

Immunotherapy for Melanoma: OVERRATED

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Melanoma

- 4% of skin cancers, 80% of deaths
- On presentation, 85% local, 10% regional nodes, 5% distant mets
- Stage IV: 5-y survival < 10%, Median survival around 11 mo



FDA Approved

- **IL-2 (Aldesleukin) – metastatic renal ca and melanoma**
- **Dacarbazine – alkylating agent, refractory Hodgkins and metastatic melanoma**
- **Anti-CTLA4 Ab (Ipilimumab) – unresectable melanoma**
- **BRAF inhibitor (Vemurafenib) – unresectable melanoma and BRAF V600 mutation**

Immunotherapy: Provoke the Host

- **Interleukins/Interferons**
- **Vaccines**
 - **Induce immune response against tumor antigens**
- **Cellular therapies**
 - **Targeted activation of innate immune cytotoxic cells (NK cells, CD8 T cells)**
- **Antibodies against tumor antigens**

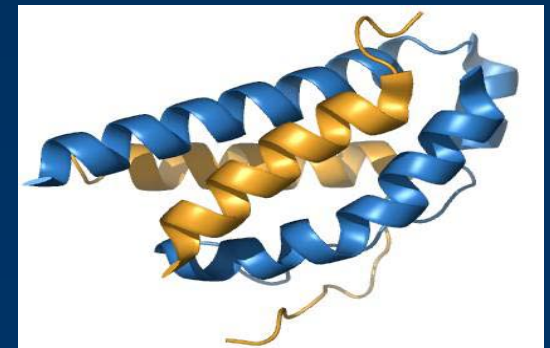
3 reasons it's overrated

- **Efficacy v. Biology**
- **Toxicity**
- **Monitoring Response**

IL-2

- **Mechanism: stimulates T cells**
- **No Controlled Trials. Series of 270 patients 1985 – 1993.**
- **Response 16%, Median PFS 8.9 mo**
- **Median OS 11.4 mo**
- **Toxicity frequently required hospital admission**

Atkins, J Clin Oncol 1999



IL-2, q8hr, 5 days
Rest 1 week
Repeat
Rest 1-2 mo, x 5 cycles



Less than 6%
complete
response

Myocardial ischemia/infarction

5%

ARDS/Respiratory Failure

4-16%

Vomiting/Diarrhea

55%

Increased Cr/Anuria

8-35%

Coma/Confusion

1-30%

Hepatic dysfunction

13-51%

Low plts, anemia, low WBC

21-43%

Skin

15-27%

Toxicity-related Death

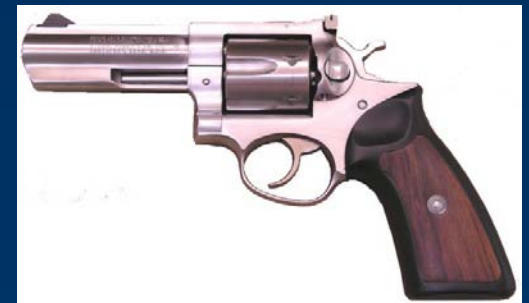
2.2%

- **In patients who responded, no relapse for 30 months**
- **Without a control group, can you distinguish results of treatment versus biology of the cancer?**
- **Dacarbazine chemotherapy – response 7-12%, community tolerated toxicity profile**

gp 100 vaccine

- **Mechanism:** stimulates immune response to melanoma specific antigen gp 100
- **IL-2 plus gp 100 v. IL-2 alone, RCT**
- **Median PFS 2.2 v. 1.6 mo**
- **Median OS 17.8 v. 11.1 mo ($p=0.06$)**
- **Additional toxicities:**
 - **Arrhythmias**
 - **Metabolic derangements**

Schwartzentruber, NEJM 2011



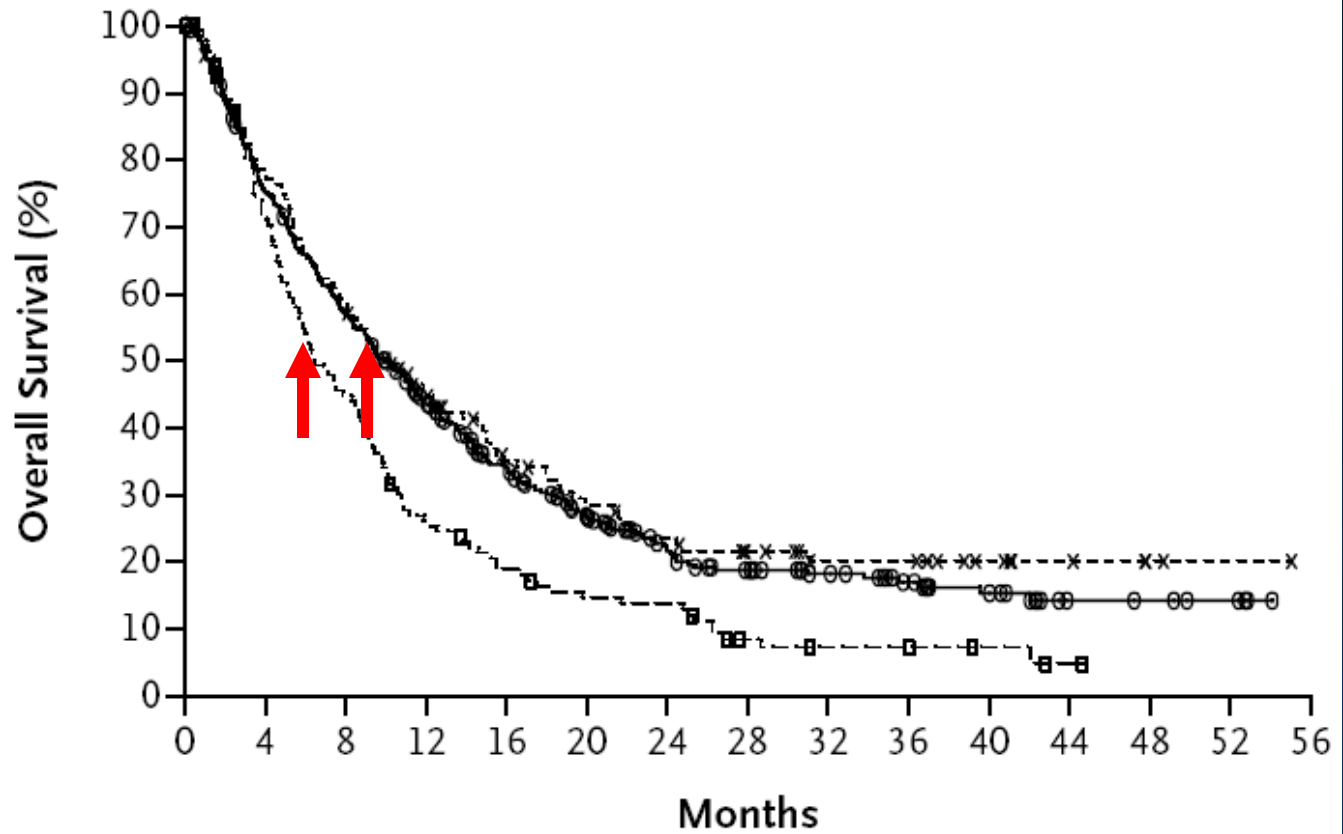
- **Only 7 of 37 patients who received the vaccine developed anti-peptide reactivity**

There was no relationship between the development of anti-peptide reactivity and the objective clinical response.

CTLA4 Antibody

- **Mechanism: inhibits the T-cell suppressor protein CTLA4**
- **CTLA4 Ab v. gp 100 v. both, DB, RCT**
- **Median PFS 3 mo in all groups**
- **Median OS 10 v. 6 v. 10 mo**

A Overall Survival



No. at Risk

lpi plus gp100	403	297	223	163	115	81	54	42	33	24	17	7	6	4	0
lpi	137	106	79	56	38	30	24	18	13	13	8	5	2	1	0
gp100	136	93	58	32	23	17	16	7	5	5	3	1	0	0	0

Hodi, NEJM 2010

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AJCC Melanoma Staging

<i>Subcategory</i>	<i>Metastases</i>	<i>LDH</i>	<i>10y survival</i>
M1a	Distant skin, SQ, nodes	Normal	16%
M2a	Lung	Normal	2-3%
M3a	Other viscera	Elevated	6%

Melanoma TMA

Expression of MAGE-C1/CT7 and MAGE-C2/CT10 Predicts Lymph Node Metastasis in Melanoma Patients

Curioni-Fontecedro PLOS 2011

Bim Expression Is Reduced in Human Cutaneous Melanomas

Dai, J Invest Derm 2008

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation