OSU MedNet 21

Continuing Medical Education in the 21st Century

The Ohio State University Medical Center

One Moment Please

New Features

Enlarge Slides

Links

Chapters **Polling**

Use the email function to let us know what you think

One Moment Please

Skin Cancer

Thomas Olencki, DO
David Carr, MD

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

Planning Committee Disclosures

The following planning committee members have no relevant financial relationships with commercial interests to disclose:

Jame Allen, MD

Barbara Berry

Derrick Freeman

The following planning committee members' educational unit does not have a financial interest or affiliation with an organization that may receive direct benefit from the subject of the proposed CME activity, and they will not be personally compensated for their role in the planning or execution of this proposed CME activity by an organization other than The Ohio State University:

Jame Allen, MD

Barbara Berry

Derrick Freeman

The following program is a Continuing Medical Education Activity sponsored by The Ohio State University Medical Center. The design and production of this CME Activity is the sole responsibility of The Ohio State University Medical Center.

Accreditation Statement

The Ohio State University Medical Center, Center for Continuing Medical Education (CCME) is accredited by the Accreditation Council for Continuing Medical Education (ACCME®) to provide continuing medical education for physicians.

AMA Designation Statement

The Ohio State University Medical Center, Center for Continuing Medical Education designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

As an enduring material this CME Activity is approved for three years from original release. Original release 09/09/11. Termination date 09/09/14.

CCME Disclosure Statement

As a provider of AMA PRA Category 1 Continuing Medical Education, it is the policy of CCME to adhere to the ACCME Standards for Commercial Support to avoid any conflict of interest and/or commercial bias and must ensure balance, independence, objectivity and scientific rigor in all its sponsored educational activities. All individuals who are in a position to control content of an educational activity, including presenters, panel members and moderators, must to disclose any relevant financial relationships that create a conflict of interest.

Nothing in this program is intended to imply that any off-label or unapproved product use discussed is reimbursed by any government or private payor or that submission of a claim for such use is proper.

Presentation may include discussion of services and unapproved or off-label usage of

Speaker Disclosures

• The following presenters for this educational activity disclose that they have the following relationships with commercial interests to disclose.

Thomas Olencki, DO

Advisory Board Membership – Genentech
Grants/Research support – Genentech, Bristol Myers-Squibb

David Carr, MD – Consultant – Healthy Advice

• Dr. Olencki's presentation will include discussion of unapproved or "off-label" usage of commercial products and/or services

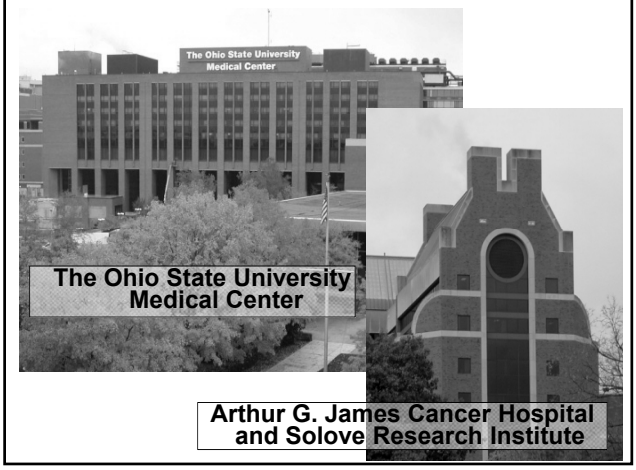
Thomas Olencki, DO

David Carr, MD

Agenda Disclaimer

CCME presents this activity for educational purposes only. Participants are expected to utilize their own expertise and judgment while engaged in the practice of medicine. The content of the presentations is provided solely by presenters who have been selected for presentations of recognized expertise in their field.

This activity will review the treatment of Skin Cancer.

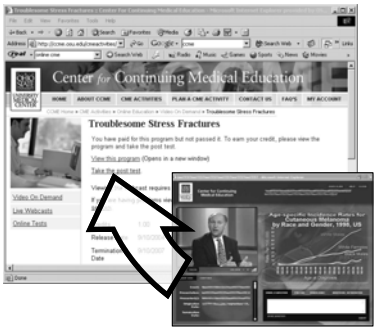


OSU MedNet 21

Continuing Medical Education in the 21st Century

The Ohio State University Medical Center

Thomas Olencki, DO
David Carr, MD



ccme.osu.edu

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

OSU MedNet 21

Continuing Medical Education in the 21st Century

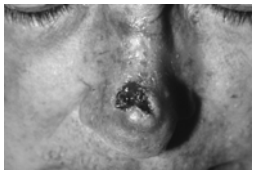
The Ohio State University Medical Center

Jim Allen, MD
Professor of Internal Medicine
The Ohio State University Medical Center

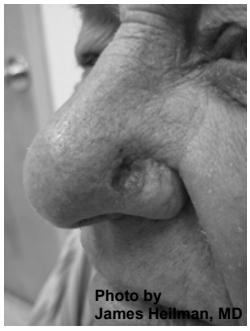
Madison, Wisconsin

Skin Cancer

Melanoma



Squamous Cell Carcinoma



Basal Cell Carcinoma

Thomas Olencki, DO
David Carr, MD

Challenges with treating melanoma with chemotherapy

Video Presentation

Mohs Surgery

Mohs Surgery: Overview & Indications

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

Video Presentation

Q & A with Dr. David Carr

Video Presentation

Dr. David Carr's Key Point

Review of 2 New Meds for Therapy of Metastic Melanoma

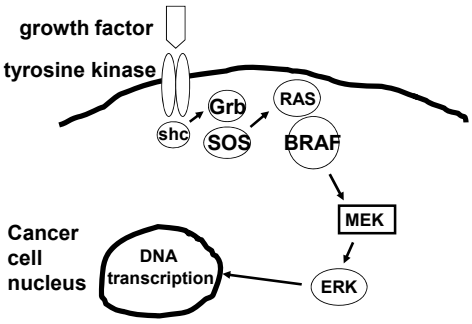
Thomas Olencki, DO
Clinical Professor of Medicine
Division of Medical Oncology
Ohio State University College of Medicine

Prognosis of metastatic melanoma

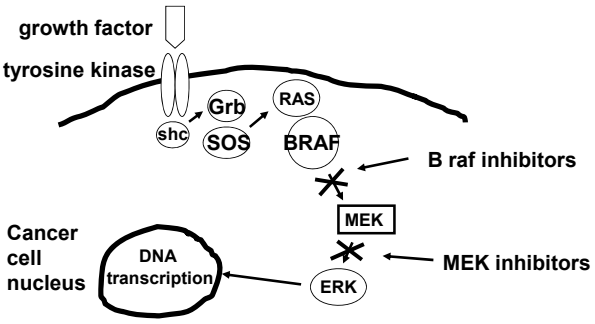
FDA Approved Drugs For Treatment Of Metastatic Melanoma

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

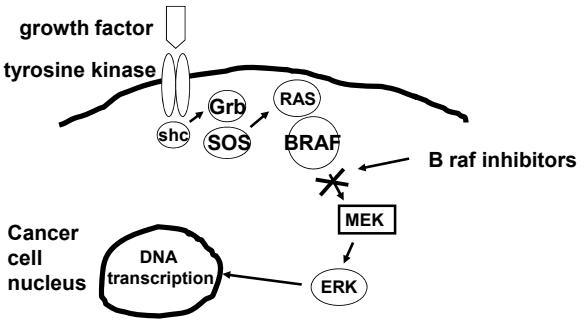
MAP Kinase Pathway And Targeted Therapy



MAP Kinase Pathway And Targeted Therapy



MAP Kinase Pathway And Targeted Therapy



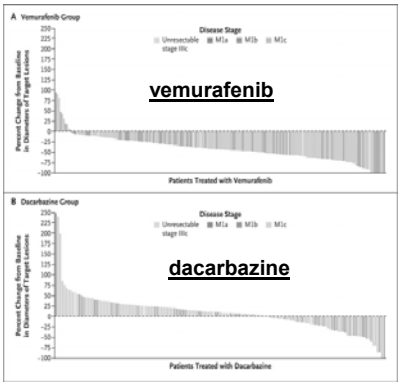
B raf Mutation

- 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

Waterfall Plot of Best Tumor Response



Chapman, NEJM 364:2507, 2011

Phase III 1st Line Vemurafenib vs Dacarbazine

Open 1/2010 to 12/2010

675 pts with B raf mutation metastatic melanoma

RANDOMIZE

- Vemurafenib 960 mg BID PO — 336 pts
- DTIC IV — 336 pts

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%	

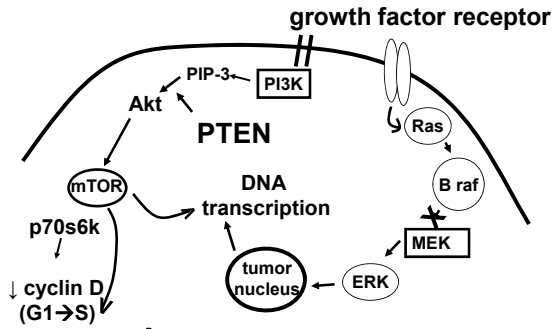
* CR, + PR, + SD

Chapman, NEJM 364:2507, 2011

Problems With Current Targeted Therapy

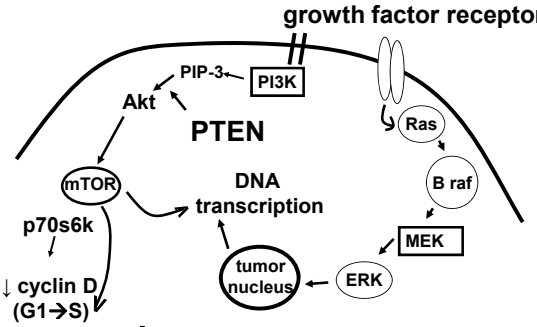
- Blocking B raf may up regulate C raf and other pathways
- B raf and MEK inhibitors "work" only if mutation present
- Significant clinical resp. usually of short duration
  - alternative signaling pathways take over
- Multiple signal transduction pathways may need to be blocked simultaneously
  - but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

PI3 And MAP Kinase Inhibitors



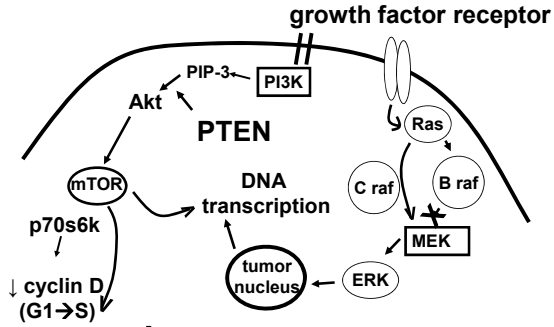
HIFα → Cox-2 → angiogenesis and other protein translation

PI3 And MAP Kinase Inhibitors



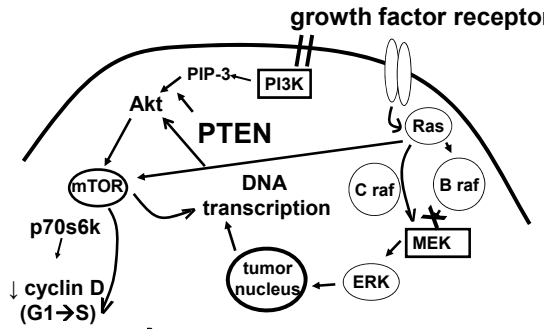
HIFα → Cox-2 → angiogenesis and other protein translation

PI3 And MAP Kinase Inhibitors



HIFα → Cox-2 → angiogenesis and other protein translation

PI3 And MAP Kinase Inhibitors

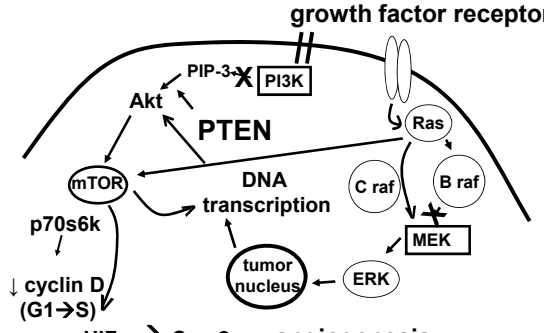


HIFα → Cox-2 → angiogenesis
and other protein translation

So, what is all the news about?

ASCO 2010
Sunday June 6, 2010

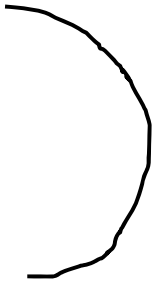
PI3 And MAP Kinase Inhibitors



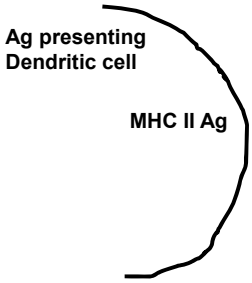
HIFα → Cox-2 → angiogenesis
and other protein translation

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

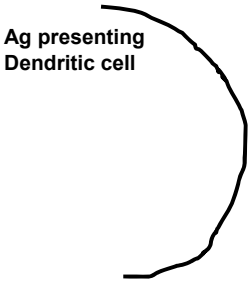
Cytotoxic T Lymphocyte Assoc Protein-4 (CTLA-4)



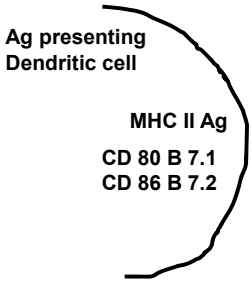
Cytotoxic T Lymphocyte Assoc Protein-4 (CTLA-4)



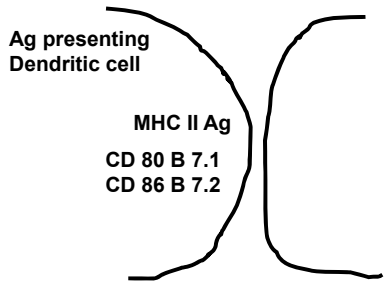
Cytotoxic T Lymphocyte Assoc Protein-4 (CTLA-4)



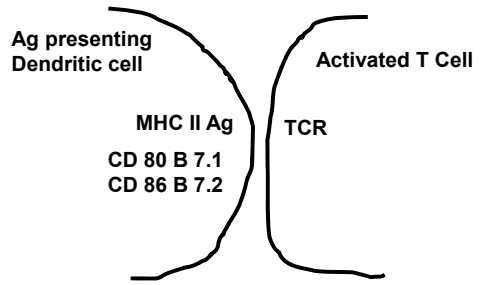
Cytotoxic T Lymphocyte Assoc Protein-4 (CTLA-4)



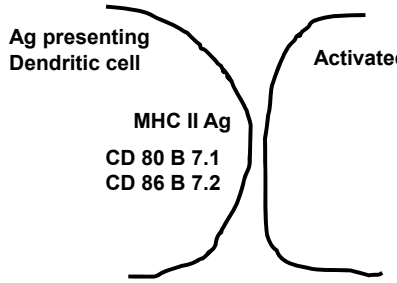
Cytotoxic T Lymphocyte Assoc Protein-4 (CTLA-4)



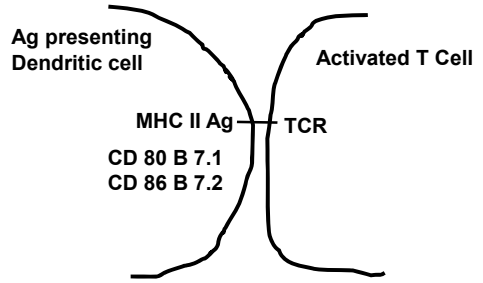
Cytotoxic T Lymphocyte Assoc Protein-4 (CTLA-4)



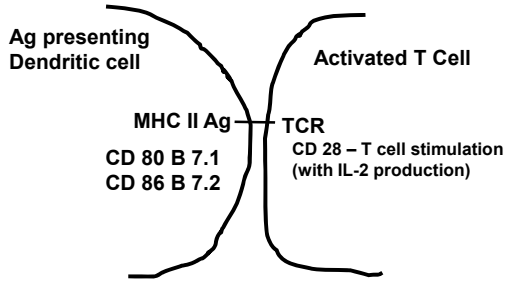
Cytotoxic T Lymphocyte Assoc Protein-4 (CTLA-4)



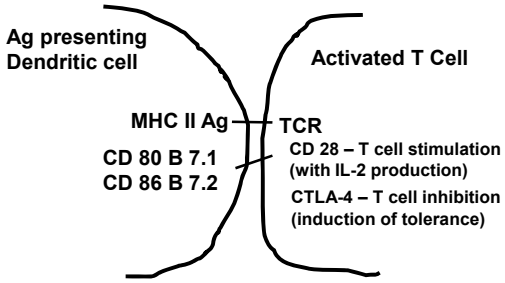
Cytotoxic T Lymphocyte Assoc Protein-4 (CTLA-4)



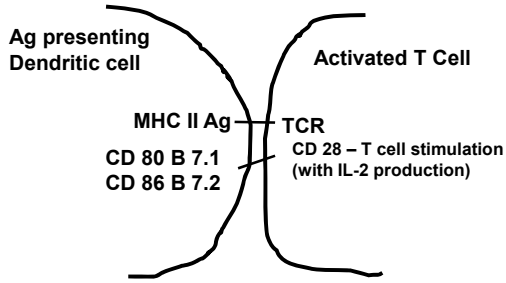
Cytotoxic T Lymphocyte Assoc Protein-4 (CTLA-4)



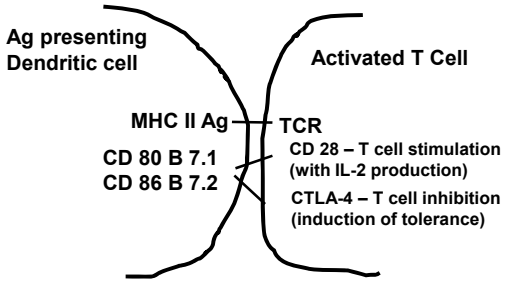
Cytotoxic T Lymphocyte Assoc Protein-4 (CTLA-4)



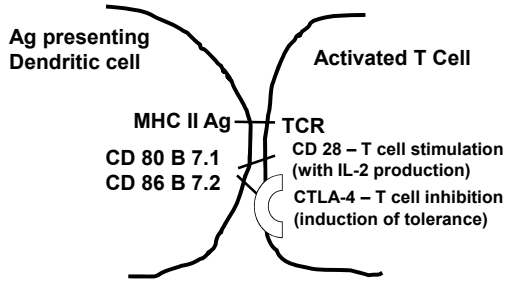
Cytotoxic T Lymphocyte Assoc Protein-4 (CTLA-4)



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



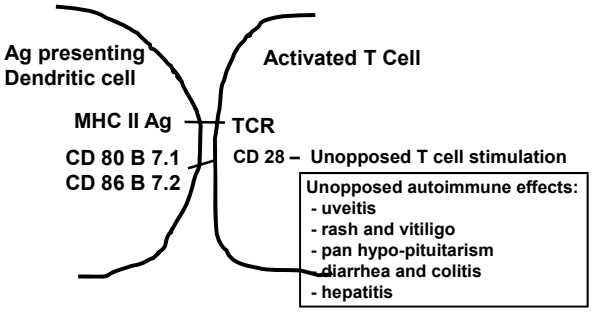
Cytotoxic T Lymphocyte Assoc Protein-4 (CTLA-4)



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)

CTLA-4 (2)



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

RANDOMIZE

- Ipilimumab 3 mg/kg IV
- Ipilimumab 3 mg/kg IV & gp 100
- gp 100 vaccine

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

Phase III Ipilimumab +/- Dacarbazine – 1st Line

Open 8/2006 to 1/2008

502 pt with untreated metastatic melanoma

RANDOMIZE

- Ipilimumab 10 mg/kg IV + DTIC — 250 pts
- All drugs → q 3wks x 4
- DTIC 850 mg/m^2 — 252 pts

Maintenance given in pts with stable to responding disease

Robert, NEJM 364:2517, 2011

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 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

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

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

Signs and symptoms of recurrent melanoma

Skin cancer prevention: Advice for patients

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

Immuno-suppression and skin cancer

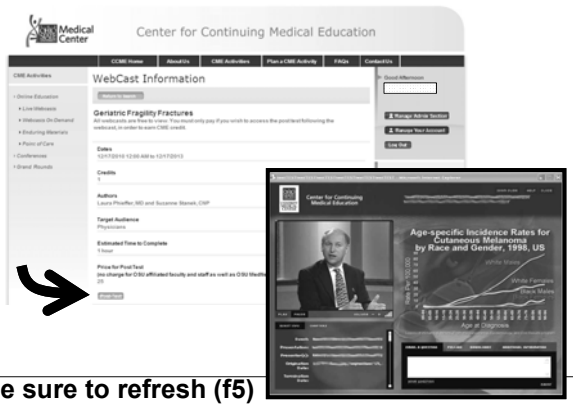
Today's Poll Results

poll results will continue to be tabulated

POLLING

Skin Cancer

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



Be sure to refresh (f5)