Summary of 15th Annual MMIG Meeting

(Merkel cell carcinoma Multi-center Interest Group)

Friday, June 4th, 2021

Virtual event (Zoom)

Prepared by:

Lauren Zawacki, Candice Church, Kelsey Cahill, Krista Lachance and Paul Nghiem

Announcements:

1) First MMIG meeting over Zoom- highest number of attendees (see pages 5-8)!

2) If you would like to view the meeting recording, please contact Krista Lachance (kcs27@uw.edu)

3) Please contact Paul Nghiem (pnghiem@uw.edu) or Krista Lachance (kcs27@uw.edu) if you would like to present at next year's meeting.

Speakers/Topics (detailed in following pages):

1. **Introduction of Polish MCC collaborators**
   Monika Dudzisz-Śledź and Piotr Rutkowski (Maria Sklodowska-Curie National Research Institute of Oncology)
2. **Molecular characterization of classical and variant MCC cell lines**
   Jürgen Becker (University of Duisburg-Essen)
3. **Repurposing Disulfiram for the treatment of MCC**
   Natasha Hill (National Institutes of Health)
4. **Immunotherapy responders after treatment discontinuation: A potentially concerning recurrence rate?**
   Yassi Moshiri (University of Washington)
5. **Circulating tumor DNA as a biomarker for MCC tumor burden**
   Lisa Zaba (Stanford University)
6. **MDM2 Inhibitor [KRT-232] Therapy in p53 WT MCC Patients Refractory to PD-1/L1 Immunotherapy: preliminary results and observations**
   Michael Wong (MD Anderson Cancer Center)
7. **Brainstorming session for the 2nd International MCC Symposium**
   Paul Nghiem (University of Washington)

1. **Introduction of Polish MCC collaborators**
   Monika Dudzisz-Śledź and Piotr Rutkowski (Maria Sklodowska-Curie National Research Institute of Oncology)

   - Multi-center collaboration (Warsaw, Wroclaw, Gliwice & Cracov, Poland)
   - Retrospective study on locally advanced and metastatic/ unresectable MCC
     - Locally Advanced (n=161)
       - Perioperative radiotherapy improves treatment outcomes and reduces disease progression but does not impact overall survival
       - Male gender, nodal involvement at diagnosis, the absence of SLNB in patients without clinical metastasis in lymph nodes were associated with lower disease specific survival and overall survival
     - Metastatic/ Unresectable MCC (N=36)
       - Prognosis of these patients is poor and avelumab in the 2nd line allows achieving better results, which are similar to clinical trial results
   - Plan to submit study findings to a journal

2. **Molecular characterization of classical and variant MCC cell lines**
   Jürgen Becker (University of Duisburg-Essen)

   - Variant MCC (vMCC) cell lines: grow adherently and lack neuroendocrine markers such as chromogranin A[1]
   - Classical MCC (cMCC) cell lines: have neuroendocrine growth pattern and grow in suspension as loose or compact spheroids[1]
   - Clustering of mRNA & miRNA expression and DNA methylation suggest that vMCCs have closer gene signatures to SCC, when compared to cMCCs
   - Despite similarities between vMCCs and SCCs they still exhibit clear differences:
     - Canonical Head & Neck SCC marker, miR-205, is not expressed in vMCCs
     - In contrast to SCCs, vMCCs have a low expression of E-cadherin
   - CMCCs and vMCCs may represent two distinct states or different forms of neoplastic transformation; specifically, hypermethylation of the neuroendocrine genes HES6 and INSM1, and intermediate expression of ISL1 and CHGA suggest that vMCCs may be locked in an incomplete neuroendocrine transformation process.

[1] Gravemeyer J, Lange A, Ritter C, et al. Classical and Variant Merkel Cell Carcinoma Cell Lines Display Different Degrees of Neuroendocrine Differentiation and Epithelial-Mesenchymal Transition. *J Invest Dermatol*. 2021;141(7):1675-1686.e4. doi:10.1016/j.jid.2021.01.012

3. **Repurposing Disulfiram for the treatment of MCC**
   Natasha Hill (National Institutes of Health)

- National Center for Advancing Translational Sciences (NCATS) High-throughput Drug Screen
    - Disulfiram selectively reduces MCC cell viability
        - Disulfiram: binds and inhibits aldehyde dehydrogenase (anti-MCC activity likely due to off-target effects)
- Copper (Cu) increases disulfiram potency in MCC
    - Combination is cytostatic and cytotoxic
    - Disulfiram and copper do not induce apoptosis
- Potential mechanism for disulfiram + Cu anticancer activity:
    - Synergizes with etoposide (VP16) in MCC
    - Induce autophagy and immunogenic cell death
- Small clinical trial with disulfiram / Cu plus avelumab
    - Disulfiram 500 mg PO daily (patients must abstain from alcohol use)
        - If not tolerated, dose reduce in 125 mg increments.
    - 2 mg of Copper as Copper Gluconate daily with meal (OTC supplement)
    - Disulfiram / Cu plus VP16 possible PO combination for patients who fail immunotherapy or can't reach infusion center.

4. **Immunotherapy responders after treatment discontinuation: A potentially concerning recurrence rate?**
   Yassi Moshiri (University of Washington)

- Frequent MCC recurrences post-immunotherapy (IMTX) discontinuation
- Study aims to assess MCC recurrence risk after discontinuation of IMTX in a Seattle based cohort (N=183)
- Overall response rate of 60% is comparable to prior first-line IMTX clinical trials (of note, this cohort includes immune-suppressed pts, that were not included in trials)
- Continuing IMTX is associated with lower risk of MCC recurrence
- Those with complete responses tended to have fewer recurrences after d/c of immuno-tx compared to patients with progressive disease
- Risk of MCC recurrence after IMTX discontinuation is greater than for melanoma

5. **Circulating tumor DNA as a biomarker for MCC tumor burden**
   Lisa Zaba (Stanford University)

   - No clinically available blood test that provides recurrence monitoring data for all patients regardless of Merkel polyomavirus serologic status
   - Study aimed to see if circulating tumor DNA (ctDNA) can be used as a biomarker to detect MCC recurrences (n=25)
   - ctDNA tracking can be useful for MCC pts regardless of tumor viral status
     - Currently looking at correlation between tumor size and level of ctDNA
   - 6 sites are now or will soon open for multi-center study
   - Contact Lisa Zaba (lisa.zaba@stanford.edu) if you would like to utilize the ctDNA test for your MCC patients

6. **MDM2 Inhibitor [KRT-232] Therapy in p53 WT MCC Patients Refractory to PD-1/L1 Immunotherapy: preliminary results and observations**
   Michael Wong (MD Anderson Cancer Center)

   - 1st clinical proof-of-concept for inhibiting the MDM2 pathway in p53(wt) MCC
   - Safety and efficacy data continue to inform KRT-232 dose and schedule optimization
   - Opportunity exists to explore combination approaches of KRT-232 and anti-PD-1/L1 agents
   - Preliminary evidence suggests encouraging benefit in a subset of patients
   - New combination arm with avelumab has been added for patients with p53 (wild type) metastatic MCC who are anti-PD-1/L1 treatment-naïve

7. **Brainstorm session on 2nd International MCC Symposium**

   Paul Nghiem (University of Washington)

   - Seattle MCC team will host; likely in a warmer climate (during winter)
   - Aiming for first or second quarter of 2022 for a two-day event
   - Survey was sent out to MMIG members, but if you did not fill it out there is still time to do so! https://forms.gle/xAGDXvcEyu4Hf9zG8

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

Homepage for MMIG is available at: https://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.

In attendance (n=104) at the 2021 Virtual MMIG Meeting:

Akaike, Tomoko	University of Washington, Seattle, US
Ananthapadmanabhan, Varsha	Dana-Farber Cancer Institute, Boston, US
Asioli, Sofia	University of Bologna, Bologna, Italy
Becker, Jurgen C	German Cancer Center Consortium, Essen, Germany
Berry, Liz	Oregon Health & Science University, Portland, US
Bhatia, Shailender	University of Washington, Seattle, US
Bierma, Marika	University of Washington, Seattle, US
Blom, Astrid	Ambroise Pare Hospital, Boulogne, France
Bollin, Kathryn	Scripps MD Anderson, San Diego, US
Brodey, Philip	San Francisco, US
Brownell, Isaac	National Institutes of Health, Bethesda, US
Butler, Marcus	Ontario Institute for Cancer Research, Toronto, Canada
Cahill, Kelsey	University of Washington, Seattle, US
Chandra, Sunandana	Northwestern University, Chicago, US
Cherny, Shira	University of Washington, Seattle, US
Choi, Jaehyuk	Northwestern University, Chicago, US
Daud, Adil	University of California, San Francisco, US
DeCaprio, Jim	Dana-Farber Cancer Institute, Boston, US
Devlin, Phillip	Dana-Farber Cancer Institute, Boston, US
Dlugosz, Andrzej A	University of Michigan, Ann Arbor, US

Doolittle-Amieva, Coley	University of Washington, Seattle, US
Dudzisz Sledz, Monika	Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
Duprat, Joao	A C Camargo Cancer Center, Sao Paulo, Brazil
Fecher, Leslie	University of Michigan, Ann Arbor, US
Fischer, Nicole	University Medical Center, Hamburg Eppendorf, Germany
Fonseca, Allene	University of Washington, Seattle, US
Friedlander, Phillip	Mount Sinai Hospital, New York, US
Frost, Thomas	
Gao, Ling	Long Beach VA / University of California, Irvine, US
Garman, Khalid	National Institutes of Health, Bethesda, US
Gastman, Brian	Cleveland Clinic, Cleveland, US
Gunnell, Lindsay	University of Washington, Seattle, US
Harms, Paul	University of Michigan, Ann Arbor, MI
Harwood, Catherine	University of London, London, UK
Hausen, Axel zur	Maastricht University, Maastricht, Netherlands
Herrera-Martinez, Miguel	University of Tennessee, Memphis, US
Hill, Natasha	National Institutes of Health, Bethesda, US
Hippe, Dan	Fred Hutchinson Cancer Research Center, Seattle, US
Hsu, Charles	University of Arizona Cancer Center, Tucson, US
Huang, Victor	University of California, Davis, US
Iyer, Jayasri	The Everett Clinic, Bothell, US
Jani, Saumya	University of Washington, Seattle, US
Jing, Lichen	University of Washington, Seattle, US
Koelle, David	University of Washington, Seattle, US
Kulikauskas, Rima	University of Washington, Seattle, US
Lachance, Krista	University of Washington, Seattle, US
Lee, Katie	
Lee, Junghyun	University of Washington, Seattle, US
Lewis, Karl	University of Colorado, Denver, US

Liao, Yi-Hua	National Taiwan University Hospital, Taipei, Taiwan
Lin, Anna	
Lobo, Matheus	A C Camargo Cancer Center, Sao Paulo, Brazil
Masuccim, Giuseppe	Karolinska University Hospital, Stockholm, Sweden
Mechling, Beth	Kartos Therapeutics
Mehmi, Inder	The Angeles Clinic and Research Institute, Los Angeles, CA
Miao, Lingling	National Institutes of Health, Bethesda, US
Miller, David	Massachusetts General Hospital, Boston, US
Morningstar, Carina D	University of Washington, Seattle, US
Morris, Valerie	EMD Serono
Moshiri, Yassi	University of Washington, Seattle, US
Nakamura, Motoki	Nagoya City University, Nagoya, Japan
Nghiem, Paul	University of Washington, Seattle, US
Park, Song	University of Washington, Seattle, US
Park, Soo	University of California, San Diego, US
Parvathaneni, Upendra	University of Washington, Seattle, US
Patil, Supriya	Fred Hutchinson Cancer Research Center, Seattle, US
Pfohler, Claudia	Saarland University Medical School, Homburg, Germany
Rabinowits, Guilherme	Miami Cancer Center, Miami, US
Rady, Peter	McGovern Medical School, Houston, US
Reddy, Sunil	Stanford Medical Center, Palo Alto, US
Reed, Danielle	
Reinstein, Zachary	Northwestern University, Chicago, US
Rodriguez, Juan	EMD Serono
Rutkowski, Piotr	Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
Saiag, Philippe	Ambroise Pare Hospital, Boulogne, France
Samlowski, Wolfram	Comprehensive Cancer Centers of Nevada, Las Vegas, US
Schmerling, Rafael	Beneficencia Portuguesa de Sao Paulo, Sao Paulo, Brazil
Schrama, David	University of Wurzburg, Wurzburg, Germany

Shalhout, Sophia	Massachusetts General Hospital, Boston, US
Silk, Annie	Dana-Farber Cancer Institute, Boston, US
Sondak, Vernon	Moffitt Cancer Center, Tampa, US
Su, Zhen	EMD Serono
Tal, Abdel Kader	Perrysburg, US
Tetzlaff, Michael	University of California, San Francisco, US
Thakuria, Manisha	Brigham and Women's Hospital, Boston, US
Thirumaran, Ranjit	Pfizer, Seattle, US
Topalian, Suzanne	Johns Hopkins University, Baltimore, US
Tsai, Kenneth	Moffitt Cancer Center, Tampa, US
Tsuruta, Daisuke	Osaka City University
Turaka, Aruna	Maui Memorial Medical Center, Wailuku, US
Ugurel, Selma	University of Essen, Essen, Germany
Uyei, Anne	Kartos Therapeutics
Venkatesh, Kaushik	National Institutes of Health, Bethesda, US
Verhaegen, Monique	University of Michigan, Ann Arbor, US
Vezeridi, Michael	Brown University, Providence, US
Vilasi, Serena	Georgetown Lombardi Comprehensive Cancer Center, Washington DC, US
Villabona, Lisa	Karolinska University Hospital, Stockholm, Sweden
Wang, Richard	UT Southwestern, Dallas, US
Wong, Tak-Wah (Ken)	National Cheng Kung University Hospital, Tainan, Taiwan
Wong, Michael	MD Anderson Cancer Center, Houston, US
Wu, Cheng-Lin	National Cheng Kung University Hospital, Tainan, Taiwan
Yu, Siegrid	University of California, San Francisco, US
Zaba, Lisa	Stanford Medical Center, Palo Alto, US
Zawacki, Lauren	University of Washington, Seattle, US