Emerging Therapies for Cutaneous Malignancies

Genevieve Kelly

AAD Highlights Meeting

Thurs 15th March 2018

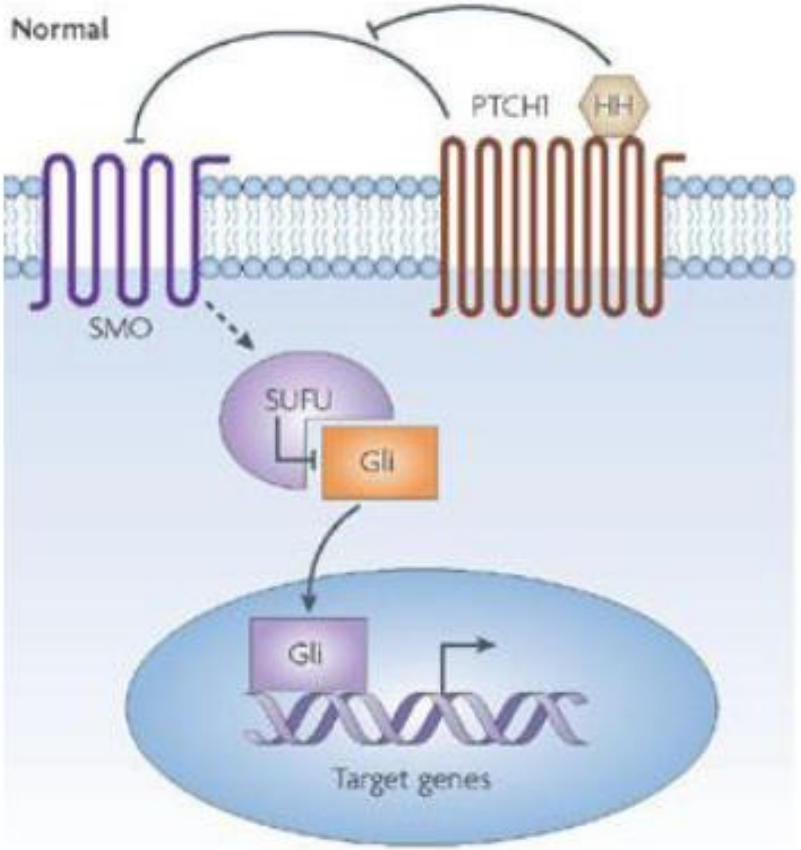
Topics

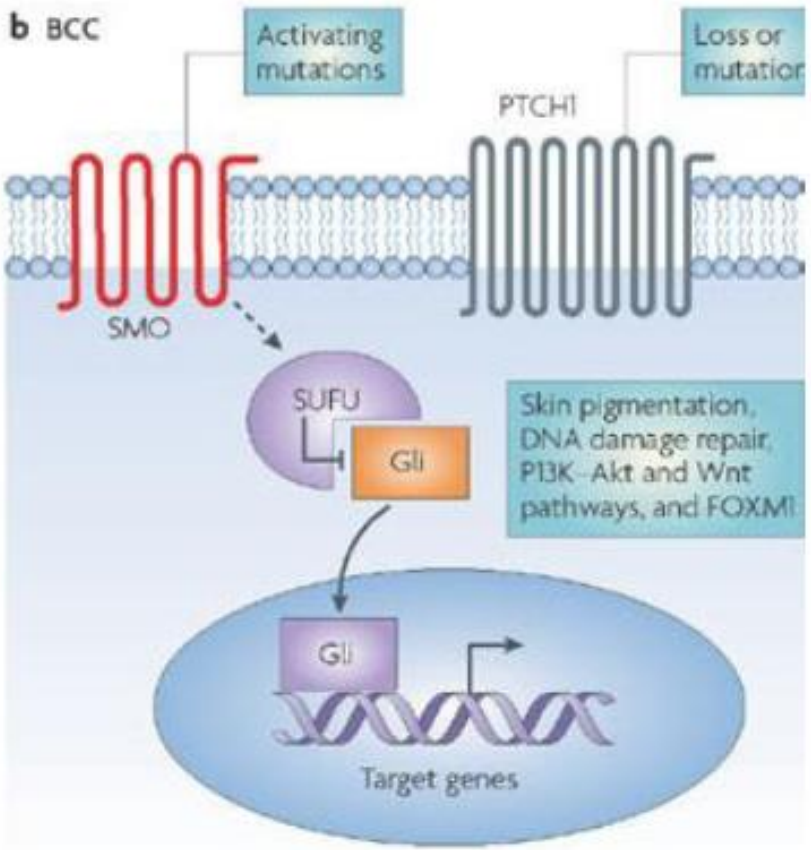
- Basal Cell Carcinoma
- Squamous Cell Carcinoma
- Merkel Cell Carcinoma
- Cutaneous Lymphoma
- Malignant Melanoma

Basal Cell Carcinoma

Update on therapy for advanced BCC

Hedgehog signaling pathway





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 sudy: anti-tumour activity in patients with mBCC and laBCC. RR 58%. Median duration of response 12.8months*
  - 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
  - Treatment of advanced basal cell carcinoma with sonidegib: perspective from the 30-month update of the BOLT trial. Chen L, Aria AB, Silapunt S et al. Future Oncol. 2018;14:515-525.

Monitoring:
CK (Sonidegib)
B HCG

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

*LoRusso PM et al. Clin Cancer Res. 2011;17;2502-2511
**Sekulic A et al. New Engl J Med.2012;366:2171-9

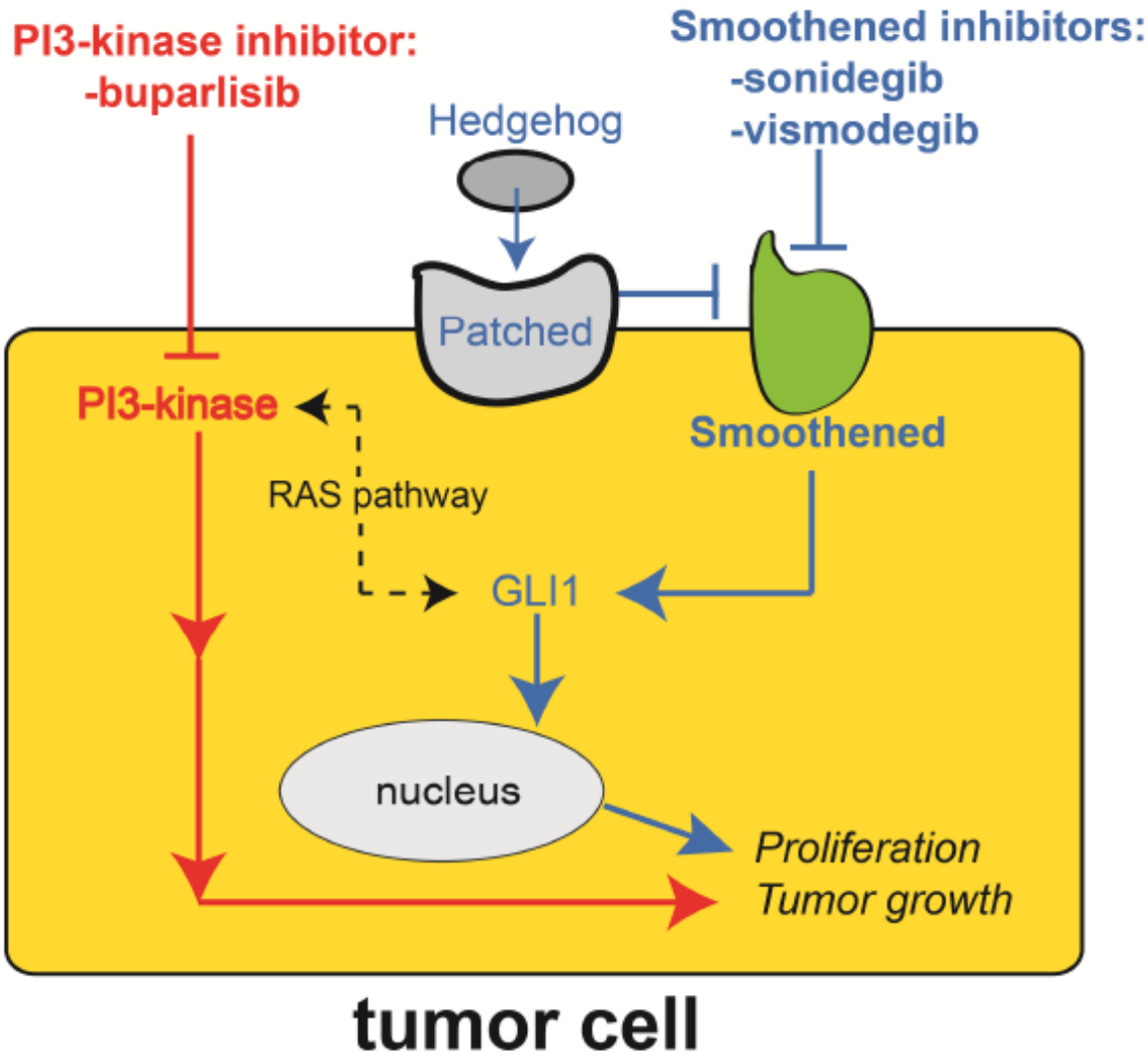
- Recurrent disease while on Smoothened inhibition
  - 20%
  - Can be discontiguous
- If resistant to Vismodegib, Sonidegib unlikely to work*
- Resistance due to mutations in Smoothened: drug binding pocket inaccessible to the drug.
- But if has E518A mutation in Smoothened: may respond to Sonidegib 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%***

*An Investigator-Initiated open label trial of Sonidegib in Advanced BCC resistant to Vismodegib. Danial et al. Clin Cancer Res:22(6)Mar 2016

**JAAD Case Rep.2017 Dec 18;4:10-12. Intracranial regression of an advanced basal cell carcinoma using sonidegib and itraconazoleafter failure with vismodegib. Yoon J, Apicelli AJ 3rd, Pavlopoulos TV.

***Kwon et al. Jamer Acad Dermatol, Vol 75,1:213-215

Smoothened Inhibition Resistance: PI3K pathway



Accepted Manuscript

An exploratory open-label, investigator-initiated study to evaluate the efficacy and safety of combination sonidegib and buparlisib for advanced basal cell carcinomas

Duy Cong Tran, BS, Ann Moffat, BA, Richard Brotherton, RN, Alana Pague, BS, Gefei
Alex Zhu, MD, Anne Lynn S. Chang, MD

- 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

Research

JAMA Dermatology | Original Investigation

Association Between Programmed Death Ligand 1 Expression in Patients With Basal Cell Carcinomas and the Number of Treatment Modalities

Julia Chang, MS; Gefei A. Zhu, MD; Christine Cheung, BS; Shufeng Li, MS; Jinah Kim, MD, PhD; Anne Lynn S. Chang, MD

CASE REPORT OPEN

Metastatic basal cell carcinoma with amplification of PD-L1: exceptional response to anti-PD1 therapy

Sadakatsu Ikeda[1,2,3,7], Aaron M Goodman[1,2,7], Philip R Cohen[4], Taylor J Jensen[5], Christopher K Ellison[5], Garrett Frampton[6], Vincent Miller[6], Sandip P Patel[1,2] and Razelle Kurzrock[1,2]

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

Category	Definition
T0	In situ SCC
T1	0 risk factors*
T2a	1 risk factor
T2b	2-3 risk factors
T3	4 risk factors or bone invasion

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

Parameters	Low risk	High risk
Clinical		
Location*/size†	Area L <20 mm Area M‡ <10 mm	Area L ≥20 mm Area M ≥10 mm Area H§
Borders	Well defined	Poorly defined
Primary vs recurrent	Primary	Recurrent
Immunosuppression	No	Yes
Site of prior radiation therapy or chronic inflammatory process	No	Yes
Rapidly growing tumor	No	Yes
Neurologic symptoms	No	Yes
Pathologic		
Degree of differentiation	Well to moderately differentiated	Poorly differentiated
High-risk histologic subtype‖	No	Yes
Depth (thickness or Clark level)¶	<2 mm, or I, II, III	≥2 mm or IV, V
Perineural, lymphatic, or vascular involvement	No	Yes

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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.

†Greatest tumor diameter, including peripheral rim of erythema.

‡Location independent of size may constitute high risk.

§Area H constitutes high-risk on the basis of location, independent of size.

‖Adenoid (acantholytic), adenosquamous (showing mucin production), desmoplastic, or metaplastic (carcinosarcomatous) subtypes.

¶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 excisional 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.

Guidelines of care for the management of cutaneous squamous cell carcinoma.
Work Group; Invited Reviewers, Kim JYS, Kozlow JH, Mittal B, Moyer J, Olenecki T, Rodgers P.
J Am Acad Dermatol. 2018 Mar;78:560-578. Epub 2018 Jan 10. PMID: 29331386

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 inibitors: Nivolumab (Opdivo, BMS) and Pembrolizumab (Keytruda, Merck)

EGFR Inhibition in cSCC

- Maubec *et* al.: Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin.
  - 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
- Foote *et al.*: Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma.
  - 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

CrossMark

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).

William *et al.*, J Am Acad Dermatol. 2017 Dec;77(6):1110-1113.e2.

Immunotherapy for SCC

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

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

PR, partial response.

Drug therapy of advanced cutaneous squamous cell carcinoma: is there any evidence? Ribero S, Stucci LS, Daniels GA, Borradori L. Curr Opin Oncol. 2017;29:129-135.

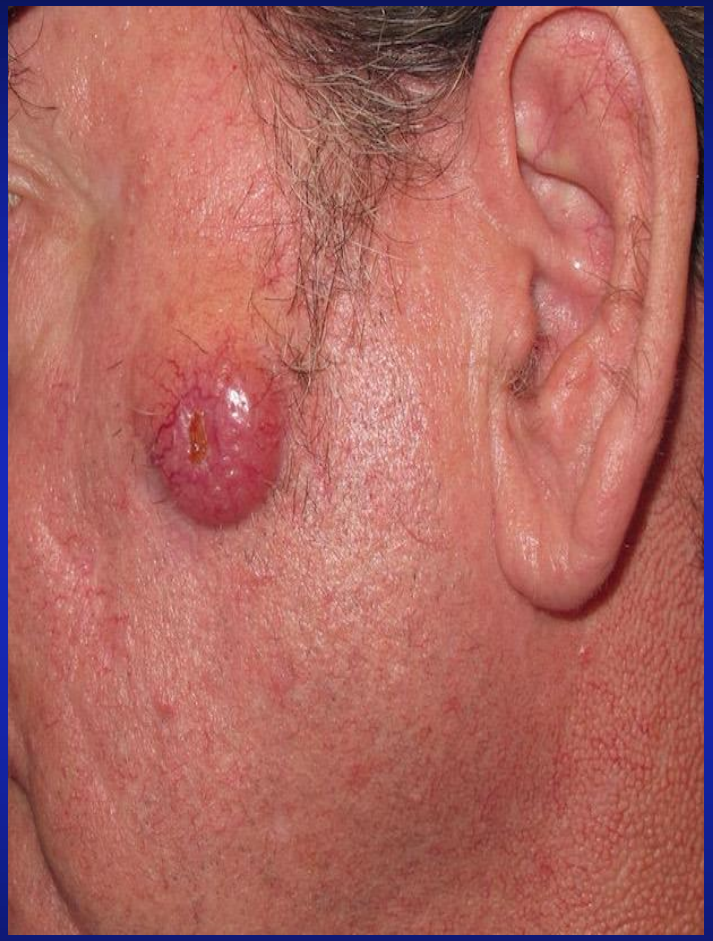
- ClinicalTrials.gov
  - NCT02760498
  - PD1 monoclonal antibody, REGN2810 (Cemiplimab)
  - Phase 2 interventional clinical trial May 2016-May 2019.

- 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

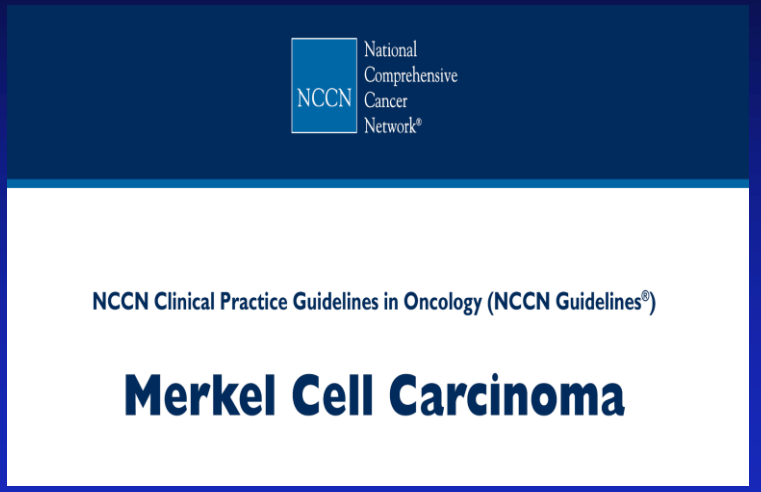
Why is MCC important?

- 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]



1. Becker et al., Ann Oncol, 2010
2. 2007-2013 SEER Cancer Stat Facts.
3. Paulson et al, J Am Acad Dermatol, 2017

Current Management & Limitations



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)

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 (MCV or MCPyV). MCV 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 MCV-positive MCCs, viral DNA was integrated within the tumor genome in a clonal pattern, suggesting that MCV infection and integration preceded clonal expansion of the tumor cells. Thus, MCV 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 polyomavirus infections 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

Molecular Virology Program, University of Pittsburgh Cancer Institute, University of Pittsburgh, 5117 Centre Avenue, Suite 1.8, Pittsburgh, PA 15213, USA.

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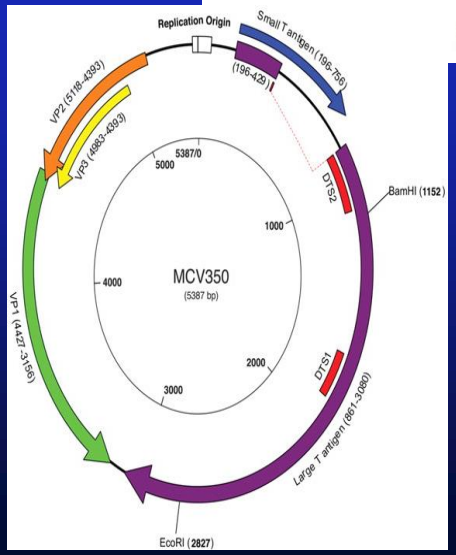
22 FEBRUARY 2008 VOL 319 SCIENCE www.sciencemag.org

Moore/Chang
(KSHV)

Present in 8/10 MCCs

Validated in dozens of studies

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



Schematic of
MCPyV genome

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2015

Mutational landscape of MCPyV-positive and MCPyV-negative merkel cell carcinomas with implications for immunotherapy

Gerald Goh[1,2], Trent Walradt[3], Vladimir Markarov[4], Astrid Blom[5], Nadeem Riaz[6,7], Ryan Doumani[5], Krista Stafstrom[5], Ata Moshiri[5], Lola Yelistratova[5], Jonathan Levinsohn[3], Timothy A. Chan[4,6], Paul Nghiem[5,7,8], Richard P. Lifton[1,2], Jaehyuk Choi[3,9,10]

Priority Report

Cancer Research

The Distinctive Mutational Spectra of Polyomavirus-Negative Merkel Cell Carcinoma

Paul William Harms[1,2,3], Pankaj Vats[1,4], Monique Elise Verhaegen[3], Dan R. Robinson[1], Yi-Mi Wu[1,2], Saravana Mohan Dhanasekaran[1,2], Nallasivam Palanisamy[1,2,5], Javed Siddiqui[1,2], Xuhong Cao[1,6], Fengyun Su[1], Rui Wang[1,2], Hong Xiao[1,2,5], Lakshmi P. Kunju[1,2], Rohit Mehra[1,2,5], Scott A. Tomlins[1,2,7,8], Douglas Randall Fullen[2,3], Christopher Keram Bichakjian[3], Timothy M. Johnson[3], Andrzej Antoni Dlugosz[3,9], and Arul M. Chinnaiyan[1,2,6,7,8]

Priority Report

Cancer Research

UV-Associated Mutations Underlie the Etiology of MCV-Negative Merkel Cell Carcinomas

Stephen Q. Wong[1], Kelly Waldeck[1], Ismael A. Vergara[1], Jan Schröder[1,2,3], Jason Madore[4], James S. Wilmott[4], Andrew J. Colebatch[1,5], Ricardo De Paoli-Iseppi[4], Jason Li[1], Richard Lupat[1], Timothy Semple[1], Gisela Mir Arnau[1], Andrew Fellowes[1], J. Helen Leonard[6], George Hruby[4], Graham J. Mann[4], John F. Thompson[4], Carleen Cullinane[1], Meredith Johnston[1], Mark Shackleton[1,7], Shahneen Sandhu[1,7], David D.L. Bowtell[1,5,7], Ricky W. Johnstone[1,7], Stephen B. Fox[1,5,7], Grant A. McArthur[1,7], Anthony T. Papenfuss[1,2,7,8], Richard A. Scolyer[4], Anthony J. Gill[9], Rodney J. Hicks[1,7], and Richard W. Tothill[1,5]

UV driven MCC
→ High mutational burden

3 studies in late 2015...

Original Article

Cancer, 2017

Viral Oncoprotein Antibodies as a Marker for Recurrence of Merkel Cell Carcinoma: A Prospective Validation Study

Kelly G. Paulson, MD, PhD[1,2,5]; Christopher W. Lewis, BS[1]; Mary W. Redman, PhD[4]; William T. Simonson, MD, PhD[3]; Aaron Lisberg, MD[1]; Deborah Ritter, MS[3]; Chihiro Morishima, MD[3]; Kathleen Hutchinson, MS[3]; Lola Mudgistratova, BA[1]; Astrid Blom, MD[1]; Jayasri Iyer, MD[1]; Ata S. Moshiri, MD, MPH[1]; Erica S. Tarabadkar, MD[1]; Joseph J. Carter, PhD[6]; Shailender Bhatia, MD[2,5]; Masaoki Kawasumi, MD, PhD[1]; Denise A. Galloway, PhD[6]; Mark H. Wener, MD[3]; and Paul Nghiem, MD, PhD[1,5]

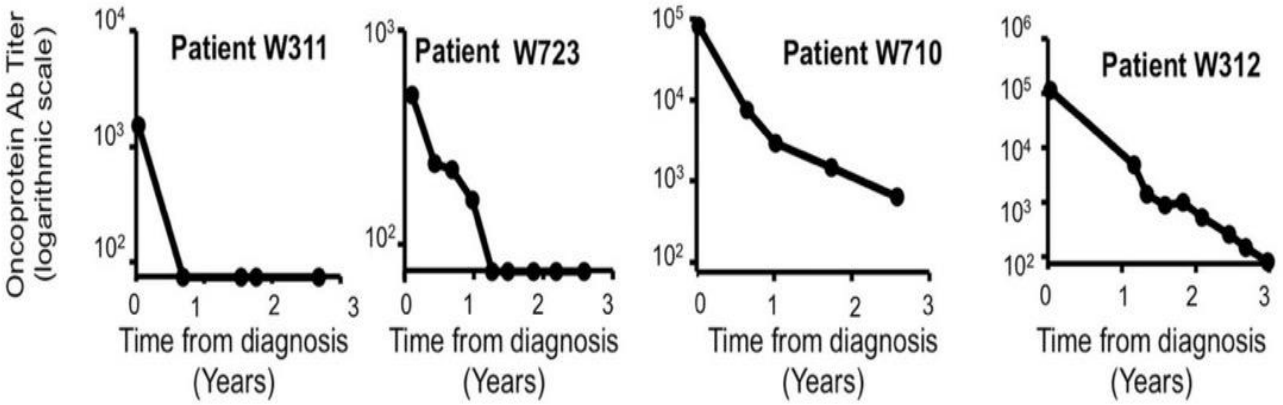
BACKGROUND: Merkel cell carcinoma (MCC) is an aggressive skin cancer with a recurrence rate of >40%. Of the 2000 MCC cases per year in the United States, most are caused by the Merkel cell polyomavirus (MCPyV). Antibodies to MCPyV oncoprotein (T-antigens) have been correlated with MCC tumor burden. The 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.

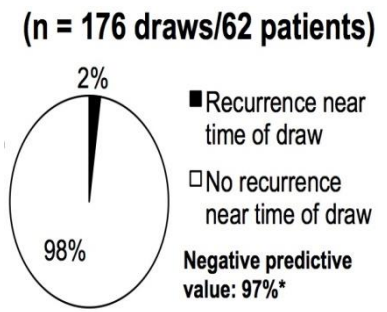
A prospective study of antibodies to MCPyV oncoprotein

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

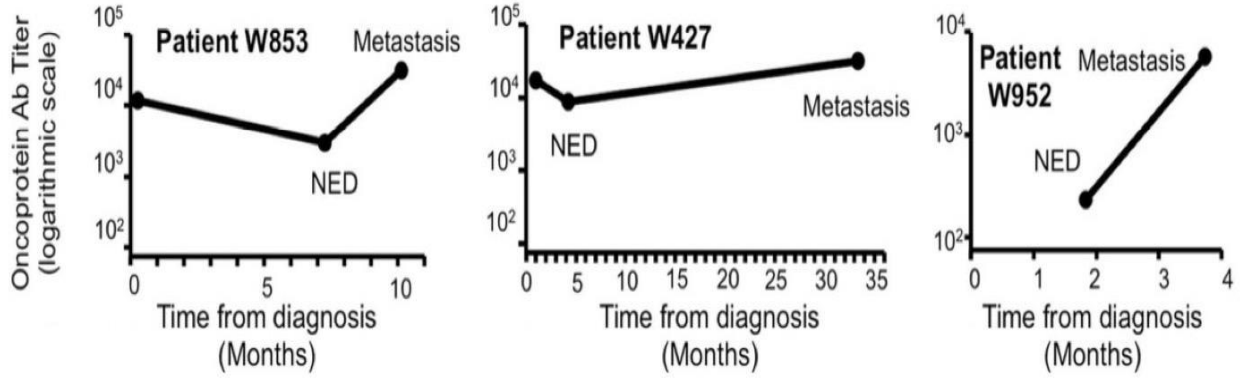
Falling/negative titers



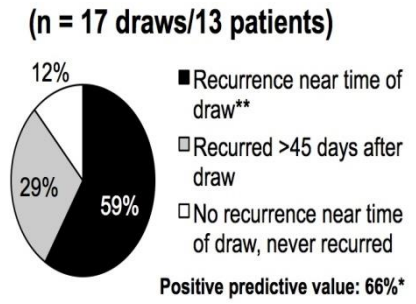
98% reassured



Increasing titers



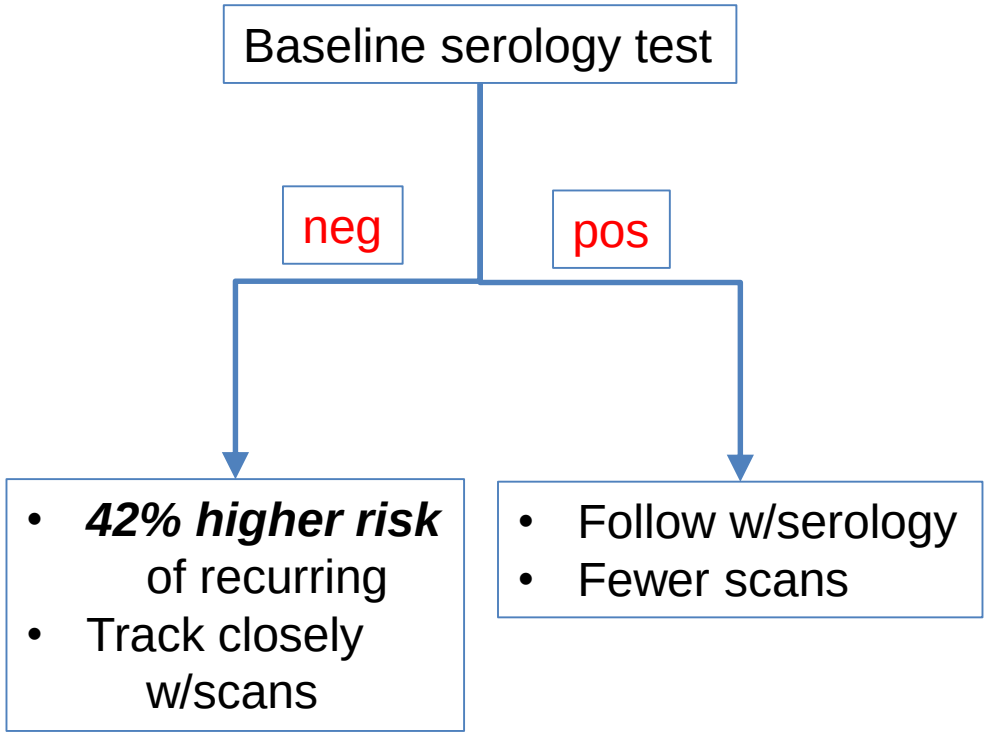
88% have/will recur



Paulson, et al, Cancer 2016

Assay available as of January 2014...

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



Response Rates for Systemic MCC drugs

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

Immunotherapy changed NCCN guidelines

NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Merkel Cell Carcinoma

2016 and before	2017	2018
Chemotherapy only	Pembrolizumab was listed	Checkpoint immunotherapies are preferred to chemotherapy
Disseminated Disease: As clinical judgment indicates: • Cisplatin ± etoposide • Carboplatin ± etoposide • Topotecan • (CAV): Cyclophosphamide, doxorubicin (or epirubicin), and vincristine	**Disseminated Disease:** • Clinical trial (preferred) As clinical judgement dictates: • Cisplatin ± etoposide • Carboplatin ± etoposide • Topotecan • (CAV): Cyclophosphamide, doxorubicin (or epirubicin), and vincristine • Pembrolizumab	**Disseminated Disease:** • Clinical trial (preferred) • Avelumab[2] • Pembrolizumab[2] • Nivolumab[2] • 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

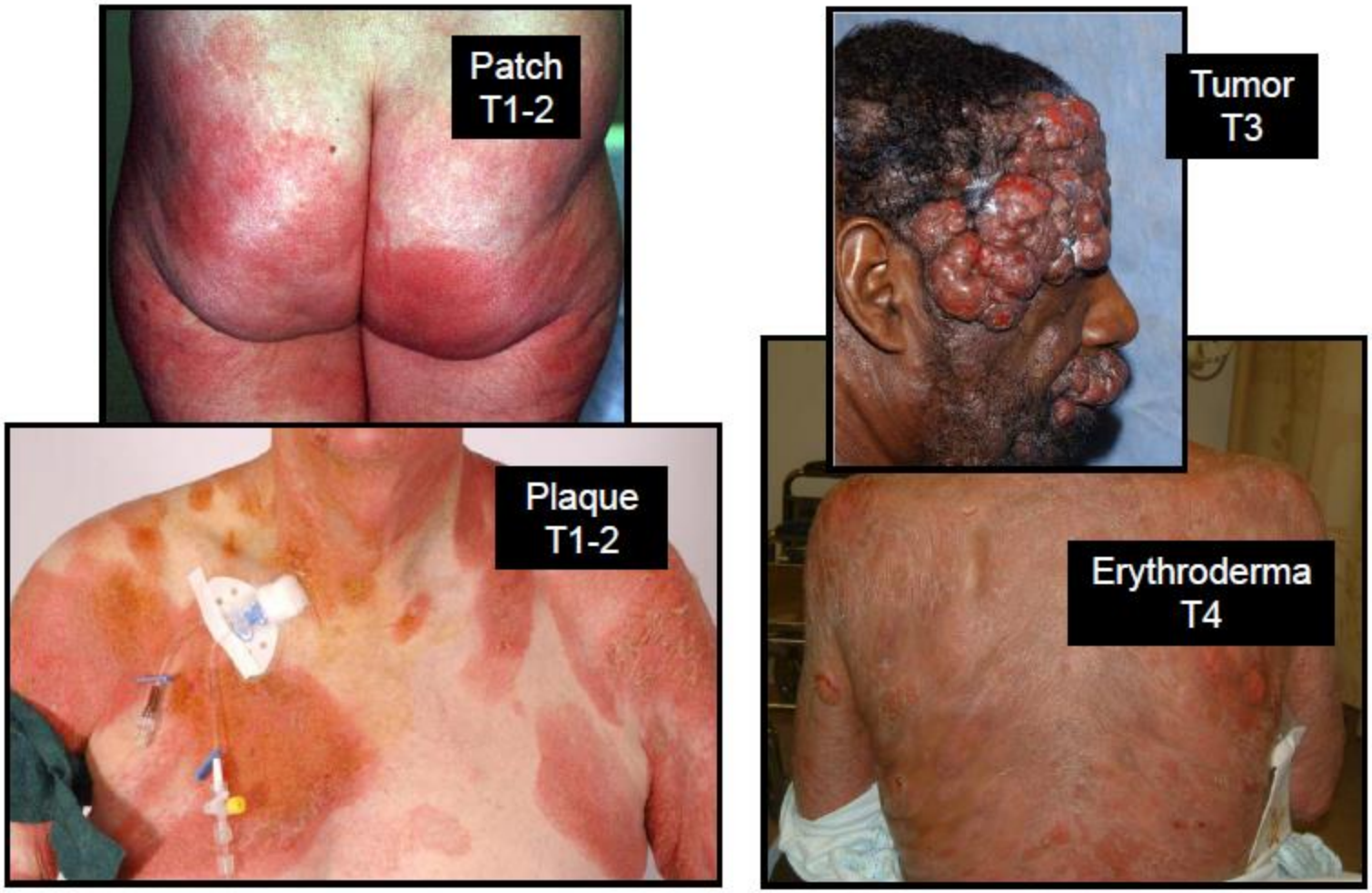
CTCL: Introduction

- Rare group of extranodal non-Hodgkin Lymphoma with heterogenous characteristics, severe pruritus and infectious complications.
- Most common forms are Mycosis Fungoides (MF) and Sezary Syndrome (SS)
- Advanced stage MF or SS, stages IIB-IVB manifest as cutaneous tumours, erythroderma, extracutaneous disease.
- Associated with decreased QOL and shortened survival compared with early stage disease

2016 WHO Mature T and NK neoplasms
Mycosis fungoides and variants/subtype
Sézary syndrome
Cutaneous CD30+ T-cell lymphoproliferative disorders • Lymphomatoid papulosis • Cutaneous anaplastic large cell lymphoma
Subcutaneous panniculitis-like T-cell lymphom
Cutaneous γ/δ T-cell lymphoma
Hydroa vacciniforme-like lymphoproliferative disorder*
Extranodal NK-/T-cell lymphoma, nasal type
Adult T-cell leukemia/lymphoma
Cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
Cutaneous acral CD8+ T-cell lymphoma*
Cutaneous CD4+ small/medium T-cell lymphoproliferative disorder*
Follicular T-cell lymphoma*
Peripheral T-cell lymphoma, NOS

*Changes from 2008 classification; provisional entities are in *italics*, Blood 2016

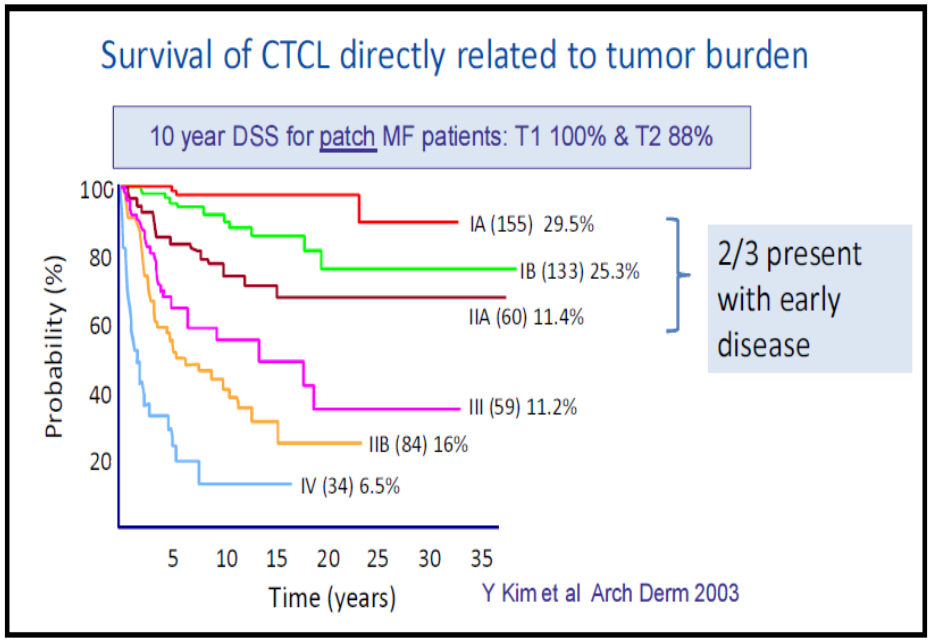
Mycosis Fungoides
Treatment of varying skin manifestations



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

Clinical stage	T	N	M
1A	1	0	0
1B	2	0	0
2A	1,2	1	0
2B	3	0,1	0
3	4	0,1	0
4A	1-4	2,3	0
4B	1-4	0-3	1



Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood.2007;110:1713–1722.

NCCN National Comprehensive Cancer Network® CTCL guidelines: T1 (<10% BSA)

For limited/localized skin involvement (Skin-Limited/Local)

- **Topical corticosteroids[b]**
- **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)[c]**
- **Topical imiquimod**

NCCN National Comprehensive Cancer Network® CTCL guidelines: T2 (BSA>10%)

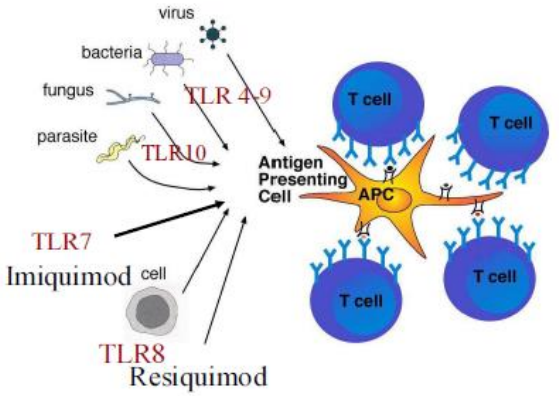
For generalized skin involvement (Skin-Generalized)

- **Topical corticosteroids[b]**
- **Topical chemotherapy (mechlorethamine [nitrogen mustard], carmustine)**
- **Phototherapy (UVB, nbUVB, for patch/thin plaques; PUVA for thicker plaques)[c]** UVA1
- **Total skin electron beam therapy (TSEBT) (12-36 Gy)[d] (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

Skin Therapy	CR	ORR
Topical steroids	45-65%	75-95%
→ **Bexarotene gel**	20-35%	50-75%
→ **Topical NM**	25-70%	50-90%
nbUVB	45-75%	75-100%
PUVA	50-80%	85-100%
TSEBT (≥30 Gy)	80-90%	100%

Toll-like receptor agonists



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

Blood 2016

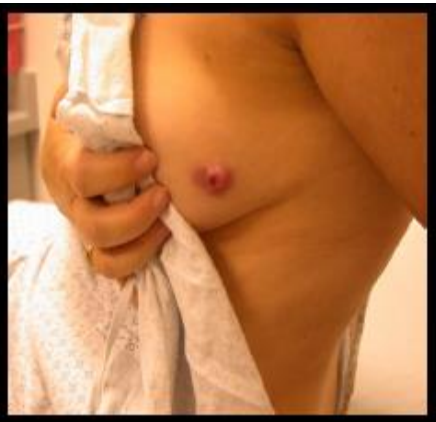
Alain H. Rook,[1] Joel M. Gelfand,[1] Maria Wysocka,[1] Andrea B. Troxel,[1] Bernice Benoit,[1] Christian Surber,[2,3] Rosalie Elenitsas,[1] Marie A. Buchanan,[1] Deborah S. Leahy,[1] Rei Watanabe,[4,5] Ilan R. Kirsch,[6] Ellen J. Kim,[1] and Rachael A. Clark[5,7]

Treatment of advanced MF and SS

Skin Directed Therapy (SDT)	Non-Cytotoxic systemic therapy	Cytotoxic Systemic Therapy/Biologics	Bone Marrow Transplant
PUVA	Extracorporeal photopheresis (ECP)	Methotrexate	
Spot Radiation	Interferon	Doxorubicin	
Total Skin Electron Beam Radiotherapy	Bexarotene	Gemcitabine	
	Histone Deacetylase (HDAC) inhibitors – Romidepsin, Vorinostat	Pralatrexate	
		Brentuximab	

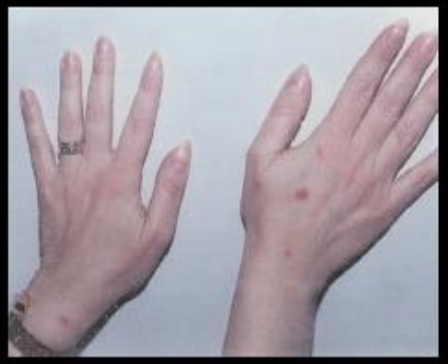
Efficacy of Approved Systemic Agents in CTCL

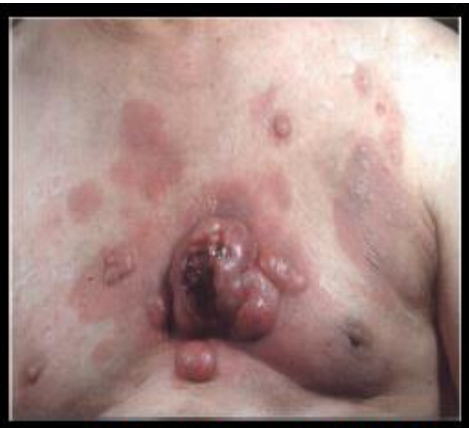
		Efficacy Data			
Agent (Class)	Indication	Study	N	ORR	DOR
Romidepsin (HDAC inhibitor)	Patients with CTCL who have received systemic therapy	Pivotal	96	34%	15 mo
		Supportive	71	35%	11 mo
Denileukin diftitox (Fusion protein)	Tumors that express CD25	Pivotal	71	30%	4 mo
Bexarotene (Retinoid x-receptor activator)	Cutaneous manifestations	Pivotal	62	32%	5+ mo
Vorinostat (HDAC inhibitor)	Cutaneous manifestations	Pivotal	74	30%	6+ mo
		Supportive	33	24%	4 mo



Primary cutaneous Anaplastic T-cell Lymphoma

Lymphomatoid Papulosis





Transformed CD30+ Mycosis Fungoides

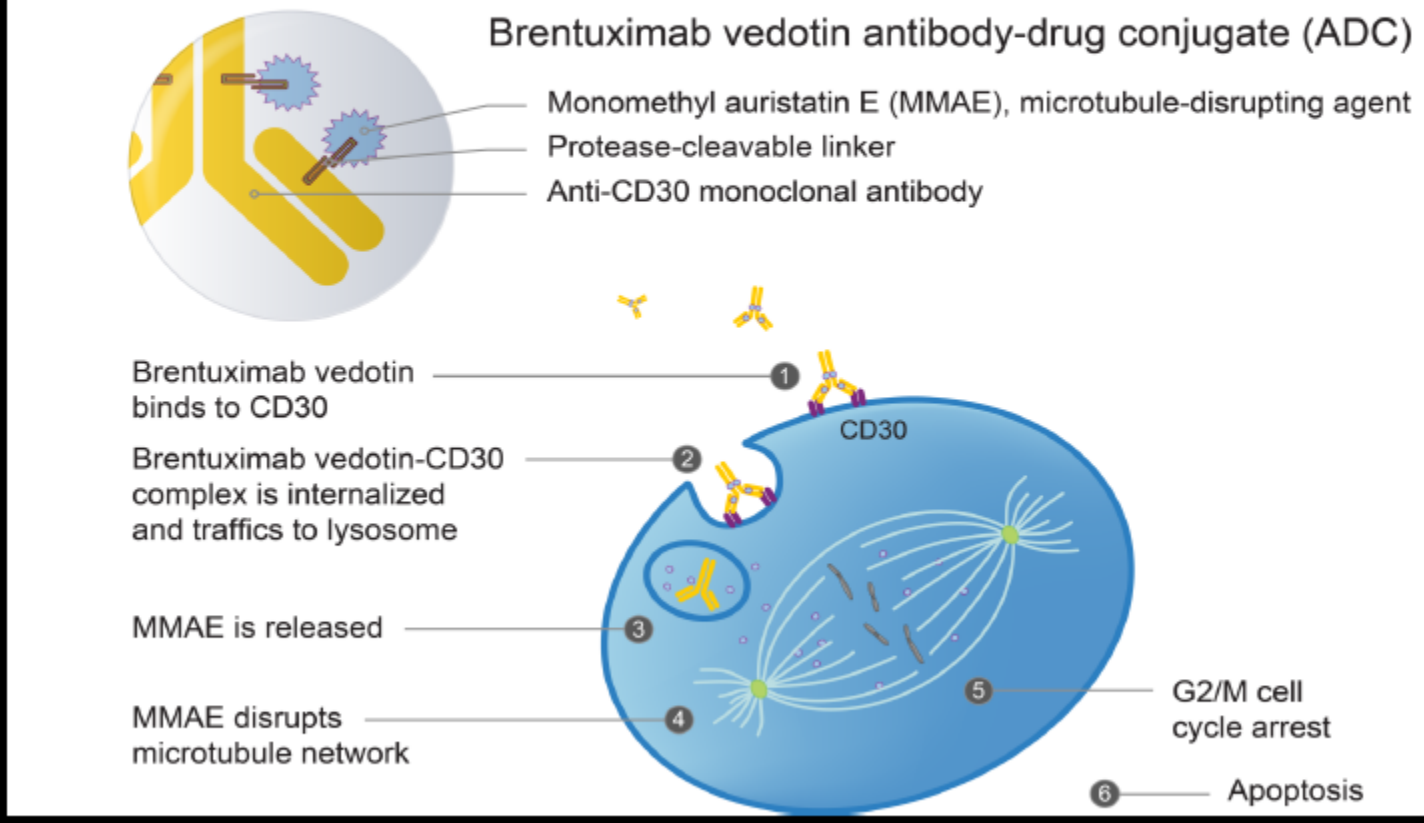
CD30+ Cutaneous T cell lymphomas

- Lymphomatoid Papulosis LyP
- Primary Cutaneous ALCL c-ALCL

CD30+ Lymphoproliferative Disorders

- Mycosis Fungoides MF or T-MF
- Secondary Cutaneous ALCL
- PTCL-NOS HTLV-1 ATL
- Hodgkin Lymphoma HL

Brentuximab Vedotin Mechanism of Action



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

J Clin Oncol 2015;33:3750-58

Youn H. Kim, Mahkam Tavallaee, Uma Sundram, Katrin A. Salva, Gary S. Wood, Shufeng Li, Sima Rozati, Seema Nagpal, Michael Krathen, Sunil Reddy, Richard T. Hoppe, Annie Nguyen-Lin, Wen-Kai Weng, Randall Armstrong, Melissa Pulitzer, Ranjana H. Advani, and Steven M. Horwitz

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

J Clin Oncol 2015;33:3759-65

Madeleine Duvic, Michael T. Tetzlaff, Pamela Gangar, Audra L. Clos, Dawen Sui, and Rakhshandra Talpur

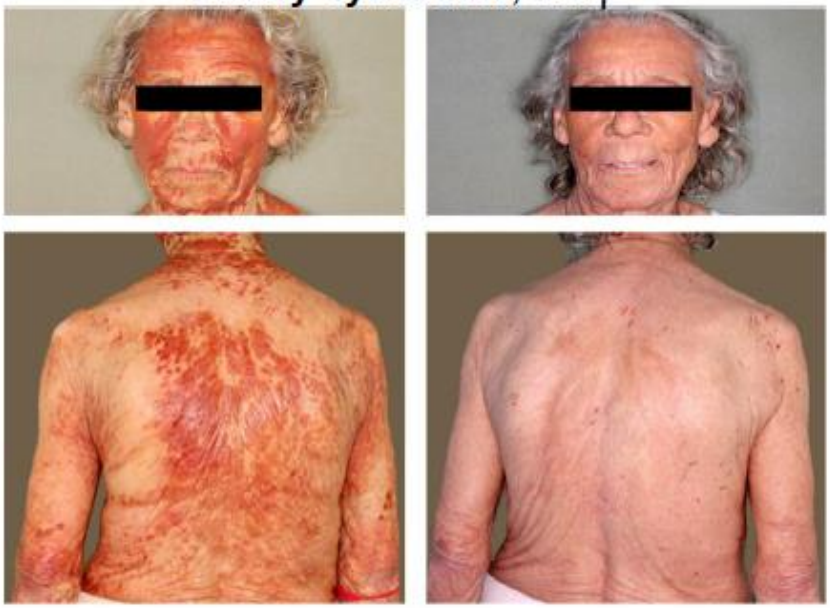
Response rates of 54-70% in MF/SS in 2 phase II studies

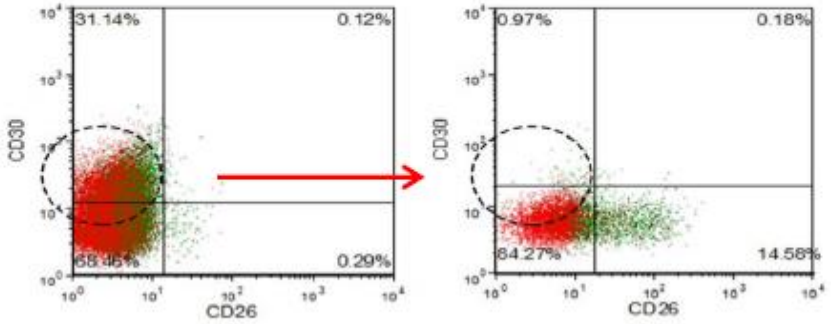
PC CD30+ LPD included in MDACC

- LyP, n=16, ORR 100% (69% CR)
- pc ALCL, n=4, ORR 100% (all CR)

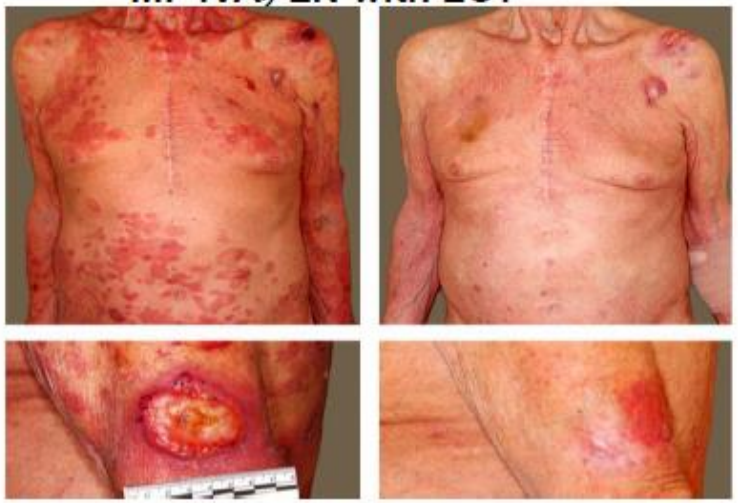
Great clinical response to brentuximab vedotin in MF/SS

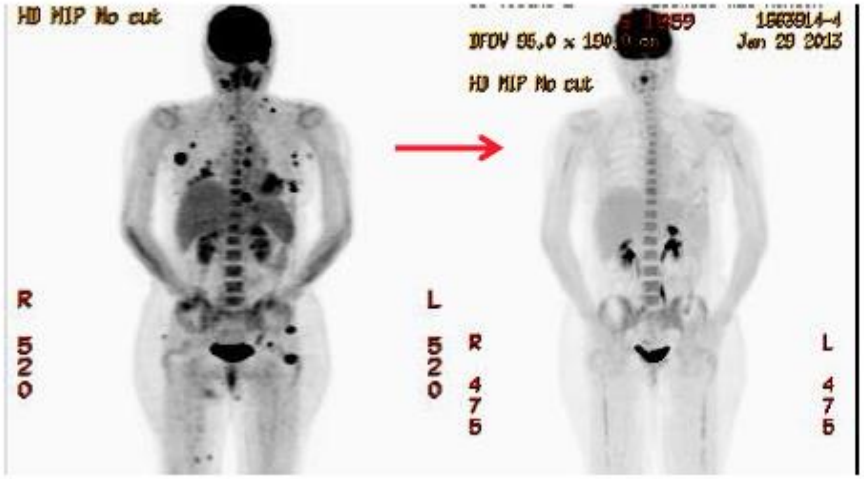
Sézary syndrome, IVA_1



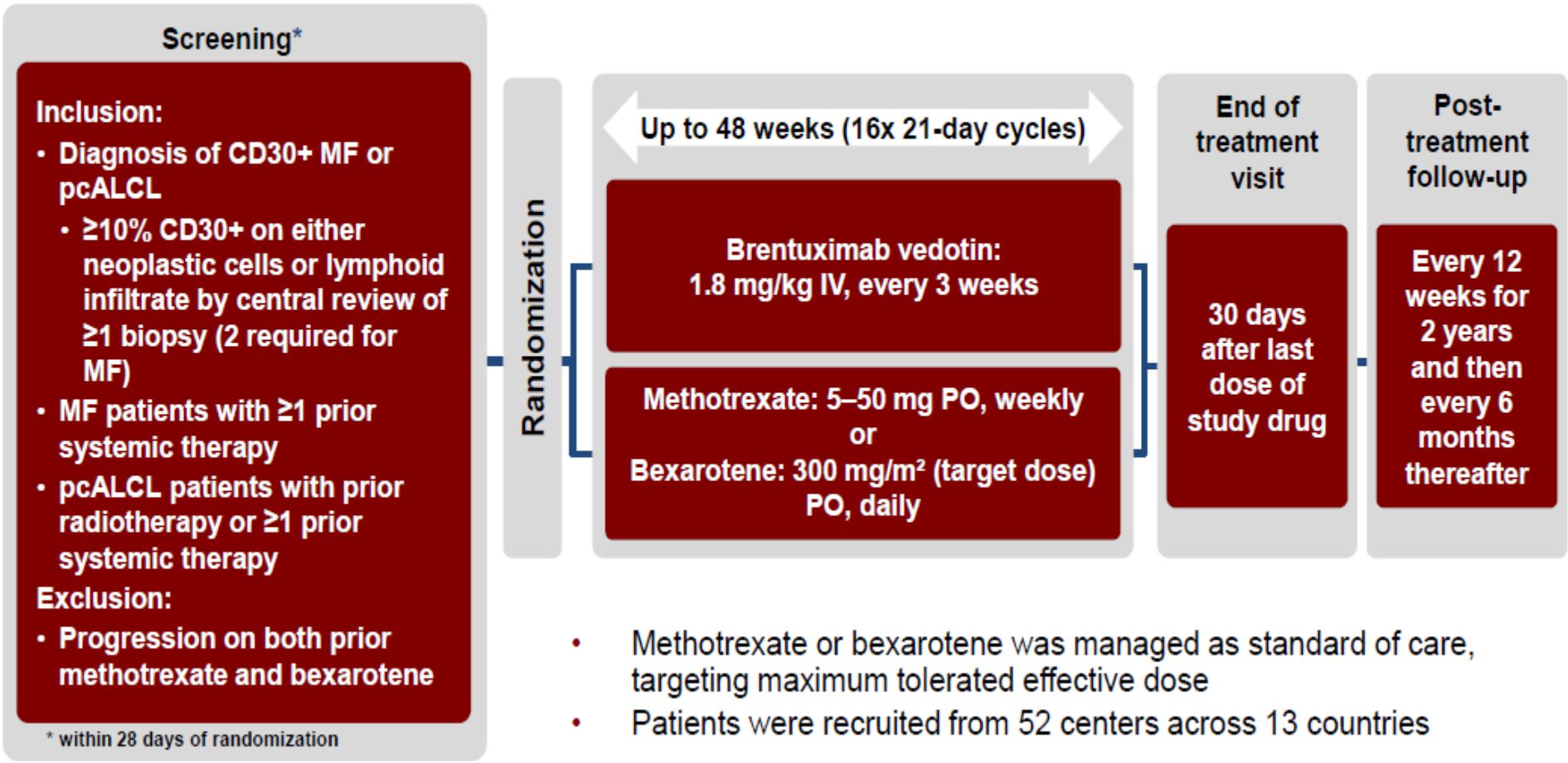


MF IVA_2 LN with LCT





ALCANZA: a randomized, open-label, phase 3 trial of brentuximab vedotin vs. physician's choice (methotrexate or bexarotene) in patients with CD30+ CTCL



- Methotrexate or bexarotene was managed as standard of care, targeting maximum tolerated effective dose
- Patients were recruited from 52 centers across 13 countries

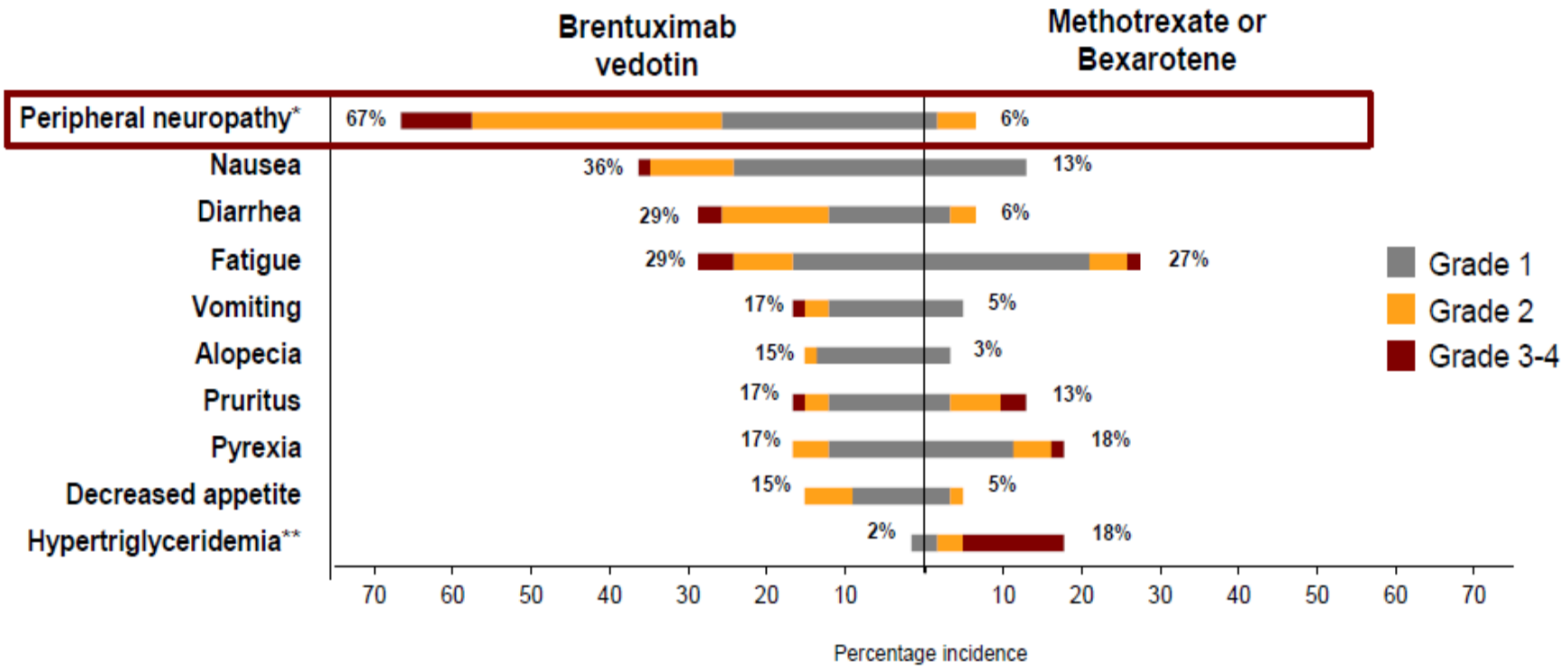
IV, intravenously; PO, orally

Prince HM, Kim YH, et al. Lancet 2017;390:555–66.

56.3% Brentuximab arm vs 12.5% Physician's choice MTX or bexarotene achieved objecti ve 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



*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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Mycosis Fungoides/Sezary Syndrome

Systemic agents in MF/SS
Real-time updates!

SYSTEMIC THERAPIES

Category A (SYST-CAT A)

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

2018 BV in Cat A

Category B (SYST-CAT B)

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

SYSTEMIC THERAPIES (continued)

Category C (SYST-CAT C)[j] (alphabetical order)

- Bortezomib (category 3)
- Brentuximab vedotin[h]
- Gemcitabine
- Liposomal doxorubicin
- Low- or standard-dose pralatrexate
- Romidepsin
- See regimens listed on TCEL-B 2 of 5 (PTCL-NOS)[k]

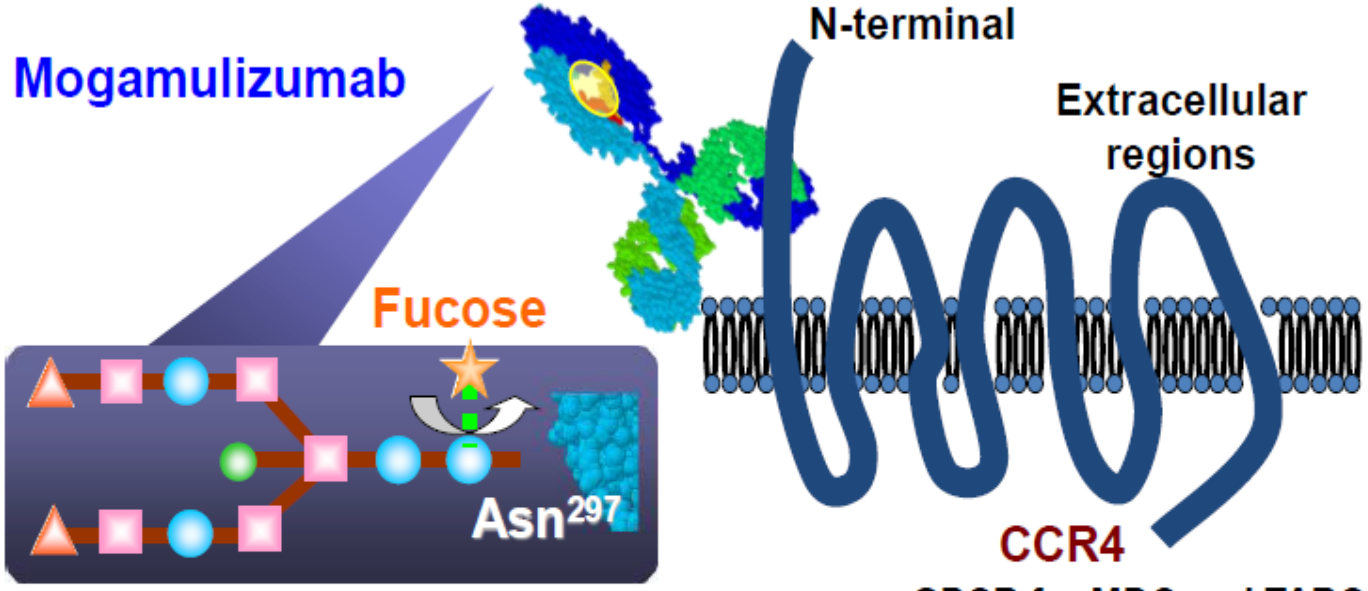
Brentuximab vedotin added 2018
to Category A systemic therapy option
Phase 3 study results & FDA approval

Footnote "h" for brentuximab vedotin (BV)

[h]A 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.

(Miles, Kim, et al. Lancet 2018;390:555, Duvic et al. JCO 2015;33:3759, Kim et al. JCO 2015;33:3750)

Mogamulizumab: *First-in-class defucosylated humanized anti-CCR4 mAb*



Higher ADCC due to a defucosylated Fc region by POTELLIGENT®[1-3]

GPCR for MDC and TARC[4]
Markers for Type II helper T cells and regulatory T cells (FoxP3+)[5]
Involved in lymphocyte trafficking to skin[6]
Over-expressed in ATL, PTCL, and CTCL[4,7]

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

1. Shinkawa et al. J Biol Chem 2003;278:3466.
2. Ishii et al. Clin Cancer Res 2010;16:1520.
3. Niwa et al. Cancer Res 2004;64:2127.
4. Ishida et al. Clin Cancer Res 2004;10:5494.
5. Ishida et al. Cancer Res 2006;66:5716-22.
6. Campbell et al. Nature 1999;400:776.
7. Ni et al. Clin Cancer Res 2015;21:274.

12/2017 ASH meeting

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, MD[1]; Martine Bagot, MD[2]; Lauren Pinter-Brown, MD[3]; Alain H. Rook, MD[4]; Pierluigi Porcu, MD[5]; Steven Horwitz, MD[6]; Sean Whittaker, MD[7]; Yoshiki Tokura, MD, PhD[8]; Maarten Vermeer, MD[9]; Pier Luigi Zinzani, MD[10]; Lubomir Sokol, MD, PhD[11]; Stephen Morris, MD[7]; Ellen J. Kim, MD[4]; Pablo L. Ortiz-Romero, MD[12]; Herbert Eradat, MD[13]; Julia Scarisbrick, MBChB, FRCP, MD[14]; Athanasios Tsianakas, MD[15]; Craig Elmets, MD[16]; Stephane Dalle, MD, PhD[17]; David Fisher, MD, PhD[18]; Ahmad Halwani, MD[19]; Brian Poligone, MD, PhD[20]; John Greer, MD[21]; Maria Teresa Fierro, MD[22]; Amit Khot, MD[23]; Alison J. Moskowitz, MD[6]; Karen Dwyer[24]; Junji Moriya[24]; Jeffrey Humphrey, MD[24]; Stacie Hudgens[25]; Dmitri O. Grebennik[24]; Kensei Tobinai, MD, PhD[26]; Madeleine Duvic, MD[27] for the MAVORIC Investigators

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

Mogamulizumab: Anti-CCR4 Monoclonal Antibody
FDA priority review granted

Response outcomes

	Mogamulizumab	Vorinostat
ORR[a,b], n/N (%)	**52/186 (28)**	**9/186 (5)**
MF[c]	**22/105 (21)**	**7/99 (7)**
SS[b]	**30/81 (37)**	**2/87 (2)**
Stage IB/IIA	7/36 (19)	5/49 (10)
Stage IIB	5/32 (16)	1/23 (4)
Stage III	5/22 (23)	0/16 (0)
Stage IV	35/96 (36)	3/98 (3)
DOR, median, months	**14**	**9**
MF	13 (n=22)	9 (n=7)
SS	17 (n=30)	7 (n=2)
ORR[a] n/N (%) mogamulizumab after crossover	**41/136 (30)**	

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

- Median relative dose intensities for mogamulizumab were 97.5% and for vorinostat was 95.1%

ORR=overall response rate; DOR=duration of response.

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)

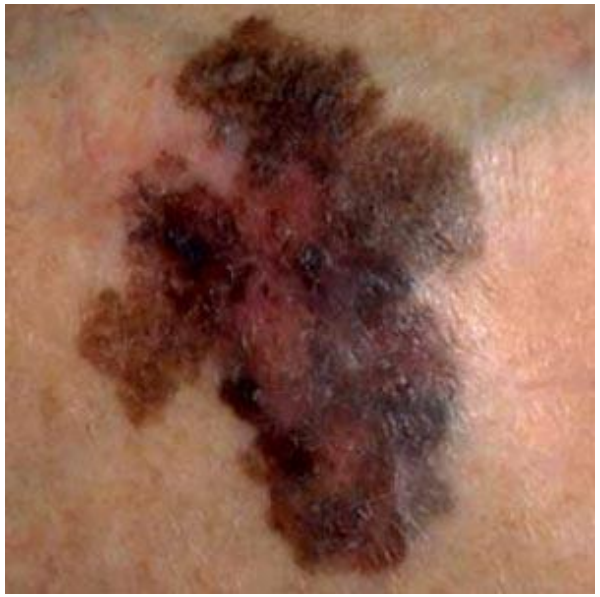
Stanford University SOM

Investigative sites/site PI:

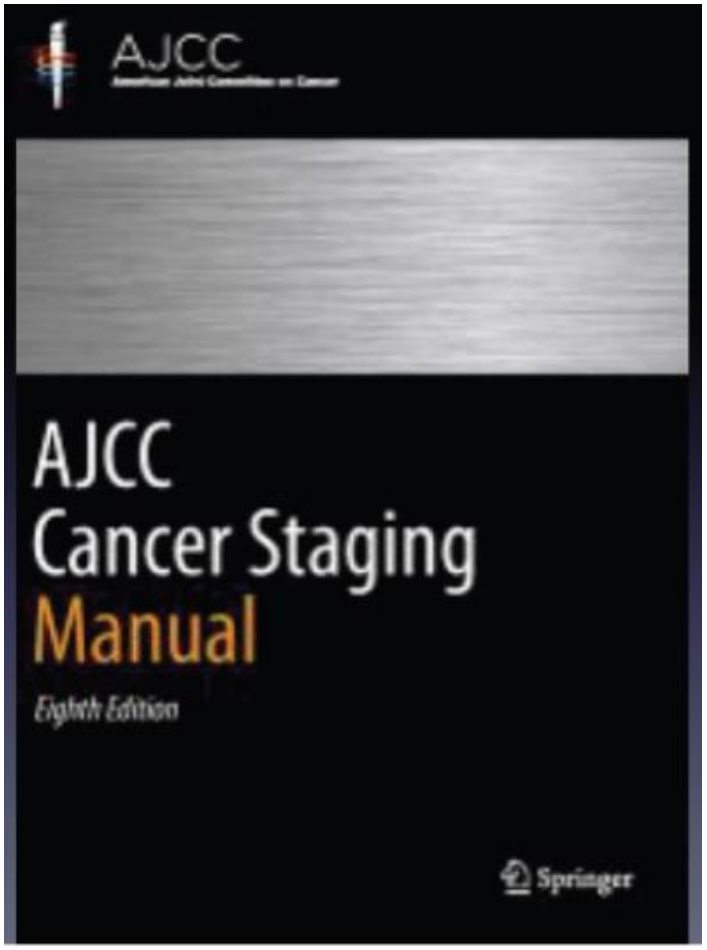
A Rook (U Penn), F Foss (Yale), PG Porcu (OSU), A Moskowitz (MSKCC), A Shustov (SCCA), L Sokol (Moffitt), S Shanbhag (Johns Hopkins)

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

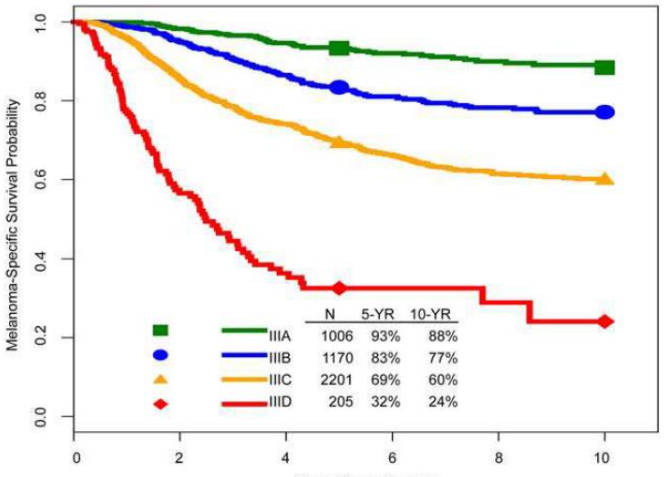
Gershenwald JE, Scolyer RA, Hess KR et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual.CA Cancer J Clin. 2017;67:472-492. PMID: 29028110

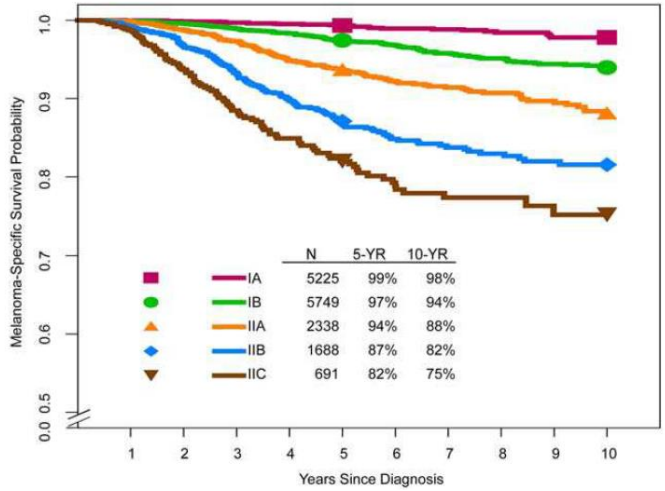
Changes in AJCC 8th Edition	
Definition of primary tumour (T)	• Tumour thickness recorded to the nearest 0.1mm, not 0.01mm • T1a <0.8mm without ulceration • T1b melanomas include those 0.8-1mm with or without ulceration and those <0.8mm with ulceration • Mitotic rate is no longer a T1 category criterion
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 N1/2/3c: 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 eith high LDH: M1c(1) (elevated LDH no longer defines M1c as per 7th edition)

TABLE 5. AJCC Clinical Prognostic Stage Groups (cTNM)[a]

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

[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





Gershenwald JE, Scolyer RA, Hess KR et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual.CA Cancer J Clin. 2017;67:472-492. PMID: 29028110

- 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

FDA Approval 2015

Alexander M M Eggermont, Vanna Chiarion-Sileni, Jean-Jacques Grob, Reinhard Dummer, Jedd D Wolchok, Henrik Schmidt, Omid Hamid, Caroline Robert, Paolo A Ascierto, Jon M Richards, Céleste Lebbé, Virginia Ferraresi, Michael Smylie, Jeffrey S Weber, Michele Maio, Cyril Konto, Axel Hoos, Veerle de Pril, Ravichandra Karra Gurunath, Gaetan de Schaetzen, Stefan Suciu, Alessandro Testori

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy

Nov 2016

A.M.M. Eggermont, V. Chiarion-Sileni, J.-J. Grob, R. Dummer, J.D. Wolchok, H. Schmidt, O. Hamid, C. Robert, P.A. Ascierto, J.M. Richards, C. Lebbé, V. Ferraresi, M. Smylie, J.S. Weber, M. Maio, L. Bastholt, L. Mortier, L. Thomas, S. Tahir, A. Hauschild, J.C. Hassel, F.S. Hodi, C. Taitt, V. de Pril, G. de Schaetzen, S. Suciu, and A. Testori

But new adjuvant options in 2018…

The NEW ENGLAND JOURNAL of MEDICINE

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Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma

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ABSTRACT

BACKGROUND

Combination therapy with the BRAF inhibitor dabrafenib plus the MEK inhibitor trametinib improved survival in patients with advanced melanoma with *BRAF* V600 mutations. We sought to determine whether adjuvant dabrafenib plus trametinib would improve outcomes in patients with resected, stage III melanoma with *BRAF* V600 mutations.

METHODS

In this double-blind, placebo-controlled, phase 3 trial, we randomly assigned 870 patients with completely resected, stage III melanoma with *BRAF* V600E or V600K mutations to receive oral dabrafenib at a dose of 150 mg twice daily plus trametinib at a dose of 2 mg once daily (combination therapy, 438 patients) or two matched placebo tablets (432 patients) for 12 months. The primary end point was relapse-free survival. Secondary end points included overall survival, distant metastasis–free survival, freedom from relapse, and safety.

RESULTS

At a median follow-up of 2.8 years, the estimated 3-year rate of relapse-free survival was 58% in the combination-therapy group and 39% in the placebo group (hazard ratio for relapse or death, 0.47; 95% confidence interval [CI], 0.39 to 0.58; P<0.001). The 3-year overall survival rate was 86% in the combination-therapy group and 77% in the placebo group (hazard ratio for death, 0.57; 95% CI, 0.42 to 0.79; P=0.0006), but this level of improvement did not cross the prespecified interim analysis boundary of P=0.000019. Rates of distant metastasis–free survival and freedom from relapse were also higher in the combination-therapy group than in the placebo group. The safety profile of dabrafenib plus trametinib was consistent with that observed with the combination in patients with metastatic melanoma.

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FDA Approval Nivolumab Dec 2017

ORIGINAL ARTICLE

Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma

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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 (≥15 years of age) who were undergoing complete resection of stage IIIB, IIIC, or IV melanoma to receive an intravenous infusion of either nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks (453 patients) or ipilimumab at a dose of 10 mg per kilogram every 3 weeks for four doses and then every 12 weeks (453 patients). The patients were treated for a period of up to 1 year or 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 70.5% (95% confidence interval [CI], 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, 0.65; 97.56% CI, 0.51 to 0.83; P<0.001). Treatment-related grade 3 or 4 adverse events were reported in 14.4% 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 42.6% of the patients, respectively. Two deaths (0.4%) related to toxic effects were reported in the ipilimumab group more than 100 days after treatment.

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*A complete list of the CheckMate 238 collaborators is provided in the Supplementary Appendix, available at NEJM.org.

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