The Challenge of Bringing Forward New Agents for Systemic Therapy of Melanoma

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Melanoma in 2008

- Epidemic Proportions of Disease
- Primary/Regional Prognostic Assessment
- Advanced/Distant Metastatic Disease
  - New Chemotherapy, Cytokine, Antibody & Vaccine Options
  - Relevance of Immunobiology to Disease/Response:
    - Cytokines and Immunoregulation
    - Tumor Antigens & Vaccines
    - Dendritic Cells, T cells,
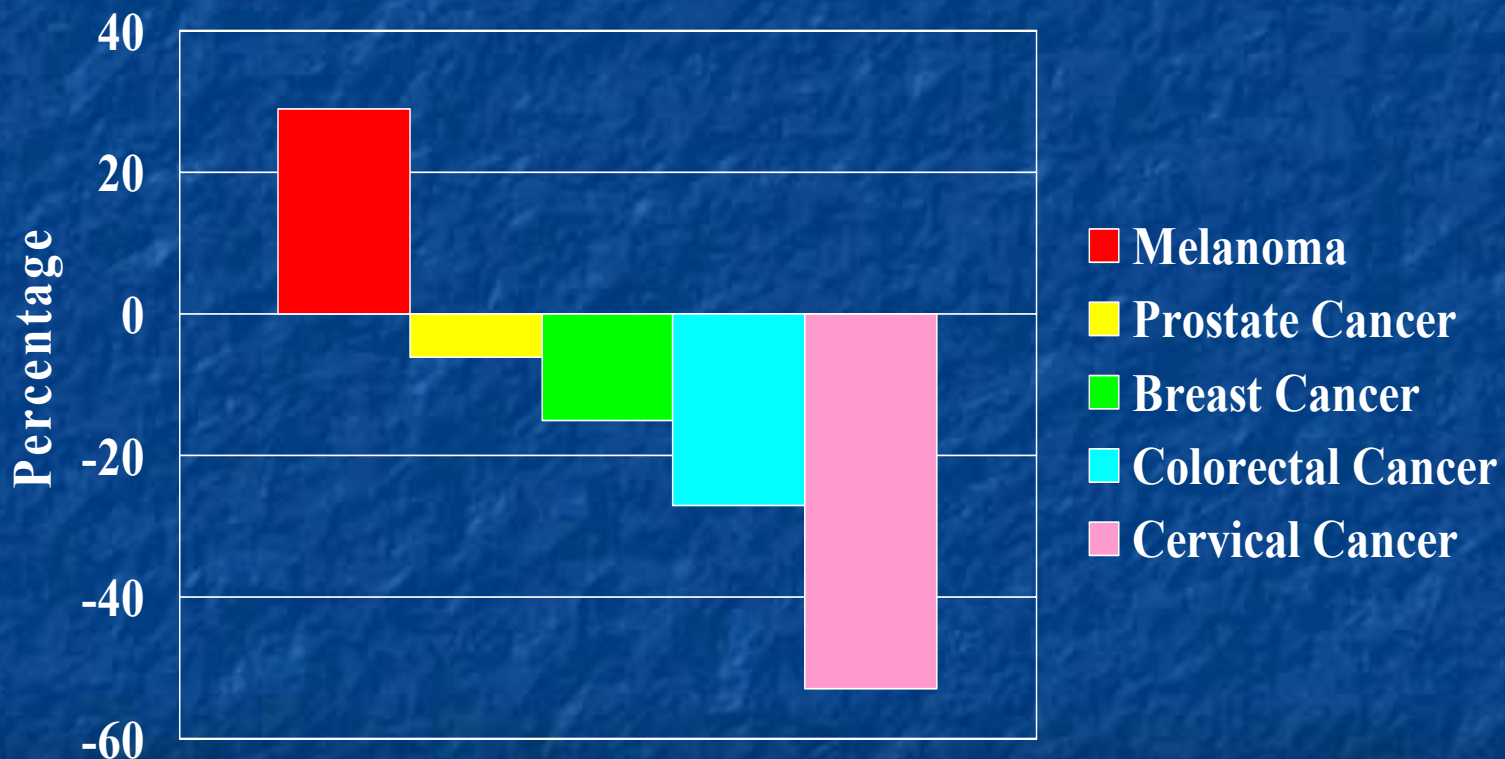   - Immunostimulatory and Disinhibitory Antibodies

Incidence and Prognosis

- 59,940 New cases of melanoma of the skin in 2007
  - ~8110 Deaths
  - 4% of new skin cancers
  - Majority of skin cancer deaths

Disease Stage	5-Yr Survival
Localized	95%
Regional	65%
Distant	15%

Jemal. *CA Cancer J Clin*. 2007;57:43.

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

Which primary melanomas will be lethal?

The Initial Forum: Stage IV Melanoma

- M1a
  - Defined by site in skin/soft tissue/nodes without elevation of LDH

- M1b
  - Defined by site in skin/ST/N and/or lung without elevation of LDH

- M1c
  - Defined by visceral site of involvement beyond lung or other distant site with elevation of LDH

(Usefully applied for multiple clinical trials)

Systemic Therapy of Advanced Melanoma

Stage IV (inoperable) survival <5% at 5+ years

- Only one approved cytotoxic agent in use
  - Dacarbazine (Temozolomide) with 6.8-12% response in modern trials, rarely durable

- Only one (biological) agent approved in modern times
  - High-dose IL-2, with 15% response and 5% durable responses

High Dose IL-2 Therapy Approved 1998
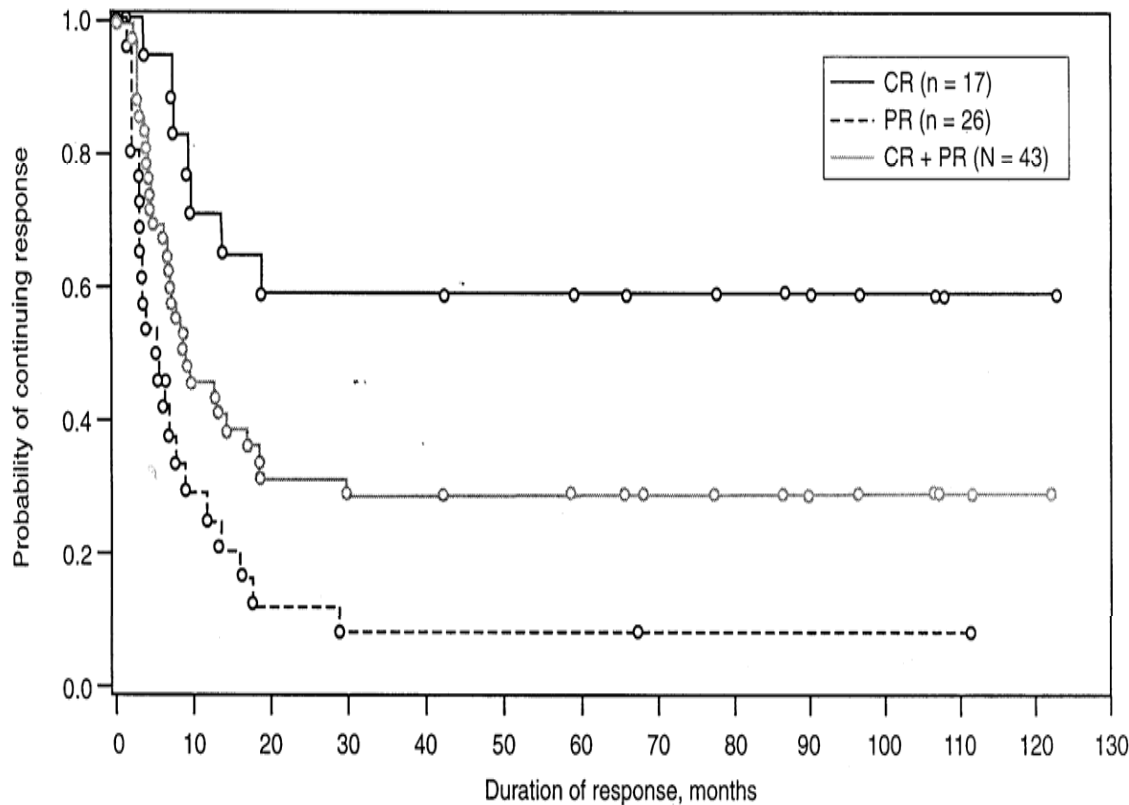
- RR: 16% (43 / 270)
- Durable responses in 6%
  - Median Duration 8.9 mos
  - CR: not reached

(N=270, collected phase II studies)

Atkins et al., JCO 1999

Interleukin-2 Summary

- High-dose bolus IL-2 approved by FDA in 1998
- Response rate ~16% of which 5-6% are durable remissions
- Toxicity and supportive care an issue
- Low dose IL-2 is not as effective
- Uncertain that any new agent with similar impact would receive approval

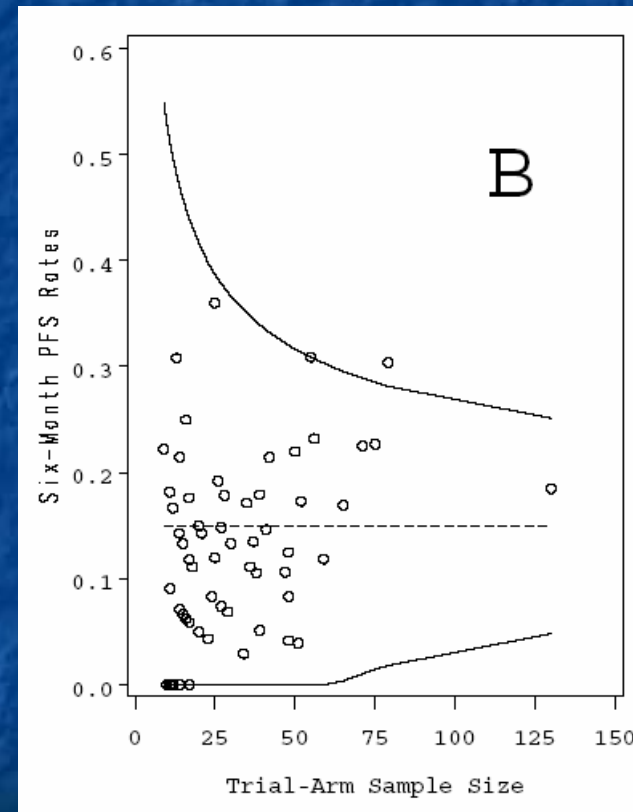Cooperative Group Meta-analysis of 70 Phase II Trials, 2100 Patients, 35 Years
Benchmarks for OS and PFS Endpoints

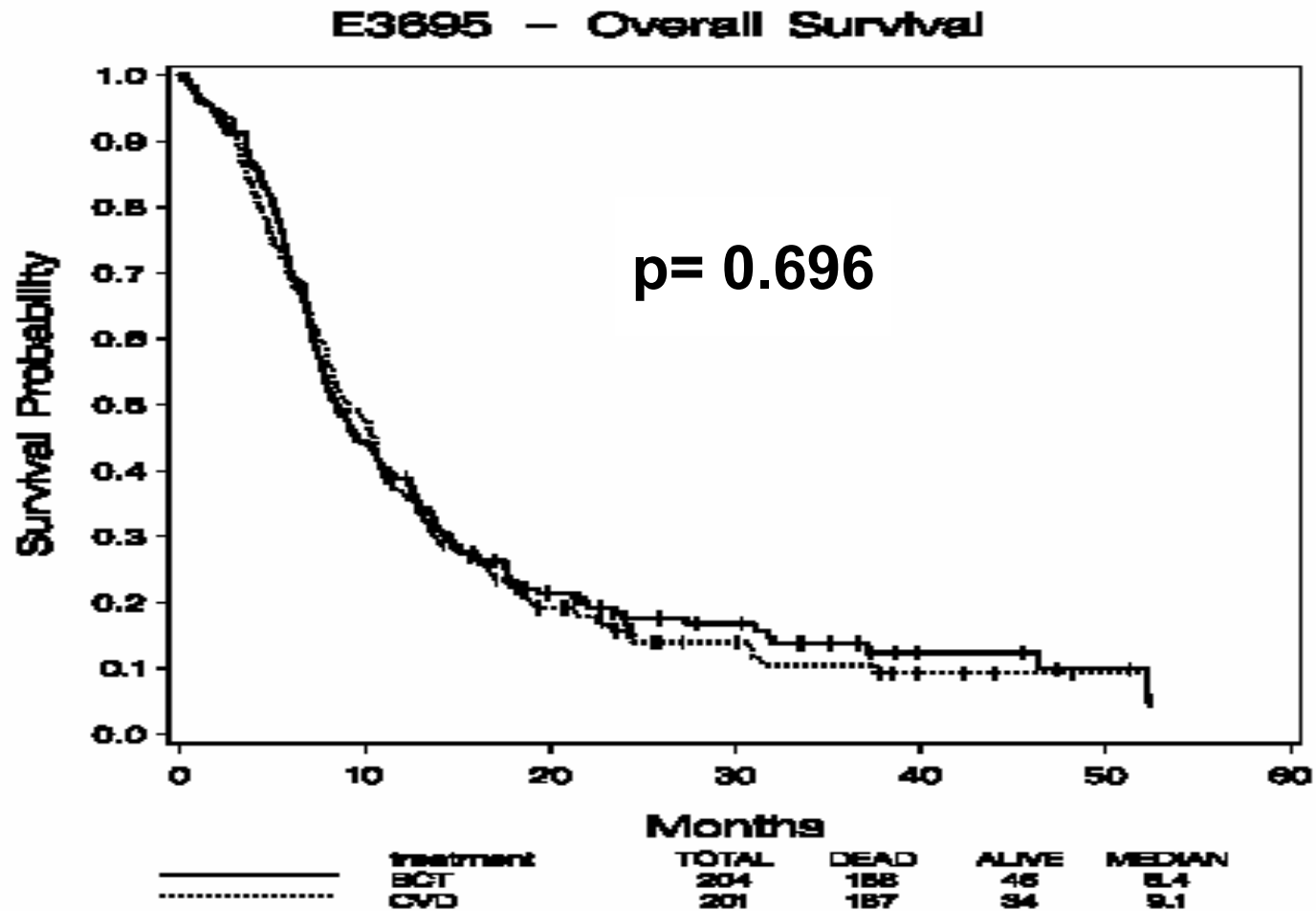**Survival at 1 year 30%**
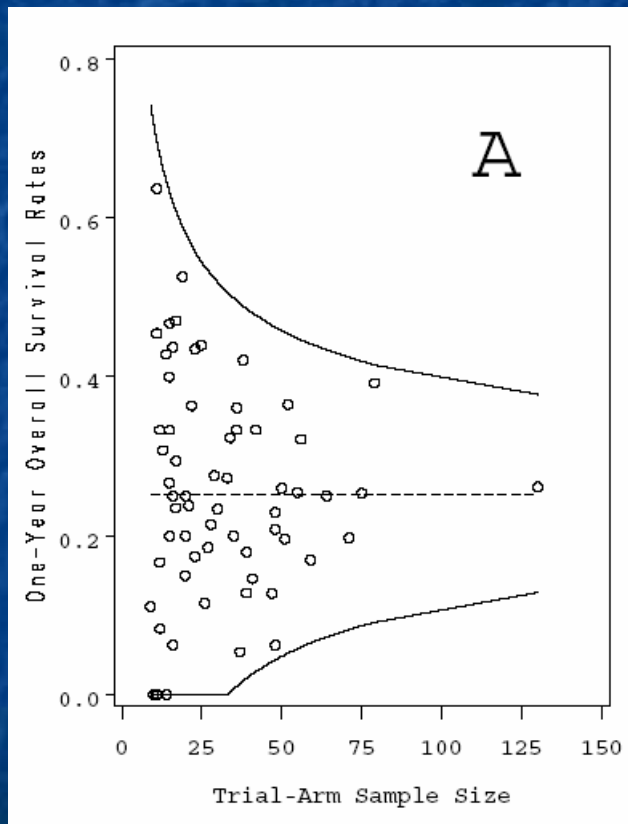
**Progression Free
Survival at 1 year 18%**

One year OS➜ 25%

Six month PFS➜ 15%

Numbers of patients➜

Numbers of patients➜

E3695: Survival Data

E3695 — Overall Survival

p= 0.696

treatment	TOTAL	DEAD	ALIVE	MEDIAN
BCT	204	188	46	6.4
CVD	201	187	34	9.1

Why so little impact of chemotherapy and combinations to date upon melanoma?

- Tumor cell drug resistance:
  – Mismatch Repair
  – Alkl guanine alkyl transferase (AGAT)
  – Base Excision Repair
- Specific molecular mechanisms of progression
  – BRAF mutated in 70% of melanoma
  – STAT3 constitutively activated in melanoma
- Tumor cell resistance to apoptosis
 – BCL2
  – Survivin

Summary

- No combination of agents is yet better than the single agent dacarbazine

- HD IL-2 produces long-term remissions in 5-10% of patients (very selected)

- Randomized multi-center phase III trials to date have all failed to reach primary endpoints with significant differences

Active stage IV melanoma is associated with immunological tolerance and Th2-type rather than effective Th1-type immune responses to MAGE-A6 & EphA2
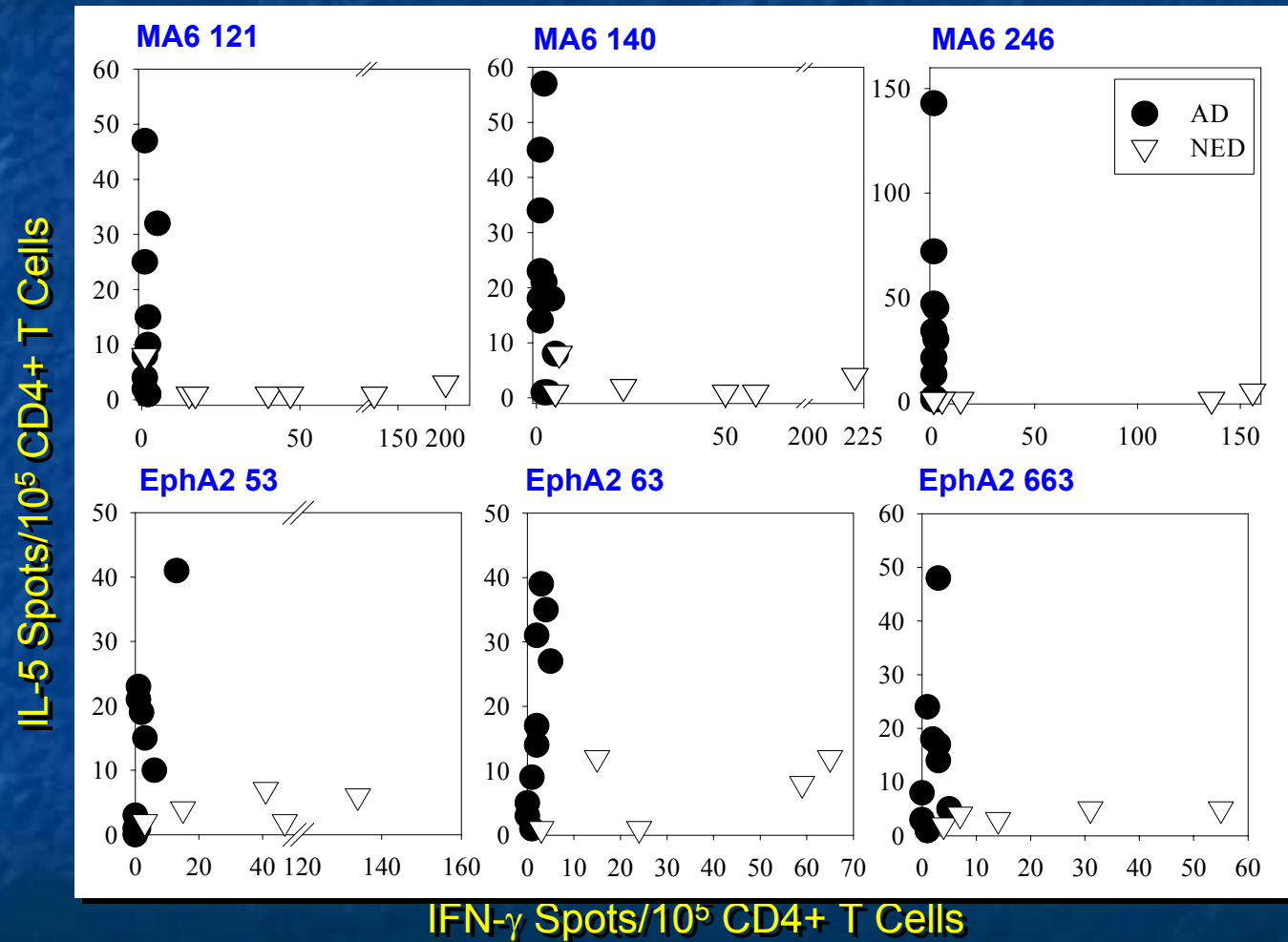
*AD = Active Disease; NED = No evidence of Disease.
Patients exhibited Th1-type immunity to Flu/EBV Th Epitopes
Tatsumi et al., J. Exp. Med. 196:619 (2002); Tatsumi et al., Cancer Res. 2003.
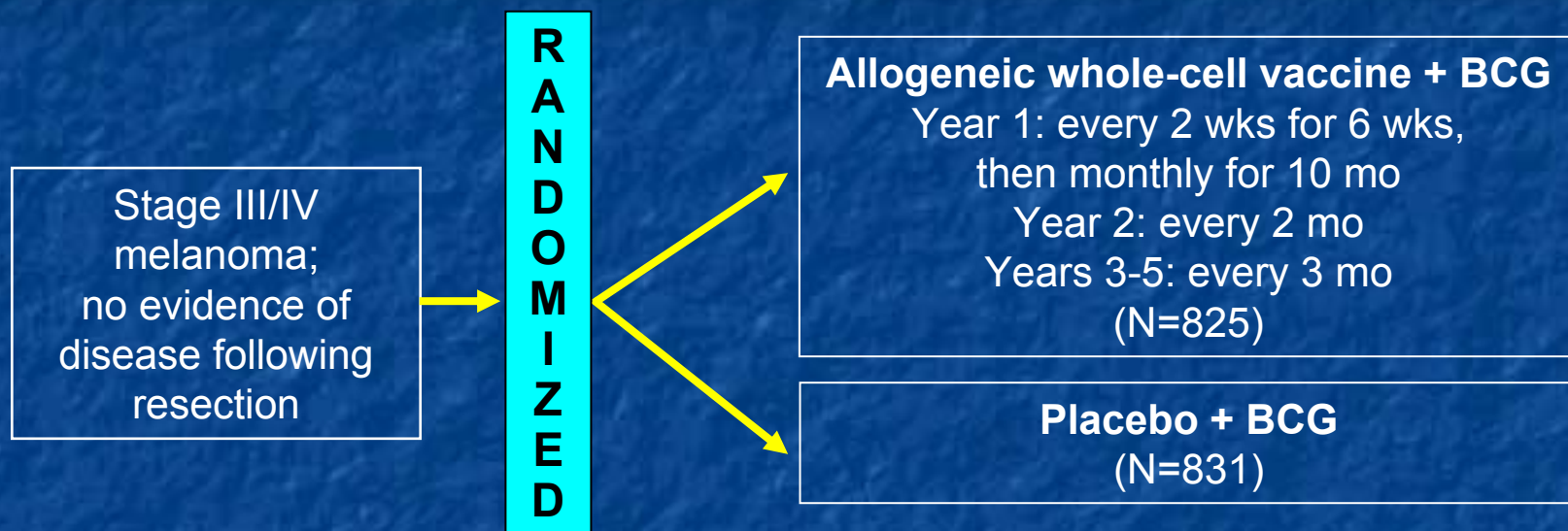
Adjuvant Trials have given more unequivocal results

- Vaccines, Adoptive Cellular/Passive Ab Transfer
    - Crude whole cell vaccines (Canvaxin)
    - Antibody (B cell)-inducing Gangliosides (GMK)
    - Effector T cell-inducing peptides (E1696; E4697; E1602); proteins, DNA

- Interferons & Cytokines
    - IFNγ (E4687, S8710)
    - IL-2 (S0008)
    - GM-CSF [peptide vaccines] (E4697)
    - IFNα2—the single agent established in current standard practice through mature phase III randomized controlled multicenter cooperative group investigations

Key: *statistically significant negative impact in Phase III Trial; Trial results pending; ph II or III evidence of significant benefit*

MMAIT: Phase III Trial of Allogeneic Melanoma Vaccine in Resected, Metastatic Melanoma

Stage III/IV melanoma; no evidence of disease following resection

R A N D O M I Z E D

Allogeneic whole-cell vaccine + BCG
Year 1: every 2 wks for 6 wks, then monthly for 10 mo
Year 2: every 2 mo
Years 3-5: every 3 mo
(N=825)

Placebo + BCG
(N=831)

	Stage III			Stage IV		
	Vaccine	**Placebo**	*P*	**Vaccine**	**Placebo**	*P*
DFS	43 mo	>60 mo	0.047	8.3 mo	7.2 mo	0.418
5-Yr DFS	47%	52%		27%	21%	
OS	>69 mo	>69 mo	0.04	32 mo	39 mo	NR
5-Yr OS	59%	68%		40%	45%	

BCG=Bacille Calmette-Guérin; DFS=disease-free survival.

MMAIT: Results

MMAIT-IV

DFS

MMAIT-III

DFS

OS

OS

Morton. *ASCO.* 2007 (abstr 8508).
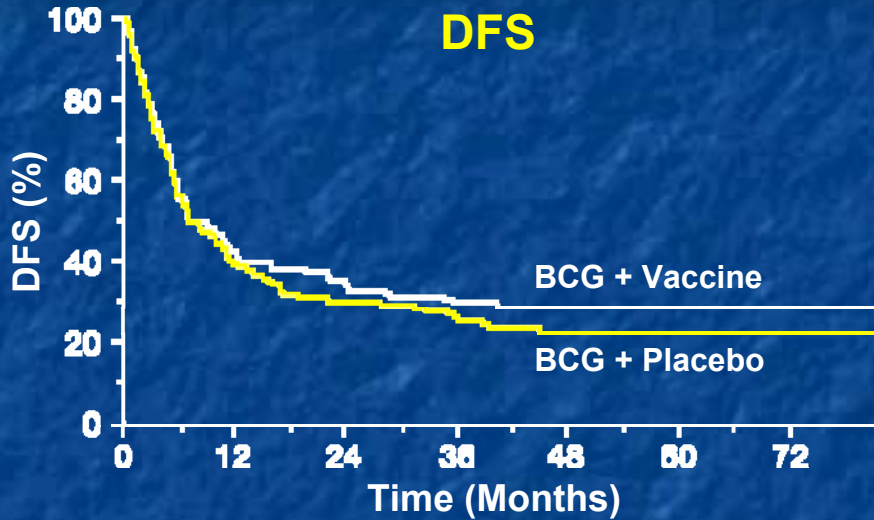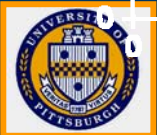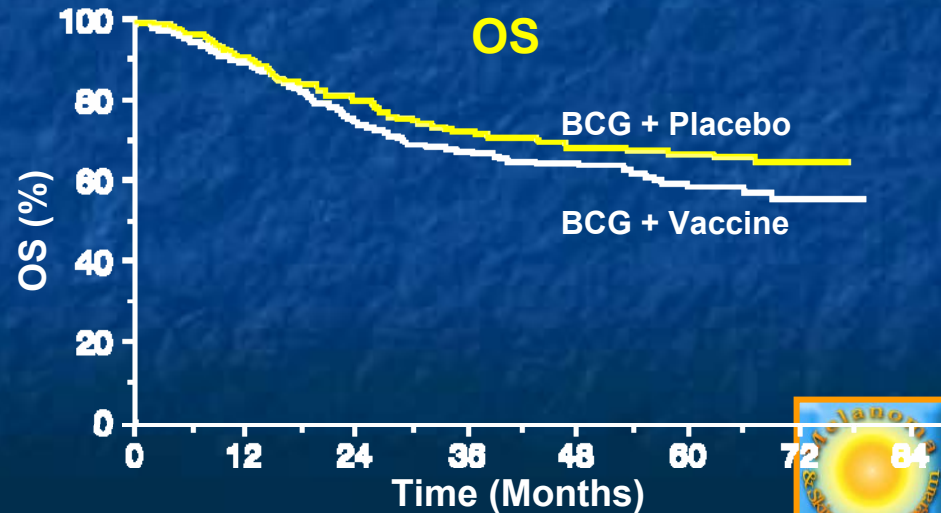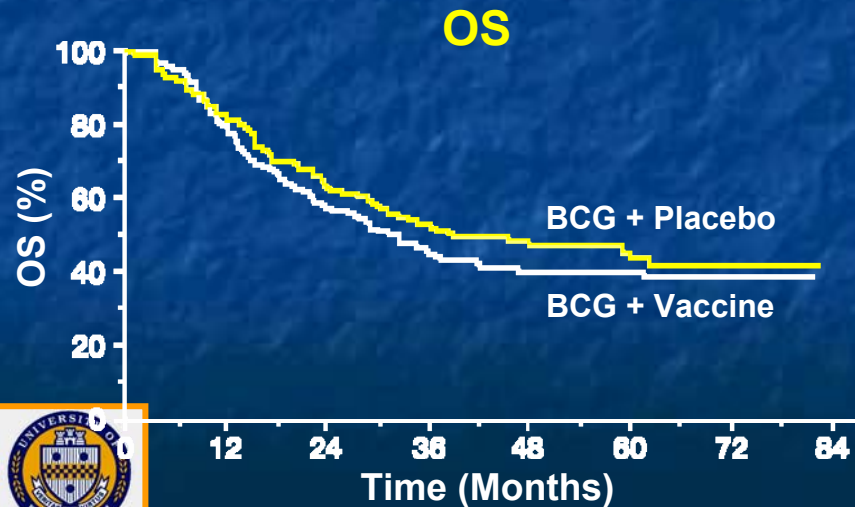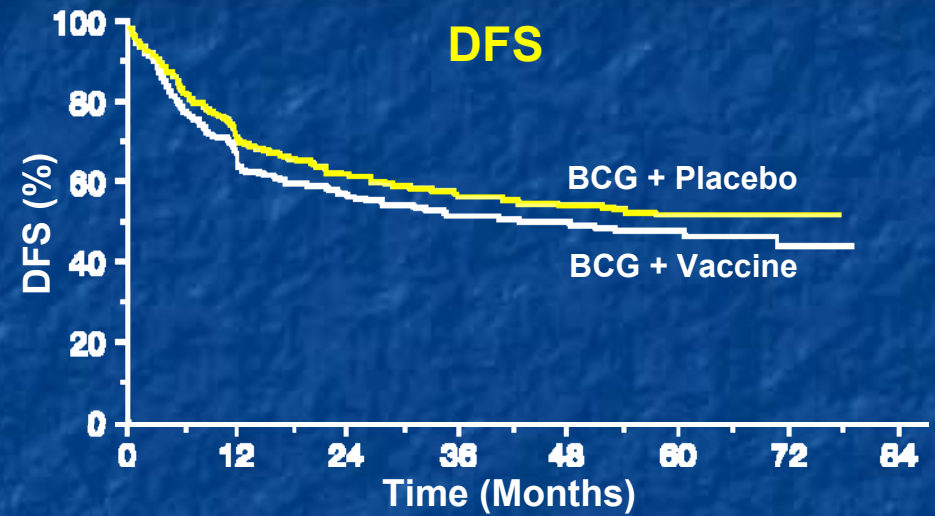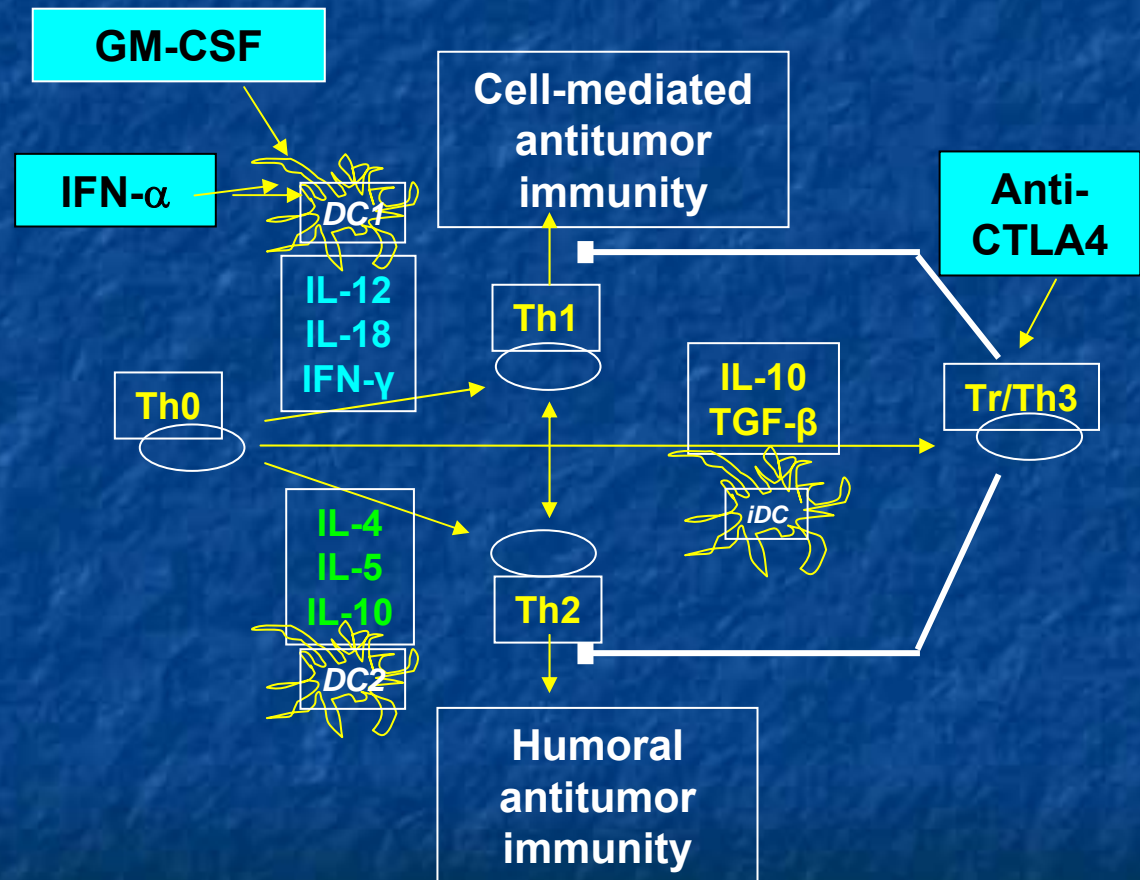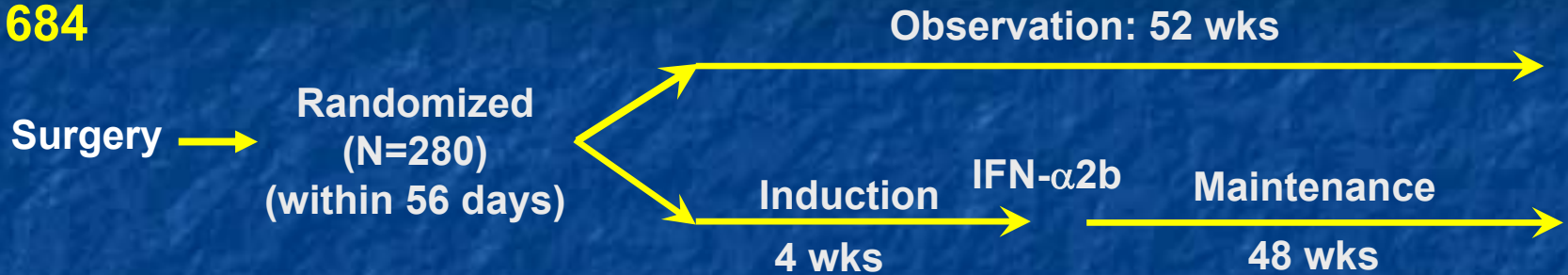
Established and New Potential Adjuvant Immunotherapy For Melanoma

- IFNs augment effector cell numbers and function, repolarizing the response to tumor cells

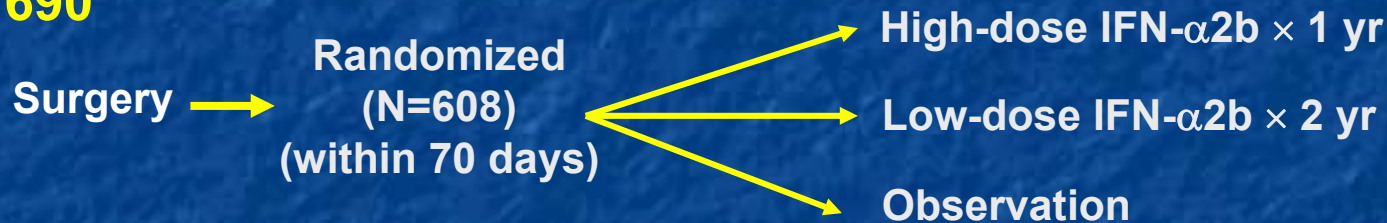- IFNs also inhibit proliferation and induce melanization in melanoma

Mature Phase III Trials of Adjuvant HDI for Stage IIB-III Melanoma

E1684

Observation: 52 wks

Surgery → Randomized (N=280) (within 56 days)

Induction 4 wks → IFN-α2b → Maintenance 48 wks

E1690

Surgery → Randomized (N=608) (within 70 days)

- High-dose IFN-α2b × 1 yr
- Low-dose IFN-α2b × 2 yr
- Observation

E1694

Surgery → Randomized (N=774)

- GM2-KLH/QS-21 (GMK) x 96 wks
- High-dose IFN-α2b x 52 wks

HDI=high-dose interferon.

Kirkwood. *J Clin Oncol.* 1996;14:7; Kirkwood. *J Clin Oncol.* 2000;18:2444; Kirkwood. *J Clin Oncol.* 2001;19:2370.

E1684, E1690, and E1694: Durable Impact upon RFS* and Significant Impact on OS**

E1684: IFN vs Observation**

HR=1.38
P_2=0.02
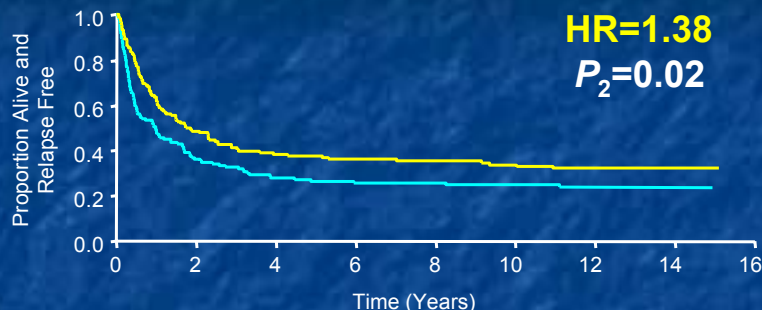
Time Interval (Years)

	0-2	2-4	4-6	6-8	8-10	10-12	12-14	14-16
Observ.	89/140	12/51	3/39	0/35	1/32	1/29	0/15	0/3
IFN	73/146	14/68	3/53	1/50	2/48	2/44	0/31	0/10

(No. events/No. at risk)

E1690: IFN vs Observation*

HR=1.24
P_2=0.09
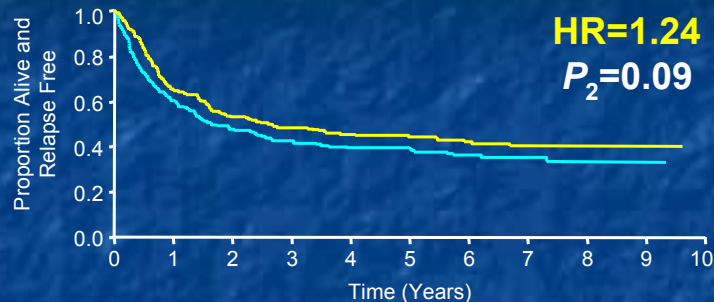
Time Interval (Years)

	0-2	2-4	4-6	6-8	8-10
Observ.	105/212	16/94	5/72	2/44	0/13
IFN	98/215	15/108	5/85	2/53	0/20

(No. events/No. at risk)

E1694: IFN vs GMK**

HR=1.33
P_2=0.006
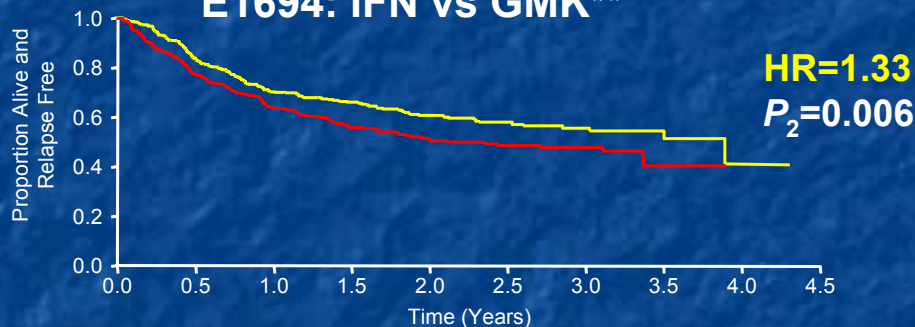
Time Interval (Years)

	0-1	1-2	2-3	3-4	4-5
IFN	118/436	28/257	8/123	3/47	0/3
GMK	153/439	40/240	6/113	3/40	0/0

(No. events/No. at risk)

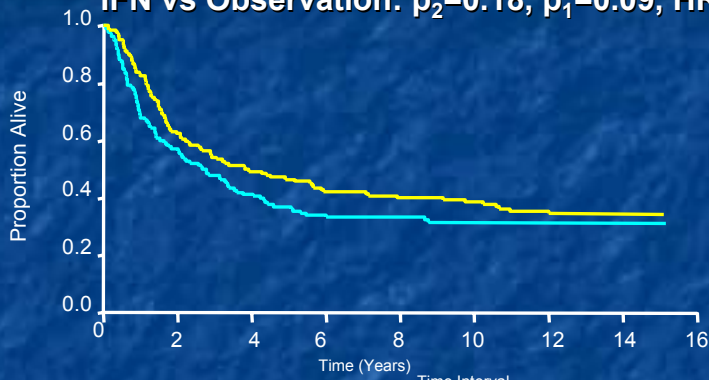RFS=relapse-free survival.

Kirkwood. *Clin Cancer Res.* 2004;10:1670.

Overall survival benefit for pivotal E1684 to >10 years is confirmed by E1694

E1684

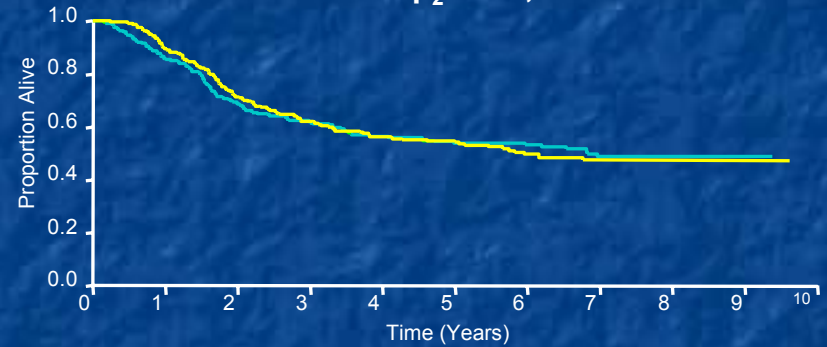**IFN vs Observation: p_2=0.18, p_1=0.09, HR=1.22**

Group	0-2	2-4	4-6	6-8	8-10	10-12	12-14	14-16
Observation	60/140	22/80	10/57	1/46	2/43	0/38	0/21	0/6
Interferon	54/146	19/90	10/70	3/60	2/56	5/52	0/35	0/10

(# events/# at risk)

E1690

IFN vs Observation: p_2=0.98, HR=1.00

Group	0-2	2-4	4-6	6-8	8-10
Observation	66/212	26/145	6/116	5/79	0/22
Interferon	61/215	32/153	12/116	3/74	0/24

(# events/# at risk)

E1694

IFN vs GMK: p_2=0.04, HR=1.32
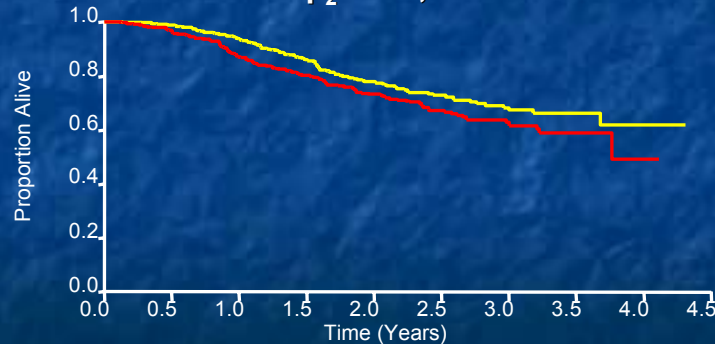
Group	0-1	1-2	2-3	3-4	4-5
Interferon	26/438	55/378	18/199	3/76	0/5
GMK	55/439	48/357	20/182	4/59	0/2

(# events/# at risk)

Kirkwood JM, et al. *Clin Cancer Res.* 2004:10:1670

Issues with high-dose IFNα survival benefits

- Two independent trials demonstrate significant durable survival benefits of IFNα
  - But a third does not: change in entry requirement of lymphadenectomy and asymmetric crossover after FDA approval of HDI provides a plausible explanation
- Benefit upon overall survival and relapse-free survival are not parallel after 10 yrs
  - Non-melanoma causes of death at >10 yrs may erode survival differences (EORTC 18952 ↑cardiac deaths?
  →Need analysis of death causes, salvage patterns
- Cost/Toxicity
  - >90% of E1694 patients without relapse completed 1 year of therapy, and cost efficacy is ~ other accepted therapies
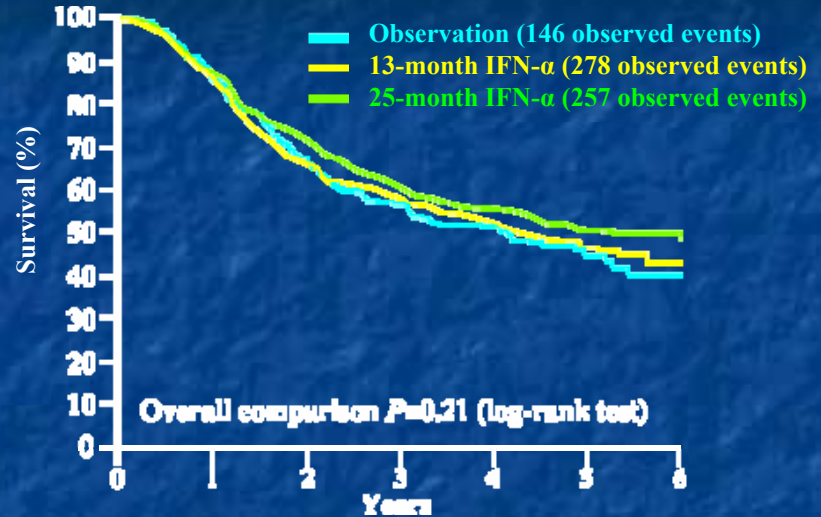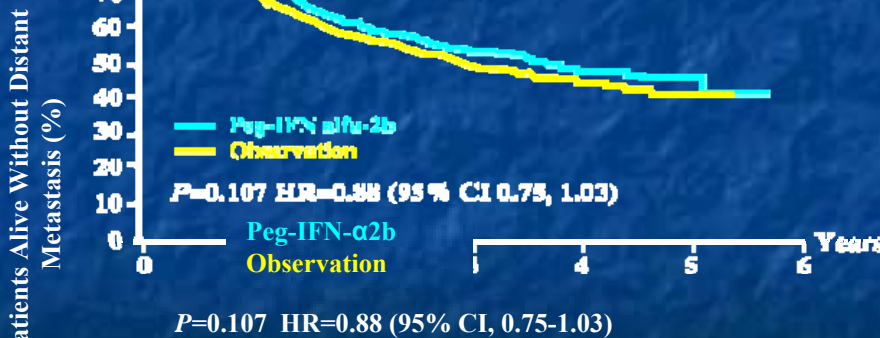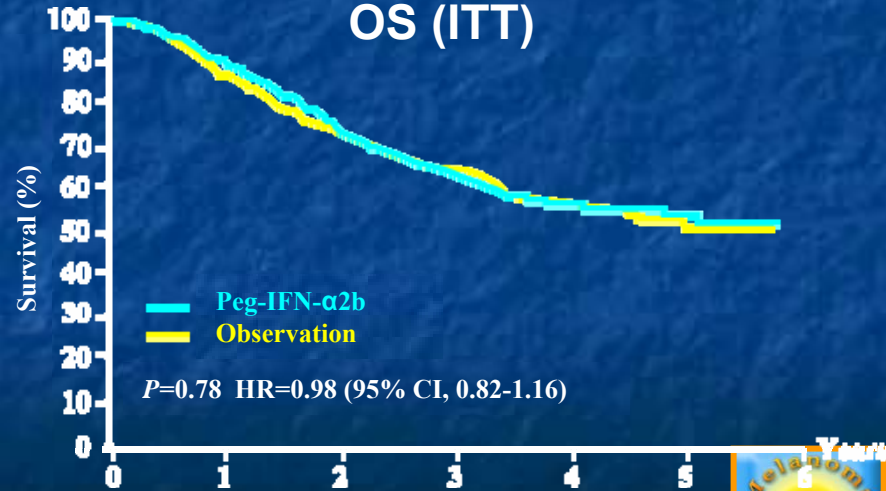
E18952 and E18991: Results
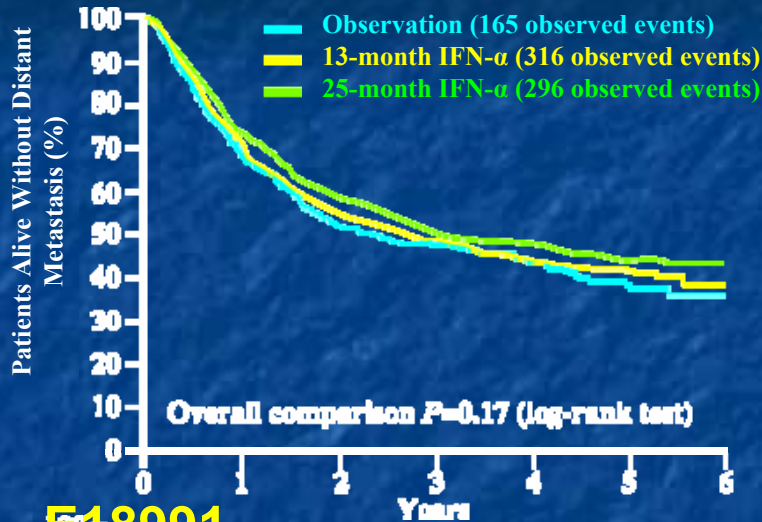
CI=confidence interval; DMFS=distant metastasis–free survival; ITT=intent to treat. Eggermont. *Lancet.* 2005;366:1189; Eggermont. *ASCO.* 2007 (abstr 8504).

Adjuvant IFN Therapy: Tolerability and Treatment Duration

Trial	Regimen	Endpoint	Patients Remaining on IFN Therapy
E1684	20 MU/m^2/day 1 mo, then 10 MU/m^2 3/wk 48 wks	6.9 yrs	~60% Received ≥80% of target dose
E1690	20 MU/m^2/day 5/wk 1 mo, then 10 MU/m^2 3/wk 48 wks	4.3 yrs	59% Required dose delay or reduction
E1694	20 MU/m^2/day 5/wk 1 mo, then 10 MU/m^2 3/wk 48 wks	16 mo	90%
E18952	10 MU 5/wk 4 wks, then 10 MU 3/wk	13 mo	84%
E18952	10 MU 5/wk 4 wks, then 5 MU 3/wk	25 mo	80%
E18991	6 µg/kg/wk 8 wks, then 3 µg/kg/wk	5 yrs	30%
WHO 16	3 MU 3/wk	3 yrs	100%
French Group	3 MU 3/wk	18 mo	65%

Kirkwood. *J Clin Oncol.* 1996;14:7; Kirkwood. *J Clin Oncol.* 2000;18:2444; Kirkwood. *J Clin Oncol.* 2001;19:2370; Eggermont. *Lancet.* 2005;366:1189; Eggermont. *ASCO.* 2007 (abstr 8504); Cascinelli. *Lancet.* 2001;358:866; Grob. *Lancet.* 1998;351:1905.

How to improve the therapeutic index?

→Dissect the roles of induction *vs.* maintenance

- All positive trials of IFNα utilized IV induction at 20MU/m^2 (C$_{max}$ >10,000u/ml)
- Is one month of IV IFNα2b both necessary and sufficient?
  - Intergroup E1697

E1697 - A randomized study of four weeks of high-dose interferon alpha-2b in stage T3-T4 or N1 (microscopic) melanoma

Hypothesis: Induction IV IFN is necessary and sufficient to achieve durable adjuvant benefit in intermediate-risk melanoma patients

STRATIFICATION

Pathologic Lymph Node Status

Known
Unkown

Lymph Node Staging Procedure

Sentinel Lymph Node Procedure
Elective Lymph Node Dissection
No Lymphadenectomy

Breslow Depth

1.5 - 3 mm
3.1 - 4 mm
> 4 mm

Ulceration of Primary Lesion

Yes
No

Disease Stage

Lymph Node Positive

Lymph Node Negative

RANDOMIZE

Arm A:

Observation

Arm B:

4 week high-dose IFN alfa-2b (Intron A)

20 MU/m^2/d qd IV for 5 consecutive days out of 7 (M-F) every week times 4 weeks

Gaps in Therapy of Melanoma

- More precise markers of prognosis
  - Treat only those at risk of relapse

- Markers to predict treatment benefit
  - Treat only those capable of response
    - Anti-tumor immunity
   - Autoimmunity to pigment cell markers, other tissue antigens

Neoadjuvant Therapy in Patients with Stage III Melanoma
UPCI 00-008

- Biomarker discovery to better predict treatment efficacy

- Define molecular mechanisms of treatment
  - Which of the multiple known actions are critical?
  - Direct pro-apoptotic, anti-angiogenic, or indirect immunomodulatory effects?

- Clinical response assessment at 4 weeks for correlation with RFS and OS

UPCI 00-008 Schema

Moschos et al., 2006
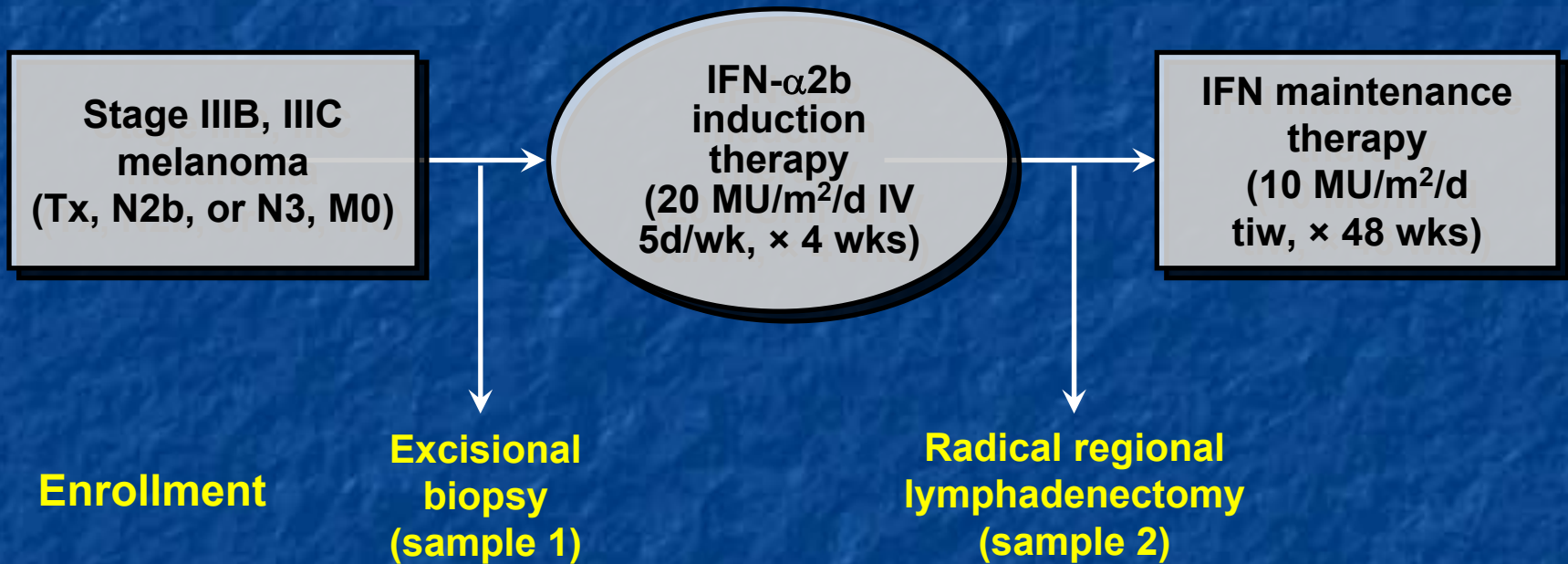
Results

- 20 patients enrolled
  - (age median 59, range 40-78; 13 males)
- 11 with recurrent disease
  - 15 completed 4 weeks of HDI
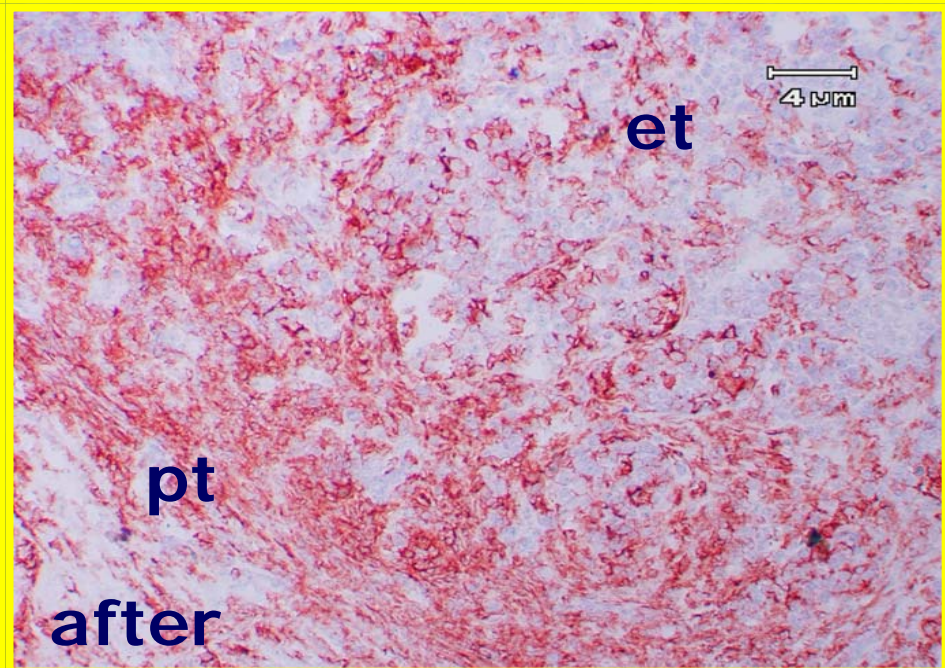- Objective Response at 4 weeks of treatment:
  Clinical

  1 complete, 10 partial

  Pathologic

  3 complete, 2 microscopic residual disease
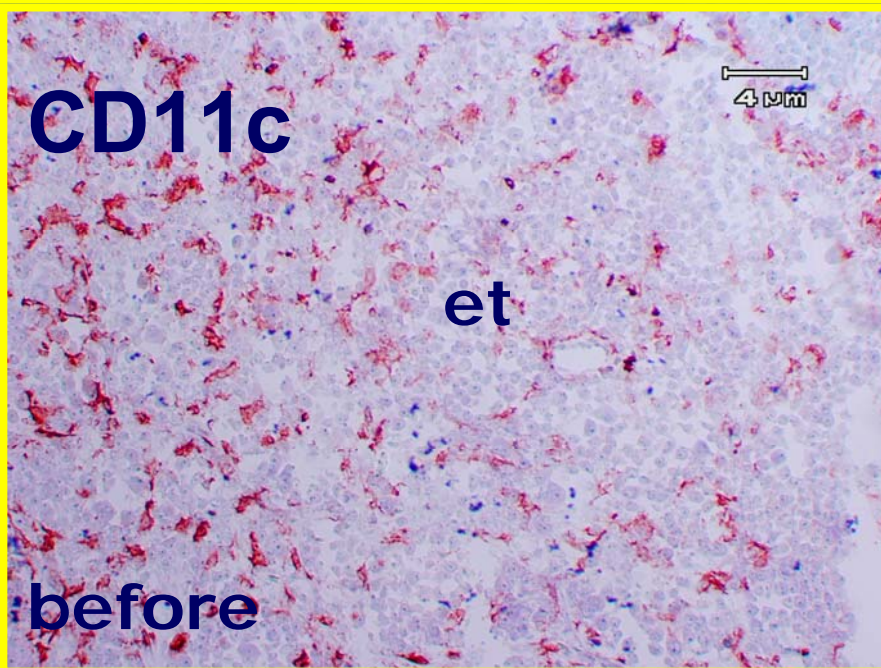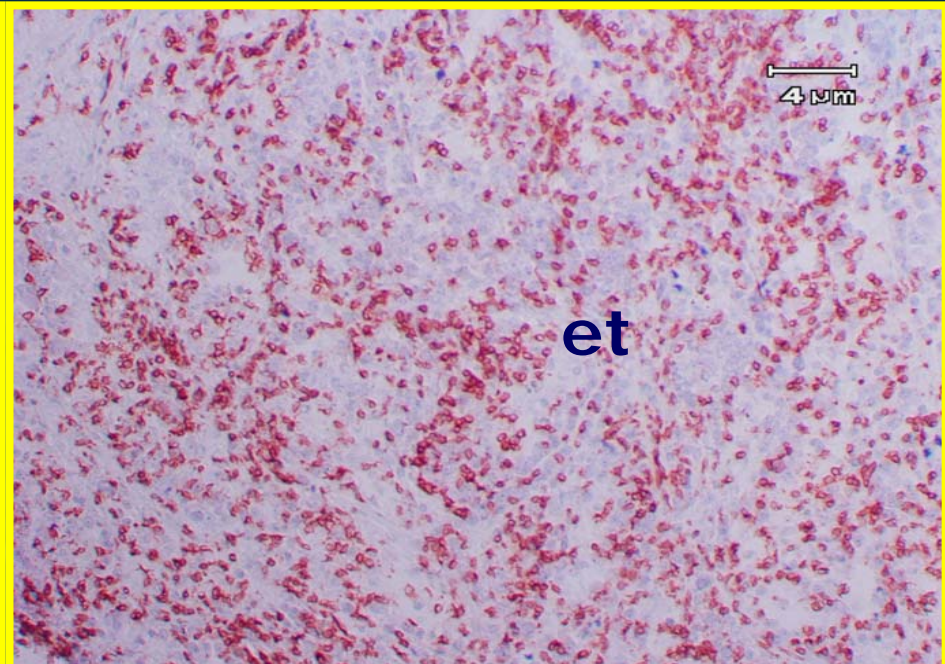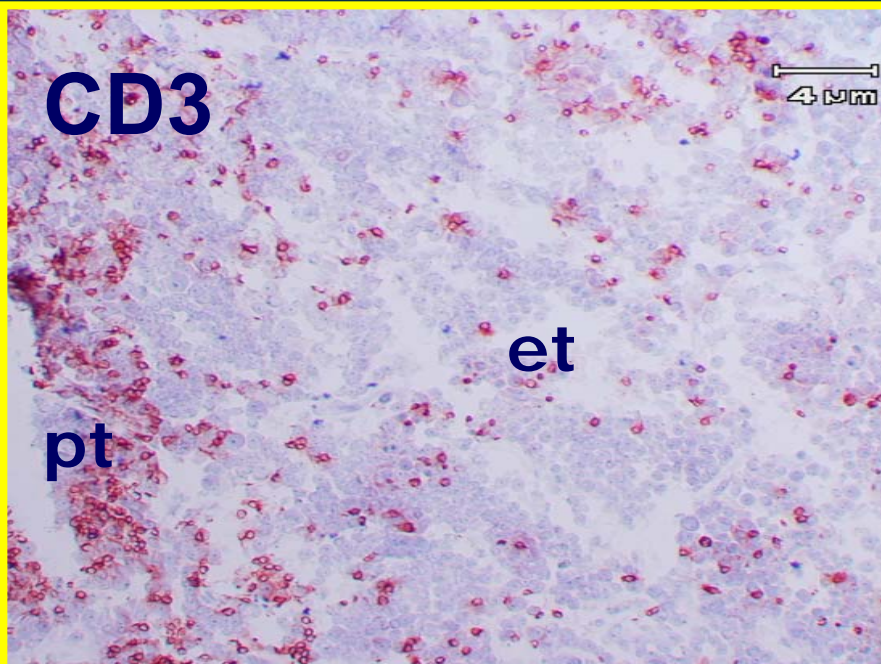
HDI increases the number of immunologically relevant cells infiltrating regional lymph node metastatic tumor
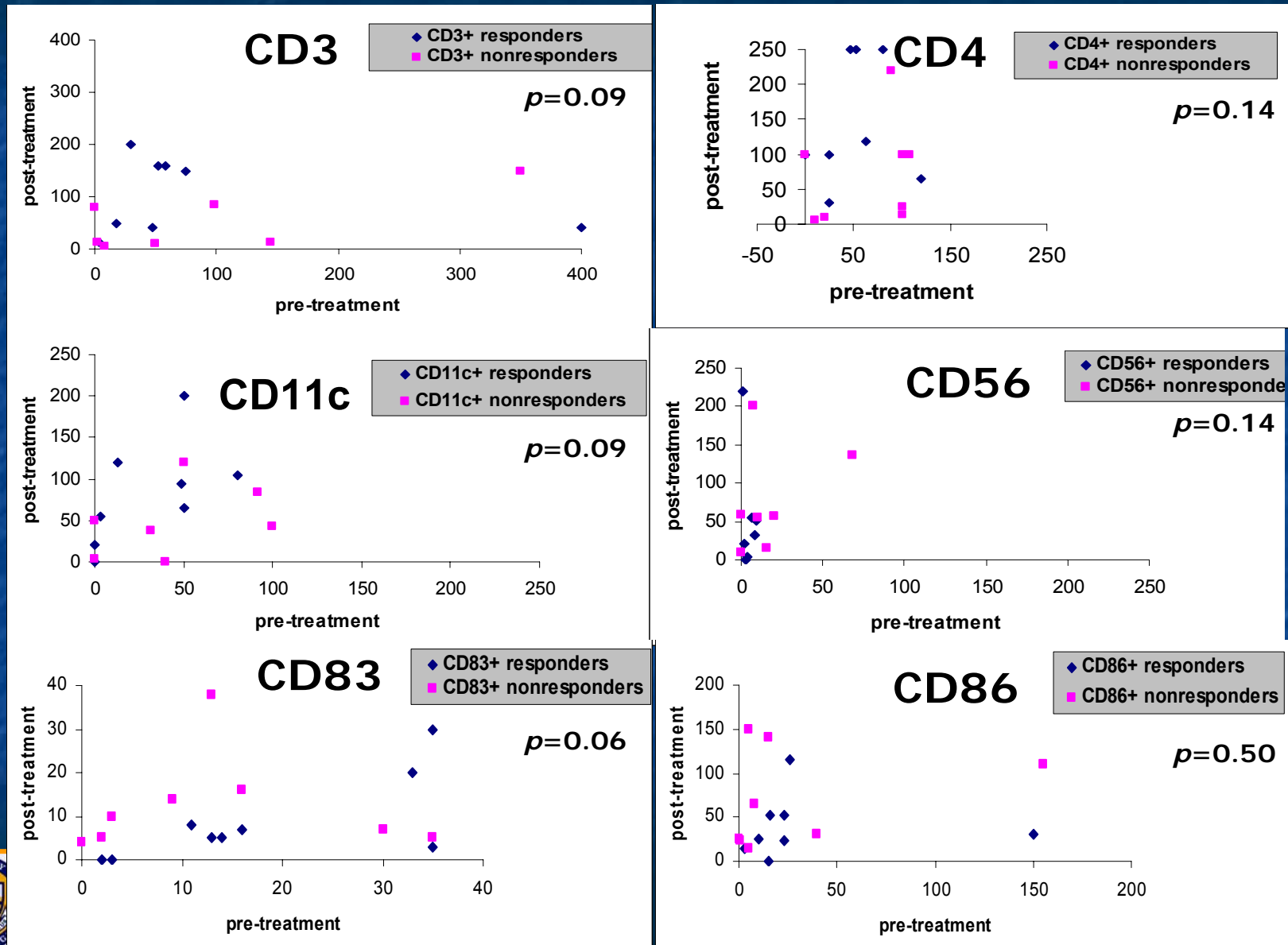
HDI Down-Regulates pSTAT3 Tyr705 And STAT3 Expression in Tumor Cells

Pretreatment   **Post treatment**

H&E

IHC

A   B

C   D

E

negative control

6 μm
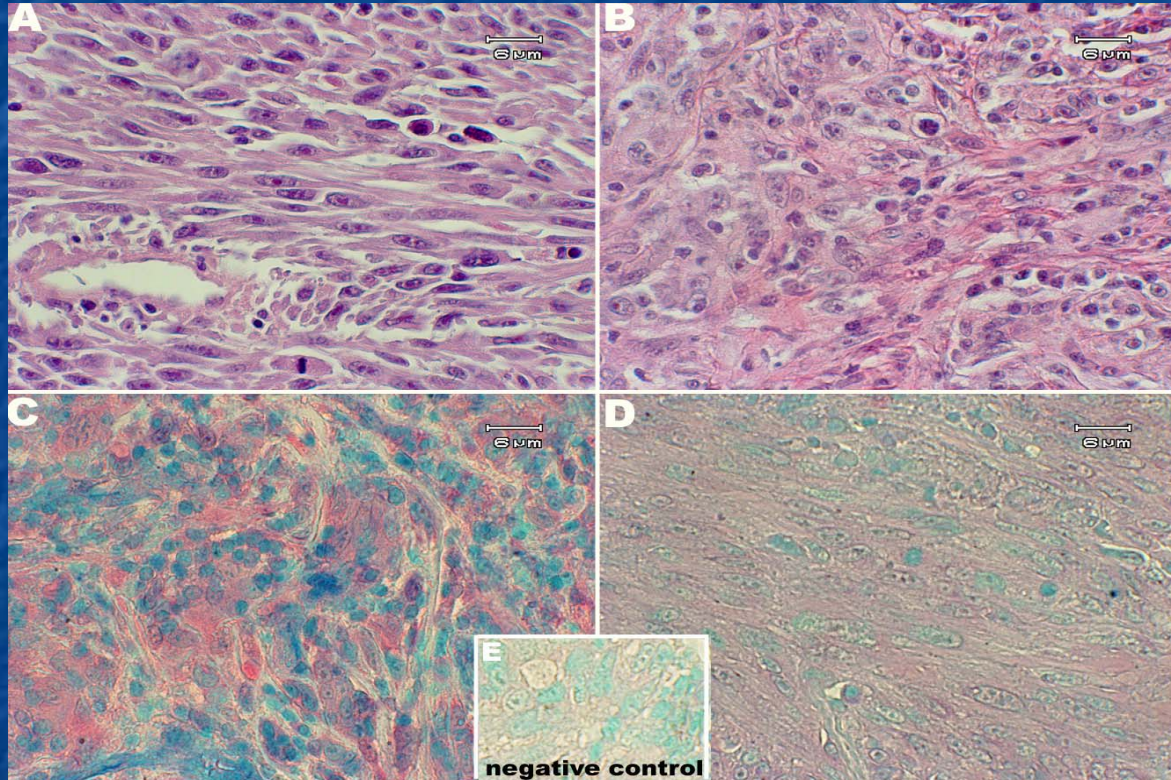
Blue = pSTAT3tyr705
Red = STAT3

Wang et al., Clin Cancer Res 2007

HDI Down-Regulates pSTAT3 Tyr705 and STAT3 in Regional Lymph Node Metastases of Melanoma

Wang et al., Clin Cancer Res 2007
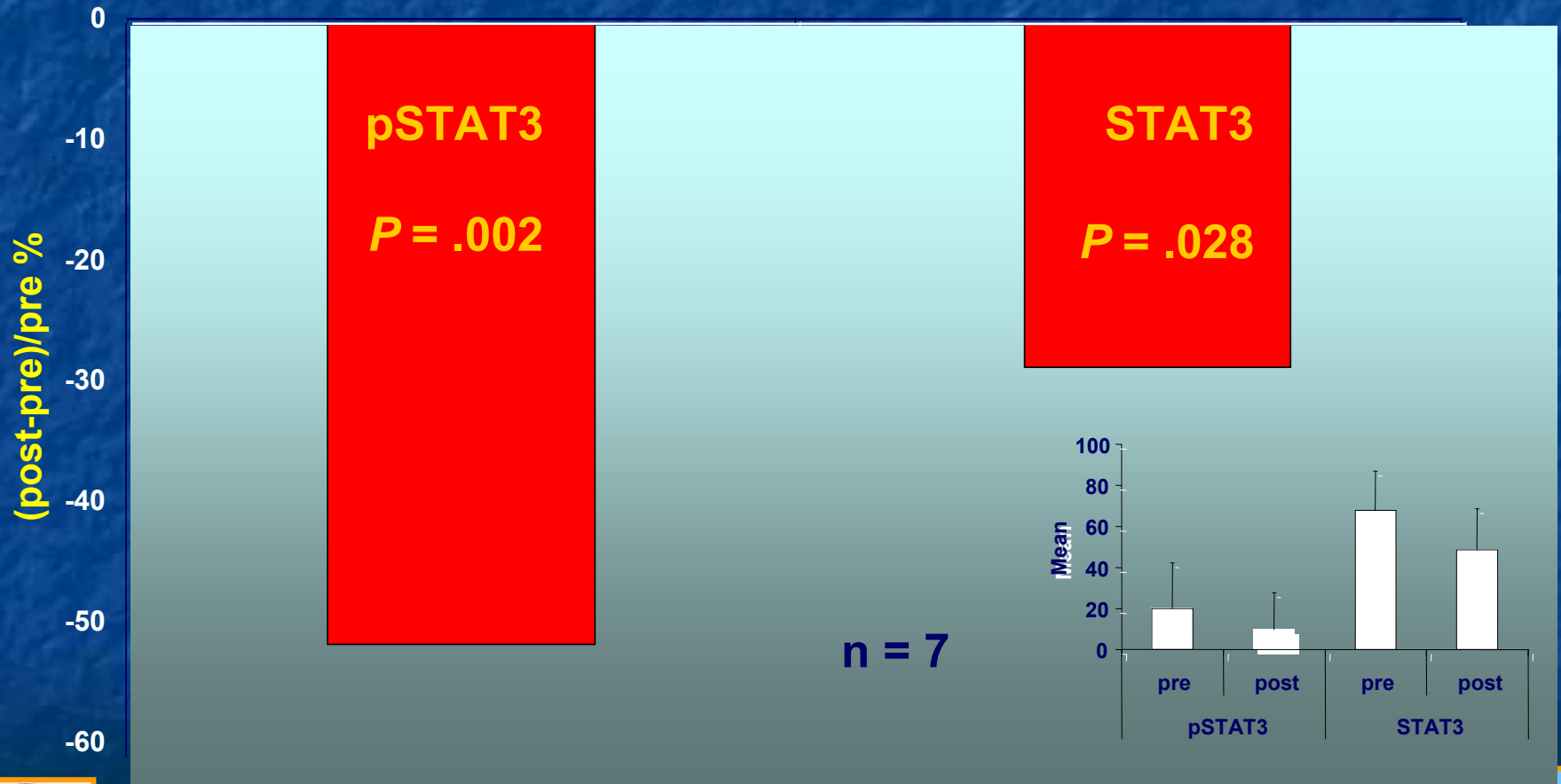
HDI Up-regulates pSTAT1 Tyr701 and Down-regulates pSTAT3 Tyr705 in Melanoma

Wang et al., Clin Cancer Res 2007
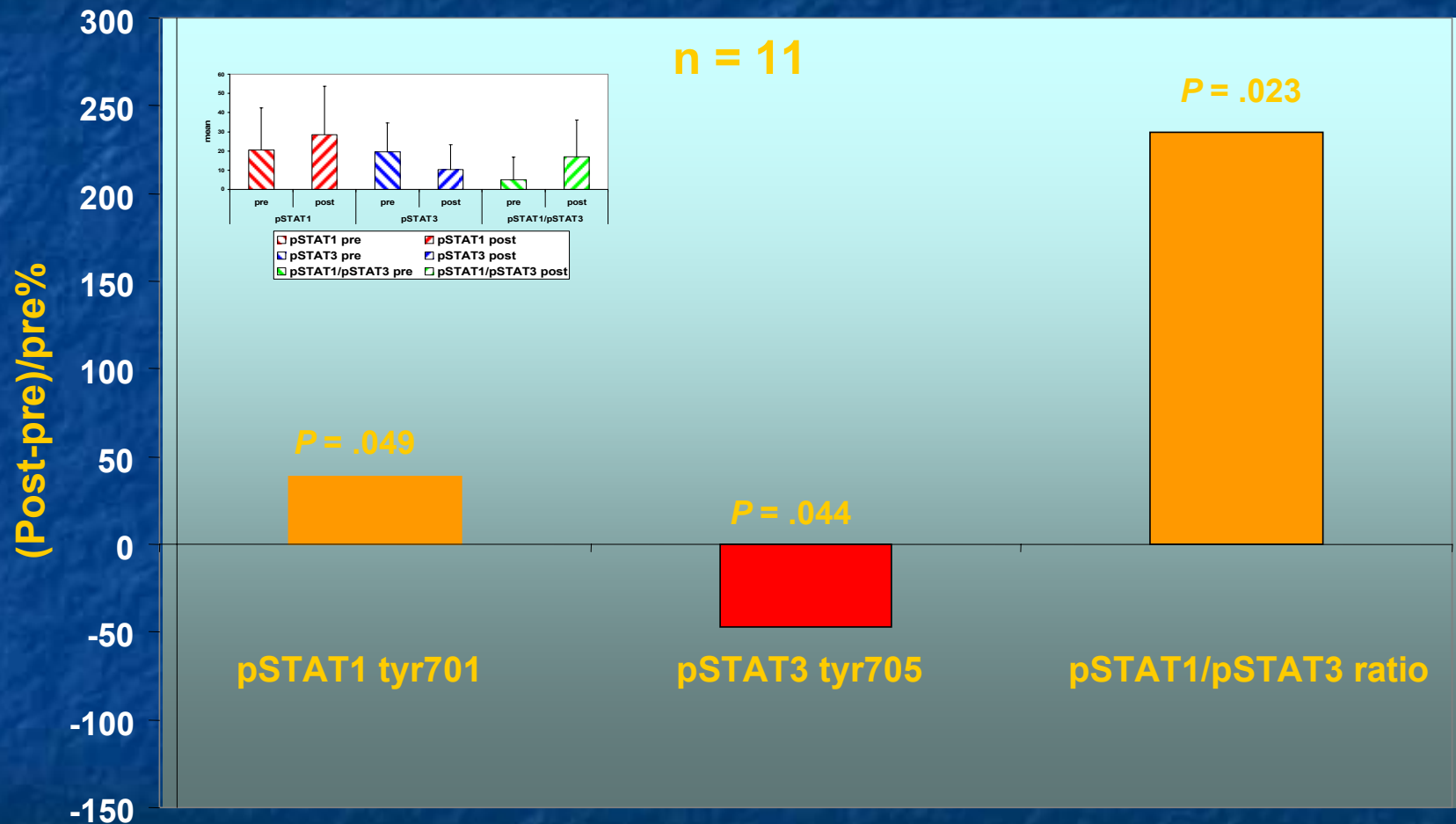
Conclusions from Neoadjuvant High-Dose IFN-α2b Trial 00-008

- Clinical response at day 29 is improved
  - 55% of patients with objective response
  - Radiographic and pathologic criteria
  - Relapse-free and overall survival data too early for final assessment
- Molecular and immunologic effects:
  - ↓ pSTAT3/STAT3, IFNAR2
  - ↑ pSTAT1, pSTAT1/3 ratio, and TAP2
  - ↑ CD3 T cell and CD11c dendritic cell populations in tumor

Prognostic Significance of Autoimmunity

- Subset analysis of phase III trial
- 200 Patients with stage IIB/IIIC melanoma

Stage IIB/IIIC melanoma

Arm 1: IFN-α2b 15 MU/m^2 5 x weekly for 4 wks, then observation
(N=96)

Arm 2: Same as Arm 1 + IFN-2b 10 MU 3 x weekly for 48 wks
(N=104)
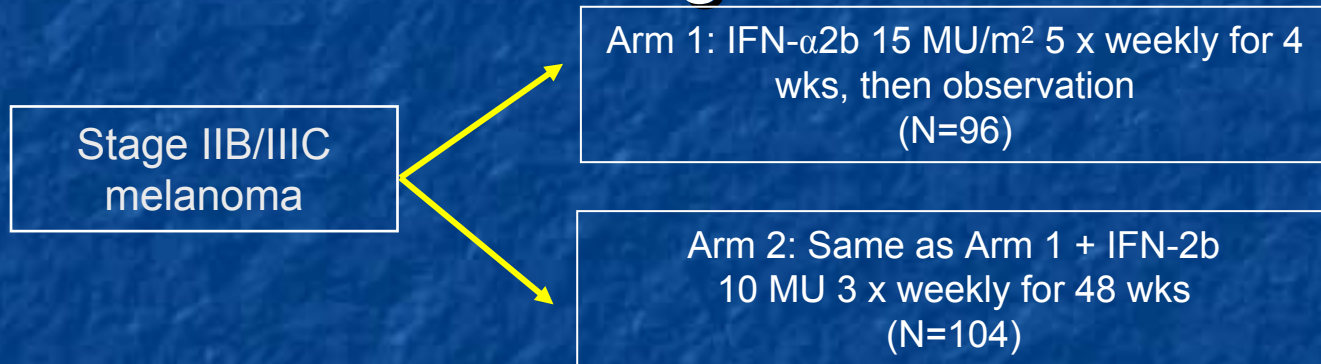
Manifestation of Autoimmunity	N	%
Antinuclear Antibodies	12	6
Anticardiolipin Antibodies	10	5
Vitiligo	11	6
Clinical Manifestations	19	10
Multiple Manifestations	16	8

Gogas et al., *N Engl J Med*. 2006;354:709.

Multivariate Analysis for OS in High-Risk Melanoma Patients Receiving HDI

Positive Autoimmunity Status	RFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
At 3 mo	0.15 (0.06-0.37)	<0.001	0.07 (0.02-0.28)	<0.001
At 12 mo	0.08 (0.03-0.22)	<0.001	0.02 (<0.01-0.15)	<0.001
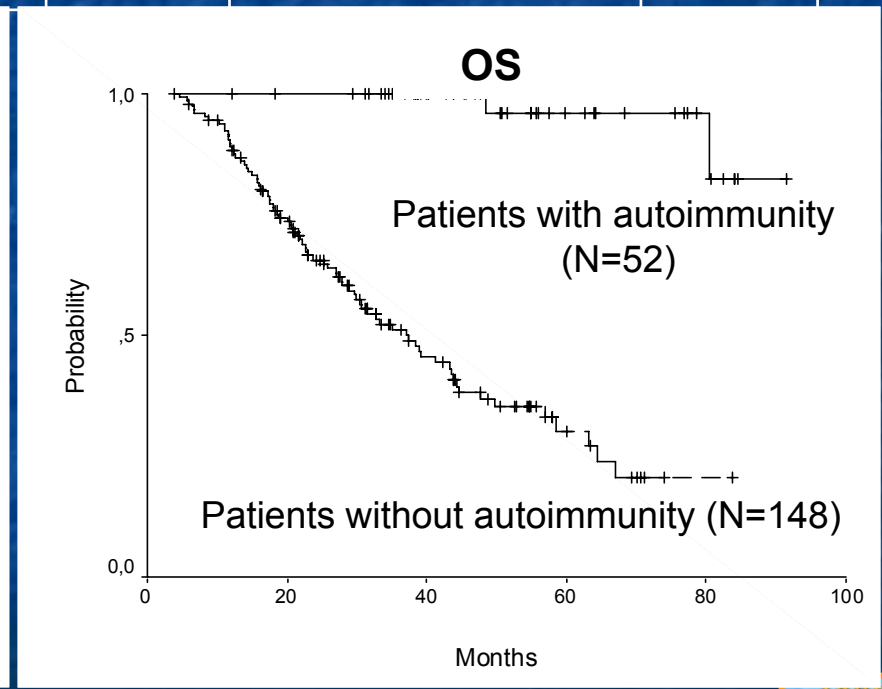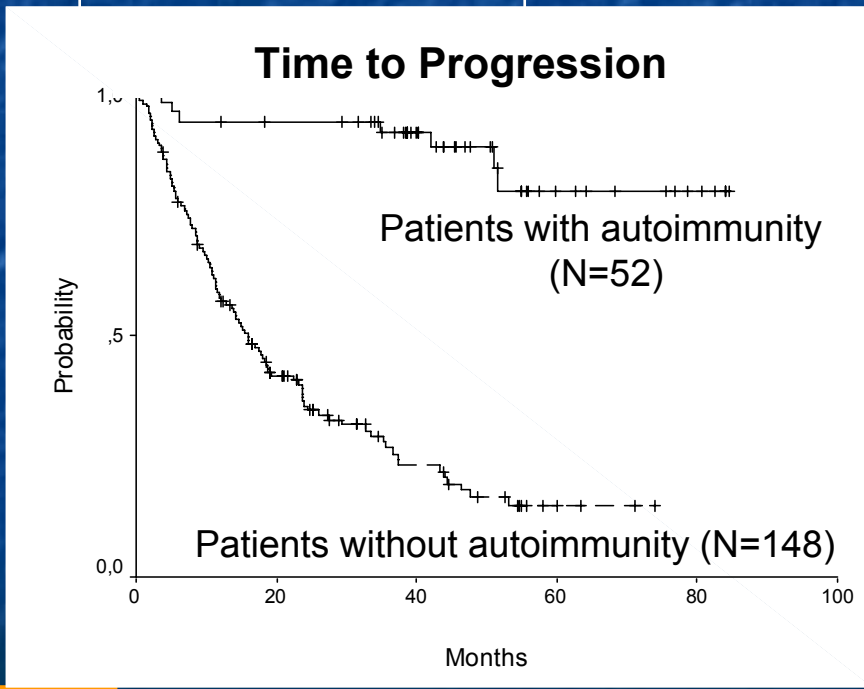
HDI=high-dose IFN-α2b.

Gogas. *N Engl J Med.* 2006;354:709.

Autoimmunity Is Correlated With Improved Outcomes in Melanoma

- Development of vitiligo, thyroiditis, and autoantibodies to other endocrine targets predicts reduced relapse risk and improved DFS and OS
  - Results confirmed in subset analyses of 13A/98 (phase III), E1694 (phase II), and E2696 (phase II)
- Induction of autoimmunity is a common thread for active immunomodulatory therapies of this disease
  - Spontaneous vitiligo is a favorable attribute
    - For disease outcome
    - For response to therapy: IL-2; anti–CTLA-4; IFN
- **Autoimmunity to endocrine and pigment cell targets is a surrogate for immunity to tumor antigens yet to be defined**

Gogas. *N Engl J Med.* 2006;354:709; Stuckert. *ASCO.* 2007 (abstr 8506); Stuckert. *AACR.* 2007 (abstr 166); Nordlund. *J Am Acad Derm.* 1983;9:689; Phan. *J Clin Oncol.* 2001;19:3477; Phan. *Proc Natl Acad Sci U S A.* 2003;100:8372.

Biomarkers of Disease Progression

- **Blood LDH: reanalysis of GM301 and E18951**
  - Trials had identical eligibility
  - Higher LDH correlated with decreased OS in advanced melanoma
  - Elevations predictive of nonresponse to oblimersen treatment
    - Patients with nonelevated baseline LDH had higher OS (12.3 mo vs 9.9 mo; P=0.0009) and ORR (20.8% vs 7.2%; P=0.002) in oblimersen + DTIC arm vs DTIC arm

- **S100**
  - S100 ≥0.08 μg/L is an independent prognostic marker for RFS and OS)
  - S100B is a prognostic marker for DMFS in patients with stage III melanoma

Keilholz. *ASCO.* 2007 (abstr 8552); Stuckert. *ASCO.* 2007 (abstr 8506); Suciu. *ASCO.* 2007 (abstr 8518).

Multiplexed Analysis of Serum Biomarkers

- High-throughput xMAP multiplex immunobead assay
  - Tested 29 analytes: cytokines, chemokines, angiogenic factors, growth factors, and soluble receptors
  - Serum of 378 matched healthy subjects vs 179 patients with melanoma from ECOG E1694
    - Phase III trial of HDI vs ganglioside vaccine in resected, high-risk, cutaneous melanoma

- Serum concentrations of many markers were found to be higher in patients with resected, high-risk melanoma than in healthy individuals

E1694

Surgery → Randomized N=774 → GMK x 96 wks

Randomized N=774 → High-dose IFN-α2b x 52 wks

Yurkovetsky. *Clin Cancer Res.* 2007;13:2422; Kirkwood. *J Clin Oncol.* 2001;19:2370.

Predictive Role of Pretherapy Serum Cytokine Levels for IFN Adjuvant Therapy

Patients Receiving HDI
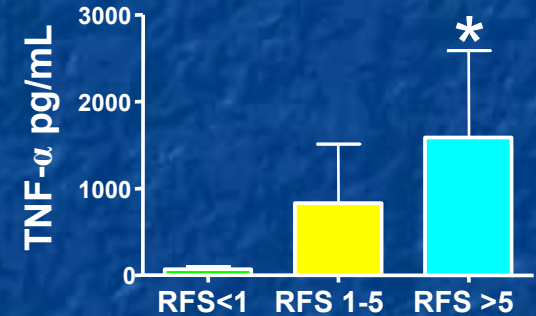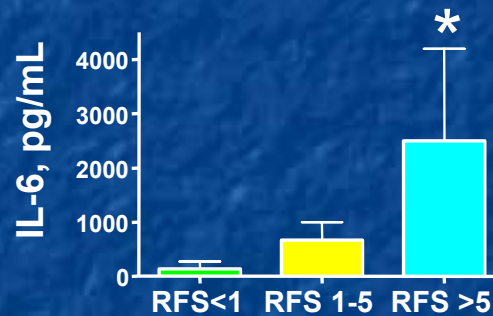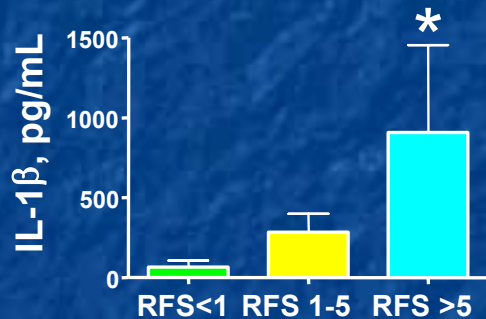
Patients Receiving GMK
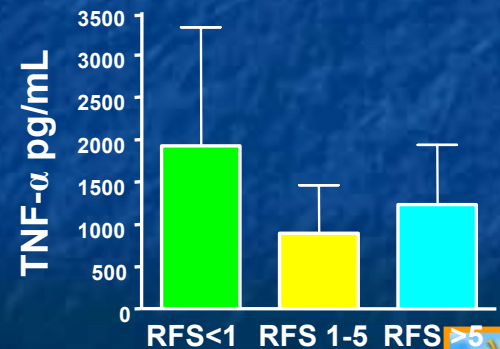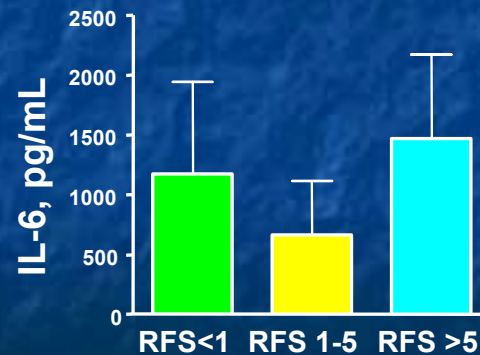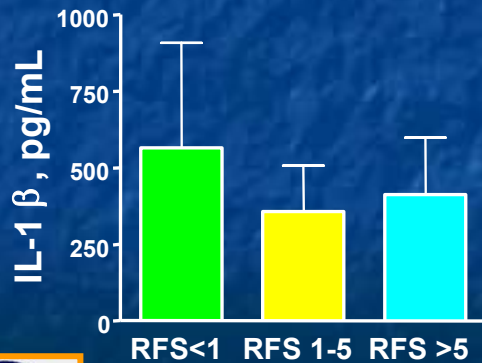
Conclusions

- IL-2, IFNα, and anti CTLA4 blocking antibodies induce durable remission in metastatic disease through mechanisms that appear to be immunological, and variably associated with induction of autoimmunity to normal tissues
- Adjuvant arena may be the most informative for new biological agents

CTLA-4

APC Activated T cell Anti-CTLA-4 antibody blocks CTLA-4/B7 interaction Activated T cell
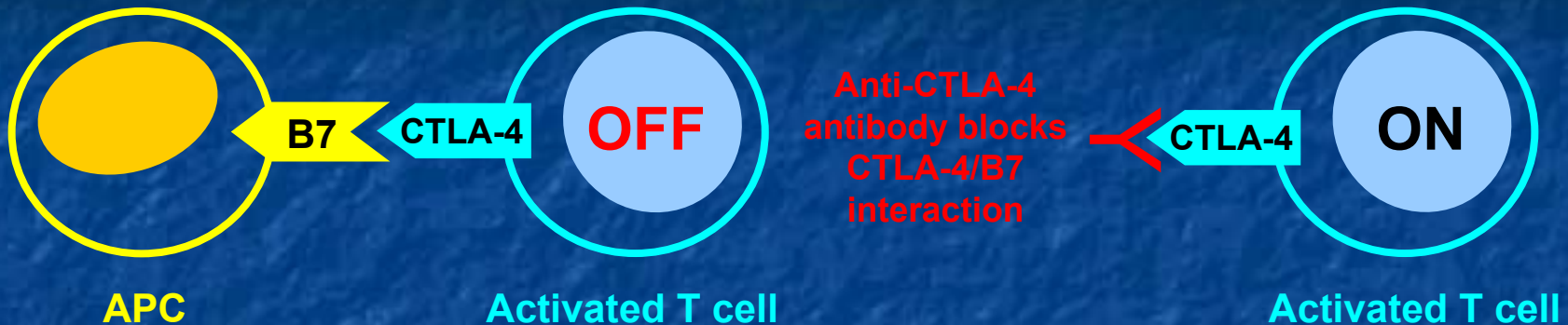
- Glycoprotein expressed on the surface of activated T cells
- Downregulates T-cell response
  - Decrease in IL-2 production
  - Arrest of cell cycle progression
- Anti-CTLA-4 monoclonal antibody antitumor activity in murine models

Anti-CTLA4 Blocking Antibodies

- Potent new inducer of autoimmunity associated with durable antitumor effects in advanced melanoma

- Potentially greater impact in adjuvant setting vs. microscopic disease?

CTLA-4 Antagonistic mAbs in Clinical Development

Antibody Name	Former Names	Type of Antibody	Ig Subtype	Plasma Half-life
Ipilimumab	MDX010 BMS-734,016	Fully human	IgG1	12-14 days
Tremelimumab	CP-675,206 ticilimumab	Fully human	IgG2	22 days

	IgG1	IgG2	IgG3	IgG4
Antibody-dependent Cellular Cytotoxicity	+++	±	+++	+
Complement Fixation	++	+	+++	–
Plasma Half-life	23 days	23 days	9 days	23 days

Ribas. *J Clin Oncol.* 2005; Benjamini. *Immunology: A Short Course.* 3rd ed. New York, NY: Wiley-Liss, Inc. 1996; Paul, ed. *Fundamental Immunology.* 3rd ed. New York, NY: Raven Press, Ltd. 1993; Korman. *Adv Immunol.* 2006;90:297.

Published Full Text Manuscripts of Antitumor Activity of Anti–CTLA-4 mAb in Melanoma

	Antibody	Combination	mAb Dose	Dose	Patients With Measurable Melanoma	ORR
Hodi, 2003	Ipilimumab (MDX010)	No	3 mg/kg	Single	7	0%
Attia, 2005 Phan, 2003	Ipilimumab (MDX010)	gp100 peptides	3 mg/kg	q3w	56	7%
Maker, 2005	Ipilimumab (MDX010)	HD IL-2	0.1-3 mg/kg	q3w	36	8%
Maker, 2006	Ipilimumab (MDX010)	No	3-9 mg/kg	q3w	46	5%
Ribas, 2005	Tremelimumab (CP-675,206)	No	0.01-15 mg/kg	Single	29	4%
Reuben, 2006	Tremelimumab (CP-675,206)	No	10-15 mg/kg	q1m or q3m	30	5%

Hodi. *Proc Natl Acad Sci U S A.* 2003;100:4712; Attia. *J Clin Oncol.* 2005;23:6043; Phan. *Proc Natl Acad Sci U S A.* 2003;100:8372; Maker. *Ann Surg Oncol.* 2005;12:1005; Maker. *J Immunol.* 2006;29:455; Ribas. *J Clin Oncol.* 2005;23:8968; Reuben. *Cancer.* 2006;106:2437.

Phase I/II Trial: Tremelimumab in Stage III/IV Melanoma

Stage III/IV melanoma

Arm 1: CP-675,206
10 mg/kg monthly
(N=20)

Arm 2: CP-675,206
15 mg/kg every 3 mo
(N=10)
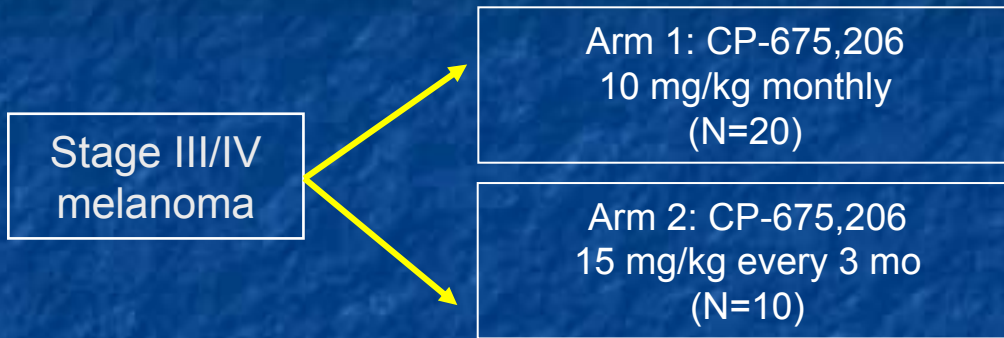
Response	IRAE+	IRAE–
N	12	18
ATR	4	1

	IRAE	**Adverse Events**		
		Grade 1	Grade 2	Grade 3
10 mg/kg	Diarrhea	1	4	5
(N=20)	Dermatitis	8	1	1
15 mg/kg	Diarrhea	1	2	0
(N=10)	Dermatitis	3	0	0

- IRAE+/ATR+ correlation between CTLA-4 and glucocorticoid-induced TRFR transcripts (*P*=0.015)

- IRAE–/ATR– PD1 receptor (*P*=0.000)

ATR=antitumor response; IRAE=immune-related adverse event.

Reuben. *Cancer*. 2006;106:2437.

Phase I/II Trial: Tremelimumab in Stage III/IV Melanoma (Cont.)

Phase I

Cohort 1:
Tremelimumab 3 mg/kg
monthly ≤12 mo (N=3)

Cohort 2:
Tremelimumab 6 mg/kg
monthly ≤12 mo (N=3)

Cohort 3:
Tremelimumab 10 mg/kg
monthly ≤12 mo (N=8)

RANDOMIZED

Phase II

Arm 1:
Tremelimumab 10 mg/kg
monthly
(N=44)

Up to 1 Year

Arm 2:
Tremelimumab 15 mg/kg
every 3 mo
(N=46)
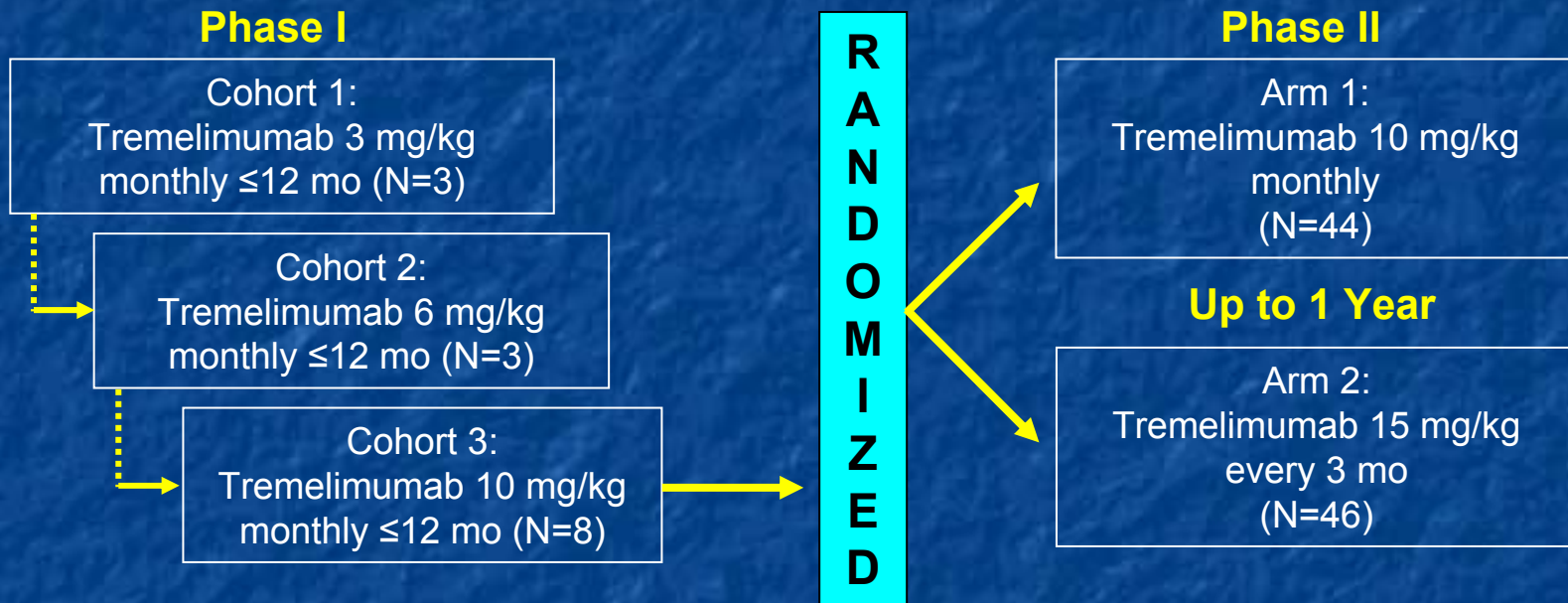
Dose Level	Phase I			Phase II	
	3 mg/kg monthly	6 mg/kg monthly	10 mg/kg monthly	10 mg/kg monthly	15 mg/kg every 3 mo
OS	8 mo	6 mo	22.7 mo	10.2 mo	11.5 mo
1-Yr OS	58%			32%	46%

Gomez-Navarro, ASCO, 2007 (abstr 8524)
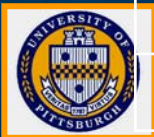
Phase II Trial: Tremelimumab in Advanced Melanoma

Stage I Randomized

Stage II Nonrandomized

Stage III/IV unresectable melanoma

Arm 1: Tremelimumab 10 mg/kg monthly (N=18)

Arm 2: Tremelimumab 15 mg/kg every 3 mo (N=18)

If 3 objective responses, proceed to stage II

Arm 1: Tremelimumab 10 mg/kg monthly (N=26)

Arm 2: Tremelimumab 15 mg/kg every 3 mo (N=28)
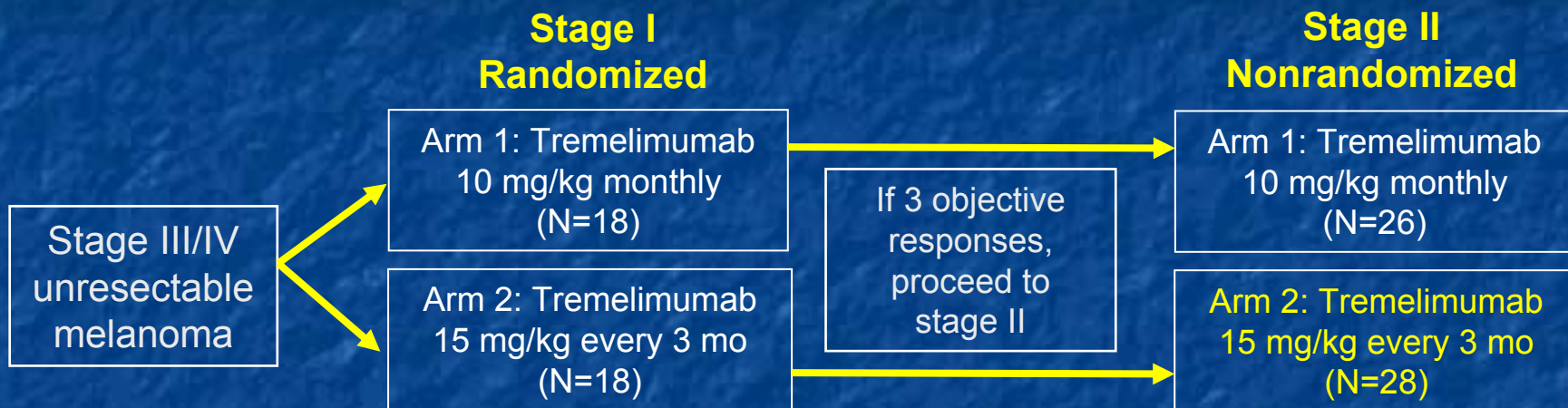
Toxicities*	Arm 1		Arm 2	
	Grade 3	Grade 4	Grade 3	Grade 4
Diarrhea/Colitis	25%	2.5%	13%	0%
Nausea/Vomiting	5%	0%	0%	0%
Pancreatitis/Lipase	2.5%	0%	2.5%	2.5%
Arthritis	2.5%	0%	0%	0%
Skin Rash	2.5%	0%	2.5%	0%

*Toxicity increases with continued dosing.

Phase I/II Trial: Ipilimumab in Patients With Unresectable Stage III/IV Melanoma

Unresectable metastatic melanoma

A: Ipilimumab 2.8, 3, or 5 mg/kg
Days 1, 57, and 85 (N=34)

B: Ipilimumab 7.5, 10, 15, or 20 mg/kg
Single doses (N=30)

C: Ipilimumab 10 mg/kg every 3 wks
Days 1, 22, 43, and 64 (N=24)
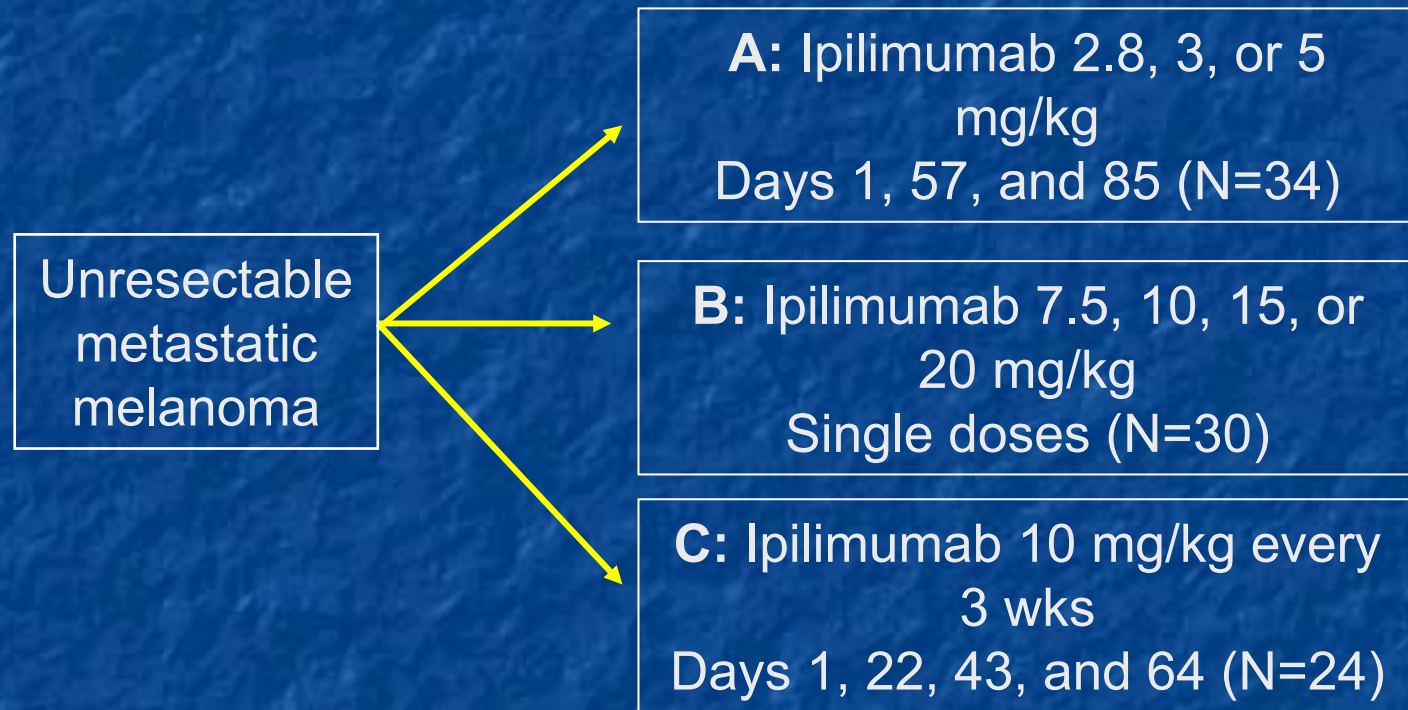
Phase I/II Trial: Ipilimumab in Patients With Unresectable Stage III/IV Melanoma

Cohort	Response		Duration	Disease Control Rate
A (N=34)	ORR	1 PR	246 days	15%
	SD	4	29, 61, 168, 172 days	
B (N=30)	ORR	1 CR	211 days	13%
	SD	3	37, 109, 395 days	
C (N=23)	ORR	1 CR, 1 PR	263, 275 days	39%
	SD	7	99, 190, 194, 194, 246, 351, 379 days	

Weber. *J Clin Oncol.* 2007;25:477S (abstr 8523).

Phase I/II Trial: Ipilimumab in Patients With Unresectable Stage III/IV Melanoma: Results

- IRAE
  - Overall incidence: 72%
  - All patients with ORR and 13/14 SD had IRAE
  - Most events grade 1/2 and reversible
- 25 Patients had SAEs
- 9 Patients across all doses had ipilimumab-related SAEs
  - 1 Patient perforated bowel @ 2 doses of ipilimumab 10 mg/kg
- Ipilimumab-related SAEs
  - Diarrhea, colitis, nausea, cerebral edema, gastrointestinal perforation, and abdominal pain

Proposed US Intergroup E1607 Phase III trial: Anti-CTLA4 Antibody CP-675,206 vs. Placebo

Anti-CTLA4 Antibody CP-675,206

SURGERY

**Patients with
T (any) N2 post IFN
-or-
any resectable M1a
or M1b**

Placebo
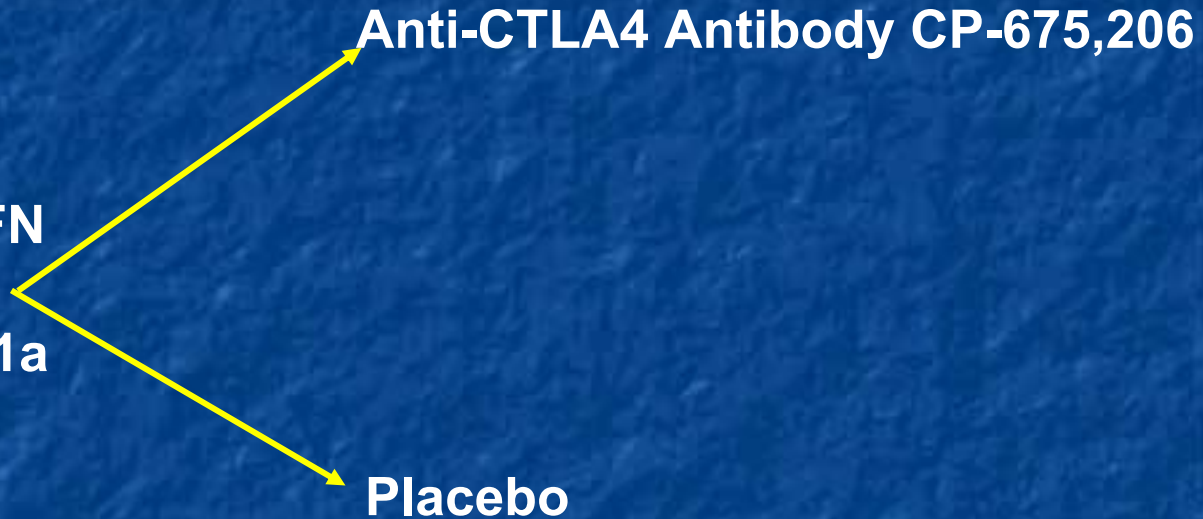
Primary endpoints: Survival, progression-free interval

Secondary Analyses: Autoimmune, antitumor responses

Building the Next Generation Adjuvant Therapy

- Anti-CTLA4 for IFN failures in stage IIIB
  - Intergroup ECOG-SWOG study E1607(Tremelimumab 15mg/kg q3mos) is in planning;
  - EORTC study of MDX-010 10 mg/kg q 3 wks is in planning

- Combinations of IFNα and other agents
  - Vaccines$\rightarrow$Recall and polarize response w/IFN (04-125)
  - Cytotoxic Antibodies$\rightarrow$Improve ADCC with IFN (07-023)
  - Anti-CTLA4: Tremelimumab combined w/IFN (05-125)

- Neoadjuvant studies may afford a rapid avenue to evaluate therapeutic efficacy and mechanism of candidate agents & combinations

Opportunities

- Evaluate more specific anti-tumor immune responses induced by established and investigational agents

  (IL-2, IFNα, anti-CTLA4 blocking antibodies)

- Identify genetic determinants of capacity to induce effective antitumor immunity

- Define specific prognostic and predictive markers of immunity in conjunction with ongoing/new trials of immunomodulators