Abstract #423

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

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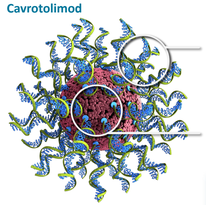
BACKGROUND

- Cavrotolimod (AST-008) is a spherical nucleic acid toll-like receptor 9 (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 analyses 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.[1,2]
- This analysis provides updated results of the Phase 1b stage of AST-008-102, an ongoing Phase 1b/2 study (NCT03684785).

Cavrotolimod



TLR9 agonist oligonucleotides – potent inducers of immunity
- Cytokines/chemokine signaling (IP-10, IL-12) for immune cell trafficking
- T cell activation
- NK cell activation

Benign lipid nanoparticle
- Scaffold for SNA structure

Oligonucleotides + nanoparticle = SNA
- Increased cellular and endosomal uptake → Location of TLR9 target

STUDY DESIGN

- Open-label, multicenter, 3+3 dose-escalation study of intratumoral cavrotolimod in combination with IV pembrolizumab in patients with advanced solid tumors
- Key eligibility criteria
  - Inoperable advanced or metastatic solid tumor
  - ≥ 1 cutaneous/subcutaneous/nodal RECIST-evaluable tumor lesion accessible for repeated IT injection
  - ≥ 1 RECIST-evaluable tumor lesion to remain noninjected throughout the study to observe systemic immune effects
- Assessments
  - Safety and tolerability; cavrotolimod and pembrolizumab pharmacokinetics
  - Peripheral blood pharmacodynamics: serum cytokines; peripheral immune cell populations
  - Intratumoral pharmacodynamics: tumor gene expression profiling (NanoString), multiplex 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)

BASELINE CHARACTERISTICS

	N (%)
Age, mean, years (range)	62.8 (30-86)
Male	15 (75%)
Caucasian	20 (100%)
Cancer type	
Melanoma	10 (50%)
Merkel cell carcinoma	5 (25%)
Cutaneous squamous cell carcinoma	2 (10%)
Head & neck squamous cell carcinoma	2 (10%)
Leiomyosarcoma	1 (5%)
Metastatic disease	19 (95%)
Prior anti-PD-1	
History of anti-PD-1 use	19 (95%)
Best prior response: progressive disease	12 (60%)
Last prior response: progressive disease	17 (85%)
Time since last dose ≤12 weeks (N=19)	15 (79%)
Prior lines of systemic therapy	
1	7 (35%)
2	5 (25%)
3+	8 (40%)

SAFETY

- Majority (98%) of treatment-related AEs were G1/2
- G1/2 injection site reactions and flu-like symptoms were the most commonly reported AEs, observed in 100% of patients at the highest dose (32 mg)

	2 mg (n=3)	4 mg (n=3)	8 mg (n=5)	16 mg (n=3)	32 mg (n=6)	Overall (n=20)
AE, related	3 (100)	1 (33)	4 (80)	3 (100)	6 (100)	17 (85)
G3 AE, related*	0	0	0	0	2 (33)	2 (10)
G4 AE, related	0	0	0	0	0	0
Serious AE†	0	0	1 (20)	0	0	1 (5)
Serious AE, related	0	0	0	0	0	0
DLT	0	0	0	0	0	0
Death from AE	0	0	0	0	0	0

*G3 AE, related: agitation (32 mg), injection site reaction (32 mg). †SAE: aspiration pneumonia, unrelated. Data cut off 9 Oct 2020. AEs shown as n (%).

PHARMACODYNAMICS

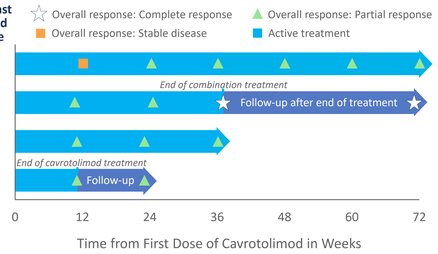
Cavrotolimod + Pembrolizumab Combination Therapy (Fold-Change vs Baseline)	
Injected tumors	**Noninjected tumors**
Cytotoxic cells: 4.3*	Cytotoxic cells: 1.3
Granzyme B: 4.7*	Granzyme B: 1.8
IFN-γ mRNA: 2.5*	IFN-inducible genes (MX1, IFI27, IFIT1 mRNA): 1.8–2.1*
CD3 D,E,G: 4.2*, 3.1, 4.6*	CD3 D,E,G mRNA: 1.1, 1.1, 1.3

Data from mRNA expression analysis (NanoString) of tumor biopsies. Cavrotolimod 2–32 mg + pembrolizumab (C3D1) vs baseline (C1D1). N = 9. *p<0.05 for two-sided t-test.

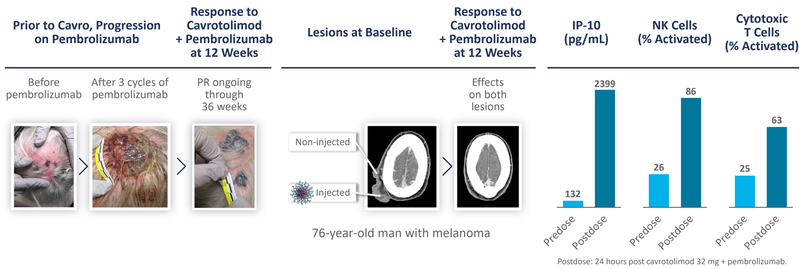
EFFICACY

- Confirmed ORR was 21% (4 [1 CR, 3 PR] 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 4 responders actively progressing on PD-1 blockade at the time of study enrollment
- Shrinkage of injected and non-injected tumor lesions distant from site of injection

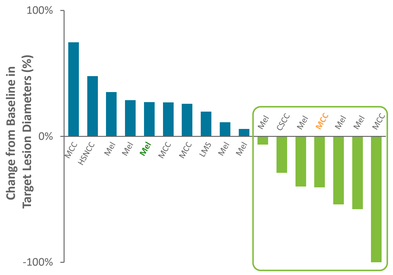
Tumor	Cavro Dose	Prior Anti-PD-1 Last Response	Time Between Last Dose of PD-1 and First Cavro Dose
Merkel	4 mg	Progressive disease	3 weeks
Merkel	2 mg	Relapsed off anti-PD-1	69 weeks
Melanoma	32 mg	Progressive disease	6 weeks
Melanoma	32 mg	Progressive disease	8 weeks



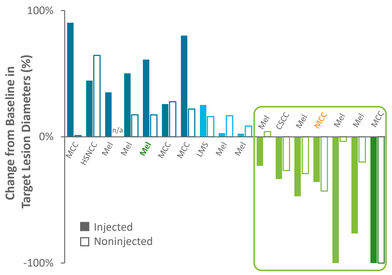
Response in Refractory Melanoma Patient with Progression on Anti-PD-1 at Enrollment



Target Tumor Response: Sum of Injected and Noninjected Lesions

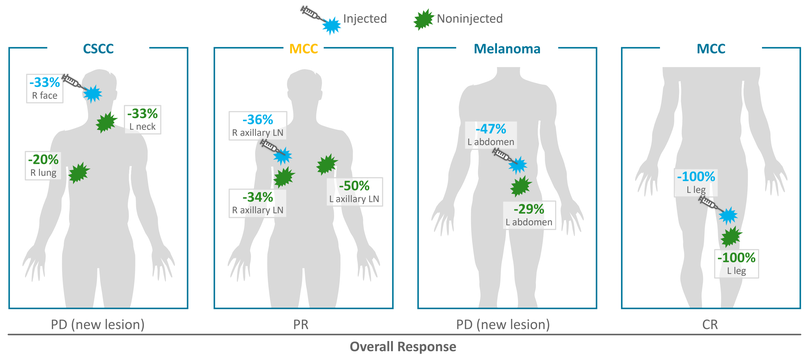


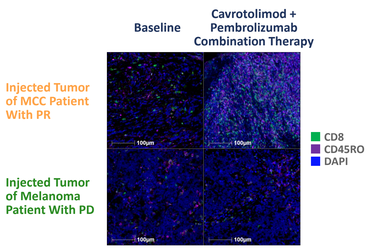
Target Tumor Response: Sum of Injected Lesions vs Sum of Noninjected Lesions



n/a: in one patient, injected and noninjected lesions fused.

Tumor Regression Observed in Distant, Noninjected Target Lesions





- Initial multiplex immunohistochemistry results (n=2) showed an increase in CD8⁺ T cells (green) and CD45RO⁺ memory T cells (purple) in the injected tumor lesion of the responder patient after treatment with cavrotolimod and pembrolizumab.
- This is in contrast with the injected tumor lesion of the patient who demonstrated progression, which did not show similar T cell infiltration.
- On-treatment biopsies were obtained on cycle 3 day 1, 5 weeks after initiation of cavrotolimod and 3 weeks after initiation of pembrolizumab.

CONCLUSIONS

- Cavrotolimod IT in combination with pembrolizumab was generally safe and well tolerated at the studied doses.
- Confirmed ORR was 21% (4 [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 4 responders were progressing on PD-1 blockade at the time of study enrollment.
- Systemic immune activation 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 2 stage, which is studying cavrotolimod IT in combination with pembrolizumab or cemiplimab in patients with PD-1-refractory locally advanced or metastatic Merkel cell carcinoma or cutaneous squamous cell carcinoma.[3]

REFERENCES

[1]Milhem MM, Perez CA, Hanna GJ et al. Phase 1b/2 Study of an Intratumoral TLR9 Agonist Spherical Nucleic Acid (AST-008) and Pembrolizumab: Evidence of Immune Activation. AACR 2020.
[2]Exicure cavrotolimod KOL day. https://event.webcasts.com/viewer/event.jsp?ei=1367836&tp_key=540c2194f5
[3]Milhem MM, Perez CA, Hanna GJ et al. AST-008: A Novel Approach to TLR9 Agonism with PD-1 Blockade for Anti-PD-1 Refractory Merkel Cell Carcinoma (MCC) and Cutaneous Squamous Cell Carcinoma (CSCC). ASCO 2020.