Cancer Immunotherapy Perspective

Michael B. Atkins, M.D.
Deputy Director
Georgetown-Lombardi Comprehensive Cancer Center

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Disclosures (1)

Consultant:

BMS, Merck, Novartis, Genentech/Roche, Pfizer, Nektar, Celldex

Disclosures (2)

I am a Medical Oncologist, not a health economist

Last formal economics training – 1976

Gerald Ford

Transfer Factor
H Sherwood Lawrence

Disclosures (3)

All opinions are my own and do not necessarily represent those of SITC or even the IO community….

Cancer Immunotherapy Principles (1)

- The host immune system is the dominant active enemy faced by a developing cancer
- All “successful” cancers must solve the challenges of overcoming defenses erected by host immune system.
- Many of these defenses serve to inactivate the immune system

Cancer Immunotherapy Principles (2)

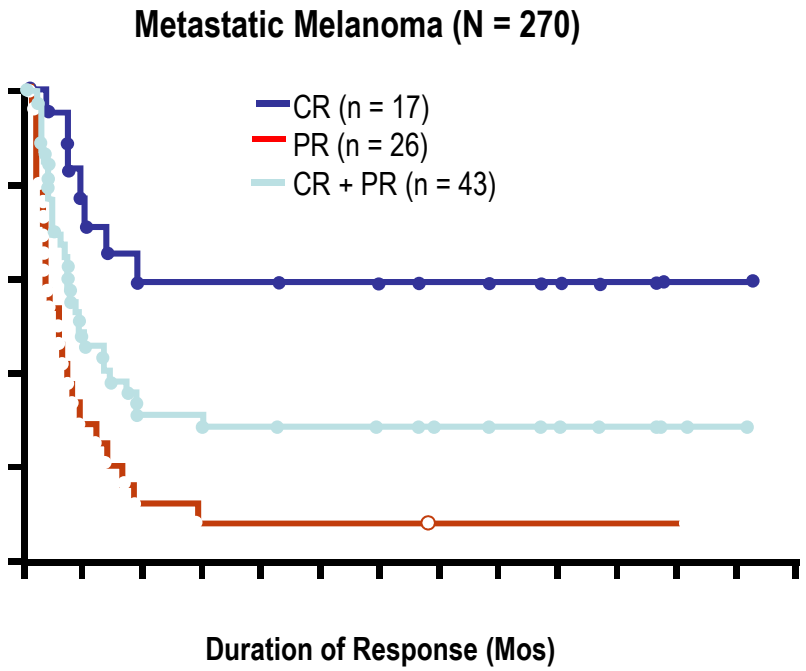
- “Treating the immune system so that it can treat the cancer” Jedd Wolchok

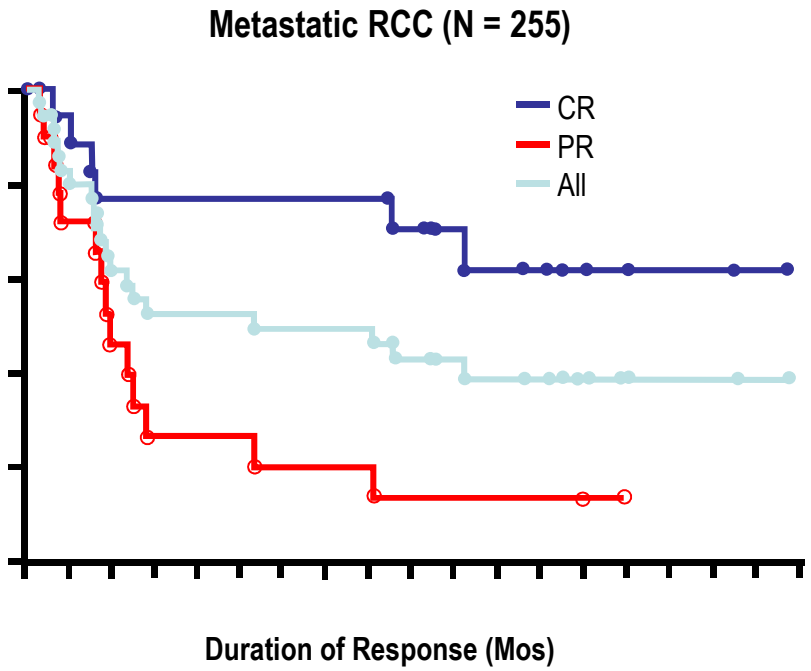
- Because the activated immune system can target many tumor antigens simultaneously, and deepen and broaden over time, IT can cure patients with metastatic cancer

- The hallmark of effective immunotherapy is the tail on the curve

HD IL-2 Therapy - Thirty Year History
Durable Responses/Cures

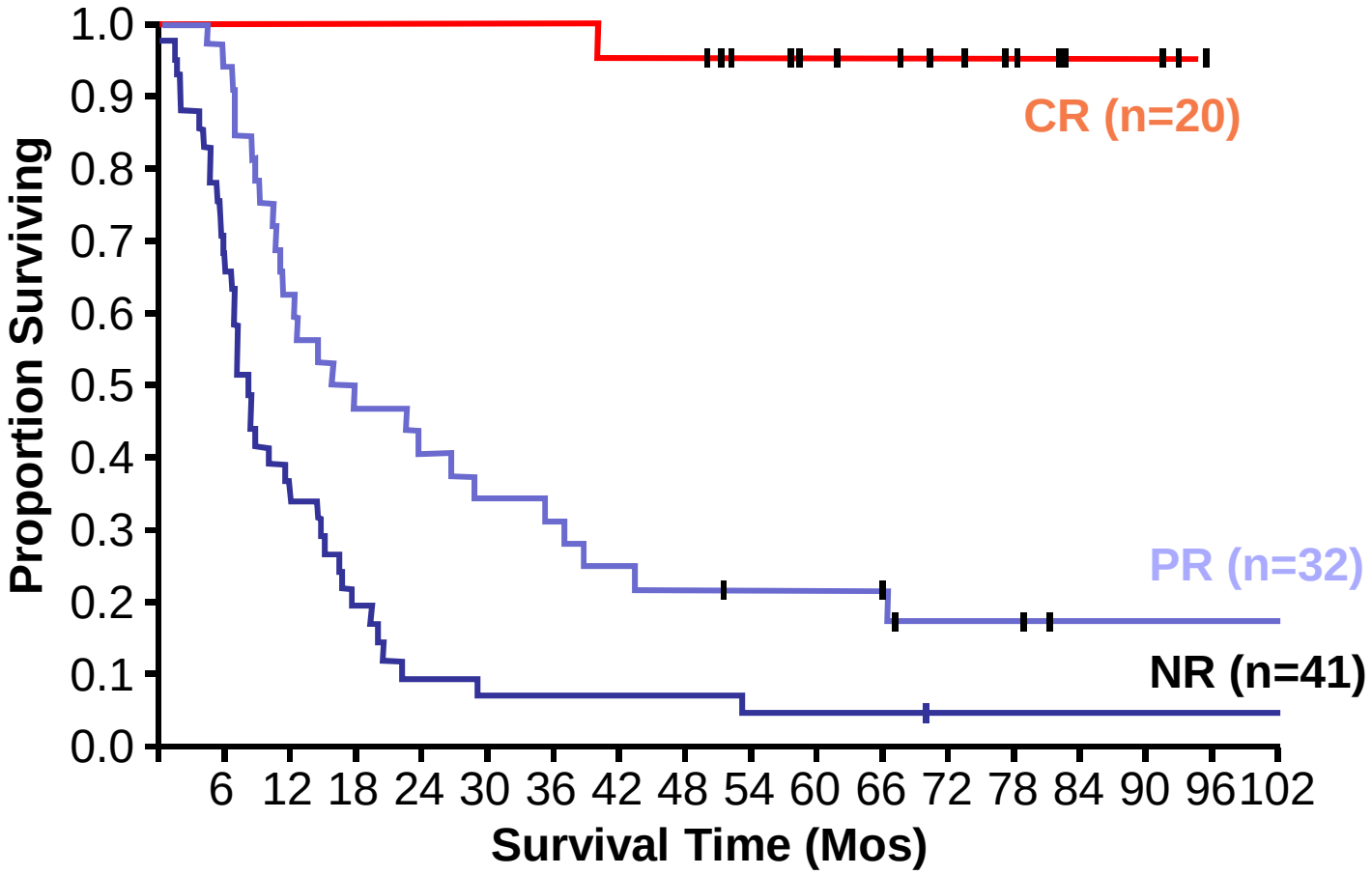
- HD IL-2 produces durable responses in ~10% of patients with advanced melanoma or RCC
- Few relapses in patients responding for over 2.5 years (likely cured)
- FDA approval in 1992 (RCC) and 1997 (melanoma)





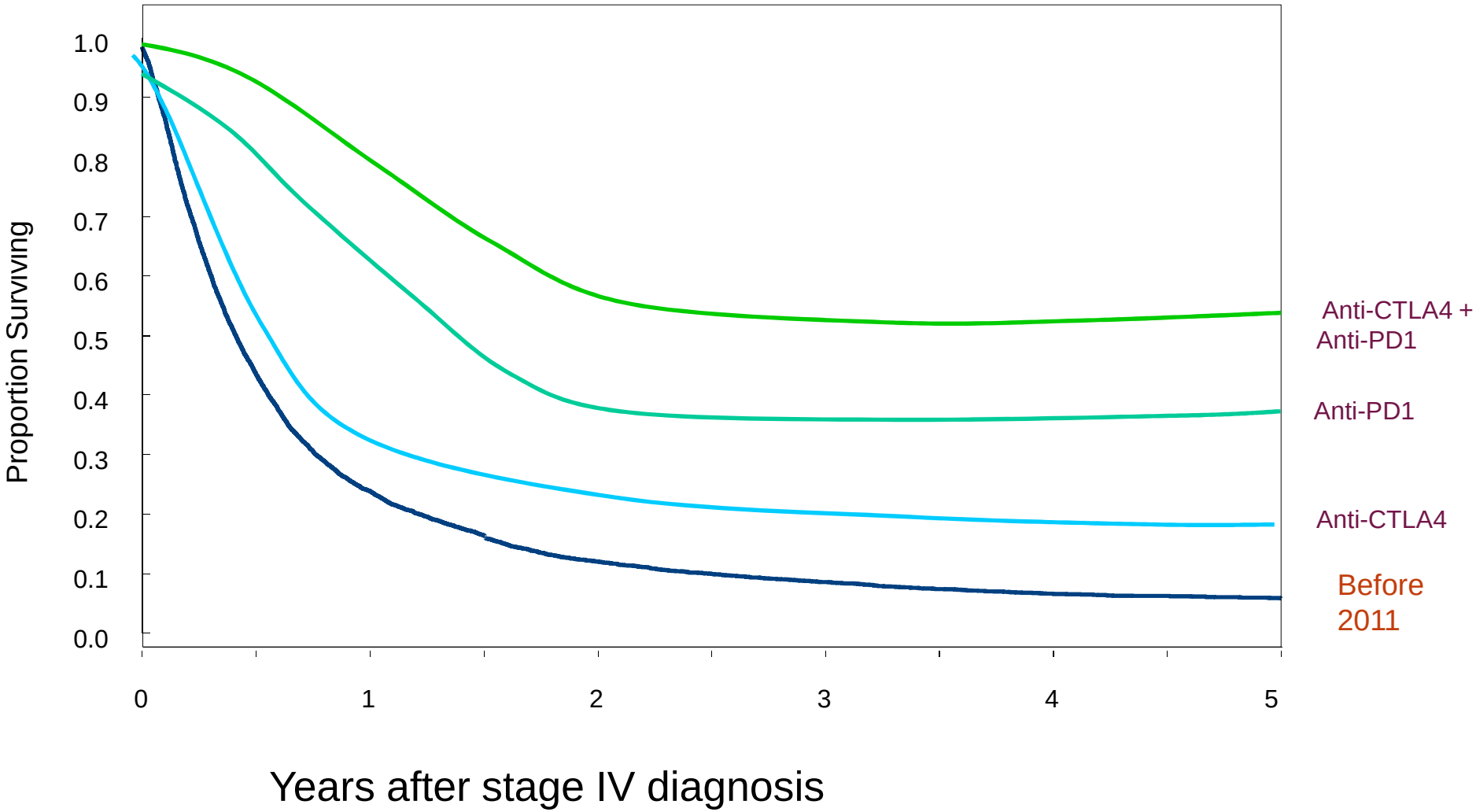
Atkins MB, et al. J Clin Oncol. 1999;17:2105-2116. McDermott DF, et al. Expert Opin Biol Ther. 2004;4:455-468.

Tumor-Infiltrating Lymphocytes + IL-2 in Metastatic Melanoma: OS



Robbins PF, et al. Nat Med. 2013;19:747-752.

Overall Survival for Patients with Stage IV Melanoma



Spectrum of PD-1/PD-L1 Antagonist Activity

Active

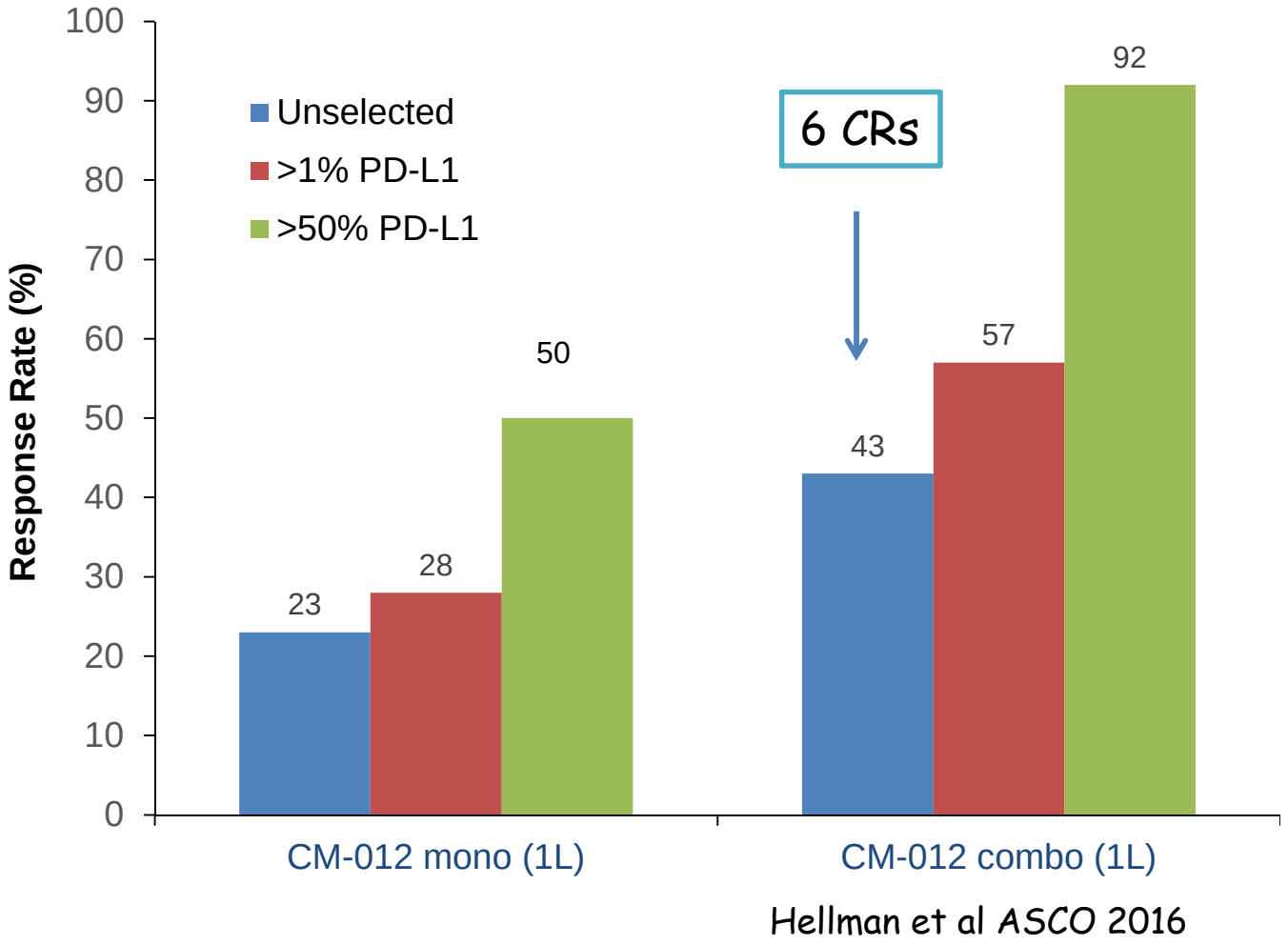
- **Melanoma**
- **Renal cancer (clear cell)**
- **NSCLC – adenocarcinoma and squamous cell**
- **Head and neck cancer**
- **Urothelial (bladder) cancer**

15 for 16
Phase III Trials

- Small cell lung cancer
- Gastric and GE junction
- **Mismatch repair deficient tumors (colon, cholangiocarcinoma)**
- Triple negative breast cancer
- Ovarian cancer
- Glioblastoma
- Hepatocellular carcinoma
- Thymic carcinoma
- Mesothelioma
- Cervical cancer
- **Hodgkin Lymphoma**
- Diffuse large cell lymphoma
- Follicular lymphoma
- T-cell lymphoma (CTCL, PTCL)
- **Merkel Cell**

Nivo + ipi benefit
Melanoma
NSCLCa
RCC
Urothelial Ca

Combination I-O (IPI/NIVO) vs nivo alone in NSCLCa



Hellman et al ASCO 2016

What is “Value”?

$$\text{Value} = \frac{\text{Net Outcomes: beneficial-detrimental}}{\text{Financial Cost}}$$

For IO relative to other therapies most value formulas tend to:

- Overestimate the financial cost
- Overestimate the detriments (toxicities)
- Underestimate the benefits

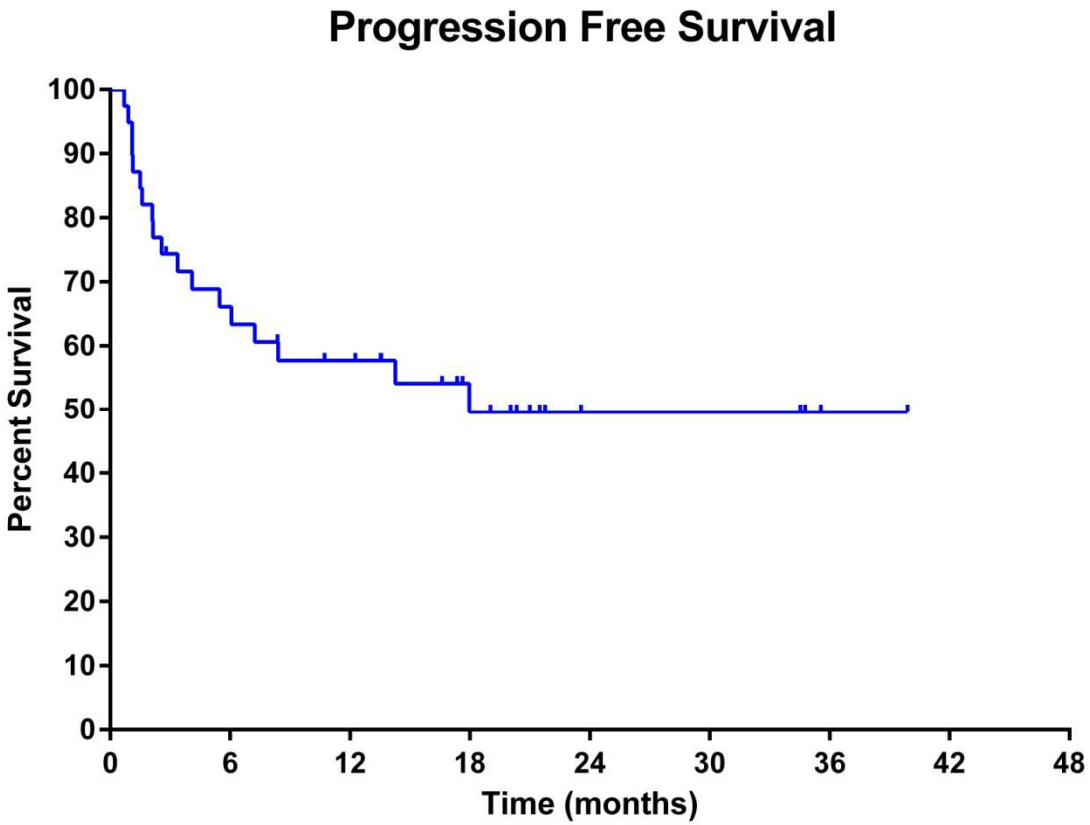
Overestimating the Costs of IT (1)

- Costs not amortized over the longer horizons of benefit (Need cure rate model)
  - Absence of the need for subsequent Rx ignored
- Many patients are being over-treated with IT
  - “Effective” IT should be a max of 6-12 months
  - Benefits of activated immune system persist long after treatment stops
  - Many radiologic “PRs” are actually pathologic “CRs”
  - Residual disease after 1 year needs to be biopsied/ resected if possible

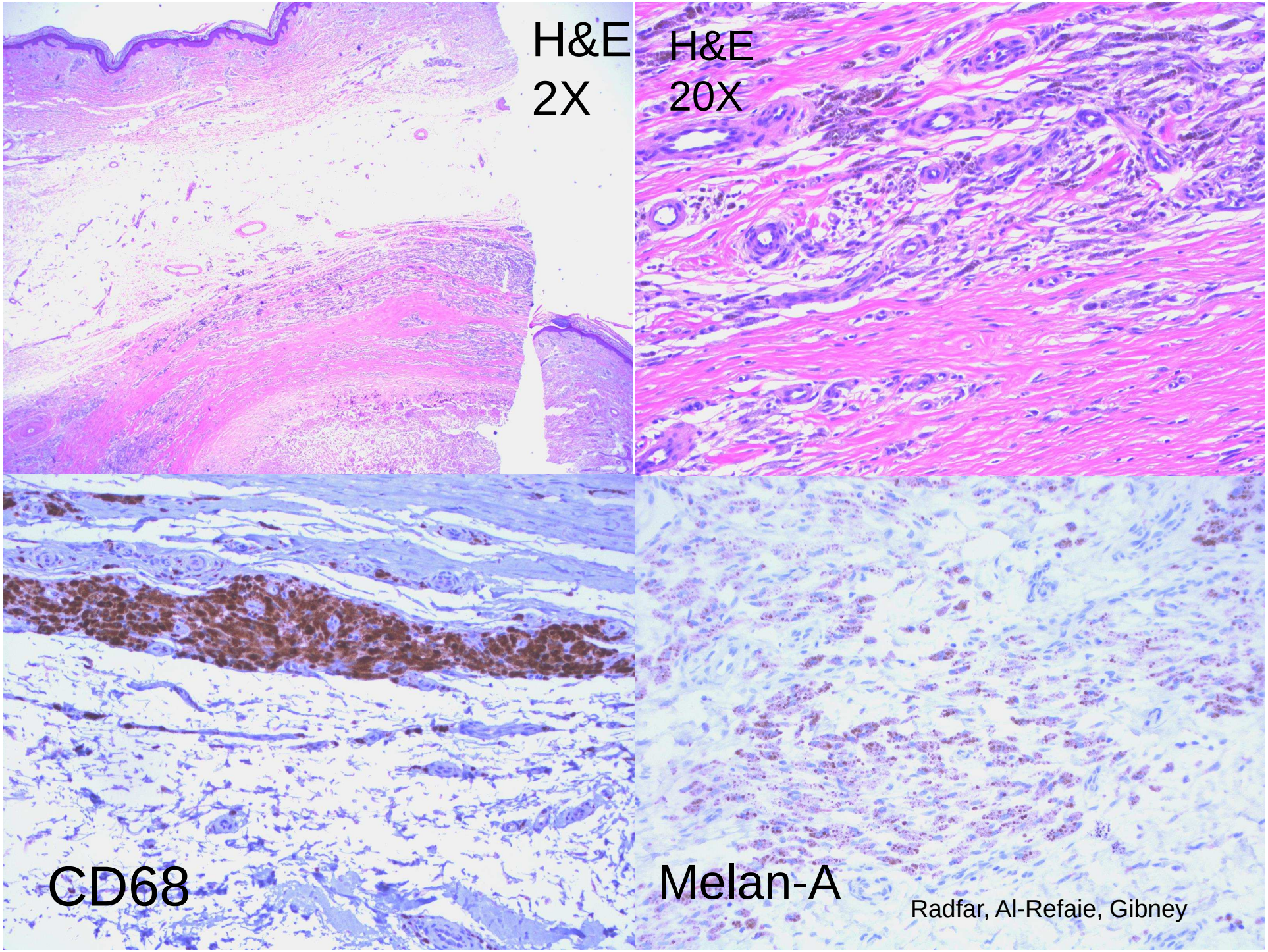
MGUH Experience with in Patients with metastatic melanoma treated with nivo/ipi

N = 41 (39 Eval)
Median f/up -18 mos

RR = 23/39 (59%)
- 5 CR (13%)
- 18 PR (46%)
- 3 SD (8%)
- 13 PD (33%)



Gibney, Gardner et al.


H&E
2X
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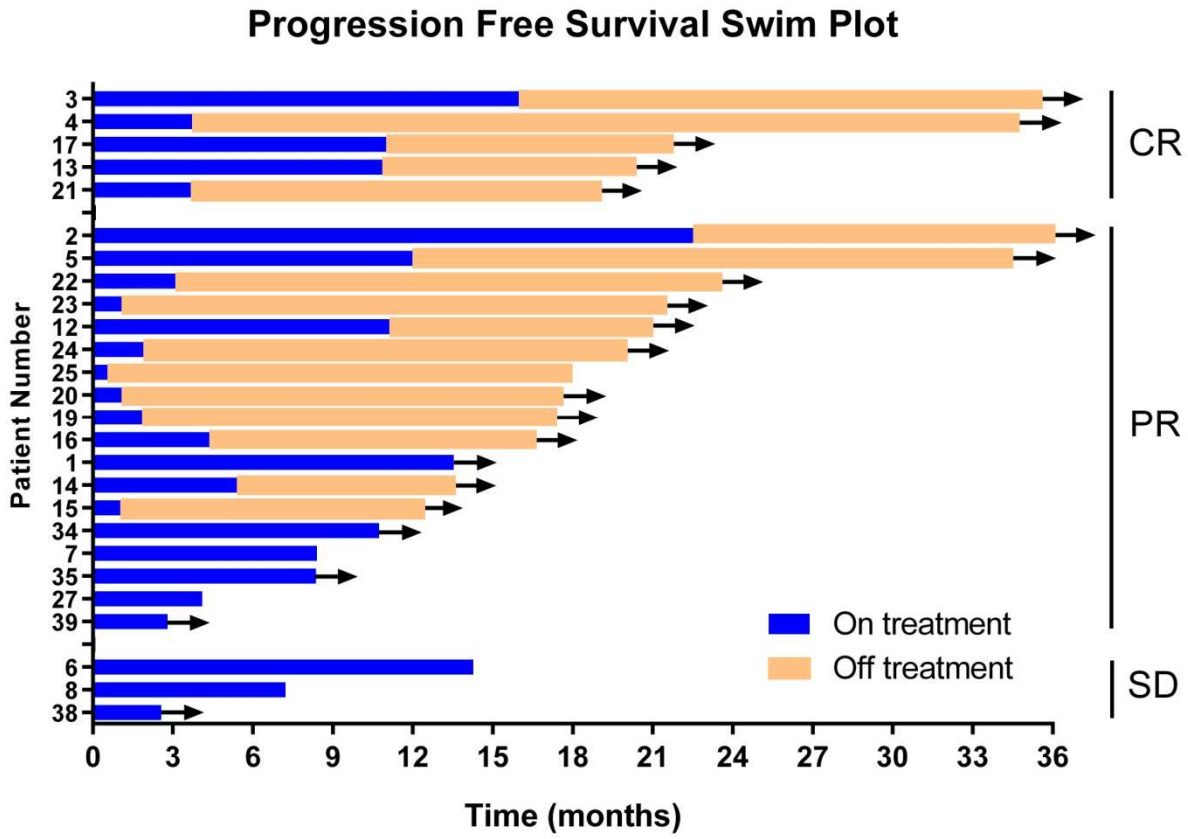
Melan-A
Radfar, Al-Refaie, Gibney

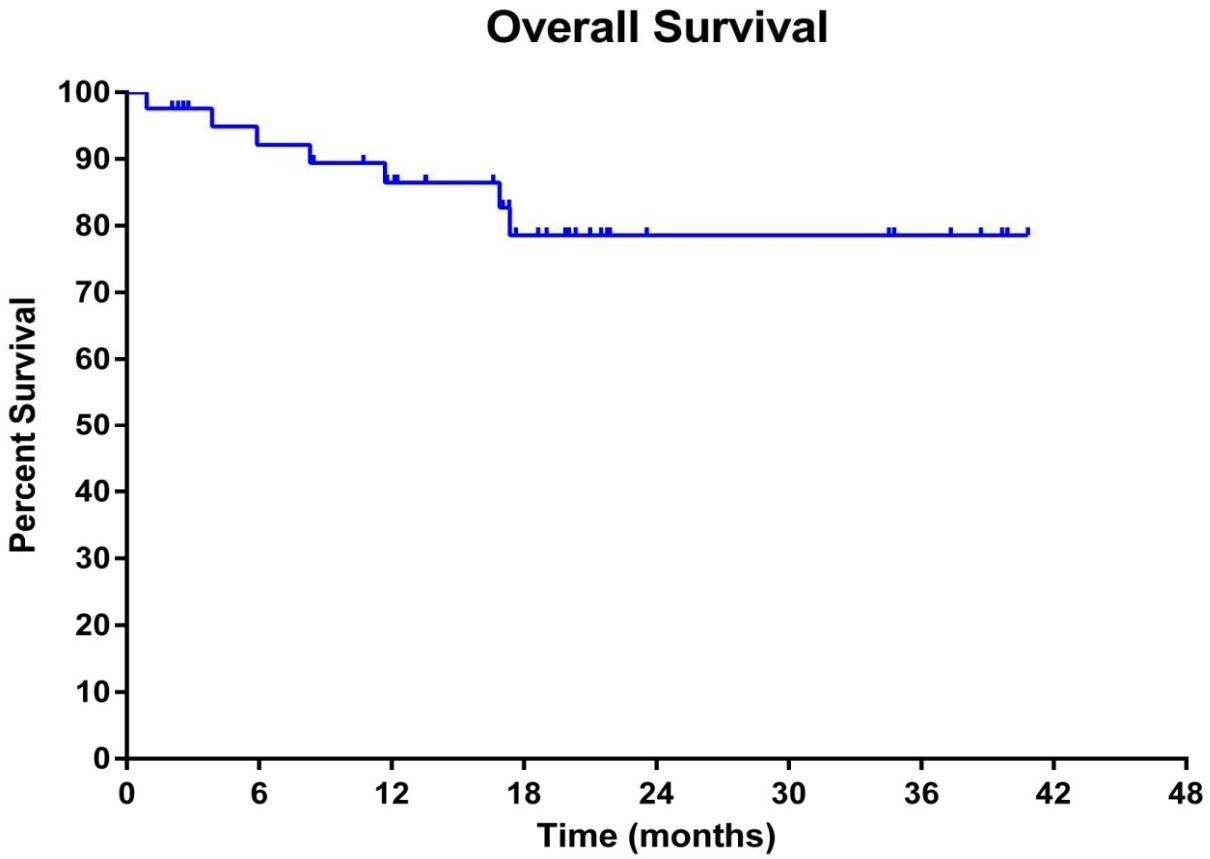
Majority of Responding patients to Nivo/Ipi will continue to respond after stopping Treatment



15/16 patients continue to respond after stopping Rx
5/5 CR; 11/12 PR

Gibney, Gardner et al

MGUH Experience: OS in Patients with Metastatic Melanoma Treated with Nivo/Ipi



7 deaths in 41 patients
Median F/up 18 months

Gibney, Gardner et al.

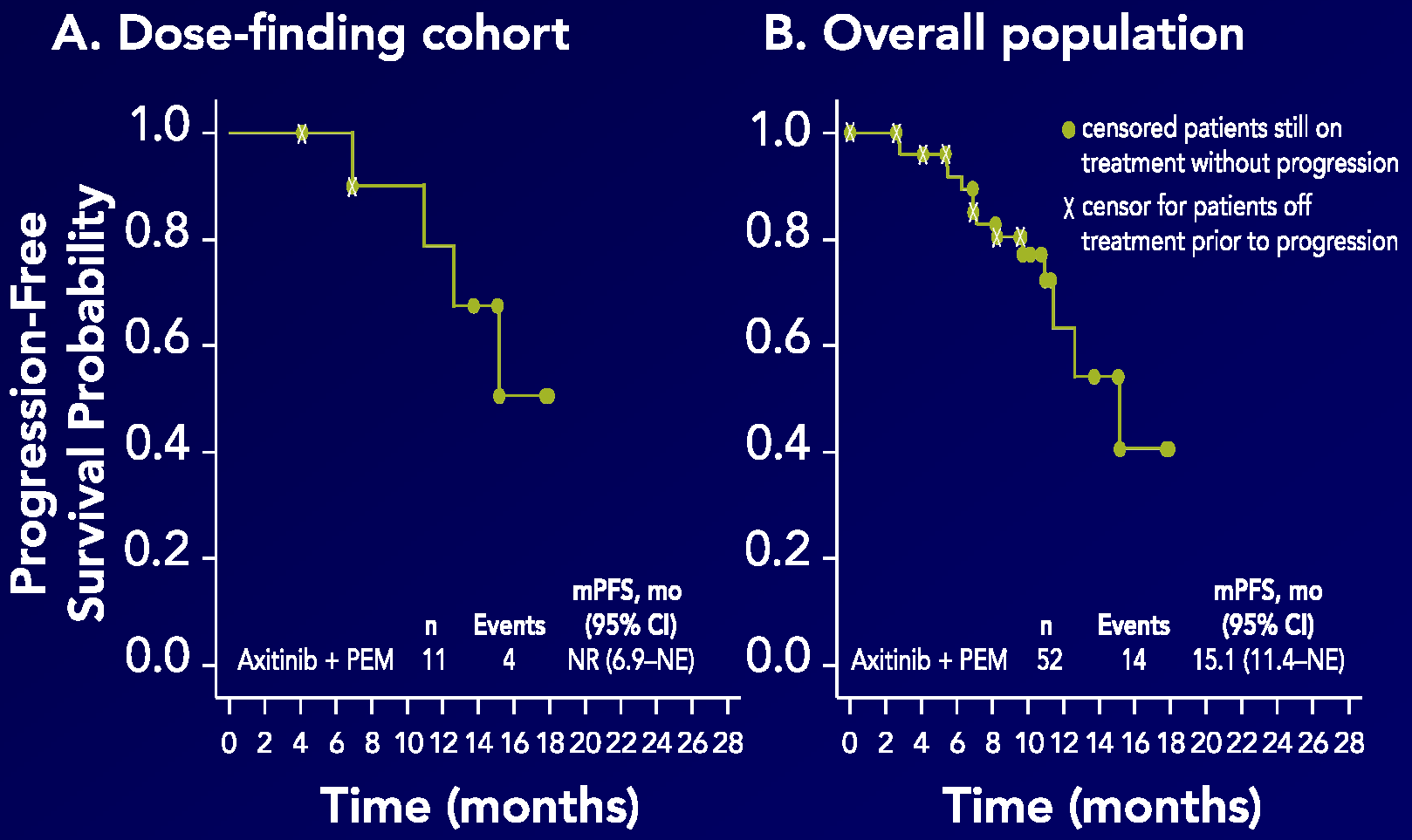
Overestimating the Costs of IT (2)

- Combinations of IOs may actually be cheaper than single agents - if work faster (require less drug);
  - Ipi/nivo regimen:
    - Added cost of nivo in the first 12 weeks is $12,500
    - Half the patients stop Rx before wk 12 due to toxicities
    - Toxicities frequently managed as outpatient
    - 2/3rd of these patients continue to respond
    - Most do not need additional therapy

Opportunities for Further Reducing Costs (1)

- Avoiding IO/Non-IO combinations that don't allow for Rx cessation
  - impossible to tell which approach is responsible for benefit
  - longer PFS = longer time on therapy= >> drug costs

Axitinib in Combination With Pembro in Patients With Advanced RCC: Preliminary Safety and Efficacy Results
Progression Free Survival



CI=confidence interval; mPFS=median progression-free survival; NE=not estimable; NR=not reached; PEM=pembrolizumab

Atkins et al ESMO 2016 Abst 2577

Opportunities for Further Reducing Costs (2)

- Reducing drug waste (Bach PB, et al BMJ 2016)
  - Estimated to be billions of dollars/yr
- Reducing drug administration costs/markups
- Biomarkers
  - Selecting the right drug/or combination for the right patient (Herbst-talk)
- More efficient drug development (less “dry wells”)
- Competition

The Cancer Letter – October 11, 2016

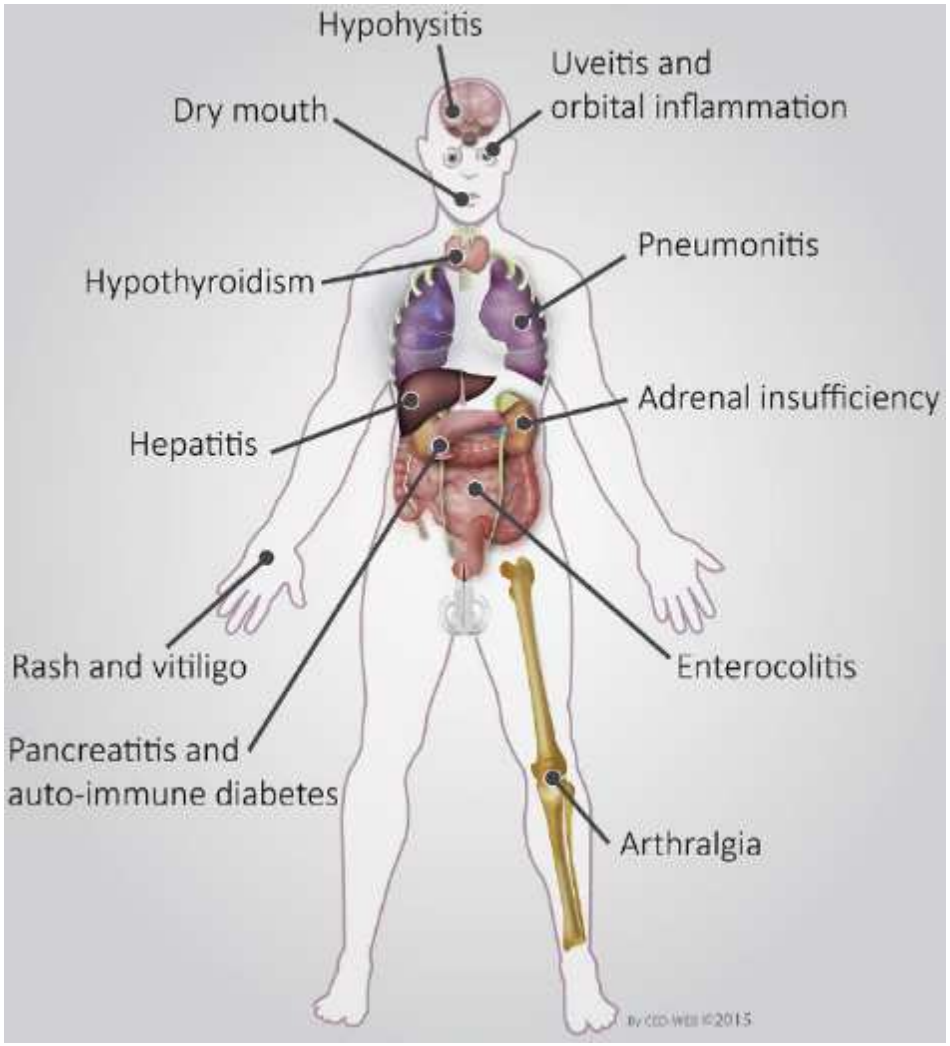
"With 20 Agents, 803 Trials, and 166,736 Patient Slots, Is Pharma Investing Too Heavily in PD-1 Drug Development?"

Bigger questions are-

Where will all of these patients come from?

If multiple similar agents are approved, will cost finally be a differentiator?

Overestimating the Toxicities (1)



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Frontline Nivo + Ipi Data: Toxicity

- Toxicities are severe but manageable
  - Rate of treatment related AEs is similar across age groups and disease stage
  - 80% AEs resolve within 4-6 weeks with immune modulatory Rx (not endocrine)
  - Few treatment related deaths (069 = 3, 067 = 0)
- Toxicity did not interfere with response

Hodi et al, Larkin et al

Overestimating the Toxicities (2)

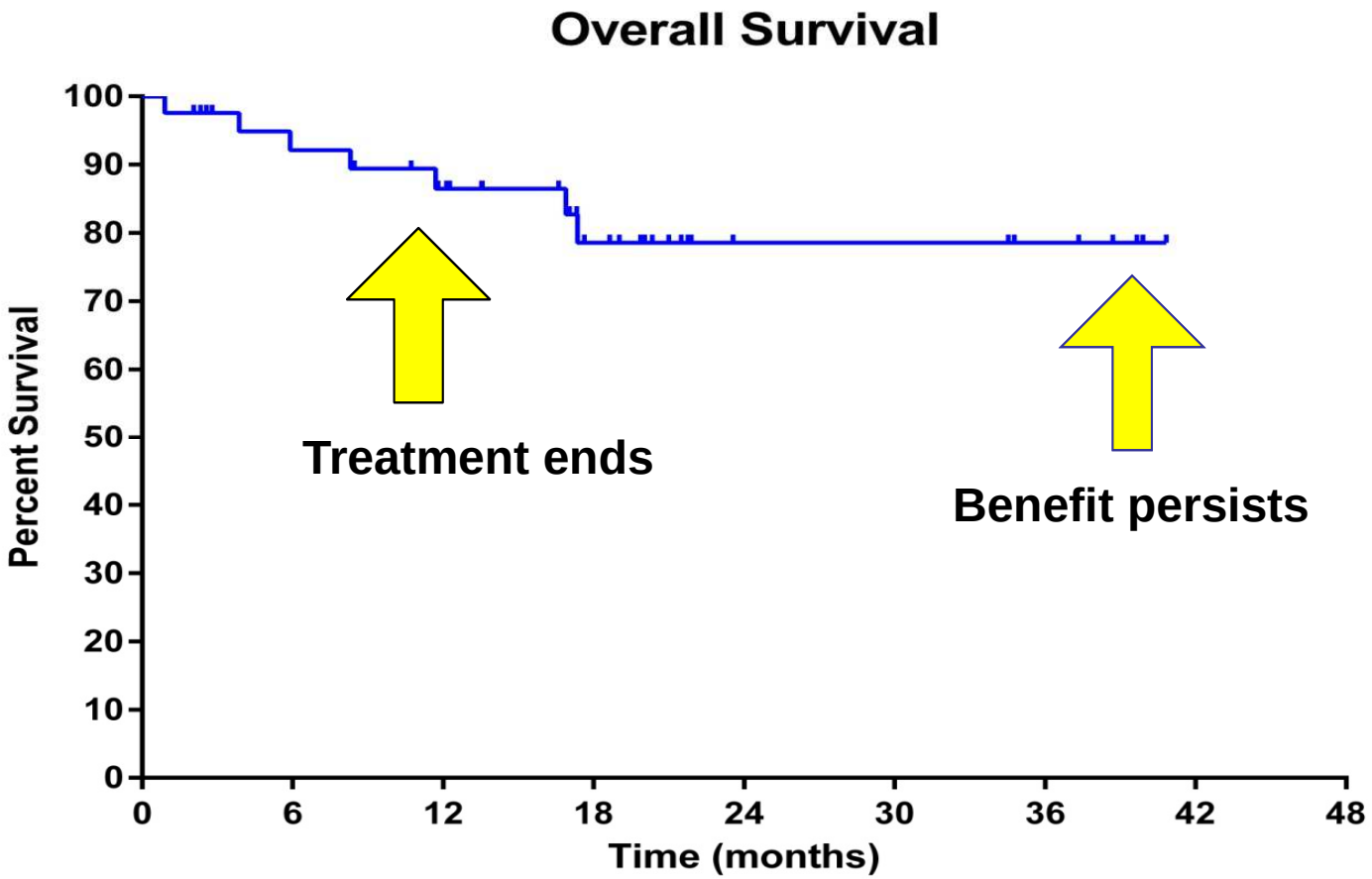
- Death following non-curative therapy typically not counted as a toxicity (in comparisons)

- Opportunities exist to reduce toxicity
  - Less ipilimumab
  - Substitute for ipilimumab (many options)
  - Better management of toxicities (education)

Underestimating the Benefits of IT (1)

- Time horizons need to account for long duration of benefits including “treatment free survival”
  - Benefits to patients
  - Benefits to family and colleagues

Combination I/0 Achieves “Many” Patients’ Preferred Outcome- Treatment Free Survival or “TFS”



7 deaths in 41 patients
Median F/up 18 months

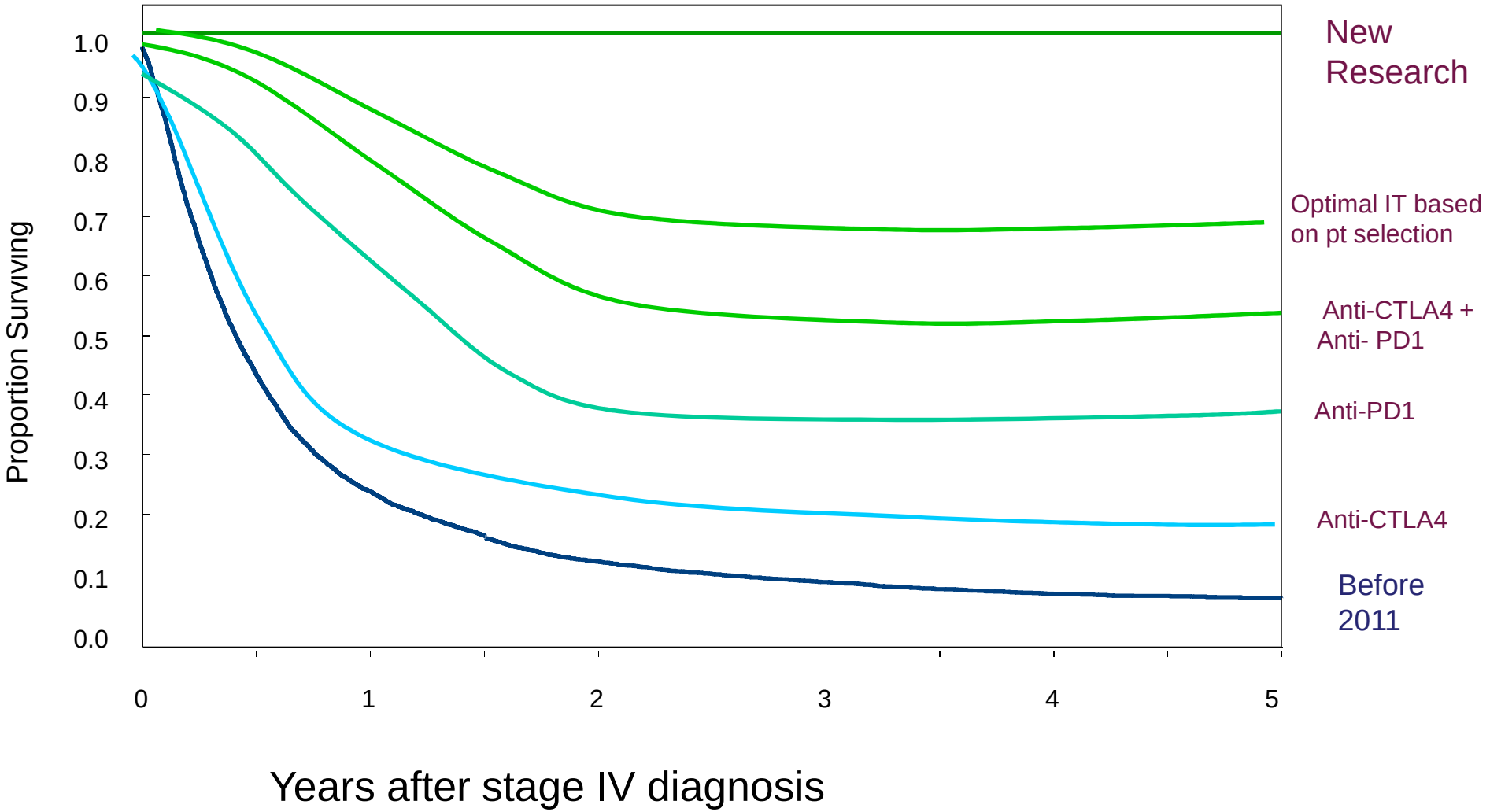
TFS = Travel Full Survival

Underestimating the Benefits of IT (2)

- Benefits to Society need to be considered[#]
  - Annual benefit of curing cancer ~ $47 trillion
  - Annual benefit of curing 1% of cancer ~ $500B
  - Improvements in health are complementary
    - E.g better Rx of heart disease increases the value of curing cancer
- Curative treatments options become the floor for time immemorial and are platforms on which to build

Murphy, Topel Economic Value of Medical Research 1998

Future Overall Survival for Patients with Stage IV Melanoma



Conclusions (1)

- Cancer Immunotherapy is different than tumor-directed therapy
- Current value models
  - Overestimate the treatment costs necessary to achieve maximum benefit
  - Overestimate the impact of acute, but reversible toxicities
  - Underestimate the value of long term survival – treatment free survival
  - Do not consider adequately the societal factors

Conclusions (2)

- New value models that better incorporate the properties of IT are needed.

Acknowledgements