Montefiore Einstein Center for Cancer Care

Management of Advanced Melanoma

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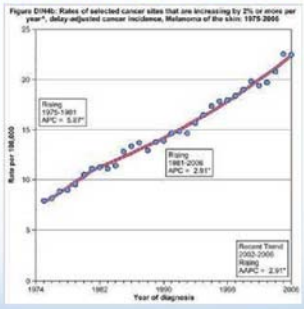
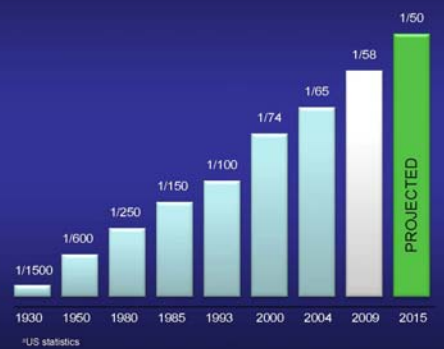
Statistics

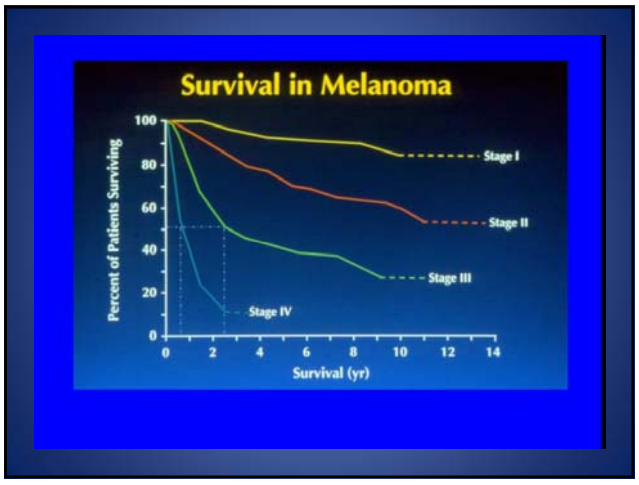
- 68,000 people are diagnosed with melanoma each year in U.S.
- 8,700 people die of melanoma each year in U.S.
- Sixth most common cancer in U.S.

Melanoma Rates Are Increasing



Lifetime Risk of Developing Melanoma[a]





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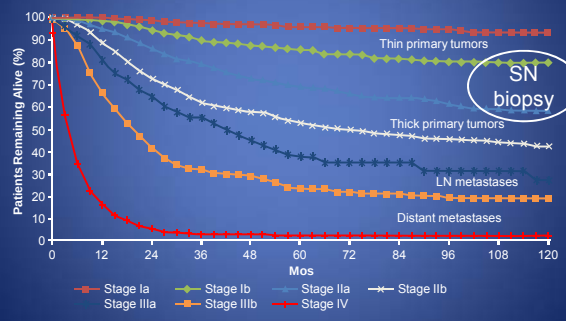
Adjuvant Therapy for Melanoma

Practice Considerations

- What is high-risk melanoma?

Melanoma: 10-Yr OS



Häfner AC, et al. Br J Cancer. 1992;66:856-861.

Practice Considerations

- What is high-risk melanoma?
- Why treat? What is the objective of therapy?

What Is the Objective of Therapy?

- The "gold standard" and ultimate goal is to improve OS
- Delay of relapse/recurrence is also beneficial

"OS is better than RFS but RFS is better than nothing"

Practice Considerations

- What is high-risk melanoma?
- Why treat? What is the objective of therapy?
- What agent should we use?

Adjuvant IFN alfa Regimens: 2013

Schedule	Dose	Frequency	Duration
Low dose			
	3 MIU	3 x wkly	18-24 mos
Intermediate dose			
Induction	10 MIU	5 x wkly	4 wks
Maintenance	10 MIU	3 x wkly	12-24 mos
	5 MIU	3 x wkly	24 mos
High dose			
Induction	20 MIU/m²	5 x wkly	4 wks
Maintenance	10 MIU/m²	3 x wkly	11 mos
Short course			
Induction x 1	20 MIU/m²	5 x wkly	4 wks
Intermittent			
Induction x 3	20 MIU/m²	20 MIU/m²	5 x wkly for 4 wks q4m

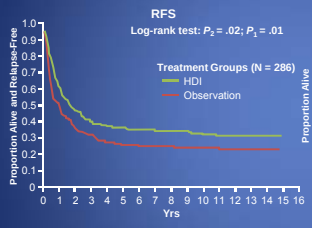
Eggermont AM, et al. Ann Oncol. 2009;20:vi30-vi34. Eggermont AM, et al. Lancet. 2008;372:1189-1196. Agarwala SS, et al. ASCO 2011. Abstract 8505.

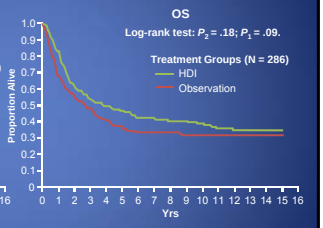
HDI alfa-2b Trials for AJCC Stage IIB/III Melanoma

Study	Eligibility	N	Treatment Agent/Dosage/Duration	Effect on RFS	Effect on OS
ECOG 1684[1]	T4, N1	287	IFN alfa-2b 20 MU/m²/d IV x 1 mo 10 MU/m² SC TIW x 11 mos	+ at 6.9-12.6 yrs	+
ECOG 1690[2]	T4, N1	642	IFN alfa-2b 20 MU/m²/d IV x 1 mo 10 MU/m² SC TIW x 11 mos vs 3 MU/day SC TIW x 2 yrs	+ at 4.3-6.6 yrs	–
ECOG 1694[3]	T4, N1	880	IFN alfa-2b 20 MU/m²/d IV x 1 mo 10 MU/m² SC TIW x 11 mos vs GMK vaccine x 96 wks	+ at 1.3-2.1 yrs	+
NCCTG 837052[4]	T3,T4,N1	262	IFN alfa-2a 20 MU/m²/day IM TIW x 3 mos	– at ~7 yrs	–

1. Kirkwood JM, et al. J Clin Oncol. 1996;14:7-17. 2. Kirkwood JM, et al. J Clin Oncol. 2000;18:2444-2458. 3. Kirkwood JM, et al. J Clin Oncol. 2001;19:1430-1436. 4. Creagan ET, et al. J Clin Oncol. 1995;13:2776-2783.

HDI in Stage IIB/III Melanoma (ECOG 1684): Efficacy at 12.6-Yr Follow-up





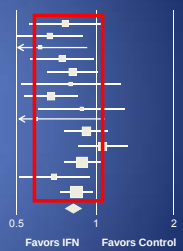
	Total	Dead or Relapsed	Alive or Relapse Free	Median
Observation	140	106	34	1.0
HDI	146	95	51	1.7

	Total	Dead	Alive	Median
Observation	140	95	45	2.7
HDI	146	93	53	3.8

Kirkwood JM, et al. Clin Cancer Res. 2004;10:1670-1677.

Meta-Analysis: Effect of IFN on RFS

Study	HR	LL	UL	SE	N	Events (IFN/ Control)
NCCTG (Creagan, 1995)	0.76	0.56	1.04	0.16	264	77/85
E1684 (Kirkwood, 1996)	0.67	0.50	0.88	0.14	287	90/103
AMCG (Pehamberger, 1998)	0.61	0.40	0.93	0.21	311	37/57
FCGM (Grob, 1998)	0.74	0.56	0.98	0.14	499	100/119
E1690 (Kirkwood, 2000)	0.81	0.65	1.01	0.11	642	236/254
SMG (Cameron, 2001)	0.80	0.52	1.23	0.22	96	32/35
E1694 (Kirkwood, 2001)	0.67	0.53	0.85	0.12	880	98/151
WHO (Cascinelli, 2001)	0.88	0.60	1.28	0.20	444	162/158
E2696 (Kirkwood, 2001)	0.59	0.32	1.07	0.31	107	28/38
UKCCCR (Hancock, 2004)	0.91	0.75	1.10	0.10	674	211/215
EORTC18871 (Kleeberg, 2004)	1.05	0.84	1.31	0.11	484	159/218
EORTC18952 (Eggermont, 2005)	0.88	0.75	1.03	0.08	1388	596/328
DeCOG (Garbe, 2008)	0.69	0.51	0.94	0.16	296	84/102



Adjuvant IFN (various doses and durations) improved RFS in almost every study: 18% increase (P < .001)

Mocellin S, et al. J Natl Cancer Inst. 2010;102:493-501.

Historical Data: Summary

- IFN alfa-2b has been the only agent to show success in randomized trials
- Side effects associated with IFN
- All other adjuvant therapy trials to date with vaccines, chemotherapy, and other immunotherapy agents have been negative
- Adjuvant RT improves local control but not distant relapse

Conclusions:

- High-risk melanoma is defined as T4N0 and T (any), N+
- Although OS benefit of adjuvant therapy is not consistent, RFS is a "bridge"
- IFN alfa-2b is the only approved agent (HDI for 1 yr or peg IFN for up to 5 yrs)
- 1-mo induction alone is not effective
- Certain subsets of patients may benefit more than others, but this needs confirmed in randomized studies

Adjuvant Therapy in 2013: Considerations

- Death and relapse risk are still accurately predicted by analysis of the PN and SN
  - Many deaths occur from node-negative melanoma
- Ipilimumab and BRAF-targeted therapy (for *BRAF*-mutated tumors) prolong survival in metastatic disease
- Adjuvant therapy is now the "bridge" between treatment
  of the primary tumor and stage IV disease

Comments/Clinical Implications New questions and priorities

5. Which agent(s) and for how long?
6. Do we build upon these results or start over?
7. What is the appropriate control arm?
8. When and how do we test for mutation status (BRAF, ckit)?
9. What is the best endpoint (RFS, OS)?
10. Role of chemo, role of vaccines-more unclear

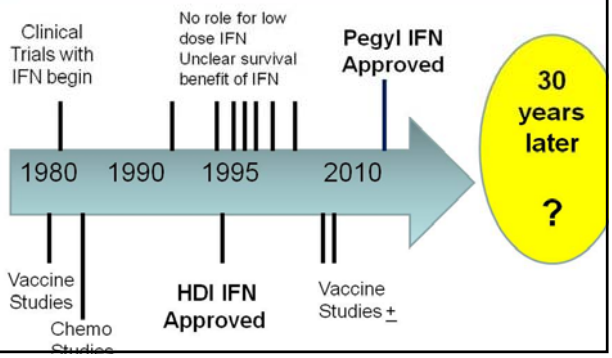
Comments/Clinical Implications

4) Further " tweaking" of IFN dose, schedule, route, type, is not going to move the field forward.

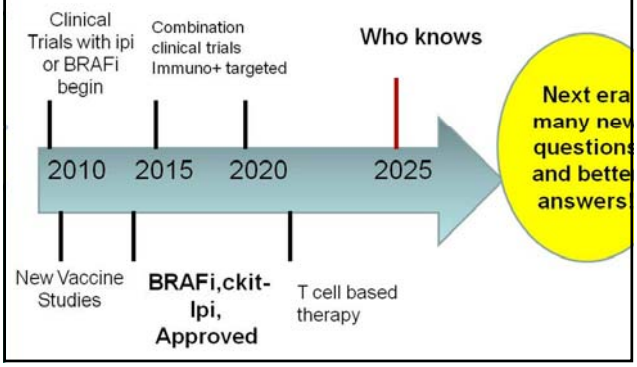
New Phase III Adjuvant Studies

Study Sponsor	Agents to be Tested	Primary Endpoint	Accrual Goal	Study Status
BMS	Ipi vs No treatment	RFS	950	Accrual complete
EORTC	Peg IFN 2 yrs. vs no Rx. (ulcerated melanoma > 1 mm.	RFD	1200	Start Date April 2012
GSK DERMA	MAGE 3 Vaccine vs placebo	DFS	1300	Open to accrual
ECOG 1609	Ipi vs HD IFN	RFS	1500	Open to accrual
Genetech/ Roche	Vem 960 mg vs placebo (1 year)	DFS	725	Start Date 2012
GSK	Dabrafenib (BRAFi) +Trametinb (MEKi) vs no placebo	RFS	852	Start Date 2012

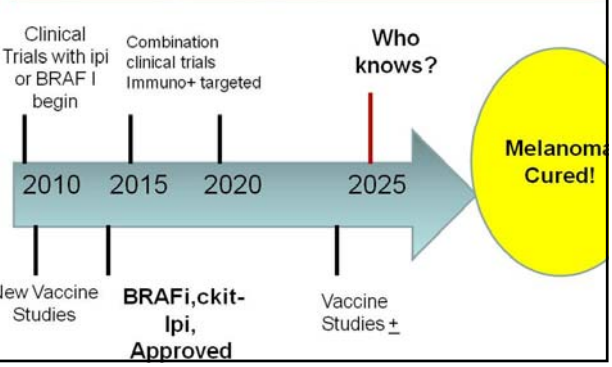
Adjuvant Therapy of Melanoma Not a Straightforward Path



Adjuvant Therapy of Melanoma A New Beginning, A New Path Forward



Adjuvant Therapy of Melanoma A New Beginning, A New Path Forward



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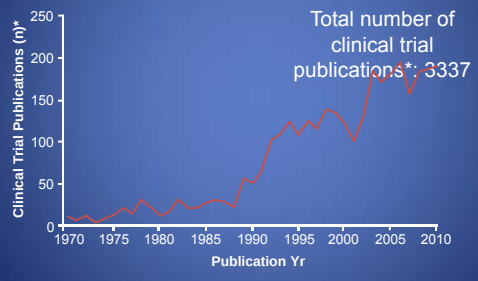
Metastatic Disease

Historical Perspective: "Advanced Melanoma is a Bad disease"

- 9th most common malignancy but 2nd in terms of potential life years lost
- Mortality"
  1. Increasing compared to other cancers
  2. Median Survival stuck at 6 – 9 months

1. Therapy:
   1. Few effective medical options
   2. Number of positive Phase I trials: 0
- Medical Investigator Community: Demoralized

> 3000 Trials Between 1970 and 2010 Had No Real Clinical Impact

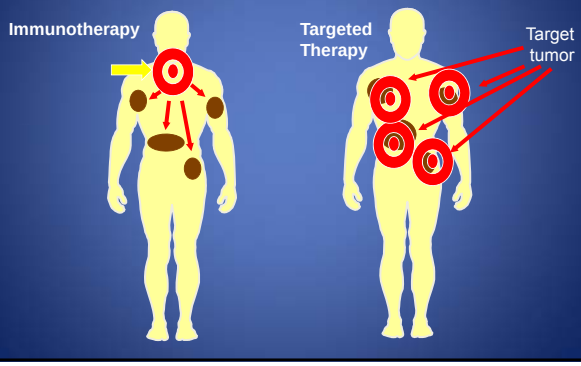


*Data collected using PubMed; search criteria: "melanoma clinical trial."
US National Library of Medicine and National Institutes of Health.

Why not Chemotherapy?

- Chemotherapy has never demonstrated its ability to confer complete, durable responses
- Response rates of chemotherapy range between 5-15%.
- Responses are generally partial
- PFS averages 3 months
- All the usual toxicities associated with chemotherapy

Metastatic Melanoma: Treatment Advances



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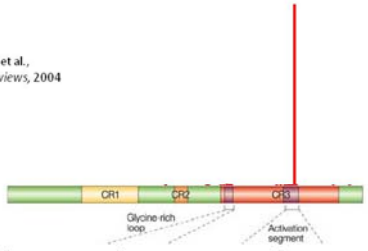
Targeted Therapy

Targeting B-RAF: How we got here

1. Transformative potential of cancer genome characterization

BRAF Mutations in Melanoma

Wellbrock et al., *Nature Reviews*, 2004

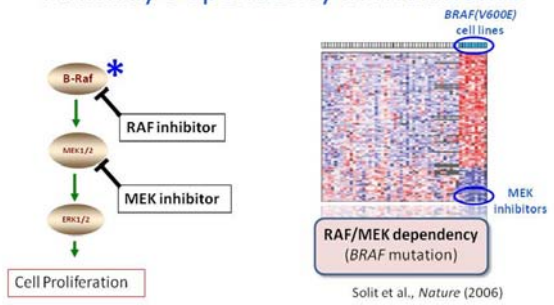


- Discovered by systematic cancer sequencing (Davies et al., *Nature*, 200
  - Discovery set of 15 tumor/normal pairs (only 1 melanoma!)
  - Validation in 378 pairs
- Valine to Glutamate (or Lysine) substitution at codon 600 is the most common (>90%) and therapeutically relevant mutation
  - $BRAF^{V600E}$, $BRAF^{V600K}$

Targeting B-RAF: How we got here

1. Transformative potential of cancer genome characterization
2. "Druggable" dependencies linked to genetic alterations

BRAF Mutation Engenders a MAP Kinase Pathway Dependency in Melanoma



Solit et al., *Nature* (2006)

Targeting B-RAF: How we got here

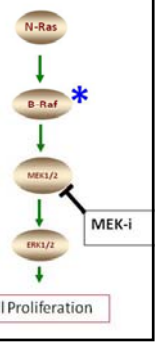
1. Transformative potential of cancer genome characterization
2. "Druggable" dependencies linked to genetic alterations
3. Multiple negative clinical trials
   - Suboptimal drug pharmacodynamics
   - No patient stratification based on genetics
   - Possible "off target" dose limiting toxicities

Early Clinical Trials of MEK Inhibition in Melanoma

CI-1040: no tumor shrinkage observed
Reinhart et al., JCO 2004
Lorusso et al., JCO 2005

PD-0325901: ocular toxicity observed; development dropped

AZD6244: no benefit compared to standard chemotherapy in melanoma
Dummer et al., ASCO (2008)



Caveats to early RAF/MEK trials

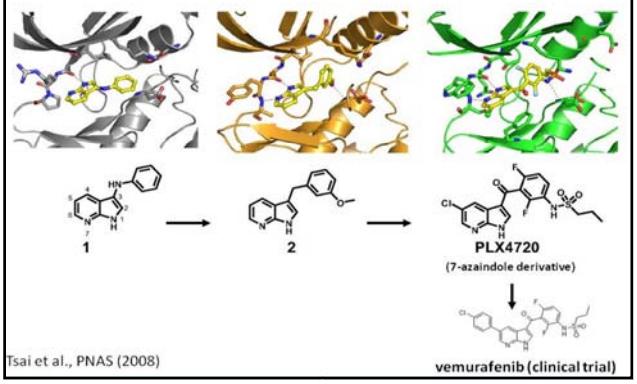
- Suboptimal drug pharmacodynamics
- No patient stratification based on genetics
- Possible "off-target" dose-limiting toxicities

➢ The "right" clinical experiment had not yet been performed!

Targeting B-RAF: How we got here

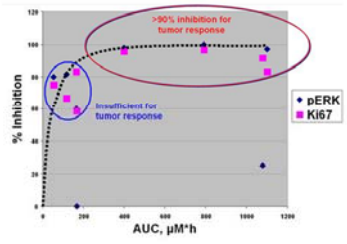
1. The transformative potential of cancer genome characterization
2. "Druggable" dependencies linked to recurrent genetic alterations
3. Multiple negative clinical trials before success was achieved
4. "Pillars" of therapeutic success

Pillar #1: design of a highly selective inhibitor



Tsai et al., PNAS (2008)

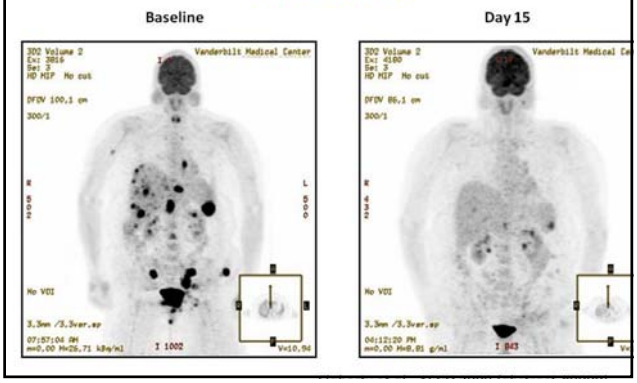
Pillar #2: Achieving optimal target and pathway inhibition



- >90% pathway inhibitio is critical to achieve significant reductions in FDG uptake

Puzanov…Flaherty, ASCO 2009

Pillar #3: Genetic profiling to identify *BRAF*^{V60} melanomas



BRAF Inhibitors

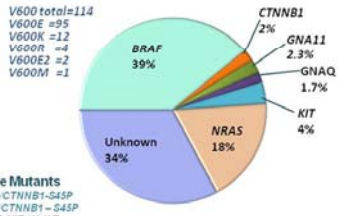
- B-RAF is a protein kinase within the RAS-RAF pathway
- Mutations of the BRAF gene result in activation of the BRAF protein
- Approximately 50% of all melanoma patients harbor a BRAF mutation and 90% occur at the V600E position
- Activated BRAF promotes cell proliferation
- BRAF inhibitors bind to the mutated BRAF and renders it inactive leading to disease control

Melanoma Molecular Profiling Results

7/1/10-3/31/11

Melanoma Panel: 297 patients

190/297 (64%) Patients with Mutation
102/297 (34%) No Mutation Identified
5/297 (2%) No Results Obtained



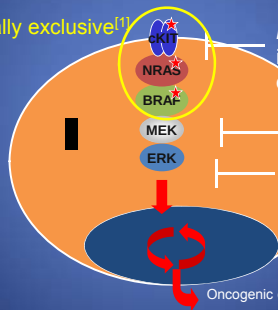
6 Double Mutants

NRAS-Q13R:CTNNB1-S45P
NRAS-Q61L:CTNNB1 – S45P
**NRAS-G12C:KIT-K642E*
BRAF-V600E:CTNNB1 – S37C
BRAF-V600E:CTNNB1-S45P
BRAF-V600K:CTNNB1 – S45F

- Mutations V600E/K/R/ associated with sensitivi BRAF inhibitor vemurafe or GSK2118436 or MEK inhibitor GSK21101212
- Mutations in CKIT K642 L576P, and V559A associ with imatinib - nilotinib, sunitinib sensitivity
- Mutations in NRAS, GN GNA11,CTTNB1 all unkn sensitivity

MAP Kinase Pathway Targeting in Melanoma

cKIT, NRAS, BRAF mutated in ~ 70% of melanomas, usually mutually exclusive[1]



KIT inhibitors: imatinib, nilotinib, dasatinib[4]

BRAF inhibitors: vemurafenib, dabrafenib[4]

MEK inhibitors: trematenib, TAK733[4]

1. Sosman JA, et al. ASCO 2011 Educational Book. 2. Arkenau HT, et al. Br J Cancer. 2011;104:392-398. 3. Thomas N, et al. Cancer Epidemiol Biomarkers Prev. 2007;16:991-997. 4. Nikolaou VA, et al. J Invest Dermatol. 2012;132:854-863.

BRAF Mutation Testing

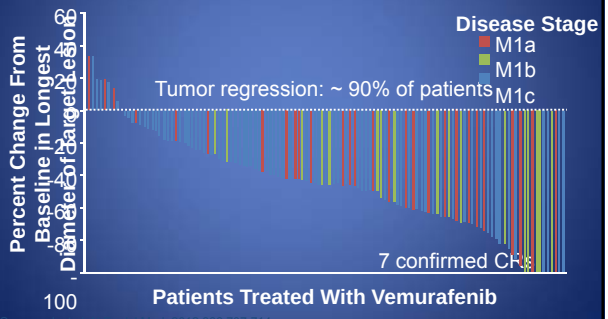
- *BRAF* mutations are present throughout melanoma disease progression
  - If metastasis biopsy not available, most recent melanoma surgery sample adequate (eg, lymph node)
- *BRAF* mutation testing is commercially available
  - FDA-approved method used in vemurafenib clinical trials
  - *cobas* 4800 BRAF V600 Mutation Test

BRIM 2 trial objective

- To confirm the ORR and anti-tumor activity of vemurafenib in previously treated patients with $BRAF^{V600}$-mutated melanoma

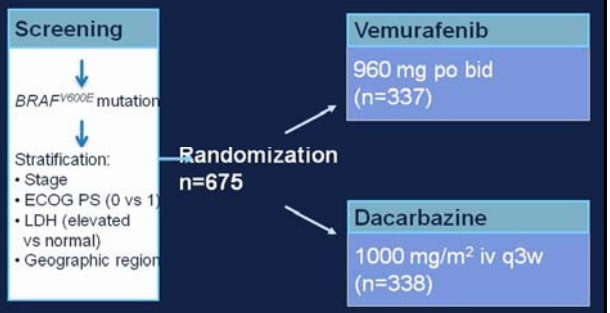
BID, twice daily; IRC: independent review committee; ORR, overall response rate; OS, overa survival; PFS, progression-free survival

BRIM-2 Phase II Study of Vemurafenib in Metastatic Melanoma: Tumor Regression



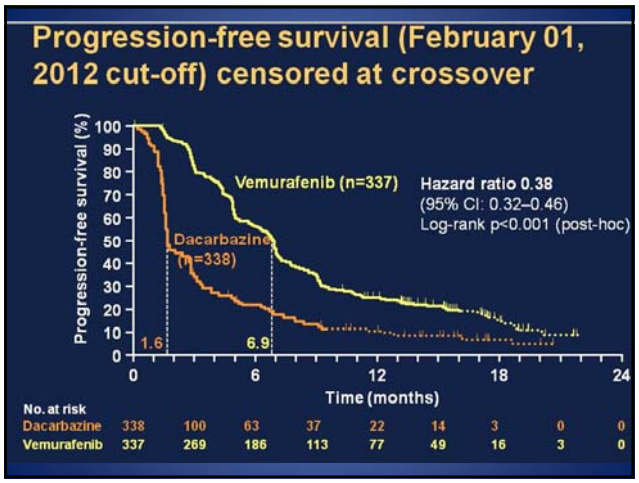
Sosman J, et al. N Engl J Med. 2012;366:707-714.

Phase III BRIM-3 trial: Study design

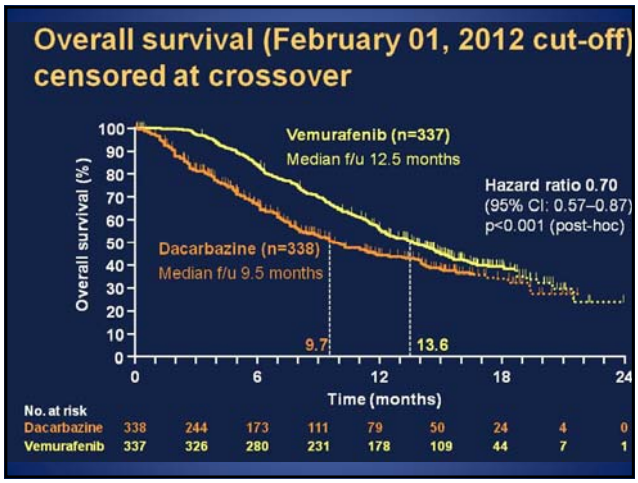


Co-primary endpoints were OS and PFS

Progression-free survival (February 01, 2012 cut-off) censored at crossover



Overall survival (February 01, 2012 cut-off) censored at crossover



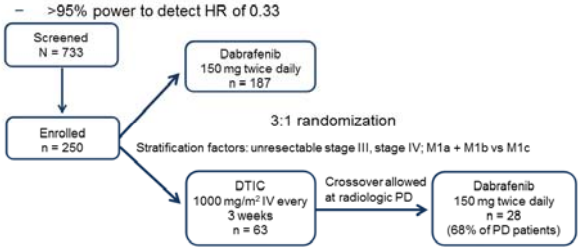
Conclusions

- With a median of 12.5 months follow-up, vemurafenib continues to be associated with improved efficacy compared with dacarbazine:
  - Improved OS (median 13.6 months, HR 0.70)
    - Initial analysis HR 0.37 indicates marked effect on early deaths
  - Improved PFS (median 6.9 months)
  - Improved confirmed objective response rate (57%)
  - Efficacy seen across all subgroups
- Consistent safety profile

Are their other Inhibitors ??

BRAF Inhibitor: Dabrafenib
BREAK-3 Front-Line Study Design

- Primary endpoint: Investigator-assessed PFS
- >95% power to detect HR of 0.33



Secondary objectives: OS, ORR in both groups and after crossover, PFS2 (after crossover), duration of response, safety/tolerability, and BRAF mutation assay validation

Audio
Dr. Pavlick

Hauschild A et al. ASCO 2012 Annual Meeting. Abstract LBA8500.

ASCO University | ASCO Tumor Boards

Dabrafenib Study

- RR, PFS and OS similar to Vemurafenib studies
- Different Toxicity pattern:
  1. KA and SCC was seen in 7% vs. 11% and 19% with vemurafenib
  2. Pyrexia in 15%, rare in vemurafenib

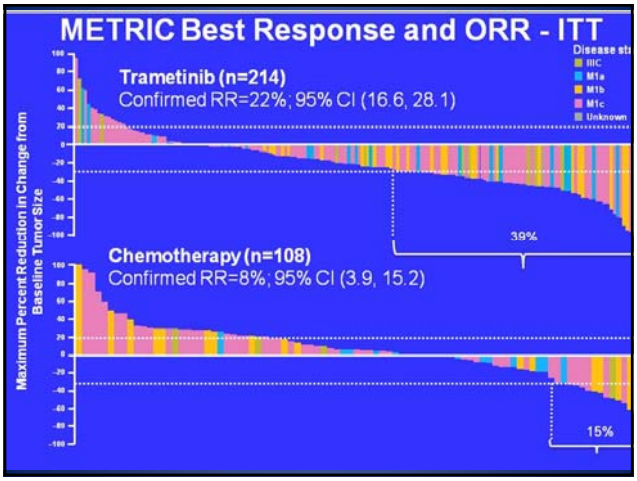
Given similar efficacy, toxicity differences may determine utilization

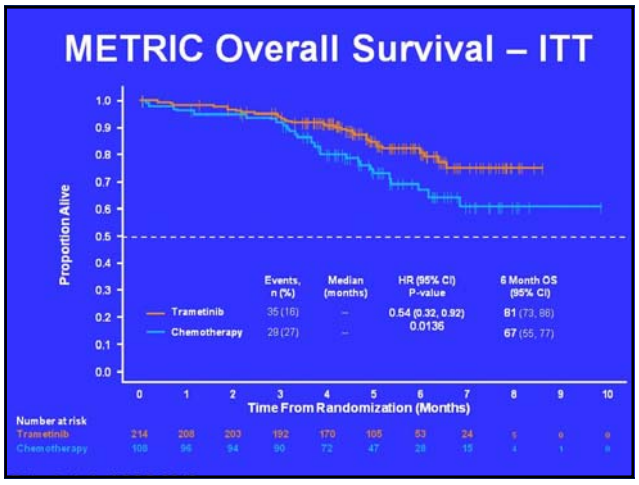
METRIC Phase 3 Study: Efficacy of Trametinib, a potent and selective MEK inhibitor, in progression-free survival and overall survival, compared with chemotherapy in patients with BRAF$^{V600E/K}$ mutant advanced or metastatic melanoma

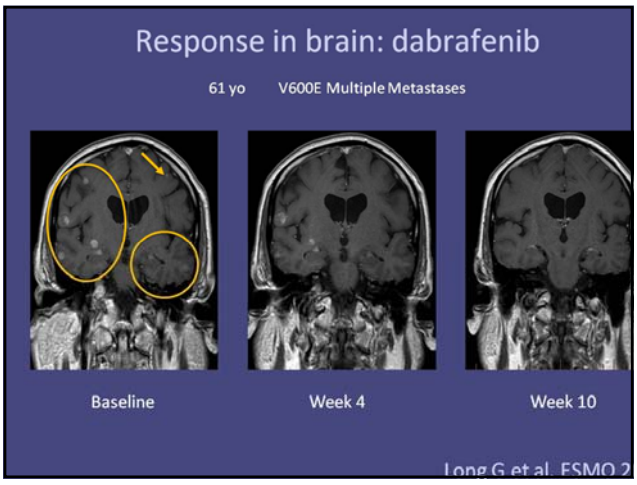
C. Robert, K.T. Flaherty, P. Hersey, P.D. Nathan, C. Garbe, M.M. Milhem, L.V. Demidov, J.C. Hassel, P. Rutkowski, P. Mohr, R. Dummer, U. Trefzer, J.M.G. Larkin, J. Utikal, M. Casey, L.J. Sherman, W.A. Crist, F.S. Wu, K. Patel, and D. Schadendorf

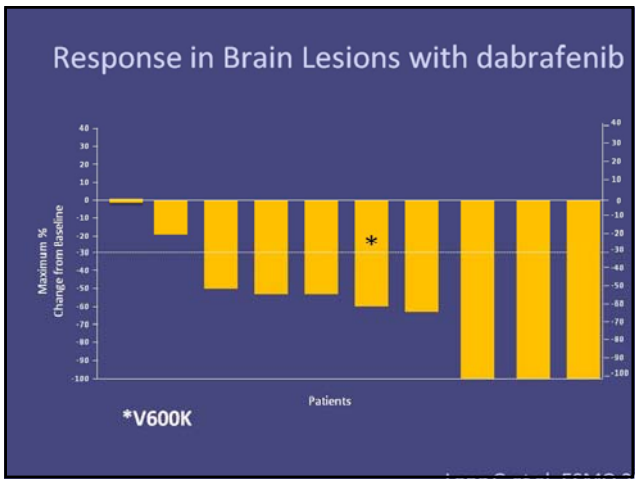
[1]Institut Gustave Roussy, Villejuif, France; [2]Massachusetts General Hospital, Boston, Massachusetts, USA; [3]Melanoma Institute Australia, University of Sydney, Sydney, New South Wales, Australia; [4]Mount Vernon Cancer Centre, Northwood, Middlesex, UK; [5]University Medical Center, Tuebingen, Germany; [6]Department of Internal Medicine, University of Iowa, Iowa City, Iowa, USA; [7]N.N.Blokhin Russian Cancer Research Center, Moscow, Russia; [8]Department of Dermatology, University Hospital Heidelberg, Heidelberg, Germany; [9]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Center Institute of Oncology, Warsaw, Poland; [10]Elbekliniken, Buxtehude, Germany; [11]Department of Dermatology, University of Zurich, Zurich, Switzerland; [12]Department of Dermatology, Venerology and Allergy, Charité -Universitätsmedizin Berlin, Germany; [13]Department of Medicine, Royal Marsden Hospital, London, UK; [14]Skin Cancer Unit, German Cancer Research Center, Heidelberg, Germany and Department of Dermatology, Venereology and Allergology, University Medical Center Mannheim, Ruprecht-Karl University of Heidelberg, Mannheim, Germany; [15]GlaxoSmithKline, Oncology, Philadelphia, Pennsylvania, USA; [16]Department of Dermatology, University Hospital Essen, Essen, Germany

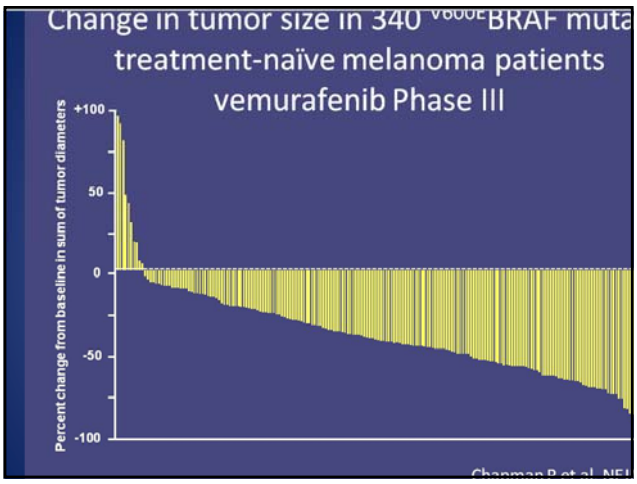
METRIC Best Response and ORR - ITT



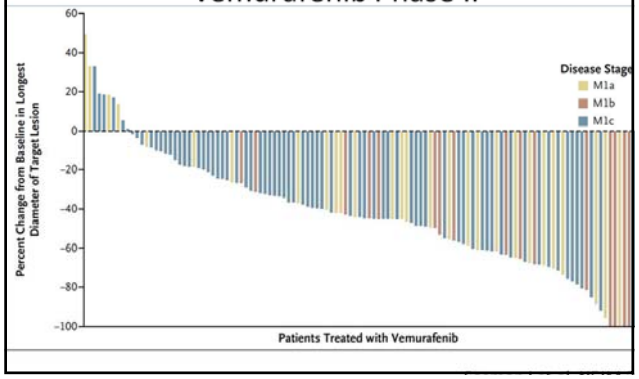

METRIC Overall Survival – ITT
Proportion Alive
Time From Randomization (Months)
Events, n (%)
Median (months)
HR (95% CI) P-value
6 Month OS (95% CI)
Trametinib
Chemotherapy
35 (16)
29 (27)
0.54 (0.32, 0.92)
0.0136
81 (73, 88)
67 (55, 77)
Number at risk
Trametinib 214 208 203 192 170 105 53 24 5 0 0
Chemotherapy 108 96 94 90 72 47 28 15 4 1 0


Response in brain: dabrafenib
61 yo V600E Multiple Metastases
Baseline
Week 4
Week 10
Long G et al. ESMO 2


Response in Brain Lesions with dabrafenib
Maximum % Change from Baseline
Patients
*V600K


Change in tumor size in 340 V600EBRAF muta
treatment-naïve melanoma patients
vemurafenib Phase III
Percent change from baseline in sum of tumor diameters
+100
50
0
-50
-100

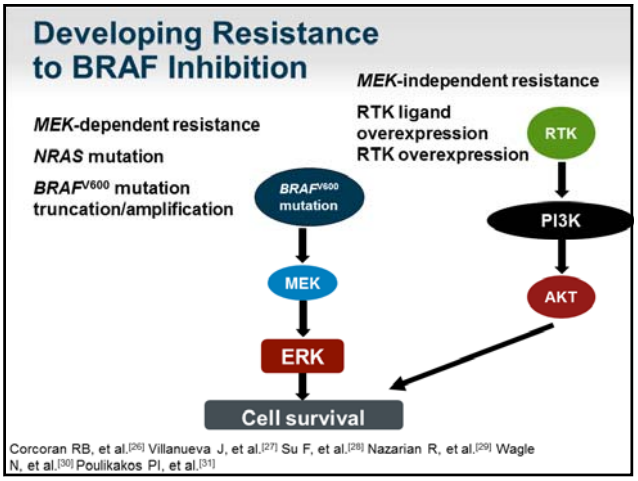
Change in tumor size in 122 ^{V600L}BRAF mutant 2nd-nth line melanoma patients vemurafenib Phase II



Conclusions

- BRAF inhibitors represents effective palliative therapy who present with symptomatic metastatic disease
- Early antitumor activity consistently observed regardless of line of therapy
- Is there a risk of diminished response/duration of response if withheld until patients are symptomatic (high LDH)?

Developing Resistance to BRAF Inhibition

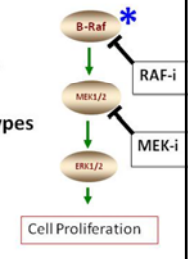


Corcoran RB, et al.[26] Villanueva J, et al.[27] Su F, et al.[28] Nazarian R, et al.[29] Wagle N, et al.[30] Poulikakos PI, et al.[31]

Targeting RAF (and MEK) in Melanoma: Present Situation

Clinical responses to both types of inhibitors

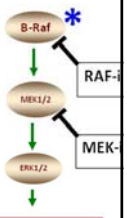
Resistance (*de novo* and acquired) to both types of inhibitors



Targeting RAF (and MEK) in Melanoma: The Path Forward

Clinical responses to both types of inhibitors

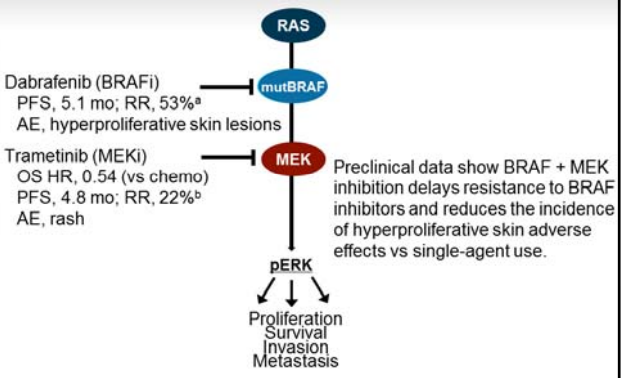
Resistance (*de novo* and acquired) to both types of inhibitors



Goals:

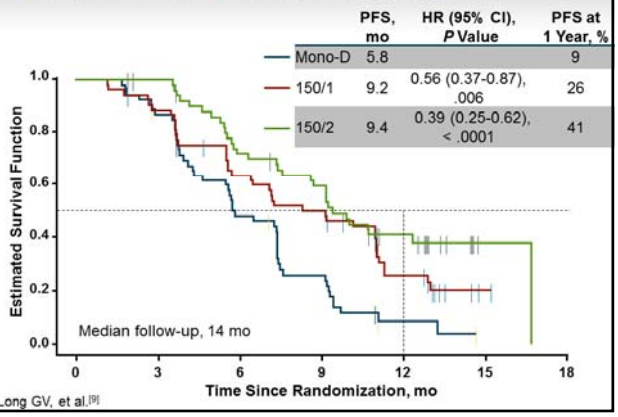
- Define the spectrum of resistance mechanisms
  (even before clinical data is fully available)
- Speed the development of rational therapeutic combinations

Combining BRAF/MEK Inhibitors



a. Hauschild A, et al.[3]
b. Flaherty K.[32]

Phase 2 Trial of Dabrafenib With or Without Trametinib: PFS



Long GV, et al.[9]

Combination Therapy

Combination therapies appear to improve duration of response and overall survival in BRAF mutated patients

Toxicities are not additive and appear manageable

Clinical trials ongoing to expand on targeted therapy combinations. The combination of dabrafenib and trametinib, both FDA-approved agents, appears to have limited efficacy in patients who have progressed on previous BRAF-targeted therapy

Molecular Therapy of Melanoma

- Therapeutic options dictate evaluation of MM for mutations, V600E, V600k, C-Kit. ? NRAS, others
  - WT tumors derive no benefit and may be harmed
- Response duration > 6.7 mos median
- Phased III Brim study: OS and PFS positive
- Resistance via pathway reactivation, both MEK and non-MEK dependent

Targeted BRAF inhibitors have replaced initial chemotherapy for systemic therapy of symptomatic patients with mutated tumors

FDA Approved Molecular Therapy

BRAF Inhibitors:

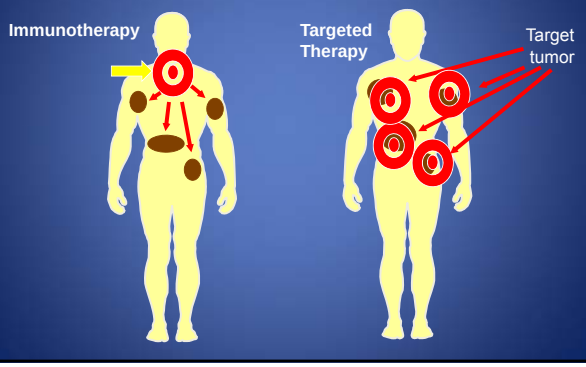
-Vemurafenib (Velboraf)

-Dabrafenib (Taflinar)

MEK Inhibitors:

-Trametinib (Mekinist)

Metastatic Melanoma: Treatment Advances



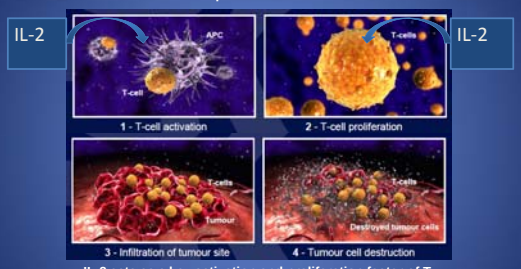
Immunotherapy

Selected Novel Immunotherapeutic Concepts in Advanced Melanoma

- FDA approved
  - IL-2
  - Ipilimumab (CTLA-4 blocking mAb)
- Investigational
  - Nivolumab, lambrolizumab (PD-1 blocking mAb)
  - MPDL3280A (PD-L1 blocking mAb)
  - T-VEC (an oncolytic virus)

Interleukin-2: A Key Modulator of T-Cell Activation and Proliferation

Enhances active non-specific immune function

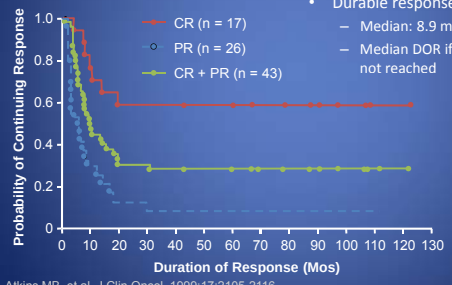


IL-2 acts as a key activation and proliferation factor of T-cells and may have a role in T-cell recruitment

Abbas AK and Lichtman AH. *Cellular and Molecular Immunology*. 2003

High-Dose IL-2 Therapy in Metastatic Melanoma

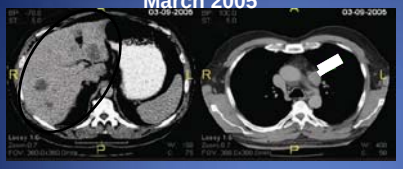
- ORR: 16% (43/270)
- Durable responses
  - Median: 8.9 mos
  - Median DOR if CR achieved: not reached



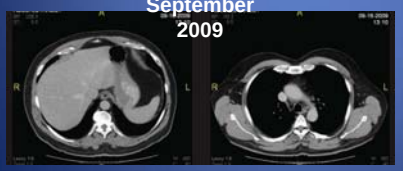
Atkins MB, et al. J Clin Oncol. 1999;17:2105-2116.

mM Case Study: Clinical & Radiographic Response Despite Tumor Burden

March 2005



September 2009



History
- Dx: 6/2000 - T2a
- Recurrance 3/2005 – M1c

March 2005
- Heavy hepatic tumor burden/hepatic dysfunction
- Mediastinal LAD (shown) and a subpleural nodule (not shown)

Treatment & Outcomes
- 2005 – Proleukin x 3 courses
- 2006 - Resumed working
- 2008 - CT A/P – few small areas of liver attenuation

September 2009
- No identifiable liver lesions and normal LFTs
- No mediastinal LAD

Results not typical

Metastatic Melanoma IL-2 Key Points:

- 16% response rate (6% CR, 10% PR)[1]
- 45% of responders were long-term survivors beyond 5 years (range: >70 mo to >150 mo)
- Median duration of response for CRs had yet to be reached[1]
- Disease progression not observed in any patient responding for longer than 30 months[1]

76

Atkins, J Clin Oncol, 1999; 70:2105-2116 ;

Relationship of MAPKinase pathway mutations and response to HD IL-2

Mutation	All	CR/PR	SD/PD	P-value
BRAF	60	14(23%)	46 (77%)	0.05
NRAS	15	7 (47%)	8 (53%)	
WT	26	3 (12%)	23 (88%)	

A significantly larger proportion of patients with BRAF or NRAS mutant tumors achieved CR/PR compared to those with WT tumors.

Joseph, Sullivan et al- JIT 201

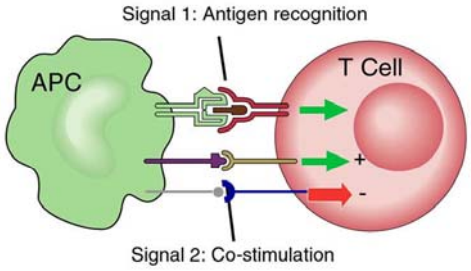
Montefiore Montefiore Einstein Center for Cancer Care

Checkpoint Inhibitors

Activation of Naive T Cells Requires Two Indep. Signals Delivered by the Same APC

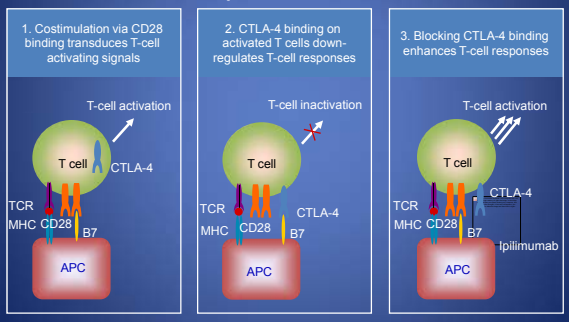
- Primary signal: MHC class II + antigen on antigen presenting cells binds to the T cell receptor
- Costimulatory signal required to activate the T cell
  - The principal costimulatory molecules expressed on APCs are B7 molecules that bind T cell protein CD28

T cell activation



- **There are positive and negative second signals**

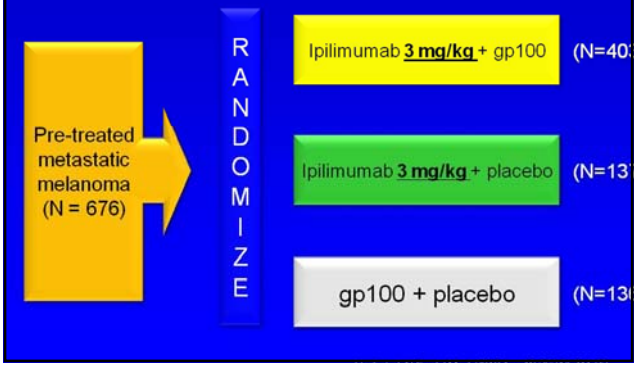
Ipilimumab a Member of Novel Class of Immunotherapeutic Abs: Anti–CTLA-4

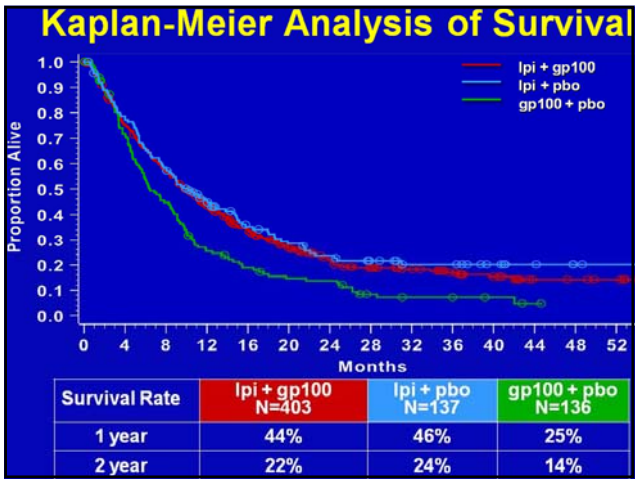


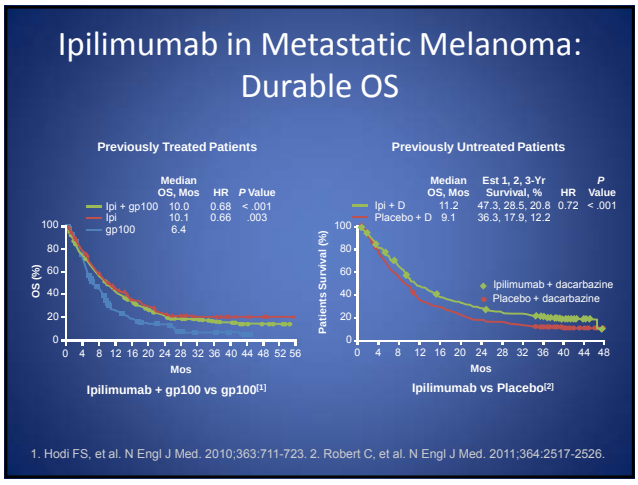
Ipilimumab Registration Trials

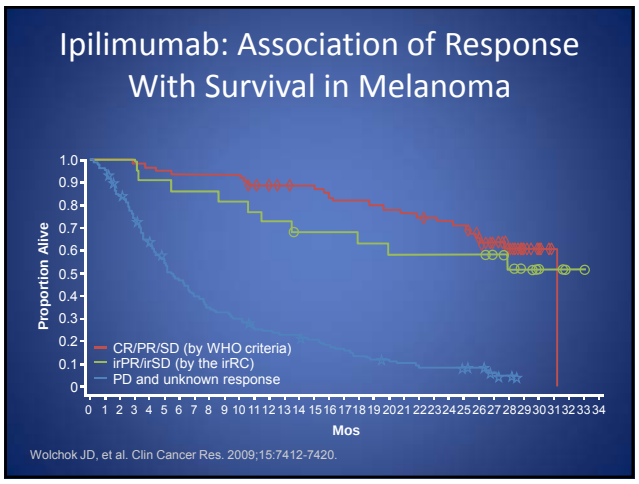
- Pivotal 2nd line trial MDX010-20 (n=650)
  - 3 arm study
  - OS primary endpoint
  - Positive trail reported in June, 2010 ASCO
- First-line CA184-024, randomized placebo controlled in combination with DTIC
  - OS primary endpoint
  - Positive study reported June, 2011 ASCO

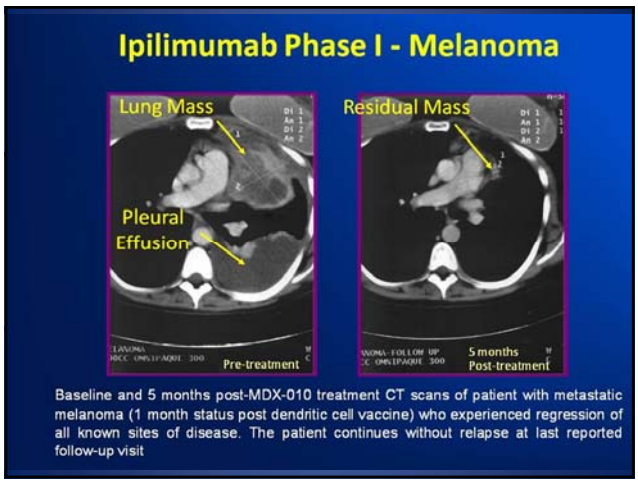
Ipilimumab in Metastatic Melanoma: Phase III Randomized Second-line Study Design




Kaplan-Meier Analysis of Survival
Ipi + gp100
Ipi + pbo
gp100 + pbo
Proportion Alive
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 4 8 12 16 20 24 28 32 36 40 44 48 52
Months
Survival Rate | Ipi + gp100 N=403 | Ipi + pbo N=137 | gp100 + pbo N=136
1 year | 44% | 46% | 25%
2 year | 22% | 24% | 14%


Ipilimumab in Metastatic Melanoma: Durable OS
Previously Treated Patients
Median OS, Mos | HR | P Value
Ipi + gp100 10.0 | 0.68 | < .001
Ipi 10.1 | 0.66 | .003
gp100 6.4
OS (%)
Mos
Ipilimumab + gp100 vs gp100[1]
Previously Untreated Patients
Median OS, Mos | Est 1, 2, 3-Yr Survival, % | HR | P Value
Ipi + D 11.2 | 47.3, 28.5, 20.8 | 0.72 | < .001
Placebo + D 9.1 | 36.3, 17.9, 12.2
Patients Survival (%)
Ipilimumab + dacarbazine
Placebo + dacarbazine
Mos
Ipilimumab vs Placebo[2]
1. Hodi FS, et al. N Engl J Med. 2010;363:711-723. 2. Robert C, et al. N Engl J Med. 2011;364:2517-2526.

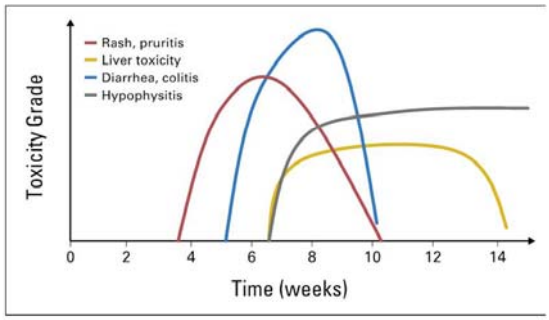

Ipilimumab: Association of Response With Survival in Melanoma
Proportion Alive
CR/PR/SD (by WHO criteria)
irPR/irSD (by the irRC)
PD and unknown response
Mos
Wolchok JD, et al. Clin Cancer Res. 2009;15:7412-7420.


Ipilimumab Phase I - Melanoma
Lung Mass
Pleural Effusion
Pre-treatment
Residual Mass
5 months
Post-treatment
Baseline and 5 months post-MDX-010 treatment CT scans of patient with metastatic melanoma (1 month status post dendritic cell vaccine) who experienced regression of all known sites of disease. The patient continues without relapse at last reported follow-up visit

Ipilmumab IrAEs

- Usually occur during the first 12 weeks of therapy
- Steroids can be sued to manage almost all the IrAEs – may require prolonged steroid taper
- IrAEs can wax and wane
- Each IrAe has different kinetics of onset

Kinetics of induction of irAEs with ipilimumab



"Miracle survivors": A reproducible event with CTLA4 blocking monoclonal antibodies

Ipilimumab Facts:

- Positive impact in overall survival in two randomized Phase III trials
  - Potential to induce durable CRs in 10 – 15% of patients
  - Responses usually take time (1 - 4 months) and have a variety of response patterns
  - Clinically significant immune related toxicities occur in 15% of patients, i.e. skin, GI, hepatic, endocrine related

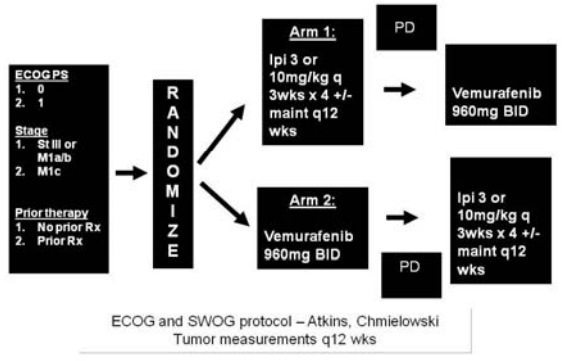
Ipilimumab-Current Issues

- Regimen: DTIC or not?
- Line of therapy: First line vs second line?
- Dose: 3mg/kg vs 10 mg?
- Schedule: Maintenance or not?
- Role in the adjuvant setting?
- Combinations
  - Bevacizumab
  - GM-CSF
  - HD IL-2
  - PD1 Ab
  - BRAF inhibitors

Treatment Selection in BRAF mutated Melanoma

- BRAFi therapy may not be the best initial option in V600E mutated patients
- Current data suggests that for some patients with V600E mutations starting with immunotherapy offers them the possibility of long term benefit without compromising their response to subsequent BRAFi therapy
- Prospective trail data is necessary to address this issue

E1612: Ipi vs Vemurafenib

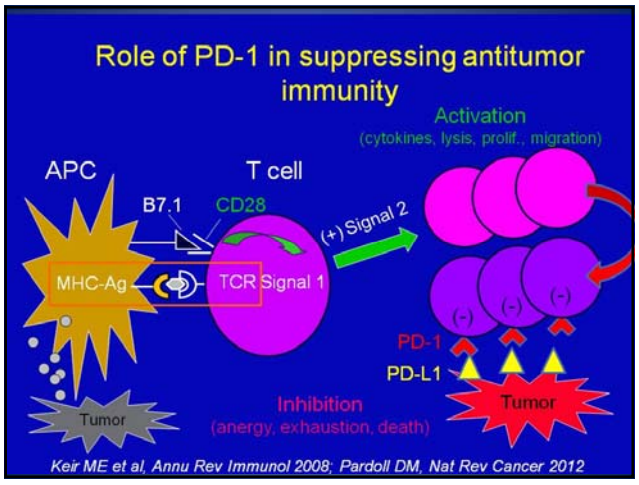


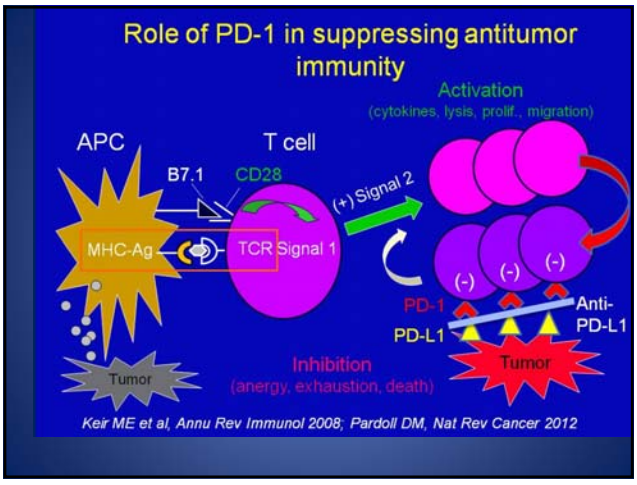
ECOG and SWOG protocol – Atkins, Chmielowski
Tumor measurements q12 wks

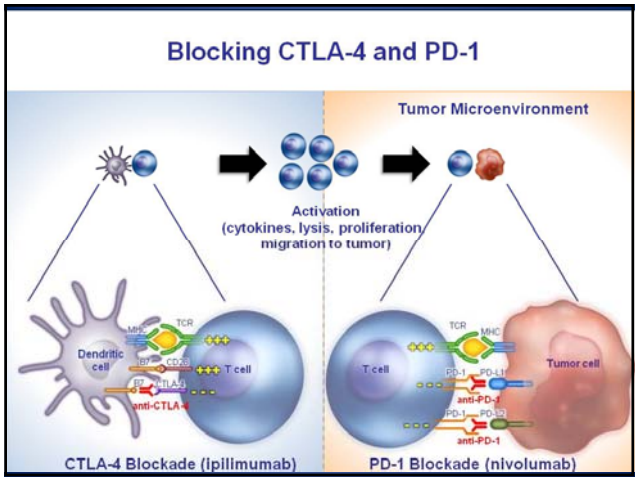
Presented By Michael B. Atkins, MD at 2012 Annual Meeting

Montefiore Montefiore Einstein Center for Cancer Care

Other Checkpoint Inhibitors



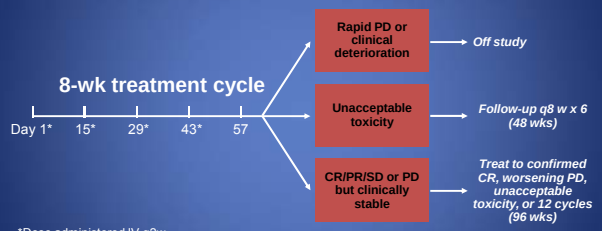




PD-1/PD-L1 Pathway Agents in Developmer

Company	Agent	Structure	Status
Amplimune/GSK	AMP-224	Fc fusion protein to PD-L2	Phase I
Bristol Myers Squibb	BMS-936558	Fully human, IgG 4 Ab	Phase II RCC, others solid tumors
Curetech/Teva	CT-011	Humanized monoclonal	Phase II melanoma, R
Genentech/Roche	GP-28328	PD-L1 Ab	Phase I
Merck	MK-3475	Humanized, IgG 4 Ab	Phase I

Phase I Nivolumab Multidose Regimen



*Dose administered IV q2w.

Scans done at baseline and following each 8-wk treatment cycle.

Eligibility: advanced MEL, RCC, NSCLC, CRC, or CRPC with PD after 1-5 systemic therapies.

Topalian SL, et al. N Engl J Med. 2012;366:2443-2454.

Clinical Activity of BMS-936559 in 160 Response-Evaluable Patients*

Tumor Type**	Dose (mg/kg)	No. Patients (N=160)	ORR*** No. Patients (%)	Duration of Response Range (months)
Melanoma	0.3–10	52	9 (17)†	2.8 to 23.5+
NSCLC	1–10	49	5 (10)	2.3+ to 16.6+
All Squamous		13	1 (8)	-
All Non-Squamous		36	4 (11)	-
RCC	10	17	2 (12)	4 to 17
Ovarian	3 and 10	17	1 (6)	1.3+

*Response-evaluable patients who initiated treatment by August 1, 2011

**To date there have been no objective responses in patients with colorectal or pancreatic cancer. No patients with gastric c breast cancer were evaluable as of the date of data analysis.

***ORR was assessed using modified RECIST v1.0 criteria

†Includes three CRs

Summary and Conclusions

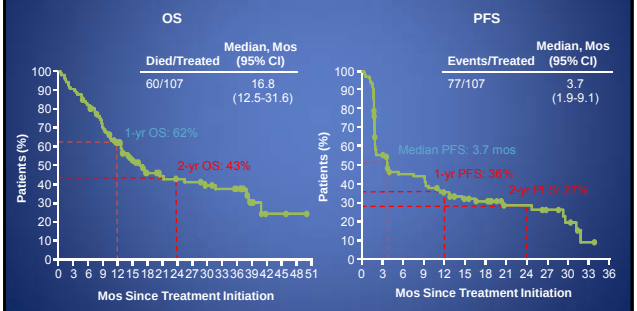
- CA210-001 trial is currently ongoing
- BMS-936559 at 0.3 to 10 mg/kg can be administered safely in an outpatient setting to heavily pretreated patients
- BMS-936559 induced durable tumor regressions and prolonged stabilization of disease in a proportion of patients with advanced NSCLC, MEL, RCC, and ovarian cancer
- Data from this first-in-human trial further validates the importance of the PD-1/PD-L1 pathway as a target for cancer immunotherapy in multiple histologies

Nivolumab in Melanoma: Efficacy

- ORR (n = 107)
  - 31% (dose range 0.1-10 mg/kg)
    - 41% at 3 mg/kg
  - 4% unconventional responses
  - 45% of responses evident at 8 wks
  - Median response duration of 2 years
- Survival outcomes
  - Median OS 16.8 months across doses
  - Survival rate
    - 62% at 1 yr
    - 43% at 2 yr
  - Median PFS 3.7 months across doses

Sznol M et al. ASCO 2013. CRA9006.

Nivolumab Phase I Study: Survival of Patients With Melanoma



Sznol M, et al. ASCO 2013. Abstract CRA9006. Used with permission.

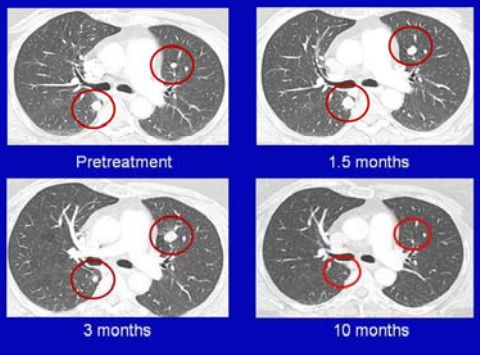
PD-1 Blockade With Nivolumab: Toxicities

Anti-PD-1–Related Adverse Event, n (%)	All Grades	Grade 3/4
Any select event	54 (58)	5 (5)
Skin	36 (38)	2 (2)
Gastrointestinal	18 (19)	2 (2)
Endocrinopathies	13 (14)	2 (2)
Hepatic	7 (7)	1 (1)
Infusion reaction	6 (6)	--
Pulmonary	4 (4)	--
Renal	2 (2)	1 (1)

- Do not ignore early respiratory symptoms, since pneumonitis can occur rarely and can be fatal if not treated promptly with immunosuppressants
- Renal insufficiency can also occur rarely
- Endocrinopathies and enterocolitis are more characteristic of ipilimumab toxicity but should also be considered in patients receiving a PD-1–blocking drug

Sznol M et al. ASCO 2013. CRA9006. Topalian SL, et al. N Engl J Med. 2012;366:2443-2454.

Complete Response in a Patient With Melanoma Treated With 3 mg/kg BMS-936559



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All target lesions in
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Completed treatme
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Clinical Activity of BMS-936558 in Melanoma Patients

Pop	Dose (mg/kg)	Pts n	ORR n (%)	Duration of Response (mo)	SD ≥24 wk n (%)	PFSR at 24 wk (%)
All MEL	0.1-10	94	26 (28)	1.9+ to 24.9+	6 (6)	41
MEL	0.1	14	4 (29)	5.6 to 7.5+	1 (7)	40
	0.3	16	3 (19)	1.9+ to 3.8+	1 (6)	31
	1	27	8 (30)	5.3+ to 24.9+	3 (11)	45
	3	17	7 (41)	9.2+ to 22.4+	1 (6)	55
	10	20	4 (20)	17.0 to 24.6+	0	30

- ORR was assessed using modified RECIST v1.0.
- 3 melanoma patients had a persistent reduction in baseline target lesions in the presence of new lesions but were not classified as responders for the

PD-L1 Expression in Melanoma

- PD-L1-positive metastatic lesions correlated with improved survival ir 56 patients with stage III-IV melanoma[1]
- In patients with MEL, NSCLC, CRC, RCC, or CRPC treated with BMS-936558 (n=42), PD-L1 expression in pretreatment tumor biopsies correlated with clinical outcomes[2]
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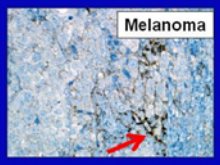


Immunohistochemical staining with anti-PD-L1 monoclonal antibody 5H1 of melanoma lymph node metastasis

[1]Taube JM, et al. *Science Transl Med.* 2012;4:127ra37 [2]Topalian SL et al. 201

MPDL3280A Phase I Study: Efficacy

- ORR: 29% (n = 38; dose range: 1-20 mg/kg)
  - Responses reported in cutaneous and mucosal melanoma, but not ocular
- SD (≥ 24 wks): 5%
- PFS at 24 wks: 43%

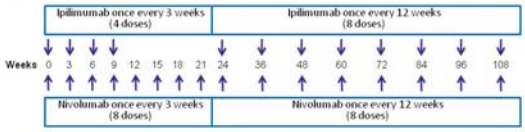
Patients with PD-L1–positive tumor tissue had a higher rate

Efficacy (n = 38)	PD-L1 Positive	PD-L1 Negative	All
ORR, n/n (%)	4/15 (27)	3/15 (20)	11/38 (2
PR + SD, %	87	20	58

Combined Immunotherapies

Phase I Study: Schedule

Concurrent Cohorts



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- **Data as of Feb 2013 for 86 patients**

Presented by: Jedd D. Wolchok, MD, PhD PRESENTED AT: ASCO Annual '13 Meeting

Presented By Jedd D. Wolchok, MD, PhD at 2013 ASCO Annual Meeting

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- About one third of patients (31%) had rapid and deep tumor regressions

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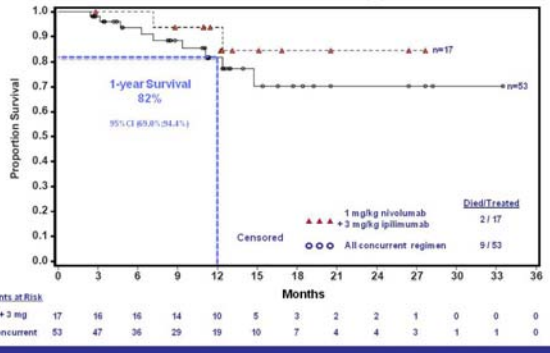

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Presented by: Jedd D. Wolchok, MD, PhD PRESENTED AT: ASCO Annual '13 Meeting

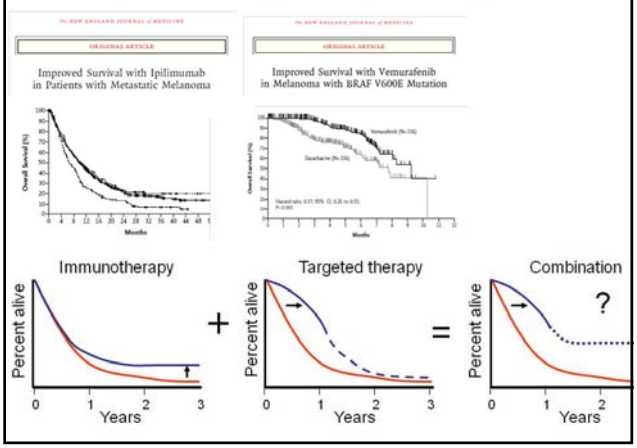
Presented By Jedd D. Wolchok, MD, PhD at 2013 ASCO Annual Meeting

Key Ongoing Phase III ImmunoTx Studies in Advanced and Metastatic Melanoma

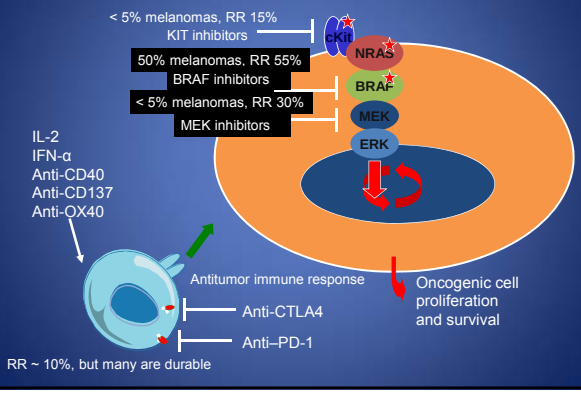
Regimen Comparison	Planned N	Endpoints
Ipilimumab vs placebo[1]	950	Primary: RFS Secondary: OS, DMFS, safety
Nivolumab vs dacarbazine[2]	410	Primary: OS Secondary: PFS, ORR, PD-L1 expression as biomarker, HRQoL
Ipilimumab 3 mg/kg vs 10 mg/kg[3]	700	Primary: OS Secondary: PFS, ORR, DCR, DoR, SD duration
Nivolumab vs nivolumab/ipilimumab vs ipilimumab[4]	915	Primary: OS Secondary: PFS, ORR, OS based on PD-L1 expression
Ipilimumab vs high-dose interferon alfa-2b[5]	1000	Primary: RFS, OS Secondary: safety, QoL

1. ClinicalTrials.gov. NCT00636168. 2. ClinicalTrials.gov. NCT01721772. 3. ClinicalTrials.gov. NCT01515189. 4. ClinicalTrials.gov. NCT01844505. 5. ClinicalTrials.gov. NCT01274338.

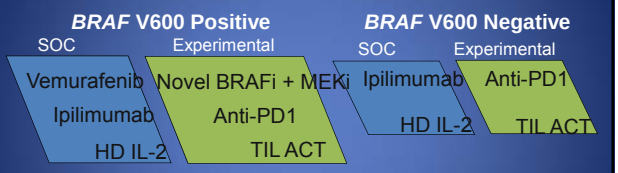
Combining immunotherapy and targeted therapy for melanoma



Can we combine Immunotherapy and Targeted therapy?



Treatment of Advanced Melanoma in 2013



Questions for the future

- Immunotherapy vs. BRAFi as 1st line therapy
- Sequencing of treatments
- Combinations:
  - BRAF + MEK inhibitors
  - Different Immunotherapies
  - Immunotherapy + BRAFi
- Treatment of BRAF resistance
- Treatment of uncommon BRAF mutations

We have a bright sunrise over the (old) graveyard of melanoma drug developmen

PD1/PDL1 inhibitors
BRAF inhibitors
CTLA4 blockage
MEK inhibitors
>10 articles in the NEJM 2010-12

Conclusions

- Immunotherapy is a reality for the treatment of metastatic melanoma:
  - High dose IL-2: FDA approved
  - Ipilimumab: FDA approved
  - Adoptive cell transfer therapy: Experimental
- The possibility of deriving long term benefit with IL-2 or ipilimumab in patients with metastatic melanoma allows accepting the side effects of the therapy
- The combination of ipilimumab and BRAF inhibitors outside a clinical trial is currently an untested combination

PRESENTED AT: ASCO Annual Meeting

Presented By Antoni Ribas, MD at 2011 ASCO Annual Meeting

PD-1/PD-L1 Pathway in Solid Tumors

- PD-L1 associates with the PD-1 receptor on T cells.
  - Also binds to B7.1 (CD80)
- PD-L1 and PD-L2 are expressed and inducible on both lymphoid and non-lymphoid tissues including many tumors
  - PD-L2 expression appears much more restricted
- Tumors may use PD-L1 to protect against a T cell-mediated immune response[1,2]
- PD-L1 up-regulation in tumors correlates with decreased immune activation and poor clinical outcomes
  - RCC; poor prognosis[3]
  - NSCLC; PD-L1+ regions contain fewer TIL[4]
  - Ovarian cancer; poor prognosis and decreased TIL[5]

1.Keir ME et al. *Annu Rev Immunol*. 2008; 2. Pardoll DM. *Nat Rev Cancer*. 2012; 3. Thompson RH, et al. *Cancer Res*. 2006; 4. Konishi J, et al. *Clin Cancer Res*. 2004; 5. Zou W, Chen L. *Nat Rev Immunol*. 2008.

4

Presented By Scott S. Tykodi, MD, PhD at 2012 Annual Meeting

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Tumor Type**	Dose (mg/kg)	No. Patients (N=160)	ORR*** No. Patients (%)	Duration of Response Range (months)
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*Response-evaluable patients who initiated treatment by August 1, 2011
**To date there have been no objective responses in patients with colorectal or pancreatic cancer. No patients with gastric or breast cancer were evaluable as of the date of data analysis.
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Presented By Scott S. Tykodi, MD, PhD at 2012 Annual Meeting

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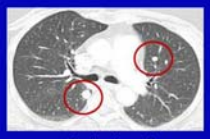
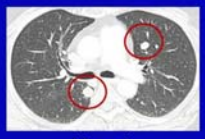
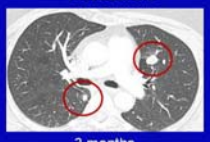

Pretreatment


1.5 months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10 months

A 61-year-old female previously treated with temozolomide.

All target lesions in lung.

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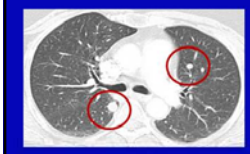
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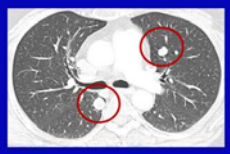
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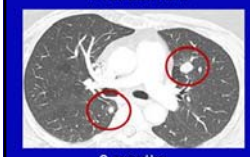
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Presented By Scott S. Tykodi, MD, PhD at 2012 Annual Meeting

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Presented By F. Stephen Hodi, MD at 2012 Annual Meeting

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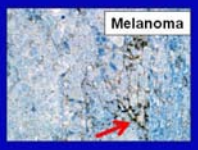

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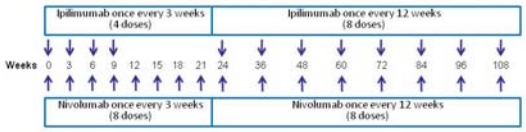
Phase I Study: Schedule

Concurrent Cohorts



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Presented by: Jedd D. Wolchok, MD, PhD PRESENTED AT: ASCO Annual '13 Meeting

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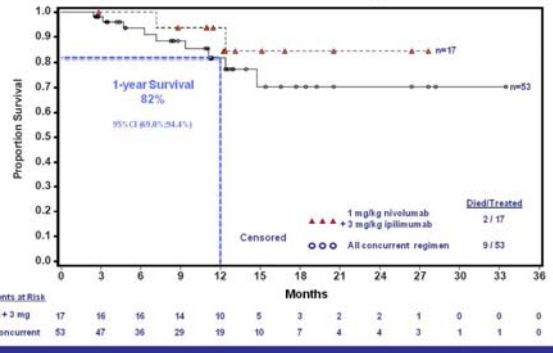

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Presented by: Jedd D. Wolchok, MD, PhD PRESENTED AT: ASCO Annual '13 Meeting

Presented By Jedd D. Wolchok, MD, PhD at 2013 ASCO Annual Meeting

Advanced Melanoma-Current Perspective

Despite recent advances–

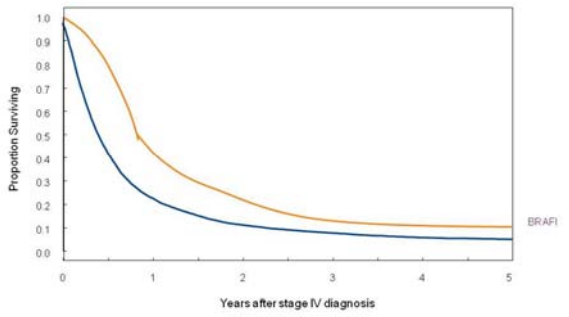
"Metastatic melanoma is still a bad disease"

Although we pause to celebrate this remarkable progress, there is still much work to do to raise the bar even higher

PRESENTED BY: Michael B. Atkins PRESENTED AT: ASCO Annual '12 Meeting

Presented By Michael B. Atkins, MD at 2012 Annual Meeting

Overall Survival for Patients with BRAF^{V600E} Melanoma: 2012



PRESENTED BY: Michael B. Atkins PRESENTED AT: ASCO Annual '12 Meeting

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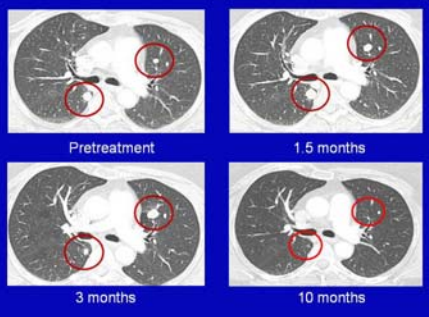

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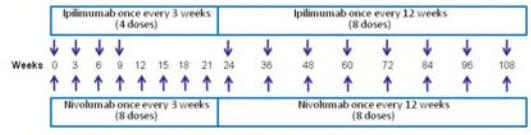

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Dose (mg/kg)		Response Evaluable Patients n	CR n	PR n	Objective Response Rate % [95% CI]	Aggregate Clinical Activity Rate % [95% CI]	≥80% Tumor Reduction at 12 wk n (%)
Nivolumab	Ipilimumab						
0.3	3	14	1	2	21 [5-51]	50 [23-77]	4 (29)
1	3	17	3	6	53 [28-77]	65 [38-86]	7 (41)
3	1	15	1	5	40 [16-68]	73 [45-92]	5 (33)
3	3	6	0	3	50 [12-88]	83 [36-100]	0
Concurrent		52	5	16	40 [27-55]	65 [51-78]	16 (31)

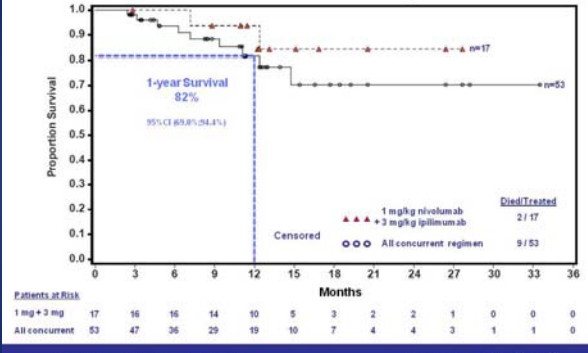
- With concurrent treatment of nivolumab + ipilimumab, 40% (range 21-53%) of patients had confirmed objective responses
- About one third of patients (31%) had rapid and deep tumor regressions

Presented by: Jedd D. Wolchok, MD, PhD

PRESENTED AT: ASCO Annual '13 Meeting

Presented By Jedd D. Wolchok, MD, PhD at 2013 ASCO Annual Meeting

Preliminary Survival of Patients Treated with the Concurrent Regimen



Presented by: Jedd D. Wolchok, MD, PhD

PRESENTED AT: ASCO Annual '13 Meeting

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Conclusions

- The concurrent combination of nivolumab and ipilimumab induced objective response rates appearing higher than published monotherapy values
- The nature of the responses appeared to be distinctly different from those of the nivolumab and ipilimumab monotherapies
  - Responses were rapid and deep
  - At the combined doses chosen for phase 3 study, all responding patients achieved deep or complete responses
- Treatment-related adverse events managed using standard protocols
  - No treatment-related deaths
- Clinical activity in patients who previously progressed on ipilimumab and then received nivolumab
- Based on these results, a phase 3 trial is open to investigate the efficacy of the concurrent nivolumab/ipilimumab combination vs. nivolumab vs. ipilimumab in patients with advanced melanoma (NCT01844505)
  - This combination is also being investigated in non-small-cell lung cancer and renal cell carcinoma

Presented by: Jedd D. Wolchok, MD, PhD

PRESENTED AT: ASCO Annual '13 Meeting

Presented By Jedd D. Wolchok, MD, PhD at 2013 ASCO Annual Meeting

Advanced Melanoma-Current Perspective

Despite recent advances–

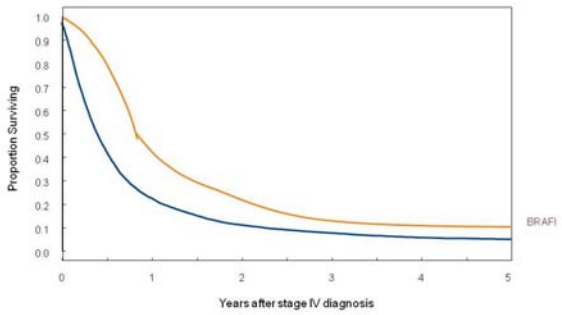
"Metastatic melanoma is still a bad disease"

Although we pause to celebrate this remarkable progress, there is still much work to do to raise the bar even higher

PRESENTED BY: Michael B. Atkins PRESENTED AT: ASCO Annual '12 Meeting

Presented By Michael B. Atkins, MD at 2012 Annual Meeting

Overall Survival for Patients with BRAF^{V600E} Melanoma: 2012



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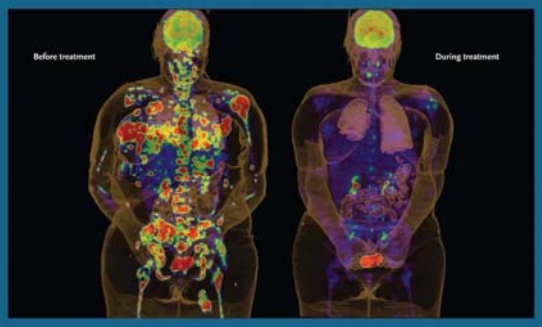
Targeting Treatment to a Specific Variant in the Melanoma Gene



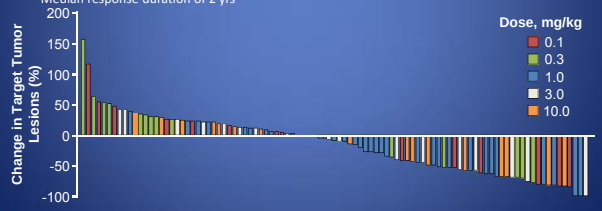
McDermott U et al. N Engl J Med 2011;364:340-350

The NEW ENGLAND JOURNAL of MEDICINE

Presented By Jeffrey Alan Sosman, MD at 2011 ASCO Annual Meeting

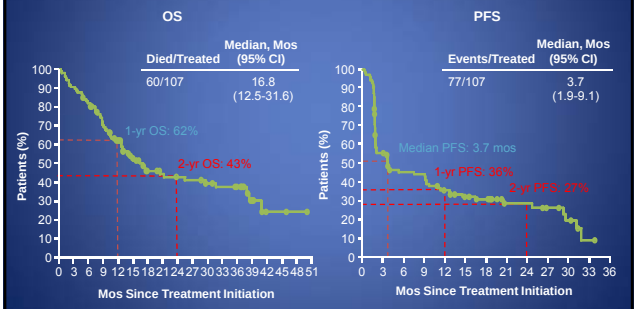
Nivolumab Phase I Study: Tumor Response in Melanoma

- ORR: 31% (across doses)
  - 41% at 3 mg/kg
  - 4% unconventional responses
  - 45% of responses evident at 8 wks
- Median response duration of 2 yrs



Sznol M et al. ASCO 2013. Abstract CRA9006. Used with permission.

Nivolumab Phase I Study: Survival of Patients With Melanoma



Sznol M, et al. ASCO 2013. Abstract CRA9006. Used with permission.

Nivolumab Phase I Study: Safety in Melanoma

- Generally well tolerated
- Grade 3/4 AEs occurred in 21% of patients, with no grade ≥ 3 pneumonitis

AE, %	Any Grade	Grade 3/4
Any select AE*	54	5
Skin	36	2
Gastrointestinal	18	2
Endocrinopathies	13	2
Hepatic	7	1
Infusion reaction	6	0
Pulmonary	4	0
Renal	2	1

*Potential immunologic etiologies.

Sznol M, et al. ASCO 2013. Abstract CRA9006.

Nivolumab + Ipilimumab: Phase I Study

- Concurrent therapy study design:

Patients with stage III or IV melanoma with ≤ 3 previous therapies (n = 53) → **Wks 0-9 Ipilimumab + Nivolumab** q3w x 4 cycles → (0.3-5 escalatin) → **Wks 12-21 Nivolumab** q3w x 4 cycles → umab → **Wks 24-108 Ipilimumab + Nivolumab** q12w x 8 cycles

- Sequenced therapy study design

Patients with stage III or IV melanoma with ≥ 3 previous doses of ipilimumab (n = 33) → **Nivolumab** (1 or 3 mg/kg) q2w for up to 48 doses

Wolchok JD, et al. N Engl J Med. 2013;[Epub ahead of print]. Wolchok JD et al. ASCO 2013. Abstract 9012.

Nivolumab + Ipilimumab: Efficacy

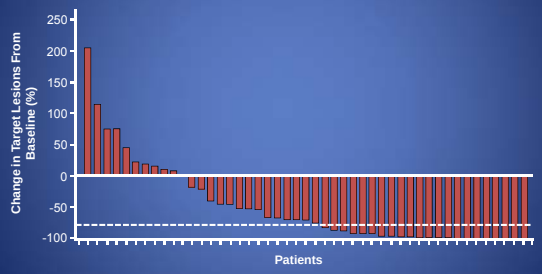
Clinical activity in concurrent regimen

Cohort	Nivolumab + Ipilimumab, mg/kg	Response Evaluable Patients, n	CR, n	PR, n	ORR, %	≥ 80% Tumor Reduction at 12 Wks, n (%)
1	0.3 + 3	14	1	2	21	4 (29)
2	1 + 3	17	3	6	53	7 (41)
2a	3 + 1	15	1	5	40	5 (33)
3	3 + 3	6	0	3	50	0
All	-	52	5	16	40	16 (31)

- ORR: 20% (1 CR, 5 PR)
- 4 patients had ≥ 80% tumor reduction at first scheduled 8-wk tumor assessment

Wolchok JD, et al. N Engl J Med. 2013;[Epub ahead of print]. Wolchok JD, et al. ASCO 2013. Abstract 9012.

Nivolumab + Ipilimumab: Tumor Response With Concurrent Therapy



- Responses ongoing in ~ 90% of responding patients after a follow-up of ~ 13 mos

Wolchok JD, et al. N Engl J Med. 2013;[Epub ahead of print]. Wolchok JD, et al. ASCO 2013. Abstract 9012.

Nivolumab + Ipilimumab: Safety

Treatment-Related Adverse Event, n (%)	Concurrent All Cohorts (n = 53)		Sequenced All Cohorts (n = 33)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any adverse event	49 (93)	28 (53)	24 (73)	6 (18)
Rash	29 (55)	2 (4)	3 (9)	0
Diarrhea	18 (34)	3 (6)	3 (9)	0
AST	11 (21)	7 (13)	0	0
ALT	11 (21)	6 (11)	1 (3)	0
Lipase	10 (19)	7 (13)	4 (12)	2 (6)
Pulmonary	3 (6)	1 (2)	1 (3)	0
Renal	3 (6)	3 (6)	0	0
Endocrinopathy	7 (13)	1 (2)	3 (9)	2 (6)
Uveitis	3 (6)	2 (4)	0	0

Combining 3 mg/kg of each agent exceeded the MTD; 1 mg/kg nivolumab + 3 mg/kg ipilimumab chosen going forward

Wolchok JD, et al. N Engl J Med. 2013;[Epub ahead of print]. Wolchok JD, et al. ASCO 2013. Abstract 9012.

Nivolumab in Advanced Melanoma: Expert Perspectives

- Nivolumab (anti-PD-1 mAb) appears promising in early trials
  - Durable responses and generally well tolerated as a single agent
  - Nivolumab + ipilimumab: robust tumor responses
    - Currently being evaluated in a phase III trial
  - Biomarkers: Absence of PD-L1 tumor expression does not predict absence of response to PD-1 targeted therapy

ClincalTrials.gov. NCT01844505

MPDL3280A, an Anti–PD-L1 Antibody: Phase I Study in Metastatic Melanoma

- MPDL3280A targets PD-L1, thereby blocking binding of PD-L1 to its receptors (PD-1 and B7.1)
- MPDL3280A specifically engineered to reduce ADCC activation and avoid depleting activated T cells

Patients with malignant melanoma
- ECOG PS 0-1 (n = 44)

→ **MPDL3280A** Administered to successive groups with escalating doses q3w x 16 cycles

- Standard 3+3 protocol [illegible] /kg
- Primary endpoints: safety and tolerability; determine MTD

Hamid O, et al. ASCO 2013. Abstract 9010.

MPDL3280A Phase I Study: Efficacy

- ORR: 29% (n = 38; dose range: 1-20 mg/kg)
  - Responses reported in cutaneous and mucosal melanoma, but not ocular
- SD (≥ 24 wks): 5%
- PFS at 24 wks: 43%

Patients with PD-L1–positive tumor tissue had a higher rate

Efficacy (n = 38)	PD-L1 Positive	PD-L1 Negative	All
ORR, n/n (%)	4/15 (27)	3/15 (20)	11/38 (29)
PR + SD, %	87	20	58

Hamid O, et al. ASCO 2013. Abstract 9010.

MPDL3280A Phase I Study: Safety

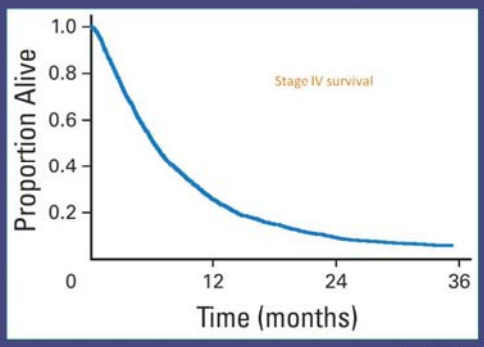
- No MTD or DLT reported
- Most adverse events were transient grade 1/2 not needing tre

Most Common Adverse Event, Regardless of Cause, %	All Dose Cohorts (N = 44)	
	Any Grade	Grade 3/4
Fatigue	59	2
Diarrhea	30	2
Pruritus	25	0
Arthralgia	16	2
Rash	16	0

- Grade 3/4 toxicities reported in 36% of patients; most common included hyperglycemia (9%), increased ALT (7%), and increased AST (5%)
- No pneumonitis or colitis seen within study group.

Hamid O, et al. ASCO 2013. Abstract 9010.

Metastatic melanoma: race against time



Korn et al. JCO 2008

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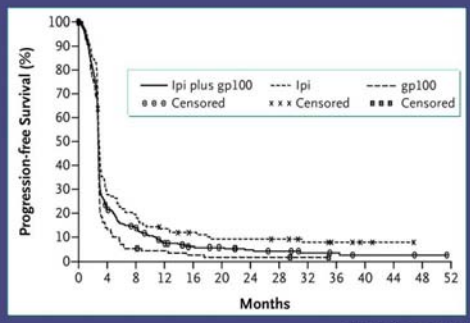
Progression-free survival: ipilimumab



Hodi FS et al. NEJM 2010

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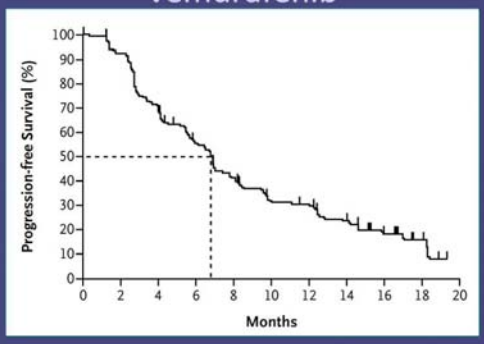
Progression-free survival: vemurafenib



Ribas A et al. NEJM 2012

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Patients who "need" a response

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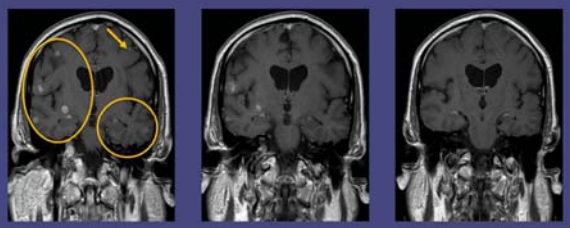
Response in brain: dabrafenib

61 yo V600E Multiple Metastases



Baseline Week 4 Week 10

Long G et al. ESMO 2010

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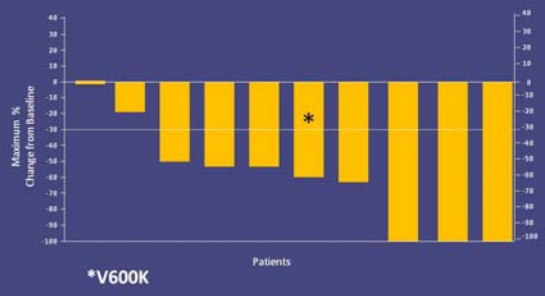
Response in Brain Lesions with dabrafenib



*V600K

Long G et al. ESMO 2010

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Line of therapy

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Change in tumor size in 340 ^{V600E}BRAF mutant, treatment-naïve melanoma patients vemurafenib Phase III

Chapman P et al. NEJM 2012

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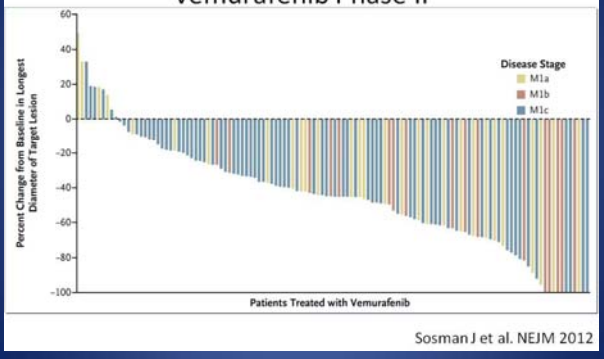
Change in tumor size in 122 ^{V600E}BRAF mutant, 2nd-nth line melanoma patients vemurafenib Phase II



Sosman J et al. NEJM 2012

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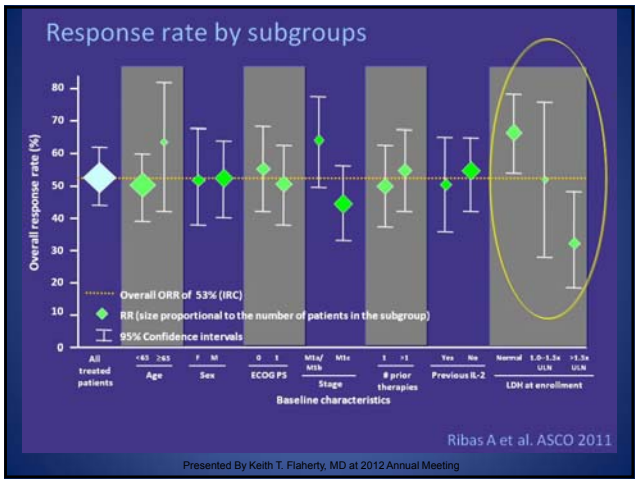

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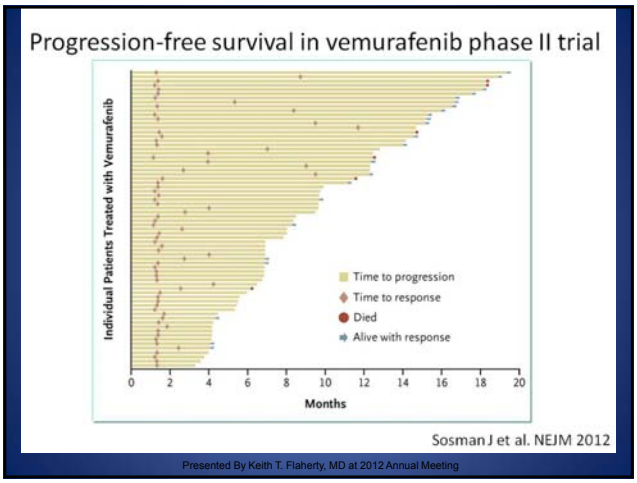

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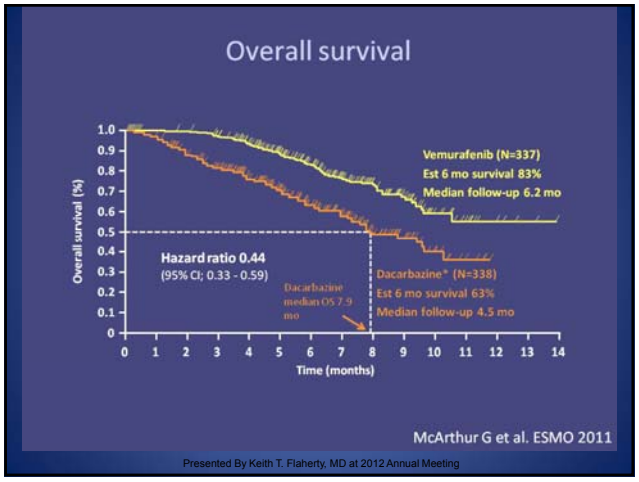

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Conclusions

- BRAF inhibitors represents effective palliative therapy who present with symptomatic metastatic disease
- Early antitumor activity consistently observed regardless of line of therapy
- Is there a risk of diminished response/duration of response if withheld until patients are symptomatic (high LDH)?

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Patient characteristics

	Dacarbazine (n=338)	Vemurafenib (n=337)
Median age, years	52.5	56.0
Male, n (%)	181 (54)	200 (59)
ECOG PS, n (%)		
0	230 (68)	229 (68)
1	108 (32)	108 (32)
Stage, n (%)		
Unresectable IIIc	13 (4)	20 (6)
M1a	40 (12)	34 (10)
M1b	65 (19)	62 (18)
M1c	220 (65)	221 (66)
LDH >ULN	142 (42)	142 (42)

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Number of patients receiving anti-cancer therapies after initial treatment on BRIM-3

Subsequent anti-cancer therapy	Dacarbazine (n=338)	Vemurafenib (n=337)
Any	149 (44%)	122 (36%)
Ipilimumab	73 (22%)	60 (18%)
Dabrafenib	5 (1.5%)	0
Crossover to vemurafenib	83 (25%)	–

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Ipilimumab use after BRIM-3, by disease stage

Stage	Dacarbazine	Vemurafenib
IIIc, IV M1a/M1b	26% (31/118)	18% (21/116)
IV M1c	19% (43/220)	18% (39/221)

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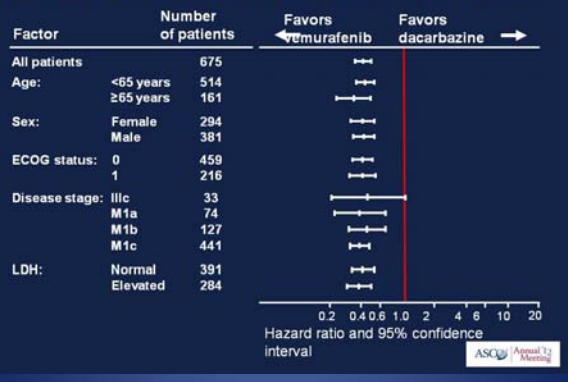
Progression-free survival by baseline characteristic (February 01, 2012 cut-off) censored at crossover



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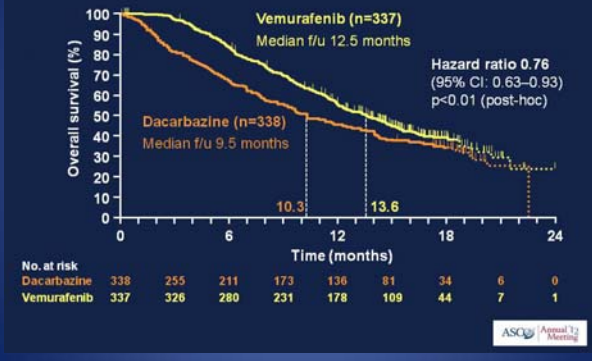
Overall survival (February 01, 2012 cut-off) not censored at crossover



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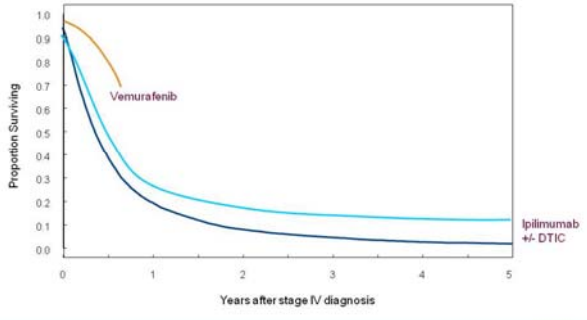
Stage IV Melanoma 2010-11: Raising the Bar



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BRIM 3: Key Points/Comments (1)

- Median OS for vemurafenb confirmed to be better than for DTIC
  - Impact of cross-over/censoring difficult to assess
  - Reassuring that OS benefit maintained even if when pts who crossed over from DTIC to vemurafenib are not censored (HR 0.76 vs 0.70)

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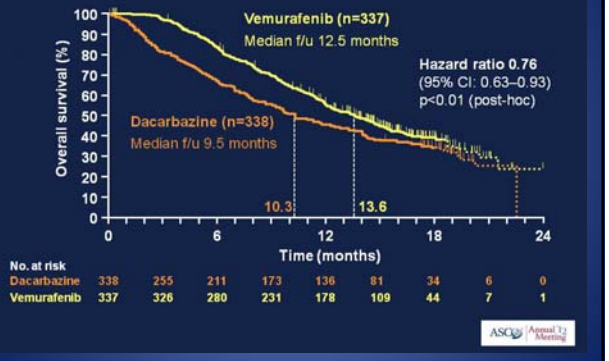
Overall survival (February 01, 2012 cut-off) not censored at crossover



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BRIM 3: Key Points/Comments (2)

- Median OS in BRIM3 (13.6 months) < BRIM2 (16 mos)
  - Did first line patients have more aggressive disease?
  - Was there less continuation of vemurafenib after PD on BRIM3?
- Forrest plot suggests no benefit for stage IIIC, M1a and M1b populations relative to DTIC

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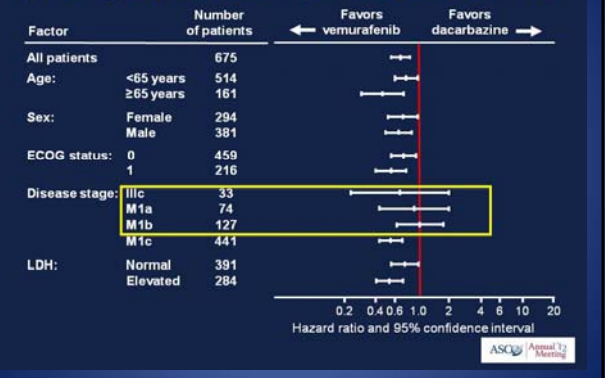
Overall survival by baseline characteristic (February 01, 2012 cut-off) censored at crossover



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BRIM 3: Key Points/Comments (2)

- Median OS in BRIM3 (13.6 months) < BRIM2 (16 mos)
  - Did Phase III patients have more aggressive disease?
  - Was there less continuation of vemurafenib after PD on BRIM3?
- Forrest Plot suggests no benefit for stage IIIC, M1a and M1b populations relative to DTIC
  - Could this be related to disproportiate ipilimumab use? Efficacy?
  - Does this suggest that these patients might be better served by receiving immune therapy first?

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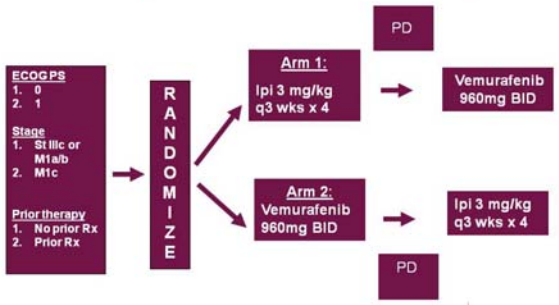
E1612: Ipi to Vem vs Vem to Ipi



ECOG and SWOG protocol – Atkins, Chmielowski
Tumor measurements q12 wks

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BREAK-MB: Key Points/Comments (1)

- Dabrafenib is active and safe in patients with $BRAF^{V600E/K}$ melanoma and brain metastases (previously untreated or treated)
  - Intracranial disease control in > 80% and median OS > 31 wks
  - Less active for patients with $BRAF^{V600K}$ mutations, but perhaps more active than expected
- Progression in EC sites as likely as IC (Azer et al Abs # 8558)
- Based on this data, there is no reason to preclude dabrafenib use in patients with $BRAF^{V600E/K}$ melanoma and brain metastases

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BREAK-MB: Key Points/Comments (2)

- The role of local therapy to the CNS is not addressed in this study.
  - Efficacy is clearly sufficient to replace WBRT
  - Role of SRS or surgery also in question
    - Historically important
    - Dabrafenib +/- SRS trial could be considered, particularly in patients with extensive systemic metastases and lack of CNS symptoms

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BRAFi Resistance: Key Points/Comments (1)

- *BRAF*-mutant melanoma escapes BRAF inhibition mainly via re-activation of MAPK pathway signaling
  - Multiple mutations identified in N-RAS and MEK
  - Previous results suggested high frequency of BRAF trunkations
  - Less evidence presented for alternative (MEK-independent) PI3K driven resistance mechanism

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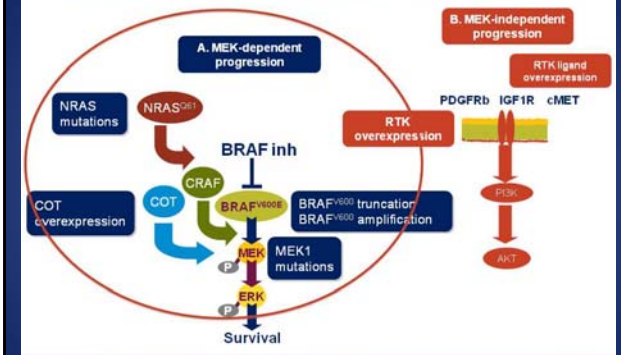
Resistance to BRAF inhibition: Many hypotheses



Nazarian et al. Nature 2010; Johannessen et al. Nature 2010; Poulikakos et al. Nature 2011; Shi et al. Nature Com 2012; Villanueva et al. Cancer Cell 2010; Wagle et al. JCO 2011; Straussman et al. AACR 2012

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BRAFi Resistance: Key Points/Comments (2)

- *NRAS*^{Q61} mutations found in 3/13 patients at resistance
  - More sensitive assays might pick such mutations up at baseline
  - Argues for adding a MEK inhibitor in such patients

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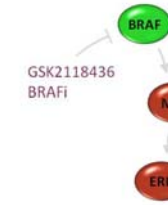
Dabrafenib + trametinib trial data



GSK2118436 BRAFi

GSK1120212 MEKi

- Squamous cell carcinoma < 1%
- Decreased skin toxicity

BRAFi refractory

# of Pts	Complete Response	Partial Response	Stable disease	Disease Control
13	0	2 (15%)	8 (62%)	10 (77%)

BRAFi naïve patients

# of Pts	Complete Response	Partial Response	Stable disease	Disease Control
58	5 (9%)	30 (52%)	20 (34%)	54 (93%)

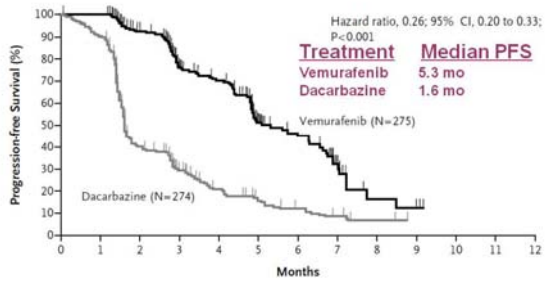
Update by Jeff Weber today
Phase III trials of combined RAFi +MEKi proceeding

Infante et al. ASCO 2011

PRESENTED AT: ASCO Annual '12 Meeting

Presented By Michael B. Atkins, MD at 2012 Annual Meeting

Vemurafenib vs. Dacarbazine (DTIC) – PFS

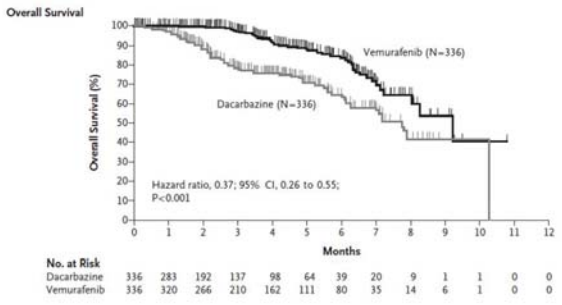


Chapman et al. N Engl J Med 2011; 364:2507-2516

PRESENTED AT: ASCO Annual '12 Meeting

Presented By Patricia LoRusso, DO at 2012 Annual Meeting

Vemurafenib vs. Dacarbazine (DTIC) – OS



Chapman et al. N Engl J Med 2011; 364:2507-2516

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METRIC Phase 3 Study: Efficacy of Trametinib, a potent and selective MEK inhibitor, in progression-free survival and overall survival, compared with chemotherapy in patients with BRAF$^{V600E/K}$ mutant advanced or metastatic melanoma

C. Robert, K.T. Flaherty, P. Hersey, P.D. Nathan, C. Garbe, M.M. Milhem, L.V. Demidov, J.C. Hassel, P. Rutkowski, P. Mohr, R. Dummer, U. Trefzer, J.M.G. Larkin, J. Utikal, M. Casey, L.J. Sherman, W.A. Crist, F.S. Wu, K. Patel, and D. Schadendorf

[1]Institut Gustave Roussy, Villejuif, France; [2]Massachusetts General Hospital, Boston, Massachusetts, USA; [3]Melanoma Institute Australia, University of Sydney, Sydney, New South Wales, Australia; [4]Mount Vernon Cancer Centre, Northwood, Middlesex, UK; [5]University Medical Center, Tuebingen, Germany; [6]Department of Internal Medicine, University of Iowa, Iowa City, Iowa, USA; [7]N.N.Blokhin Russian Cancer Research Center, Moscow, Russia; [8]Department of Dermatology, University Hospital Heidelberg, Heidelberg, Germany; [9]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; [10]Elbekliniken, Buxtehude, Germany; [11]Department of Dermatology, University of Zurich, Zurich, Switzerland; [12]Department of Dermatology, Venerology and Allergy, Charité-Universitätsmedizin Berlin, Germany; [13]Department of Medicine, Royal Marsden Hospital, London, UK; [14]Skin Cancer Unit, German Cancer Research Center, Heidelberg, Germany and Department of Dermatology, Venereology and Allergology, University Medical Center Mannheim, Ruprecht-Karl University of Heidelberg, Mannheim, Germany
[15]GlaxoSmithKline, Oncology, Philadelphia, Pennsylvania, USA; [16]Department of Dermatology, University Hospital Essen, Essen, Germany

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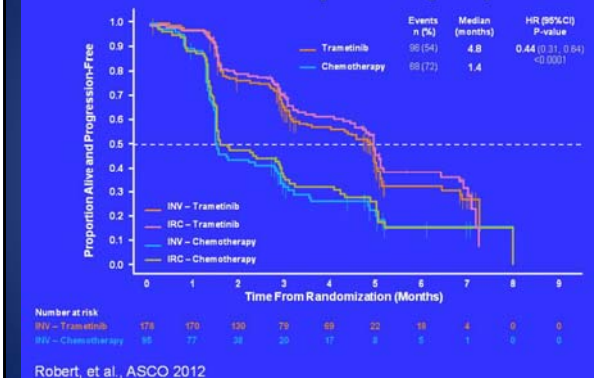
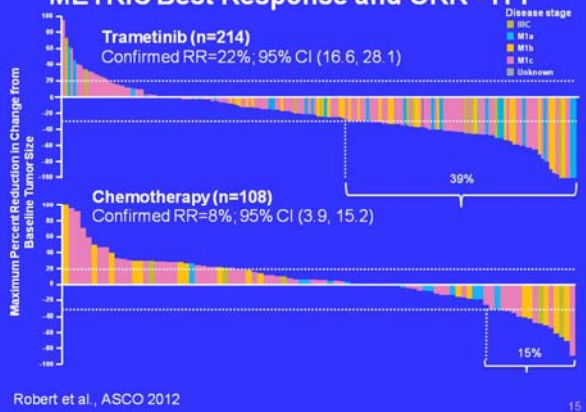
METRIC PFS – Primary Efficacy Population



Robert, et al., ASCO 2012

Presented By Patricia LoRusso, DO at 2012 Annual Meeting

METRIC Best Response and ORR - ITT



Robert et al., ASCO 2012

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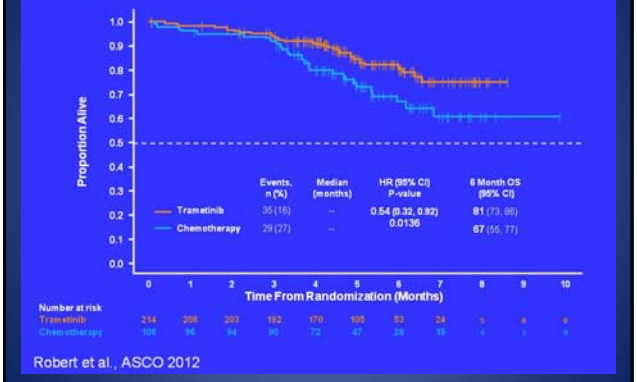
METRIC Overall Survival – ITT



Robert et al., ASCO 2012

Presented By Patricia LoRusso, DO at 2012 Annual Meeting

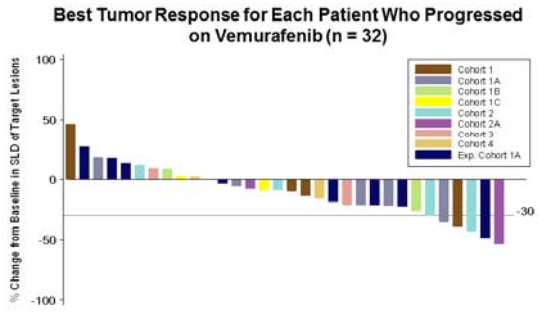
Toxicities Associated With BRAF and MEK Inhibitors

Toxicity, No. (%)*	Monotherapy D (n = 53)	Combination D + T 150/1 (n = 54)	Combination D + T 150/2 (n = 55)
Skin papilloma	8 (15)	4 (7)	2 (4)
Hyperkeratosis	16 (30)	3 (6)	5 (9)
Squamous cell carcinoma/ keratoacanthoma	10 (19)	1 (2) *P* = .004	4 (7) *P* = .09
Acneiform rash	2 (4)	6 (11)	9 (16)
Reduced ejection fraction	0	2 (4)	5 (9)
Chorioretinopathy	0	0	1 (2)

*No cases of retinal vein occlusion were reported.

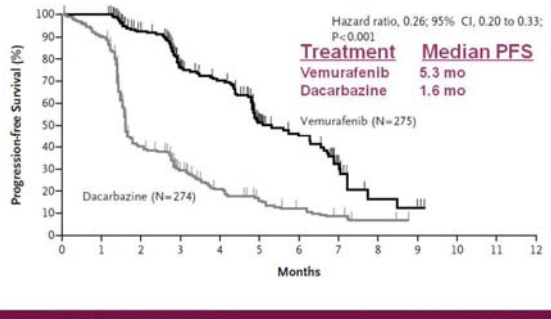
Long GV, et al.[9]

BRIM-7 Trial Results: Vemurafenib + GDC-0973



Gonzalez R, et al.[10]

Vemurafenib vs. Dacarbazine (DTIC) – PFS



Chapman et al. N Engl J Med 2011; 364:2507-2516

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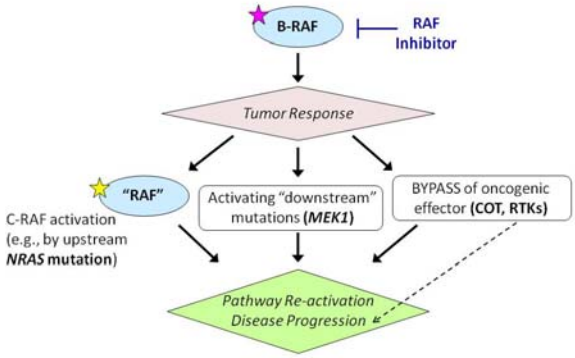
Mechanisms of Resistance to RAF/MEK inhibition in melanoma

- *MEK1* mutations (e.g., *MEK1*$^{P124L/S}$) (MEK inhibition)
  - Emery et al., *PNAS* (2009)
- COT overexpression , C-RAF activation (RAF inhibition)
  - Johannessen et al., *Nature* (2010)
- *NRAS* mutation, PDGFR overexpression (RAF inhibition)
  - Nazarian et al., *Nature* (2010)
- IGF1R overexpression (RAF inhibition)
  - Villanueva et al., *Cancer Cell* (2010)
- *BRAF* amplification (MEK inhibition)
  - Corcoran et al., *Sci. Signal.* (2010)
- *MEK1* mutation (*MEK1*^{C121S}) (RAF inhibition)
  - Wagle et al., *J. Clin. Oncol.* (2011)

Presented By Levi A. Garraway, MD, PhD at 2011 ASCO Annual Meeting

Resistance to RAF Inhibition: Emerging Themes



Presented By Levi A. Garraway, MD, PhD at 2011 ASCO Annual Meeting

Background

- ~50% of melanomas have a *BRAF*^{V600} activating mutation, promoting cell proliferation and opposing apoptosis[1]
- Vemurafenib is a potent inhibitor of mutated BRAF[2]
- Phase I clinical data show favorable response rates with vemurafenib[3]
- No prior systemic therapies for metastatic melanoma have had objective tumor response rates >20% in large multicenter trials[4-6]

[1]Gray-Schopfer V *et al.* Nature 2007;445:851. [2]Bollag *et al.* Nature 2010;467:596. [3]Flaherty *et al.* NEJM 2010;363:809. [4]Chapman *et al.* J Clin Oncol 1999; 17:2745. [5]Middleton *et al.* J Clin Oncol 2000;18:158. [6]Tsao *et al.* N Engl J Med 2004;351:998

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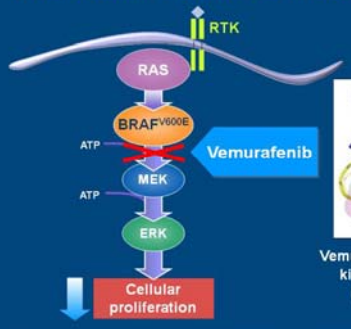
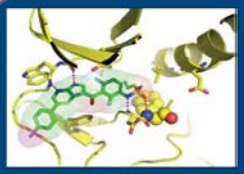
The target: BRAF kinase

An important mediator of cellular proliferation





Vemurafenib co-structure with the kinase domain of BRAF^{V600E} (Bollag *et al.*, Nature 2010)

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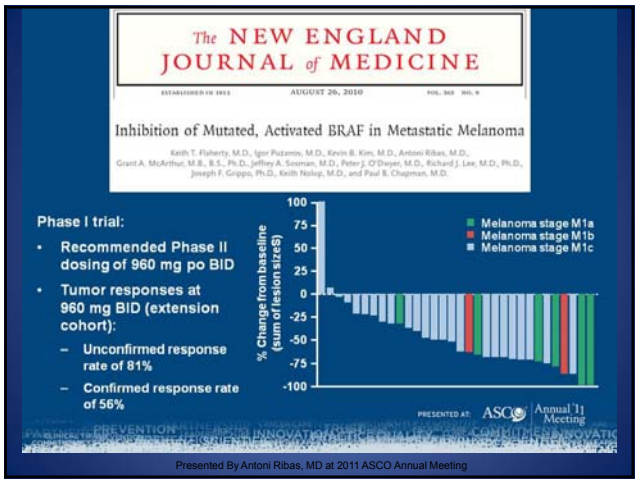

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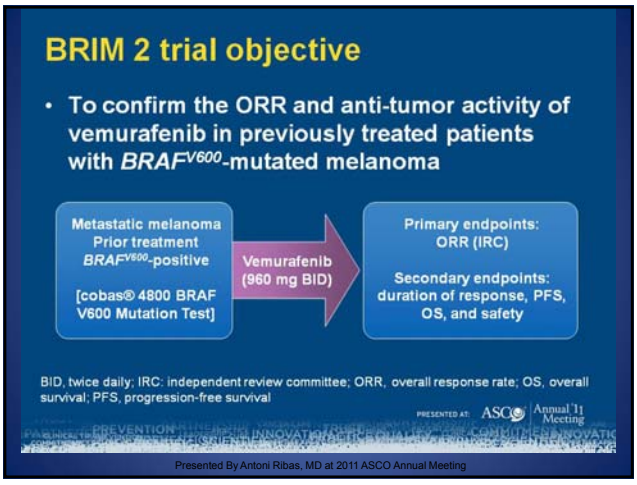

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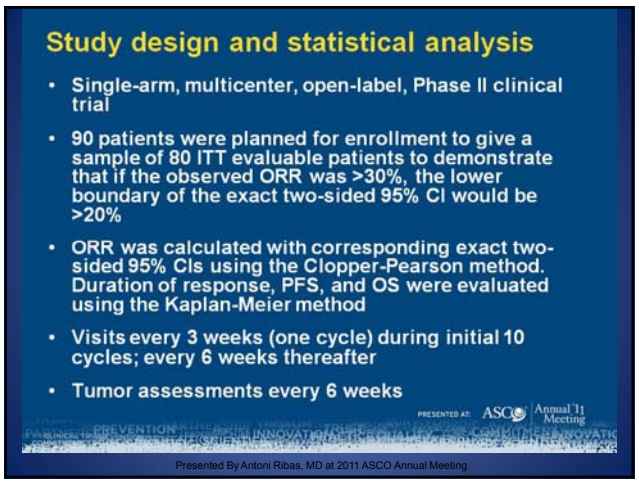

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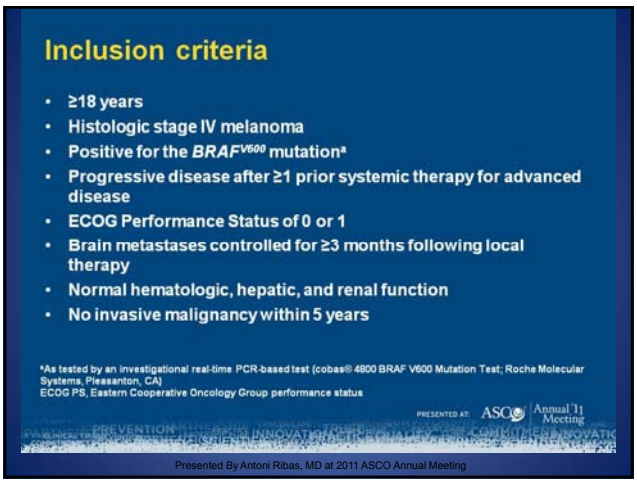

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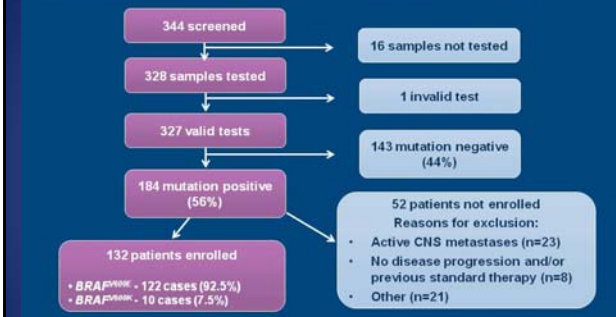
Trial enrollment and *BRAF*^{V600} mutation screening



Additional details about the cobas® 4800 BRAFV600 Mutation Test in Bloom K *et al.*, abstract #10523; Poster Discussion, Sat June 4

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Patient demographics and baseline disease characteristics

n=132

Characteristic	n (%)	Characteristic	n (%)
Sex		Stage at diagnosis	
Female	51 (39)	M1a	33 (25)
Male	81 (61)	M1b	18 (14)
Race		M1c	81 (61)
Caucasian	130 (98)	Serum LDH	
Hispanic	2 (2)	Normal	67 (51)
Age (yr) (median 51.5)		Elevated	65 (49)
<65	107 (81)	No. prior therapies	
≥65	25 (19)	1	67 (51)
ECOG		2	36 (27)
0	61 (46)	≥3	29 (22)
1	71 (54)	Previous ipilimumab or tremelimumab	
Previous IL-2		No	125 (95)
No	81 (61)	Yes	7 (5)
Yes	51 (39)		

IL-2, interleukin-2; LDH, lactate dehydrogenase

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Study Status

- Enrollment: October 2009–March 2010
- 13 centers: 10 USA; 3 Australia
- Data cut-off date: January 31, 2011
- Median follow-up: 10 months (range 0.6 to 14.7)

Treated (n=132)	n (%)
Still on treatment	35 (27)
Discontinued	97 (73)
Disease progression	89
Adverse event	4
Death	1
Consent withdrawal	1
Other	2

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Assessment of Primary Endpoint: Tumor Responses by Independent Review Committee (IRC)

- ORR 53% by IRC
- ORR 57% by investigator assessments (INV)
- RR, including unconfirmed, 69% (INV)
- PR in 4 of 10 *BRAF*^{V600K} patients

Error bars represent 95% confidence intervals

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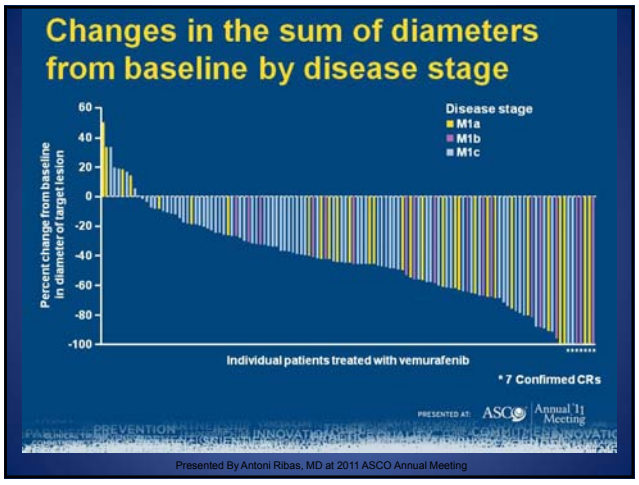
Changes in the sum of diameters from baseline by disease stage
Disease stage
M1a
M1b
M1c
Percent change from baseline in diameter of target lesion
60
40
20
0
-20
-40
-60
-80
-100
Individual patients treated with vemurafenib
* 7 Confirmed CRs
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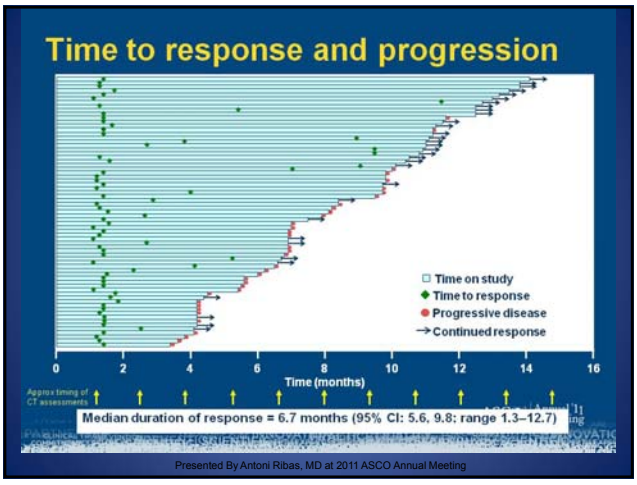
Time to response and progression
Time on study
Time to response
Progressive disease
Continued response
0
2
4
6
8
10
12
14
16
Time (months)
Approx timing of CT assessments
Median duration of response = 6.7 months (95% CI: 5.6, 9.8; range 1.3–12.7)
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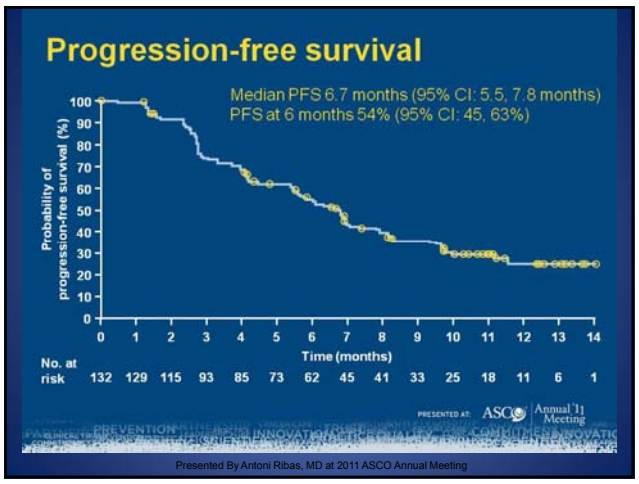
Progression-free survival
Median PFS 6.7 months (95% CI: 5.5, 7.8 months)
PFS at 6 months 54% (95% CI: 45, 63%)
Probability of progression-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Time (months)
No. at risk
132 129 115 93 85 73 62 45 41 33 25 18 11 6 1
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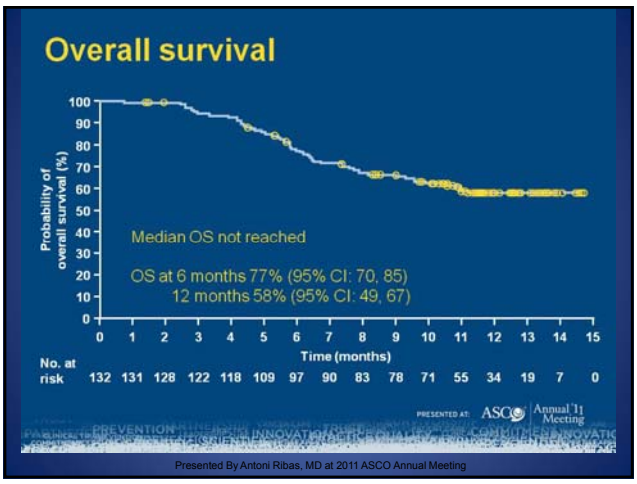
Overall survival
Probability of overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
Median OS not reached
OS at 6 months 77% (95% CI: 70, 85)
12 months 58% (95% CI: 49, 67)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time (months)
No. at risk
132 131 128 122 118 109 97 90 83 78 71 55 34 19 7 0
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Drug-related AEs

Includes AEs reported in ≥20 patients

	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Overall	130 (99)	79 (60)	5 (4)[1]
Arthralgia	78 (59)	8 (6)	–
Rash	69 (52)	9 (7)	–
Photosensitivity reaction	69 (52)	4 (3)	–
Fatigue	56 (42)	2 (2)	–
Alopecia	48 (36)	–	–
Pruritus	38 (29)	3 (2)	–
Skin papilloma	38 (29)	–	–
cuSCC / KA[2]	34 (26)	34 (26)	–
Nausea	30 (23)	2 (2)	–
Elevated liver enzymes	23 (17)	8 (6) [3]	4 (3)[4]

[1]One patient with 2 grade 4 AEs
[2]Cases of cuSCC/KA were generally managed with simple excision and did not generally require dose modification
[3]Managed with dose reduction; one removed from study
[4]Led to discontinuation of therapy

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Dose modifications and AEs leading to drug modifications/interruptions

	n (%)
Patients with dose modifications	59 (45)
Dose reductions – final dose:	
720 mg BID	37
480 mg BID	21
<480 mg BID	1
Patients with dose interruptions	85 (64)
Median average daily dose (%)	1740 mg/day (91)

- Common AEs leading to dose modifications/interruptions were rash, arthralgia, LFT abnormalities (GGT elevation), and photosensitivity
- 4 patients discontinued drug for AEs:
  - Retinal vein occlusion
  - Jaundice, blood bilirubin increased, fatigue, AST, ALT
  - Delirium
  - Cellulitis

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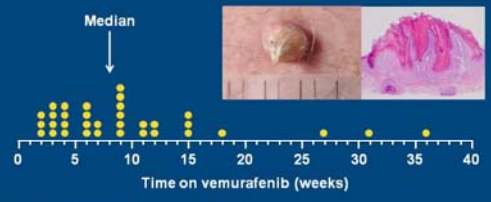
Time to incidence of first cuSCC/KA



- Median time 8 weeks (2–36)
- Median number of cuSCC/KAs per patient 1 (range 1 to 7)
- Each dot represents weeks to development of first cuSCC/KA lesion

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Conclusions

- BRIM 2 met its primary endpoint with an ORR of 53% and a 95% CI that excludes an ORR of 20%
- The toxicity profile at 960 mg BID is manageable, with most AEs being reversible with dose modification or interruption
- The longer follow up of this study complements the benefit in OS of BRIM 3 (LBA#4, Chapman *et al*)
- Together they provide evidence that vemurafenib is an effective agent for treatment of patients with *BRAF*^{V600} mutation-positive melanoma

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Practice Considerations

- What is high-risk melanoma?
- Why treat? What is the objective of therapy?
- What agent should we use?
- What regimen, dose, and schedule?
- Can we personalize therapy to specific patients?

Adjuvant Therapy of Melanoma: History

- Microbial/chemical immunomodulators (BCG, levamisole)
- Chemotherapy, chemobiotherapy, BMT
- Vaccines
  - Whole cell and cell-derived antigen
  - Peptide and protein antigen (T cell)
  - Ganglioside antigen (B cell)
- Passive (antibody) and adoptive (cellular) transfer
- IFN
- Radiation

Adjuvant IFN alfa Regimens: 2012

Schedule	Dose	Frequency	Duration
Low dose			
	3 MIU	3 x wkly	18-24 mos
Intermediate dose			
Induction	10 MIU	5 x wkly	4 wks
Maintenance	10 MIU	3 x wkly	12-24 mos
	5 MIU	3 x wkly	24 mos
High dose			
Induction	20 MIU/m²	5 x wkly	4 wks
Maintenance	10 MIU/m²	3 x wkly	11 mos
Short course			
Induction x 1	20 MIU/m²	5 x wkly	4 wks
Intermittent			
Induction x 3	20 MIU/m²	20 MIU/m²	5 x wkly for 4 wks q4m

Eggermont AMM, et al. Ann Oncol. 2009;20:vi30-vi34. Eggermont AM, et al. Lancet. 2008;372:1189-1196. Agarwala SS, et al. ASCO 2011. Abstract 8505.

LDI alfa for High-Risk Melanoma

Randomized Trial	Stage	N	Dose	Duration	Outcome vs Observation
WHO-16[1]	III	444	3 MU SC TIW	3 yrs	OS, RFS (*P* = NS)
UKCCCR[2]	IIB, III	654	3 MU SCTIW	2 yrs	OS, RFS (*P* = NS)
ECOG-1690[3] (HDI vs LDI vs observation)	IIB, III	608	3 MU SC TIW	2 yrs	OS, RFS (*P* = NS)

- Adjuvant treatment with LDI did not improve outcome in trials of patients with high-risk, node-positive melanoma (stage IIb/III)

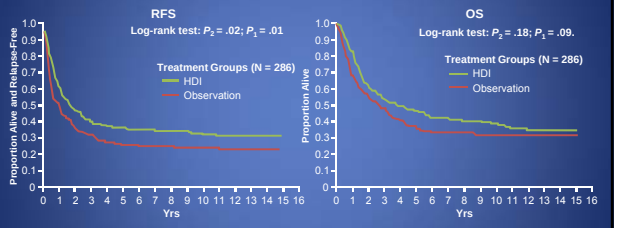
1. Cascinelli N, et al. Lancet. 2001;358:866-869. 2. Hancock BW, et al. ASCO 2001. Abstract 1393. 3. Kirkwood JM, et al. ASCO 2001. Abstract 1395.

HDI alfa-2b Trials for AJCC Stage IIB/III Melanoma

Study	Eligibility	N	Treatment Agent/Dosage/Duration	Effect on RFS	Effect on OS
ECOG 1684[1]	T4, N1	287	IFN alfa-2b 20 MU/m²/d IV x 1 mo 10 MU/m² SC TIW x 11 mos	+ at 6.9-12.6 yrs	+
ECOG 1690[2]	T4, N1	642	IFN alfa-2b 20 MU/m²/d IV x 1 mo 10 MU/m² SC TIW x 11 mos vs 3 MU/day SC TIW x 2 yrs	+ at 4.3-6.6 yrs	–
ECOG 1694[3]	T4, N1	880	IFN alfa-2b 20 MU/m²/d IV x 1 mo 10 MU/m² SC TIW x 11 mos vs GMK vaccine x 96 wks	+ at 1.3-2.1 yrs	+
NCCTG 837052[4]	T3,T4,N1	262	IFN alfa-2a 20 MU/m²/day IM TIW x 3 mos	– at ~7 yrs	–

1. Kirkwood JM, et al. J Clin Oncol. 1996;14:7-17. 2. Kirkwood JM, et al. J Clin Oncol. 2000;18:2444-2458. 3. Kirkwood JM, et al. J Clin Oncol. 2001;19:1430-1436. 4. Creagan ET, et al. J Clin Oncol. 1995;13:2776-2783.

HDI in Stage IIB/III Melanoma (ECOG 1684): Efficacy at 12.6-Yr Follow-up



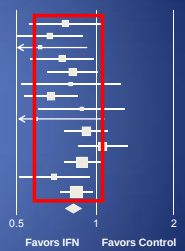
	Total	Dead or Relapsed	Alive or Relapse Free	Median
Observation	140	106	34	1.0
HDI	146	95	51	1.7

	Total	Dead	Alive	Median
Observation	140	95	45	2.7
HDI	146	93	53	3.8

Kirkwood JM, et al. Clin Cancer Res. 2004;10:1670-1677.

Meta-Analysis: Effect of IFN on RFS

Study	HR	LL	UL	SE	N	Events (IFN/ Control)
NCCTG (Creagan, 1995)	0.76	0.56	1.04	0.16	264	77/85
E1684 (Kirkwood, 1996)	0.67	0.50	0.88	0.14	287	90/103
AMCG (Pehamberger, 1998)	0.61	0.40	0.93	0.21	311	37/57
FCGM (Grob, 1998)	0.74	0.56	0.98	0.14	499	100/119
E1690 (Kirkwood, 2000)	0.81	0.65	1.01	0.11	642	236/254
SMG (Cameron, 2001)	0.80	0.52	1.23	0.22	96	32/35
E1694 (Kirkwood, 2001)	0.67	0.53	0.85	0.12	880	98/151
WHO (Cascinelli, 2001)	0.88	0.60	1.28	0.20	444	162/158
E2696 (Kirkwood, 2001)	0.59	0.32	1.07	0.31	107	28/38
UKCCCR (Hancock, 2004)	0.91	0.75	1.10	0.10	674	211/215
EORTC18871 (Kleeberg, 2004)	1.05	0.84	1.31	0.11	484	159/218
EORTC18952 (Eggermont, 2005)	0.88	0.75	1.03	0.08	1388	596/328
DeCOG (Garbe, 2008)	0.69	0.51	0.94	0.16	296	84/102



Adjuvant IFN (various doses and durations) improved RFS in almost every study: 18% increase (P < .001)

Mocellin S, et al. J Natl Cancer Inst. 2010;102:493-501.

HDI Duration: Short (Induction Only) vs Prolonged (PegIFN)

- Hypothesis: much of the benefit of HDI in melanoma may be driven by the 1-mo IV induction phase
- Other trials have suggested that longer duration of treatment with a lower dose may be beneficial
- Therefore, the question of short-duration intensive therapy vs long-duration, less-intensive therapy is being evaluated in clinical trials

Phase III ECOG 1697 Study: HDI alfa-2b Induction vs Observation in T3 Melanoma

Patients with intermediate- and high-risk T3* melanoma
(N = 1150)

Resection

IFN alfa-2b
20 MU/m^2/day for 5 days/wk x 4 wks
(n = 581)

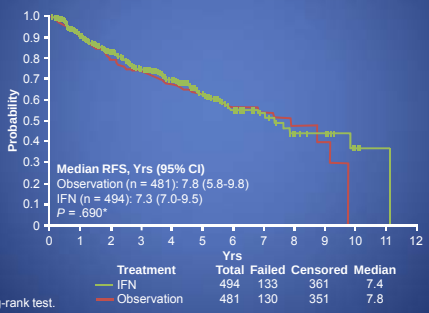
Observation
(n = 569)

*Breslow thickness > 1.5 mm (AJCC 6th ed) or > 2.0 mm (AJCC 7th ed) **or** any thickness with microscopically positive nodal disease (N1a-N2a).

- Primary endpoint: RFS (time to recurrence or death without recurrence)
- Secondary endpoint: OS

Agarwala SS, et al. ASCO 2011; Abstract 8505.

HDI alfa-2b vs Observation in T3 Melanoma (E1697): RFS

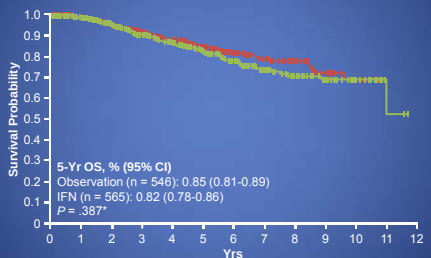


Treatment	Total	Failed	Censored	Median
IFN	494	133	361	7.4
Observation	481	130	351	7.8

*Stratified log-rank test.

Agarwala SS, et al. ASCO 2011; Abstract 8505.

HDI alfa-2b vs Observation in T3 Melanoma (E1697): 5-Yr OS



Treatment	Total	Dead	Alive	Median
IFN	565	86	479	—
Observation	546	70	476	—

*Stratified log-rank test.

Agarwala SS, et al. ASCO 2011; Abstract 8505.

HDI alfa-2b vs Observation in T3 Melanoma (E1697): Conclusions

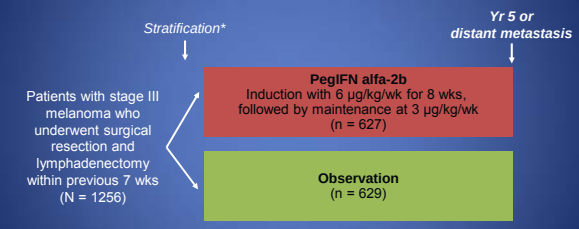
- Adjuvant therapy with the induction phase alone was not sufficient to improve RFS or OS
- The approved 1-yr adjuvant HDI regimen of induction followed by maintenance should not be shortened to 4 wks

PegIFN alfa-2b: Dosing

Schedule	Dose	Frequency	Duration
Induction	6 µg/kg SC	qw	8 wks
Maintenance	3 µg/kg SC	qw	Up to 5 yrs

Eggermont AM, et al. Lancet. 2008;372:117-126.

Phase III EORTC 18991 Study of Adjuvant PegIFN alfa-2b in Stage III Melanoma

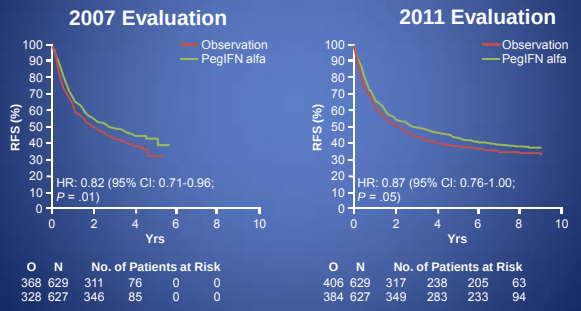


*Patients stratified according to microscopic vs palpable nodal involvement (N1 vs N2), number of nodes (1 vs 2-4 vs 5+), Breslow score, ulceration of primary tumor, sex, and treatment center.

- Primary endpoints: RFS, DFS

Eggermont AM, et al. ASCO 2011. Abstract 8506b.

Phase III EORTC 18991 Study of Adjuvant PegIFN alfa-2b in Stage III Melanoma: RFS

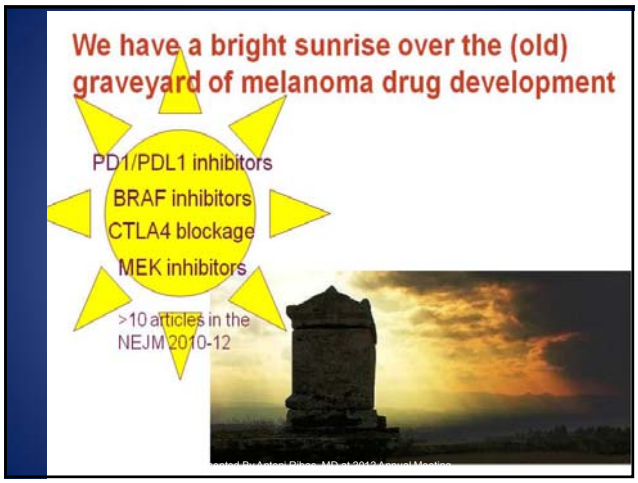


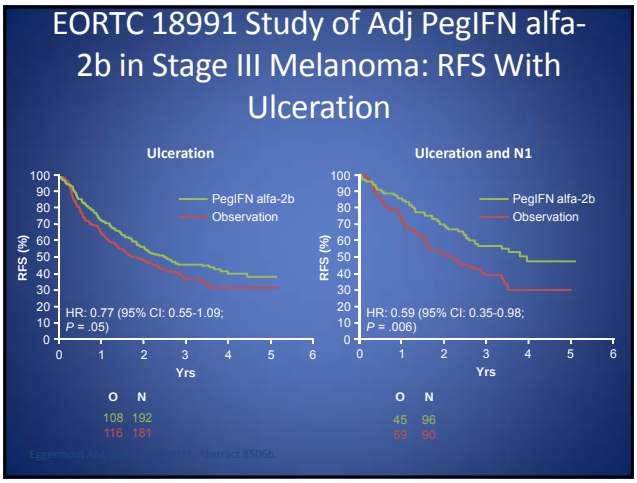
Eggermont AM, et al. ASCO 2011. Abstract 8506b.

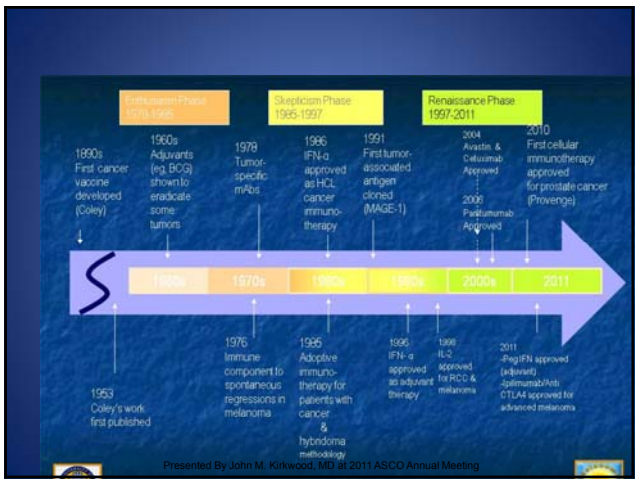
The Effectiveness of HDI Is Not Stage Dependent

Trial/Yr	Eligibility	N	Patients With LN Micromets, n			Subgroup findings
			Total	IFN	Obs Only	
E1684 1996	IIB, III	280	34	2	14	Major impact on patients with clinically evident LN-positive disease
E1690 2000	IIB, III	608	68	18	29	Major impact on patients with LN-positive disease, particularly those with 2-3+ lymph nodes
E1694 2001	IIB, III	774	316	149	166	HDI was of the most benefit for patients with no LN involvement (IIB) (*P* = .01)
M. D. Anderson 2007	III	486	110	42	68	Stage IIIA absolute increase in RFS of 9% (*P* = .09); *P* = .02 after adjustment for multiple variables

Anaya DA, et al. Cancer. 2009;112:2030-2037.


We have a bright sunrise over the (old) graveyard of melanoma drug development
PD1/PDL1 inhibitors
BRAF inhibitors
CTLA4 blockage
MEK inhibitors
>10 articles in the NEJM 2010-12


EORTC 18991 Study of Adj PegIFN alfa-2b in Stage III Melanoma: RFS With Ulceration
Ulceration
Ulceration and N1
PegIFN alfa-2b
Observation
RFS (%)
Yrs
HR: 0.77 (95% CI: 0.55-1.09; P = .05)
HR: 0.59 (95% CI: 0.35-0.98; P = .006)
O N
108 192
116 181
45 96
59 90


Enthusiasm Phase 1979-1995
Skepticism Phase 1985-1997
Renaissance Phase 1997-2011
1890s First cancer vaccine developed (Coley)
1960s Adjuvants (eg, BCG) shown to eradicate some tumors
1976 Immune component to spontaneous regressions in melanoma
1978 Tumor-specific mAbs
1985 Adoptive immunotherapy for patients with cancer & hybridoma methodology
1986 IFN-α approved as HCL cancer immunotherapy
1991 First tumor-associated antigen cloned (MAGE-1)
1995 IFN-α approved as adjuvant therapy
1998 IL-2 approved for RCC & melanoma
2004 Avastin & Cetuximab Approved
2006 Panitumumab Approved
2010 First cellular immunotherapy approved for prostate cancer (Provenge)
2011 -PegIFN approved (adjuvant) -Ipilimumab/Anti CTLA4 approved for advanced melanoma
1953 Coley's work first published
1970s
2000s
2011
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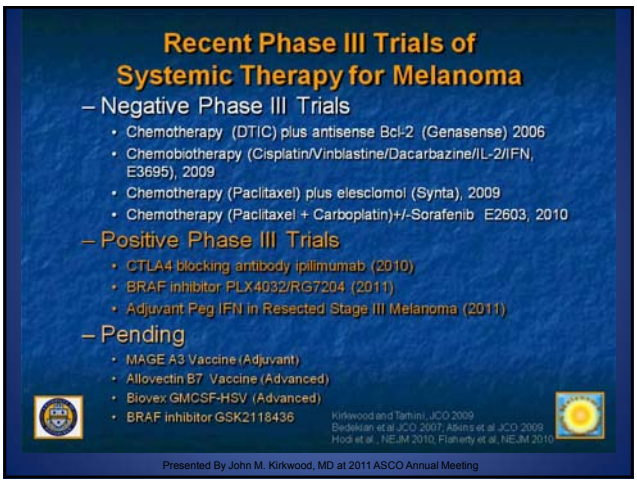

Recent Phase III Trials of Systemic Therapy for Melanoma
– Negative Phase III Trials
• Chemotherapy (DTIC) plus antisense Bcl-2 (Genasense) 2006
• Chemobiotherapy (Cisplatin/Vinblastine/Dacarbazine/IL-2/IFN, E3695), 2009
• Chemotherapy (Paclitaxel) plus elesclomol (Synta), 2009
• Chemotherapy (Paclitaxel + Carboplatin)+/-Sorafenib E2603, 2010
– Positive Phase III Trials
• CTLA4 blocking antibody ipilimumab (2010)
• BRAF inhibitor PLX4032/RG7204 (2011)
• Adjuvant Peg IFN in Resected Stage III Melanoma (2011)
– Pending
• MAGE A3 Vaccine (Adjuvant)
• Allovectin B7 Vaccine (Advanced)
• Biovex GMCSF-HSV (Advanced)
• BRAF inhibitor GSK2118436
Kirkwood and Tarhini, JCO 2009
Bedikian et al, JCO 2007; Atkins et al JCO 2009
Hodi et al., NEJM 2010; Flaherty et al, NEJM 2010
Presented By John M. Kirkwood, MD at 2011 ASCO Annual Meeting

Molecular Therapy of Melanoma

- Therapeutic options dictate evaluation of metastatic melanoma for V600E, K driver mutations in patients with metastatic disease
  - WT tumor patients derive no benefit/may be harmed
- Response duration >6.7 mos median
- Phase III BRIM Trial Closed Feb 2011
  - Survival and progression-free goals met
  - Resistance via pathway reactivation
    - Primary resistance in a minority ~10-15%
    - Acquired resistance through MEK, non-MEK dependent pathways in most patients by 7+mos

Chapman, et al., Proc ASCO 2011

Presented By John M. Kirkwood, MD at 2011 ASCO Annual Meeting

Transformational Results in 2011

- BRAF inhibitors rapidly induce response in a majority of patients with V600E mutant tumors
  - BRAF mutation status is a primary determinant of therapeutic strategy for melanoma after staging, symptom assessment, & performance status (PS)
    - WT tumor patients derive no benefit/may be harmed
  - Targeted BRAF inhibitors will displace initial chemotherapy for systemic therapy of symptomatic patients with stage IV V600E melanoma as approved & available
    - **Opportunity for rational combinations with immunotherapy**

Presented By John M. Kirkwood, MD at 2011 ASCO Annual Meeting

Transformational Results in 2011

- Immunotherapy with anti-CTLA4 blocking mAb improves survival of advanced disease
  - Immunotherapy is a leading consideration for therapy of asymptomatic metastatic disease
  - Anti-CTLA4 blocking antibodies induce durable and probably curative effects in >10% of pts
  - Benefits accompanied by autoimmune toxicities (immune-related adverse events or ir-AE)
  - Biomarkers that predict therapeutic benefit are needed to refine application of therapy

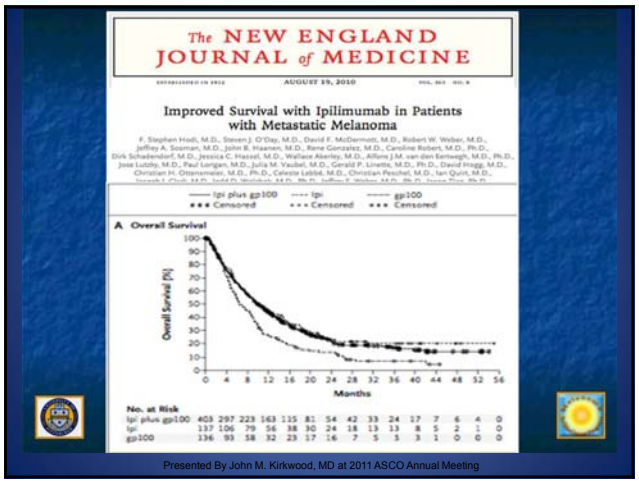
Presented By John M. Kirkwood, MD at 2011 ASCO Annual Meeting

Ipilumumab

- Immunotherapy with anti-CTLA4 blocking mab improves survival of advanced melanoma
  - -Induces durable and possibly curative effects in approximately 10-15% of patients
  - -Benefits accompanied by autoimmune toxicities (ir-AEs)
  - -Biomarkers that predict therapeutic benefit needed to select patients

Montefiore Einstein Center for Cancer Care

EINSTEIN



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Ipilimumab Registration Trials

- **Pivotal Second Line MDX010-20 Trial in HLA-A2 Positive Patients (N=650)**
- **3 arms 3:1:1 ipi/gp100 vaccine, ipi alone, gp100 alone**
- **OS primary endpoint**
- **Positive trial reported 2010 June 3 ASCO**

- **First Line CA184-024 Trial, Randomized Placebo-Controlled trial in combination with DTIC (N=500)**
- **Ipilimumab/DTIC *vs.* Placebo/DTIC**
- **OS primary endpoint**
- **Event driven analysis delayed 2+ years since closure of tremelimumab phase III trial and reported 2011 June 5 at ASCO**

DTIC=dacarbazine; ipi=ipilimumab; OS=overall survival

Hodi et al., NEJM 2010; Wolchok ASCO 2011

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Renaissance for Immunotherapy of Melanoma

- Immunotherapy demonstrates survival and progression-free benefits in the advanced & adjuvant disease settings
  - Ipilimumab joins IL-2 and IFNα as standard therapy of melanoma
    - Autoimmunity is a key to benefit of each
    - Nodal station of progression is critical to adjuvant therapy and under prospective study
    - Role of combinations with vaccines, molecular therapy and chemotherapy require further study
    - PD-1, TIM-3 are further checkpoints of interest for future trials alone and in combination

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Renaissance for Melanoma Therapy & Combinations

- Identification of driver mutations has opened an era of molecular therapy for melanoma based on tumor mutation analysis
  - BRAF (cutaneous and other)
    - Combinations may improve benefits, toxicity
    - Role in brain metastasis (Long et al, Proc ESMO 2010)
  - C-Kit (acral and mucosal)
- Signature of chemotherapy resistance has been identified and drug resistance abrogation is under study (Tawbi et al., 2009)

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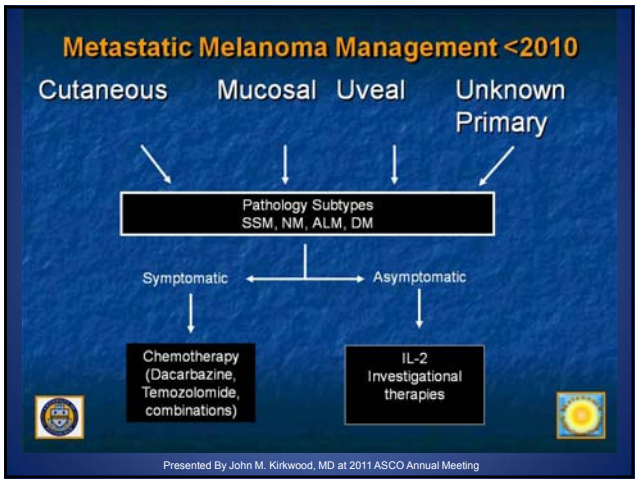
Metastatic Melanoma Management <2010
Cutaneous
Mucosal
Uveal
Unknown Primary
Pathology Subtypes
SSM, NM, ALM, DM
Symptomatic
Asymptomatic
Chemotherapy (Dacarbazine, Temozolomide, combinations)
IL-2 Investigational therapies
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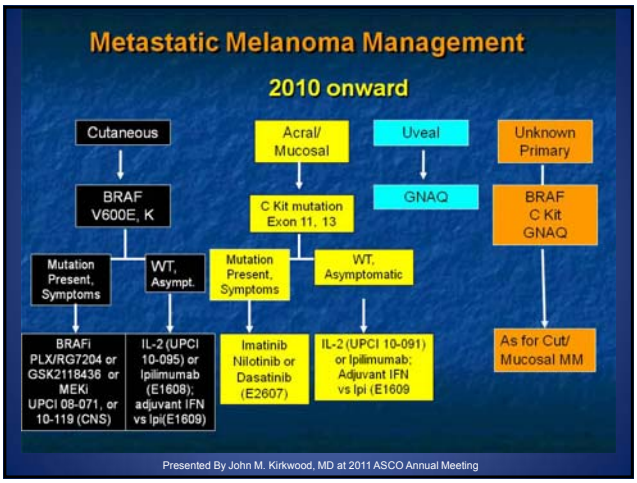
Metastatic Melanoma Management
2010 onward
Cutaneous
Acral/ Mucosal
Uveal
Unknown Primary
BRAF V600E, K
C Kit mutation Exon 11, 13
GNAQ
BRAF C Kit GNAQ
Mutation Present, Symptoms
WT, Asympt.
Mutation Present, Symptoms
WT, Asymptomatic
BRAFi PLX/RG7204 or GSK2118436 or MEKi UPCI 08-071, or 10-119 (CNS)
IL-2 (UPCI 10-095) or Ipilimumab (E1608); adjuvant IFN vs Ipi(E1609)
Imatinib Nilotinib or Dasatinib (E2607)
IL-2 (UPCI 10-091) or Ipilimumab; Adjuvant IFN vs Ipi (E1609
As for Cut/ Mucosal MM
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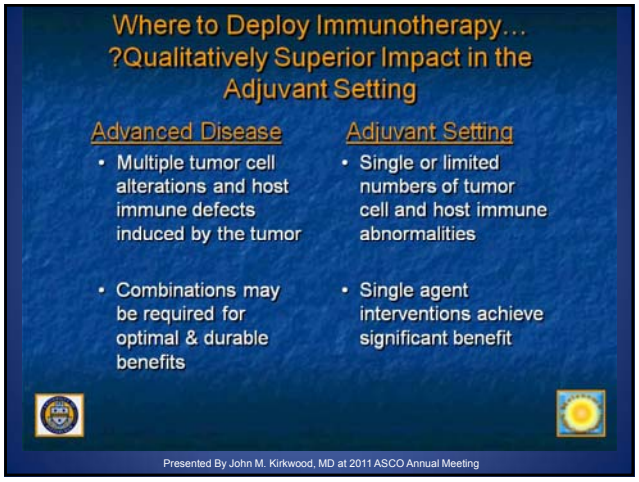
Where to Deploy Immunotherapy…
?Qualitatively Superior Impact in the Adjuvant Setting
Advanced Disease
• Multiple tumor cell alterations and host immune defects induced by the tumor
• Combinations may be required for optimal & durable benefits
Adjuvant Setting
• Single or limited numbers of tumor cell and host immune abnormalities
• Single agent interventions achieve significant benefit
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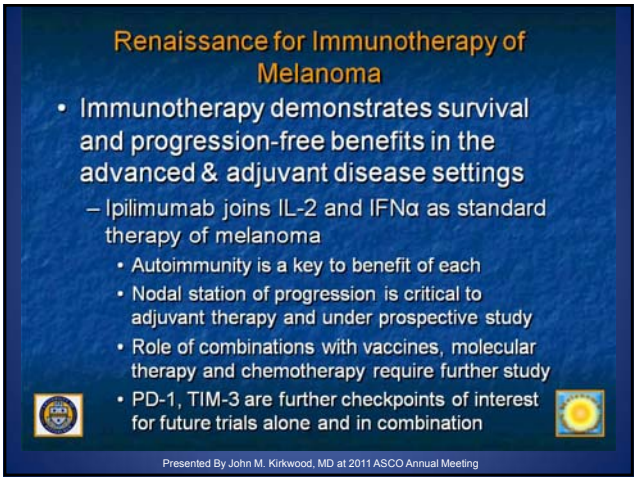
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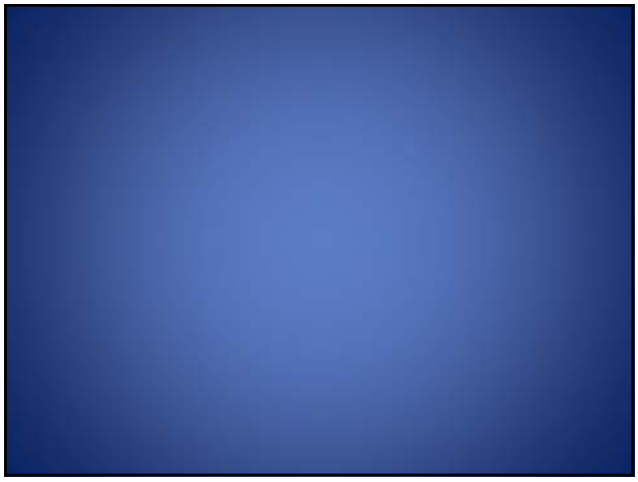
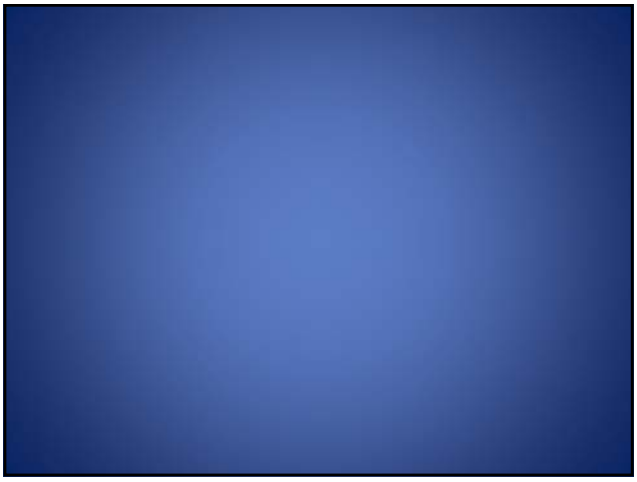




Differences between blocking CTLA4/B7 and blocking PD-1/PD-L1

	CTLA4	PD-1
Receptor T cell expression	~48 h after antigen exposure	Upon chronic antigen exposure
Ligand expression	CD80 (B7.1)/CD80 (B7.2) by APCs	PD-L1 (B7-H1) by tumors and inflamed tissues PD-L2 (B7-DC) by APCs
Knock out mouse phenotype	Early death from autoimmunity	Late onset autoimmunity
Prediction upon blockade	Less specific for antitumor T cells	More specific for antitumor T cells

PRESENTED BY: ANTONI RIBAS, MD PRESENTED AT: ASCO Annual '12 Meeting

Presented By Antoni Ribas, MD at 2012 Annual Meeting

Conclusions

- Expanded access programs should be open when an agent has demonstrated unquestionable patient benefit
- Ipilimumab should continue to be administered at 3 mg/kg x 4 doses
  - Awaiting 3 vs 10 mg/kg randomized trial
- PD-1/PD-L1 inhibitors are likely the most impacting new agents in metastatic melanoma (and possibly other cancers)

PRESENTED BY: ANTONI RIBAS, MD PRESENTED AT: ASCO Annual '12 Meeting

Presented By Antoni Ribas, MD at 2012 Annual Meeting

[TITLE]

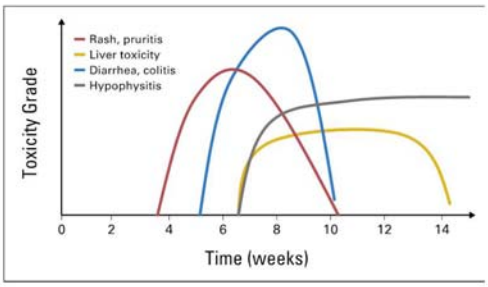
Ipilimumab Treatment and irAEs: Basic issues

- Most irAEs occur during the first 12 weeks of therapy, i.e. during induction
- Steroids can be used to manage almost all irAEs
- Prolonged steroid tapers can be required
- irAEs can wax and wane, particularly colitis
- Late irAEs can occur: one episode has been seen at month 47 during maintenance
- Each irAE has different kinetics of onset:
  - Skin first, then colitis, then hypophysitis and finally hepatitis

Attia. *J Clin Oncol*. 2005;23:6043; Downey. *Clin Cancer Res*. 2007;13:6681; Lutzky. ASCO 2009 (abstr 9034); van Elsas. *J Exp Med*. 1999;190:355; Weber. *J Clin Oncol*. 2008;26:5950

Presented By Jeffrey S. Weber, MD, PhD at 2012 Annual Meeting

Kinetics of induction of irAEs with ipilimumab



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irAE Management

- Patient education for early recognition of irAEs
- Aggressive work-up and management for moderate/severe events
- Nonspecific complaints may reflect endocrine (eg, pituitary) toxicity
- Established therapies (eg, corticosteroids) are effective
- Algorithms established for work-up, treatment, and reporting of irAEs

Beck et al. *J Clin Oncol*. 2006;24:2283.

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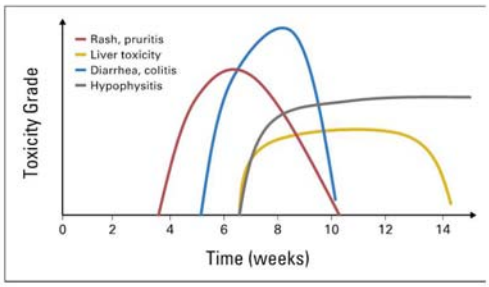

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