Summary of 12th Annual MMIG Meeting  
(Merkel cell carcinoma Multi-center Interest Group)  
Friday March 3, 2017  
American Academy of Dermatology Annual Meeting  
Orlando, FL  
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 San Diego, California on Friday February 16th, 2018 (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. Determining if a subsequent MCC is a second primary or a metastasis: How & why to answer the question  
   Kelly Harms (University of Michigan)  
2. Optimizing surveillance for MCC using new relapse-free survival data & oncoprotein antibodies  
   Paul Nghiem (University of Washington)  
3. Does tumor viral status predict drug response in vitro?  
   Isaac Brownell (NIH)  
4. Immune Therapy Clinical Trials in Merkel Cell Carcinoma: Updates  
   Song Park (University of Washington)  
5. Do we need a “network” for clinical trials in MCC?  
   Mike Wong (MD Anderson)
1. Determining if a subsequent MCC is a second primary or a metastasis: How & why to answer the question
Kelly Harms (University of Michigan)

Drs. Harms and Bichakjian’s team performed a study of the genetic similarity between four pairs of the primary and subsequent MCCs.

From the MCC database at Michigan Medicine, 4 cases were identified with clinical designation of “2nd primary” MCC and sufficient tumor volume for the study. Next-generation sequencing (NGS) was used to determine if the 2 tumors were clonally related (thus metastatic) or genetically distinct (thus a true 2nd primary tumor). NGS of 409 cancer relevant genes were analyzed for similarity index of copy number alterations (CNA) and specific mutations, where high similarity index indicates high proportion of CNA or specific mutations shared between the two tumors.

Similarity index for CNA of the studied cases showed high similarity for 2 cases (2, 3) and low similarity for the other 2 cases (1, 4). Similarity index for specific mutations showed none of the four pairs had shared specific point mutations for all 4 cases, suggesting that copy number alterations may be a more consistent predictor of clonal relatedness than sequencing of the targeted cancer related genes.

Interestingly, in all cases, the subsequent tumor from a given patient had the same viral status, suggesting that, within each patient, the subsequent tumors are induced by the same pathway (UV vs. viral).

Multiple MCC primaries is rare but possible, representing 1.5 percent of the MCC patient population. If the clinical scenario suggests a 2nd primary MCC, we would treat it as a primary lesion with excision and staging with SLNB. Molecular studies may help to distinguish whether the tumor is a metastasis or indeed a 2nd primary.

- Original publication from Dr. Harms
Harms K et al, Molecular profiling of multiple primary Merkel Cell Carcinoma to distinguish genetically distinct tumors from clonally related metastases, JAMA dermatolol. JAMA Dermatol. Published online April 12, 2017.

- Other relevant publications:

Eluri M et al, Multiple Merkel cell carcinomas: Late metastasis or multiple primary tumors? A molecular study, JAAD Case Rep. 2017 Mar 20;3(2):131-134
2. Optimizing surveillance for MCC using new relapse-free survival data & oncoprotein antibodies
Paul Nghiem (University of Washington)

Recurrence data for MCC on a stage-specific basis has not been available in the past. Such data can be very useful in patient management, especially 1-2 years after the diagnosis when residual risk begins to decrease, and decisions should be made about follow-up and scan frequency. Although not yet peer-reviewed and “published”, these data are now available at http://www.merkelcell.org/prognosis.

The MCPyV specific oncoprotein antibody titer test, which was developed in 2010, also can be used for improving management of MCC. In a prospective validation study of 219 patients, this test was useful regardless of whether patients did or did not make antibodies. Seronegative patients were at a 42% increased risk of recurrence and thus need to be followed quite closely with imaging studies, as the antibody test would not be useful for ongoing surveillance. Seropositive patients whose titer decreased over time had a 97% chance of being free of detectable disease at the time of blood draw. In contrast, if the oncoprotein antibody titer increased, 88% of patients either had detectable disease at the time of blood draw or, in some cases, an increase in antibody titer preceded the clinical detection of tumor by many months. In seropositive patients, disease status can be tracked by oncoprotein antibody titer, and potentially decrease the frequency of scans. More information on this test is available at https://merkelcell.org/testing-and-diagnosis/serology/

3. Does tumor viral status predict drug response in vitro?
Isaac Brownell (NIH)

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Drs. Gelb and Brownell investigated drug candidates to identify the pathophysiology underlying MCPyV positive and MCPyV negative MCC and develop new treatment options for MCC patients. As nearly half of MCC patients are either ineligible or unresponsive to PD1 pathway inhibitors, the need for novel therapies remains great. In collaboration with the National Center for Advancing Translational Sciences (NCATS) two drug libraries were screened, the NCATS Pharmaceutical Collection of 2,400 approved drugs, and the Mechanism Interrogation PlatE (MiPE) (~1,900 clinically-relevant, oncology-focused, and mechanistically annotated compounds). High throughput drug screening identified agents that reduce MCC viability for 3 virus-positive and 3 virus-negative cell lines. ~4,300 compounds from both libraries were screened for 11 concentrations each, by observing cell viability after 72 hours using CellTiter-Glo (luminescence).

MCPyV positive and negative MCC cells clustered distinctly in drug response,
suggesting biological differences between MCPyV positive and negative MCC. In addition, some agents were effective for all MCC cell lines. For example, topoisomerase inhibitors showed activity for both MCPyV positive and negative MCC cells, while apoptosis-inducers were selective for MCPyV positive cells. A RASGAP/ERK inhibitor was selective for MCPyV negative cells. Interestingly, among topoisomerase inhibitors, topotecan (topo I inhibitor), which is used as a salvage treatment, showed better potency and efficacy for all cell lines than etoposide (topo II inhibitor), which is used as a first-line agent for neuroendocrine carcinomas in general, suggesting the possibility of using topotecan as first-line treatment instead of as salvage. An apoptosis-inducer potently and selectively reduced MCPyV positive MCC cell viability through induction of intrinsic apoptosis, and the drug’s target was overexpressed in MCPyV positive MCC. This implies that MCPyV positive MCC cells use a distinct and druggable mechanism to evade apoptosis. Dr. Brownell’s team also performed screenings for synergistic effects between apoptosis inducers and MiPE library compounds at different dose combinations. From this study, they found that CDK inhibitors were synergistic with apoptosis-inducers in both MCPyV positive and negative MCC.

In conclusion, this study demonstrated that viral status impacts single-agent response in MCC, and specific drug combinations synergize in both MCPyV positive and negative MCC cells. Combining apoptosis-inducers and CDK inhibitors may be a novel therapeutic option for MCC patients.

4. Immune Therapy Clinical Trials in Merkel Cell Carcinoma: Updates
Song Park (University of Washington)

Dr. Park reviewed 6 ongoing immune therapy clinical trials in MCC.

The pembrolizumab (anti PD-1) trial, which is the first study of immune checkpoint blockade in MCC, showed a 56% response rate and 67% progression free survival at 6 months in the initial study. This result prompted recommendation of pembrolizumab for the treatment of disseminated disease in the 2017 NCCN guidelines. The trial was expanded to include 50 patients from over 25 sites, and all of the slots were taken or reserved as of 4/11/2017. The avelumab (anti-PDL1) study used the drug as a 2nd line therapy for patients with distant metastatic, chemotherapy-refractory MCC, and showed a 32% response rate. (Happily, this drug was FDA approved for metastatic MCC on March 23, 2017). Currently, a trial using avelumab in the 1st line is enrolling. The nivolumab trial has multiple arms, including monotherapy, combination treatment with ipilimumab, and neoadjuvant treatment arms. The ipilimumab and nivolumab combination arm is now open. The clinical trial combining adoptive T -cell therapy with avelumab targets multiple interactions between the tumor and the T cells by using autologous MCPyV specific T cells, MHC I up-regulation with radiation or interferon, and avelumab as triple
therapy. The NK-92 trial utilizes irradiated natural killer cells together with a modified version of IL-15. Lastly, the adjuvant PD-L1 trial in MCC is now under development, and will likely be the first phase 3 randomized clinical trial in MCC in the US. Knowing that MCC has high a risk of recurrence and distant metastasis, we suspect there may be a beneficial role for adjuvant use of immunotherapy.

Multiple immunotherapy trials are available now at many sites. And more trials are in the pipeline to open in the near future.

**Links to Clinical Trials in MCC:**
Avelumab: [https://clinicaltrials.gov/ct2/show/NCT02155647](https://clinicaltrials.gov/ct2/show/NCT02155647)
Pembrolizumab: [https://clinicaltrials.gov/ct2/show/NCT02267603](https://clinicaltrials.gov/ct2/show/NCT02267603)
Avelumab and Adoptive T cells: [https://clinicaltrials.gov/ct2/show/NCT02584829](https://clinicaltrials.gov/ct2/show/NCT02584829)
Nivolumab: [https://clinicaltrials.gov/ct2/show/NCT02488759](https://clinicaltrials.gov/ct2/show/NCT02488759)
NK-cells: [https://clinicaltrials.gov/ct2/show/NCT02465957](https://clinicaltrials.gov/ct2/show/NCT02465957)

5. **Do we need a “network” for clinical trials in MCC?**
Mike Wong (MD Anderson)

Dr. Wong presented his vision for a network and modular trial design/operation among MCC experts. There are only a small number of MCC patients, and drug companies do not have a deep understanding of this disease. Therefore, patients in great need are not well served by multiple competing approaches to the same problem, we are unable to run trials in a timely manner, trials do not have enough statistical power to properly answer the hypothesis and are unable to pool enough specimens to run biomarker studies.

We could overcome these limitations by creating a modular clinical trial design, a clearing house for trials, a formal network of centers (investigators) interested in MCC clinical trials, and a centralized registry for patients. Dr. Wong envisions that modular trials will be constituted with consensus on target population, inclusion/exclusion criteria, screening, ‘intervention’, trial conduct - scans, labs, biopsy, statistical analysis, follow up care, registry, etc. The ‘intervention’ portion would be modified for each treatment option. To run such modular trials, we need to agree on what is high risk disease, best practice, real world practice, where we deviate, and the statistical threshold for a ‘signal’. With this modular design, we could go through the IRB process more quickly and use the small number of MCC patients nationally. It lowers the barrier to individual investigator, enabling even ‘smaller’ institutions to be involved thereby expanding the pool of patients and MCC investigators. We will get better and better at doing MCC trials as those processes are iterative. If all trials are the same, we know what to expect and can pick up small changes. But with this network and a modular trial design, the allocation of credit, individual budget, protection of intellectual property will become more challenging,
requiring consensus before action. And it will be difficult to mix and match different therapies.

On the consensus for the necessity of a network and modulated trials we should act now. We can do virtual meetings, develop milestones and goals and get funded.
In attendance at the 2017 Orlando, FL MMIG meeting:
Afanasiev, Olga (Stanford)
Akaike, Tomoko (St. Luke International Hospital, Japan)
Bickakjian, Chris (University of Michigan)
Brownell, Isaac (NIH)
Choi, Jaehyuk (Northwestern University Feinberg School of Medicine)
Colunga, Aric (University of Washington)
Gao, Ling (UAMS)
Gorgun, Cem (EMD Serono)
Guilherme, Rabinowits (DF/HCC)
Guitera, Pascale (Sydney University, Australia)
Harms, Kelly (University of Michigan)
Huang, Victor (BWH/DFCI, Harvard)
Inoue, Takuya (Japan)*
Messina, Jane (Moffitt)
Miller, David (BIDMC/MGH, Harvard)
Nagase, Kotaro (Japan)*
Nghiem, Paul (University of Washington)
Nguyen, Jannett (NIH)
Park, Song (University of Washington)
Russell, Jeff (Moffitt)
Schoenfeld, Jason (University at Buffalo)
Soon, Seaver (Scripps Clinic)
Su, Zhen (EMD serono)*
Thomas, Hannah (University of Washington)*
Vanderven, Natalie (University of Washington)*
Wang, Richard C. (UT Southwestern)*
Weiss, Jonathan (Lahey Clinic)
Wong, Michael (MD Anderson)
Yu, Siegrid (UCSF)
Zeitouni, Nathalie (University of Tucson)
Zhang, Lin (EMD Serono)

*Joined online via GTM

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:
http://merkelcell.org/MMIG.html

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.