A Phase 1 Dose Escalation Study of TSR-033, an Anti-LAG-3 Monoclonal Antibody, in Patients With Advanced Solid Tumors

Kelly Stratton,1 Aurélien Marabelle,2 Geoffrey I. Shapiro,1 Jong Chul Park,3 Solmaz Sahebjam,4 Srirnayee Ghosh,5 Jian Chen,6 Michelle Kneissl,6 Ying Wang,6 Anita Patnaik7

1College of Medicine, The University of Oklahoma, Oklahoma City, OK, USA; 2 Gustave Roussy Integrated Cancer Research, Villejuif, France; 3 Dana-Farber Cancer Institute, Boston, MA, USA; 4 Massachusetts General Hospital, Boston, MA, USA; 5 Moffitt Cancer Center & Research Institute, University of South Florida, Tampa, FL, USA; 6 TESARO, Inc., Waltham, MA, USA; 7 Texas Southwest Accelerated Research Therapeutics, San Antonio, TX, USA.

BACKGROUND

• Lymphocyte activation gene (LAG-3) is an immune checkpoint inhibitor receptor found on multiple immune cells, including effector T cells.
• LAG-3 interacts with major histocompatibility complex (MHC) class II on antigen-presenting cells and attenuates T-cell activation.

LAG-3 is often co-expressed with programmed death 1 (PD-1) on tumor-infiltrating lymphocytes and is associated with increased levels of exhaustion. LAG-3 expression is upregulated in response to anti-PD-1 therapy (Figures 1 and 2).

• TSR-033 is an investigational, humanized, anti-LAG-3 monoclonal antibody (immunoglobulin G4/kappa) that blocks the interaction of LAG-3 with MHC class II.

• LAG-3 blockade with TSR-033 in combination with anti-PD-1 therapy (TSR-042) boosts immune function and elicits antitumor immunity in preclinical models (Figures 3 and 4).

• Prior clinical data demonstrate that combined anti-PD-1 and anti-LAG-3 checkpoint blockade leads to increased antitumor activity compared with anti-PD-1 alone in patients who have progressed on anti-PD-1 therapy.

Figure 1. LAG-3 is a Key Immune Checkpoint That Is Frequently Co-expressed With PD-1 on Tumor-Infiltrating T Cells, Acts to Alleviate Activation, and Is Upregulated by Anti-PD-1 Treatment

Figure 2. LAG-3 Is Frequently Co-expressed With PD-1 on Tumor-Infiltrating Lymphocytes (A). CD8+ T Cells With Co-expression of PD-1 and LAG-3 Are Associated With A More "Exhausted" Phenotype As Assessed By Lower Frequency of Granzyme B+ T cells Are More "Exhausted," and Is Upregulated Following PD-1 Blockade in a Humanized Mouse NSCLC Model (C)

METHODS

Inclusion Criteria

• Patients aged ≥18 years with advanced (unresectable) or metastatic solid tumors who had disease progression or treatment intolerance after treatment with available therapies.

• Adequate organ function and Eastern Cooperative Oncology Group (ECOG) performance status score.

Exclusion Criteria

• Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-LAG-3 agent that resulted in permanent discontinuation due to an adverse event (AE).

Endpoints

• Safety and tolerability of TSR-033 as monotherapy and in combination with TSR-042 for the treatment of NSCLC and other solid tumors.

RESULTS

Patients

• Slightly over one-half of the patients enrolled in Part 1A were female, and the most common tumor sites were prostate and colon (Table 1).

• Most patients had received ≥4 prior treatment lines.

ACKNOWLEDGEMENTS

Writing and editorial support, funded by TESARO, Inc. (Waltham, MA, USA) and coordinated by Ashif Tajali, Ph.D., of TESARO, Inc., was provided by Jeremy Kennard, Ph.D., and Cara Hunsberger of Arklight Healthcare Communications (Midland, CT, USA).

REFERENCES


Society for Immunotherapy of Cancer 33rd Annual Meeting | November 7-11, 2018 | Washington, DC, USA