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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

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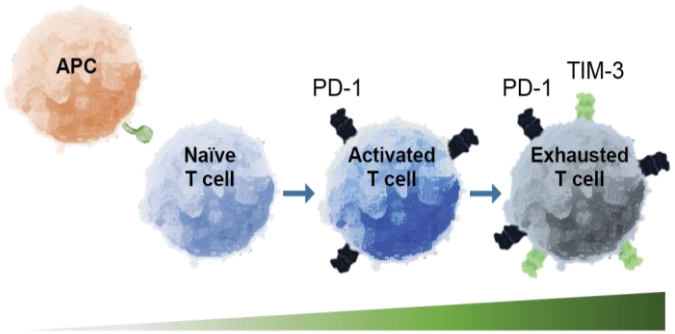
TIM-3 Is a Key Immune Checkpoint and a Next-Generation Cancer Immunotherapy Target

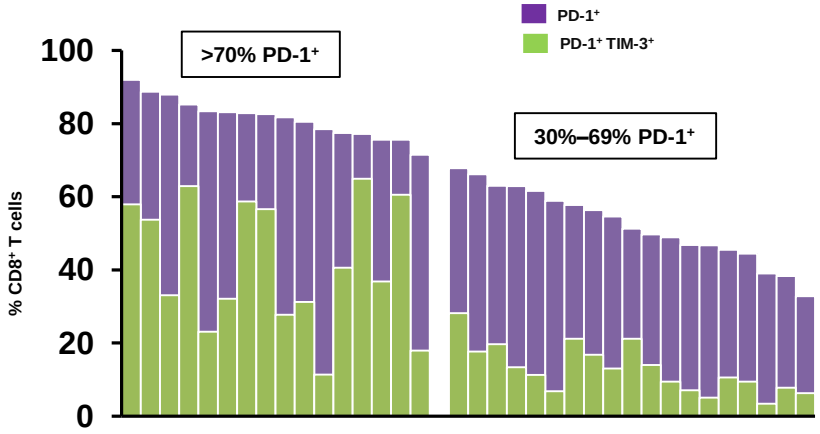
TIM-3 Biology Has Been Implicated in T-Cell Exhaustion and Immune Suppression Mediated by Myeloid Cells

CD4/8⁺ T-Cell Exhaustion



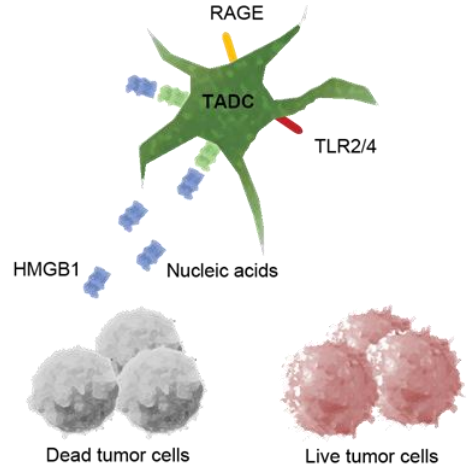
- TIM-3 is a marker of progressively exhausted CD8⁺ T cells and negatively regulates their activation
- Blocking TIM-3 results in increased proliferation and cytokine production by these cells

Diversity of Immune Profiles in NSCLC



- 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

Dendritic Cells



- 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

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-2/4=toll-like receptor-2/4; TME=tumor microenvironment; Treg=regulatory T cell. Adapted from Anderson AC. Cancer Immunol Res. 2014;2:393-398.

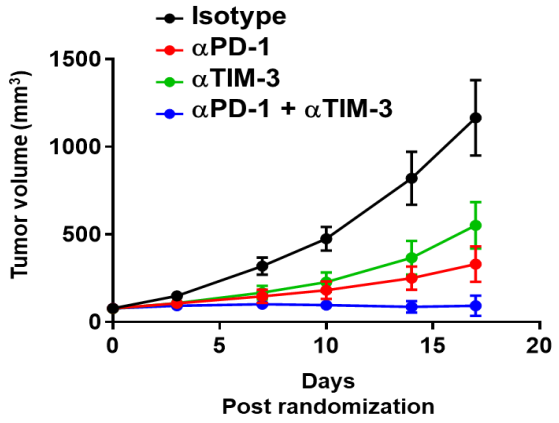
TSR-022: A Potent and Selective Anti-TIM-3 Monoclonal Antibody

- [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
  - [3A] Increases melanoma specific $CD8^+$ human T-cell proliferation
  - [3B] Increases IL-2 production by antigen specific $CD8^+$ human T cells

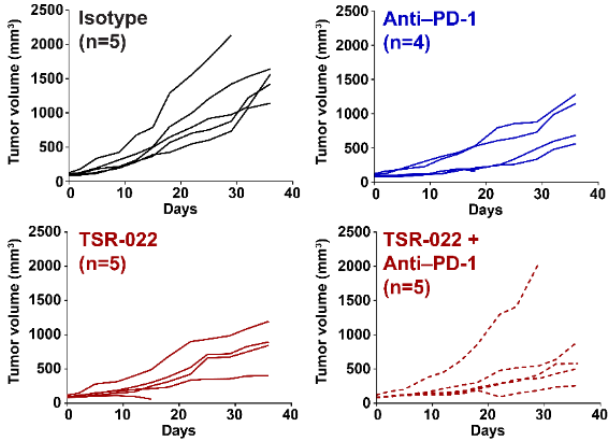
IgG4=immunoglobulin G4.

Sakuishi et al. *JEM.* 2010; Fourcade et al. *JEM* 2010.; Chiba et al. *Nat Immunol*. 2012; de Mingo Pulido et al. *Cancer Cell.* 2018.

[1] SaLN syngeneic model

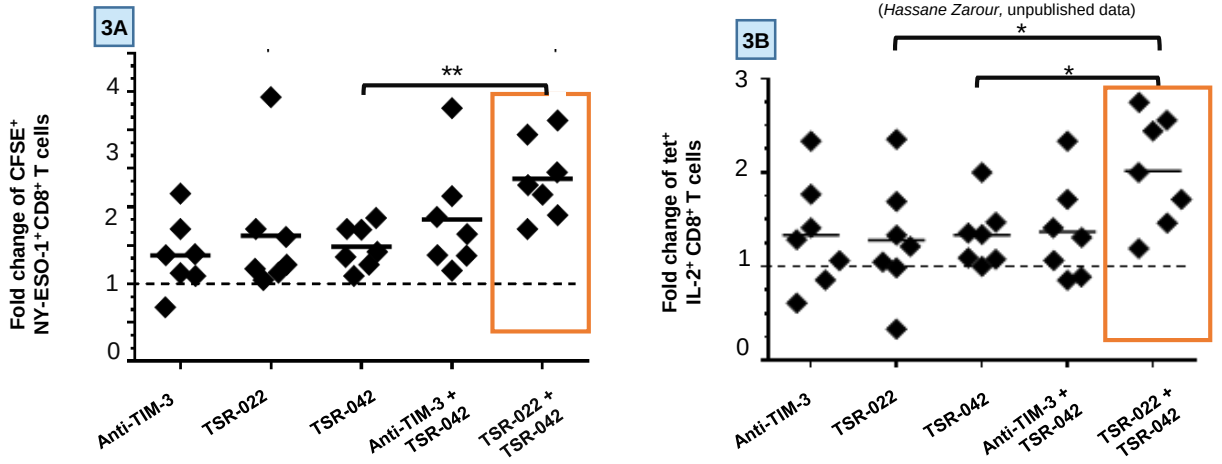


[2] HuNOG-EXL-A549 humanized mouse model



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

(*Hassane Zarour*, unpublished data)

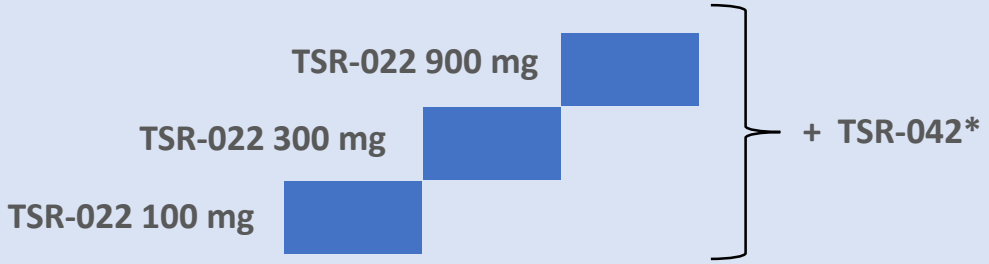


AMBER STUDY Combination Dose Escalation

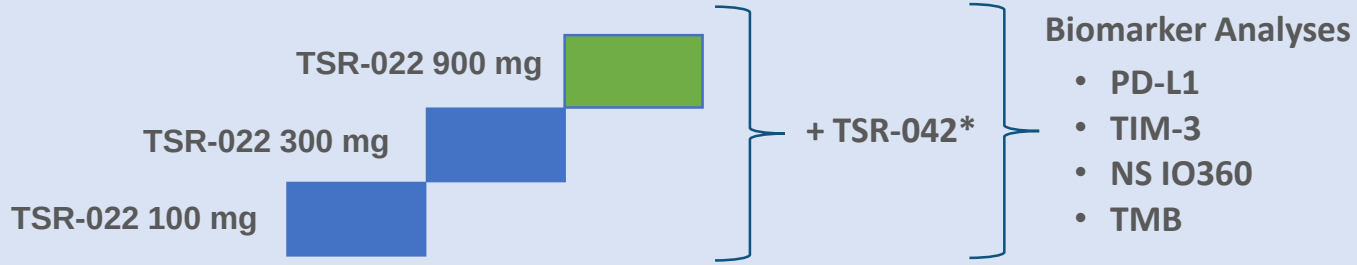
Part 1a All Comers Monotherapy Dose escalation (SITC 2017)

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



Part 2 Patients with NSCLC Expansion cohorts N=39 (ongoing)



= Complete
= Enrolling

*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

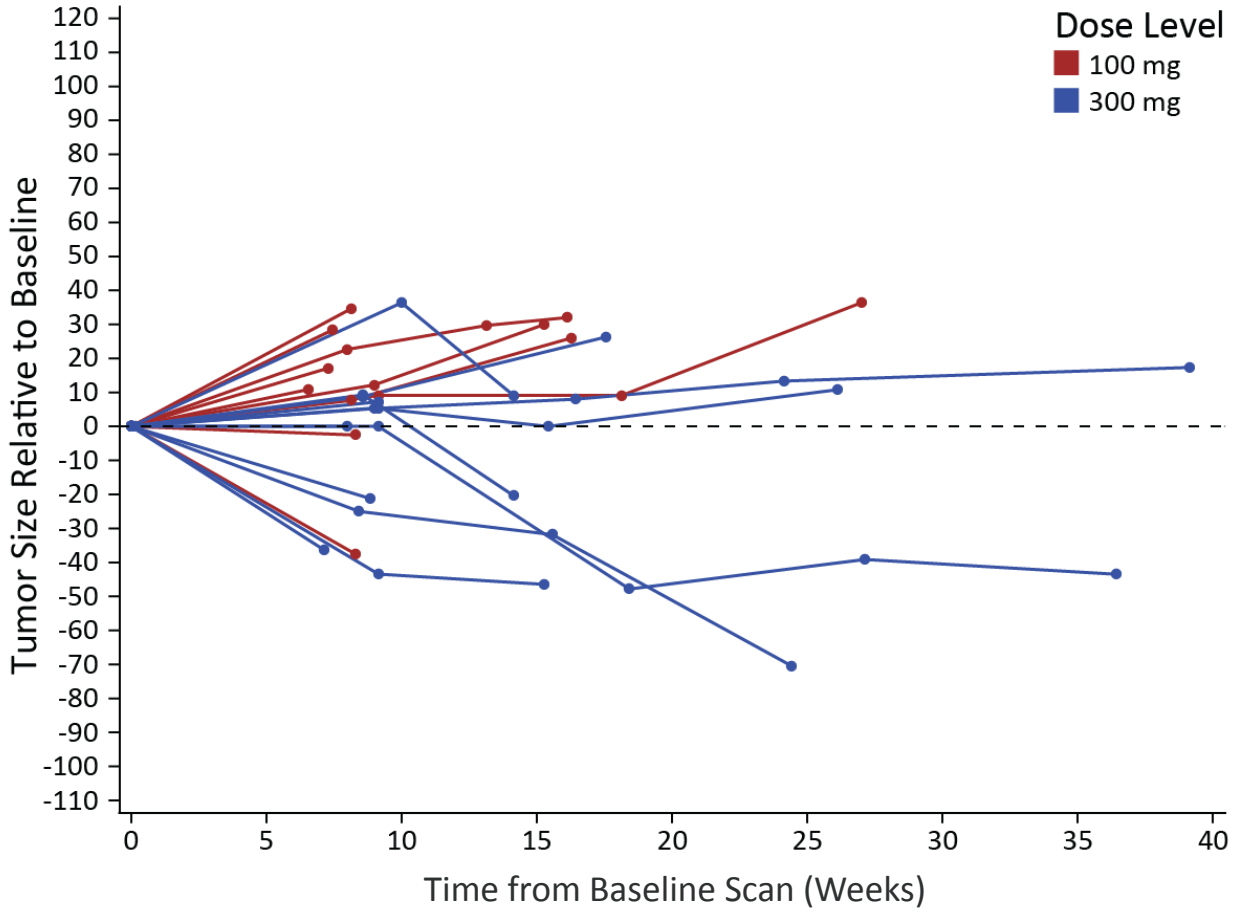
AE Preferred Term, N (%)	TSR-022 100 mg + TSR-042* (N=13)		TSR-022 300 mg + TSR-042* (N=19)		TSR-022 900 mg + TSR-042* (N=22)		Total (N=54)	
	All grade	Grade 3-4	All grade	Grade 3-4	All grade	Grade 3-4	All grade	Grade 3-4
Fatigue	2 (15.4)	0	2 (10.5)	0	4 (18.2)	0	8 (14.8)	0
Rash	1 (7.7)	1 (7.7)**	3 (15.8)	0	2 (9.1)	0	6 (11.1)	1 (1.9)**
Hypothyroidism	1 (7.7)	0	1 (5.3)	0	2 (9.1)	1 (4.5)***	4 (7.4)	1 (1.9)***
Chills	1 (7.7)	0	1 (5.3)	0	1 (4.5)	0	3 (5.6)	0
Nausea	1 (7.7)	0	1 (5.3)	0	1 (4.5)	0	3 (5.6)	0
Pruritus	0	0	2 (10.5)	0	1 (4.5)	0	3 (5.6)	0

- 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.

AE=adverse event; TEAE=treatment-emergent adverse event.

Combination Dose Escalation: Clinical Activity

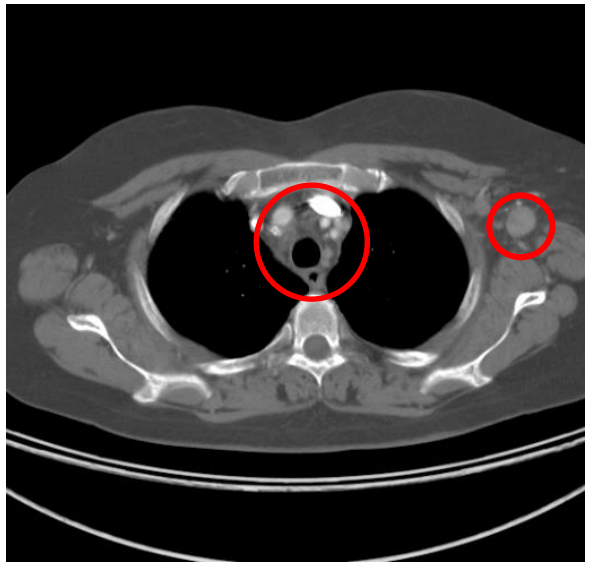


Confirmed Response in NSCLC Patient Progressing on Nivolumab

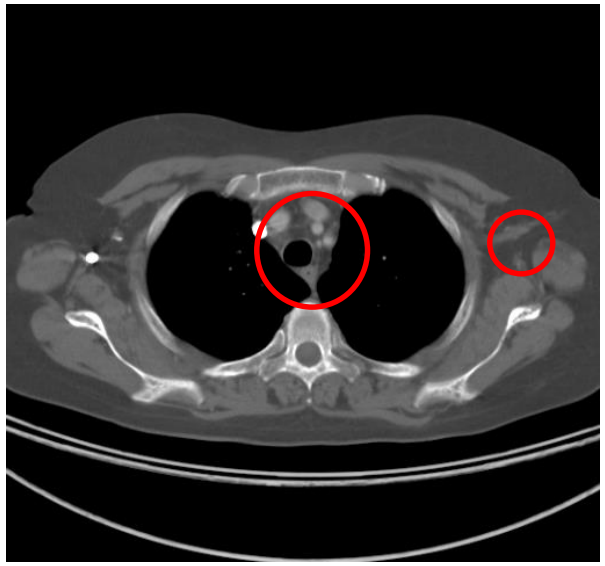
Well tolerated with early signs of clinical activity

- 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

Feb 23, 2017



Apr 20, 2017



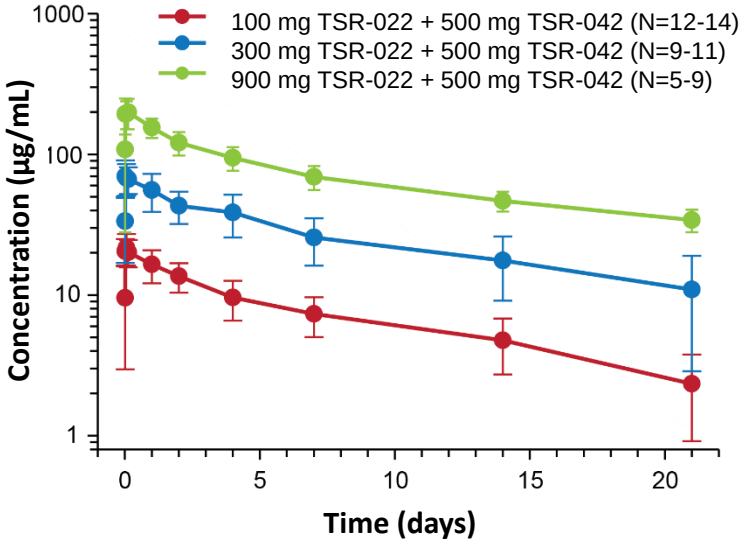
- 63 year-old female diagnosed with Stage IV NSCLC
- Prior treatment included 1L chemotherapy, 2L anti-PD-1, 3L Tarceva
- Progression noted on all previous therapies
- 72% shrinkage

PR=partial response; RO=receptor occupancy.

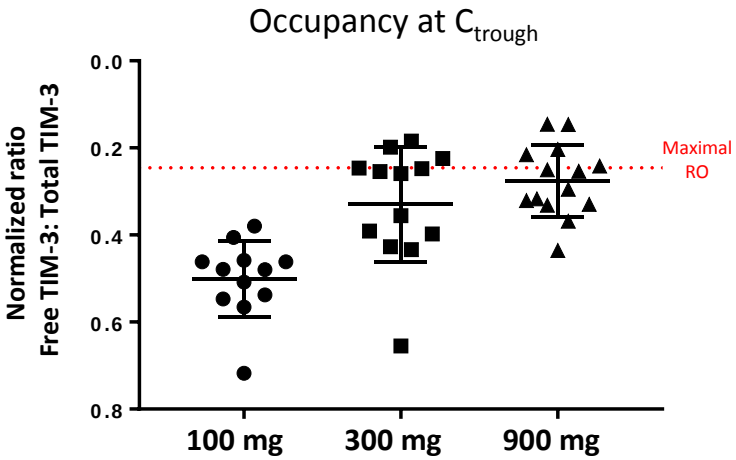
Combination Dose Escalation

900 mg dose required for effective exposure throughout dose interval

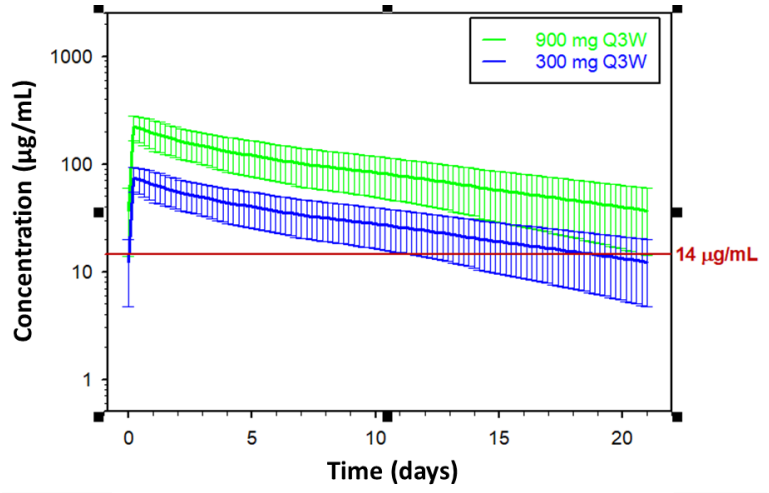
TSR-022 PK is dose proportional



TSR-022 RO is maximal at 900 mg



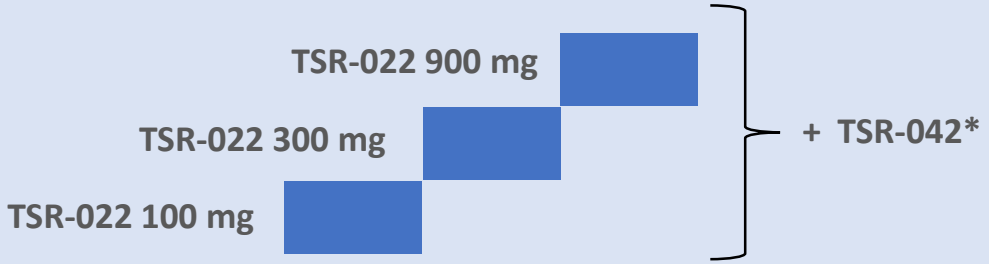
MLR EC_{90} is maintained at 900 mg



PK=pharmacokinetics; Q3W=every 3 weeks.

AMBER: Part 2 Expansion Cohorts

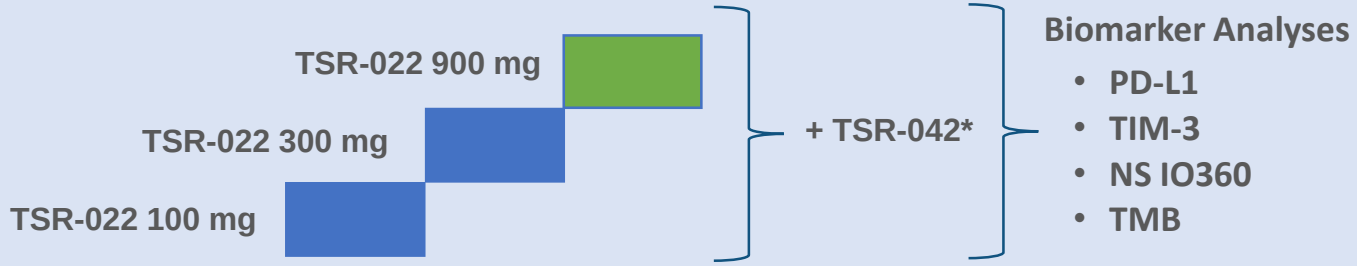
All Comers Combination Dose Escalation N=54



= Complete

= Enrolling

Patients with NSCLC Expansion Cohorts N=39 (ongoing)



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

Characteristic	TSR-022 + TSR-042 N=39
Age, y	
Median (range)	66 (35 - 86)
Sex	
Male	22
Female	17
ECOG performance status score	
0	9
1	30
PD-L1 status	
TPS ≥1%	16
TPS <1%	8
Unknown	15

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

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

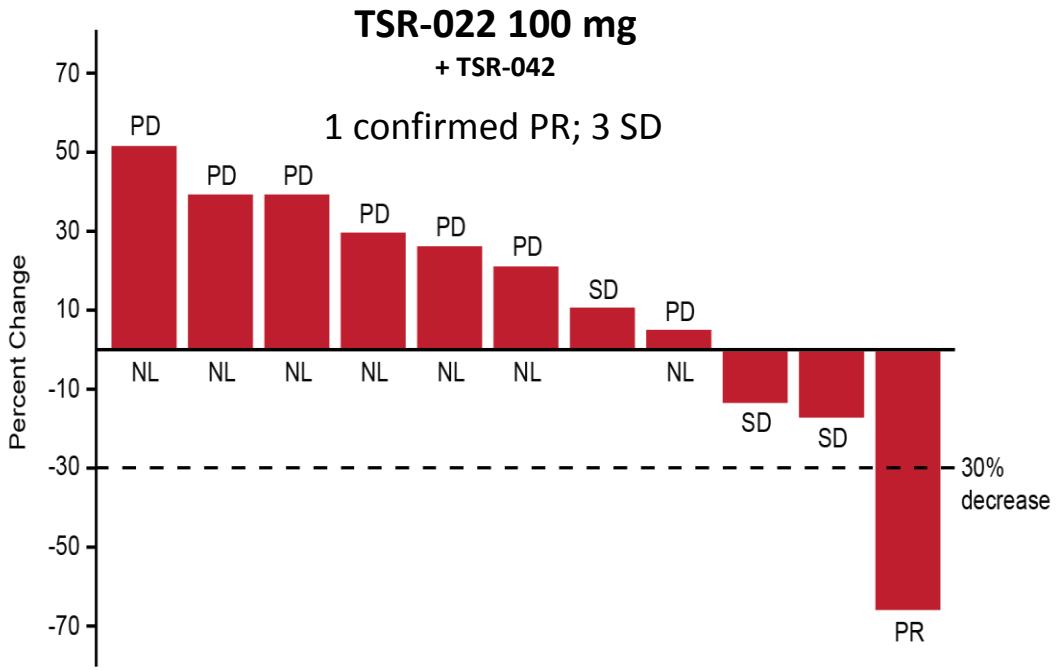
AE Preferred Term, n (%)	100 mg (N=14)		300 mg (N=25)		Total (N=39)	
	All Grade	Grade 3	All Grade	Grade 3	All Grade	Grade 3
Fatigue	5 (35.7)	1 (7.1)	5 (20.0)	0	10 (25.6)	1 (2.6)
Lipase increased	1 (7.1)	1 (7.1)*	2 (8.0)	1 (4.0)	3 (7.7)	2 (5.1)
Decreased appetite	0	0	3 (12.0)	0	3 (7.7)	0
Pruritus	1 (7.1)	0	2 (8.0)	0	3 (7.7)	0
Arthralgia	0	0	2 (8.0)	0	2 (5.1)	0
Diarrhea	1 (7.1)	0	1 (4.0)	0	2 (5.1)	0
Rash	1 (7.1)	0	1 (4.0)	0	2 (5.1)	0
Rash maculopapular	0	0	2 (8.0)	0	2 (5.1)	0
Weight decreased	0	0	2 (8.0)	0	2 (5.1)	0

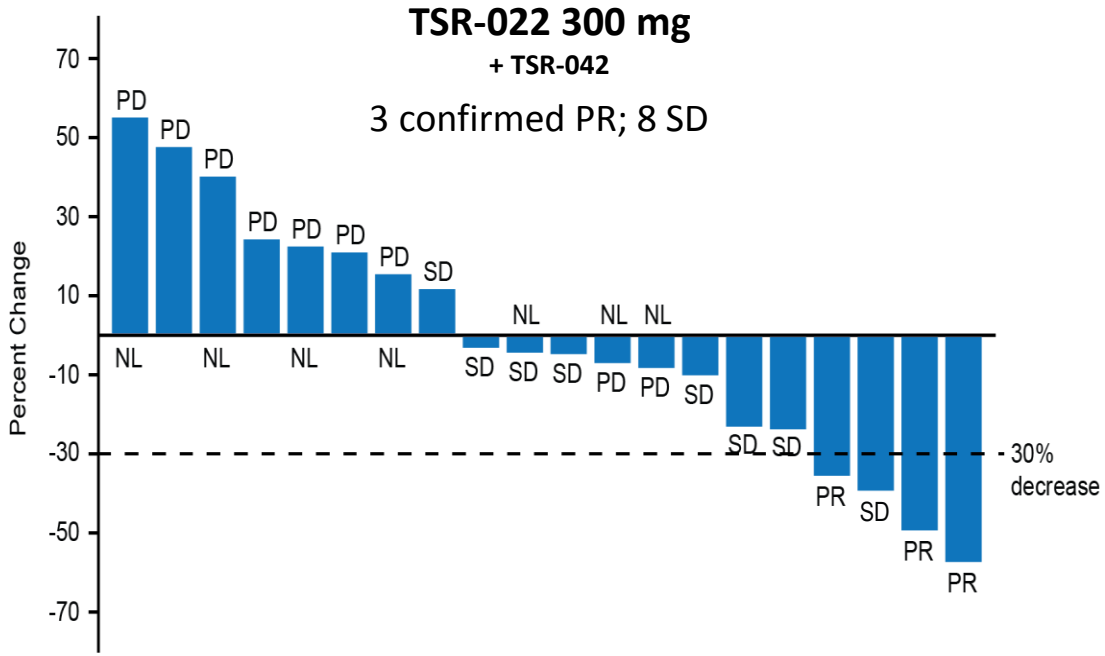
*Grade 4 lipase increased seen in 1 patient.
There were 2 (5.1%) patients with related irAEs: hypothyroidism and pancreatitis.
AE=adverse event; irAE=immune-related adverse event.

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



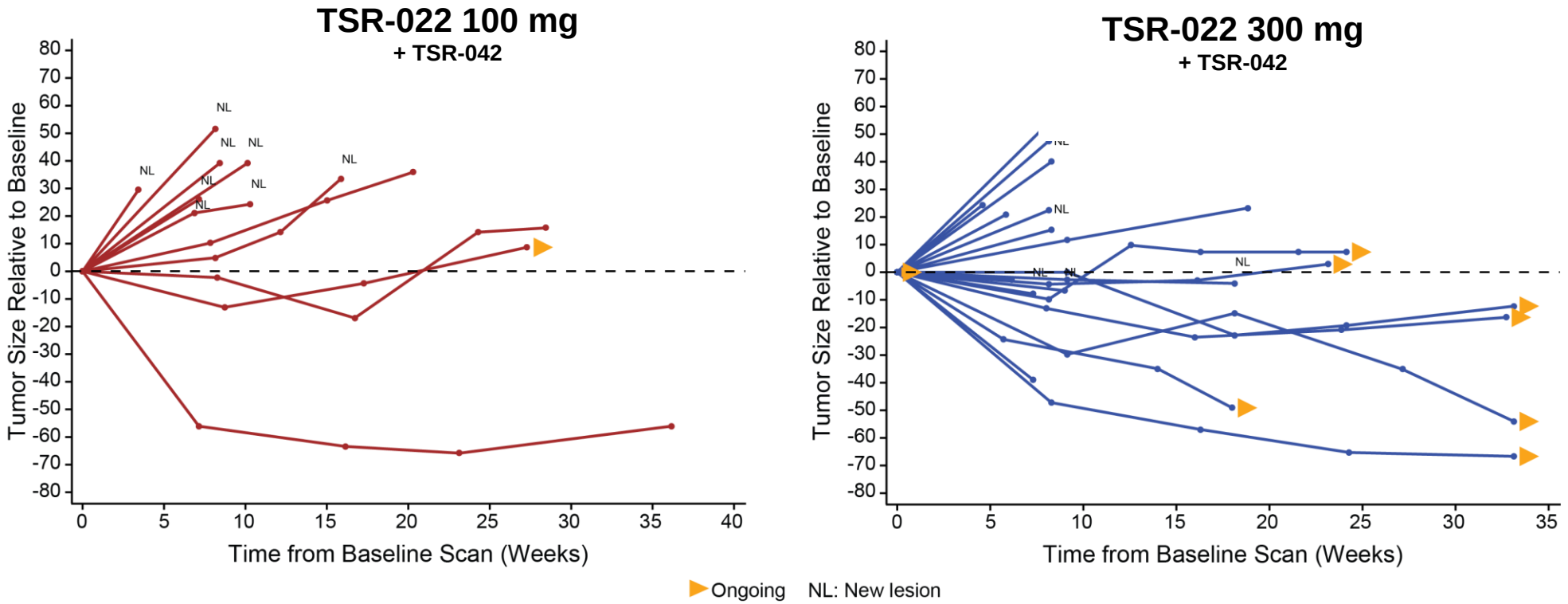


*One patient with scan was not evaluable and hence not included in figure.
NL=new lesion; PD=progressive disease; PR=partial response; SD=stable disease.

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

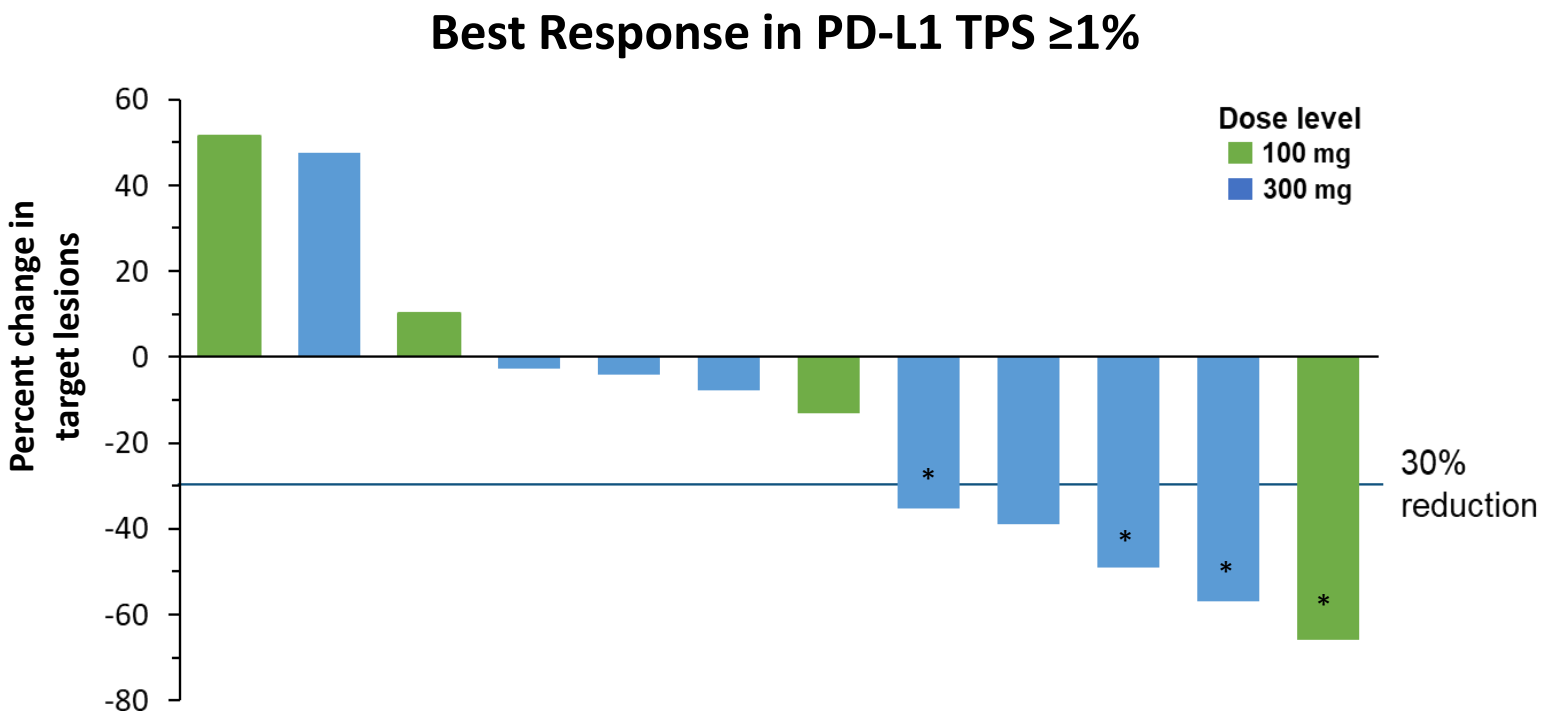
Emerging evidence for dose response in post-anti-PD-(L)1 NSCLC

Percent change in sum of target lesion dimensions over time



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

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

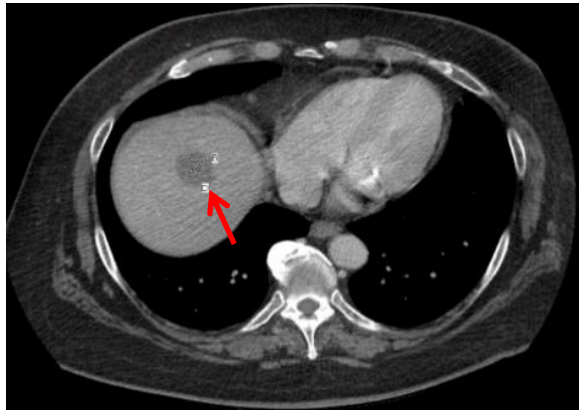


- 4 confirmed PR (3 by RECIST and 1 by irRECIST; 3 ongoing)
  - 1 in the 100 mg cohort
  - 3 in the 300 mg cohort

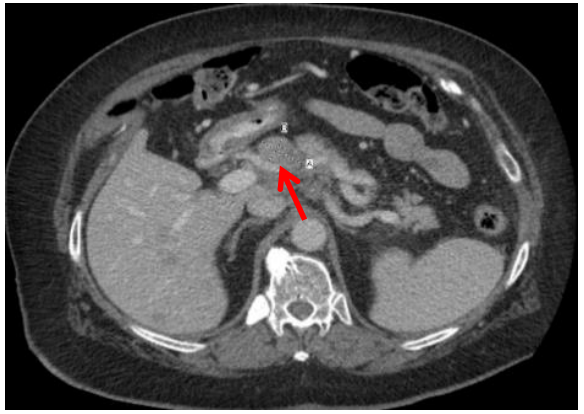
*Response was confirmed.

Ongoing Durable PR in PD-1 Refractory Patient

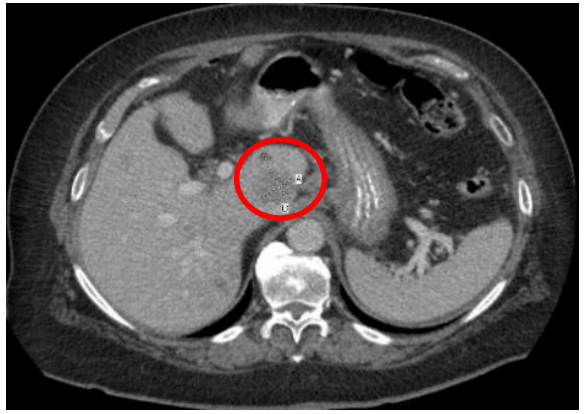
Pretreatment



Hepatic dome tumor (22×21 mm)



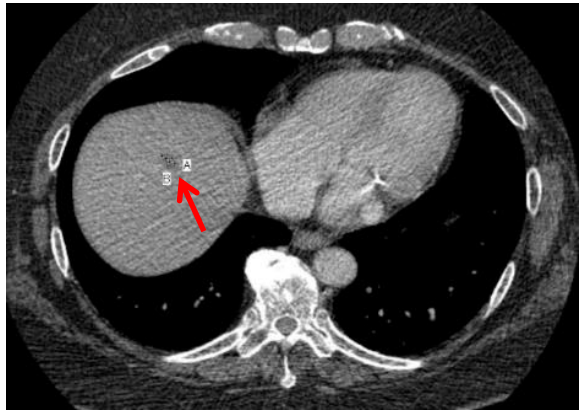
Periportal LN tumor (32×20 mm)



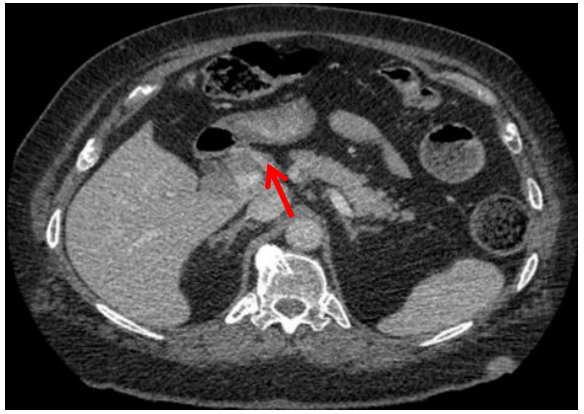
R hepatic lobe tumor (36×23 mm)

- 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

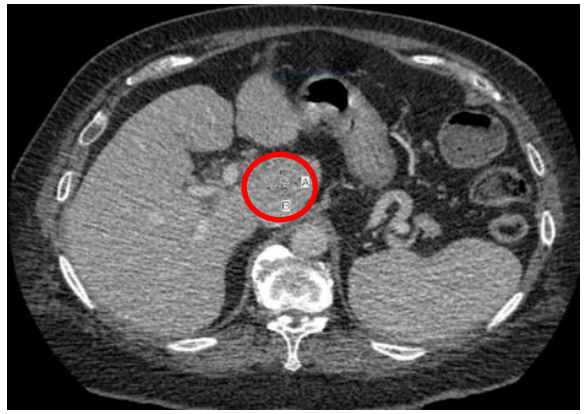
After 6 cycles, ongoing PR by RECIST version 1.1



Hepatic dome tumor (11×7 mm)



Periportal LN tumor (resolved)



R hepatic lobe tumor (17×16 mm)

LN=lymph node.

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 theTSR-022 900 mg dose level is ongoing in the NSCLC cohort.

Thank you