

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.

Acknowledgements Holly Dressman, PhD of the Duke Center for Genomic and Computational Biology for her assistance with the Nanostring samples; Jenna Goodwin, Carol Ann Wiggs, and Jennifer Nixon of the Duke Clinical Melanoma Research Team for their assistance with the melanoma tissue acquisition protocol; Tadas Rimkus of Nanostring for his assistance with analysis

Trial Registration NCT02694965

Ethics Approval This study was approved by Duke University's Institutional Review Board, protocol number Pro00059349

Consent Not applicable

REFERENCES

1. Luke JJ, B.R., Spranger S, Sweis RF, Lingen MW, Lengyel E, Zha Y, Gajewski TF. Wnt/Beta-catenin pathway activation correlates with immune exclusion across most human cancers. *Journal of Clinical Oncology* 2016;34(15).
2. Hugo W, et al. Genomic and transcriptomic features of response to anti-pd-1 therapy in metastatic melanoma. *Cell* 2016;165(1): p. 35–44.
3. DeVito NC, X.C., Zhao F, Evans KS, Theivanthiran B, Lewicki J, Hoey T, Hurwitz H, Strickler JH, Hanks BA. Paracrine wnt-β-catenin signaling inhibition as a strategy to enhance the efficacy of anti-PD-1 antibody (Ab) therapy in a transgenic model of melanoma. *Journal of Clinical Oncology*, 2017. 35(no. 15_suppl).
4. Zhao F, et al. Paracrine Wnt5a-beta-Catenin signaling triggers a metabolic program that drives dendritic cell tolerization. *Immunity* 2018;48(1): p. 147–160 e7.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0425>

426

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

¹Reinhard Dummer*, ²Georgina V Long, ³Anna Pavlick, ⁴Michael Postow, ⁵Antoni Ribas, ⁶Caroline Robert, ⁷Richard A Scolyer, ⁷Janis Taube, ⁸Michael Tetzlaff, ⁹Jason Liao, ⁹Sama Ahsan, ⁹Scott Diede, ¹⁰Hussein Tawbi. ¹University Hospital of Zurich, Zurich, SC, Switzerland; ²Melanoma Inst Australia, Univ of Sydney, Sydney, Australia; ³Weill Cornell Medicine, New York, NY, USA; ⁴Memorial Sloan Kettering Cancer Center, New York, NY, USA; ⁵David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; ⁶Gustave Roussy and Paris-Sud University, Villejuif-Paris, France; ⁷Johns Hopkins Univ School of Medicine, Baltimore, MD, USA; ⁸UCSF Dermatopathology Service, San Francisco, CA, USA; ⁹Merck and Co., Inc., Kenilworth, NJ, USA; ¹⁰MD Anderson Cancer Center, Houston, Texas, USA

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 treatment arms evaluating ≥ 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 IIIB/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 pathological 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 pathological partial response rates for substudy 02C.

Results N/A

Conclusions N/A

Acknowledgements The authors thank the patients and their families for participating in these trials and all investigators and site personnel. Medical writing and/or editorial assistance was provided by Neha Tuli-Wildemore, MBBS, PhD, and Doyel Mitra, PhD, of the ApotheCom pembrolizumab team (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

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

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0426>