# The Future of Immunotherapy (Is Bright)

**Nikhil I. Khushalani, MD**
Associate Member, Cutaneous Oncology
H. Lee Moffitt Cancer Center
Associate Professor, USF Morsani College of Medicine

# Disclosures

- Research Funding (Institute)
  - BMS, Merck, Amgen, GSK
  - NCCN (general research support from Roche, Spectrum, Pfizer)
- Advisory Board
  - Castle Biosciences, BMS, EMD Serono
- Data Safety Monitoring Board
  - AstraZeneca
- I *will* be discussing non-FDA approved treatments during my presentation today.

*The content of this presentation has been entirely controlled and prepared by Dr. Khushalani, who is not acting as an agent or spokesperson for any company. No company had the right of final approval of the content and/or edits of this presentation*

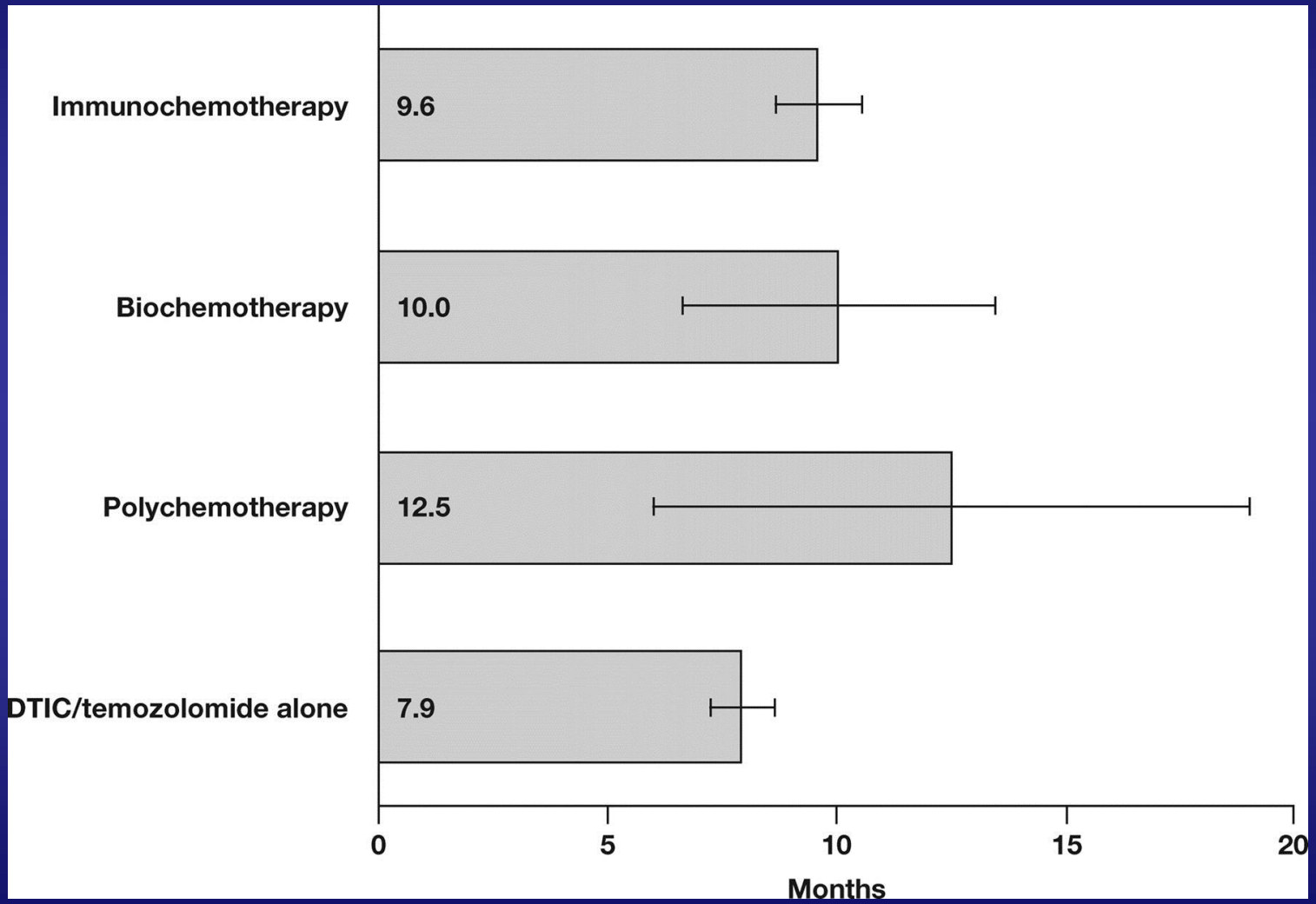
# Objectives

- Highlight salient advances in immunology in cancer medicine
- Using melanoma as a model disease, highlight the changing field of immunology applications in cancer
- Identify economic challenges in immunotherapy and discuss practical strategies to lower cost

# Melanoma in the ‘Dark Ages’ Pre-2011

- Chemotherapy
- High-dose Interleukin-2 (IL-2)
- Clinical Trials

# Survival in Metastatic Melanoma: (Pre-Checkpoint Inhibitor Era)

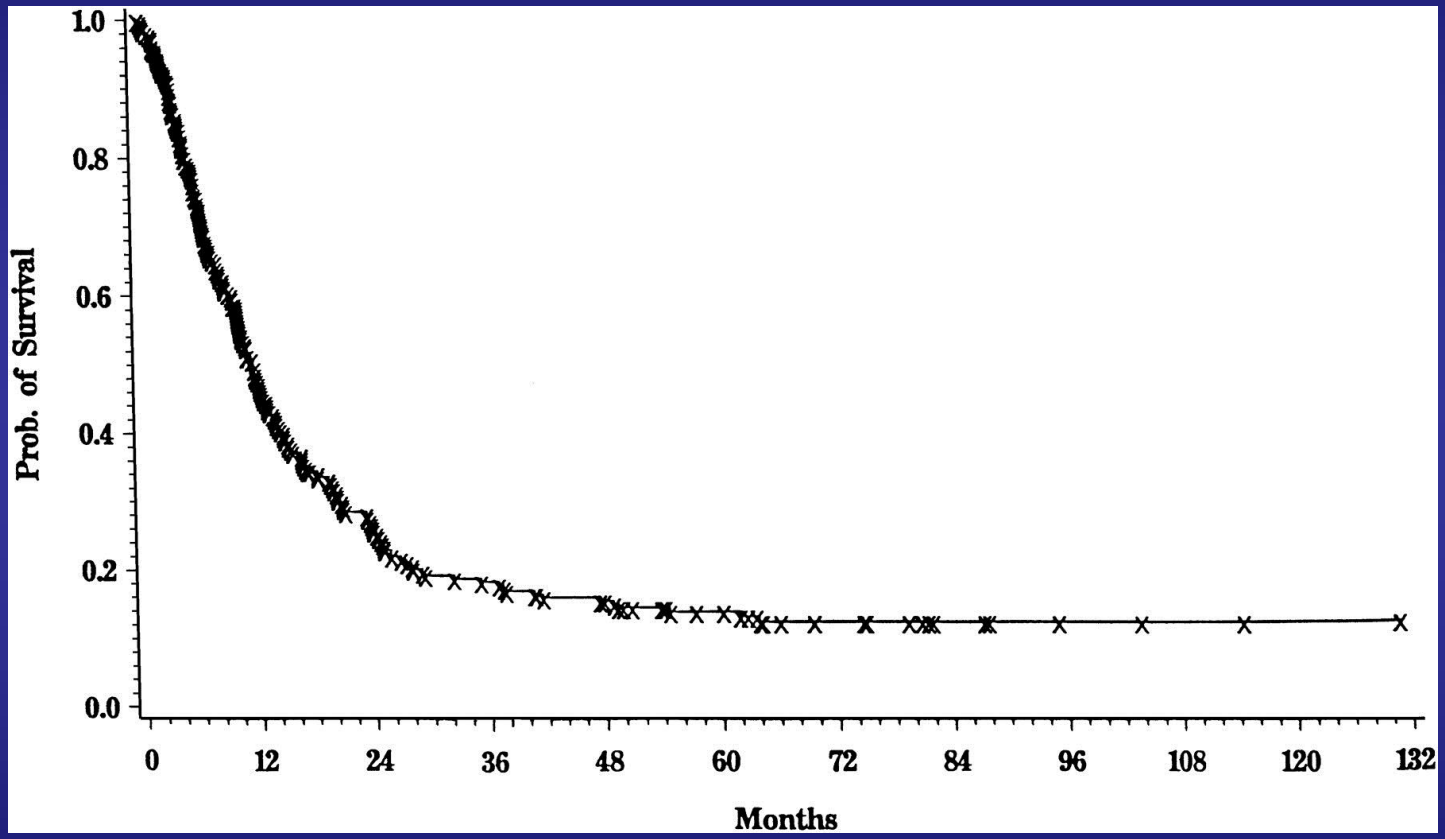



Garbe C et al. *The Oncologist* 2011;16:5-24

# And then there were five


The Economist. June 6, 2015

# Overall Survival with HD IL-2 in Melanoma




Atkins M B et al. JCO 1999;17:2105-2105

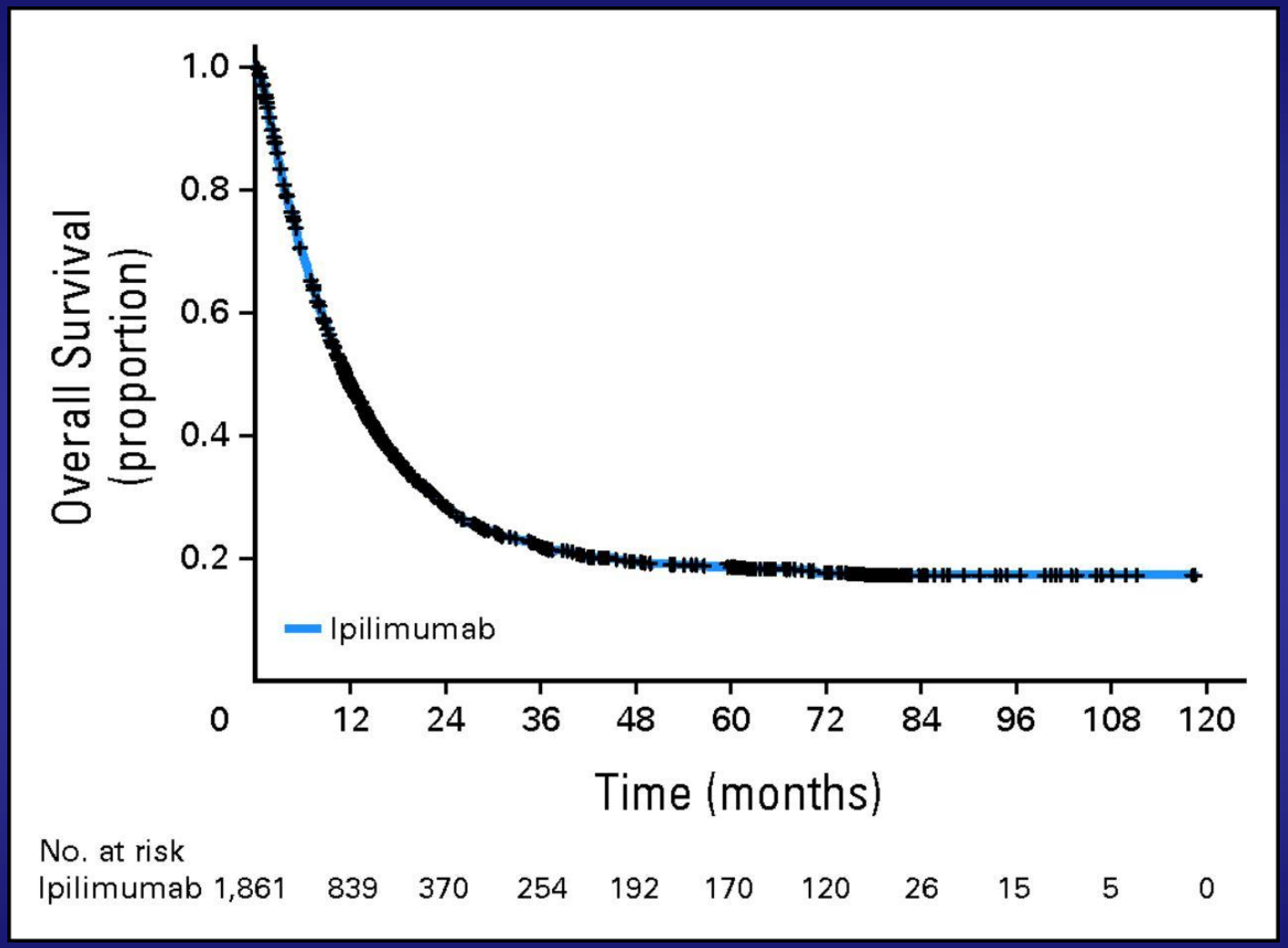
# Can Cure be a Reality in Metastatic Disease?

- N=4846
  - 1861 (on clinical trials)
  - 2985 (off protocol use)
- Median OS = 9.5 months (11.4m in 1861 pts)
- 3-year survival 22%
- No patient who survived beyond 7 years had died
  - (7-year survival = 17%)
- Longest OS survival is 9.9 years

**YES**

Schadendorf D. *J Clin Oncol* 2015, 33:1889

# Pooled Analysis: OS



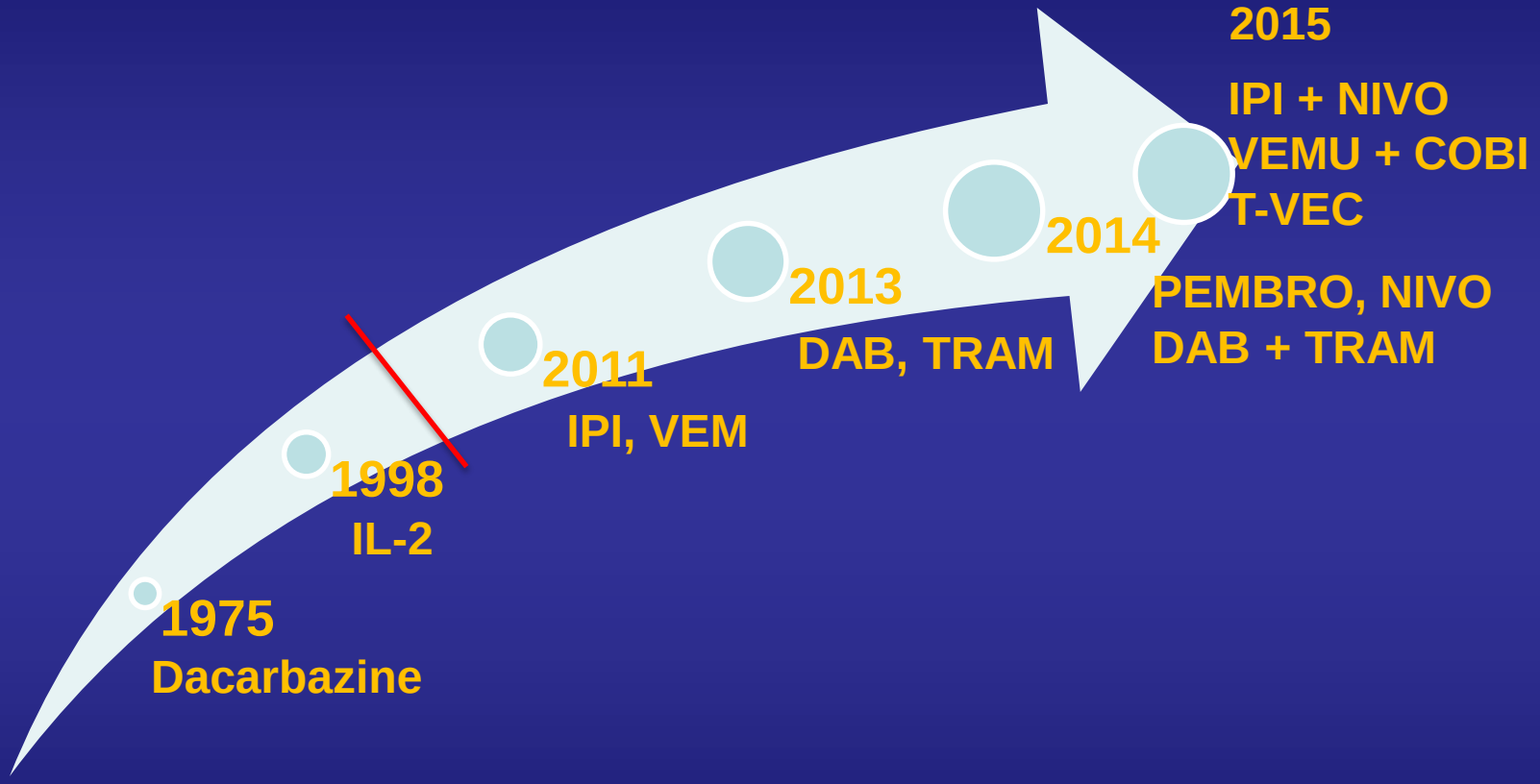

Schadendorf D. *J Clin Oncol* 2015, 33:1889

BREAKTHROUGH OF THE YEAR 2013

# CANCER IMMUNOTHERAPY

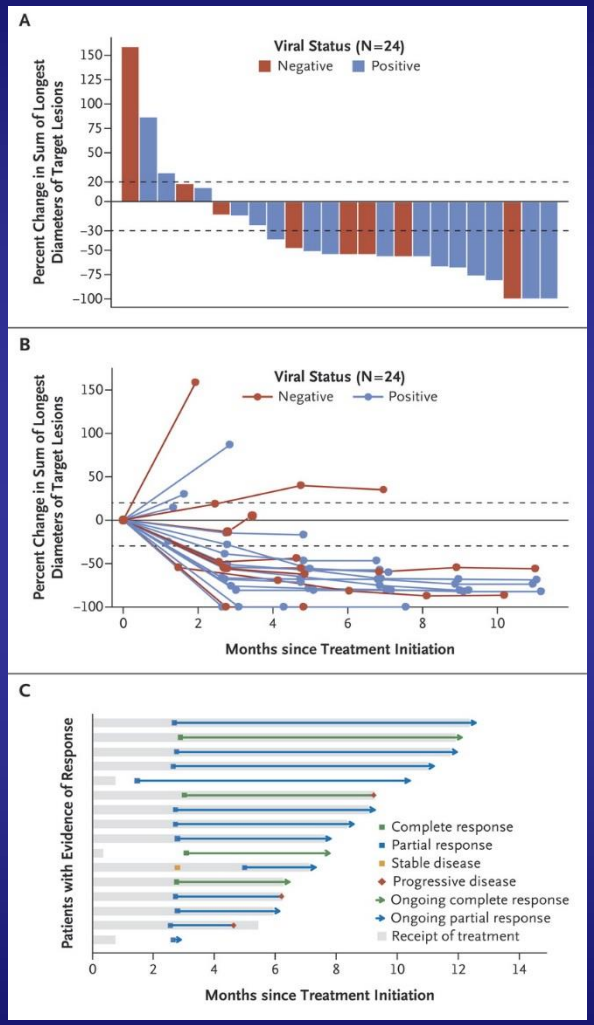
20 DECEMBER 2013 VOL 342 SCIENCE www.sciencemag.org

# Therapeutic Timeline in Melanoma




IL = interleukin; IPI = ipilimumab; VEM = vemurafenib; DAB = dabrafenib; TRAM = trametinib: PEMBRO = pembrolizumab; NIVO = nivolumab; VEMU = vemurafenib; COBI = cobimetinib; TVEC = talimogene laherparepvec.

# PD-1 Blockade in Merkel Cell Carcinoma



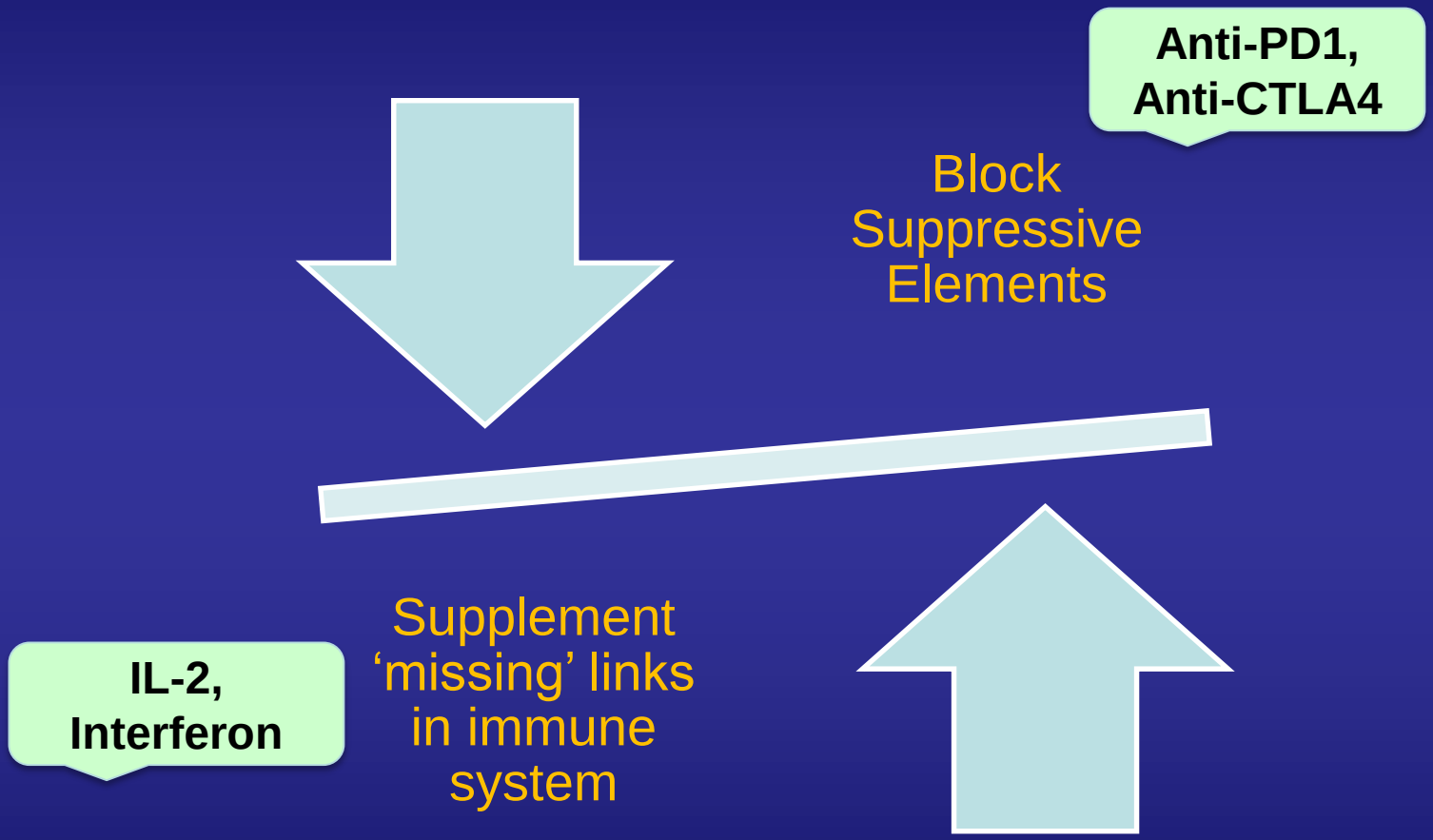

Nghiem PT et al. N Engl J Med 2016;374:2542-2552.

# My Vision for a Better Tomorrow

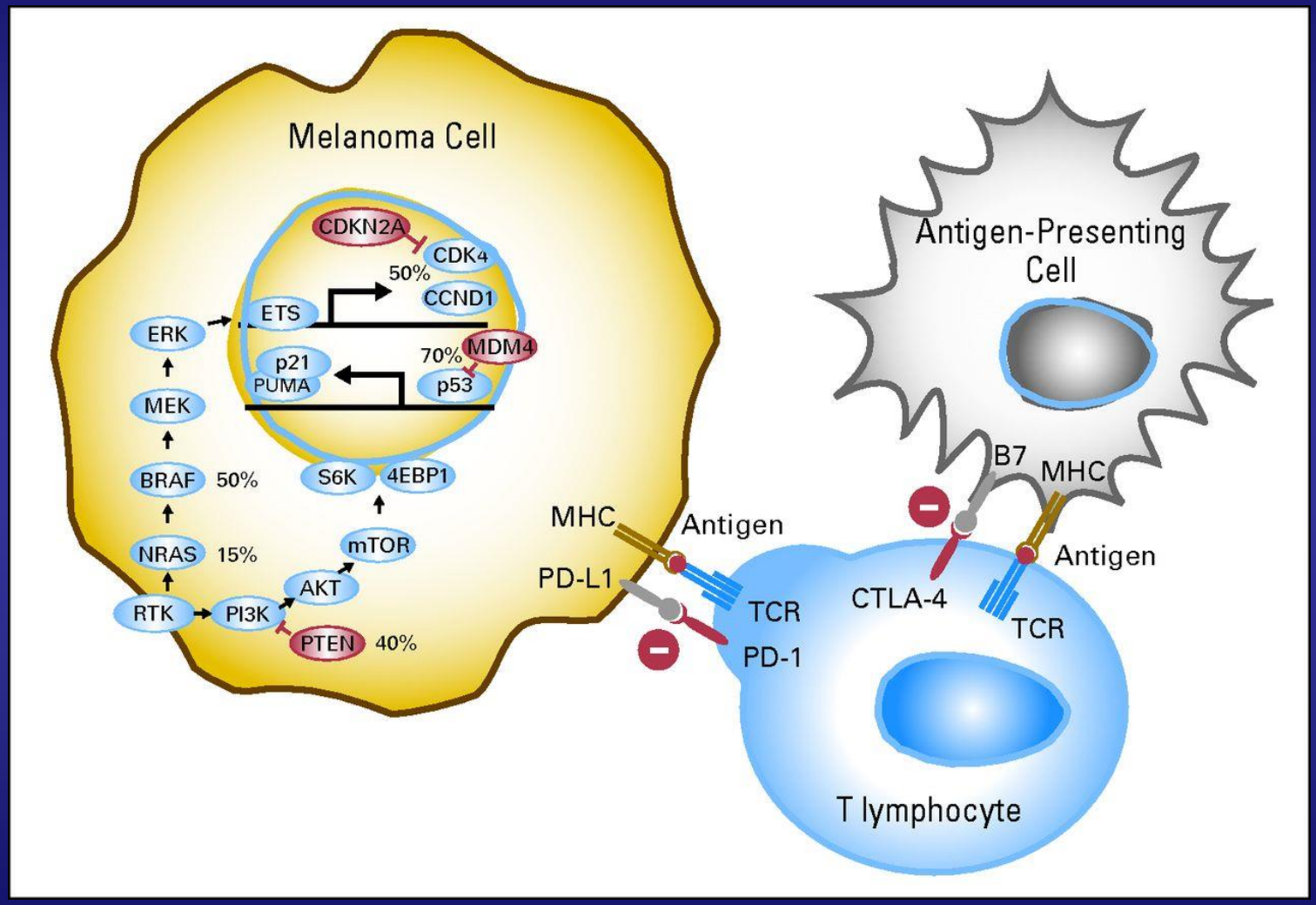
# Some Thoughts

1. Biomarker discovery
   – Who benefits and why
2. Identification of other immune pathways
3. Optimal duration of immunotherapy
4. Cost of success
   - A steep price to pay?

# Strategies to win the host versus tumor battle

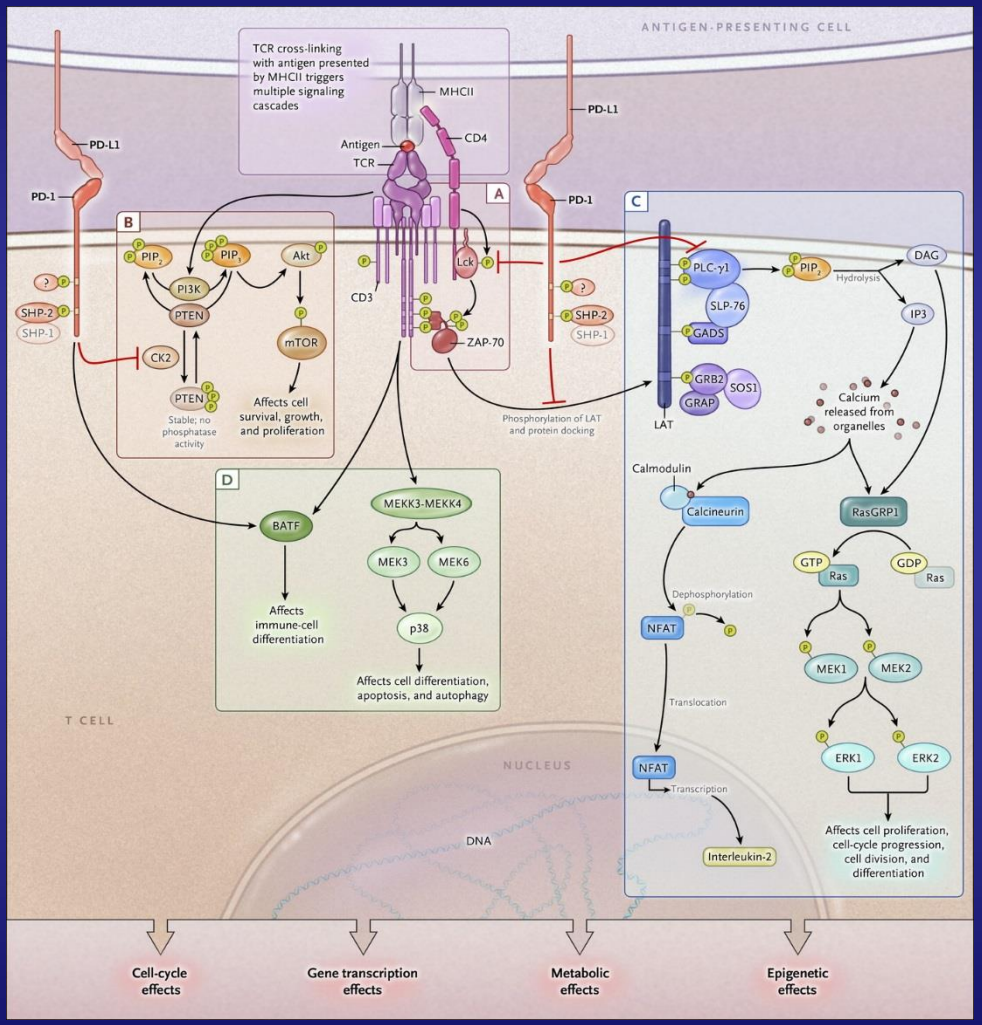


# Therapeutic Biology in Melanoma



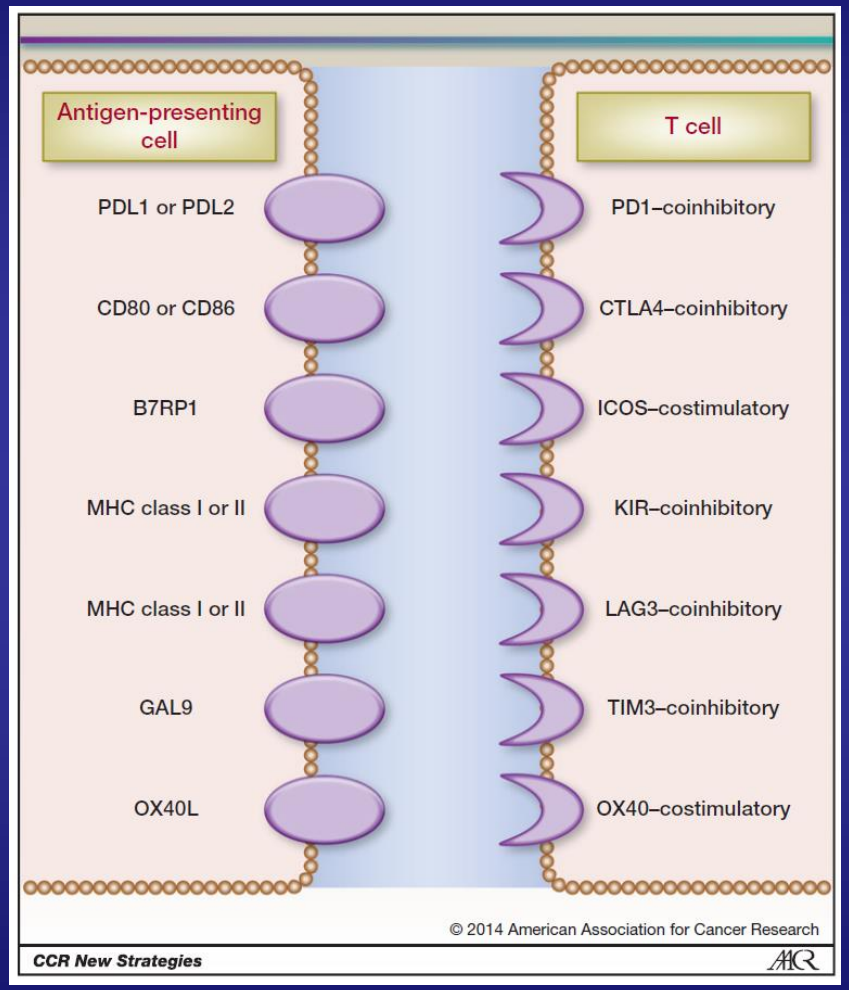

McArthur G A , and Ribas A JCO 2013;31:499-506

# Effects of PD-1 on Major Signaling Pathways in T Cells



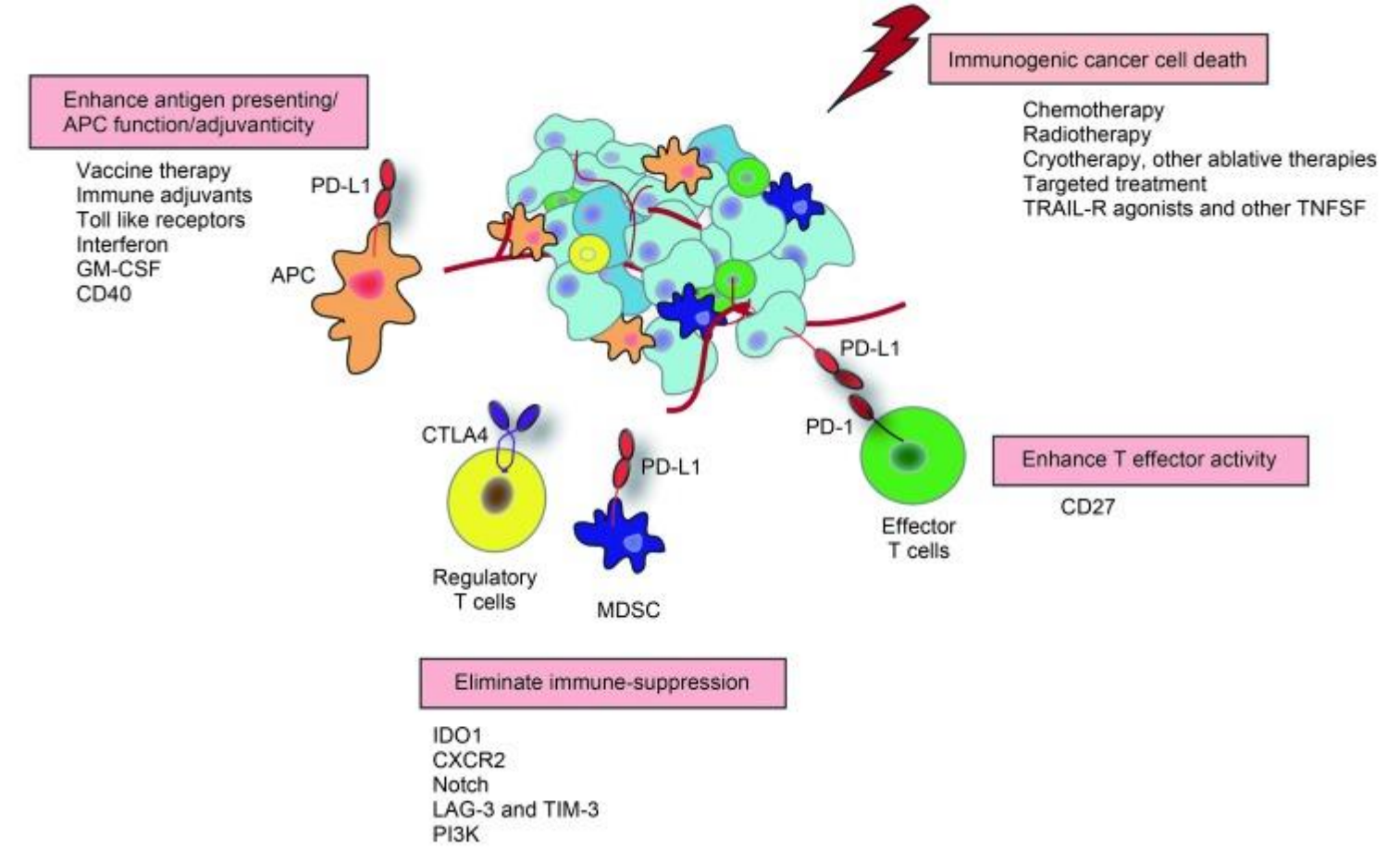

Boussiotis VA. N Engl J Med 2016;375:1767-1778

# Other Immune Targets



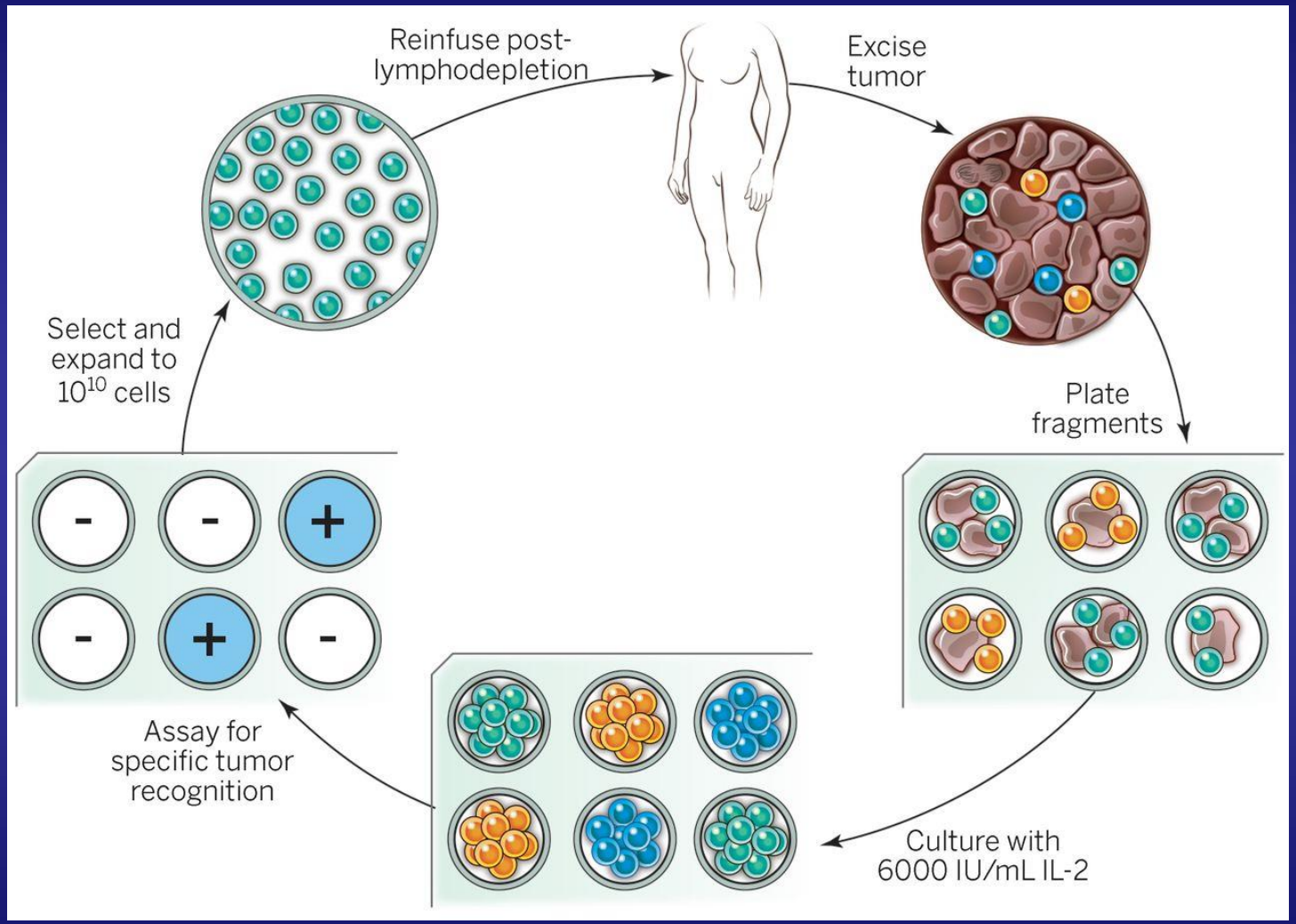

Forde et al, Clin Cancer Res 2014;20:1067

# Future Combinations




Harris et al. Cancer Biol and Med 2016;13:171

# Adoptive Cell Transfer




Srosenberg and Restifo. *Science* 2015;348:62-68

# Ongoing Melanoma Tumor Infiltrating Lymphocyte (TIL) Trials at Moffitt

- Vemurafenib + TIL (to be changed to Vem + Cobi + TIL): for BRAF V600-mutant melanoma
- Nivolumab (+ 41BB ex-vivo) + TIL
- TIL alone

***It ain't over TIL(L) it's over!***

# Real Life Decision Making

- 56-year-old man is found to have melanoma metastatic to lung and subcutaneous sites
- BRAF V600E mutant
- KPS of 90%; normal LDH
- No other significant co-morbidity

**OPTIONS ???**

# Options ???

1. Combined BRAFi + MEKi
2. Ipilimumab + Nivolumab
3. Single agent anti-PD1 therapy alone
4. Ipilimumab alone
5. Dacarbazine
6. Other

*Do we have markers to help us make the best choice?*

# So How Do We Choose?

- Burden of disease (symptoms or not)
- Functional status
- BRAF status
- Co-morbidities (eg. autoimmune disease)

# Predicting Response

- Clinical
- Tissue Based
  - PD-L1 expression
  - Tumor infiltrating lymphocytes
  - Mutational load of tumor
  - Neo-antigens
  - Intra-tumor heterogeneity

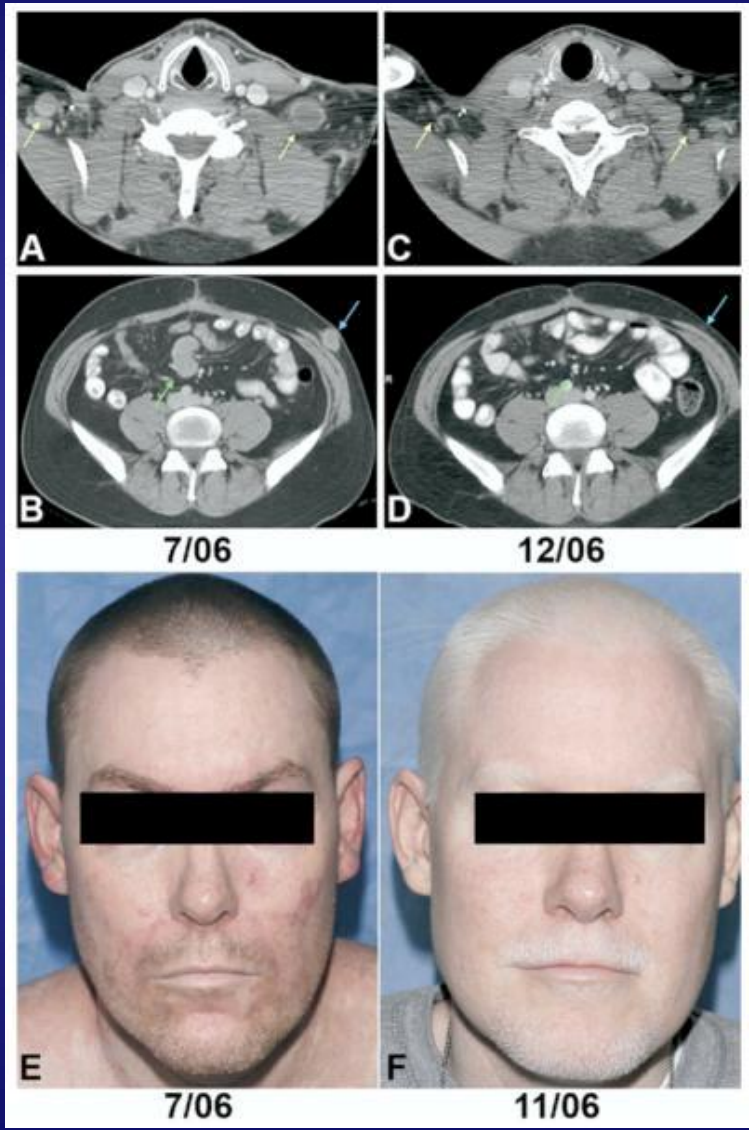
Teng et al. Cancer Discov 2016;6:818

# Phenotype and Prognosis

- Model using LDH (≤2.5), Relative Eosinophil Count (≥1.5%), Relative Lymphocyte Count (≥17.5%), and Location of Metastases (Soft tissue/lung)
- n-=616 (discovery, confirmation, validation)
- Results:
  - 4/4: 84% 1-yr survival, RR 58%
  - 0/4: 15% 1-yr survival, RR 3%

Weide et al. Clin Cancer Res, epub May 2016

# Melanoma & Vitiligo




Melanoma pts responding to immunotherapy can develop vitiligo

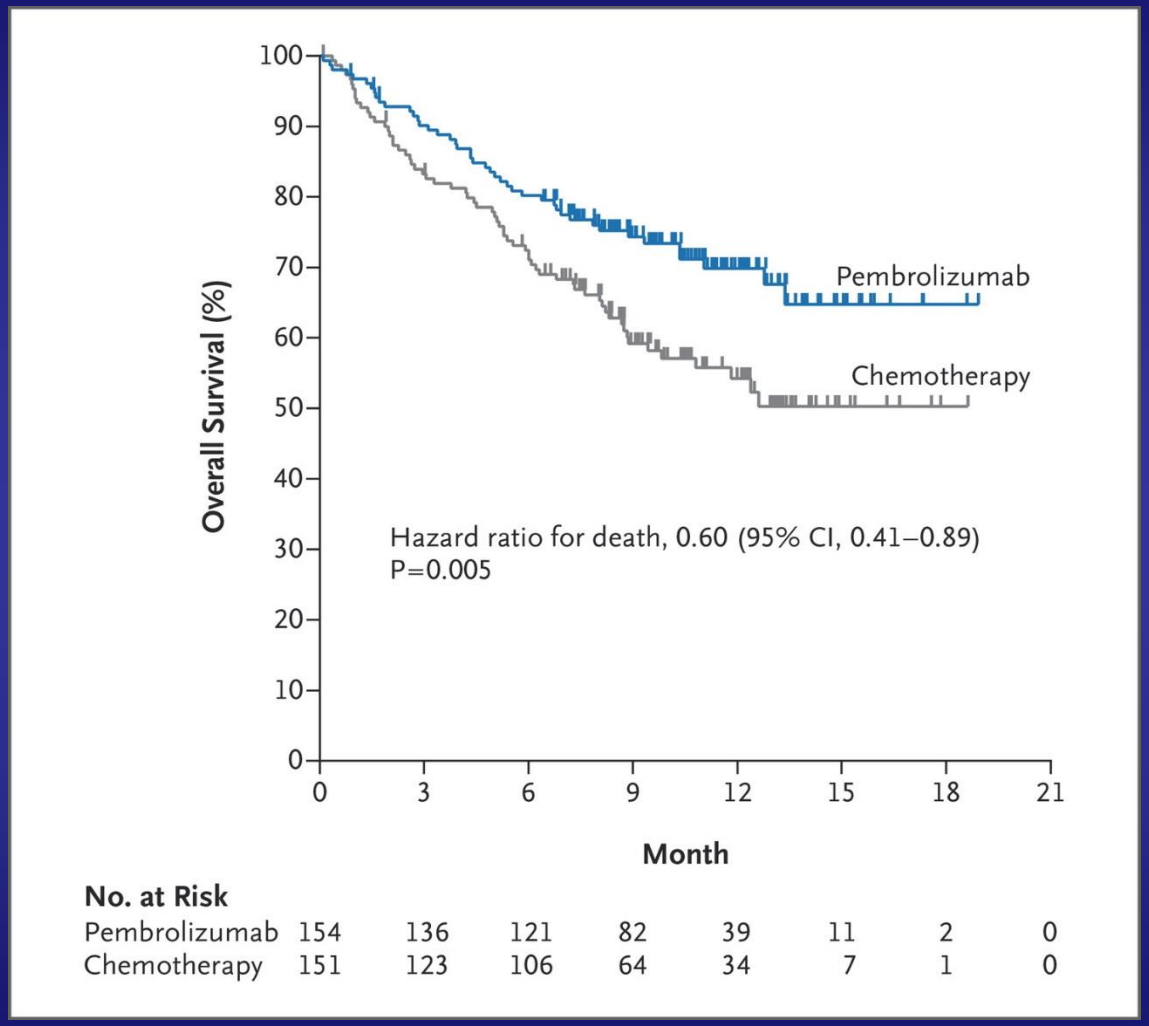
Yeh, S, et al. 2009. *Opthalmology*. 116: 981-989.

# PD-L1 Expression

- IHC on archival tissue pre-Rx
- Variable definitions of positive results
  - 1%, 5%, Any
- PD-L1 negative tumors also respond
- Combination Ipi + Nivo elicits a higher RR & mPFS (55%, 11.2m) compared to Nivo (41%, 5.3m) in PD-L1 – tumors*

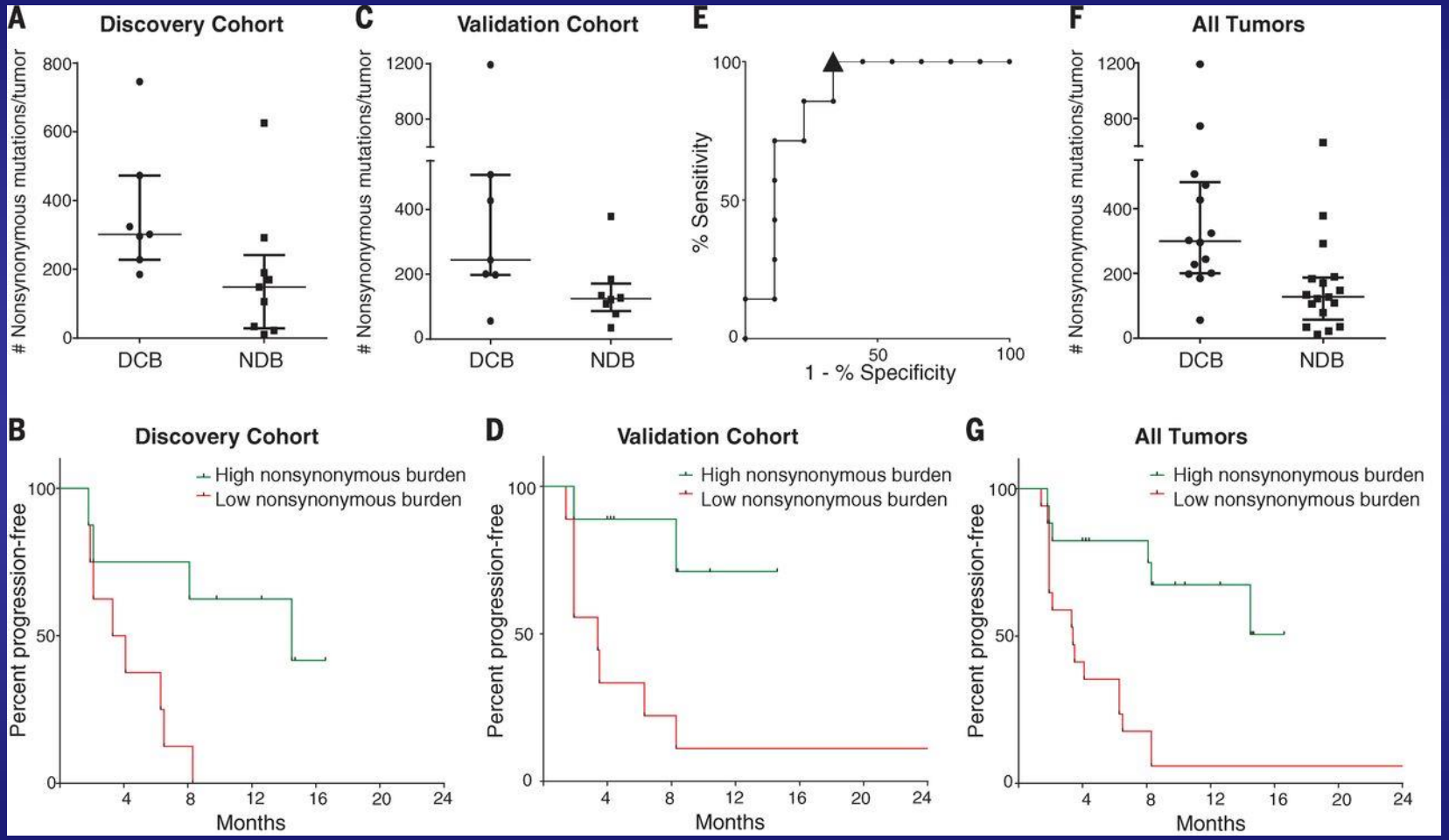
***Larkin J et al. N Engl J Med 2015;373:23-34.**

# Yet Different in NSCLC…



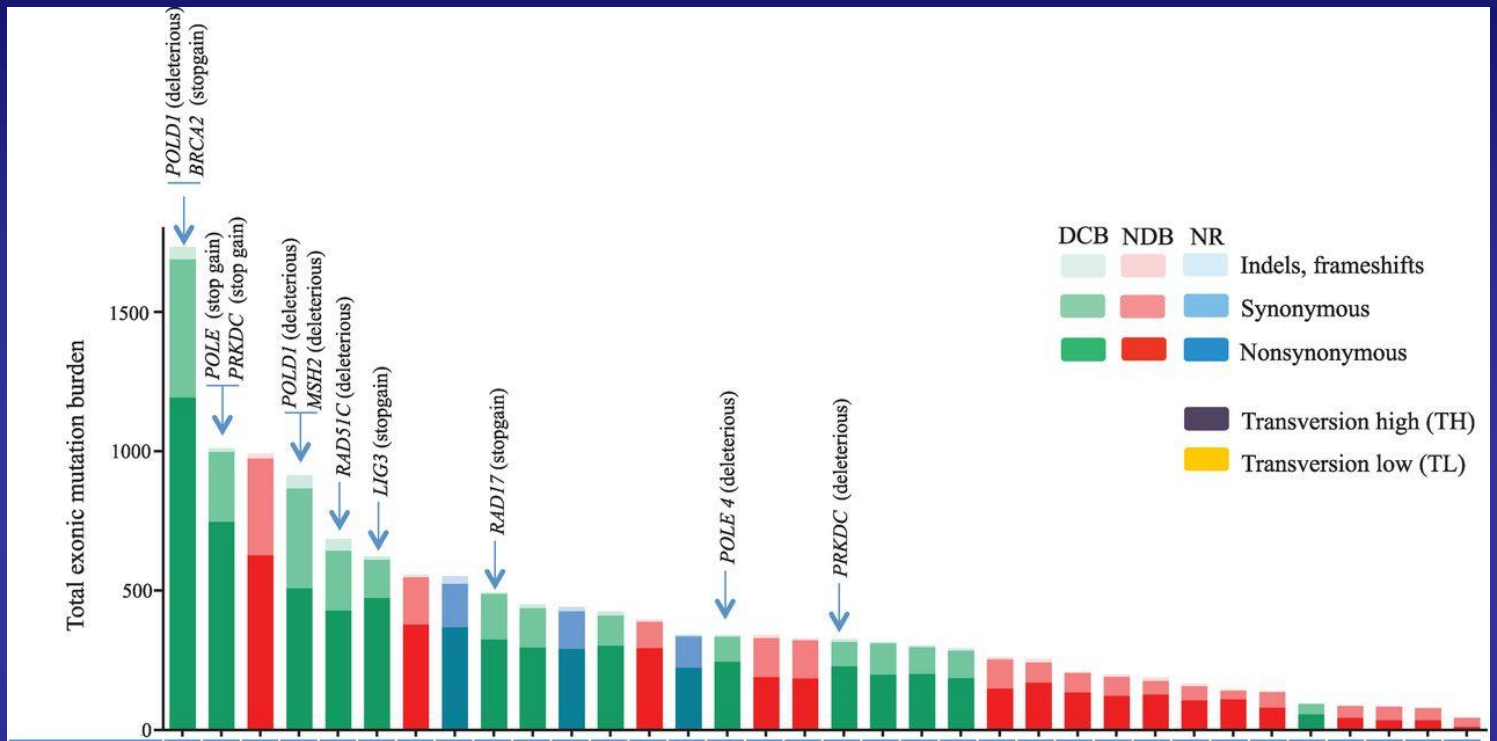

Reck M et al. N Engl J Med 2016;375:1823-1833.

# Nonsynonymous mutation burden associated with clinical benefit of anti–PD-1 therapy




Naiyer A. Rizvi et al. Science 2015;348:124-128

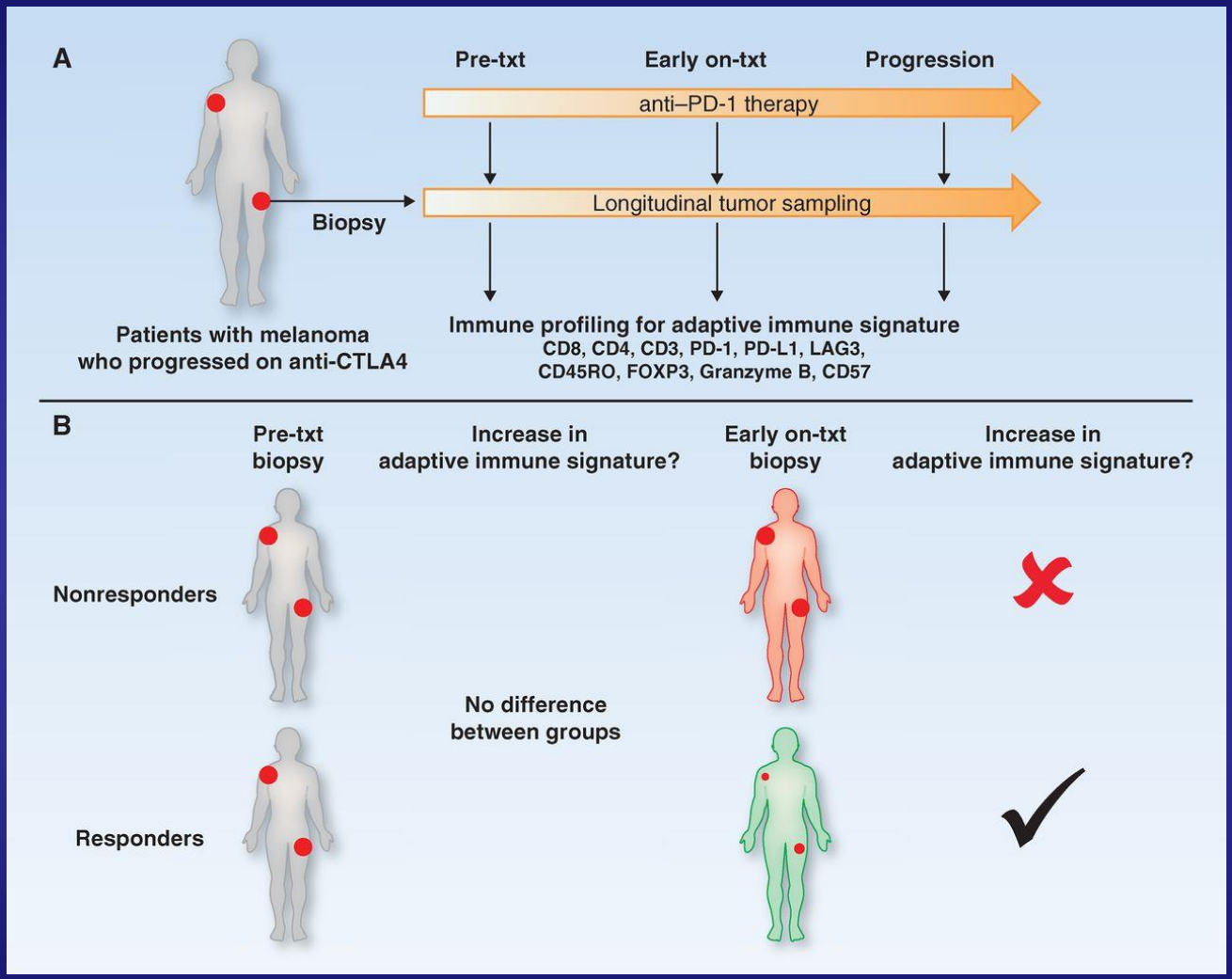
# Mutation Burden and Clinical Response




| Study ID | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cohort | V | D | D | V | V | D | V | V | D | D | V | D | D | V | V | V | D | D | V | V | D | D | D | V | V | V | D | V | V | V | D | V | D | D |
| Objective Response | PR | PR | PD | SD | PR | PR | PD | SD | PR | PR | PR | SD | PD | PR | SD | PD | PD | PR | PR | PR | SD | SD | PD | PD | PD | PD | PD | SD | SD | PR | SD | PD | PD | SD |
| PFS (months) | 8 | 14 | 2 | 8 | 14 | 16 | 2 | 4 | 15 | 13 | 4 | 8 | 2 | 4 | 8 | 3 | 3 | 10 | 27 | 10 | 8 | 7 | 2 | 2 | 1 | 2 | 2 | 4 | 6 | 8 | 4 | 2 | 2 | 6 |
| Ongoing response | ++ | ++ | | | ++ | ++ | | ++ | | ++ | ++ | | | ++ | ++ | | | ++ | ++ | ++ | | | | | | | | | | | | | | |
| Smoking signature | TH | TH | TH | TL | TH | TH | TL | TH | TH | TH | TH | TH | TH | TH | TH | TL | TL | TH | TL | TL | TH | TL | TH | TL | TL | TL | TL | TL | TL | TL | TL | TL | TL | TL |

Naiyer A. Rizvi et al. Science 2015;348:124-128

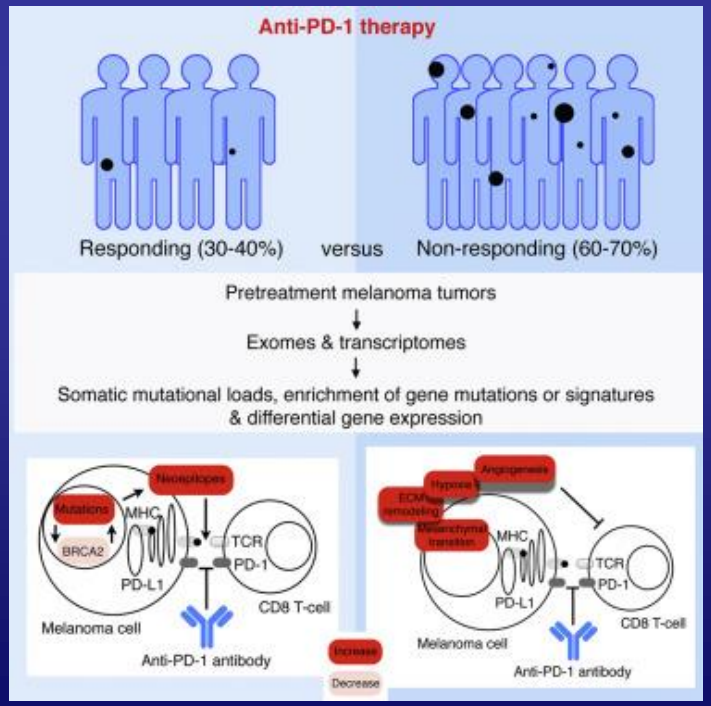
# Increase in adaptive immune signature in early on-treatment biopsies predicts patients who respond to PD-1 blockade.




Teng et al. Cancer Discov 2016;6:818
Chen et al. Cancer Discov 2016;6:827

# Determining Resistance Mechanisms to PD-1 Blockade

- High mutational loads – better survival
- BRCA2 mutations enriched in anti-PD1 responders
- Pathways of interferon-receptor signaling and antigen presentation
  - JAK 1 & 2 loss of function mutations
  - B2M mutation
- IPRES signature (innate anti-PD1 resistance)




**Hugo et al. Cell 2016;165:35**
**Zaretsky et al. NEJM, 2016;375:819**

# Liquid Biopsies

- **BRAF V600E ctDNA**
  - Allele specific PCR assay
  - 388 serum samples from 48 TIL patients (NCI)
  - Strong correlation b/w +/- early ctDNA peak and likelihood of response
  - If peak + clearance – high likelihood of CR

**Xi et al. Clin Cancer Res, Aug 2016 (epub)**

# A Foray into Pharmacoeconomics

# The Rising Cost of Healthcare in the United States

- Cost of cancer care (US)
  - ➢$125B (2010) → $158B (2020)
- Healthcare spending (US)
  - ➢$70B (1970) → $2.6T (2010) → $4.8T (2021)

**Mariotto AB. JNCI 2011;103:117**
**CMS 2012, California Healthcare Foundation**

# Same Case Scenario

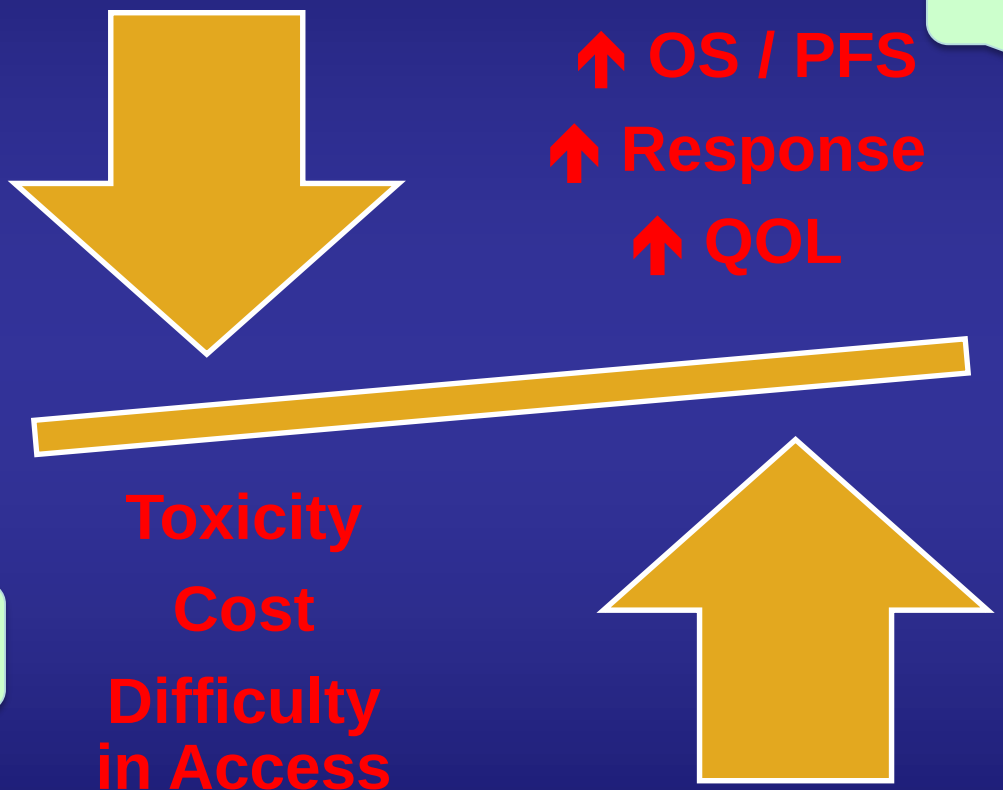
- M/56, BRAF V600E mutant melanoma
- Metastatic disease to distant lymph nodes + lung; normal LDH (M1b disease)
- Options ??

# A Typical Case Scenario

- IL-2 (1 course): **$115,000**
- IPI (4 doses); mPFS 3m: **$159,000**
- PEMBRO (8 doses); mPFS 6m: **$ 83,000**
- DAB+TRAM; mPFS 10m: **$226,000**
- Clinical trial(s)
- Hospice care

**= $$$$$$**

# The Teeter Totter Named Value



# Costs of Cancer Care

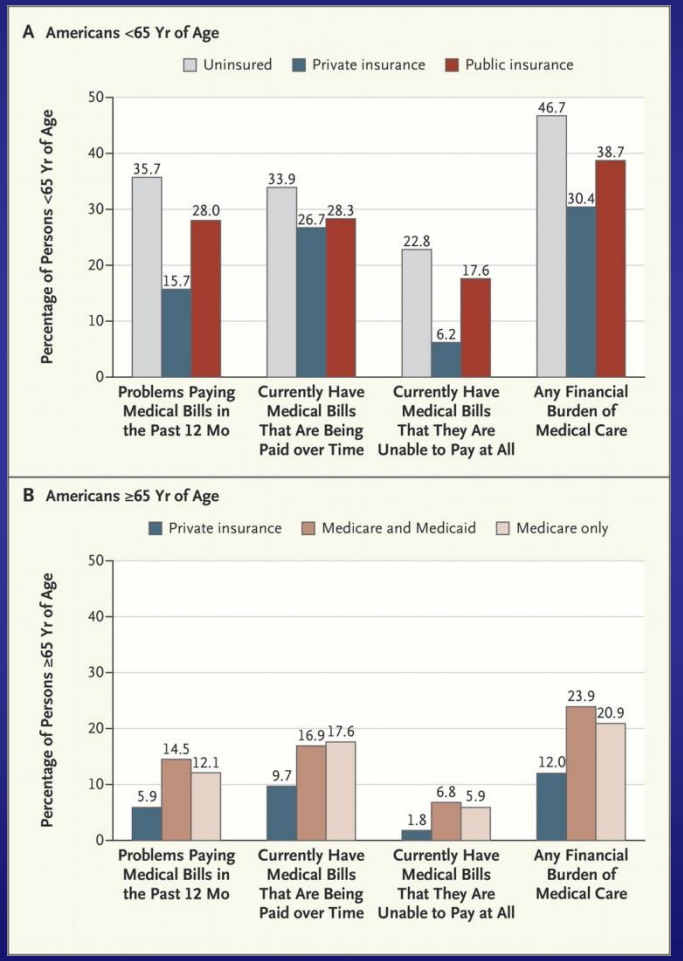
- Median out-of-pocket expenses: **US $1730-4727 / year**
- Direct
  - In-patient / Out-patient care / Supportive care
  - MD charges
  - Drugs and devices
- Indirect
  - Disability payments
  - Medical related absenteeism (22.3 more workdays lost for a cancer patient)
  - Lost productivity
  - Travel / accommodation costs

**Bestvina et al. Future Oncol 2014;10:2189-99**

# Financial Toxicity

*"It is important to be aware not only of the physical toxicity but also the financial toxicity of cancer treatment"*

Gary Lyman, MD, HICOR, Hutch News, May 7 2014




Ubel PA et al. N Engl J Med 2013;369:1484-1486.

# Solutions

- Physicians
- Patients
- Industry
- Policy makers
- Healthcare stakeholders
- Third-party payors

# Patient-MD

- Cost communication
  - Only 15% oncologists are cognizant of their patient's financial well-being
- Price transparency

# Dose Rounding of Ipilimumab

- FDA approved dose 3mg/kg/dose X 4
- Acquisition cost $120/mg

  **80kg person = $115,200 per course**
- Supplied in 50mg & 200mg vials
- Dose rounding to nearest 50mg (up or down)
- 63 doses in 22 pts at RPCI
- Cost savings = **$155,400**
- **Potential for annual US cost savings = $22 M**

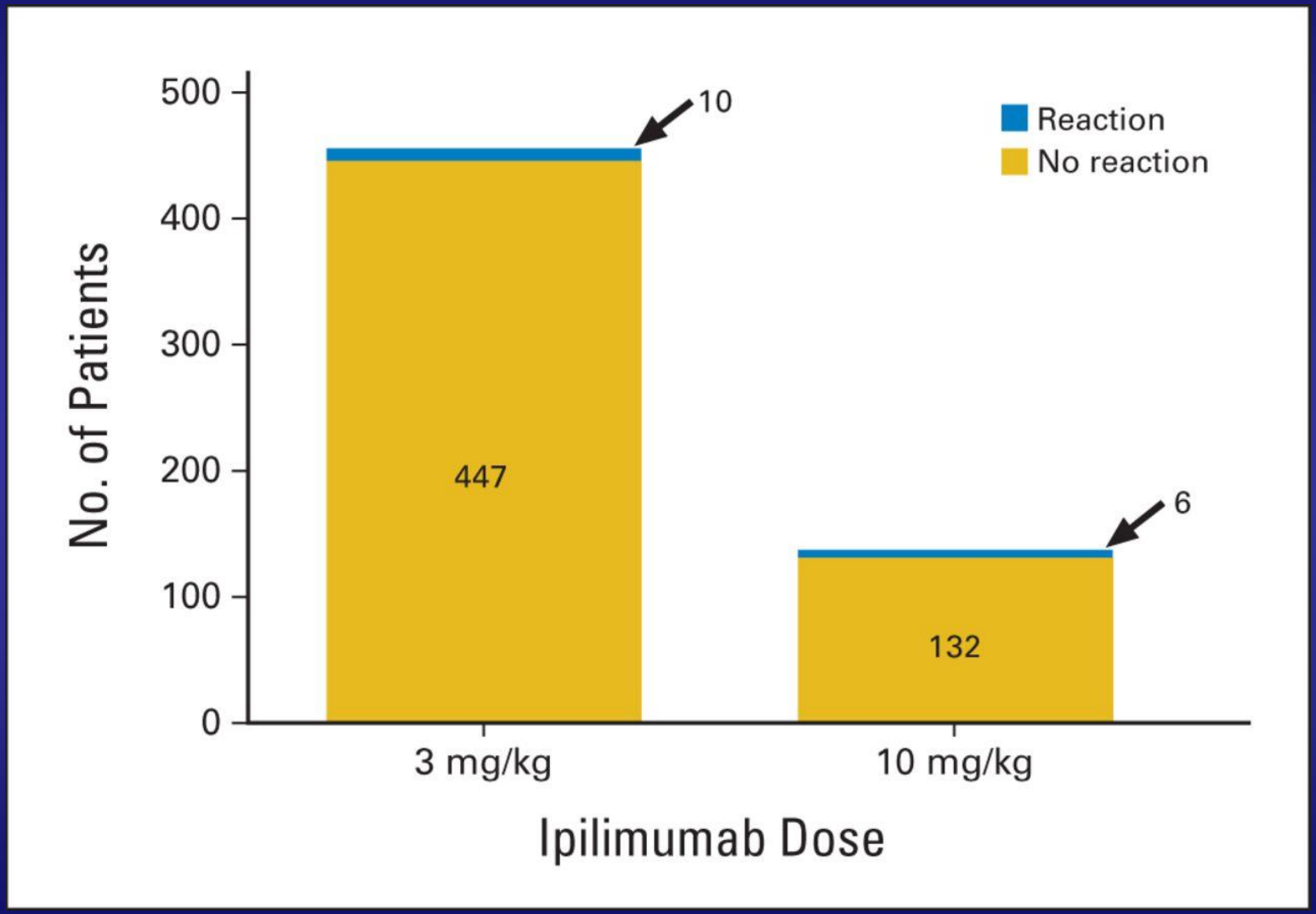
**Jarkowski A at al. J0PP 2014;20:47-50**

# Ipilimumab over 30 minutes

- **Rationale**
  - Both 3mg/kg and 10mg/kg dose typically infused over 90 minutes
- **Single institution**
  - N=595 (at both doses; over 90 mins)
  - N=127 (3mg/kg; over 30 mins)

Parisa Momtaz et al. JCO 2015;33:3454-3458

# Infusion Related Reactions (90m)




Parisa Momtaz et al. JCO 2015;33:3454-3458

# Prospective Cohort (n=120)

- Infusion-related reactions (IRR): 7 (5.8%)
  - All at second dose
  - Grade II (6); Grade III (1)
- **Conclusions:**
  - IRRs with 30m infusion are acceptably low
  - Incidence is slightly higher than 90m infusion (p=0.06)
  - Improves patient convenience and more efficacious use of infusion center

# Modeling the cost of immune checkpoint inhibitor-related treatment and toxicities

*Neil T. Mason, MBA, Nikhil I. Khushalani, MD, Jeffery S. Weber, MD, PhD,*
*Scott J. Antonia, MD, PhD, Howard L. McLeod, PharmD*
*Tampa, Florida*

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## Background

- Immune checkpoint inhibitors that target PD-1 (nivolumab and pembrolizumab) and CTLA-4 (ipilimumab) have demonstrated significant improvements in overall survival for patients with metastatic disease
- Single agent immune checkpoint therapy yields a clinical response in 11-32% of patients[1]
- Up to 53% of patients experience serious, Grade 3-5 toxicities[1]
- Efficacy and toxicity are not clearly correlated meaning some patients receive benefit without experiencing toxicities while others suffer severe adverse events with not benefit[2,3]
- Most economic analyses use published literature and results from clinical trials to determine cost-effectiveness, though results from clinical practice often differ from clinical trials[4]
- This model utilizes patient data from Moffitt Cancer Center to estimate the average cost of treatment with immune checkpoint inhibitors based on average duration of treatment and reported toxicity rates from the electronic health record (EHR) and billing data.

## Methods

Drug costs were obtained from the Redbook average wholesale cost per dose and the average number of doses received by patients at H. Lee Moffitt Cancer Center (N=627). Major toxicities associated with each drug were identified from package inserts, peer-reviewed literature, and Moffitt Cancer Center patient data. Toxicity costs were obtained from peer-reviewed literature and data obtained at Moffitt Cancer Center. Incidences of toxicities were obtained from the Total Cancer Care database using ICD-9/ICD-10 billing codes (Table 1). The weighted average cost of managing toxicities associated with each drug was calculated and compared to the total anticipated cost of therapy. All cost estimates are in 2015 USD.

**Table 1. Incidence and estimated cost of Immunotherapy-related toxicites in patients receiving ipilumumab, nivolumab, or pembrolizumab**

| Toxicity | ICD-9 | ICD-10 | Incidence Ipilimumab | Incidence Nivolumab | Incidence Pembrolizumab | Estimated Cost |
|---|---|---|---|---|---|---|
| Anemia | 285.3 285.9 | D64.89 | 42.9% | 59.4% | 34.0% | $851[4] |
| Colitis | 558.9 | K52.1 K52.89 K52.9 | 10.2% | 10.9% | 9.7% | $8563[4] |
| Dermatitis from drug | 692.9 693.0 | R21 | 18.1% | 10.9% | 18.8% | $764[7] |
| Diarrhea | 787.91 | R19.7 | 26.4% | 15.8% | 40.3% | $775[4] |
| Dyspnea | 786.09 | R06.00 | 8.4% | 31.7% | 8.3% | $3345[4] |
| Fatigue | 780.79 | R53.83 | 72.0% | 87.1% | 91.0% | $2069[4] |
| Fever | 780.6 | R50 | 17.8% | 22.8% | 20.8% | $3304[4] |
| Hepatitis | 571.3 571.42 | K75.4 K75.9 | 1.0% | 1.0% | 3.5% | $529[8] |
| Hypo/ Hyperthyroidism | 244.9 242.9 | E03.9 | 33.5% | 39.6% | 38.2% | $583[9] |
| Hypopituitarism | 253.2 253.7- 9 | E23 | 20.4% | 4.0% | 7.6% | $4979[4] |
| Myalgia/Pain | 729.1 | M79.1 | 8.1% | 7.9% | 5.6% | $1947[4] |
| Nausea/Vomiting | 787.01/.02 | R11.0 R11.10 R11.2 | 47.9% | 59.4% | 54.9% | $1442[4] |
| Nephritis | 580-583 | N00-N09 | 1.6% | 2.0% | 0.0% | $4218[4] |
| Neutropenia | 288 | D70.8/.9 | 21.5% | 16.8% | 26.4% | $859[4] |
| Oliguria/Anuria | 788.5 | R34 | 1.0% | 0.0% | 0.0% | $3807[4] |
| Pancreatitis | 577.0/.1 | K85.9 | 1.8% | 1.0% | 2.8% | $3590[9] |
| Peripheral neuropathy | 356 357.6 | G61.0 G62.0 G62.8 G62.9 | 12.8% | 33.7% | 16.7% | $3960[10] |
| Pneumonitis | 516.32/.33 | J84 | 0.5% | 0.0% | 0.7% | $2580[11] |
| Renal Failure | 584.5- 9 | N17.0 N17.9 | 13.9% | 9.9% | 13.9% | $8854[12] |
| Seizures | 780.39 | R56.9 | 0.0% | 0.0% | 5.6% | $2167[4] |
| Thrombocytopenia | 287.5 | D69.59 D69.6 | 12.0% | 14.9% | 10.4% | $854[6] |
| Ventricular arrhythmia | 427.89 427.9 | I49.01 | 0.0% | 18.8% | 0.0% | $2246[4] |

**Table 2. Estimated cost of immune checkpoint inhibitor therapy including cost of managing toxicities**

| Treatment | # of Patients | Average # of Doses | Cost Per Dose | Estimated Cost of Therapy | Estimated Average Cost of Toxicities | Total Cost of Treatment | % of Total Cost Related to Toxicity |
|---|---|---|---|---|---|---|---|
| Ipilimumab | 382 | 3.3 | $30,694 | $101,290 | $8,216 | $109,506 | 6.3% |
| Nivolumab | 101 | 6.3 | $6,043 | $38,078 | $9,616 | $47,686 | 17.6% |
| Pembrolizumab | 144 | 8.0 | $7,251 | $58,008 | $8,547 | $66,555 | 16.0% |

## Results

Ipilimumab has the highest estimated cost of therapy at $101,290. Nivolumab and pembrulizumab had lower estimated costs of therapy of $30,078 and $58,008, respectively. The estimated cost of toxicity is similar for all three drugs with nivolumab estimated to be most costly (Table 2). Ipilimumab is estimated to cost the most per patient driven by the cost of drug. However, toxicities make up a much larger proportion of the cost of care for the PD-1 inhibitors.

## Conclusion

- Immune checkpoint inhibitors are clearly valuable treatments with the potential to significantly extend survival for patients with metastatic disease
- Nivolumab and pembrolizumab therapy cost less on average than ipilimumab due to the high cost per dose of ipilimumab and average number of doses received for each drug
- The estimated costs to manage toxicities was very similar between the three drugs
  - Nivolumab had the highest cost driven by a disproportionate incidence of peripheral neuropathy (33.7%), dyspnea (31.7%), and ventricular arrhythmia (18.8%)
- Nivolumab and pembrolizumab are estimated to cost less and yield better outcomes than treatment with ipilimumab, which will likely increase PD-1 inhibitor use and possibly replace ipilimumab in the clinical pathway
- Trials combining a PD-1 inhibitor with a CTLA-4 inhibitor have demonstrated significant improvements in efficacy with concomitant increases toxicities.[12]
  - Extrapolating from this model, it is clear that these regimens would be extremely, and possibly prohibitively, costly
- In order to improve the cost-benefit ratio of expensive immunotherapies, new diagnostics must be developed to identify patients most likely to respond or those most likely to suffer from catastrophic toxicities that could be prevented or preemptively managed to contain the overall cost of care.

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# Schedule and Duration of Therapy

- How much drug is enough?
  - Treat to best response and stop?
  - Treat 2 cycles beyond complete response?
  - Stop and go approach?
- Intermittent dosing for targeted therapy?
  - SWOG 1320 (NCT02196181)

# Costs Yet Unaccounted For…

- **Cost of toxicity management**
  - Steroids, infliximab, other immunosuppressive agents (Immune-check point inhibitors)
  - Dermatologic surveillance (BRAF inhibitors)
  - Need for intensive monitoring for cardiomyopathy (MEK inhibitors)

# Conceptualizing my vision for a better tomorrow

*‘Fiscally responsible personalized medicine’*

# Summary

- Immunotherapy is potentially curative in cancer medicine, yet not all will benefit
- Rationale development of combination therapy should aim to improve efficacy and reduce toxicity
- The challenge for better pharmacoeconomic value in cancer care must be a shared undertaking