Melanoma: The Basics and New Directions in Treatment

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I have no financial disclosures

Objectives

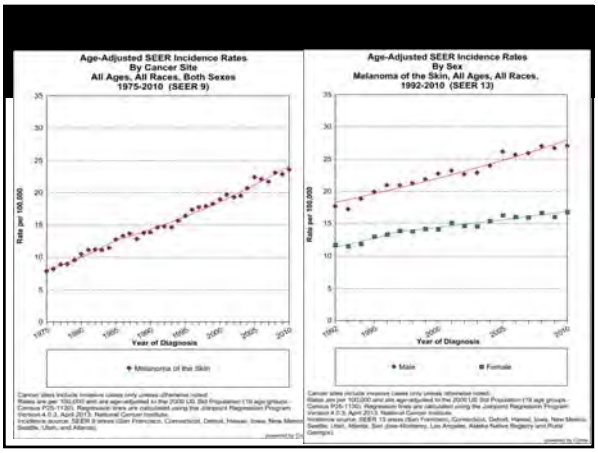
- Review the epidemiology and risk factors for melanoma
- Review the staging of melanoma
- Discuss appropriate management of early-stage melanoma
- Describe new agents and/or targets in the treatment of metastatic melanoma

History

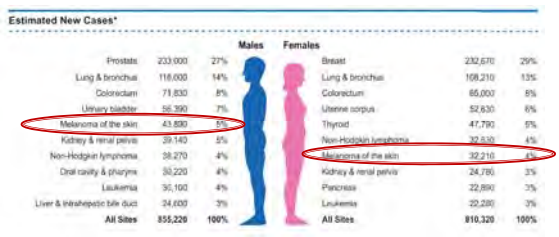
- John Hunter first discovered in 1787
  - Operated on the first identified melanoma
  - Described it as a "cancerous fungous excrescence"
  - Preserved in the Museum of the Royal College of Surgeons of England
  - 1968 – microscopic exam confirmed it to be metastatic melanoma
- 1840 – Samuel Cooper formally acknowledged that advanced melanoma was untreatable.
  - Stated that the only chance for benefit depends upon early removal of the disease
  - >1.5 centuries later this still remains essentially true
- 1956 - Henry Lancaster first identified association with melanoma and sunlight intensity

Epidemiology

- 2014 estimated statistics:
  - 76,100 new melanomas will be diagnosed in 2014
    - 43,890 in men
    - 32,210 in women
- Most common fatal malignancy in young adults
- Incidence is rapidly rising
  - Rising every year steadily for the past 30 years
- 9,710 people estimated to die this year from melanoma in the US



2014 US Cancer Statistics



Estimated New Cases*

	Males			Females		
Prostate	233,000	27%		Breast	232,670	29%
Lung & bronchus	116,000	14%		Lung & bronchus	108,210	13%
Colorectum	71,830	8%		Colorectum	65,000	8%
Urinary bladder	56,390	7%		Uterine corpus	52,630	6%
Melanoma of the skin	43,890	5%		Thyroid	47,790	5%
Kidney & renal pelvis	39,140	5%		Non-Hodgkin lymphoma	32,930	4%
Non-Hodgkin lymphoma	38,270	4%		Melanoma of the skin	32,210	4%
Oral cavity & pharynx	38,220	4%		Kidney & renal pelvis	24,780	3%
Leukemia	30,190	4%		Pancreas	22,890	3%
Liver & intrahepatic bile duct	24,600	3%		Leukemia	22,280	3%
All Sites	855,220	100%		All Sites	810,320	100%

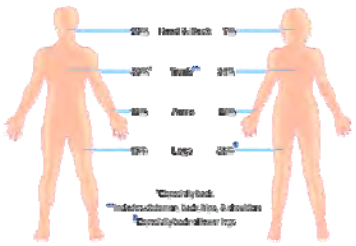
Origin of Melanomas

- Skin – 90%
- Unknown – 5%
- Eyes – 2-3%
- Mucous membranes – 2%
- Remote internal site – 0.2%

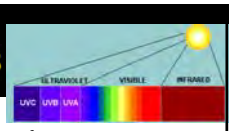
ORIGIN OF ALL MELANOMAS ON THE SKIN

- Clear skin – 65%
- Pre-existing moles – 30%
- Age spots (>70 y/o) – 5%

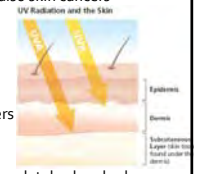
Location of Melanomas



Ultraviolet light types

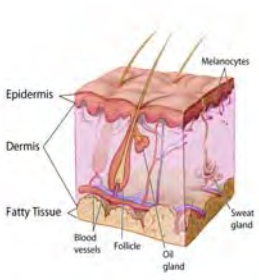


- Ultraviolet A (UVA)
  - Most common kind of sunlight at the earth's surface
  - Reach beyond the top layer of human skin
  - Cause cells to age and can damage DNA.
  - Linked to long-term skin damage (wrinkles), but also skin cancers
- Ultraviolet B (UVB)
  - Mostly absorbed by the ozone layer
  - Do not penetrate the skin as deeply
  - Cause direct damage to DNA
  - Linked to sunburns & primary cause of skin cancers
- Ultraviolet C (UVC)
  - Most dangerous, but do not reach the ground (completely absorbed by the ozone layer)



UV light

- The sun's UV rays can damage your skin in as little as 15 minutes
- Based on our information we have today, there are *no* safe UV rays.



Indoor Tanning

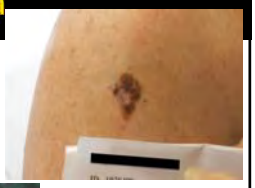
- Indoor tanning is linked with BCC, SCC, melanoma and ocular melanoma
- Exposes you to both UV-A & UV-B
- Exposes you to the same intensity UVB as the sun and 10 to 13 times greater UVA intensity than the sun.
- A single tanning bed session increases your risk of melanoma by 22%.

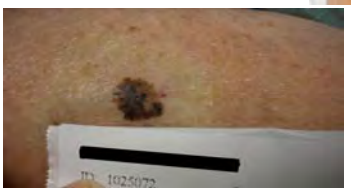
Indoor Tanning

- In 2009, the World Health Organization International Agency for Research on Cancer (IARC) classified UV light emitted from tanning beds as a class 1 human carcinogen
- Especially dangerous for young ages
  - Use prior to age 35 ⟶75% higher risk
  - Banned in many countries for <19 y/o
- Some US states are now restricting their use
- Also ⇧your risk of ocular melanoma

Types of Melanoma

- Superficial Spreading
- Nodular
- Lentigo maligna melanoma
- Acral lentiginous



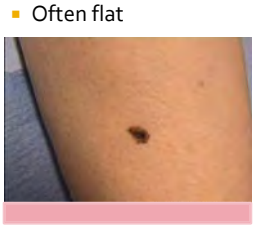


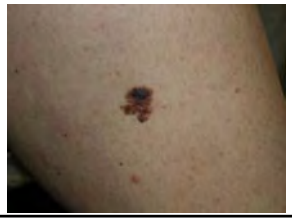
A – asymmetry
B – border irregularity
C – color variegation
D – diameter
E – evolving

+ Itching/Bleeding

Superficial Spreading

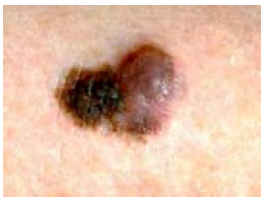
- Most common type, 70%
- Often arises in a precursor mole
- Spreads along the epidermis for months before it begins to penetrate downward
- Often flat

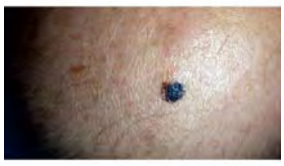




Nodular

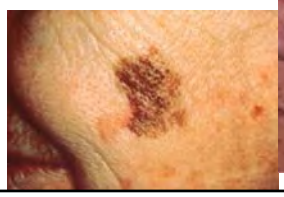
- 2nd most common, 15-30%
- Grows downward earlier
- Often dome-shaped. Bluish coloration often
- Often arises de novo (normal skin)
- More common in men

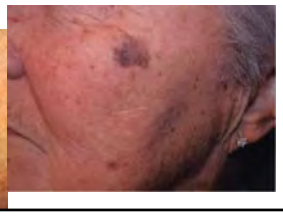




Lentigo maligna melanoma

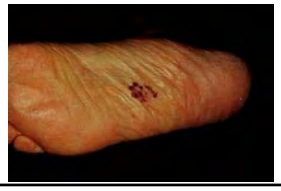
- Arises from a pre-existing lentigo, not a mole
- Very slow growing. Takes years to develop
- Older adults
- Often on the face or chronically-exposed areas





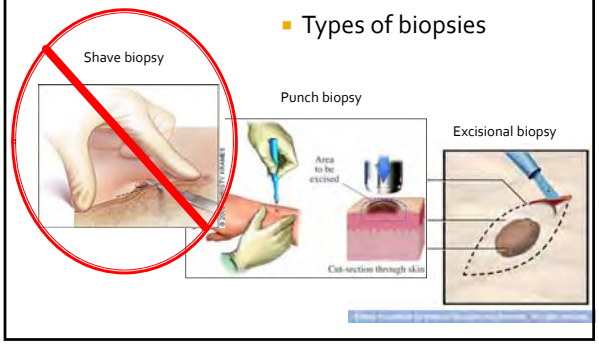
Acral lentiginous

- <5% of all melanomas
- More often seen in Asians & African-Americans
- Palms, soles, nail beds, mucosal membranes
- Highly irregular borders
- Often diagnosed much later in the disease course



Diagnosis

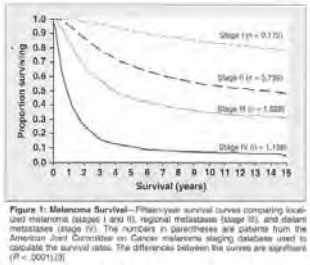
- Types of biopsies



Prognostic factors

- MOST IMPORTANT: Breslow depth
  LN involvement, # of LNs
- Ulceration
- Mitotic rate
- Absence of TIL
- Presence of microscopic satellitosis
- Extremities vs trunk/head
- Increasing age
- Gender (male worse)

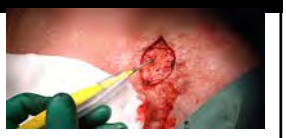
Survival according to stage

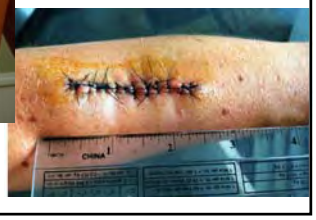


When detected early, melanoma has an excellent cure rate.

Wide re-excision

2cm margins minimum





Update: SLNB in Thin Melanoma

Rational for SLN biopsy

- Microscopic LN involvement is the most important predictor of prognosis in patients with clinically node negative melanoma
- Minimally invasive approach to nodal staging
- Additional therapies improve disease outcomes for the node-positive patients

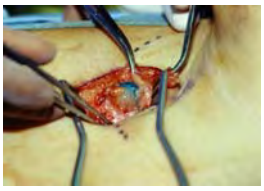
Review of "thin" melanoma

- Thin melanoma (≤1.0 mm) accounts for 70% of newly diagnosed cases
- 10yr mortality rate: IA = 12%; IB = 17%
  - Small group develop dissemination/death
  - High incidence=important issue
- Meta-analysis: Rate of nodal mets:
  - <0.75mm →2.7%
  - 0.75-1mm→6.2%

Andtbacka, RH. JNCCN 2009; 7(3): 308-319

What risk of LN metastasis warrants a SLN biopsy?

1 %
3 %
5 %
10 %
15 %
20 %



NCCN guideline revision 1/2013:
- Discuss and consider SLNB for melanoma >0.75mm Breslow depth

Treatment

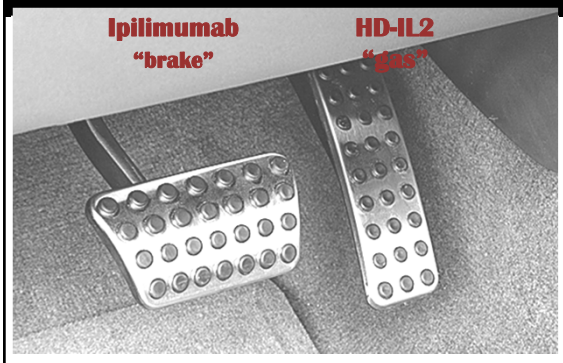
- Wide re-excision (2cm margins)
- SLNB – for >0.75mm or high risk features
- Therapeutic lymph node dissection
  - Positive SLNB
  - Clinically enlarged regional LN
- Adjuvant therapy
  - Breslow >4mm or node-positive
  - IFN, pegIFN, trial
- Adjuvant XRT
  - ENE or multiple nodes

Metastatic Melanoma

Treatment Options for Metastatic Melanoma

- Surgical resection of metastases
- Chemotherapy: IV Dacarbazine (DTIC)
  - Response rate <10% and median time to progression of <2 months
- Immunotherapy:
  - HD-IL2
  - Ipilimumab
- Targeted agents
  - BRAF inhibitors (vemurafenib, dabrafenib)
  - MEK inhibitors (trametinib)
- Clinical trial

Immunotherapy



HD-IL2

--the "gas"--

HD-IL2 (Proleukin)

- Approved 1998 based on phase II data
- Given inpatient
- Max 2 courses (1 course = 2 cycles)
- 1 cycle = iv q8hrs x 14 max doses, repeat after 7-10 days rest
- one month between courses; give only if response or SD
- VERY toxic, but short-lived, manageable SE

Acute toxicities

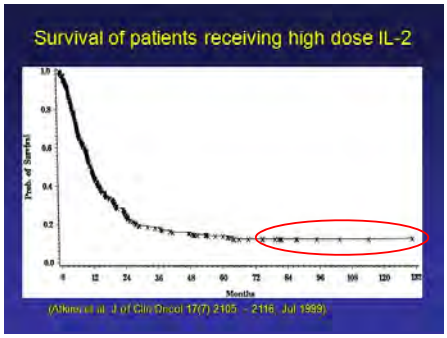
- Hypotension 71%
- Oliguria 63%
- Chills 52%
- Vomiting 50%
- Dyspnea 43%
- Rash 42%
- Hyperbilirubinemia 40%
- Thrombocytopenia 37%
- Confusion 34%

"Capillary Leak" syndrome

HD-IL2

		median duration of response
CR	6%	59+ mos
PR	10%	6 mos
CR+PR	16%	9 mos

Few patients experience durable response to high dose IL-2



HD-IL2 (Proleukin)

- Very toxic acutely
- Patient selection more strict
  - Better results with non-visceral mets
  - Better results with normal LDH
- Must be off all steroids >1 month!
- Low RR, but durable remissions

Ipilimumab (Yervoy)

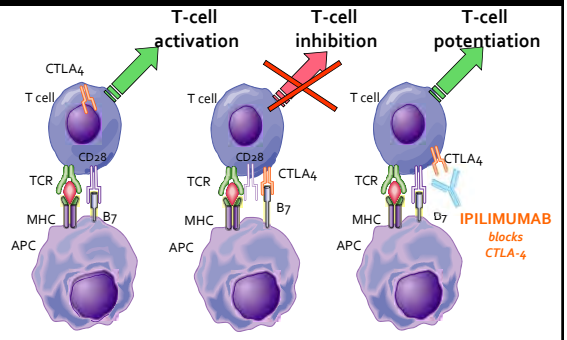
-- the "brake"--

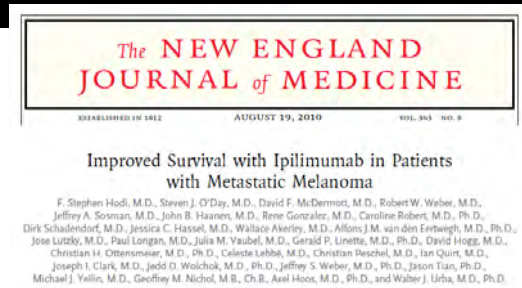
Ipilimumab (Yervoy)

- CTLA-4:
  - Down-regulates T-cell activation
- Ipilimumab (Yervoy):
  - Fully human monoclonal antibody
  - Blocks CTLA-4 receptor
  - Potentiates T cell activation

Korman, Peggs and Allison: Adv. In Immunol. 2006;90:297-339

Ipilimumab: Mechanism of Action



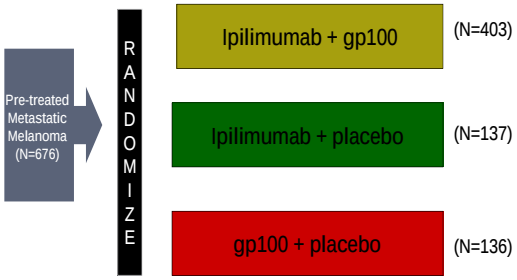

The NEW ENGLAND JOURNAL of MEDICINE

AUGUST 19, 2010

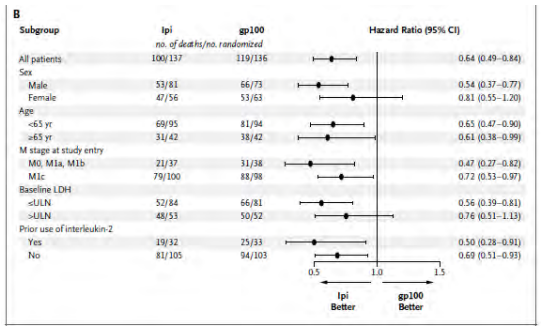
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

MDX010-20: Study Design



Ipilimumab improved survival in all subgroups


B

Subgroup	Ipi	gp100	Hazard Ratio (95% CI)
	no. of deaths/no. randomized		
All patients	100/137	119/136	0.64 (0.49–0.84)
Sex			
Male	53/81	66/73	0.54 (0.37–0.77)
Female	47/56	53/63	0.81 (0.55–1.20)
Age			
<65 yr	69/95	81/94	0.65 (0.47–0.90)
≥65 yr	31/42	38/42	0.61 (0.38–0.99)
M stage at study entry			
M0, M1a, M1b	21/37	31/38	0.47 (0.27–0.82)
M1c	79/100	88/98	0.72 (0.53–0.97)
Baseline LDH			
≤ULN	52/84	66/81	0.56 (0.39–0.81)
>ULN	48/53	50/52	0.76 (0.51–1.13)
Prior use of interleukin-2			
Yes	19/32	25/33	0.50 (0.28–0.91)
No	81/105	94/103	0.69 (0.51–0.93)

0.5 1.0 1.5

Ipi Better | gp100 Better

Trial results

- 1 year OS: 46 vs 25%
- 2 year OS: 24 vs 14%
- medial OS: 10 vs 6 mos
- ORR ~ 11%
- median duration of response – not yet reached (44 mos)

Previously untreated stage IV

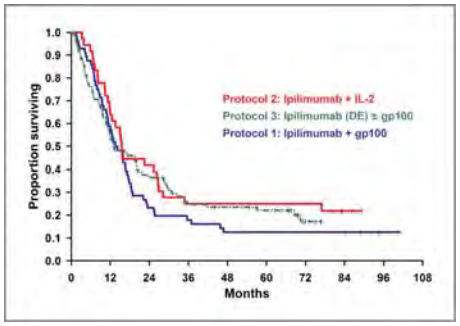
- Ipilimumab + DTIC vs. DTIC +placebo
- mOS – 11.2 mos vs. 9.1 mos (p=0.0009)
  - HR 0.72

Pooled Analysis of Ipi Outcomes

- 12 studies
- 1861 patients
- mOS – 11.4 mos
  - 3 year OS – 22%
  - 7 year OS – 17%
    - No deaths after 7 years
- Longest survival -9.9 yrs
- Plateau starts at ~36 mos

Schadendorf D, Hodi FS, Robert C, et al.. Presented at: European Cancer Congress 2013; September 27-October 1, 2013.

Overall survival for all patients, separated by protocol.



Prieto P A et al. Clin Cancer Res 2012;18:2039-2047

Ipi dosing

- Intravenous
- 3mg/kg q 3weeks x 4 doses
- No immediate SE

Unique SE of Ipi

- Immune-mediated/inflammatory
- Can occur with any organ system
- 60% develop some immune-related AE
  - Grade 3-4, only 10%
- Can occur weeks AFTER therapy
- Prompt attention and treatment is vital!
  - Rx: early steroids
    - Prednisone 1-2mg/kg
    - Taper only when grade 1, and taper over >1 month

Immune-mediated AE

- Enterocolitis
  - Incidence 31% (6% severe)
  - Risk of perforation, sepsis, death
  - Avg – 6-7 weeks after start of treatment
  - Diarrhea, abd pain, blood/mucous in stool
  - Severe is >7 stools/day
  - Can involve upper GI tract as well

Immune-mediated AE

- Dermatitis
  - Incidence 40% (2.5% severe)
  - Pruritus, rash, vitiligo, alopecia
  - Avg – 3 weeks
  - Can be severe: Stevens-Johnson, TEN
  - Mild-mod: treat symptomatically
  - Severe: high dose steroids

Immune-mediated AE

- Endocrinopathies
  - Incidence 2.3% (1.8% severe)
  - Avg – 11 weeks
    - Some up to 6 months later
  - Hypophysitis & hypopituitarism
  - Hypothyroidism or Grave's hyperthyroidism
  - Adrenal insufficiency
  - Hypogonadism
  - Pituitary swelling
    - Headache, vision changes, diplopia

Immune-mediated AE (~1%)

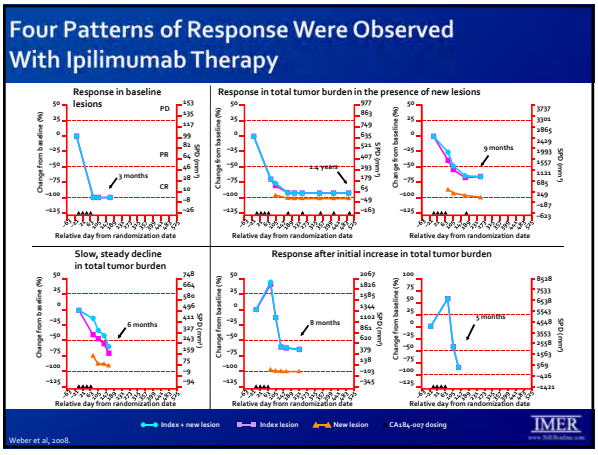
- Hepatitis
- Nephritis
- Vasculitis
- Neuropathy (incl. enteric)
- Uveitis/conjunctivitis/scleritis
- Pleuritis/pericarditis
- AI pancreatitis
- Guillain-Barre
- Temporal arteritis

.....etc.....

Unique kinetics of response

- Patients may have prolonged SD followed by late regression
- Some patients have an initial response with slow induction of a CR
- Others have new lesions, meaning PD, but then have either prolonged stability or a subsequent response
- Another pattern is progression of target lesions followed by subsequent regression and stability
- This suggests an ongoing immune response

Weber et al, 2008.

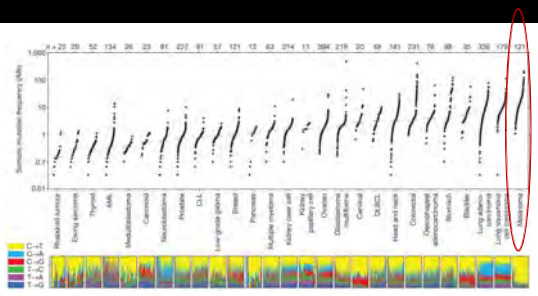


Ipi summary

- Can have late, prolonged responses
- Low RR, but potential for durable remissions
- Educate on side effects
  - can occur 6 months after last treatment
  - Severe SE requiring prompt initiation of steroids
- Can re-induce

Sporadic Gene Mutations

- BRAF oncogene (50-60%)
  - More common in minimally exposed areas
- NRAS mutations (15%)
  - Mutually exclusive from BRAF mutations
- KIT mutations
  - Mucosal melanomas, acral, lentigo

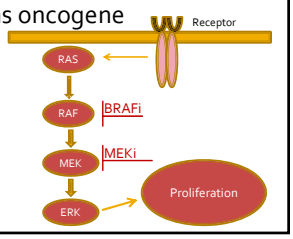


MS Lawrence *et al. Nature* 2013; 499: 214-18

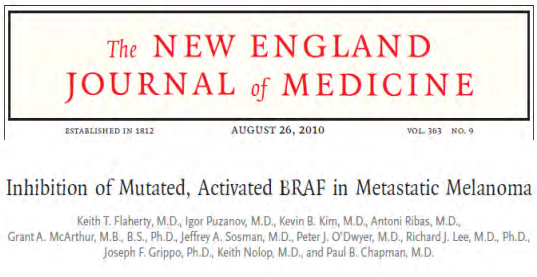
BRAF-mutated melanoma

BRAF mutations

- Protein kinase; member of the Raf family
- Regulates MAP kinase/ERK signaling pathway
  - Involved in cell division and differentiation
- Acquired mutations act as oncogene
- 40-50% melanomas
  - V600E most common



Targeting the BRAF pathway



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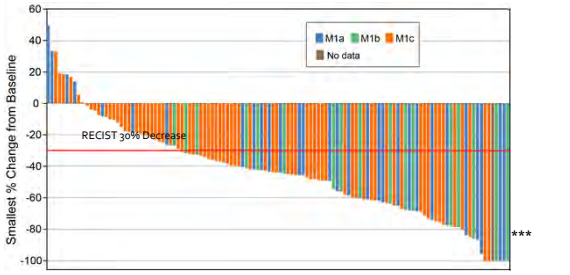
ESTABLISHED IN 1812 AUGUST 26, 2010 VOL. 363 NO. 9

Inhibition of Mutated, Activated BRAF in Metastatic Melanoma

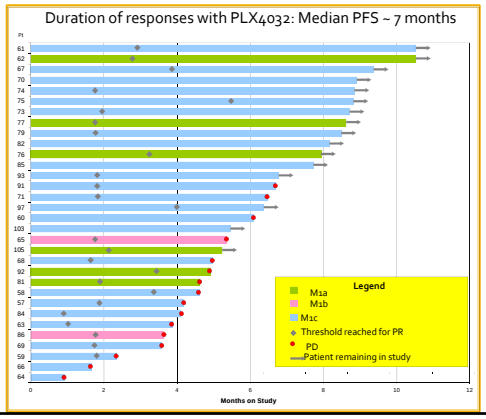
Keith T. Flaherty, M.D., Igor Puzanov, M.D., Kevin B. Kim, M.D., Antoni Ribas, M.D., Grant A. McArthur, M.B., B.S., Ph.D., Jeffrey A. Sosman, M.D., Peter J. O'Dwyer, M.D., Richard J. Lee, M.D., Ph.D., Joseph F. Grippo, Ph.D., Keith Nolop, M.D., and Paul B. Chapman, M.D.

RECIST Responses to vemurafenib (960 mg bid) in 132 Patients with BRAF^{V600E} Mutant Melanoma



Sosman, Kim, et al. Society for Melanoma Research, Sydney, Australia, 2010

Duration of responses with PLX4032: Median PFS ~ 7 months



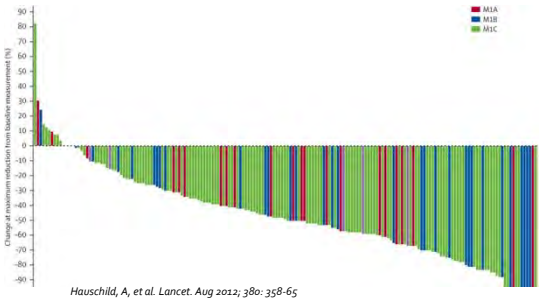
Phase III Trial

- 2011
- 675 patients randomized to vemurafenib vs DTIC
- Previously untreated unresectable stage IIIC or IV with V600E BRAF mutations (675 pts)
- Interim analysis:
  - HR for OS 0.37 (95% CI 0.26 to 0.55; p<0.0001)
  - HR for PFS 0.26 (95% CI 0.20 to 0.33; p<0.0001)
- Crossover then was allowed.
- Relatively well tolerated
  - Skin toxicity
  - Arthralgia
  - Fatigue
  - Alopecia
  - QTc prolongation

Dabrafenib

- Newly approved BRAF inhibitor (May 2013)
- Similar results as vemurafenib
  - 3:1 randomization to dabrafenib vs dacarbazine (crossover allowed)
  - First-line therapy
  - PFS improved (HR 0.33)
    - 5.1mos vs 2.7 mos
  - ORR 52% (CR 3%)
  - No OS benefit
- No photosensitivity
- Fevers

Maximum tumor change



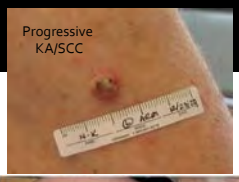
Hauschild, A, et al. Lancet. Aug 2012; 380: 358-65

Skin toxicities with BRAFi:

Squamous cell carcinomas
Basal cell carcinomas
Keratoacanthomas
Photosensitivity
Papular rash
Verrucous rash
Alopecia
Melanoma

Do NOT stop drug!

- Treat with local therapy only
- Aggressive UV protection

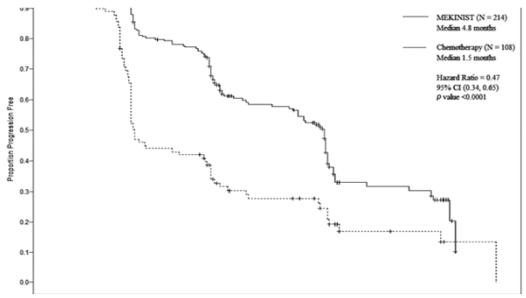


BRAF inhibitor toxicities

Trametinib

- MEK inhibitor
- Newly approved for first line in BRAF mutated melanoma (May 2013)
- 2:1 Trametinib vs DTIC or Taxol
  - Improved PFS (HR 0.47)
    - 4.8 mos vs 1.5 mos
  - ORR 22%
  - OS data not yet mature
- SE: rash, diarrhea, CM, RVO, retinal detachment

PFS



Trametinib

- Also approved for V600K mutations
- Jan 2014 – approved in combo with BRAFi
  - Combined in attempt to delay resistance
  - Phase II Trial
    - Prolonged PFS (9.4 vs 5.8 mos)
    - Decreased skin toxicity (5% vs 19%)
    - Increased pyrexia (71% vs 26%)

Dabrafenib/Trametinib combo

- COMBI-d trial, presented ASCO 2014
  - Phase III, Dabrafenib + Trametinib ***VS***. Dabrafenib + Placebo
  - 423 pts with advanced ds and V600E or V600K mutation
  - Median follow-up: 9 months
- PFS prolonged (9.3 vs 8.8 mos, HR 0.75, 95% CI 0.57-0.99)
- ORR improved (67 vs 51%)
- Unable to evaluate OS yet
- Substantial differences in toxicity
  - DECREASED: SCC/keratoacanthoma (2% vs 9%), hyperkeratosis, hand-food syndrome (5% vs 21%), alopecia
  - INCREASED: Diarrhea (24% vs 14%), hypertension (22% vs 14%)
  - More dose interruptions with combo due to pyrexia and chills (51% vs 28%)

Perfect drug?

- Short PFS
- ?increased rate of tumor growth at time of progression
- Acquired resistance
  - Can combine with MEK inhibitor
    - Trametinib
  - HSP90 molecules

Treatment options when I started:

- Clinical trial
- HD-IL2
- Cytotoxic chemotherapy

Treatment options now (3 years later):

- Metastatectomy
- Clinical trial
- HD-IL2
- Ipilimumab
- Vemurafenib
- Dabrafenib
- Trametinib
- Dabrafenib +Trametinib
- Cytotoxic chemotherapy
- [Anti-PD1 antibody]

Choice of therapy

- BRAF status
- Patient's overall well-being
- Symptomatology
- Extent of disease
- Need for steroids

What to tell your patients: Prevention is KEY!

- Aggressive sun protective measures
- Monthly self-skin checks
- Annual full body skin exam by a practitioner
- When in doubt, have it checked out

Thank you!