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GARNET: Preliminary Safety, Efficacy, Pharmacokinetic, and Biomarker Characterization from a Phase 1 Clinical Trial of TSR-042 (Anti-PD-1 Monoclonal Antibody) in Patients with Recurrent/Advanced NSCLC

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GARNET TSR-042 CLINICAL TRIAL

BACKGROUND

- TSR-042 is an investigational humanized anti-programmed death 1 (PD-1) monoclonal antibody that binds with high affinity to the PD-1 receptor and effectively blocks its interaction with the PD-1 ligands PD-L1 and PD-L2.
- TSR-042 is the only anti-PD-1 therapy administered as a monotherapy every 3 weeks (Q3W) for 4 doses then every 6 weeks (Q6W) until disease progression.[1,2]
- In clinical trials, preliminary data show that TSR-042 has activity and safety profiles that are similar to approved anti-PD-1 therapies.[3]
- The ongoing GARNET trial (NCT02715284) is evaluating TSR-042 as monotherapy in patients with advanced solid tumors.
- GARNET included a weight-based dose escalation study (part 1) and a fixed-dose safety study (part 2A), both completed[3]; the results of these studies were used to determine the recommended phase 2 dose (RP2D; 500 mg Q3W for the first 4 cycles then 1000 mg Q6W).
- The study is now enrolling patients with specific tumor types into 4 expansion cohorts (part 2B; ongoing), including endometrial cancer and non-small cell lung cancer (NSCLC).
- Here, we present safety, efficacy, and biomarker data from the previously treated recurrent or advanced NSCLC cohort.

OBJECTIVES

Primary

- To evaluate the clinical activity of TSR-042 at the RP2D in patients with previously treated recurrent or advanced NSCLC.
- To evaluate the safety and tolerability of TSR-042 at the RP2D.

Secondary

- To further characterize the pharmacokinetic (PK) profile of TSR-042.

METHODS

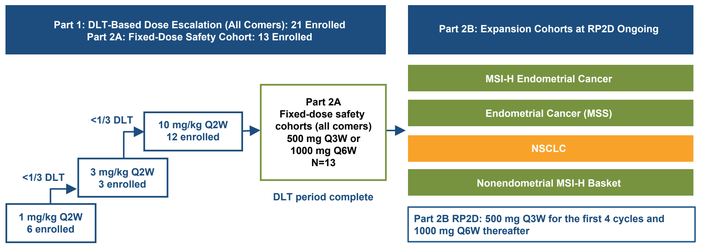
Patients

- Subjects with previously treated recurrent or advanced NSCLC.
- Key exclusion criteria included:
  - Prior therapy with agents targeting PD-1, PD-L1, or PD-L2.
  - Uncontrolled central nervous system metastases and/or carcinomatous meningitis, or additional malignancy that progressed or required active treatment within the last 2 years.
  - Active autoimmune disease that required systemic treatment in the last 2 years.

Study Design

- GARNET is a multicenter, open-label, first-in-human phase 1 dose escalation study with expansion cohorts designed to assess the safety, PK, pharmacodynamics, and clinical activity of the PD-1 inhibitor TSR-042 in patients with advanced solid tumors (**Figure 1**).

Figure 1. GARNET Phase 1 Study



DLT=dose-limiting toxicity; MSI-H=microsatellite instability-high; MSS=microsatellite stable; NSCLC=non-small cell lung cancer; Q2W=every 2 weeks; Q3W=every 3 weeks; Q6W=every 6 weeks.
For more information on this trial: https://clinicaltrials.gov/ct2/show/NCT02715284.

- The part 2B expansion cohort portion of GARNET is evaluating clinical activity, safety, and PK/pharmacodynamics of TSR-042 at the RP2D.
- The primary efficacy endpoints include objective response rate (ORR) and duration of response (DOR) per immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) assessed by investigators.
- Safety parameters include treatment-emergent adverse events (TEAEs), immune-related AEs (irAEs) of interest, and clinical laboratory values.

Assessments

- Antitumor activity was assessed by investigators using irRECIST.
  - Radiographic evaluations and serum-based tumor marker testing were conducted 12 weeks after the first dose and every 6 weeks thereafter.
- Serum and peripheral blood mononuclear cells were collected for PK and receptor occupancy (RO) analyses, respectively.
- Tumor PD-L1 expression was measured and PD-L1 tumor proportion scores (TPS) were categorized as <1%, 1-49%, and ≥50% (centrally assessed).
- Safety was evaluated by TEAEs, irAEs of interest, and clinical laboratory measures.

RESULTS

Patients

- At present, 67 patients in the NSCLC cohort were treated with TSR-042 at the RP2D.
- Patient demographics and prior lines of therapy are presented in **Table 1**. Patients in this cohort received a median of 1 prior line of therapy for advanced or metastatic disease.

Table 1. Demographic and Baseline Characteristics

Characteristics	NSCLC (n=67)
Age, mean (SD), yrs	64.8 (9.55)
Median	66.0
Q1, Q3	58.0, 71.0
Min, Max	40, 83
Age group n (%), yrs	
<65	30 (44.8)
≥65 to <75	25 (37.3)
≥75	12 (17.9)
Sex n (%)	
Male	40 (59.7)
Female	27 (40.3)
Median number of prior regimens	1.0
Median number of prior regimens for metastatic disease (range)[a]	1.0 (0-4)

[a]Hormonal therapy was excluded. NSCLC=non-small cell lung cancer; SD=standard deviation.

PK AND PHARMACODYNAMIC SUMMARY

- The C_{last} for the 500 mg Q3W and 1000 mg Q6W dosing were shown to be equivalent (**Table 2**).

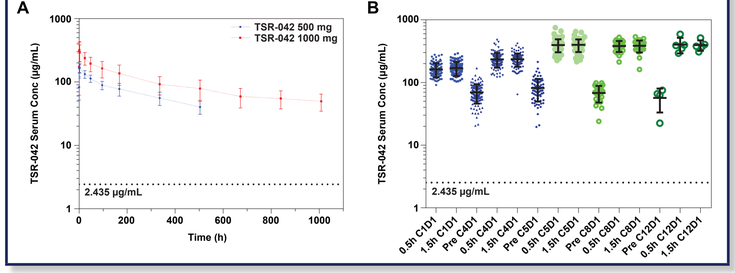
Table 2. PK Summary: 500 mg (Q3W) vs. 1000 mg (Q6W)

Dose Regimen (mg)	C_{max} (µg/mL)	C_{last}[a] (µg/mL)	T_{max} (h)	$AUC_{0\text{-}last}$[b] (h*µg/mL)
500 Q3W (N=6)	174 ± 35.2	40.2 ± 9.31	1.0 (0.5 - 3.0)	36424 ± 6674
1000 Q6W (N=7)	322 ± 101	43.7 ± 18.2[c]	1.5 (0.5 - 3.0)	91376 ± 26808

Mean ± SD for all but T_{max} (median [range]).
[a]C_{last} for 500 mg Q3W was at 504 h while for 1000 mg, it was at 1008 h. [b]$AUC_{0\text{-}last}$ for 500 mg Q3W was from 0 to 504 h and for 1000 mg Q6W from 0 to 1008 h. [c]n=5.

- Serum concentrations required for full RO were achieved at doses of 500 mg and 1000 mg after single and multiple dosing for all patients tested. The lowest TSR-042 concentration observed for a full RO (2.435 ug/mL) is shown as a dotted line (**Figure 2**).

Figure 2. (**A**) Concentration Versus Time Profile Following Single-Dose Administration of TSR-042 (GARNET Part 2A). (**B**) Sparse PK for GARNET Part 2B (4 x 500 mg Q3W followed by 1000 mg Q6W) Maintain at Least an 8-Fold Margin for Full RO Through the Course of Treatment



SAFETY

- TEAEs were reported in 62 patients with previously treated recurrent or advanced NSCLC (92.5%; **Table 3**).

Table 3. Treatment-Emergent Adverse Event (TEAEs) in ≥10% of Patients, Safety Population

AE Preferred Term	Cohort E: NSCLC (N=67) n (%)
Subjects with at least one TEAE	62 (92.5)
Fatigue	23 (34.3)
Nausea	11 (16.4)
Decreased appetite	10 (14.9)
Diarrhea	10 (14.9)
Constipation	9 (13.4)
Cough	9 (13.4)
Arthralgia	9 (13.4)
Dyspnea	8 (11.9)
Anemia	7 (10.4)
Pruritus	7 (10.4)
Back pain	7 (10.4)

NSCLC=non-small lung cancer.

- Treatment-related TEAEs were reported in 42 patients (62.7%) (**Table 4**).

Table 4. Treatment-Related Treatment-Emergent Adverse Event (TEAEs) in ≥10% of Patients, Safety Population

AE Preferred Term	Cohort E: NSCLC (N=67) n (%)
Subjects with at least one treatment-related TEAE[a]	42 (62.7)
Fatigue	16 (23.9)
Nausea	7 (10.4)
Pruritus	7 (10.4)

[a]Related, possibly related, and missing relationship adverse events are considered as related adverse events.

- Grade ≥3 treatment-related TEAEs were reported in 4 patients (6.0%), including rash (n=1), fatigue (n=1), lipase increased (n=1), and transaminases increased (n=1).
- Two patients had related serious AEs, including pancreatitis (n=1) and transaminases increased (n=1).
- Three patients had treatment-related TEAEs leading to treatment discontinuation, including lipase increased (n=1), pleural effusion (n=1), and transaminases increased (n=1).
- No death related to study drug was reported.

CLINICAL ACTIVITY

- At the October 25, 2018 cutoff date, 47 patients with previously treated recurrent or advanced NSCLC had at least 1 tumor assessment or discontinued treatment prior to first postbaseline tumor assessment due to AEs or withdrawal of consent. The best overall tumor response by irRECIST is shown in **Table 5**.
  - ORR was 31.9% (95% CI 19.1, 47.1). There were 15 patients who achieved partial responses (13 confirmed, 2 unconfirmed; patients with unconfirmed responses have not progressed).
  - Nine of 15 responses (60.0%) are ongoing (**Figure 3**).

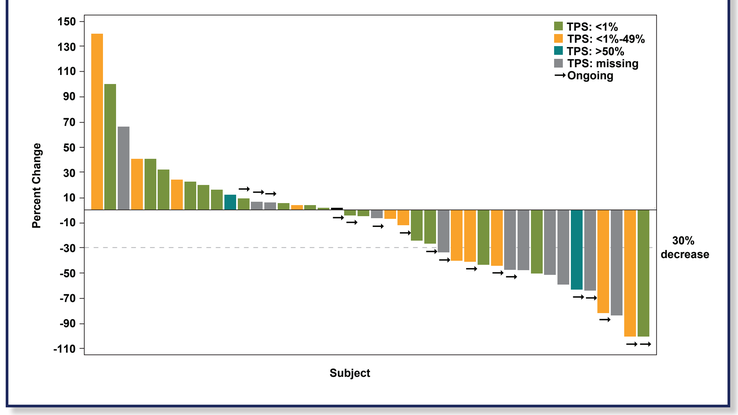
Table 5. Tumor Response Summary Based on irRECIST

Characteristics	Cohort E: NSCLC (N=47) n (%)
Best overall response by irRECIST, n (%)	
irCR	0
irPR[a]	15 (31.9)
irSD	14 (29.8)
irPD	12 (25.5)
Not done	6 (12.8)
Overall response rate[a]	**15 (31.9)**
Overall response rate 95% CI	19.1, 47.1
Response ongoing	9/15 (60.0)
Disease control rate[b]	29 (61.7)
Disease control rate 95% CI	46.4, 75.5

irCR=complete response, irPR=partial response, irSD=stable disease, irPD=progressive disease.
[a]Included 2 unconfirmed irPR: one patient still receiving treatment and the other patient discontinued due to AE and has not progressed.
[b]Disease control rate: (irCR+irPR+irSD).
Median duration of response was not reached.

- Best percentage change in the sum of target lesions by PD-L1 TPS status is presented in **Figure 3**.

Figure 3. Change in Total Tumor Burden from Baseline by PD-L1 TPS Status



- Treatment with TSR-042 resulted in durable tumor responses regardless of PD-L1 TPS score (**Table 6**).

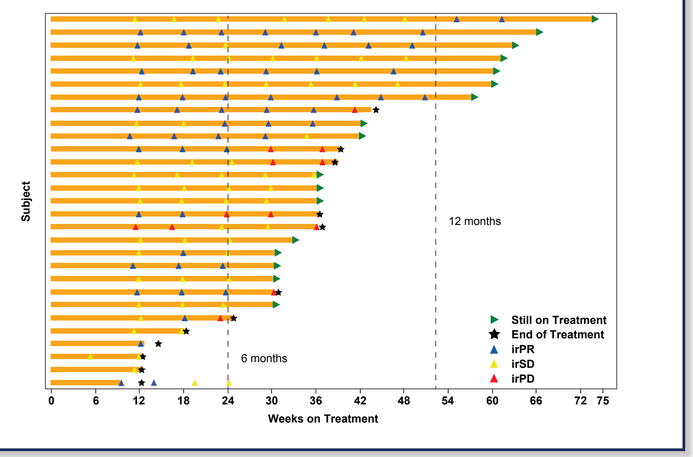
Table 6. Tumor Responses by PD-L1 TPS Score by irRECIST

Characteristics	TPS: <1% (N=19) n (%)	TPS: 1-49% (N=13) n (%)	TPS: >50% (N=2) n (%)	TPS: missing (N=13) n (%)	All (N=47) n (%)
Best overall response by irRECIST, n (%)					
irCR	0	0	0	0	0
irPR[a]	3 (15.8)	5 (38.5)	1 (50.0)	6 (46.1)	15 (31.9)
irSD	8 (42.1)	2 (15.4)	0	4 (30.8)	14 (29.8)
irPD	7 (36.8)	3 (23.1)	1 (50.0)	1 (7.7)	12 (25.5)
Not done	1 (5.3)	3 (23.1)	0	2 (15.4)	6 (12.8)
Overall response rate[a]	**3 (15.8)**	**5 (38.5)**	**1 (50)**	**6 (46.1)**	**15 (31.9)**
Overall response rate 95% CI	3.4, 39.6	13.9, 68.4	1.3, 98.7	19.2, 74.9	19.1, 47.1
Response ongoing	1/3 (33.3)	4/5 (80)	1/1 (100)	3/6 (50)	9/15 (60)
Disease control rate[b]	11 (57.9)	7 (53.8)	1 (50)	10 (76.9)	29 (61.7)
Disease control rate 95% CI	33.5, 79.7	25.1, 80.8	1.3, 98.7	46.2, 95.0	46.4, 75.5

TPS=tumor proportion score, irCR=complete response, irPR=partial response, irSD=stable disease, irPD=progressive disease.
[a]Included 2 unconfirmed irPR: one patient (TPS: 1-49%) still receiving treatment and the other patient (TPS missing) discontinued due to AE and has not progressed.
[b]Disease control rate: (irCR+irPR+irSD).
Median duration of response was not reached.

- Duration of exposure in patients with disease control is presented in **Figure 4**.

Figure 4. Duration of Exposure in Patients with DCR (irCR+irPR+irSD) Based on irRECIST



CONCLUSIONS

- TSR-042 is an anti-PD-1 monoclonal antibody that binds with high affinity to the PD-1 receptor.
- TSR-042 is administered at 500 mg Q3W for the first 4 cycles and 1000 mg Q6W thereafter, which is less frequent than approved PD-1 inhibitors.
- At this unique dosing schedule, TSR-042 achieved serum concentrations sufficient for full RO throughout the dosing cycle.
- TSR-042 was well tolerated; the safety profile was characteristic of approved PD-1 inhibitors.[4]
- TSR-042 produced a robust response rate (ORR 31.9%). Responses were durable in this population with previously treated recurrent or advanced NSCLC.
- Activity was observed across all PD-L1 TPS categories. Encouraging activity was observed despite the fact that the vast majority (94%) of patients with available PD-L1 status had a TPS <50%.

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