Melanoma
A Medical Oncology Perspective

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Epidemiology

- 76,690 new diagnoses expected in 2013
- 9480 deaths
- 5th most common cancer in men
- 7th most common cancer in women
- Incidence is increasing faster than any other potentially preventable cancer in the U.S
- Lifetime risk for a male is 1/39 and for a woman is 1/58

Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63:11.

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Risk Factors

- Familial
- Atypical Nevi
- High nevus count
- Sun or ultraviolet exposure
- Phenotypic traits
- A history of melanoma or non-melanomatous skin cancer
- Immunosuppression

Role Of The Medical Oncologist

- To reduce the likelihood of systemic recurrence in patients with stage III (node positive) disease
- To treat systemic disease
  - To improve quality of life
  - To extend life

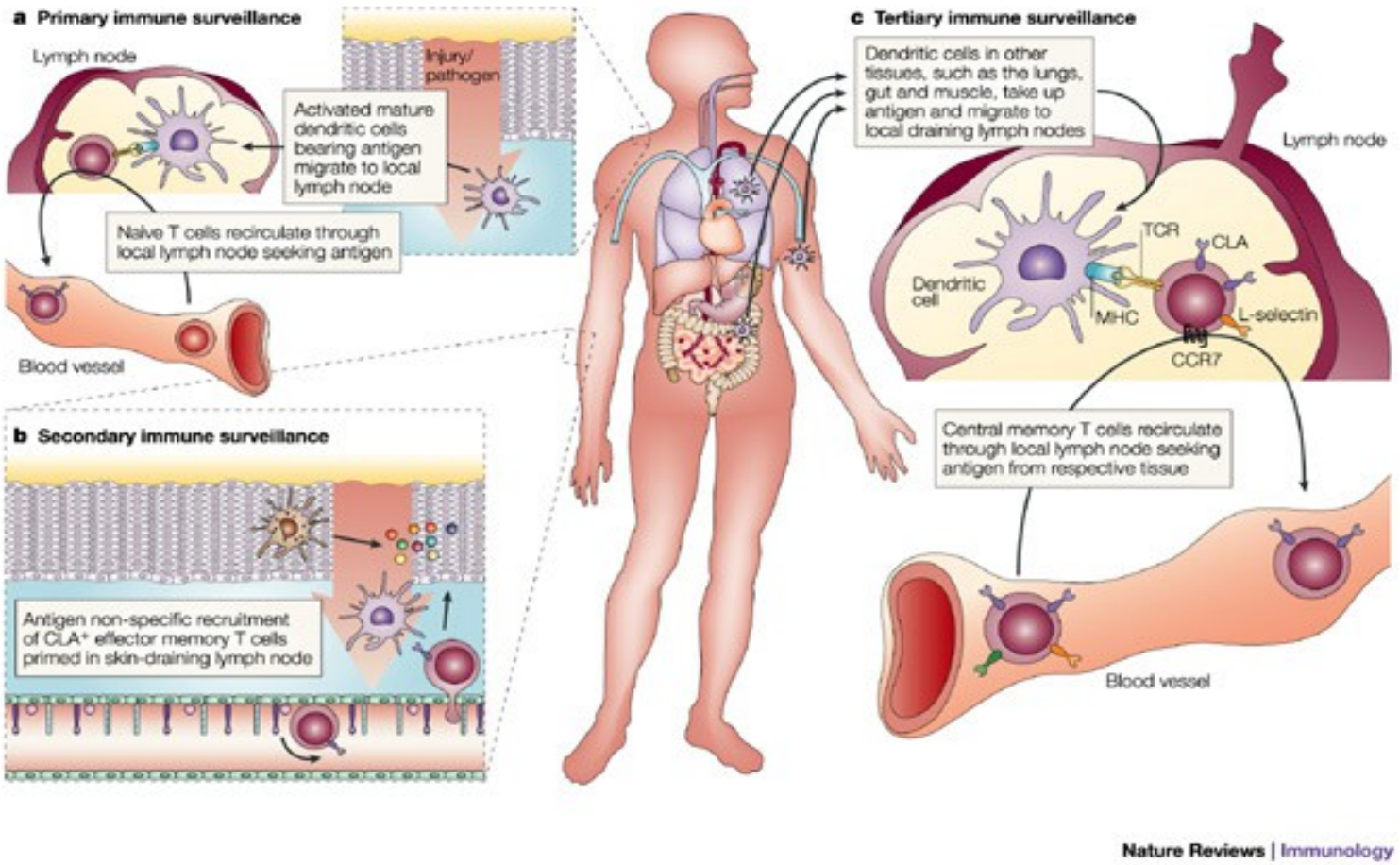
Early Stage Disease

- Surgical excision is the treatment of choice
  - Curative in most cases
- Sentinel lymph node involvement is the single most important factor predicting recurrence
  - 5 year DFS with a negative SLNB is 83.2%
  - 5 year DFS with a positive SLNB is 53.4%

- SLNB followed by completion lymphadenectomy improved 5-year OS in patients with a positive SLN from 52.4% to 72.3%
- Indications:
  - Melanomas ≥1 mm thick
  - <1 mm thick with high risk features (ulceration, LVI, high mitotic rate)

-Sentinel lymph node biopsy for melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Joint Clinical Practice Guideline. J Clin Oncol 2012.

Immune Surveillance



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Stage III Disease

- ECOG 1684
  - 287 patients with stage IIb or III disease
  - Randomized to 1 year of HD IFNa-2b or close observation
  - At median follow-up of seven years:
    - 9 month prolongation in RFS (11% increase at 5 years) in treated patients
    - 1 year improvement in median survival (3.8 vs 2.8) years favored IFN

Kirkwood JM, et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. J Clin Oncol. 1996;14(1):7.

- Intergroup E1690
  - ECOG 1684 vs. LD IFNa vs. observation in stage II-III patients
  - No OS benefit
  - RFS benefit with HD IFNa

Kirkwood, JM et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. J Clin Oncol. 2000;18(12):2444.

Interferon

- Cytopenias
- Liver toxicity
- Fatigue
- Depression
- Thyroid dysfunction

Metastatic Disease

- Surgical metastectomy
- Immunotherapy
- Cytotoxic therapy
- Radiation therapy

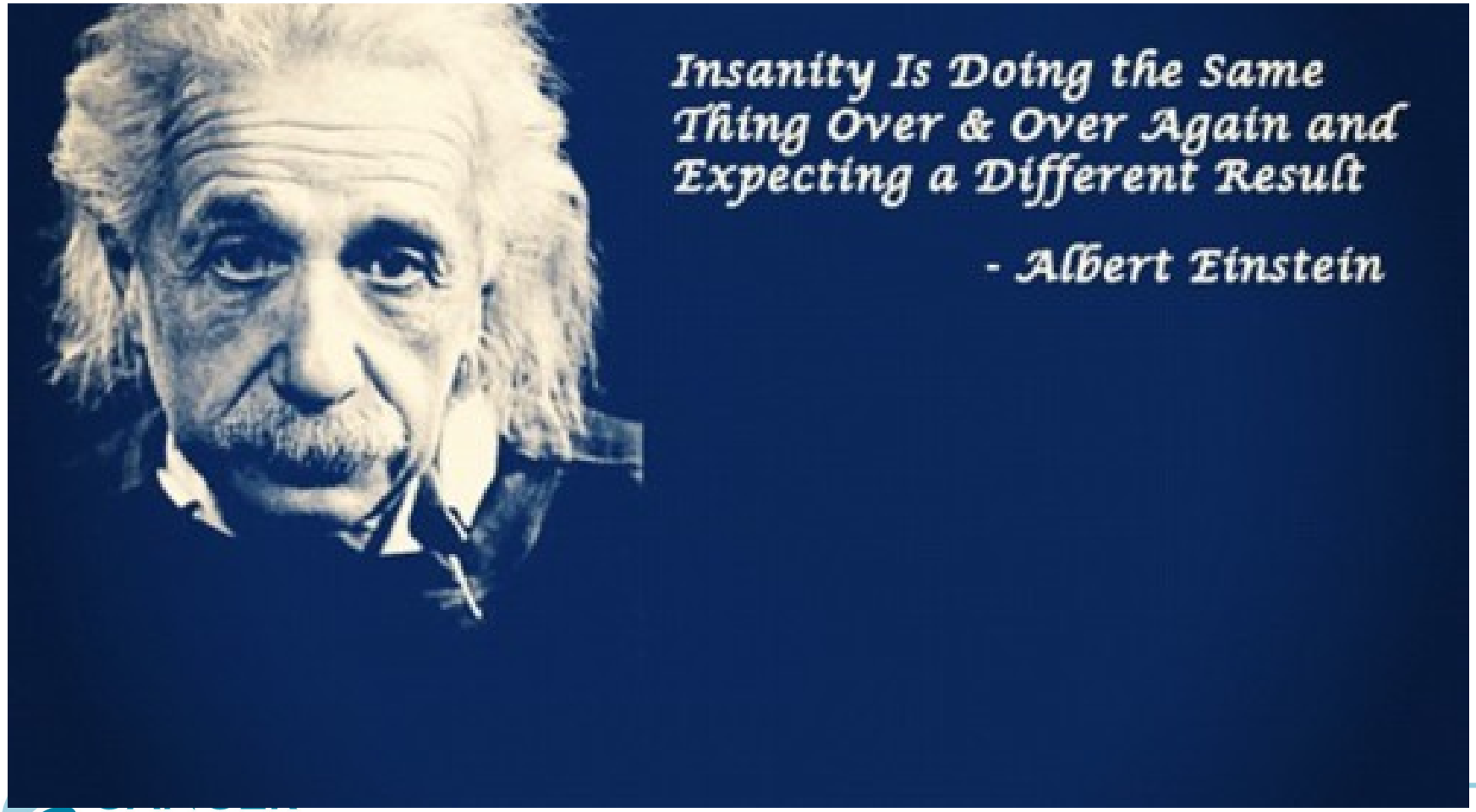
High Dose IL-2

- IV every 8 hours D1-5 and 15-19; 6-12 week cycle
- 15-20% of patients respond
- 4-6% have complete responses
- At 6 years 44% of responders were alive
- No patient with a CR more than 30 months progressed

Tarhini AA et al. Durable complete responses with high-dose bolus interleukin-2 in patients with metastatic melanoma who have experienced progression after biochemotherapy. J Clin Oncol 2007; 25:3802

Cytotoxic Therapy

- DTIC
  - Only FDA-approved cytotoxic agent
  - No phase III trials demonstrate an OS benefit
  - RR 8-20%
    - Usually partial, lasting 4-6 months
  - 2% of patients live 6 years
- Other options
  - temozolamide, platinum/taxane, nitrosureas fotemustine



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Cytotoxics

- Temozolamide
- Platinum/Taxane
- Nitrosureas fotemustine

- All the same.

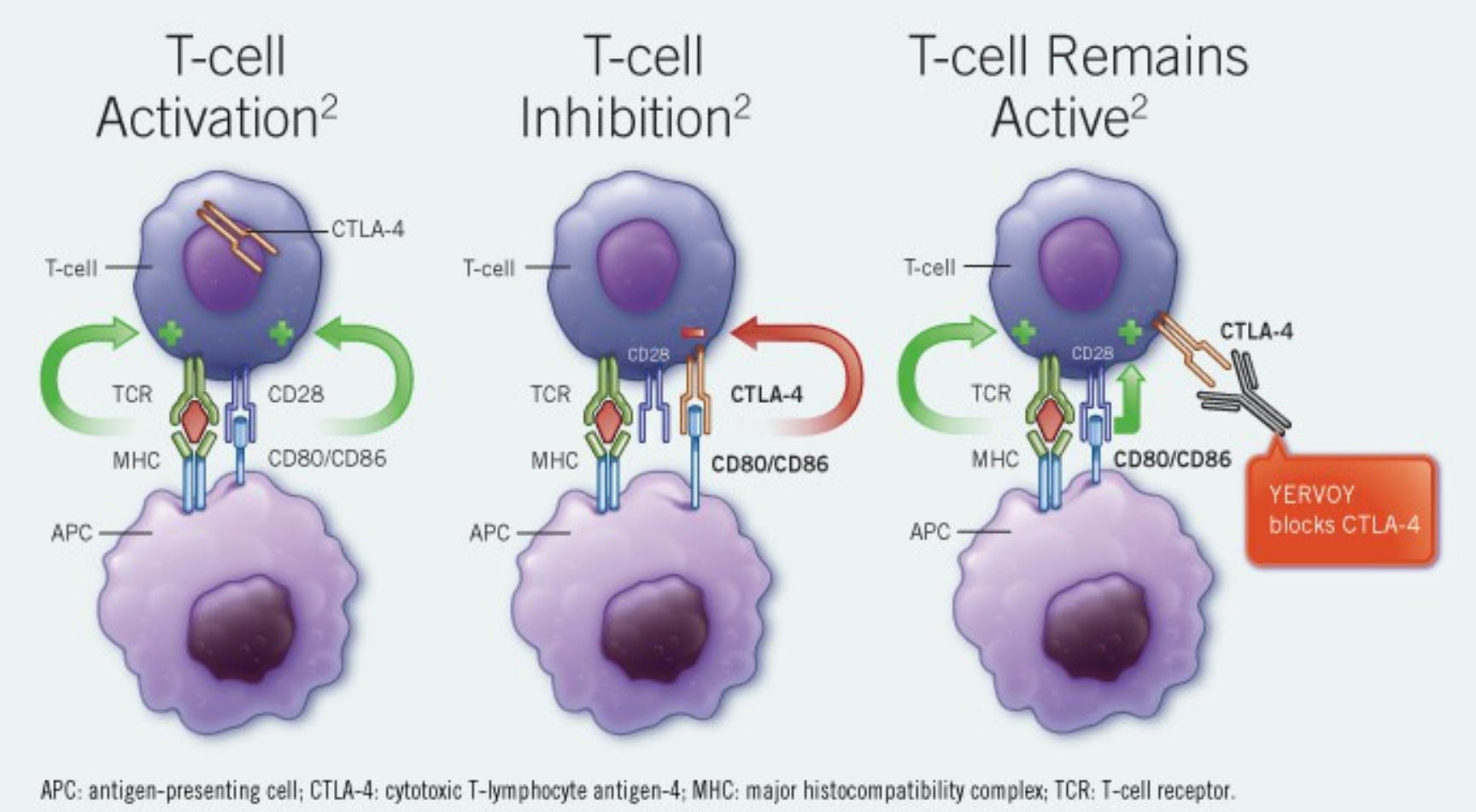
CTLA-4

- Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a negative regulator of T-cell activation
- What if it were possible to inhibit this, and therefore its interactions with CD80 and CD86?
- T-cell activation and proliferation would be agumented

Ipilumimab

- Monoclonal antibody against CTLA-4
- Presumed MOA
  - Break down tolerance to tumor-associated antigens in the melanoma
  - Given every three weeks 4 times

New Approachs



https://www.hcp.yervoy.com/Pages/mechanism-of-action.aspx

- Was demonstrated to improve OS in two randomized trials

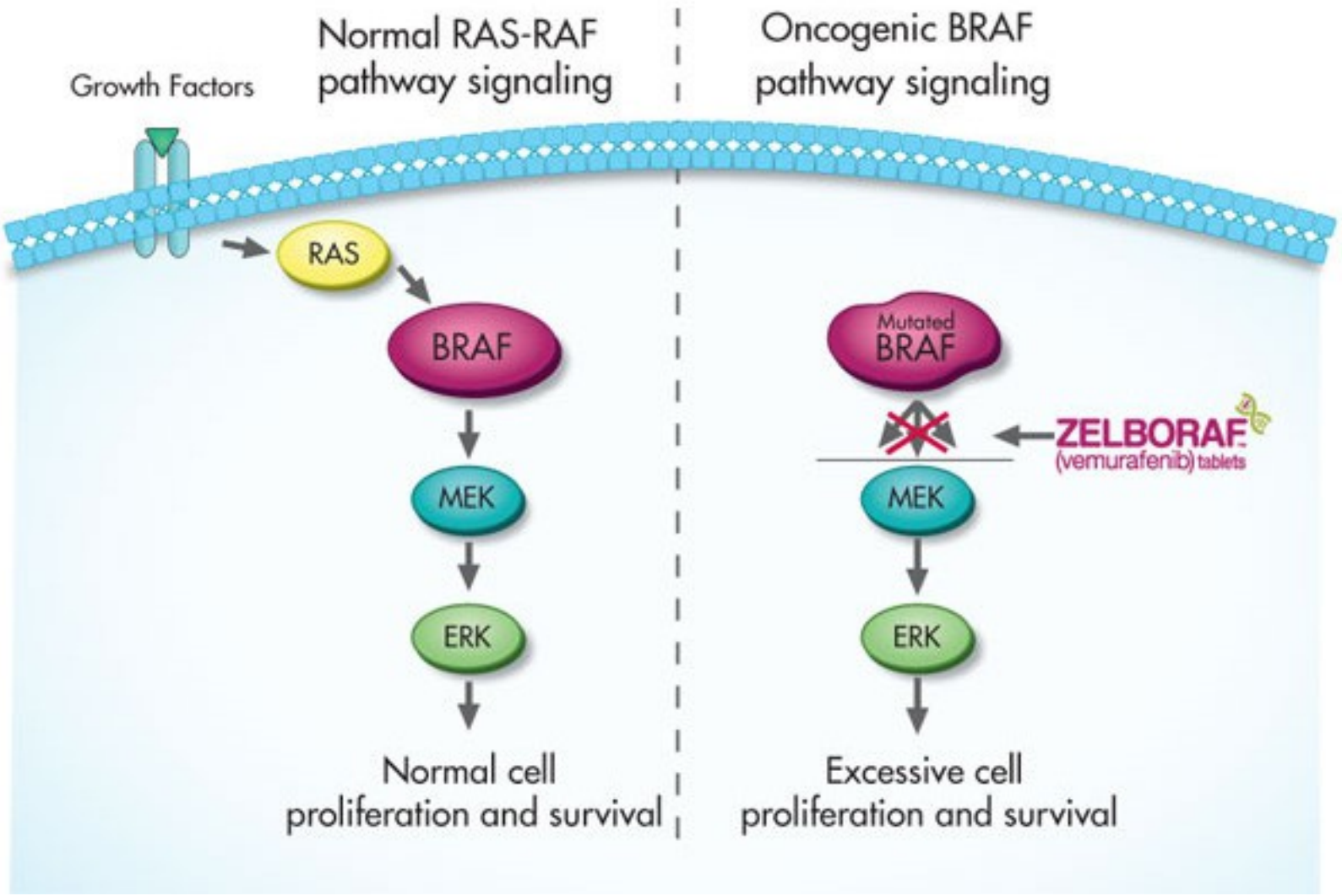
Year	OS% (ipi+DTIC)	OS% (ipi)
1	47	36
2	29	18
3	21	12

- Responses can be delayed – have been noticed even after 30 months
- In the 9% of patients that achieved a CR in early studies, all but one were ongoing at 54-99 months

Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011; 364:2517.
Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363:711.

BRAF Inhibition

- Mutations of BRAF are present in ~50% of melanomas
- May be associated with a more aggressive clinical course
- Activates MAPK pathway



http://www.zelboraf.com/dermatology/moa/

Vemurafenib

- BRIM-3
  - Vemurafinib vs DTIC
    - OS 13.6 vs 9.7 months with median f/u of 12. 5 months
    - RR 57% vs 8.6%
- Daily oral tablet

Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011; 364:2507.

Chapman PB, et al. Updated overall survival (OS) results for BRIM-3, a phase III randomized, open-label, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patients with BRAFV600E-mutated melanoma. J Clin Oncol 2012.

Summary

- Melanoma is rapidly increasing in incidence
- No major advancements have occurred since the 1970's, when DTIC was approved
- Two agents are new standards of care for metastatic melanoma and the first agents to demonstrate OS benefits

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Thank you.