

Prognostic Factors for Patients with Stage IV Melanoma

Michael B. Atkins, M.D.
Beth Israel Deaconess Medical Center
Harvard Skin Cancer SPORE

Financial Disclosure

- ◆ Genentech – Advisory Board
- ◆ Prometheus - Advisory Board
- ◆ Merck - Advisory Board
- ◆ BMS - Advisory Board

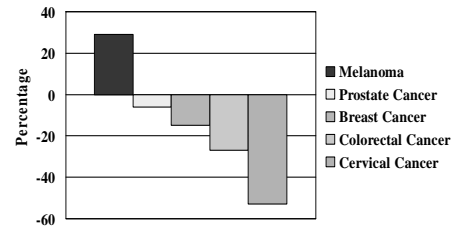
Melanoma : Epidemiology 2011

Incidence: >60,000 / 8100 deaths
3% of all cancers
1% of all cancer deaths
12 fold increase since 1935

Lifetime risk: 1 in 75 Americans
1 in 25 Australians

9th most common malignancy, but 2nd in terms of years of potential life lost

Changes in Overall Cancer Mortality (1975-2003), United States

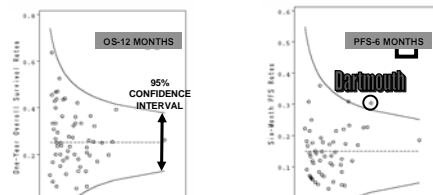


US SEER Cancer Registry, 2003

Advanced Melanoma Prior to 2010: A Bad Disease

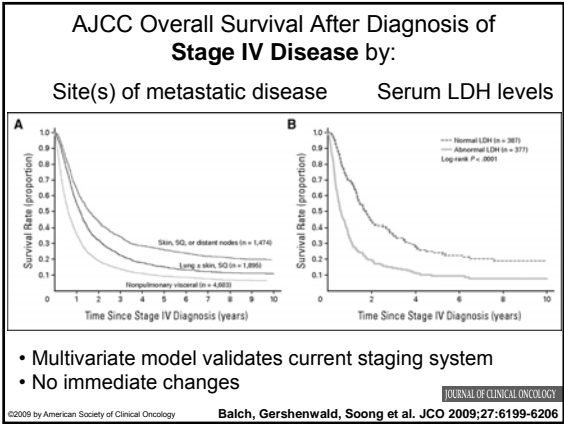
- ◆ Mortality:
 - Increasing compared to other cancers
 - Median survival remains 6-9 months in most studies
- ◆ Therapies: few effective medical options
 - Treatments had either limited (IFN) or no effect on overall survival (DTIC, IL-2)
 - Significant toxicity (HD IL-2)
 - Number of positive Phase III trials = 0

Statistical Consistency of Endpoints Across Trials



With 70 phase II evaluations of INACTIVE agents, we would expect at least 3 "positive" trials by chance alone

Korn et al. *J Clin Oncol* 2008;26:527-534

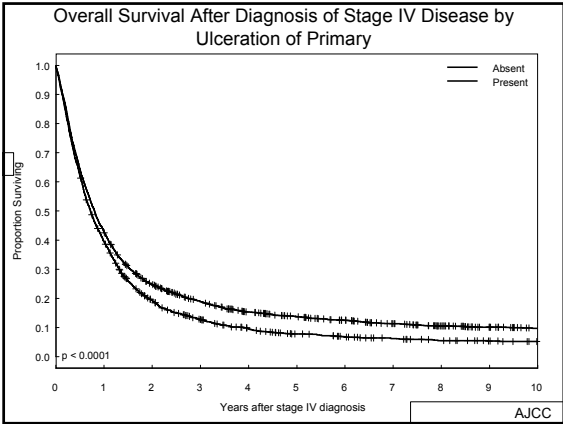
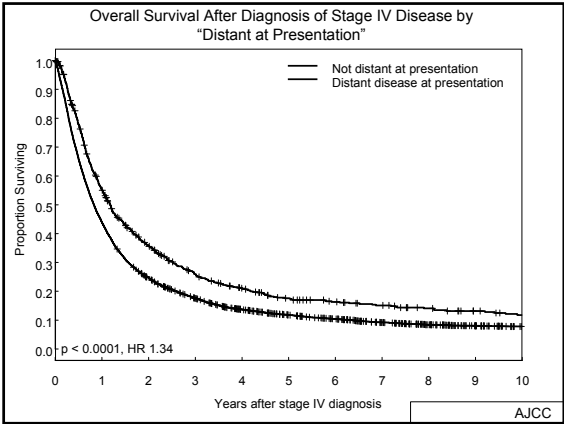
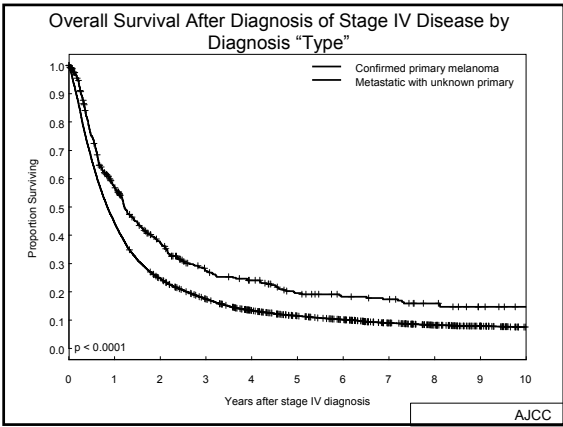
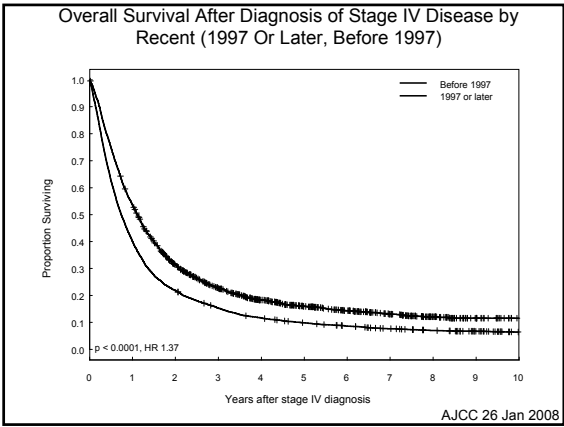


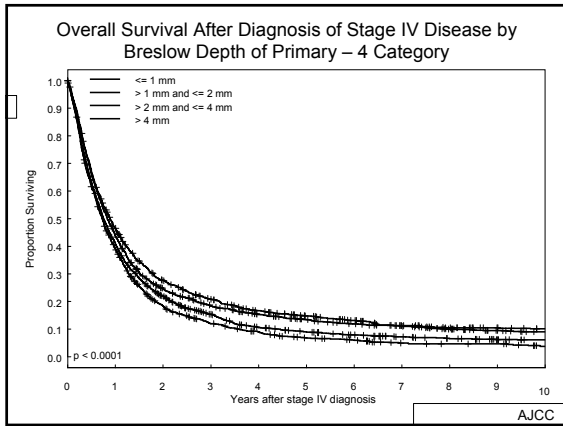
Staging Factors: AJCC Update

Serum LDH appears to be the most important factor

- Median OS and % alive at 1 yr is double for pts with normal LDH relative to elevated LDH
- Differences at 1 year are minimally influenced by sites of disease

Gershenwald, Kirkwood, Flaherty





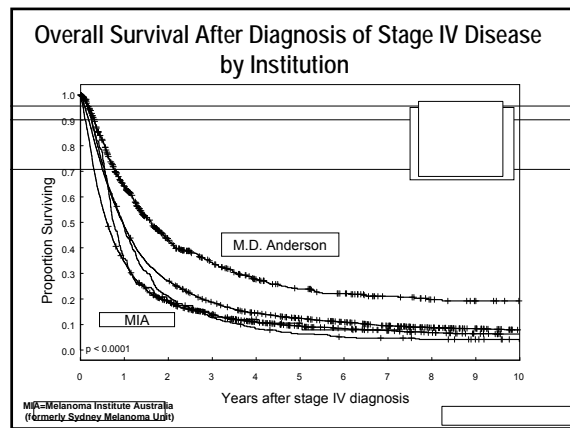
Breslow Depth Among Patients with Known Primary Melanoma Histology

BRESLOW (mm)	Frequency	Percent	Cumulative Percent
0 - 0.5	284	4.32	4.32
> 0.5 - 1	996	15.15	19.46
> 1 - 2	1817	27.63	47.10
> 2 - 3	1321	20.09	67.18
> 3 - 4	793	12.06	79.24
> 4 - 5	485	7.38	86.62
> 5 - 6	244	3.71	90.33
> 6	636	9.67	100.00

J. Gershenwald

AJCC 26 Jan 2008

- ### Covariates in Multivariate Cox Models
- M category (anatomic site only)
 - LDH at stage IV diagnosis
 - Year of stage IV diagnosis (“AJCC edition”)
 - Age at stage IV diagnosis
 - Gender
 - Primary site (cutaneous, mucosal, unknown)
 - Number of recurrent sites (organ)
 - Disease-free interval (primary to stage IV)
 - Institution
- J. Gershenwald
- AJCC



- ### Key Questions
- Why is MD Anderson Stage IV patient outcome better than for MIA?
 - Do these differences represent institution- or country-specific effects?

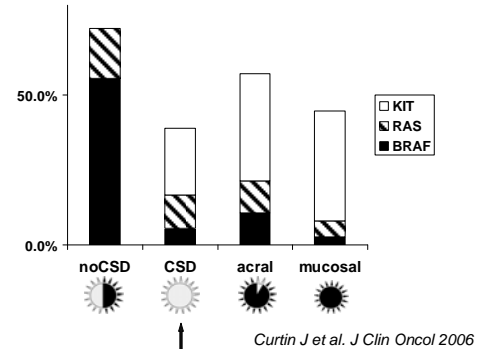


University of Sydney Visiting Professorship: Potential Hypotheses

Differences are related to-

- **Lead time bias**
 - Differences in time frames
 - Extent of disease at Stage IV diagnosis
 - Imbalance in prognostic features at Stage IV diagnosis
 - Intensity of follow-up prior to Stage IV diagnosis
- **Therapeutic approaches**
- **Cancer biology**

Oz vs US - Potential Biology Differences



OZ vs US- Potential Biology Differences

- ◆ Australia melanoma more likely in chronic sun damaged skin
- ◆ Distribution of CSD skin is more widespread
- ◆ Is this reflected in differences in melanoma molecular biology?
- ◆ Can differences in molecular basis of melanoma influence outcome?

Bastian AACR
Work with Richard Scolyers at MIA

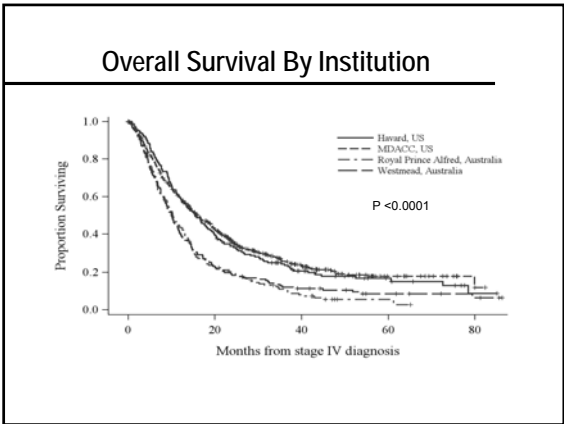
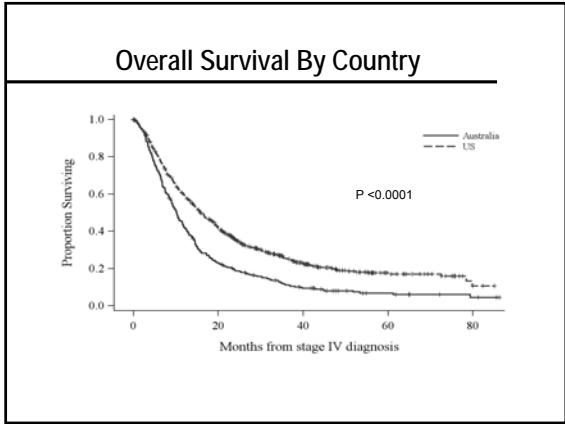
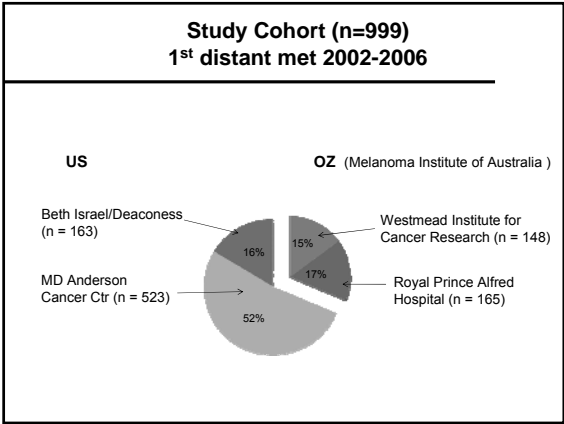
Methods: PHAMOUS Study

- Patients diagnosed with 1st distant metastasis 1/02-12/06
 - LDH incorporated into AJCC staging in 2002
 - Minimum 3 year follow-up
 - Modern imaging and current therapies
- Study cohort
 - Australia – 2 centers (from MIA database)
 - Westmead Institute for Cancer Research
 - Royal Prince Alfred Hospital
 - USA – 2 centers (from institutional databases)
 - M. D. Anderson Cancer Center
 - Beth Israel/Deaconess Medical Center
- Create and populate an expanded AJCC database for each patient – (institutional databases and chart reviews)
- Compare outcomes between centers and countries controlled for known prognostic factors and treatment

Data Elements added to 7th Edition AJCC Database Dictionary

- Performance Status @ time of Stage IV dx
 - LDH @ time of Stage IV dx
 - Number of distant metastatic sites
 - Type of surveillance to detect distant mets
 - Development/Treatment of CNS mets
 - F/up frequency prior to Stage IV dx
 - Adjuvant therapy
 - Treatment of distant metastatic disease
 - Surgery (Intent)
 - Chemotherapy
 - Immunotherapy
 - Patients with multiple primary melanomas
- } **Not well covered in AJCC Database**
} Focus of this analysis

Step 1: Confirm survival differences exist
in a confined time frame



Explore Hypotheses-Step 2

Differences are related to-

- Lead time bias
 - Differences in time frames
 - Extent of disease at Stage IV diagnosis
 - Imbalance in prognostic features at Stage IV diagnosis
 - Intensity of follow-up prior to Stage IV diagnosis
- Therapeutic approaches
- Cancer biology

Clinicopathologic Factors: Some favor US vs OZ

Variable	US	OZ	P value
N (evaluable)	686	313	N/A
Gender (% male)	64.2	69.7	0.104
Age: Median (Range)	54.8 (12-92)	56.2 (17-84)	0.271
ECOG PS*: 0 (%)	53.4	59.9	
> 0 (%)	46.6	40.1	0.071
Site of Distant Disease: (%)			
Soft tissue M1a	13.6	9.9	0.0004
Lung M1b	33.1	23.6	
Other visceral M1c*	53.3	66.5	
Serum LDH*: Normal (%)	64.2	52.9	0.0055
Elevated (%)	35.8	47.1	
# of Metastatic Sites: 1 (%)	25.2	34.1	0.012
>1 (%)	74.8	65.9	
Disease-free Interval (mos) median (range)	23.5 (0-442)	29.5 (0-400)	0.043

*excludes high LDH only 10 (11%) missing ECOG PS; 286 (28%) missing LDH

Overall Survival - Univariate analysis

	US	OZ	P value
OS - months (95% CI)	15.9 (14.4-18.0)	10.2 (9.0-11.6)	<0.0001

Multivariate Analysis

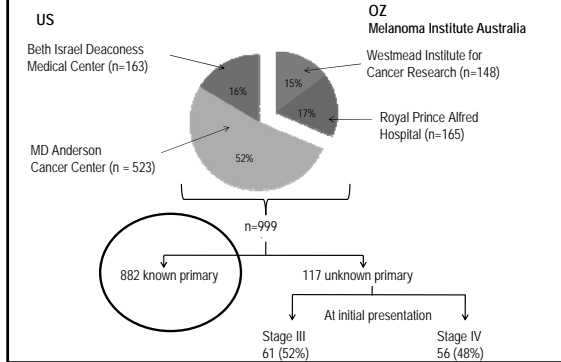
Parameter	Chi-Square	P>Chi-sq	Hazard Ratio	95% Confidence Limits	
Oz (vs US)	34.9	<0.0001	1.57	1.34	1.82
M1b (vs M1a)	3.5	0.061	1.27	0.99	1.64
M1c (vs M1a)	24.5	<0.0001	1.86	1.44	2.33
# of met sites >1 (vs 1)	18.2	<0.0001	1.44	1.22	1.70
LDH high (vs LDH lo)	26.8	<0.0001	1.55	1.31	1.83
LDH unkn (vs LDH lo)	6.2	0.013	1.25	1.05	1.49
ECOG > 0 (vs ECOG 0)	28.8	<0.0001	1.51	1.30	1.75
ECOG Unkn (vs ECOG 0)	3.4	0.063	0.79	0.60	1.02

Explore Hypotheses-Step 2

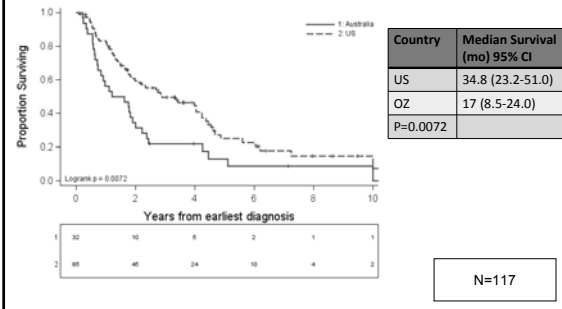
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Study Cohort - 1st Distant Metastasis 2002-2006



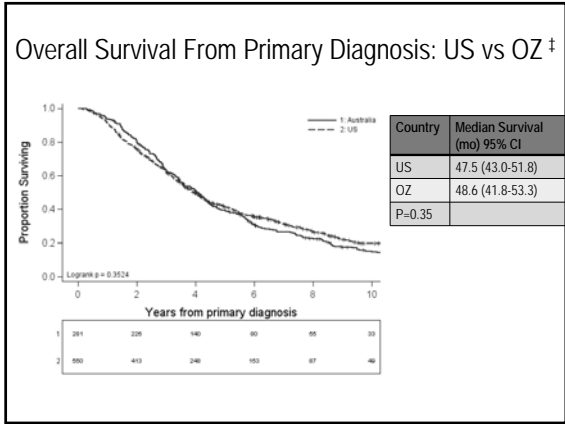
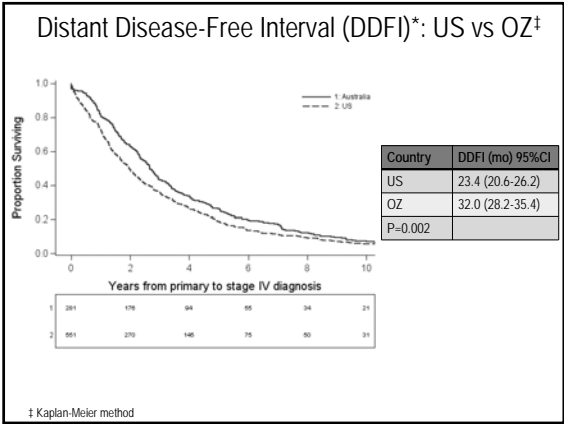
Overall Survival for Unknown Primary Melanoma: US vs OZ †



Results for Patients with Known Primary Melanoma-N=882

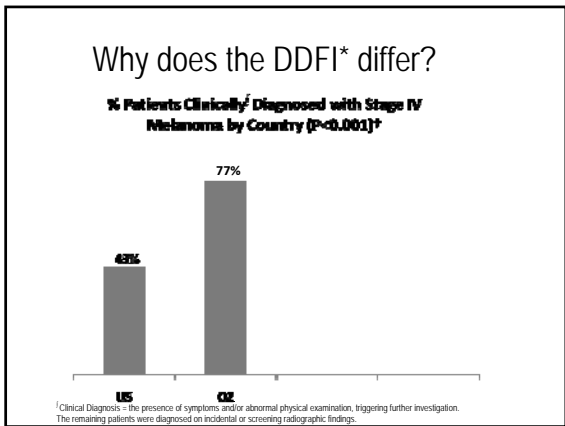
Clinicopathological Features of Stage IV Melanoma; US vs OZ †

Parameter at Stage IV diagnosis	US	OZ	P
Sex	Male 376 (63%)	198 (70%)	0.0230
	Female 225 (37%)	83 (30%)	
Age: Median, range (years)	59 (13-92)	59 (17-85)	0.2443
M Stage	M1a 83 (14%)	27 (10%)	0.0019
	M1b 194 (32%)	67 (24%)	
	M1c 324 (54%)	187 (66%)	
Number of Sites of Metastases	1 335 (56%)	84 (30%)	<0.0001
	>1 266 (44%)	197 (70%)	
ECOG	0 292 (53%)	146 (59%)	0.1422
	>0 254 (47%)	100 (41%)	
LDH	Normal 302 (66%)	102 (55%)	0.0150
	Elevated 158 (34%)	83 (45%)	
DDFI* Median, range (months)	23.5 (0-44.3)	32.0 (0-400.3)	<0.0001



Why does the DDFI* differ?

		US	OZ	
Clinical Diagnosis of Stage IV Melanoma	Yes	252 (43%)	205 (77%)	P<0.0001
	No	339 (57%)	61 (23%)	



Multivariate Analysis of OS from Diagnosis of Primary Melanoma (342 deaths/411 total)[‡] (Preliminary)

Parameter		HR	95% CI	P
Country	OZ	1.15	0.91-1.46	0.232
	US	1.00		
Age at Primary Melanoma (# years)		1.01	1.00-1.02	0.010
Sex	Male	1.15	0.92-1.45	0.223
	Female	1.00		
Breslow Thickness (# mm)		1.04	1.02-1.07	0.002
Mitoses (# /mm ²)		1.02	1.01-1.04	0.012
Ulceration	Present	0.93	0.73-1.19	0.572
	Absent	1.00		
Regional Lymph Node	Microscopic	1.23	0.95-1.59	0.120
	Macroscopic	0.91	0.58-1.43	
	Regional Unspecified	0.72	0.30-1.75	
	None	1.00		
Number of Lymph Nodes (#)		1.12	1.06-1.16	<0.0001
Satellites or Intransit Metastases	Yes	1.56	1.03-2.38	0.038
	No	1.00		

- ### PHAMOUS STUDY: Conclusions
- In patients with stage IV melanoma and an unknown primary;
- Overall survival is longer in the US compared with OZ from first melanoma
 - Differences in tumour biology or treatment may explain this difference, and are currently being explored; however, this group is small and heterogeneous.
- In patients with stage IV melanoma and a known primary melanoma:
- There appears to be no difference in overall survival between US and OZ from diagnosis of primary melanoma.
 - A clinical diagnosis of stage IV melanoma is more common in OZ, with a corresponding longer DFI compared with US
 - It is likely "lead-time bias" significantly contributes to the survival difference observed between OZ and US from diagnosis of stage IV melanoma.

Acknowledgments

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Reflections on Current Staging and Statistics

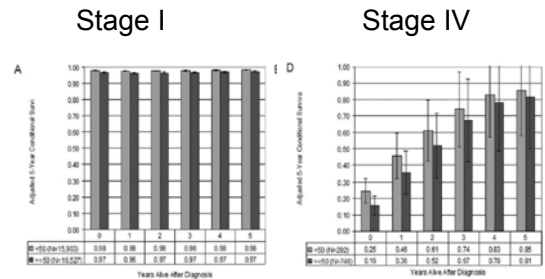
- ◆ Despite tremendous strides **limitations exist in traditional melanoma staging systems**
 - Estimates of survival based only on time of diagnosis
 - Lead time bias can dwarf prognostic characteristics
 - TNM staging applies to large cohorts of patients – not truly individualized
 - Systems do not take into account biologic/molecular features of the tumor
 - Systemic do not consider the impact of therapy

J. Gershenwald

Potential Staging Advances

- ◆ Conditional survival endpoints
- ◆ Country specific adjustments (standardized f/up patterns)
- ◆ Individual Melanoma Outcome prediction tools
- ◆ Incorporation of molecular and biologic variables- predictive biomarkers
 - Immune infiltrates
 - BRAF mutational status
 - VEGF/LDH levels

Conditional Stage-Specific and Melanoma Specific Survival



Xing et al., Cancer 2010

ajcc
Individualized Melanoma Patient Outcome Prediction Tools
Developed based on the American Joint Committee on Cancer Melanoma Database

By Seng-jaw Soong PhD, Shouluan Ding PhD, Daniel C. Cote MD, Charles M. Balch MD, Jeffrey Gershenwald MD, John F. Thompson MD and the American Joint Committee on Cancer, Melanoma Task Force

III. Use of Melanoma Prediction Tools: If you would like to use these tools, please click to proceed.

Options:
 Predicting Individual Melanoma Patient's Survival Outcome From Initial Diagnosis.

www.melanomaprognosis.org

Soong et al., Ann Surg Oncol, 2010

ajcc
Individualized Melanoma Patient Outcome Prediction Tools
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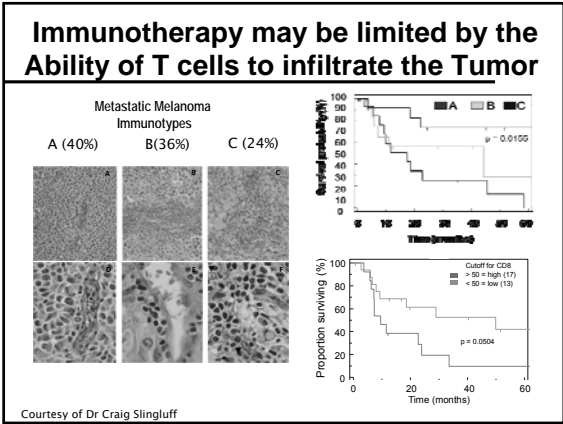
By Seng-jaw Soong PhD, Shouluan Ding PhD, Daniel C. Cote MD, Charles M. Balch MD, Jeffrey Gershenwald MD, John F. Thompson MD and the American Joint Committee on Cancer, Melanoma Task Force

Estimated Survival Rates (95% Confidence Interval)

1-Year	2-Year	5-Year	10-Year
67.3%	57%	31.3%	10.8%
(57.5% - 78.7%)	(46.1% - 70.3%)	(21.3% - 45.8%)	(4.4% - 26.1%)

Soong et al., Ann Surg Oncol, 2010

Incorporation of Biomarkers Into Staging

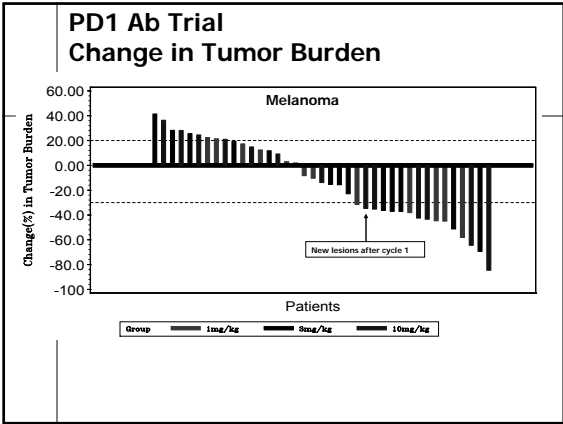
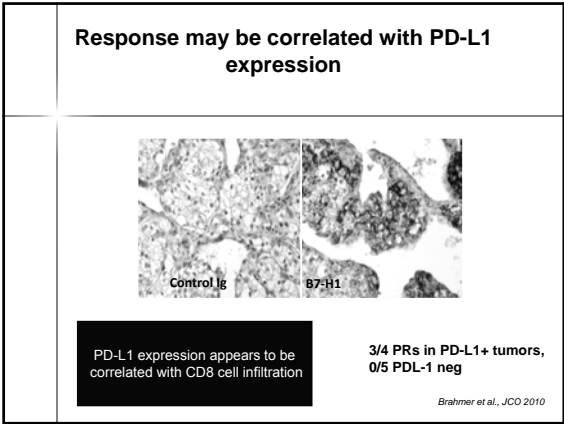
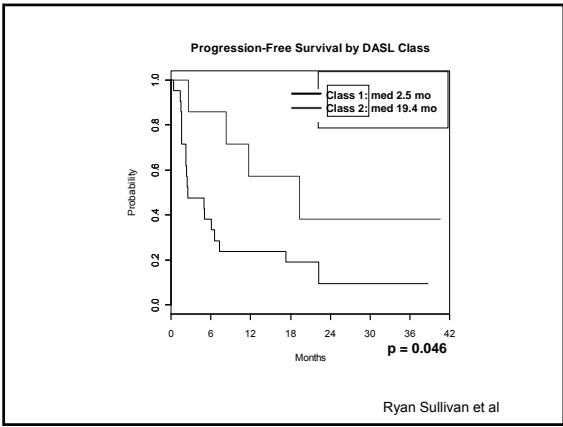


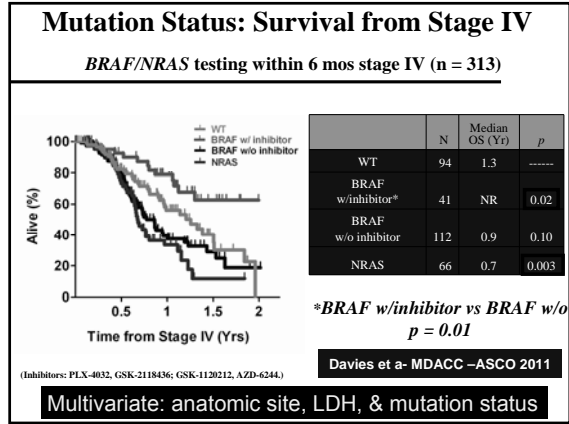
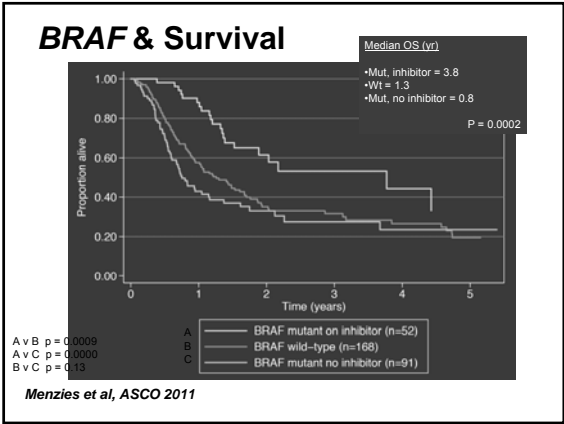
HD IL-2 Selection: Efficacy Data

- **Class 2**
 - Better PFS
 - $p = 0.046$
 - Better RR
 - $p = 0.0384$
 - 1-sided FET
 - OS similar
 - $p = 0.19$

	DASL Class 1: Antigenic (n=21)	DASL Class 2 Immune (n=7)
Response (%)		
Complete	2 (10%)	2 (29%)
Partial	6 (28%)	4 (57%)
Total	8 (38%)	6 (86%)
Durable (>18 mo)	3* (14%)	3* (43%)
Survival (mo)		
Median OS	22.8	27.0
Median PFS	2.5	19.4

Ryan Sullivan et al



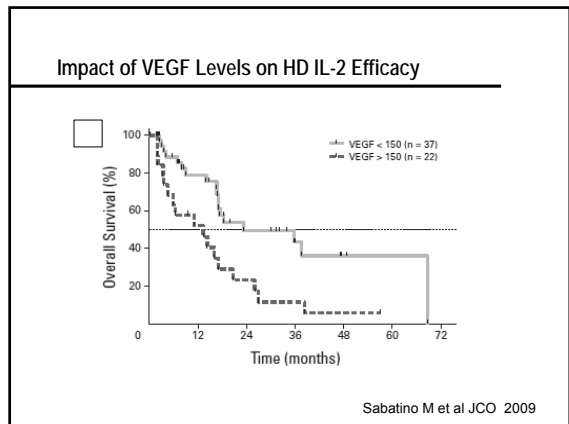
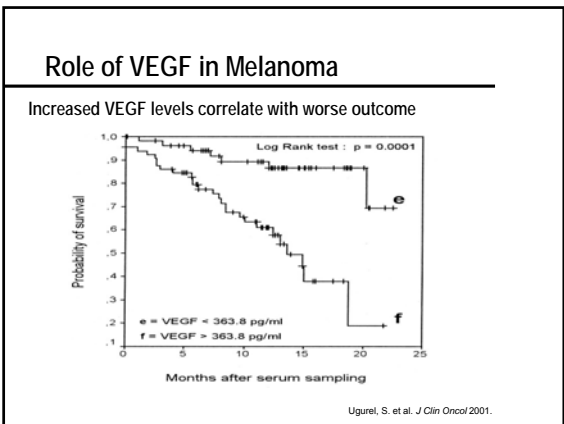
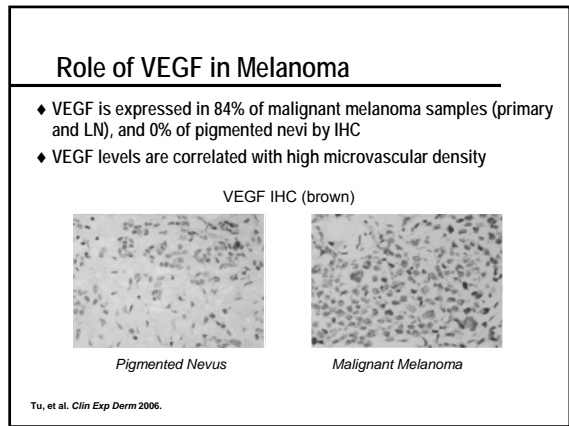


Relationship of MAPKinase Pathway mutations and response to HD IL-2

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. More data is needed.

ph, Sullivan et al- JIT 2011 (in p



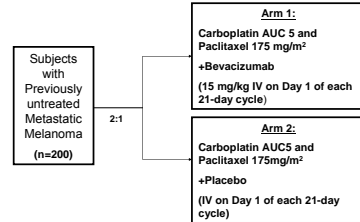
Elevated LDH is a negative predictor for Response to HD IL-2

LDH	All	CR	PR	CR/PR	P-value
Normal	176	13 (7%)	24 (14%)	37 (21%)	0.05
Elevated	32	0	2 (6%)	2 (6%)	

LDH is a HIF dependent factor
? Possible correlation with VEGF
Suzman et al

Sh, Sullivan et al- JIT 2011 (in p

Carbo/Paclitaxel +/- Bev (BEAM) Trial: Schema



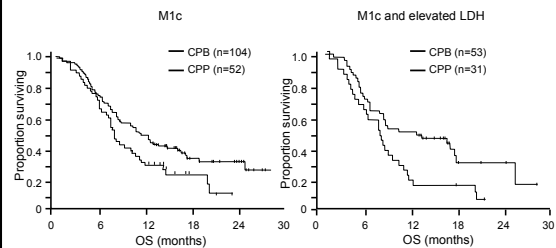
Stratification:
 • Performance Status: 0 vs. 1
 • Stage: M1a/M1b vs. M1c (visceral involvement or abnormal LDH)
Key Statistical Assumptions:
 • PFS HR: 0.67 (improvement from 4 to 6 months)

Subgroup OS analysis

Baseline risk factor	Total (n)	CPP (n=71)		CPB (n=143)		HR (95% CI)	CPB better	CPP better
		Median n (months)	9.2	Median n (months)	12.3			
All patients (unstratified)	214	71	9.2	143	12.3	0.79 (0.56-1.13)		
Baseline ECOG PS								
0	148	48	11.4	100	16.7	0.69 (0.44-1.08)		
1	66	23	7.5	43	7.3	1.08 (0.61-1.91)		
M classification								
M1a	19	8	17.9	11	10.2	2.36 (0.62-9.02)		
M1b	39	11	NE	28	18.5	1.28 (0.42-3.90)		
M1c	156	52	7.9	104	11.1	0.64 (0.44-0.95)		
Baseline LDH								
Normal	128	39	17.9	89	13.4	1.25 (0.73-2.13)		
Abnormal	84	31	7.5	53	8.5	0.53 (0.32-0.88)		

NE = not estimable

BEAM Trial: Phase II Carbo/paclitaxel +/- Bev: Exploratory OS analysis in poor prognosis patients



No. of patients at risk												
CPB	104	77	50	17	8	0	53	36	24	4	2	0
CPP	52	36	15	4	0	0	31	18	4	3	0	0

O'Day ECCO 2009

Conclusions

- Prognostic Factors for Stage IV Disease a work in progress
 - Clinical factors defined
 - F/up assessment techniques still a major component
- Opportunities exist for expanding prognostic variables to include laboratory tests and link to specific therapies.
- These approaches may allow for both more personalized treatment selection and prognostic assessment that can further facilitate clinical decision making and trial design