A Phase 1 Study of TSR-022 (Anti-TIM-3) in Combination with TSR-042 (Anti-PD-1)

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Presenter Disclosure Information

Diwakar Davar, MD

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All authors participated in poster design.
TIM-3 Is a Key Immune Checkpoint and a Next-Generation Cancer Immunotherapy Target

TIM-3 Biology Has Been Implicated in T-Cell Exhaustion and Immune Suppression Mediated by Myeloid Cells

- TIM-3 is a marker of progressively exhausted CD8+ T cells and negatively regulates their activation
- Blocking TIM-3 results in increased proliferation and cytokine production by these cells
- TIM-3 is highly expressed on CD8+ T cells from freshly isolated NSCLC tumors
- High levels of expression correlated with increased levels of PD-1 expression
- TIM-3 is expressed on tumor-associated DCs and may negatively regulate DC/T-cell activation
- Expression on macrophages can influence MDSC activity in TME

CD4/8+ T-Cell Exhaustion

Diversity of Immune Profiles in NSCLC

Dendritic Cells

- APC=antigen-presenting cell; CD=cluster of differentiation; DC=dendritic cell; HMGB1=high mobility group protein 1; MDSC=myeloid-derived suppressor cells; PD-1=programmed cell death receptor 1; RAGE=receptor for advanced glycation end products; TADC=tumor-associated dendritic cells; TIM-3=T-cell immunoglobulin and mucin-domain containing-3; TLR=toll-like receptor; TME=tumor microenvironment; Treg=regulatory T cell. Adapted from Anderson AC. Cancer Immunol Res. 2014;2:393-398. Travers et al. AACR 2017
TSR-022: A Potent and Selective Anti-TIM-3 Monoclonal Antibody

1. In preclinical models, combination treatment with anti-PD-1 and anti-TIM-3 antibodies produces anti-tumor activity that surpasses that of monotherapy approaches.

2. TSR-022 is a humanized anti-TIM-3 IgG4 monoclonal antibody that binds to TIM-3 with high affinity and has potent in vitro and in vivo activity.

3. TSR-022 in combination with TSR-042 enhances the anti-tumor immune response in comparison to monotherapy.
   - Increases melanoma specific CD8+ human T-cell proliferation.
   - Increases IL-2 production by antigen specific CD8+ human T cells.

TSR-022, when combined with PD-1 blockade, increases the proliferation and production of IL-2 by human tumor specific T cells.

IgG4=immunoglobulin G4.
**AMBER STUDY Combination Dose Escalation**

**Part 1a All Comers Monotherapy**

**Dose escalation (SITC 2017)**

- Escalated to 10 mg/kg without DLT
- Several patients with stable disease
- One PR in patient with leiomyosarcoma at high dose (10 mg/kg)

**Part 1c All Comers Combination**

**Dose escalation N=54**

- TSR-022 900 mg
- TSR-022 300 mg
- TSR-022 100 mg

**Part 2 Patients with NSCLC**

**Expansion cohorts N=39 (ongoing)**

- TSR-022 900 mg
- TSR-022 300 mg
- TSR-022 100 mg

**Biomarker Analyses**

- PD-L1
- TIM-3
- NS IO360
- TMB

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*The TSR-042 dose was 500 mg every three weeks. DLT=dose-limiting toxicity; NS IO360=nanostring IO360 panel; NSCLC=non-small cell lung cancer; TMB=tumor mutation burden.
Combination Dose Escalation: Safety

Includes Treatment-related TEAEs Observed in ≥5% of Patients

<table>
<thead>
<tr>
<th>AE Preferred Term, N (%)</th>
<th>TSR-022 100 mg + TSR-042* (N=13)</th>
<th>TSR-022 300 mg + TSR-042* (N=19)</th>
<th>TSR-022 900 mg + TSR-042* (N=22)</th>
<th>Total (N=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grade</td>
<td>Grade 3-4</td>
<td>All grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (15.4)</td>
<td>0</td>
<td>2 (10.5)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (7.7)</td>
<td>1 (7.7)**</td>
<td>3 (15.8)</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1 (7.7)</td>
<td>0</td>
<td>1 (5.3)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>1 (7.7)</td>
<td>0</td>
<td>1 (5.3)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (7.7)</td>
<td>0</td>
<td>1 (5.3)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>0</td>
<td>2 (10.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

• No DLTs were observed

*The TSR-042 dose was 500 mg.
**Grade 3 rash seen in 1 patient.
***Grade 4 hypothyroidism seen in 1 patient.
Combination Dose Escalation: Clinical Activity

![Graph showing tumor size relative to baseline over time from baseline scan (weeks). The graph compares two dose levels: 100 mg and 300 mg.]

- **Dose Level**
  - 100 mg (red)
  - 300 mg (blue)

**Axes:**
- X-axis: Time from Baseline Scan (Weeks)
- Y-axis: Tumor Size Relative to Baseline

**Legend:**
- Red line: 100 mg dose
- Blue line: 300 mg dose
Confirmed Response in NSCLC Patient Progressing on Nivolumab

Well tolerated with early signs of clinical activity

- All comers patient population
  - Metastatic, late stage patients with extensive prior therapy
- No dose-limiting toxicities observed with the combination
  - AE profile consistent with IO drug class
- Confirmed PR observed at first TSR-022 dose level in NSCLC patient progressing on nivolumab

- 63 year-old female diagnosed with Stage IV NSCLC
- Prior treatment included 1L chemotherapy, 2L anti-PD-1, 3L Tarceva
- Progression noted on all previous therapies
- 72% shrinkage

PR=partial response; RO=receptor occupancy.
Combination Dose Escalation

900 mg dose required for effective exposure throughout dose interval

**TSR-022 PK is dose proportional**

- 100 mg TSR-022 + 500 mg TSR-042 (N=12-14)
- 300 mg TSR-022 + 500 mg TSR-042 (N=9-11)
- 900 mg TSR-022 + 500 mg TSR-042 (N=5-9)

**TSR-022 RO is maximal at 900 mg**

- Occupancy at C_{trough}

**MLR EC_{90} is maintained at 900 mg**

PK=pharmacokinetics; Q3W=every 3 weeks.
AMBER: Part 2 Expansion Cohorts

**All Comers Combination Dose Escalation**  
N=54

<table>
<thead>
<tr>
<th>Dose</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>TSR-022 100 mg</td>
<td>Complete</td>
</tr>
<tr>
<td>TSR-022 300 mg</td>
<td>Complete</td>
</tr>
<tr>
<td>TSR-022 900 mg</td>
<td>Complete</td>
</tr>
<tr>
<td>+ TSR-042*</td>
<td></td>
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</tbody>
</table>

**Patients with NSCLC Expansion Cohorts**  
N=39 (ongoing)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSR-022 100 mg</td>
<td>Complete</td>
</tr>
<tr>
<td>TSR-022 300 mg</td>
<td>Complete</td>
</tr>
<tr>
<td>TSR-022 900 mg</td>
<td>Enrolling</td>
</tr>
<tr>
<td>+ TSR-042*</td>
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</table>

**Biomarker Analyses**
- PD-L1
- TIM-3
- NS IO360
- TMB

**Additional Key Inclusion Criteria (Part 2):**
- Measurable disease by RECIST
- Tumor biopsy available
- Prior anti-PD-1 or anti-PD-L1 treatment

*The TSR-042 dose was 500 mg every 3 weeks.

NSCLC=non-small cell lung cancer; NS IO360=Nanostring IO360 panel; TMB=tumor mutation burden; RECIST=Response Evaluation Criteria in Solid Tumors
Part 2: Post-Anti-PD-(L)1 NSCLC Cohort

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TSR-022 + TSR-042 N=39</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>66 (35 - 86)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
</tr>
<tr>
<td>ECOG performance status score</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>PD-L1 status</td>
<td></td>
</tr>
<tr>
<td>TPS ≥1%</td>
<td>16</td>
</tr>
<tr>
<td>TPS &lt;1%</td>
<td>8</td>
</tr>
<tr>
<td>Unknown</td>
<td>15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior Therapy</th>
<th>TSR-022 + TSR-042 N=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lines of prior therapy</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>≥4</td>
<td>18</td>
</tr>
<tr>
<td>Prior anti-PD-(L)1 antibody*</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>14</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>23</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>5</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
</tr>
</tbody>
</table>

ECOG PS=Eastern Cooperative Oncology Group; PD-L1=programmed cell death ligand 1; TPS=tumor proportion score.
*None of the patients had maximal treatment on prior PD-1 (e.g. 2 years)
Treatment-Related Adverse Events: Post-Anti-PD-(L)1 NSCLC Expansion Cohort

Includes Treatment-Related AEs Observed in ≥5% of Patients

<table>
<thead>
<tr>
<th>AE Preferred Term, n (%)</th>
<th>100 mg (N=14)</th>
<th>300 mg (N=25)</th>
<th>Total (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grade</td>
<td>Grade 3</td>
<td>All Grade</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (35.7)</td>
<td>1 (7.1)</td>
<td>5 (20.0)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>1 (7.1)</td>
<td>1 (7.1)*</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>0</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (7.1)</td>
<td>0</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0</td>
<td>0</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (7.1)</td>
<td>0</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (7.1)</td>
<td>0</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Rash maculopapular</td>
<td>0</td>
<td>0</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>0</td>
<td>0</td>
<td>2 (8.0)</td>
</tr>
</tbody>
</table>

*Grade 4 lipase increased seen in 1 patient.
There were 2 (5.1%) patients with related irAEs: hypothyroidism and pancreatitis.
AE=adverse event; irAE=immune-related adverse event.
Part 2: TSR-022 in Combination with TSR-042 Demonstrated Clinical Activity

Emerging evidence for dose response in post-anti-PD-(L)1 NSCLC

Percentage Change in Sum of Target Lesion Dimensions

<table>
<thead>
<tr>
<th>TSR-022 100 mg + TSR-042</th>
<th>TSR-022 300 mg + TSR-042</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 confirmed PR; 3 SD</td>
<td>3 confirmed PR; 8 SD</td>
</tr>
</tbody>
</table>

*One patient with scan was not evaluable and hence not included in figure.
NL=new lesion; PD=progressive disease; PR=partial response; SD=stable disease.
Part 2: TSR-022 in Combination with TSR-042 Demonstrated Clinical Activity

Emerging evidence for dose response in post-anti-PD-(L)1 NSCLC

Percent change in sum of target lesion dimensions over time

TSR-022 100 mg + TSR-042

TSR-022 300 mg + TSR-042
Part 2: TSR-022 in Combination with TSR-042 Demonstrated Clinical Activity

Objective Responses in PD-L1 Positive (TPS ≥1%) Patients

Best Response in PD-L1 TPS ≥1%

- 4 confirmed PR (3 by RECIST and 1 by irRECIST; 3 ongoing)
  - 1 in the 100 mg cohort
  - 3 in the 300 mg cohort

*Response was confirmed.
Ongoing Durable PR in PD-1 Refractory Patient

Pretreatment

Hepatic dome tumor (22×21 mm)

Periportal LN tumor (32×20 mm)

R hepatic lobe tumor (36×23 mm)

After 6 cycles, ongoing PR by RECIST version 1.1

Hepatic dome tumor (11×7 mm)

Periportal LN tumor (resolved)

R hepatic lobe tumor (17×16 mm)

- 69-year-old patient with metastatic NSCLC
- Treated with nivolumab for 2.5 months
- Treated with TSR-022 300 mg + TSR-042 500 mg Q3W
Conclusions

• TSR-022 is a potent and selective anti-TIM-3 antibody that is being developed in combination with the anti-PD-1 antibody TSR-042.

• Treatment with TSR-022 in combination with TSR-042 was well tolerated.

• TSR-022 in combination with TSR-042 demonstrated clinical activity in patients who have progressed on anti-PD-1 treatment.

• Objective responses observed were in PD-L1 positive (TPS ≥1%) patients, indicating the potential for biomarker enrichment.

• A dose response trend was observed, with greater evidence of anti-tumor activity in the population receiving the 300 mg dose compared to the 100 mg dose.

• TSR-022 PK was dose proportional with the 900 mg dose required for effective exposure throughout dose interval in most patients.

• Enrollment at the TSR-022 900 mg dose level is ongoing in the NSCLC cohort.
Thank you