Emerging Therapies for Cutaneous Malignancies

Genevieve Kelly
AAD Highlights Meeting
Thurs 15th March 2018
Topics

- Basal Cell Carcinoma
- Squamous Cell Carcinoma
- Merkel Cell Carcinoma
- Cutaneous Lymphoma
- Malignant Melanoma
Basal Cell Carcinoma

Update on therapy for advanced BCC
Over-expression of the Hedgehog signalling pathway in BCCs
Oral Smoothened Inhibitors

**Vismodegib-150mg PO OD**
- FDA approved for metastatic and locally advanced BCC
  - Phase 1 study: anti-tumour activity in patients with mBCC and laBCC. RR 58%. Median duration of response 12.8 months*
  - Phase 2 Trial: Pivotal Trial. NEJM. Overall response rate 30% in mBCC and 42% laBCC: lead to FDA approval**

**Sonidegib-200mg PO OD**
- FDA approved for locally advanced BCC

Side effects:
- Muscle spasm (50% by 2/12)
- Taste disturbance (50% by 1/12)
- Alopecia (50% by 6/12)
- Increased risk of SCC

Monitoring:
- CK (Sonidegib)
- B HCG

*LoRusso PM et al. Clin Cancer Res. 2011;17;2502-2511
• Recurrent disease while on Smoothened inhibition  
  – 20%  
  – Can be discontiguous  
• If resistant to Vismodegib, Sonidegib unlikely to work*  
• Resistance due to mutations in Smoothened: drug binding pocket inaccessible to the drug.  
• But if has E518A mutation in Smoothened: may respond to Sonidegib after failing Vismodegib  
• Case report of Sonidegib + Itraconazole for advanced BCC in to ethmoid sinus and brain after treatment failure with Vismodegib**  
• Neoadjuvant vismodegib – decreased final surgical defect by 34.8%***  

Smoothened Inhibition Resistance: PI3K pathway

- PI3-kinase inhibitor: buparlisib
- Smoothened inhibitors: sonidegib, vismodegib
- Hedgehog
- Patched
- Smoothened
- RAS pathway
- GLI1
- Nucleus
- Tumor growth
- Proliferation

Tumor cell
Sonidegib + Buparlisib (PI3K inhibitor)
  – All had failed Vismodegib monotherapy
71% (5 of 7) of patients experienced stable disease or partial response
ORR 14.3%
Terminated early. 50% Grade 3 AEs
  • PI3K inhibitor class recently FDA approved: ?
  Combination may be possible with less toxic PI3K inhibitor
PDL1 inhibition in BCC

Investigator initiated trial for Pembrolizumab ± Vismodogib for metastatic BCC underway.....
Squamous Cell Carcinoma

Emerging therapies
Grading and Staging

- Universally accepted staging system for risk stratification is not yet available
- Until 2010, cutaneous SCC (cSCC) was grouped in AJCC staging with multitude of other cutaneous malignancies
- AJCC 8th edition: cSCC of head and neck
  - Unsatisfactory prognostication among stage groups
- Alternative Brigham and Women’s Hospital System
  - BWH staging does not address nodal/metastasis classification, superior prognostication for patients with localised cSCC
### Table II. Brigham and Women’s Hospital tumor classification system

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>In situ SCC</td>
</tr>
<tr>
<td>T1</td>
<td>0 risk factors*</td>
</tr>
<tr>
<td>T2a</td>
<td>1 risk factor</td>
</tr>
<tr>
<td>T2b</td>
<td>2-3 risk factors</td>
</tr>
<tr>
<td>T3</td>
<td>4 risk factors or bone invasion</td>
</tr>
</tbody>
</table>

Reprinted with permission. Copyright ©2013 American Medical Association. All rights reserved.

SCC, Squamous cell carcinoma.

*Risk factors include tumor diameter 2 cm or larger, poorly differentiated histology, perineural invasion, and tumor invasion beyond the subcutaneous fat (excluding bone, which automatically upgrades to T3).
Table III. National Comprehensive Cancer Network stratification of low versus high risk cSCC

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location*size(^\d)</td>
<td>Area L &lt; 20 mm</td>
<td>Area L ≥20 mm</td>
</tr>
<tr>
<td></td>
<td>Area M(^\d) &lt; 10 mm</td>
<td>Area M ≥10 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Area H(^\d)</td>
</tr>
<tr>
<td>Borders</td>
<td>Well defined</td>
<td>Poorly defined</td>
</tr>
<tr>
<td>Primary vs recurrent</td>
<td>Primary</td>
<td>Recurrent</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Site of prior radiation therapy or chronic inflammatory process</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Rapidly growing tumor</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Pathologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree of differentiation</td>
<td>Well to moderately differentiated</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>High-risk histologic subtype(^\d)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Depth (thickness or Clark level)(^\d)</td>
<td>&lt;2 mm, or I, II, III</td>
<td>≥2 mm or IV, V</td>
</tr>
<tr>
<td>Perineural, lymphatic, or vascular involvement</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Reprinted with permission.\(^3\)

cSCC, Cutaneous squamous cell carcinoma.

*Area L consists of trunk and extremities (excluding hands, feet, nail units, pretibia, and ankles); area M consists of cheeks, forehead, scalp, neck, and pretibia; and area H consists of central face, eyelids, eyebrows, periorbital skin, nose, lips, chin, mandible, preauricular and postauricular skin/sulci, temple, ear, genitalia, hands, and feet.

\(^\d\)Greatest tumor diameter, including peripheral rim of erythema.

Location independent of size may constitute high risk.

\(^\d\)Area H constitutes high-risk on the basis of location, independent of size.

\(^\d\)Adenoid (acantholytic), adenosquamous (showing mucin production), desmoplastic, or metaplastic (carinosarcomatous) subtypes.

\(^\d\)A modified Breslow measurement should exclude parakeratosis or scale/crust and should be made from base of the ulcer is present. If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow-margin excision biopsy.
**Table IV.** Recommendations for grading and staging of cSCC

Stratification of localized SCCs using the NCCN guideline framework is recommended for clinical practice. Clinicians should refer to the BWH tumor classification system to obtain the most accurate prognostication of patients with localized cSCC.

*BWH, Brigham and Women’s Hospital; cSCC, cutaneous squamous cell carcinoma; NCCN, National Comprehensive Cancer Network; SCC, squamous cell carcinoma.*

Systemic Agents for cSCC

- Regional disease should be treated with lymph node dissection and postoperative radiation
- Clinical data for distant metastatic cSCC is limited
  - First line (NCCN): Cisplatin, 5-fluorouracil
  - Second line: EGFR inhibition
    - Monoclonal Antibodies: Cetuximab (Erbitux, Lilly), Panitumumab (Vectibix, Amgen)
    - Tyrosine Kinase Inhibitors: Erlotinib (Tarceva, Genentech), Gefitinib (Iressa, AstraZenica)
  - Emerging: Immunotherapy/checkpoint inhibition
    - Anti PD-1 inhibitors: Nivolumab (Opdivo, BMS) and Pembrolizumab (Keytruda, Merck)
EGFR Inhibition in cSCC

  - Open-label trial for chemotherapy-naïve patients with unresectable (17) or metastatic SCC (16 nodal, 3 distant)
  - 6 week response: 3% CR, 8% PR, 58% SD
  - Open label trial of 16 patients, 14 with prior XRT and 7 with prior chemotherapy
  - Best response: 13% CR, 18% PR, 38% SD.
  - The median PFS and overall survival were 8 and 11 months respectively.

Maubec et al., J Clin Onc 2011
Foote et al., Ann Oncol 2014
Gefitinib for patients with incurable cutaneous squamous cell carcinoma: A single-arm phase II clinical trial

EGFR Inhibition in cSCC- 2018 Update

- Phase II Study of Iressa in Treatment of Recurrent or Metastatic cSCC (MD Anderson, 2017)
- 40 patients with locoregional or metastatic disease not amenable to surgery or radiation; 37 evaluable for response
- 250 PO QD until progression or intolerable toxicity, median treatment time 3.4 months (0.9-33.5)
- Favorable toxicity profile; AEs included 70% acneiform rash and 53% diarrhea (grade 1-2)
- PR in 6 patients and SD in 13 patients at 8 weeks
  - ORR at 16% and disease control rate of 51%.
  - All PRs were in locoregional patients; none in metastatic.
- Median overall survival 12.9 months (95% CI 8.5-25.0). Median progression-free survival 3.8 months (95% CI, 2.2-5.7).

# Immunotherapy for SCC


## Table 2. Immunotherapy protocols encompassing immune checkpoint antibodies for treatment of advanced cutaneous squamous cell carcinoma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cases</th>
<th>Treatment</th>
<th>Drugs</th>
<th>Outcomes</th>
<th>Progression-free survival</th>
<th>Significant adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day et al. [73**]</td>
<td>Lung and liver metastatic SCC</td>
<td>Third line</td>
<td>Ipilimumab</td>
<td>PR</td>
<td>8 months</td>
<td>Hypophysitis</td>
</tr>
<tr>
<td>Winkler et al. [74**]</td>
<td>Lymph node metastatic SCC</td>
<td>First line</td>
<td>Pembrolizumab</td>
<td>PR</td>
<td>5 months</td>
<td>None</td>
</tr>
<tr>
<td>Chang et al. [75**]</td>
<td>Locally advanced SCC</td>
<td>Second line</td>
<td>Pembrolizumab</td>
<td>PR</td>
<td>5 months</td>
<td>Fatigue, weight loss and arthralgias</td>
</tr>
<tr>
<td>Lipson et al. [76**]</td>
<td>Kidney-transplanted patient</td>
<td>Second line</td>
<td>Pembrolizumab</td>
<td>PR</td>
<td>8 months</td>
<td>Allograft rejection</td>
</tr>
<tr>
<td></td>
<td>Metastatic SCC</td>
<td>Third line</td>
<td>Pembrolizumab</td>
<td>PR</td>
<td>7 months</td>
<td>Fatigue, brain edema</td>
</tr>
<tr>
<td>Borradori et al. [77**]</td>
<td>Metastatic SCC</td>
<td>Third line</td>
<td>Pembrolizumab</td>
<td>PR</td>
<td>7 months</td>
<td>Fatigue, weight loss, hyponatremia</td>
</tr>
<tr>
<td></td>
<td>Locally advanced SCC</td>
<td>Fourth line</td>
<td>Pembrolizumab</td>
<td></td>
<td>4 months</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Locally advanced SCC</td>
<td>Second line</td>
<td>Nivolumab</td>
<td>PR</td>
<td>7 months</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Metastatic SCC</td>
<td>Fourth line</td>
<td>Nivolumab</td>
<td>PR</td>
<td>6 months</td>
<td>None</td>
</tr>
</tbody>
</table>

PR, partial response.
• ClinicalTrials.gov
  – NCT02760498
  – PD1 monoclonal antibody, REGN2810 (Cemiplimab)
  – Phase 2 interventional clinical trial May 2016-May 2019.

• NCT02883556 (CARSKIN) a French multicenter, open-label, nonrandomized phase 2 trial, designed to evaluate the efficacy and safety of pembrolizumab in 39 pts with unresectable and/or metastatic cSCCs, naive of chemotherapy and of EGFR inhibitors
Merkel Cell Carcinoma: Therapeutic Update
Why is MCC important?

• More lethal than melanoma
  – ~40% mortality\(^1\) (~8% for melanoma)\(^2\)

• Optimal therapy is unique among skin CAs

• A new polyomavirus is associated with MCC
  – We need better (immuno) therapies

• Reported incidence increasing
  – Quintupled since 1986
  – ~2,500 new cases/yr in the US in 2017\(^3\)
  – > 3,300 new cases/yr in 2025 (projected)\(^3\)

Local disease: Surgery & Radiation
- >95% of pts ‘free of detectable disease’...
- But MCC recurs in nearly half

Metastatic or locally advanced disease:
- (Used to be) chemotherapy (‘small cell regimen’)
- Shrinks MCC in most cases, but over half progress by 3 months

→ Need better therapies
A new human virus that causes cancer  (in 2008)

Moore/Chang
(KSHV)

Present in 8/10 MCCs

Validated in dozens of studies

~80% driven by virus
~20% driven by UV

Clonal Integration of a Polyomavirus in Human Merkel Cell Carcinoma

Huichen Feng, Masahiro Shuda, Yuan Chang,* Patrick S. Moore*

Merkel cell carcinoma (MCC) is a rare but aggressive human skin cancer that typically affects elderly and immunosuppressed individuals, a feature suggestive of an infectious origin. We studied MCC samples by digital transcriptome subtraction and detected a fusion transcript between a previously undescribed virus T antigen and a human receptor tyrosine phosphatase. Further investigation led to identification and sequence analysis of the 5387-base-pair genome of a previously unknown polyomavirus that we call Merkel cell polyomavirus (MCPyV). MCPyV sequences were detected in 8 of 10 (80%) MCC tumors but only 5 of 59 (8%) control tissues from various body sites and 4 of 25 (16%) control skin tissues. In six of eight MCPyV-positive MCCs, viral DNA was integrated within the tumor genome in a clonal pattern, suggesting that MCPyV infection and integration preceded clonal expansion of the tumor cells. Thus, MCPyV may be a contributing factor in the pathogenesis of MCC.

Polyomaviruses have been suspected as potential etiologic agents in human cancer since the discovery of murine polyoma virus (MuPyV) by Gross in 1953 (1). However, although polyomaviruses can produce tumors in animal models, there is no conclusive evidence that they play a role in human cancers (2). These small double-stranded DNA viruses (~5200 base pairs (bp)) encode a variably spliced oncoprotein, the tumor (T) antigen (3, 4), and are divided into three genetically distinct groups: (i) avian polyomaviruses, (ii) mammalian viruses related to MuPyV, and (iii) mammalian polyomaviruses related to simian virus 40 (SV40) (5). All four known human polyomaviruses (BK virus (BKV), JCV, KIV, and WUV (6, 7)) belong to the SV40 subgroup. In animals, integration of polyomavirus DNA into the host genome often precedes tumor formation (8).

Merkel cell carcinoma (MCC) is a neuroectodermal tumor arising from mechanoreceptor Merkel cells (Fig. 1A). MCC is rare, but its incidence has tripled over the past 2 decades in the United States to 1500 cases per year (9). It is one of the most aggressive forms of skin cancer; about 50% of advanced MCC patients...
UV driven MCC → High mutational burden

3 studies in late 2015...
Viral Oncoprotein Antibodies as a Marker for Recurrence of Merkel Cell Carcinoma: A Prospective Validation Study

Kelly G. Paulson, MD, PhD1,2,5; Christopher W. Lewis, BS1; Mary W. Redman, PhD4; William T. Simonson, MD, PhD3; Aaron Lisberg, MD1; Deborah Ritter, MS2; Chihiro Morishima, MD3; Kathleen Hutchinson, MS3; Lola Mudgistrateova, BA1; Astrid Blom, MD1; Jayasri Iyer, MD1; Ata S. Moshiri, MD, MPH1; Erica S. Tarabadkar, MD1; Joseph J. Carter, PhD6; Shailender Bhatia, MD2,5; Masaoki Kawasaki, MD, PhD1; Denise A. Galloway, PhD6; Mark H. Wener, MD3; and Paul Nghiem, MD, PhD1,5

BACKGROUND: Merkel cell carcinoma (MCC) is an aggressive skin cancer with a recurrence rate of >40%. Of the 2000 MCC cases per year in the United States, most are caused by the Merkel cell polyomavirus (MCPyV). Antibodies to MCPyV oncoprotein (T-antigens) have been correlated with MCC tumor burden. The present study assesses the clinical utility of MCPyV-oncoprotein antibody titers for MCC prognostication and surveillance. METHODS: MCPyV-oncoprotein antibody detection was optimized in a clinical laboratory. A cohort of 219 patients with newly diagnosed MCC were followed prospectively (median follow-up, 1.9 years). Among the seropositive patients, antibody titer and disease status were serially tracked. RESULTS: Antibodies to MCPyV oncoproteins were rare among healthy individuals (1%) but were present in most patients with MCC (114 of 219 patients [52%]; P < .01). Seropositivity at diagnosis independently predicted decreased recurrence risk (hazard ratio, 0.58; P = .04) in multivariate analyses adjusted for age, sex, stage, and immunosuppression. After initial treatment, seropositive patients whose disease did not recur had rapidly falling titers that became negative by a median of 8.4 months. Among seropositive patients who underwent serial evaluation (71 patients; 282 time points), an increasing oncoprotein titer had a positive predictive value of 66% for clinically evident recurrence, whereas a decreasing titer had a negative predictive value of 97%. CONCLUSIONS: Determination of oncoprotein antibody titer assists in the clinical management of patients with newly diagnosed MCC by stratifying them into a higher risk seronegative cohort, in which radiologic imaging may play a more prominent role, and into a lower risk seropositive cohort, in which disease status can be tracked in part by oncoprotein antibody titer. Cancer 2016;000:000–000. © 2016 American Cancer Society.

KEYWORDS: Merkel cell carcinoma (MCC), Merkel cell polyomavirus (MCPyV), oncoprotein, serology, skin cancer, T antigen.
A prospective study of antibodies to MCPyV oncoprotein

- NIH-funded
- 465 patients prospectively studied w/1035 blood draws
- 219 had 1st draw <90 days after diagnosis
- Median f/u 1.9 years

Falling/negative titers
- 98% reassured

Increasing titers
- 88% have/will recur

Run by UW Lab Medicine (50 ul serum)
Cost ~$300 (modest vs CT scan)
Helps both virus-pos and virus-neg patients...

Baseline serology test

- **42% higher risk** of recurring
- Track closely w/scans
- Follow w/serology
- Fewer scans

Assay available as of January 2014...

*About the Disease Testing & Diagnosis Treatment Prognosis Helpful Resources*

**Serology test**
A blood test for recurrence and disease status in Merkel cell carcinoma.

Purpose of the Merkel virus serology test

The *Merkel polyomavirus* serology test is a blood test that is helpful in managing MCC patients (whether they make these antibodies or not) so that possible disease recurrence can be detected early, when it can be most effectively treated. A baseline oncoprotein antibody test (ideally within 2-3 months of when a patient had evidence of disease) is useful for all MCC patients. This is because patients who do not produce antibodies are at higher risk of having a recurrence and will need to be followed closely by imaging scans. In contrast, patients who produce oncoprotein antibodies can be followed over time using this test which decreases the need for imaging scans.
# Response Rates for Systemic MCC drugs

<table>
<thead>
<tr>
<th>Agents</th>
<th>Response</th>
<th>Study</th>
<th>Status in MCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>55% ORR</td>
<td>1st line treatment, retrospective study for 62 patients, Iyer et al., 2016, Cancer Medicine</td>
<td>Included in NCCN guidelines based on historical/clinical experience</td>
</tr>
<tr>
<td>Avelumab (Anti-PD-L1)</td>
<td>56% ORR</td>
<td>1st line trial, D’Angelo et al., ASCO 2017 Abstract No. 9530</td>
<td>FDA-approved: 1st and ≥ 2nd line, 3/2017</td>
</tr>
<tr>
<td>Pembrolizumab (Anti-PD-1)</td>
<td>56% ORR</td>
<td>1st line trial, Nghiem et al., 2016, NEJM</td>
<td>NCCN guideline for MCC, 2018</td>
</tr>
<tr>
<td>Nivolumab (Anti-PD-1)</td>
<td>73% ORR</td>
<td>1st and ≥ 2nd line, Topalian, et al., AACR 2017 Abstract No. CT074</td>
<td>NCCN guideline for MCC, 2018</td>
</tr>
</tbody>
</table>
# Immunotherapy changed NCCN guidelines

<table>
<thead>
<tr>
<th>2016 and before</th>
<th>2017</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy only</td>
<td>Pembrolizumab was listed</td>
<td>Checkpoint immunotherapies are preferred to chemotherapy</td>
</tr>
</tbody>
</table>

**Disseminated Disease:**
As clinical judgment indicates:
- Cisplatin ± etoposide
- Carboplatin ± etoposide
- Topotecan
  - (CAV): Cyclophosphamide, doxorubicin (or epirubicin), and vincristine

- Pembrolizumab

**Disseminated Disease:**
As clinical judgement dictates:
- Cisplatin ± etoposide
- Carboplatin ± etoposide
- Topotecan
  - (CAV): Cyclophosphamide, doxorubicin (or epirubicin), and vincristine

- Pembrolizumab

**Disseminated Disease:**
As clinical trial (preferred)

- Avelumab
- Pembrolizumab
- Nivolumab

- As clinical judgment dictates for patients with contraindications to checkpoint immunotherapy
- Cisplatin ± etoposide
- Carboplatin ± etoposide
- Topotecan
  - (CAV): Cyclophosphamide, doxorubicin and vincristine
Cutaneous T Cell Lymphoma

Update and emerging therapies
CTCL: Introduction

- Rare group of extranodal non-Hodgkin Lymphoma with heterogeneous characteristics, severe pruritus and infectious complications.
- Most common forms are Mycosis Fungoides (MF) and Sezary Syndrome (SS)
- Advanced stage MF or SS, stages IIIB-IVB manifest as cutaneous tumours, erythroderma, extracutaneous disease.
- Associated with decreased QOL and shortened survival compared with early stage disease
<table>
<thead>
<tr>
<th>2016 WHO Mature T and NK neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis fungoides and variants/subtype</td>
</tr>
<tr>
<td>Sézary syndrome</td>
</tr>
<tr>
<td>Cutaneous CD30+ T-cell lymphoproliferative disorders</td>
</tr>
<tr>
<td>- Lymphomatoid papulosis</td>
</tr>
<tr>
<td>- Cutaneous anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
</tr>
<tr>
<td>Cutaneous γ/δ T-cell lymphoma</td>
</tr>
<tr>
<td>Hydroa vacciniforme-like lymphoproliferative disorder*</td>
</tr>
<tr>
<td>Extranodal NK-/T-cell lymphoma, nasal type</td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma</td>
</tr>
<tr>
<td>Cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma</td>
</tr>
<tr>
<td>Cutaneous acral CD8+ T-cell lymphoma*</td>
</tr>
<tr>
<td>Cutaneous CD4+ small/medium T-cell lymphoproliferative disorder*</td>
</tr>
<tr>
<td>Follicular T-cell lymphoma*</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma, NOS</td>
</tr>
</tbody>
</table>

*Changes from 2008 classification; provisional entities are in *italics*, Blood 2016
Mycosis Fungoides
Treatment of varying skin manifestations

- Patch T1-2
- Tumor T3
- Plaque T1-2
- Erythroderma T4
MF staging

TNM

- **T stage**
  - T1: limited patches (T1A)/plaques (T1B) <10% BSA
  - T2: patches (T2A)/plaques (T2B) >10% BSA
  - T3: tumours (1 or more)
  - T4: >80% BSA

- **N stage**
  - N1: clinically abnormal lymph nodes. Pathology negative for CTCL
  - N2: no clinically abnormal peripheral lymph nodes. Pathology positive for CTCL
  - N3: clinically abnormal peripheral lymph nodes. Pathology positive for CTCL

- **M stage**
  - M0: no visceral organ involvement
  - M1: visceral organ involvement

---


---

**Survival of CTCL directly related to tumor burden**

10 year DSS for patch MF patients: T1 100% & T2 88%

2/3 present with early disease
CTCL guidelines: T1 (<10% BSA)

For limited/localized skin involvement (Skin-Limited/Local)
- Topical corticosteroids
- Topical chemotherapy (mechlorethamine [nitrogen mustard], carmustine)
- Local radiation (8-36 Gy)
- Topical retinoids (bexarotene, tazarotene)
- Phototherapy (UVB, nbUVB for patch/thin plaques; PUVA for thicker plaques)
- Topical imiquimod

CTCL guidelines: T2 (BSA>10%)

For generalized skin involvement (Skin-Generalized)
- Topical corticosteroids
- Topical chemotherapy (mechlorethamine [nitrogen mustard], carmustine)
- Phototherapy (UVB, nbUVB, for patch/thin plaques; PUVA for thicker plaques)
- Total skin electron beam therapy (TSEBT) (12-36 Gy) (reserved for those with severe skin symptoms or generalized thick plaque or tumor disease, or poor response to other therapies)

Skin directed therapies more effective than systemic therapies for patch/plaque MF

<table>
<thead>
<tr>
<th>Skin Therapy</th>
<th>CR</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical steroids</td>
<td>45-65%</td>
<td>75-95%</td>
</tr>
<tr>
<td>Bexarotene gel</td>
<td>20-35%</td>
<td>50-75%</td>
</tr>
<tr>
<td>Topical NM</td>
<td>25-70%</td>
<td>50-90%</td>
</tr>
<tr>
<td>nbUVB</td>
<td>45-75%</td>
<td>75-100%</td>
</tr>
<tr>
<td>PUVA</td>
<td>50-80%</td>
<td>85-100%</td>
</tr>
<tr>
<td>TSEBT (≥30 Gy)</td>
<td>80-90%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Topical resiquimod can induce disease regression and enhance T-cell effector functions in cutaneous T-cell lymphoma

Blood 2016

Alain H. Rook, Joel M. Gelfand, Maria Wysocka, Andrea B. Troxel, Bernice Benoit, Christian Surber, Rosalie Elenitsas, Marie A. Buchanan, Deborah S. Leahy, Rei Watanabe, Ilan R. Kirsch, Ellen J. Kim, and Rachael A. Clark
## Treatment of advanced MF and SS

<table>
<thead>
<tr>
<th>Skin Directed Therapy (SDT)</th>
<th>Non-Cytotoxic systemic therapy</th>
<th>Cytotoxic Systemic Therapy/Biologics</th>
<th>Bone Marrow Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUVA</td>
<td>Extracorporeal photopheresis (ECP)</td>
<td>Methotrexate</td>
<td></td>
</tr>
<tr>
<td>Spot Radiation</td>
<td>Interferon</td>
<td>Doxorubicin</td>
<td></td>
</tr>
<tr>
<td>Total Skin Electron Beam Radiotherapy</td>
<td>Bexarotene</td>
<td>Gemcitabine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Histone Deacetylase (HDAC) inhibitors – Romidepsin, Vorinostat</td>
<td>Pralatrexate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brentuximab</td>
<td>Brentuximab</td>
<td></td>
</tr>
<tr>
<td>Agent (Class)</td>
<td>Indication</td>
<td>Study</td>
<td>N</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------------------------------------------------</td>
<td>-----------</td>
<td>----</td>
</tr>
<tr>
<td>Romidepsin (HDAC inhibitor)</td>
<td>Patients with CTCL who have received systemic therapy</td>
<td>Pivotal</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supportive</td>
<td>71</td>
</tr>
<tr>
<td>Denileukin diftitox (Fusion protein)</td>
<td>Tumors that express CD25</td>
<td>Pivotal</td>
<td>71</td>
</tr>
<tr>
<td>Bexarotene (Retinoid x-receptor activator)</td>
<td>Cutaneous manifestations</td>
<td>Pivotal</td>
<td>62</td>
</tr>
<tr>
<td>Vorinostat (HDAC inhibitor)</td>
<td>Cutaneous manifestations</td>
<td>Pivotal</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supportive</td>
<td>33</td>
</tr>
</tbody>
</table>
Lymphomatoid Papulosis

Primary cutaneous Anaplastic T-cell Lymphoma

CD30+ Cutaneous T cell lymphomas

- Lymphomatoid Papulosis (LyP)
- Primary Cutaneous ALCL (c-ALCL)
- Mycosis Fungoides MF or T-MF
- Secondary Cutaneous ALCL
- PTCL-NOS HTLV-1 ATL
- Hodgkin Lymphoma HL

Transformed CD30+ Mycosis Fungoides
Brentuximab Vedotin Mechanism of Action

Brentuximab vedotin antibody-drug conjugate (ADC)

- Monomethyl auristatin E (MMAE), microtubule-disrupting agent
- Protease-cleavable linker
- Anti-CD30 monoclonal antibody

1. Brentuximab vedotin binds to CD30
2. Brentuximab vedotin-CD30 complex is internalized and traffics to lysosome
3. MMAE is released
4. MMAE disrupts microtubule network
5. G2/M cell cycle arrest
6. Apoptosis

©2012 Seattle Genetics, Inc. Bothell, WA 98021. All rights reserved.
Two ISTs published together in 2015

Journal of Clinical Oncology

Original Report

Phase II Investigator-Initiated Study of Brentuximab Vedotin in Mycosis Fungoides and Sézary Syndrome With Variable CD30 Expression Level: A Multi-Institution Collaborative Project


Response rates of 54-70% in MF/SS in 2 phase II studies

Journal of Clinical Oncology

Original Report

Results of a Phase II Trial of Brentuximab Vedotin for CD30+ Cutaneous T-Cell Lymphoma and Lymphomatoid Papulosis

Madeleine DuVic, Michael T. Tetzlaff, Pamela Gangar, Audra L. Clos, Dawn Sui, and Rakhshanda Talpur

PC CD30+ LPD included in MDACC

- LyP, n=16, ORR 100% (69% CR)
- pc ALCL, n=4, ORR 100% (all CR)
**Great clinical response to brentuximab vedotin in MF/SS**

Sézary syndrome, IVA₁

MF IVA₂, LN with LCT

![Images of skin conditions and graphs](image-url)
56.3% Brentuximab arm vs 12.5% Physician’s choice MTX or bexarotene achieved objective global response lasting at least 4 months

**BRENTUXIMAB- Antibody/drug conjugate against CD30**

**FDA approval granted November 2017**
Commonly reported (≥15% of patients) treatment-emergent AEs

<table>
<thead>
<tr>
<th></th>
<th>Brentuximab vedotin</th>
<th>Methotrexate or Bexarotene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy*</td>
<td>67%</td>
<td>6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>36%</td>
<td>13%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29%</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29%</td>
<td>27%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17%</td>
<td>5%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>15%</td>
<td>3%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>17%</td>
<td>13%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17%</td>
<td>18%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>Hypertriglyceridemia**</td>
<td>2%</td>
<td>18%</td>
</tr>
</tbody>
</table>

*No Gr 4 peripheral neuropathy was reported in the brentuximab vedotin (26% Gr 1, 32% Gr 2, 9% Gr 3) or physician’s choice arms (2% Gr 1, 5% Gr 2). At last follow-up (median 22.9 months), 36/44 (82%) patients in the brentuximab vedotin arm had improvement or resolution of peripheral neuropathy.

**Elevated triglycerides, were reported in 2% of patients receiving brentuximab vedotin versus 30% of patients receiving bexarotene (14% Gr 3, 8% Gr 4).

Length of drug exposure: median 12 cycles (36 weeks) of BV vs. 17 weeks of bexarotene or 9 weeks of methotrexate.
NCCN Guidelines Version 2.2018
Mycosis Fungoides/Sezary Syndrome

SYSTEMIC THERAPIES

Category A (SYST-CAT A)
- Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid], acitretin)
- Interferons (IFN-alpha, IFN-gamma)
- HDAC-inhibitors (vorinostat, romidepsin)
- Extracorporeal photopheresis
- Methotrexate (≤100 mg q week)
- Brentuximab vedotin

Category B (SYST-CAT B)
- Preferred therapies (alphabetical order)
  - Brentuximab vedotin
  - Gemcitabine
  - Liposomal doxorubicin
  - Low-dose pralatrexate
- Other therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphamide
  - Temozolomide
  - Methotrexate (>100 mg q week)
  - Pembrolizumab (category 2B)
  - Bortezomib (category 3)

SYSTEMIC THERAPIES (continued)

Category C (SYST-CAT C)
- Brentuximab vedotin
- Gemcitabine
- Liposomal doxorubicin
- Low- or standard-dose pralatrexate
- Romidepsin
- See regimens listed on TCEL-B 2 of 5 (PTCL-NOS)

Brentuximab vedotin added 2018 to Category A systemic therapy option
Phase 3 study results & FDA approval

Footnote “h” for brentuximab vedotin (BV)

hA randomized phase 3 trial comparing BV with physician’s choice of bexarotene or MTX, showed superior clinical outcome of BV in CD30+ MF and pcALCL. CD30+ was defined as CD30 expression >10% of total lymphoid cells in at least 1 or minimal 2 skin biopsies required to evaluate for eligibility. 44% of eligible MF had at least 1 screening biopsy with CD30 <10%. In 2 previously reported investigator-initiated studies, clinical responses with BV was observed across all CD30 expression levels including in those with negligible CD30 expression by IHC.
Mogamulizumab: First-in-class defucosylated humanized anti-CCR4 mAb

Higher ADCC due to a defucosylated Fc region by POTENTIAL®

G Protein-Coupled Receptor for MDC and TARC
Marker for Type II helper T cells and regulatory T cells (FoxP3+)
Involved in lymphocyte trafficking to skin
Over-expressed in ATL, PTCL, and CTCL

ADCC, antibody-dependent cellular cytotoxicity; Fc, fragment crystallizable; GPCR, G-protein-coupled receptor; MDC, macrophage derived chemokine; TARC, thymus -and activation-regulated chemokine.

Anti-CCR4 Monoclonal Antibody, Mogamulizumab, Demonstrates Significant Improvement in PFS Compared to Vorinostat in Patients with Previously Treated Cutaneous T-Cell Lymphoma: Results from the Phase 3 MAVORIC Study

Youn H. Kim, MD1; Martine Bagot, MD2; Lauren Pinter-Brown, MD3; Alain H. Rook, MD4; Pierluigi Porcu, MD5; Steven Horwitz, MD6; Sean Whittaker, MD7; Yoshiki Tokura, MD, PhD8; Maarten Vermeer, MD9; Pier Luigi Zinzani, MD10; Lubomir Sokol, MD, PhD11; Stephen Morris, MD7; Ellen J. Kim, MD4; Pablo L. Ortiz-Romero, MD12; Herbert Eradat, MD13; Julia Scarisbrick, MBChB, FRCP, MD14; Athanasios Tsiaknakas, MD15; Craig Elmets, MD16; Stephane Dalle, MD, PhD17; David Fisher, MD, PhD18; Ahmad Halwani, MD19; Brian Poligone, MD, PhD20; John Greer, MD21; Maria Teresa Fierro, MD22; Amit Kho, MD23; Alison J. Moskowitz, MD6; Karen Dwyer24; Junji Moriya24; Jeffrey Humphrey, MD24; Stacie Hudgens25; Dmitri O. Grebennik24; Kensei Tobinai, MD, PhD26; Madeleine Duvic, MD27 for the MAVORIC Investigators

1Stanford University, Stanford, CA, USA; 2Hôpital Saint Louis, APHP, Inserm U976, Université Paris 7, France; 3University of California Irvine, Orange, CA, USA; 4University of Pennsylvania, Philadelphia, PA, USA; 5Thomas Jefferson University, Philadelphia, PA, USA; 6Memorial Sloan Kettering Cancer Center, New York, NY, USA; 7Guy's and St Thomas' Hospital, London, UK; 8Hamamatsu University School of Medicine, Hamamatsu, Japan; 9Leiden University, Leiden, The Netherlands; 10Institute of Hematology “Seràgnoli,” University of Bologna, Bologna Italy; 11Moffitt Cancer Center, Tampa, FL, USA; 12Department of Dermatology, Institute I-12, Hospital 12 de Octubre Medical School, University Complutense Madrid; 13UCLA Medical Center, Santa Monica, CA, USA; 14University Hospital Birmingham, Birmingham, UK; 15University Hospital Münster, Münster, Germany; 16University of Alabama, Birmingham, AL, USA; 17Hospices Civils de Lyon, Claude Bernard Lyon 1 University, Lyon, France; 18Dana-Farber Cancer Institute, Boston, MA, USA; 19University of Utah, Salt Lake City, UT, USA; 20Rochester Skin Lymphoma Center, Fairport, NY, USA; 21Vanderbilt University Medical Center, Nashville, TN, USA; 22University of Turin, Turin, Italy; 23Peter MacCallum Cancer Centre, Melbourne, Australia; 24Kyowa Kirin Pharmaceutical Development, Inc., Princeton, NJ, USA; 25Clinical Outcome Solutions, Tucson, AZ, USA; 26National Cancer Center Hospital, Choc-ku, Tokyo, Japan; 27McGill University Health Centre, Montreal, Quebec, Canada; 28National Cancer Institute Hospital, Choc-ku, Tokyo, Japan

Mogamulizumab: Anti-CCR4 Monoclonal Antibody
FDA priority review granted
## Response outcomes

<table>
<thead>
<tr>
<th></th>
<th>Mogamulizumab</th>
<th>Vorinostat</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR&lt;sup&gt;a,b&lt;/sup&gt;, n/N (%)</td>
<td>52/186 (28)</td>
<td>9/186 (5)</td>
</tr>
<tr>
<td>MF&lt;sup&gt;c&lt;/sup&gt;</td>
<td>22/105 (21)</td>
<td>7/99 (7)</td>
</tr>
<tr>
<td>SS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30/81 (37)</td>
<td>2/87 (2)</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>5/32 (16)</td>
<td>1/23 (4)</td>
</tr>
<tr>
<td>Stage III</td>
<td>5/22 (23)</td>
<td>0/16 (0)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>35/96 (36)</td>
<td>3/98 (3)</td>
</tr>
<tr>
<td>DOR, median, months</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>MF</td>
<td>13 (n=22)</td>
<td>9 (n=7)</td>
</tr>
<tr>
<td>SS</td>
<td>17 (n=30)</td>
<td>7 (n=2)</td>
</tr>
</tbody>
</table>

**ORR**<sup>a</sup> n/N (%) mogamulizumab after crossover: 41/136 (30)

<sup>a</sup>ORR is the percentage of patients with confirmed CR or confirmed PR; <sup>b</sup>P<0.0001; <sup>c</sup>P=0.004.

- Median relative dose intensities for mogamulizumab were 97.5% and for vorinostat was 95.1%
Cancer Immunotherapy Trials Network  
NCI Protocol # CITN-10  

A Phase 2 Study of MK-3475 (pembrolizumab) for the Treatment of Relapsed/Refractory MF/SS  

Coordinating Center: M Cheever  
CITN, Fred Hutchinson Cancer Research Center  

Principal Investigator: H Kohrt  
Y Kim (Co-PI)  
Stanford University SOM  

Investigative sites/site PI:  
A Rook (U Penn), F Foss (Yale), PG Porcu (OSU), A Moskowitz (MSKCC), A Shustov (SCCA), L Sokol (Moffitt), S Shanbhag (Johns Hopkins)
Malignant Melanoma
what’s new?

- The new staging system
- Treatment of advanced melanoma
  - Adjuvant treatment
The new staging system- AJCC 8th edition

- In use since January 2018
- Changes in T, N and M categories

<table>
<thead>
<tr>
<th>Changes in AJCC 8th Edition</th>
<th></th>
</tr>
</thead>
</table>
| **Definition of primary tumour (T)** | • Tumour thickness recorded to the nearest 0.1mm, not 0.01mm  
• T1a <0.8mm without ulceration  
• T1b melanomas include those 0.8-1mm with or without ulceration and those <0.8mm with ulceration  
• Mitotic rate is no longer a T1 category criterion |
| **Loco/Regional Metastases (N)** | • Clinically occult vs clinically detected  
• Microsatellites, satellites, or in-transit mets = denoted by ‘c’  
• N-category criterion based upon the number of tumour-involved regional lymph nodes  
  - N1: 1 lymph node involved  
  - N2: 2-3 lymph nodes involved  
  - N3: >4 lymph nodes involved  
  - N1/2/3a: 1 occult nodes  
  - N1/2/3/b: clinically detected nodes  
  - N1/2/3/c: microsatellites, satellites, in-transit mets |
| **AJCC Prognostic Stage Groups** | • Stage IIIA better prognosis (93%) than Stage IIC (82%)  
• Stage IIID (32%) |
| **Definition of Distant Metastasis (M)** | • M1a non-visceral (distant cutaneous, subcutaneous, nodal)  
• M1b: lung mets  
• M1c: visceral mets  
• M1d: CNS mets  
• If elevated LDH: ‘1’ added at end  
  • eg lung mets with high LDH: M1b(1)  
  • eg visceral mets with high LDH: M1c(1)  
  (elevated LDH no longer defines M1c as per 7th edition) |
TABLE 5. AJCC Clinical Prognostic Stage Groups (cTNM)\textsuperscript{a}

<table>
<thead>
<tr>
<th>WHEN T IS...</th>
<th>AND N IS...</th>
<th>AND M IS...</th>
<th>THEN THE CLINICAL STAGE GROUP IS...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>0</td>
</tr>
<tr>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
<td>IA</td>
</tr>
<tr>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
<td>IB</td>
</tr>
<tr>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
<td>IB</td>
</tr>
<tr>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>IIA</td>
</tr>
<tr>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
<td>IIA</td>
</tr>
<tr>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
<td>IIB</td>
</tr>
<tr>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
<td>IIB</td>
</tr>
<tr>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
<td>IIC</td>
</tr>
<tr>
<td>Any T, Tis</td>
<td>≥N1</td>
<td>M0</td>
<td>III</td>
</tr>
<tr>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>IV</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, eighth edition (2017) published by Springer.

• Management of advanced melanoma
Adjuvant treatment

Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial


The NEW ENGLAND JOURNAL of MEDICINE

Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy


FDA Approval 2015

Nov 2016
But new adjuvant options in 2018...

Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma


ABSTRACT

Background
Nivolumab and ipilimumab are immune checkpoint inhibitors that have been approved for the treatment of advanced melanoma. In the United States, ipilimumab has also been approved as adjuvant therapy for melanoma on the basis of recurrence-free and overall survival rates that were higher than those with placebo in a phase 3 trial. We wanted to determine the efficacy of nivolumab versus ipilimumab for adjuvant therapy in patients with resected advanced melanoma.

Methods
In this randomized, double-blind, phase 3 trial, we randomly assigned 906 patients (435 patients in each group) to receive nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks or ipilimumab at a dose of 10 mg per kilogram every 4 weeks for 6 doses and then every 12 weeks (453 patients). The patients were treated for a period of up to 5 years until disease recurrence, a report of unacceptable toxic effects, or withdrawal of consent. The primary end point was recurrence-free survival in the intention-to-treat population.

Results
At a minimum follow-up of 18 months, the 12-month rate of recurrence-free survival was 76.3% (95% confidence interval, 66.1 to 74.5) in the nivolumab group and 60.8% (95% CI, 56.0 to 65.2) in the ipilimumab group (hazard ratio for disease recurrence or death, 0.55; 95% CI, 0.42 to 0.70; P=0.0006). Treatment-related grade 3 or 4 adverse events were reported in 34.4% of the patients in the nivolumab group and in 45.9% of those in the ipilimumab group; treatment was discontinued because of any adverse event in 9.7% and 46.0% of the patients, respectively. Two deaths (0.4%) related to toxic effects were reported in the ipilimumab group more than 104 days after treatment.
Summary

• **BCC**
  – Smoothened inhibition + PI3K inhibitors
  – Immunotherapy: Pembrolizumab±Vismodegib in trial
• **SCC**
  – Alternative staging system
  – EGFR inhibition
  – Immunotherapy – Cemiplimab, Pembrolizumab in trial
• **Merkel Cell Carcinoma**
  – Serology: antibodies to MCPyV oncoprotein for tracking recurrence
  – Immunotherapy now preferable over chemotherapy for advanced disease
• **CTCL**
  – Brentuximab Vedotin for CD30+ CTCL
  – Mogamulizumab (anti-CCR4 agent)
  – Immunotherapy in trial (Pembrolizumab)
• **Malignant Melanoma**
  – New staging system (AJCC 8\textsuperscript{th} edition)
  – Adjuvant therapy for resected stage 3 disease: Nivolumab