# Summary of 9th Annual MMIG Meeting (2014)

**(Merkel cell carcinoma Multi-center Interest Group)**

## Friday March 21st, 2014
## American Academy of Dermatology Annual Meeting
## Denver, CO
## Prepared by Drs. Paul Nghiem & Astrid Blom

*edited 3/30/14*

## Announcements:

1) If anyone is interested in presenting at next year's MMIG meeting in San Francisco please send Paul an email (pnghiem@uw.edu) with a proposed topic that is relevant to MCC patient care or translational research.

2) The Seattle team has recruited 1057 cases (often with blood, tissue, and/or DNA) and is currently tracking the "status" of ~440 live patients. We will not regularly add more patients to our longitudinal cohort at this point, with the focus shifting towards clinical trials (3 active now) and staying up-to-date on our existing cohort.

**Speakers/Topics (detailed in following pages):**

**1) Rationale and efficacy of single-fraction radiation therapy for metastatic MCC lesions**
Paul Nghiem (UW/Seattle)

**2) Update from the NCCN and Michigan MCC Group**
Chris Bichakjian (UM/Ann Arbor)

**3) Validation of a serologic assay for MCC recurrence/monitoring**
Astrid Blom (UW/Seattle)

**4) Towards a revised MCC staging system for the AJCC Staging Manual 8th Edition**
Arthur Sober (MGH/Boston)

**5) Updates on immunetherapy clinical trials for MCC**
Isaac Brownell (NCI/Bethesda)

## 1) Rationale and efficacy of single-fraction radiation therapy for metastatic MCC lesions

Paul Nghiem (UW/Seattle)

Radiation is often used in an adjuvant setting in MCC to improve loco-regional control and is almost always 'fractionated'. New approaches are needed to treat MCC patients with distant metastases in whom life expectancy is low and focus on quality of life is important. "Single dose" radiation offers several advantages over fractionated treatment: it enhances immunity by upregulating MHC-I, avoids killing T cells with later treatments, has essentially no side effects and can be combined with other immune therapies.

Dr. Nghiem reviewed the Seattle experience of 27 patients (93 tumors) who were treated with single dose XRT (1 x 8 Gy) for metastatic MCC. The patients were broken down into 2 risk strata: "Low Risk" patients who were not immunosuppressed and had never had chemotherapy, and High Risk patients who were immunosuppressed and/or had received prior chemotherapy. Of the total of 86 evaluable tumors, only 2 did not respond to SFXRT, while 40 achieved a complete response, regardless of size. Virtually no side-effects were observed and several patients achieved prolonged complete remissions of their disease, although no abscopal effects (regression of untreated lesions) were recorded. While response rates were similar in low-risk and high-risk patients, there was a significant difference in the durability of control for the target lesions among the 2 groups: only 9% of the targeted lesions showed subsequent progression after SFXRT in low-risk patients, while 30% did in the high-risk group ($p=0.02$).

In summary, SFXRT is efficacious with excellent palliation, provides durable responses compared with chemotherapy, has virtually no side effects and can treat metastatic disease almost anywhere in the body. It is also cost effective compared to fractionated radiation, convenient for patients who live far away from a Radiation Oncology center and can potentially synergize with the immune system.

**References: (data from the Seattle cohort is in preparation for submission)**

Lee Y, Auh S, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood. 2009 Jul 16;114(3):589-95.

## 2) Update from the NCCN and Michigan MCC Group

Chris Bichakjian (UM/Ann Arbor)

Several updates were recently made to the 2014 version of the NCCN guidelines for MCC:
- In the initial work-up, the footnote about imaging will state that PET/CT may be preferred to CT in some circumstances.
- Adjuvant chemotherapy will no longer be suggested as an option for SLNB-positive patients.
- SLNB will be described as an "important staging tool" and no longer considered optional for head & neck lesions.
- Expeditious initiation of XRT will be recommended and should not be delayed by extensive surgery.
- Principles of pathology will be more detailed, along the lines of the ones found in melanoma (Breslow, mitoses, etc).

Dr. Bichakjian reviewed the Michigan experience of 113 patients with MCC who were treated without XRT to the primary site with a mean follow-up of 31 months. The majority of the lesions were less than 1cm in diameter (64 less than 1cm, 41 between 1-2 cm and 8 greater than 2 cm) and SLNB negative (80 negative, 33 positive). Among these lesions, there were a total of 3 local/satellite "in field" recurrences (2.7%). The total recurrence rate (local, regional and distant) was 21.2% (24/113 lesions). Among the 24 recurrences, 17 patients had nodal disease at the time of presentation and the remaining 7 developed regional or distant recurrences without local recurrence. These findings led Dr. Bichakjian to conclude that in a highly selected and "micro-managed" group, very low local recurrence rates can be achieved with wide excision of primary MCC without adjuvant radiation therapy to the primary site. Furthermore, in this cohort adjuvant radiation did not seem to be required to prevent in-transit/regional or distant recurrences.

Dr. Bichakjian then reviewed the total Michigan cohort of 237 MCC patients (237 tumors). Demographics and tumor characteristics are similar to other cohorts. As expected, disease-specific survival is significantly correlated with nodal disease (absent vs microscopic vs macroscopic). More surprisingly, among a small number of tumors for which ulceration information was available, the presence of ulceration (n=22) seems to significantly lower survival, even in a multivariate analysis.

## 3) Validation of a serologic assay for MCC recurrence/monitoring
Astrid Blom (UW/Seattle)

Dr. Blom reviewed the 3½-year Seattle experience with MCPyV oncoprotein antibody testing on 1342 serum samples from 104 population controls and 519 MCC patients. When blood draws were done within 90 days of initial diagnosis, 52% of MCC patients (n=217) produced antibodies to the viral oncoprotein, while less than 2% of normal controls did. In patients who produced oncoprotein antibodies and did not recur, the antibody decay rate varied, with a median time to seronegativity of 255 days.

A major finding of the study was that producing antibodies to the viral oncoprotein confers a significantly better MCC-specific survival, cutting the risk of death from the disease approximately in half. This remained true after multivariate analysis including age at diagnosis, sex, immune suppression and stage at diagnosis ($p<0.01$).

131 patients made oncoprotein antibodies and had subsequent blood draws. Oncoprotein antibody titers steadily fell or remained stably negative in 227 of 231 samples from patients who remained disease-free (specificity = 98%). Of the 17 patients that progressed within 30 days of a blood draw, 14 had at least a 20% increase in oncoprotein antibody titer (sensitivity = 82%). In four of these patients, the increasing titers preceded recognition of recurrent disease and initiated further workup that revealed occult recurrent/metastatic disease. The negative predictive value of the test was 99%. These results suggest that, for patients who produce them at the time of diagnosis, antibodies to the MCPyV oncoprotein can be used to detect early recurrence of MCC and may reduce the need for frequent surveillance by computed tomography. The assay is now available at UW Lab Medicine and can be ordered by any physician across the country, with results available within a few weeks. The cost of the test is approximately $200, although the facility that draws and ships the blood may charge extra for those services. For details about the test, just Google the keywords (MCC, antibody, serology) and the webpage with relevant information will appear (http://www.merkelcell.org/sero).

**Reference: (Manuscript for validation study is in preparation)**
Paulson K, Carter J, et al. Antibodies to merkel cell polyomavirus T antigen oncoproteins reflect tumor burden in merkel cell carcinoma patients. Cancer Res. 2010 Nov 1;70(21):8388-97.

## 4) Towards a revised MCC staging system for the AJCC Staging Manual 8th Edition

Arthur Sober (MGH/Boston)

A new American Joint Committee on Cancer (AJCC) staging system for cancers, including MCC, will be derived over the next few years.

Dr. Sober reviewed the organizations that founded and sponsor the AJCC in Chicago. For more than five decades the AJCC has played a leadership role in the USA as the organization that provides oversight of cancer staging for most solid tumors seen in clinical practice. It is a task force made up of experts in the clinical, statistical, and registration areas. The first edition dates back to 1977 and its central goal is for hospital tumor registrars to have standardized reporting classifications. Historically, AJCC staging mirrored TNM staging and was purely anatomical, but recent editions have included microscopic features (i.e. ulceration, mitoses, etc) and will most likely soon include biomarkers (LDH, genetic alterations, etc).

The upcoming Non-Melanoma Skin Expert Committee is composed of Dermatologists (4), Medical Oncologists (2), Surgical Oncologists (7), Radiation Oncologists (3), Radiologists (1) and Pathologists (4). The AJCC 8$^{th}$ edition Authoring Wave for NMSC will be between 9/15/14 and 3/20/15, with the Post-Authoring Wave (data collection, statistics, publishing) taking place from 12/7/15 to 9/30/15. Likely changes in the 8$^{th}$ edition MCC staging will include the effect of lymphovascular invasion on worsening prognosis and a further refinement of staging for patients with regional nodal involvement (cases with unknown primary versus those with a known primary). The 8$^{th}$ edition should be published about 3 years from now.

## 5) Updates on immunotherapy clinical trials for MCC

Isaac Brownell (NCI/Bethesda)

Dr. Brownell outlined clinical trials evaluating the utility of immunotherapy in patients with MCC. There is literature to support the idea that the Merkel cell polyomavirus functions as an immune target in MCC: 1) the tumor expresses non-self viral antigens, 2) patients generate T-antigen reactive T cells and antibodies that correlate with tumor load, and 3) high antibody titers for VP1 correlate with progression-free survival. Furthermore, several points suggest that MCC should respond to immunotherapy: higher incidence and worse prognosis in immunocompromised populations, spontaneous regression, responses to DNCB (contact sensitizer), TNFa and interferon, and improved prognosis with CD8+ tumor-infiltrating lymphocytes.
Currently, there are 4 active immunotherapy trials for MCC.

Aude Chapuis leads the MCPyV-reactive autologous T cell therapy for metastatic MCC phase I/II trial at the Fred Hutchinson Cancer Research Center. Patients are treated with adoptive CD8+ MCPyV-

reactive T cells after MHC-I upregulation with XRT or intra-lesional IFN.

2 trials rely on intra-lesional immunotherapy. The first one, open at the Fred Hutchinson Cancer Research Center and at UCSF, is a Phase II Interleukin-12 Plasmid and in Vivo Electroporation for Merkel cell carcinoma. The second is a Phase I, single arm proof of concept with TLR4 agonist GLA-SE and is to enroll 10 patients at the FHCRC.
Dr Brownell made the interesting observation that contact sensitizers might also be effective for MCC. Indeed, one case report showed an impressive response of MCC to DNCB. In another study in 50 melanoma patients treated with DPCP, 46% had complete clearance of their cutaneous disease and a further 38% had partial response. In particular, one patient treated for fungating recurrent melanoma on the thigh had a complete regression of bilateral inguinal disease and lung metastases.

The last trial for MCC is a phase II using tenascin-C-targeting human F16IL2 monoclonal fusion protein and paclitaxel vs paclitaxel alone. It is taking place within the European Immomec group (IMmune MOdulating strategies for treatment of MErkel cell Carcinoma) under the leadership of Jürgen Becker in Austria.

Finally, Dr Brownell detailed 3 upcoming immunotherapy trials for MCC. The first one is a single arm, early phase II trial of anti PD-1 as first line therapy for advanced MCC and will be led by the Cancer Immunotherapy Trials Network (CITN). The second is a combination of ipilimumab (anti CTLA-4) and nivolumab (anti PD-1) for MCC. This combination has shown very promising results in melanoma (53% objective response with adverse effects similar to monotherapy) and Chris Lao at U Michigan is seeking SWOG support to open the trial in MCC. Finally, a trial for anti-PDL1 in second line is in the pipeline.

**References:**

- Herrmann G, Groth W, et al. Complete remission of Merkel cell carcinoma of the scalp with local and regional metastases after topical treatment with dinitrochlorbenzol. J Am Acad Dermatol 2004 Jun;50(6):965-9.
- Damian S, Saw R, et al. Topical immunotherapy with diphencyprone for in transit and cutaneously metastatic melanoma. J Surg Oncol. 2014 Mar;109(4):308-13.
- Wolchok J, Kluger H, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013 Jul 11;369(2):122-33.

## In attendance at the Denver 2014 MMIG meeting:

Asgari, Maryam
Berg, Daniel
Bichakjian, Chris
Blom, Astrid
Boldrick, Jennifer
Brewer, Jerry
Brownell, Isaac
Frohm, Marcus
Gao, Ling
Huang, Victor
Jaimes, Natalia
Kwong, Bernice
Lai, Jennifer
Martinez, John Carlos
Nambudiri, Vinod
Nghiem, Paul
Otley, Clark
Perlis, Cliff
Seely, Jill
Sober, Arthur
Stasko, Tom
Swetter, Susan
Thakuria, Manisha
Verhaegen, Monique
Vetto, John
Yu, Siegrid
Zeitouni, Nathalie

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**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 contains photos, meeting summaries and more at:*
*http://merkelcell.org/MMIG.html*

*MMIG is funded in part by donations from Merkel cell carcinoma patients.*

*Please note that in some 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.*