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

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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-A2M10+ 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 a dose of lymphodepletion (fludarabine 30 mg/m2 on days 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.4 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. Tumor-infiltrating lymphocyte therapy has shown activity in several solid tumors. 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, 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. Melanoma-associated antigen A10 (MAGE-A10) is a cancer/testis protein associated with many cancers. MAGE-A10 expression has been described in varying frequencies in NSCLC. MAGE-A10 expression by protein using immunohistochemistry (IHC) or by RNA using reverse transcription PCR 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.

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 GLYDGMEHL peptide derived from the MAGE-A10 CTAs. 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 × (% of 1+ cells) + 2 × (% of 2+ cells) + 3 × (% of 3+ cells). Patients had an Eastern Cooperative Oncology Group performance status of 0 or 1, adequate organ function, pulmonary function with mechanical parameters ≥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 ≥50%, and measurable disease by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST V.1.1) before lymphodepletion (not required before leukapheresis).

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 ≥6x106 in the expansion group only. The intermittent 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 postinfusion biopsy samples were collected anytime from 2 months to 1 week prior to lymphodepletion and from 3 to 8 weeks after infusion, respectively.
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, 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.16 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, lymphodepleting 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, insertionional 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 (MHC-I) 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 (IFNγ), 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 (2G6), rabbit monoclonal primary antibody; Roche Diagnostics, Indianapolis, Indiana, USA) using the DISCOVERY Teal HRP detection kit (Roche Diagnostics) (online supplemental methods).

CD3, MHC-I, 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. 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, with modifications described in the online supplemental methods. The following gene signatures were used for analyses: APM, CD3+ T cells, CD8+ T cell, NanoString Technologies; Seattle, Washington, USA), and T-cell exhaustion.

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 \(6.77 \times 10^9\) 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).

In dose group 1, there was a protocol-defined DLT of grade 4 CRS (detailed below) in patient 1, who received \(0.1 \times 10^9\) (±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 ≥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/platellet 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,* | MAGE-A10 H-score† | Actual ADP-A2M10 dose, cells×10⁹ | 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                            | SD→PR$          |
|            |            |     |                 |                        |                   |                   | 5.23§                           |                 |
|            |            |     |                 |                        |                   |                   | 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 × (% of 1+ cells) + 2 × (% of 2+ cells) + 3 × (% of 3+ 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, hypertension, 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...
and antibiotics, which resolved symptoms. The transient increase in CRS-associated serum cytokines, such as IFNγ, 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 BMMC, 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 figure 1), although the small number of patients limits the conclusions that can be drawn. 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).

### Table 3: AEs in ≥20% of patients by grade following first infusion: mITT population

| Preferred term | Any grade | Grade 3 | Grade 4 | Grade 5 |
|----------------|-----------|---------|---------|---------|
| Patients with any AEs | 11 | 10 | 10 | 2* |
| Leukopenia/lymphocyte count decreased | 11 | 1 | 10 | 0 |
| Anemia/RBC count decreased | 10 | 0 | 10 | 0 |
| Neutropenia/neutrophil count decreased | 10 | 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 | 5 | 0 | 0 | 0 |
| Decreased appetite | 4 | 0 | 0 | 0 |
| Fatigue | 4 | 0 | 0 | 0 |
| Pneumonia | 4 | 0 | 1 | 0 |
| Alopecia | 3 | 0 | 0 | 0 |
| CRS | 3 | 0 | 1 | 0 |
| Diarrhea | 3 | 0 | 0 | 0 |
| Pancytopenia | 3 | 0 | 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.
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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 MHCI 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 MHCI 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 CD5+ 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, MHCI, 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 5×10⁹ 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 (0.08–0.12×10⁹, group 1; 0.5–1.2×10⁹, group 2; and 1.2–15×10⁹, 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 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 mg/m²/day for 3 days and intravenous fludarabine 30 mg/m²/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)疫苗 (NCT01343043), a lymphodepletion regimen including a higher dose of cyclophosphamide 1800 mg/m²/day for 2 days with fludarabine 30 mg/m²/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.

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There are reported cases of prolonged cytopenias with lymphodepletion regimens administered prior to adoptive T-cell therapy. Aplastic anemia has been observed after high-dose lymphodepletion similar to that employed in the patient treated in this trial. In addition, cyclophosphamide and fludarabine have either bone marrow failure or aplasia, respectively, listed as warnings/precautions in their prescribing information. 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 BMMC 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⁺ BMMC 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
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Figure 3  Variability of MAGE-A10 and MHCI 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 MHCI 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) MHCI expression was assessed using MHCI 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; MHCI, major histocompatibility complex I; NE, not evaluable; PD, progressive disease; SCC, squamous cell carcinoma; SD, stable disease; wks, weeks.

determined by IFNγ release) to any of the HLA-A2+ CD34+ BMMC 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 ≥1×10⁹ and doses of ≥5×10⁹ afamitresgene autoleucel (ADP-A2M4).11 In this trial, three patients received a dose of ≥5×10⁹ 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 CD8α 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-0044001 (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. 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, may further represent a path toward overcoming local tolerance and inhibitory mechanisms.

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