Safet y and Preliminary Efficacy of Intratumoral Cavrotolimod (AST-008), a Spherical Nucleic Acid TLR9 Agonist, in Combination With Pembrolizumab in Patients With Advanced Solid Tumors

SI O’Day,1 CA Perez,2 TM Wise-Draper,1 GH Hanna,3 S Bhatia,3 CM Kelly,2 DE Laux,4 A Daud,5 S Chandra,1 MA Shaheen,1 L Hernandez-Aya,4 CC Yeung,5 KS Smythe,5 EM deGoma,15 WL Daniels,6 DE Feltner,2,5 SLinderal,5 HE Michel,10 AS Bexon,2,15 M Bexon,9 and MM Milhem11,15

Presenter: Steven J. O’Day (O’Day@jwci.org)

1Mayo Cancer Institute, Santa Monica, CA; 2Tyler Cancer Center at University of Miami, Miami, FL; 3Kettering Cancer Center, Cincinnati, OH; 4Ohio State University Comprehensive Cancer Institute, Columbus, OH; 5New Yorker Cancer Institute, Boston, MA; 6University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA; 7Memorial Sloan Kettering Cancer Center, New York, NY; 8University of Colorado Cancer Center, Aurora, CO; 9University of Iowa Health Care, Iowa City, IA; 10UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; 11Northwestern University Feinberg School of Medicine, Chicago, IL; 12University of Arizona Cancer Center, Tucson, AZ; 13University of California Irvine, Irvine, CA; 14University of Pittsburgh Medical Center/Children’s Hospital of Pittsburgh, Pittsburgh, PA; 15Sloan-Kettering Institute, New York, NY; 16Exicure, Inc, Chicago, IL; 17Bexon Consulting, Upper Montclair, NJ

Background

- Cavrotolimod (AST-008) is a spherical nucleic acid toll-like receptor (TLR9) agonist designed to robustly activate innate and adaptive immune responses.
- Cavrotolimod is in development for the treatment of advanced solid tumors in combination with PD-1 blockade.
- Prior analysis demonstrated that cavrotolimod, alone and in combination with PD-1 blockade, increased circulating levels of Th1-type cytokines and activated peripheral T cells and NK cells.

This analysis provides updated results of the Phase 1b study of cavrotolimod in patients with advanced solid tumors in combination with pembrolizumab.1–5

CONCLUSIONS

- Cavrotolimod/PD-1 combination was generally safe and well-tolerated at the studied doses.
- Confirmed ORR was 21% (6 [1 CR, 3 PR] of 19 evaluable) across all doses and 33% (2 PR of 6) at the highest and recommended Phase 2 dose.
- Durable and ongoing responses in all responders, with PFS at least 6 months and up to 16 months.
- Three of four responders actively progressing on PD-1 blockade at the time of study enrollment.
- Stroke of injected and non-injected tumor lesions distant from site of injection.

REFERENCES

1Milhem MM, Perez CA, Hanna GS et al. Phase 1/2 Study of an Intratumoral TLR9 Agonist Against Spherical Nucleic Acid (AST-008) and Pembrolizumab: Evidence of Immune Activation. ASCO 2020. 3 weeks

2Exicure cavrotolimod KOL day.

3Initial multiplex immunostaining results (n=2) showed an increase in C/E+B cells (green) and C/OS/D5 (red) tumor T cells (purple) in the injected tumor lesion of the responder patient after treatment with cavrotolimod/PD-1 blockade.

4This is in contrast with the injected tumor lesion of the patient who demonstrated progression, which did not show similar T cell infiltration.

5On treatment biopsies were obtained on cycle 4 day 1, 5 days after initiation of cavrotolimod and 3 weeks after initiation of pembrolizumab.

STUDY DESIGN

- Open-label, multicenter, 3+3 dose-escalation study of intratumoral cavrotolimod in combination with IV/ subcutaneous pembrolizumab in patients with advanced solid tumors
- Key eligibility criteria:
  - Irreparable advanced or metastatic solid tumor
  - ≥1 cutaneous/subcutaneous/red B-cell RECT-evaluable tumor lesion accessible for repeated If injection
  - A RECT-evaluable tumor lesion to remain non-injected throughout the study to observe systemic immune effects.
- Assessments:
  - Safety and tolerability, cavrotolimod and pembrolizumab pharmacokinetics
  - Peripheral blood and tumor infiltrating lymphocytes
  - Intratumoral pembrolizumab tumor grade expression profiling (Novocure), multiple immunohistochemistry
  - Tumor response assessment by RECIST 1.1
- Dosing schedule:
  - Cavrotolimod: IT: once weekly x 8 weeks → once every 3 weeks
  - Pembrolizumab: IV: once every 3 weeks (starting week 3)

Efficacy

- Confirmed ORR was 21% (6 [1 CR, 3 PR] of 19 evaluable) across all doses and 33% (2 PR of 6) at the highest and recommended Phase 2 dose.
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Conclusions

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- Confirmed ORR was 21% (6 [1 CR, 3 PR] of 19 evaluable) across all doses and 33% (2 PR of 6) at the highest and recommended Phase 2 dose.
- Durable and ongoing responses in all responders, with PFS at least 6 months and up to 16 months.
- Three of four responders were progressing on PD-1 blockade at the time of study enrollment.
- Systemic immune activity was supported by shrinkage of noninjected tumors, systemic and intratumoral pharmacodynamic activity, and adverse events of flu-like symptoms.
- The highest dose, 32 mg, was selected for the Phase 2a dose, which is studying cavrotolimod IT in combination with pembrolizumab or in combination in patients with PD-1 refractory locally advanced or metastatic Merkel cell carcinoma or cutaneous squamous cell carcinoma.

103±16 (pg/mL) 63±17 (pg/mL) 4 mg 121±10 (pg/mL) 126±19 (pg/mL) 8 mg