Update on the Adjuvant Therapy of Malignant Melanoma

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Case Presentation

- 48 year-old healthy man
- Presented to his dermatologist five years ago with an elevated pigmented lesion on his heel
- Diagnosed as wart and treated topically
- Never went away, then grew back
- Sought further medical attention….

Case, continued

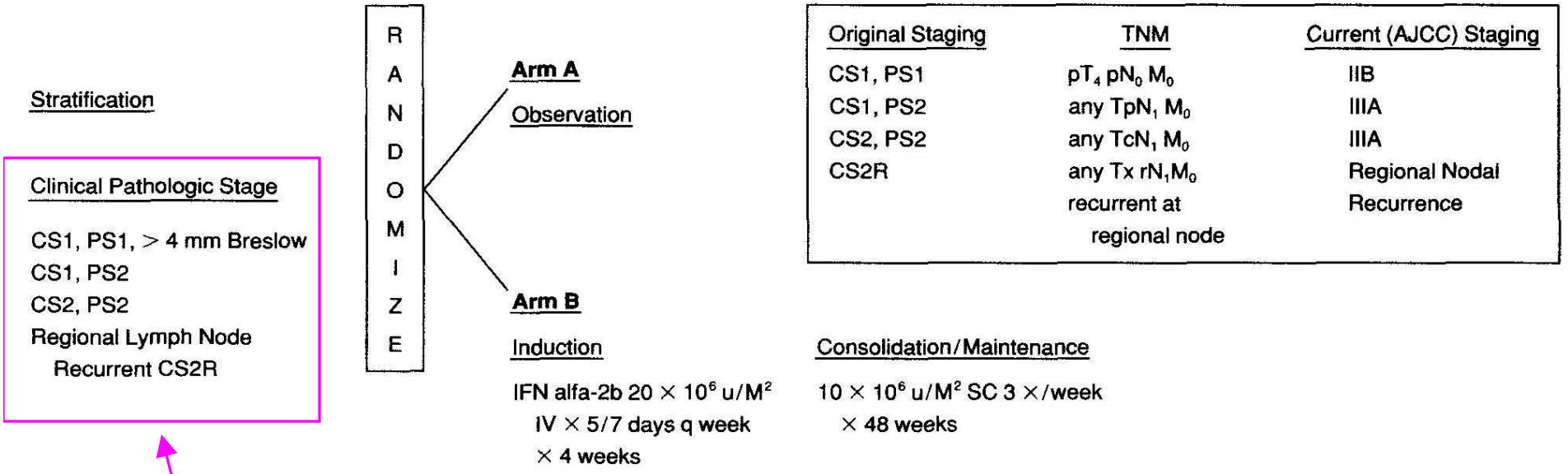
- Had large black lesion on his heel
- Biopsy:
- Referred to Dr. Roger Perry at EVMS for wide local excision and sentinel lymph node procedure
- Pathology…..

Case, continued

- On basis of pathology findings he was advised to undergo high-dose interferon therapy for a year

- Rationale for treatment…

Randomized Interferon Trial



Original Staging	TNM	Current (AJCC) Staging
CS1, PS1	$pT_4\ pN_0\ M_0$	IIB
CS1, PS2	any $TpN_1\ M_0$	IIIA
CS2, PS2	any $TcN_1\ M_0$	IIIA
CS2R	any Tx rN_1M_0 recurrent at regional node	Regional Nodal Recurrence

High-risk patients

Kirkwood et al *J. Clin. Onc.* 14:7-17, 1996

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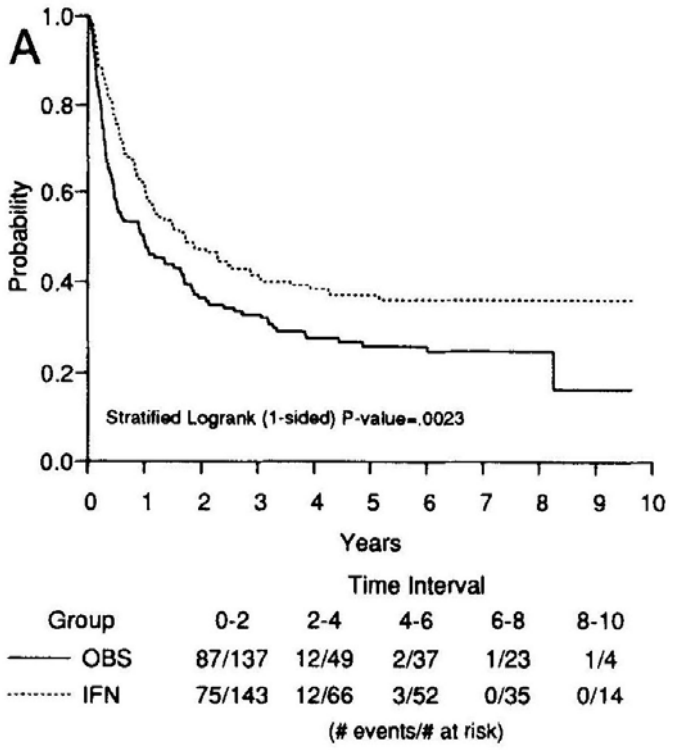
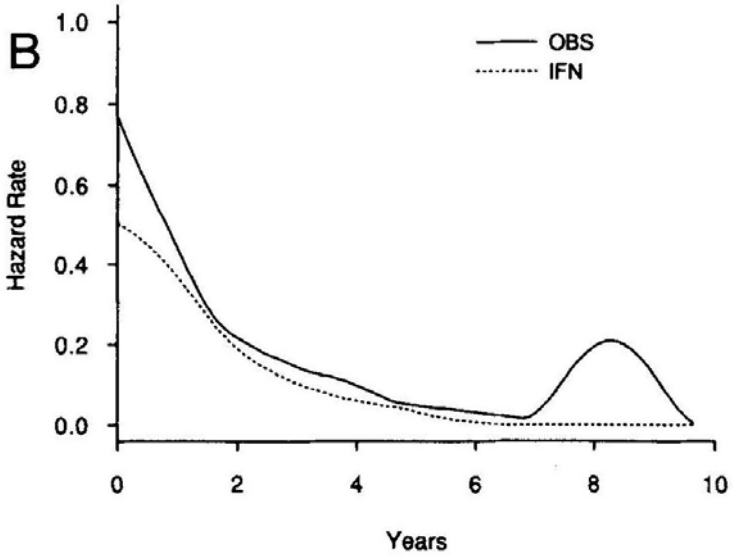
Relapse-free survival and hazard of relapse

KIRKWOOD ET AL





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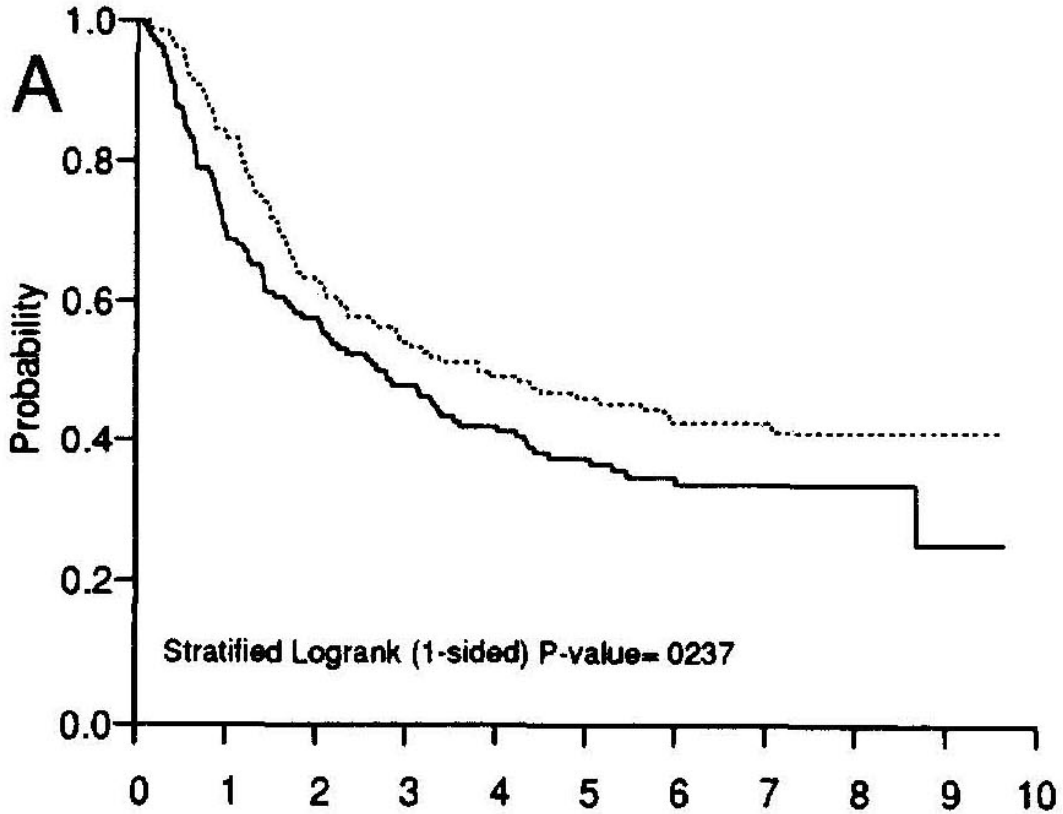
Overall Survival

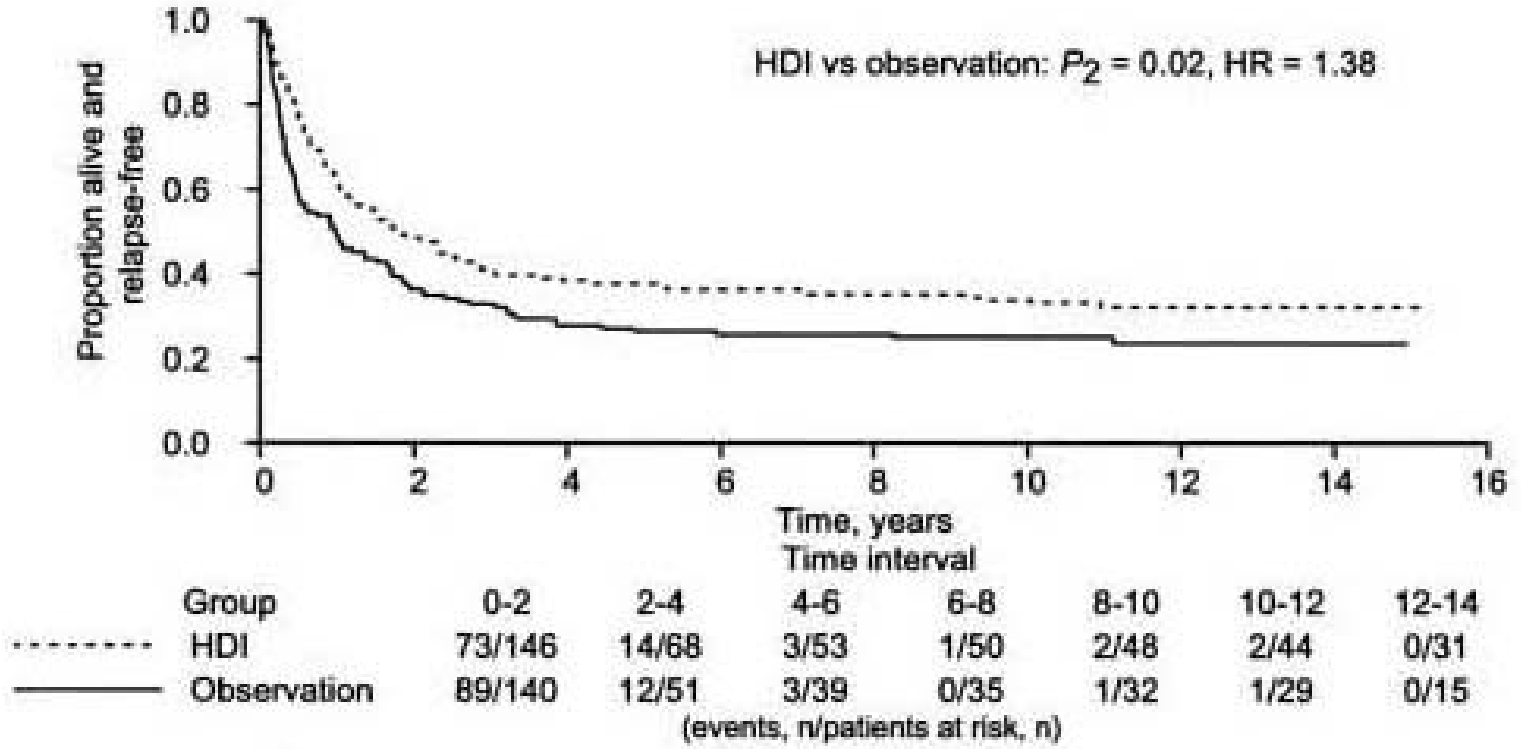


Group	Time Interval 0-2	2-4	4-6	6-8	8-10
—— OBS	58/137	21/78	9/56	1/33	1/7
····· IFN	53/143	19/89	8/69	1/44	0/17

Subset Analysis

- Only patients with positive nodes benefitted from treatment with α-interferon
  - Nodes could be grossly positive or microscopically positive at diagnosis, or could have become positive months to years after initial primary removed
  - Patients with deep (>4.0 mm) melanomas were entered on trial but as a subset did not benefit from interferon if nodes were negative

Subsequent Long-Term Analysis



Three subsequent trials by same group have largely confirmed this observation.

Case, continued

- On basis of pathology findings he was advised to undergo high-dose interferon therapy for a year
- Took treatment
  - 30 lb weight loss
  - Weakness and fatigue
    - Had to take LOA from job as lineman for Dominion Virginia Power
  - Became subclinically hypothyroid, treated to normalization of TSH
- What is the significance of hypothyroidism?

Autoantibodies or Manifestations of Autoimmunity in Patients Treated with Interferon Alfa-2b

Table 2. Autoantibodies or Manifestations of Autoimmunity in Patients Treated with Interferon Alfa-2b.*

Autoantibodies or Manifestations of Autoimmunity	All Patients (N=200)	Induction-Therapy Group (N=96)	Extended-Therapy Group (N=104)
		no. of patients (%)	
Autoantibodies or autoimmune disorders	52 (26)	23 (24)	29 (28)
Antithyroid antibodies	43 (22)	16 (17)	27 (26)
Antinuclear antibodies	12 (6)	2 (2)	10 (10)
Anticardiolipin antibodies	10 (5)	2 (2)	8 (8)
Vitiligo	11 (6)	5 (5)	6 (6)
Clinical manifestations	19 (10)	2 (2)	17 (16)
With autoantibodies	16 (8)	2 (2)	14 (13)
Without autoantibodies (vitiligo)	3 (2)	1 (1)	2 (2)
Multiple manifestations of autoimmunity	16 (8)	1 (1)	15 (14)

* Patients in the induction-therapy group received interferon alfa-2b (15 million IU per square meter of body-surface area per day, intravenously, five days per week for four weeks) followed by observation. Patients in the extended-therapy group received the same induction dose for 4 weeks, followed by subcutaneous therapy (10 million IU per day thrice weekly) for an additional 48 weeks.

Gogas H et al. *N Engl J Med* 2006;354:709-718

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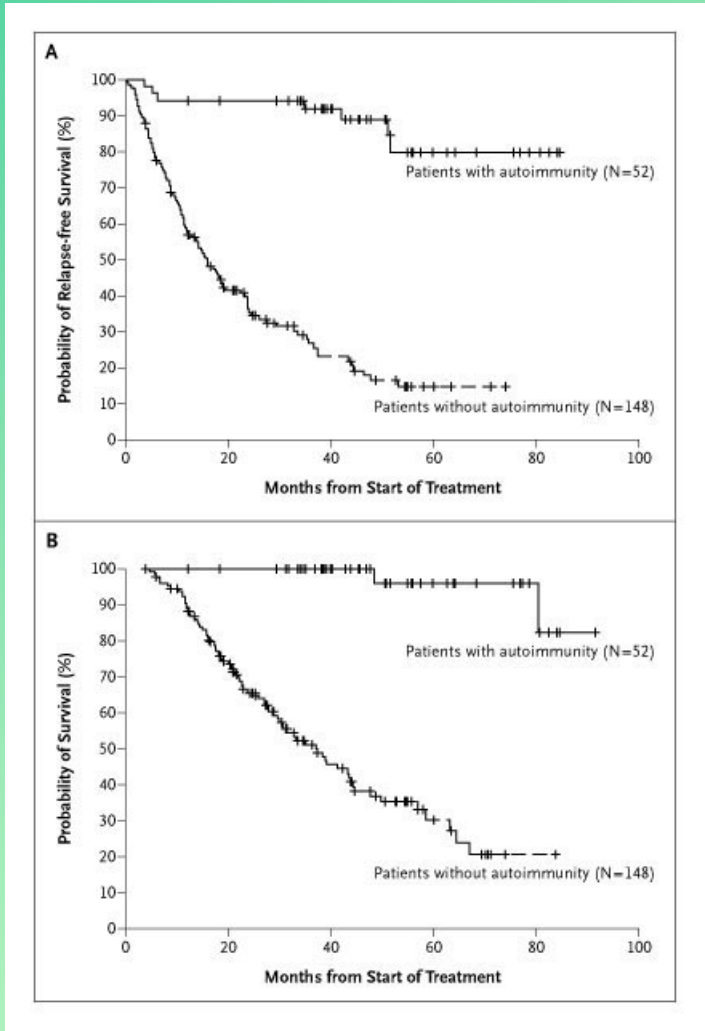
Relapse-free Survival (Panel A) and Overall Survival (Panel B) among Patients Treated with HD IFN with or without Autoimmunity



Gogas H et al. *N Engl J Med* 2006;354:709-718

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Univariate Cox Regression Models of Relapse-free Survival and Overall Survival

Table 3. Univariate Cox Regression Models of Relapse-free Survival and Overall Survival.*

Variable	Relapse-free Survival			Overall Survival		
	Rate	Median Duration (95% CI)	P Value†	Rate	Median Duration (95% CI)	P Value†
	no. of events/ no. of patients	*mo*		*no. of events/ no. of patients*	*mo*	
Age (yr)			0.71			0.71
<52	59/98	31.3 (14.3–48.3)		44/98	63.3 (41.6–85.0)	
≥52	56/102	28.0 (17.9–38.0)		38/102	58.7 (NE)	
Group‡			0.94			0.82
Induction therapy	54/96	24.0 (6.4–41.7)		39/96	58.7 (40.0–77.5)	
Extended therapy	61/104	32.9 (21.2–44.6)		43/104	63.3 (39.5–87.2)	
Sex			1.00			0.58
Male	61/104	28.0 (13.8–42.1)		45/104	57.0 (34.9–79.2)	
Female	54/96	27.7 (13.3–42.1)		37/96	58.7 (40.5–76.9)	
Breslow thickness (mm)			0.33			0.90
0–2.0	16/30	18.6 (NE)		11/30	80.8 (NE)	
2.1–4.0	31/47	23.7 (8.0–39.5)		21/47	43.8 (NE)	
>4.0	59/107	35.7 (20.4–51.0)		43/107	58.7 (40.0–77.5)	
Clark level			0.22			0.12
II or III	19/42	NR (NE)		13/42	80.8 (NE)	
IV or V	83/138	26.1 (14.2–38.1)		60/138	47.9 (27.7–68.2)	
Vascular invasion			<0.001			0.02
No	54/111	43.8 (27.3–60.3)		39/111	80.8 (51.6–110.0)	
Yes	42/58	16.0 (8.7–23.2)		29/58	37.6 (18.1–57.1)	
Ulceration			0.61			0.48
No	22/39	35.7 (11.1–60.3)		17/39	57.0 (31.7–82.3)	
Yes	74/130	32.9 (19.1–46.7)		51/130	64.6 (45.8–83.3)	
Regression			0.39			0.77
No	69/117	23.8 (9.2–38.4)		49/117	63.6 (45.3–81.4)	
Yes	27/52	36.6 (18.9–54.3)		19/52	NR (NE)	
Lymph-node involvement			0.02			0.01
No	25/55	51.1 (37.7–64.8)		13/55	NR (NE)	
Yes	84/138	19.0 (12.5–25.4)		63/138	48.6 (31.5–65.7)	
Autoimmunity			<0.001§			<0.001§
No	108/148	16.0 (12.5–19.3)		80/148	37.6 (28.9–46.3)	
Yes	7/52	NR (NE)		2/52	NR (NE)	

* CI denotes confidence interval, NE not evaluable, and NR not reached.
† P values were calculated with the use of the Wald test.
‡ Patients in the induction-therapy group received interferon alfa-2b (15 million IU per square meter of body-surface area per day, intravenously, five days per week for four weeks) followed by observation. Patients in the extended-therapy group received the same induction dose for 4 weeks, followed by subcutaneous therapy (10 million IU per day thrice weekly) for an additional 48 weeks.
§ The P value is for autoimmunity status as a time-varying covariate.

Case, continued

- Finished therapy without major incident
- Continued on thyroid hormone
- Went back to work
- Resumed pre-treatment exercise program

Case, continued

- Presented in December, 2009 with colorless subcutaneous nodule midway between knee and groin on same side as original tumor
- FNA positive for in-transit metastasis
- Underwent PET/CT….

Case, continued

- Based on PET/CT findings underwent total excision of dermal tumor and exploration of external iliac node through a pelvic laparotomy incision…four hours of surgery
- Pathology….

Case, continued

- Patient is now surgically debulked
- What is to be done?
  - HLA typed to look at eligibility for NCI trial
  - Not appropriate HLA type for their program
  - Acceptance deferred until develops further overt metastases
- Broad inquiry initiated of leading melanoma experts in US
- GM-CSF (Leukine) started

Case #2 65 y.o. WM

- Presented in October 2008
- Mole left thigh gradually darkened over a two-year period
- Excised by Dr. Grenga on referral from PCP
- Pathology….
- Clark Level III Breslow 1.25 mm with ulceration, vertical and radial growth phase identified, lymphocytic response present
- Sentinel lymph node procedure successful: two negative nodes identified
- No additional treatment recommended

Case #2, continued

- Did well for only 13 months
- Developed clinically enlarged lymph node
- PET scan performed….positive in groin
- Underwent lymph node dissection
- 5/10 lymph nodes removed contained melanoma
- Started on high-dose interferon in January, 2010

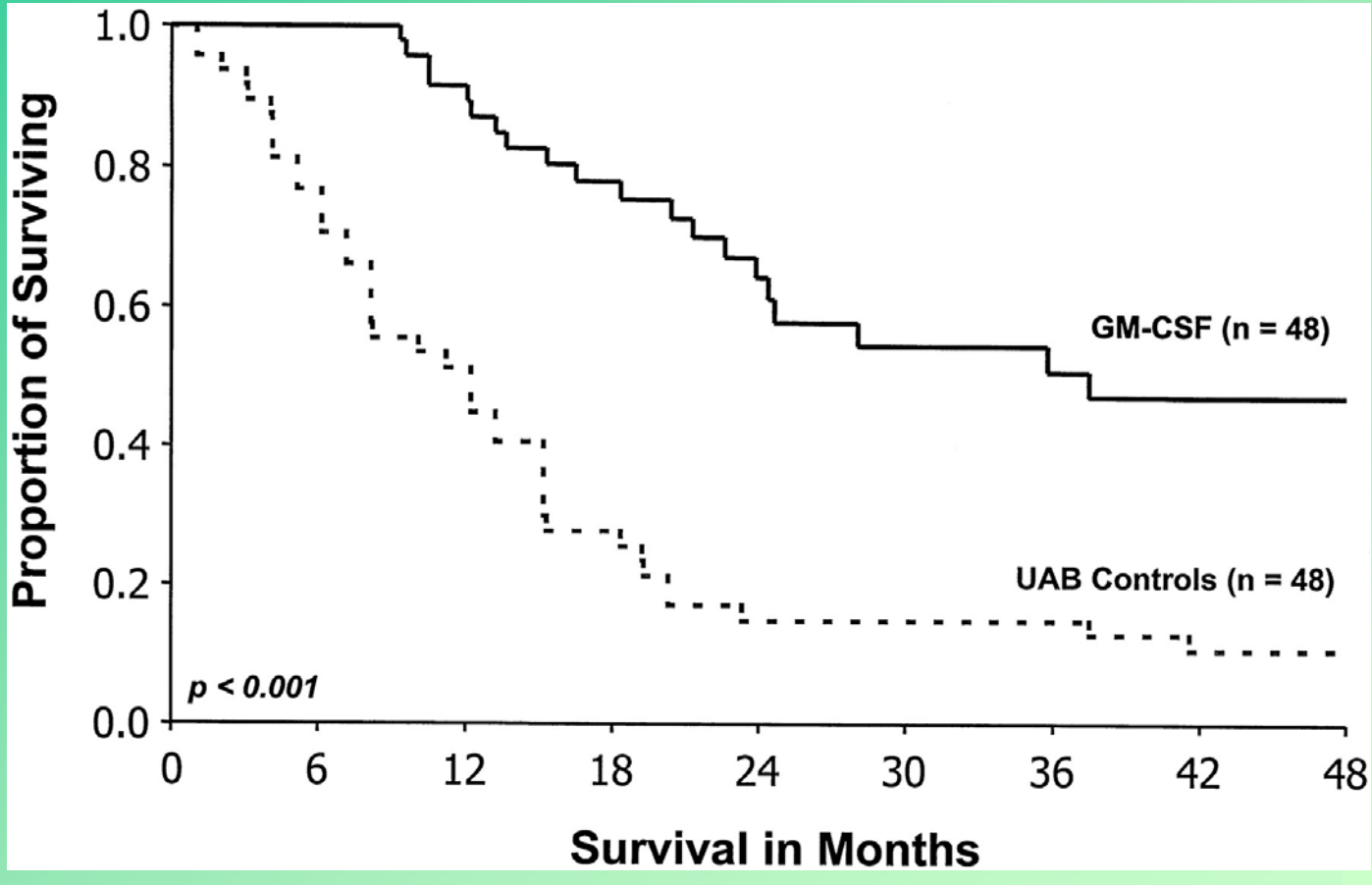
Case #2, continued

- Baseline WBC 3,500; subsequent hematologic intolerance demonstrated with inability to deliver full doses of IFN
- Bone marrow biopsy performed….
- Non-diagnostic bone marrow
- While on reduced interferon after only six weeks developed further intracutaneous recurrence…excised *in toto*
- Interferon continued because of uncertainty as to whether he was true interferon failure

Case #2, continued

- After three months on interferon in May 2010 developed additional intracutaneous disease in skin adjacent to prior groin dissection site
- PET scan showed no other disease
- Further recurrence removed *in toto*
- Recommended he start GMCSF (leukine)
- Patient went to MCV for second opinion
- They recommended isolated limb perfusion with chemotherapy
- Final disposition pending

Patients with high-risk malignant melanoma treated with GM-CSF following debulking vs. matched historical controls



Spitler, L. E. et al. *J Clin Oncol*; 18:1614-1621 2000

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GM-CSF for debulked Stage IV patients with malignant melanoma: the new standard of care in 2000 and beyond?

- Spitler 2000 paper attacked
  - Used historical controls – not a randomized trial
  - Numbers of patients relatively small
  - Results could not be replicated elsewhere
  - Briefly fell into disfavor among the melanoma cognoscenti
  - Many of the relapses occurred very soon after stopping therapy….clue?

GMCSF relook using prolonged therapy

Prior Therapy	No. Patients	Percent
Prior therapy or procedure (all types)	43	44
Surgery (excluding excision and reexcision of primary and regionallymph node dissection)	25	26
Biologic therapy*	25	26
High-dose interferon	13	13
Vaccine	10	10
Levamisole	1	1
Other	3	3
Chemotherapy single agent regimen	3	3
Chemobiotherapy	2	2
Radiotherapy	1	1
Other	1	1

*Two subjects received more than one biologic therapy (both received high-dose interferon and vaccine).

Spitler et al. *J. Immunotherapy* 32:632-7, 2009

Characteristics of Study Population

Characteristic	No. Patients	Percent
AJCC Stage		
IIB	2	2.0
IIC	3	3.1
IIIA	13	13.3
IIIB	27	27.5
IIIC	29	29.6
IVM1a	6	6.1
IVM1b	8	8.2
IVM1c	10	10.2
Sex		
Male	68	69.4
Female	30	30.6
Age (y)		
Mean (± SD)	53.1 (± 12.41)	
Median (min, max)	53.5 (15, 84)	

Spitler et al. *J. Immunotherapy* 32:632-7, 2009

Also non-randomized trial, but patients were treated for three years

Survival Statistics in Treatment Group

Overall melanoma-specific survival

Recurrence-free survival

Difference between two curves is local recurrences totally resected

Change in biology?

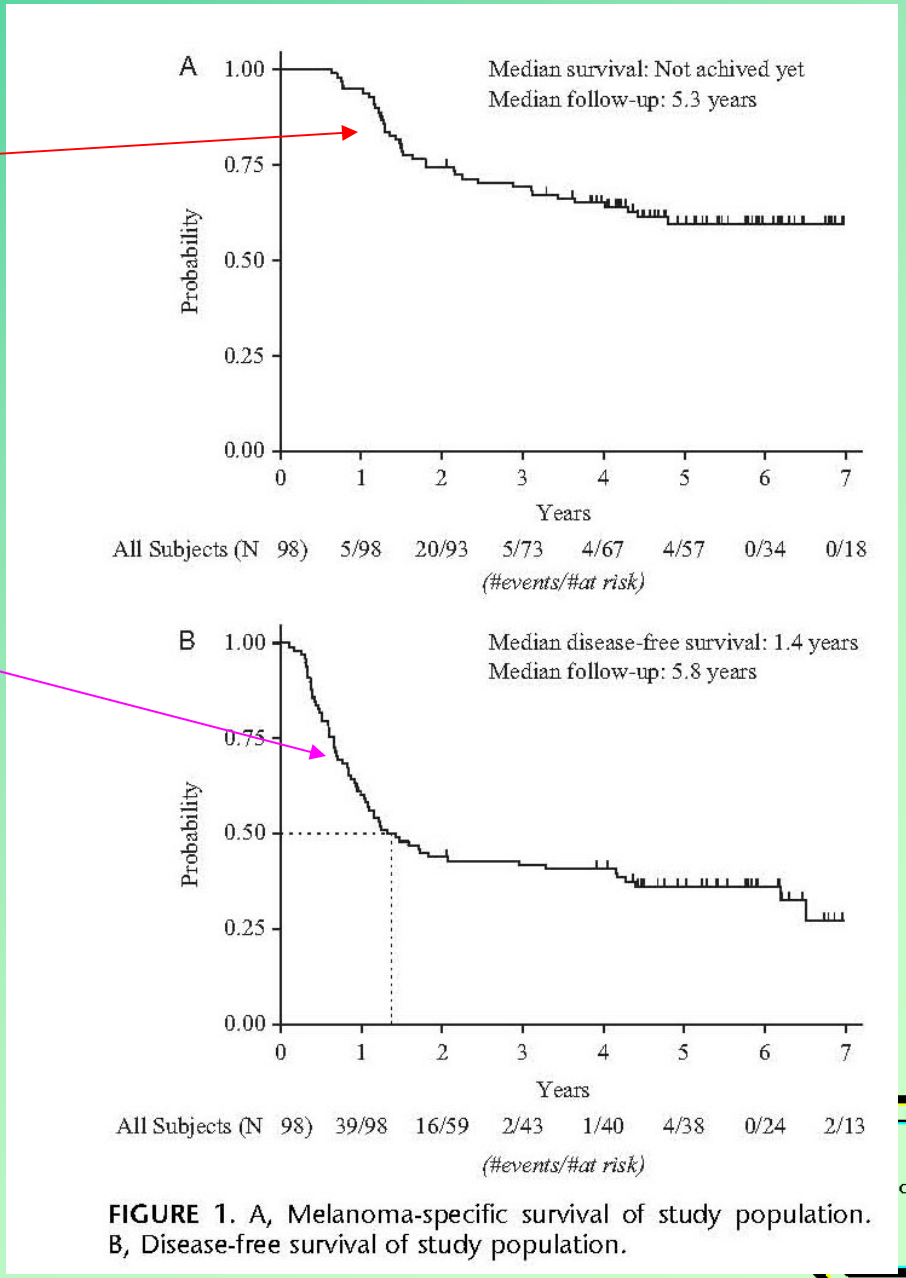

FIGURE 1. A, Melanoma-specific survival of study population. B, Disease-free survival of study population.

Adverse Events from Leukine

Characteristic	No. Patients	Percent
Skin	79	80.6
Injection site reaction	67	68.4
Erythema	56	57.1
Pruritus	31	31.6
Urticaria	10	10.2
Rash	4	4.1
Desquamation	1	1.0
Flu-like symptoms	53	54.1
Fatigue	47	48.0
Myalgia	10	10.2
Sweats	5	5.1
Chills/rigors	4	4.1
Fever	3	3.1
Arthralgia	2	2.0
Gastrointestinal	8	8.2
Nausea	5	5.1
Abdominal pain	2	2.0
Loose stools	1	1.0
Gastric discomfort	1	1.0
Vomiting	1	1.0
Neurologic	6	6.1
Headache	6	6.1
Cardiac	7	7.1
Chest pain	6	6.1
Congestive heart failure	1	1.0
Respiratory	5	5.1
Dyspnea	5	5.1
Wheezing	1	1.0
Pain	5	5.1
Bone	3	3.1
Joint	2	2.0
Sternal	1	1.0
Circulatory	1	1.0
Edema	1	1.0
Other*	17	17.3

Potential Time Bomb…

TABLE 4. Summary of Results of Epidemiologic Analysis

	Melanoma Patients	AML Cases*	Crude Risk %	95% CI (%)	Incidence Rate	95% CI
Clinical study	98	2	2.04	0.25-7.4	541/100,000 person-years	6.8/100,000-1500/100,000 person-years
GRPD	13,291	3	0.02	0.005-0.066	3.2/100,000 person-years	0.26/100,000-7.8/100.000 person-years
SEER	93,396	48	0.05	0.037-0.068	Data for calculation not available	Data for calculation not available

*Cases of AML observed in patients with a previous diagnosis of melanoma.

AML indicates acute myelogenous leukemia; CI, confidence interval; GRPD, general practice research database; SEER, surveillance epidemiology and end results.

No AML seen in earlier study with shorter treatment regimen

What Happens Next?

- In clinical practice in the community only GM-CSF has shown the potential to prolong life in patients who have failed to be cured with adjuvant α-interferon
- The Eastern Cooperative Oncology Group is conducting a larger trial in this patient population
  - Randomization between GM-CSF and a vaccine
  - No true control arm
  - Time will tell about efficacy and risk of leukemia; question of true efficacy may not be answered in this trial, however, without no-treatment control arm

Conclusions

- Adjuvant α-interferon in patients with high-risk melanoma improves overall survival if nodes are involved
- Entire benefit seen in patients who exhibit evidence of acquired autoimmunity
- GM-CSF in debulked adjuvant setting may offer meaningful second-line therapy
- Increased risk of leukemia bears watching in this group of patients with an otherwise very poor prognosis from their underlying disease
- On-going trials may or may not answer question of efficacy of this approach; probably will answer question of safety
- My bias: try this approach or refer patients to institutions specializing in the treatment of high-risk melanoma (UPMC or NCI)