Alloplex Biotherapeutics

CLINICAL STUDY MONOGRAPH

Summary of the SUPLEXA-101 Clinical Study

A Completed First-in-Human Signal Finding Study

Safety, clinical activity and immune pharmacodynamics of SUPLEXA, an autologous, non-engineered NK/NKT-like cell therapy in metastatic solid tumors

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ABOUT THIS DOCUMENT

- *A consolidated account of SUPLEXA-101 (NCT05237206), assembled from the final clinical study report and the conference poster record. The study asked whether a non-engineered, autologous cell product, manufactured from about 50 mL of blood (not requiring leukapheresis) and administered as a single agent without lymphodepleting chemotherapy or cytokine support, could be administered repeatedly to end-stage solid tumor patients. The answer was affirmative, with no dose-limiting toxicity and no treatment-related serious or high-grade toxicities observed across more than 220 administered doses. The study also produced clinical responses and stable disease as determined by RECIST criteria, with benefit concentrated in dMMR/MSI-H colorectal cancer and clear cell renal cancer, and with immune pharmacodynamic changes that track with that benefit. The primary safety endpoint was therefore achieved, as was the secondary signal finding objective.*
- *Beyond that, the study provided a trove of longitudinal samples for exploratory analyses. These samples revealed unexpected findings concerning how SUPLEXA cells migrate throughout the body, one of which indicated that SUPLEXA may migrate to the bone marrow. Taken together, the positive safety findings, the observation of single-agent anti-tumor activity in some solid tumors, and the bone marrow migration potential all feed into the strategic decision to prioritize the hematologic malignancies, acute myelogenous leukemia (AML) and smoldering multiple myeloma (SMM).*
- ***Note:** recent preclinical experiments in collaboration with the Dana-Farber Cancer Institute (DFCI) and the Hackensack Meridian Health Network (HMHN) confirm that SUPLEXA can be made from the most diseased AML and MM blood samples. Because SMM is a precursor state to full multiple myeloma, SUPLEXA manufacture from SMM samples follows from the MM result. This positions Alloplex to request a pre-IND meeting with the FDA to plan an IND application.*

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SECTION 1

Executive summary

Five statements carry this document.

First, the primary endpoint was met without qualification. Thirty-five participants received a minimum of three infusions and 31 continued into an optional extension of up to nine further doses. There were no dose-limiting toxicities, no treatment-related Grade ≥3 events, no treatment-related serious adverse events, no injection-site reactions, and no clinically significant laboratory, vital sign or ECG findings. Three participants (8.6%) had any treatment-related event at all; every one was Grade 1 or 2 and resolved without a change in dosing[1].

Second, this was achieved without the toxicity that usually accompanies adoptive cell therapy. No lymphodepleting chemotherapy, no cytokine support and no concurrent checkpoint inhibitor were used. That was a design choice made so that any signal could be attributed to SUPLEXA alone, and its consequence is that the tolerability result is clean enough to carry into combination development without a sequencing problem[1,6].

Third, single-agent activity was measurable in this signal finding study, in a heterogeneous population spanning 14 different tumor types. Of 32 response-evaluable participants, one achieved a complete response and two achieved partial responses. The overall objective response rate was 9.4% (95% CI 2.0–25.0) in this mixed population, but among the CRC-MSI-H participants (n = 3) the objective response rate was 66.7%[6]. A further 19 had stable disease, giving an overall clinical benefit rate of 68.8% (95% CI 50.0–83.9). Median time to progression and median progression-free survival were both 19.29 weeks[1].

Fourth, the activity is not randomly distributed across tumor types. Two of the three objective responders had colorectal cancer subsequently confirmed as dMMR/MSI-H, and both of these had already progressed on chemotherapy and PD-1 blockade. The third objective responder had renal cell cancer. A third dMMR/MSI-H colorectal participant

achieved stable disease. Three of three profiled dMMR/MSI-H colorectal participants therefore derived clinical benefit, which is the single most consequential observation in the dataset[1,6].

Fifth, exploratory studies indicate that the immune changes accompanying treatment are measurable and track with benefit. Participants with clinical benefit entered the study with higher NK cells and lower PMN-MDSCs than those without. Treatment produced reproducible increases in activated (SIGLEC-1^{+}) classical monocytes and modulation of IL-6 and cKit-centered plasma protein networks. In a single-arm study, these findings convert a tolerability result into a testable development hypothesis[7,9].

The Sponsor closed the study in February 2024 on the basis that the predefined endpoints had been met.

TABLE 1

The study at a glance

ITEM	DETAIL
Study	SUPLEXA-101 — Phase 1, first-in-human, open-label, non-comparative, single-agent, basket design
Registration	ClinicalTrials.gov NCT05237206
Sponsor / CRO	Alloplex Australia Pty. Ltd. (Collingwood, VIC) / Novotech (Australia) Pty Ltd (Sydney)
Sites	3 centers in Australia: Cancer Research South Australia; Southern Oncology Clinical Research Unit; Gallipoli Medical Research Foundation
Period	First participant enrolled 04 May 2022; last participant completed 14 June 2024; terminated by the Sponsor 18 February 2024 on endpoints met
Population	Adults with histologically or cytologically confirmed measurable metastatic solid tumors who had exhausted standard options
Intervention	SUPLEXA autologous therapeutic cells, IV, target ~2.5 billion cells weekly × 3, then an optional extension (amended to ~5 billion cells every 2 weeks)
Enrollment	46 screened → 35 treated; 100% received all three planned doses; 31 continued into the extension
Analysis sets	Safety 35 (100%); DLT-evaluable 15 (42.9%); response-evaluable 32 (91.4%)

Source: clinical study report, Sections 5, 6, 9 and 10[1].

TABLE 2

Headline results

ENDPOINT	RESULT	POPULATION / NOTE
Dose-limiting toxicities	0	First 15 participants, assessed 1 week after doses 1 and 2
Treatment-related Grade ≥3 TEAEs	0	Safety population, N = 35
Treatment-related SAEs	0	All 8 SAEs in 6 participants judged unrelated
Participants with any related TEAE	3 (8.6%)	All Grade 1–2; all resolved without dose change
Objective response rate	9.4% (95% CI 2.0–25.0)	1 CR + 2 PR of 32 response-evaluable
Objective response rate, CRC-MSI-H	66.7%	2 of 3 profiled CRC-MSI-H participants
Clinical benefit rate	68.8% (95% CI 50.0–83.9)	CR + PR + stable disease (22 of 32)
Median time to progression	19.29 weeks (7.14–NE)	Response-evaluable population
Median progression-free survival	19.29 weeks (7.14–NE)	19 of 32 with progression or death
Median overall survival	Not evaluable	3 deaths (9.4%) during the observation period
Median time to clinical benefit	8.57 weeks (7.29–10.00)	Exploratory endpoint (TTCB)
Median duration of clinical benefit	16.14 weeks (8.71–NE)	Exploratory endpoint (DOCB)

CI = confidence interval; CR = complete response; NE = not evaluable, the upper limits being unreachable within the follow-up available; PR = partial response; SAE = serious adverse event; TEAE = treatment-emergent adverse event. Source: clinical study report Sections 11 and 12, Tables 14.2.1–14.2.7 and 14.3.3.1[1].

SECTION 2

The platform and why it is built this way

Cell therapy for cancer has been dominated by two strategies, each of which carries a structural limitation. Engineered approaches (CAR-T and its successors in NK, γδ T, iNKT, macrophage and iPSC-derived formats) require a target antigen that reliably separates tumor tissue from normal tissue. That constraint has been manageable in B-cell malignancy, where CD19 is shared with a dispensable normal compartment, and far harder in solid tumors, where most candidate antigens are also carried by normal cells. Tumor-infiltrating lymphocyte approaches sidestep the antigen problem by starting from cells that have already entered the tumor. However, as they begin from a population that demonstrably failed to control the disease, they require tumor tissue, and they have carried a persistent manufacturing burden.

Alloplex took a third route: rather than select one immune cell type and one engineering concept, use naturally occurring immunostimulatory mechanisms to convert a patient's own circulating leukocytes into a multi-lineage NK/NKT-like effector population. The intellectual ancestor to the approach is the GVAX cellular vaccine, in which a tumor line was engineered to express a single immunomodulator to modulate the immune system in vivo. Alloplex extended that idea combinatorially, engineering a melanoma line to express a curated set of immunomodulatory proteins, added in successive rounds with functional testing after each cycle until the in vitro functional assays saturated. Those are the ENLYST induction reagents[5] used to make autologous, non-engineered SUPLEXA by in vitro stimulation of patient-derived PBMC.

2.1 What SUPLEXA cells are

SUPLEXA™ is the product of exposing patient PBMCs to ENLYST™ cells. It is composed of NK and NKT-like cells, the latter component further fractioned into TCRαβ$^+$ and TCRγδ$^+$ cells of the CD4$^+$ or CD8$^+$ phenotype. SUPLEXA is notable for the absence of B cells, myeloid cells and regulatory T cells. Four major properties define it.

PROPERTY	BASIS
Migratory	Chemokine receptors and adhesion molecules supporting trafficking to bone marrow, lymph node and the tumor microenvironment
Cytolytic	High granzyme, perforin and granulysin expression, with broad killing of tumor cell lines and of patient-derived colorectal and lung organoids in vitro, without damage to normal resting cells
Antigen-presenting	High MHC class II (HLA-DR) with the T-cell costimulatory molecules CD80, CD86 and CD40 — features usually associated with professional antigen-presenting cells rather than effectors
Immunomodulatory	Rapid, measurable remodeling of the patient's peripheral myeloid compartment after infusion

Source: SITC 2024 Poster 378[7]; SITC 2023 Poster 381[9]; ISCT 2021 Poster 411[11].

The combination of direct cytolysis with antigen-presenting capacity is the mechanistically distinctive claim.

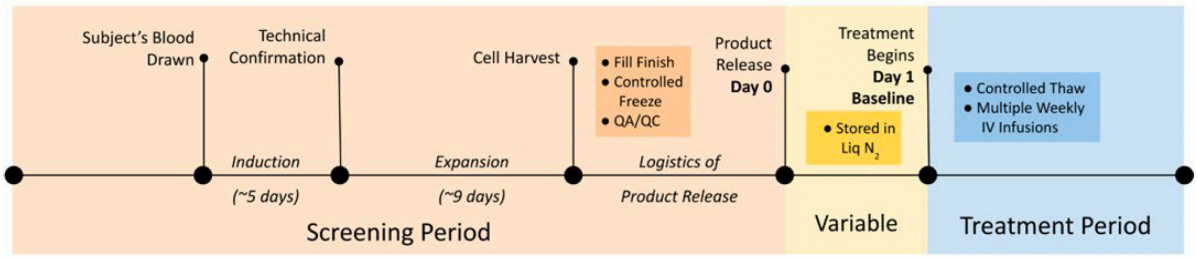
2.2 Manufacturing

Manufacturing is short, xeno-free, and requires neither primary tumor tissue, PBMC fractionation, nor genetic modification. Approximately 50 mL of whole blood is collected; PBMCs are co-incubated with freeze/thaw non-viable ENLYST cells for a five-day induction; the activated cells are expanded for nine days in IL-7 and IL-15; the product is harvested and cryopreserved. The process yields roughly a 300-fold expansion with low inter-subject variability in composition[10,11]. In this study SUPLEXA was manufactured under GMP by a contract manufacturer in Australia and supplied as approximately 2.5 billion cells in 100 mL of cryopreservative solution (PlasmaLyte with 28 mM glucose, 3.5% human serum albumin, 50% EZ-CPZ and 10% DMSO)[1].

One operational consequence deserves stating plainly. Participants who did not show adequate blast formation at the manufacturing facility during screening did not proceed: two of the 46 screened were not treated for that reason. That is a manufacturing feasibility rate, and it belongs in the design assumptions of any successor trial rather than in a footnote.

FIGURE 1A

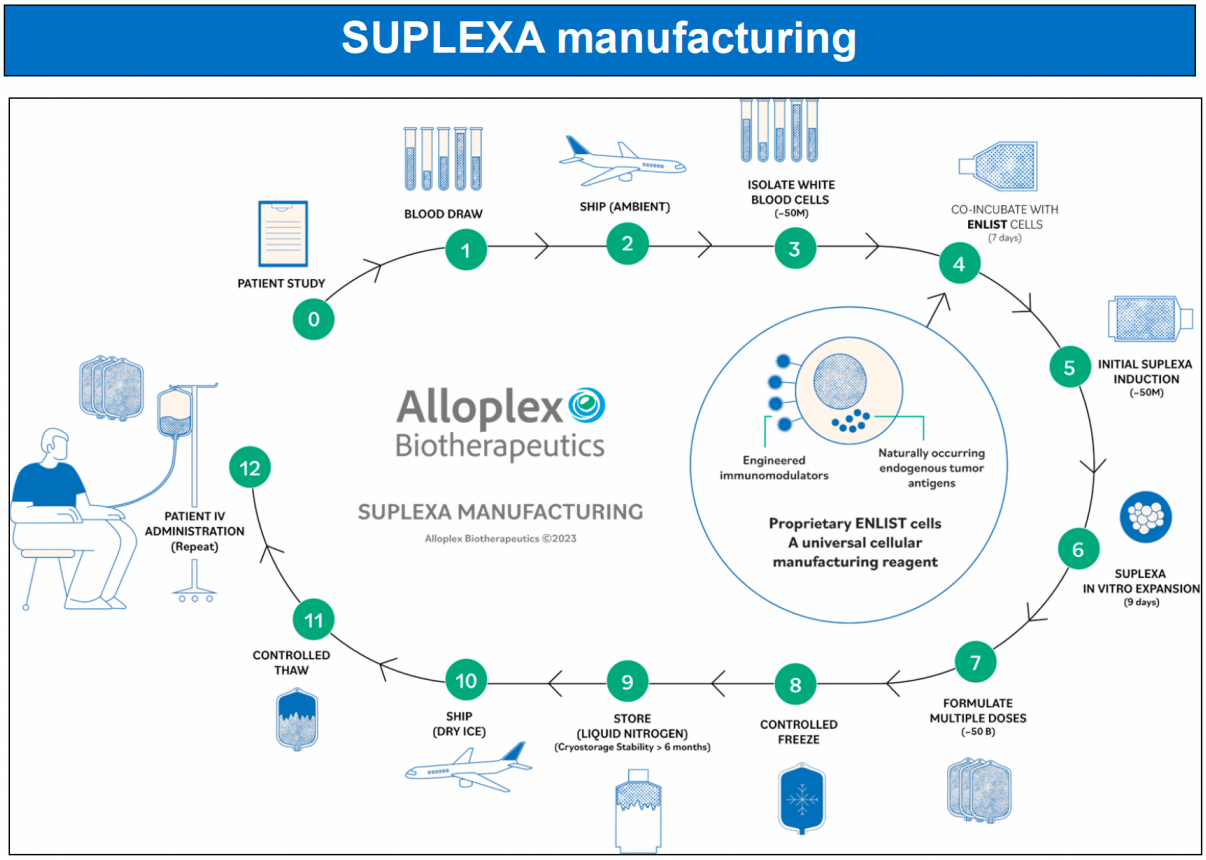
SUPLEXA screening and manufacturing period



Note: treatment period was minimally 3 doses 1 week apart. Abbreviations: IV = intravenous; Liq N2 = liquid nitrogen; QA = quality assurance; QC = quality control.

FIGURE 1B

SUPLEXA manufacturing schematic



50 mL whole blood → PBMC isolation → 5-day ENLYST induction → 9-day IL-7/IL-15 expansion → harvest, QC and cryopreservation → IV infusion.

2.3 The preclinical foundation

Before the clinical study, SUPLEXA was characterized by 47- and 48-marker mass cytometry, tested for cytolysis against a panel of tumor lines (M14, K562, PC3, COLO205) by flow cytometry, profiled for cytokine release during killing by 33-plex Luminex, and tested against patient-derived colorectal and non-small cell lung organoids, where imaging showed dose-dependent infiltration and killing[10,11]. In vivo activity was shown in a single-dose xenograft model and in a repeat-dose patient-derived xenograft model. The clinical dose was anchored to those studies: mice received approximately 28 times the intended human regimen of three doses of ~2.5 billion cells[1].

SECTION 3

How the study was run

SUPLEXA-101 was a Phase 1, first-in-human, non-comparative, open-label, basket-design study conducted at three Australian centers. The solid tumor cohort enrolled participants with measurable disease radiographically confirmed as Stage II to IV who were neither receiving nor under the residual influence of immunosuppressive therapy. A planned hematologic malignancy cohort was never recruited, and its objectives and criteria are therefore out of scope here.

TABLE 3

Objectives and endpoints

LEVEL	OBJECTIVE	ENDPOINTS
Primary	Safety and tolerability of SUPLEXA in malignant solid tumors	Incidence of DLTs; incidence of AEs and SAEs overall, by severity, by relationship, and those leading to discontinuation
Secondary	Efficacy by Investigator assessment under RECIST v1.1, or by change in tumor-derived blood biomarkers	Objective response rate (CR + PR); time to progression
Exploratory	Additional efficacy outcomes	Clinical benefit rate; duration of clinical benefit (DOCB, replacing DOR); time to clinical benefit (TTCB, replacing TTR); PFS; OS; change in plasma biomarkers
Exploratory	Anti-tumor activity under iRECIST	iORR; iPFS; iDOR; iDCR
Exploratory	Disease biomarkers in blood	Change from baseline in whole-blood immune cell phenotyping and related pharmacodynamic assays

DOR and TTR were replaced by DOCB and TTCB in the statistical analysis plan. Source: clinical study report Section 8 and Section 9.7.7.2[1]; statistical analysis plan[3].

3.1 Screening, treatment and follow-up

Screening ran over two visits across up to five weeks. At the first visit, blood was drawn for safety laboratories (~5 mL), for manufacturing of Batch 1 (~50 mL) and for exploratory studies (~20 mL). Participants meeting the laboratory criteria and showing adequate blast formation proceeded to the second screening visit.

Eligible participants received infusions on Day 1, Week 1 and Week 2 at a target of approximately 2.5 billion cells, with each bag given over about an hour with recommended prophylactic pre-treatment. The first three participants were dosed at least a week apart, observed in clinic for six hours after each infusion and contacted every business day between infusions; no further participants were dosed until the Data Safety Monitoring Board had reviewed their data. Subsequent participants were observed for at least 90 minutes after each infusion.

After the three mandatory doses, participants could continue on an optional extension at the discretion of the Investigator, treating physician and Sponsor Medical Monitor, and with the participant’s agreement — initially weekly ~2.5 billion cell doses, changed by Protocol Amendment 3 to ~5 billion cells every two weeks once early safety and pharmacodynamic data suggested infusion burden could be reduced. A second batch could be manufactured from a further draw, with a gap of up to 60 days permitted. Treatment continued until doses were exhausted, disease progressed, toxicity became unacceptable, or another reason for discontinuation arose.

Imaging of chest, abdomen and pelvis was performed 6–12 weeks after the first infusion and every 6–12 weeks thereafter, with response assessed by the Investigator under RECIST v1.1 and under iRECIST where immune progression was suspected. Because pseudo-progression and delayed response are well recognized with immunotherapies, participants could continue beyond RECIST-defined progression, with confirmation sought at the next imaging timepoint 4–8 weeks later. All scans were retained for possible retrospective blinded independent central review. Follow-up ran every 8 weeks for up to 48 weeks after the last dose, then every 12 weeks for survival and disease status up to 24 months.

3.2 Safety architecture

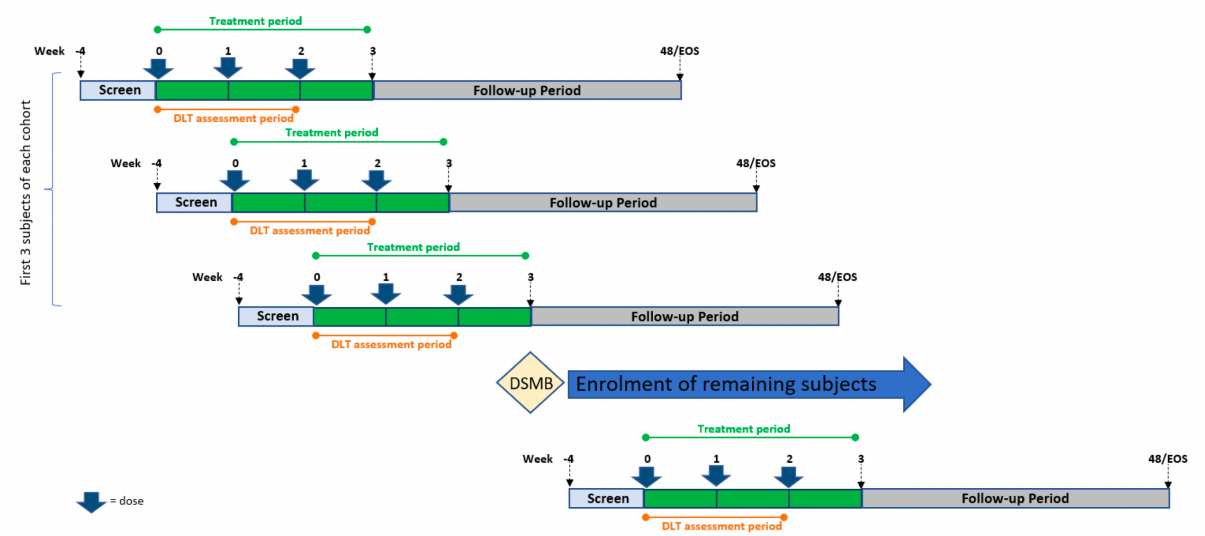
Dose-limiting toxicity was assessed in the first 15 participants, one week after the first dose and one week after the second, graded by NCI CTCAE v5.0. Hematologic criteria covered Grade 4 neutropenia lasting ≥7 days, febrile neutropenia, Grade 4 thrombocytopenia or Grade 3 with clinically significant bleeding, and unexplained Grade 4 anemia. Non-hematologic criteria covered Grade ≥3 toxicity, with carve-outs for short-lived Grade 3 events manageable with standard of care — inflammatory reactions attributable to local anti-tumor response, fatigue ≤3 days, gastrointestinal events ≤3 days, and rash or pruritus not requiring corticosteroids — plus explicit hepatic laboratory criteria.

A Data Safety Monitoring Board — composed of at least three independent medical experts, the Principal Investigator and a statistician, with non-voting CRO and Sponsor representation — reviewed unblinded safety data throughout. Predefined suspension triggers included any non-progression death within 30 days of dosing, two or more Grade ≥4 DLTs, or three or more Grade ≥3 immunological, cytokine release syndrome or tumor lysis syndrome events assessed as related.

The study was conducted under ICH GCP, the Declaration of Helsinki and the NHMRC National Statement, with Human Research Ethics Committee approval and written informed consent from every participant[1,2].

FIGURE 2

Study schema



Screening and manufacturing (Day -35 to Day 1) → three weekly infusions with staggered dosing and DLT windows → optional extension → follow-up to end of study. Abbreviations: DLT = dose-limiting toxicity; DSMB = Data Safety Monitoring Board; EOS = end of study.

SECTION 4

Who was treated

Forty-six participants were screened. Eight were screen failures and three were not treated — two for insufficient blast formation during manufacturing, one because of a pre-treatment adverse event (hospitalization for cholecystitis). The remaining 35 were treated and constitute the safety analysis population. All 35 received the three planned doses and 31 continued into the optional extension, receiving between one and nine additional doses.

Only three participants (8.6%) were recorded as completing the study. This reflects the Sponsor’s decision to close it rather than any tolerability problem. Reasons for non-completion were progressive disease and Sponsor termination (8 participants each, 22.9%), participant withdrawal (6, 17.1%), physician decision and start of new anti-cancer therapy (3 each, 8.6%), and adverse events and death (2 each, 5.7%).

TABLE 4

Demographics and baseline characteristics (safety analysis population, N = 35)

CHARACTERISTIC	VALUE
Age, years — mean (SD)	63.6 (10.1); median 64.0; range 34–81
Sex — n (%)	Female 18 (51.4%); male 17 (48.6%)
Race — n (%)	White 31 (88.6%); Asian 4 (11.4%); all 35 not Hispanic or Latino
Body mass index, kg/m² — mean (SD)	26.63 (6.40); median 25.99; range 19.9–53.8
ECOG performance status — n (%)	0: 24 (68.6%); 1: 11 (31.4%)
Diagnosis confirmation — n (%)	Histological 33 (94.3%); cytological 2 (5.7%)
Stage at screening — n (%)	IV: 34 (97.1%); II: 1 (2.9%)
Time since initial diagnosis, months — mean (SD)	59.8 (59.5); median 46.0; range 4.6–338.2
Most common primary sites — n (%)	Kidney 11 (31.4%); ovary 4 (11.4%); colon 3 (8.6%); cervix 2 (5.7%); lung 2 (5.7%)

CHARACTERISTIC	VALUE
Most common metastatic sites — n (%)	Lymph node 20 (57.1%); lung 18 (51.4%); liver 8 (22.9%); bone 5 (14.3%)
Prior therapy	All 35 had prior anti-tumor medication (chemotherapy 22; immunotherapy 22; other 13); 30 prior surgeries; 19 prior radiotherapies

The single participant recorded as Stage II had kidney cancer with pulmonary metastases and would, per the Principal Investigator, have been Stage IV; all 35 had metastatic disease at screening. Source: clinical study report Tables 7 and 8, and Tables 14.1.3 and 14.1.5[1].

This is a difficult population by design: heavily pre-treated, metastatic, out of standard options, and with roughly two-thirds having already received immunotherapy. Any reading of the efficacy signal must be set against that baseline.

4.1 Exposure and compliance

Compliance with the three planned doses was 100%. One participant (2.9%) had an infusion interruption and delay on Day 1 because of nausea; no other interruptions or delays occurred. Mean total infused volume was approximately 352 mL at each scheduled timepoint. Across the study, more than 220 doses were administered (range: 3 to 20 doses per participant)[1,6] — a breadth of exposure that materially strengthens the tolerability conclusion, because it tests the product across cumulative dose rather than at a single point.

4.2 Protocol deviations

Four participants (11.4%) had one major protocol deviation each: one eligibility deviation (screening eGFR of 37 mL/min, considered not clinically significant but meeting an exclusion criterion), one entry deviation (manufacturing blood draw taken one day within the required anti-tumor therapy washout period), and two operational deviations relating to consent form handling. All other deviations were minor, and none was considered to affect the assessment of study objectives or the integrity of the data.

SECTION 5

Safety and tolerability

The primary objective was met without qualification. No dose-limiting toxicities occurred among the 15 DLT-evaluable participants. Across the full safety population there were no treatment-related Grade ≥3 events, no treatment-related serious adverse events, and no treatment-related events leading to discontinuation of treatment or of the study.

TABLE 5

Overall summary of treatment-emergent adverse events (safety analysis population, N = 35)

CATEGORY	PARTICIPANTS, N (%)	EVENTS, M
Any TEAE	25 (71.4%)	125
Any DLT-related TEAE	0	0
Any severe TEAE (Grade ≥3)	6 (17.1%)	10
By maximum severity		
Mild (Grade 1)	9 (25.7%)	66
Moderate (Grade 2)	10 (28.6%)	49
Severe (Grade 3)	3 (8.6%)	7
Life-threatening (Grade 4)	2 (5.7%)	2
Fatal (Grade 5)	1 (2.9%)	1
Any treatment-related TEAE	3 (8.6%)	7
Any SAE	6 (17.1%)	8
TEAEs leading to withdrawal from study treatment	2 (5.7%)	2
TEAEs leading to discontinuation from study	2 (5.7%)	2
Infusion-related TEAEs	2 (5.7%)	2
TEAEs leading to death	1 (2.9%)	1

Severity rows count participants by maximum severity; five participants experienced at least one Grade 3 event, two of whom also experienced higher-grade events. Source: clinical study report Table 9, Table 14.3.3.1 and Section 12.1.2.2[1].

5.1 The related events

Three participants (8.6%) had seven events judged related to study treatment, all Grade 1 or 2, all resolved with no change to dosing: Grade 1 arthralgia, Grade 1 muscle spasms (two events), Grade 1 paresthesia and Grade 2 maculopapular rash in one participant; Grade 1 parosmia in a second; Grade 2 back pain in a third. No participant reported injection-site pain, tenderness, erythema, induration, swelling or bruising.

5.2 The unrelated events

The most common all-causality events, each judged unrelated, were fatigue (8 participants, 22.9%), constipation (6, 17.1%), nausea (5, 14.3%) and cough (5, 14.3%). Grade 3 events in five participants comprised ascites, intestinal obstruction, astroviral gastroenteritis, hyperkalemia, back pain, musculoskeletal chest pain and pleural effusion. Two participants had Grade 4 events (rectal hemorrhage; dyspnea) and one had a Grade 5 pulmonary embolism. Eight serious adverse events occurred in six participants (17.1%) — intestinal obstruction, colitis, astroviral gastroenteritis, back pain, rectal hemorrhage, ascites, pulmonary embolism and dyspnea — with no serious event reported by more than one participant and all assessed as unrelated. One further serious event, pneumonia, occurred during screening before any dosing.

5.3 Laboratory, vital sign and cardiac safety

Mean hematology and biochemistry values showed no trends over time and no clinically significant abnormal values were reported; the same held for dipstick and microscopic urinalysis. Vital signs showed no trends and no clinically significant abnormalities. ECG parameters likewise showed no trends, with no participant experiencing an on-treatment QTc above 450 msec or a change from baseline greater than 30 msec at Week 1, Week 2 or Week 48/end of study. Most participants maintained an ECOG performance status of 0 or 1 throughout; two had transient deterioration, one returning to baseline at the next visit.

What this profile is worth. This safety result is unusual for an adoptive cell therapy in solid tumors, and it was obtained without lymphodepleting preconditioning or cytokine support, across more than 220 administered doses and up to 20 doses in a single patient. The absence of compounding toxicity is what makes combination development a near-term option rather than a sequencing problem, and it is the property on which the Phase 2 designs in Section 8 depend.

SECTION 6

Clinical activity

Thirty-two of the 35 treated participants were evaluable for response. Best overall response was based on unconfirmed tumor response.

TABLE 6

Best overall response and derived endpoints (response-evaluable population, N = 32)

OUTCOME	N (%)	ESTIMATE (95% CI)
Complete response	1 (3.1%)	—
Partial response	2 (6.3%)	—
Stable disease	19 (59.4%)	—
Progressive disease	10 (31.3%)	—
Objective response rate (CR + PR)	3 (9.4%)	9.4% (2.0–25.0)
Clinical benefit rate (CR + PR + SD)	22 (68.8%)	68.8% (50.0–83.9)
Median time to progression	—	19.29 weeks (7.14–NE)
Median progression-free survival	—	19.29 weeks (7.14–NE)
Median time to clinical benefit	—	8.57 weeks (7.29–10.00)
Median duration of clinical benefit	—	16.14 weeks (8.71–NE)
Median overall survival	—	Not evaluable (3 deaths, 9.4%)

NE = not evaluable; upper confidence limits were not estimable given the follow-up available. Source: clinical study report Tables 14.2.1–14.2.7[1].

6.1 The three responders

All three participants with an objective response maintained at least a partial response until the end of their participation.

Participant 0117 (colon primary, lymph node metastases; prior chemotherapy and PD-1 blockade) achieved a complete response of target and non-target lesions by Week 24, maintained through Week 48; a target lesion CR with overall PR persisted at Week 60, when the participant withdrew because of inability to attend visits. Mesenteric lymph node lesions fell from 15 mm at screening to 5 mm from Week 24 through Week 60.

Participant 0111 (colon primary, peritoneal metastases; prior chemotherapy and PD-1 blockade) achieved a partial response by Week 24 that was maintained to the Week 84 assessment, when the participant completed the study. Peritoneal lesions fell from 52 mm at screening to 24 mm by Week 84.

Participant 0113 (kidney primary, pulmonary metastases; prior PD-1 blockade) achieved a partial response of target lesions by Week 72, maintained through Week 84 at study completion. Pulmonary lesions fell from 10 mm at screening to 7 mm by Week 72 and 9 mm at Week 84.

Participants 0117 and 0111 were both subsequently confirmed by the Investigator, through non-study assessments, as having dMMR/MSI-H disease; a third dMMR/MSI-H colorectal participant, 0119, achieved stable disease[1]. That three of three profiled dMMR/MSI-H colorectal participants derived clinical benefit — two of them objective responses after progression on both chemotherapy and checkpoint blockade — is the observation that sets the development path.

6.2 Tumor burden over time

Mean baseline sum of target lesion diameters was 80.1 mm (SD 50.5). From Week 24 onward the mean percentage change from baseline was negative among participants remaining on study, ranging from –4.19% (SD 24.76; n = 14) at Week 24 to –29.72% (SD 24.00; n = 5) at Week 48, and a mean decrease was still present at Week 84 (–19.23%; SD 20.71; n = 4). These later timepoints reflect a progressively smaller and self-selected group and should be read as descriptive rather than as an estimate of average effect.

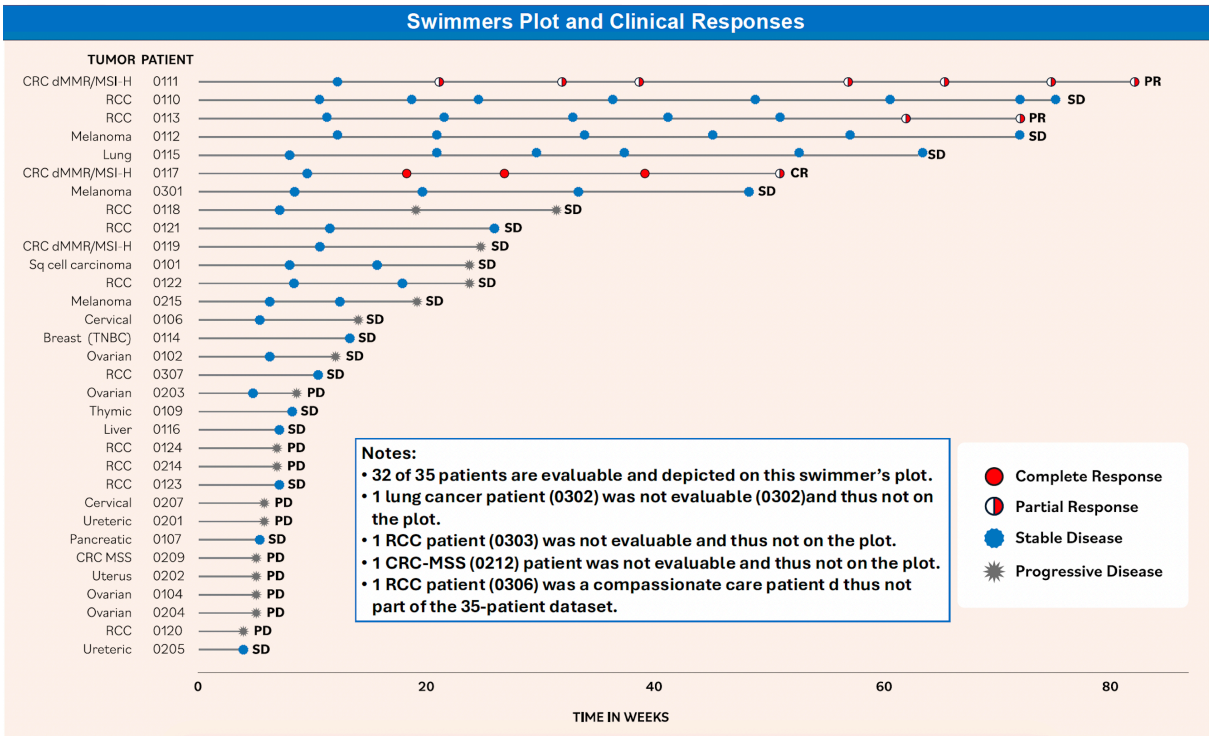
6.3 Progression and survival

Median time to progression was 19.29 weeks, with progression-free rates of 66.9% at 12 weeks, 40.3% at 24 weeks and 35.8% at 36 weeks and beyond. Median progression-free survival was identical at 19.29 weeks, with rates of 61.2%, 36.9% and 32.8% at the same timepoints; 19 of 32 participants (59.4%) had progression or death. Median overall survival was not evaluable given follow-up duration, with a survival rate of 88.6% (95% CI 68.5–96.2) at 12 weeks and beyond; three participants died, two from disease progression and one from the pulmonary embolism described in Section 5.

iRECIST assessment was applied at single timepoints in three participants, supplementary to their RECIST assessments; no confirmed progressive disease was reported under iRECIST. No statistical or analytical issues arose, no covariate or multiplicity adjustments were made, no subgroup analyses were performed, and no interim analysis was conducted.

FIGURE 3

Swimmer plot of overall tumor response by timepoint



Response-evaluable population (n = 32), annotated by tumor type including CRC-dMMR/MSI-H, CRC-MSS, ccRCC, melanoma, lung and TNBC, showing dosing and response duration.

SECTION 7

Translational and pharmacodynamic findings

Blood was collected at baseline and at multiple points during and after treatment. Three analytical streams ran in parallel: mass cytometry with custom 48-marker panels focused on myeloid or T/NK compartments; transcriptional profiling of SUPLEXA cells and PBMCs by bulk RNA sequencing and NanoString; and plasma protein profiling by 40-analyte Luminex and the Olink Discovery panel (3,072 proteins) at baseline, Week 1 and Week 2[7,9]. These analyses are exploratory and are the subject of detailed reporting elsewhere; what follows is a summary of the record as presented to date.

7.1 The product itself

Mass cytometry across all 35 clinical batches showed the expected NK cell and NKT-like cell lineage composition, containing γδ T cells, CD4 single-positive and CD8 single-positive T cells, and CD4/CD8 double-negative T cells. Acquisition of the defining functional phenotype was consistent across batches: HLA-DR and CD86 for antigen presentation, granzyme B and granulysin for cytolysis, and NKG2D as an activation marker. Notably, the downregulating protein PD-1 is not expressed and NKG2A is observed only at very low levels. Transcriptionally, cell killing, cell proliferation and cytolytic networks were highly elevated relative to starting PBMCs, with IFN-γ and granzyme A among the most significantly upregulated genes by both sensitive transcriptomic and proteomic methods, indicating positive regulation of cytolytic activity.

Interpatient variation is found primarily at the level of lineage subset composition — the NK to NKT-like ratio, which can vary significantly with the starting PBMC — but the activation signature is otherwise remarkably consistent across all SUPLEXA samples prepared.

7.2 Baseline immune state and clinical benefit

Analysis of baseline PBMCs separated participants who derived clinical benefit from those who did not. Those with benefit entered with higher NK cells and lower polymorphonuclear myeloid-derived suppressor cells. Across the 15 profiled participants spanning CRC-MSI-H,

CRC-MSS, ccRCC, melanoma, lung and breast cancer, the pattern held with sufficient consistency to justify prospective testing as a selection biomarker in the future.

7.3 On-treatment changes

Longitudinal myeloid mass cytometry showed a pharmacodynamic increase in activated classical monocytes (SIGLEC-1^{+}) after dosing, illustrated in detail for two dMMR/MSI-H colorectal participants across baseline, Week 1, Week 2, three months and six months. Earlier analyses had shown that participants entering with high baseline PMN-MDSC (>20%) shifted toward profiles resembling normal healthy controls over the first weeks of treatment. Plasma proteomics by Luminex and Olink, analyzed by STRING network and gene ontology enrichment, showed modulation of networks centered on IL-6 and on the hematopoietic factor cKit, with distinguishable trajectories between immune-suppressed and inflammatory patient profiles.

Why this matters. In a single-arm study with modest objective response numbers, reproducible pharmacodynamic changes that track with clinical benefit are what convert a tolerability result into a development hypothesis. These data provide a dose- and schedule-optimization readout that does not depend on RECIST, and a candidate basis for selecting the population most likely to respond.

The full immunophenotypic characterization of the product and of the longitudinal patient samples — including the composite mass cytometry profile of all 35 clinical batches and the baseline and longitudinal profiling that distinguishes participants with and without clinical benefit — is a detailed technical analysis in its own right and is not reproduced here. It is presented in the SITC 2023 and SITC 2024 scientific posters[7,9], which, together with the clinical posters, are available on the Alloplex Biotherapeutics website[12].

SECTION 8

Interpretation and what follows operationally

8.1 What the study establishes

A non-engineered autologous cell product manufactured from 50 mL of blood can be given repeatedly to heavily pre-treated metastatic cancer patients without lymphodepletion or cytokine support, and without dose-limiting toxicity, related serious adverse events or related high-grade toxicity, across more than 220 administered doses. Single-agent activity is measurable in that setting: one complete and two partial responses, 19 participants with stable disease, and a clinical benefit rate of 68.8%. The activity is not randomly distributed — every profiled dMMR/MSI-H colorectal participant derived clinical benefit, including two objective responders who had already progressed on chemotherapy and PD-1 blockade. Furthermore, treatment produces reproducible, measurable changes in the peripheral immune compartment, with baseline immune composition differing between participants who do and do not benefit.

The study is also notable for the consistency of manufacturing at a low cost of goods, owing in large measure to the easily obtained starting material and the avoidance of genetic engineering, as well as to the absence of any need for chemotherapy preconditioning of the patient or cytokine support — both procedural elements that contribute a great deal of toxicity to the patient.

8.2 What it does not establish

The study was single-arm, open-label and non-comparative, with Investigator-assessed response in a deliberately heterogeneous basket population in search of an activity signal. There is no control arm against which to benchmark stable disease or progression-free survival in a mixed-tumor population. Response was based on best overall RECIST response as supported by regular imaging evaluations. Further follow-up ended when the study was closed in February 2024, which is why median overall survival and several upper confidence limits are not evaluable, and why later-timepoint tumor burden statistics rest on very small numbers. The biomarker findings are exploratory and hypothesis-building, drawn

from modest sample numbers, and are used only for internal strategic purposes and for planning additional studies. The primary safety conclusions rest on the full population across a wide exposure range, and the secondary efficacy findings take their direction from the signal seeking nature of the study.

8.3 The combination hypothesis for solid tumors

Checkpoint inhibitors work by removing a brake — blocking PD-1 or CTLA-4 signaling that would otherwise downregulate an anti-tumor T-cell response. That mechanism presupposes the existence of primed anti-tumor host T cells. In cancer patients the antigen-presenting compartment that primes those T cells is known to be defective, and an abundance of suppressive Tregs and MDSCs compounds the problem. When T-cell priming represents the rate-limiting bottleneck, checkpoint blockade has limited therapeutic leverage. Consequently, despite their clinical success, checkpoint inhibitors achieve response in only 25–30% of unselected patients.

SUPLEXA is unusual among effector cell therapies in carrying antigen-presenting machinery — high MHC class II with CD86 — alongside its cytolytic apparatus, and in demonstrably remodeling the peripheral myeloid compartment after infusion. The hypothesis is therefore mechanistically specific rather than generically additive: SUPLEXA may serve not only to lyse tumor cells but also to prime an anti-tumor host T-cell response and shift the myeloid environment toward one permissive to their function, complementing precisely what checkpoint blockade requires[6]. The clinical observation that two participants responded to SUPLEXA after progressing on PD-1 blockade is consistent with that model.

8.4 A path forward in solid tumors

A randomized, open-label, two-arm Phase 2 study is under development in front-line dMMR/MSI-H colorectal cancer, comparing checkpoint-inhibitor standard of care against the same standard of care plus SUPLEXA[6]. Two features of that design follow directly from the Phase 1 experience. Every participant receives active standard of care, which is both ethically cleaner and practically necessary if the question is synergy rather than replacement. And front-line patients are less fragile than the end-stage population studied here, which matters for a therapy requiring repeated manufacturing draws and infusions. The benchmark to beat is the current 12-month progression-free survival of approximately

55% in this setting. Because there is no overlapping toxicity between SUPLEXA and checkpoint blockade, the combination can be tested at full doses of both agents. This trial design has been granted Fast Track status by the FDA.

8.5 Strategically superior paths forward exist in the hematologic malignancies (AML and SMM)

Acute myelogenous leukemia (AML) and smoldering multiple myeloma (SMM) are two hematologic malignancies that originate in the bone marrow. Each is a spectrum of indications with suboptimal standards of care that delay but do not arrest disease progression.

The exploratory finding from the Phase 1 experience indicates that SUPLEXA cells can traffic to the bone marrow, increasing the local concentration of cytolytic activity where the responsible leukemic stem cells reside. Solid tumors present the more difficult problem: they are often found at the center of a fibrotic tumor microenvironment that helps them evade immune surveillance. By contrast, the highly vascularized nature of the bone marrow suggests that SUPLEXA effector cells can more readily contact tumor cells there. Combined with a large body of evidence that SUPLEXA cells kill a broad array of tumor cells upon contact, this suggests that SUPLEXA may be therapeutic in the marrow setting.

Using the same design as planned for solid tumors — a two-arm study of standard of care alone versus standard of care plus SUPLEXA — provides all of the same advantages outlined above. Every participant receives active standard of care, so no one is denied the best available therapy, and it is established that the standards of care in the identified indications are not toxic to SUPLEXA cells. Hematologic malignancies also carry a practical advantage over solid tumors: both progression of disease and response to therapy can be monitored with highly sensitive assays applied to a simply obtained peripheral blood sample. That not only simplifies the study but significantly decreases the cost of producing unequivocal results.

It is anticipated that the FDA should be equally receptive to the hematologic indications as it was to the CRC-MSI-H solid tumor indication.

SECTION 9

Where the primary underlying data resides

This document consolidates material that currently exists across one regulatory report and six conference presentations, the latter available on the Alloplex Biotherapeutics website[12]. The table below maps each section to its primary source so that any statement can be traced without re-reading the full clinical study report.

TABLE 7

Where the underlying data sit

SECTION OF THIS DOCUMENT	PRIMARY SOURCE
2. Platform rationale and historical context	Borriello & Lederer, Immuno-Oncology Insights 2023[5]
2.2 Manufacturing and product characterization	ISCT 2021 Poster 411[11]; SITC 2021 Poster 164[10]; clinical study report Section 9.4.2 (Table 1) and Figure 1[1]
2.3 Preclinical cytolysis and organoid killing	SITC 2021 Poster 164[10]; clinical study report Section 7[1]
3. Design, conduct, ethics, statistical methods	Clinical study report Sections 5–9[1]; protocol[2]; statistical analysis plan[3]
4. Disposition, demographics, exposure, deviations	Clinical study report Section 10; Tables 14.1.1–14.1.5; Listings 16.2.1–16.2.5[1]
5. Safety results	Clinical study report Section 12; Tables 14.3.3.1–14.3.5.3; Listings 16.2.7–16.2.9[1]
6. Efficacy results	Clinical study report Section 11; Tables 14.2.1–14.2.7; Figures 14.2.2.1–14.2.7[1]
6. Final clinical update (35-patient dataset)	SITC 2024 Poster 608[6]; interim 28-patient dataset, SITC 2023 Poster 727[8]
7. Translational and pharmacodynamic findings	SITC 2024 Poster 378[7]; SITC 2023 Poster 381[9]; clinical study report Appendix 16.1.11[1]

SECTION OF THIS DOCUMENT	PRIMARY SOURCE
8. Interpretation and conclusions	Clinical study report Section 13[1]; SITC 2024 Poster 608[6]

9.1 Investigators and contributors

Sponsor: Alloplex Biotherapeutics (F Borriello and S Gargosky).

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Principal Investigators: Dr Rohit Joshi (Cancer Research South Australia, Adelaide); Dr Ganessan Kichenadasse (Southern Oncology Clinical Research Unit, Bedford Park); Dr Jeffrey Goh (Gallipoli Medical Research Foundation, Greenslopes). Additional site investigators contributing to the presented datasets include V Atkinson, S Bishnoi, W Joubert, V Kwatra, G Nisyrios and M Okera.

Translational analyses: led by J Lederer with J Pulford, E Murzin and D Younger (Brigham and Women’s Hospital / Harvard Medical School).

CRO trial oversight: Novotech (Sydney). Regulatory support: Syner-G BioPharma Group.

Acknowledgment: Above all, this work depended on the 35 participants and their families who consented to a first-in-human study at a point in their illness when standard options had been exhausted.

SECTION 10

References

1. Alloplex Australia Pty. Ltd. SUPLEXA-101 clinical study report, Version 1.0, 28 November 2024, and appendices 16.1.1 to 16.2.8. Internal document.

2. Alloplex Australia Pty. Ltd. SUPLEXA-101 protocol, initial HREC-approved Version 2.2 dated 28 December 2021, with subsequent amendments. Clinical study report Appendix 16.1.1. Internal document.

3. Novotech (Australia) Pty Ltd. SUPLEXA-101 statistical analysis plan, Final Version 1.0, 19 June 2023. Clinical study report Appendix 16.1.9. Internal document.

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5. Borriello F, Lederer JA. Alloplex Biotherapeutic's SUPLEXA cells represent a new type of autologous adoptive cellular therapy for cancer. Immuno-Oncology Insights. 2023; 4(3), 89–104. doi: 10.18609/ioi.2022.013

6. Joshi R, Goh JC, Kichenadasse G, et al. Final safety and efficacy update of SUPLEXA-101, a first-in-human, single-agent study of SUPLEXA therapeutic cells in metastatic solid tumors. SITC 2024, Poster 608.

7. Pulford J, Murzin E, Younger D, et al. Transcriptional and proteomic insights into the immunomodulatory nature of SUPLEXA cells: an autologous cellular therapy for cancers. SITC 2024, Poster 378.

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10. Borriello F, Keegan J, Lederer JA. Potent tumor organoid infiltration and killing by PBMC-derived effector cells. SITC 2021, Poster 164.

11. Borriello F, Keegan J, Lederer JA. Characterization of a novel autologous pan-cancer cellular immunotherapy. ISCT 2021, Poster 411.

12. Alloplex Biotherapeutics, Inc. Scientific presentations and publications, including the SITC and ISCT posters cited above. Available on the company website, alloplexbio.com.

References 1 to 3 are internal documents. Literature cited within the clinical study report itself is listed in Section 15 of that report and is not reproduced here.

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