Methods AST-008-102 is an ongoing Phase 1b/2 study (NCT03684785). The Phase 1b dose escalation stage examined intratumoral (IT) cavrotolimod at doses of 2, 4, 8, 16, and 32 mg in combination with pembrolizumab in patients with advanced solid tumors. Cavrotolimod was dosed once weekly for 8 weeks and once every 3 weeks thereafter. The Phase 2 dose expansion stage is examining cavrotolimod 32 mg IT in combination with IV pembrolizumab for the treatment of advanced Merkel cell carcinoma (MCC) and in combination with IV cemiplimab for the treatment of advanced cutaneous squamous cell carcinoma (CSCC). Both cohorts are enrolling patients with documented progression of disease on PD-(L)1 blockade. This analysis provides interim results of the Phase 1b stage.

Results In the Phase 1b stage, 20 patients were enrolled across all planned dose levels. No dose-limiting toxicities, grade (G)4 toxicities, or treatment-related serious adverse events (AEs) were observed. The most common AEs were injection site reactions (ISRs) and flu-like symptoms. All treatment-related AEs were < G3 except agitation and ISR (1 each). At data cutoff, ORR is 21% (4 of 19 evaluable patients) in a heterogeneous population with solid tumors. All 4 responders (2 melanoma and 2 MCC patients) have ongoing responses, with duration of response exceeding 52 weeks in 2 patients. Three of 4 responders had disease progression on PD-1 blockade at the time of enrollment, and one patient had a prior response to PD-1 blockade, but subsequently relapsed off therapy. Regression of both injected and noninjected lesions was observed. Gene expression analyses demonstrated increased IT infiltration by cytotoxic immune cells in both injected and noninjected tumors. The highest dose (32 mg) was selected for the Phase 2 stage.

Conclusions IT administration of cavrotolimod appears to be safe and well tolerated in combination with pembrolizumab. Durable responses have occurred in patients previously experiencing progressive disease on PD-1 blockade.

Trial Registration NCT03684785

Ethics Approval The study was approved by Institutional Review Boards of Dana-Farber Cancer Institute (IRB #18-584), John Wayne Cancer Institute (WIRB #20183064), University of Miami (IRB #20180957), University of Iowa (IRB #201810763), University of Cincinnati (WIRB #20183064), University of Washington (WIRB #20183064), MSKCC (IRB #20-174), UC San Francisco (WIRB #20183064), U Colorado (WIRB #20183064), Northwestern (IRB #STU00211083), U Arizona (WIRB #20183064), UC Irvine (WIRB #20183064), U Pitt (WIRB #20183064), and Washington University (WIRB #20183064).

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425 INVESTIGATION OF WNT LIGAND SIGNALING REGULATORS AS A PREDICTOR OF ANTI-PD-1 RESPONSE IN METASTATIC MELANOMA

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Background Responses to anti-PD-1 antibodies (aPD1) have changed the therapeutic landscape of metastatic melanoma, however predictive biomarkers of resistance are lacking. Beta-catenin pathway activation has been inversely correlated with tumor-infiltrating T lymphocytes in melanoma as well as several other solid tumors.1 However, activating mutations involving this pathway are rare, implying that the modulation of upstream Wnt ligand/Fzd receptor (Wnt/Fzd) signaling could be a critical regulator of anti-tumor immunity. Indeed, expression of certain Wnt ligands has been associated with inferior responses to checkpoint inhibitor immunotherapy in metastatic melanoma patients.2 In addition, we have further found tumor-derived paracrine and autocrine Wnt ligand signaling to drive dendritic cell tolerization and to be associated with escape from aPD1 therapy in transgenic mouse models.3

4 No studies to date have focused on the impact of the various regulators and components of proximal Wnt/Fzd receptor signaling on resistance to aPD1 therapy in melanoma patients. We therefore developed a unique Wnt/Fzd pathway panel using Nanostring technology to examine alterations in Wnt ligands, their receptors, and regulators as a predictor of aPD1 resistance.

Methods To test whether this panel could identify aPD1 resistant patients, Nanostring analysis was performed on archival FFPE tissue specimens of 12 responding (R) and 12 nonresponding (NR) metastatic melanoma patients (pts) taken prior to aPD1 monotherapy. Response was assessed radiographically by week 12 RECIST criteria.

Results Several components of both canonical and non-canonical Wnt ligand signaling, including regulators of autocrine/paracrine signaling, were upregulated in aPD1 NR pts

Abstract 425 Table 1 Most significantly upregulated Wnt ligands, receptors, and pathway components in patients that do not respond to aPD1

<table>
<thead>
<tr>
<th>Gene Category</th>
<th>Genes Upregulated in NRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wnt Receptor</td>
<td>FZD1</td>
</tr>
<tr>
<td>Wnt Receptor</td>
<td>FZD6</td>
</tr>
<tr>
<td>Wnt Co-Receptor</td>
<td>LRP5</td>
</tr>
<tr>
<td>Wnt Ligand</td>
<td>WNT2B</td>
</tr>
<tr>
<td>Wnt Ligand</td>
<td>WNT4</td>
</tr>
<tr>
<td>Wnt Ligand</td>
<td>WNT9A</td>
</tr>
<tr>
<td>Wnt Activator</td>
<td>PYGO1</td>
</tr>
<tr>
<td>Wnt Regulator</td>
<td>SFRP2</td>
</tr>
<tr>
<td>Wnt Regulator</td>
<td>DKK2</td>
</tr>
</tbody>
</table>

Abstract 425 Figure 1 Volcano plot of the top 30 genes from the nanostring panel comparing responders (red) and nonresponders (blue)
compared to R pts (figure 1, table 1). GZMB, CD8, and IFNG were among cytotoxic T cell related genes upregulated in Rs. Upregulation of SFRP2 and DKK2 in NR pts, classically negative feedback regulators of Wnt ligands, are a reflection of enhanced Wnt ligand signaling activity.

Conclusions This study supports the importance of paracrine and autocrine Wnt ligand signaling in the regulation of effector T cell responses and aPD1 resistance in cancer. In addition to predicting response to aPD1 checkpoint inhibitor immunotherapy, these findings further suggest that this Wnt signaling panel could serve as a predictive marker of immunologic response to Wnt ligand inhibitors, such as the PORCN inhibitors, which are currently under development. We continue to accrue additional pts to further validate these findings. Future studies will include a comparison of pre-treatment and on-treatment biopsies to evaluate these markers as predictors of adaptive aPD1 resistance.

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Trial Registration NCT02694965

Ethics Approval This study was approved by Duke University’s Institutional Review Board, protocol number Pro00039349

Consent Not applicable

REFERENCES


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MK-3475-U02: PHASE 1/2 STUDY OF INVESTIGATIONAL AGENTS WITH OR WITHOUT PEMBROLIZUMAB VERSUS PEMBROLIZUMAB MONOTHERAPY IN MELANOMA

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Background Pembrolizumab is a standard of care for the treatment of unresectable or metastatic melanoma and an adjuvant treatment of melanoma with involvement of lymph node(s) following complete resection. However, new treatment options are needed to reduce the tumor burden before surgery and improve overall outcomes in patients with advanced melanoma.

Methods MK-3475-U02 is a phase 1/2, rolling arm, multicenter, open-label, adaptive design study to evaluate the safety and efficacy of investigational agents with or without pembrolizumab or pembrolizumab alone for the treatment of melanoma. Patients will be enrolled in 1 of the 3 substudies. Substudy 02A will include patients with programmed death-1 (PD-1)–refractory melanoma (progressed after ≥2 doses of anti-PD-1/programmed death ligand-1 [PD-L1] therapy) randomized equally to arms treating patients ≥1 investigational agent(s) with or without pembrolizumab. Enrollment is planned for up to ~100 patients per arm. Substudy 02B will include patients with unresectable stage III or stage IV melanoma not amenable to local therapy. Patients will be randomized 2:1 to combination (≥1 investigational agent(s) with or without pembrolizumab) or monotherapy (pembrolizumab alone) stratified by baseline lactate dehydrogenase status (normal/elevated) and prior adjuvant therapy with a PD-1 inhibitor (yes/no). Enrollment is planned for ~90 patients in the combination arm and ~45 in the control arm. Substudy 02C will include patients with stage IIIIB/IIIC/IIID melanoma who are candidates for neoadjuvant therapy. Patients will be randomly assigned to combination (≥1 investigational agent(s) with or without pembrolizumab) or monotherapy (pembrolizumab alone). Surgical resection will be performed 6 weeks after the first dose of neoadjuvant study intervention. Enrollment is planned for ~25 patients in combination and ~15 in the pembrolizumab monotherapy arms. Treatment will continue for up to 2 years (up to 1 year neoadjuvant/adjuvant therapy for substudy 02C), until disease progression, unacceptable toxicity, or study discontinuation. The primary end points include safety (adverse events and study intervention discontinuations) for all 3 substudies; objective response rate by blinded independent central review per Response Evaluation Criteria in Solid Tumors 1.1 for substudies 02A and 02B, and pathologic complete response (pCR) as assessed by central review of the pathology results for substudy 02C. Secondary end points include duration of response for substudies 02A and 02B, and recurrence-free survival, near pCR, and pathologic partial response rates for substudy 02C.

Results N/A

Conclusions N/A

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Trial Registration NCT04305041, NCT04305054, NCT04303169

Ethics Approval The study protocol and all amendments were approved by the relevant Institutional Review Board or ethics committee at each study site. All patients provided written informed consent to participate in the clinical trial.

Consent N/A

REFERENCE

N/A

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