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2013 Conference on Clinical Cancer Research

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Facilitating the Development of Immunotherapies: Intermediate Endpoints for Immune Checkpoint Modulators

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Immune Checkpoint Modulators

Jim Allison, Ph.D.
The University of Texas
MD Anderson Cancer Center

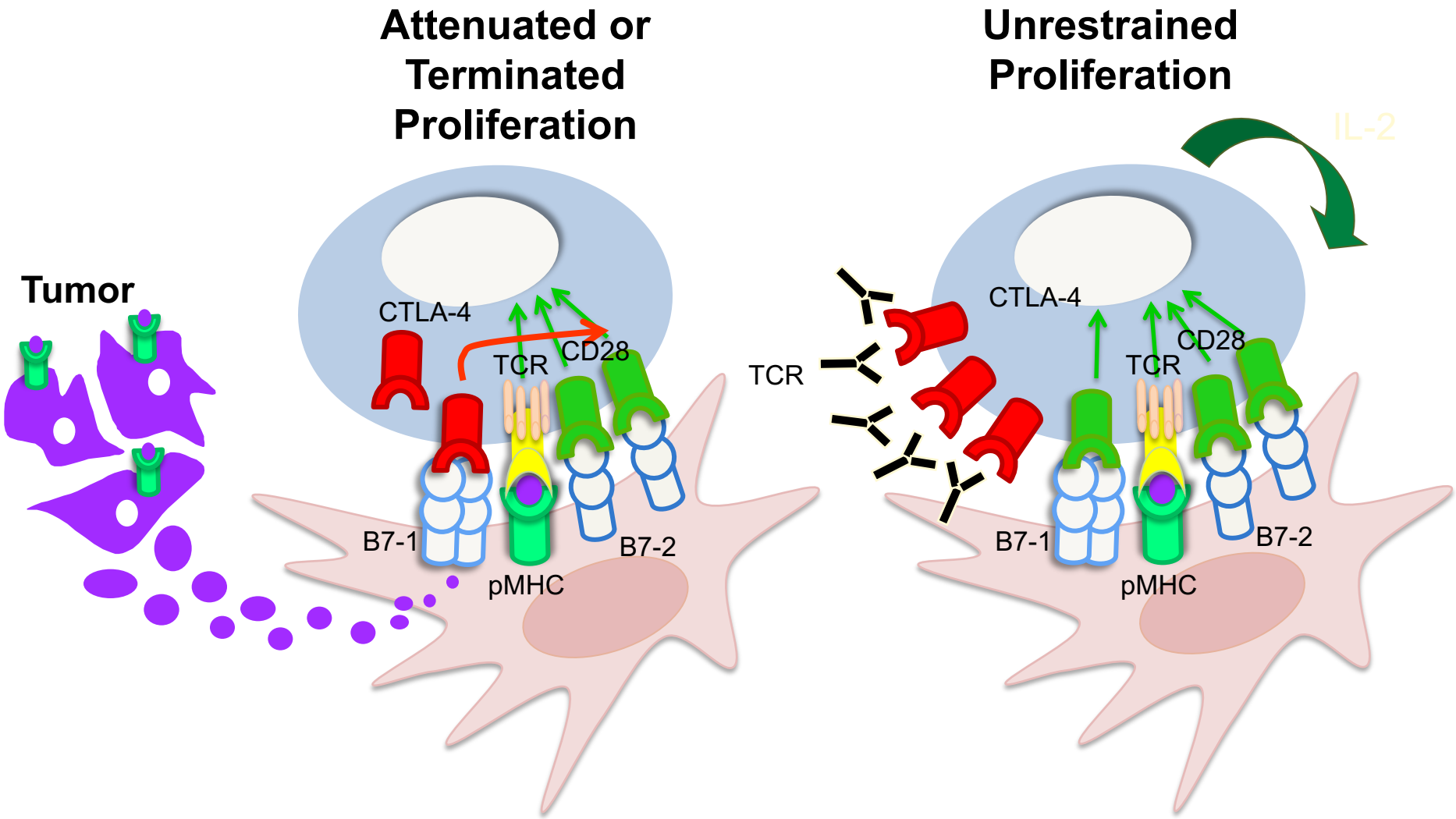
Why immunotherapy?

Specificity

Memory

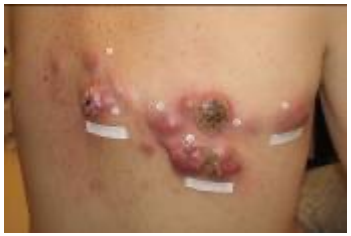
Adaptability

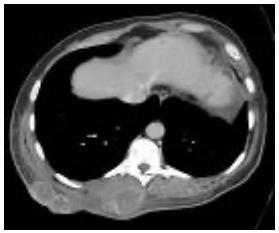
CTLA-4 Blockade Enhances Tumor-Specific Immune Responses



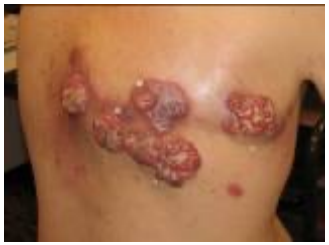
Evolution of Response: Patient Example

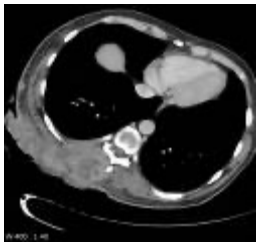
Screening



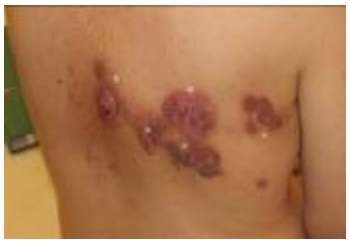


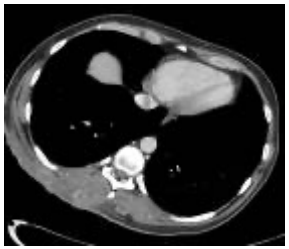
Week 12
Initial increase in
total tumor burden (mWHO PD)



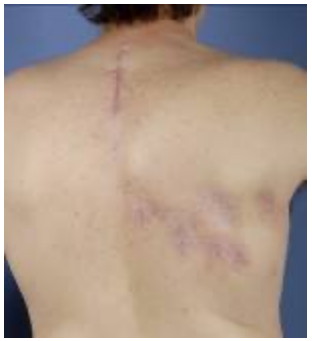


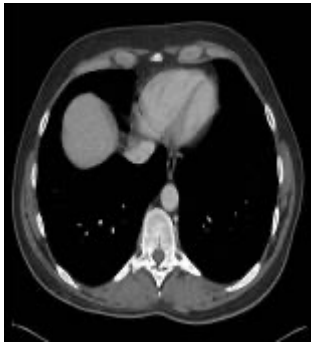
Week 16
Responding





Week 72
Durable & ongoing response
without signs of IRAEs





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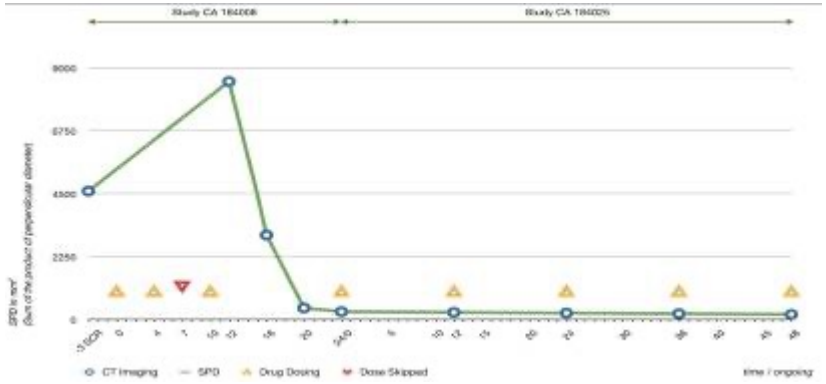
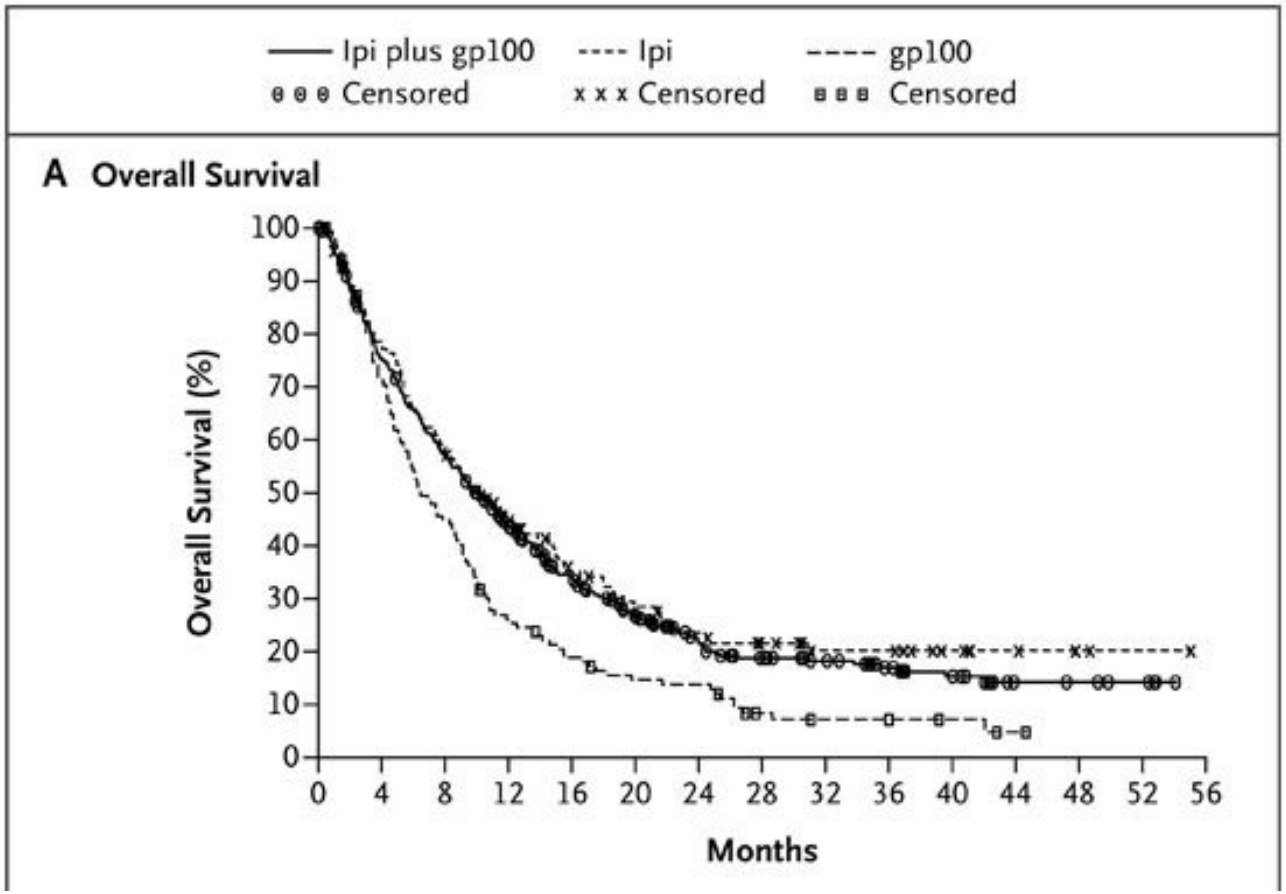


Harmankaya

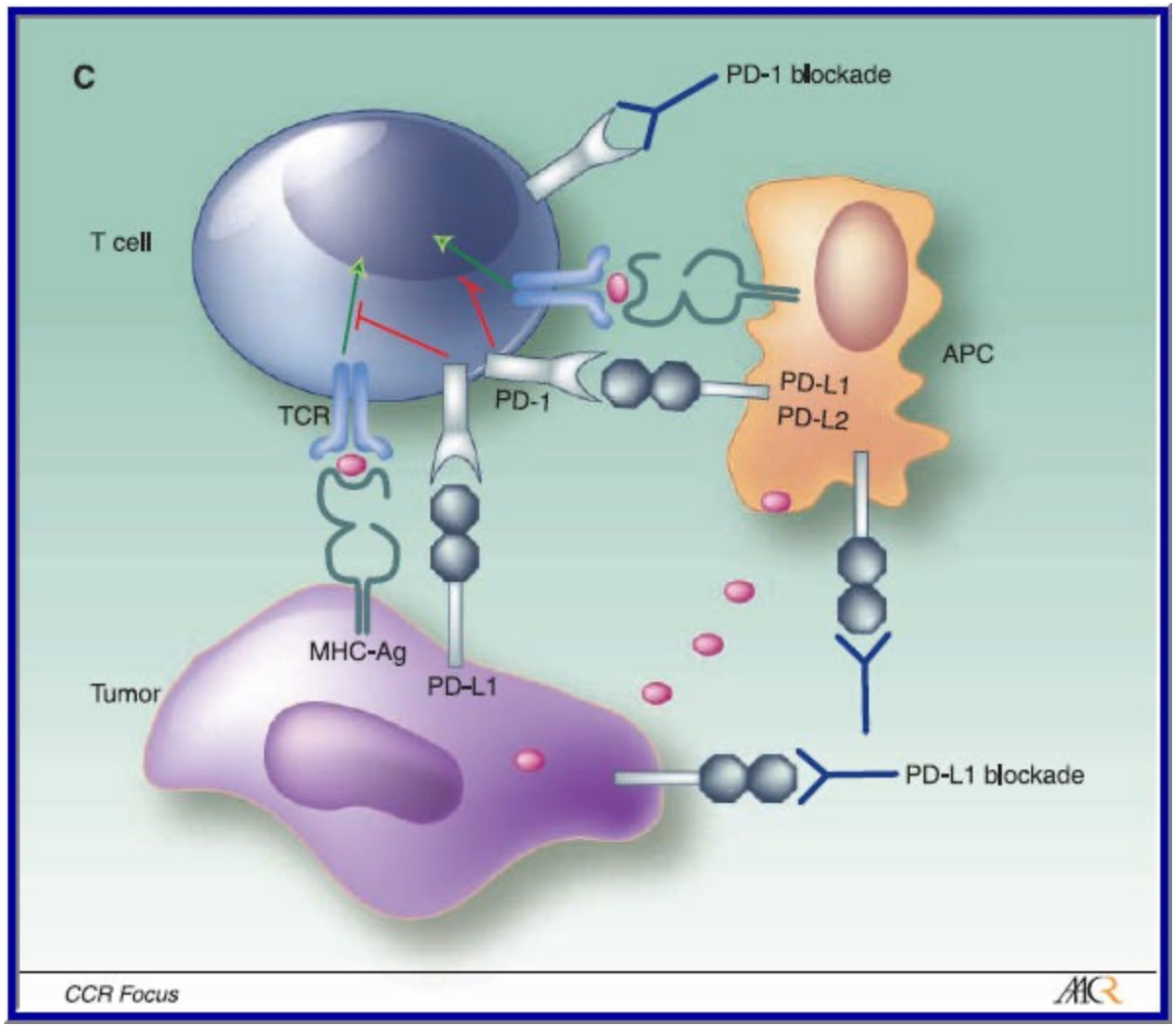
Kaplan-Meier Analysis of Survival



Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

Hodi et al. NEJM 2010

Programmed Death 1



http://www.melanoma.org/community/mpip-melanoma-patients-information-page/video-how-anti-pd-1-therapy-works-imumne-system

Anti – PD-1 (BMS-936558)

296 Patients with Metastatic Cancer
1, 3, 10 mg/kg, MTD not reached

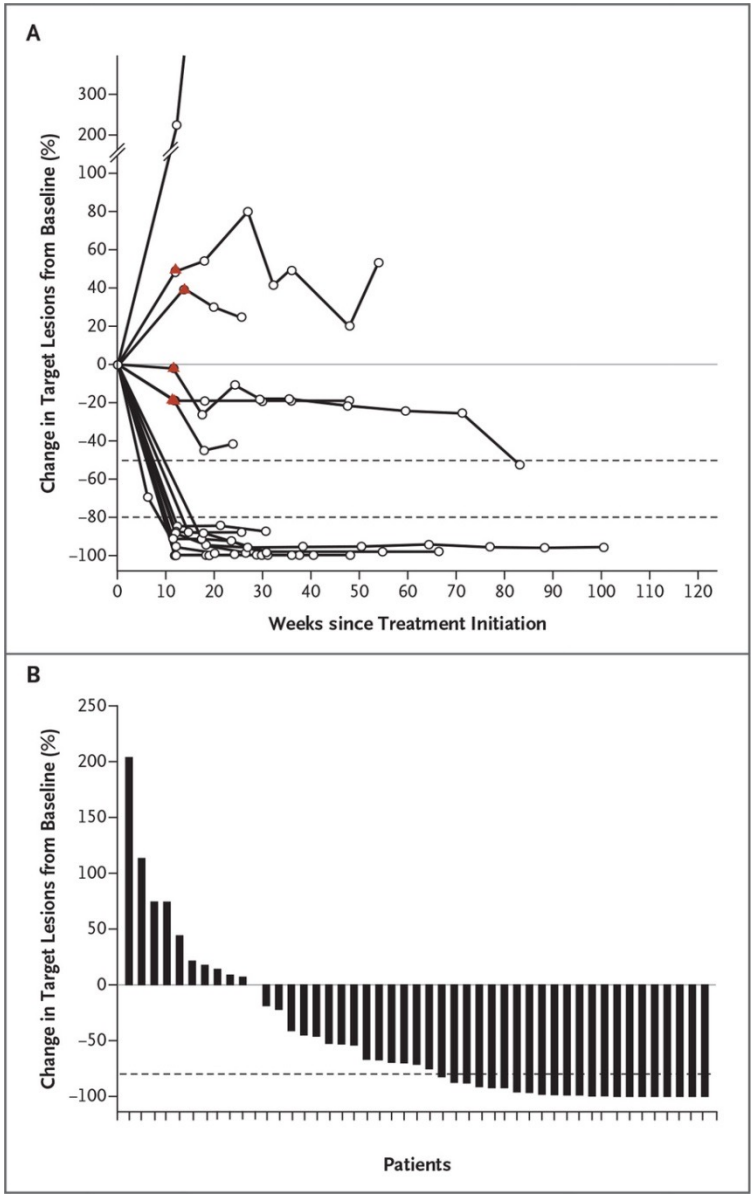
Safety: Adverse events similar to Ipilimumab, but 4% pneuomonitis (3 deaths)

Clinical Activity:

- **Melamona (n= 94): 28% CR/PR, 6% SD**
- **NSCLC (n=76): 18% CR/PR, 7% SD**
- **RCC (n= 33): 27% CR/PR, 27% SD**
- ***CRC (n=19), CRPC (n=13): No responses***

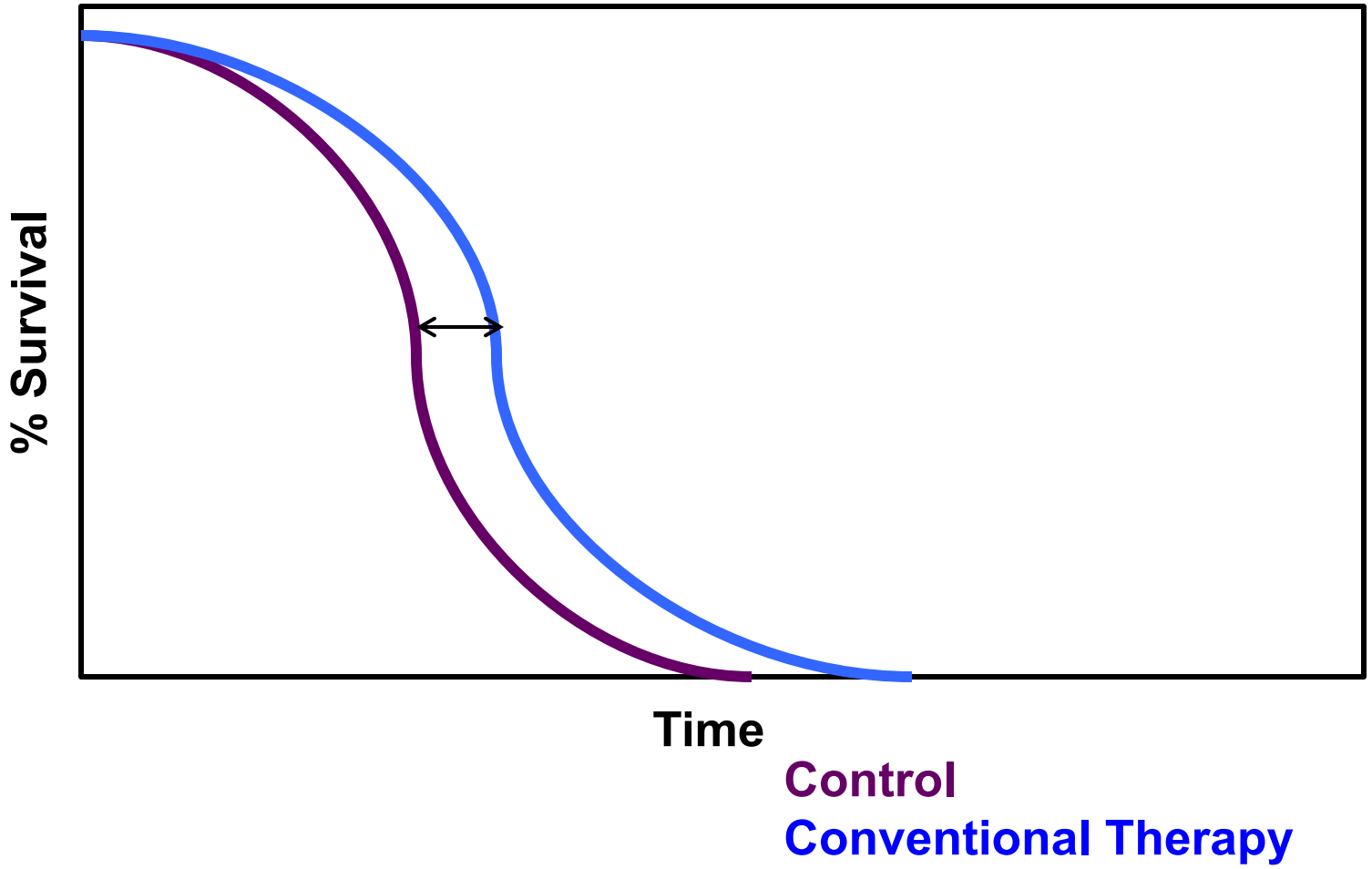
Topalian ASCO, NEJM 2012

Clinical Activity in Melanoma Patients Receiving Ipilimumab (αCTLA-4) and Nivolumab (αPD-1)

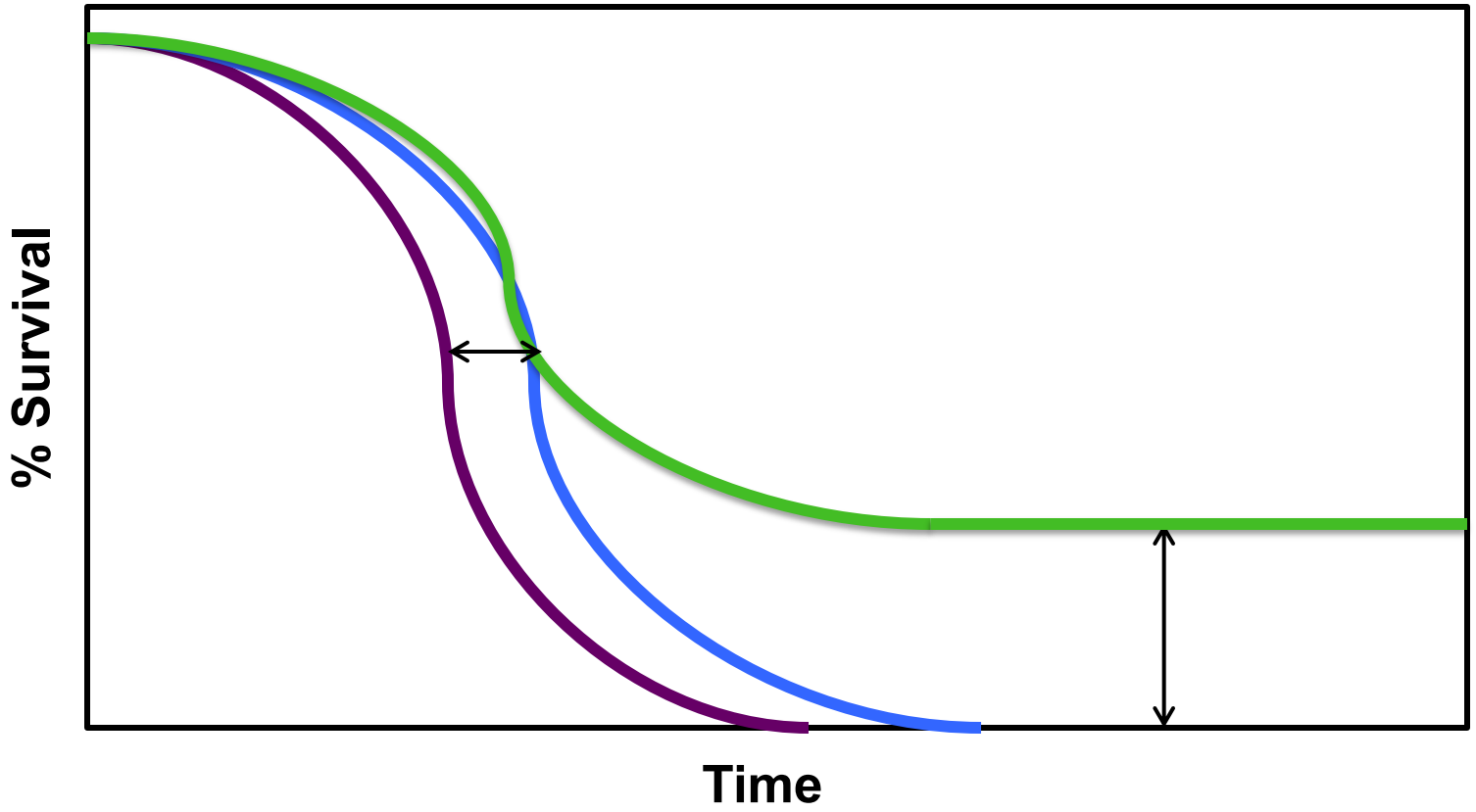


ASCO 2013
NEJM 6/2/2013

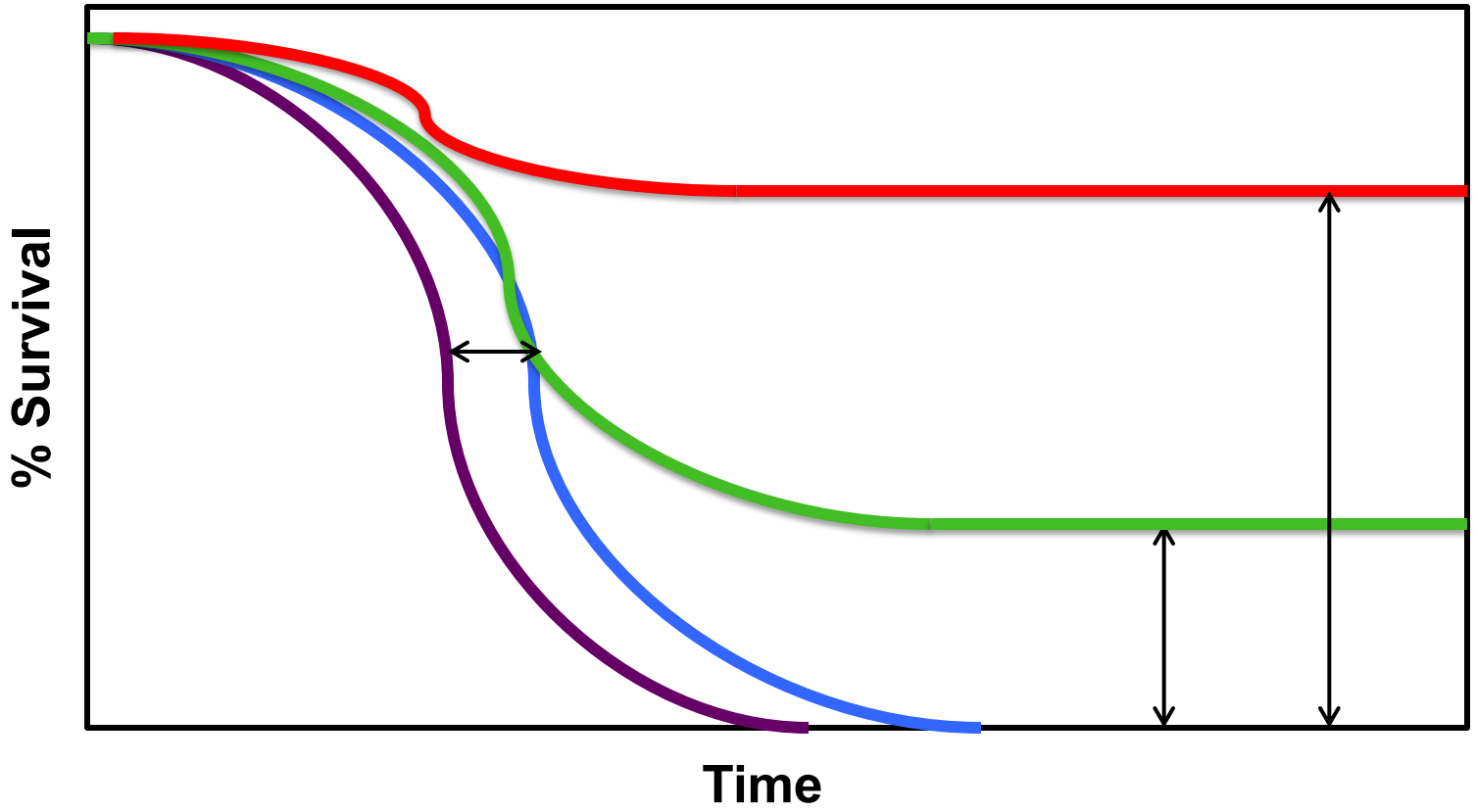
Improving Survival with Combination Therapy



Improving Survival with Combination Therapy



Improving Survival with Combination Therapy



Speakers

- **Jim Allison, Ph.D.**, U.Texas MD Anderson Cancer Center
- **Mark Gorman**, Survivor and Advocate
- **Ramy Ibrahim, M.D.** MedImmune
- **Axel Hoos, M.D., Ph.D,** Glaxo-Smith Kline
- **Tai-Tsang Chen, Ph.D.,** Bristol-Myers Squibb
- **Steve Rosenberg, M.D., Ph.D.,** National Cancer Institute
- **Amy McKee, M.D.,** FDA-CDER
- **Celia Witten, M.D., Ph.D.,** FDA-CBER
- *Contributors:* **Renzo Canetta, M.D.**, **Suzanne Topalian, M.D.**

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Mark Gorman

Long-term Survivor of Metastatic Melanoma And Patient Advocate

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Immunotherapies: Dosing Challenges

Ramy Ibrahim, M.D.
MedImmune

Conventional dose/schedule selection and anti-cancer development

- Preclinical data from efficacy studies to identify target exposures in human
- Escalate doses in FTIH studies to assess safety and achieve target exposures (or higher) to increase likelihood of early signal
- Determine the MTD after DLTs are observed
- Select MTD for further development in randomized studies to assess efficay
- Initiate registrational studies

Novelties with immune-modulators and implications on dose/schedule selection

- Animal data might not inform dose selection
  - Cross reactivity and finding surrogate has limitations
- The “target” is the immune system and not the cancer
  - Complexity of the interaction between the immune system and cancer
  - Patients might have different threshold or sensitivity to immune priming
    - We need to identify a dose that achieves appropriate exposure while accommodating inter-patient variability
- Immune targets are dynamic
  - Variability in target level, site of expression, tumor type and tumor burden
- Animal data and PK modeling might only inform the starting dose and identify a target exposure range

Novelties with immune-modulators and implications on dose/schedule selection (cont)

- Dose escalation till “toxicity” is not a viable approach
    - None of the PD1/PDL1 targeting antibodies reached an MTD
    - Activity observed at multiple dose levels
    - Early phase clinical PK, target related biomarkers, markers of immune response and clinical activity should be leveraged
    - Need for novel phase I designs to inform dose selection

Novelties with immune-modulators and implications on dose/schedule selection (cont)

- Dose-ranging comparative studies may not necessarily better inform dose selection
  - Tremelimumab development
    - Randomized phase II suggested 15 mg/kg q3mo to be associated with more favorable risk: benefit
    - Phase III study suggested 15mg/kg Q 3 months not to maintain desired AUC
    - Currently exploring monthly dosing
- Beside dose/schedule, what about duration of treatment?
- Due to the early and sometimes dramatic signal of activity, programs progress quickly from large phase 1 to phase 3
  - How to design better studies to inform registrational studies

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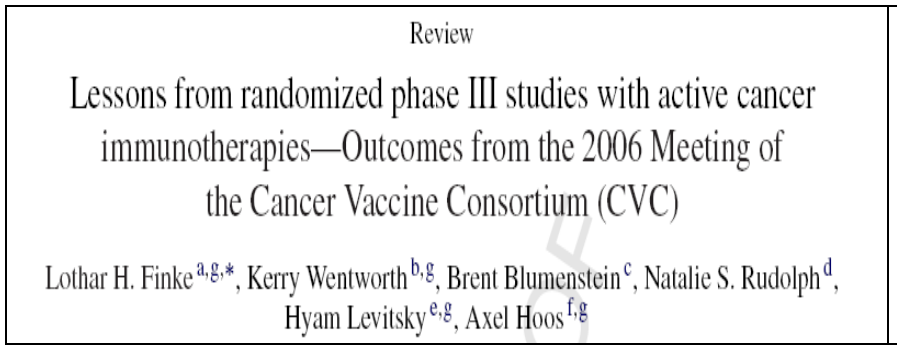
Delayed Treatment Effects of Cancer Immunotherapies

Axel Hoos, M.D., Ph.D.
Glaxo-Smith Kline

A Methodological Framework for Immuno-Oncology

Challenge: ***Clinical trial endpoints are not immunotherapy-focused***

Solution: ***Adjustment of endpoints to immunotherapy biology***

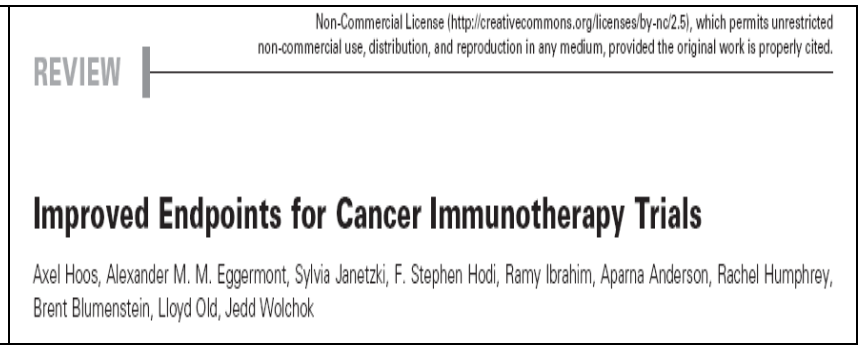


Review

Lessons from randomized phase III studies with active cancer immunotherapies—Outcomes from the 2006 Meeting of the Cancer Vaccine Consortium (CVC)

Lothar H. Finke[a,g,*], Kerry Wentworth[b,g], Brent Blumenstein[c], Natalie S. Rudolph[d], Hyam Levitsky[e,g], Axel Hoos[f,g]

Vaccine 2007



REVIEW

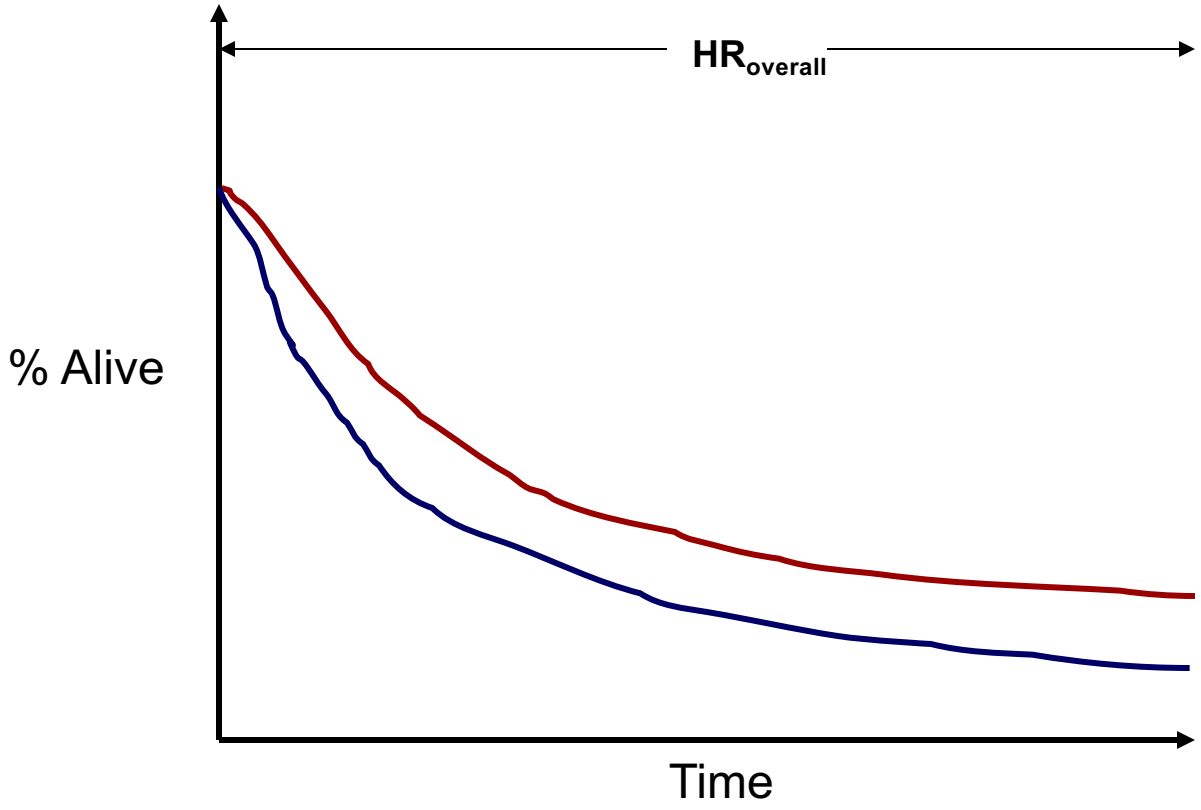
Improved Endpoints for Cancer Immunotherapy Trials

Axel Hoos, Alexander M. M. Eggermont, Sylvia Janetzki, F. Stephen Hodi, Ramy Ibrahim, Aparna Anderson, Rachel Humphrey, Brent Blumenstein, Lloyd Old, Jedd Wolchok

J Natl Cancer Inst 2010

Cancer Immunotherapy Consortium

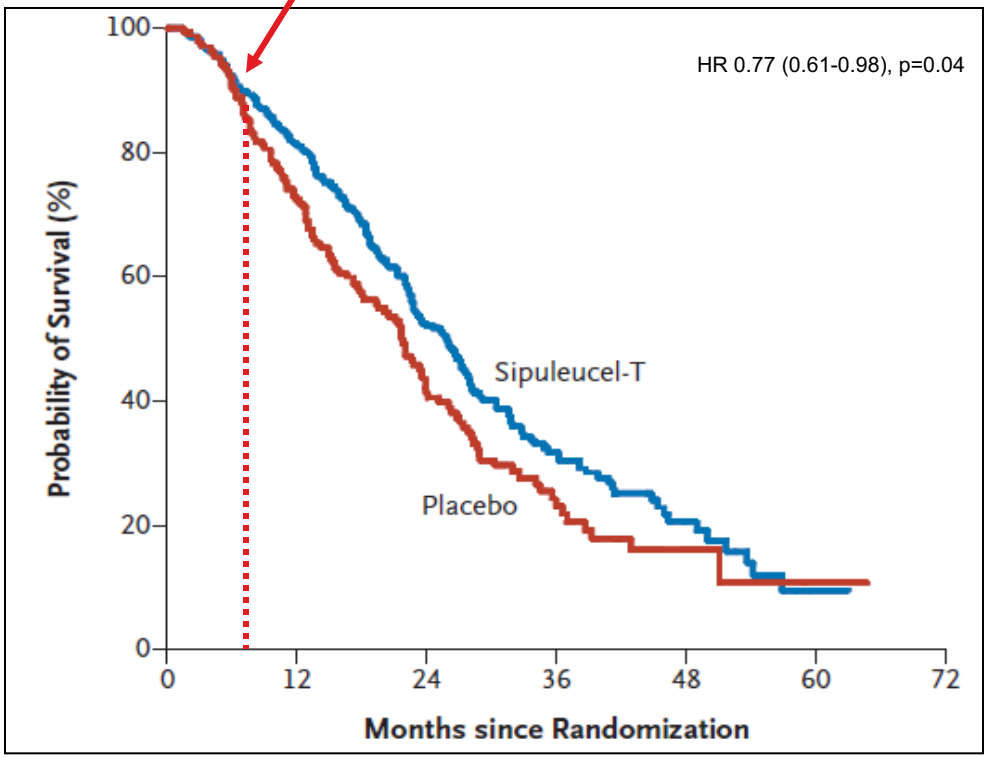
Survival: Conventional Design Assumptions



- No events occur before separation of curve
- Proportional hazard applies

Delayed Separation – Sipuleucel-T

Separation of curves
at ~8 months



Sponsor:
Dendreon

Agent:
autologous dendritic cell vaccine

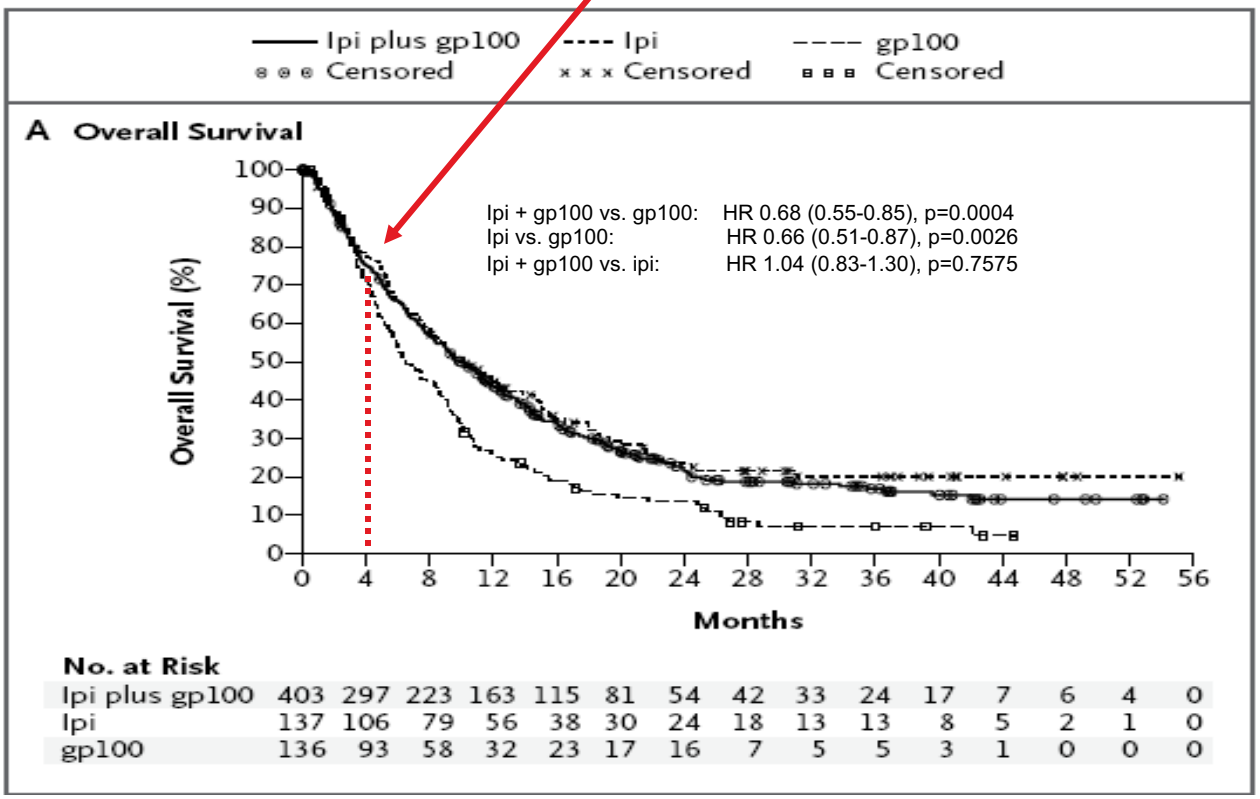
Disease:
hormone-refractory prostate cancer

Kantoff et al., New Engl. J. Med. 2010

CIC Cancer Immunotherapy Consortium

Delayed Separation – Ipilimumab

Separation of curves
at ~4 months



Sponsor:
BMS

Agent:
Anti-CTLA-4 mAb

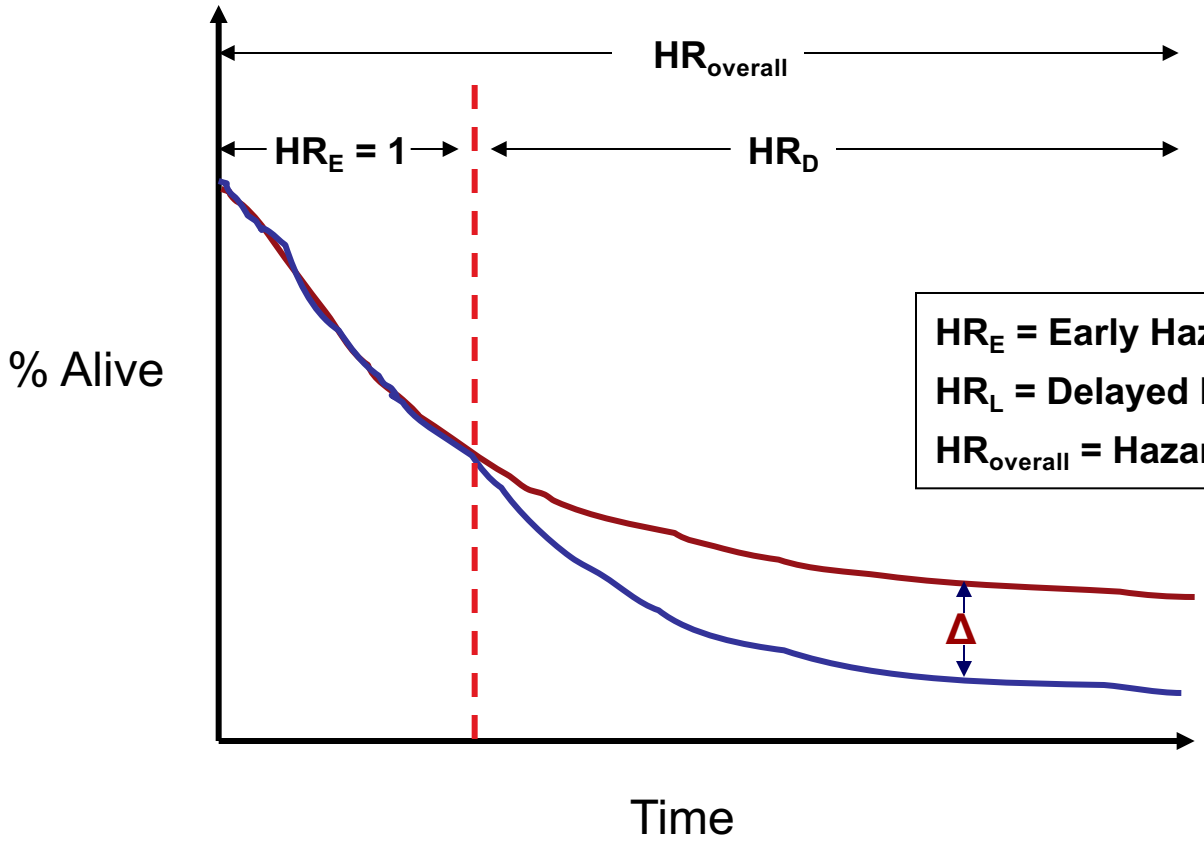
Disease:
Metastatic melanoma

Hodi et al., New Engl. J. Med. 2010

CIC Cancer Immunotherapy Consortium

Implications of Delayed Separation of Curves

- Model Scenario -



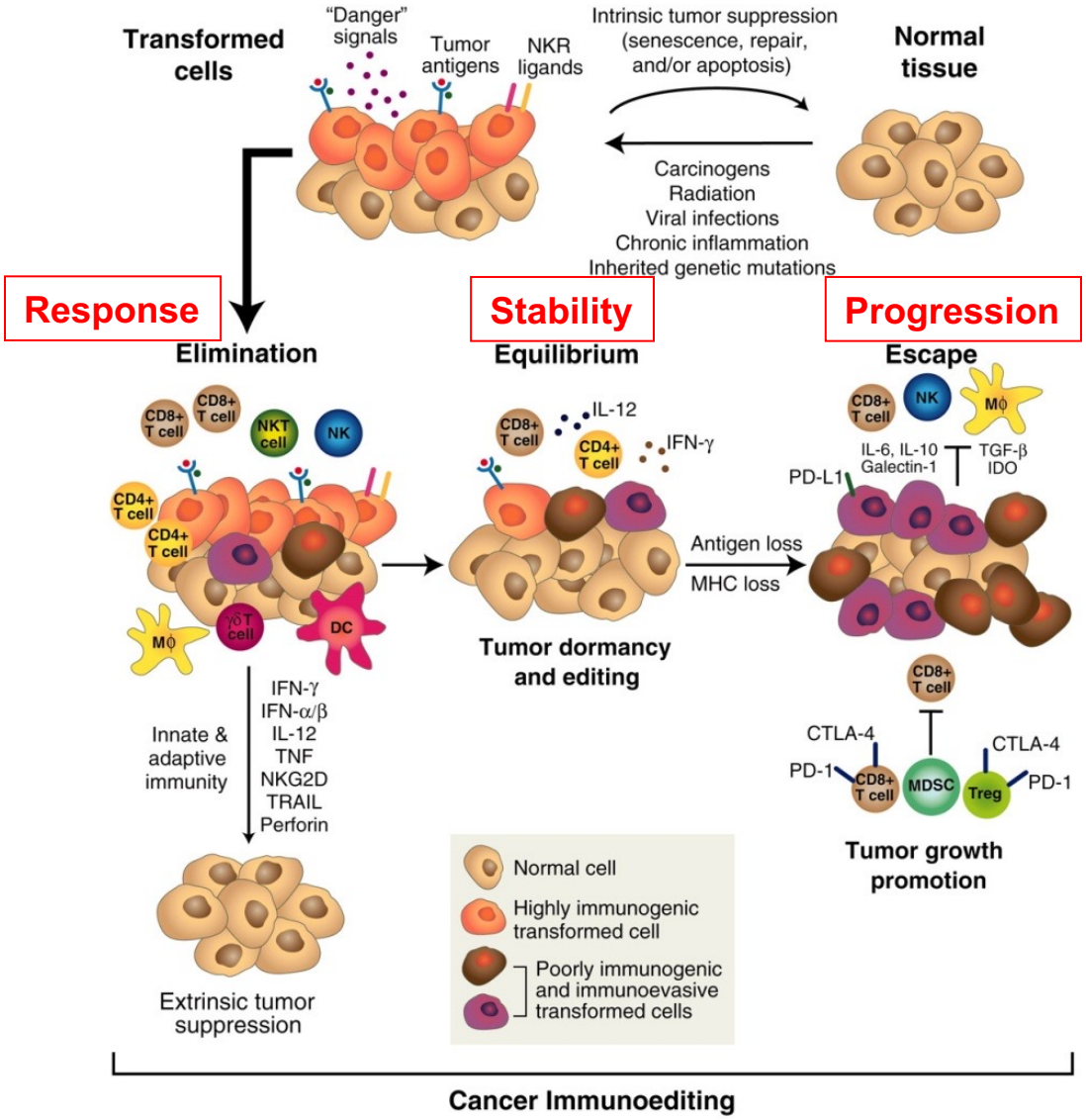
HR_E = Early Hazard Ratio (before Separation)

HR_L = Delayed Hazard Ratio (after separation)

$HR_{overall}$ = Hazard ratio for entire curve

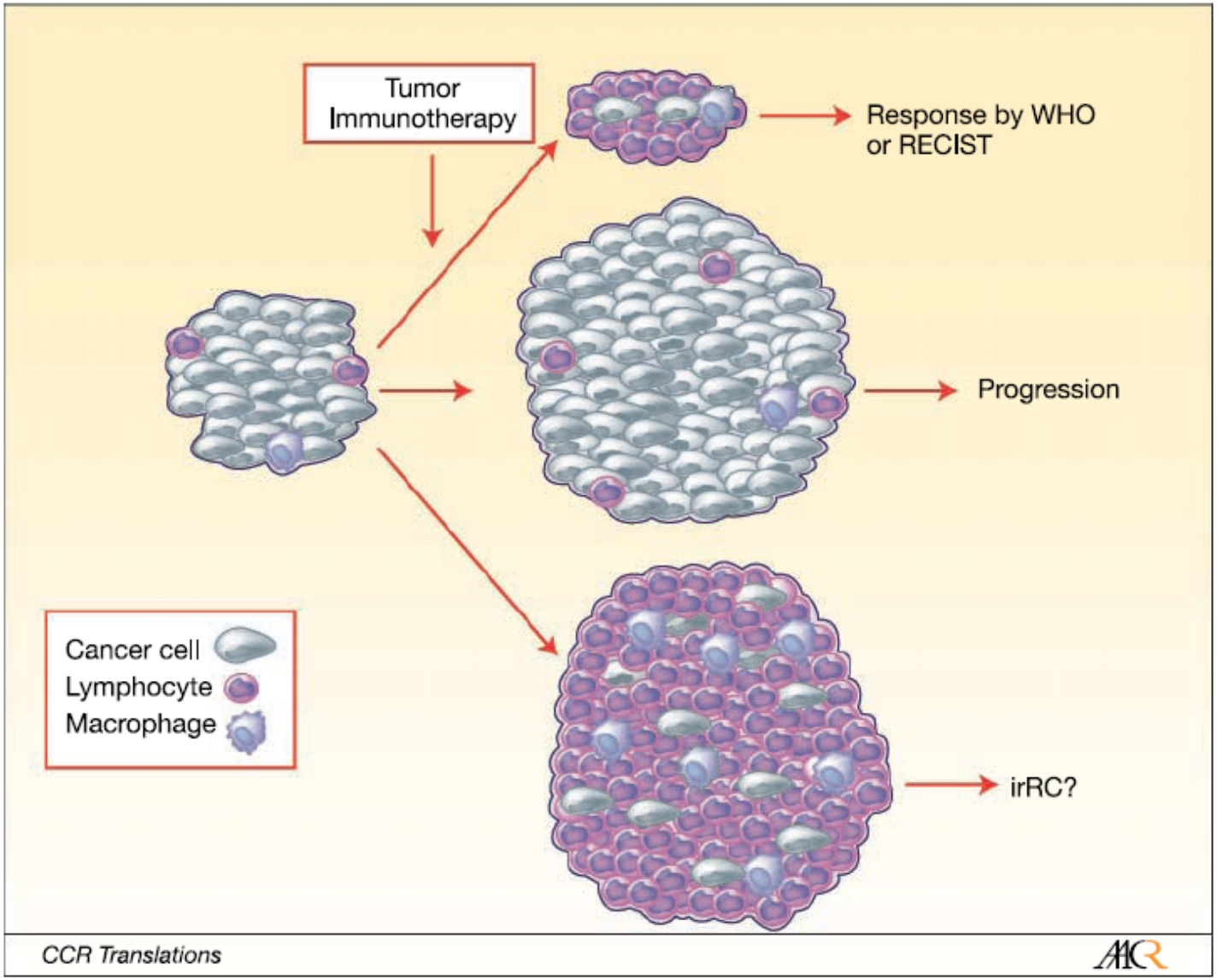
- Large Δ after separation needed to compensate for no effect before separation

Interactions between Immune System and Tumor



Schreiber R., *Science* 2011

Tumor Volume Increase Due to Lymphocyte Infiltration

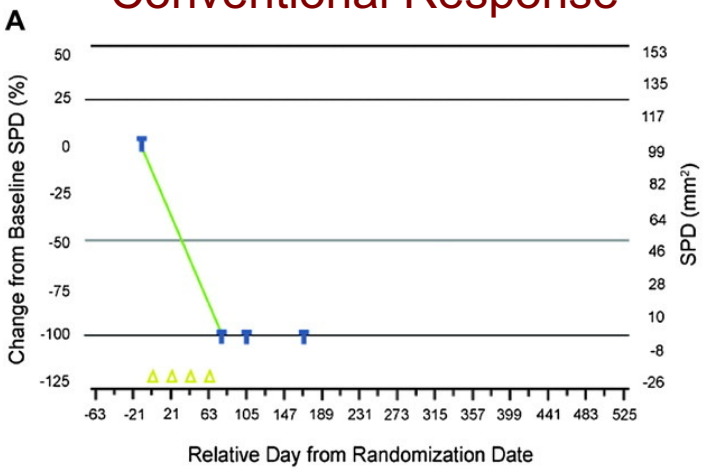


Ribas et al., Clin Cancer Res 2009; 15:7116–8

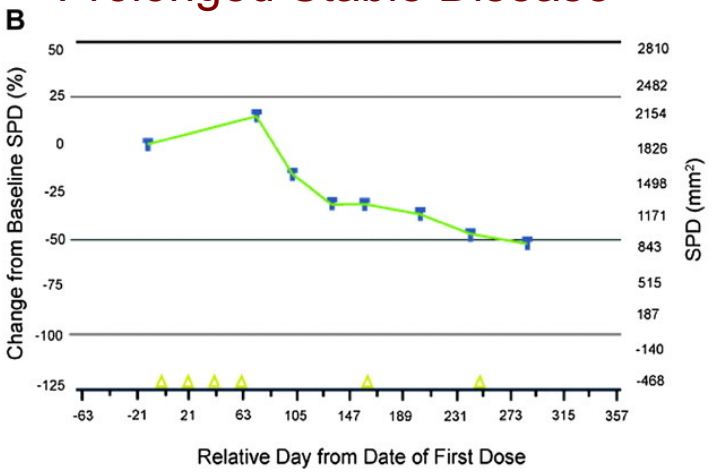
Cancer Immunotherapy Consortium

Immunotherapy Patterns of Response

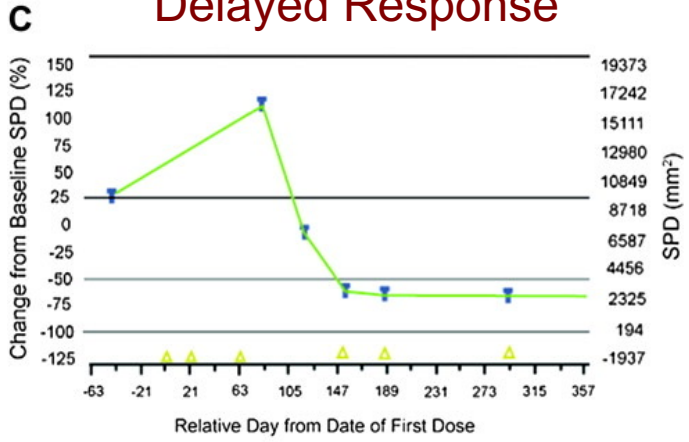
Conventional Response



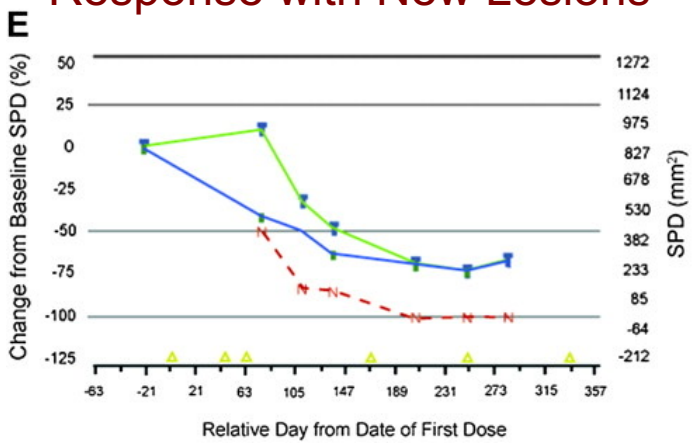
Prolonged Stable Disease



Delayed Response



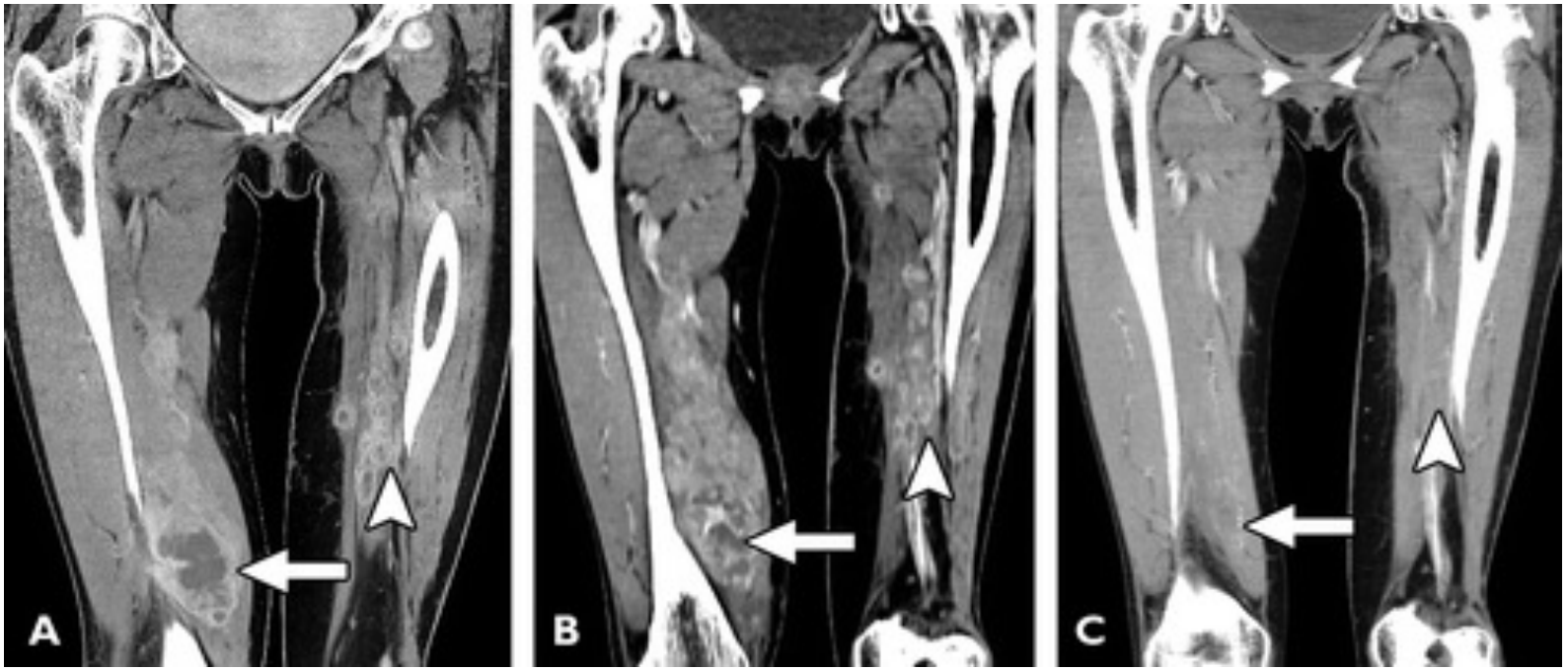
Response with New Lesions



Wolchok JD, et al. *Clin Cancer Res.* 2009;15:7412-7420

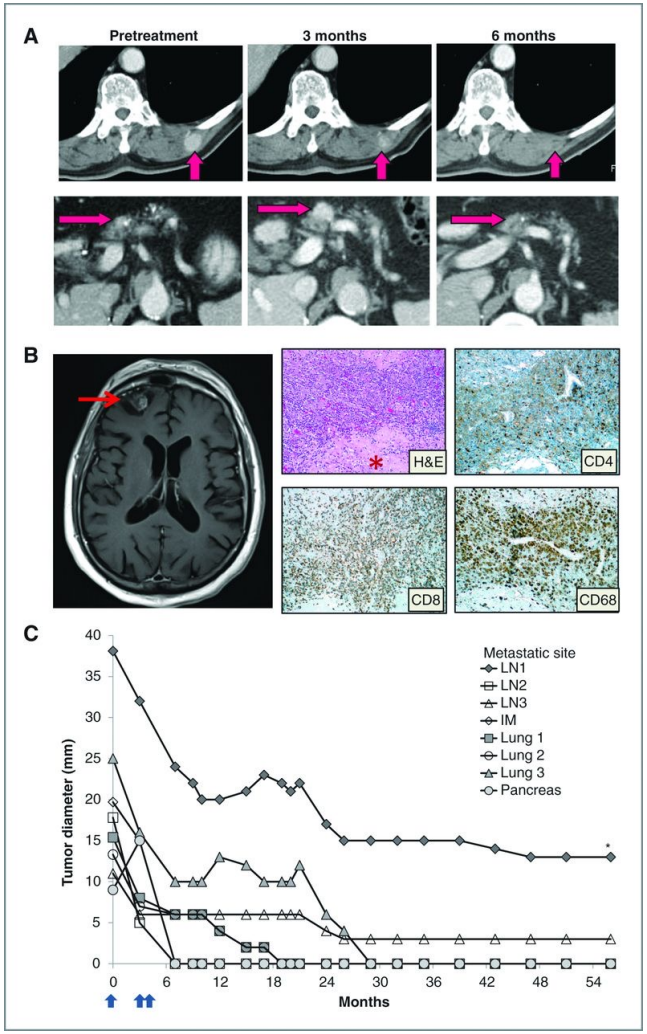
Hoos A et al. *JNCI J Natl Cancer Inst* 2010;102:1388-1397

Anti-CTLA-4 (Ipilimumab): Delayed Response



O'Regan, KN, et al. AJR 2011

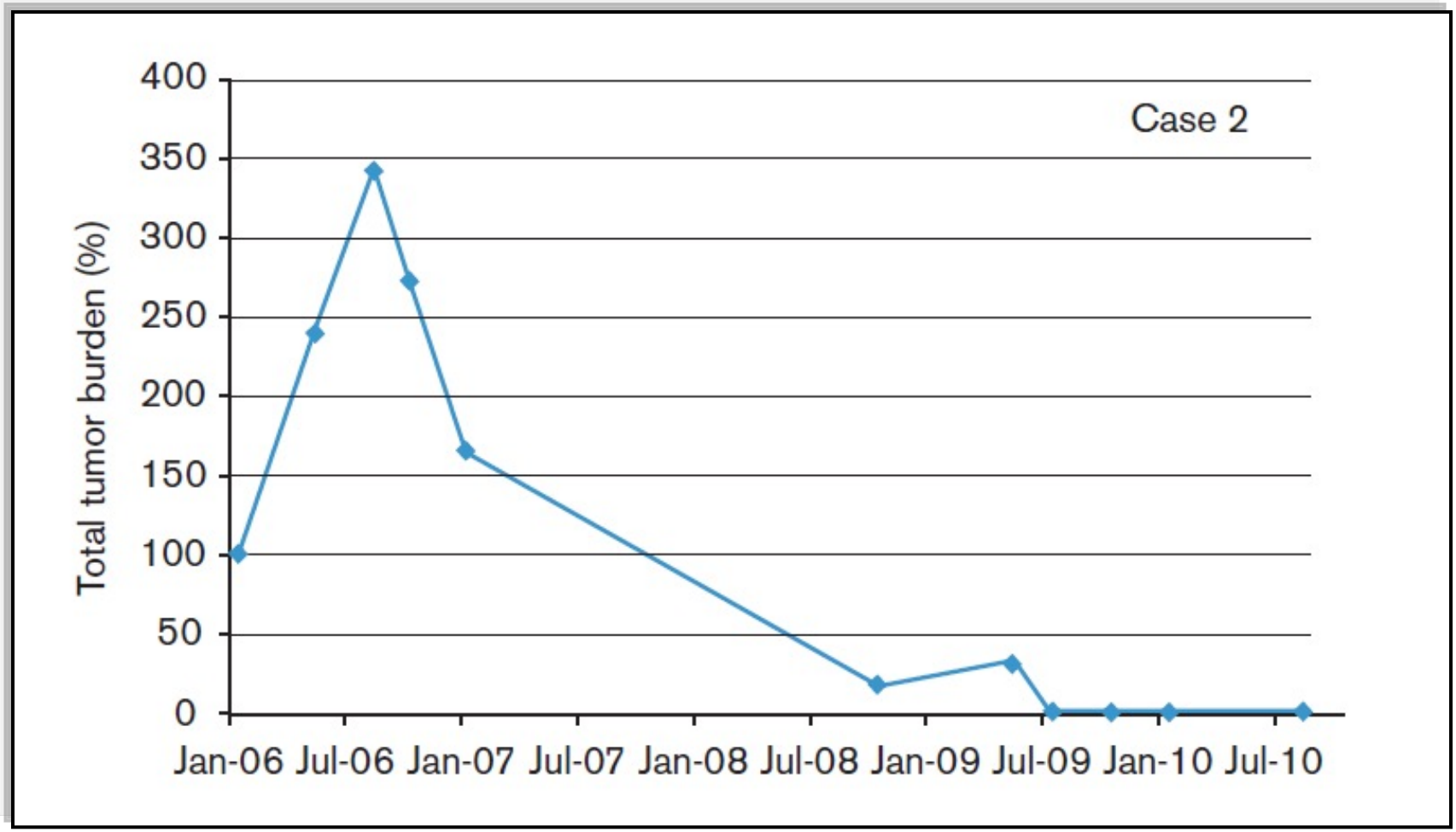
Regression of metastatic RCC following anti-PD-1 therapy, with “immune-related” response characteristics.



Lipson E J et al. Clin Cancer Res 2013;19:462-468

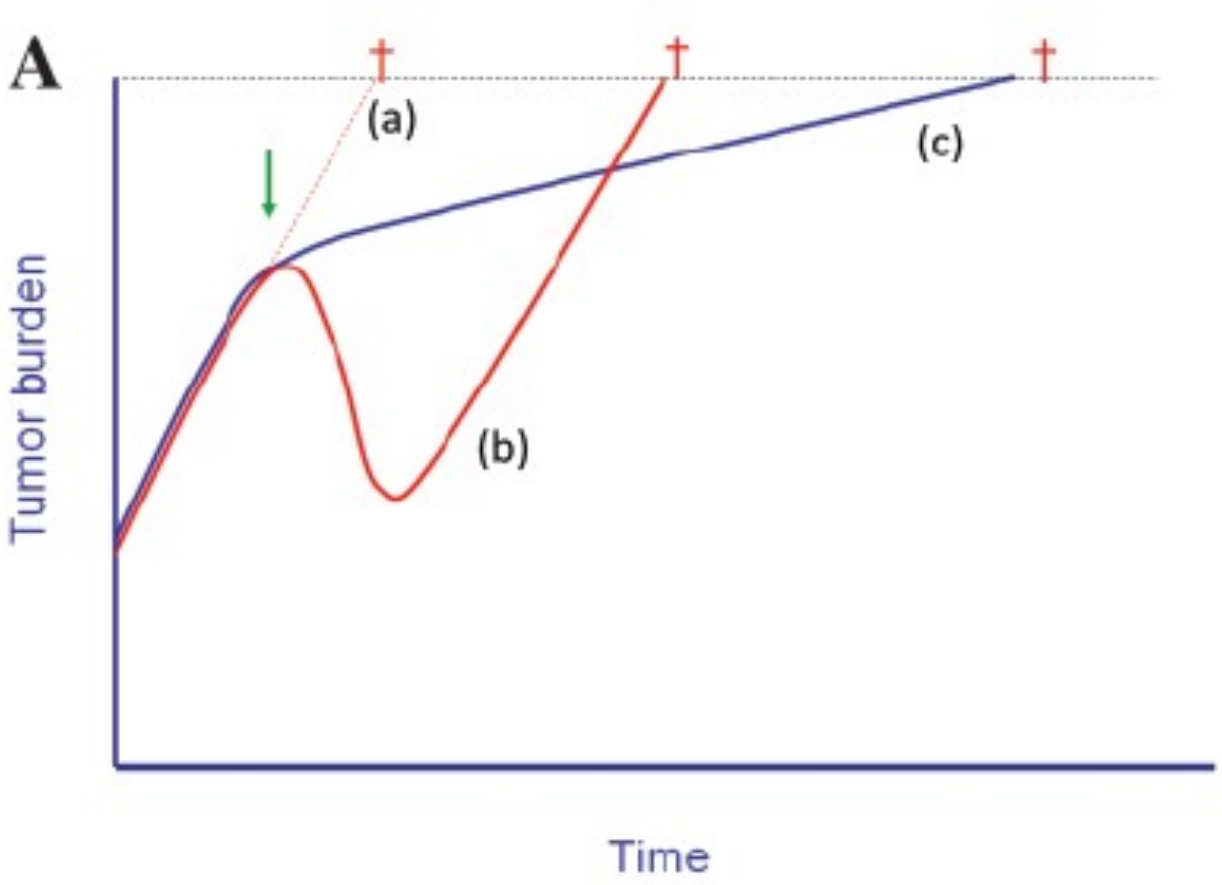
Clinical Cancer Research

Autologous DC + IFN α2b in Advanced Melanoma: Delayed Response



Wilgenhof S. et al., *Melanoma Res.* 2011

Tumor Growth Rate: Potential Impact on Survival



Schlom J., J. Natl. Cancer Inst. 2012

Available Tools

- Statistical methods for analyzing survival
- Immune-related Response Criteria
- Tumor growth kinetics

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Intermediate Endpoints for Immune Checkpoint Modulators: Milestone OS Analysis

Tai-Tsang Chen, Ph.D.
Bristol-Myers Squibb

Rationale

- Unique characteristics of immune checkpoint modulators
  - Survival probability (long term survival)
  - Delayed clinical effect

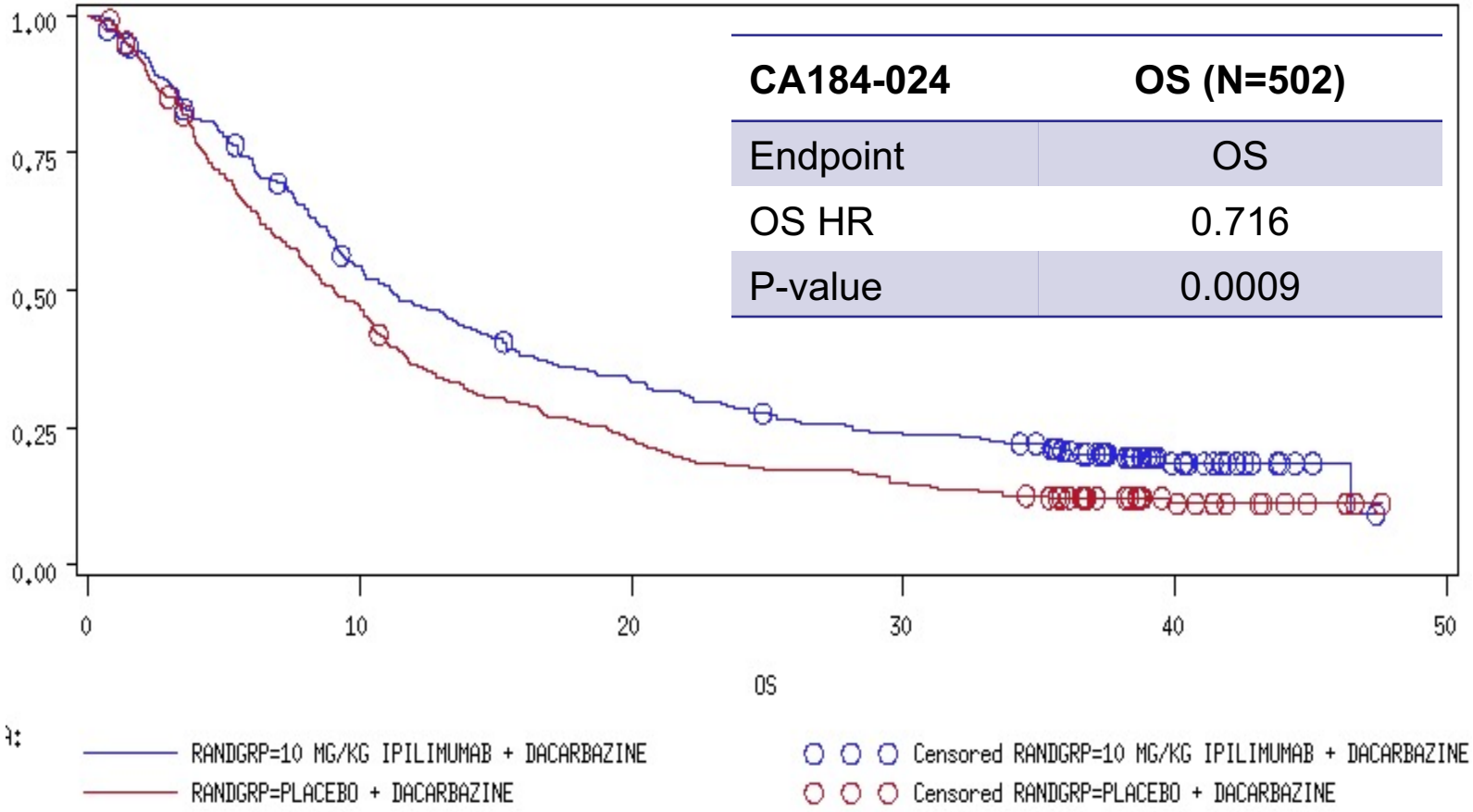
- Key challenges of log-rank analysis as sole characterization of overall survival
  - Does not capture key attribute of survival probability (or long term survival)
  - Time to final analysis may continue to lengthen based on kinetics of survival effect

Milestone OS Analysis

- Milestone survival is defined as the Kaplan-Meier survival probability at a pre-specified milestone, e.g., 2 years

- Study design and analysis consideration
  - Primary endpoint: overall survival
  - Intermediate endpoint: milestone survival probability
  - Population includes patients with a minimal follow-up duration, i.e., ≥ milestone duration
  - Hierarchical testing procedure

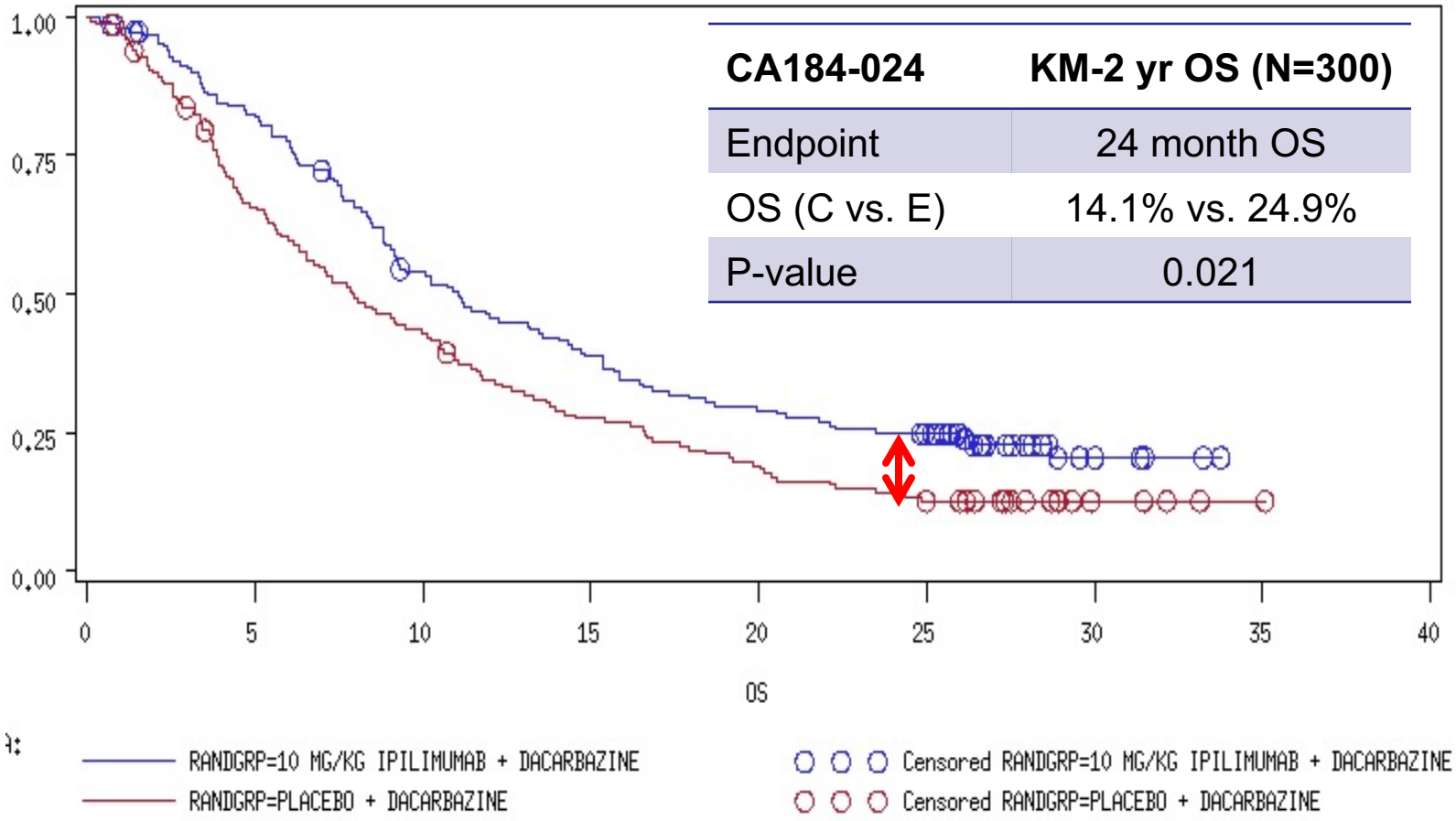
Example*: Ipilimumab+DTIC vs. DTIC Final OS Analysis



CA184-024	OS (N=502)
Endpoint	OS
OS HR	0.716
P-value	0.0009

* Roberts, C. et al. NEJM, 2011, 364: 2517-2526.

Example*: Ipilimumab+DTIC vs. DTIC Intermediate 2-year Milestone OS Analysis



CA184-024	KM-2 yr OS (N=300)
Endpoint	24 month OS
OS (C vs. E)	14.1% vs. 24.9%
P-value	0.021

* Roberts, C. et al. NEJM, 2011, 364: 2517-2526.

Pros and Cons

- Pros
  - Potential earlier assessment of benefit/risk
  - Greater statistical power when delayed treatment effect is present
  - Direct characterization of survival probability (long term survival effect)
  - Predictable timing of analysis
  - Both intermediate and final endpoints are overall survival
- Cons
  - Challenge in maintaining study integrity post milestone analysis, i.e., unblinding prior to final OS analysis
  - Does not account for the totality of OS data
  - Only appropriate for a registration trial when prior data enable an understanding of appropriate milestone time point selection

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Steven Rosenberg, M.D., Ph.D.

National Cancer Institute

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Amy McKee, M.D.

FDA
Center for Drug Evaluation and Research

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Celia Witten, M.D., Ph.D.

FDA
Center for Biologics Evaluation and Research

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