One Moment Please

One Moment Please

Skin Cancer

Thomas Olencki, DO
David Carr, MD

Today's Webcast
Friday, 09/09/11, Noon

New Features

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Thomas Olencki, DO

David Carr, MD

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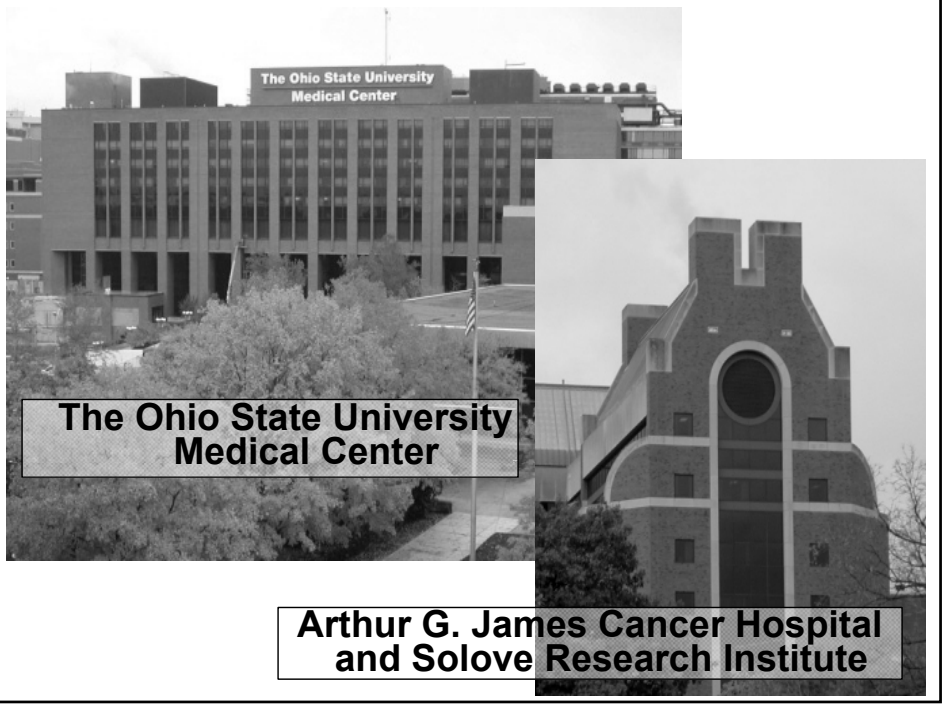
This activity will review the treatment of Skin Cancer.

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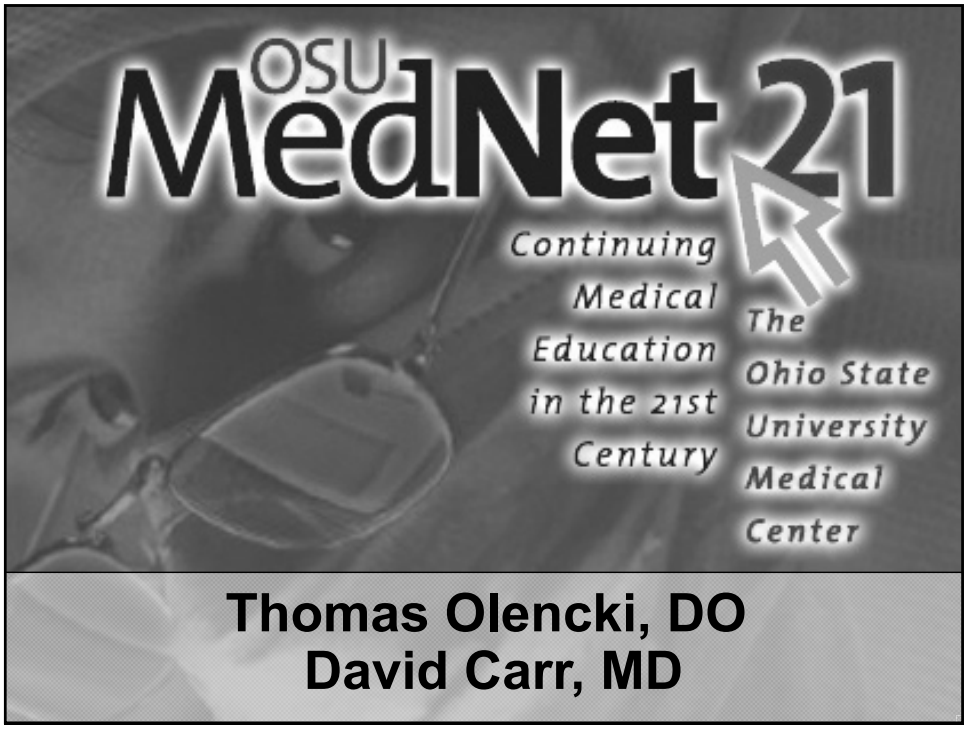
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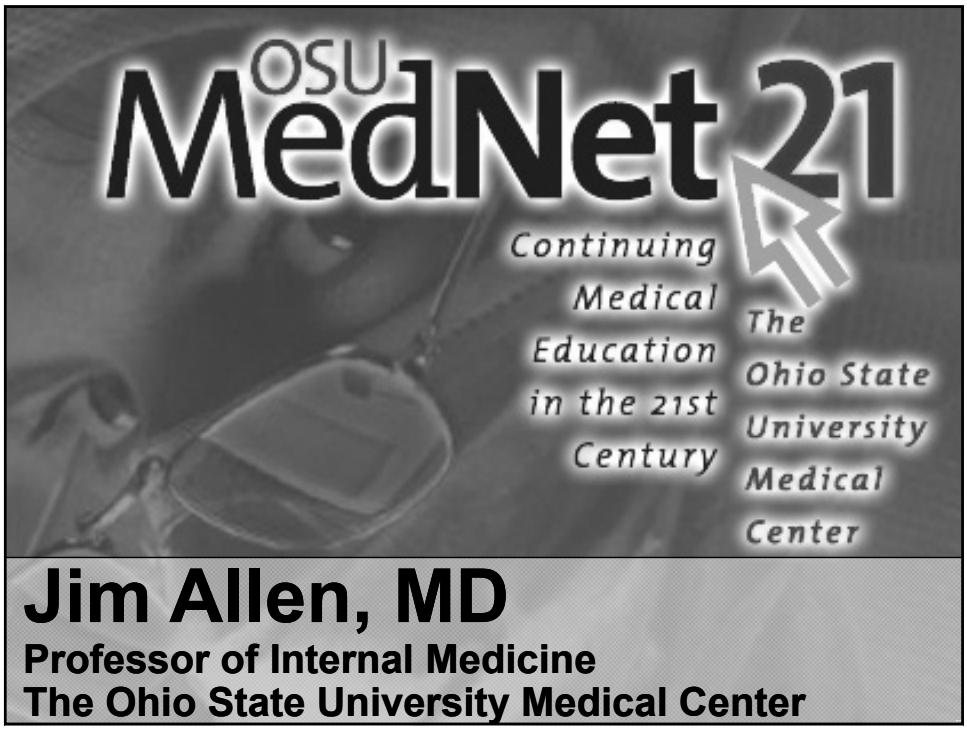
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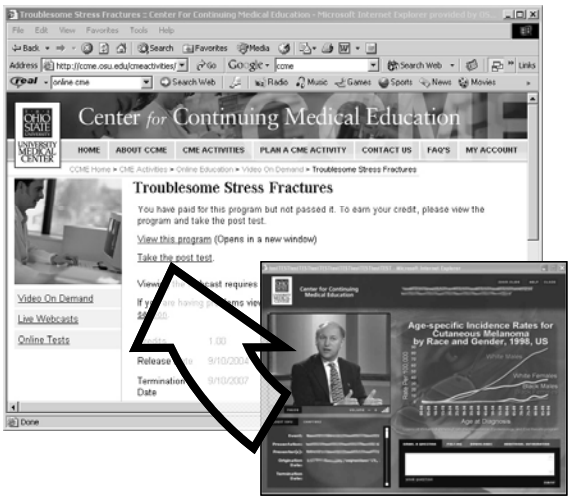
Professor of Internal Medicine
The Ohio State University Medical Center



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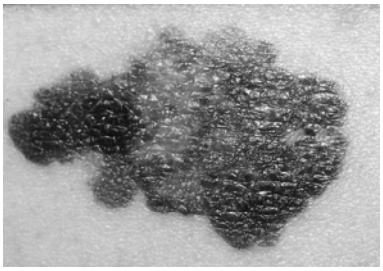
CME tracking, 24/7, current therapies, post-tests

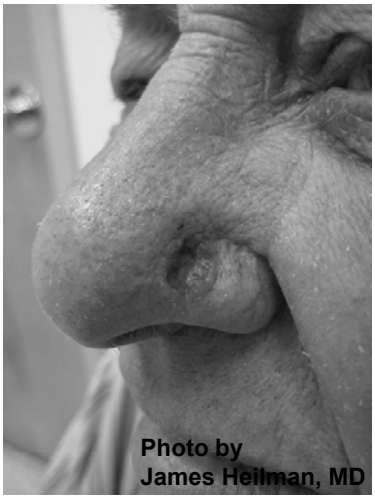
Madison, Wisconsin

Skin Cancer

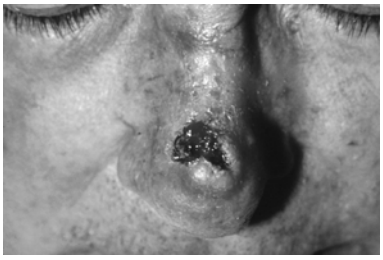
Thomas Olencki, DO
David Carr, MD



Melanoma



Basal Cell Carcinoma



Squamous Cell Carcinoma

Challenges with treating melanoma with chemotherapy

Mohs Surgery: Overview & Indications

David Carr, MD
Assistant Professor
Division of Dermatology
The Ohio State University College of Medicine

Video Presentation

Mohs Surgery

Video Presentation

Q & A with Dr. David Carr

Video Presentation

Dr. David Carr's Key Point

Prognosis of metastatic melanoma

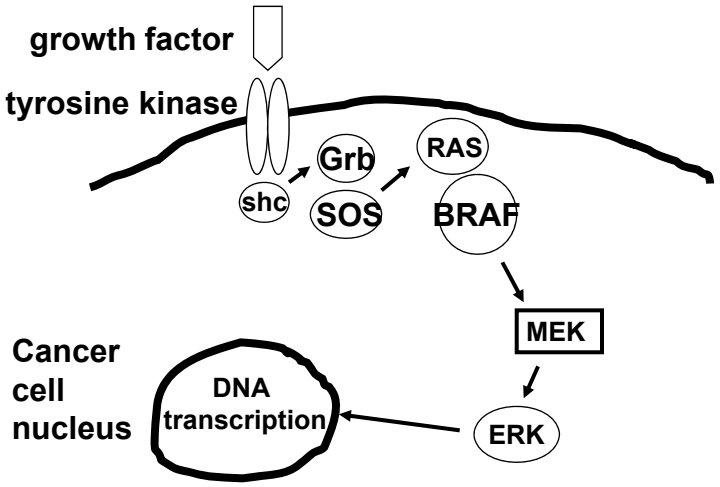
Review of 2 New Meds for Therapy of Metastic Melanoma

Thomas Olencki, DO
Clinical Professor of Medicine
Division of Medical Oncology
Ohio State University College of Medicine

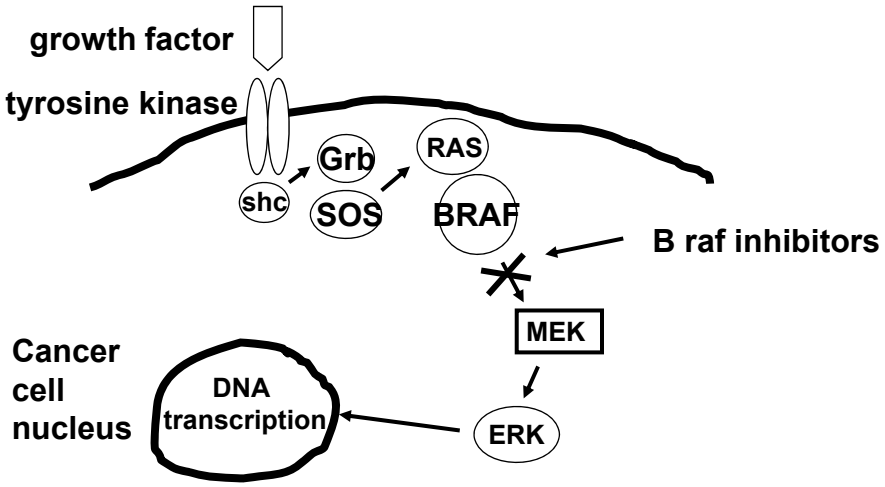
FDA Approved Drugs For Treatment Of Metastatic Melanoma

- **Dacarbazine (DTIC) – 1975**
- **Interleukin-2 (IL-2) – Jan 1998**
- **Yervoy (ipilimumab) – March 2010**
- **Zelboraf (vemurafenib) – August 2011**

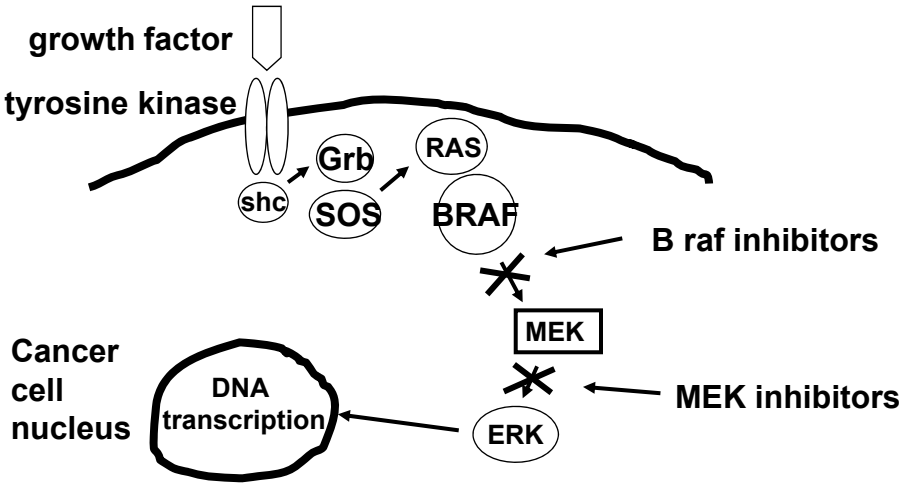
MAP Kinase Pathway And Targeted Therapy



MAP Kinase Pathway And Targeted Therapy



MAP Kinase Pathway And Targeted Therapy



B raf Mutation

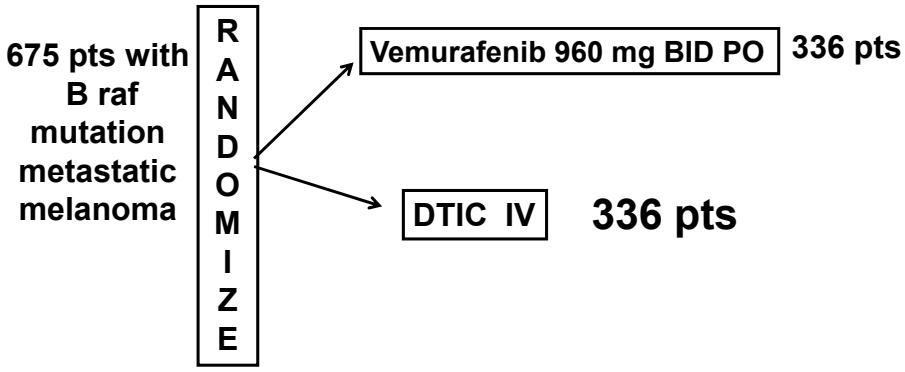
- Found in 50% of cutaneous melanomas
  - Most commonly V600 E B raf mutation
    - Results in a substitution of glutamic acid for valine at codon 600
  - May also have a B raf V 600K and B raf V 600R
  - Present in the entire spectrum of melanoma (primary to mets)
  - Activating mutation
  - Translocates to mitochondria where it binds to and inactivates Bad
    - Net effect is to decrease melanoma apoptosis

B raf Mutation

- Drugs designed to inhibit site
  - Sorafenib (Nexavar®) bound to non-mutated B raf → not active in melanoma
  - Vemurafenib (Zelboraf®) (RO 5185426, PLX 4032)
  - GSK 2118436

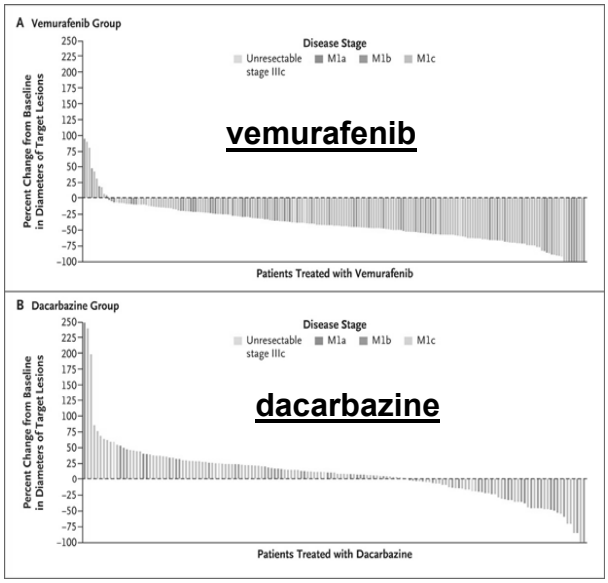
Phase III 1st Line Vemurafenib vs Dacarbazine

Open 1/2010 to 12/2010



Chapman, NEJM 364:2507, 2011

Waterfall Plot of Best Tumor Response



Chapman, NEJM 364:2507, 2011

Phase III 1st Line Vemurafenib vs Dacarbazine

- **Results**

	vemurafenib	DTIC	Korn
median PFS	5.3 mos	1.6 mos	1.7
median OS	not reached	7.9 mos	6.2
12 mos survival	44%	25%	26%
24 mos survival	22%	14%	
RR	48%	6%	
Control rate*	22%	11%	

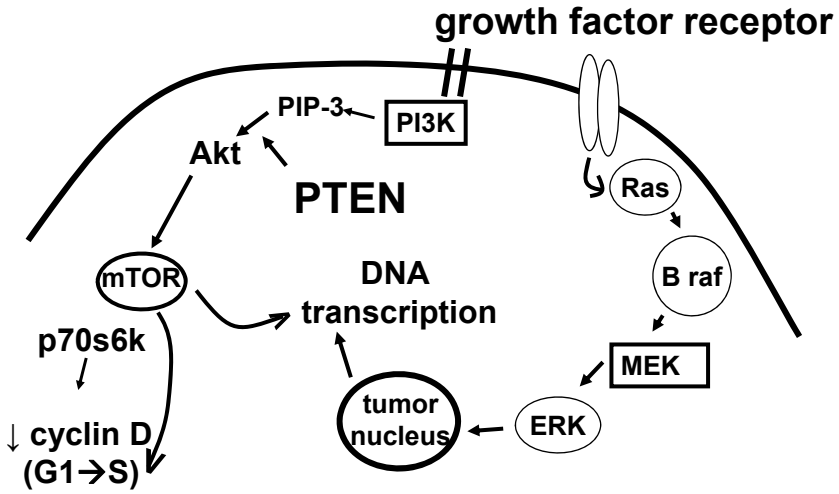
* CR, + PR, + SD

Chapman, NEJM 364:2507, 2011

Problems With Current Targeted Therapy

- Blocking B raf may up regulate C raf and other pathways
- B raf and MEK inhibitors "work" only if mutation present
- Significant clinical resp. usually of short duration
  - alternative signaling pathways take over
- Multiple signal transduction pathways may need to be blocked simultaneously
  - but this may increase side effects or "off target" effects

PI3 And MAP Kinase Inhibitors



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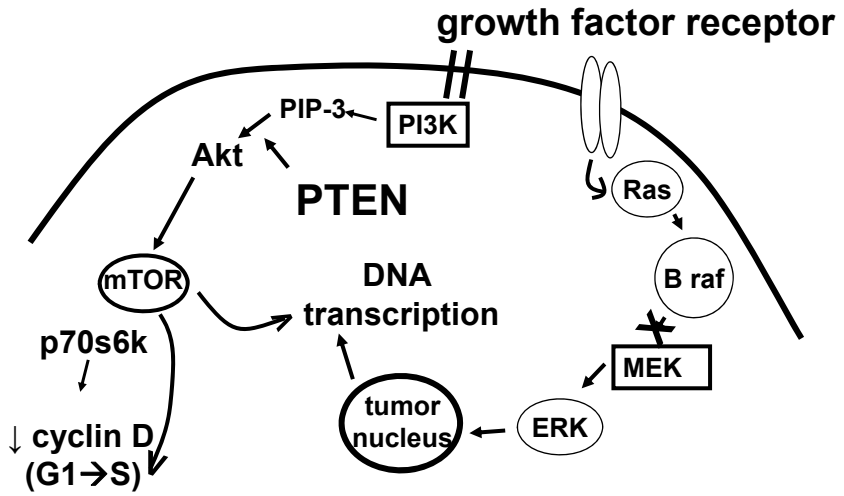
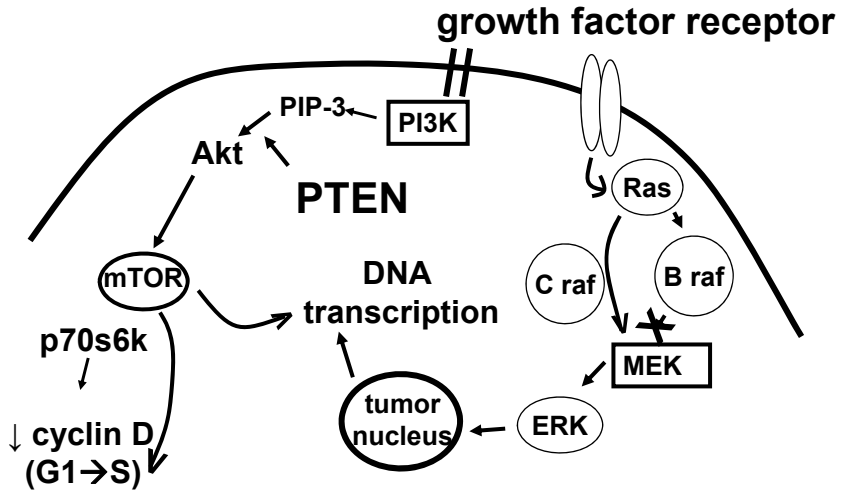


HIFα → Cox-2 → angiogenesis
and other protein translation

PI3 And MAP Kinase Inhibitors



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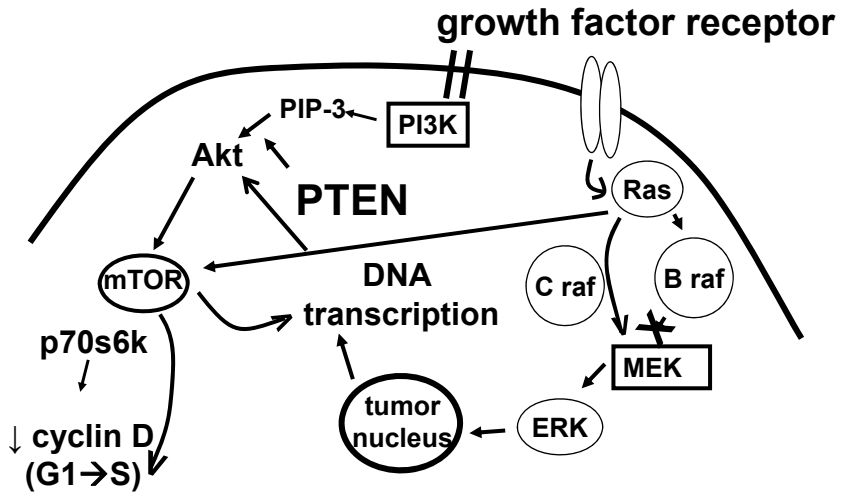

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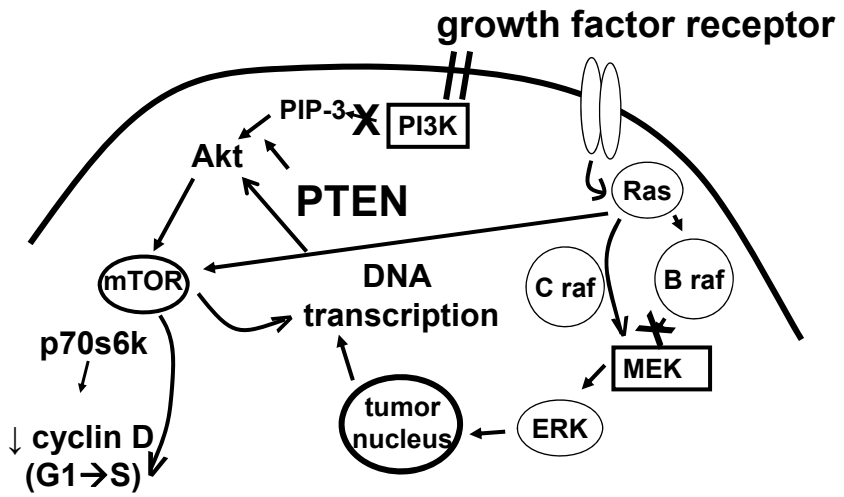

HIFα → Cox-2 → angiogenesis
and other protein translation

So, what is all the news about?

ASCO 2010
Sunday June 6, 2010

Cytotoxic T Lymphocyte Assoc Protein-4 (CTLA-4)

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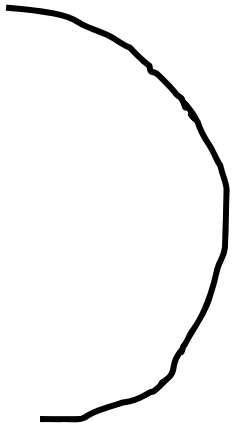

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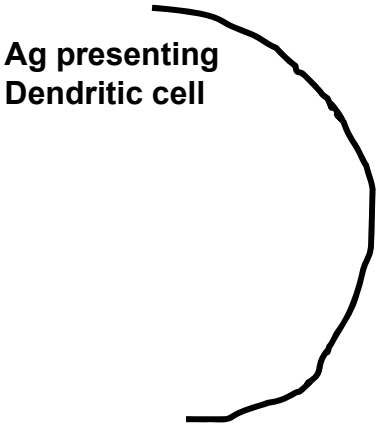

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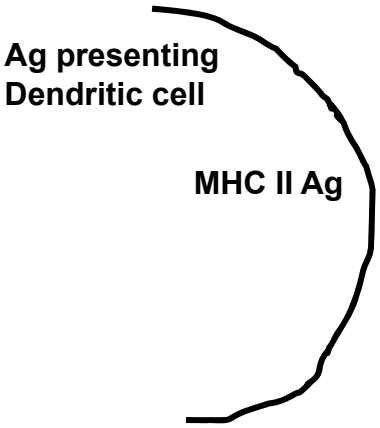

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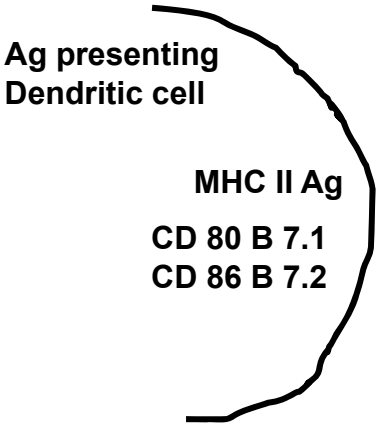

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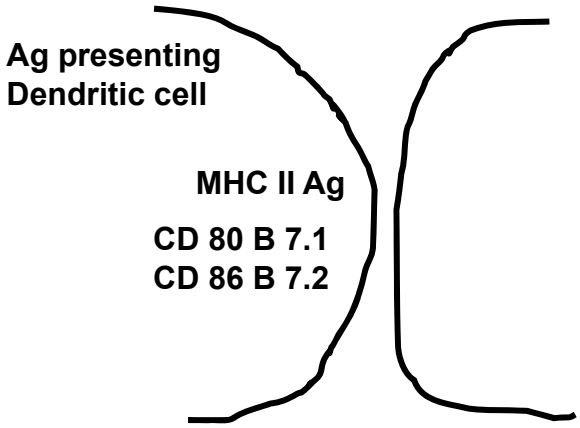

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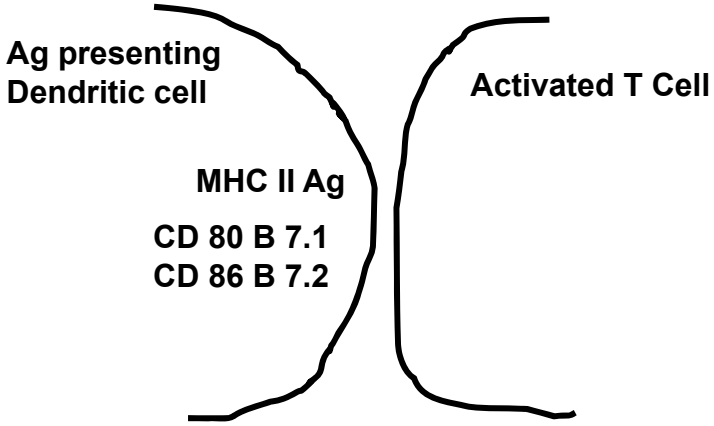

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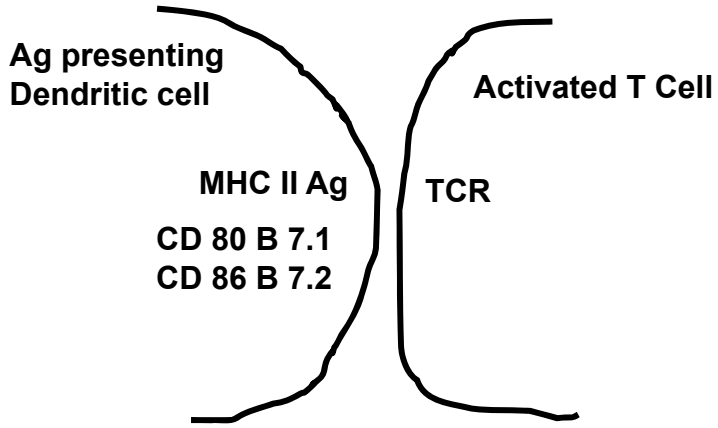

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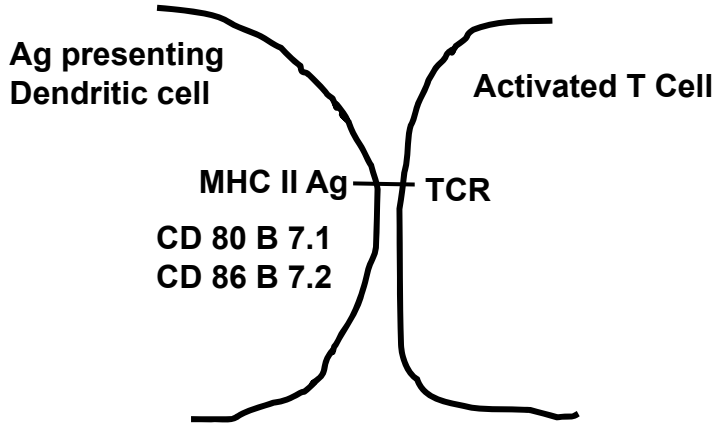

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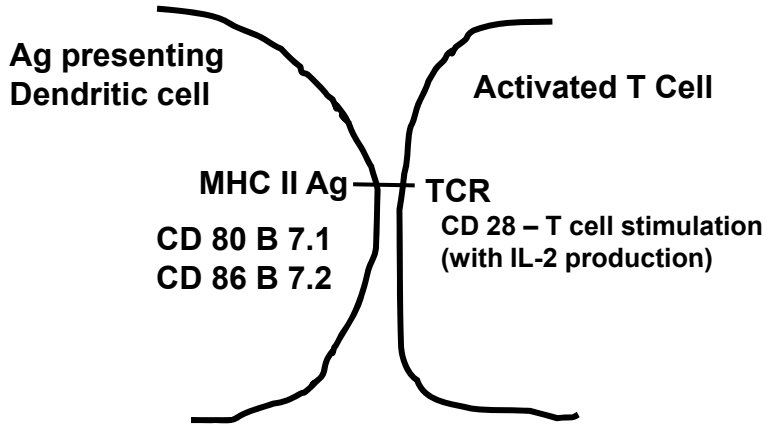

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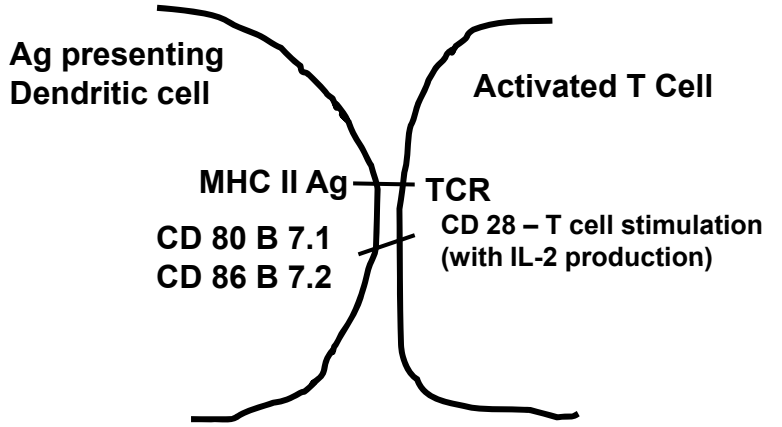

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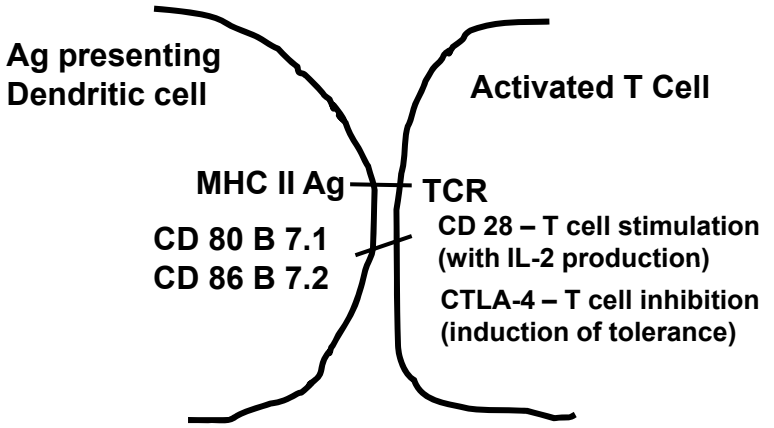

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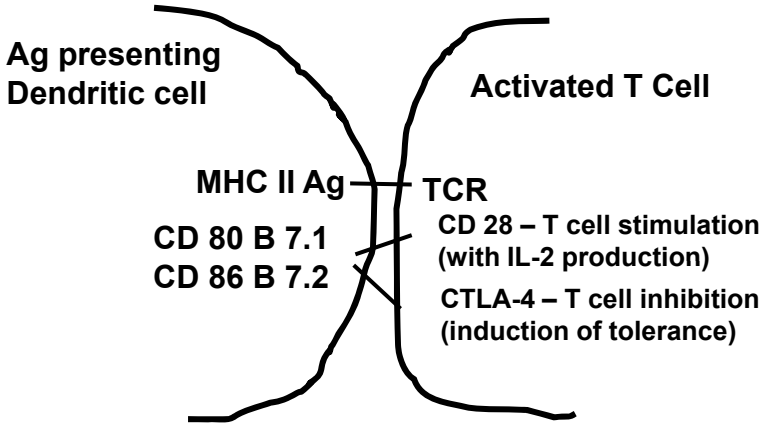

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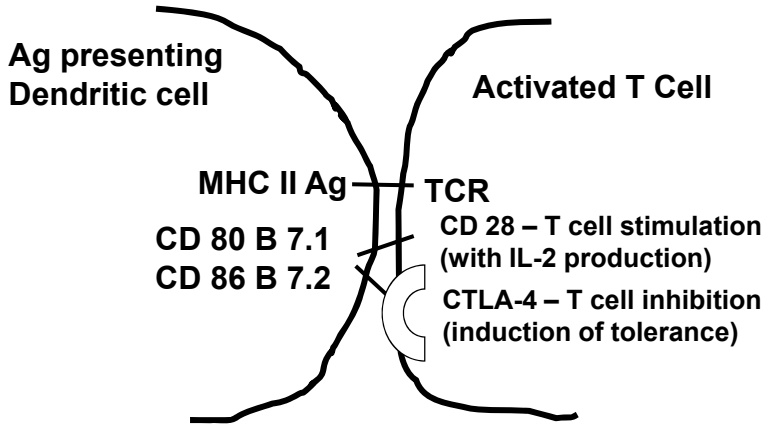
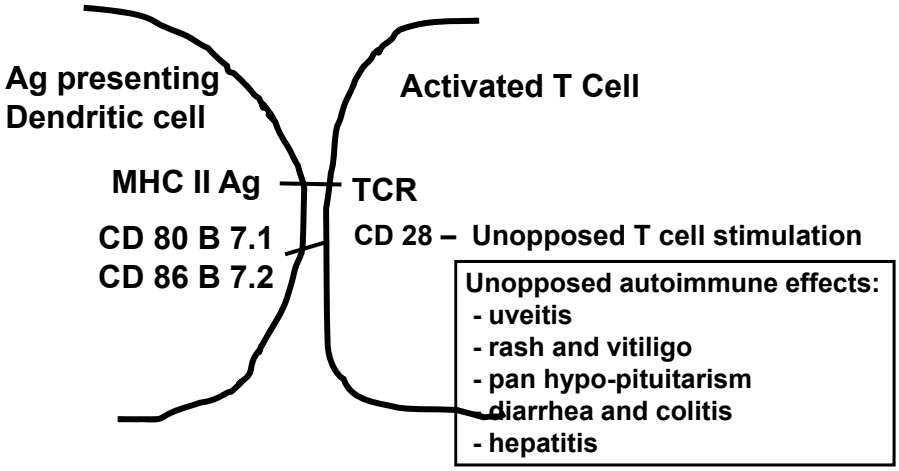


CTLA-4 (2)



CTLA-4 (3)

- anti-CTLA-4 MoAb
  - humanized IgG1k
  - $T_{1/2}$ 20 - 30 days
  - BMS/ Medarex - MDX 010 - ipilimumab
- Breaks tolerance – removes the "brake " on T cells
  - decreases T reg number and function (↓ IL-10 and TGFβ)

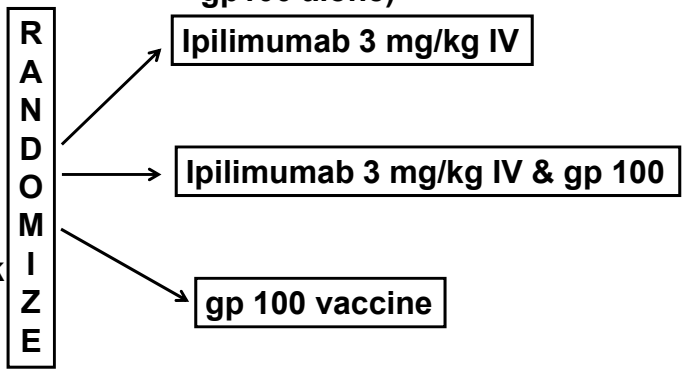
Phase III MDX010-20 – 2nd Line Tx

Open 9/2004 – 8/2008
Double blind

All drugs → q 3wks x 4 doses (3:1:1; for ipi, ipi & gp100 and gp100 alone)

676 pts with prior treated metastatic melanoma

70% had M1c poor risk visceral disease



Hodi, NEJM 363:711, 2010

Phase III MDX010-20 – 2nd Line Tx

- **Results**

	ipi	ipi and gp100	gp100	Korn
PFS	2.8 mos	2.8 mos	2.8 mos	1.7
med OS	10.1 mos	10 mos	6.4 mos	6.2
12 mos	46%	44%	25%	26%
24 mos	24%	22%	14%	
RR	11%	6%	2%	
Control rate*	29%	22%	11%	

* CR, + PR, + SD

Hodi, NEJM 363:711, 2010

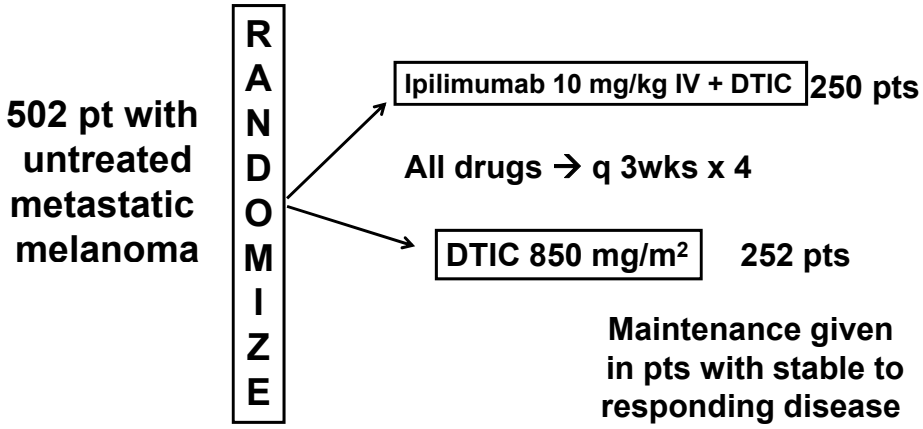
MDX010-20 Ipilimumab

- **Toxicity**
  - **60% had immune related adverse events**
  - **30% diarrhea/colitis (any grade) lasting a median of 2.3 wks (after steroids begun)**
  - **10-15% of pts have gr. 3 and 4 immune toxicity**
  - **cutaneous – maculopapular rash and vitiligo**
- **Deaths – 14 pts (2%) of drug side effects**
- **Unique feature – pts who progress may be re-challenged and still have a chance of response**

Hodi, NEJM 363:711, 2010

Phase III Ipilimumab +/- Dacarbazine – 1st Line

Open 8/2006 to 1/2008



Robert, NEJM 364:2517, 2011

Phase III MDX010-20 – 2nd Line Tx

Results

	ipi and DTIC	DTIC	Korn
PFS (stat significant)	2.8 mos	2.6 mos	1.7
med OS	11 mos	9 mos	6.2
12 mos	47%	36%	26%
24 mos	29%	18%	
RR (duration)	15% (19 mos)	10% (8 mos)	
Control rate*	33%	30%	

* CR, + PR, + SD

Robert, NEJM 364:2517, 2011

Which Is Better – High Dose IL-2 Or Ipilimumab?

- HD IL-2
  - In pt treatment
  - Side effects stop with drug infusion
  - 4% complete response rate (may be increased with surgery)
  - Pts need to be in good physical condition

Which Is Better – High Dose IL-2 Or Ipilimumab?

- Ipilimumab
  - Out pt treatment
  - Side effects continue for weeks
  - 0.5 to 1% complete response rate
  - May be done in a pt with Tx brain mets or with less physical reserve

Conclusions

- Because of short response and short survival upon progression, B raf inhibitors will need to be given in combination or sequentially with other drugs
- Uncertainty remains
  - re the effect of dacarbazine given in combination with ipi
  - whether ipi should be given 1st or 2 nd line
  - whether ipi should be given in combination or sequentially with other drugs
- As optimal therapy remains lacking, pts should be treated on clinical trials as much as possible

Signs and symptoms of recurrent melanoma

Skin cancer prevention: Advice for patients

Immuno-suppression and skin cancer

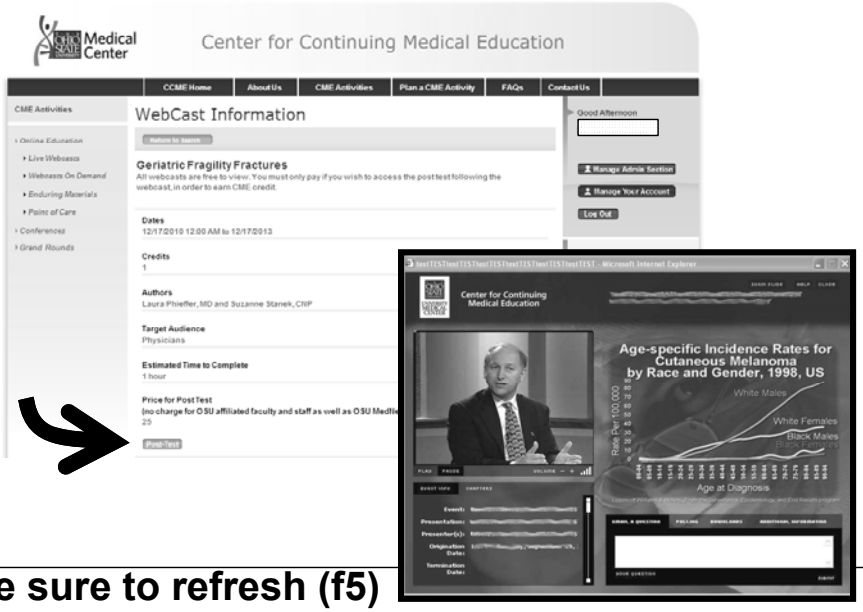
Squamous cell carcinoma and basal cell carcinoma: the role of the medical oncologist

Today's Poll Results

poll results will continue to be tabulated

POLLING

To take the post test, please return to your account at *ccme.osu.edu*



Be sure to refresh (f5)

Skin Cancer