Cytokines: Interferons, Interleukins and Beyond

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Presenter Disclosure Information

MICHAEL B. ATKINS, M.D

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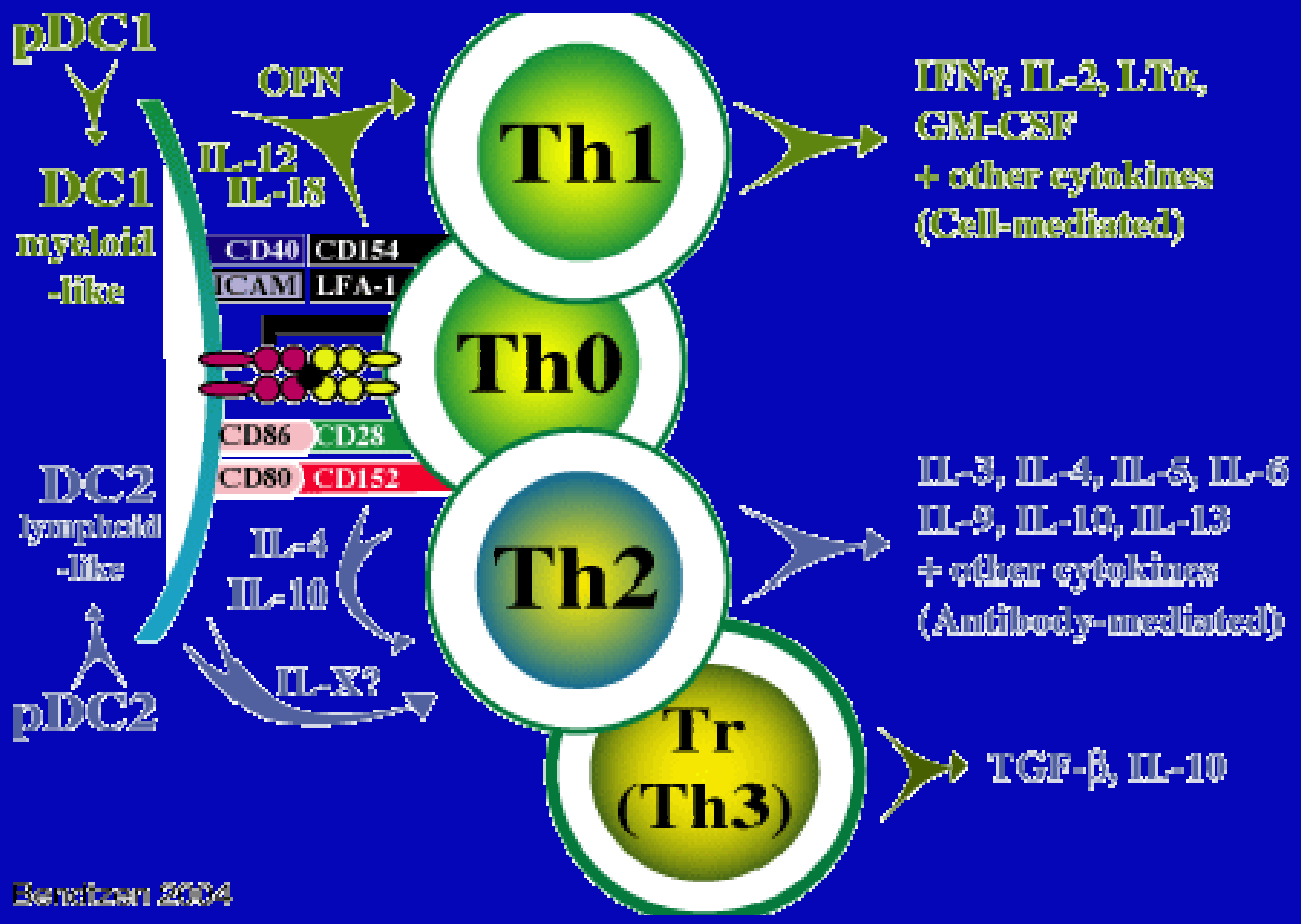
Cytokine Therapy: Learning Objectives

- Describe the players
- Understand the main effects of cytokines on immune cells
- Describe clinical utility and toxicity
  - IFN
  - IL-2
  - Other cytokines
- Current and Future Directions

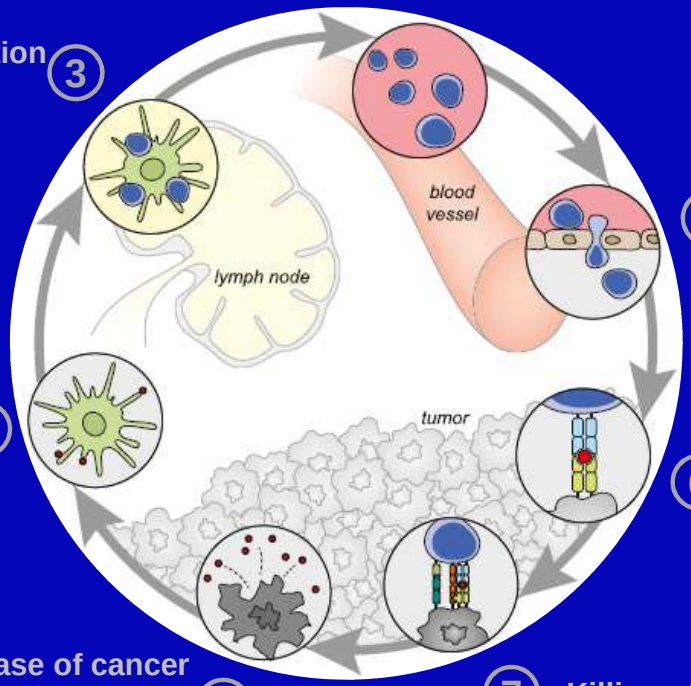
What are cytokines?

- Diverse family of immune cell regulators:
  - Interferons
  - Interleukins
  - Tumor Necrosis Factors
  - Other
- Cytokines interact with cell surface receptors and influence:
  - Gene transcription and activation (of other cytokines)
  - Proliferation
  - Cytotoxicity
  - Immunological memory
  - Movement of cells into sites of inflammation
- Cytokines trigger a cascade of immunological events

Cytokine Sources, Properties



A Roadmap of Immunotherapy-Tumor Interactions



4 Trafficking of T cells to tumors

Priming and activation 3
Anti-CTLA4
Anti-CD137 (agonist)
Anti-OX40 (agonist)
Anti-CD27 (agonist)
IL-2
IL-12
IL-15
IL-18
IL-21

5 Infiltration of T cells into tumors
Anti-VEGF

Cancer antigen presentation 2
Vaccines
IFN-α
GM-CSF
Anti-CD40 (agonist)
TLR agonists

6 Recognition of cancer cells by T cells
CARs

Release of cancer cell antigens 1
Chemotherapy
Radiation therapy
Targeted therapy

7 Killing of cancer cells
Anti-PD-L1
Anti-PD-1
IDO inhibitors

Chen DS, et al. Immunity. 2013;39:1-10.

Role of IFN alpha in Cancer Therapy

- Adjuvant therapy of Melanoma
- Treatment of RCC
  - Meta-analysis shows IFN alone produces survival advantage over chemotherapy (Coppin et al)
  - Activity inferior to sunitinib in Phase III trials
  - Bevacizumab + IFN an approved regimen
- Heme Malignancies
  - Hairy Cell Leukemia
  - CML

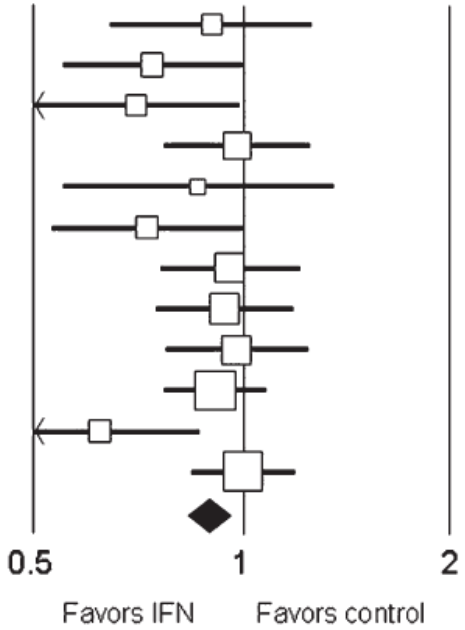
Adjuvant IFN-α Regimens

Schedule	Dose	Frequency	Duration
Low Dose			
	3 MIU	3 x weekly	18 – 24 months
Intermediate Dose			
Induction	10 MIU	5 x weekly	4 weeks
Maintenance	10 MIU	3 x weekly	12 -24 months
	5 MIU	3 x weekly	24 months
High Dose			
Induction	20 MIU/m^2	5 x weekly	4 weeks
Maintenance	10 MIU/m^2	3 x weekly	11 months

PEG IFN is equivalent to intermediate dose IFN

Meta-analysis of IFN: Impact on overall survival

	HR	LL	UL	SE	Patients	Events (IFN/control)
NCCTG (Creagan, 1995)	0.90	0.64	1.25	0.17	264	68/72
E1684 (Kirkwood, 1996)	0.73	0.54	0.99	0.15	287	81/90
FCGM (Grob, 1998)	0.70	0.49	0.98	0.17	499	59/76
E1690 (Kirkwood, 2000)	0.98	0.76	1.24	0.12	642	194/186
SMG (Cameron, 2001)	0.86	0.54	1.35	0.23	96	31/36
E1694 (Kirkwood, 2001)	0.72	0.52	0.99	0.16	880	52/81
WHO (Cascinelli, 2001)	0.95	0.76	1.20	0.12	444	146/138
UKCCCR (Hancock, 2004)	0.94	0.74	1.17	0.12	674	151/156
EORTC18871 (Kleeberg, 2004)	0.98	0.77	1.23	0.12	484	137/202
EORTC18952 (Eggermont, 2005)	0.91	0.76	1.07	0.09	1388	534/292
DeCOG (Garbe, 2008)	0.62	0.44	0.86	0.17	296	65/88
EORTC18991 (Eggermont, 2008)	1.00	0.84	1.18	0.09	1256	256/257
	0.89	0.83	0.96	0.04		



Adjuvant interferon (various doses and durations) improved overall survival 11%, (p=0.002)

Mocellin et al JNCI 2010;102:493

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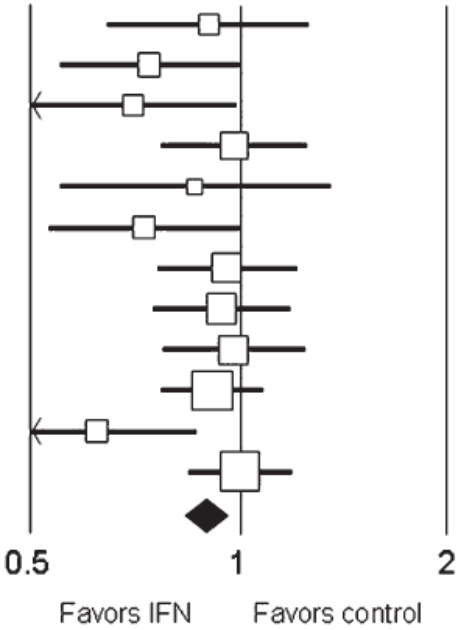

High dose IFN shows OS benefit in patients with high risk melanoma (p=0.002)

Mocellin et al JNCI 2010;102:493

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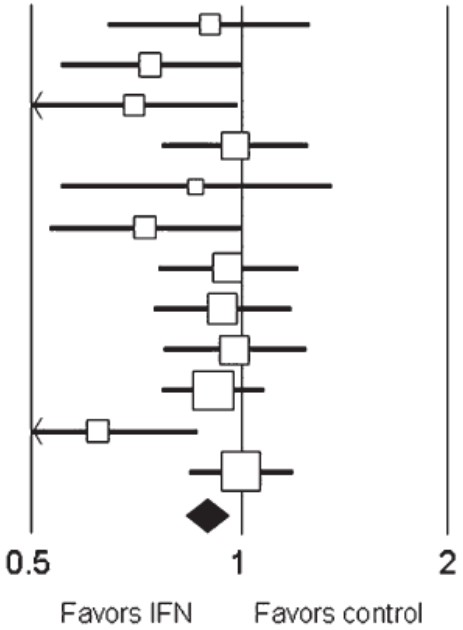
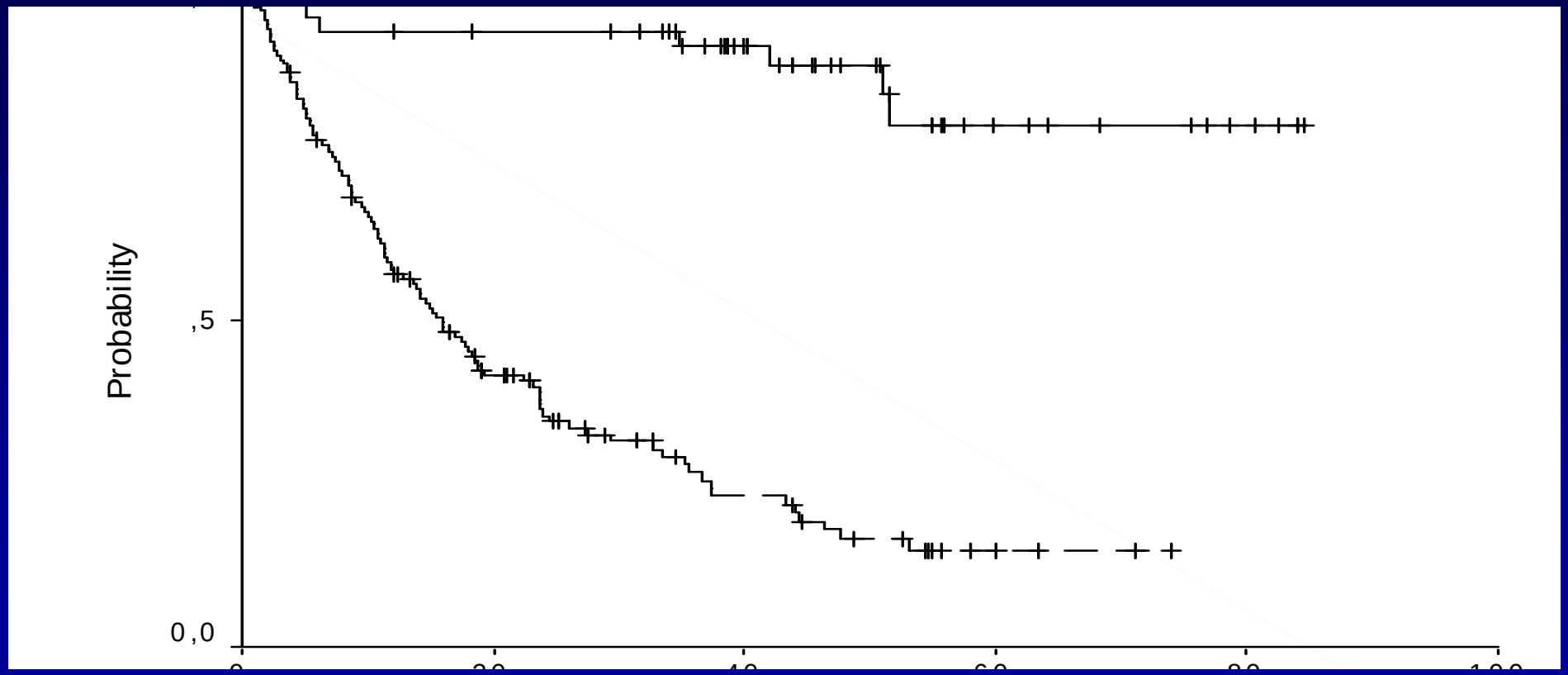


LD, ID and PEG IFN do not produce overall survival benefits in patients with high risk melanoma

Mocellin et al JNCI 2010;102:493

IFN Alpha TTP by Autoantibody Status



Gogas NEJM 2006

Adjuvant IFN: Conclusions

- HD IFN has significant RFS and likely OS benefit - *only positive trials*
- Toxicity is primarily a flu-like syndrome of variable severity; can be managed with dose reductions
- Benefit may be correlated with autoimmunity
- Benefit of IFN appears proportionate to risk: *benefits > risks of Rx when risk of relapse is > 30%*

- Full staging according to AJCC staging system is necessary to assess risk and choose treatment
- Better treatments needed

Melanoma: New Adjuvant Therapy Approaches

- Biochemotherapy (RFS but no survival benefit relative to IFN)
- Ipilimumab (EORTC Trial -FDA approved 10/15, E1609)
- BRAF inhibitors
- Anti-PD1
  - BMS : Ipi vs Nivo trial
  - SWOG- Pembro vs IFN trial or Ipi
  - EORTC- Pembro vs. placebo with crossover

HD IFN's days are numbered in melanoma adjuvant therapy

IL-2 History

1965 Factor stimulating DNA synthesis derived from lymphocyte cultures[1]

1976 Factor identified as a T-cell growth factor[2]

1983 First clinical use of lymphocyte-derived IL-2 for melanoma[3]

1984 Clinical trial of cell-line-derived IL-2 in cancer and AIDS[4]

1984 rIL-2 produced in *E coli* demonstrated the same range of biological activity as native IL-2[2]

1985 Clinical trials with rIL-2 for advanced malignancies[2]

1992 rIL-2 (aldesleukin) approved for metastatic RCC

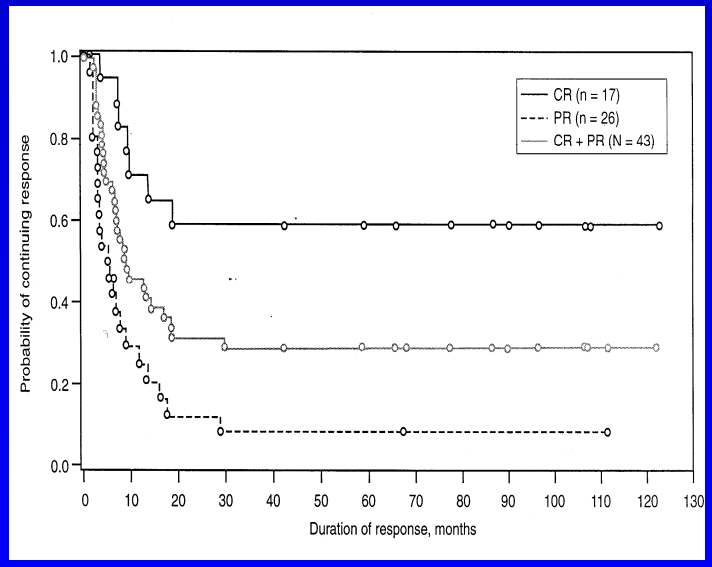
1998 rIL-2 (aldesleukin) approved for metastatic melanoma

IL-2 Treatment

- IL-2 = 600,000 international units per kg IVB q 8 hrs x 14 planned doses/ 5 days cycle;
- Second cycle given after 1 week break. Scans repeated 6 and 12 weeks.
- More IL-2 for responders (max 3 courses).

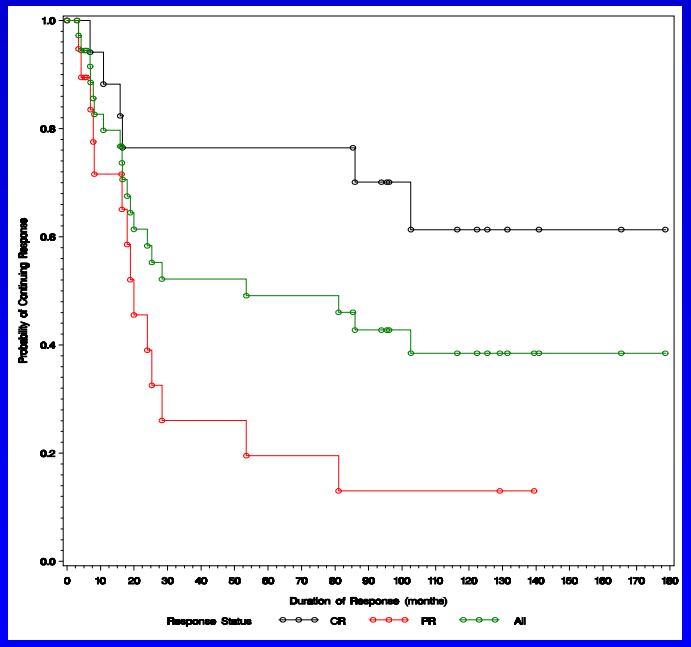
HD IL-2 Therapy- Durable Responses

Metastatic Melanoma



*Atkins et al JCO, 1999 (N=270)

Metastatic RCC



Fyfe et al JCO, 1992 (N=255)

HD IL-2 produces durable responses in 6-10% of patients with advanced Mel and RCC

Few relapses in patients responding for over 2.5 years (likely cured)

FDA approved in 1992 (RCC) and 1998 (melanoma)

IL-2 Side Effects

Physiologic Categories

- Constitutional (flu-like)
- Cardiovascular
- Gastrointestinal
- Pulmonary
- Metabolic
- Neurologic
- Hepatic
- Renal
- Dermatologic
- Capillary leak
- Hematologic/ immunologic

HD IL-2 Toxicity Management

- Approach is to provide IL-2 doses when patients are stable; skip doses in patients who are unstable
- Toxicity usually resolves in 8-24 hours
- Patients receive on average 10-12 doses in first weeks and 8-10 doses in 2nd week (18-22 doses during a 3 week course of therapy)
- Toxicity is manageable in experienced hands

High Dose IL-2 Therapy

1985

2015

A case study for what is wrong with cancer clinical development

- Uncontrolled
- No target
- No target population
- Toxic
- Inpatient
- No correlates

Proof of Principle

Phase III Trials of HD vs LD IL-2 in RCC

	Regimen	N	RR	p-value
NCI SB	HD IV IL-2	156	21%	
	vs			0.05
	LD IV IL-2	150	13%	
CWG	HD IV IL-2	95	23%	
	vs			0.02
	LD SC IL-2/IFN	91	10%	

More durable responses (9 vs 1), especially CRs (7 vs 0; p =0.01), with HD IL-2

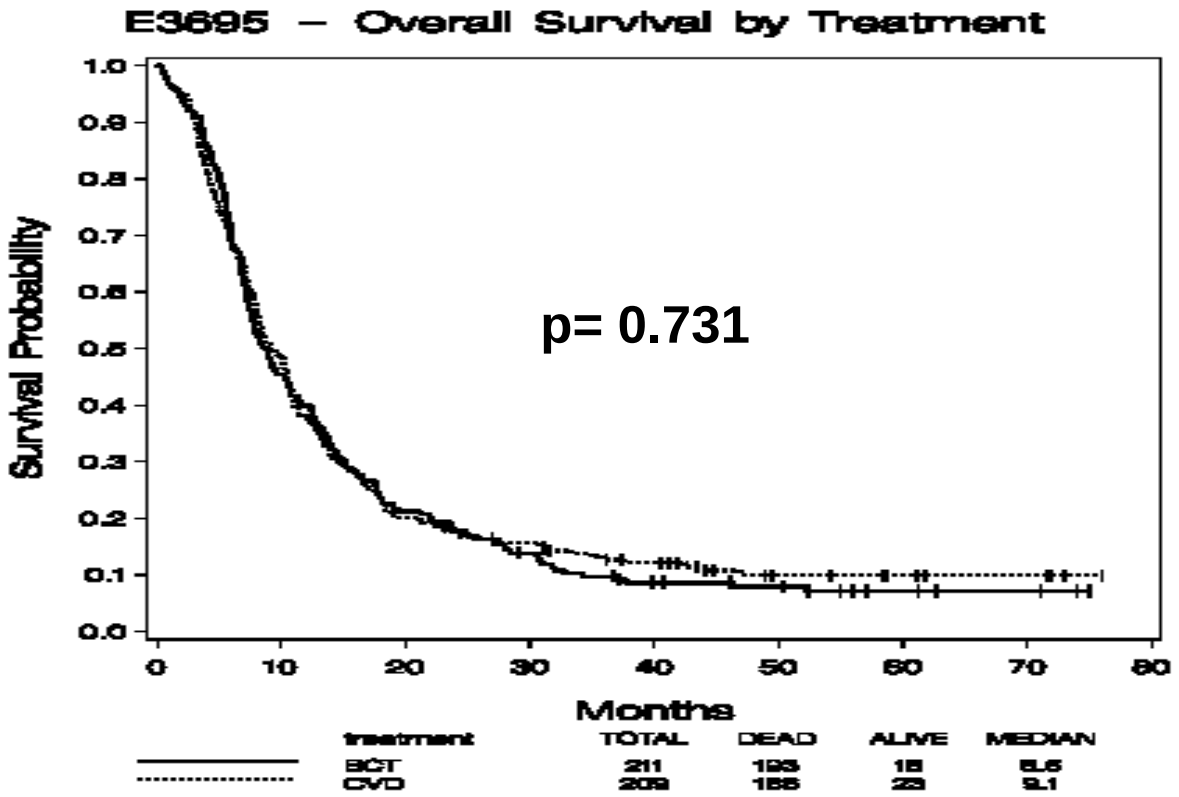
No difference in PFS, but trends in terms of OS

Yang et al JCO 2003; McDermott et al JCO 2005

Melanoma:
Biochemotherapy: "A Case Study"

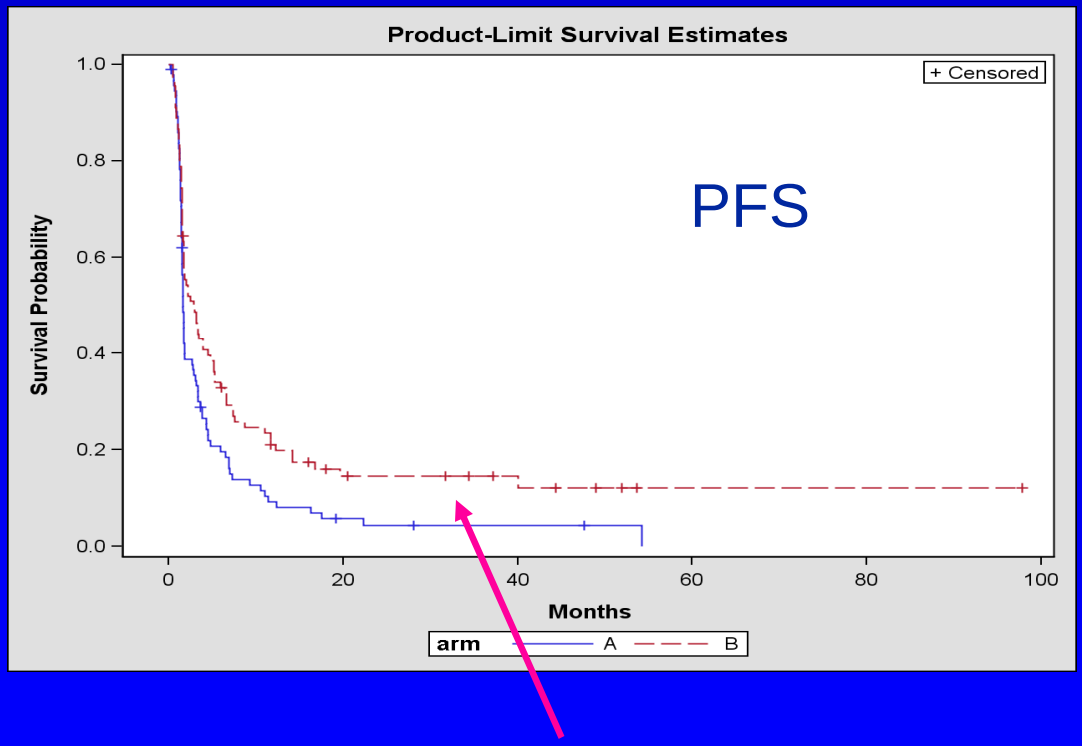
- Phase II studies and meta-analyses suggested an advantage for cisplatin / IL-2-based biochemotherapy over chemotherapy or IL-2 alone
  - 50% response rates
  - 10-20% CR, 10% durable CR
- A single institution Phase III trial confirmed benefit of BCT over chemotherapy alone
- Phase III trials were initiated through the Cooperative Group mechanism

E3695: Cocurrent Biochemotherapy (BCT) vs CVD – Final Result



Atkins et al J Clin Oncol 2008

IL-2 +/- gp100: 209-217(210M) peptide vaccine: Focusing Immune Response



Hallmark of immunotherapy:
Very few relapses beyond 2 years

Scwhartzentruber et al

MAY 10, 2010

OUR SPECIAL DOUBLE ISSUE

TIME

Didier Drogba

THE 100 MOST INFLUENTIAL PEOPLE IN THE WORLD

Sarah Palin *by Ted Nugent*
Oprah Winfrey *by Phil Donahue*
Nancy Pelosi *by Hillary Clinton*
Michael Pollan *by Alice Waters*
Lee Kuan Yew *by Henry Kissinger*
Taylor Swift *by Stevie Nicks*

... and 94 more

Bill Clinton

Lady Gaga

www.time.com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On the trail of a cancer vaccine
BY ERIC SHANTEAU
I will never forget the day I heard the words "You have cancer." They are three of the most chilling words you can ever hear, stripping you of control over your life, not to mention any confidence that life will even continue.
www.time.com

HD IL-2 Therapy (Melanoma and RCC)

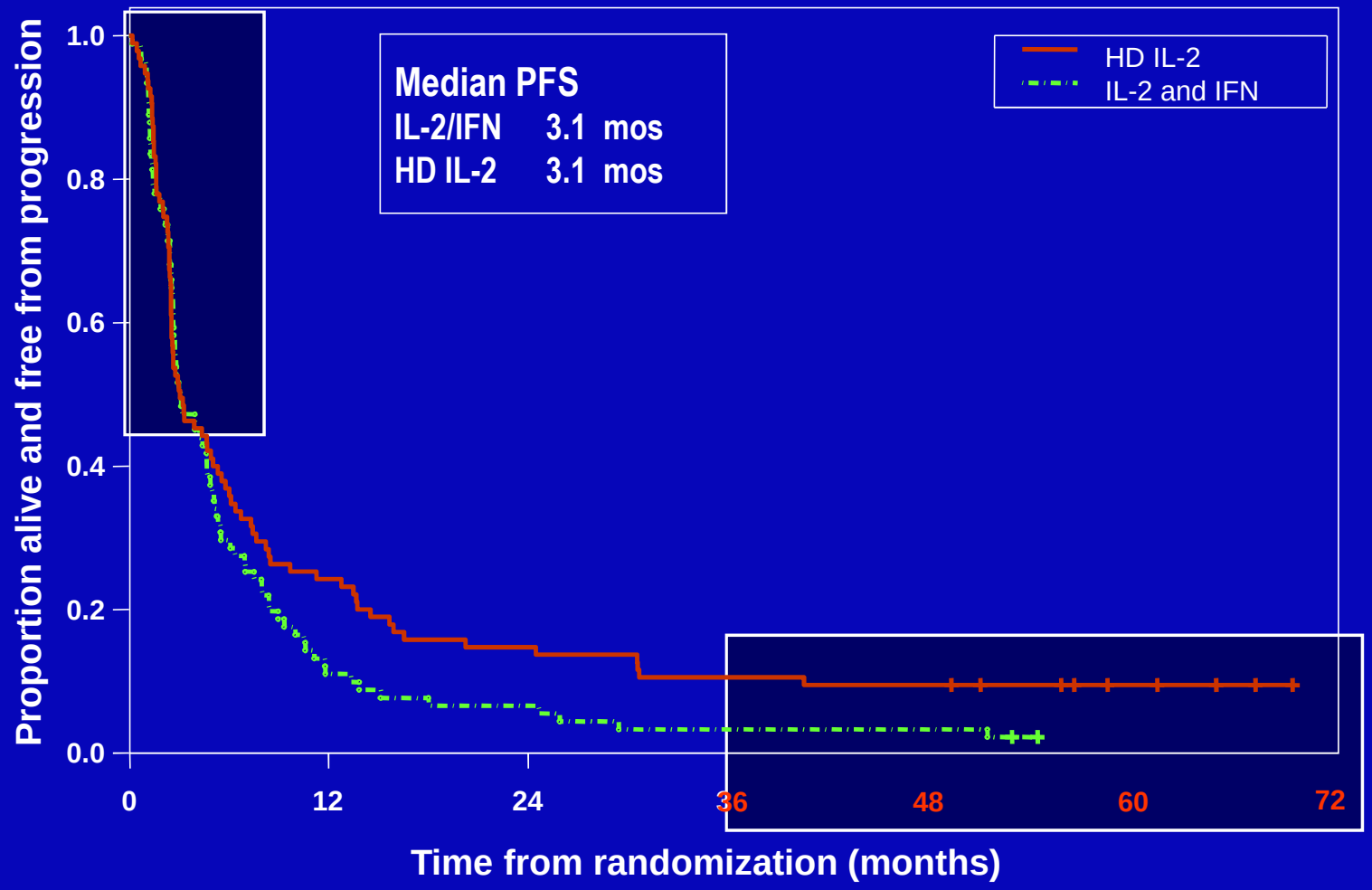
- High dose IL-2 appears to be useful, but it is toxic, inpatient, expensive and impractical; therefore its use remains limited to selected patients treated at experienced centers
- Efforts to develop more tolerable regimens have been unsuccessful
- Efforts to better select patients who might benefit from therapy were warranted
- Newer immunotherapies are needed

Treatment Selection Opportunities

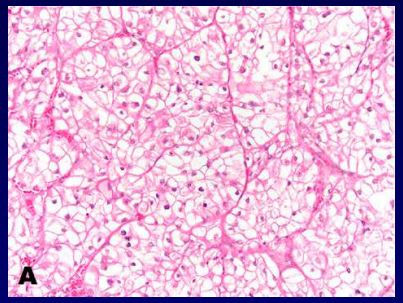
- Tumor characteristics
- Tumor microenvironment
- Host immunotype

How do we get beyond the 15-20% Response Barrier?

CWG Phase III RCC: PFS



Combined UCLA/DFHCC Model



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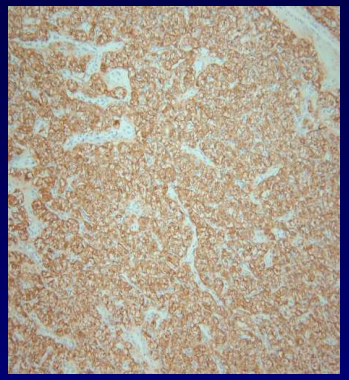


CA-9 Staining

Pathology Risk Group	Low	High
Good		
Intermed		
Poor		

Good

Poor

Atkins, et al Clin Can Res, 2005

Activity of IL-2 is greater than package Insert

Response*	%
Historical rate	14
IL-2 Select Trial (all pts n=120)*	28

p=0.0016

95% CI=20.5-37.3%

Likely explanations for improved RR include:

1) Enhanced "pre-screening"
- smaller non-clear cell population
2) Impact of alternative therapies on IL-2 referral patterns
3) Application of debulking nephrectomy
- fewer patients treated with primary in place

*Using WHO Criteria

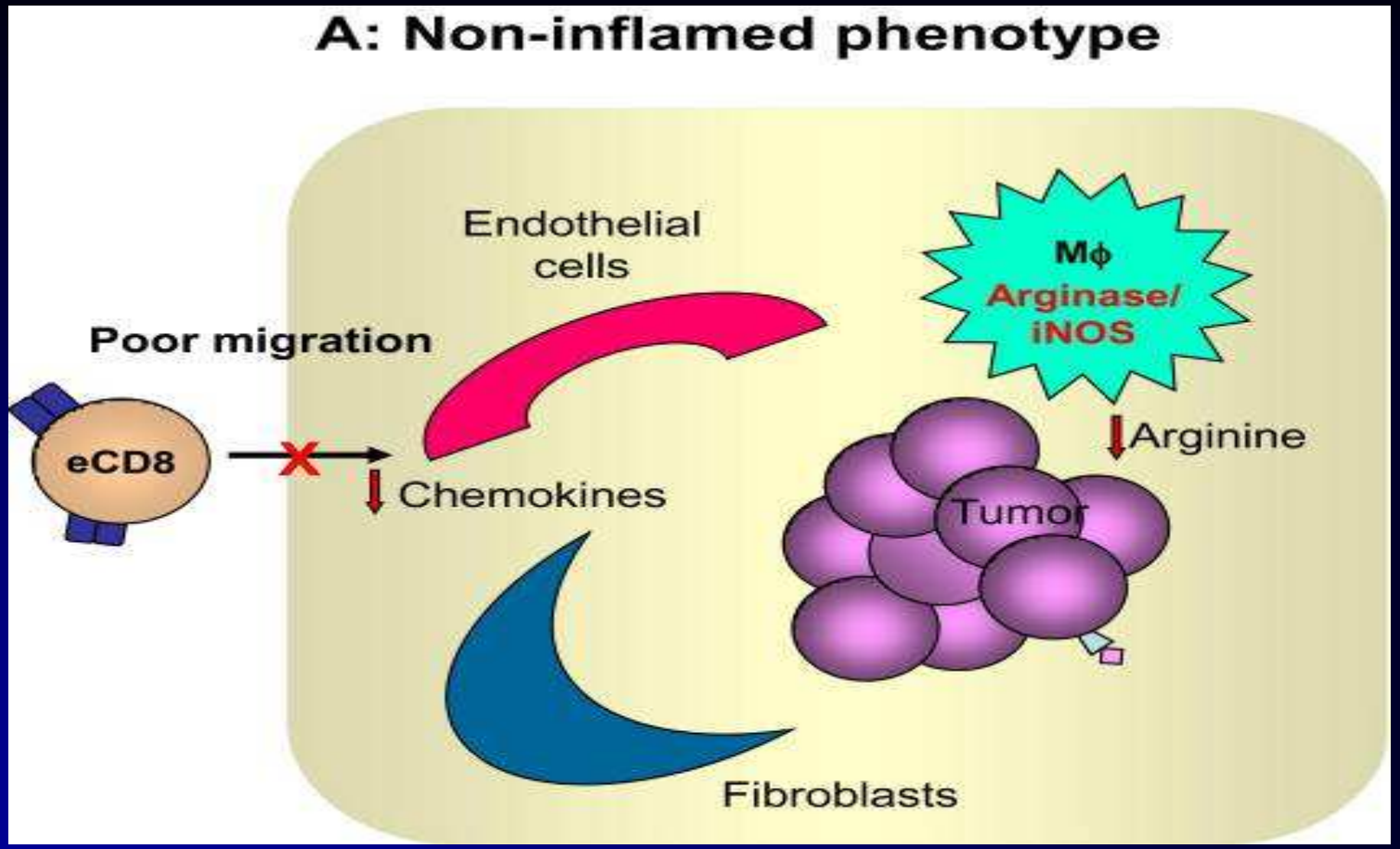
McDermott et al ASCO 2010

Response by Tumor Features

Tumor risk group	RR (95% CI)	P-value*
Good (n=11)	27% (6%-61%)	0.89
Intermediate (n= 83)	24% (15%-35%)	
Poor (n=25)	28% (12%-49%)	

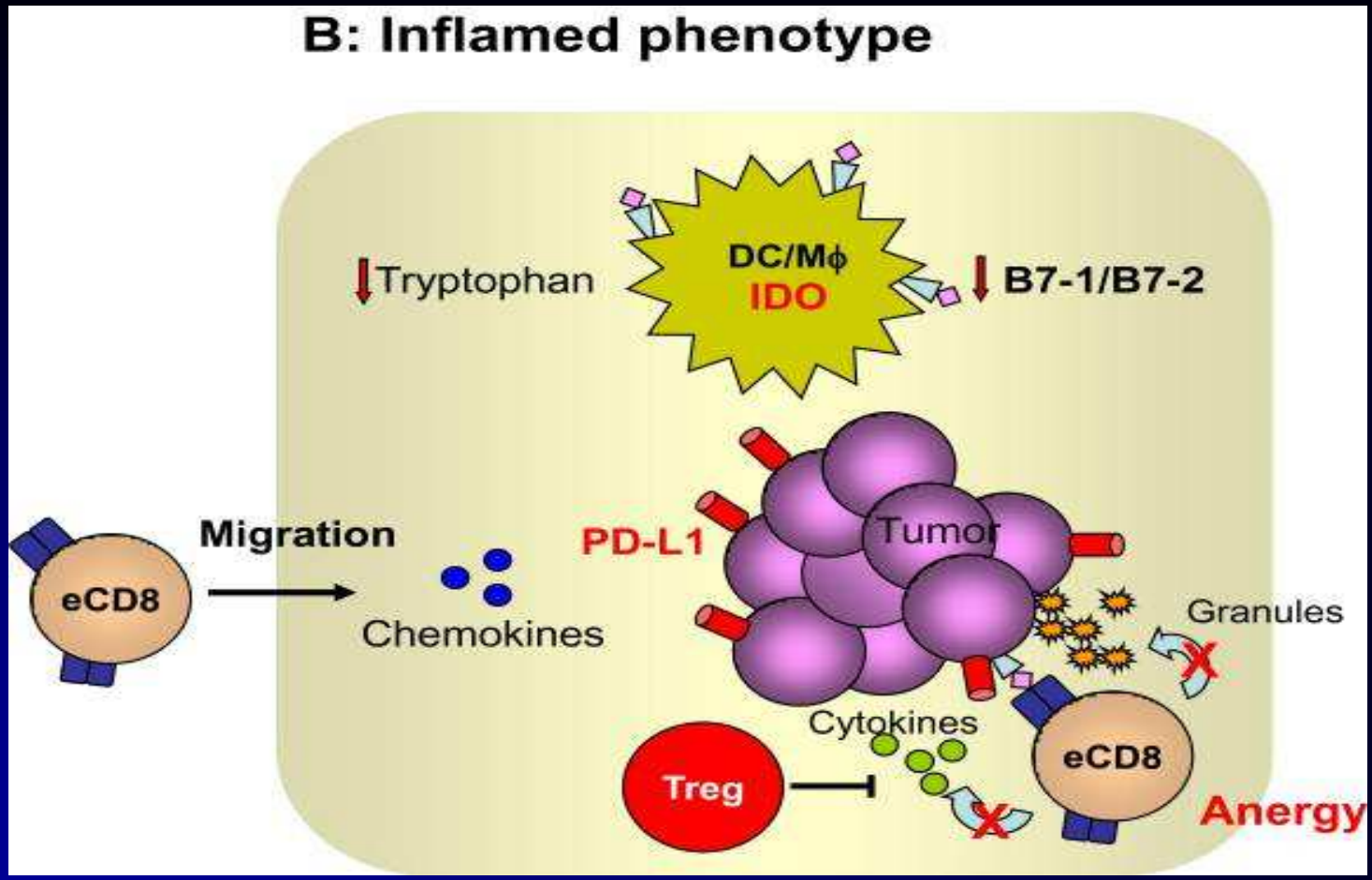
CA-9 Score		
High (>85% n=77)	22% (13%-33%)	0.19
Low (≤85% n=39)	33% (19%-50%)	

Combined Score		
Good (n=74)	23% (14%-34%)	0.39
Poor (n=42)	30% (17%-46%)	



High expression of vascular markers, macrophages, fibroblasts +
Low inflammation and chemokines, few lymphocytes =
Poor effector cell trafficking

Gajewski, Curr Opin Immun 2011



High levels of innate immune signals, chemokines for T cell recruitment
But, negative immune regulators dominate

Gajewski, Curr Opin Immun 2011

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

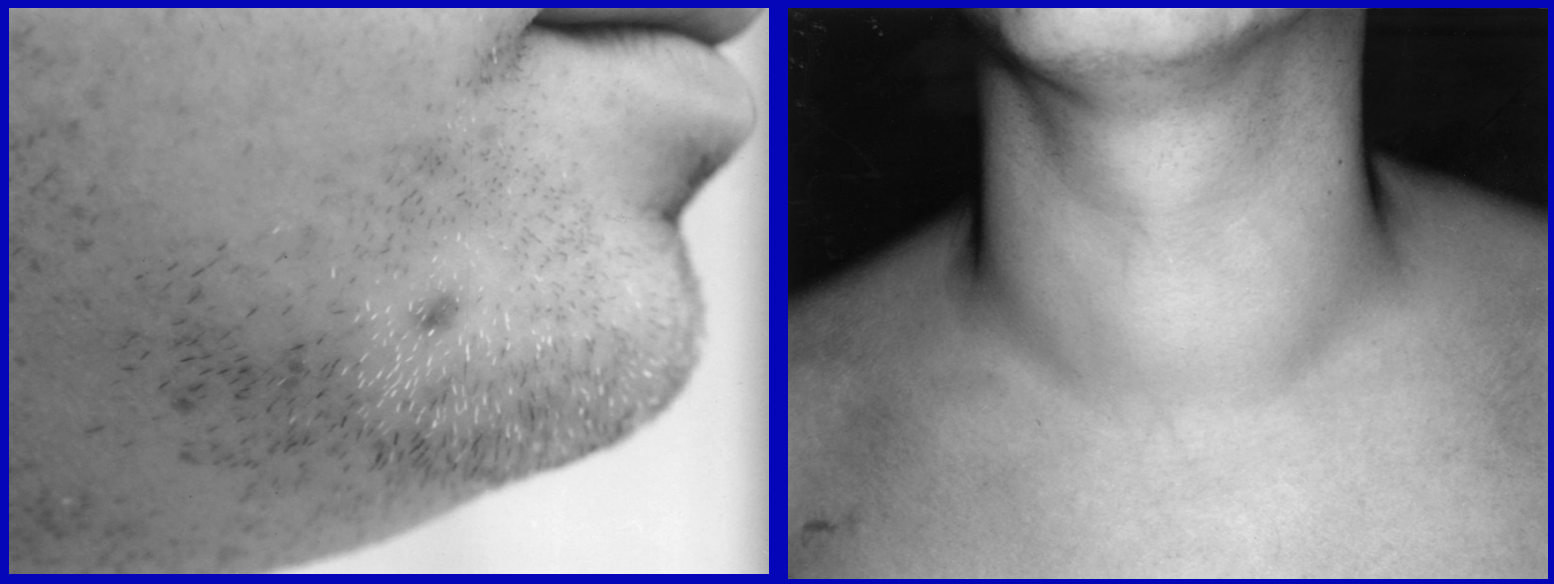
RCC: Response by tumor expression of PDL1/B7-H3

	RR	p-value*
PDL1+ Tumor		
Negative (n=95)	19%	0.012
Positive (n=18)	50%	
B7-H3 Tumor		
Negative (n=28)	10.7%	0.075
Positive (n=85)	29.4%	

McDermott, Atkins
IL-2 Select Trial Clin Ca Res 2015

IHC performed at Mayo Clinic
by Kwon, Leibovich, et al.

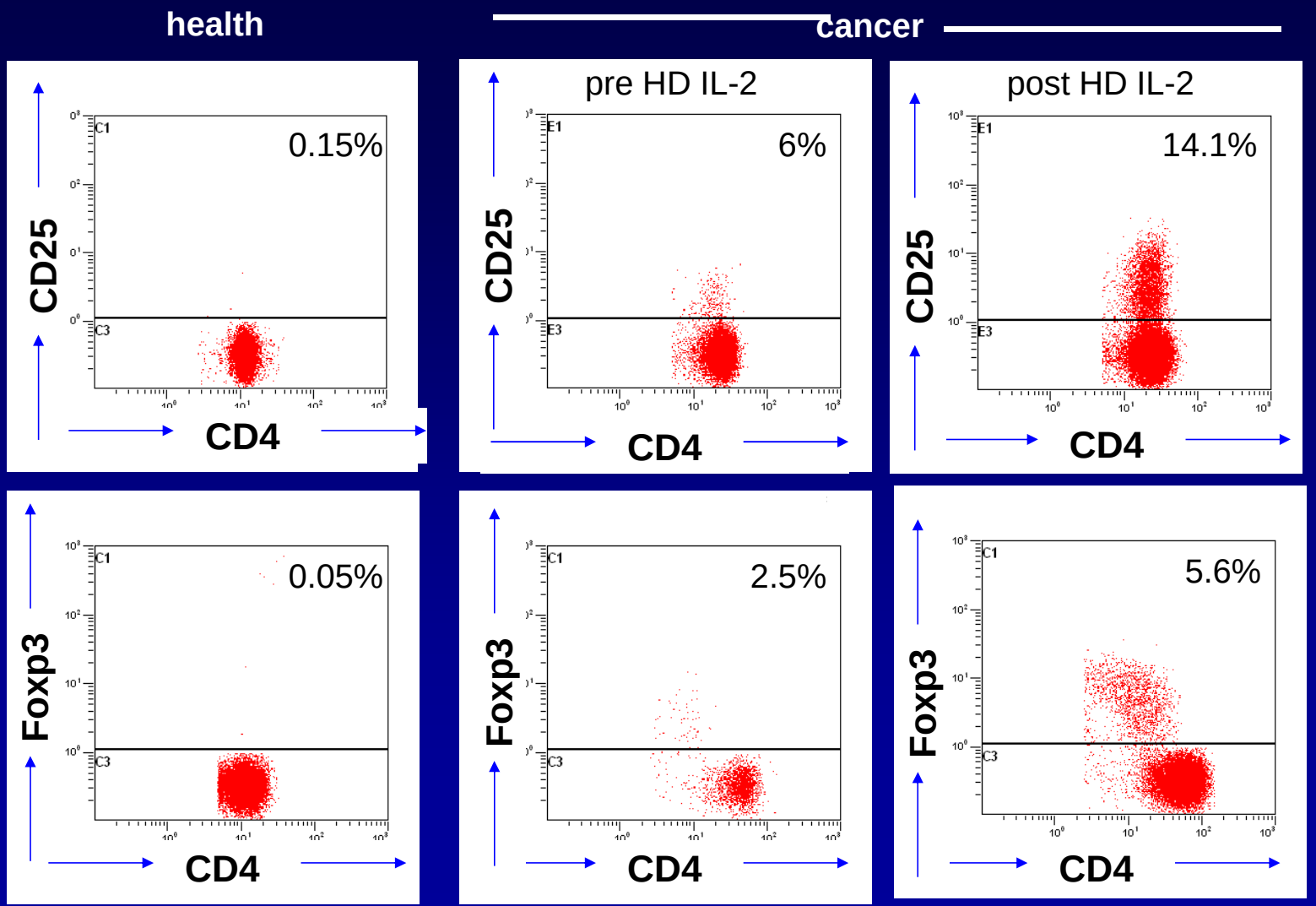
Vitiligo and hypothyroidism following HD IL-2 Rx



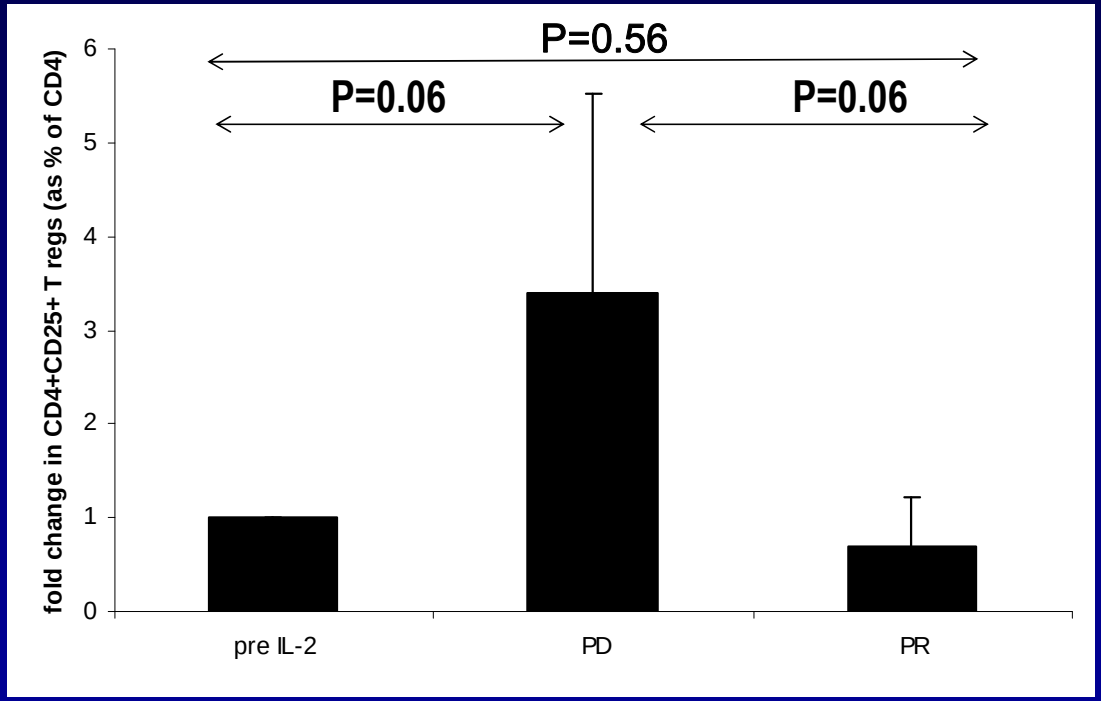
Treated May 1986 – Alive today without disease

Atkins et al NEJM, 1988

HD IL-2: Increases both $CD4^+CD25^+$ and $CD4^+Foxp3^+$ T cells



No increase in $CD4^+CD25^+$ regulatory like T cells in patients responding to HD IL-2



N=5 N=2

Beth Israel Deaconess Medical Center

Hans van der Vliet, Mark Exley, Henry Koon et al

Conclusion for Biomarker Studies

- IL-2 works best in tumors with inflamed microenvironment
- Activity primarily seen in patients with defective Tregs development – association of benefit with autoimmunity
- Sets stage for TIL and checkpoint inhibitor therapy

IL-2 and other Cytokines: Future Directions

- Develop an IL-2 that more selectively activates CD8 T cells, rather than Tregs
- Study HD IL-2 following checkpoint inhibitor therapy
- Study IL-2 in combination with checkpoint inhibitors
  - IL-2 + ipilimumab
  - IL-2 + PD1 blocker
- IL-2 in combination with T cell therapy
- Identify cytokines that are more selective T cell activators
  - IL-15, IL-21

Other Cytokines Therapy Of Cancer

Cytokine	Mechanism	Activity	Toxicity	Status
GM-CSF	DC activation	? RFS in stage IV NED MM, Synergy with Ipi	+	Combination with checkpoint inhibitors
IL-12	Th1 shift, IFN γ, Antiagniongenic	Some with IL-2	++	No current investigations
IL-15	Prolif and diff of CD8+ T cells and NK cells, more potent than IL-2	SD as best response	++	Ongoing studies
IL-18	IFN γ inducer, Fas and T cell dependent killing, Induces memory, Antiangiogenic	Little	+	Phase II in melanoma ongoing
IL-21	Stim of activated CD8+ T cells, B cell Diff Stat1 and 3 signaling	Rare responses in MM	+	Studies with checkpoint inhibitors

Take Home Messages

- IFN alpha still has a role as adjuvant treatment for patients with high risk melanoma
- HD IL-2 has a role in treatment of patients with advanced melanoma and RCC
- These roles are rapidly being replaced by checkpoint inhibitors
- Other cytokines do not have established anti-tumor activity
- Future of agents will likely be in combination with checkpoint inhibitors (many), in relapsed patients (IL-2) or to support T cell therapy (IL-2)

Lessons and Take Home Messages

•Key points

- IFNa still has a role as adjuvant treatment for pts with high risk melanoma
- HD IL-2 has a role in Rx of patients with advanced melanoma and RCC
- These roles are rapidly being replaced by checkpoint inhibitors
- Other cytokines do not have established anti-tumor activity

•Lessons learned

•Cytokines established proof of principal that immunotherapy can be curative

•Potential impact on the field

-Future of agents will likely be in combination with checkpoint inhibitors (many), in relapsed patients (IL-2) or to support T cell therapy (IL-2)