Melanoma Research Updates from 2020 AACR and ASCO Conferences

Here are a few highlights related to melanoma from the first-ever Virtual AACR Annual Meeting and Virtual ASCO Annual Meeting.

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When the COVID-19 pandemic began to spread, many of us quickly shifted to a virtual world. Labs were slowed to essential work only, enrollments in clinical trials were paused and many healthcare workers were asked to turn their attention to the growing pandemic.

While many in-person meetings were cancelled, the two largest global cancer research conferences – AACR and ASCO – quickly shifted plans, taking thousand of participants on-line to hear the latest in cancer research.

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Melanoma Updates from the American Association for Cancer Research (AACR) Annual Meeting:

- Microbiome: Erin Shanahan of University of Sydney, reported on correlative studies being performed using specimens obtained from patients in an ongoing neoadjuvant trial testing different doses of ipilimumab + nivolumab (OpACIN-Neo trial). She analyzed the fecal microbiome of patients on the trial and found that microbial diversity could be used as a predictive biomarker of response. Low gut microbiome diversity was associated with pathological non-response and higher grade immune-related adverse events (irAEs) (3-5), whereas high microbial diversity was associated with pathological response and low grade irAEs (0-2). While intriguing, the overall number of patient specimens analyzed is small (n=42), so additional confirmatory studies are needed. MRA currently has two team-science awards funded on microbiome.

- New dosing schedule for pembrolizumab: Mallika Lala of Merck presented interim results from the Keynote 555 trial that tested a dosing schedule of pembrolizumab of 400mg every 6 weeks in patients with metastatic melanoma and compared the results with historical data using the current FDA-approved schedule of 200mg every 3 weeks. Only 44 patients were given the experimental dosing schedule, but the response and durability rates were similar in both groups. Based on these data, the FDA approved the 6 week/400mg schedule. The updated, every 6 weeks dosing schedule is especially relevant during the COVID19 pandemic to limit the number of trips a patient with melanoma has to make to receive infusions.
- Triple therapy with anti-PDL1, BRAKi, MEKi: Genentech presented preliminary results of the phase 3 IMspire 150 trialand reported the addition of the checkpoint inhibitor (atezolizumab) to the BRAF/MEK inhibitors vemuafenib + cobimetinib improved outcomes compared to BRAF/MEKi plus placebo in patients with newly diagnosed BRAF-mutant advanced melanoma. The triplet combination led to a median PFS of 15.1 months versus 10.6 months in patients receiving combination BRAF/MEK inhibition. This is the first reported data on a phase 3 trial of 'triplet therapy' in patients with melanoma.
- New immune checkpoint (anti-PVRIG): In a phase 1 study, Compugen's anti-PVRIG COM701 showed promise, stopping growth in two-thirds of 28 advanced cancer patients treated, who had exhausted all other treatment options. 16 patients with advanced cancers received COM701 on its own, while 12 received COM701 in combination with nivolumab. While this is an early stage study, the results are intriguing and the treatment warrants further study. Ryan Sullivan, an MRA-funded grantee from Massachusetts General Hospital, noted: "achieving durable disease, including partial responses, is remarkable in this population……Taken together, these results support further investigation of targeting PVRIG with COM701 and suggest that targeting the PVRIG/TIGIT pathways may broaden the patient population that can benefit from immunotherapies."

Melanoma Updates from the American Society of Clinical Oncology (ASCO) Annual Meeting:

- Recognizing 10 Leaders in Cancer Care and Research: The ASCO Post each year profiles leaders

in cancer care and research. MRA salutes the ten honored leaders this year, and is thrilled that four leaders involved in melanoma research are among those profiled – including Stephen Hodi (Dana-Farber Cancer Institute), Nobel Laureate William Kaelin (Dana-Farber Cancer Institute), Steven Rosenberg (National Cancer Institute), and Jedd Wolchok (Memorial Sloan Kettering Cancer Center).

- Systems biology approaches to immunotherapy response and toxicity: Using a 'Systems biology' approach, researchers expand their analysis beyond the tumor sample to include characteristics from the patient in order to develop a more complete picture of disease and treatment response. ASCO 2020 featured six presentations that integrated tumor and immune cell genomic, gene expression, and T cell repertoire analyses to develop a model to predict melanoma response to immune checkpoint inhibition (ICI). Additional studies presented examined (i) using gene-expression profiling to predict response to ICI, (ii) using an analysis of pre-treatment autoantibodies (that is, antibodies targeting self), or (iii) harnessing the power of artificial intelligence to predict response to immunotherapy and likelihood of experiencing immune-related toxicity.

    - Valsamo Anagnoustou (Johns Hopkins University) – in work co-authored with several MRA-engaged researchers including Suzanne Topalian, Drew Pardoll and Janis Taube – analyzed melanoma tumors and the immune system in 64 patients with melanoma treated with checkpoint immunotherapy as part of the CheckMate 038 clinical trial. By integrating multiple features of the tumor and the patient's immune system, the authors were able to classify patients as high-risk or low-risk of disease progression. Large scale validation studies are currently underway.

- Cell-based therapy in patients with advanced melanoma: Amod Sarnaik (Moffitt Cancer Center) presented results (presentations slides) on the long-term follow up of treatment with lifileucel (LN-144) cryopreserved autologous tumor infiltrating lymphocyte (TIL) therapy in patients with advanced melanoma who had previously progressed on multiple prior therapies. He noted of 66 evaluable subjects, 24 had an objective response (ORR 36.4%), which included

3% with complete responses and 33.3% partial responses. An additional 43.9% of patients had stable disease. Overall the TIL infusions were safe, with adverse events consistent with widespread underlying advanced disease and anticipated with the lymphodepletion and IL-2 regimens required for cell-based infusions. It should be noted that 2 patients died within 30 days of TIL infusion, one due to intra-abdominal hemorrhage and one from acute respiratory failure; it remains unclear if this was due to intervention or disease progression. He concluded that in this clinical trial of heavily pretreated patients with metastatic melanoma, lifileucel is associated with substantial number of responses and that the median duration of response had not yet been reached with a median follow-up of 18.7 months.

- Long-term survival following PD-1 therapy in patients with advanced melanoma compared to CTLA: MRA-funded researcher, Georgina Long, presented updated survival data from patients with advanced melanoma enrolled in the phase 3 KEYNOTE-006 study with an additional 8 months of follow-up, beyond the 5-year analysis. She reported that pembrolizumab improves the long-term survival versus ipilimumab as second line therapy in patients with advanced melanoma, with 5-year overall survival of 32% for pembrolizumab and 27% with ipilimumab. It was further noted that for the 30 patients who completed first-line therapy with pembrolizumab as scheduled for 2 years and experienced a complete response, all of these patients were alive at 5 years. She concluded that pembrolizumab improved the overall survival compared to single-agent ipilimumab in patients with advanced melanoma regardless of their line of treatment.

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