Summary of 13th Annual MMIG Meeting

(Merkel cell carcinoma Multi-Center Interest Group)

Friday February 16, 2018

American Academy of Dermatology Annual Meeting

San Diego, CA

Prepared by Drs. Song Park, Paul Nghiem, and Hannah Thomas

Announcements:

1) If you are interested in presenting at next year's MMIG meeting in Washington, D.C., on Friday March 1st, 2019 (5 – 7 pm), please send Paul an email (pnghiem@uw.edu) with a proposed topic that is relevant to MCC patient care or translational research.

Speakers/Topics (detailed in following pages):

1. **Developing alternatives and adjuvants to checkpoint inhibition for MCC**
   Isaac Brownell (National Cancer Institute)

2. **Lessons from the Mole Mapper Mobile App Project: Possibilities & Pitfalls for MCC**
   Sancy Leachman (Oregon Health Sciences University)

3. **Updates on lymph node dissection vs. nodal radiation from the Michigan cohort**
   Kelly Harms (University of Michigan)

4. **Unknown primary MCC: Immunobiology and integration into the new AJCC staging system**
   Paul Nghiem (University of Washington)

5. **Immune therapy clinical trials in MCC in the metastatic and adjuvant settings**
   Song Park (University of Washington)

6. **Proposals for a national MCC registry and clinical trials platform**
   Mike Wong (MD Anderson)

1. **Developing alternatives and adjuvants to checkpoint inhibition for MCC**
   Isaac Brownell (NCI)

Dr. Brownell reviewed current and potential alternative immune and targeted therapies for MCC.

Although PD-(L)1 blocking agents demonstrated superior responses compared to chemotherapy, they are not as helpful for patients with contraindications to the drug, such as immunosuppression or severe autoimmune disease. Moreover, approximately 40% of patients who are treated with PD-(L)1 blocking agents do not respond to treatment, and a significant portion of the responders develop secondary resistance later.

In an effort to improve this response rate, various combination therapies with immune checkpoint inhibitors (ICI) are being investigated. Dr. Brownell reviewed them based on the rationale/mechanism and suggested potential new combinations. Combination of drugs targeting different immune checkpoints, such as CTLA-4, is one leading possibility. Treatment which enhances antigen presentation, by MHC upregulation (e.g. HDAC inhibitors, thalidomide analogues), radiation treatment, or oncolytic vaccine (e.g. T-VEC), can be combined with ICI. Immune adjuvants such as TLR agonists (e.g. resiquimod, poly-ICLC), contact sensitizers (e.g. DPCP), pro-inflammatory cytokines (e.g. IL-12, IFN, GM-CSF, IL-2), or inhibitors of anti-inflammatory cytokines (e.g. TGF-beta), are other possible combinations. Therapeutic vaccines, antibody drug conjugates, and CD47 blockade are also being investigated. ICI combined with cell-based therapies such as NK cells and autologous/transgenic T cells are also being explored. Combining ICI with targeted therapy such as chemotherapy, PI3K inhibitor, cabozantinib, somatostatin analogues, or mTOR inhibitors could be considered, and some of those combinations are being investigated for other cancers.

Dr. Brownell revisited the idea of high throughput small-molecule and RNAi screening to develop new treatment options for MCC, which he presented at last year's MMIG meeting. His team has identified multiple therapeutic targets including a nanoparticle kinase inhibitor. The novel kinase inhibitor showed efficacy and a favorable safety profile in a mouse model and they hope to translate this agent to a clinical trial.

In summary, while it is known that MCC is sensitive to PD-(L)1 blockade, we need new treatments to improve response rates and help patients with contraindications to PD-(L)1 blockade. Various combination treatments are possible, and new agents, including kinase inhibitors, are being investigated.

2. **Lessons from the Mole Mapper Mobile App Project: Possibilities & Pitfalls for MCC**
   Sancy Leachman (OHSU)

   Mole Mapper is a cell phone app that tracks moles and how they change and grow over time using the phone camera. It tracks rapid change or growth of moles and reminds the user to re-check the moles regularly. Through this, Mole Mapper provides individual users and clinicians quantitative information on the change of the mole. It also helps researchers gather crowdsource data for melanoma research. By analyzing mole images over time, researchers can develop new ways of evaluating moles.

   In order to use the app as a research tool, Dr. Leachman and team have built an infrastructure that helps run a research study through a phone, which performs participant surveys, keeps the de-identified data safe, and can link data with PHI to communicate with the participants via the app.

   We shared ideas about how we might utilize the infrastructure of Mole Mapper in Merkel cell carcinoma research and community activity, noting there are many differences between melanoma and MCC. These include the fact that MCC does not have distinctive clinical features or precursor lesions. A crowdsource app for MCC would thus focus more on tracking experiences and connecting patients who were already diagnosed with MCC.

   - Original publication from Dr. Leachman
     Webster DE et al., The Mole Mapper Study, mobile phone skin imaging and melanoma risk data collected using ResearchKit, Sci Data. 2017 Feb
     https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5308198/

   - Other Relevant links
     http://www.ohsu.edu/xd/health/services/dermatology/war-on-melanoma/mole-mapper.cfm
     https://itunes.apple.com/us/app/mole-mapper-melanoma-study/id1048337814?mt=8
     https://play.google.com/store/apps/details?id=edu.ohsu.molemapper&hl=en

3. **Updates on lymph node dissection vs. nodal radiation from the Michigan cohort**
   Kelly Harms (U of Michigan)

   Dr. Harms shared preliminary unpublished data from the Michigan cohort. Her team analyzed a cohort of 163 patients with stage IIIA disease. Therapeutic management with lymph node dissection versus nodal radiation were discussed; and prognostic factors based on histopathologic parameters were presented.

   - Other relevant publications:

     Iyer et al., Relationships among primary tumor size, number of involved nodes, and survival for 8044 cases of Merkel cell carcinoma, J Am Acad Dermatol. 2014 Apr;70(4):637-43.

4. **Unknown primary MCC: Immunobiology and integration into the new AJCC staging system**
   Paul Nghiem (University of Washington)

   Dr. Nghiem's team performed a study of unknown primary MCC (UP-MCC) patients and discovered that those patients have elevated markers of immunity, higher tumor mutation burden, and improved survival.

   Patients presenting with MCC-UP are nearly twice as likely to survive compared with similarly staged patients with known primary lesions (MCC-KP). This finding has been reflected in the 8th edition AJCC staging system, and MCC-KP, which used to be "IIIB" disease, is now classified as "pathologic stage IIIA" disease in the 2018 new staging system (8th edition).

   To study the immunobiology of this previously reported finding, Dr. Nghiem's team performed survival analyses and markers of immunity for 123 patients with advanced MCC from the Seattle cohort.

   As in prior studies, patients with nodal MCC-UP had strikingly improved MCC-specific survival as compared with MCC-KP patients. Surprisingly, patients presenting with distant metastatic MCC-UP also had significantly improved survival (HR, 0.296; P = 0.038). None of the 72 patients with MCC-UP were immunosuppressed as compared to 12 of the 51 (24%) patients with MCC-KP (P < 0.001). MCPyV oncoprotein antibody median titer was higher in MCC-UP patients (26,229) than MCC-KP patients (3,492; P < 0.001). In addition, the median number of nonsynonymous exome mutations in MCC-UP tumors (688 mutations) was markedly higher than MCC-KP tumors (10 mutations, P = 0.016).

In summary, in this cohort, MCC-UP patients were never immune suppressed, had higher oncoprotein antibody titers, and higher tumor mutational burdens. In addition, nodal tumors identified in MCC-UP patients did indeed arise from primary skin lesions as they contained abundant UV-signature mutations. **These findings suggest that stronger underlying immunity against MCC contributes to primary lesion elimination and improved survival.**

- Original publication from Natalie Vandeven and Dr. Nghiem
  Vandeven N et al., Merkel Cell Carcinoma Patients Presenting Without a Primary Lesion Have Elevated Markers of Immunity, Higher Tumor Mutation Burden, and Improved Survival, Clin Cancer Res. 2018 Feb 15;24(4):963-971

5. **Immune therapy clinical trials in MCC in the metastatic and adjuvant settings**
   Song Park (University of Washington)

Dr. Park reviewed ongoing immune therapy clinical trials in MCC.

PD-1 axis blocking agents are now considered to be the first line treatment option for metastatic MCC. Patients who present with clinically positive nodal disease are also known to have a very high risk of recurrence, but currently we have no data as to whether adjuvant PD-1 axis blockade will lower the recurrence rate for those patients. The Adjuvant avelumab in Merkel cell carcinoma trial (ADAM trial) was designed to assess this issue. To be eligible, patients should complete surgery ± adjuvant XRT with no evidence of disease at the time of enrollment. Patients will be randomized into treatment or placebo arms, and the trial will treat the patient for up to 2 years or until relapse or unacceptable toxicity develops. The medication or placebo will be given every 15 days for the first 4 months, then every 1 month for the next 4 months, then every 4 months until 24 months. The trial was opened in Seattle in 12/2017, and more sites will be added soon.

Regarding status of clinical trials for metastatic MCC, in clinicaltrials.gov, there were 23 active trials as of 2/9/2018. 18 of them involved a checkpoint inhibitor, and 20 trials allow prior systemic treatment including immunotherapy. Anti-PD-1 or PD-L1 antibody monotherapy studies are still ongoing in various settings, and 1st or 2nd line checkpoint blockade combination therapies are available in many locations.

- More information about ADAM trial available
  https://clinicaltrials.gov/ct2/show/NCT03271372

6. Proposals for a national MCC registry and clinical trials platform

Mike Wong (MD Anderson)

Dr. Wong presented his vision for a multicenter registry/central database and modular trial design among MCC experts.

Based on prior successful modular trials run by Pediatric Oncology Group / Children's Oncology Group, Dr. Wong envisions that modular trials will include a consensus on the priority questions, definition of 'success' (e.g. response rate, OS, PFS), inclusion/exclusion criteria, how to handle exceptions (e.g. brain metastasis), toxicity management, frequency of monitoring and evaluations, etc.

With modular design, we can go through the IRB process more quickly and present a focused vision to pharmaceutical / biotech companies. Modular trial design promotes effective and efficient testing of hypotheses and concepts. Modular trials with larger numbers of patients nationwide can potentially expose regional differences in disease biology and response to therapy.

Dr. Wong mentioned that we are already seeing the movement to modular trials in melanoma and other cancers. Trial protocols are getting more similar and handle issues such as inclusion / exclusion criteria and autoimmune toxicity in a similar way. Modular trials will have similar baseline inclusion/exclusion criteria, surgical, XRT procedure, medical therapy, and evaluations.

Regarding central databases and registries, Dr. Wong introduced several examples of other diseases including PROCLAIM, which was originally established for FDA compliant use of IL-2 in melanoma and renal cell carcinoma. This database has now expanded beyond the original purpose to other drugs and disease. Essential tasks for central databases include establishing a purpose, definitions of terms, a charter and a steering committee, rules of access.

In this project, MCC providers, pharmaceutical partners, philanthropic organizations, advocacy groups, granting agencies, as well as MCC patients will play important roles.

In attendance at the 2018 San Diego MMIG meeting

Afanasiev, Olga (Stanford)
Akaike, Tomoko (University of Washington) *
Berg, Dan (University of Washington)
Bickakjian, Chris (University of Michigan)
Brownell, Isaac (NIH)
Baker, Mairead (NIH)
Choi, Jaehyuk (Northwestern University Feinberg School of Medicine)
Freeman, Morganna*
Frezza, Michael (EMD Serono)
Gardner, Jennifer (University of Washington)
Harms, Kelly (University of Michigan)
Inoue, Takuya (Japan)*
Iyer, Jayasri (University of Washington)
James, Natalia (U Miami)
Kim, Anna (University of South Florida)
Leachman, Sancy (OHSU)
Leetouni, Hathalic (UACC, Phoenix)
Lemos, Bianca (Kaiser)
Locker, Michael (EMD serono)
Mahay, Heidi (EMD serono)
Miller, David (BIDMC/MGH, Harvard)
Nagase, Kotaro (Japan)*
Nghiem, Paul (University of Washington)
Park, Song (University of Washington)
Shantha, Erica (University of Washington)
Silk, Ann*
Somani, Ally (IU Indiana)
Soon, Seaver (Scripps Clinic)
Sunshine, Joel (Northwestern University Feinberg School of Medicine)
Tai, Patricia*
Turaka, Aruna*
Vanderven, Natalie (University of Washington)*
Weiss, Jonathan (Beth Israel Deaconess)
Wong, Michael (MD Anderson)
Yu, Siegrid (UCSF)
Zeitouni, Nathalie (University of Tucson)

*Joined online via GoToMeeting

Goals of the Merkel cell carcinoma Multi-center Interest Group (MMIG)
- Promote communication and collaborative studies on MCC
- Enhance access to patient data and specimens
- Expand evidence-based care for MCC

The homepage for MMIG is available at:
https://www.merkelcell.org/about-us/mmig/

MMIG is funded in part by donations from Merkel cell carcinoma patients.
Please note that in many cases, these summaries reflect unpublished data and are provided to help MMIG members manage their patients and give an overview of what is being done at different centers for care and research.