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Contributors

All authors meet the International Committee of Medical Journal Editors criteria for authorship of this article; take responsibility for the integrity of the work; were involved in revising and critical review of the manuscript; and approved the final version for submission. SPD, WDT, SB, BAVT, DMA and DW conceived and designed the study. SPD accessed and verified the underlying data. SPD and DW wrote the first manuscript draft and had the final responsibility for the decision to submit for publication. SPD, DMA, MA, SA, JYB, ICG, EC, GDD, MD, EF, KNG, VLK, DAL, VM, GKS, SJS, MJW, BAW, and BVVT enrolled patients and collected data. ARAR was involved in patient accrual and treatment within stipulated protocol and data collection. JAC contributed project administration. JG was an investigator. SMP enrolled patients. SMS provided study patients and performed data collection and interpretation. FT contributed to data collection, data interpretation, data curation, formal analysis, investigation, project administration, and supervision. CVM collected and interpreted data. SPD and DW wrote the first manuscript draft. LH, CM, AS, LF, EVW, EE, CL, EN, and DW collected and analysed data. JMN curated and analysed data and contributed to methodology and validation. RW, TW, and ALC collected, analysed, and interpreted data. SR curated (accessed and verified) and performed formal analysis of the underlying data. JB was the statistician.

All authors had full access to the data and vouch for the accuracy and completeness of the data and fidelity of the trial to the protocol.

Declaration of interests

EC participated in an advisory board for Adaptimmune and received research support to his institution for clinical trial activities with Adaptimmune, Novartis, Tracon, Boehringer Ingelheim, Merck, Bayer, Amgen, and Mirati.

JYB received grants to his institution from Netsarc+ and Euracan, and research support and honoraria from Adaptimmune and GSK.

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LH, TW, JB, AS, LF, EVW, EN, DW, RW, JMN, SR, and EE are employees of and have stock options in Adaptimmune. SB, CM, and CL were employees of Adaptimmune at the time of the study.

DA, ICG, DAL, ALC, GKS, and SMP have nothing to disclose.

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SPEARHEAD-1: a single-arm phase 2 trial of afamitresgene autoleucel (afami-cel) in advanced synovial sarcoma and myxoid/round cell liposarcoma

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Summary

Background—Afamitresgene autoleucel (afami-cel) showed acceptable safety and promising efficacy in a phase 1 trial (NCT03132922). This study evaluated afami-cel's efficacy in human leukocyte antigen (HLA)-A*02–positive patients with melanoma-associated antigen A4 (MAGE-A4)-expressing advanced synovial sarcoma or myxoid/round cell liposarcomas (MRCLS).

Methods—Cohort 1 of this ongoing, single-arm, open-label, phase 2 trial evaluated a single intravenous afami-cel dose after lymphodepletion in HLA-A*02–positive adult patients with metastatic/unresectable synovial sarcoma or MRCLS expressing MAGE-A4 who had received ≥1 prior line of anthracycline and/or ifosfamide-containing chemotherapy. Primary endpoint was overall response rate in cohort 1, determined by a blinded committee using Response Evaluation Criteria in Solid Tumours version 1·1 in the modified intent-to-treat population. Adverse events (AEs), including those of special interest (cytokine release syndrome, prolonged/pan-cytopenia, neurotoxicity) were monitored. Trial is registered at ClinicalTrials.gov, number NCT04044768.

Findings—Between 17 December 2019 and 27 July 2021, 52 patients with cytogenetically confirmed synovial sarcoma (n=44) and MRCLS (n=8) were enrolled and received afami-cel in cohort 1. Baseline median MAGE-A4 expression P-score was 83·5 (IQR 62–99) overall and 89·5 in patients with synovial sarcoma; H-score was 231·5 (IQR 174–294) overall and 256·5 in patients with synovial sarcoma. Patients were heavily pre-treated (median 3 [IQR 2–4] prior lines of systemic therapy). Overall response rate was 37% (19 of 52; 95% CI 23·62–51·04) overall, 39% (17 of 44) in synovial sarcoma, and 25% (2 of 8) in MRCLS; median follow-up time, 32·6 months (IQR 29–36). Cytokine release syndrome occurred in 71% (37 of 52) of patients (one grade 3 event). Cytopenias were the most common grade ≥3 AEs (lymphopenia in 50 [96%], neutropenia 44 [85%], leukopenia 42 [81%] of 52).

Interpretation—Afami-cel treatment resulted in durable responses in heavily pre-treated HLA-A*02–positive patients with MAGE-A4–expressing synovial sarcoma. Grade 1/2 cytokine release syndrome and grade 3/4 haematologic toxicities were common.

Funding—Adaptimmune.

Introduction

Synovial sarcoma (SyS) and myxoid/round cell liposarcomas (MRCLS) are rare mesenchymal malignancies comprising 5–10% of all soft tissue sarcomas. Despite initial sensitivity to chemotherapy, these aggressive tumours have poor outcomes in the metastatic setting.[1] Five-year overall survival for patients with metastases remains low (eg, 8·2% and 14·8% in two studies),[2,3] with 1-year progression-free survival and overall survival rates of 33% and 67%, respectively, reported for patients with advanced SyS receiving second-line therapies,[4] and median progression-free survival and overall survival after third-line therapies of 2·8 and 7·8 months, respectively.[3,5] Historical overall response rate to second-line therapy and beyond ranges from 4·2–14·7% in SyS,[4,6–8] versus 10%[1] to 18·2% in MRCLS with eribulin[9]; however, higher response rates (27–51%) have been reported with trabectedin.[10,11] Therefore, an unmet need for more promising therapies remains.

Though distinct diseases, SyS and MRCLS share clinical/biological features.[12] Both have high expression of cancer testis antigens, including melanoma-associated antigen A4 (MAGE-A4) and NY-ESO-1. Engineered T cells targeting NY-ESO-1 have demonstrated promising efficacy in patients with SyS and MRCLS.[13,14] SyS and MRCLS are also both characterised by unique pathognomonic chromosomal translocations.[15–17] Their immune microenvironments have limited T cells and antigen-presenting cells, low programmed death-ligand 1 expression, and low non-synonymous somatic mutations, explaining the limited efficacy of checkpoint inhibitors.[18,19]

Afamitresgene autoleucel (afami-cel) is an autologous $CD4^+$ and $CD8^+$ T-cell product transduced with a self-inactivating lentiviral vector to express an affinity-enhanced MAGE-A4–specific T-cell receptor.[20] Preliminary efficacy of afami-cel was demonstrated in a phase 1 clinical trial (NCT03132922), where an overall response rate of 44% (7 of 16 patients with advanced SyS) with median duration of response of 28 weeks was observed.[21] Here we describe cohort 1 of SPEARHEAD-1, an international phase 2 trial evaluating efficacy/safety of afami-cel in patients with refractory SyS and MRCLS.

Methods

Study design and participants

This single-arm, open-label, phase 2 trial was conducted at 23 specialist investigational sites in North America and Europe. Sites were selected based on sarcoma expertise and accreditation for implementing/administering cell therapy (appendix p 13). Trial was designed by Adaptimmune together with the authors and conducted in accordance with International Council for Harmonisation guidelines for Good Clinical Practice and principles of the Declaration of Helsinki. Protocol was approved by local or independent institutional review boards or ethics committees at participating sites. All patients provided written informed consent. Overall trial comprises three separate, independent cohorts. Rationale for cohorts 2 and 3 was to provide continued access to afami-cel and generate supplemental data in patients with advanced SyS (to be reported separately). Inclusion criteria for cohort 1 were advanced (metastatic or unresectable) SyS or MRCLS; 16–75 years of age; expression of human leukocyte antigen (HLA)-A*02:01, *02:02, *02:03, *02:06, or other *02 alleles with the same protein sequence as those in the peptide-binding domain (excluding HLA-A*02:05); a tumour sample showing MAGE-A4 expression of ≥2+ staining in ≥30% of tumour cells by a fit-for-purpose immunohistochemistry clinical trial assay (appendix p 2); had received a regimen containing either an anthracycline or ifosfamide; had measurable disease; and had adequate organ function. Trial design is shown on appendix p 4, and complete descriptions of design/eligibility criteria are provided in protocol (appendix p 72). The protocol was amended 3 times as detailed on appendix p 2, approved by local or independent institutional review boards or ethics committees at participating sites. An independent data safety monitoring board reviewed safety data during the interventional phase, after ~5, 15, and 30 patients had received afami-cel.

Procedures

Leukapheresis was performed to obtain T cells for afami-cel manufacturing at Adaptimmune with T-cell process 1·6·1.[21] $CD4^+$ and $CD8^+$ T cells were transduced with a third-generation lentiviral vector to express the affinity-enhanced T-cell receptor recognising the HLA-A*02-GVYDGREHTV MAGE-A4 antigen complex. Following expansion/quality control release testing (appendix p 2), afami-cel was cryopreserved and returned to investigational sites. Median time from leukapheresis until afami-cel was manufactured and completed release testing was 40 days (IQR 35–50). Bridging therapy was permissible between leukapheresis and lymphodepletion at investigators' discretion, provided mandatory washout periods were adhered to (cytotoxic chemotherapy 3 weeks, tyrosine kinase inhibitor 1 week, immune therapy or investigational treatment 4 weeks, corticosteroids/immunosuppressives 2 weeks). Lymphodepletion chemotherapy, consisting of intravenous fludarabine 30 mg/m^2 on 4 consecutive days (days −7 to −4) and intravenous cyclophosphamide 600 mg/m^2 on 3 consecutive days (days −5 to −3), was administered before afami-cel infusion (day −1 was immediately before infusion). Mesna/anti-microbial prophylaxis were used according to institutional practice. Afami-cel was administered by intravenous infusion on day 1 at a transduced dose range of $1{\cdot}0\times10^9$–$10{\cdot}0\times10^9$ T cells. Eligible patients could only receive a single afami-cel infusion.

Outcomes

Primary endpoint was overall response rate for SyS and MRCLS in cohort 1 only, determined by an appropriately qualified, trained, and experienced imaging review committee using Response Evaluation Criteria in Solid Tumours (RECIST) version 1·1. Independent reviewers were blinded to total duration of participant's enrolment and total number of time points presented when undertaking image review. Primary efficacy analysis was for cohort 1 only of this ongoing, multicohort trial, with clinical cut-off occurring once last patient dosed in cohort 1 had ≤6 months of follow-up post T-cell infusion or had ended the interventional phase. Although the primary endpoint was determined by independent review, investigators also assessed response to guide the patient's care throughout the trial. Secondary endpoints were treatment-emergent adverse events (AEs), including serious AEs and AEs of interest, assessment of replication competent lentivirus and T-cell clonality and insertional oncogenesis, best overall response, duration of response, time to response, progression-free survival, overall survival, evaluation of T-cell persistence, and retention of additional tumour tissue during pre-screening for validation of MAGE-A4 expression diagnostic assay (to be reported separately). AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5·0. Cytokine release syndrome was graded according to Lee 2019 criteria.[22] Exploratory endpoints included characterisation of serum cytokines and in vitro profiling of a subset of afami-cel manufactured products assessing phenotypic composition using multiparameter flow cytometry staining panels (appendix p 2).

Statistical analysis

Modified intent-to-treat population (all patients who met eligibility criteria, were enrolled in the trial, and received afami-cel) was used for primary efficacy analysis and safety

evaluations. Primary endpoint was evaluated using a two-sided exact-based Clopper-Pearson (exact binomial) 95% CI. Null hypothesis was that percentage of afami-cel–treated patients with best overall response of partial response or better would be ≤18% (ie, conservative estimate from the top of the range of the historically reported overall response rates for second-line chemotherapy). It was calculated that a sample size of 45 patients would provide ≥90% power to reject the null hypothesis assuming one-sided type I error not exceeding 0·025 and type II error not exceeding 0·1. Progression-free survival, overall survival, time to response (all measured from date of infusion), duration of response, and associated 95% CI were estimated using Kaplan-Meier methods. Censoring of data for duration of response and progression-free survival was based on US Food and Drug Administration censoring rules.[23,24] Additional post hoc analyses included Kaplan-Meier assessment of time to next treatment or death per RECIST response and overall survival per exposure to afami-cel. Analyses were performed with SAS software, version 9·4 or higher. This study is registered with ClinicalTrials.gov, NCT04044768; recruitment is closed, and follow-up is ongoing for cohort 1.

Role of the funding source

Study's funder participated in study design; data collection, analysis, and interpretation; and preparation, review, and approval of this report.

Results

Of 373 trial candidates pre-screened for HLA eligibility, MAGE-A4 expression, or both, 105 (28%) had both an eligible HLA-A*02 allele and MAGE-A4 expression at or above the pre-defined level. MAGE-A4 expression at or above the pre-defined level was observed in tumours of 87 of 142 (61%) and 27 of 58 (47%) of patients with SyS and MRCLS, respectively. Double-positive candidates were then assessed for additional inclusion/exclusion criteria both at leukapheresis and baseline assessment (appendix p 4). Withdrawn consent or change in patient status led to some candidates not being eligible, even following confirmation of HLA eligibility and MAGE-A4 expression. Between 17 December 2019 and 27 July 2021, 63 patients were enrolled into cohort 1 and underwent leukapheresis (intent-to-treat population), and 52 (modified intent-to-treat population) were treated with afami-cel (figure 1, table 1). These 52 participants were generally demographically representative of other published sarcoma populations (appendix p 14). Of 11 patients who did not receive afami-cel (reasons shown in figure 1), three had manufacturing failures/delays that might have contributed to these decisions. At 30 August 2023 data cut-off, 39 patients had entered long-term follow-up.

Most patients were heavily pre-treated, with a median 3 (range 1–12, IQR 2–4) prior lines of therapy. Median tumour MAGE-A4 expression was numerically higher in the SyS versus MRCLS groups, as measured by both H- and P-scores (table 1, appendix p 15). Fifty of 52 patients (96%) expressed HLA-A*02:01P, one patient each expressed HLA-A*02:02P and HLA-A*02:06P, and one of the HLA-A*02:01P–positive patients also expressed HLA-A*02:03P.

Overall, 20 of 52 patients (38%) received some bridging therapy between leukapheresis and afami-cel (table 1, appendix p 3). Median (range) time between leukapheresis and lymphodepletion start in the modified intent-to-treat population was 52·5 (IQR 43–73) days overall, 56 (range 34–218) days in those receiving bridging therapy, and 50 (range 35–140) days in those who did not. Afami-cel was administered at median total dose of $8{\cdot}70\times10^9$ transduced T cells (range $2{\cdot}68–9{\cdot}99\times10^9$, IQR 5·1–9·9), with median transduction efficiency of 61·5% (IQR 49–69).

Of 52 patients in the modified intent-to-treat population, overall response rate was 37% (19 of 52; 95% CI 23·62–51·04), with all having best overall response of partial response (figure 2A, 2B, appendix p 5). The trial met the protocol-defined criterion for demonstrating efficacy; lower limit of the 95% CI was greater than pre-specified null hypothesis rate of 18%. Overall response rate was 39% (17 of 44; 95% CI 24·36–54·50) in SyS and 25% (2 of 8; 95% CI 3·19–65·09) in MRCLS. There was a high level of concordance (79%) between independent- and investigator-assessed response rates (appendix p 17). Median time to initial confirmed response was 4·9 weeks (95% CI 4·29–8·14). Median duration of response was 11·6 months (95% CI 4·44–17·97) and 4·2 months (95% CI 2·86–5·52) in the SyS and MRCLS subgroups, respectively. Responses were observed across key subgroup covariates. Higher response rates were observed in patients with SyS who were female, had higher MAGE-A4 expression (MAGE-A4 H-score ≥200), had lower disease burden before lymphodepletion (sum of longest diameters of target lesions <100 mm), or did not require bridging therapy (figure 2C). Numbers of patients with MRCLS were too low to allow conclusive subgroup analysis; however, these patients were more often male, had lower MAGE-A4 expression, and had higher disease burden (baseline sum of longest diameters of target lesions ≥100 mm) than patients with SyS (table 1). At 30 August 2023 data cut-off, median follow-up time was 32·6 months (IQR 29–36) and 40.4% of survival analysis events were censored. Median progression-free survival was 3·7 months (95% CI 2·8–5·6) overall, 3·8 months (95% CI 2·8–6·4) in patients with SyS (appendix p 6), and 2·4 months (95% CI 0·9–7·4) in patients with MRCLS.

After disease progression, 20 of 44 patients with SyS started additional systemic therapy. In patients with SyS, median time to next treatment or death was 6·6 months overall and 16·8 months in patients who had RECIST response (appendix p 7); probability of being alive and additional systemic treatment free was 30% overall at 24 months.

Median overall survival was 15·4 months (95% CI 10·9–28·7) in the overall population, with an overall survival probability of 60% at 12 months. Median overall survival was not reached in patients with SyS who had RECIST response (figure 2D). Estimated overall survival probability in patients with SyS who had RECIST response was 90% at 12 months and 70% at 24 months.

All 52 patients who received afami-cel had treatment-emergent AEs (appendix p 18). Cytopenias were the most common grade ≥3 AEs; lymphopenia occurred in 50 (96%), neutropenia in 44 (85%), and leukopenia in 42 (81%) of 52 patients. Ten patients (19%) had prolonged cytopenia, defined as grade ≥3 cytopenia at week 4 post T-cell infusion, including five with neutropenia (10%), four with anaemia (8%), and three with thrombocytopenia

(6%). One patient (2%) had cytopenia that resolved at day 29, recurred around week 12, and resolved at day 110; no others had prolonged cytopenia at week 12. 48 of 52 (92%) patients had AEs related to T-cell infusion, of which haematologic toxicities were common (table 2).

Cytokine release syndrome events were mostly grade 1/2, with one patient (1·9%) experiencing a grade 3 event (table 2); these were serious events in 5 patients (10%). All serious adverse events are reported on appendix p 3. Cytokine release syndrome occurred in both the SyS and MRCLS groups (appendix p 20), early after afami-cel infusion, with median time to onset of 2 (IQR 2–3) days, with resolution in a median 3 (IQR 2–5) days. Tocilizumab was permitted for grade 1 cytokine release syndrome if symptoms persisted for ≥24 hours or if patient had comorbidities. Cytokine release syndrome was managed with supportive care, and 19 patients (37%) received tocilizumab; two required corticosteroids, and all cases resolved. One patient (2%) had immune effector cell–associated neurotoxicity syndrome (grade 1) and concomitant cytokine release syndrome; neurotoxicity syndrome resolved 1 day later.

There were no grade 5 AEs, and no deaths occurred in the first 30 days after afami-cel infusion. All 28 deaths were attributed by investigators to disease progression. No cases of replication competent lentivirus or secondary malignancies were reported.

Circulating afami-cel was detected post infusion in all patients, typically with an increase in cell exposure to a peak followed by bi-exponential decline. Levels decreased below lower limit of quantification 18 months post infusion in two patients. In most patients, peak exposure was observed in the first week post infusion across dose range evaluated. Persistence of transduced T cells showed large variations of peak and duration among patients (figure 3).

When exposure to afami-cel was measured as area under the concentration-time curve for afami-cel (measured by vector copies/μg DNA) over first 3 months post infusion, exposure above median was associated with longer overall survival (appendix p 8).

Patient serum samples taken before/after afami-cel infusion were analysed to determine levels of 22 pharmacodynamic biomarkers. Transient post-infusion increase was evident for most biomarkers, with nine showing an at least two-times increase relative to pre-infusion concentration in at least half the dataset. These included granulocyte-macrophage colony-stimulating factor and interleukin (IL)-6, with interferon-γ showing greatest magnitude of change. Others showed smaller transient rises (eg, tumour necrosis factor [TNF]-α) or negligible detectable changes (eg, IL-1β, TNF-β). Serum levels were analysed relative to cytokine release syndrome occurrence. After applying multiple hypothesis correction, post-infusion serum levels were significantly greater in patients with cytokine release syndrome versus patients without for interferon-γ (appendix p 9), IL-10, IL-15, IL-2Rα, and IL-6 (appendix p 21).

In vitro profiling of phenotypic composition was performed on samples of afami-cel taken before infusion into 30 patients. Proportions of afami-cel $CD3^+$ cells that were $CD4^+$ T-helper cells or $CD8^+$ cytotoxic T cells and expressed engineered MAGE-A4–specific T-cell receptor are shown on appendix p 10. These data show the balance of T-cell subsets

within afami-cel as well as range in transduction efficiency across patients. Memory subset immunophenotyping shows that transduced $CD4^+CD8^-$ T cells are predominantly T-cell effector memory expressing CD45RA and effector memory cells; these T-helper cells have a relatively low naive/stem cell memory (N/SCM) and central memory component (appendix p 11). Cytotoxic $CD8^+CD4^-$ T cells show a similar subset distribution but have lower proportion of effector memory cells and concomitant increase in N/SCM and central memory cells (appendix p 12).

Discussion

Clinical outcomes of patients with metastatic SyS and MRCLS remain poor; improved therapeutic strategies are needed. In this phase 2 trial involving HLA-A*02:01/02/03/06–positive and MAGE-A4–positive patients with previously treated SyS and MRCLS, treatment with lymphodepletion chemotherapy and afami-cel resulted in overall response rate of 37%, with durable responses. In meeting the primary endpoint, this trial provides proof of principle for utility of T-cell therapy for solid tumours. As expected, haematologic toxicities were the most common AEs, largely attributable to lymphodepletion chemotherapy. However, incidence of prolonged cytopenia appeared lower in this trial than has been observed in chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory large B-cell lymphoma.[25] Cytokine release syndrome occurred in most patients; however, events were mostly grade 1/2 and managed with standard treatments. These data are clinically impactful, considering poor clinical outcomes and limited effective therapies available for these patients.

Sarcomas remain complex, heterogenous malignancies characterised by >70 histological subtypes.[12] Given the rarity of these diseases, clinical trials have only been enrolling specific histological subtypes during the last decade. Further, there is a paucity of prospective randomised clinical trials evaluating efficacy of systemic therapies specifically in SyS or MRCLS; available data are limited to retrospective pooled analyses.[26] As such, statistical design of SPEARHEAD-1 defined the null hypothesis as overall response rate of ≤18%. This trial met its primary endpoint, confirming the benefit seen in the phase 1 trial of afami-cel in SyS.

In addition to varied responses noted by histology, clinical factors such as higher MAGE-A4 expression, lower disease burden at baseline, and lack of bridging therapy were associated with higher response rates. MAGE-A4 expression was reported to be 82% and 68% in SyS and MRCLS, respectively.[27] In this study, MAGE-A4 expression was measured by both P- and H-score. Median P- and H-scores were higher in SyS versus MRCLS, likely contributing to different responses seen. Although a trend was observed, the study was not powered to assess differences in response according to MAGE-A4 expression. This may be an important predictor of response and warrants further research. Patients in this trial had refractory SyS and MRCLS, which can be characterised as aggressive with high tumour burden and bulky disease (52% of patients had baseline sum of longest diameters of target lesions ≥100 mm).

A potential limitation of T-cell therapy is that antigen recognition of MAGEA-4 is restricted to specific HLA alleles. Broad applicability of afami-cel will require additional T-cell receptor constructions to expand the HLA allele repertoire for epitope presentation. An additional limitation is the logistical challenge posed by screening/manufacturing processes. Therefore, maintaining disease control while T-cell manufacturing occurs can be important. In patients with relapsed/refractory large B-cell lymphoma, bridging therapy before treatment with CAR T-cell therapy was found to be feasible and had no impact on efficacy outcomes, although those patients did experience prolonged cytopenias.[28] Both low disease burden and lack of bridging therapy correlated with improved efficacy in this trial, but responses were observed in all subgroups analysed. Baseline scans were performed after any bridging therapies were administered, washout periods were in place for bridging therapies, and time between leukapheresis and lymphodepletion was similar in those who did or did not receive bridging therapies. These clinical factors will require further investigation, as they may be relevant biomarkers to inform patient selection and timing of afami-cel.

Expansion and persistence of afami-cel in peripheral blood was observed. Increased post-infusion levels of pro-inflammatory cytokine interferon-γ were associated with increasing severity of cytokine release syndrome. An exposure–response relationship between afami-cel cellular persistence over 3 months post infusion and overall survival was observed. Additional analyses of other translational correlations are underway. There is an ongoing need to identify biomarkers of resistance to afami-cel. In previous experience in letetresgene autoleucel–treated patients with SyS, NY-ESO-1–directed T cells, loss of HLA expression, and decrease in antigen-presenting machinery correlated with lack of efficacy.[29]

Limitations of this trial include the single-arm, non-randomised design. Given this design, it is not possible to conclude that afami-cel is superior to systemic agents for refractory SyS and MRCLS. A randomised trial, however, would be difficult for several reasons; there is no globally consistent second-line therapy, so selecting a comparator would be difficult, and HLA*A-02 typing and MAGE-A4 expression requirements would entail selection of a subset of an ultra-rare disease, with an incidence of $1{\cdot}55/10^6$/year for MRCLS and $1{\cdot}67/10^6$/year for SyS.[30] Overall response rate in SPEARHEAD-1 is improved versus published data in patients with refractory SyS. The current analysis is also limited by the small number of pre- and post-infusion biopsies to evaluate markers of response and resistance such as downmodulation or loss of HLA expression and antigen presentation, this being compounded by the fact that HLA class I expression is dynamic and can be significantly increased by interferon-γ. For example, it has been reported that loss of HLA expression correlated with progression in a patient with breast cancer treated with a T-cell receptor T-cell therapy targeting a tp53 hotspot mutation. Potential contribution of fludarabine and/or cyclophosphamide from lymphodepletion chemotherapy is a potential limitation; both SyS and MRCLS are sensitive to alkylating agents. However, durable responses seen after afami-cel treatment in this heavily pre-treated population suggests that contribution, if any, of a single cycle of cyclophosphamide lymphodepletion to responses observed was minimal.

Use of CAR T-cell therapies targeting cell surface cancer antigens in haematologic malignancies is well established, but their activity in solid tumours has been disappointing.

Unlike many haematologic malignancies, solid tumours can have an immunosuppressive microenvironment that makes effective treatment with cell therapy more challenging than liquid tumours. Additionally, few solid tumours express the tumour-specific surface antigens targeted by CAR T-cells, whereas engineered T-cell receptor T-cell therapies such as afami-cel target intracellular antigens presented by HLA. This study demonstrates the ability to effectively target solid tumour cancer antigens with T-cell receptor therapy, and highlights MAGE-A4 as a new immunotherapy target for treatment of SyS. Our findings support use of afami-cel as a potentially effective treatment option for HLA-A*02–positive patients with MAGE-A4–positive SyS following progression despite prior anthracycline- or ifosfamide-based therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing statement

The clinical datasets generated and/or analysed during the current study are available upon reasonable request from the corresponding author for research only, non-commercial purposes. Such datasets include study protocol, statistical analysis plan, individual participant data that underlie the results reported in this article after de-identification (text, tables, figures, and appendices) as well as supporting documentation as required. Restrictions relating to patient confidentiality and consent will be maintained by aggregating and anonymising identifiable patient data. The clinical data will be available beginning immediately after article publication and thereafter with no time limit. Requests should be sent in writing describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement that describes the conditions for release and requirements for data transfer, storage, archiving, publication, and intellectual property. Requests should be directed to Dennis.Williams@adaptimmune.com and will be reviewed by the first and last authors, and by Adaptimmune. Responses will typically be provided within 60 days of the initial request.

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Research in context

Evidence before this study

Adoptive T-cell therapy has been greatly advanced by the use of chimeric antigen receptor T-cell therapy for certain subsets of B-cell leukaemia or lymphoma; however, autologous T-cell therapies have not yet been approved for the treatment of any solid tumours. Affinity-optimised engineered T-cell receptors have emerged as a promising tool for application of autologous T-cell therapies for solid tumours. Melanoma-associated antigen A4 (MAGE-A4), a cancer testis antigen, is expressed in germline tissue and a variety of solid tumours, including synovial sarcoma and myxoid/round cell liposarcoma, and is a promising target for cancer immunotherapy. We searched PubMed (with no limits on date or language) for publications with 'melanoma-associated antigen A4' in the title/abstract and found two publications describing clinical results. One was a case study in which a single patient with MAGE-A4–expressing uterine leiomyosarcoma, who had a complete response following prior therapy, received two infusions of autologous lymphocytes expressing a codon-optimised MAGE-A4 T-cell receptor and siRNAs to silence endogenous T-cell receptors, and continued to have a complete response. The other described the phase 1 trial of afami-cel. Afamitresgene autoleucel (afami-cel) is an autologous T-cell therapy engineered to express an affinity-enhanced T-cell receptor specifically targeting a MAGE-A4 antigen presented on cells by human leukocyte antigen (HLA)-A*02. The phase 1 trial evaluated afami-cel in HLA-eligible patients with relapsed/refractory solid tumours expressing MAGE-A4, including synovial sarcoma, ovarian cancer, and head and neck cancer. An acceptable benefit-to-risk profile and durable responses, especially in patients with synovial sarcoma, were observed. Therefore, this larger, phase 2 trial of afami-cel was performed.

Added value of this study

This trial includes an international, relatively large population of patients with the rare solid tumours, synovial sarcoma and myxoid/round cell liposarcoma, and showed that afami-cel can produce durable responses in some HLA-eligible patients with MAGE-A4–expressing tumours. It also provides further details on the safety profile associated with afami-cel, and preliminary analyses of clinical and translational correlates that will be important in the future application of afami-cel, and other autologous engineered T-cell receptor T-cell therapies, for the treatment of solid tumours.

Implications of all the available evidence

Together, data from these phase 1 and 2 trials suggest that afami-cel can produce durable responses with an acceptable benefit-to-risk profile in HLA-eligible patients with MAGE-A4–expressing advanced synovial sarcoma. These data have been used to file for US Food and Drug Administration approval, which to our knowledge, if granted, would be the first approval of an engineered T-cell therapy for solid tumours.

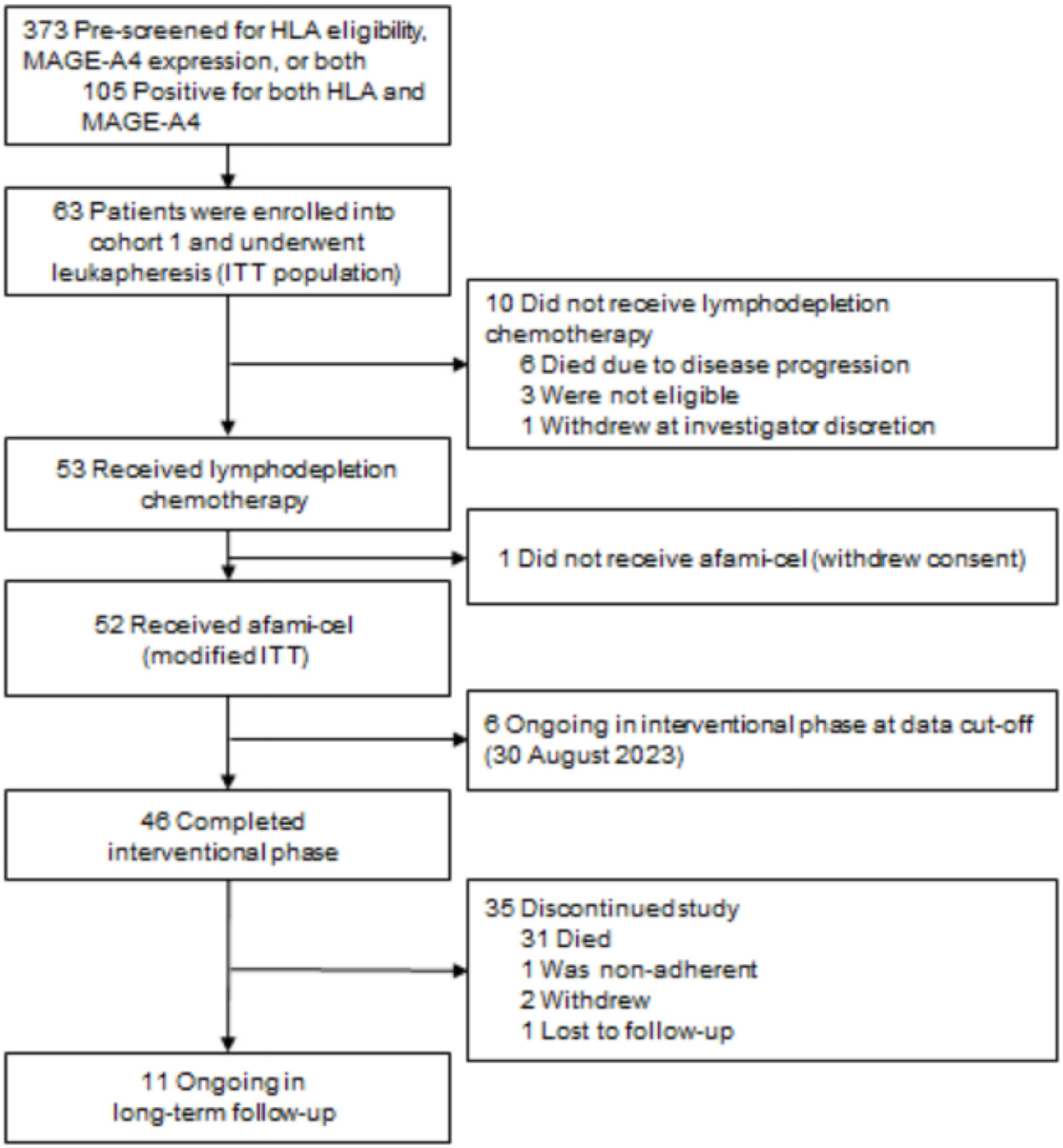

Figure 1: Randomisation and treatment

afami-cel=afamitresgene autoleucel; HLA=human leukocyte antigen; ITT=intent-to-treat; MAGE-A4=melanoma-associated antigen A4.

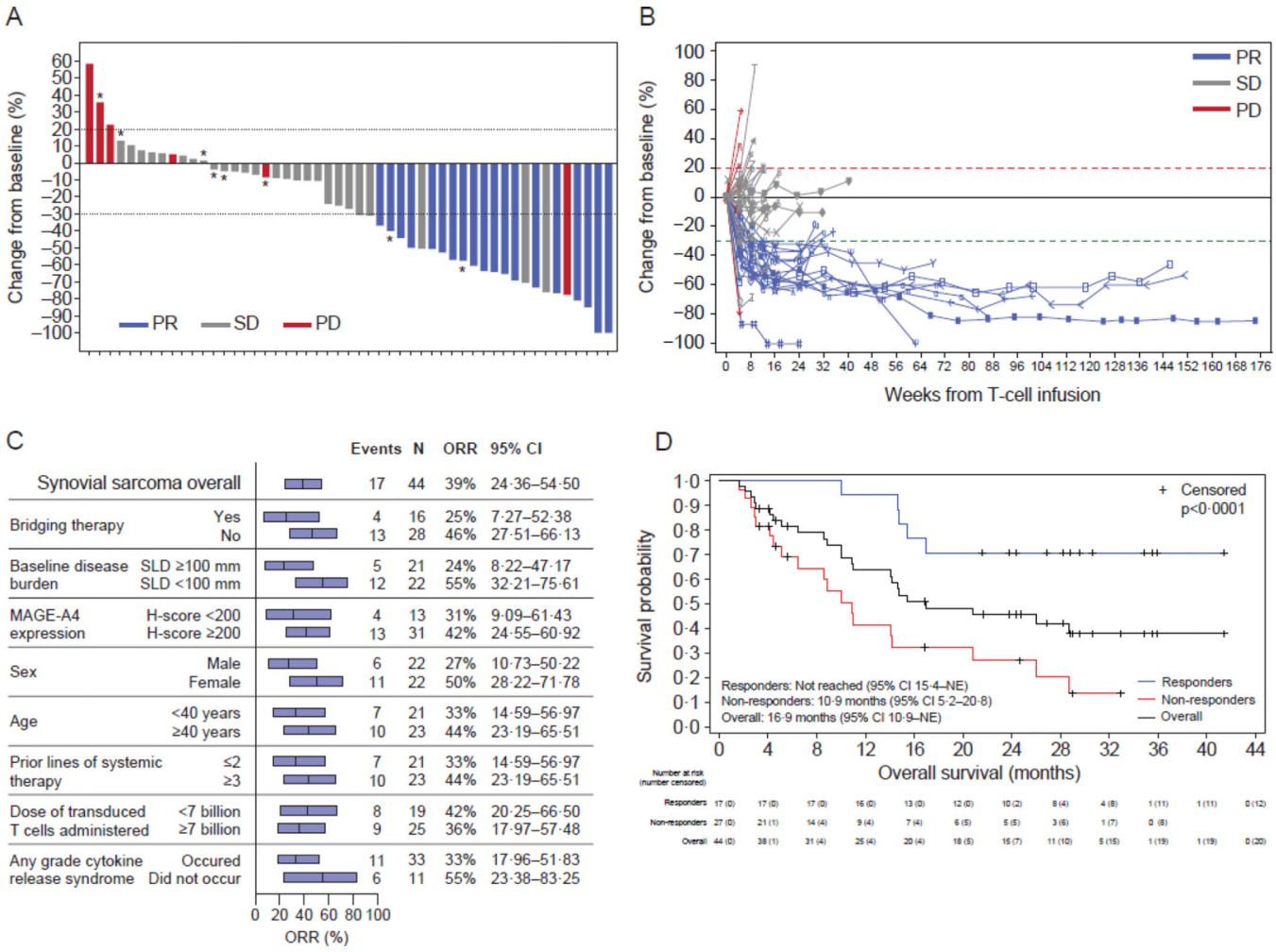

Figure 2: Response and prognostic characteristics of modified intent-to-treat patients

Maximum percentage change in sum of longest diameters in target lesions from baseline, coloured by best overall response (n=51, patients who did not have a scan are not shown), patients with MRCLS indicated with * (A), change in sum of longest diameters in target lesion from baseline over time (B), forest plot of overall response rate in different subgroups of patients with synovial sarcoma (C), Kaplan-Meier plot of overall survival in patients with synovial sarcoma (D). p-values estimated using the log-rank method. Patients who have a maximum decrease in size of the target lesion of ≥30% may still be classified as having SD or PD due to other RECIST version 1·1 criteria, such as behaviour of non-target lesions. MAGE-A4=melanoma-associated antigen A4; MRCLS=myxoid/round cell liposarcoma; NE=not estimable; ORR=overall response rate; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours; SD=stable disease; SLD=sum of longest diameters of the target lesions.

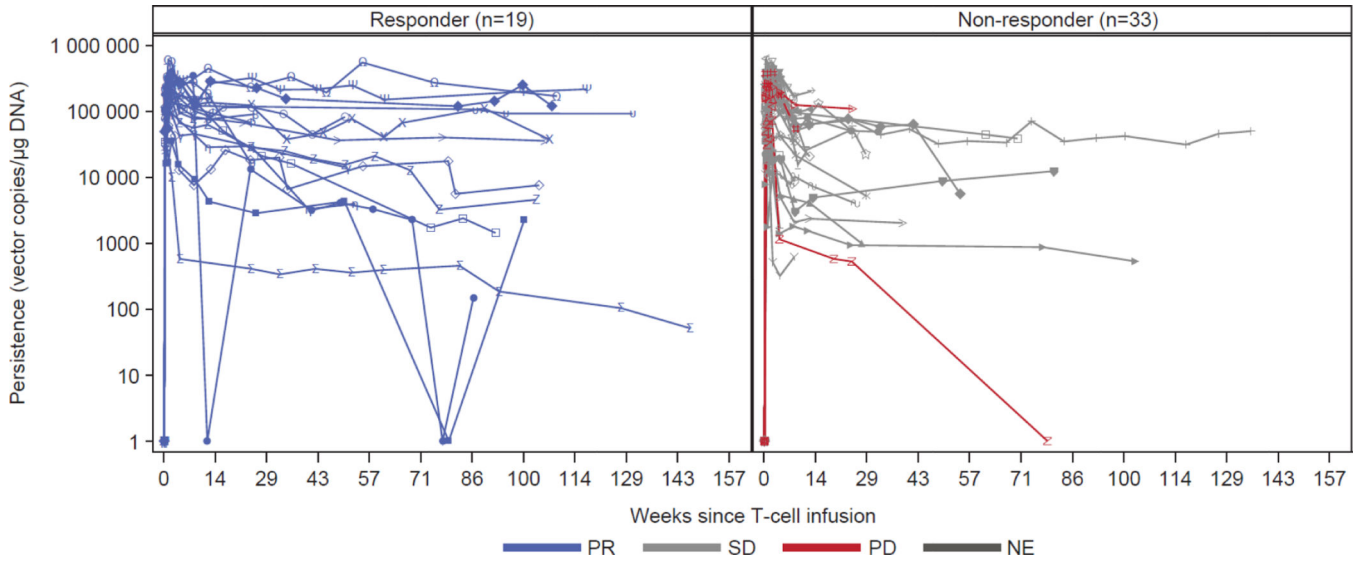

Figure 3: Afami-cel persistence and serum interferon-γ profile.

Afami-cel persistence over time, comparing responders (PR) and non-responders (SD and PD). The high positive result in the week 24 sample following a negative result at week 12 was detected as an anomaly and triggered an investigation that showed without ambiguity that the week 12 sample did not belong to that patient. NE=not estimable; PD=progressive disease; PR=partial response; SD=stable disease.

Table 1:

Demographics and disease characteristics (modified intent-to-treat population)

	Synovial sarcoma (n=44)	Myxoid/round cell liposarcoma (n=8)	Overall (N=52)
Age at consent, years, median (IQR)	40·5 (31–46)	43·5 (33–55)	41·0 (31–47)
Female, n (%)	22 (50%)	2 (25%)	24 (46%)
Male, n (%)	22 (50%)	6 (75%)	28 (54%)
Race, n (%)			
Asian	3 (7%)	0	3 (6%)
Black or African American	2 (5%)	0	2 (2%)
White	39 (89%)	6 (75%)	45 (87%)
Missing	0	2 (25%)	2 (4%)
Ethnicity			
Hispanic or Latino	2 (5%)	0	2 (4%)
Not Hispanic or Latino	38 (86%)	5 (63%)	43 (83%)
Not reported	4 (9%)	2 (25%)	6 (12%)
Unknown	0	1 (13%)	1 (2%)
Geographic region, n (%)			
Europe	12 (27%)	1 (13%)	13 (25%)
North America	31 (70%)	6 (75%)	37 (71%)
United Kingdom	1 (2%)	1 (13%)	2 (4%)
Histological grade, n (%)			
Well differentiated	0	2 (25%)	2 (4%)
Moderately well differentiated	9 (25%)	0	9 (17%)
Poorly differentiated	22 (50%)	4 (50%)	26 (50%)
Undifferentiated	4 (9%)	1 (13%)	5 (10%)
Unknown	9 (20%)	1 (13%)	10 (19%)
Stage of cancer at last staging, n (%)			
II	2 (5%)	0	2 (4%)
III	1 (2%)	0	1 (2%)
IV	35 (80%)	6 (75%)	41 (79%)
Unknown *	6 (14%)	2 (25%)	8 (15%)
Prior lines of systemic therapy, n (%)			
1	7 (16%)	3 (38%)	10 (19%)
2	14 (32%)	1 (13%)	15 (29%)
3	9 (20%)	0	9 (17%)
4+	14 (32%)	4 (50%)	18 (35%)
Received bridging therapy, n (%)			
Yes	16 (36%)	4 (50%)	20 (38%)
Pazopanib	11 (25%)	0	11 (21%)

	Synovial sarcoma (n=44)	Myxoid/round cell liposarcoma (n=8)	Overall (N=52)
Trabectedin	1 (2%)	2 (25%)	3 (6%)
Ifosfamide	3 (7%)	0	3 (6%)
Doxorubicin	1 (2%)	1 (13%)	2 (4%)
Docetaxel	0	1 (13%)	1 (2%)
No	28 (64%)	4 (50%)	32 (62%)
ECOG performance status score, n (%)			
0	23 (52%)	4 (50%)	27 (52%)
1	20 (45%)	4 (50%)	24 (46%)
2[†]	1 (2%)	0	1 (2%)
Baseline sum of longest diameters in target lesions ≥100 mm, n (%)	21 (48%)	6 (75%)	27 (52%)
MAGE-A4 expression H-score at pre-screening, median (IQR)[‡]	256·5 (182–299)	179·0 (142–197)	231·5 (174–294)
MAGE-A4 expression P-score at pre-screening, median (IQR)[§]	89·5 (68–100)	62·5 (46–76)	83·5 (62–99)

ECOG=Eastern Cooperative Oncology Group; IQR=interquartile range; MAGE-A4=melanoma-associated antigen A4.

[*] Formal staging was not required for inclusion.

[†] The baseline ECOG performance status score for this patient was actually 1, but the August 30, 2023, data cut-off included this error due to a transcription error from the hospital's dictation software.

[‡] H-score is derived by (3× percentage of strongly staining cells) + (2× percentage of moderately staining cells) + percentage of weakly staining cells, giving a range of 0–300.

[§] P-score is derived by (% tumour staining at intensity 2+) + (% tumour staining at intensity 3+).

Table 2:

Adverse events related to T-cell infusion in the modified intent-to-treat cohort as of 29 March 2023

Data are n (%). Grade 1 and 2 events are reported here if they occurred in over 10% of patients. All grade 3 and 4 events are shown. No treatment-related deaths occurred.

	Grade 1 or 2	Grade 3	Grade 4	Overall (N=52)
Cytokine release syndrome	36 (69%)	1 (2%)	0	37 (71%)
White blood cell count decreased/leukopenia	1 (2%)	8 (15%)	5 (10%)	14 (27%)
Pyrexia	10 (19%)	1 (2%)	1 (2%)	12 (23%)
Neutrophil count decreased/neutropenia	1 (2%)	5 (10%)	6 (12%)	12 (23%)
Lymphocyte count decreased/lymphopenia	0	4 (8%)	5 (10%)	9 (17%)
Nausea	6 (12%)	0	0	6 (12%)
Fatigue	6 (12%)	0	0	6 (12%)
Platelet count decreased/thrombocytopenia	3 (6%)	1 (2%)	2 (4%)	6 (12%)
Weight decreased	2 (4%)	1 (2%)	0	3 (6%)
Febrile neutropenia	1 (2%)	2 (4%)	0	3 (6%)
Anaemia/haemoglobin decreased	1 (2%)	2 (4%)	0	3 (6%)
Dyspnoea	1 (2%)	1 (2%)	0	2 (4%)
Hyponatraemia	0	1 (2%)	0	1 (2%)
Pleural effusion	0	1 (2%)	0	1 (2%)
Pleuritic pain	0	1 (2%)	0	1 (2%)
Pulmonary embolism	0	1 (2%)	0	1 (2%)
Deep vein thrombosis	0	1 (2%)	0	1 (2%)
Superior vena cava occlusion	0	1 (2%)	0	1 (2%)
Empyema	0	1 (2%)	0	1 (2%)
Anuria	0	1 (2%)	0	1 (2%)
Hepatic cytolysis	0	1 (2%)	0	1 (2%)