 21 Daudi S, Eng KH, Mhawech-Fauceglia P, et al. Expression and immune responses to MAGE antigens predict survival in epithelial ovarian cancer. *PLoS One* 2014;9:e104099.
- 22 Tajima K, Obata Y, Tamaki H, et al. Expression of cancer/testis (CT) antigens in lung cancer. *Lung Cancer* 2003;42:23–33.
- 23 Gure AO, Chua R, Williamson B, et al. Cancer-testis genes are coordinately expressed and are markers of poor outcome in non-small cell lung cancer. *Clin Cancer Res* 2005;11:8055–62.
- 24 Border EC, Sanderson JP, Weissensteiner T, et al. Affinity-enhanced T-cell receptors for adoptive T-cell therapy targeting MAGE-A10: strategy for selection of an optimal candidate. *Oncoimmunology* 2019;8:e1532759.
- 25 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
- 26 Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014;124:188–95.
- 27 US Food and Drug Administration. Long term follow-up after administration of human gene therapy products. Guidance for industry. Available: <https://www.fda.gov/media/113768/download> [Accessed 21 Jul 2021].
- 28 US Food and Drug Administration. Testing of retroviral vector-based human gene therapy products for replication competent retrovirus during product manufacture and patient follow-up. Guidance for industry. Available: <https://www.fda.gov/media/113790/download> [Accessed 21 Jul 2021].
- 29 European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on follow-up of patients administered with gene therapy medicinal products. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-follow-up-patients-administered-gene-therapy-medicinal-products_en.pdf [Accessed 21 Jul 2021].
- 30 Şenbabaoğlu Y, Gejman RS, Winer AG, et al. Tumor immune microenvironment characterization in clear cell renal cell carcinoma identifies prognostic and immunotherapeutically relevant messenger RNA signatures. *Genome Biol* 2016;17:231.
- 31 Rhodes M, Danaheer P, Dennis L, et al. Using the PanCancer immune profiling advanced analysis module. Available: https://www.nanostring.com/wp-content/uploads/2020/12/WP_MK1190_PanCancer_Immune_Profiling_Advanced_Analysis.pdf [Accessed 21 Jul 2021].
- 32 Woroniecka K, Chongsathidkiet P, Rhodin K, et al. T-cell exhaustion signatures vary with tumor type and are severe in glioblastoma. *Clin Cancer Res* 2018;24:4175–86.
- 33 D'Angelo SP, Tap WD, Glod J. Open label non-randomized multi-cohort pilot study of genetically engineered NYESO-1 spear T-cells in HLA-A2+ patients with synovial sarcoma (NCT01343043). Abstract ID: 2804636. *Connective Tissue Oncology Society* 2017 <https://www.ctos.org/Portals/0/PDF/2017%20CTOS%20Final%20Program.pdf>
- 34 US Food and Drug Administration. Yescarta biologics license application clinical review memorandum. Available: <https://www.fda.gov/media/109149/download> [Accessed Apr 2021].
- 35 US Food and Drug Administration. Kymriah biologics licence application clinical review memorandum. Available: <https://www.fda.gov/media/107973/download> [Accessed Apr 2021].
- 36 Chodon T, Comin-Anduix B, Chmielowski B, et al. Adoptive transfer of MART-1 T-cell receptor transgenic lymphocytes and dendritic cell vaccination in patients with metastatic melanoma. *Clin Cancer Res* 2014;20:2457–65.
- 37 Nguyen LT, Saibil SD, Sotov V, et al. Phase II clinical trial of adoptive cell therapy for patients with metastatic melanoma with autologous tumor-infiltrating lymphocytes and low-dose interleukin-2. *Cancer Immunol Immunother* 2019;68:773–85.
- 38 US Food and Drug Administration. Cyclophosphamide United States prescribing information. Baxter Healthcare Ltd. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/012141s090,012142s112lbl.pdf [Accessed Apr 2021].
- 39 European Medicines Agency. Cyclophosphamide summary of product characteristics. Baxter Healthcare Ltd. Available: <https://www.medicines.org.uk/emc/product/1815/smpc> [Accessed Apr 2021].
- 40 Zito Marino F, Bianco R, Accardo M, et al. Molecular heterogeneity in lung cancer: from mechanisms of origin to clinical implications. *Int J Med Sci* 2019;16:981–9.
- 41 Cohen EE, Dunn L, Neupane P, et al. SPEARHEAD-2 trial design: a phase II pilot trial of ADP-A2M4 in combination with pembrolizumab in patients with recurrent or metastatic head and neck cancer. *Ann Oncol* 2020;31(Suppl 4):S685.
- 42 Vasileiou S, Lulla PD, Tzannou I, et al. T-cell therapy for lymphoma using nonengineered multiantigen-targeted T cells is safe and produces durable clinical effects. *J Clin Oncol* 2021;39:1415–25.