306 PREDICTORS OF IMMUNOTHERAPY BENEFIT IN MERKEL CELL CARCINOMA

Alec Kacew*, Harita Dhaneeswaran, Gabriel Starrett, Manisha Thakuria, Nicole LeBoeuf, Ann Silk, James DeCaprio, Glenn Hanna. The University of Chicago, Chicago, IL, USA; Dana-Farber Cancer Institute, Boston, MA, USA; CCR/NCI, Bethesda, MD, USA

Background Merkel cell carcinoma is a rare cancer for which the standard-of-care is immune checkpoint blockade in the recurrent/metastatic setting. However, immunotherapy is not effective in all patients. A greater understanding of molecular mechanisms and potential predictive biomarkers are unmet needs for clinicians and researchers.

Methods We undertook a retrospective analysis of 45 patients treated at our institution from 2013 to 2020 to understand the clinical and genomic correlates of clinical benefit from immunotherapy. We gathered data from the electronic health record, including provider notes and results from our institutional next-generation sequencing panel of actionable genomic alterations.

Results Our cohort predominantly included individuals with stage III disease at diagnosis and stage IV disease at the time of diagnosis of recurrent/metastatic disease. Most patients received immunotherapy in the first line. 43% of patients experienced an objective response to immunotherapy (median duration of response 24.2 months, 95% confidence interval 8.8–not reached) and median overall survival was 15.5 months (95% confidence interval 9.0–28.7) (median follow-up 25.2 months). Lower stage at diagnosis of primary disease and shorter disease-free interval between completion of initial treatment and recurrence were each associated with greater odds of response (odds ratio 0.06, p<0.04 for stage; odds ratio 0.75, p=0.05 for disease-free interval). The most common single-nucleotide variants among the sequenced cohort were those in TP53 (59%) and RB1 (51%). Single-nucleotide variants in the ARID2 and NTRK1 genes were associated with response without Bonferroni correction (p=0.05), while none of Merkel cell polyomavirus status, total mutational burden, ultraviolet mutational signatures, and copy-number alterations predicted outcomes (figure 1).

Conclusions Patients with shorter disease-free interval after definitive treatment may be particularly suitable candidates for immunotherapy. Our molecular findings point to ARID2 and NTRK1 as potential predictive markers and/or therapeutic targets (e.g., with Trk inhibitors), although this association needs to be confirmed in a larger sample.

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Ethics Approval The study was approved by the Dana-Farber institutional review board, protocol numbers 11-104 and 17-000.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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307 ATEZOLIZUMAB PLUS VEMURAFENIB AND COBIMETINIB PROVIDES FAVORABLE SURVIVAL OUTCOMES IN PATIENTS WITH HIGH TUMOR MUTATION BURDEN AND PROINFLAMMATORY GENE SIGNATURE IN THE PHASE 3 IMSPIRE150 STUDY


1University of Colorado Comp. Cancer Ctr, Aurora, CO, USA; 2Istituto Nazionale Tumori IRCCS, Napoli, Italy; 3Gustave Roussy and Université Paris-Sud, Villejuif-Paris; 4Instituto do Câncer do Estado, São Paulo, Brazil; 5Oncoclinica, Móstoles, Spain; 6Hospital Universitario Virgen Macarena, Seville, Spain; 7University of Szeged Szent-Györgyi, Szeged, Hungary; 8IRCCS Istituto Europeo di Oncologia, Milan, Italy; 9Greater Poland Cancer Centre, Poznan, Poland; 10Genentech, Inc., South San Francisco, CA, USA; 11Harper Forbes, 12Ralf Gutzmer, 13Grant McArthur. 1Karl Lewis*, 2Paolo Ascierto, 3Caroline Robert, 4Rodrigo Munhoz, 5Gabriella Liszkay, 6Luis De La Cruz Marino, 7Judit Olah, 8Paola Queirolo, 9Jackeck Mackiewicz, 10Kalpit Shah, 11Harper Forbes, 12Christian Hertig, 13Yiping Yan, 14Ralf Gutmer, 15Grant McArthur.

University of Colorado Comp. Cancer Ctr, Aurora, CO, USA; Gustave Roussy and Université Paris-Sud, Villejuif-Paris; Instituto do Câncer do Estado, São Paulo, Brazil; Oncoclinica, Móstoles, Spain; Hospital Universitario Virgen Macarena, Seville, Spain; University of Szeged Szent-Györgyi, Szeged, Hungary; IRCCS Istituto Europeo di Oncologia, Milan, Italy; Greater Poland Cancer Centre, Poznan, Poland; Genentech, Inc., South San Francisco, CA, USA; Harper Forbes, Ralf Gutzmer, Grant McArthur.

Background The phase 3 IMspire150 study (NCT02908672) showed that first-line atezolizumab (A) combined with vemurafenib (V) + cobimetinib (C) improved progression-free survival (PFS) vs placebo (P) + V + C in patients with BRAFV600 mutation–positive advanced melanoma (15.1 vs 10.6 months; hazard ratio [HR] 0.78; 95% CI 0.63–0.97; P=0.0249). Insights into the clinical benefit of the A+V+C triple combination in prognostic molecular subgroups of patients can inform treatment selection and future clinical research.

Methods 514 patients were randomized 1:1 to A+V+C (n=256) or P+V+C (n=258). The efficacy endpoints analyzed included PFS and duration of response (DOR) estimated using the Kaplan-Meier method. Outcomes were based on investigator-assessed best overall response per Response Evaluation Criteria in Solid Tumors v1.1. Patients were primarily categorized into binary subgroups defined by tumor mutation burden (TMB; low or high: <10 or ≥10 mutations/Mb, respectively) or by the < or ≥ median values.

Abstract 306 Figure 1 Mutation landscape by immune checkpoint inhibitor response. Mutational plot showing the most frequently mutated genes (top-to-bottom, ≥15%) ordered by response and by total number of SNVs, with gene frequency listed at left (%), and Fisher exact test p values (response versus no response) at right. Asterisks denote values less than 0.05 (significant before Bonferroni correction, for which cutoff for significance is 0.0001 for our panel of 447 genes). The bar graph at top shows the total number of panel single nucleotide variants detected per sample by mutation signature. Blank MCPyV and TMB denote unknown values.