AAD HIGHLIGHTS 2017

Susan O'Gorman

Update: New Modalities in the Diagnosis, Staging and Prognostication of Melanocytic Lesions

Rajendra Singh, MD

Associate Professor
Icahn School of Medicine at Mt. Sinai
New York, NY 10029

What Molecular Tests are Available?

- Fluorescent in situ hybridization (FISH)
- Comparative genomic hybridization (CGH)
- Gene Expression Profile Testing-myPATH

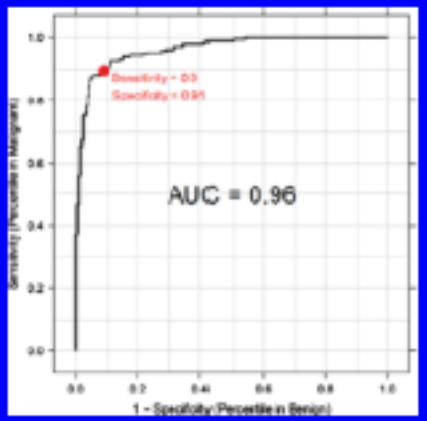
Gene Expression Profile Testing

- myPath Melanoma (Myriad Genetics)
- 23 genes
- 90% sensitivity; 91% specificity
- Primary tumor only
- Price $900

Evaluating benign nevi and melanomas using a gene expression signature

Using a training set of 464 melanocytic lesions, a 23 gene signature yields an area under the curve of (AUC) 96%

- RT-PCR of RNA from FFPE tissue



Clinical validation study: Melanoma Diagnostic score

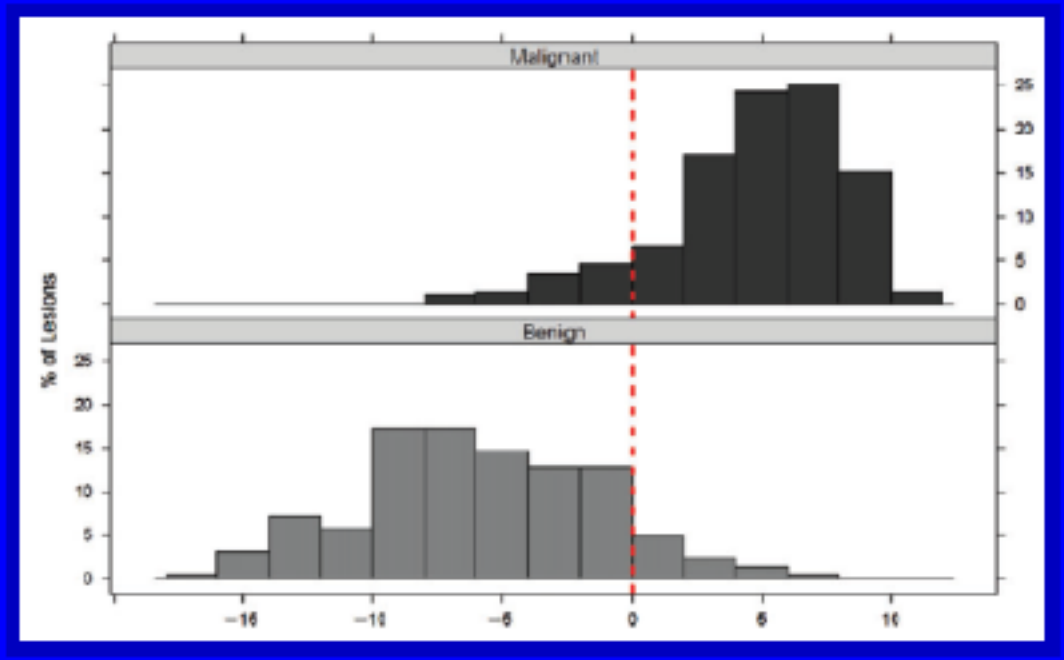
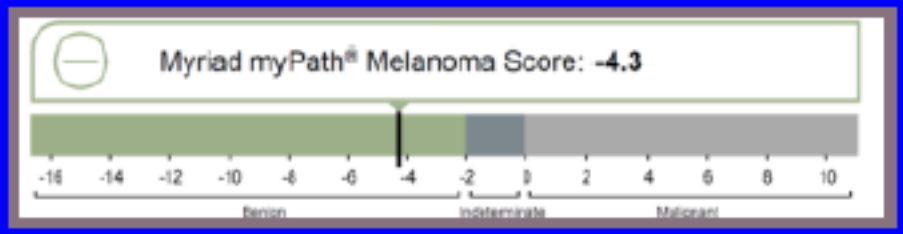


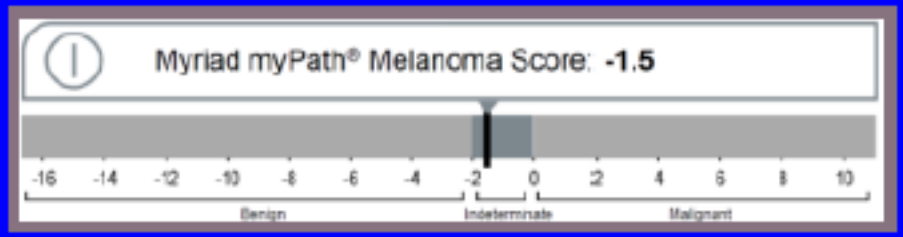
Image reproduced from Clarke LE. J. Cutan Pathol (2015); 42: 244-252.

Melanoma Diagnostic Score

Benign
-16 to -2



Indeterminate
-2 to 0



Malignant
>0-10

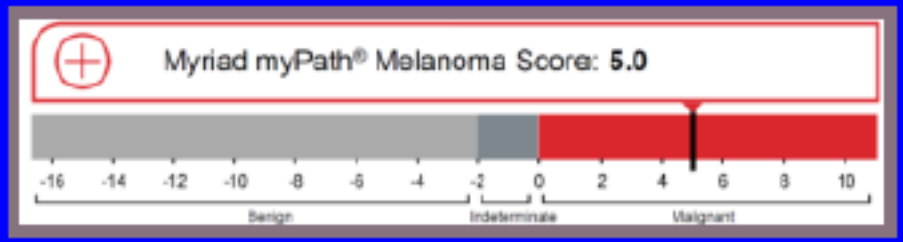


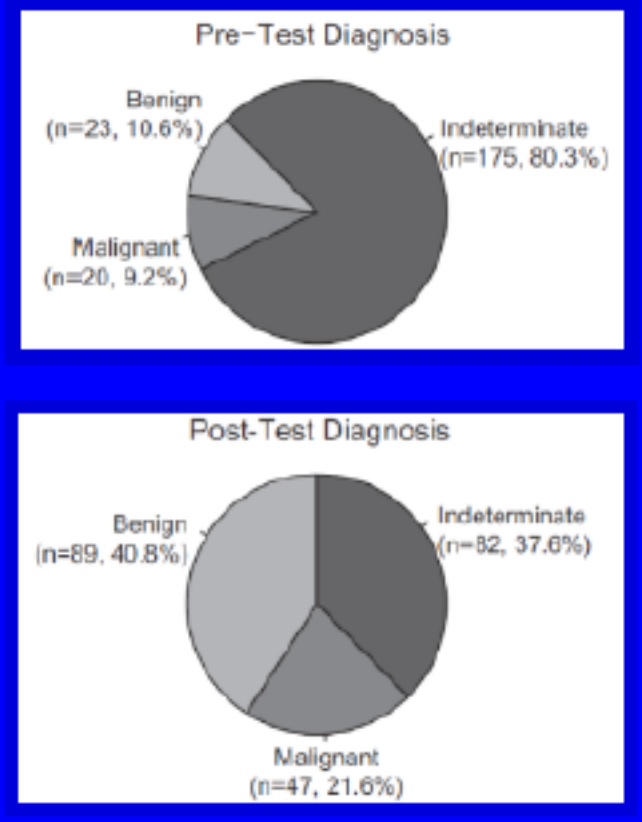
Image reproduced from https://www.myriad.com/products-services/melanoma/mypath-melanoma/

Sensitivity Analysis

Melanoma Subtype	Validation I Sensitivity (n = 201)	Validation II Sensitivity (n = 177)
Lentigo maligna melanoma	*93.3%*	*89.7%*
Nodular melanoma	*100%*	*91.4%*
Superficial spreading melanoma	*90.9%*	*94.8%*
All melanomas	*94.0%*	*91.5%*

Adapted from Clarke LE et al, Cancer (2016) 00, 1-12.

Does MyPath change diagnostic practice?



Adapted from Cochareli CJ et al, Medicine (2016) 95, 40.

MYRIAD myPath® Melanoma

"…a clinically validated test to be used as an adjunct to histopathology when the distinction between a benign nevus and a malignant melanoma cannot be made confidently by histopathology alone."
(Not FDA approved)

https://www.myriad.com/products-services/melanoma/mypath-melanoma/

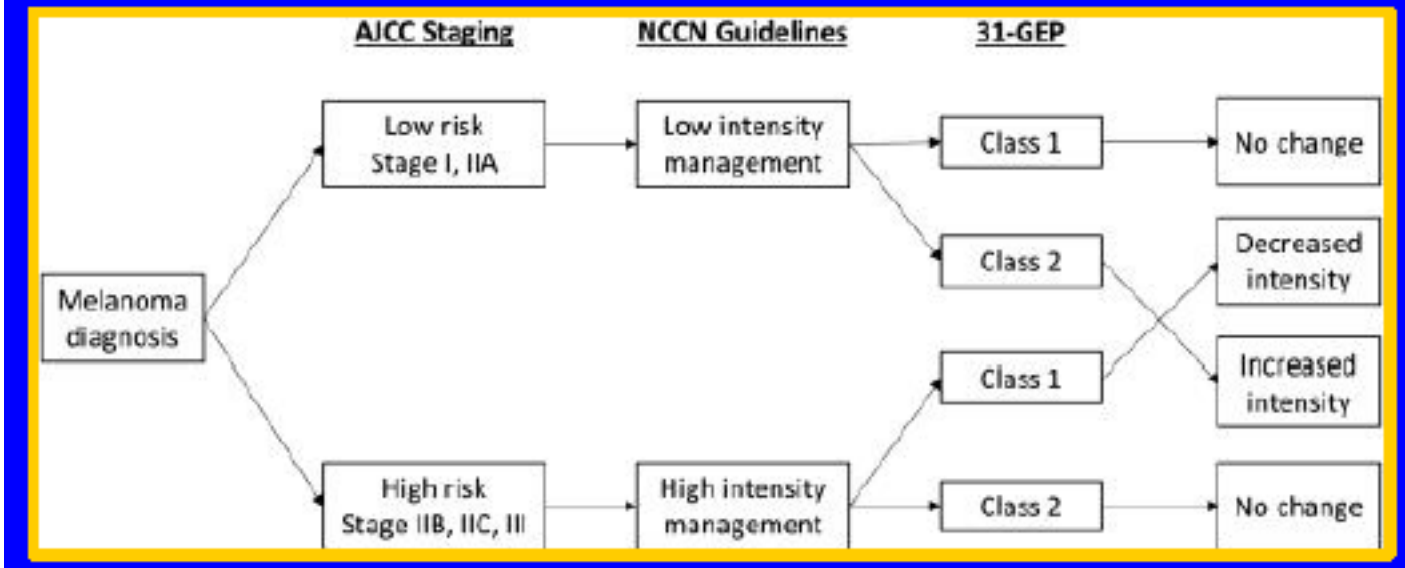
- Currently, the only prognostic techniques for melanoma are AJCC criteria and Sentinel Lymph Node status
- Is it possible to identify patients who will develop more aggressive disease?

GENE EXPRESSION PROFILING

- Genetic Testing to Assist in Prognosis of Melanoma
- FDA approved test developed by Castle Bioscience, Friendswood, Texas
- Uses formalin-fixed, paraffin-embedded tissue
- Quantifies expression of 31 genes from primary tumor to develop a Gene Expression Profile (GEP)
- Applies a validation algorithm to classify patients as Class 1 (low) vs Class 2 (high) risk of developing metastatic disease within 5 years

Gene Expression Profile Testing

- Prognosis was Independent of Breslow thickness, ulceration status, SLNB, and mitotic index in predicting metastatic disease
- Bill $7900 (avg. collection $1500)

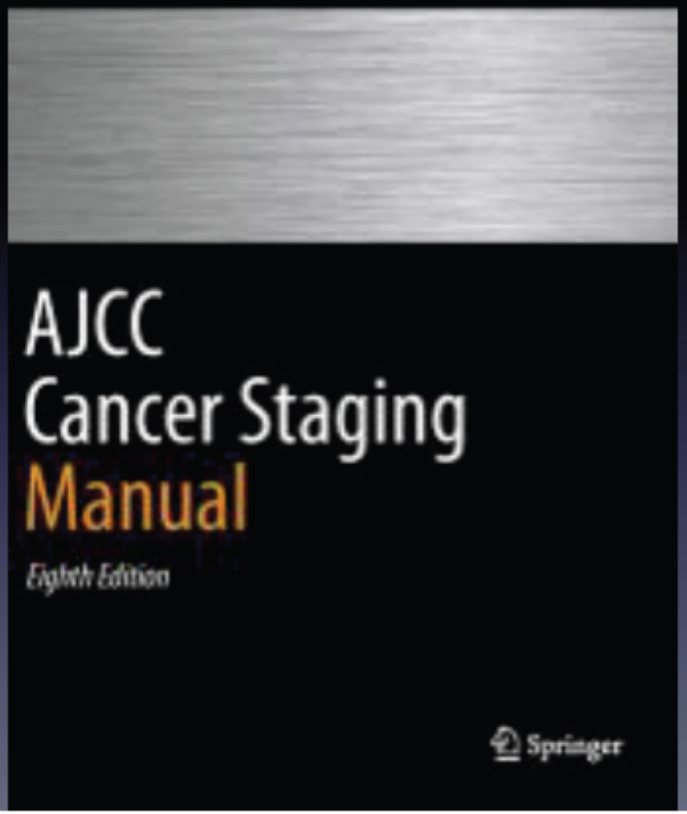


Change in clinical management by AJCC stage

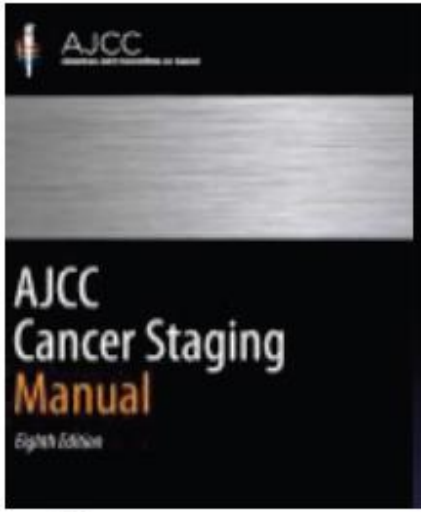
Berger AC, et al, Current Medical Research and Opinion, 2016; 32:9: 1599-1604.

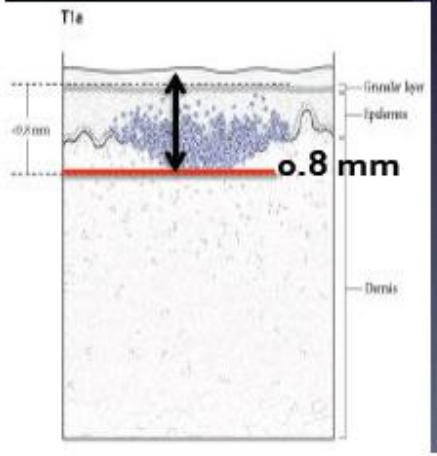
Translating Evidence into Practice: Primary Cutaneous Melanoma Guidelines

Jinah Kim, MD, PhD
Section of Dermatopathology
Stanford University Medical Center



- Starts Jan 1, 2018
- All newly diagnosed cases through Dec 31, 2017 should be staged with the 7th edition





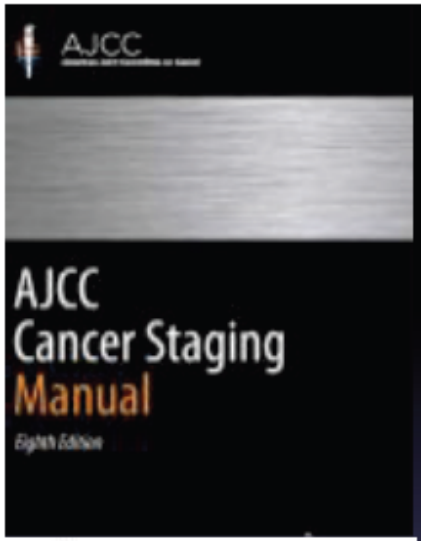
AJCC 8th ed

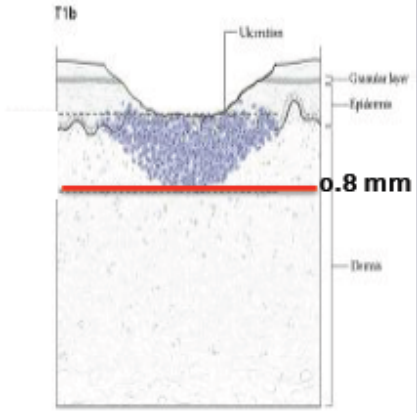
Definition of Primary Tumor (T)

- T-category tumor thickness cutoffs maintained
- Except substratification of T1:

Melanomas <0.8 mm in thickness= T1a

Melanomas 0.8 mm - 1.0 mm = T1b

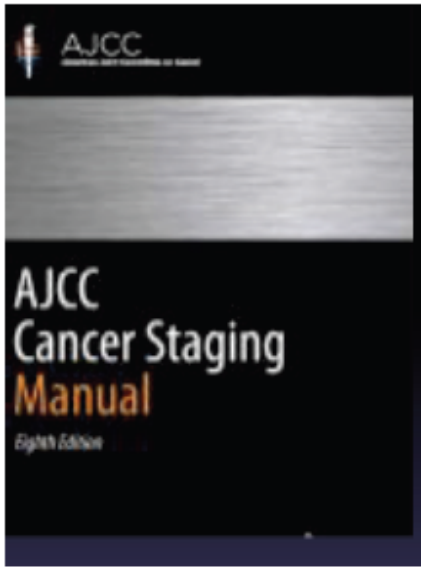


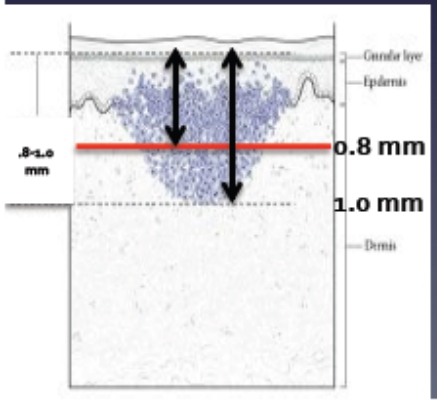


AJCC 8th ed

Definition of Primary Tumor (T)

- **T1b** melanomas now are defined:
- 0.8 to 1.0 mm in thickness regardless of ulceration
- Ulcerated melanomas <0.8 mm in thickness

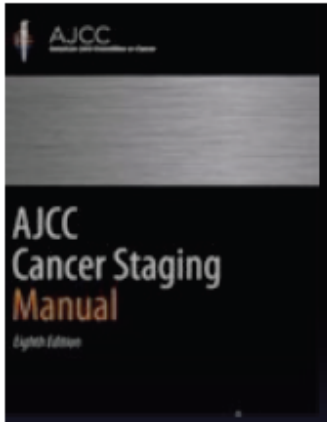




AJCC 8th ed

Definition of Primary Tumor (T)

- Tumor thickness recorded to the nearest 0.1 mm
- Melanomas measured to be in the range of 0.75 to 0.84 mm are reported as 0.8 mm in thickness; hence T1b



Definition of Primary Tumor (T)

- Tumor mitotic rate was removed as a staging criterion for **T1** tumors
- Remains an overall important prognostic factor that should continue to be recorded for all patients with T1-T4 primary cutaneous melanoma

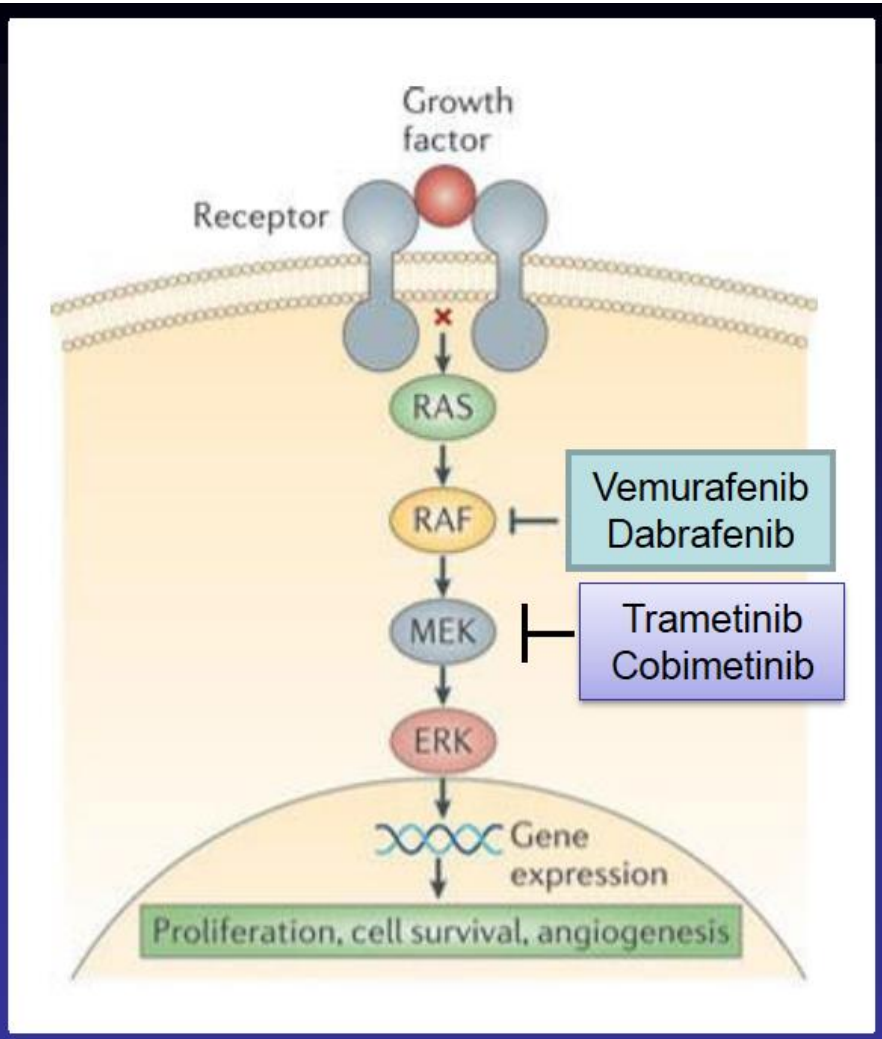
Update on Therapy for Metastatic Melanoma

Emily Y. Chu, M.D., Ph.D.
Assistant Professor of Dermatology
& Pathology and Laboratory Medicine
University of Pennsylvania

March 3, 2017
AAD Annual Meeting
Orlando, FL

FDA approved medications for advanced melanoma

- Targeted kinase inhibitors
  - BRAF inhibitors (vemurafenib, dabrafenib)
  - MEK (trametinib, cobimetinib)
- Immunotherapy agents
  - Ipilimumab
  - PD-1 inhibitors (nivolumab, pembrolizumab)
  - Talimogene laherparepvec/T-VEC



Flaherty et al, Nat Rev Drug Disc 2011

Vemurafenib

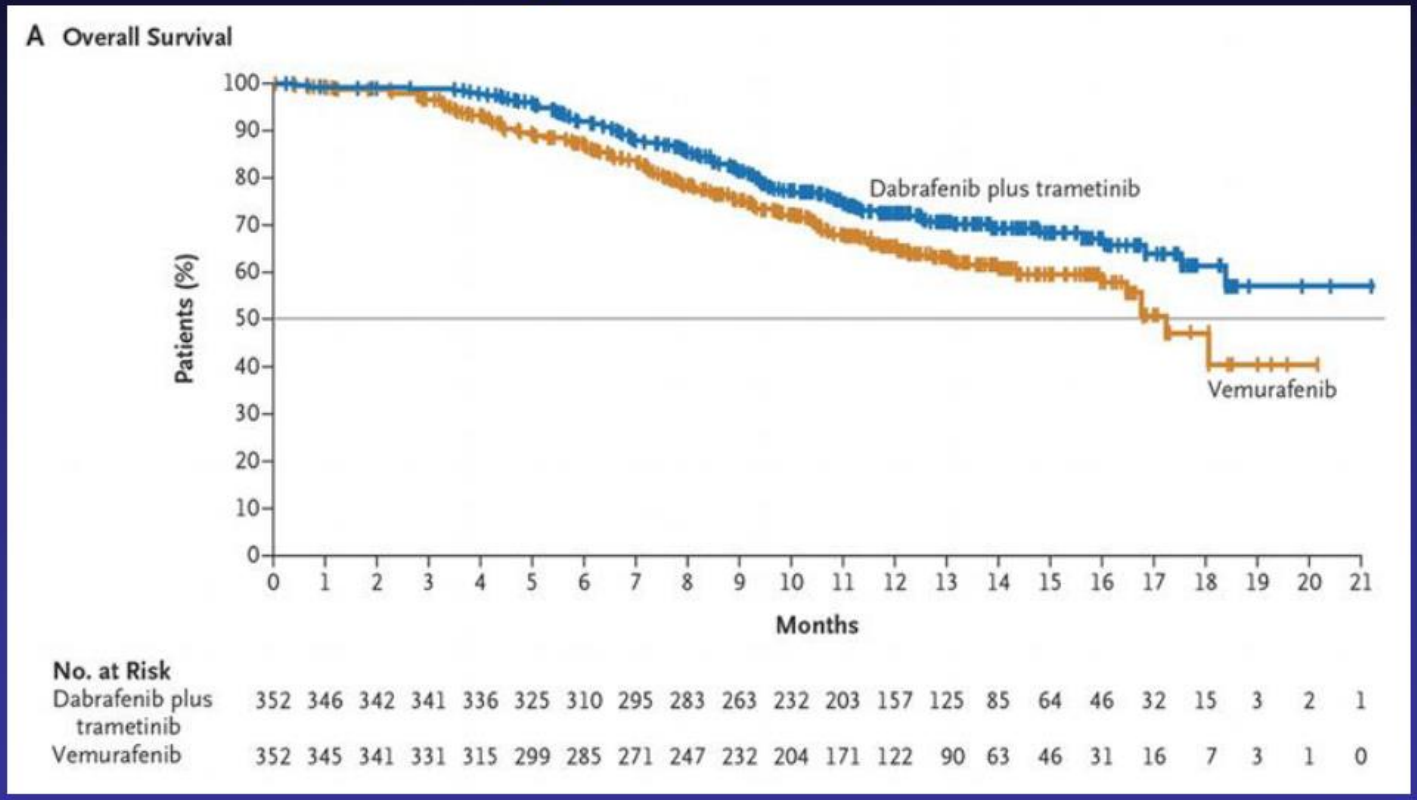
- Up to 80% of patients with the BRAF V600E mutation will have at least a partial response within weeks

- The majority of patients will experience relapse
  - Secondary mutations develop within melanomas in response to therapy
  - Median time to progression: 6-7 months
  - **Few long term responders**

Other targeted therapy agents

- Da**BRAF**enib
  - BRAF inhibitor
  - Similar response rate to vemurafenib
- Tra**ME**tinib/Cobi**ME**tinib
  - MEK inhibitors
  - Side effect profile is different (hypertension, decreased EF)

Combination BRAFi + MEKi superior to single agent BRAFi



Robert et al, NEJM 2015

Decreased #'s of SCCs and KAs with vemurafenib and cobimetinib treatment compared to vemurafenib + placebo

Table 3. Common Adverse Events.*

Adverse Event	Vemurafenib and Placebo (N=239)				Vemurafenib and Cobimetinib (N=254)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)							
Any adverse event	21 (9)	70 (29)	117 (49)	22 (9)	19 (7)	66 (26)	125 (49)	34 (13)
Most common adverse events†								
Diarrhea	51 (21)	16 (7)	0	0	99 (39)	29 (11)	16 (6)	0
Nausea	43 (18)	12 (5)	2 (1)	0	75 (30)	22 (9)	2 (1)	0
Vomiting	21 (9)	6 (3)	2 (1)	0	41 (16)	10 (4)	3 (1)	0
Rash	46 (19)	27 (11)	12 (5)	0	55 (22)	29 (11)	13 (5)	2 (1)
Photosensitivity reaction	25 (10)	12 (5)	0	0	48 (19)	18 (7)	6 (2)	0
Hyperkeratosis	49 (21)	14 (6)	5 (2)	0	23 (9)	3 (1)	0	0
Fatigue	42 (18)	24 (10)	7 (3)	0	48 (19)	24 (9)	9 (4)	0
Pyrexia	43 (18)	10 (4)	0	0	49 (19)	13 (5)	4 (2)	0
Arthralgia	53 (22)	31 (13)	12 (5)	0	54 (21)	23 (9)	6 (2)	0
Alopecia	55 (23)	14 (6)	1 (<1)	0	33 (13)	1 (<1)	1 (<1)	0
Increased alanine aminotransferase	17 (7)	11 (5)	14 (6)	1 (<1)	16 (6)	15 (6)	28 (11)	1 (<1)
Increased aspartate aminotransferase	15 (6)	10 (4)	4 (2)	1 (<1)	17 (7)	18 (7)	21 (8)	0
Increased creatine kinase	6 (3)	1 (<1)	0	0	23 (9)	27 (11)	17 (7)	9 (4)
Selected adverse events								
Cutaneous squamous-cell carcinoma	0	0	27 (11)	0	0	1 (<1)	6 (2)	0
Keratoacanthoma	1 (<1)	1 (<1)	18 (8)	0	0	0	2 (1)	0
Chorioretinopathy	1 (<1)	0	0	0	17 (7)	12 (5)	1 (<1)	0
Retinal detachment	0	0	0	0	9 (4)	6 (2)	5 (2)	1 (<1)
Decreased ejection fraction	0	4 (2)	3 (1)	0	2 (1)	14 (6)	3 (1)	0
QT-interval prolongation	8 (3)	2 (1)	3 (1)	0	6 (2)	2 (1)	1 (<1)	0

* The safety population was analyzed according to the study treatment received. Eight patients assigned to the control group received investigational cobimetinib as a result of dispensing errors. Two patients (one in each study group) did not receive the assigned study drug and were therefore excluded from the safety analysis. Multiple occurrences of a specific adverse event for a patient were counted once at the highest grade of the occurrence, according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. For example, if a patient had two episodes of a specific toxic event, one grade 3 and one grade 4, the patient was counted only once, in the grade 4 column. Similarly, in the "Any adverse events" row, if a patient had, for example, three separate events of grade 1, 3, and 4, the patient was counted only once, in the grade 4 column.

† The most common adverse events were those that occurred in at least 20% of the patients in either study group.

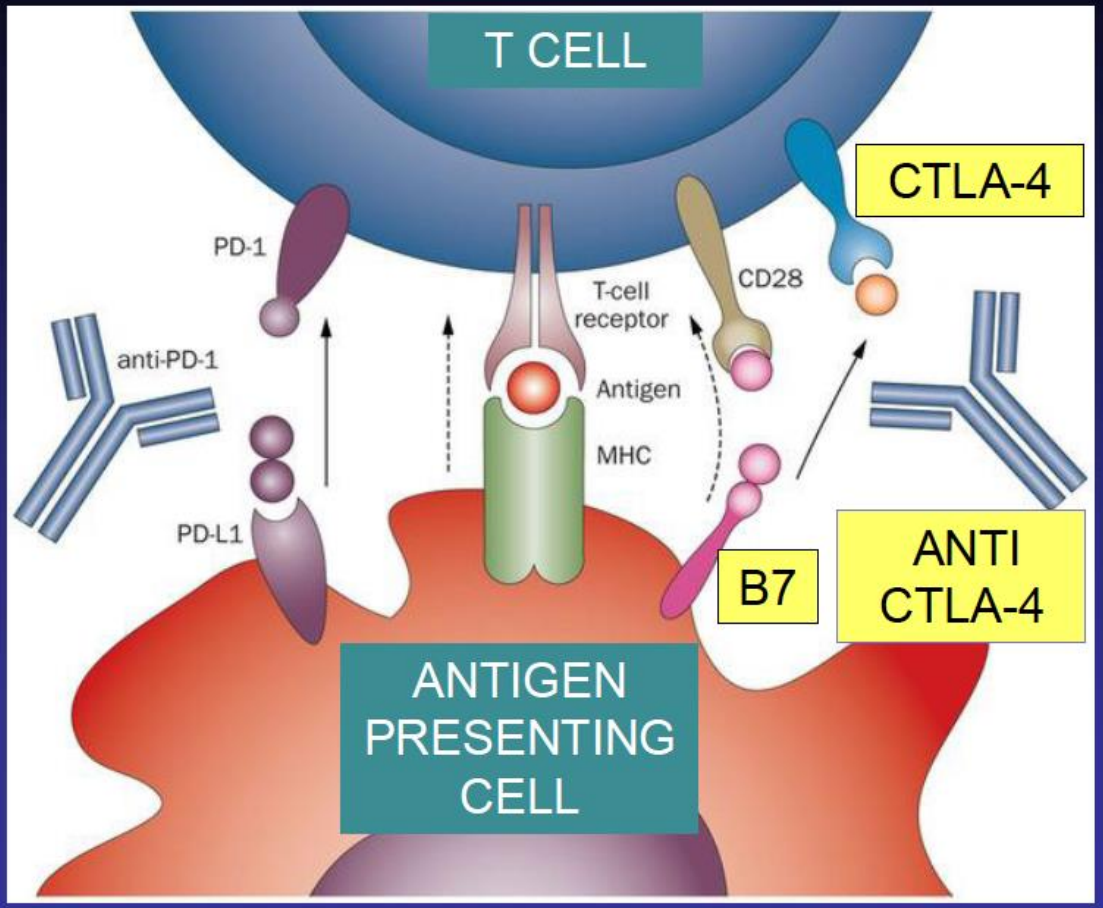
Larkin J et al. N Engl J Med 2014

FDA approved medications for advanced melanoma

- Targeted kinase inhibitors
  - BRAF inhibitors (vemurafenib, dabrafenib)
  - MEK (trametinib, cobimetinib)

- Immunotherapy agents
  - Ipilimu**mab**
  - PD-1 inhibitors (nivolu**mab**, pembrolizu**mab**)
  - Talimogene laherparepvec/T-VEC

Ipilimumab



- Cytotoxic T-lymphocyte antigen-4 antibody
  - Enhances immune response/antitumor activity
  - Inhibit **CTLA-4**, which is a negative regulator of T- cell activation

Drake CG et al, Nature Reviews Clinical Oncology, 2014

Ipilimumab

- 4 IV doses, 3 weeks apart
  - Effect often seen towards the end of dosing
  - 10 – 15% of patients will respond
  - But many of these patients will have durable response

Ipilimumab

- Toxic side effects
  - General activation of immune system, leading to immune-related issues
    - Diarrhea/colitis, hepatitis
    - Hypophysitis
    - Skin manifestations
      - Morbilliform eruption
      - Pruritus
      - Vitiligo

Hodi et al, NEJM, 2010

Pseudoprogression and Immunotherapy

VOLUME 33 · NUMBER 31 · NOVEMBER 1 2015

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

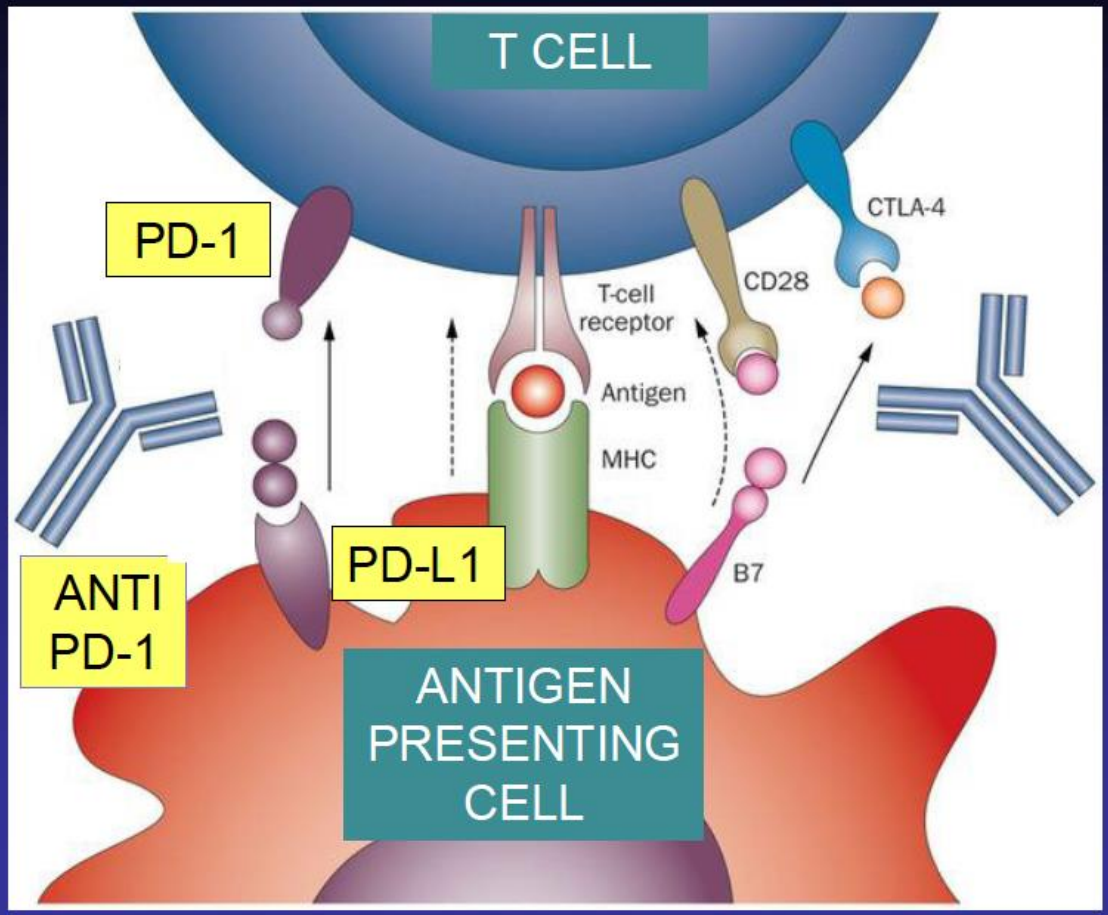
Pseudoprogression and Immune-Related Response in Solid Tumors

Victoria L. Chiou and Mauricio Burotto, *Center for Cancer Research, National Cancer Institute, Bethesda, MD*

- Some experience initial increase in radiologic tumor size → bx shows inflammatory cell infiltrate → subsequent decreased tumor burden
- Need to distinguish pseudoprogression from actual progression of disease

Chiou et al, J Clin Oncology 2015
Di Giacomo et al., Cancer Immunol Immunother 2009

PD-1 inhibitors



- Programmed cell death-1 antibodies
  - Enhances immune response/antitumor activity
  - Inhibit **PD-1**, which plays an important role in downregulating the immune system by preventing the activation of T-cells, which in turn reduces autoimmunity and promotes self-tolerance

Drake CG et al, Nature Reviews Clinical Oncology, 2014

Nivolumab and Pembrolizumab

- IV dosing, indefinitely (?)
- Higher response rate than ipilimumab
  - 30% will have objective response
- More rapid response
- Fewer side effects
  - 10% discontinued pembrolizumab in clinical trials

Are two drugs better than one?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D. Wolchok

Larkin et al., NEJM 2015

Combination nivolumab/ipilimumab is more effective than monotherapy

- Nivolumab
  - PFS: 6.9 months
- Nivolumab + Ipilimumab
  - PFS: 11.5 months
- Ipilimumab
  - PFS: 2.9 months

Larkin et al., NEJM 2015

Can predictive biomarkers help predict who will response to PD-1 inhibitors?

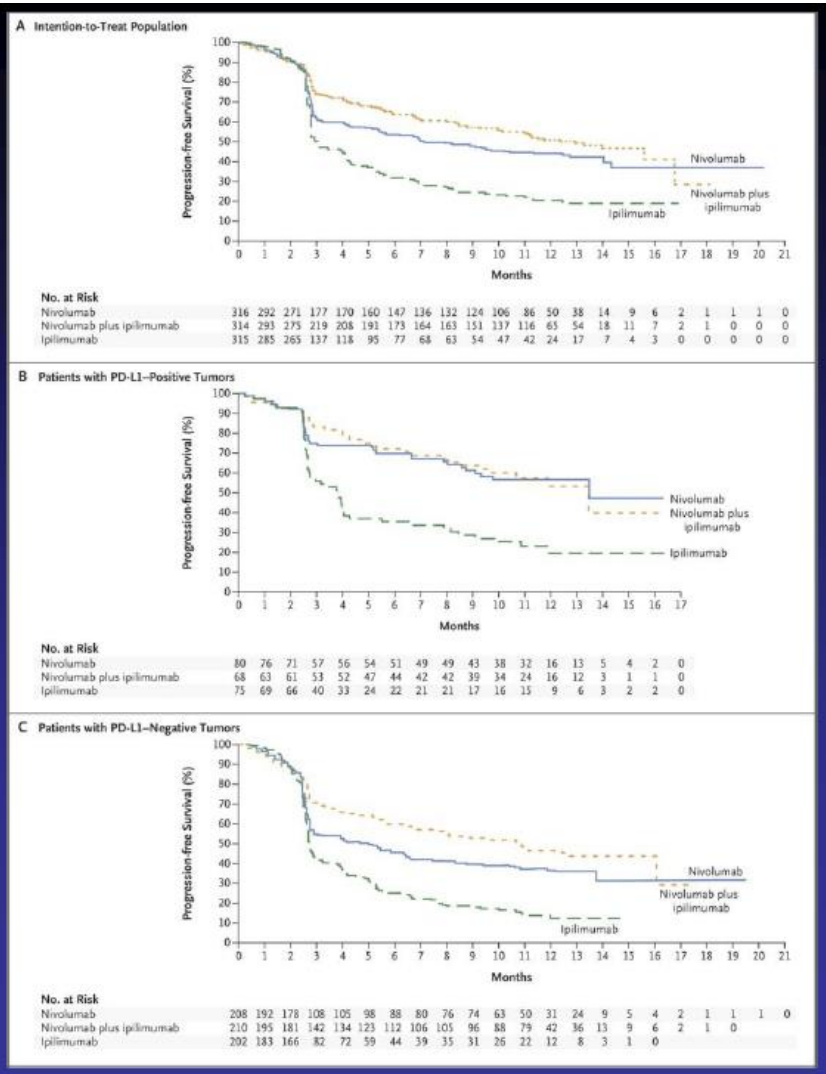
- PD-L1 expression
- Tumor infiltrating lymphocytes
- Other immune regulatory molecules
- Baseline tumor size
  - Smaller baseline tumor size is prognostic of survival and predictive of response with pembrolizumab

Joseph et al, ASCO 2014

Progression-free survival according to PD-L1 tumor status

- Among patients with a positive PD-L1 tumor status, medial PFS was
  - 14.0 months in the nivolumab group
  - 14.0 months in the nivolumab + ipilimumab group
  - 3.9 months in the ipilimumab group
- Among patients with a negative PD-L1 tumor status, the median PFS was
  - 5.3 months in the nivolumab group
  - 11.2 months in the nivolumab + ipilimumab group
  - 2.8 months in the ipilimumab group

Larkin et al., NEJM 2015



Increased efficacy comes at a cost: more side effects

- 55% grade III/IV adverse events, compared to
  - 16% for nivolumab alone
  - 27% for ipilimumab alone
- 43% had to stop
- 27% did not get 4 cycles of drug
- 3% of patients in original Phase II study died from drugs

Targeted Therapy (BRAFi / MEKi)	Immune Therapy (ipilimumab and/or PD-1)
Only works in V600E/K mutations	**Anyone**
Higher Likelihood of Response	
Shorter Time to Response	
Long-term benefit is unproven	**Long-term response can occur**

(courtesy Tara Gangadhar and Ravi Amaravadi)

FDA approved medications for advanced melanoma

- Targeted kinase inhibitors
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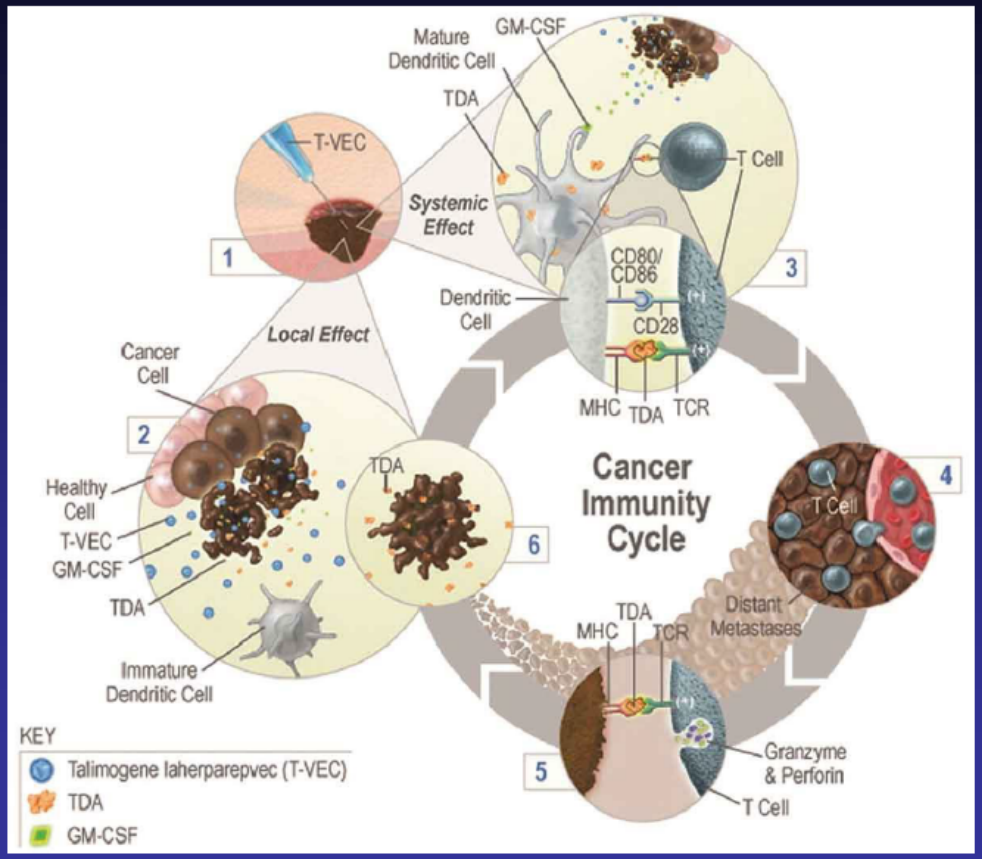
  - MEK (trametinib, cobimetinib)
- Immunotherapy agents
  - Ipilimumab
  - PD-1 inhibitors (nivolumab, pembrolizumab)
  - Talimogene laherparepvec/T-VEC

Talimogene Laherparepvec (T-VEC)

- Approved by the FDA in October 2015 for treatment of unresectable Stage IIIB, IIIC, or IV melanoma
- First in class oncolytic virus based on modified HSV-1
  - Injectable therapy, directed into tumor tissue
  - Modified via deletion of 2 nonessential viral genes
- Designed to selectively replicate in and lyse tumor cells while promoting regional and systemic antitumor immunity
  - Should not harm normal tissue

Proposed mechanism of action of T-VEC



- T-VEC selectively replicates in tumor cells and lyses them → release of progeny virus and tumor-derived antigens (TDAs)
- T-VEC modified to include 2 copies of human GM-CSF → promotes maturation and function of dendritic cells → activate anti-tumor T-cells through presentation of processed TDAs

Harrington et al, 2015

Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma

Robert H.I. Andtbacka, Howard L. Kaufman, Frances Collichio, Thomas Amatruda, Neil Senzer, Jason Chesney, Keith A. Delman, Lynn E. Spitler, Igor Puzanov, Sanjiv S. Agarwala, Mohammed Milhem, Lee Cranmer, Brendan Curti, Karl Lewis, Merrick Ross, Troy Guthrie, Gerald P. Linette, Gregory A. Daniels, Kevin Harrington, Mark R. Middleton, Wilson H. Miller Jr, Jonathan S. Zager, Yining Ye, Bin Yao, Ai Li, Susan Doleman, Ari VanderWalde, Jennifer Gansert, and Robert S. Coffin

See accompanying article on page 2812

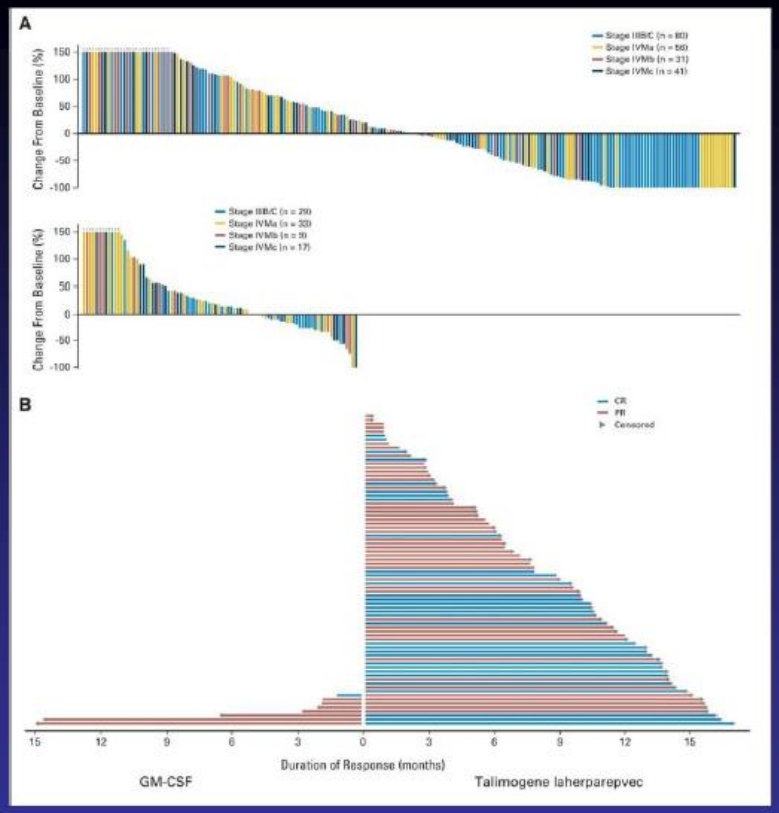
A B S T R A C T

Purpose
Talimogene laherparepvec (T-VEC) is a herpes simplex virus type 1–derived oncolytic immunotherapy designed to selectively replicate within tumors and produce granulocyte macrophage colony-stimulating factor (GM-CSF) to enhance systemic antitumor immune responses. T-VEC was compared with GM-CSF in patients with unresected stage IIIB to IV melanoma in a randomized open-label phase III trial.

Patients and Methods
Patients with injectable melanoma that was not surgically resectable were randomly assigned at a two-to-one ratio to intralesional T-VEC or subcutaneous GM-CSF. The primary end point was durable response rate (DRR; objective response lasting continuously ≥ 6 months) per independent assessment. Key secondary end points included overall survival (OS) and overall response rate.

Results
Among 436 patients randomly assigned, DRR was significantly higher with T-VEC (16.3%; 95% CI, 12.1% to 20.5%) than GM-CSF (2.1%; 95% CI, 0% to 4.5%]; odds ratio, 8.9; $P < .001$). Overall response rate was also higher in the T-VEC arm (26.4%; 95% CI, 21.4% to 31.5% *v* 5.7%; 95% CI, 1.9% to 9.5%). Median OS was 23.3 months (95% CI, 19.5 to 29.6 months) with T-VEC and 18.9 months (95% CI, 16.0 to 23.7 months) with GM-CSF (hazard ratio, 0.79; 95% CI, 0.62 to 1.00; $P = .051$). T-VEC efficacy was most pronounced in patients with stage IIIB, IIIC, or IVM1a disease and in patients with treatment-naive disease. The most common adverse events (AEs) with T-VEC were fatigue, chills, and pyrexia. The only grade 3 or 4 AE occurring in ≥ 2% of T-VEC–treated patients was cellulitis (2.1%). No fatal treatment-related AEs occurred.

Conclusion
T-VEC is the first oncolytic immunotherapy to demonstrate therapeutic benefit against melanoma in a phase III clinical trial. T-VEC was well tolerated and resulted in a higher DRR ($P < .001$) and longer median OS ($P = .051$), particularly in untreated patients or those with stage IIIB, IIIC, or IVM1a disease. T-VEC represents a novel potential therapy for patients with metastatic melanoma.



- **78 patients in T-VEC arm showed response, 56/78 were ongoing at time of end point assessment**
- **8 pts in GM-CSF arms responded**

Andtbacka et al, JCO 2015

On the horizon…

- More combination therapies (simultaneous vs sequential)
- Adjuvant studies (vemurafenib, pembrolizumab)

Ted Rosen, MD
Professor of Dermatology
Baylor College of Medicine
Houston, Texas

MEDICAL THERAPY FOR BASAL CELL CARCINOMA

Baylor College of Medicine

Hedgehog Pathway Inhibitors

- Directly suppress SMO which is upregulated due to mutation in its suppressor (PTCH)
- Currently approved: vismodegib and sonidegib
  - Vismo: 150mg/day and Soni: 200mg/day
- Same AE profile, which is accompanied by high dropout rate in studies and in real life
- Muscle cramps, alopecia, taste abnormalities, weight loss, fatigue, nausea, diarrhea, and decreased appetite
- Soni, maybe Vismo: Monitor CPK (rhabdomyolysis)
- Embryotoxic and teratogenic

Future ONCOLOGY

REVIEW

Managing adverse events associated with vismodegib in the treatment of basal cell carcinoma

Kate Fife*[1], Robert Herd[2], Susan Lalondrelle[3], Ruth Plummer[4], Amy Strong[1], Sarah Jones[5] & John T Lear[6]

Future Oncol. 2017;13:175-184

Table 2. Time to onset and management strategies for taste disturbances, muscle cramps and alopecia.

AE	Symptoms	Time to onset in clinical trials (months)	Severity	Management strategies (in order of priority)	AE resolution upon stopping vismodegib
Taste disturbance	Loss of taste Sour to sweet Sweet to sour Metallic taste Change of taste of alcohol Food tasting bland Sensitivity to spicy foods	1.4–6.5	Mild/moderate	Managing expectations Food swaps to identify food that is pleasant in the context of taste changes Dietetic referral Monitoring blood to check for raised creatinine levels Treatment breaks (>4 weeks may be needed)	Yes (2–6 months after stopping vismodegib)
Muscle cramps	Cramps in hands/feet Cramps in abdomen Often experienced after physical activities	1.3–2.8	Mild/moderate	Quinine (200 mg) Treatment breaks (4–8 weeks) Gentle exercise of affected areas Muscle relaxants (e.g., baclofen 15–30 mg daily; temazepam 10–20 mg daily)	Yes (1 month after stopping vismodegib)
Alopecia	Can be patchy or cover the whole head Includes body hair	3.4–5.5	Mild/moderate	Managing expectations Wig referral	Yes (usually 6–12 months, occasionally longer)

AE: Adverse event.

Future Oncol. 2017;13:175-184

Intermittent Dosing: Reduce AEs, Retain Rx Effect?

Research Letter ONLINE FIRST

January 18, 2017

A Novel Alternate Dosing of Vismodegib For Treatment of Patients With Advanced Basal Cell Carcinomas

Lauren R. Becker, MD[1]; Angela E. Aakhus, MD[1]; Hilary C. Reich, MD[1]; et al

» Author Affiliations | Article Information

JAMA Dermatol. Published online January 18, 2017. doi:10.1001/jamadermatol.2016.5058

N=2, Both Gorlin Syn
1-2 Months on
2 Months off

JAMA Dermatol. 2016 Feb;152(2):223-4

N =7 (1 Gorlin Syn)
1 Week on
1-3 Weeks off

JAMA Dermatol. 2017 Jan 18.
doi: 10.1001/jamadermatol.2016.5058.

Observation FREE

February 2016

Intermittent Vismodegib Therapy in Basal Cell Nevus Syndrome

Xinyi Yang[1]; Scott M. Dinehart, MD[2]

» Author Affiliations | Article Information

JAMA Dermatol. 2016;152(2):223-224. doi:10.1001/jamadermatol.2015.3210

THE LANCET
Oncology

Lancet Oncol 2017; Feb 7
http://dx.doi.org/10.1016/S1470-2045(17)30072-4

Articles

Two intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas (MIKIE): a randomised, regimen-controlled, double-blind, phase 2 trial

Prof Brigitte Dréno, MD, Prof Rainer Kunstfeld, MD, Prof Axel Hauschild, MD, Prof Scott Fosko, MD, David Zloty, MD, Bruno Labeille, MD, Prof Jean-Jacques Grob, MD, Susana Puig, MD, Frank Gilberg, PhD, Daniel Bergström, PhD, Damian R Page, PhD, Gary Rogers, MD, Prof Dirk Schadendorf, MD

Published: 07 February 2017

Vismodegib: Intermittent Dosing Trial

- 229 adult patients, mostly immunocompetent and good overall functional status; 37% Gorlin Synd.
- Assigned to two treatment groups for 72 wk trial
  - QD Induction x 3 mo, then 2mo off, 3 mo on x 3 cycles
  - QD induction x 6 mo, then 2mo off, 2 mo on x 3 cycles
- BOTH treatment regimens were effective
  - 54-62.7% reduction from baseline in number BCC
  - 57-76% had at least 50% reduction in number BCC
  - 64-72% experienced NO new BCC by EOT
- Adverse events were still common; 23% Dropout rate

Lancet Oncol 2017; Feb 7
http://dx.doi.org/10.1016/S1470-2045(17)30072-4

Drugs in R&D
pp 1–8

Hepatotoxicity with Vismodegib: An MD Anderson Cancer Center and Research on Adverse Drug Events and Reports Project

Authors | Authors and affiliations

Beatrice J. Edwards ✉, Dennis W. Raisch, Smita S. Saraykar, Ming Sun, Josh A. Hammel, Hai T. Tran, Nathaniel Wehr, Rasha Arabyat, Dennis P. West

Open Access | Original Research Article

First Online: 06 January 2017

DOI: 10.1007/s40268-016-0168-2

Cite this article as:
Edwards, B.J., Raisch, D.W., Saraykar, S.S. et al. Drugs R D (2017). doi:10.1007/s40268-016-0168-2

Hepatotoxicity signal
Two severe liver toxicity cases
94 addt'l reports, 35 serious

Drugs R D. 2017 Jan 6. doi: 10.1007/s40268-016-0168-2.

Predicting Hedgehog Pathway Inhibitor Resistance????

European Journal of Dermatology

Immunohistochemical markers of advanced basal cell carcinoma: CD56 is associated with a lack of response to vismodegib

Volume 26, numéro 5, September-October 2016

Auteurs
Jean-Marie Castillo [1]
Anne-Chantal Knol [2]
Jean-Michel Nguyen [2 3]
Amir Khammari [2 4]
Mélanie Saint-Jean [4]
Brigitte Dreno [2 4 5 *]

Eur J Dermatol. 2016;26:452-459

Original Investigation

Hedgehog Pathway Inhibitor Therapy for Locally Advanced and Metastatic Basal Cell Carcinoma

A Systematic Review and Pooled Analysis of Interventional Studies

Audrey A. Jacobsen, BA; Adam S. Aldahan, BS; Olivia B. Hughes, BS; Vidhi V. Shah, BA; John Strasswimmer, MD, PhD

IMPORTANCE Hedgehog pathway inhibitors (HPIs) were made available by US Food and Drug Administration approval in 2012 for vismodegib and 2015 for sonidegib. Both target the Smoothened molecule and are indicated for locally advanced basal cell carcinoma (laBCC) and metastatic basal cell carcinoma (mBCC).

Cochrane-type systematic analysis
Included pivotal study plus other published trials & case series
Total trials = 8 and Total patients clinically evaluable = 704
Objective response laBCC weighted average 64.7%
Complete response weighted average 31.1%
AE-related discontinuation of therapy average 28.2%

JAMA Dermatol. 2016;152:816-24.

Original Investigation

Hedgehog Pathway Inhibitor Therapy for Locally Advanced and Metastatic Basal Cell Carcinoma

A Systematic Review and Pooled Analysis of Interventional Studies

"This analysis supports the opinion that vismodegib may be more useful as a means to control laBCC than to provide a definitive cure."

Cochrane-type systematic analysis
Included pivotal study plus other published trials & case series
Total trails = 8 and Total patients clinically evaluable = 704
Objective response laBCC weighted average 64.7%
Complete response weighted average 31.1%
AE-related discontinuation of therapy average 28.2%

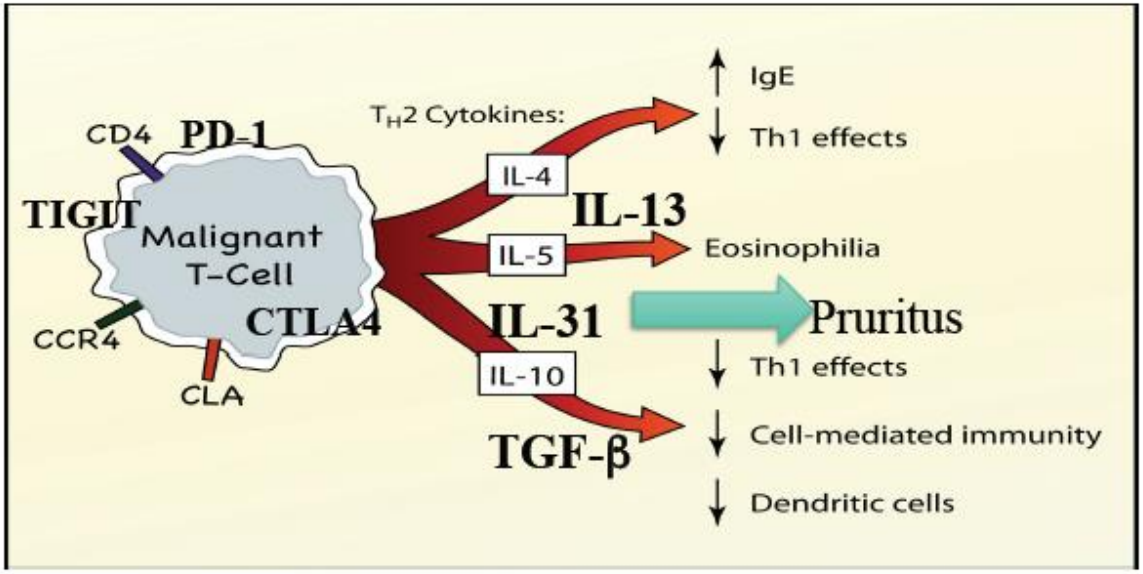
JAMA Dermatol. 2016;152:816-24.

New Systemic Immune Strategies in CTCL

Youn H Kim, MD

Department of Dermatology
Multidisciplinary Cutaneous Lymphoma Group
Stanford Cancer Institute & School of Medicine

Sezary Cell: Receptors and Soluble Factors



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

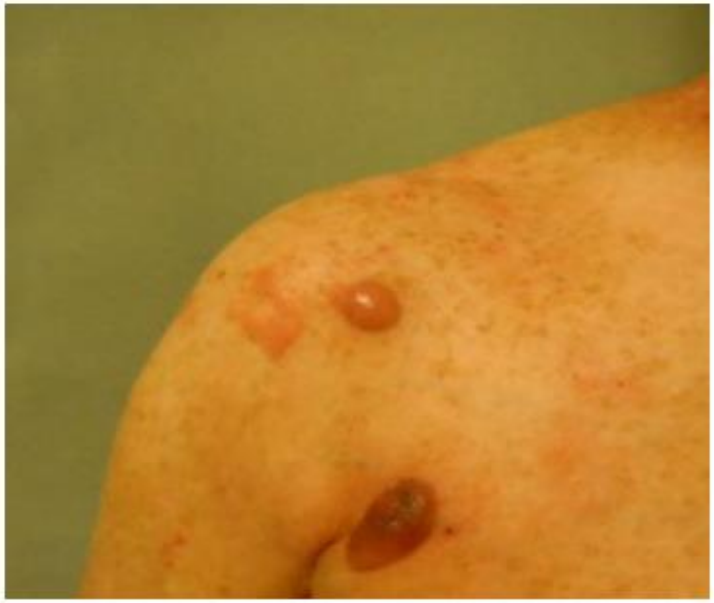
Y Kim (Co-PI)

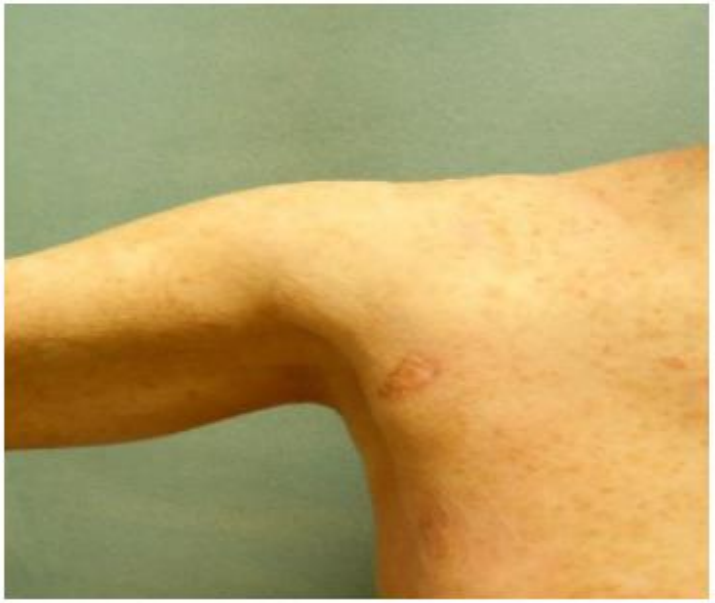
Stanford University SOM

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)

Refractory Stage IIB: Response to Anti-PD-1 After Progression on 9 Previous Treatments





National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
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)[e]
- Interferons (IFN-alpha, IFN-gamma)
- HDAC-inhibitors (vorinostat, romidepsin)[e]
- Extracorporeal photopheresis[f]
- Methotrexate (≤100 mg q week)

Category B (SYST-CAT B)

- First-line therapies (alphabetical order)
  - Brentuximab vedotin
  - Gemcitabine
  - Liposomal doxorubicin
  - Low-dose pralatrexate
- Second-line therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphamide
  - Temozolomide
  - Methotrexate (>100 mg
  - Pembrolizumab[g] (category 2B)
  - Bortezomib (category 3)

Pembrolizumab added based on ASH 12/2016, abstract #181

SYSTEMIC THERAPIES (conti

Category C (SYST-CAT C)[h] (alp

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

COMBINATION THERAPIES

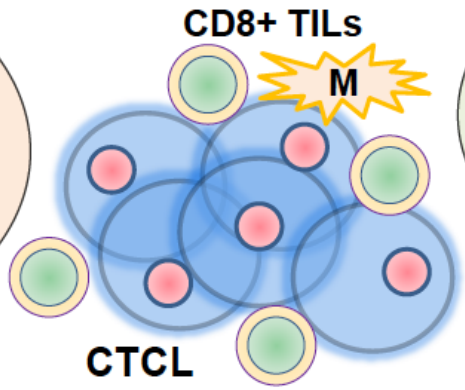
Skin-directed + Systemic

- Phototherapy + retinoid
- Phototherapy + IFN
- Phototherapy + photopheresis[f]
- Total skin electron beam + photopheresis[f]

Systemic + Systemic

- Retinoid + IFN
- Photopheresis[f] + retinoid
- Photopheresis[f] + IFN
- Photopheresis[f] + retinoid + IFN

Newer therapies in clinical development in CTCL



Tumor cell surface molecules

CD25,
2, CCR4,
R3DL2)

Brentuximab vedotin
Mogamulizumab
Anti-CD25 fusion toxin
Anti-CD3 fusion toxin
Anti-CD37 ADC
Anti-KIR3DL2 mab

Microenvironment, immune mechanisms (e.g., PD-1, PD-L1, CTLA-4, SIRPα/CD47, IDO, MDSC

Anti-PD-1/PD-L1 mAbs
Anti-CTLA-4 mAbs
Anti-CD47 mAb/SIRPα Fc decoy, anti-SIRPα mAb
IDO inhibitor
Lenalidomide
Treg depleting agents

Proteosome inhibitors
PI3k inhibitors
mTOR inhibitors
Jak inhibitors
Syk-Jak dual inhibitor
ITK inhibitor
Anti-apoptotic agents
Anti-miR-155
New HDAC inhibitors
Demethylating agents
New anti-folates (pralatrexate)

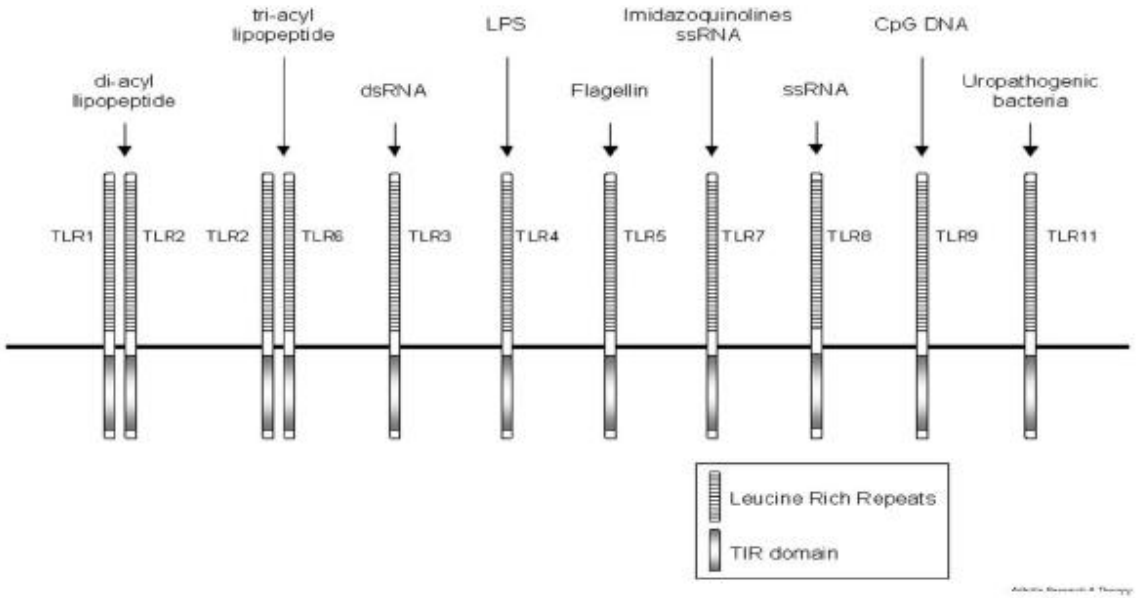
Tumor proliferation, metabolism, survival, progression mechanisms:
Signal transduction/transcription activation pathways *(e.g. TNFR2, proteasome, AKT/PI3K/mTOR, JAK/STAT, ITK)*
Apoptotic pathways *(e.g. Bcl/Bax, TNFR, Fas, miRNAs)*
Epigenetics *(e.g., histone, non-histone proteins)*
Metabolic/survival pathways *(e.g., RFC-1, PARP)*

Multiple combination therapies under investigation

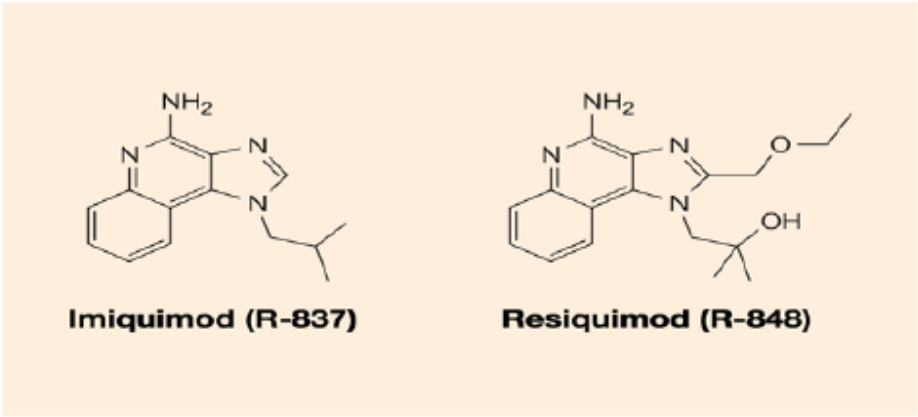
Activation of the Innate Immune Response as Therapy for CTCL

Alain H. Rook, M.D.
Professor of dermatology
University of Pennsylvania
Perelman School of Medicine

Toll Like Receptors

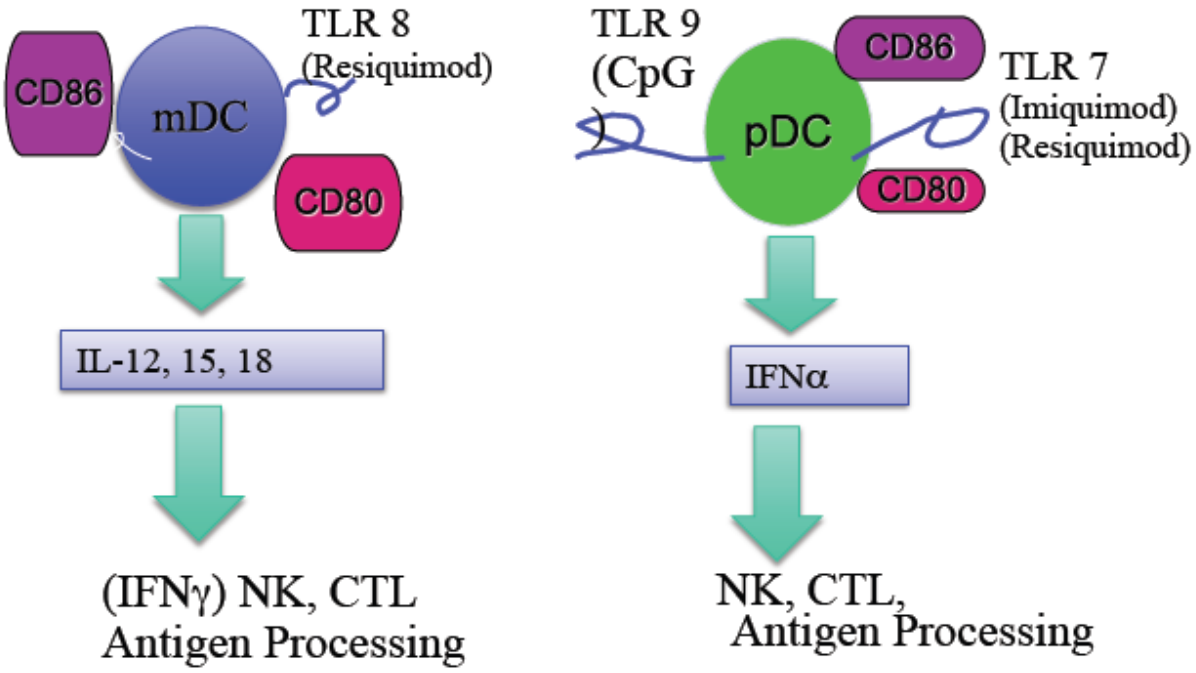


Imidazoquinolines Are Powerful TLR Agonists



Nature Reviews | Drug Discovery

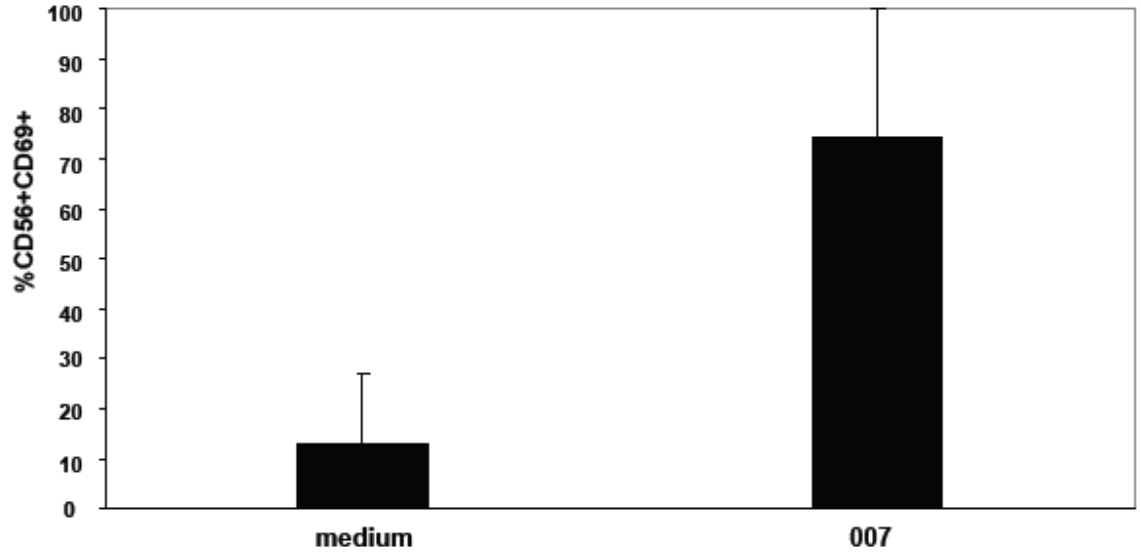
Toll Like Receptor Agonists Are Therapeutically Active for Cutaneous T-Cell Lymphoma



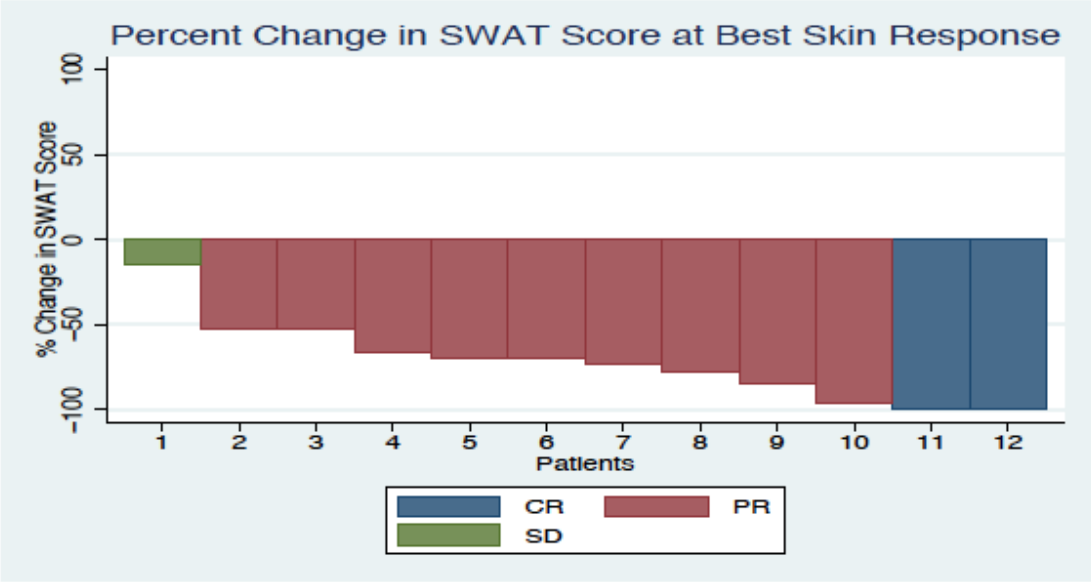
Resiquimod(007)

- **Combined TLR 7 & 8 agonist**
- **Bioavailability 10 times > imiquimod**
- **Potency up to 100 times > imiquimod**
- **1g application induces a systemic IFN alpha response**

Resiquimod Activates a High Percentage of NK Cells That are in the Blood of Sezary Syndrome Patients



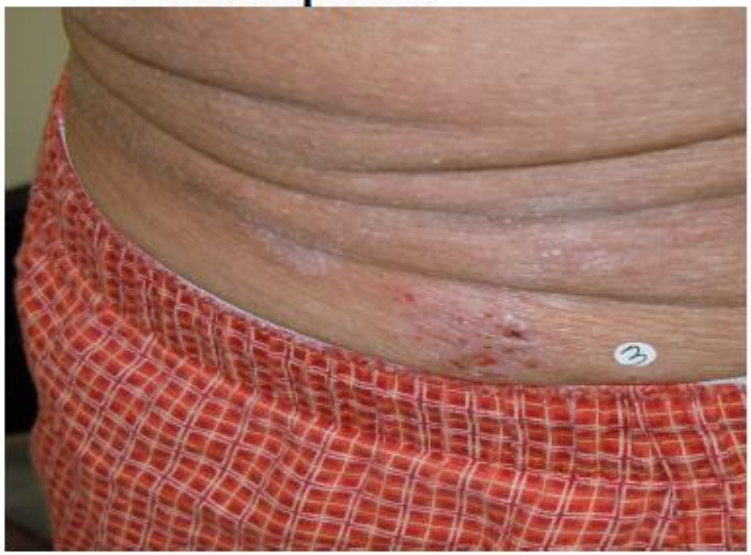
Resiquimod Phase I Trial Responses



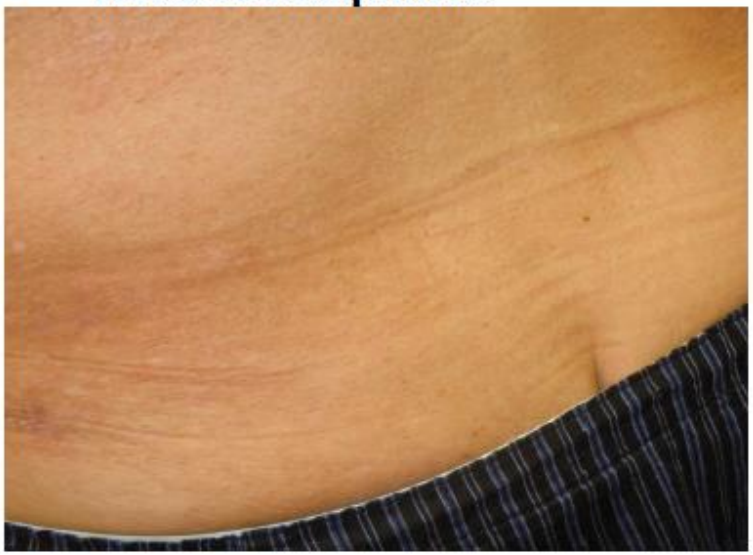
Rook, et al. Blood. Sept 17, 2015

Clinical Response to Resiquimod

Pre-Resiquimod



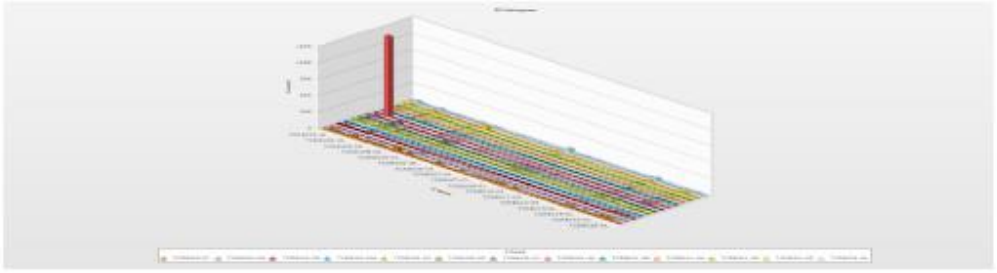
Week 12 Resiquimod



Patient 11

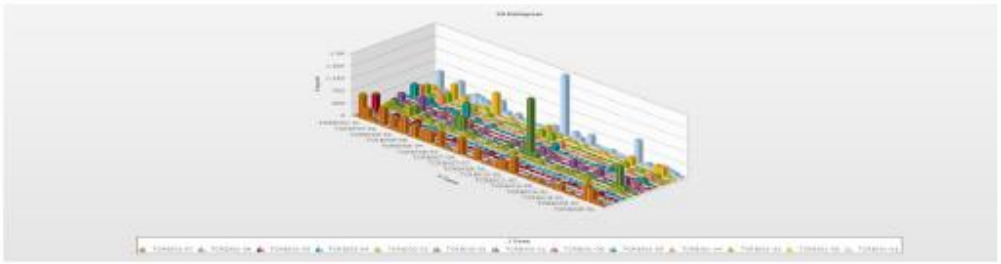
Clearance of Malignant Clone and Restoration of Clonal Diversity

Pre-treatment



Clone:
19% T cells

8 weeks

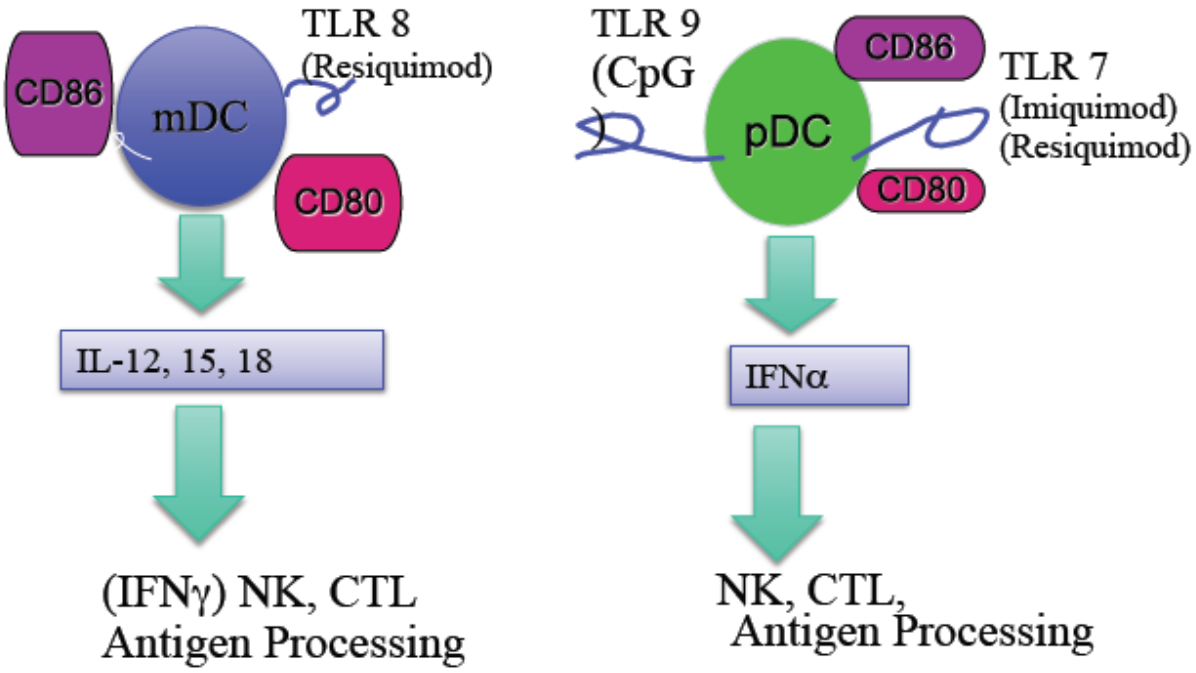


Clone:
0% T cells

Resiquimod Trial for CTCL

- **Well tolerated topical drug with grade I skin toxicity**
- **Ease of application**
- **High clinical response rates of both treated and untreated lesions among refractory early stage CTCL**
- **Among 12 patients 10/12 responses (7 PR; 3CR; 2 stable disease)**
- **Evidence for systemic immune activation**
- **Phase II, multicenter, placebo controlled trial planned**

Toll Like Receptor Agonists Are Therapeutically Active for Cutaneous T-Cell Lymphoma



Phase I trial of a Toll-like receptor 9 agonist, PF-3512676 (CPG 7909), in patients with treatment-refractory, cutaneous T-cell lymphoma.

Kim YH1, Girardi M, Duvic M, Kuzel T, Link BK, Pinter-Brown L, Rook AH.

- **A phase I designed to test safety but not efficacy with weekly Sub Q injections**
- **Dose escalation trial with low concentrations not effective**
- **High concentrations produced responses even at stage IV**

Phase I Trial of CpG 7909

- **28 patients with highly refractory CTCL**
- **9 responses**
- **3 complete responses (including 2 with late stage disease)**
- **Significant activity in advanced CTCL:future trials are warranted**

Potential Role of TLR Agonists in CTCL Therapy

Single-agent immunostimulator

Effective agent in combination regimens

- **Photopheresis**
- **Cytokines (particularly IFN gamma)**
- **Retinoids**
- **PUVA**
- **Electron beam**
- **Anti-PD-1**

***In situ* vaccination therapy**

- **Low-dose RT + intratumoral CPG**

  (Ongoing clinical trial at Stanford)

THANK YOU !