Abstract No. 2526

A Phase 1, Open-Label, Dose Escalation Study of the Safety and Tolerability of T3011 in Advanced Cutaneous or Subcutaneous Malignancies

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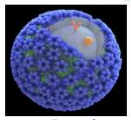
INTRODUCTION to MVR-T3011

I. MVR-T3011

- Genetically modified, replication-competent, next generation oncolytic HSV-1
- 2 payload genes encoding active domain of IL-12 and anti-PD-1 antibody

II. Immunotherapy with MVR-T3011

- Immunogenic Cell Death induced by T3011 infection
- Extra "double-barrel" effect of antitumor immune modulation by payload expression



III. Advanced Malignancy Remains a Highly Unmet Medical Need

- Immunotherapy has transformed cancer therapy and resulted in long-term disease-free survival in a number of advanced malignancies. Recent data also led to regulatory approvals of anti-PD-1/PD-L1 regimens as part of first- or second-line therapies
- Unmet needs in patients with disease progression following Immunotherapy treatment remain high, especially PD-1/PD-L1, presumably due to insufficient T cell activities
- Therapies such as oncolytic viruses that activate and orchestrate both innate and adaptive immunity may have the potential to overcome immune escape and to improve clinical outcome

METHODS

Study Design

- Phase 1, multi-center, open label, dose escalation (3+3 study design) and dose expansion study
- In Phase 1 dose escalation, subjects were treated with T3011 given intratumorally as a single agent Q2W at one of 3 dose levels (PFU/mL)
  - Cohort 1 (n=3) T3011 dose 1×10^6 (PFU/mL)
  - Cohort 2 (n=3) T3011 dose 1×10^7 (PFU/mL)
  - Cohort 3 (n=5) T3011 dose 5×10^7 (PFU/mL)
- Response assessments performed every 8 weeks by RECIST Version 1.1
- Histologically confirmed diagnosis of advanced malignancies
- Disease progression after standard of care (SOC) therapy or in the opinion of the Investigator unlikely to benefit from SOC therapy
- Once Recommended Phase 2 Dose (RP2D) established, T3011 single agent dose expansion will start

Study Objectives

Primary:

- To evaluate the safety and tolerability of escalating doses of T3011
- To determine the RP2D of single agent T3011

Secondary and Exploratory:

- To evaluate the clinical activity of T3011
- To evaluate the immunogenicity of T3011
- To evaluate the pharmacokinetics and viral shedding of T3011
- To characterize pharmacodynamic markers, including immunomodulatory and cancer-related changes, following T3011 exposure

Key Eligibility Criteria

- Histologically confirmed diagnosis of advanced malignancy.
- Disease progression after SOC therapy or in the opinion of the Investigator unlikely to benefit from SOC therapy
- Measurable disease per RECIST Version 1.1
- Must have at least 1 tumor lesion with a longest dimension of ≥ 10 mm (≥ 15 mm for the short axis for malignant lymph node lesions) accessible for intratumoral injection of T3011
- Adequate bone marrow, hepatic and renal function

Definition of Dose-Limiting Toxicity (DLT)

DLTs will be evaluated during dose escalation. The DLT evaluation period will include the first 2 doses of T3011, approximately 4 weeks.

AEs are assessed by CTCAE Version 5.0. Main DLTs criteria include:

- T3011 related Grade 3 or greater non-hematologic toxicity
- Grade 4 neutropenia (ANC < 0.5 × 10^9/L) persisting for ≥ 7 days and/or complicated by infection; ANC < 1.0 × 10^9/L with a temperature of ≥ 38.3ºC for greater than 1 hour; Grade 4 thrombocytopenia (platelets < 25 × 10^9/L); and Grade 3 thrombocytopenia with clinically significant bleeding

RESULTS (AS OF 13 APRIL 2021)

Demographic and Baseline Characteristics

	1x10⁶ PFU/mL (N=3) n (%)	1x10⁷ PFU/mL (N=3) n (%)	5x10⁷ PFU/mL (N=5) n (%)	Total (N=11) n (%)
Median age, years (range)	72 (52, 85)	58 (36, 74)	51 (50, 74)	58 (36, 85)
Male/Female	0/3	2/1	2/3	4/7
Diagnosis - n(%)				
Melanoma	3 (100.0)	1 (33.3)	3 (60.0)	7 (63.6)
Lung Cancer	0	2 (66.7)	0	2 (18.2)
Squamous Cell Carcinoma	0	0	1 (20.0)	1 (9.1)
Sarcoma	0	0	1 (20.0)	1 (9.1)
Disease stage at Screening - n (%)				
IIIB	0	0	1 (20.0)	1 (9.1)
IIIC	1 (33.3)	0	2 (40.0)	3 (27.3)
IV	2 (66.7)	3 (100.0)	1 (20.0)	6 (54.5)
Missing	0	0	1 (20.0)	1 (9.1)
Time from Initial Diagnosis to First T3011 Dose (Years)				
n	3	3	4	10
Mean	5.11	2.13	5.07	4.20
SD	4.921	0.521	4.978	3.967
Median	3.16	1.84	5.05	2.29
Min, Max	1.5, 10.7	1.8, 2.7	0.6, 9.5	0.6, 10.7

Subject Disposition

	1x10⁶ PFU/mL (N=3) n (%)	1x10⁷ PFU/mL (N=3) n (%)	5x10⁷ PFU/mL (N=5) n (%)	Total (N=11) n (%)
All-Treated Analysis Set	3	3	5	11
Dose Limiting Toxicity (DLT) Evaluable Analysis Set	3	3	4*	10 (90.9)
Participants who are ongoing in the study	3 (100.0)	1 (33.3)	5 (100.0)	9 (81.8)
Total subjects who discontinued study	0	2 (66.6)	0	2 (18.2)
Withdrawal by subject	0	1 (33.3)	0	1 (9.1)
Progressive Disease	0	1 (33.3)	0	1 (9.1)

*Study is ongoing and 4/5 subjects in Cohort 3 completed the DLT period. The 5th subject is under DLT observation

T3011 Dosing Summary

	1x10⁶ PFU/mL (N=3) n (%)	1x10⁷ PFU/mL (N=3) n (%)	5x10⁷ PFU/mL (N=5) n (%)	Total (N=11) n (%)
No. of T3011 Doses Received, Median (Min-Max)	12 (10 – 13)	6 (4 – 9)	2 (1 – 5)	5 (1 – 13)
Treatment Duration (months), Median (Min – Max)	5.62 (5.1 - 5.6)	2.33 (1.4 - 4.2)	0.53 (0.0 - 1.9)	1.91 (0.0 - 5.6)

SAFETY SUMMARY

T3011 Treatment-Related TEAEs >15% of Subjects

Treatment Related AEs	1x10⁶ PFU/mL (N=3) n (%)		1x10⁷ PFU/mL (N=3) n (%)		5x10⁷ PFU/mL (N=5) n (%)		Total (N=11) n (%)	
Preferred Term	**Grade 1, 2**	**Grade ≥3**	**Grade 1, 2**	**Grade ≥3**	**Grade 1, 2**	**Grade ≥3**	**Grade 1, 2**	**Grade ≥3**
Subjects with at least one TEAE	3 (100.0)	0	1 (33.3)	1 (33.3)	1 (20.0)	0	5 (45.5)	1 (9.1)*
Fatigue	1 (33.3)	0	1 (33.3)	0	1 (20.0)	0	3 (27.3)	0
Headache	1 (33.3)	0	1 (33.3)	0	0	0	2 (18.2)	0
Injection site pain	0	0	2 (66.7)	0	0	0	2 (18.2)	0
Nausea	0	0	1 (33.3)	0	1 (20.0)	0	2 (18.2)	0

*One subject experienced a Grade 3 Pneumonitis

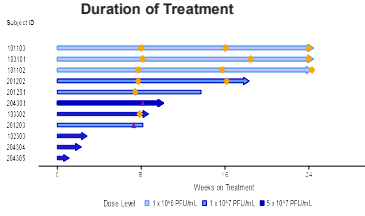
T3011 was well tolerated with repeat dosing

- Injection site pain, headache, fatigue and nausea were the most common treatment-related AEs and all were Grade 1 and 2 in severity
- One subject experienced Grade 3 Pneumonitis possibly related to T3011 and withdrew consent at Week 13

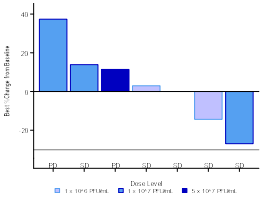
EFFICACY ASSESSMENT

- Response was assessed using RECIST Version 1.1 criteria
- Baseline and Week 9 core biopsy were required when possible and were analyzed using immunonohistochemistry and specific fluorescence staining for T-cell identification

Duration of Treatment



% Change by RECIST v1.1 in Evaluable Subjects



- Tumor assessment was conducted at baseline and every 8 weeks. At the first disease assessment, of the 8 evaluable subjects, 6 showed stable disease by RECIST Version 1.1. 1 subject discontinued due to progressive disease and 1 subject continued on study after progressive disease at Week 9
- All subjects in the first Cohort have had stable disease for over 6 months and all are continuing on study as of 13 Apr 2021.

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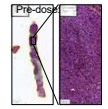
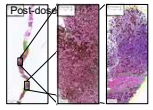
Case Report 1: Subject 101103

A 52-year-old Female with Metastatic Melanoma (Post PD-1/CTLA-4 Antibody)

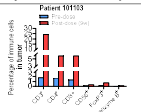
- First T3011 dose ($1x10^9$ PFU/mL): 30 Sep 2020
- Biopsy samples were taken at baseline and prior to Week 9 dosing
- Post treatment biopsies of injected lesion showed:
  - Significant reduction of tumor cells
  - Large area of necrosis
  - Significant increase of CD4+, CD8+ and NKT cells
- On-target effect demonstrated T3011 mechanism of action
- Subject remains on study

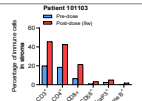


75-80% Tumor cells



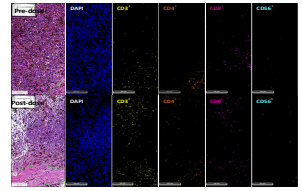
3-5% Tumor Cells, large necrosis





101103 - Tumor	Percentage %	
Targets	Pre-dose	Post-dose (9w)
CD3(+)	1.78%	24.19%
CD4(+)	1.67%	5.77%
CD8(+)	1.33%	5.72%
CD56(+)	0.12%	0.33%
FoxP3(+)	0.20%	0.72%
Granzyme B(+)	0.05%	0.15%

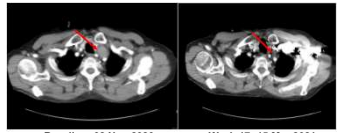
101103 - Stroma	Percentage %	
Targets	Pre-dose	Post-dose (9w)
CD3(+)	19.84%	45.54%
CD4(+)	18.42%	42.46%
CD8(+)	6.45%	21.44%
CD56(+)	0.87%	3.23%
FoxP3(+)	2.39%	4.94%
Granzyme B(+)	0.28%	1.78%



Case Report 2: Subject 201202 Achieved 27% Tumor Reduction by RECIST Version 1.1

A 74-year-old Male subject diagnosed with NSCLC Mar 2018

- Prior treatments included pemetrexed, carboplatin, and pembrolizumab with maintenance pembrolizumab
- Received the first T3011 dose ($1x10^7$ PFU/mL) on 23 Nov 2020
- Week 9 scans showed SD and further lesion reduction (-27%) at Week 17 of injected lesion
- Subject remains on study

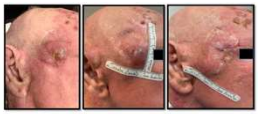


Baseline: 02 Nov 2020 Week 17: 15 Mar 2021

Case Report 3: Subject 102303

A 74-year-old Male with nodal infratemporal fossa squamous cell carcinoma (SCC)

- Prior treatments include radiotherapy; Clinical Trial MGA271/MGA012 (immunotherapy)
- Received the first T3011 dose ($5x10^7$ PFU/mL) on 24 Mar 2021
- Evidence of changes in the injected target lesion include inflammatory reaction on Week 2 and significant lesion shrinkage on Week 5
- Subject remains on study

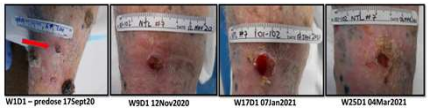


W1D1: predose 24Mar2021 W2D1: 01Apr2021 W5D1: 22Apr2021

Case Report 4: Subject 101102

A 85-year-old Female with Metastatic Melanoma

- Multiple cutaneous lesions, N-ras Gene mutation
- Prior treatment included anti-PD-1 Antibody
- Received the first T3011 dose ($1x10^6$ PFU/mL) on 17 Sep 2020
- Changes in the injected non-target lesion include inflammatory reaction on Week 9 and lesion changes/necrosis from Week 9 to Week 25
- Subject remains on study



W1D1 – predose 17Sept20 W9D1 12Nov2020 W17D1 07Jan2021 W25D1 04Mar2021

SUMMARY & CONCLUSION

- Repeat T3011 IT injections were well tolerated in subjects with advanced solid tumors and accessible injectable lesions
- Injection site pain, headache, fatigue and nausea were the most common treatment-related AEs and all were Grade 1 and 2 in severity
- 11 subjects have been enrolled and received between 1 to 13 doses of T3011
- Preliminary efficacy is encouraging. Stable disease was achieved in 75% of evaluable subjects and tumor shrinkage was observed in some subjects who had at least one efficacy assessment in the first 2 Cohorts
- Tumor biopsy results following treatment showed tumor necrosis, significant decrease of tumor cells, and significant increase of infiltrating lymphocytes indicating on-target activity further demonstrating T3011's mechanism of action
- IL-12 and anti-PD-1 antibody were not detected in the blood at any time point following injection
- Measurement of viral shedding by blood, urine, saliva and injection site swab showed very limited evidence of viral shedding with one occurrence of viral DNA presence at injection site 1 hour following injection
- T3011 as a next generation oHSV therapy has an acceptable safety profile and can stimulate innate immune response resulting in tumor necrosis, tumor cell reduction and lymphocyte infiltration
- This Phase 1 study of T3011 is ongoing (ClinicalTrials.gov identifier: NCT04370587)