Poster: 608

Final safety and efficacy update of SUPLEXA-101, a First-in-Human, Single-Agent Study of SUPLEXA Therapeutic Cells in Metastatic Solid Tumors

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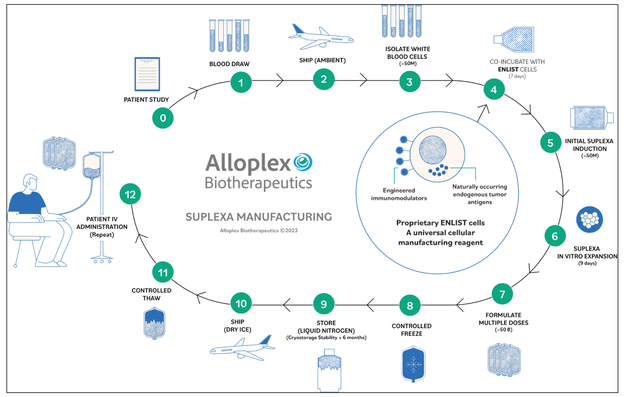
Background

SUPLEXA therapeutic cells are an autologous, non-engineered cell therapy derived from patient PBMCs isolated from about 50 mL of whole blood. They are composed of highly activated immune cells and are broadly cytolytic against an array of tumor cell lines in vitro without harming normal cells. SUPLEXA cells express features that enable direct tumor lysis as well as characteristics of antigen presenting cells ('APCs'). This first-in human study is a non-comparative, open-label, single-agent survey study designed to address safety and clinical activity in subjects with various solid tumors. Notably, no other active agents were used in these end-stage patients, thus toxicity from chemotherapeutic preconditioning and cytokine support was avoided.

SUPLEXA manufacturing



Note: Only 50 mL of whole blood is required per patient.

Study Design

This poster reports on SUPLEXA-101, 35 patients with histologically or cytologically confirmed measurable solid tumors, radiographically confirmed metastatic cancer who had exhausted standard options. All eligible subjects received a minimum of 3 weekly dose of SUPLEXA of approx. 2.5 billion cells per dose. At the discretion of the Investigator, Sponsor Medical Monitor and in agreement with the subject, additional SUPLEXA infusions were administered when available. Response was assessed by imaging on an 8-12 schedule.

Objectives	Endpoints
Assess Safety and tolerability of SUPLEXA in subjects with malignant solid tumors.	-Incidence of DLTs, AEs, SAEs.
Assess the efficacy of SUPLEXA based on RECIST evaluation criteria.	-Overall Response Rate (ORR). -Time-to-Progression (TTP).
Clinical Exploratory Endpoints	-Progression-free Survival (PFS). -Duration of Response (DOR). -Time to Response (TTR). -Clinical Benefit Rate (CBR). -Overall Survival (OS).
Scientific Exploratory Studies (results presented in an additional poster)	-Interpatient comparison of SUPLEXA batches. -Evaluation of longitudinal blood samples in individual patients assessing for changes in cellular composition and inflammatory cytokines.

Summary of Demographics and Baseline Characteristics

All patients had exhausted standard therapeutic options including chemotherapy and immune checkpoint inhibitors (ICIs).

Parameter	Statistics	Solid Tumor
Age	(N), Mean (SD)	(35), 63.6 years (10.1)
Gender	Male, Female	18, 17
Race	Caucasian, Asian	31, 4
ECOG Status	(Total), 0, 1, 2, 3, 4	(35), 24, 11, 0, 0, 0

Safety (treatment emergent adverse events)

Parameter	Statistics	Solid Tumors
Total subjects	N	35
Subjects with at least one TEAE	N, Not-related (NR), Related (R)	25, 22, 3
Subjects reporting TEAEs by severity	Total; grade 1, 2, 3, 4, 5	25; 9, 10, 3, 2, 1
Subjects with at least one **serious** TEAE	Affected subjects, Gastrointestinal disorders, Infections, Musculoskelatal, Respiratory	6 4 1 1 2
Subjects reporting drug **related** TEAEs	Subjects with at least 1 related TEAE; grade 1, 2, 3, 4, 5 Musculoskelatal, (N; grade 1, 2, 3, 4, 5) Arthralgia, (N; grade 1, 2, 3, 4, 5) Back Pain, (N; grade 1, 2, 3, 4, 5)	3; 1, 2, 0, 0, 0 2; 1, 1, 0, 0, 0 1; 1, 0, 0, 0, 0 1; 1, 0, 0, 0, 0

Note: Critically, there were no DLTs identified, no injection site reactions, no serious drug related adverse events. no laboratory abnormalities, no abnormalities in vital signs and ECGs

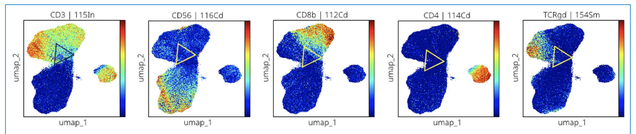
Best Overall Response and Event-free Survival

Best Overall Tumor Response	N (%)
Clinical Benefit Rate (CBR)	22 (68.8)
Overall Response Rate ORR)	3 (9.4)
Complete Response (CR)	1 (3.1)
Partial Response (PR)	2 (6.3)
Stable Disease (SD)	19 (59.4)
Progressive Disease (PD)	10 (31.3)

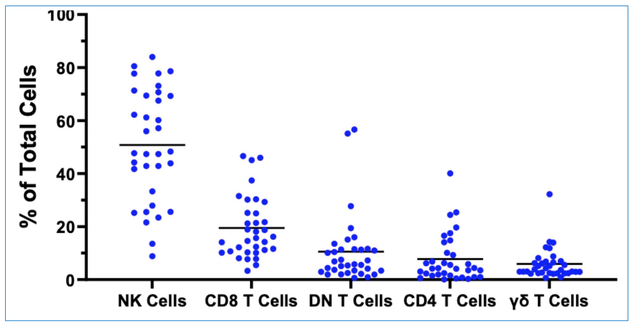
	Statistics	Solid Tumors
Descriptive	N	32
	Event	19
	Censored	13
Time to Event (weeks)	Median (95% CI)	19.3 (7.1, NE)
Event-free Rate (%) (95% CI)	12 weeks	61.2 (41.8 -75.1)
	24 weeks	36.9 (19.3 -54.6)
	36 weeks	32.8 (16.1 -50.6)
	48 weeks	32.8 (16.1 -50.6)

Composite CyTOF Data for 35 SUPLEXA Clinical Batches

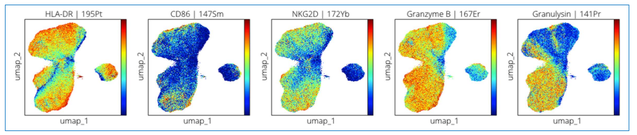
A: Lineage markers



Note: Cells within the triangle are double negative (DN) T Cells.

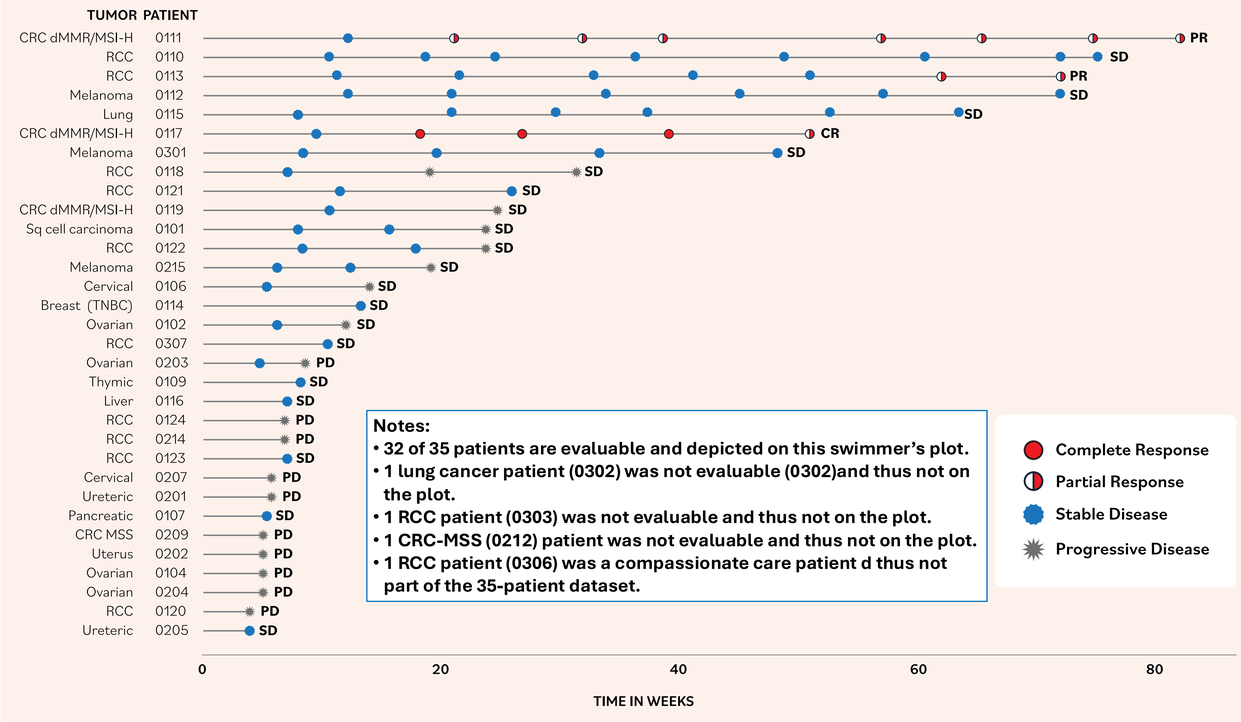


B: Activation markers

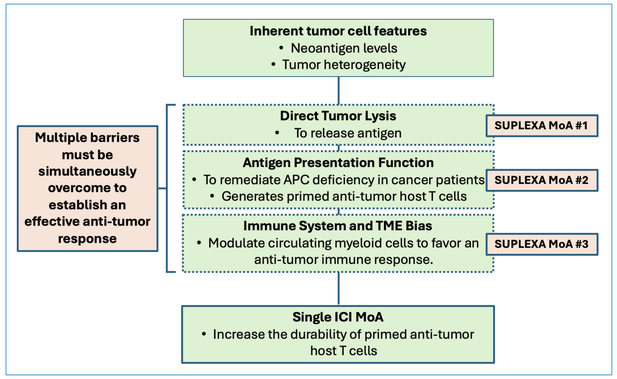


Note: HLA-DR Class II is required for antigen presentation, CD86 is a T cell costimulatory molecule, NKG2D is an NK activation molecule involved in cytolysis, Granzyme B and Granulysin are cytolytic proteins.

Swimmers Plot and Clinical Responses



SUPLEXA mechanisms provide a strong rationale for synergy with immune checkpoint inhibitors



It is widely accepted that the key mechanism by which ICI act on the immune system is by blocking the activation of a checkpoint protein (e.g. PD-1 and CTLA4) which would otherwise down-regulate the anti-tumor host T cell response. This means that ICI are dependent on the availability of anti-tumor host T cells for their activity. As cancer patients have a known defect in the antigen presenting cells that prime anti-tumor host T cells, this may provide a bottle neck which when combined with an abundance of suppressive Tregs and MDSC, restrains a functional anti-tumor immune response. We hypothesize that the multiple mechanisms of SUPLEXA shown above, are complementary to that of ICIs and should result in an increased availability of primed anti-tumor host T cells and an alteration in the myeloid compartment that results in an immune environment more permissive to their function.

Conclusions

All study endpoints were achieved. Safety was established over a wide dose range (3-20 doses of 2.5B cells per patient) and a total of >220 administered doses. No related DLTs, injection site reactions or drug related serious adverse events were identified throughout the course of the study. Signs of clinical efficacy were demonstrated with a CR and two PRs and a number of long-lasting SD responses in various tumor types including, CRC-dMMR/MSI-H, ccRCC, melanoma, lung cancer and TNBC.

Based on these positive first-in-human single-agent clinical trial results in select tumor types – supported by laboratory evidence that SUPLEXA cells modulate the immune environment of treated patients – a Phase 2 study of SUPLEXA combined with ICIs in front-line CRC-dMMR/MSI-H patients is under development. Since SUPLEXA possesses APC-like properties, we hypothesize that SUPLEXA cells may facilitate the production and function of anti-tumor primed T cells. Since the mechanism of action for immune checkpoint inhibitors depends on the presence of such primed T cells, we suggest that a combination of SUPLEXA with ICIs may result in synergistic activity with an improvement in the current 12-month PFS of ~55%.

This Phase 2 study will be open label 2-arm comparing the standard of care ICI against ICI combined with SUPLEXA. The advantage of such a study is that all participants receive ICI standard of care, and as front-line patients are less fragile.

For further information, see accompanying poster, Poster 378, 'Transcriptional and proteomic insights into the immunomodulatory nature of SUPLEXA cells: An autologous cellular therapy for cancers'

Acknowledgments

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