Cytokines: Interferons, Interleukins and Beyond

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Disclosures

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- I am neither employed nor do I have equity interests in any company or entity whose products/drugs will be discussed today.
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- Speakers Bureau: Prometheus

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Implementation of an Interleukin-2 National Registry: an opportunity to improve cancer outcomes

Michael K Wong[1*], Howard L Kaufman[2*], Gregory A Daniels[3], David F McDermott[4], Sandra Aung[5], James N Lowder[5] and Michael A Morse[6]

Journal for ImmunoTherapy of Cancer

Durable responses and reversible toxicity of high-dose interleukin-2 treatment of melanoma and renal cancer in a Community Hospital Biotherapy Program

Roxanne Payne[1], Lyn Glenn[1], Helena Hoen[1], Beverley Richards[1], John W Smith II[2], Robert Lufkin[2], Todd S Crocenzi[1], Walter J Urba[1] and Brendan D Curti[1*]

High dose interleukin-2 (Aldesleukin) - expert consensus on best management practices-2014

Janice P Dutcher[1*], Douglas J Schwartzentruber[2], Howard L Kaufman[3], Sanjiv S Agarwala[4], Ahmad A Tarhini[5], James N Lowder[6] and Michael B Atkins[7]

HD IL-2 extends OS in malignant melanoma
April 18, 2015

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Learning Objectives

- Understand the main effects of cytokines on immune cells.
- Identify the main patient selection criteria for IL-2-based immunotherapy.
- Describe the mechanisms for toxicity related to IL-2 administration.
- Describe the rationale for considering IL-2 immunotherapy.

Overview

- Primer on how T cells work
- Cytokines in the immune system
- IL-2
  - Clinical applications
  - Toxicity anecdotes
  - Clinical response

T Cell Mechanics

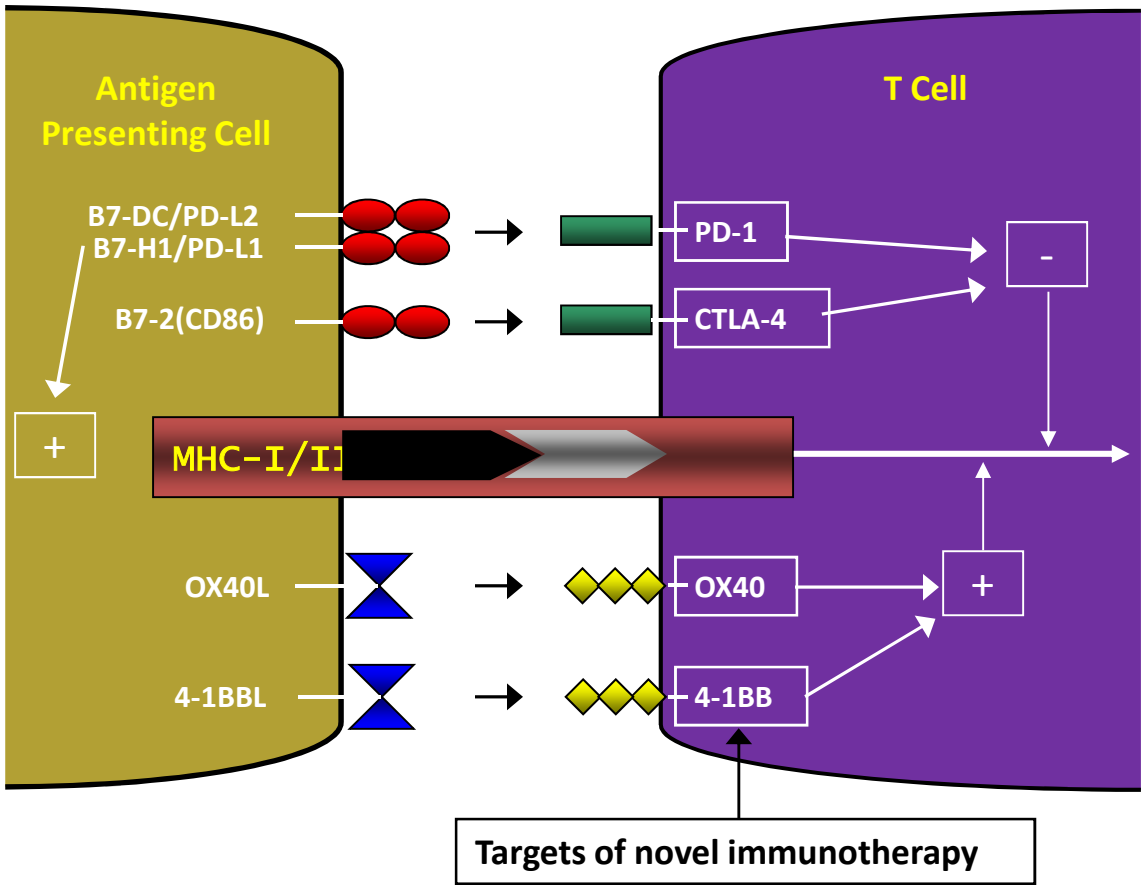
T-cell receptor: antigen/MHC

CD28 B7

CTLA-4 B7

Vaccine?

T Cell Regulatory Pathways



TNFR family TNF family B7 family CD28 family

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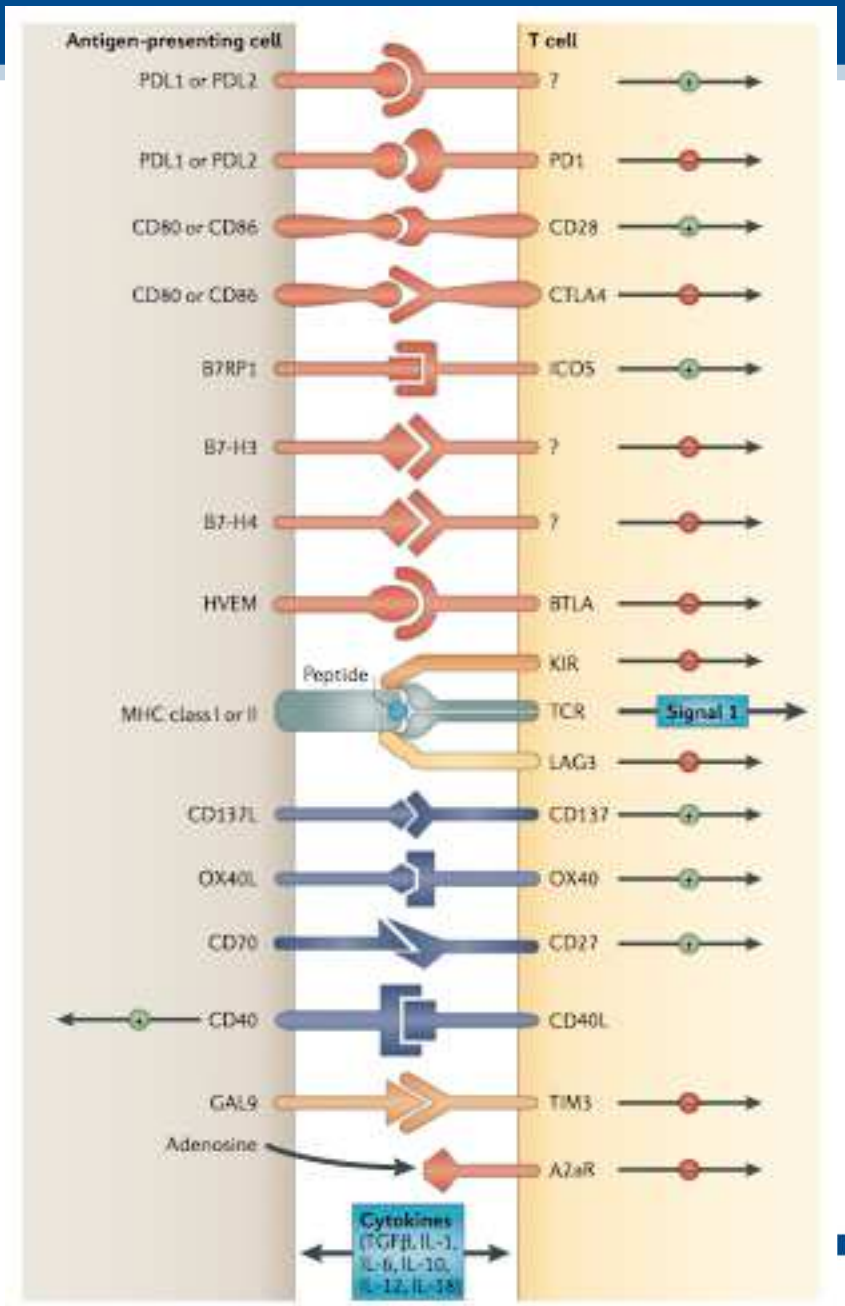
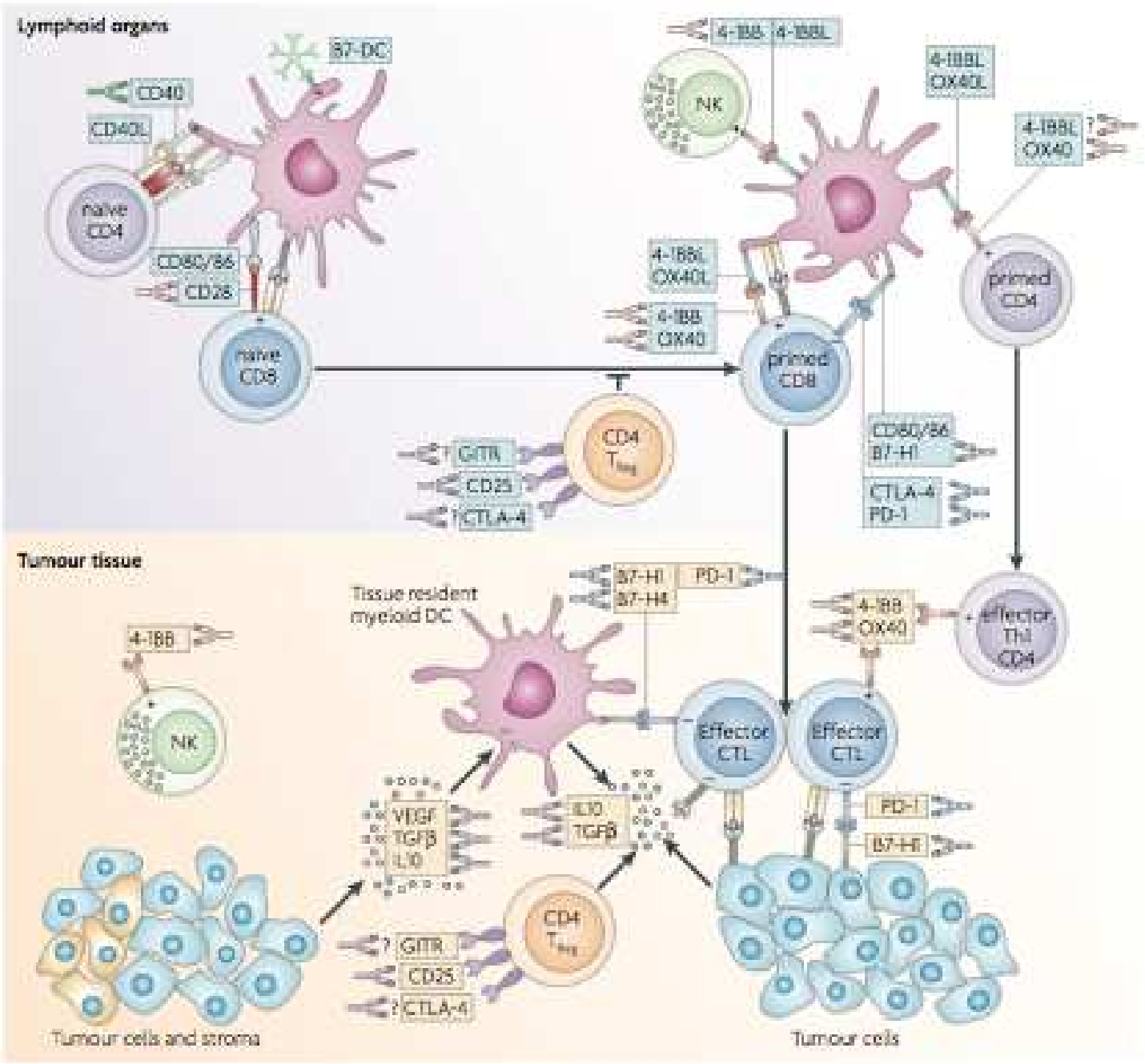
Adapted from: Melero et al. *Nature Rev Cancer*. 2007;7:95.

More regulatory pathways . . .



Pardoll, Nature April 2012



Melero et al., Nature Reviews February 2007

What are cytokines?

- Diverse family of immune cell regulators:
  - Interleukins
  - Chemokines
  - Tumor Necrosis Factors
  - Interferons
- 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

More Details

- Interleukins
  - Type 1: γ-chain (IL-2, IL-15, IL-4, IL-13, IL-7, IL-9, IL-21); β-chain (IL-3, IL-5, GM-CSF); IL-6-like (IL-6, IL-11, IL-27, IL-30, IL-31); IL-12 family (IL-12, IL-23, IL-27, IL-35)
  - Type 2: IL-10 family (IL-10, IL-22, IL-19, IL-20, IL-24, IL-26, IFN type III)
  - Ig superfamily (IL-1α, IL-1β)
  - IL-17 family (IL-17, IL-25)
- Interferons
  - Alpha, beta, gamma (around 36 total)
- Chemokines
  - CCL (CCL1 – CCL28)
- TNF
  - . . .

Cytokines That Have Been Tested in Humans

- IL-1-α
- IL-1-β
- IL-2
- IL-7
- IL-12
- IL-21
- Interferons
- TNFs

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EDITORIAL

Present Status and Future Prospects for Adjuvant Therapy of Melanoma: Time to Build upon the Foundation of High-dose Interferon Alfa-2b

Stergios J. Moschos, John M. Kirkwood, University of Pittsburgh Cancer Institute, Pittsburgh, PA Panagiotis A. Konstantinopoulos, State University of New York Upstate Medical Center, Syracuse, NY

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Interferon Factoids

- Remains the only FDA-approved adjuvant therapy for stage III melanoma
- Relapse-free survival consistent across 30 years of investigation
- Overall survival benefit remains controversial (3 – 5% range and not with low dose regimens)
- Findings of ECOG 1609 (IFN vs Ipilimumab in stage III melanoma) will be of interest.

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

Major Selection Criteria for IL-2

- Metastatic renal cancer or melanoma
- Normal pulmonary and cardiac function as assessed by PFTs and ETT
- “Relatively” normal renal and hepatic function
- Controlled brain metastases
- No active infection
- No active autoimmune disease requiring steroids (vitiligo and autoimmune hypothyroidism OK)

IL-2 Treatment

- IL-2 = 600,000 international units per kg IVB x 14 planned doses.
- Manage clinical consequences of immune activation.
- Second cycle given after 2 week break. Scans repeated one month later.
- More IL-2 for lucky responders (up to 3 courses (6 cycles) maximum).

IL-2 Side Effects

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

HYPOTENSION

Cardiac Tachy or Bradydysrhythmias

FATIGUE

RENAL FAILURE

Hepatic Dysfunction

ACIDOSIS

Weight gain/Fluid Retention

RASH

Hypoxia

Pleural effusions

Hypothyroidism

DIARRHEA

Mucositis

Desquamation

Lymphopenia

Peripheral neuropathy

Splenomegaly

Vomiting

Pulmonary Infiltrates

HEART ATTACK

NAUSEA

ITCHING

Arthralgias/myalgias

Thrombocytopenia

VITILIGO

Hyperbilirubinemia

Mental status changes

Stroke-like syndromes

Infection

Electrolyte abnormalities

Abdominal visceral perforation

CHILLS

Anorexia

Vivid Dreams

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Bleeding/Clotting

DEATH

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Physiology of IL-2-Induced Capillary Leak

- Nitric oxide
- TNF, IL-1
- Lymphocyte activation and movement through blood vessels
- Activation of prostaglandin pathways

Criteria to Consider Holding IL-2 Doses

- Sinus tachycardia 150
- A. fibrillation/SVT
- Hypotension
- Phenylephrine
  - 1-1.5 μg/kg/min or higher
- Neurotoxicity
  - Vivid dreams
  - Emotional lability
  - Transient confusion
- Ileus/abdominal distention
- Diarrhea >1000 cc
- Severe nausea/vomiting
- Shortness of breath at rest
- 3-4 L/min O_2 by NC for saturation >90%
- Rales one third of the way up chest
- Significant oliguria
- Significant elevation in serum creatinine
- Weight gain 15% over baseline

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Schwartzentruber et al., J Immunother 24:287-293, 2001

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Criteria to Consider Stopping IL-2

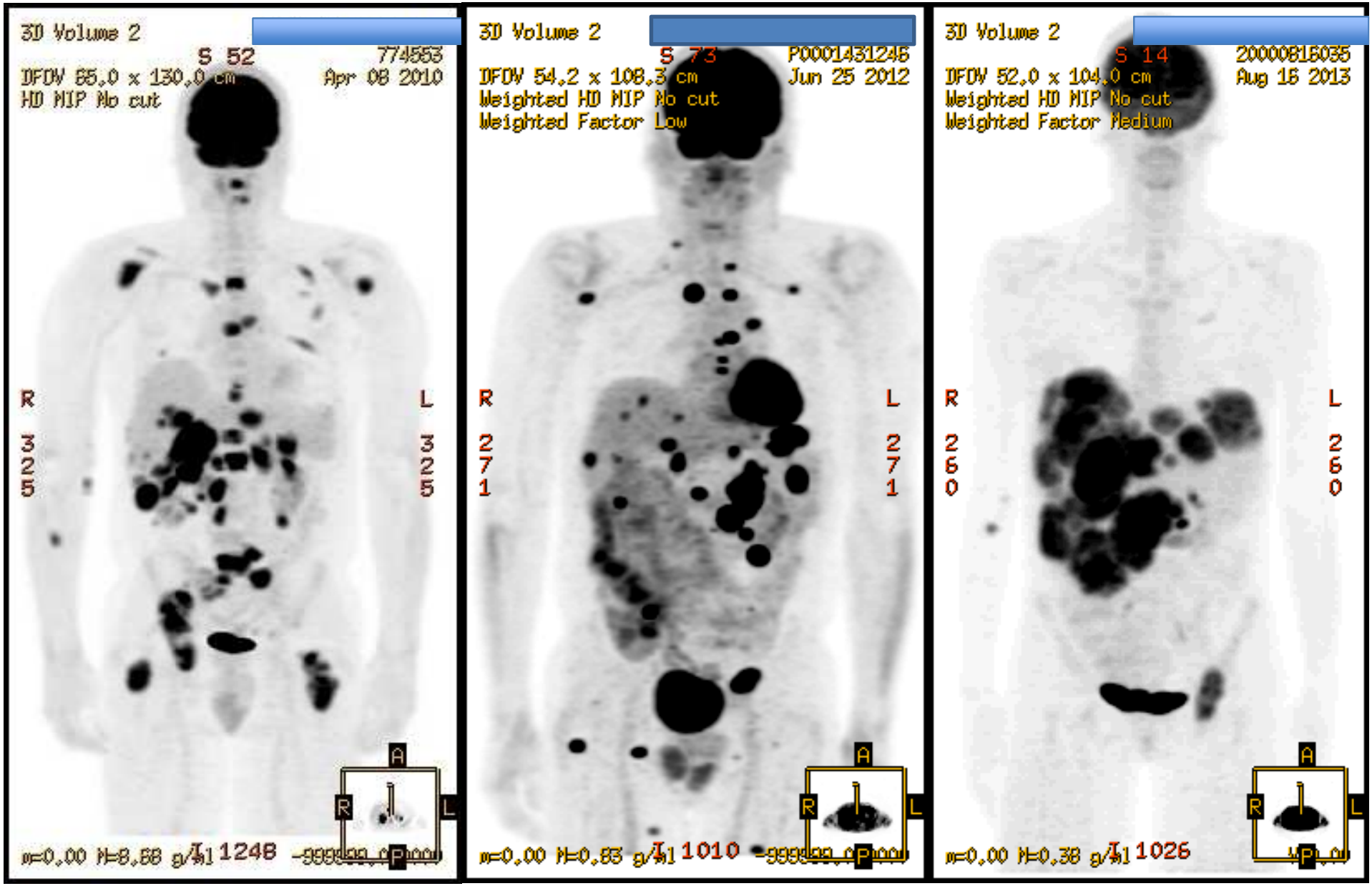
- Uncontrolled sinus tachycardia >150
- EKG changes of ischemia
- Uncontrolled atrial fibrillation/supraventricular tachychardia
- Ventricular arrhythmias
- Elevated CPK-MB
- Moist desquamation
- Diarrhea 1000 cc/shift × 2
- Vomiting unresponsive to medication
- Severe abdominal distention affecting breathing
- Severe abdominal pain, unrelenting
- Phenylephrine
  - 3.0 µg/kg/min
  - Prolonged need for high doses
- Frank blood in sputum, emesis, stool
- Platelets <30,000/µL
- Strong clinical suspicion of or documented infection

Criteria to Consider Stopping IL-2 (cont)

- Mental status changes not resolved in 2 hr
- Obtundation or coma
- Hallucinations
- Cortical blindness
- Limb or gait ataxia
- Speech difficulties
- >4 L/min O_2 by NC or 40% O_2 mask to maintain saturation >90%
- Endotracheal intubation
- Rales halfway up chest
- Pleural effusion requiring tap or chest tube while on therapy
- Significant oliguria or elevation in serum creatinine not improved by holding dose or low-dose dopamine
- Exacerbation of autoimmune and inflammatory disorders

Why do we offer this difficult (barbaric) treatment?

What is the Diagnosis?



Clinical History

- 52 year old white man presented with abdominal discomfort. Cholelithiasis suspected. US shows multiple hepatic masses. Biopsy shows melanoma (no primary evident). He volunteers for a clinical trial combining SBRT radiation + high-dose IL-2 (600,000 international units/kg IVB q8h x 14 planned doses). After dose 4 his SBP is 68/44, pulse 120, O2 sat 94% on RA.
- What would you do?

IL-2-Induced Hypotension: Physiology

- Capillary leak from:
  - Nitric oxide
  - IL-1
  - TNF . . .
- Activated T cell trafficking
- Decreased cardiac contractility
- Analog to “warm shock” (e.g.: sepsis without the bugs)

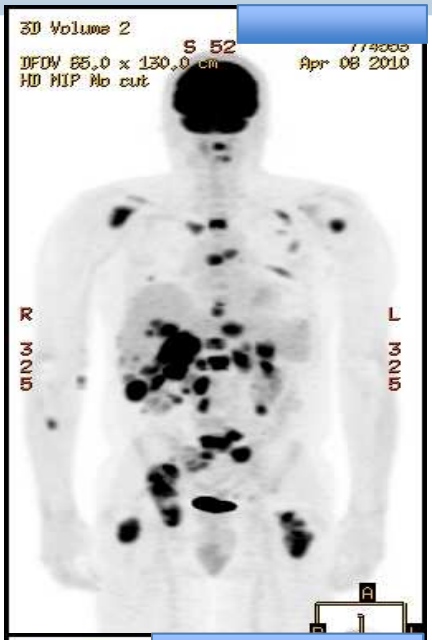
IL-2 Hypotension: Management

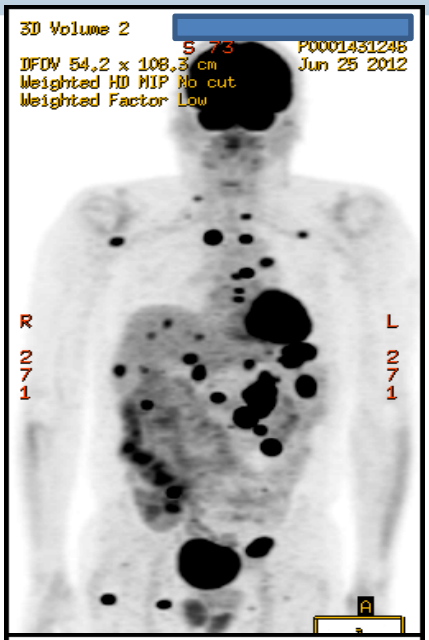
- Fluid bolus (e.g.: 250 NS x 3 (within 24 hours)) to achieve SBP > 85 mm Hg.
- Phenylephrine 40 µg/min IV titrated to maintain SBP > 85 mmHg
- In "IL-2-selected" patients, the usual 200 µg/min "maximal" dose used in the ICU is not relevant. Doses of phenylephrine > 5 µg/kg/min can be used.
- Clinical assessment of organ perfusion is key to pressor management. For patients with a high "SITS" (severe IL-2 toxicity score), then ICU transfer, norepinephrine.
- For cytokine circulatory collapse then consider hetastarch or methylene blue infusions, high-dose steroids, anti-TNF antibodies.

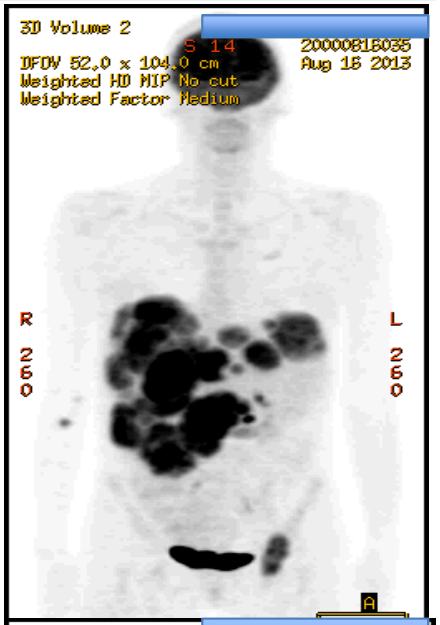
Clinical History continued

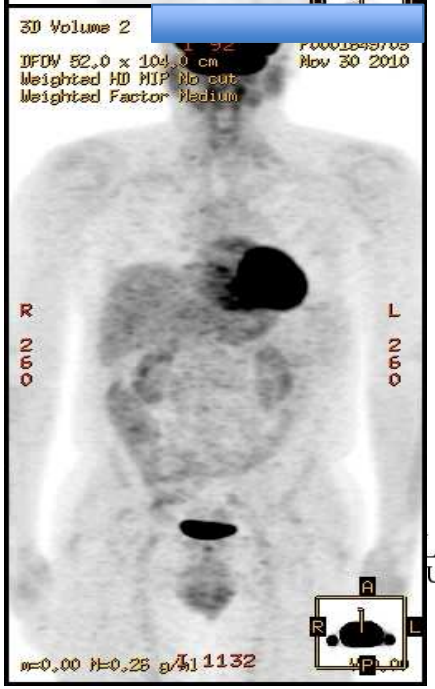
- Blood pressure was 75/45 mmHg after 3 NS boluses. Phenyephrine was started and within two hours the SBP was 80/50 mmHg at a phenyephrine dose of 325 µg/min. He then developed atrial fibrillation and BP decreased to 70/40. He was transferred to the ICU for amiodarone drip, and further pressor titration. He converted to NSR and within 10 hours was off phenylephrine.
- His response after IL-2 + SBRT was:

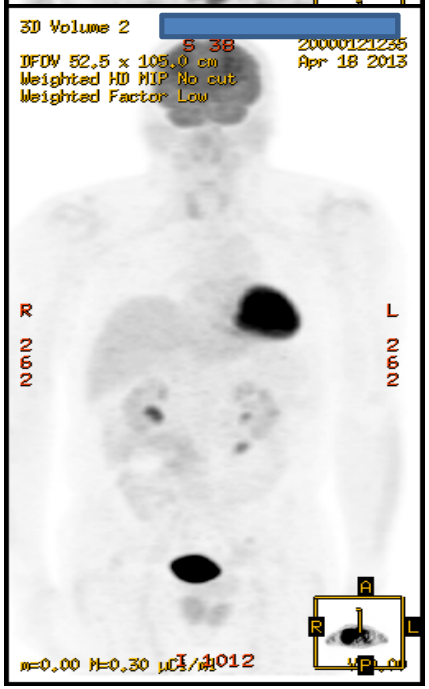
Befores and Afters

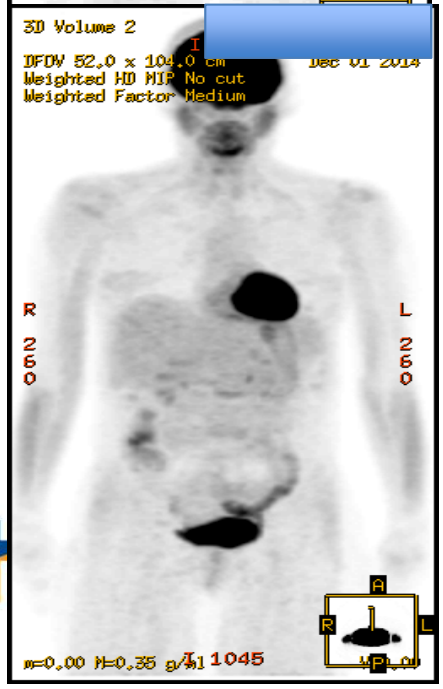




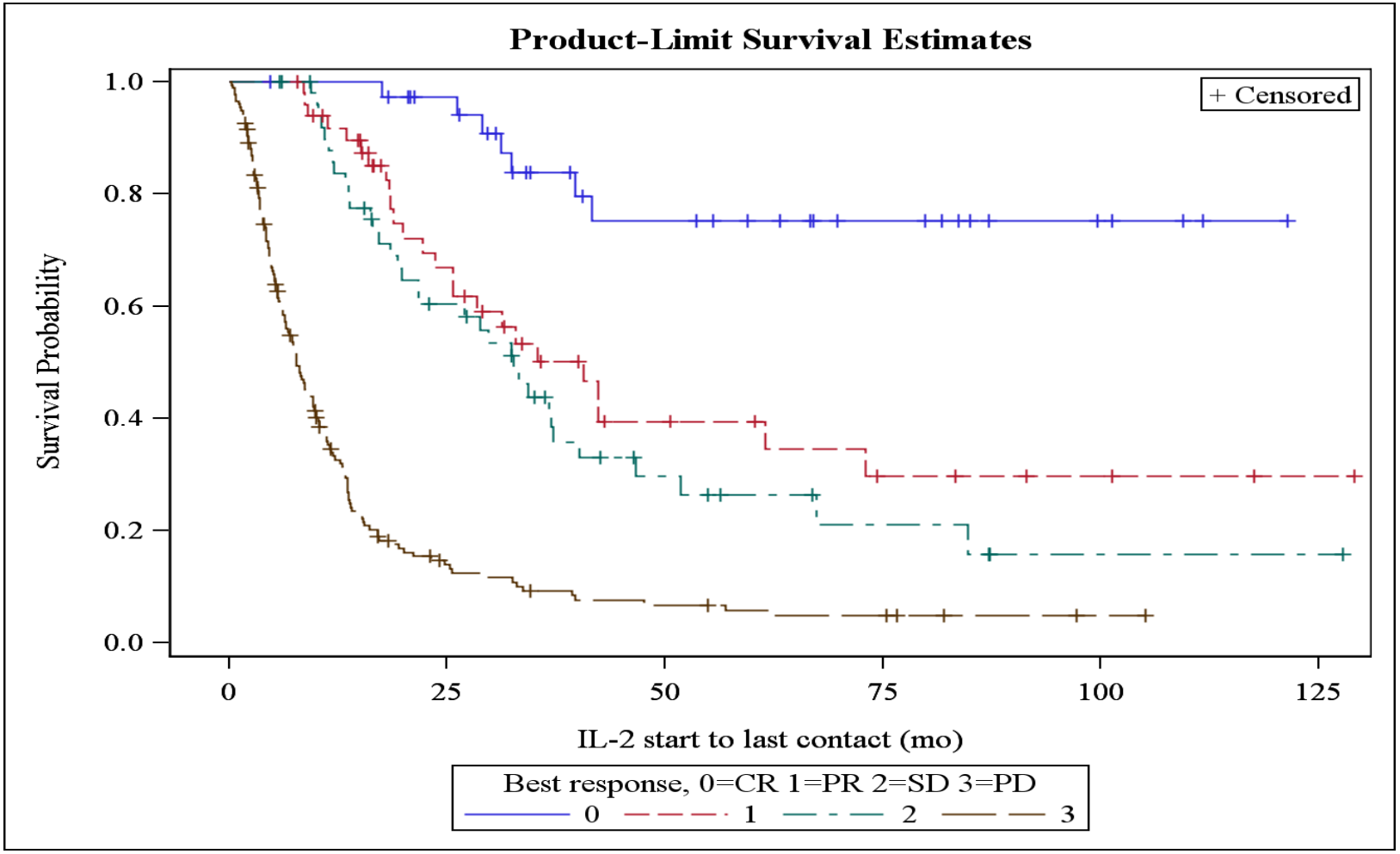








High-dose IL-2: Melanoma Survival



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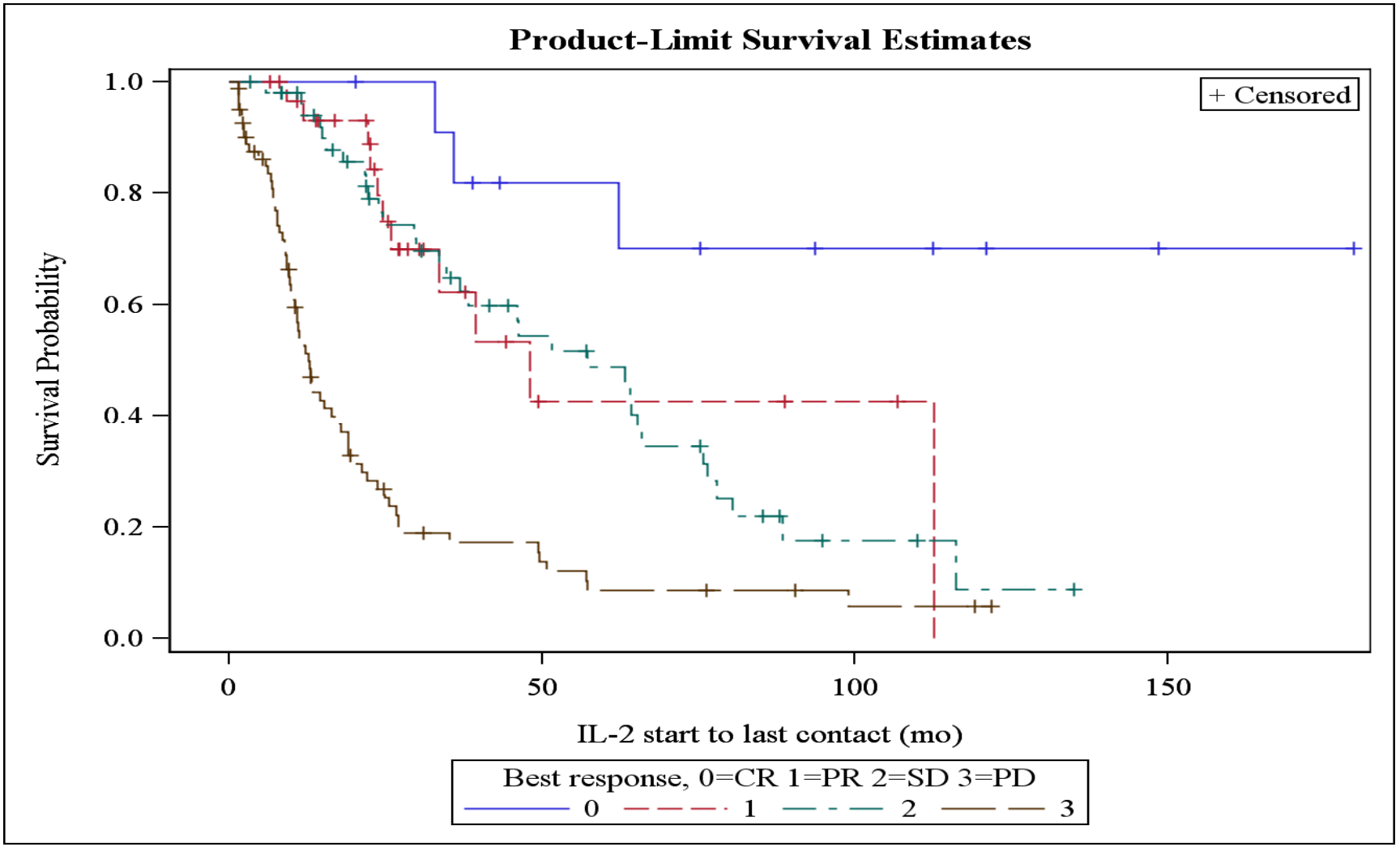
High-dose IL-2: RCC Survival



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Conclusions

- IL-2 can be administered safely at sites experienced in cytokine toxicity management.
- Patients have significant, but reversible toxicity during IL-2.
- Objective responses occur that translate into a survival benefit in selected patients with melanoma and renal cell carcinoma.