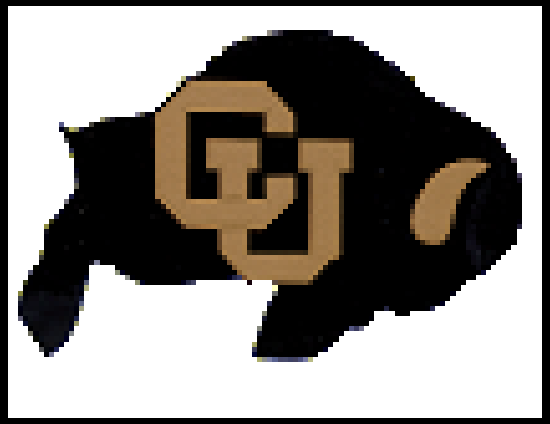
Immunotherapy: a Valuable Treatment Strategy for Melanoma



Marshall T Bell
Research Resident
University of Colorado
Grand Rounds
Nov. 21, 2011

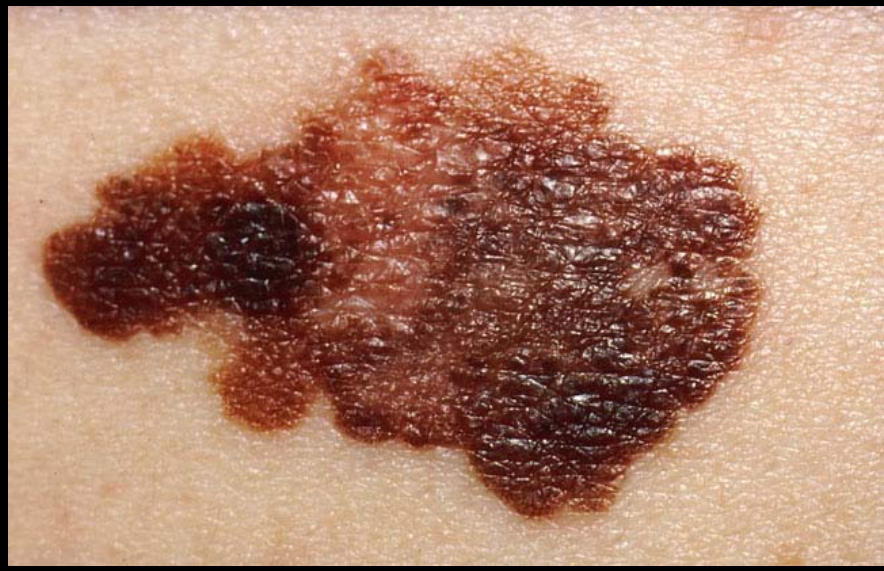
Melanoma

- Most common form of cancer in adults ages 25-29
- 3-5% of skin cancers but 65-75% of deaths
- Most common metastasis to small bowel
- Prognosis
  - Pts with melanoma *in situ* 99.9% 5 year survival
  - Pts that progress to stage IV disease median survival <1 yr

Cameron(2011) ,Lens (2004)

Diagnosis -ABCD's

- Asymmetry
- Borders-irregular
- Color
- Diameter- >6mm
- Excision



Stages

Stage	Description	
IA	Tumor depth = ≤ 1.0 mm without ulceration and Clark level II/III	No lymph node involvement or distant metastases
IB	Tumor depth = ≤ 1.0 mm with ulceration or Clark level IV or V Or tumor depth = 1.01-2.0 mm without ulceration	
IIA	Tumor depth = 1.01-2.0 with ulceration Or tumor depth = 2.01-4.0 mm without ulceration	
IIB	Tumor depth = 2.01-4.0 mm with ulceration Or tumor depth = > 4.0 without ulceration	
IIC	Tumor > 4.0 mm with ulceration	
IIIA	Tumor of any thickness without ulceration, with 1-3 lymph nodes containing micrometastasis	
IIIB	Tumor of any thickness without ulceration with 1-3 positive nodes, at least 1 containing macrometastasis Or tumor of any thickness with ulceration and 1-3 positive nodes and micrometastasis, or in-transit met(s)/satellites(s) without metastatic nodes	
IIIC	Tumor of any thickness with ulceration with 1-3 lymph nodes, at least 1 containing macrometastasis Or tumor of any thickness with 4 or more metastatic nodes, or matted nodes, or in-transit metastases/satellites with metastatic nodes(s)	
IV	Tumor of any thickness with or without ulceration and with or without lymph node involvement with distant metastases to other organ systems	

Source: Adapted from Kim, Reintgen, & Balch, 2002.

Surgical Management

- Biopsy to assess thickness
- Excision with margins
  - <1mm - 1 cm margin
  - >1mm – 2 cm margin
- Sentinel lymph node biopsy
  - All patients with clinical or radiographically negative disease and lesion greater than 1mm or ulcerated
- Regional lymphadenectomy for +SLN or microscopic metastatic disease
- Surgical resection of metastatic disease in appropriate candidates

Cameron (2011)

Immunotherapy

- Lymphocytic infiltrates are a primary prognostic factor for outcome
- Multiple pro-inflammatory cytokines are significantly elevated in patients with relapse free survival longer than 5 years as compared to RFS of 1 yr
  - IL-1B, IL-1α, IL-6, TNF-α, MIP-1α, MIP1-β
- T-Cell infiltrates after IFNα-2b therapy are also predictive of improved prognosis

Weber (2011)

Current Strategies

- IL-2
- IFNα
- Vaccines
- CTLA4 Antibodies

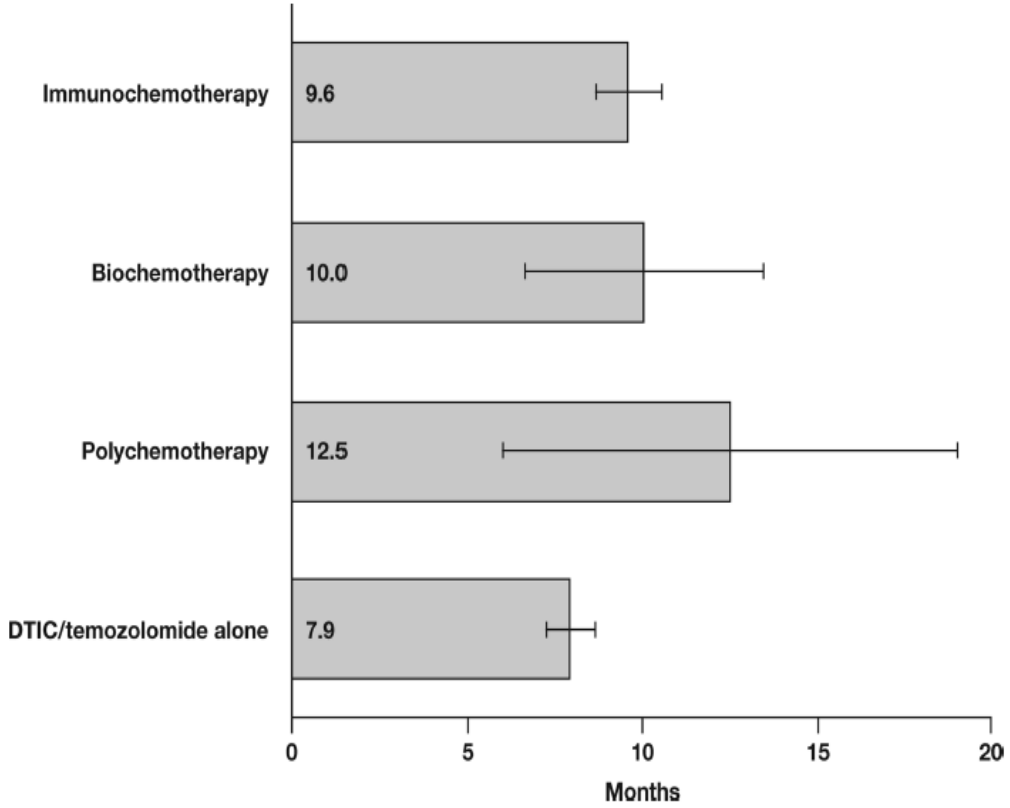


Figure 3. Overall survival of patients treated with different therapies for melanoma. The data analyzed are listed in Table 1. On this figure, the error bars represent the 95% confidence interval. Abbreviation: DTIC, dacarbazine.

Garbe (2011)

The Opposition

Dr Yu

- Doesn't believe in taking risks to help others
- Skeptical about “Fancy Science”
- Didn’t vote for Obama because she is against HOPE

Bell (2011)

Interleukin-2

- Glycoprotein that binds receptors on T-helper and T-effectors cells
- T-cell growth factor
- Potent antitumor activity *in vivo*
- Induces release of cytokines augmenting the immune response

- Weber 2011

IL-2 Therapy-Early Phase II

- 1990 *Journal of Clinical Oncology*
- 47 patients with histological confirmed metastatic melanoma
- Anticipated survival of at least 4 months
- Two five day courses of high dose IL-2 one week apart

Table 2. Characteristics of Responding Patients

Patient No.	Age (years)	Sex	PS	No. of Doses of IL-2 in Phase 1	No. of Doses of IL-2 in Phase 2	Sites of Response	Response	Duration (months)
1	47	F	0	13	11	LN, skin liver	PR	15+
2	60	M	0	12	5	Liver, lung	PR	9
3	58	M	0	13	9	LN	CR	14
4	64	F	1	13	11	Liver, lung, skin	PR	16
5	60	M	0	13	8	Subcutaneous mass, lung	PR	5
6	32	M	0	12	13	Lung	CR	20+
7	31	M	0	9	10	Lung, adrenal, LN, mesenteric mass, skin	PR	4
8	66	M	1	15	0	LN	PR	3
9	53	M	1	9	6	LN	PR	7
10	62	M	0	13	7	Liver, LN	PR	6+

Abbreviation: LN, lymph node.

!!!!!

22% of patient with complete or partial responses
Median Response was 8 months

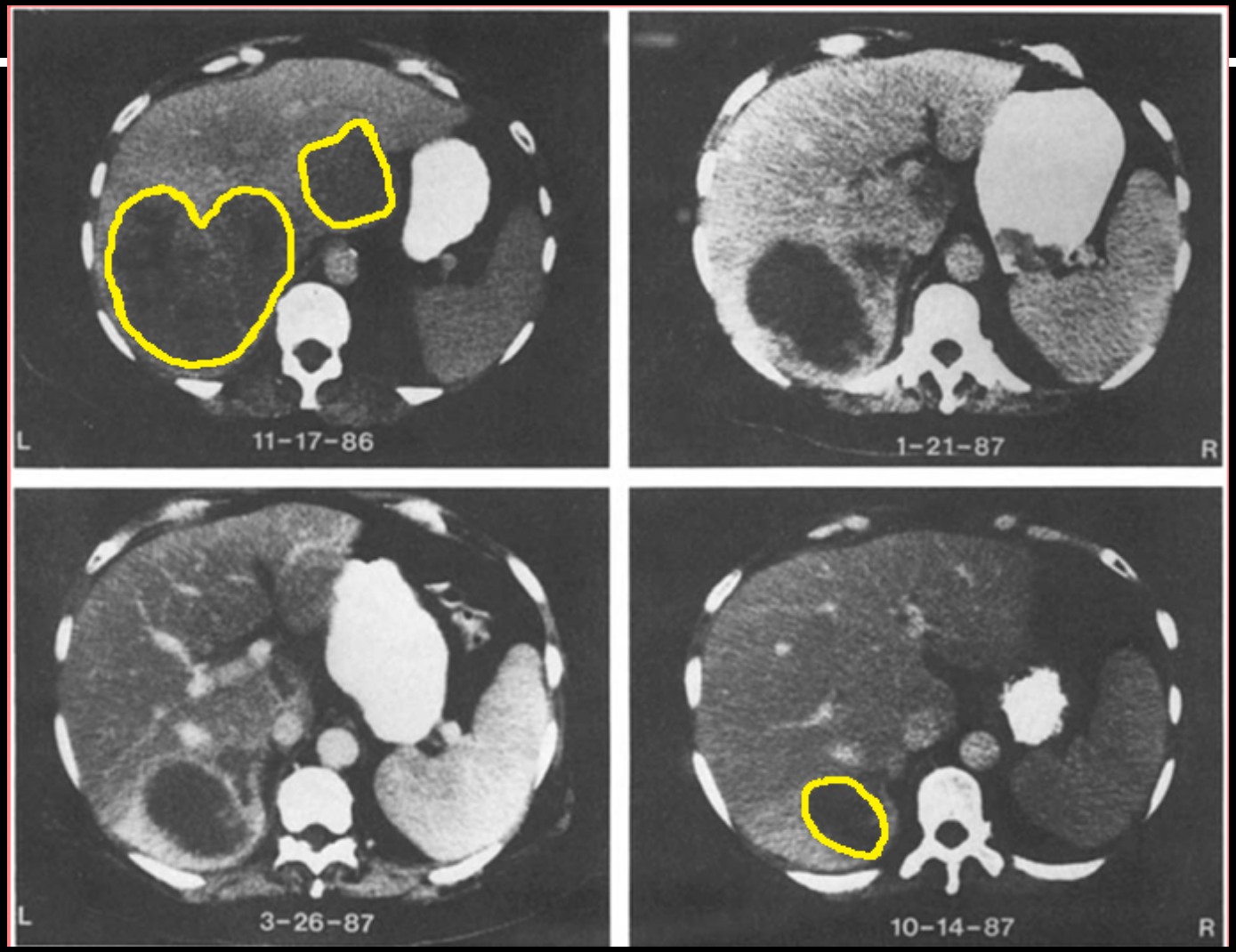

L
11-17-86
1-21-87
R
L
3-26-87
10-14-87
R

Table 3. Toxicity of Treatment With IL-2 in 47 Patients

	Toxicity Level	No. of Patients (%)
Cardiopulmonary		
hypotension	Requiring pressors for up to 48 hours	32 (68)
	Pressors for > 48 hours after stopping drug	2 (4)
Ventricular arrhythmia	Cause hypotension	0 (0)
	Ventricular tachycardia	2 (4)
Myocardial ischemia	Transient angina	1 (2)
	Myocardial infarction	3 (6)
Pulmonary	Dyspnea at rest	11 (23)
	Intubation required	3 (6)
Weight gain > 10%		6 (13)
Renal		
Increase in creatinine	5.1-10 × upper limits of normal	14 (30)
	> 10 × upper limits of normal	1 (2)
Oliguria	< 80 cc output over 8-hour period	11 (23)
	Anuria > 8 hours	17 (36)
Gastrointestinal		
Increase in alkaline phosphatase	5.1-1.0 × upper limit of normal	8 (17)
Increase in bilirubin	5.1-10 × upper limit of normal	7 (15)
	> 10 × upper limit of normal	1 (2)
Diarrhea	Requiring therapy	11 (23)
Nausea and vomiting	Requiring therapy	13 (28)
Hematologic		
Neutropenia	WBC, 0.5-0.9	4 (9)
	< 0.5	2 (4)
Thrombocytopenia	25-49 platelets/μl	12 (26)
	< 25 platelets/μl	1 (2)
Other		
Cutaneous	Desquamation	6 (13)
Neurologic	Somnolence	6 (13)
	Coma	1 (2)
	Disorientation requiring help with activities of daily living	10 (21)
Fever > 40°C		6 (13)
Death on study		1 (2)

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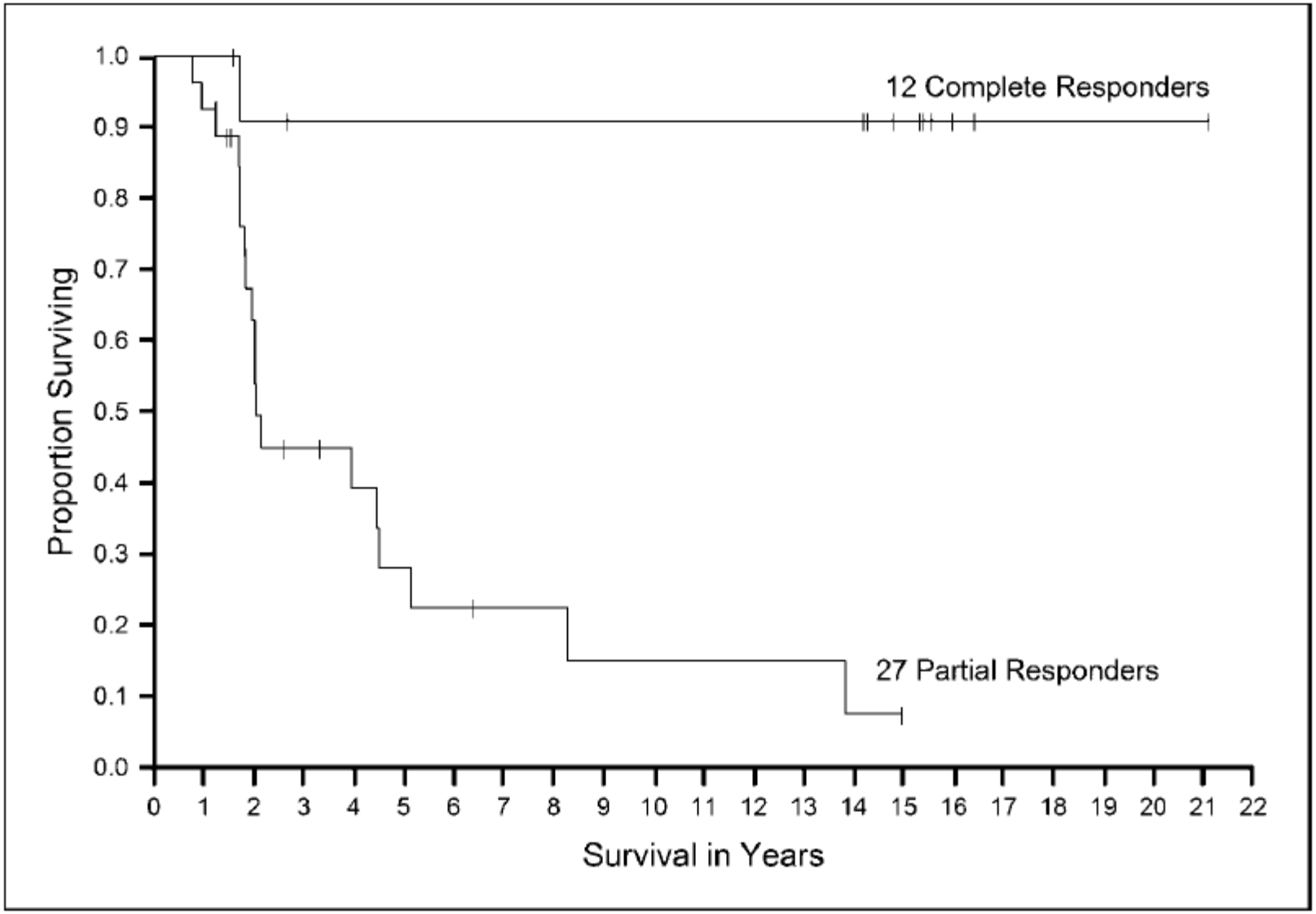
Treatment of Metastatic Melanoma Using Interleukin-2 Alone or in Conjunction with Vaccines

- *Clinical Cancer Research*, 2008
- Biopsy proven metastatic melanoma
- 305 patients receiving IL-2 alone from 1985-03

- 13% objective response rate
  - 9% partial response
  - 4% complete response rate
  - Median duration of partial and complete responses was 24 and >176 months
  - Median survival 12.8 months in all patients

- Smith 2008


12 Complete Responders
27 Partial Responders
Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Survival in Years

IL-2 with Vaccines

- 379 patients with IL-2 treatment + Vaccine
  - Multiple other vaccines (gp209-2m, MART-1, gp100)
- IL-2 + all vaccines
  - Objective response rate-15%
  - PR-12%, CR3%
  - Median duration Response 9.4 & 7.8 months
- IL-2 + gp100:209 (n=150)
  - OR rate 22.3%

Table 1. Second-Line Metastatic Melanoma Treatment Comparison[10-13]

Response	Temozolomide[10,a] (n = 34)	Interleukin-2[11,b] (n = 305)	Paclitaxel[12,c] (n = 18)	Paclitaxel + Carboplatin[12,d] (n = 16)	Temozolomide + Docetaxel[13,e] (n = 38)
Objective response rate, %[f]	1	13	11	0	13
Complete response, %	0	4	0	0	0
Partial response, %	1	9	11	0	13
Stable disease, %	18	NR	17	19	13
Progression-free survival, mo	1	NR	1.8	1.9 (n =15)	2
Overall survival, mo	2.2	12.8	7.2 (n =19)	6.9	6.5

NR = not reported.
[a]Temozolomide 150 mg/m^2 orally on days 1-5 of 28-day cycle.
[b]Interleukin-2 720,000 units/kg intravenously every 8 hours for 12-15 doses, every 14 days.
[c]Paclitaxel 100 mg/m^2 intravenously weekly for 6 weeks, 8-week cycle.
[d]Paclitaxel 80 mg/m^2 with carboplatin 200 mg/m^2 intravenously weekly for 6 weeks, 8-week cycle.
[e]Docetaxel 80 mg/m^2 intravenously on day 1 with temozolomide 150 mg/m^2 orally on days 1-5, 28-day cycle.
[f]Objective response rate = complete response + partial response.

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Objective response rate, %[f]	1	13	11	0	13
Complete response, %	0	4	0	0	0
Partial response, %	1	9	11	0	13
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IFN-α

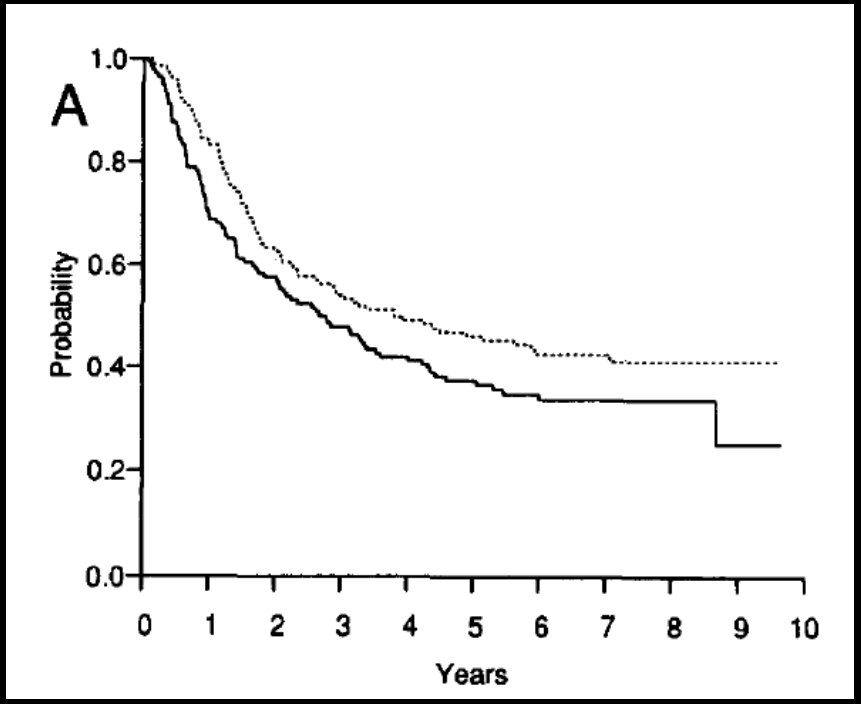
- Activate macrophages and natural killer cells
- Up-regulate antigen presentation to T-lymphocytes

Trial EST 1684

- 1996, *Journal of Clinical Oncology*
- Randomized controlled trial
- 252 patients stage IIb or III disease and lymphadenectomy
- 48 weeks of treatment with IFNα-2b Vs. observation
- Median follow up 7 yrs

Results

- 5 Year Survival Rates
  - 46% with IFNα2b
  - 37% with observation
- Relapse Free Survival
  - 1.72 yrs with IFNα
  - 0.98 yrs with observation
- P-Value 0.0023



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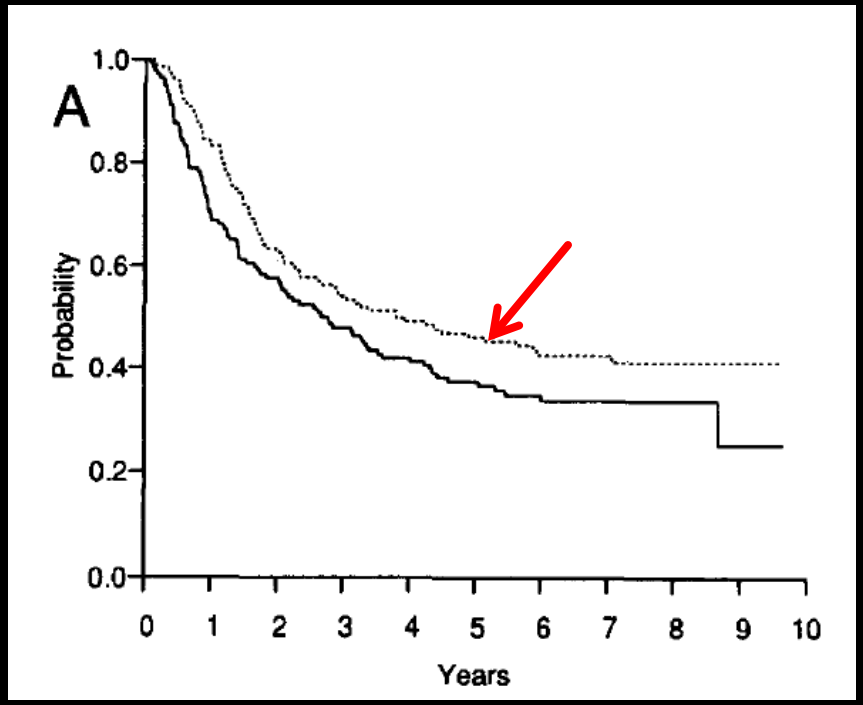

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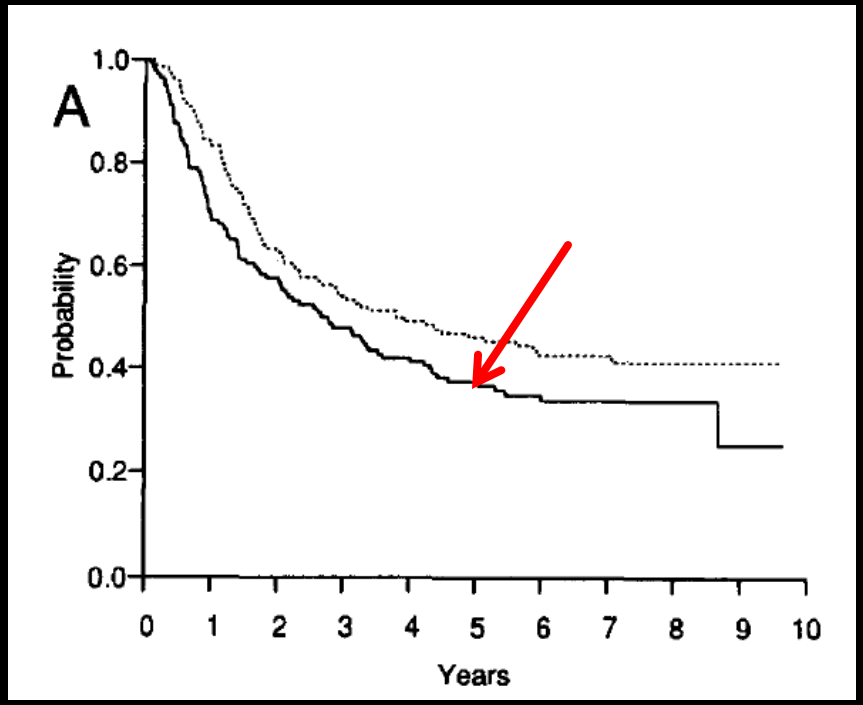

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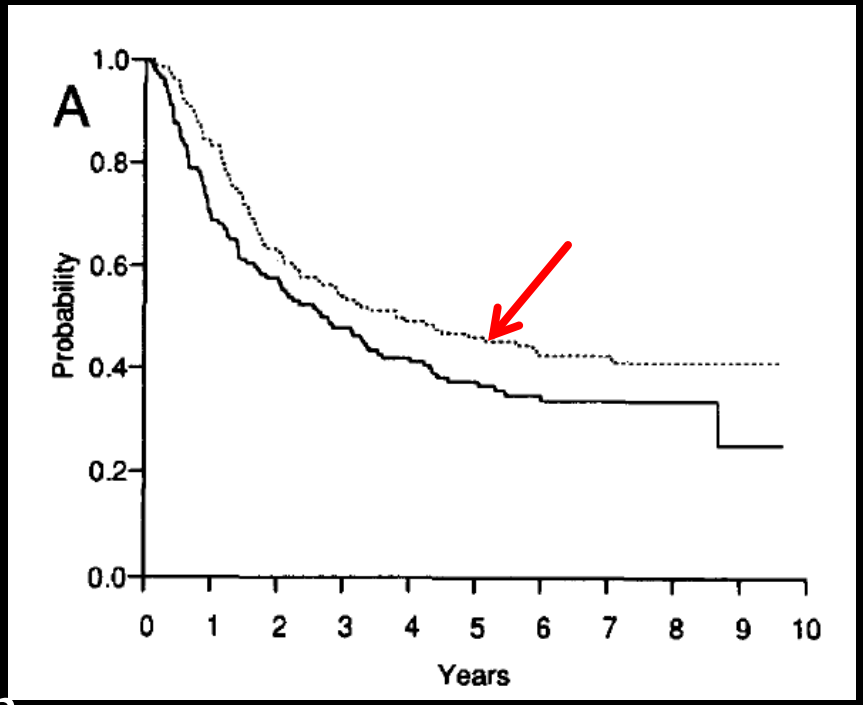

Vaccines

- Presentation of antigen activates CD8+ cytotoxic T-cells and NK cells
- Over 100 different melanoma associated antigens have been described

- Largest Phase III trial MMAIT III and IV 2007
  - 700 stage III resected and 500 Stage IV resected stopped due to lack of efficacy

Morgan 2008

Cytotoxic T-lymphocyte Antigen4 Anitbodies

- CTLA4 antigen that binds T-cells and attenuates T- cells response
- Immune check point that induces cell arrest and inhibits cell proliferation
- Ipilimumab -human monoclonal antibody that blocks CTLA-4 to promote anti-tumor immunity

Korman (2006)

Ipilimumab monotherpay in patients with pretreated advanced melanoma

- *Lancet,* 2011
- Phase II dose-ranging study
- 217 pts with Stage III or IV unresectable melanoma
- All patients had received previous treatment with multiple other agents
- Randomized 0.3, 3 or 10 mg/kg

Wolchok 2011

	Ipilimumab 0·3 mg/kg (n=73)	Ipilimumab 3 mg/kg (n=72)	Ipilimumab 10 mg/kg (n=72)
Best overall response			
Complete response	0	0	2
Partial response	0	3	6
Stable disease	10	16	13
Progressive disease	43	41	36
Unknown (progressive disease by clinical observation only)	20	12	15
Best overall response rate*	0% (0·0–4·9)	4·2% (0·9–11·7)	11·1% (4·9–20·7)
Disease control rate†	13·7% (6·8–23·8)	26·4% (16·7–38·1)	29·2% (19·0–41·1)
Number (%) with disease control ≥24 weeks (complete or partial response or stable disease) [95% CI]	0 (0%) [0·0–4·9]	2 (3%) [0·3–9·7]	5 (7%) [2·3–15·5]
Median (95% CI) overall survival (months)	8·6 (7·7–12·7)	8·7 (6·9–12·1)	11·4 (6·9–16·1)
Survival at 1 year	39·6% (28·2–51·2)	39·3% (28·0–50·9)	48·6% (36·8–60·4)
Survival at 18 months	23·0% (13·4–33·6)	30·2% (19·8–41·4)	34·5% (23·4–46·2)
Survival at 24 months	18·4% (9·6–28·2)	24·2% (14·4–34·8)	29·8% (19·1–41·1)
Median (IQR) survival follow-up (months)	8·3 (3·5–15·3)	8·7 (4·0–22·3)	10·7 (3·6–23·3)
Progression-free survival at 24 weeks‡	2·7% (0·0–7·3)	12·9% (0·0–25·9)	18·9% (7·9–28·9)

Data are number of patients (%) or rate (95% CI), unless otherwise indicated. *Number of patients with complete or partial response/N. †Number of patients with complete or partial response, or stable disease/N. ‡Calculated with the Kaplan-Meier product-limit method for all patients, which includes censoring, and therefore the rates for progression-free survival are different from disease control rates.

Table 2: **Summary of efficacy results**

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

- *New England Journal of Medicine* June 2011
- Phase III
- 502 patients with metastatic melanoma, previously untreated
- Ipilimumab + Dacarbazine or Dacarbazine alone
- Primary endpoint overall survival

- Roberts 2011

Table 2. Efficacy Results.

End Point	Ipilimumab plus Dacarbazine (N = 250)	Placebo plus Dacarbazine (N = 252)	Hazard Ratio with Ipilimumab plus Dacarbazine (95% CI)	P Value
Primary end point: overall survival				
No. of deaths	196	218	0.72 (0.59–0.87)	<0.001
Survival — % (95% CI)				
1 yr	47.3 (41.0–53.6)	36.3 (30.4–42.4)		
2 yr	28.5 (22.9–34.2)	17.9 (13.3–22.8)		
3 yr	20.8 (15.7–26.1)	12.2 (8.2–16.5)		
Secondary end points				
Disease progression — no. of events	203	223	0.76 (0.63–0.93)	0.006
Best overall response — no. (%)*	38 (15.2)	26 (10.3)		
Complete response	4 (1.6)	2 (0.8)		
Partial response	34 (13.6)	24 (9.5)		
Stable disease — no. (%)*	45 (18.0)	50 (19.8)		
Progressive disease — no. (%)	111 (44.4)	131 (52.0)		
Response not evaluated — no. (%)†	56 (22.4)	45 (17.9)		

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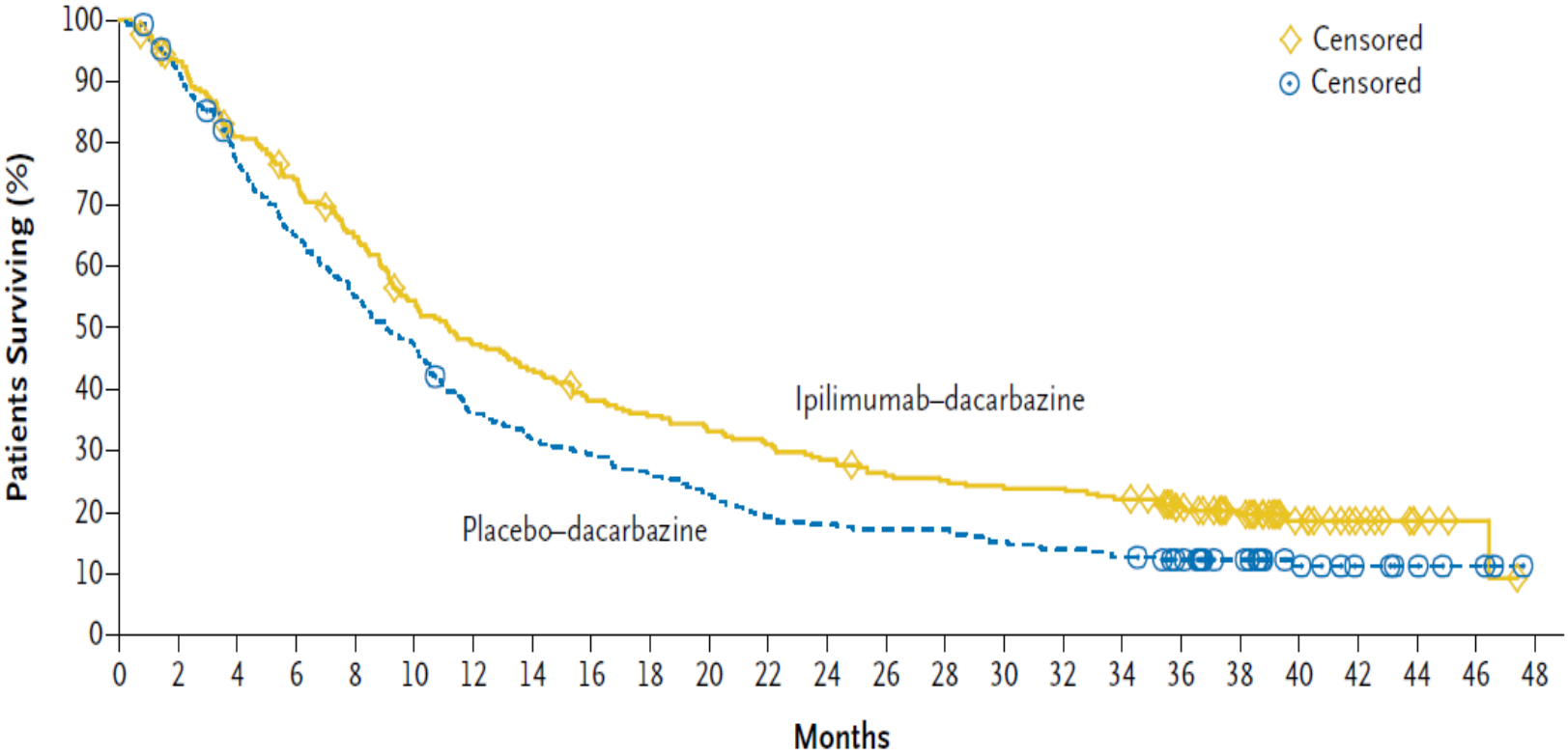

Median overall survival 11.2 Vs. 9.1 months

COLORADO SURGERY

Conclusion

- Immunotherapy is a valuable approach to melanoma
- IL-2 at high doses can achieve long term durable responses
- IFN has a significance impact on relapse free progression and overall survival in patients with stage IIB or III disease
- CTLA4 antibodies have shown improved longer term survival in conjunction with other agents
- Our surgery department is great