Phase 1 studies of agenT-797, a novel allogeneic invariant natural killer T cell therapy, for the treatment of patients with solid tumors or multiple myeloma

Poster 647

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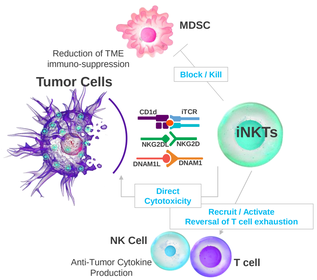
Background

Invariant natural killer T (iNKT) cells are a subset of T cells that regulate both innate and adaptive immunity, making them an ideal immunotherapy. MiNK Therapeutics is advancing an allogeneic iNKT cell product (agent-797) for the treatment of immune related diseases, including cancer. These data are presented from two ongoing phase 1 studies of agenT-797 alone or combined with pembrolizumab or nivolumab in relapsed/refractory (r/r) solid tumors (NCT05108623) and r/r multiple myeloma (MM) (NCT04754100).

iNKT Mechanisms of Action

- iNKTs exert anti-cancer attributes through TCR dependent and independent effector mechanisms and recognition of:
  - CD1d ligands in the TME and activation through the invariant TCR
  - Stress-signals through activating NK receptors, NKG2D, DNAM1
- Significantly improve function of exhausted T cells **(MiNK Poster # 372)**
- Modulates myeloid biology through MDSC suppression or killing
- Recruitment and activation of NK & T cells through cytokine secretion and modulation of TME



Clinical Trials

Solid Tumor Study (NCT05108623)

Phase 1 open-label study to assess safety, tolerability and preliminary clinical activity (per RECIST 1.1) of allogeneic INKT cells (agenT-797) +/- pembro or nivo in patients with r/r solid tumors.

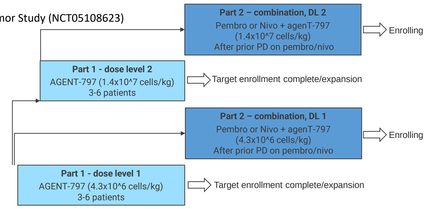
- 3+3 design with single I.V. administration of agenT-797 alone or in combo with pembro or nivo at 4.3 x 10^6 cells/kg, or 1.4 x 10^7 cells/kg (**Figure 1**).
- Endpoints included safety, persistence of agenT-797, response (per RECIST 1.1), time to response, duration of response, progression-free survival.

Multiple Myeloma Study (NCT04754100)

A Phase 1, open-label study to assess safety, tolerability, and preliminary clinical activity of allogeneic iNKT cells (agenT-797) in subjects with r/r Multiple Myeloma (MM) after at least 3 prior lines of therapy (proteasome inhibitor, immunomodulatory. agent and anti-CD38 antibody).

- 3+3 design with single I.V. administration of agenT-797 at 1.4 or 4.3 x 10^6 cells/kg or 1.4 x 10^7 cells/kg.
- Endpoints: safety, agent-797 persistence, response rate (I Myeloma Working Group; Kumar 2016), time to response, duration of response, progression-free survival.

Figure 1 Solid Tumor Study (NCT05108623)



Patient Demographics and Disposition (accrual ongoing)

Table 1. Patient demographics and disposition of Solid Tumor Study

Solid Tumor	DL1, MonoTx	DL1, ComboTx	DL2, MonoTx	Total
agenT-797 dose level	4.3 x 10^6 cells/kg	4.3 x 10^6 cells/kg	1.4 x 10^7 cells/kg	
monoTx/comboTx	agent-797 monotherapy	agent-797 in combination with pembro or nivo	agent-797 monotherapy	
Subjects dosed (n)	8	3	14	25
Age				
Median (range)	60 (30-73)	62 (62-76)	57 (54-66)	62 (30-76)
Sex, n (%)				
Male	2 (25.0)	3 (100.0)	11 (78.6)	16 (64.0)
Female	6 (75.0)	0	3 (21.4)	9 (36.0)
Patient disposition				
Early Discontinuation	6 (75.0)	1 (33.3)	2 (14.3)	9 (36.0)
Death	1 (12.5)	0	0	1 (4.0)
Disease Progression	5 (62.5)	1 (33.3)	2 (14.3)	8 (32.0)

PI reported data as of 12OCT22

Table 2. Patient demographics and disposition of Multiple Myeloma Study

Mutiple Myeloma	Cohort 1	Cohort 2	Cohort 3	Total
agenT-797 dose level	1.4 x 10^6 cells/kg	4.3 x 10^6 cells/kg	1.4 x 10^7 cells/kg	
Subjects dosed (n)	3	6	3	12
Age				
Median (range)	50 (49-53)	56.5 (49-74)	58 (51-67)	54 (49-74)
Sex, n (%)				
Male	3 (100.0)	3 (50.0)	2 (66.7)	6 (58.3)
Female	0	3 (50.0)	1 (33.3)	2 (41.7)
Patient disposition				
Early Discontinuation	3 (100.0)	2 (33.3)	1 (33.3)	6 (50.0)
Disease Progression	3 (100.0)	2 (33.3)	1 (33.3)	6 (50.0)

PI reported data as of 12OCT22

Results

Single-dose agenT-797 Demonstrates No CRS or Neurotoxicity

At multiple doses, no neurotoxicity and no cytokine release syndrome (CRS) grade ≥ 3 has been observed in either the solid tumor study or the multiple myeloma study. In solid tumors, the most severe TRAE was anemia (n=1, grade 3) and no grade ≥ 3 AE was observed in the multiple myeloma study. agent-797 is tolerated at all dose levels tested and no MTD has been determined.

Table 3. Summary of AEs in Solid Tumors

Solid Tumor Study	DL1 MonoTx (n=8)	DL1 ComboTx (n=3)	DL2 MonoTx (n=14)	Total (n=25)
Dose level	4.3 x 10^6 cells/kg	4.3 x 10^6 cells/kg	1.4 x 10^7 cells/kg	
	n (%)	n (%)	n (%)	n (%)
Any AE	**7 (87.5)**	**2 (66.7)**	**9 (64.3)**	**18 (72.0)**
Any AE of grade >= 3	6 (75.0)	0	2 (14.3)	8 (32.0)
Any TRAE	**1 (12.5)**	**1 (33.3)**	**1 (7.1)**	**3 (12.0)**
Any TRAE of grade >= 3	1 (12.5)	0	0	1 (4.0)
Any irTRAE	0	0	0	0
Any TRAE leading to discontinuation	0	0	0	0
Any TRAE leading to dose interruption	0	0	0	0
Any TRAE leading to death	0	0	0	0

PI reported data as of 12OCT22

- No DLTs were reported by the subjects treated to date.
- TEAEs were observed in 18/25 subjects. The most common TEAEs were fatigue (n=9), nausea (n=6) and constipation (n=4). TEAEs of grade ≥3 (n=10) were consistent with disease progression. One TRAE of grade ≥3 (n=1; anemia)

Table 4. Summary of AEs in Multiple Myeloma

Multiple Myeloma Study	Cohort 1 (n=3)	Cohort 2 (n=6)	Cohort 3 (n=3)	Total (n=12)
Dose Level	1.4 x 10^6 cells/kg	4.3 x 10^6 cells/kg	1.4 x 10^7 cells/kg	
	n (%)	n (%)	n (%)	n (%)
Any AE	**3 (100.0)**	**3 (50.0)**	**2 (66.7)**	**8 (66.7)**
Any AE of grade >= 3	0	1 (16.7)	1 (33.3)	2 (16.7)
Any TRAE	**3 (100.0)**	**0**	**0**	**3 (37.5)**
Any TRAE of grade >= 3	0	0	0	0
Any TRAE leading to discontinuation	0	0	0	0
Any TRAE leading to dose interruption	0	0	0	0
Any TRAE leading to death	0	0	0	0

PI reported data as of 12OCT22

- No DLTs or related AEs were reported to date.
- TEAEs were observed in 8/12 subjects; the most common were fatigue (n=3), dizziness. (n=3), and anemia (n=3). TEAEs of grade ≥3 were observed in two subjects (n=2; thrombocytopenia)
- No TRAEs were observed

agenT-797 Does not Induce Cytokine Release Syndrome (CRS)

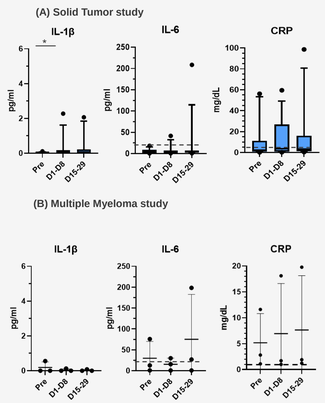


Figure 2. Serum levels of key indicators of CRS; IL-1β, IL-6, C-Reactive Protein (CRP) determined over 29 days. **(A)** Solid Tumor study (n=14), **(B)** MM study (n=3).

Data for both studies by day 1 pre-infusion (Pre; single timepoint), early post-infusion window (0.5 hr post infusion on day 1 to day 8; D1-D8) and a late post-infusion time window (days 15-29; D15-29).

Data corresponded to measured persistence of agent-797 in the periphery. Upper limit of biomarker levels in healthy people shown as dashed line (--). Where no upper normal serum level is indicated, scale of Y-axis represents half the upper normal serum level. Significant changes post dosing are indicated with asterisks (* p<0.05; ** p<0.01; data analyzed by one-way ANOVA). No significant post-infusion changes outside normal serum levels was observed for any of the markers of CRS.

Reduction in Target and Non-Target Lesions (Solid Tumor) in Heavily Pre-treated Patients

- Reduction of target & off-target lesions with agent-797 alone [27% (3/11)] & in combo with pembro/nivo [66% (2/3)].
- Disease stabilization in patients refractory to standard of care and after progression on checkpoint inhibitors alone.

Primary Tumor	# Prior Lines	BORR	Progression on last line of therapy
Pancreatic	3	SD	Gemcitabine, Abraxane
Thymoma	4	SD	Cisplatin, Etoposide
Cervical	3	PD	Pembrolizumab, Tisotumab Vedotin
Rectal	3	PD	Folfiri, Bevacizumab
Urothelial	4	PD	Trodelvi
Pancreatic	2	PD	Gemcitabine, Abraxane
NSCLC	4	PD	ABBV-155, Docetaxel
Breast	11	PD	Capecitabine
NSCLC	6	SD	Pembrolizumab
Gastric	2	SD	Oxaliplatin, Leucovorin, Fluorouracil, Nivolumab
Renal	2	PD	Pembrolizumab, Axitinib
Appendiceal	3	SD	Lonsurf
Prostate	6	PD	Carboplatin, Cabazitaxel
Pancreatic	3	PD	Xeloda

Early data cut with median follow-up ~ 18 weeks. PI reported data as of 19OCT22

Figure 3

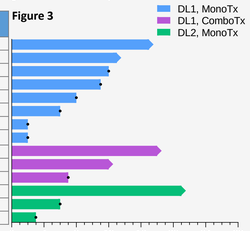


Table 5: First patient dosed May 2022; 14 patients evaluable (≥1 on-treatment scan). PD; progressive disease, SD: Stable disease with number of weeks of SD indicated. As of 19OCT22, 27 patients have been dosed; assessment of disease status is underway.

Figure 3. Patient status since administration of agent-797. Arrowhead indicates ongoing SD; Dots indicates PD.

On-Treatment Disease Assessment (Multiple Myeloma) in Heavily Pre-treated Patients

Table 6

Disease	Dose Level (cells/kg)	BORR	# Prior Lines	Prior I/O (any line)
r/rMM	1.4 x 10^6	SD10	6	Daratumumab, Nivolumab
r/rMM	1.4 x 10^6	PD	6	Daratumumab, Elotuzumab
r/rMM	1.4 x 10^6	PD	4	Daratumumab
r/rMM	4.3 x 10^6	PD	4	Daratumumab
r/rMM	4.3 x 10^6	PD	3	Daratumumab
r/rMM	4.3 x 10^6	SD2+	7	Daratumumab, Elotuzumab
r/rMM	1.4 x 10^7	PD	2	Daratumumab
r/rMM	1.4 x 10^7	PD	6	Daratumumab

Table 6. First patient dosed April 2021; as of October 2022, 12 patients dosed with 8 evaluable patients. Evaluable patients had at least one on-treatment disease assessment. PD; progressive disease, SD: Stable disease with number of months of SD indicated. '+' indicates the response is ongoing.

Figure 4

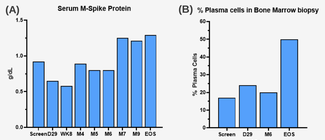


Figure 4. MM Case study: Patient 01-001 is a 49-year-old Male with r/r Multiple Myeloma having undergone 6 lines of prior treatment (1. doxorubicin, cisplatin, vincristine, thalidomide, Velcade; 2. Nivolumab; 3. Daratumumab, pomalidomide; 4. ASCT, melphalan; 5. Daratumumab; 6. Carfilzomib, dexamethasone, Revlimid). Single-dose agent-797 at DL1 April 2021 with Day 29 biopsy indicating disease stabilization (SD)/Minimal Response (MR) which remained through month 10. **(A)** During the duration of stable disease, a significant reduction of M-Spike protein was observed, as well as **(B)** a concurrent stabilization of plasma cell levels in bone marrow.

Peripheral Persistence is Consistent with Rapid Translocation of agenT-797 to Tissues

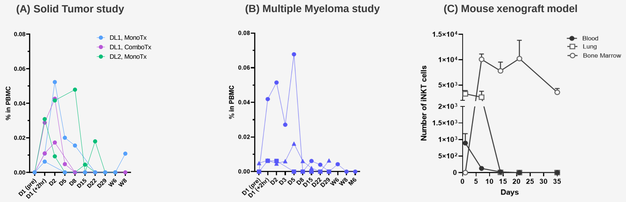
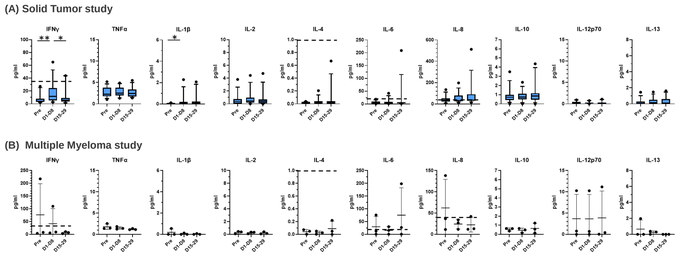


Figure 5. Persistence of agent-797 in cancer studies. Quantification of agent-797 in patient PBMC of BMMC by digital PCR based on genetic markers unique to donor material. Each line represents data from one patient. **(A)** Solid Tumor study. Peripheral detection of agent-797 in dose level 1 (DL1: 4.3x10^6 cells/kg) treated patients on monotherapy, dose level 1 (DL1: 4.3x10^6 cells/kg) in combination with pembro or nivo, and dose level 2 (DL2: 1.4x10^7 cells/kg) agent-797 alone. Transient detection of agent-797 up to day 22 post-infusion. **(B)** Multiple Myeloma study, cohort 1 (1.4x10^6 cells/kg). Detection of agent-797 in PBMC up to day 8 post infusion. **(C)** Dynamics of tissue distribution of agent-797 in a murine xenograft model (model presented by MiNK Therapeutics in poster #400 at SITC 2021), demonstrating rapid translocation of agent-797 to tissue following i.v. injection. The observed transient post-infusion persistence of agent-797 in patient blood is consistent with the dynamics of blood-to-tissue distribution of agent-797 in vivo. To determine tissue persistence of agent-797 a cell-free DNA (cfDNA)-based assay is in development with readouts in 2022.

agent-797 Demonstrates Modulation of Peripheral Cytokines



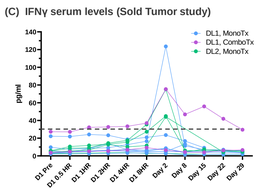


Figure 6. Pre- and post- infusion serum levels of select pro-inflammatory and anti-inflammatory cytokines. Data in both studies analyzed as described for Figure 2. **(A)** Solid Tumor study (n=14), **(B)** Multiple myeloma study (n=3). Upper limit of biomarker levels in healthy people shown as dotted line (--). Where no upper normal serum level is indicated, scale of Y-axis represents half the upper normal serum level. Significant changes post dosing are indicated with asterisks (* p<0.05; ** p<0.01; data analyzed by one-way ANOVA). The most significant post-dosing change was observed for IFNγ in the solid tumor study. **(C)** Data for IFNγ data from the Solid Tumor study for each patient in detail. Each line represents data from a single patient. Blue: DL1, monotherapy; Magenta: DL 1, combination therapy; Green : DL2, monotherapy.

A significant increase in for IFNγ levels is observed on Day 2 of treatment in a number of patients. IFNγ release (either directly by iNKT cells or through iNKT cell mediated transactivation of NK cells) is a hallmark of iNKT activation and function, and increased detection in serum may indicate iNKT activation at tumor site. No corresponding increase in serum IFNγ levels is observed in the Multiple Myeloma study, or in the use of agent-797 in COVID-19/ARDS **(MiNK Poster# 649)**, suggesting this biosignature to be unique in the solid tumor setting.

Conclusions

- agenT-797 alone and in combination with anti-PD-1 is well tolerated across multiple doses and shows early signals of clinical and biomarker activity in patients with solid tumor cancers, multiple myeloma, and severe viral acute respiratory distress (**MiNK Poster #649**).
- agenT-797 shows early clinical activity in solid tumors with reduction of target and off-target lesions in patients treated with monotherapy [27% (3/11)] and in combination with pembrolizumab or nivolumab [66% (2/3)] with disease stabilization in patients refractory to standard of care and after progression on checkpoint inhibitors alone.
- Observations are consistent with iNKTs ability to reinvigorate exhausted CD8+ T cells **(MiNK Poster #372)**, enable T cell trafficking to tumor (**MiNK Poster #358**), and improve effector functions within the tumor microenvironment (**MiNK Poster #372**).
- agenT-797 can be administered without lymphodepletion, is tolerable in patients with r/r multiple myeloma after at least 3 prior lines of therapy, and shows early signals of durable disease stabilization and modulation of M-spike protein.
- agenT-797 can be dosed to 1000x10^6 cells in severe immune diseases of cancer and infections without cytokine release syndrome or neurotoxicity **(MiNK Posters #647, #649).**
- agenT-797 demonstrates transient persistence in the periphery consistent both with MiNK in vivo data (SITC 2101 Posters #205, #400) describing rapid translocation of agent-797 from blood into tissues and with our study of agent-797. Persistence data from a proprietary cf DNA-based assay will readout by end of year.
- agenT-797 continues to advance in multiple Phase 1/2 clinical studies alone and in combination (anti-PD-1; **NCT05108623**), viral ARDS (**NCT04582201**) and multiple myeloma (**NCT04754100**).

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