American Association for Cancer Research

FINDING CURES TOGETHER℠

Immuno-Oncology Drug Development Workshop

October 13 &14, 2016

Hyatt Regency on Capitol Hill

Washington, DC

American Association for Cancer Research

FINDING CURES TOGETHER℠

Day 2 Introduction

Suzanne Topalian, MD

Workshop Co-Chair

Regulatory Pathways for Approval

Considerations for Alternate Endpoints

Maitreyee Hazarika, M.D.

Office of Hematology and Oncology Products, Office of New Drugs,
Center for Drug Evaluation and Research, FDA

FDA-AACR Immuno-Oncology Drug Development Workshop

October 13-14, 2016

Disclosures

- No financial relationships to disclose
- Will not discuss off-label use of approved products

Requirements for FDA Approval

- Substantial evidence of effectiveness in adequate and well-controlled studies with acceptable safety
- FDA examines evidence in context of the disease, line of therapy, available therapy, study design, endpoints, and magnitude of evidence
- Ability to generate product labeling that:
  - Defines appropriate patient population for whom the drug is indicated
  - Provides adequate information to enable safe and effective use

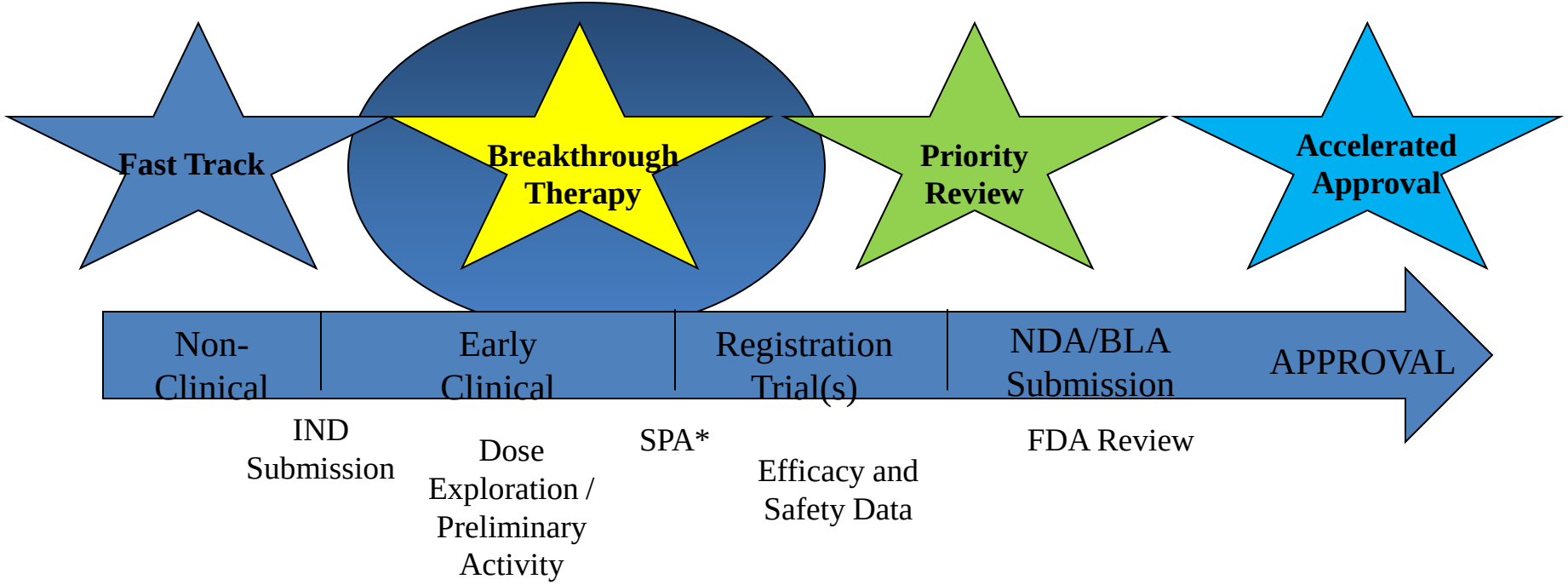
Regulatory Pathways for Approval

- Regular Approval
  - Approval based on demonstration of direct clinical benefit or effect on an established surrogate
- Accelerated Approval
  - Intent to treat serious or life-threatening illnesses
  - Approval based on a surrogate or intermediate endpoint reasonably likely to predict clinical benefit
  - Provides meaningful therapeutic benefit over available therapy
  - Requires confirmatory clinical studies to verify and/or describe actual clinical benefit

FDA Expedited Programs: Goals

- Address an unmet medical need in the treatment of a serious or life-threatening condition
- Facilitate and expedite development and review of promising new drugs
- Ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies' benefits justify their risks
- Allow for earlier attention to investigational agents that have promise in treating such conditions, including earlier consultation with FDA

FDA Expedited Programs



*Special Protocol Assessment

Slide from Paul Kluetz, MD

Codevelopment of Two or More Investigational Drugs

- Combination intended to treat a serious disease or condition
- Compelling biological rationale for use of combination
- Contribution of individual agents to the treatment effect of the agents used in combination
- Safety evaluation for potential increased risks
- Early and frequent interaction with FDA to facilitate development

Considerations of Endpoints Supporting Past Approvals

Overall Survival (OS)

- Direct evidence of clinical benefit
- Randomized controlled studies
- Superiority or non-inferiority
- Larger studies
- Long follow-up
- May be confounded by cross-over and subsequent therapy

Tumor-assessment Endpoints

Objective Response Rate (ORR), Progression-free Survival (PFS), Disease-free Survival, Relapse-Free Survival, Time to Tumor Progression*

- Surrogate for clinical benefit
  - Accelerated or regular approval depends on magnitude of effect, effect duration, disease setting, and risk-benefit to available therapy
- Adjuvant setting after definitive surgery or radiotherapy
- Single-arm or randomized controlled studies
- Smaller sample size
- Blinded external review (or audit)
- Clinical significance: benefit vs. risk

* Based on RECIST criteria

Endpoints Based on Symptom Assessment

Patient Reported Outcomes (PRO)

- Quality of life, physical functioning, tumor related symptoms, and symptomatic adverse events
- Patient perspective of direct clinical benefit
- Randomized blinded studies
- Fit for purpose tool for measurement
- Missing or incomplete data
- Interpretation: clinical significance of small changes

Approval of an Application

- 21 CFR 314.105(c)

FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards for safety and effectiveness

- FDA applies flexibility regarding the evidence required to support approval to address particular challenges posed by each disease

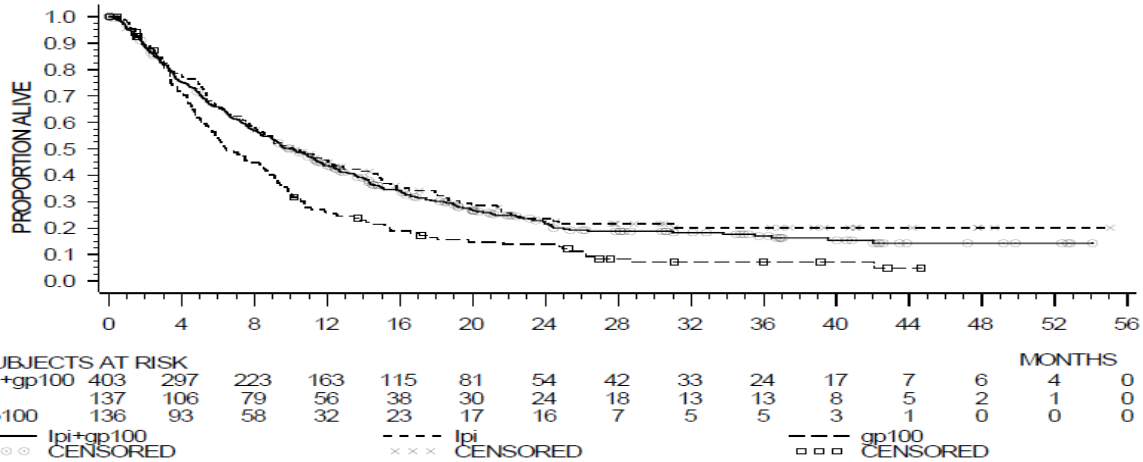
Innovative Endpoints

- Pathologic complete response
  - pertuzumab in neoadjuvant breast cancer
- Spleen volume reduction and patient reported outcomes (total symptom score)
  - ruxolitinib in myelofibrosis
- Red blood cell transfusion independence
  - lenalidomide in MDS
- Major cytogenetic / hematologic response
  - imatinib, nilotinib in CML

Melanoma

- Ipilimumab (anti-CTLA4) vs. gp100
  - ORR: 10.9% vs. 1.5%; median duration of response not reached in either arm
  - OS: HR 0.66 (95% CI: 0.51, 0.87); median OS 10 vs. 6 months

Ipilimumab Kaplan-Meier (K-M) curves for OS

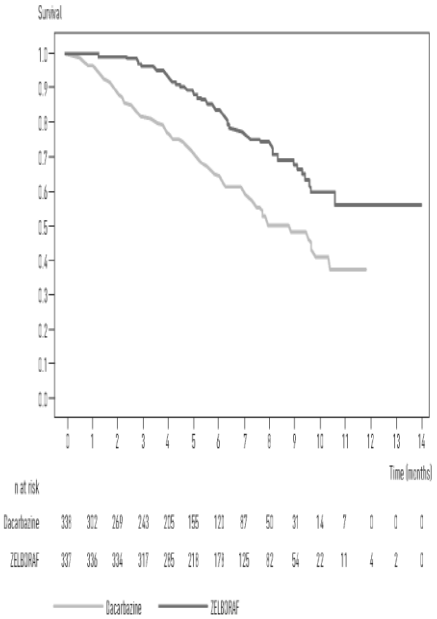


(Ipilimumab USPI)

Melanoma

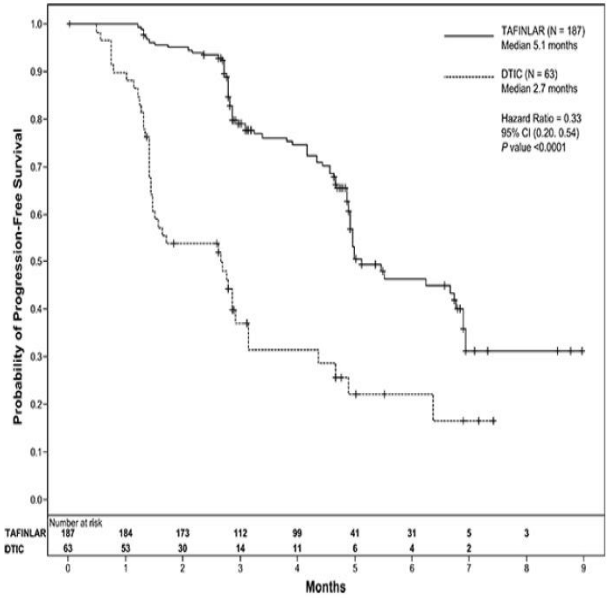
- Targeted (BRAF inhibitor or BRAF+MEK inhibitor) therapy

Vemurafenib K-M OS



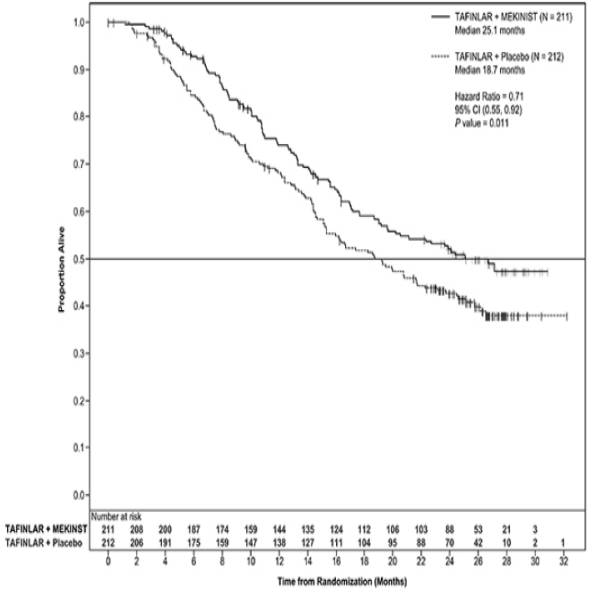
(Vemurafenib USPI)

Dabrafenib K-M PFS



(Dabrafenib USPI)

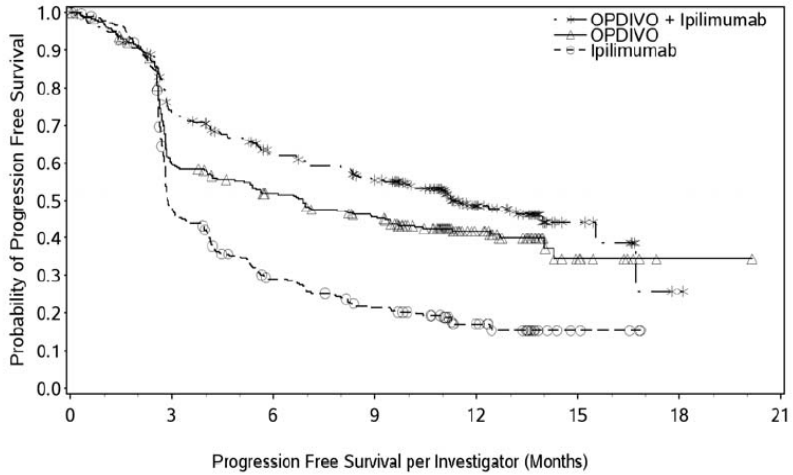
Dabrafenib + Trametinib K-M OS



(Dabrafenib USPI)

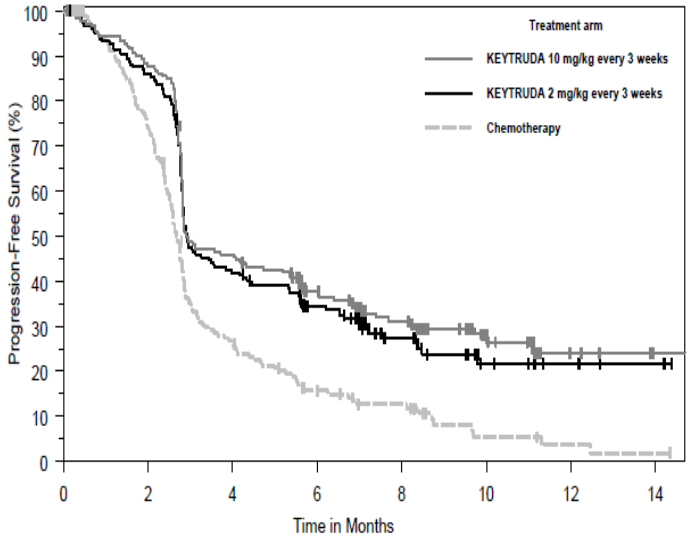
Melanoma

- Nivolumab and pembrolizumab (anti-PD1) K-M curves for PFS



Number of Subjects at Risk								
OPDIVO + Ipilimumab	314	219	173	151	65	11	1	0
OPDIVO	316	177	147	124	50	9	1	0
Ipilimumab	315	137	77	54	24	4	0	0

(Nivolumab USPI)



Number at Risk								
KEYTRUDA 10 mg/kg:	181	158	82	55	39	15	5	1
KEYTRUDA 2 mg/kg:	180	153	74	53	26	9	4	2
Chemotherapy:	179	128	43	22	15	4	2	1

(Pembrolizumab USPI)

Immuno-oncology Drugs Considerations

- Low ORR with prolonged duration of response
- Small differences in median PFS
- Delayed separation of PFS and OS K-M curves
- Median OS may obscure long-term benefits in minority of patients
- Late plateau of survival curves likely represent long-term responders who remain progression free for years

Immuno-oncology Study Design Challenges

- Measures of clinical benefit with innovative endpoints
- Identify surrogate endpoints for OS
- Characterize clinical benefit with alternate analyses
- Improve on the tail of the survival curves
- Expedite approval: enrichment designs, reduced sample size with biomarkers, adaptive trials

Acknowledgements

- Marc Theoret, MD
- Paul Kluetz, MD
- Patricia Keegan, MD
- Amy McKee, MD
- Kirsten Goldberg, MA
- Richard Pazdur, MD

References & Resources

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Challenges in Interpreting Results Based on Traditional Endpoints

Rajeshwari Sridhara, Ph.D.

Director, Division of Biometrics V

FDA-AACR Immuno-oncology Workshop 2016

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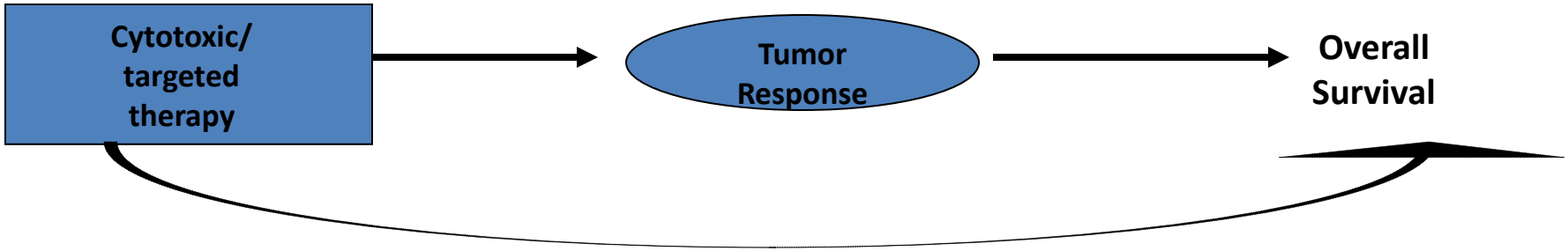
- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Traditional Endpoints

- Objective Response Rate based on RECIST criteria
- Progression-Free Survival – Time from randomization to disease progression (based on RECIST criteria) or death whichever occurs first
- Overall survival – Time from randomization to death
- Patient reported outcome (PRO) – improvement or time to deterioration

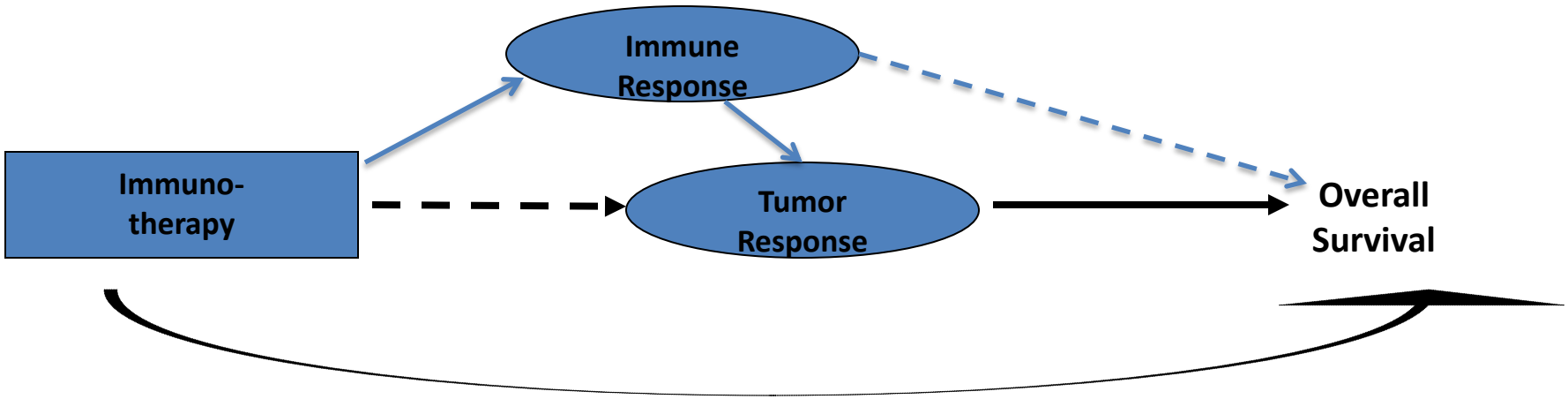
Effect of Therapeutic Interventions



Beneficial or Harmful Effects

Not Measured by Tumor Size Changes

Effect of Immuno-oncology Product



Beneficial or Harmful Effects

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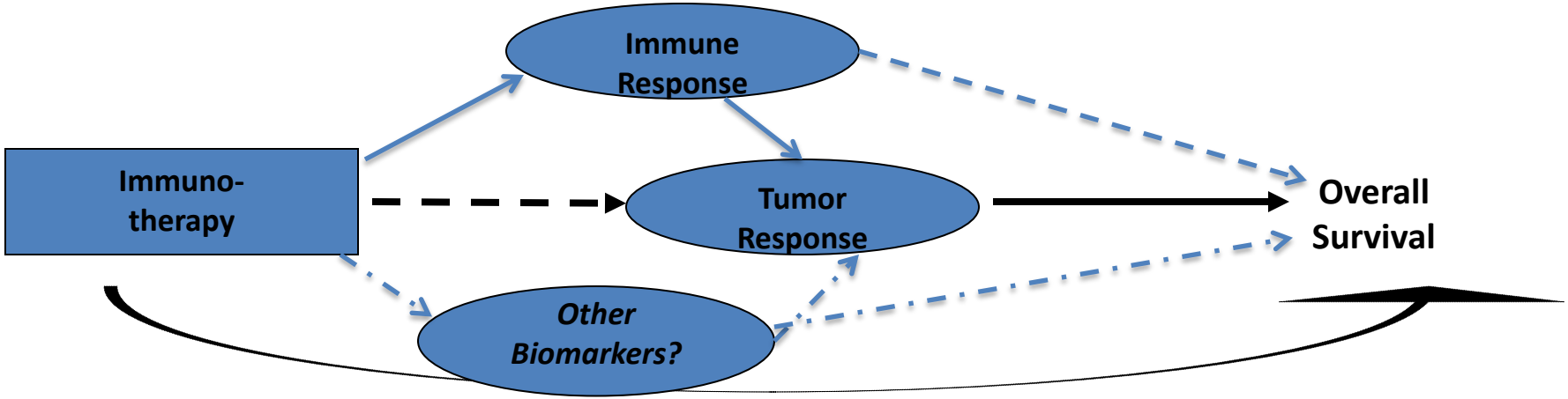
Effect of Immuno-oncology Product



Beneficial or Harmful Effects

Not Measured by Tumor Size Changes

Regulatory Considerations

- "…Evidence consisting of adequate and well-controlled investigations, including clinical investigations, by qualified scientific experts, that proves the drug will have the effect claimed by its labeling…" (Section 505(d) FD&C Act of 1962 as amended)
- Single study – consistency among different endpoints

Trial Design

- Single arm trials (analysis) – patient population generally more refractory; difficult to attribute safety concerns. Long-term safety unknown as survival is generally short; Approval pathway – accelerated generally based on ORR
- Randomized clinical trials – Optimal dose? optimal length of follow-up (based on interim results)?; optimal length of treatment – treat till disease progression? Approval pathway – can be accelerated or regular

Approved Products – Advanced Melanoma

Product	ORR	PFS HR	OS HR
Ipi+gp100 vs. gp100	5.7% vs. 1.5%	0.81	0.68
Pembro	24%	-	-
Pembro vs. Ipi	34% vs. 12% 33% vs. 12%	0.58 0.58	0.62 0.69
Pembro vs. Chemo	21% vs. 4% 25% vs. 4%	0.57 0.50	- -
Nivo	32%		
Nivo+Ipi	60% vs. 11%	0.40	
Nivo+Ipi , Nivo vs. Ipi	50% vs. 14% 40% vs. 14%	0.42 0.57	
Nivo vs. Dacarb	34% vs. 9%	0.43	0.42

Approved Products – Advanced NSCLC

Product	ORR	PFS HR	OS HR
Nivo	15%	-	-
Nivo vs. docetaxel (Sqam)			0.59
Nivo vs. docetaxel (non-squam)	19% vs. 12%	0.92	0.73
Pembro (PDL1>50%)	41%	-	-

Approved Products in Other Diseases

FDA

Renal Cell Carcinoma

- Nivo vs. Everolimus: ORR 21.5% vs. 3.9%; OS HR = 0.73

Classical Hodgkin Lymphoma

- Nivo: ORR 65%

Head and Neck Cancer

- Pembro: ORR 16%

Urothelial Carcinoma

- Atezo: 14.8% ; (PD-L1 < 5% : 9.5%, PD-L1 > 5% : 26%)

Endpoints

- Metastatic melanoma
  - Ipi – OS ↑, ORR ↗ and PFS (non-proportionality)
  - Pembro - OS ↑, ORR ↑ and PFS (non-proportionality)
  - Nivo - OS ↑, ORR ↑ and PFS (non-proportionality)
- Metastatic NSCLC
  - Pembro - ORR possibly ↑
  - Nivo - OS ↑, ORR ↗ and PFS non-proportionality
- Metastatic RCC
  - Nivo - OS ↑, ORR ↑ and PFS non-proportionality
- PRO disease dependent and has not been evaluated rigorously. No long term experience with IM products

Association Between ORR, PFS and OS

Individual level association

- Patient-level responder analysis performed to compare PFS and OS between responders and non-responders, irrespective of treatment assignment using the pooled dataset of anti PD-1 products
  - Hazard ratios of PFS and OS estimated from Cox model stratified by study
  - Kaplan-Meier estimates of PFS and OS by response status

- Spearman rank correlation for PFS vs. OS

Association between ORR, PFS and OS

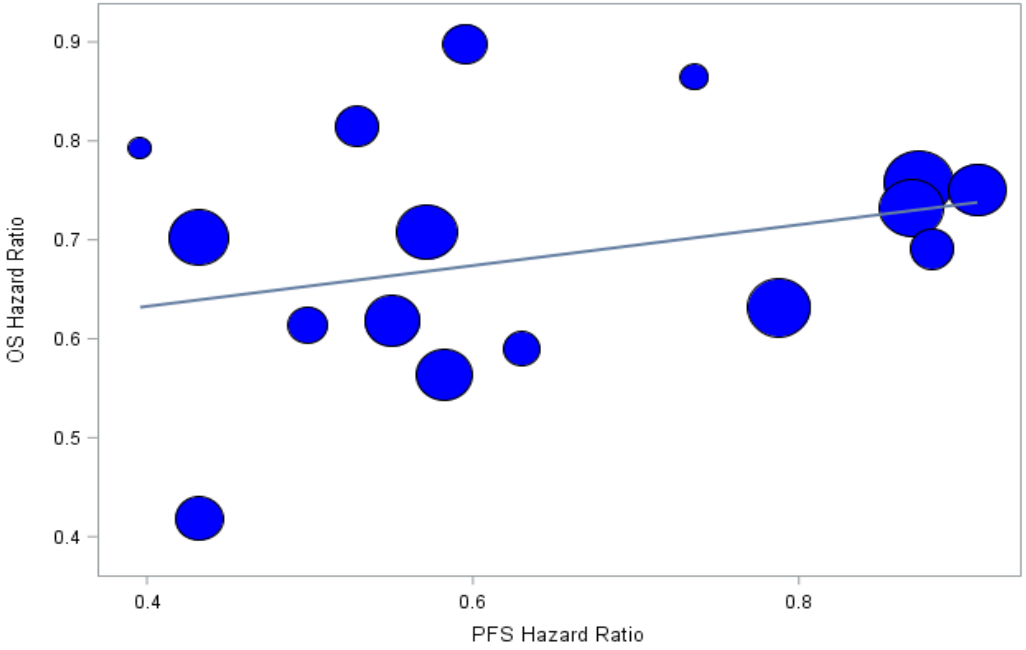
Trial level association

- Treatment effect estimates
  - ORR: odds ratio from logistic regression model
  - PFS: hazard ratio (HR) from Cox regression model
  - OS: HR from Cox regression model
- Weighted linear regression model performed on original and also log-transformed effects
  - weights equal to number of patients
  - R^2_{trial} used to quantify the proportion of variance explained by the regression

Results (Mushti, ASA Biopharm workshop 2016)

	Primary Endpoint	Secondary endpoint	N	OS HR	PFS HR	ORR Odds Ratio
Study-1	PFS (IRC), OS	ORR (IRC)	359	0.898	0.595	5.4190
Study-2	PFS (IRC), OS	ORR (IRC)	360	0.815	0.529	7.2833
Study-3	OS, PFS (IRC)	ORR (IRC)	557	0.618	0.551	3.3367
Study-4	OS, PFS (IRC)	ORR (IRC)	555	0.563	0.582	3.1270
Study-5	OS, PFS (IRC)	ORR (IRC)	687	0.732	0.869	1.6951
Study-6	OS, PFS (IRC)	ORR (IRC)	689	0.631	0.788	1.6940
Study-7	PFS (IRC)	OS, ORR (IRC)	305	0.614	0.499	2.0320
Study-8	OS	ORR, PFS (INV)	272	0.590	0.630	2.6042
Study-9	OS	ORR, PFS (INV)	821	0.758	0.873	5.9323
Study-10	ORR (IRC), OS	PFS (IRC)	182	0.864	0.736	4.9762
Study-11	OS	ORR, PFS(INV)	582	0.750	0.909	1.6742
Study-12	OS	ORR INV, PFS (INV)	418	0.418	0.432	4.1149
Study-13	PFS(INV), OS	ORR (INV)	631	0.708	0.572	3.2949
Study-14	PFS(INV), OS	ORR (INV)	629	0.702	0.432	5.7838
Study-15	ORR (INV)	PFS (INV)	142	0.792	0.396	13.5655
Study-16	OS	PFS (INV), ORR (INV)	361	0.691	0.882	2.5055

Trial-level association results: PFS vs. OS



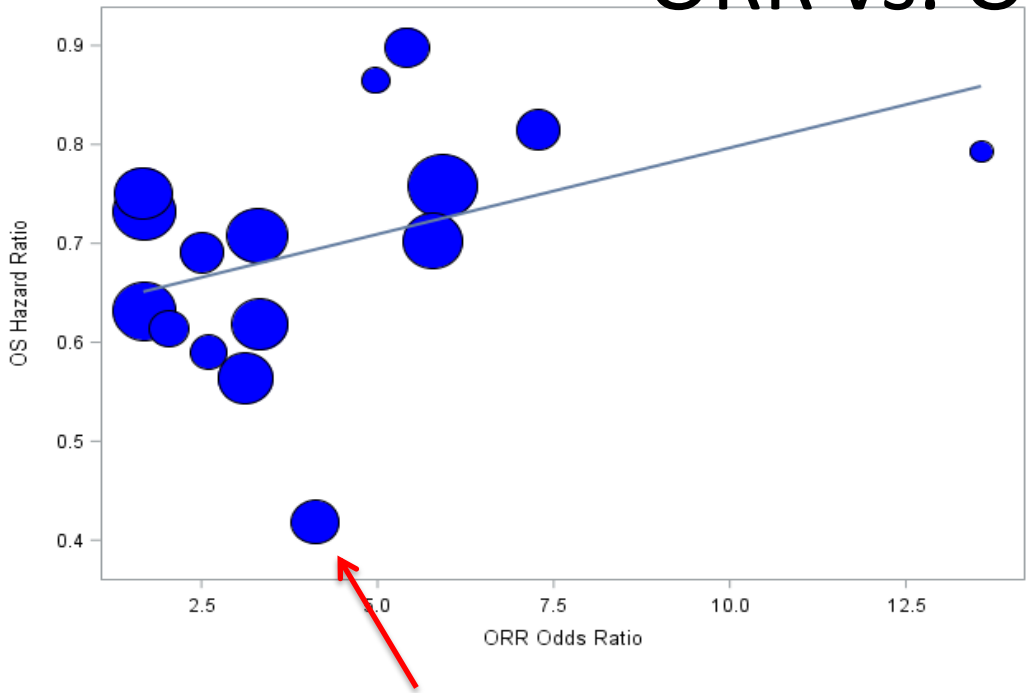
# Trials	12
# Patients	6435

$$R^2_{trial} = 0.1141$$

$$R^2_{trial}(\log - \text{transformed}) = 0.1395$$

Mushti, ASA Biopharm workshop 2016

Trial-level association results: ORR vs. OS



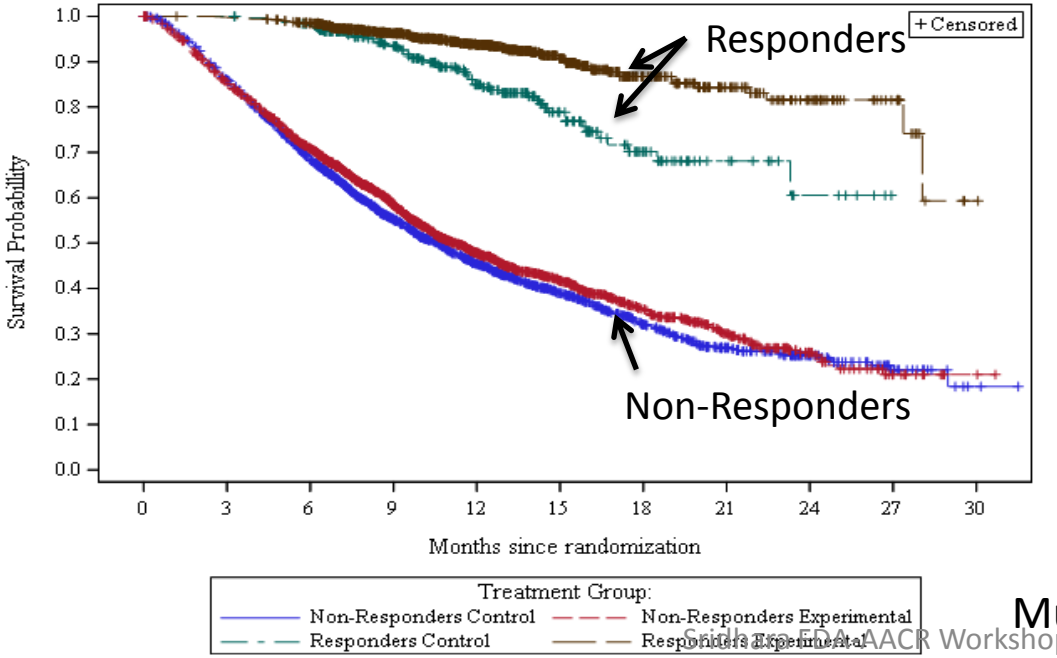
$$R^2_{trial} = 0.131$$

$$R^2_{trial}\,(\text{excluding outlier}) = 0.2357$$

Mushti, ASA Biopharm workshop 2016

Patient-level Responder analysis results for OS

- Responders were associated with better OS compared with non-responders (HR= 0.129, 95% CI: 0.11, 0.15)

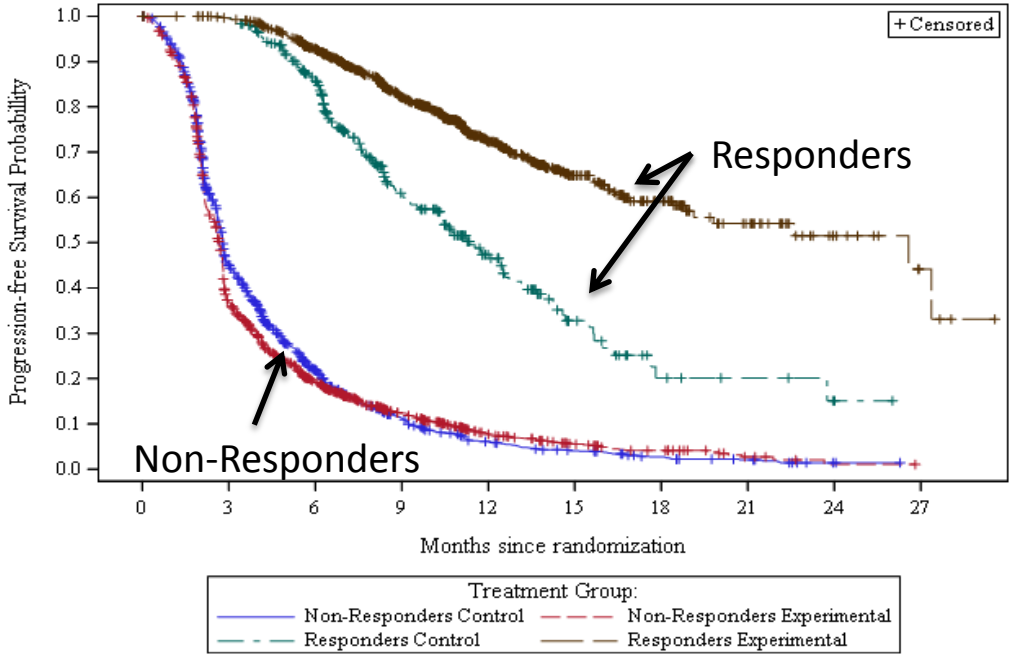


Response rates:	
Treatment group	32%
Control	12.7%

Mushti, ASA Biopharm workshop 2016

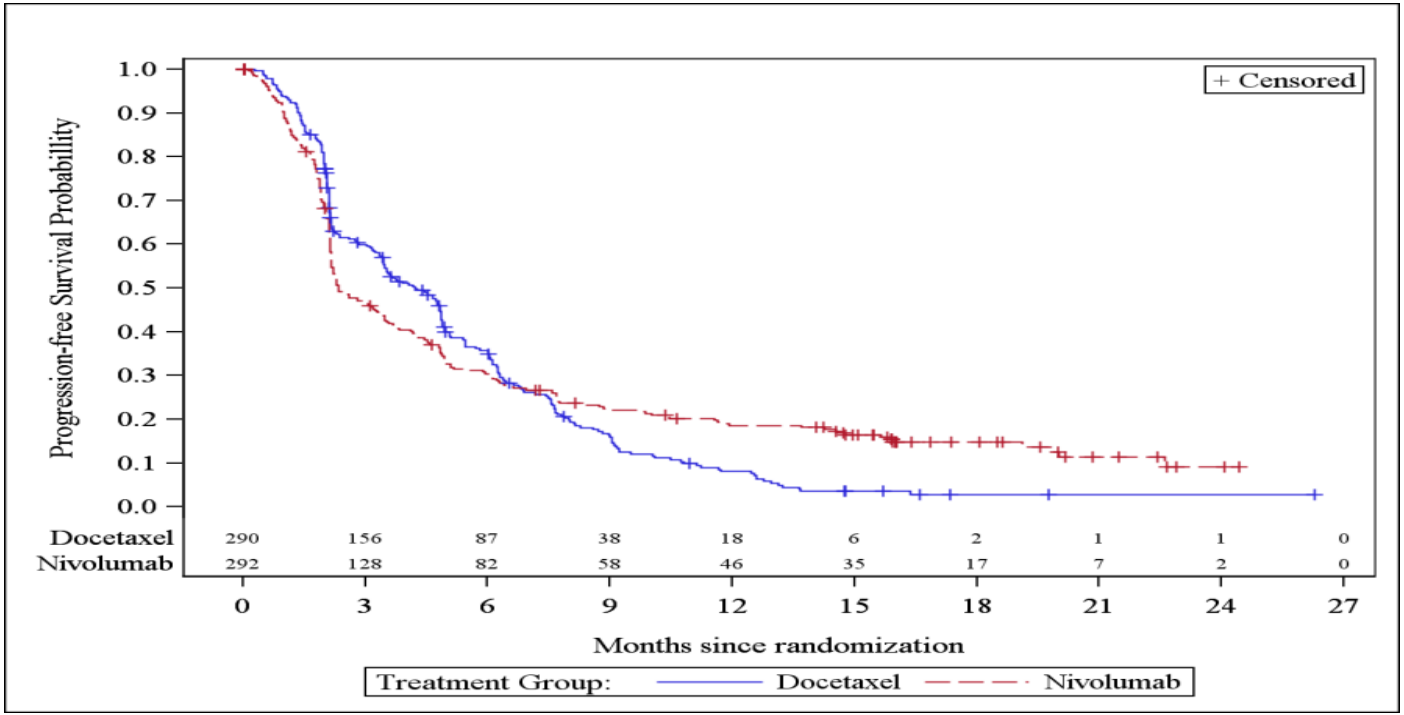
Patient-level Responder analysis results for PFS

- Responders were associated with better PFS compared with non-responders (HR= 0.118, 95% CI: 0.11, 0.13)

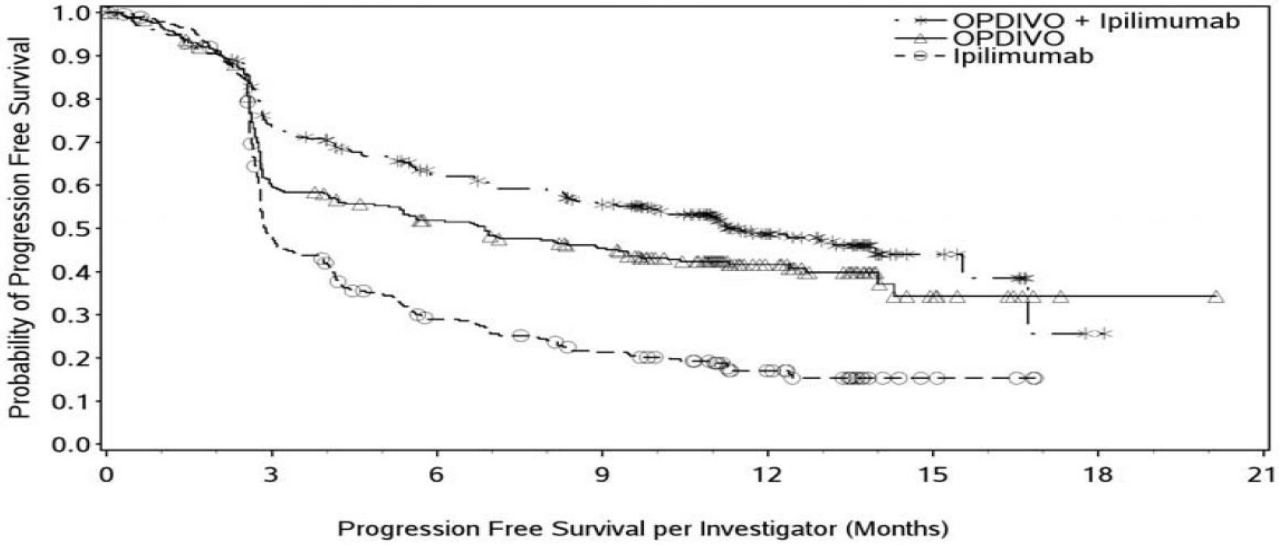


Response rates:	
Treatment group	32%
Control	12.7%

Nivolumab 2nd line non squamous mNSCLC: PFS analysis – *Pseudo Progression?*



Examples of Non-proportionality: Nivolumab, CA209067 Trial - PFS



Number of Subjects at Risk

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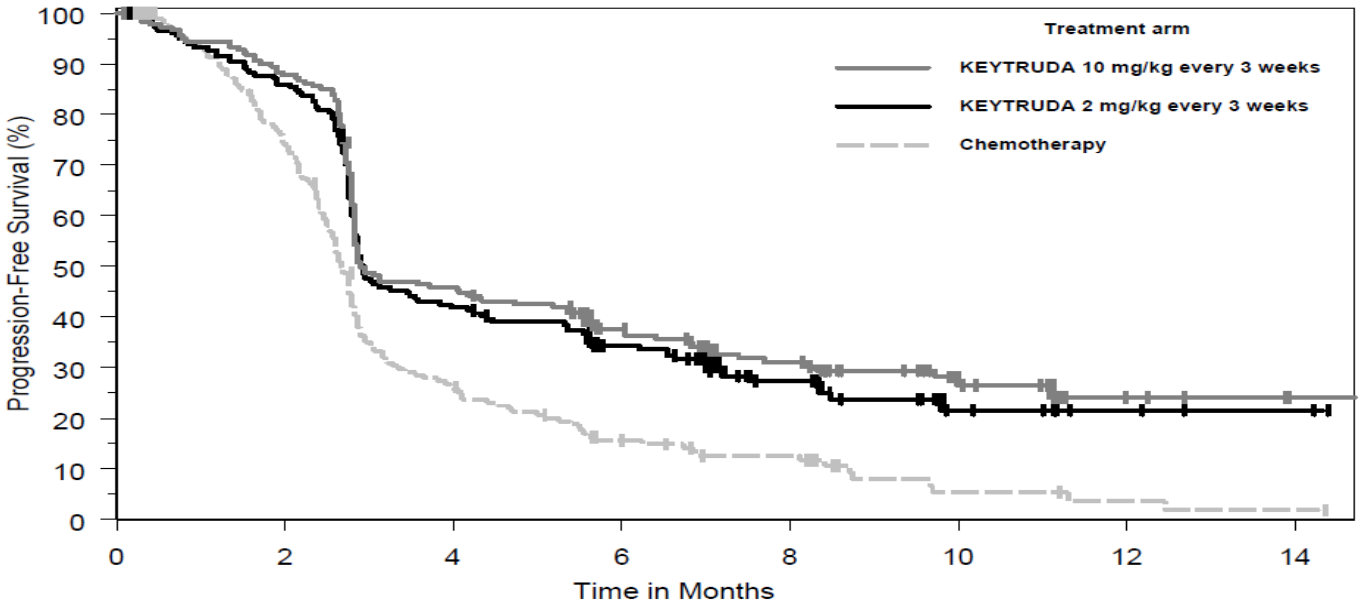
OPDIVO	316	177	147	124	50	9	1	0
Ipilimumab	315	137	77	54	24	4	0	0

Examples of Non-proportionality: Pembrolizumab, P002 Trial – PFS



Number at Risk

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Chemotherapy:	179	128	43	22	15	4	2	1

Biomarker

- PD-L1 expression > 50% restricted indication - Pembro for NSCLC with companion diagnostic
- PD-L1 expression 1%, 5% , 10%? Nivo for non-squamous NSCLC– indication not restricted, complementary diagnostic
- PD-L1 expression >1%? Nivo for metastatic melanoma – indication not restricted, complementary diagnostic
- No standard assay or threshold
- Other biomarkers?
- Unanswered: *Is there a subgroup of patients who contribute to the plateau at the end of the survival curve*

Challenges

- Going forward: what should be the primary endpoint?
  - OS clear winner. But may not be feasible – example in first-line treatment.
  - PFS – is the RECIST progression criteria accurate for IO products; in most cases proportional hazard assumption does not hold – alternate analysis methods needed to accurately summarize the late separation of curves
  - ORR inconsistent
  - What other intermediate endpoints can be used?
- Length of follow-up
  - Toxicities different from chemotherapy
  - Beyond treatment follow-up
- Future trial designs in combination with another IO product or with other targeted and cytotoxic therapies? Endpoint, Toxicity, follow-up, length of treatment?

Summary

- Current knowledge is limited
- Need for exploration of intermediate endpoints other than ORR and PFS
- Need for standardization in biomarker measurement assays
- Identification of potential subgroup with long-term benefit
- Alternative ways in which data can be summarized – address non-proportionality
- Critical consideration on duration of treatment and length of follow-up necessary
- Innovative trial designs including master protocols, enrichment and adaptive designs could be considered, if network infrastructure and resources are available to implement such designs

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Session IIIa

Endpoints for I-O Products: Considerations for Unique Efficacy Based on Unique Biology of Checkpoint Inhibitors

Moderator: Renzo Canetta, MD

Speakers:

Lawrence Schwartz, MD

Sumithra Mandrekar, PhD

Axel Hoos, PhD

Nicholas Latimer, PhD

FDA-AACR Immuno-Oncology Drug development Workshop

Traditional Endpoints
Introduction: An Historical Perspective

Renzo Canetta, MD

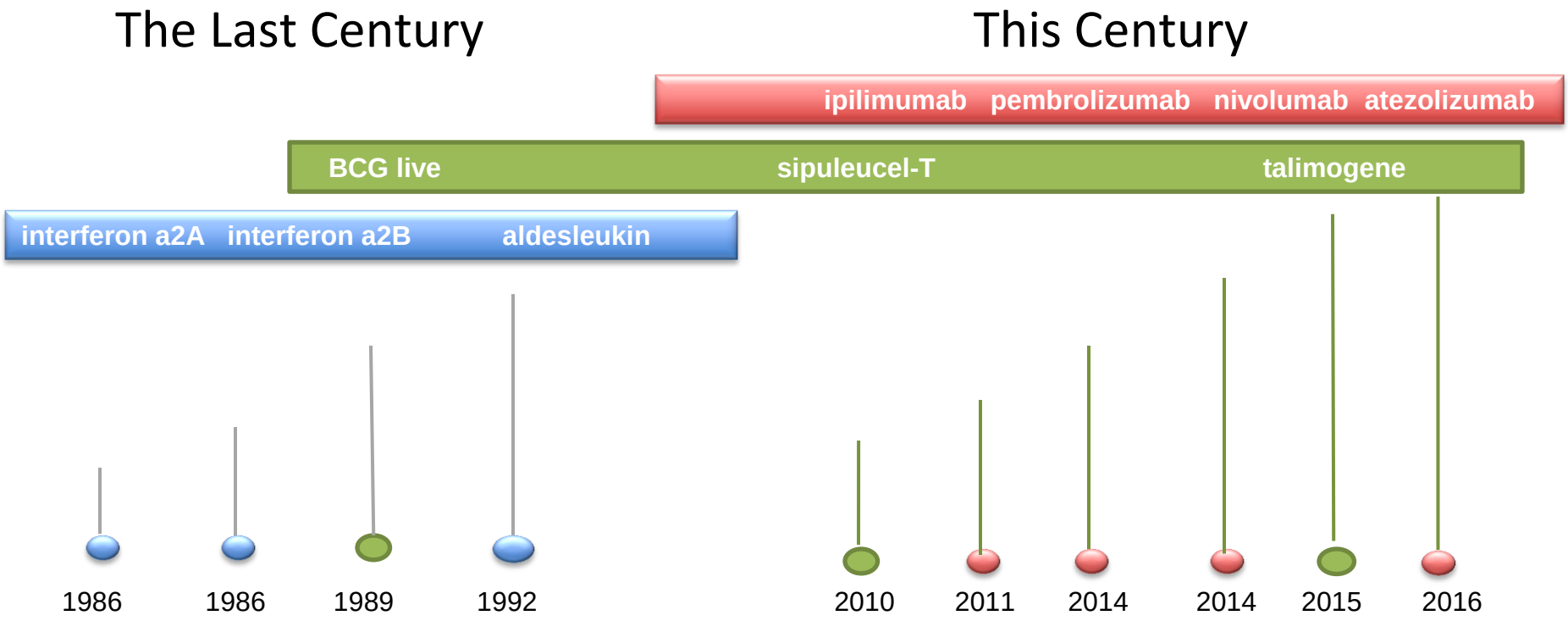
Washington, DC, October 13-14, 2016

Conflict of Interest

- I have been employed for a long time by Bristol-Myers Squibb (BMY)

- As such, I hold stocks in BMY and in two of its spin-off companies:
  - Mead Johnson Nutritionals (MJN)
  - Zimmer Biomet Holdings (ZBH)

US Approved Immunologic and Immuno-Oncologic Agents



Durable Objective Response Rate Approvals

YEAR	COMPOUND	INDICATION	CR+PR %	DURATION (median)
1986	interferon a2A	hairy cell leukemia	61	NA
1988	interferon a2A	HIV+ Kaposi's sarcoma	7-45	NA
	interferon a2B	HIV+ Kaposi's sarcoma	30	NA
	BCG live	bladder (in situ)	76	48 mos.
1992	aldesleukin	renal cell	15	54 mos.
1998	"	melanoma	16	9 mos. #
2014	pembrolizumab	melanoma (2L) **	24	median n.r.
	nivolumab	melanoma (2L) **	32	87% > 6 mos.
2015	pembrolizumab	lung nsc PD-L1+ *	41	84% > 6 mos.
	ipi+nivo combo	melanoma (1L) *	60	79% > 6 mos.
	talimogene	local melanoma	16	100% > 6 mos.
2016	pembrolizumab	head & neck *	16	82% > 6 mos.
	nivolumab	Hodgkin's disease *	65	8.7 mos.
	atezolizumab	bladder *	15	12.7 mos.

* Accelerated approval ** Accelerated approval converted to full approval later # 59+ months for CRs

Progression-Free (PFS) and Disease-Free (DFS) Survival Approvals

YEAR	COMPOUND	INDICATION	RESULTS (median,months)	HR
1986	interferon a2B	hairy cell leukemia	DFS = n.r. vs 6.8	NA
1989	BCG live	bladder (Ta/T1)	2-yr DFS = 57% vs 45%	NA
1995	interferon a2B	adj.melanoma	DFS = 20.5 vs 11.8	NA
1997	interferon a2B	follicular NHL	PFS = 34.8 vs 18	NA
2015	ipilimumab	adj.melanoma	DFS = 26 vs 17	0.75
	pembrolizumab	melanoma (2L)	PFS = 2.9 vs 2.7	0.57/0.50
	nivolumab	melanoma BRAF+ (1L)*	PFS = 6.9 vs 2.9	0.57
	ipi+nivo combo	melanoma (1L)*	PFS = 11.5 vs 2.9	0.42

* Accelerated approval

Overall Survival (OS) Approvals

YEAR	COMPOUND	INDICATION	RESULTS (median,months)	HR
1995	interferon a2A	CML (Phila+)	69 vs 55	NA
2010	sipuleucel-T	prostate	25.8 vs 21.7	0.775
2011	ipilimumab	melanoma	10 vs 6	0.66
2015	pembrolizumab	melanoma (1L)	n.r. vs n.r.	0.69-0.63
	nivolumab	melanoma BRAF- (1L)	n.r. vs 10.8	0.42
	“	lung squamous	9.2 vs 6.0	0.59
	“	lung non-squamous	12.2 vs 9.4	0.73
	“	renal cell	25.0 vs 19.6	0.73

Traditional Endpoints Concordance (or not) for Compounds Approved on OS

COMPOUND	INDICATION	PFS (median,months)	CR+PR (%)
interferon a2A	CML (Phila+)	69 vs 46 (HR NA)	60 vs 70
sipuleucel-T	prostate	NA (HR 0.95)	NA
ipilimumab	melanoma	2.86 vs 2.76 (HR 0.64)*	10.9 vs 1.5
pembrolizumab	melanoma (1L)	4.1/5.5 vs 2.8 (HR 0.58)	33/34 vs 12
nivolumab	melanoma BRAF- (1L)	5.1 vs 2.2 (HR 0.43)	34 vs 9
"	lung squamous	NA	NA
"	lung non-squamous	2.3 vs 3.9 (HR 0.92)	56 vs 36
"	renal cell	NA	21.5 vs 3.9

* In FDA BLA clinical review, not in label

Questions

- Are there unique challenges in objective response rates (ORR) and duration assessment?
- Are there unique challenges in time-to-event analyses such as disease-free survival (DFS) and progression-free survival (PFS)?
- Is overall survival (OS) still an attainable endpoint?
- Any special considerations for combinations?

Tumor measurement based endpoints: Lessons learned from the RECIST database experience

Sumithra J. Mandrekar
Mayo Clinic

FDA-AACR Public Workshop
Immuno-Oncology Drug Development
October 13-14, 2016

Collaborators

- Vassar College
  - Ming-Wen An (Co-PI)
- Mayo Clinic
  - **Dan Sargent**
  - Axel Grothey
  - Jeff Meyers
- EORTC
  - Jan Bogaerts
- Summer students

  Xinxin Dong, and Yu Han

Challenges and Successes

Response rate and RECIST based time-to-event endpoints

Successes

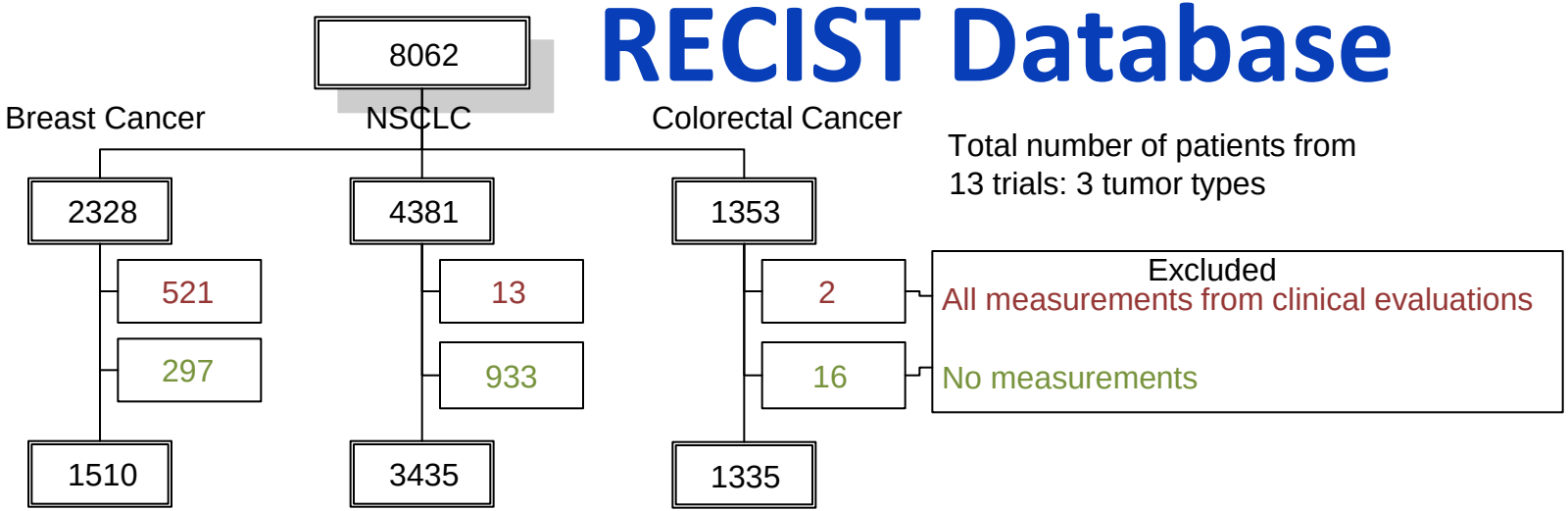
- Response is relatively simple to determine and understand for clinical trial decision making

- Response Rate is similarly simple for patients to understand

Challenges

- Data Quality
  - Missing measurements
  - Inconsistently measured lesions
  - Conflicting measurements for same lesion at same time point
  - Measurements based on clinical examination only
- Response Rate
  - Does not capture cytostatic activity
  - Categorizes otherwise inherently continuous measurements leading to a potential loss of information
- Continuous metrics
  - Handling progression due to new lesions

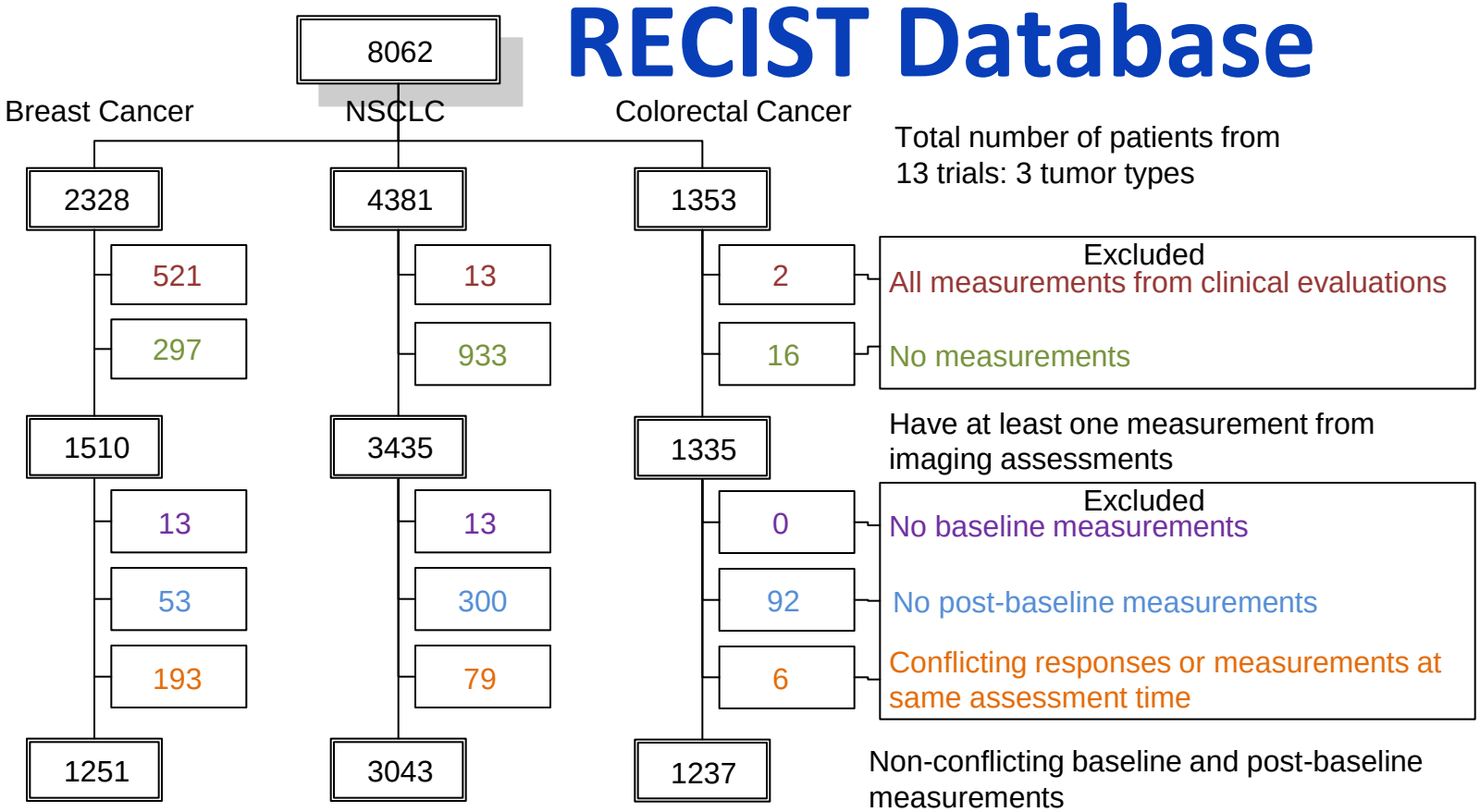
RECIST Database



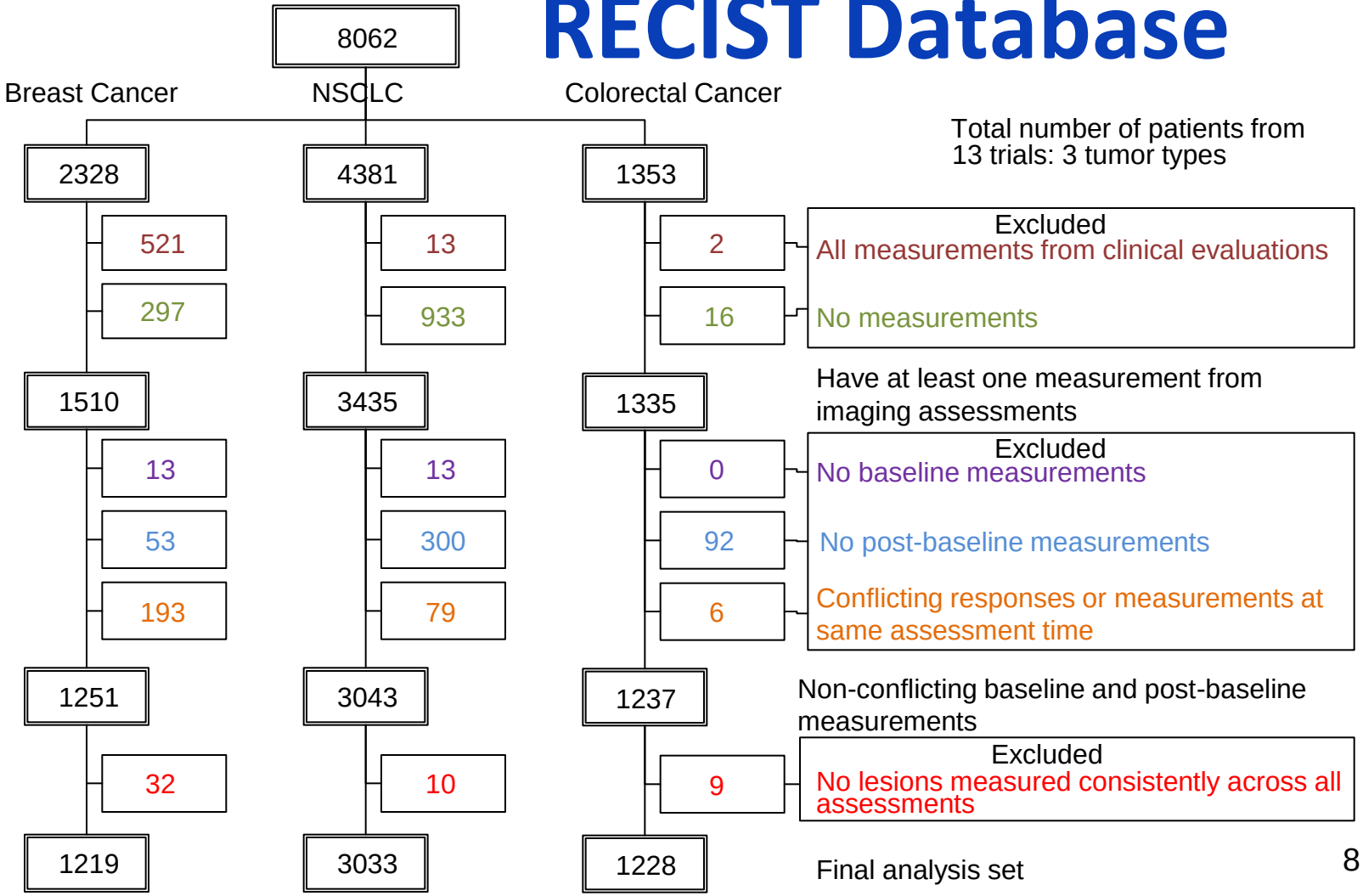
Total number of patients from 13 trials: 3 tumor types

An et al. (JNCI 2015)
Mandrekar et al. (JCO 2014)

RECIST Database



RECIST Database



Timing of Assessments

Timing of Assessments

- More frequent measurements
  - (+) more real-time monitoring about tumor activity
  - (-) Not according to clinical care and thus subject to missing measurements

Protocol Assessment Schedule by 24weeks

Study	Disease	Protocol assessment week										
Study 1	Breast	0		6			12			18		
Study 2	Breast	0		6			12			18		
Study 3	Breast	0		6			12			18		24
Study 4	Breast	0		6			12				21	
Study 5	Breast	0				9				18		24
Study 6	Breast	0	3	6		9	12		15	18	21	24
Study 7	Breast	0				9			15		21	
Study 8	Colon	0		6			12			18		24
Study 9	Colon	0			7			14			21	
Study 10	NSCLC	0		6			12			18		
Study 11	NSCLC	0		6			12			18		
Study 12	NSCLC	0	3	6			12			18		
Study 13	NSCLC	0	3	6			12			18		

Assessment Window

- Based on expected assessment times

- Sliding expected window:
  - If observed assessment time was within the +/- 2 week window, next expected was recalculated based on observed
  - Example: If current expected was 4 weeks and next expected was at 8 weeks, but current observed was at 6 weeks, then the next *adjusted expected* would be at 10 weeks instead of 8.

Assessment Window

Reasons for not being within the window (Not Perfect):

- Going off treatment early for reasons other than progression or death
- Missing an assessment followed by progression or off-treatment (without assessment)

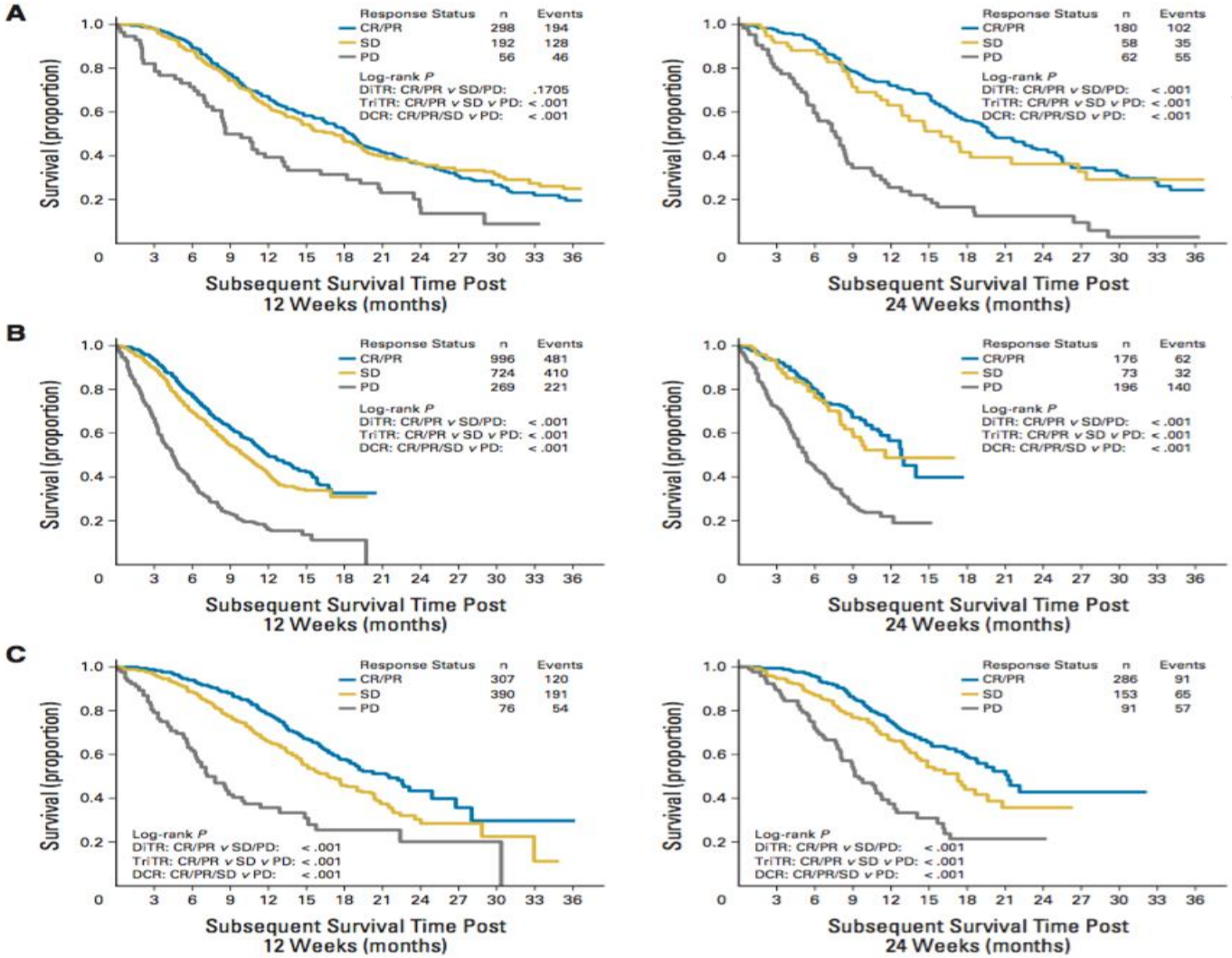
RESULTS

Alternative cutpoints and continuous metrics no better than RECIST response

Categorical Metrics

- Dichotomous Tumor Response (DiTR)
  - PD/SD vs. PR/CR (response vs. others)
- Disease Control Rate (DCR)
  - PD vs. SD/PR/CR (progression vs. others)
- Trichotomous Tumor Response (TriTR)
  - PD vs. SD vs. PR/CR

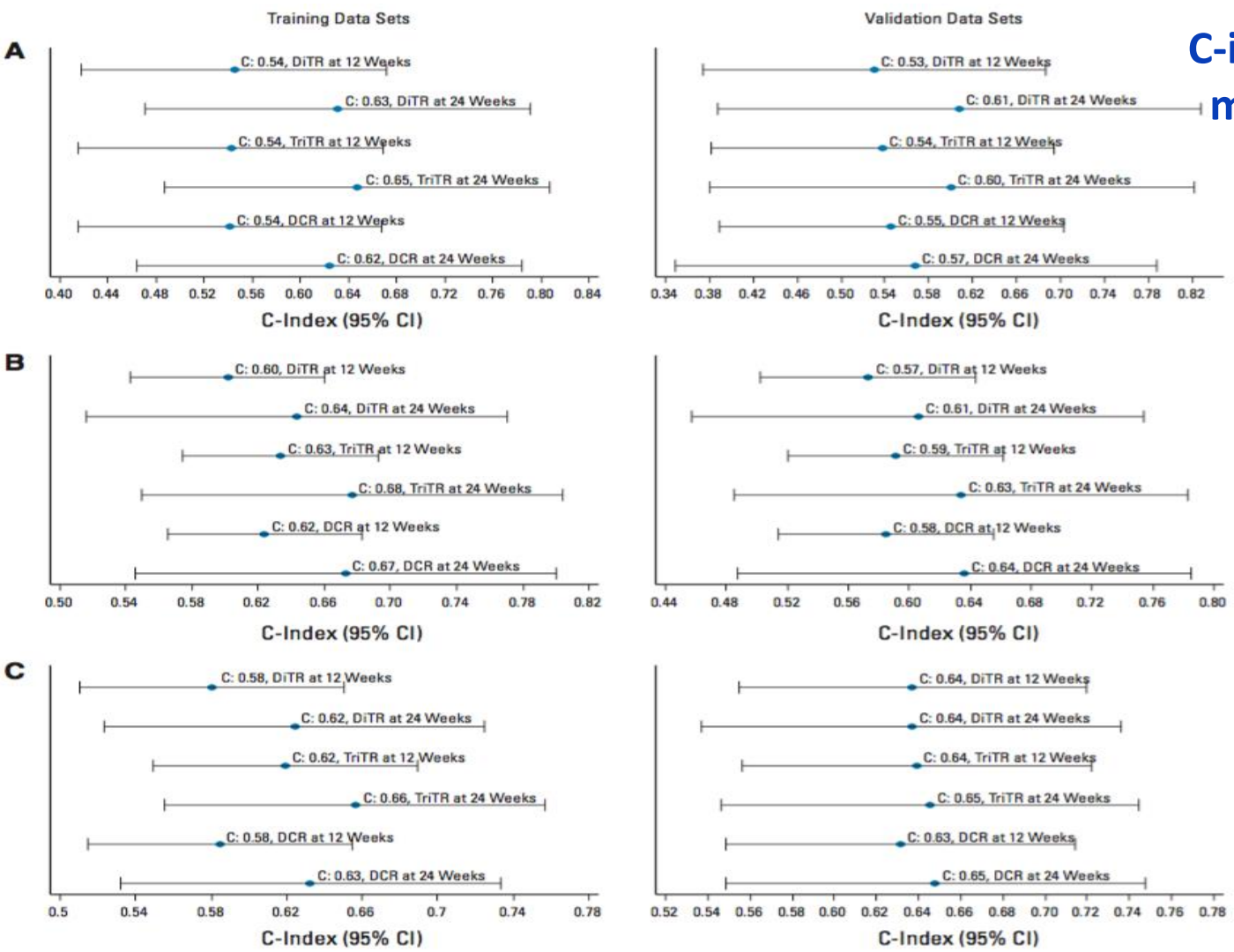
KM Curves for OS across metrics at 12 and 24 weeks landmark time points



A: Breast
B: NSCLC
C: Colorectal

Mandrekar et al. (JCO 2014)

C-indices across datasets, metrics, and time points



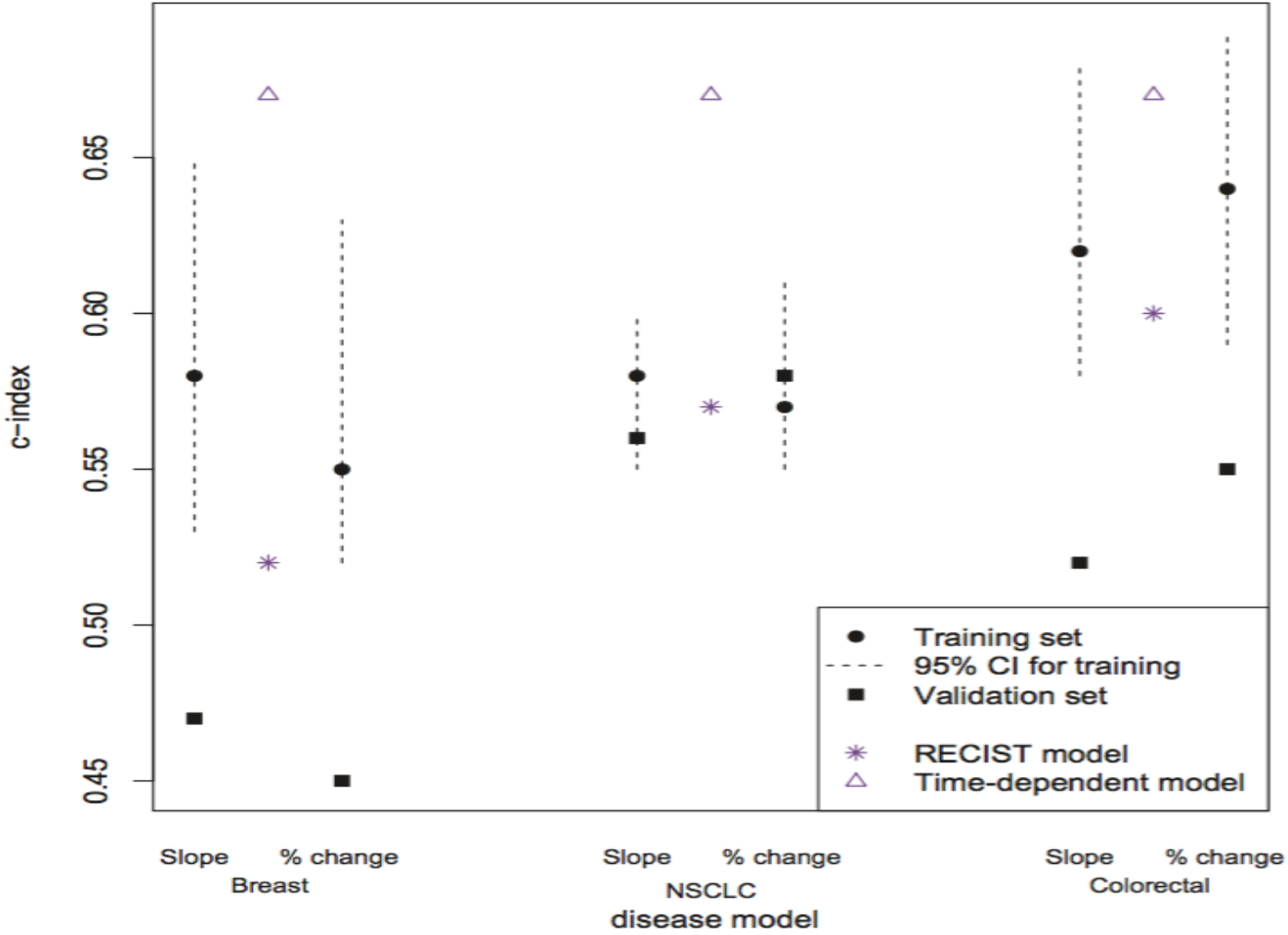
A: Breast
B: NSCLC
C: Colorectal

Mandrekar et al. (JCO 2014)

Continuous Metrics

- Absolute change in tumor size
  - Between 0 and 6 weeks, and
  - Between 6 and 12 weeks
- Percent change in tumor size
  - Between 0 and 6 weeks, and
  - Between 6 and 12 weeks

C-indices across continuous metrics, datasets



An et al. (JNCI 2015)

Summary

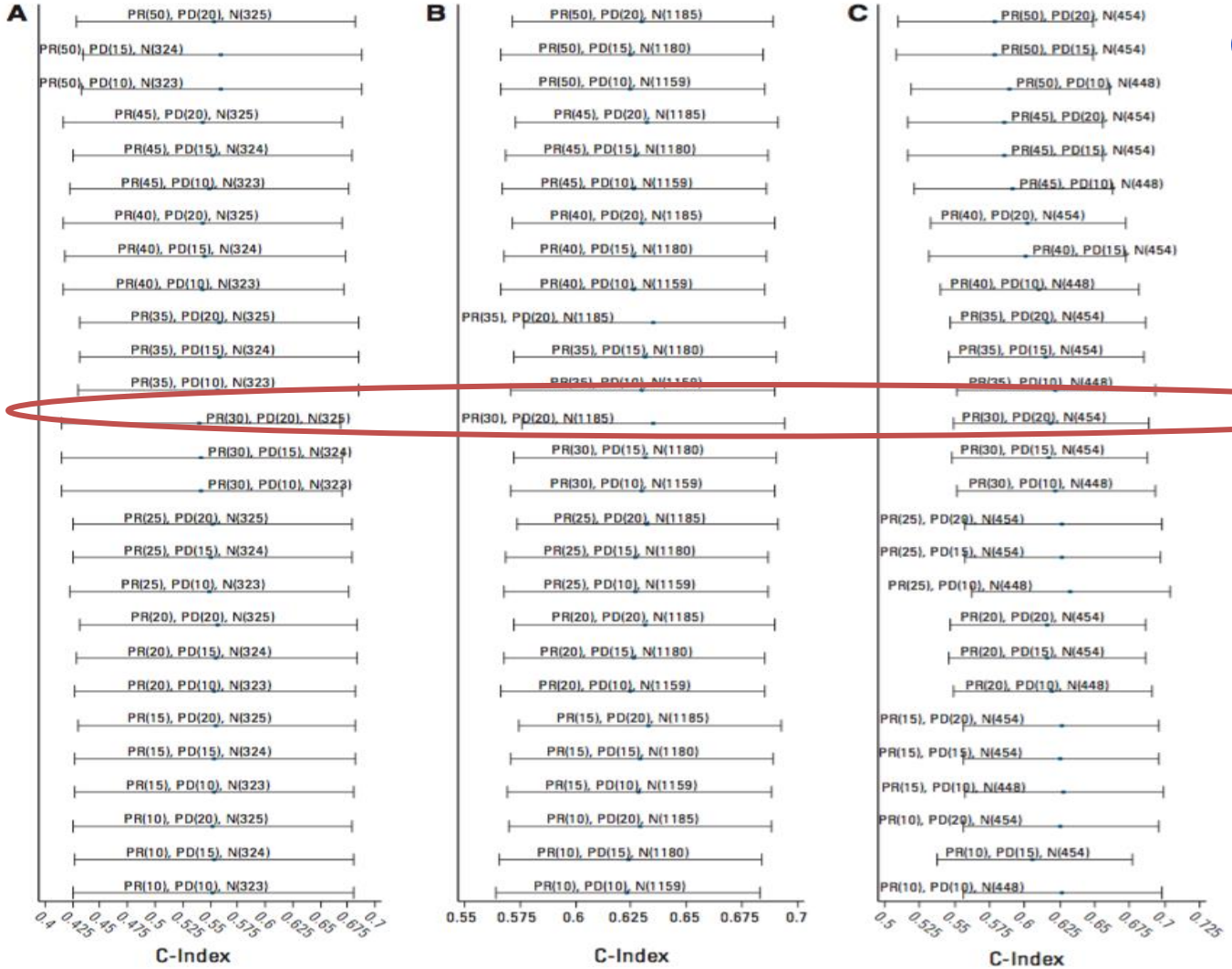
- *Metrics (TriTR, DiTR, DCR), continuous metrics*
  - Similar predictive performance (c-index)
  - Similar calibration (prediction-errors)
  - Similar PPV/NPV (positive/negative phase II yielding a positive/negative phase III)
  - Absolute and relative change in TM based metrics are no better than RECIST based TR as phase II endpoints
- *Time points (12- or 24-weeks)*
  - Overlapping CIs, comparable performance
- *Disease*
  - Breast performed poorly compared to Colon and NSCLC

Pseudo-progression, and treatment beyond progression

Pseudo-progression

- Different cutoffs for PD and PR considered:
  - PD: increase in10%, 15% and 20% from baseline
  - PR: 10% to 50% in 5% increments
    - pair (30%, 20%) corresponds to the RECIST categorization
- No change in predictive ability
- RECIST cutpoints demonstrated similar predictive ability as the alternate cutpoints

Overall Survival with the TriTR metric



RECIST cut points

A: Breast
B: NSCLC
C: Colorectal

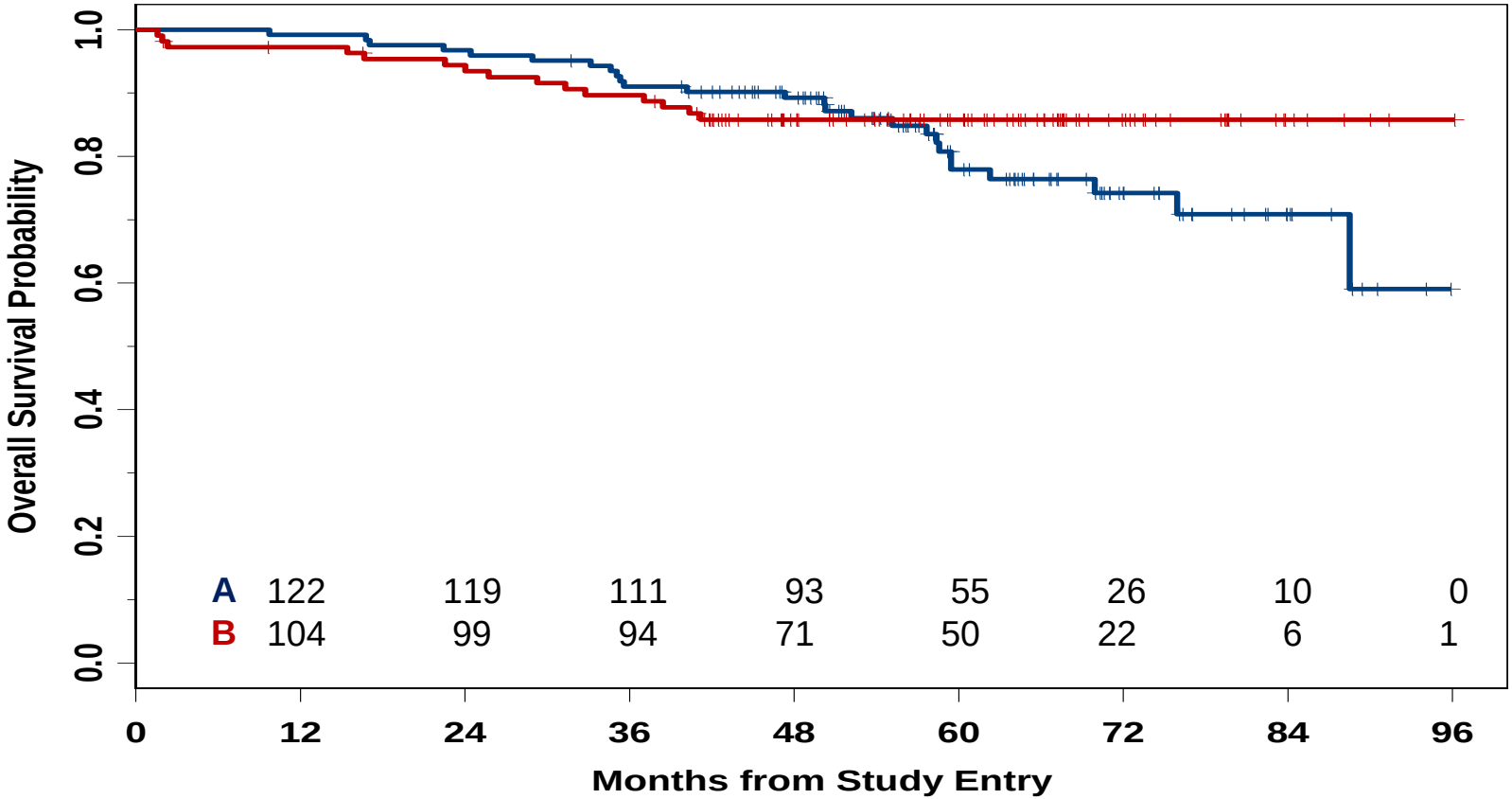
Mandrekar et al. (JCO 2014)

Treatment beyond disease progression

- Data unavailable in RECIST data warehouse

Long Term Survivors

Long term survivors: Illustration



Arm A	N = 123	Events = 26	Median = Not Reached	
Arm B	N = 109	Events = 15	Median = Not Reached	p-value = 0.28

Mixture Cure Model

- Assumes population is a mixture of individuals
  - Those who may experience the event of interest
  - Those who will never experience the event of interest and are cured
  - Each modeled separately
  - Estimate the cure rate of a treatment
    - Uses a logit link function (logistic regression)
  - Estimate the survival rate of uncured patients
    - Uses the proportional hazards model

Mixture Cure Model

- T = failure time of interest
- $1 - \boldsymbol{\pi}(\boldsymbol{z})$ = probability of a patient being cured given vector of covariates $\boldsymbol{z}$
- $S(t|\boldsymbol{x})$ = survival probability of uncured patients given vector of covariates $\boldsymbol{x}$

$$S_{pop}(t\,|\,\boldsymbol{x}, \boldsymbol{z}) = \boldsymbol{\pi}(\boldsymbol{z})S(t|\boldsymbol{x}) + 1 - \boldsymbol{\pi}(\boldsymbol{z})$$

latency incidence

Mixture Cure Model Example

Cure Probability Model				
	Estimate	**Std. Error**	**Z value**	**p-value**
Intercept	-0.28	0.31	-0.91	0.37
Arm, B vs. A	-1.49	0.46	-3.21	0.001

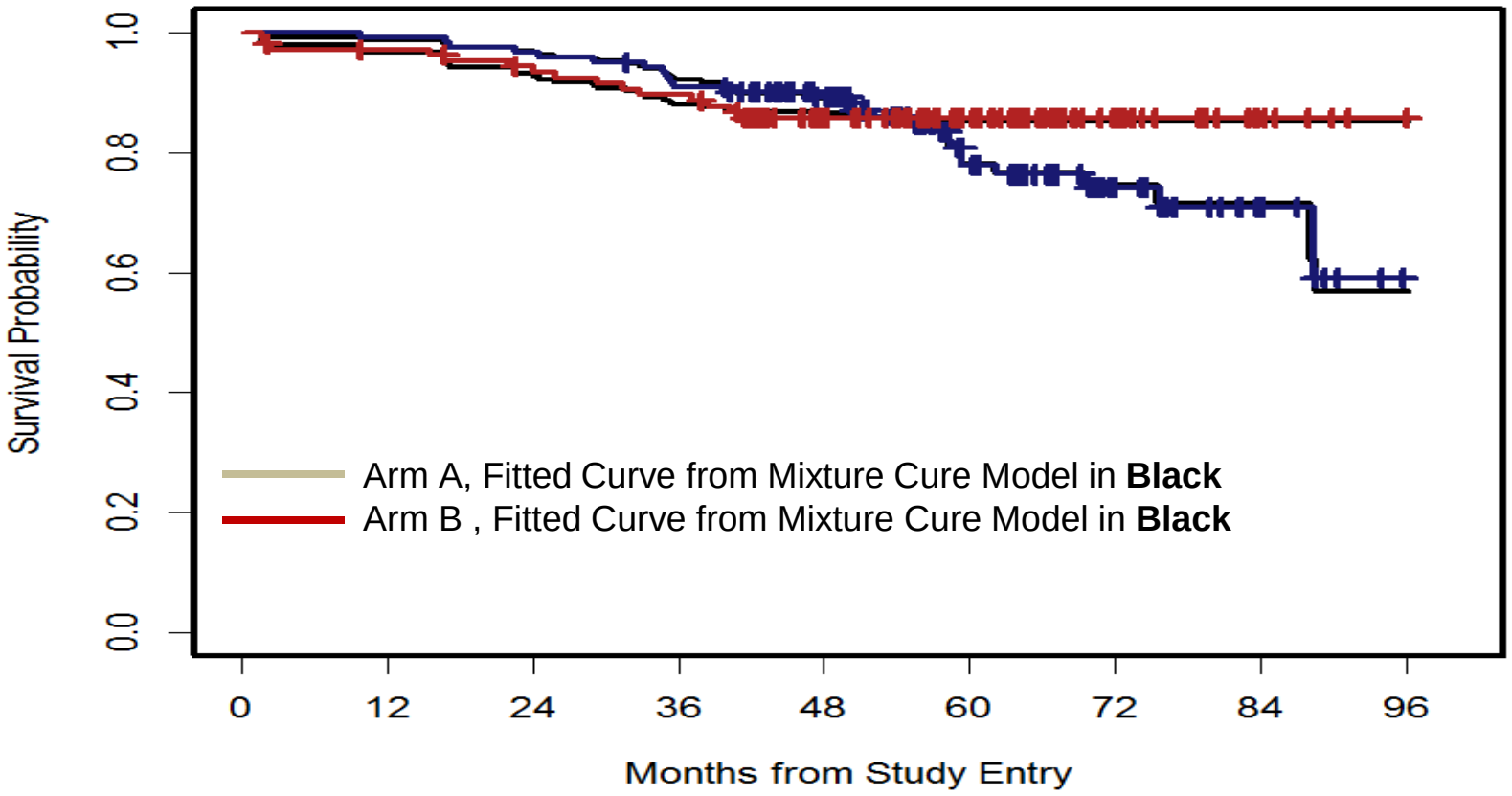
Failure Time Distribution Model				
	Estimate	**Std. Error**	**Z value**	**p-value**
Arm, B vs. A	2.15	0.52	4.16	<0.0001

$$\text{Cure Fraction} = 1 - \boldsymbol{\pi}(\mathbf{z}) = 1\text{-}\ \frac{\exp(\mathbf{bz})}{1+\exp(\mathbf{bz})}$$

$$\text{Arm A} = 1\text{-}\ \frac{\exp(-0.28)}{1+\exp(-0.28)} = 0.57$$

$$\text{Arm B} = 1\text{-}\ \frac{\exp(-0.28-1.49)}{1+\exp(-0.28-1.49)} = 0.85$$

Kaplan-Meier Plot for Overall Survival and Predicted Curves from Mixture Cure Model



Acknowledgements

- RECIST steering committee
- Supported in part by NIH grant, CA167326-01

- Amy S. Ruppert: Cure Model Slides
- Ming-Wen An and Jeffrey Meyers: RECIST slides

Thank you

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Immunotherapy Clinical Endpoints

Challenges & Opportunities

***Axel Hoos**, MD, PhD*
Senior Vice President, Oncology R&D, GSK
Co-Chair, CIC

gsk do more feel better live longer

CIC Cancer Immunotherapy Consortium

Objectives

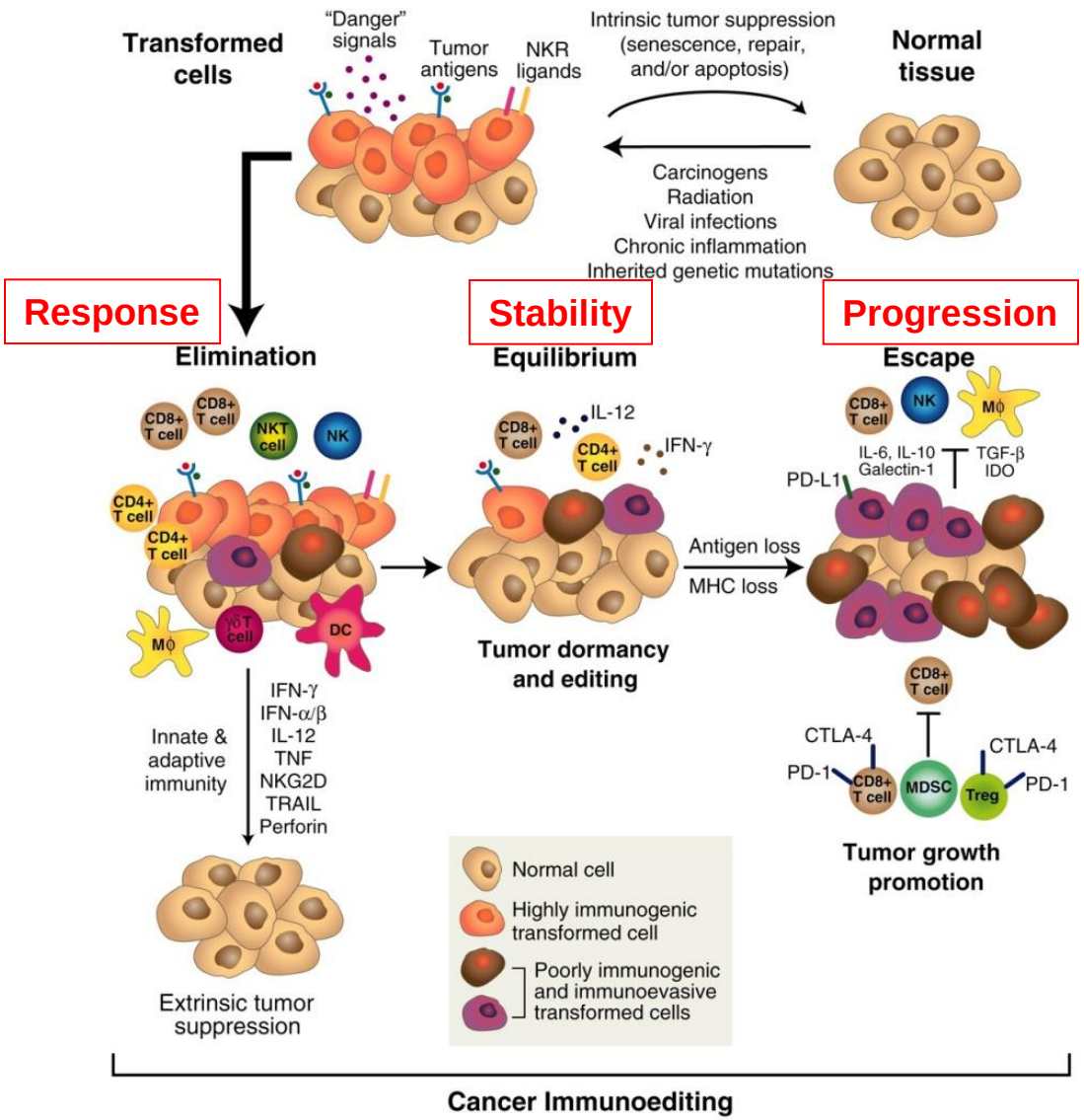
- Hypotheses from clinical observations with IO agents
- Clinical endpoint challenges
- Improving clinical endpoints
- Ultimate goals

Cancer Immunotherapy

- **Mechanism of Action:**
  - **Indirect: Targeting the immune system, not the tumor**
  - **Immune response is dynamic and complex**
- **Consequences:**
  - **No direct anti-tumor effects**
  - **Delayed clinical effects: activation of immune mechanisms before clinical activity**

CIC Cancer Immunotherapy Consortium

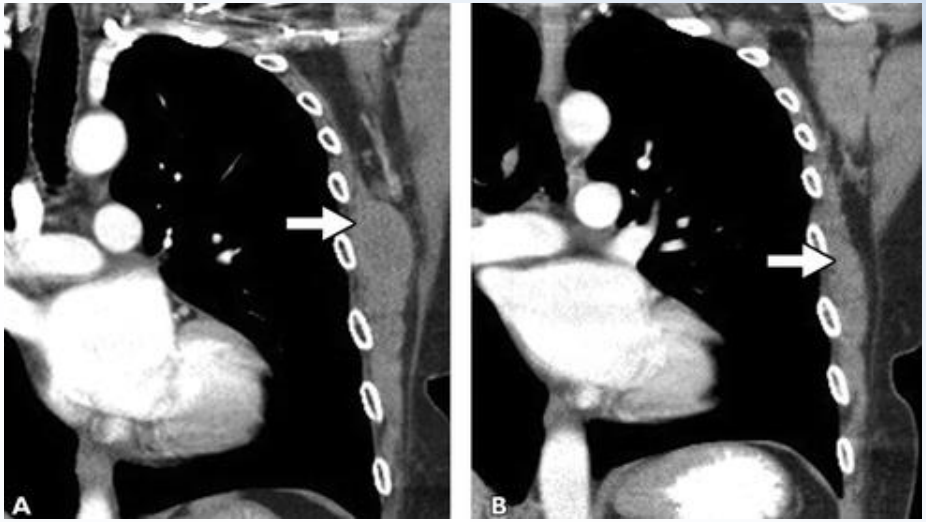
Interactions between Immune System and Tumor



Schreiber R., *Science* 2011

Clinical Observations from Ipilimumab: Driving Hypotheses

Anti-CTLA-4 (Ipilimumab): Conventional Response



O'Regan, KN, et al. AJR 2011

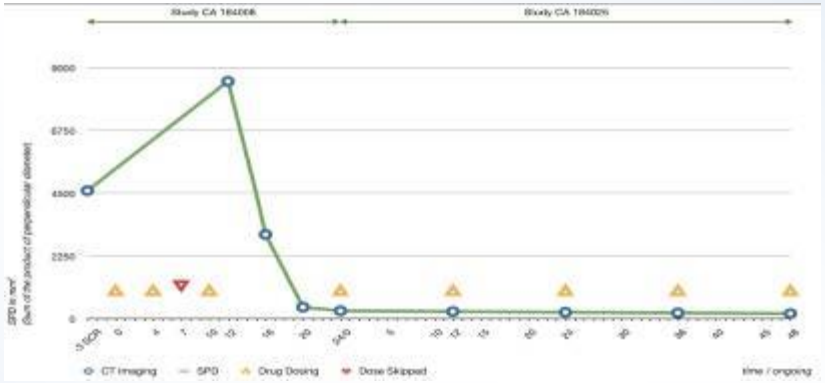
Anti-CTLA-4 (Ipilimumab): Delayed Response

Screening

Week 12
Increase in tumor burden
(mWHO PD)

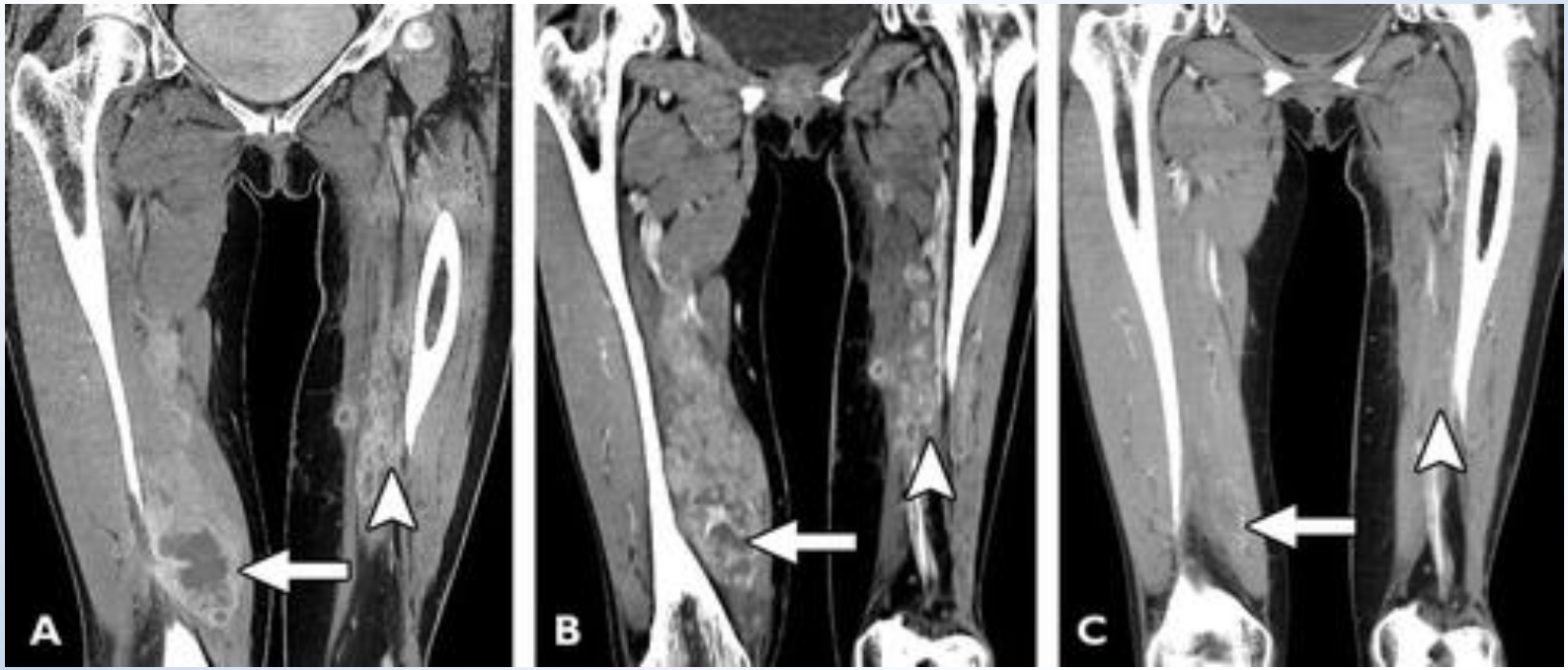
Week 16
Responding

Week 72
Durable & ongoing response
without signs of IRAEs



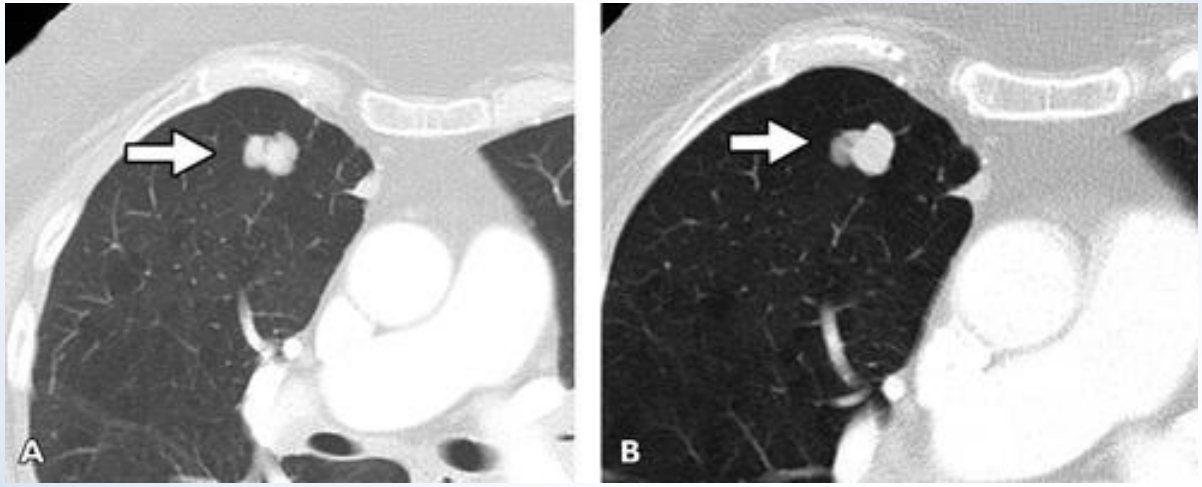
Hoos et al., J Natl Cancer Inst, 2010

Anti-CTLA-4 (Ipilimumab): Delayed Response



O'Regan, KN, et al. AJR 2011

Anti-CTLA-4 (Ipilimumab): Stable Disease

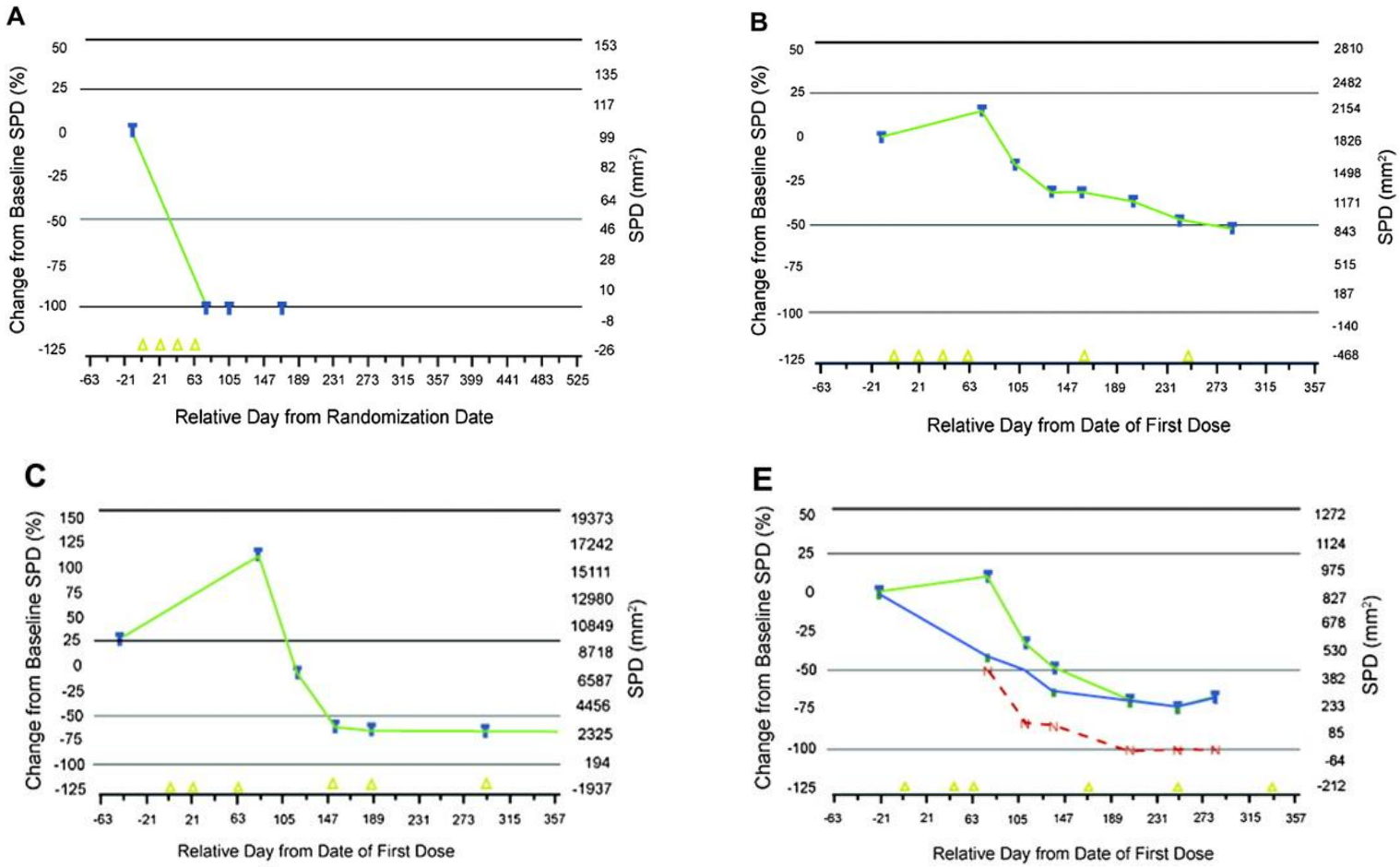


O'Regan, KN, et al. AJR 2011

Anti-CTLA-4 (Ipilimumab): Response with New Lesion

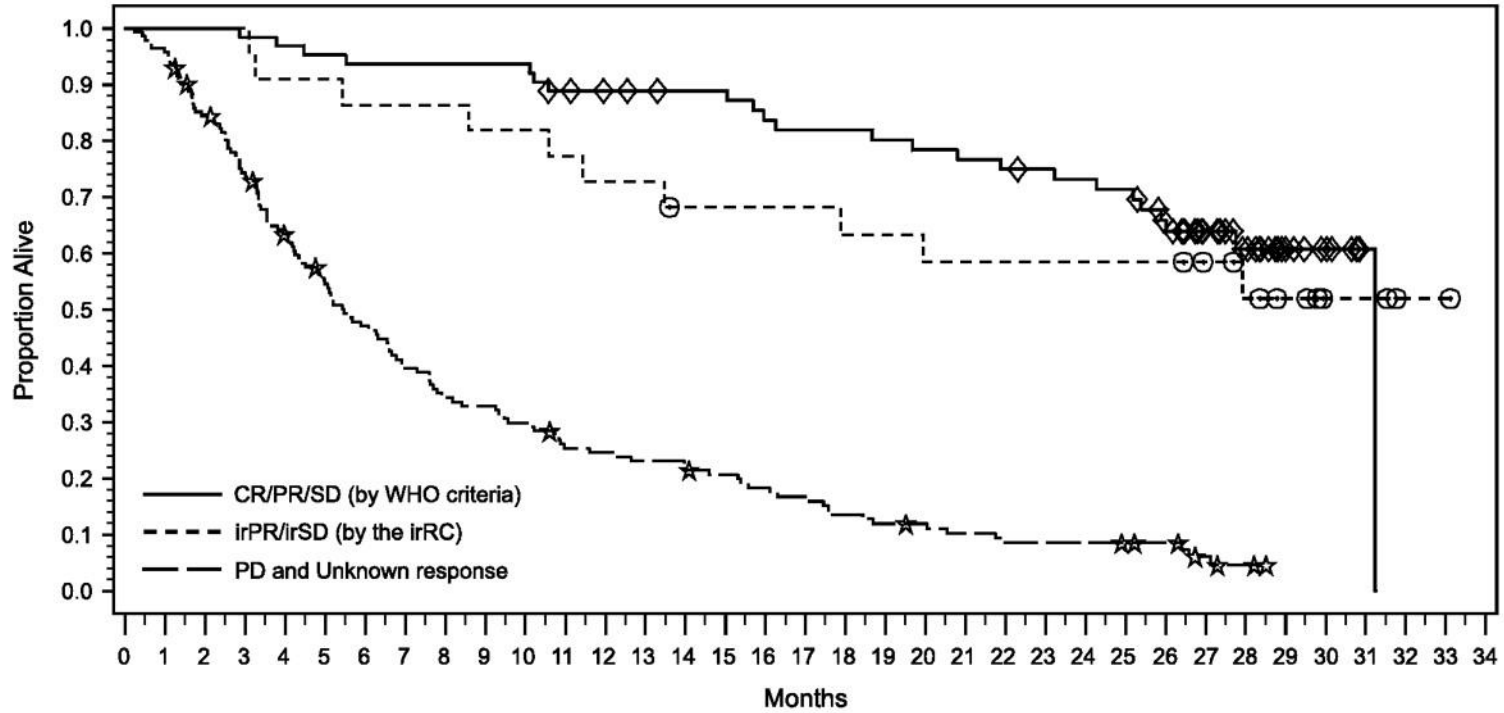
O'Regan, KN, et al. AJR 2011

Ipilimumab (anti-CTLA-4): Clinical Patterns of Response



Wolchok JD, et al. Clin Cancer Res. 2009;15:7412-7420
Hoos A et al. J Natl Cancer Inst 2010;102:1388-1397

Ipilimumab: Association of OS with Patterns of Response



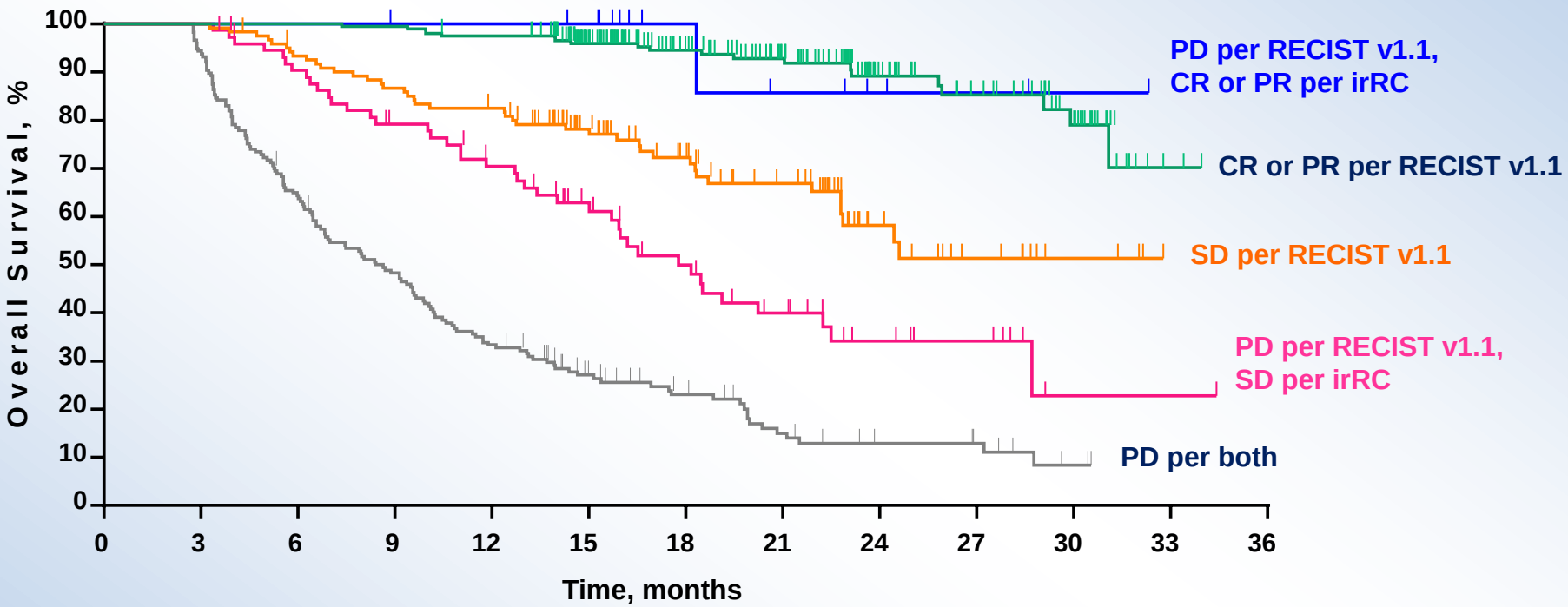
Subjects at Risk

CR/PR/SD	63	63	63	62	61	60	59	59	59	59	59	55	53	52	51	51	48	47	47	46	45	44	43	42	41	40	34	24	18	10	6	1	0	0	0
irPR/irSD	22	22	22	22	20	20	19	19	19	18	18	17	16	16	14	14	14	14	13	13	12	12	12	12	12	12	12	10	8	6	3	3	1	1	0
PD/Unkown	142	136	118	102	86	73	63	53	46	44	40	33	32	30	28	26	23	21	17	15	14	12	10	10	10	9	8	4	2	0	0	0	0	0	0

Wolchok J D et al. Clin Cancer Res 2009;15:7412-7420

©2009 by American Association for Cancer Research

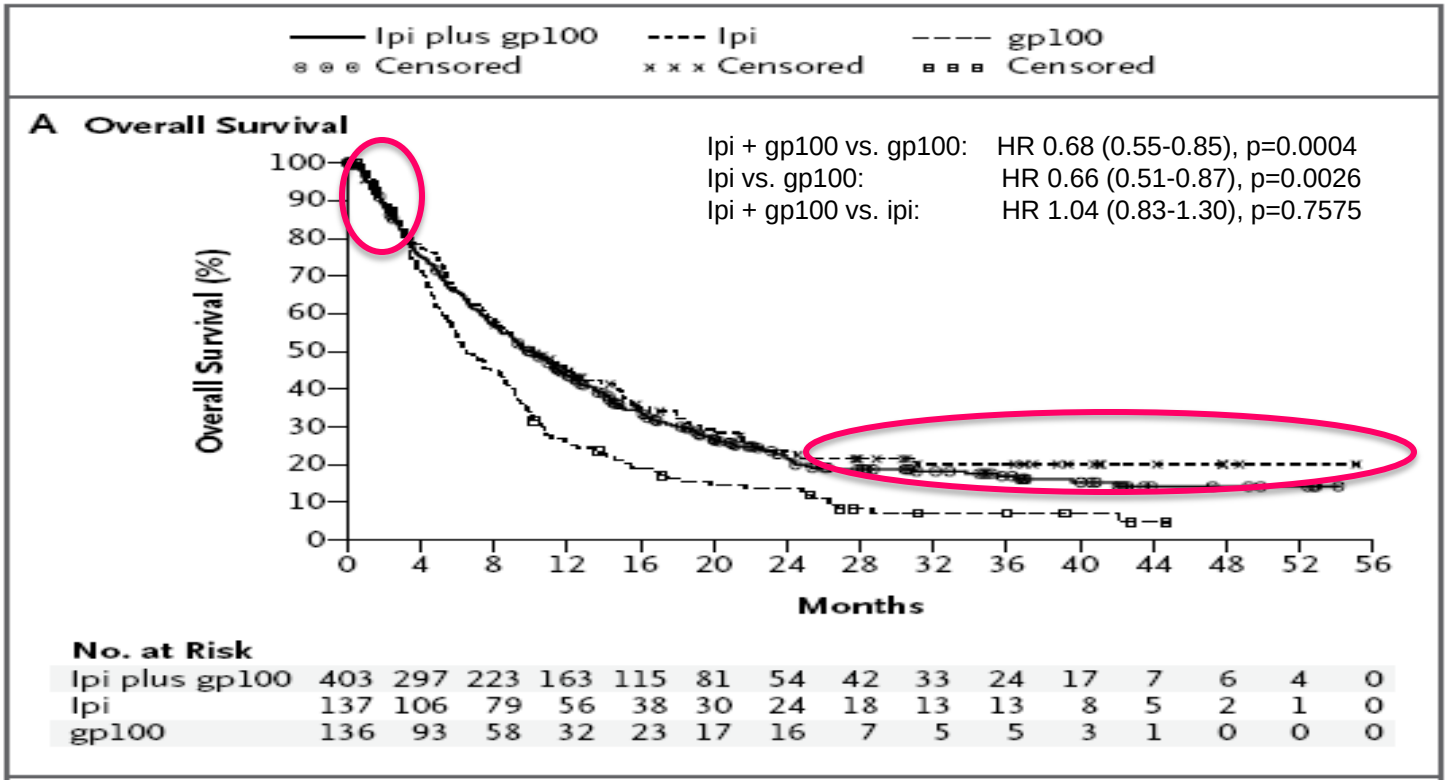
Pembrolizumab: Association of OS with Patterns of Response (n = 594; 16% irR)



205	205	205	204	199	159	118	93	53	40	21	2	0
122	122	112	104	98	73	55	43	18	10	4	0	0
15	15	15	14	14	13	7	5	3	2	1	0	0
75	75	65	55	47	36	26	18	10	7	1	1	0
177	167	113	84	58	37	25	15	9	7	2	0	0

Wolchok et al., ASCO 2014

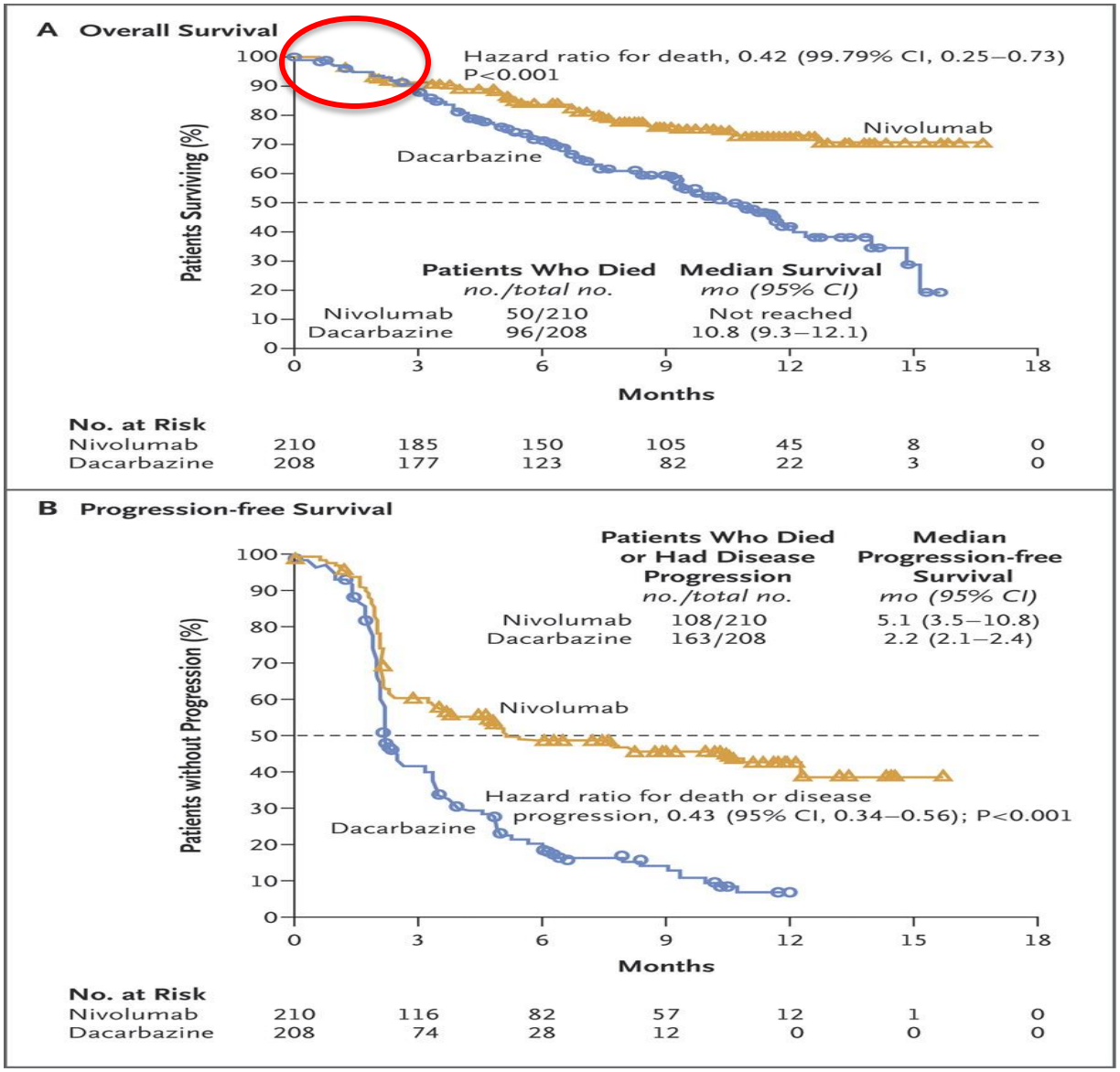
ORR - OS Relationship: Ipilimumab in Metastatic Melanoma



Ipilimumab Alone	ORR	DCR	Survival Rate at 2 years
	11%	29%	24%

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

PFS – OS Relationship: Nivolumab vs. Dacarbazine



OS HR 0.42

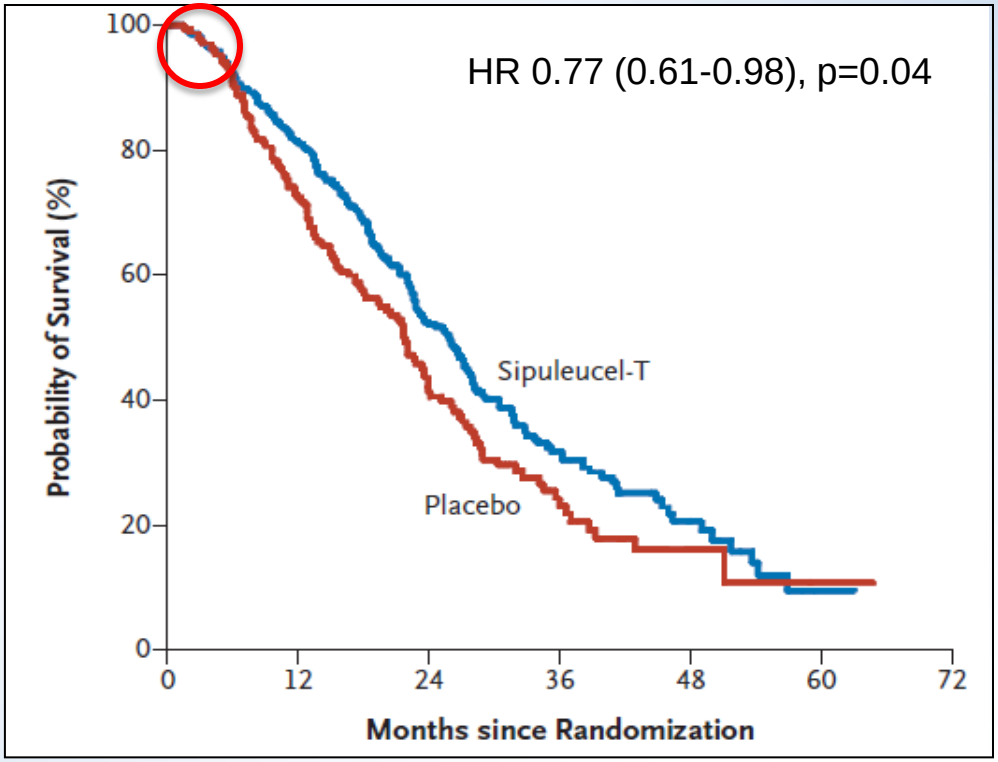
PFS HR 0.43

Robert C et al. N Engl J Med 2014

PFS -OS Relationship: Sipuleucel-T

No PFS benefit

OS HR 0.77



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

Hypotheses

- Unusual response patterns and delayed effects reflect the underlying biology of immune intervention
- Novel patterns of response or stable disease represent clinical benefit because they are associated with better survival
- Conventional chemotherapy-derived response or PFS assessment (RECIST, WHO) does not account for all benefit patterns and therefore underestimates clinical benefit.

  This may vary between types of immunotherapies.
- Evaluation of time-to-event endpoints can be impacted by delayed clinical effects (non-proportional hazards) and may require modified statistics.

ORR & PFS: Clinical (Trial) Challenges

- Conventional ORR and PFS underestimate IO drug effects
  - Potential for premature discontinuation of a new therapy
  - Potential for clinical trial failure if conventional effects are insufficient to meet study objectives
- Premature treatment discontinuation due to conventional PD
- Sequencing of therapies difficult due to potential ongoing effects of the prior agent before “true” PD

Improving clinical endpoints
ORR, PFS and OS

History: Improving Endpoints for IO Drugs

Clinical observations of unconventional "mixed" responses

Delayed Separation of KM Curves

CIC Cancer Immunotherapy Consortium

irResponse Criteria

CIC Cancer Immunotherapy Consortium

Bristol-Myers Squibb

Versions of irRC:

irRECIST
iRECIST
imRECIST
irLugano (LYRIC)

FDA AACR American Association for Cancer Research
FINDING CURES TOGETHER™

Immuno-oncology Drug Development Workshop
Hyatt Regency Washington on Capitol Hill
Columbia A&B Ballroom
Washington, DC
October 13-14, 2016

1995 - - - - 2005 2010 2015 2016

Increasing Data Availability

Ipilimumab

Tremelimumab

Pembrolizumab
(Nivolumab)
Atezolizumab
Durvalumab

Hoos et al., JIT 2007
Wolchok et al., CCR 2009

Cancer Therapy: Clinical

2009

Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria

Jedd D. Wolchok,[1] Axel Hoos,[2] Steven O'Day,[3] Jeffrey S. Weber,[4] Omid Hamid,[3] Celeste Lebbé,[5] Michele Maio,[6] Michael Binder,[7] Oliver Bohnsack,[8] Geoffrey Nichol,[9] Rachel Humphrey,[2] and F. Stephen Hodi[10]

- Confirmation of PD
- Measurement of new lesions
- Total tumor burden including new lesions
- Treatment post initial PD
- Support new endpoints
  - irORR
  - irDCR
  - irPFS

Wolchok et al., Clin Cancer Res 2009

2015

CCR 20th Anniversary Commentary

CCR 20th Anniversary Commentary: Immune-Related Response Criteria—Capturing Clinical Activity in Immuno-Oncology

Axel Hoos[1,2], Jedd D. Wolchok[2,3], Rachel W. Humphrey[4], and F. Stephen Hodi[5]

The Journal of Clinical and Translational Research
1995-2015
20th Anniversary
Clinical Cancer Research

Advances of irRC utility between 2009 and 2015

- Transferability of irRC concepts between WHO and RECIST
- Application of irRC to diseases beyond melanoma
- Inclusion of irRC concepts into regulatory guidances of FDA and EMA
- Expansion of irRC beyond the initial implementation (further adaptation)
- Demonstration of an irRC class effect across several immunotherapies

Hoos et al., Clin Cancer Res 2015

Beyond irResponse Criteria

Concept	irRC	irRECIST	iRECIST	imRECIST	irLugano (LYRIC)
Originator	CIC BMS	DFCI	RECIST Working Group	Genentech	Lymphoma Foundation & CIC
Confirmation of PD or "Unconfirmed PD"	+	+	+	+	+
Measurement of new lesions	+	+	+	+	+
Total tumor burden includes new lesions	+	+	−	+	+
Response beyond confirmed PD	−	−	−	+	−
Treatment post initial PD	+	+	+	+	+
Supports new ORR and PFS endpoints	+	+	+	+	+

CBER, FDA Guidance:
Therapeutic Cancer Vaccines

Guidance for Industry

Clinical Considerations for Therapeutic Cancer Vaccines

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD) (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
September 2009

- Delayed separation of K-M curves
- New response kinetics
- Treatment beyond progression
- Immune response measurements
- Randomized Phase 2 trials

EMA Guidance: Anti-cancer Drug Development

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, 15 December 20101
EMA/CHMP/205/95/rev.4
Oncology Working Party

Guideline on the evaluation of anticancer medicinal products in man

Draft Agreed by Working Party	**September 2011**
Adoption by CHMP for release for consultation	15 December 2011
End of consultation (deadline for comments)	31 May 2012

This guideline replaces guideline / NfG Reference.

Comments should be provided using this template. The completed comments form should be sent to ONCWPsecretariat@ema.europa.eu

Keywords	Cancer, malignancy, biomarker, targeted drugs, pharmacogenomics

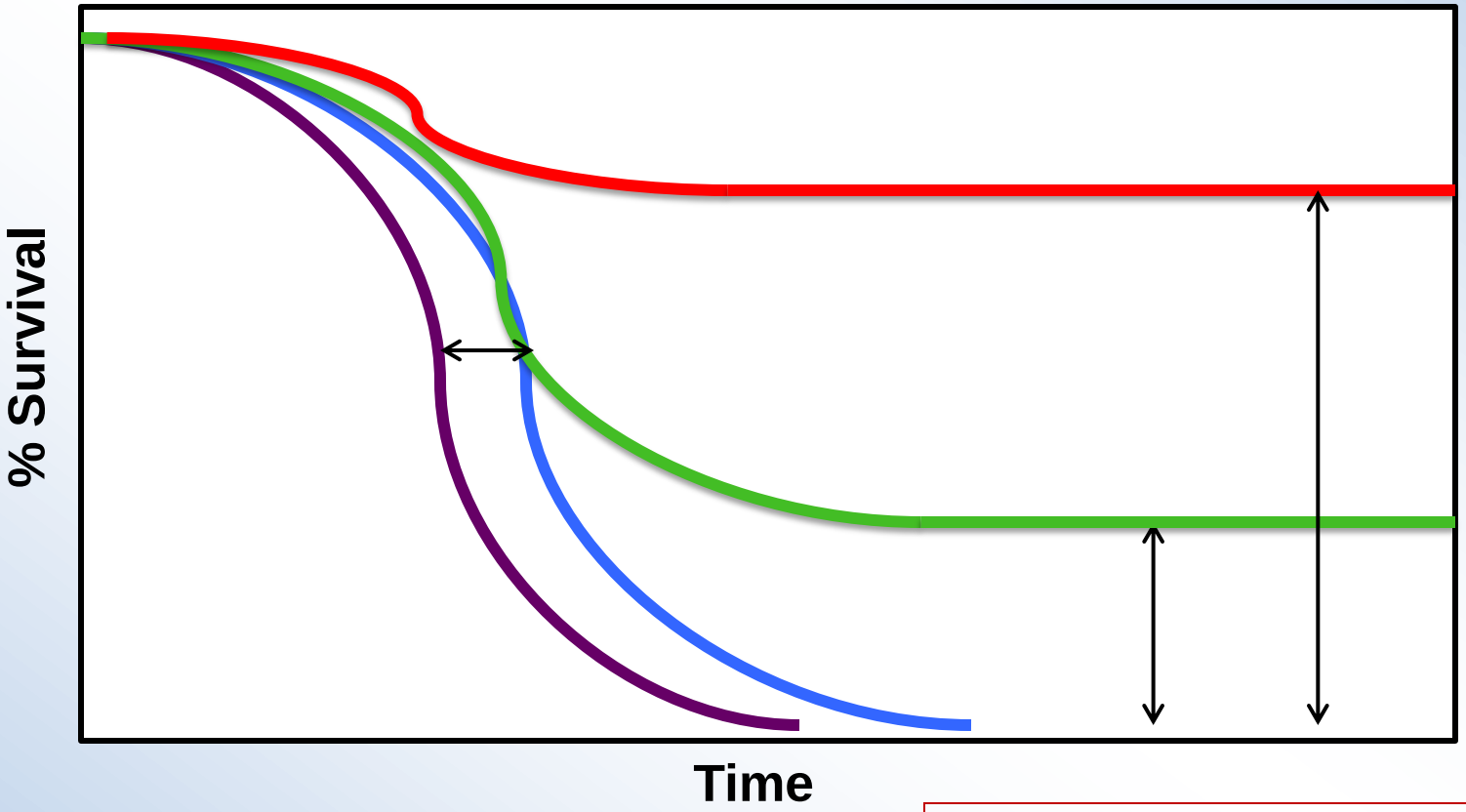
- Section on cancer immunotherapy
- Delayed effect
- Relative role of response
- Treatment beyond progression
- Randomized Phase 2 trials

CIC Workshop October 2014

- Initial ipilimumab observations are reproduced in several other IO development programs and represent a class effect.
- Novel endpoints reflect the biology of immunotherapies and more accurately capture clinical effects than standard endpoints.
- There is a correlation between the proposed new endpoints and overall survival suggesting surrogacy.
- Prospective use for exploratory and pivotal studies may be considered.

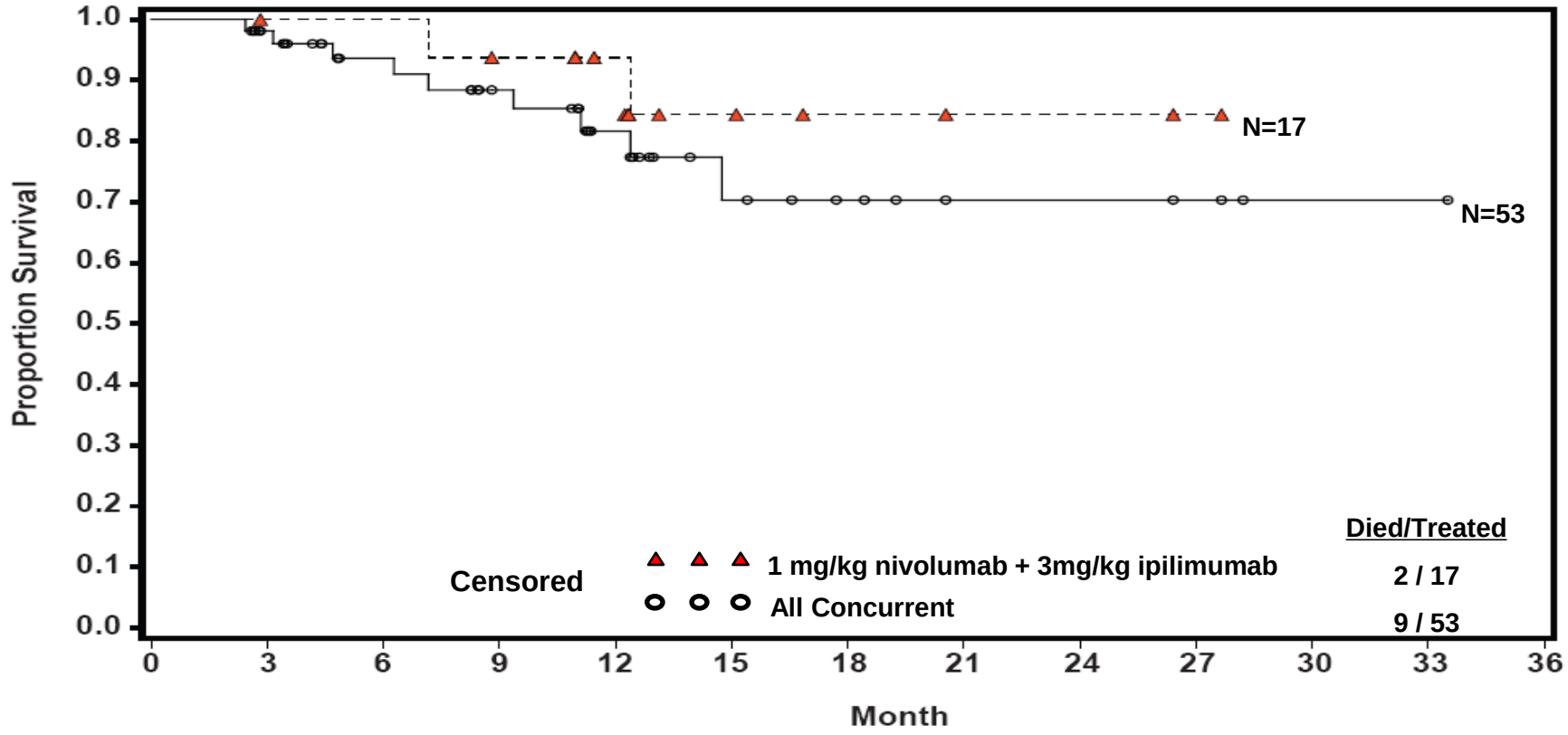
CIC Cancer Immunotherapy Consortium

Increasingly Improving Survival with Immunotherapy



Control
Conventional Therapy
Immunotherapy (e.g.anti-CTLA-4)
Future Regimens

Survival Metastatic Melanoma: Phase 1 Ipilimumab + Nivolumab



Subjects at Risk

1 mg + 3 mg	17	16	16	14	10	5	3	2	2	1	0	0	0
All concurrent	53	47	36	29	19	10	7	4	4	3	1	1	0

Wolchok et al. ASCO 2013 #9012

OS: Challenges and Solutions

Challenge	Solution
Non-proportional hazards	▪ New statistical models ▪ Overpowering of studies ▪ Sensitivity analyses
Increased duration of trials with continuously improving survival	▪ Earlier survival read-outs (eg Milestone survival) ▪ Alternative PFS endpoints (eg irPFS)
Diluting effect of other survival influencing therapies post progression	▪ Earlier survival read-outs (eg Milestone survival) ▪ Alternative PFS endpoints (eg irPFS)
Potential need for cross-over design if comparing increasingly effective therapies	▪ Alternative PFS endpoints (eg irPFS)

Ultimate Goals

- Better "Tools" – immunotherapy adapted endpoints
- Harmonize new criteria for a uniform approach
- Reflect biology in patients
- Accurately capture benefit
- Enable future trials in a context of substantially extended survival

CIC Cancer Immunotherapy Consortium

Thank you !

Estimating survival benefit in the presence of non-proportional and complex hazard functions

FDA-AACR Workshop: “Immuno-Oncology Drug Development”
Day 2 – October 14, 2016

Dr Nicholas Latimer, Senior Research Fellow, NIHR Post-doctoral Fellow, University of Sheffield, Sheffield, UK

Plan

1. Standard survival analysis
2. Parametric survival analysis
3. Immuno-Oncology
   - What are the challenges?
   - What are the solutions?
4. Conclusions

Plan

1. Standard survival analysis
2. Parametric survival analysis
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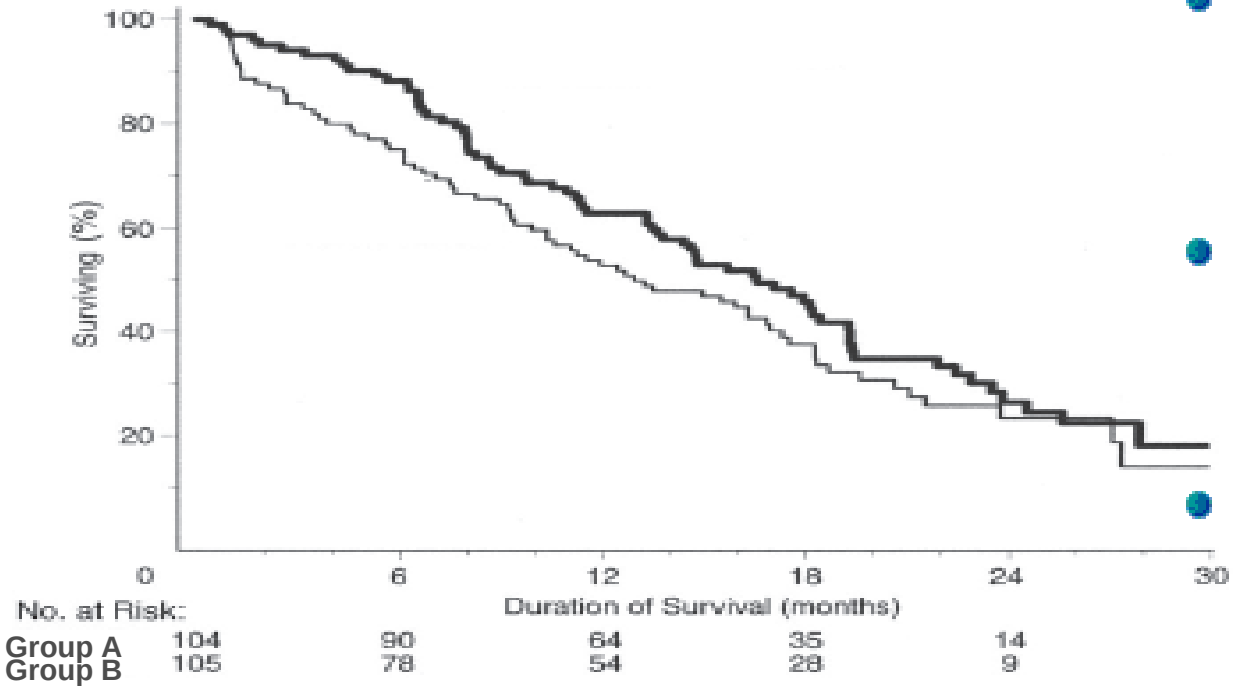
The University Of Sheffield.

Survival analysis

- **The analysis of time-to-event data from a specified time origin** (e.g. randomisation) **until the occurrence of a particular event or endpoint** (e.g. disease progression, death)
- Commonly used in evaluating effectiveness of healthcare interventions
- Results are often summarised using
  - Kaplan-Meier curves
  - Median survival
  - Hazard Ratios

Kaplan-Meier curves



- The Kaplan-Meier estimates the probability of “surviving” until time T
- We can use them to estimate medians and means
- And can use a log-rank test to compare curves statistically

Cox PH models

- **If we want to quantify the treatment effect** we can use a Cox proportional hazards regression model
- These produce **hazard ratios** (HR) which compare hazard rates between treatment groups

➔ The Cox model makes the **proportional hazards** assumption – the baseline hazard rate can change over time, but the hazard ratio cannot

Issues with standard non-parametric survival analysis

- Log-rank tests and HRs from Cox models are reliant on the proportional hazards assumption

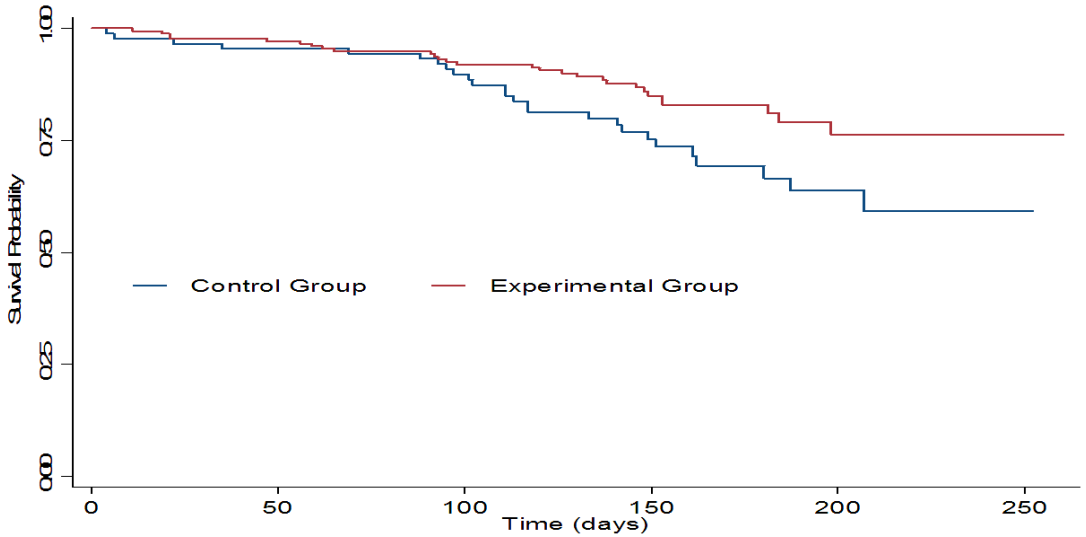
➔ If this assumption does not hold, these analyses are not useful

- What we really want to know is the survival benefit of the new treatment

➔ The truest estimate of this is the mean survival benefit – for resource allocation decisions means are more useful than medians

Issues with standard non-parametric survival analysis

- In the presence of heavy censoring, within-trial analyses may not be very informative
- Mean survival estimates from the Kaplan-Meier curve are downwardly biased ("restricted")



Number at risk						
Control Group	95	84	77	45	16	1
Experimental Group	178	171	156	88	26	2

Issues with standard non-parametric survival analysis

So…

- ➔ **If we want to estimate the mean survival benefit for the entire disease population we need to extrapolate from the trial data**
- ➔ **There is a role for parametric survival analysis**
- ➔ **This is commonly done for economic evaluation in health technology assessment** (Latimer et al. 2013; Davies et al. 2012)

Plan

1. Standard survival analysis

2. **Parametric survival analysis**

3. Immuno-Oncology

   – What are the challenges?

   – What are the solutions?

4. Conclusions

Parametric survival models

- Parametric survival models use the assumption that the survival data follows an underlying probability distribution

➔**Hence survival can be predicted beyond the end of the trial**

- Several parametric survival models exist, eg:
  - Exponential
  - Weibull
  - Gompertz
  - Log-logistic
  - Log normal
  - Generalised Gamma

➔**The key is to pick the most appropriate model**

Parametric models

Exponential

- Simplest model
- Hazard is constant over time

Weibull

- 2 parameters
- Hazard can increase or decrease monotonically

Gompertz

- 2 parameters
- Hazard can increase or decrease monotonically

Log-logistic

- 2 parameters
- Hazard may increase and then decrease

Log normal

- 2 parameters
- Hazard may increase and then decrease

Generalised Gamma

- 3 parameters
- More flexible, includes exponential, Weibull, log normal as special cases

***Note: here, we are talking about the hazard rate, not the HR!**

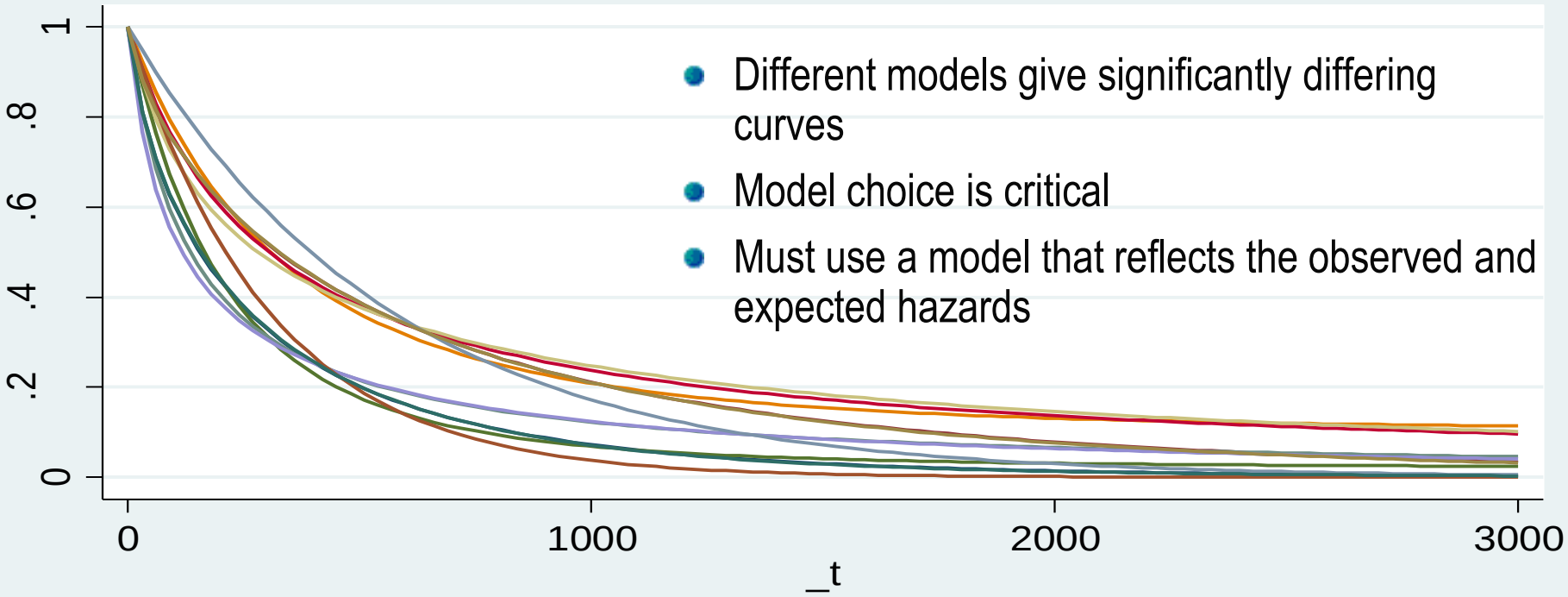
Parametric survival models

- Parametric survival models can be fitted assuming a proportional treatment effect

➔ As for Cox models, this will not be appropriate if there is not a proportional treatment effect

- Or, they can be fitted without assuming a proportional effect – e.g. by fitting models independently to each treatment group

Parametric models



- Different models give significantly differing curves
- Model choice is critical
- Must use a model that reflects the observed and expected hazards

Plan

1. Standard survival analysis

2. Parametric survival analysis

3. Immuno-Oncology

   – What are the challenges?

   – What are the solutions?

4. Conclusions

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Caveat

- Survival modelling – in any disease area – is rarely straightforward
  - Proportional hazards assumption often may not hold
  - Often there is limited long-term survival data
  - Hazard functions may not follow standard parametric distributions
- **Nevertheless, immuno-oncology appears to be characterised by certain features which have implications for survival modelling…**

Immuno-oncology – challenges

1. Immuno drugs may not exhibit a proportional treatment effect

2. Immuno drugs may be associated with a delayed effect, long-term survivors and therefore complex hazard functions

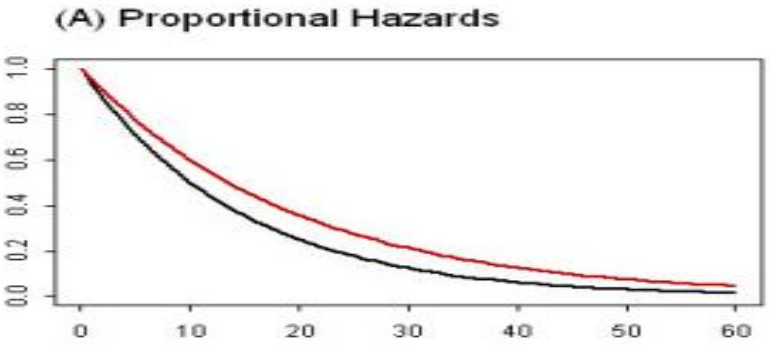
Problem: Non-PH effects

1. **Immuno drugs may not exhibit a proportional treatment effect**

➔ PH assumption is not valid

➔ Cox models and log-rank tests may not be appropriate

➔ Parametric models that assume PH may not be appropriate



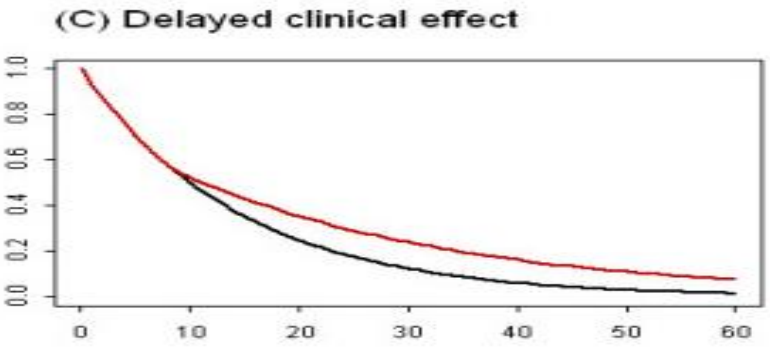


Figure adapted from Chen, 2013

Solutions: Non-PH effects

- Cox models can incorporate time-dependent treatment effects
  - But we no longer get a single, simple HR
  - But shouldn't we be more interested in mean survival anyway? – hence non-parametric analysis is not that useful

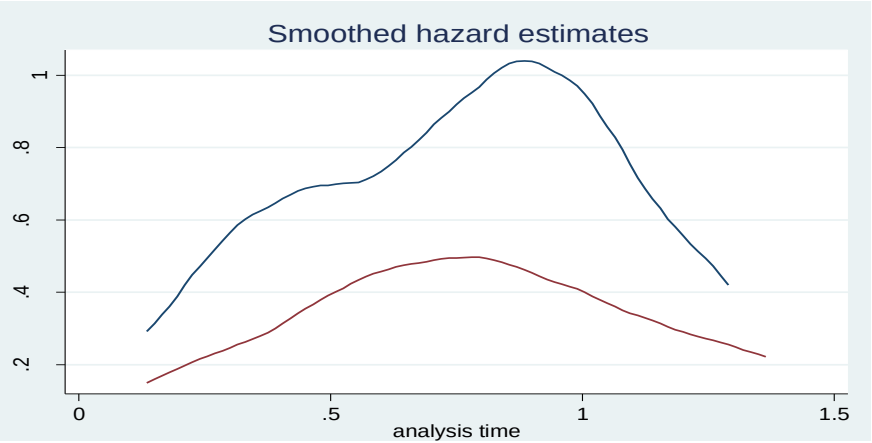
- Parametric models can be fitted independently to each treatment arm
  - Don't need to assume PH
  - May get a better estimate of the survival gain

Problem: Complex hazards

2. **Immuno drugs may be associated with a delayed effect, long-term survivors and therefore complex hazard functions**

➔ Standard parametric models may not provide a good fit to the observed (or expected) hazard & survival functions

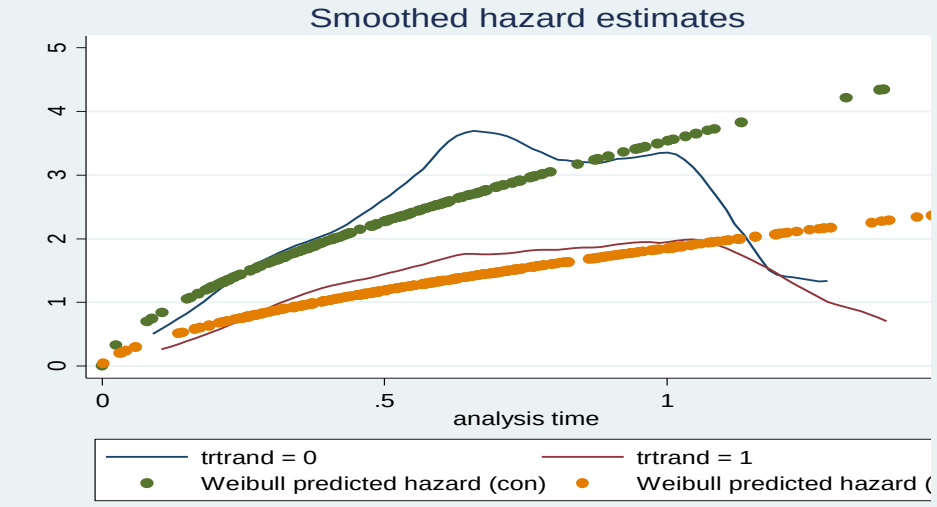
➔ So survival estimates may be poor



Solutions: Complex hazards

Flexible parametric models

- ➔ Flexible parametric models use restricted cubic splines to estimate the shape of the log-cumulative hazard function
- ➔ FPMs can accurately reflect complex hazard functions, with turning points (Royston and Parmar, 2002; Rutherford, Crowther and Lambert, 2015)…


Smoothed hazard estimates
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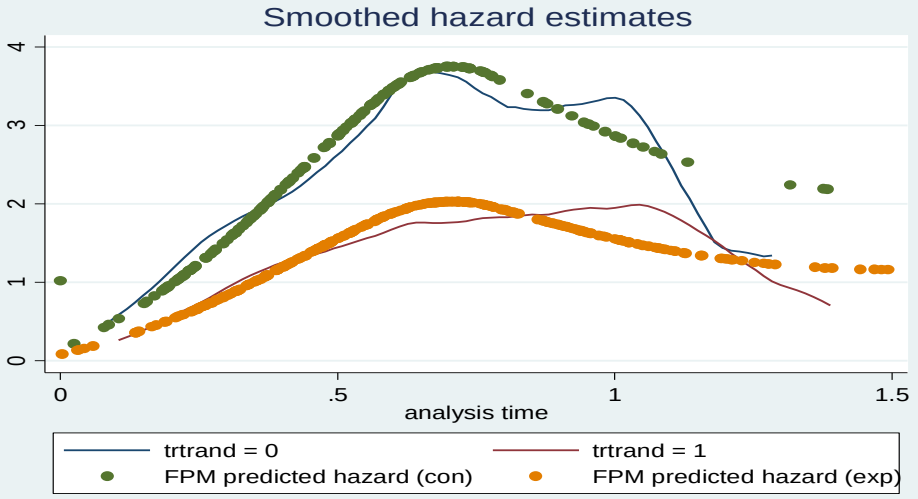
analysis time
trtrand = 0
trtrand = 1
Weibull predicted hazard (con)
Weibull predicted hazard (


Smoothed hazard estimates
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analysis time
trtrand = 0
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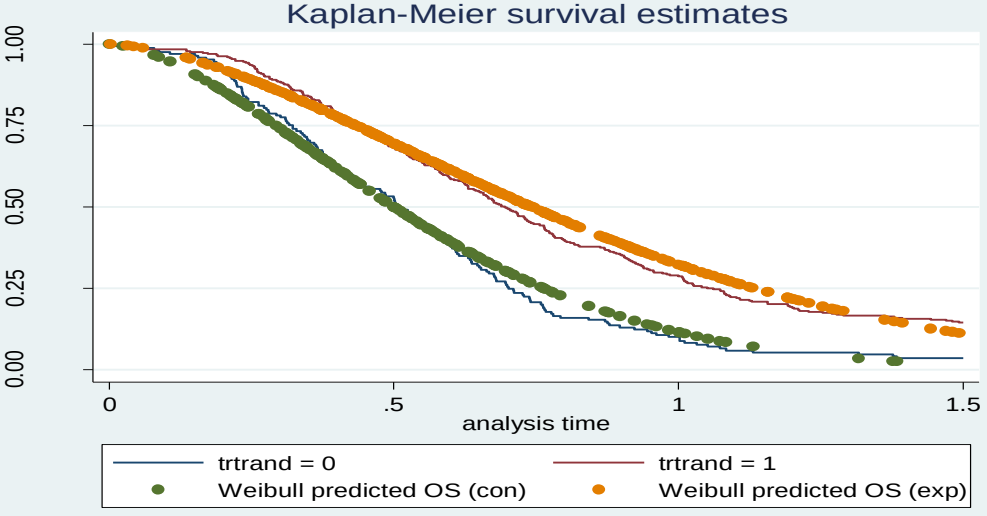
FPM predicted hazard (con)
FPM predicted hazard (exp)


Kaplan-Meier survival estimates
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analysis time
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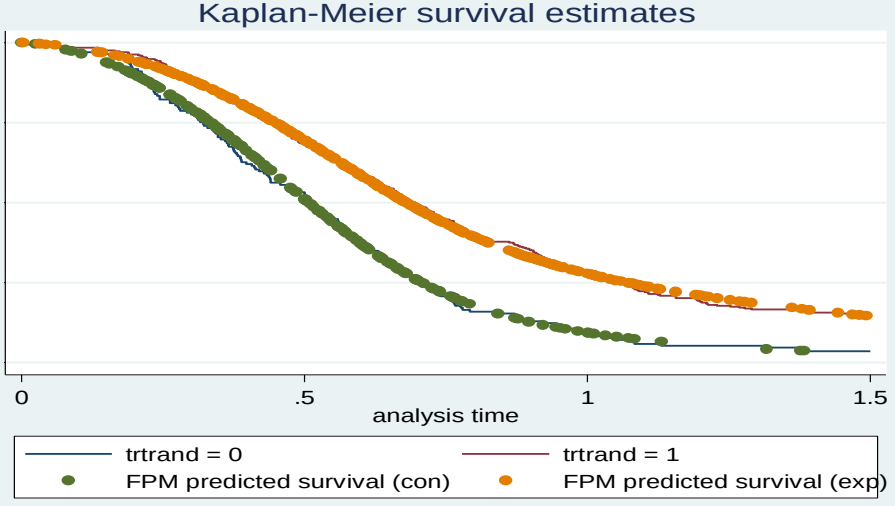
Weibull predicted OS (con)
Weibull predicted OS (exp)


Kaplan-Meier survival estimates
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analysis time
trtrand = 0
trtrand = 1
FPM predicted survival (con)
FPM predicted survival (exp)

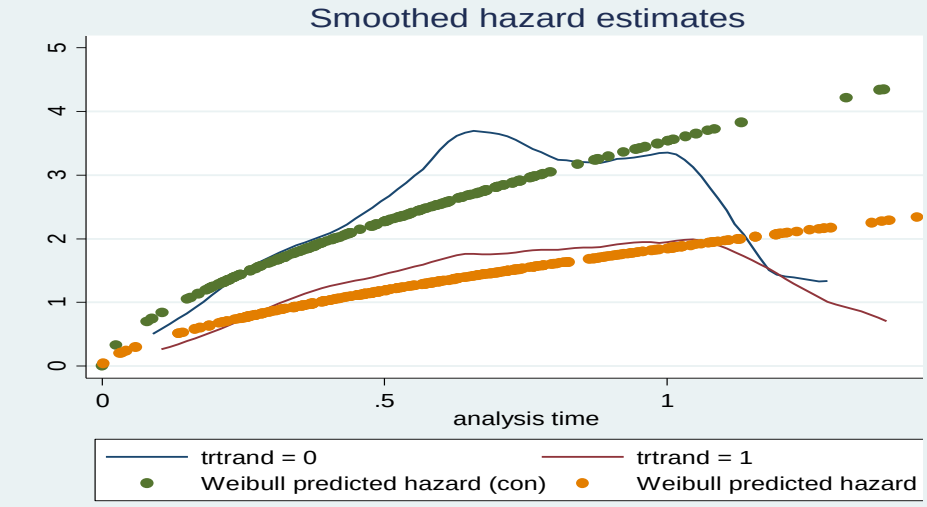
Solutions: Complex hazards

Parametric cure models

- Sometimes it might appear that a % of patients have been “cured”
- Parametric cure models can be used to estimate the cure fraction, modelling ‘cured’ and ‘uncured’ with different distributions (Chen, 2015)

Parametric mixture models

- Sometimes it might appear that there are 2 (or more) distinct groups within the population, who have different survival distributions
- Parametric mixture models can be used to model with two (or more) distinct distributions (Lambert, 2007)


Smoothed hazard estimates
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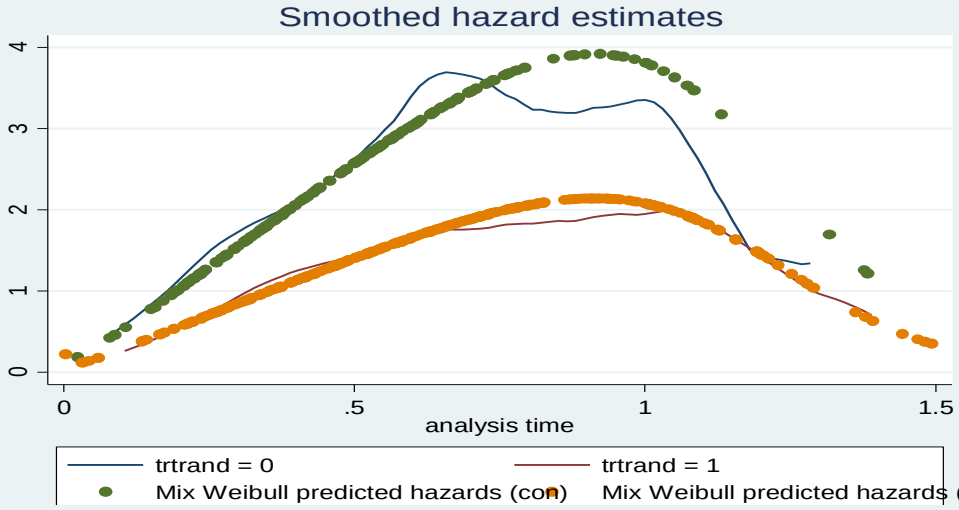
analysis time
trtrand = 0
trtrand = 1
Weibull predicted hazard (con)
Weibull predicted hazard


Smoothed hazard estimates
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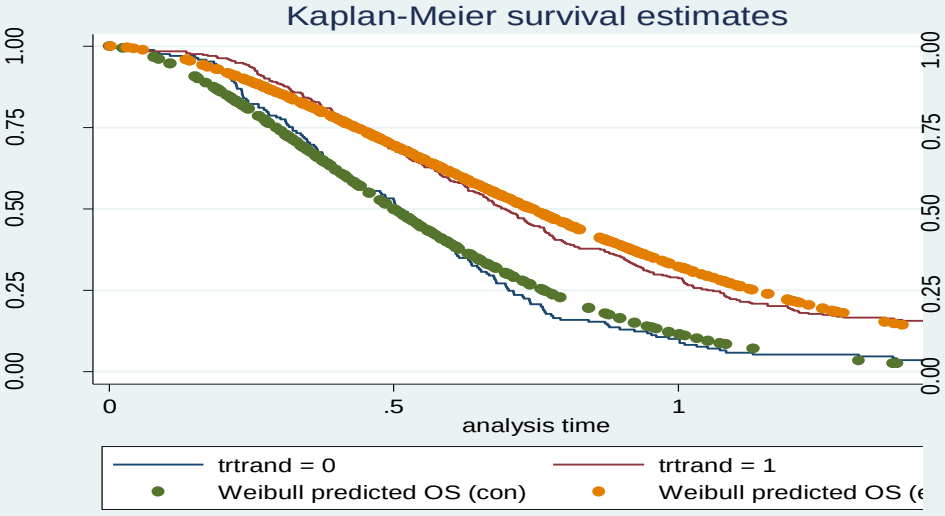
analysis time
trtrand = 0
trtrand = 1
Mix Weibull predicted hazards (con)
Mix Weibull predicted hazards


Kaplan-Meier survival estimates
0.00
0.25
0.50
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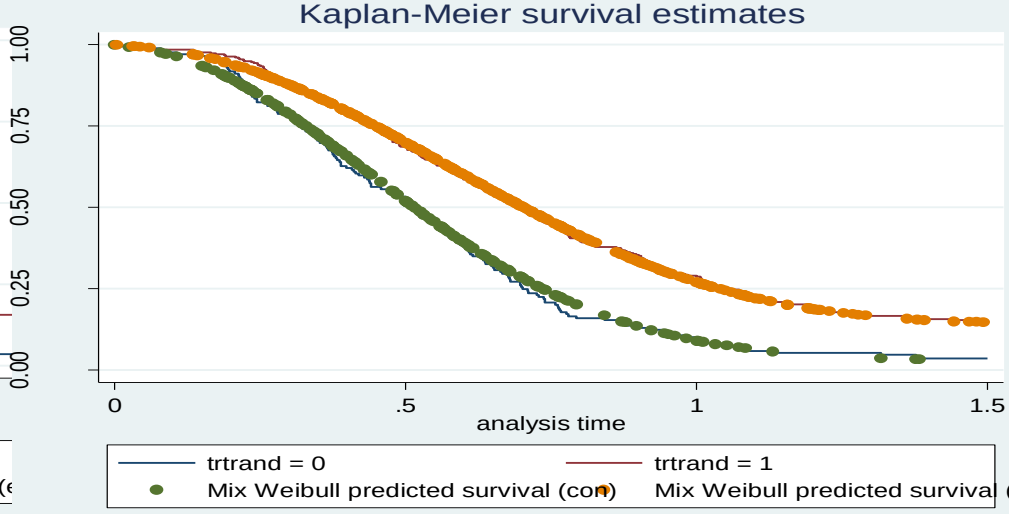
analysis time
trtrand = 0
trtrand = 1
Weibull predicted OS (con)
Weibull predicted OS (


Kaplan-Meier survival estimates
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0.25
0.50
0.75
1.00
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1.5
analysis time
trtrand = 0
trtrand = 1
Mix Weibull predicted survival (con)
Mix Weibull predicted survival

Solutions: Complex hazards

FPMs, cure and mixture models

- The FPM extrapolates beyond the data using only the final segment of the curve. This may or may not be appropriate for achieving accurate projections
- Cure/mixture models may have a preferred biological basis as they do not involve segmenting the survival curve, but…
  - Can we prove that an assumption of a cure is reasonable?
  - Can we estimate the cure fraction based on short-term trial data?
  - Can we justify an assumption of two (or more) distinct groups?
  - Still need to select appropriate parametric models

Plan

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4. Conclusions

The University Of Sheffield.

Conclusions

- Immuno-Oncology ***may*** present “non-standard” issues for survival analysis
  - HRs and log-rank tests of Kaplan-Meier curves may not be useful
  - Standard parametric models may not fit
- We may need models that allow time-dependent treatment effects, or model survival curves independently
- FPMs, cure models and mixture models offer potential solutions
  - But each requires careful justification
  - As always, demonstrating the validity of extrapolated portions of survival curves is critical

The University Of Sheffield.

References

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American Association for Cancer Research

FINDING CURES TOGETHER℠

Session IIIa Panel Discussion

Endpoints for I-O Products: Considerations for Unique Efficacy Based on Unique Biology of Checkpoint Inhibitors

Moderator: Renzo Canetta, MD

Speakers:

Lawrence Schwartz, MD
Sumithra Mandrekar, PhD
Axel Hoos, PhD
Nicholas Latimer, PhD

Panelist:

Shenghui Tang, PhD

American Association for Cancer Research

FINDING CURES TOGETHER℠

Session IIIb

Use of Alternate Efficacy Endpoints with I-O Products

Moderator: Marc Theoret, MD

Speakers:

Sirisha Mushti, PhD

Xin (Cindy) Gao, PhD

Antoni Ribas, MD, PhD

Jan Bogaerts, PhD

Daniel S. Chen, MD. PhD

Keaven Anderson, PhD

Tai-Tsang Chen, PhD

Alternate Efficacy Endpoints—use of alternate endpoints with IO products

12:15-2:45 pm session

How we assess benefit from IO agents

DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Antoni Ribas, MD, PhD

DISCLOSURES

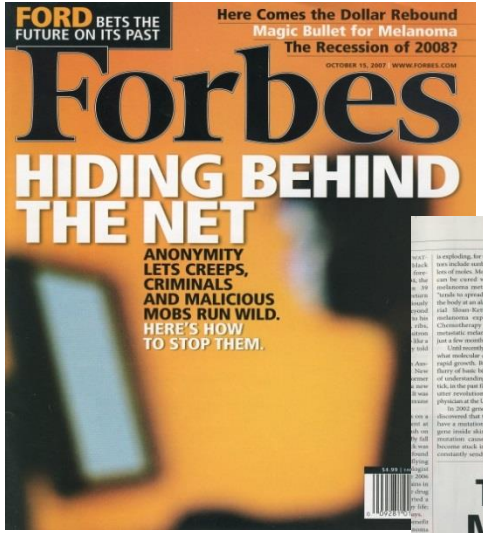
Amgen, Genentech, Merck, Novartis:

Consultant – Honoraria to UCLA

Acteris, Advaxis, Compugen, CytomX, Five Prime, Kite Pharma:

Scientific Advisory Board – Stock

Very long term responses with CTLA4 blockade

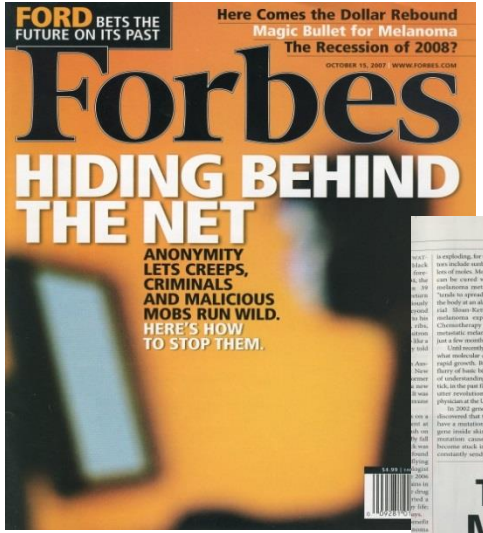


Forbes, Oct 2007

Dr Ed, 39 years old in 2004, metastatic melanoma to the liver, adrenal gland and bone, told he had months left to live.

Hi Toni, I would like that you improve my hazard ratio for survival by 0.68

Very long term responses with CTLA4 blockade

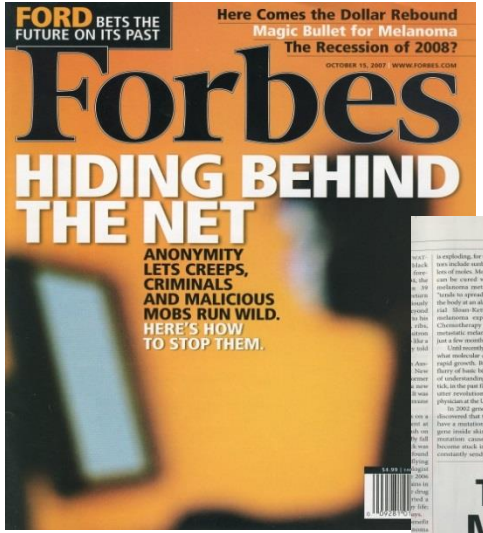


Forbes, Oct 2007

Dr Ed, 39 years old in 2004, metastatic melanoma to the liver, adrenal gland and bone, told he had months left to live.

Hi Toni, I would like to see my two daughters grow and go to college

Very long term responses with CTLA4 blockade



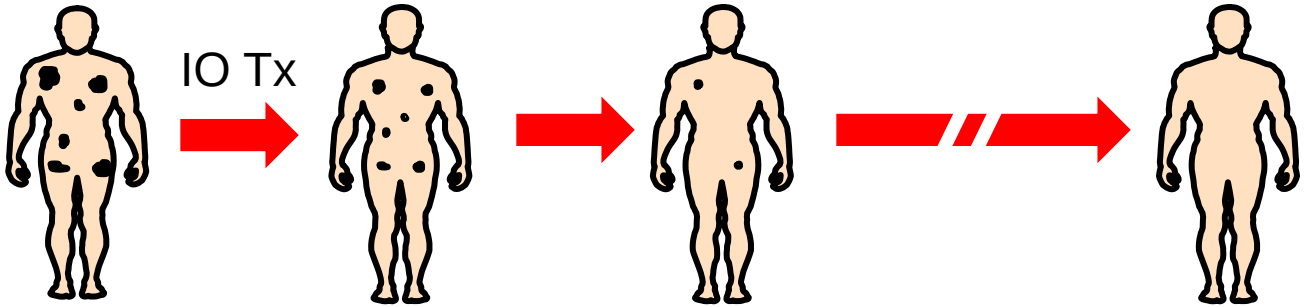
Forbes, Oct 2007

Dr Ed, 39 years old in 2004, metastatic melanoma to the liver, adrenal gland and bone, told he had months left to live.

Top of Rangitoto volcano, Auckland, New Zealand, Nov 2015.

What IO benefit analysis captures living to take your children to college?

- ORR
- PFS
- OS
- Durable response rate



What IO benefit analysis captures living to take your children to college?

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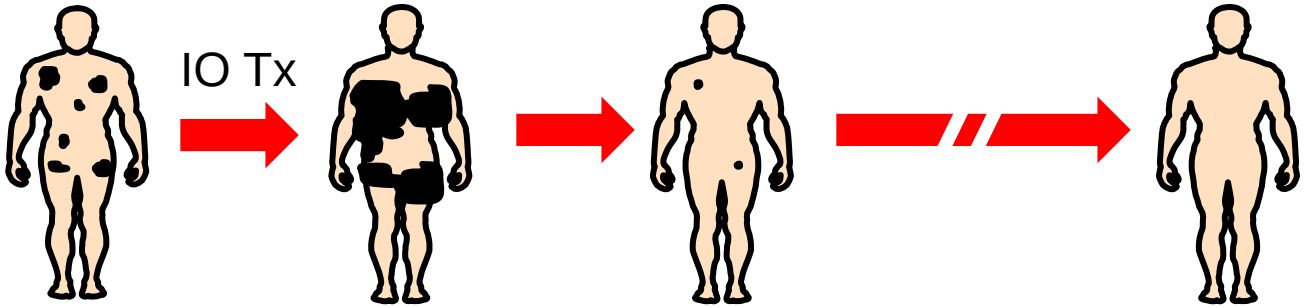


OPTiM: Phase 3 trial of talimogene laherparepvec (T-VEC) vs sc GM-CSF for unresected stage IIIB/C and IV melanoma

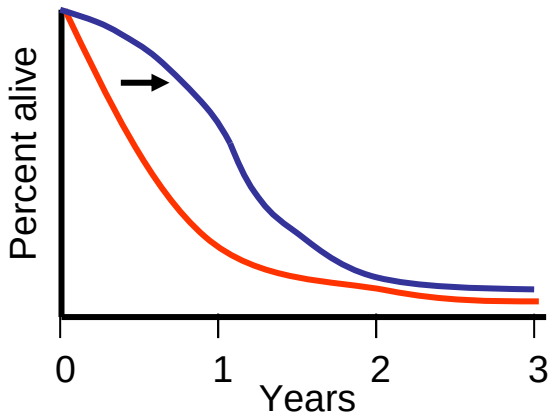
Primary Endpoint: Durable Response Rate per EAC

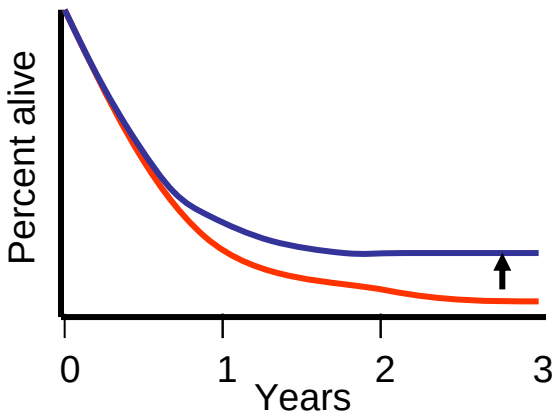
ITT Set	GM-CSF (N=141)	T-VEC (N= 295)	Unadjusted Odds Ratio
Durable Response Rate	2.1%	16.3%	8.9 95% CI: (2.7, 29.2) P < 0.0001

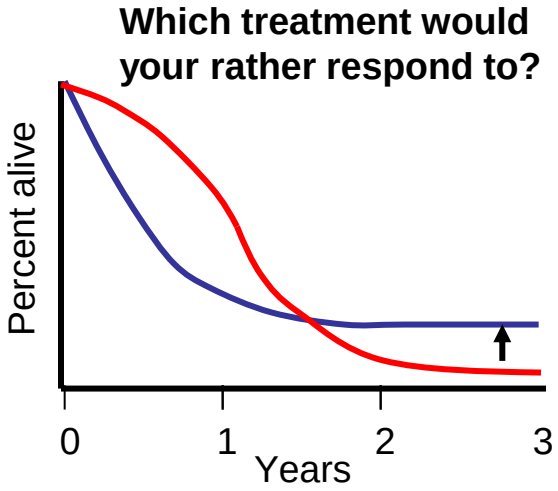
143 patients (33%) in the ITT set met the criteria to be reviewed by the EAC (ie, had best response per investigator of CR or PR or on therapy for ≥ 9 months)

Andtbacka *et al*. JCO 2013

PFS and OS are more likely to be positive when benefitting very little all patients than when benefitting a lot (maybe curing) a subset of patients







PFS	HR++++	HR +/-	HR -
OS	HR++	HR ++	HR -
DRR	OR-	OR+++	OR+++

Conclusions

- The main benefit of IO agents is inducing very long lasting responses in patients with metastatic cancer
- ORR, PFS and OS may not always capture this benefit, and may depend on the type of benefit in the control arm
  - PFS and OS usually favor a small benefit in a lot of patients than a life-changing benefit in a subset of patients
- DRR:
  - Captures the intended benefit of IO agents
  - Independent of the performance of the control arm
  - Independent of other post-progression therapies

Milestones for Survival: Overall Survival versus Earlier Endpoints

Jan Bogaerts, PhD

EORTC, Brussels

Conflicts

- No conflicts
- EORTC works with most major pharma companies and receives grants in various forms of cooperation to run studies
- Permanent member of the EMA SAG

Overview

- Some comments coming from our work on (i)RECIST
- Lack of gold standard for earlier endpoints
- Thoughts about how survival data can be interpreted

(i)RECIST

- Current status of RECIST:
  - Busy writing up the analysis of the targeted agents warehouse analysis
  - In writing: RECIST recommendations for how to use it in immunology setting: L. Seymour coordinates
  - This will be discussed at EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium, Munich (end of the year)

RECIST

- Contrast between PD per RECIST and the decision to stop treatment
- RECIST is a method to standardize and reach some degree of comparability across studies
  - Should it always define end of treatment?

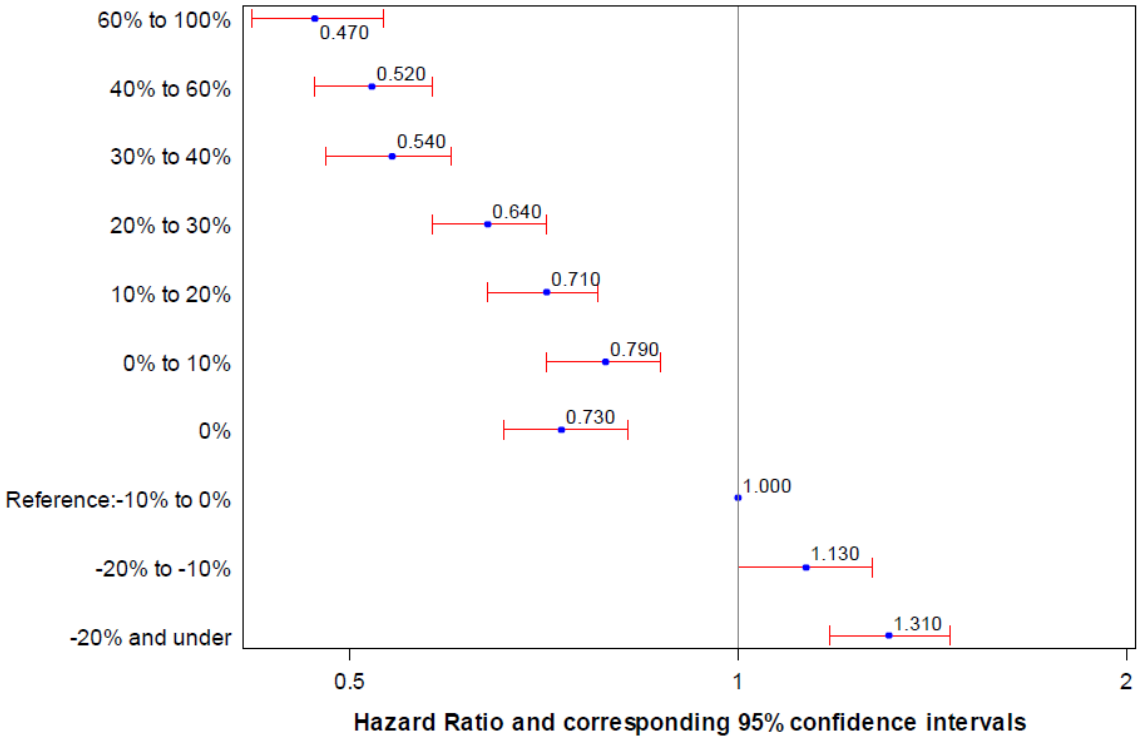
RECIST

- A ‘paradox by construction’:
- When RECIST PD is reached, the data flow stops, making it impossible to look into many interesting questions (no data)

Intermediate endpoints

- There is no gold standard for what constitutes ‘response’ or ‘progression’ (IMO)
- There will always be some degree of convention
- We can reach high degrees of correlation with OS, if not surrogacy in the Prentice sense

Any dichotomisation will show separation



Stratified by study. Adjusted for baseline sum of diameters, occurence of new lesions and progression of non-target lesions

Also in the work by S. Mandrekar et al (no 'better' split)

Temptation to maximize RR

Thanks to S. Litiere

Maio et al., JCO 2015

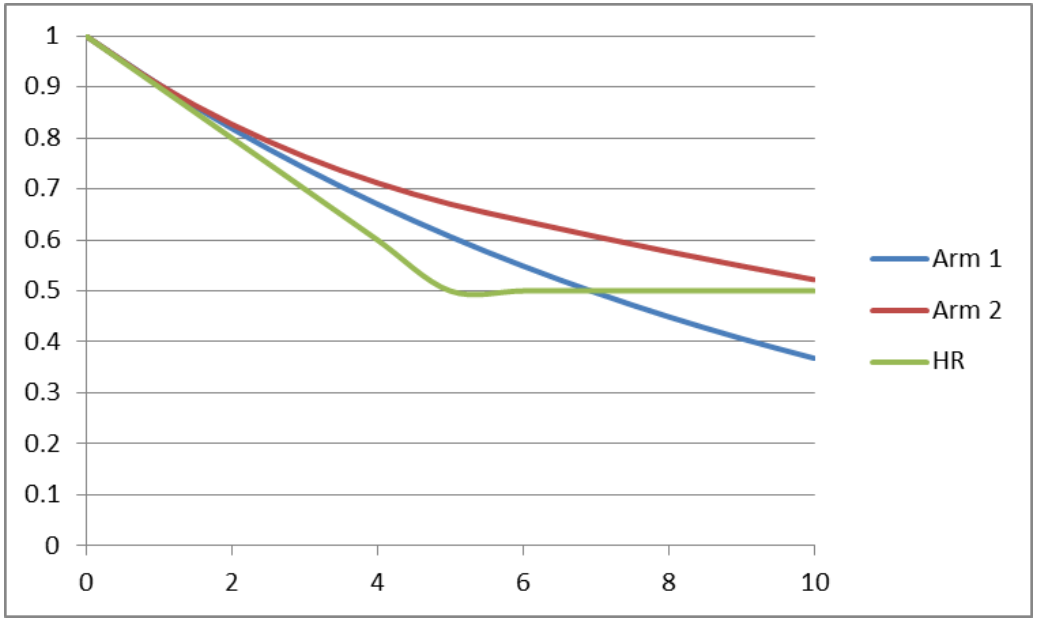
Table 4. Best Overall Response for Patients Alive at Least 5 Years

	Ipilimumab + Dacarbazine (n = 40)		Placebo + Dacarbazine (n = 20)	
Best Overall Response	No.	%	No.	%
Complete response	3	7.5	0	0
Partial response	17	42.5	7	35
Stable disease	11	27.5	8	40
Progressive disease	7	17.5	3	15
Unknown	2	5	2	10
Objective response rate		50		35

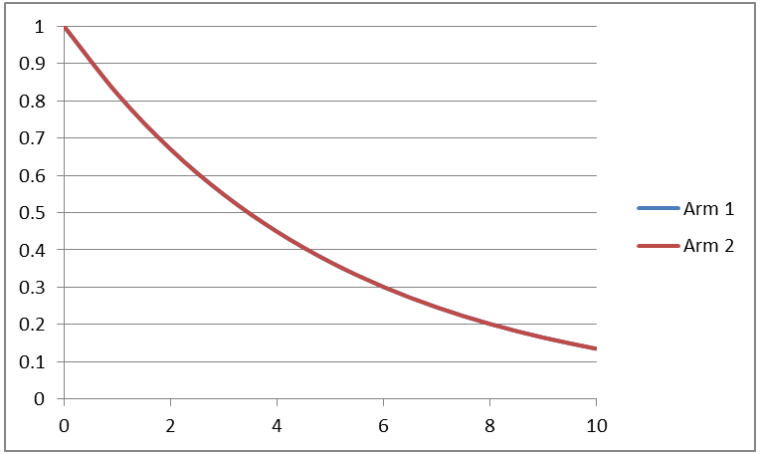
For immunotherapy

- While OS outcomes dominate, we should prepare and come to better goal setting
  - What is an acceptable “delay” or waiting time for patients to stay on treatment in ‘apparent PD’
- Definition of progression should not take a form that recognizes any level of activity
  - This question will come back if OS is not significant, while PFS is

Do we need to change stat methods?

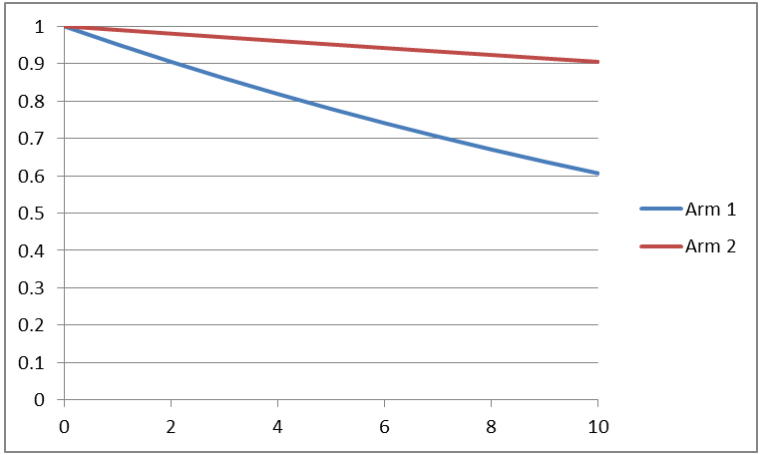


Diverging hazards
Late separation of the curve



50% of patients:

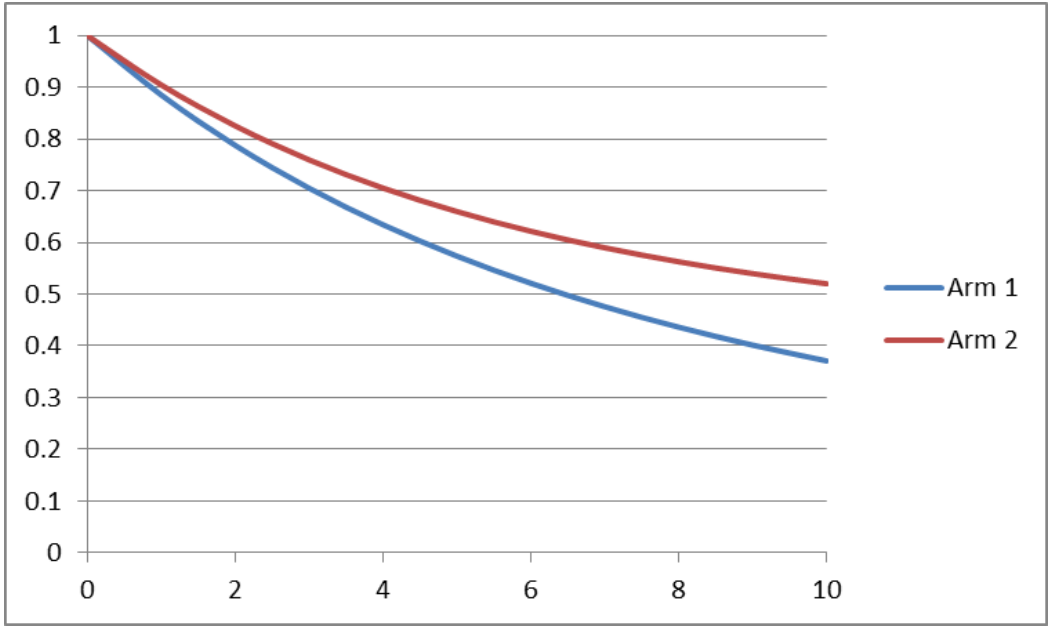
- bad prognosis group
- no effect at all (overlapping curves)



50% of patients:

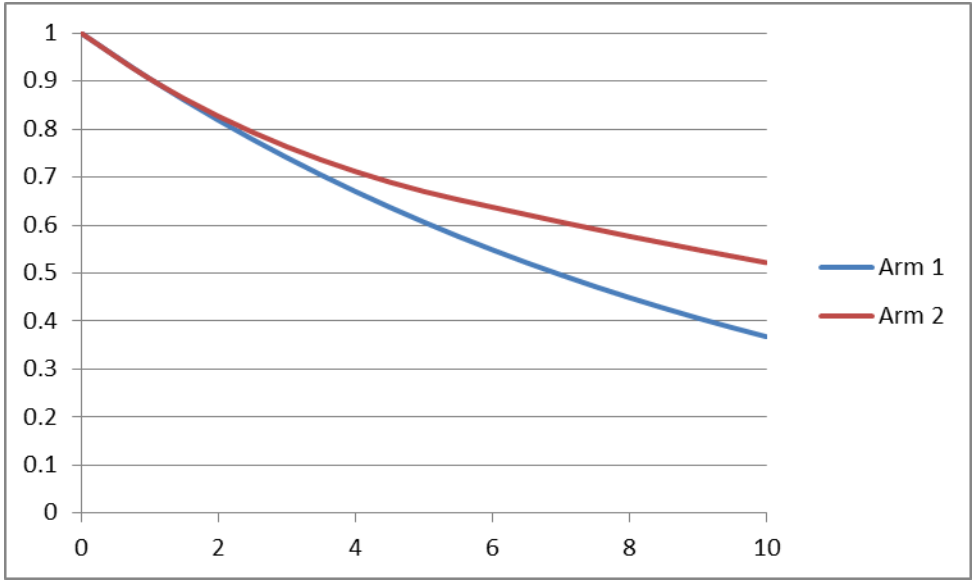
- better prognosis group
- huge effect

The ‘mix’ of those two



This is a ‘caricature’, but deserves reminding

Many mechanisms can lead to this



- Late drug effect
  - We know this is at work
- Unidentified factor
- Too broad population
- Non-compliance
- Short term effect that is not maintained
- …

Thank you

Non-Classical Response Patterns, Immune-Modified RECIST and Immune-Modified PFS:

Potential Optimization of Radiographic Endpoints for Immunotherapies

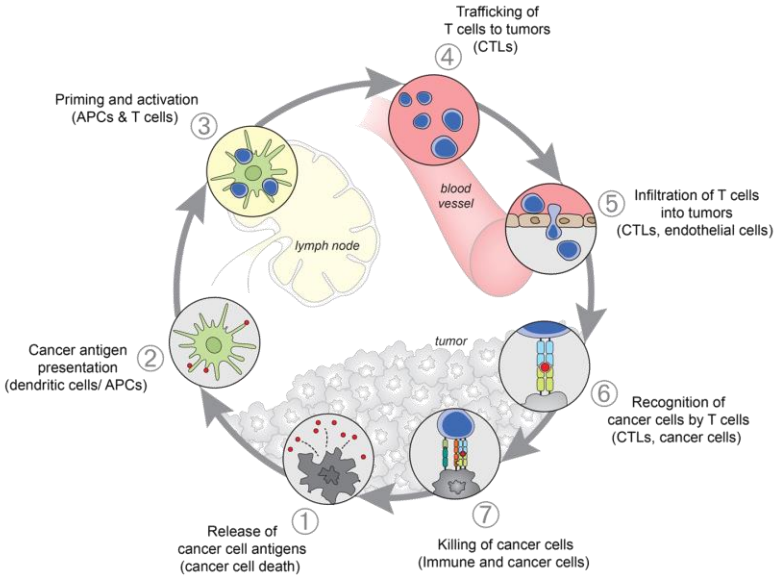
Ballinger M, Lyons B, Winslow N, Fine G, Chen DS

Dan Chen, M.D. Ph.D.
Vice President, Global Head of Cancer Immunotherapy Development
Genentech/Roche

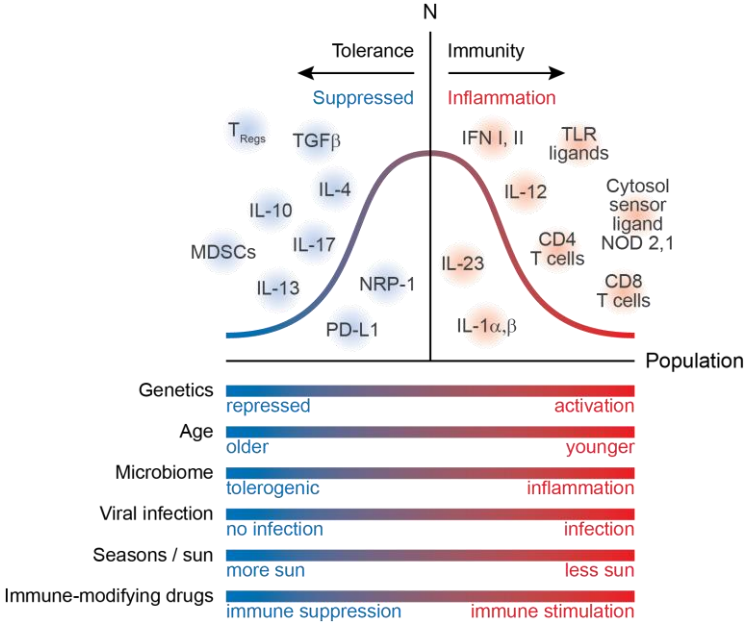
FDA-AACR Immuno-Oncology Drug Development
October 14, 2016

Immune Biology

a complex set of tumor, host and environmental factors govern strength, and timing of anti-cancer immune responses



Chen and Mellman. *Immunity* 2013



Chen and Mellman. *Publication pending 2016*

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Non-Classical Responses after Radiographic PD

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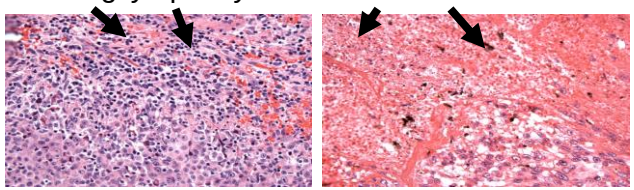
Atezolizumab monotherapy

Baseline | Week 6 | Week 12 | Week 18 | Week 46

Neck mass
Week 15
DFCI
(Hodi)

Infiltrating lymphocytes | Necrotic melanoma



Sosman et al. SMR Meeting 2013

Ipilimumab monotherapy

Screening | **12 wk** | **72 wk**

Wolchok et. al, 2009

Atezolizumab *(TECENTRIQ)*: Anti-PDL1 mAb
Ipilimumab *(YERVOY)*: Anti-CTLA mAb

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Non-Classical Responses: Reversion to SD or PR

Atezolizumab Monotherapy from Phase I study

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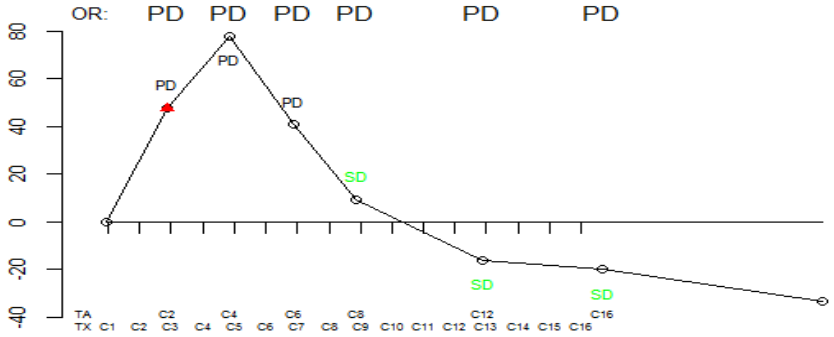
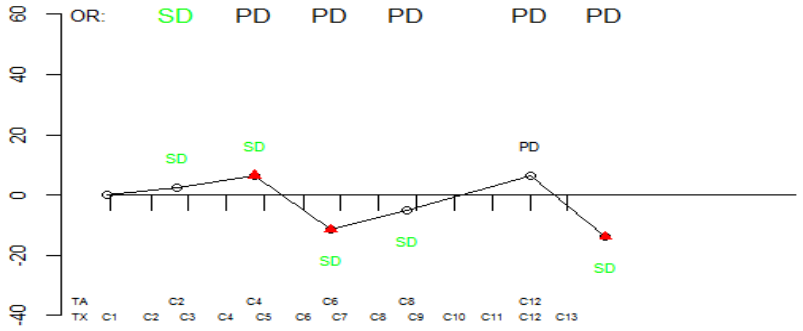
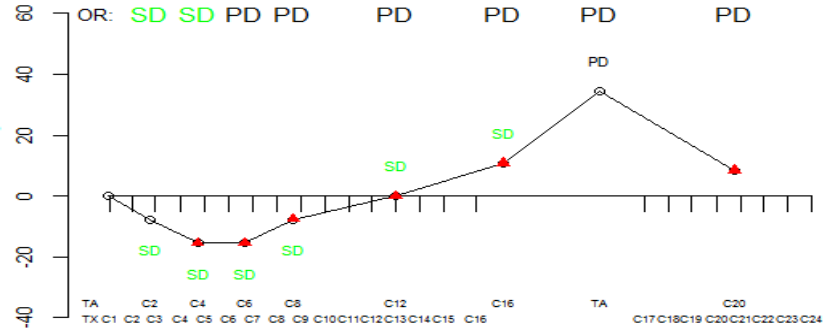
Atezolizumab monotherapy: RCC
RECIST: PD; irRC: PD



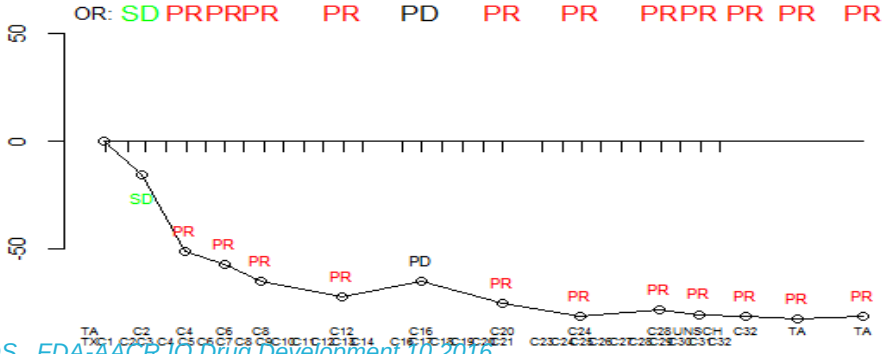
Atezolizumab monotherapy: NSCLC
RECIST: SD: irRC: SD



Atezolizumab monotherapy: NSCLC
RECIST: SD; irRC: SD



Atezolizumab monotherapy: RCC
RECIST: PR; irRC: PR



D.S. Chen, Ballinger, Chappey CIC 2014

Ballinger M, Lyons B, Winslow N, Fine G, Chen DS . FDA-AACR IO Drug Development 10 2016

Tumor burden can decrease in patients treated beyond RECIST 1.1 PD

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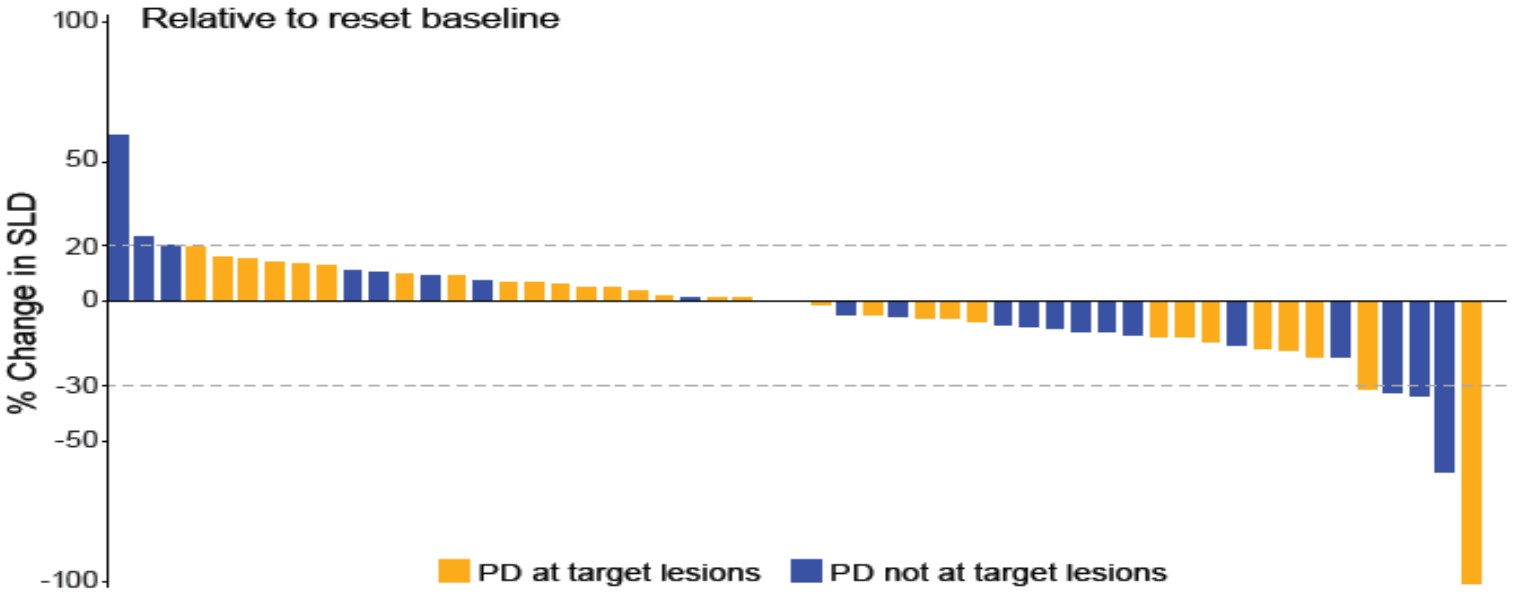
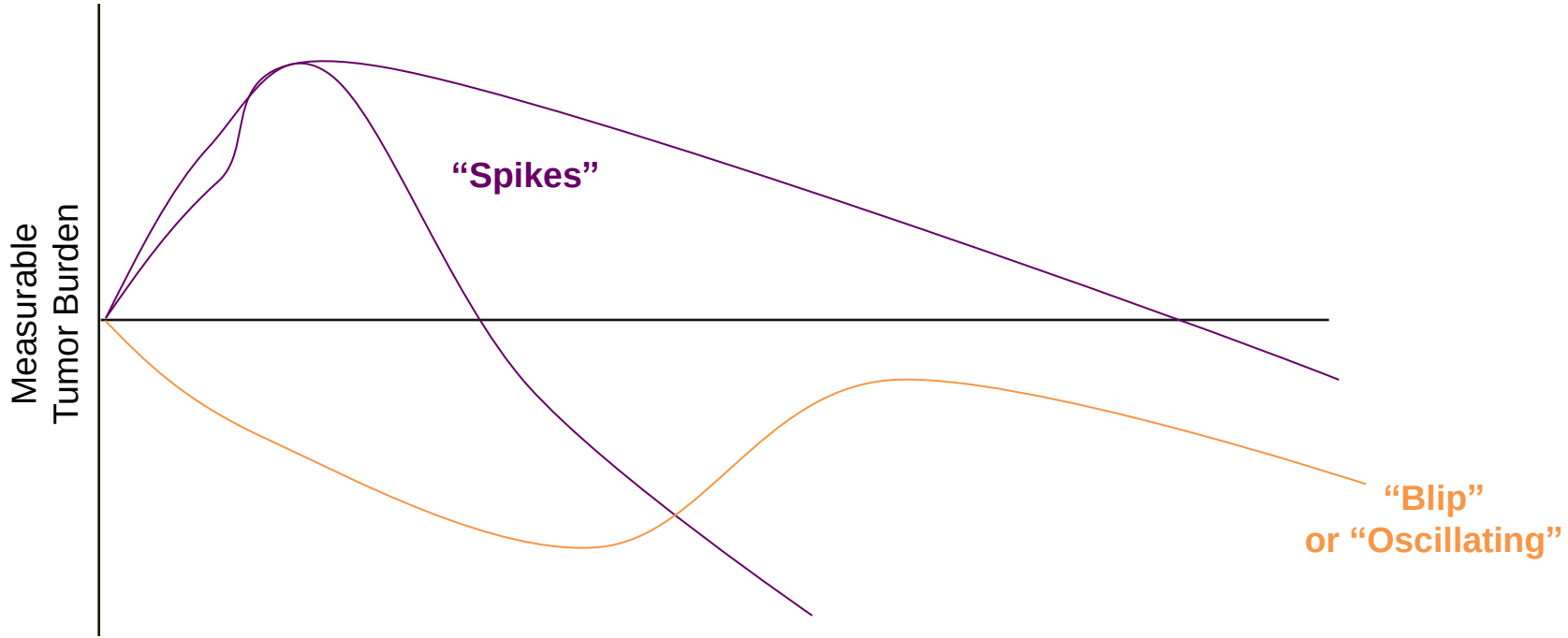
Atezolizumab treated *NSCLC patients (POPLAR study)*

Best change in target lesions from RECIST 1.1 PD for patients continuing atezolizumab beyond PD (investigator assessed)



Mazieres, et al ASCO 2016 *Ballinger M, Lyons B, Winslow N, Fine G, Chen DS . FDA-AACR IO Drug Development 10 2016*

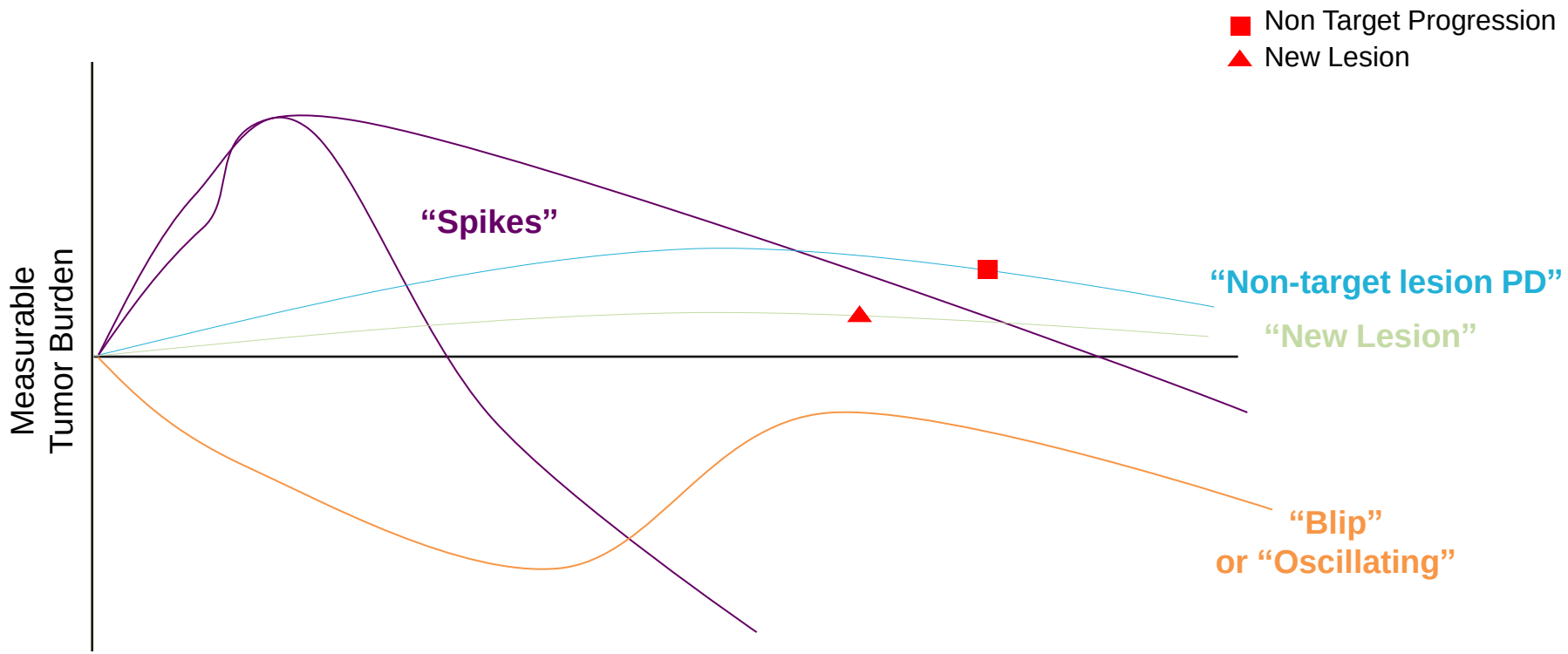
Patterns of Non-Classical Response



D.S. Chen, Ballinger, Chappey CIC 2014

Ballinger M, Lyons B, Winslow N, Fine G, Chen DS . FDA-AACR IO Drug Development 10 2016

Patterns of Non-Classical Response



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Patterns of Response with Atezolizumab:
First PD in Target Lesions that later reverts to non-PD

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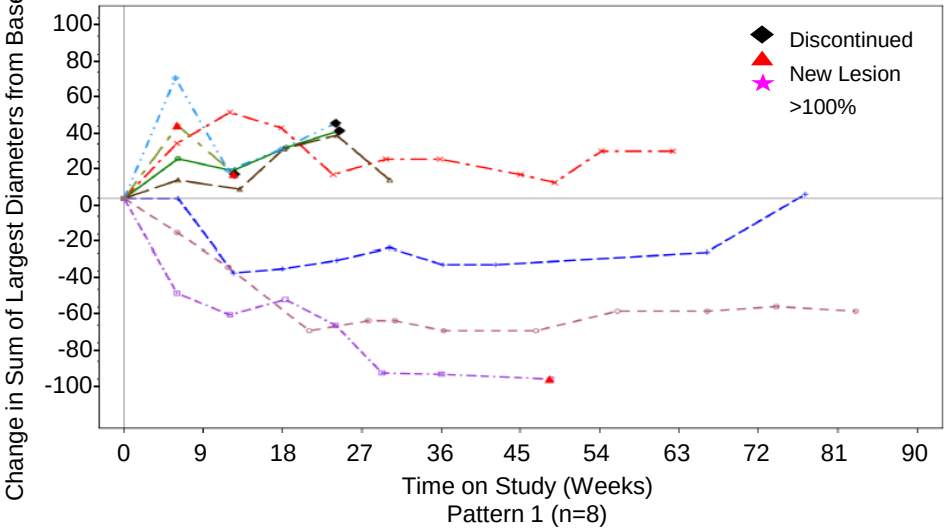
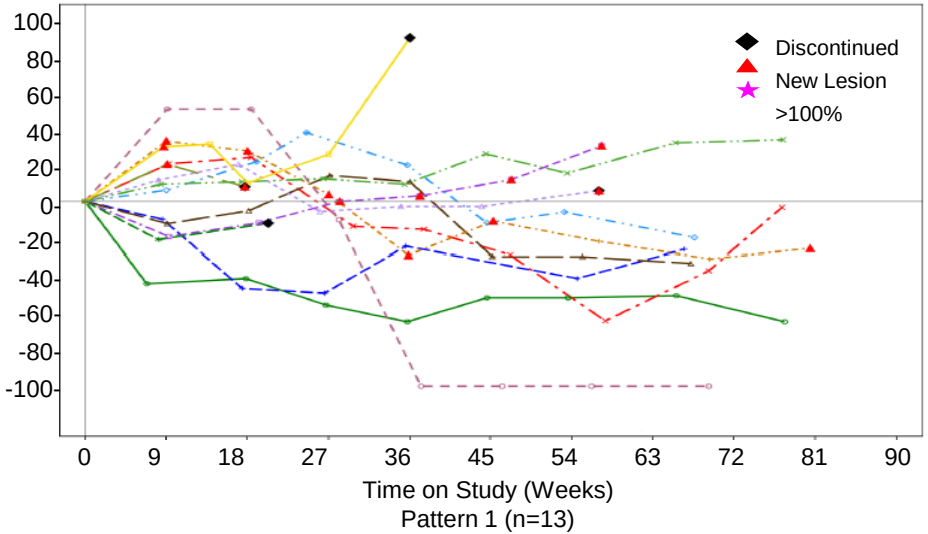
POPLAR (2L/3L NSCLC)
Sum of longest diameter



IMvigor 210 (2L+ mUC)
Sum of longest diameter



POPLAR: Randomized P2 study of Atezolizumab monotherapy in 2/3L NSCLC
IMvigor210: Atezolizumab P2 study in mUC (bladder cancer)

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Patterns of Response with Atezolizumab:
PD due to NL or NTL only

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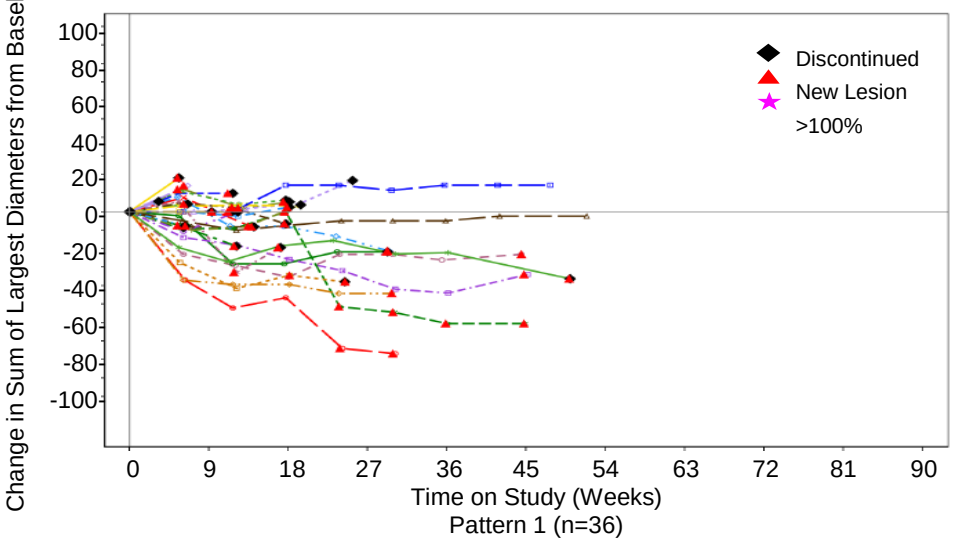
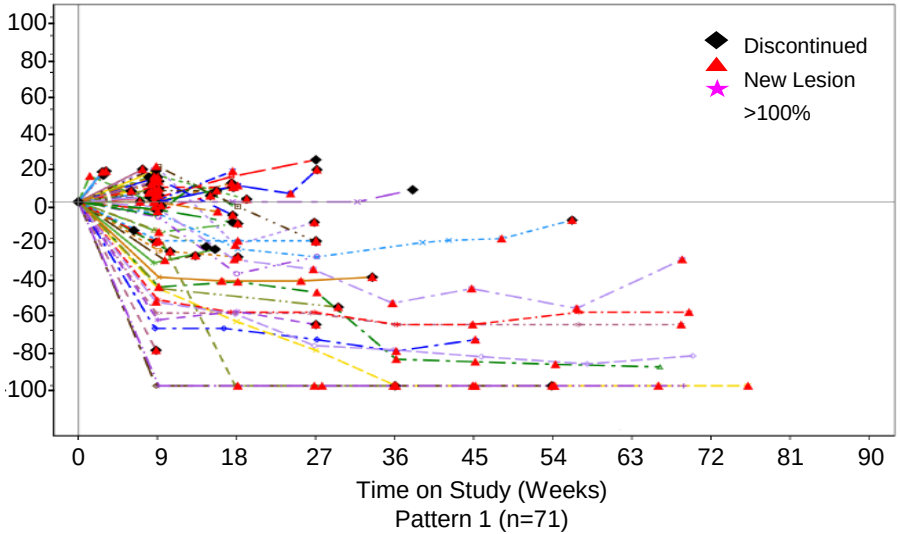
POPLAR (2L/3L NSCLC)
Sum of longest diameter



IMvigor 210 (2L+ mUC)
Sum of longest diameter



POPLAR: Randomized P2 study of Atezolizumab monotherapy in 2/3L NSCLC
IMvigor210: Atezolizumab P2 study in mUC (bladder cancer)

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Frequency of Atypical Response Patterns with Atezolizumab

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Pattern	#1 (Target Lesions Revert)	#2 (Non-target/New)
Definition	First PD due to target lesions progression that reverts to non-PD after further tumor scans	Non-Target or new Lesion PD without Target Lesion PD
Pattern addressed by imRECIST v1.0	Yes, PFS event may be negated by subsequent non-PD	Yes
Frequency in POPLAR (2L/3L NSCLC)	8/144 (5.6%)	36/144 (25%)
Frequency in IMvigor 210 (2L+ mUC)	13/310 (4.2%)	71/310 (22.9%)

Data cutoff: Dec 1, 2015

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Immune-modified Response Criteria aim to Capture Benefit that is Not Captured by RECISTv1.1

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- irRC (immune-related response criteria): derived from WHO; designed to better account for ipilimumab non-classical response patterns
- Immune-modified RECIST (imRECIST): derived from RECIST 1.1 using irRC principles
  - **Includes definitions for imPFS analysis**

	RECIST 1.1	irRC (Wolchok et al., 2009)	IM-RECIST (GNE/Roche)
Tumor burden	• Unidimensional • Up to 5 targel lesions/2 per organ	• Bidimensional per WHO • Up to 10 target lesions/5 per organ	**Unidimensional** per RECIST 1.1
New lesions	Always represent PD	• **New lesions do not categorically define PD** • Measurable new lesions incorporated into the total tumor burden. • Unmeasurable new lesions preclude CR	
Non-target lesions	Can contribute to defining CR or PD (unequivocal progression)	• **Non-Target progression does not define PD** • Can only contribute to defining CR (complete disappearance required)	
PD	• ≥ 20% increase in the SLD (RECIST) compared with baseline/nadir and/or • Unequivocal progression of non-target lesions and/or • Appearance of new lesions • Confirmation of PD not required	• **Determined only on the basis of measurable disease** • **Negated by subsequent non-PD assessment ≥ 4 weeks from the date first documented (lack of confirmation)**	
		• ≥ 25% increase in the SPD compared with baseline/nadir • Best response may occur prior to confirmed PD	• ≥ 20% increase in SLD (RECIST) compared with baseline/nadir • **Best response may occur after any number of PD assessments**

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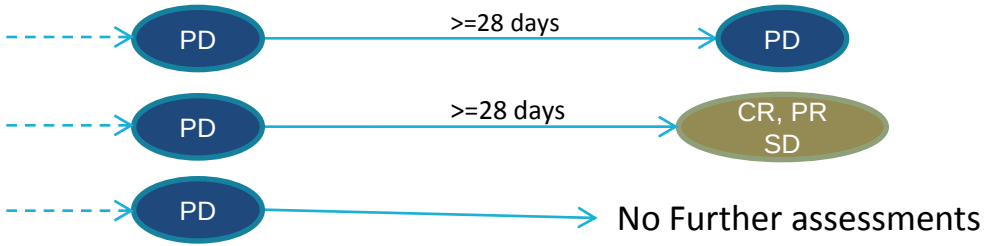
imRECIST PFS Event Definition

- PFS: PD event may be negated by subsequent non-PD assessment ≥ 4 weeks from the date first documented
  - However, PD followed by no further assessments is still counted as a PD event
  - Confirmed PD dated back to prior PD assessment



imRECIST PFS event?

Yes, dated to 1st PD

No

Yes

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imRECIST definitions extend PFS relative to RECISTv1.1

POPLAR: Atezolizimab-treated NSCLC Patients by PD-L1 IHC Expression

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Group	Median PFS (95% CI) mo	
	per RECIST 1.1	per imRECIST
All patients (n=144)	**2.7** (2.0, 4.1)	**4.3** (3.9, 7.0)
TC3 or IC3[a] (n=24)	**7.8** (2.7, 12.3)	**12.3** (7.8, 17.1)
TC2/3 or IC2/3 (n=50)	**3.4** (1.4, 6.9)	**7.8** (4.2, 12.0)
TC1/2/3 or IC1/2/3 (n=93)	**2.8** (2.6, 5.5)	**6.8** (4.1, 8.5)
TC0 and IC0 (n=51)	**1.7** (1.4, 4.2)	**4.1** (1.6, 4.4)

[a]**TC3 or IC3** = TC ≥ 50% or IC ≥ 10% PD-L1+ cells; **TC2/3 or IC2/3** = TC or IC ≥ 5% PD-L1+ cells; **TC1/2/3 or IC1/2/3** = TC or IC ≥ 1% PD-L1+ cells; **TC0 and IC0** = TC and IC < 1% PD-L1+ cells, respectively.

Data cutoff: Dec 1, 2015

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OS is increased in patients with extended imPFS
POPLAR atezolizumab arm (2L/3L NSCLC)

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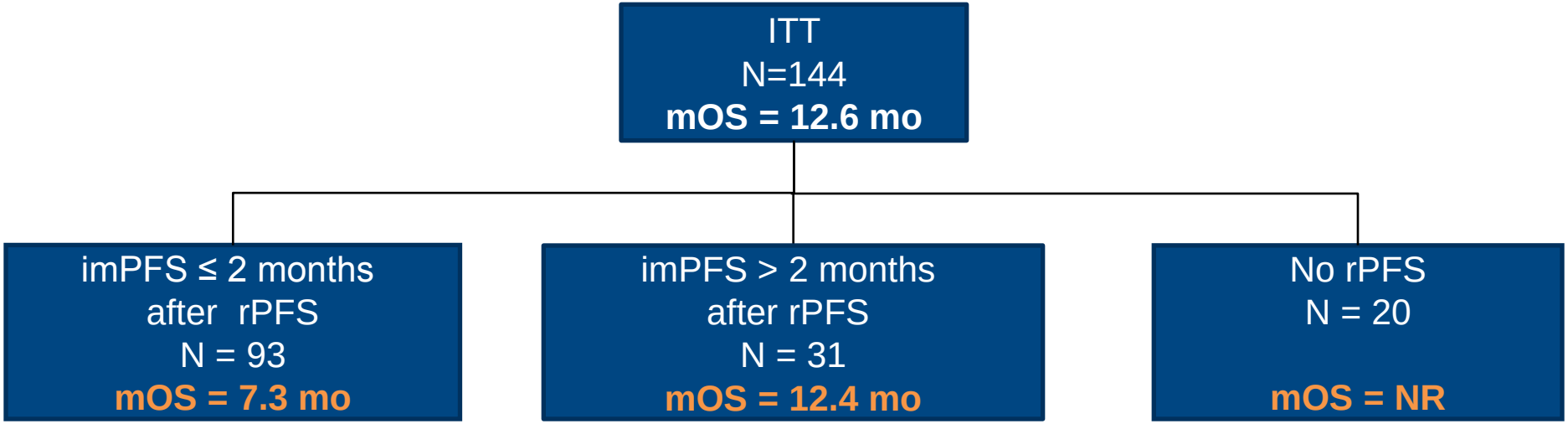
Compare OS according to difference in time between imPFS and rPFS event



Data Cut: May 2015

PFS = PFS event date, includes death
NR = not reached

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OS is increased in patients with extended imPFS

POPLAR atezolizumab arm (2L/3L NSCLC)

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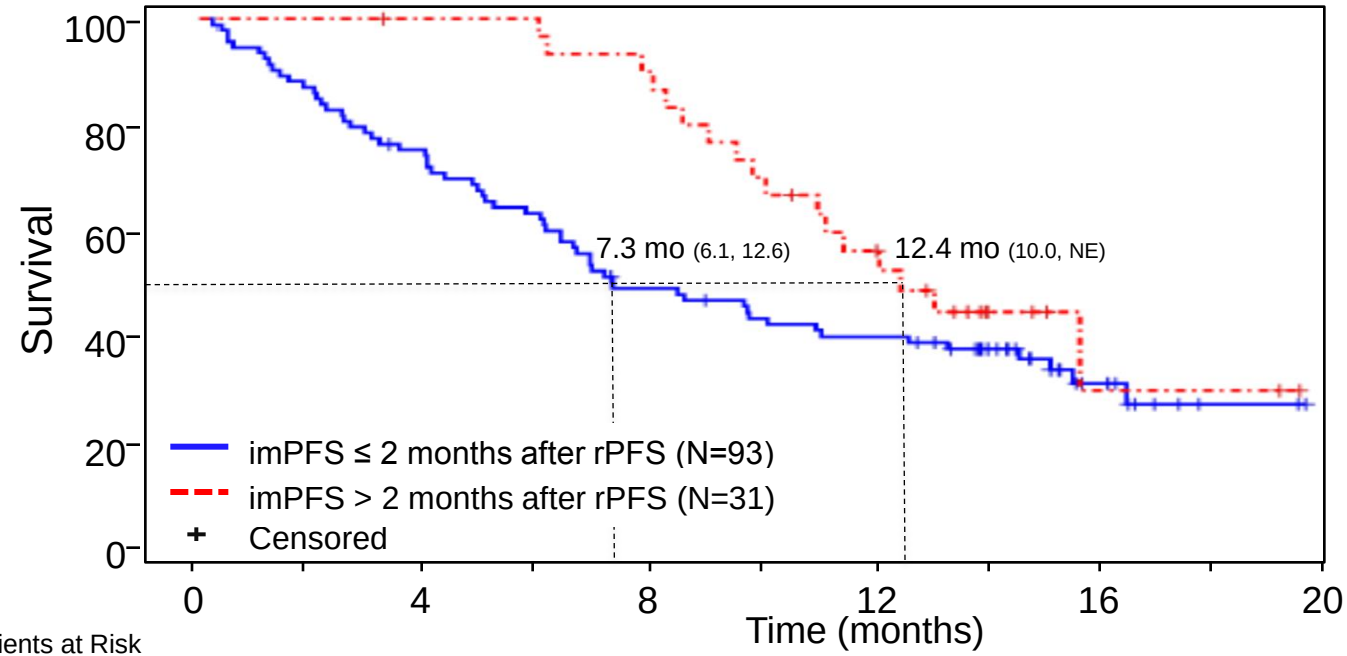

No. of Patients at Risk										
imPFS ≤ 2 months after rPFS	93	81	68	58	44	38	35	24	10	2
imPFS > 2 months after rPFS	31	31	30	29	27	21	15	5	2	2

Plot above does not include N=20 patients without a PFS event by RECIST 1.1 or imRECIST that have 100% survival

Data Cut: May 2015

Excludes Patients w/o Radiographic PFS

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OS is increased in patients with extended imPFS
IMvigor 210 (2L+ mUC)

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ITT
N=310
mOS = 7.9 mo

imPFS ≤ 2 months after rPFS
N = 238
mOS = 6.0

imPFS > 2 months after rPFS
N = 35
mOS = 13.3

No rPFS
N = 37
mOS = NR

PFS = PFS event date, includes death
NR = not reached

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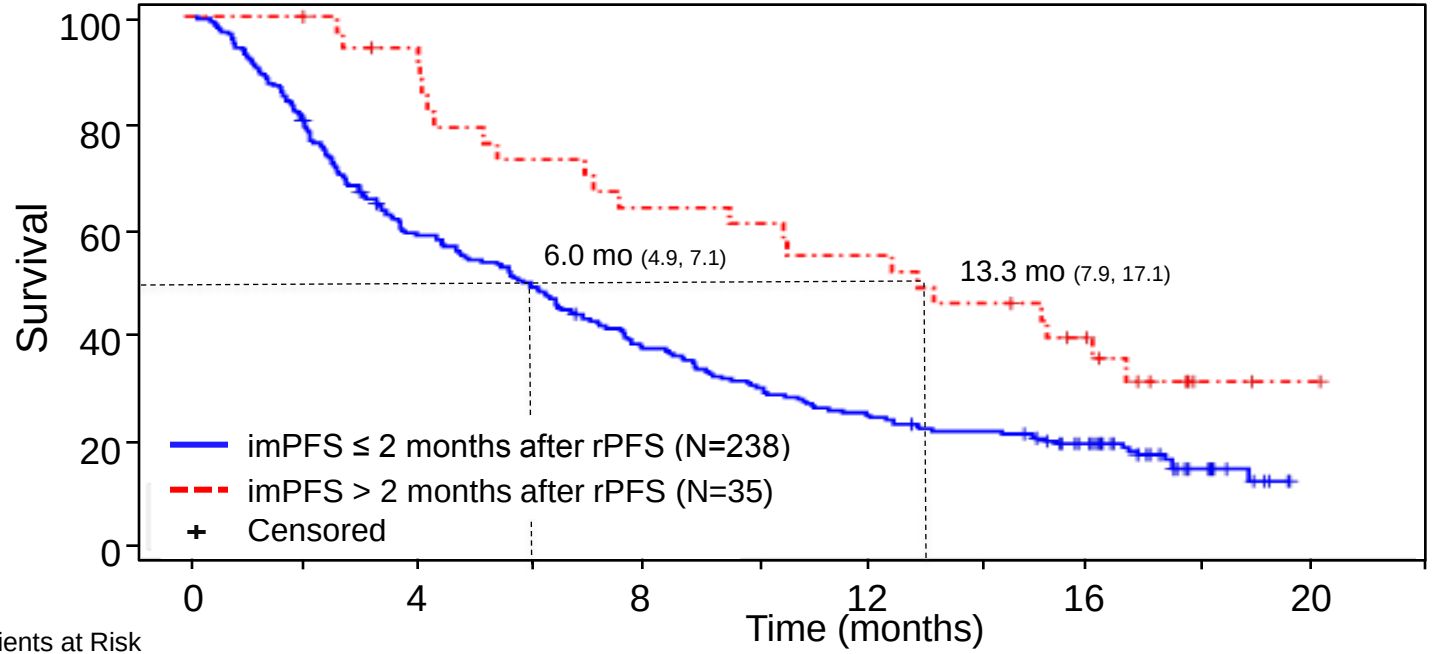
Data Cut: March 2016

OS is increased in patients with extended imPFS

IMvigor 210 (2L+ mUC)



No. of Patients at Risk											
imPFS ≤ 2 months after rPFS	238	195	127	117	90	71	57	47	37	14	2
imPFS > 2 months after rPFS	35	35	31	24	21	21	18	15	12	5	1

Plot above does not include N=37 patients without a PFS event by RECIST 1.1 or imRECIST that have 100% survival

Data Cut: March 2016

Excludes Patients w/o Radiographic PFS

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Summary

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- Anti-Cancer Immunity may be influenced by tumor, host and environmental factors
  - Responses can be immediate, delayed or can follow inflammation/tumor swelling
  - Non-classical response patterns include 1) Target lesion increase followed by reversion 2) New lesions or Non-target lesion PD in the absence of target lesion PD 3) waxing and waning cancer immune responses
- imRECIST developed to better capture non-classical response patterns and evaluate PFS with CIT
  - Incorporates most irRC principles into a RECIST 1.1 – based framework
  - PFS event may be negated by subsequent non-PD assessment
  - Presence of new lesion does not automatically imply PD
  - imPFS may be a better predictor for OS
- Results to date (NSCLC, mUC with atezolizumab monotherapy):
  - Median PFS increased per imRECIST relative to RECIST 1.1
  - Change in PFS event time (imPFS vs rPFS) associated with longer OS
  - PD associated with *new lesions only more* common than reversion

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Ongoing Analyses and Potential Modifications to imRECIST

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- Analysis of OS and imRECIST according to lesion patterns
  - Importance of Non-target lesions and new lesions to clinical outcome
  - Lymph nodes vs other lesion types
- Alternate imRECIST PFS definitions
  - Allowance for PD negation at any subsequent assessment
- Collaboration with Cross-industry, academic and Health Authority efforts to standardize criteria
  - EORTC iRECIST working group
  - Cancer Immunotherapy Consortium of the Cancer Research Institute (CIC)

Ballinger M, Lyons B, Winslow N, Fine G, Chen DS . FDA-AACR IO Drug Development 10 2016

Acknowledgements

- Steve Hodi
- Jedd Wolchok
- Jean-Charles Soria
- Josep Tabernero
- Axel Hoos
- Eric Rubin
- Roger Dansey
- Ramy Ibrahim
- Tai-Tsang Chen
- Roy Herbst
- Omid Hamid
- Jill O'Donnell-Tormey
- Roel Funke
- Daniel Waterkamp
- Alan Sandler
- Xiaodong Shen
- Ed Cha
- Cathi Ahearn
- Priti Hegde
- Bill Grossman
- Jing Yi
- Connie Irl
- Ulrich Beyer
- Colombe Chappey
- Ira Mellman
- Hartmut Koeppen
- Marcin Kowanetz
- Maria Anderson
- Ina Rhee
- Friedrich Graf Finckenstein
- James Reimann
- Cathi Ahearn
- Genentech and Roche Investigators, Cancer Immunotherapy Working Group, Cancer Immunotherapy Committee, CIC/CRI

irRECIST and Survival Modeling

Keaven M. Anderson, Ph.D.
Distinguished Scientist, Late Development Statistics
Merck & Co., Inc., Kenilworth, NJ, USA

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MERCK

Overview

- Merck's rationale for irRECIST
  - Past and recent data
  - Based presentation by Eric Rubin, Andrea Perrone: ASCO Review of irRECIST, Overview of Merck's Strategy
- Survival modeling suggestion
  - Based on 2016 ESMO presentation by Blank, Ma, et al.

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Rationale for irRECIST

- As market access to immunotherapies increases, OS will be increasingly confounded as a primary endpoint in randomized studies due to crossover
  - PFS will be increasingly important as an endpoint to assess clinical benefit for immunotherapies
- Recent analyses of randomized studies indicate that immunotherapies may yield an improvement in OS with minimal or no improvement in PFS, as assessed by RECIST 1.1
- Using RECIST 1.1 to identify progression times may underestimate PFS effect sizes for immunotherapy
- IrRECIST-like determination of disease progression correlates better with OS than RECIST 1.1-determined progression for immunotherapy in multiple cancer types
- A uniform definition of irRECIST is needed

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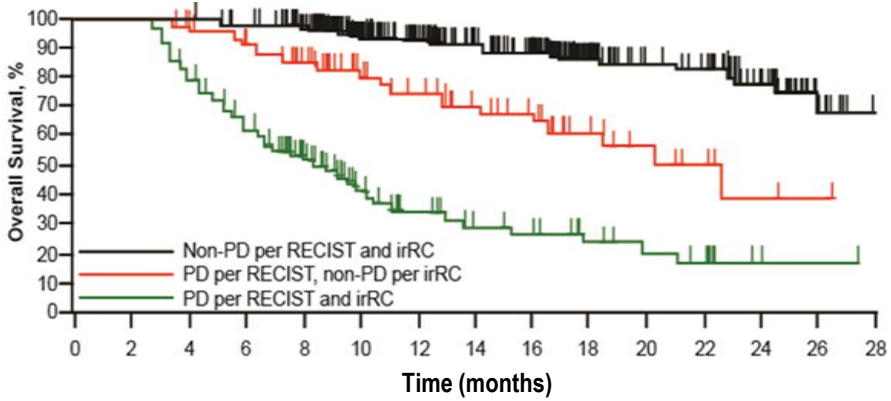
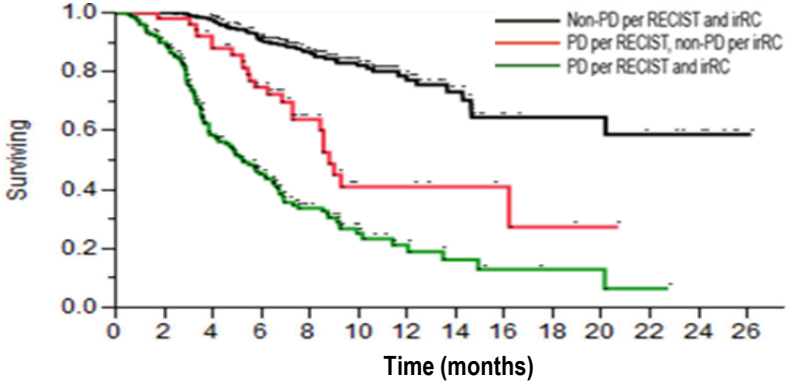
Association of Overall Survival With Tumor Response (RECIST vs irRC)

MK3475-001 Melanoma



MK3475-001 NSCLC



PD: Progressive disease
DC: Disease control, including CR, PR, and SD
NE: Not evaluable

PRESENTED AT: ASCO Annual '15 Meeting

Analysis cutoff: October 2014.

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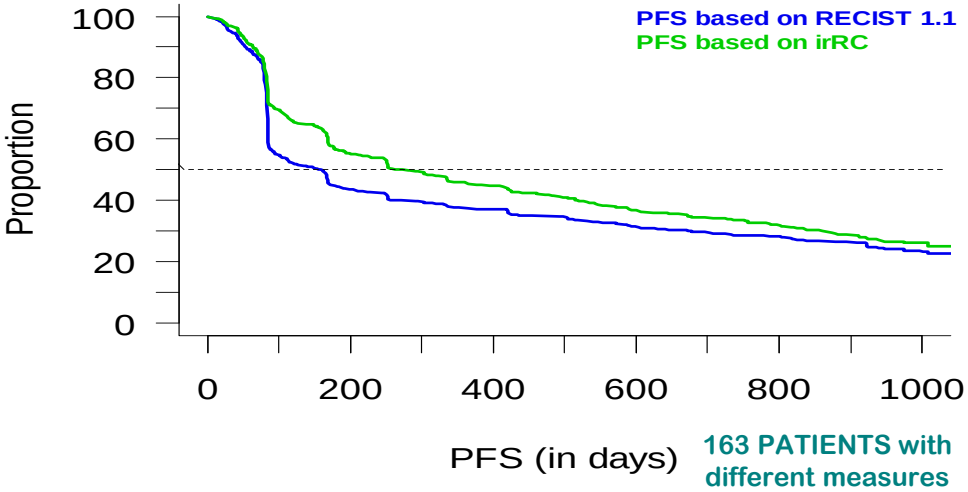
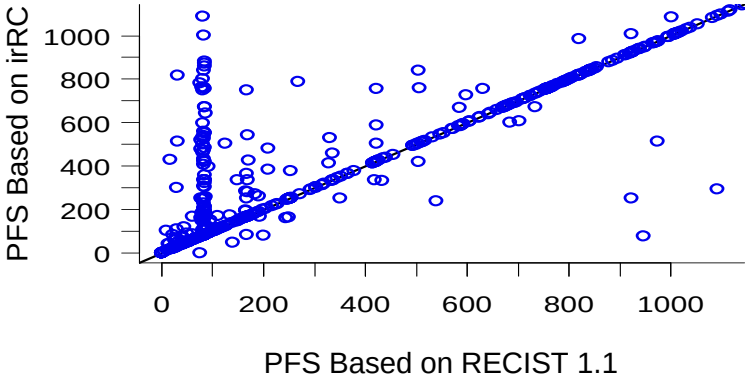
KN001 Melanoma Cohort: All Patients



163 PATIENTS with different measures

PFS Endpoint	Median PFS (months)	Difference (relative to RECIST 1.1)
Based on RECIST 1.1	5.30	NA
Based on irRC	9.24	3.94



- 492/655 (75.1%) have exactly the same PFS using RECIST 1.1 and irRC
  - 20/655 (3.1%) have longer PFS using RECIST 1.1
  - 143/655 (21.8%) have longer PFS using irRC

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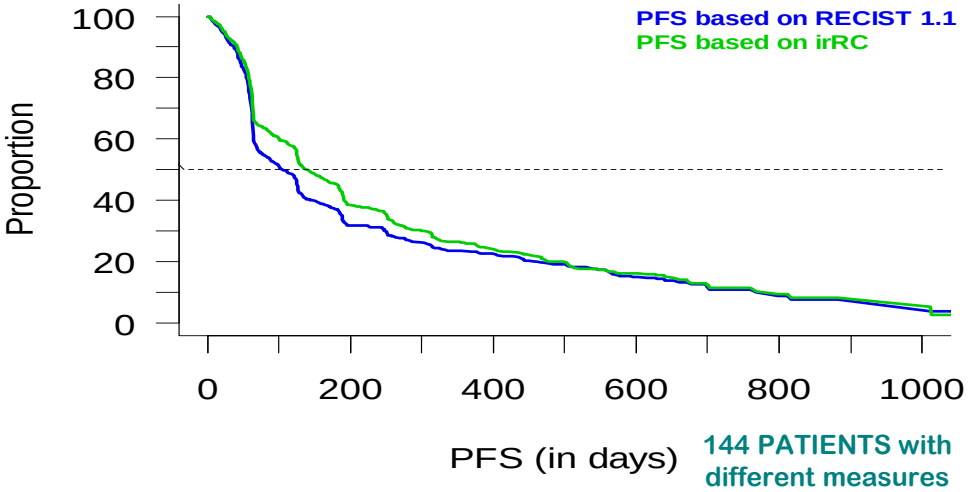
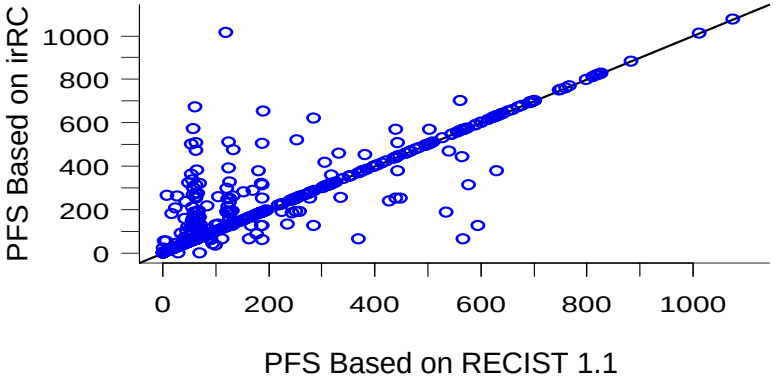
KN001 Lung Cohort: All Patients



144 PATIENTS with different measures

PFS Endpoint	Median PFS (months)	Difference (relative to RECIST 1.1)
Based on RECIST 1.1	3.49	NA
Based on irRC	4.57	1.08



- 423/567 (74.6%) have exactly the same PFS using RECIST 1.1 and irRC
  - 34/567 (6.0%) have longer PFS using RECIST 1.1
  - 110/567 (19.4%) have longer PFS using irRC

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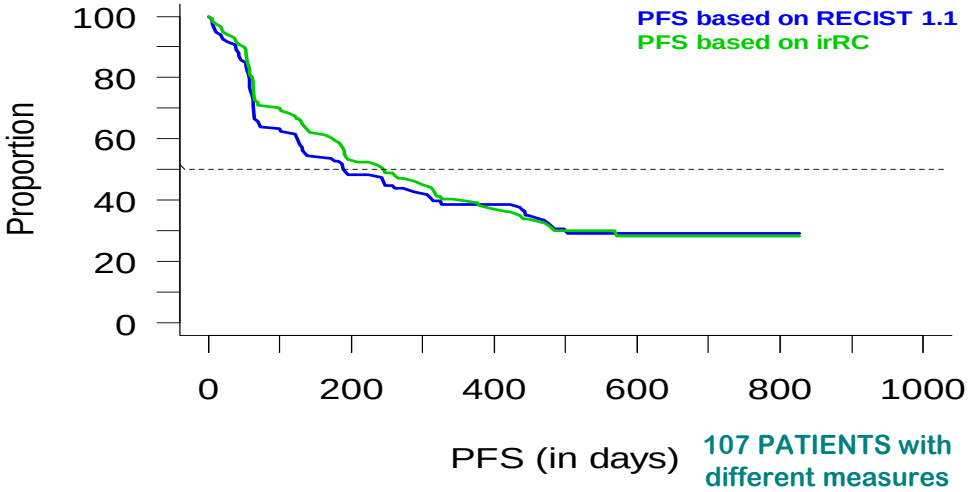
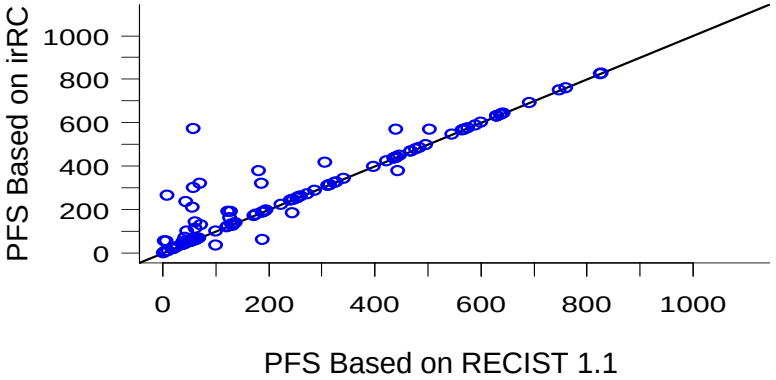
KN001 Lung Cohort: TPS ≥50%



107 PATIENTS with different measures

PFS Endpoint	Median PFS (months)	Difference (relative to RECIST 1.1)
Based on RECIST 1.1	6.32	NA
Based on irRC	8.06	1.74



- 92/119 (77.3%) have exactly the same PFS using RECIST 1.1 and irRC
  - 5/119 (4.2%) have longer PFS using RECIST 1.1
  - 22/119 (18.5%) have longer PFS using irRC

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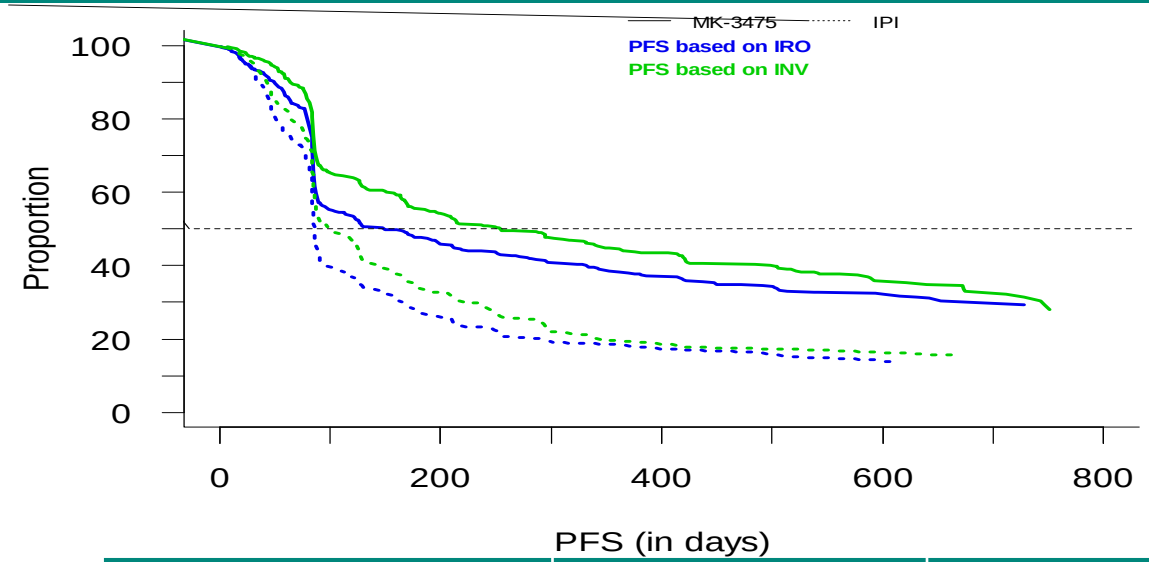
KN006 Melanoma: All patients IRO vs INV



	Median PFS (months)		Improvement in Median PFS relative to IPI (months)	
PFS Endpoint	**IPI**	**MK-3475**	**IPI**	**MK-3475**
Based on IRO	2.83	4.93	NA	2.10
Based on irRC (INV)	3.32	8.39	NA	5.07
Difference (irRC – IRO)	0.49	3.46		

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Part 1 summary

- Conventional imaging criteria by RECIST 1.1 underestimates PFS effective size of immunotherapy
- Data gathering across the industry could support use of irRECIST rather than RECIST to evaluate PFS

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Part 2: Long-term survival modeling

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Estimating Long-Term Survival: Keynote 006

- Blank, Ma et. al, ESMO, 2016
- Based on Ipilumimb-naïve advanced melanoma patient population
  - March 2015 data cutoff
- Established “cure” (long-term survival) model used to approximate Kaplan-Meier estimate
  - de Castro et al, Computer Methods and Programs in Biomedicine, 2010
- 556 randomized to two pembrolizumab arms; 278 randomized to ipilimumab

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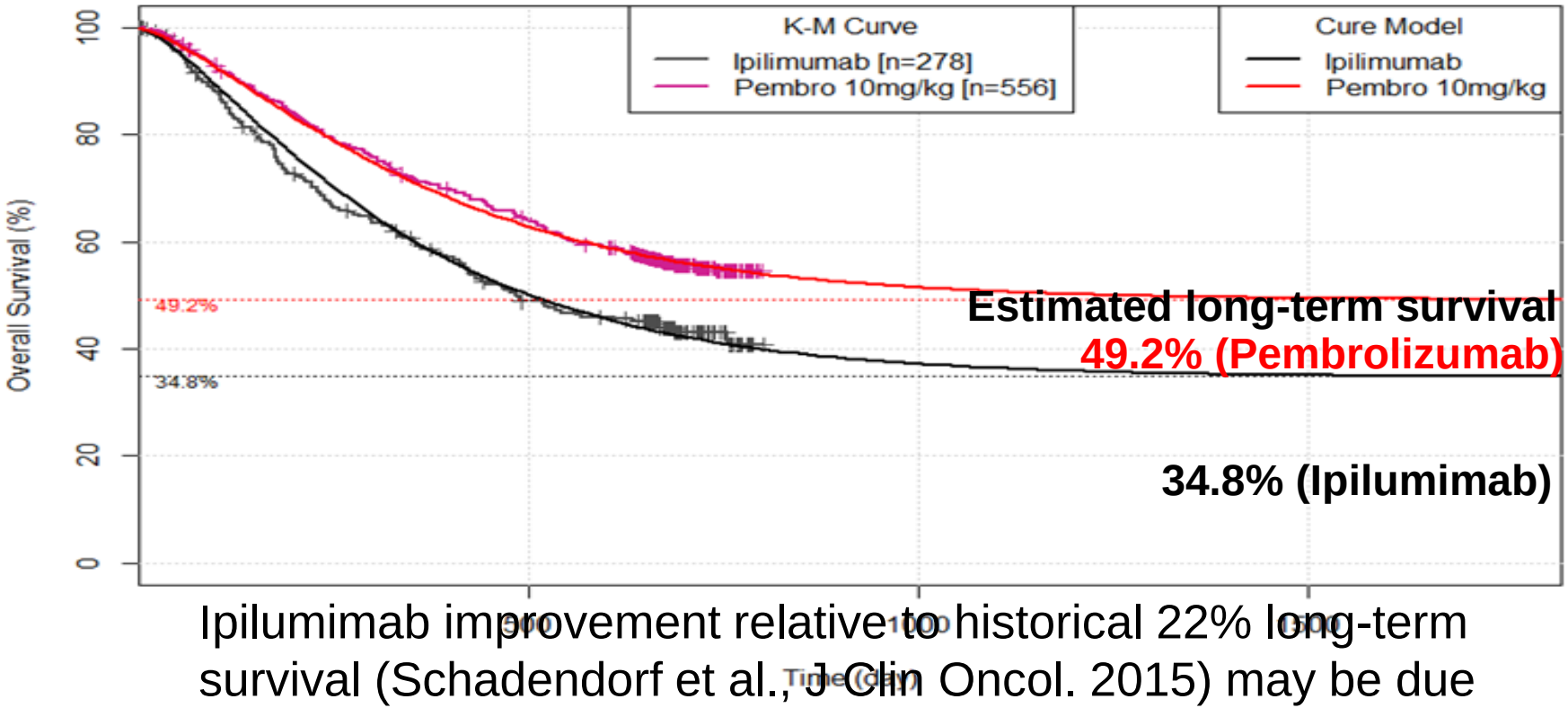
Modeling Long-Term Survival: Keynote 006



Ipilumimab improvement relative to historical 22% long-term survival (Schadendorf et al., J Clin Oncol. 2015) may be due to new therapeutic options for follow-on treatments

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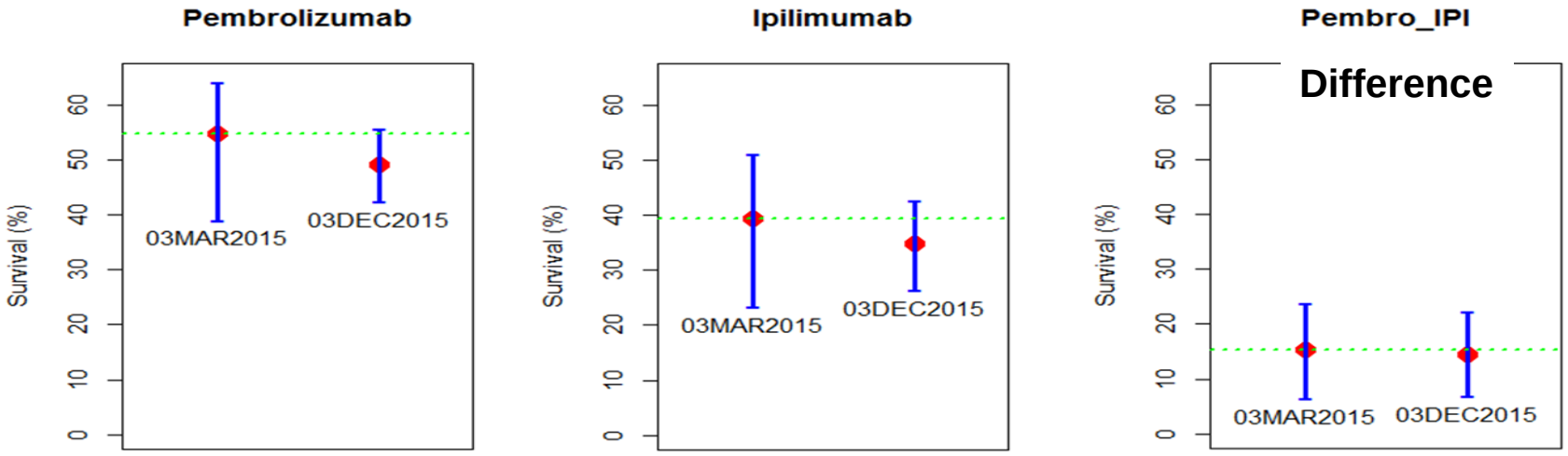
Interim Estimates of Long-Term Survival Stabilize with Increased Follow-up



- Confidence intervals (CI) useful to evaluate accuracy of long-term survival rate and benefit
  - CI shrinks with increased follow-up
- Model appears useful to project possible future survival rates

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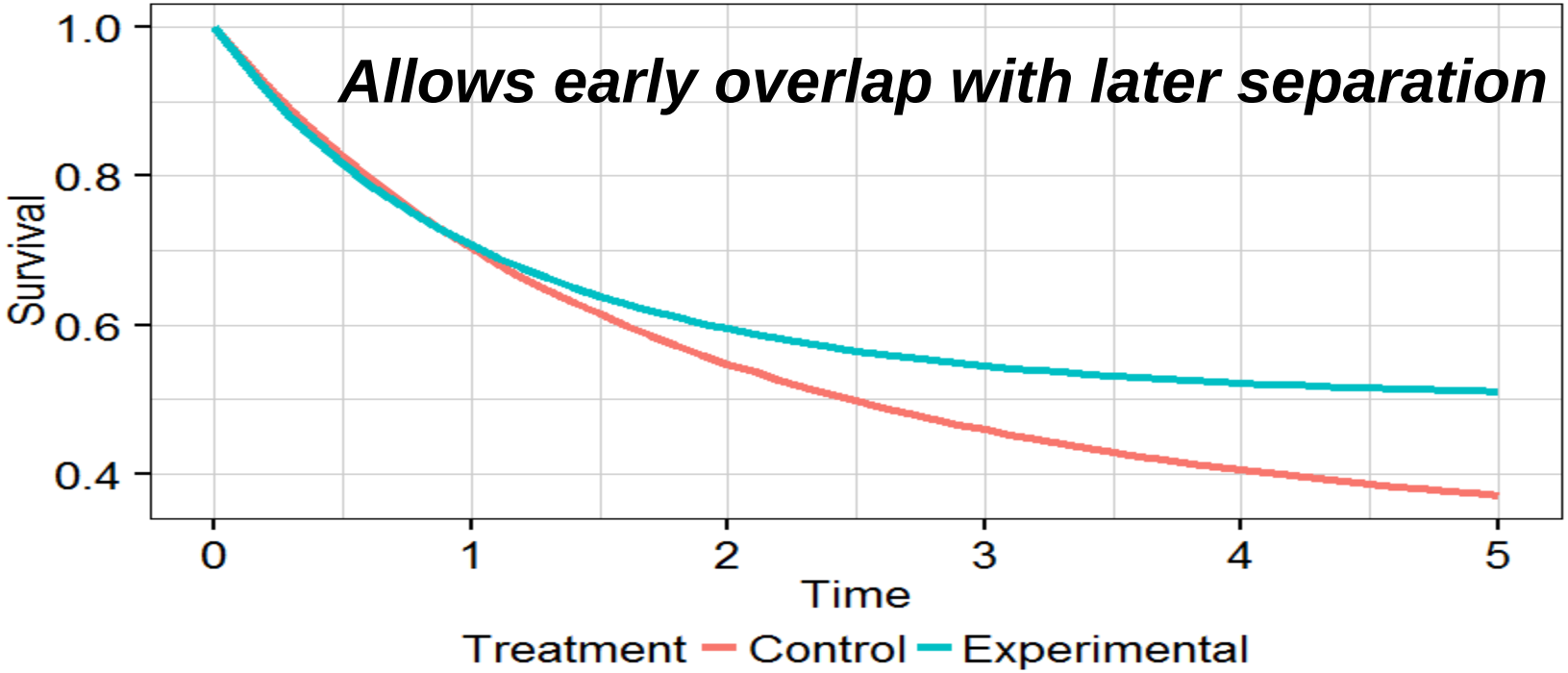
Example Hypothetical Model



Usefulness of model

- Stabilizing point estimates for ‘smooth’ Kaplan-Meier curves
- Confidence intervals (CI) useful to evaluate accuracy of long-term survival rate and benefit
  - CI shrinks with increased follow-up
- Model appears useful to project possible future survival rates
  - Covariates allowed, if needed
  - Late separation easily modeled
- Additional experience with this model may suggest use in immuno-oncology trials

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Alternative Survival Endpoints

Tai-Tsang Chen, PhD
Global Biometric Sciences, Bristol-Myers Squibb

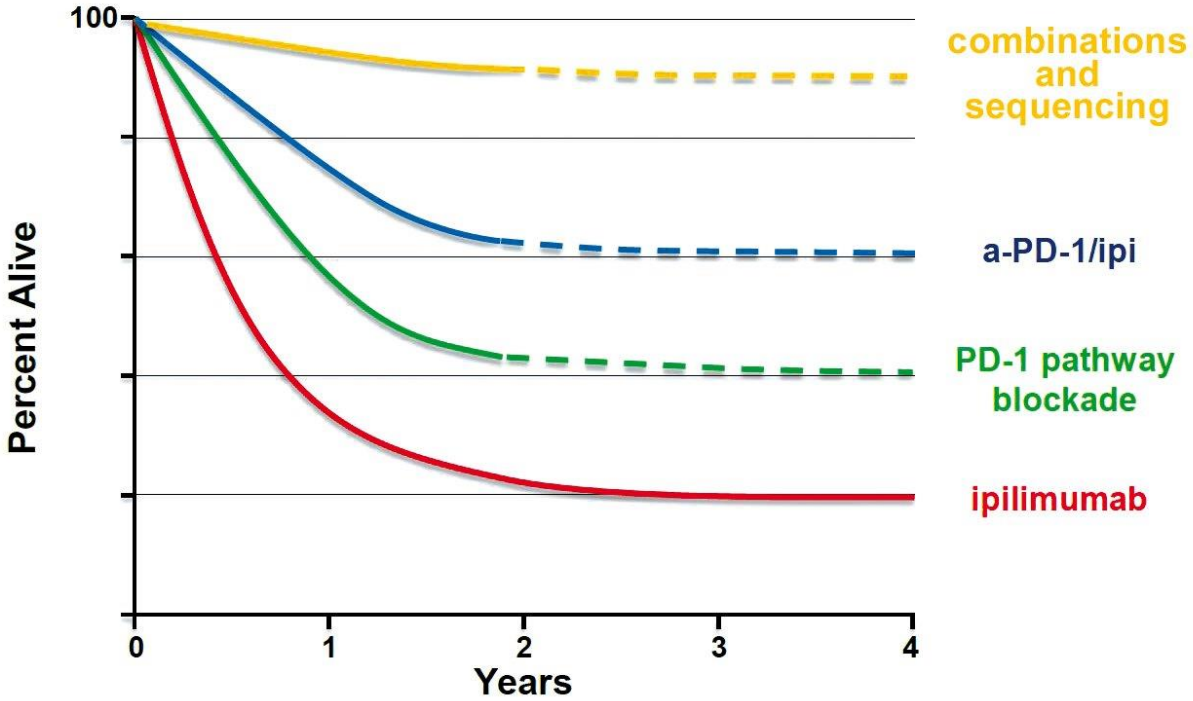
AACR-FDA Workshop, Washington, DC
October 13-14, 2016

Disclosure

- Employment: currently employed by Bristol-Myers Squibb as Head of Global Biometric Sciences in Medical and Market Access

- The views expressed in this presentation are personal based on my experience and do not necessarily reflect the views of Bristol-Myers Squibb

Promising Future and Challenges in Cancer Research



** Adapted from Walter Urba , ASCO 2013*

Focus of this Presentation

- The ultimate goal is to identify a short-term endpoint that can be used to predict clinical benefit, i.e., overall survival

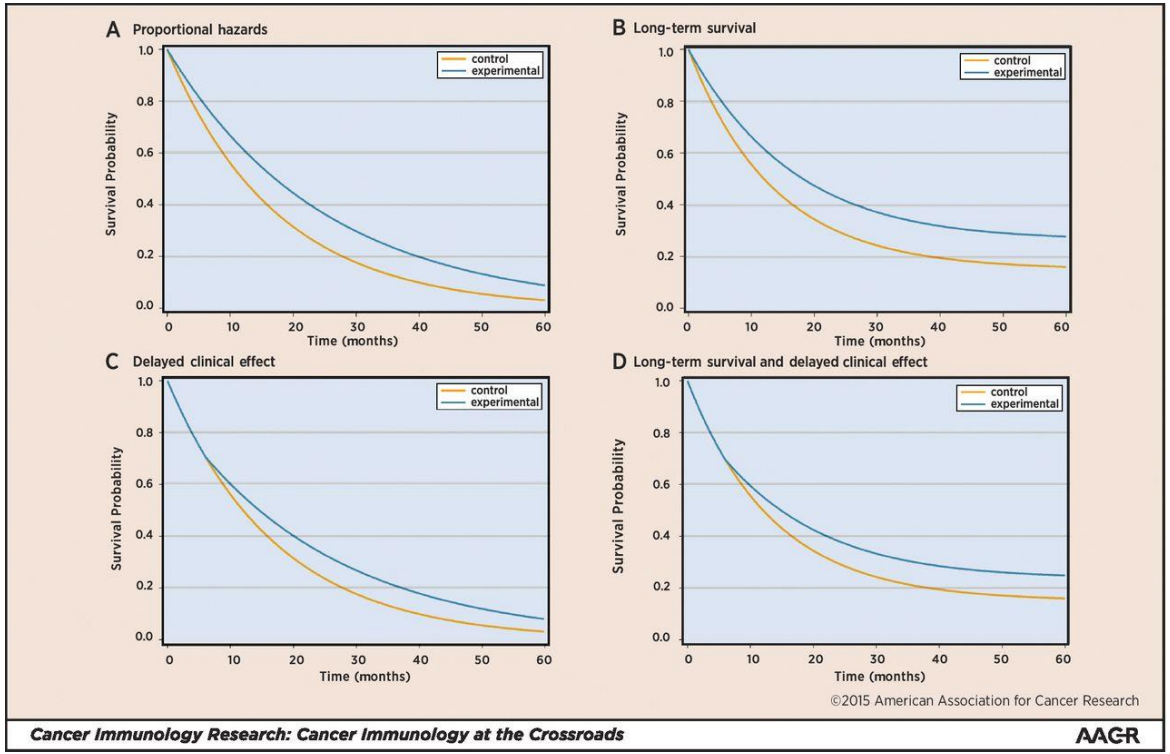
- The focus of this presentation is to introduce two alternative survival related endpoints
  - Milestone Survival
  - Restricted Mean Survival

Alternative Survival Endpoints

- Milestone Survival (MS)
  - Defined as the Kaplan-Meier survival probability at a specific time point defined a priori, such as two years
  - Can be measured by the difference or ratio

- Restricted Mean Survival Time (RMST)
  - Area Under the Kaplan-Meier Curve
  - Life expectancy for the restricted (truncated) duration
  - Can be measured by the difference or ratio

Graphical Presentation of Survival Kinetics



Comparison of Study Designs Among Survival Endpoints (One Scenario)

	PHM	PHCRM	NPHM	NPHCRM
Hazard Ratio	0.75	0.75	1/0.59	1/0.57
Delay/Long-Term Survival	NA	NA/0.1	8/NA	8/0.1
Overall Survival*	90%	91%	91%	89%
Milestone Survival (2-year)	80%	81%	88%	90%
Restricted Mean Survival (2-year)	89%	86%	84%	83%

** Log-rank test*

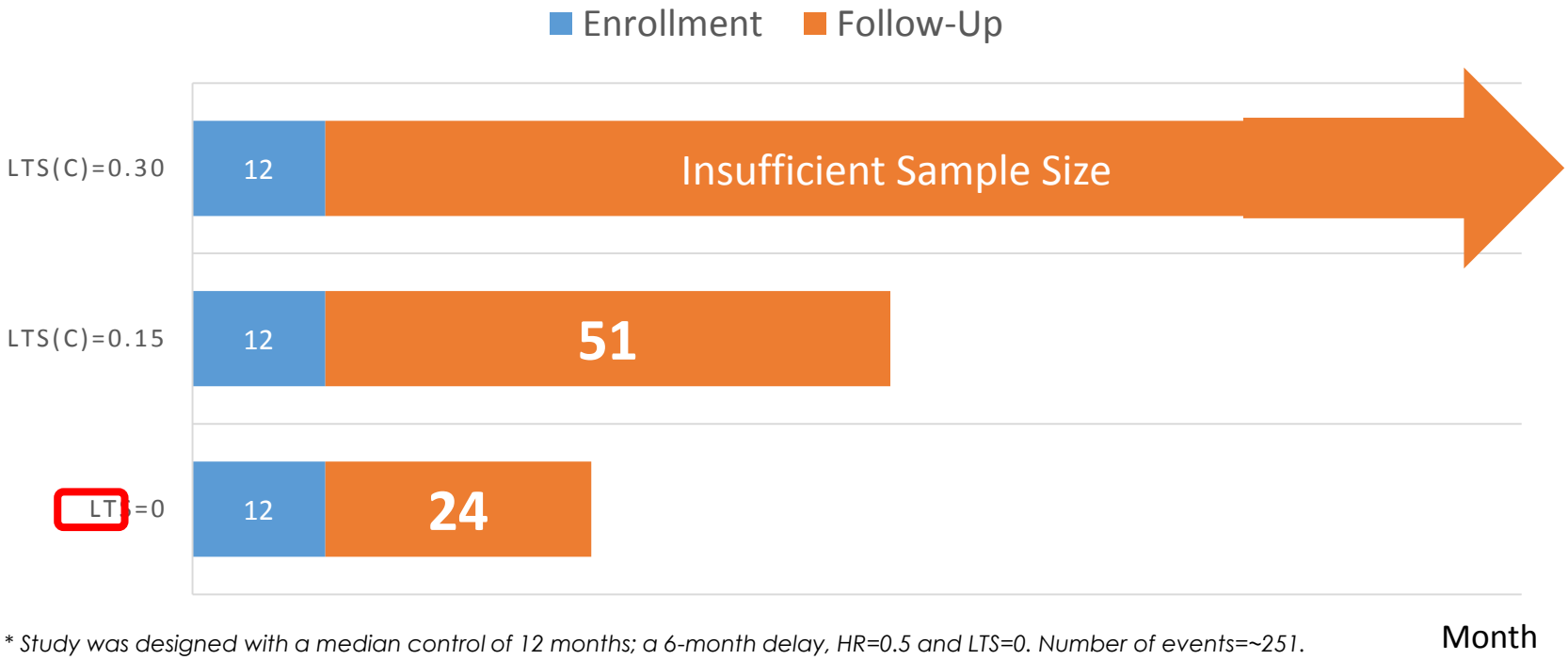
- Design Assumption
  - Minimum follow-up duration: 24 months
  - Power based on log-rank test: 90%
  - False positive rate: 5%
  - Control arm: exponential with median of 12 months

Why Alternative Survival Endpoints?

- Overall Survival (based on log-rank) remains a good clinical endpoint under the assumptions of proportional hazards and some patterns of non-proportional hazards

- Why do we consider other endpoints?
  - Non-proportionality in hazard ratio among I-O agents
  - The need for describing (time-dependent) treatment effects
  - Unpredictability of the analysis time based on OS

Impact of Misspecification of Long-Term Survival Effect on Trial Duration (N=345)



** Study was designed with a median control of 12 months; a 6-month delay, HR=0.5 and LTS=0. Number of events=~251.*

Reporting the Time-to-Event Outcome: An Illustrative Example based on Simulation

Conventional summary statistics:

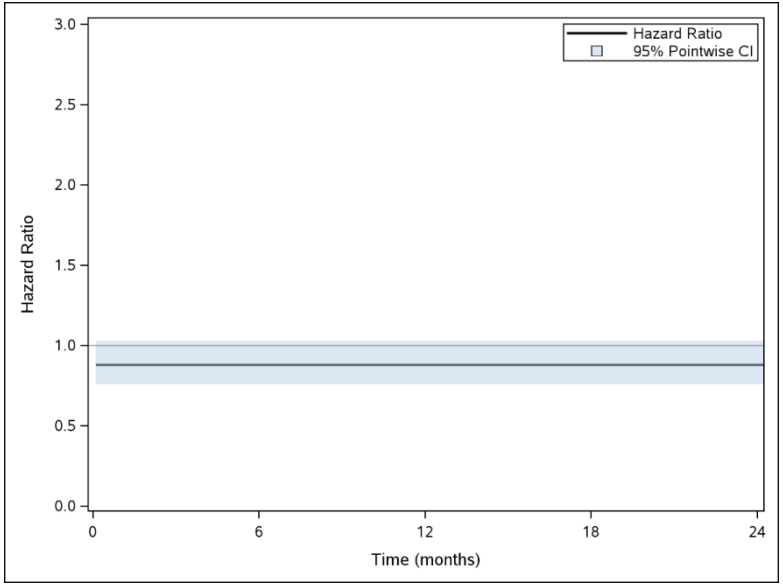
- Hazard Ratio (95% CI): 0.88 (0.76, 1.03)
- Median survival (95% CI)
  - Experimental treatment: 9.4 (8.3, 12.5)
  - Control treatment: 11.4 (9.3, 13.2)
- Log-rank statistic p-value: 0.1051

Issues:

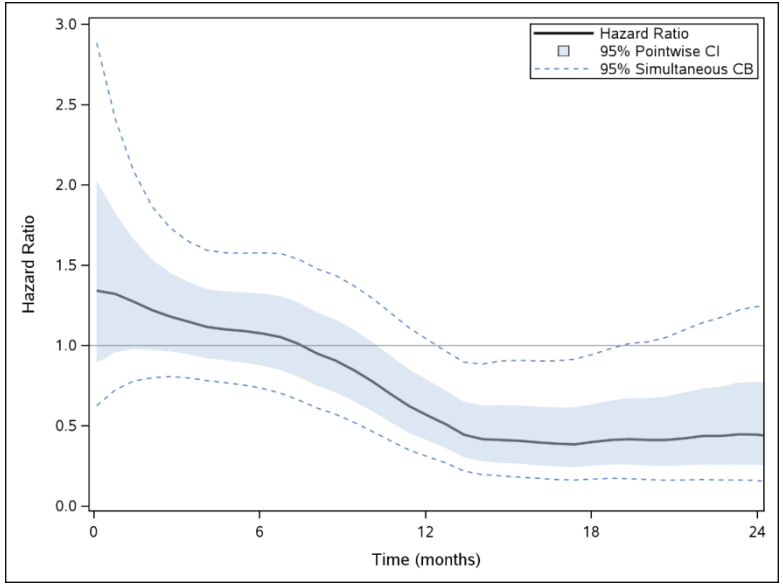
- The hazard ratio indicates that the experimental arm has
  - A better performance
  - A constant improvement in the treatment effect relative to the control
- Median survival is better in the control arm

Presentation of Hazard Ratio

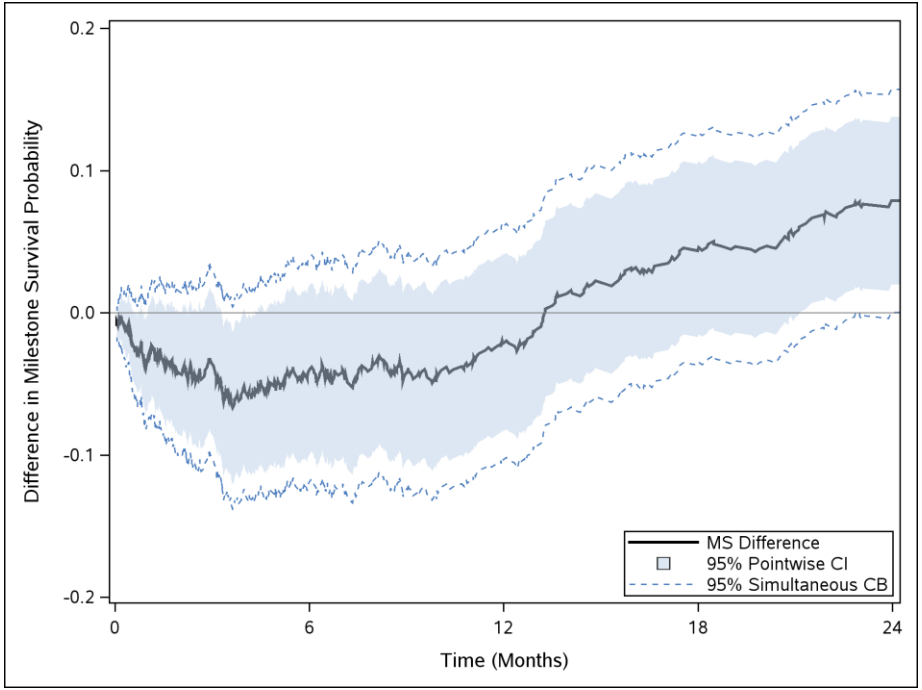
Constant Hazard Ratio



Hazard Ratio Over Time

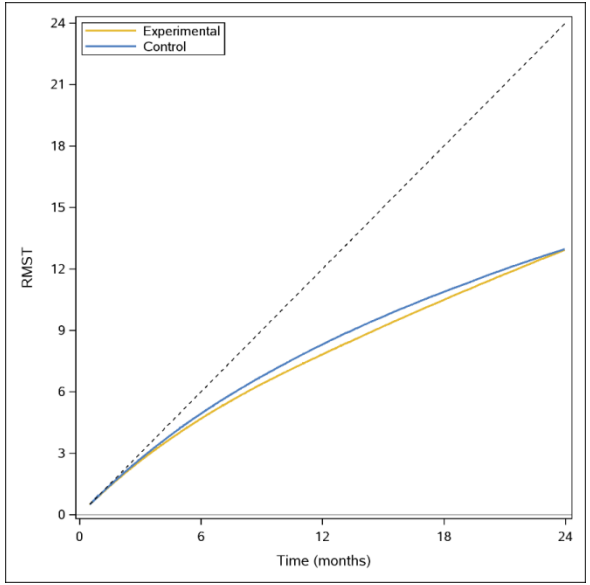


Difference in Milestone Survival Over Time

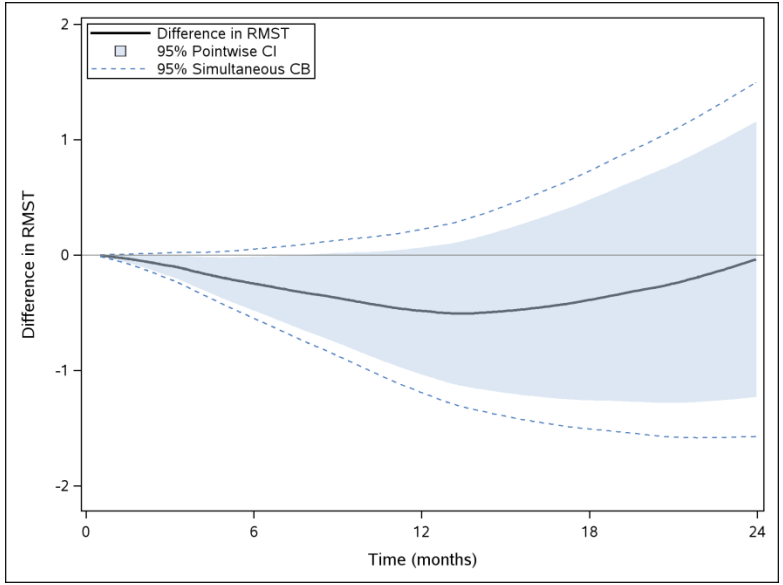


Restricted Mean Survival Over Time

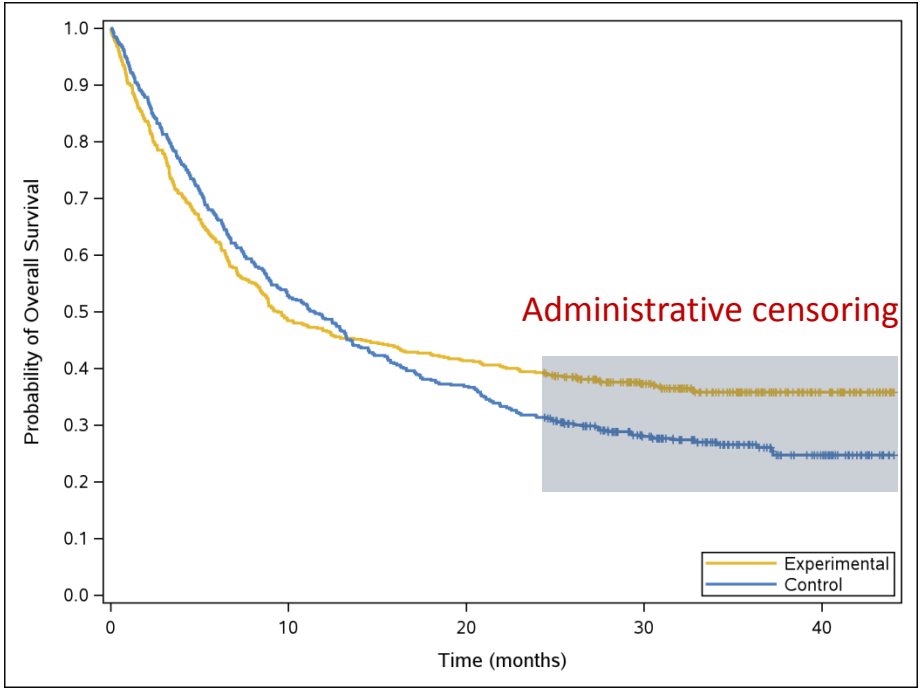
RMST by Arm



Difference in RMST



The Underlying Kaplan-Meier Curves



Summary

- Overall survival remains a very good endpoint under certain assumptions
- Alternative endpoints such as milestone or restricted mean survival
  - Predictable length of study duration (time-driven)
  - Survival endpoints
  - Allow both relative and absolute measure of treatment effects (over time)
  - More powerful under certain patterns of non-proportionality in hazard ratio
- Reporting of milestone survival, restricted mean survival and change in hazard ratio is recommended to complement KM curve

References (in chronological order)

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- Royston, P and Palmer, MKB. (2013). Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. BMRM, 13:152.
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- Tai-Tsang Chen. (2015). Milestone Survival: A Potential Intermediate Endpoint for Immune Checkpoint Inhibitors. *Journal of the National Cancer Institute*, 107(9): djv156.
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American Association for Cancer Research

FINDING CURES TOGETHER℠

Session IIIb Panel Discussion

Use of Alternate Efficacy Endpoints with I-O Products

Moderator: Marc Theoret, MD

Speakers:

Sirisha Mushti, PhD
Xin (Cindy) Gao, PhD
Antoni Ribas, MD, PhD
Jan Bogaerts, PhD
Daniel S. Chen, MD. PhD
Keaven Anderson, PhD
Tai-Tsang Chen, PhD

Panelist:

Kun He, PhD

Phase III Design Considerations for Agents with a Potential Predictive Biomarker

Edward L. Korn
Biometric Research Program
National Cancer Institute

Disclosure Information

FDA-AACR Immuno-Oncology Drug Development Public Workshop

Edward L. Korn

I have no financial relationships to disclose.

- and -

I will not discuss off label use and/or investigational use in my presentation.

- and -

The views expressed represent my own and do not necessarily represent the views or policies of the National Cancer Institute.

- Some agents may only benefit a subgroup of a histologically defined population

- Successful evaluation requires co-development of biomarkers to identify sensitive subpopulations

- Various design strategies to integrate treatment and biomarker evaluation are available

- Choice of phase III design depends on the biomarker's credentials

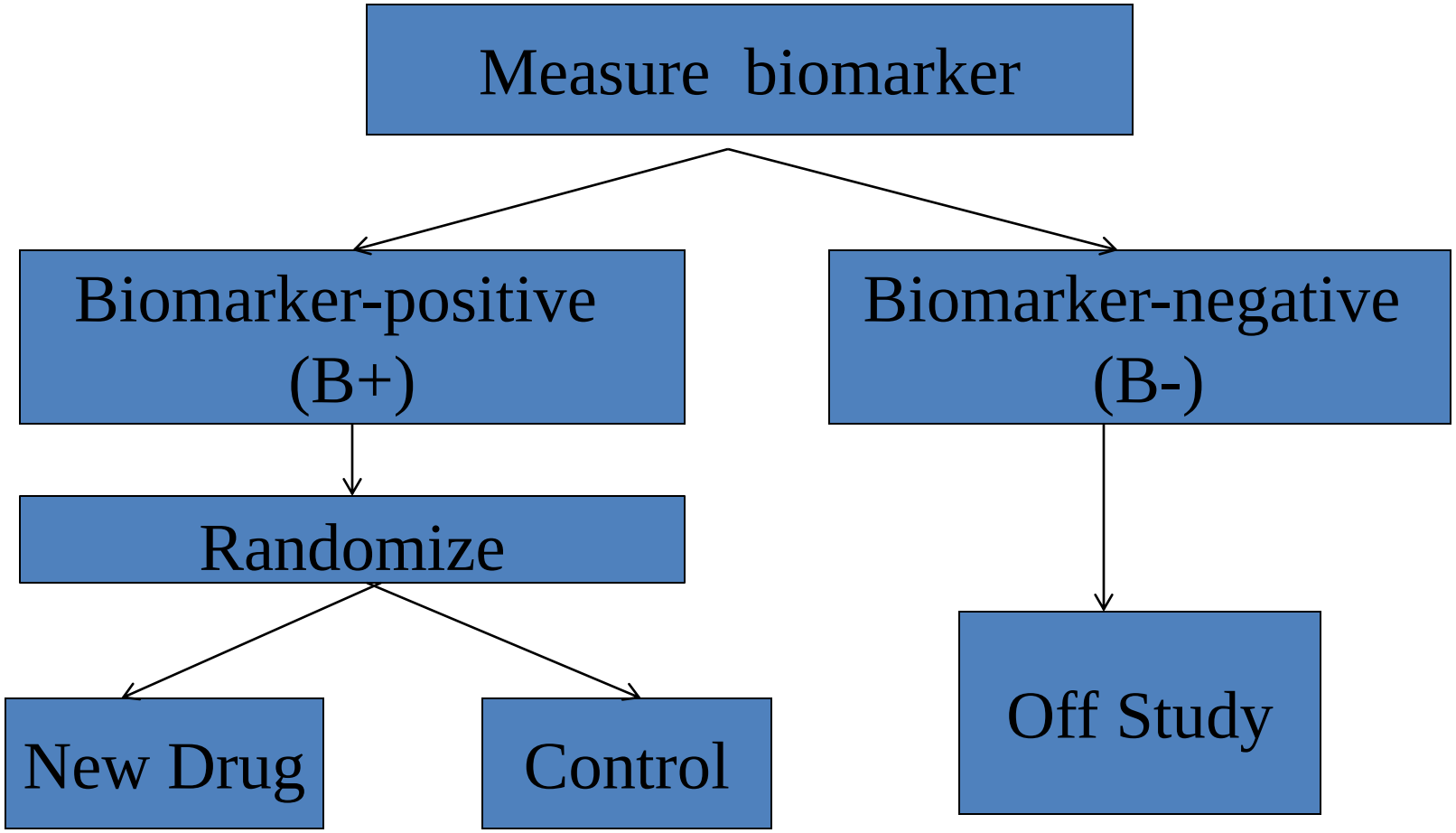
Focus of this talk

- Binary biomarker separates the population of interest into biomarker-positive (B+) and biomarker-negative (B-) subgroups
- Analytical validity of the biomarker assay has been established
- Biomarker credentials are sufficient to assume that B- patients benefit only if B+ patients benefit

Biomarker with very strong credentials:

Convincing evidence indicates that the benefits of the treatment, if any, are limited to the biomarker-positive subgroup of patients.

Biomarker with very strong credentials: use Enrichment design



Examples:

BRIM3 (metastatic melanoma)

-vemurafenib vs. standard chemotherapy

-2107 patients screened to identify 675 patients with BRAF mutation

KEYNOTE-010 (advanced NSCLC)

-pembrolizumab vs. docetaxel

-2699 patients screened to identify 1475 patients with PD-L1 expression of at least 1%

Limitations of Enrichment design:

Unless external evidence clearly limits benefit to B+ patients, a positive enrichment study leaves open:

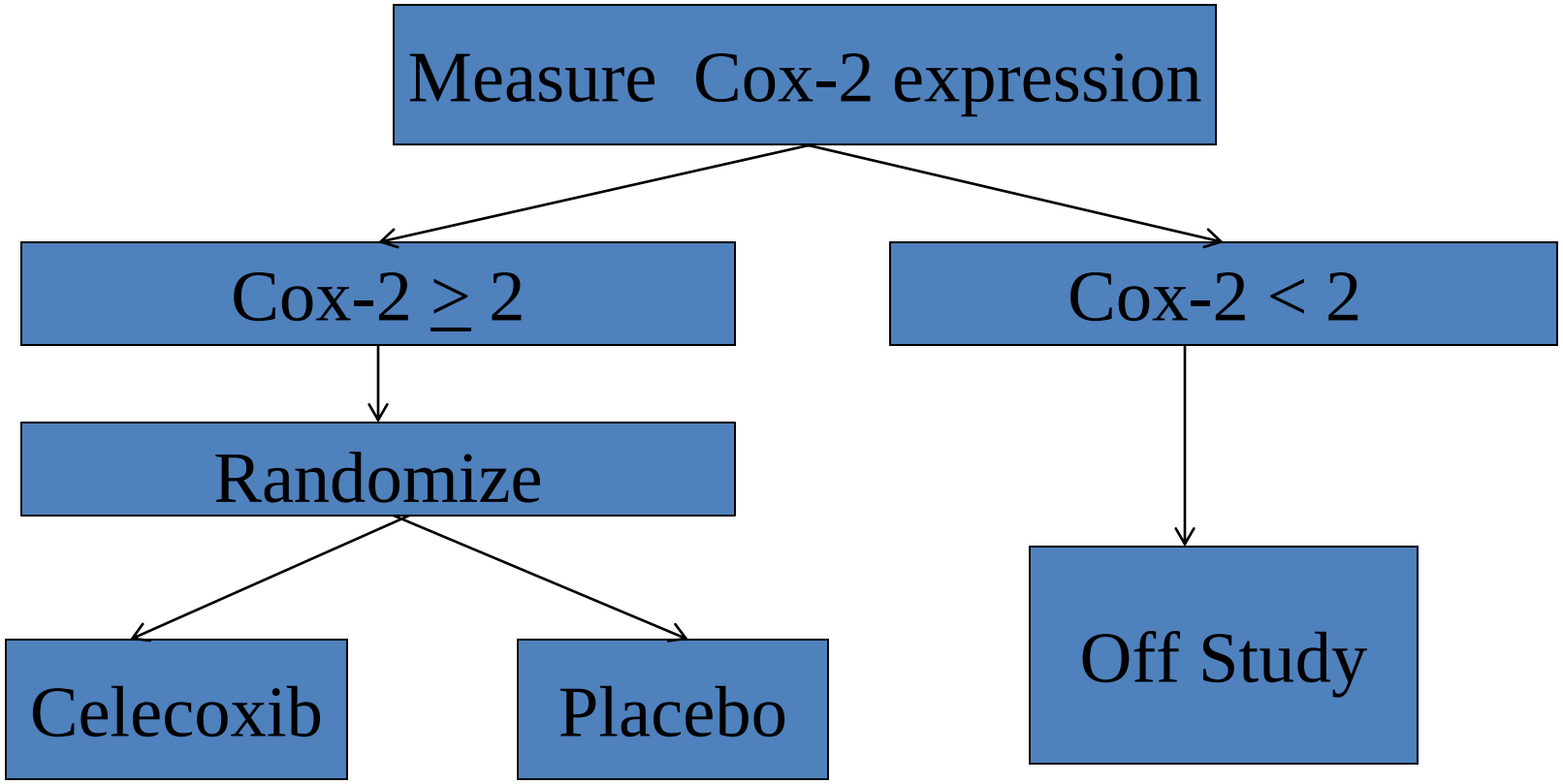
- Whether the treatment benefit extends to biomarker-negative patients
- Whether the costs and inconvenience of routine use of the biomarker to select patients for treatment are justified

Modified enrichment design (example)

CALGB 30801

Chemo+Celecoxib vs Chemo+Placebo in NSCLC

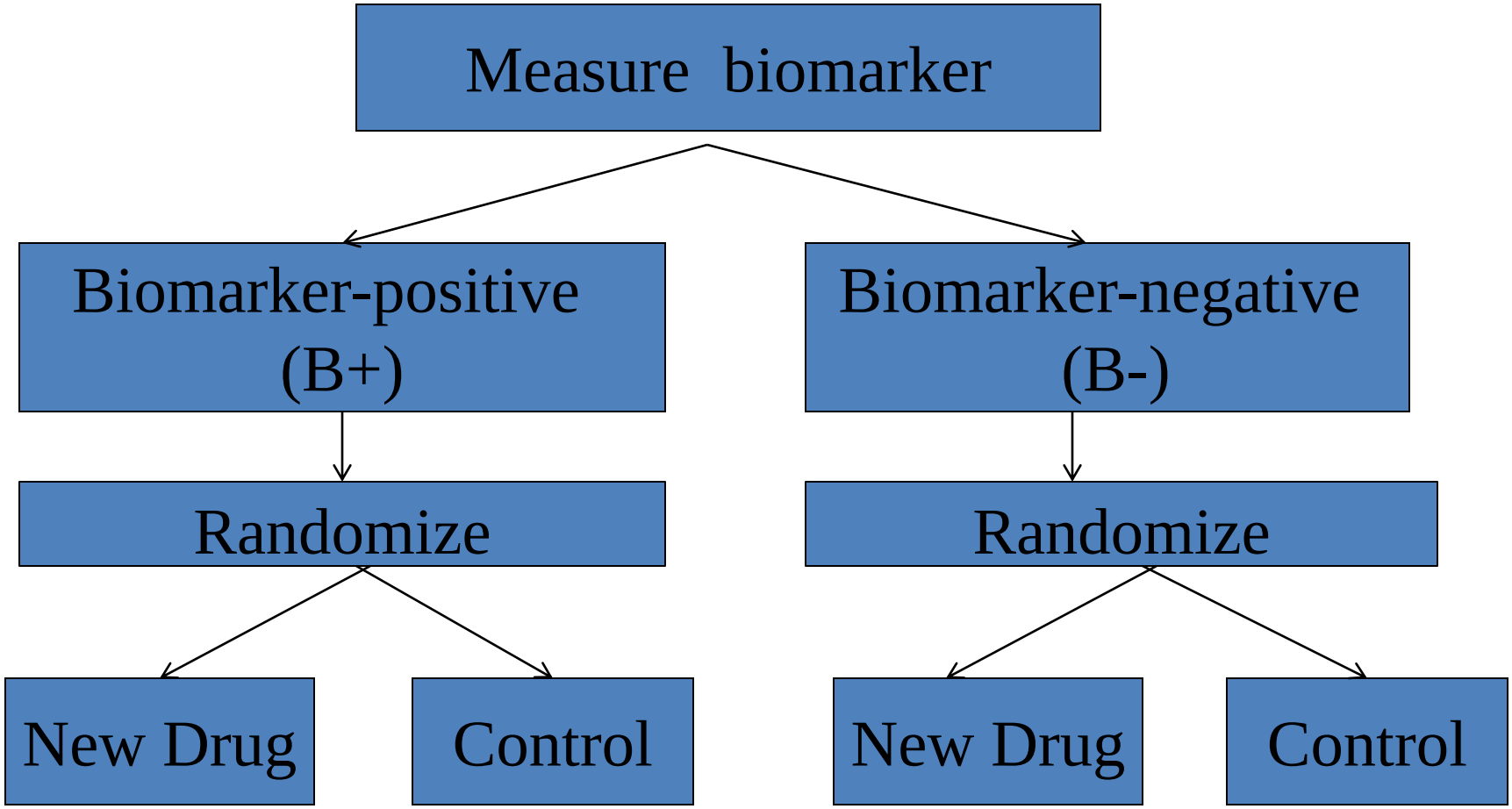
Primary analysis: Cox-2 expression index ≥ 4 subgroup



Biomarker with strong credentials:

Evidence is convincing enough to assume that the treatment is more likely to be effective (and is probably more effective) in the biomarker-positive subgroup than the biomarker-negative subgroup, but the evidence is not sufficiently compelling to rule out a clinically meaningful benefit in the biomarker-negative subgroup.

Biomarker credentials are strong: use Biomarker-stratified (randomize-all) designs



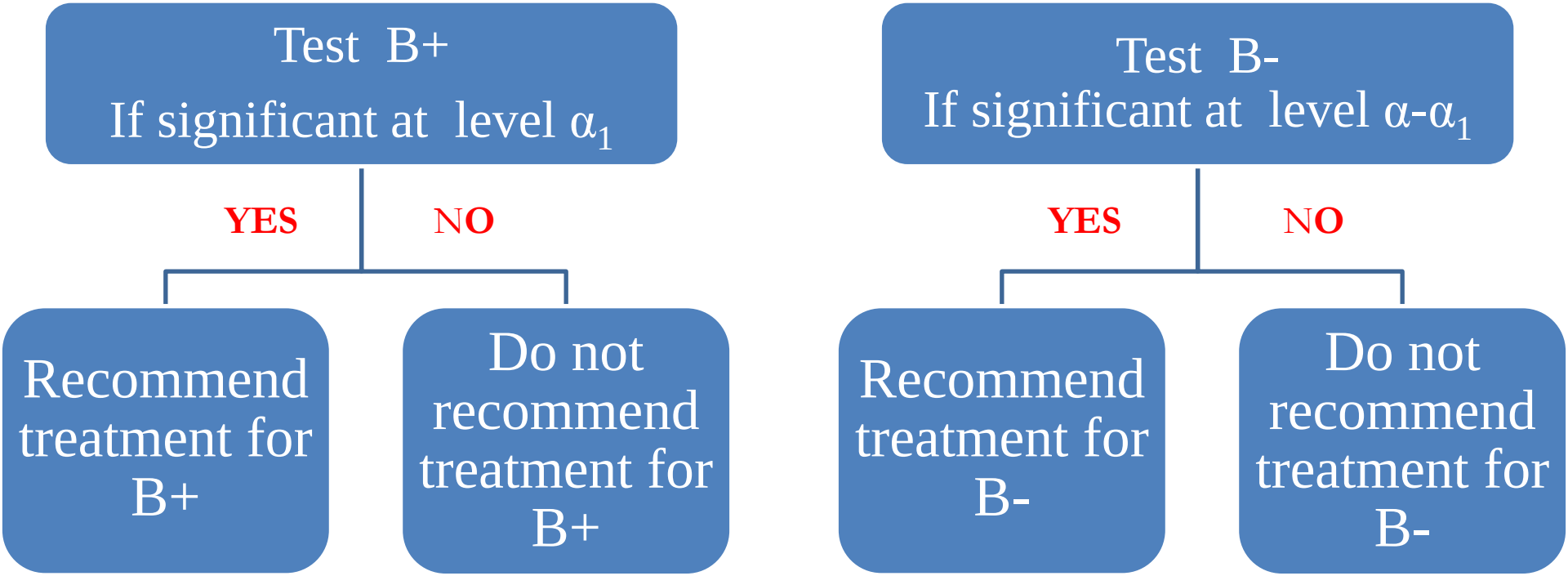
Goals of a biomarker-stratified phase III trial

- Assess benefit in each biomarker subgroup
- Recommend drug to patients who benefit
- Do not recommend drug to patients who do not benefit

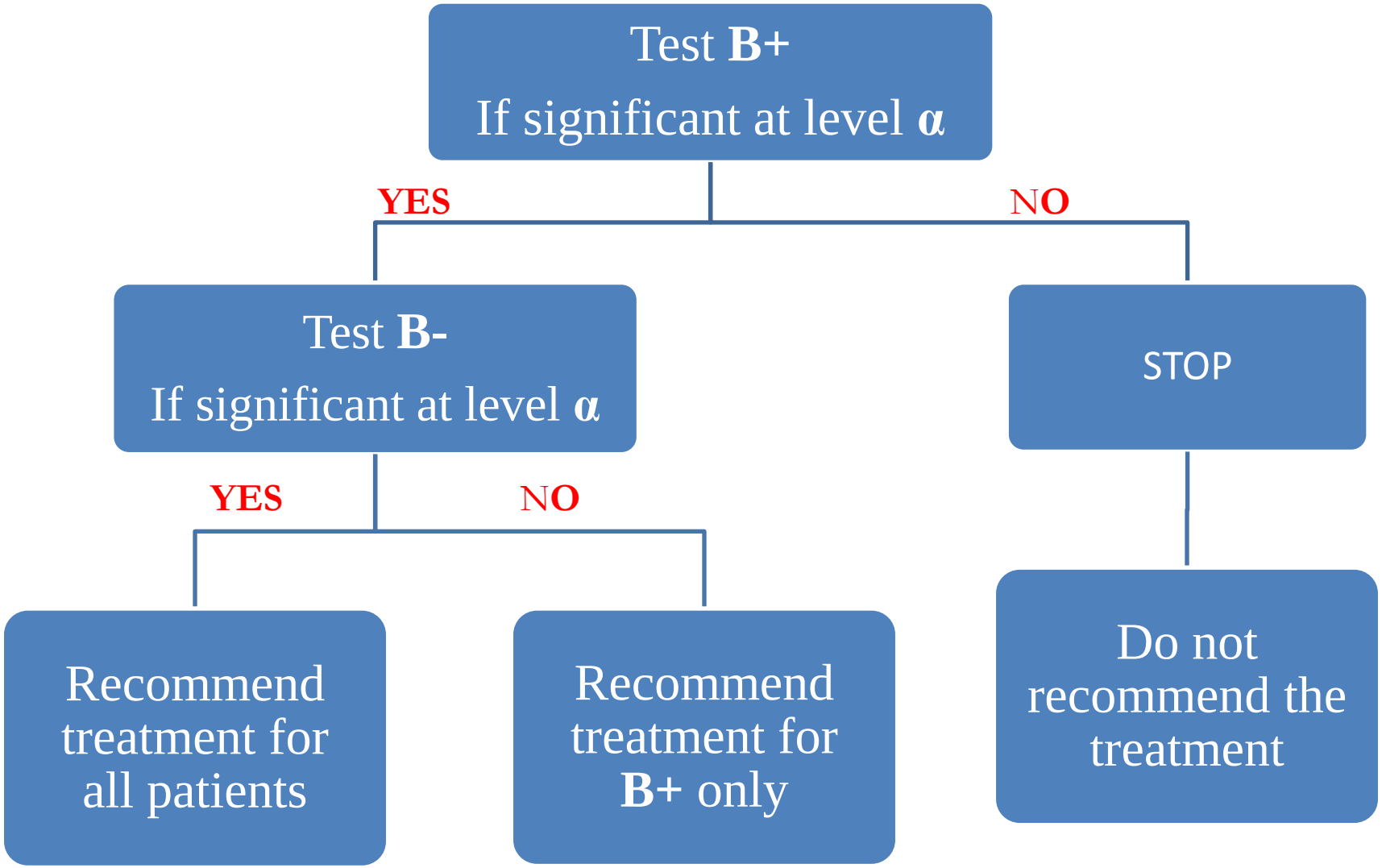
Different formal analysis strategies for biomarker-stratified trial design

- Subgroup-specific strategies
  - -parallel version
  - -sequential version
- Biomarker-positive/Overall strategies
  - -parallel version
  - -sequential version
- MaST

Subgroup-specific parallel strategy



Subgroup-specific sequential strategy



Example: PRIME study

Chemotherapy ± Panitumumab in metastatic colorectal cancer

- Biomarker: KRAS status

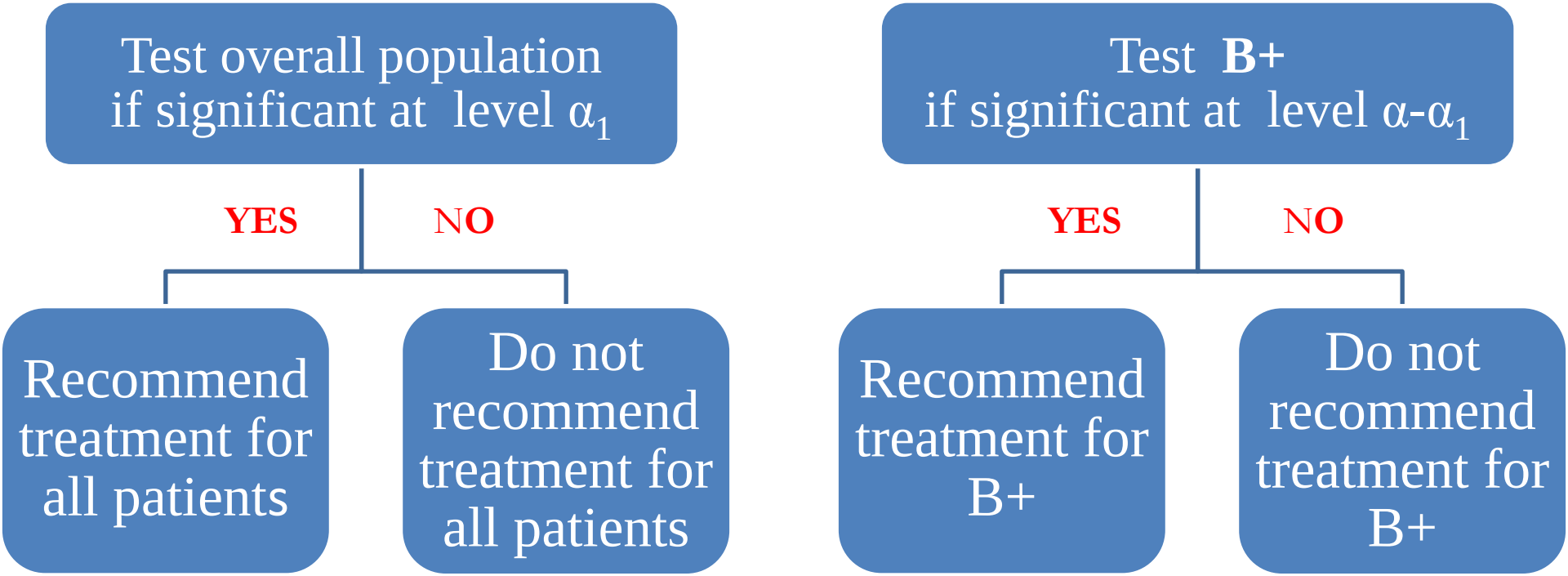
- B+ population KRAS WT (n=656)

PFS: HR=0.80 (0.66, 0.97)

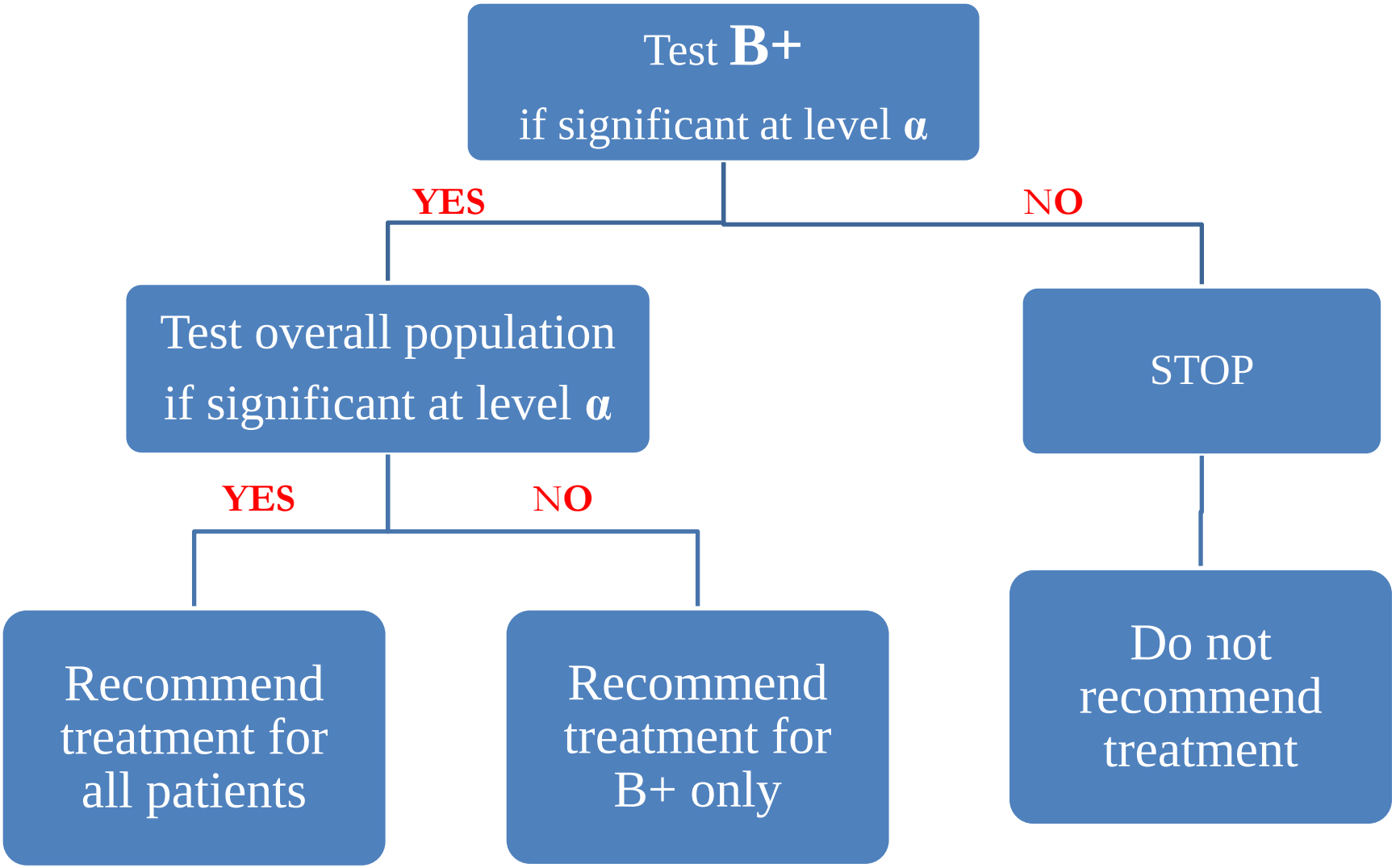
- B- population KRAS MT (n=440)

PFS: HR=1.29 (1.04, 1.62)

Biomarker-positive/overall parallel strategy



Biomarker-positive/overall sequential strategy



Example:

KEYNOTE-010 (pembrolizumab vs docetaxel)

B+ population (PD-L1$\geq$ 50%, n=442)

OS: HR=0.53 (0.40, 0.70)

Overall population (PD-L1$\geq$ 1%, n=1033)

OS: HR=0.67 (0.56, 0.80)

[*analysis plan was more complex than this]*

Example: Lapatinib+letrozole vs. Placebo +letrozole in metastatic breast cancer

- HER2-positive (n=219)
  PFS: HR=0.71 p-value=.019

- Overall population (n=1286)
  PFS: HR=0.86 p-value=.026

Problem with biomarker-positive/overall strategies

These strategies may formally recommend treatment for biomarker-negative patients even though the treatment is ineffective in these patients.

Reason: Even with no benefit in B- patients a statistically significant effect can be still observed in the overall population if the effect in B+ patients is large.

Example: Lapatinib+letrozole vs. Placebo +letrozole in metastatic breast cancer

- HER2-positive (n=219)
  PFS: HR=0.71 p-value=.019

- Overall population (n=1286)
  PFS: HR=0.86 p-value=.026

- **HER2-negative (n=952)**
  PFS: HR=0.90 p-value=.188

Example:

KEYNOTE-010

B+ population (PD-L1≥ 50%, n=442)

OS: HR=0.53 (0.40, 0.70)

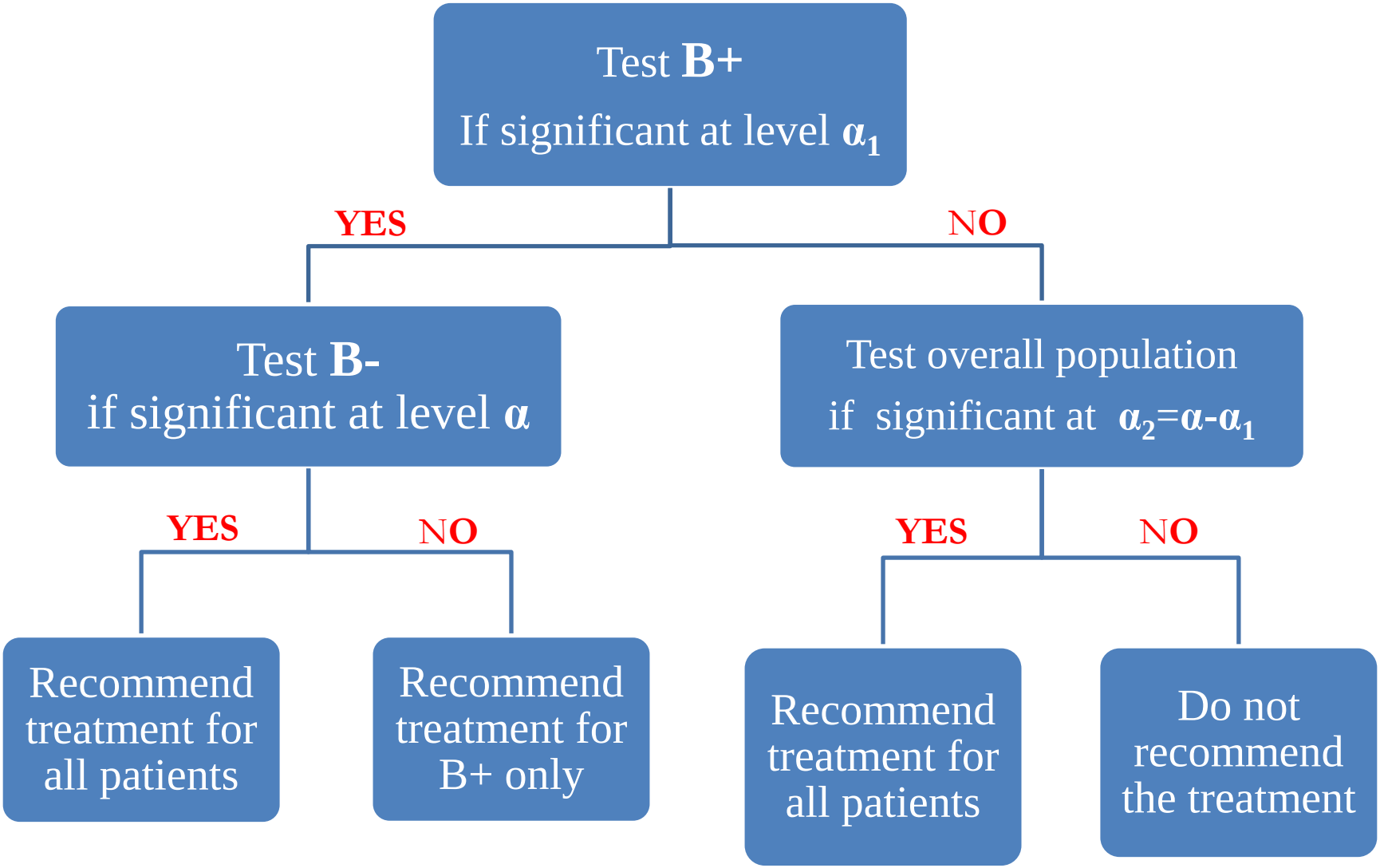
Overall population (PD-L1≥ 1%, n=1033)

OS: HR=0.67 (0.56, 0.80)

B- population (1% ≤ PD-L1< 50%, n=591)

OS: HR=0.76 (0.60, 0.96)

Marker Sequential Test MaST(α, α_1)



MaST design allows one to

- minimize the probability of recommending ineffective treatment for B- patients

- maximizing power for treatments when the treatment effect is similar in the B+ and B- subgroups.

Example using MaST design

ECOG E1910 (NCT02003222)

Blinatumomab in ALL

n=285, MAST

Biomarker: minimal residual disease after induction therapy

Recommendations

Select phase III design based on biomarker's credentials.

If the biomarker-negative patients are treated in a biomarker-stratified design, then the treatment effect in this subgroup should also be assessed.

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Trials:

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Others:

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Immuno-Oncology Combinations – Clinical Trial Design Considerations

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UHN Princess Margaret Cancer Centre

TIP Tumor Immunotherapy Program

Disclosures (2015-2016)

I have the following financial relationships to disclose:

Consultant for: Boerhinger-Ingelheim (uncompensated), Merck (compensated), Pfizer (compensated), Celgene (compensated)

Speaker's Bureau for: None

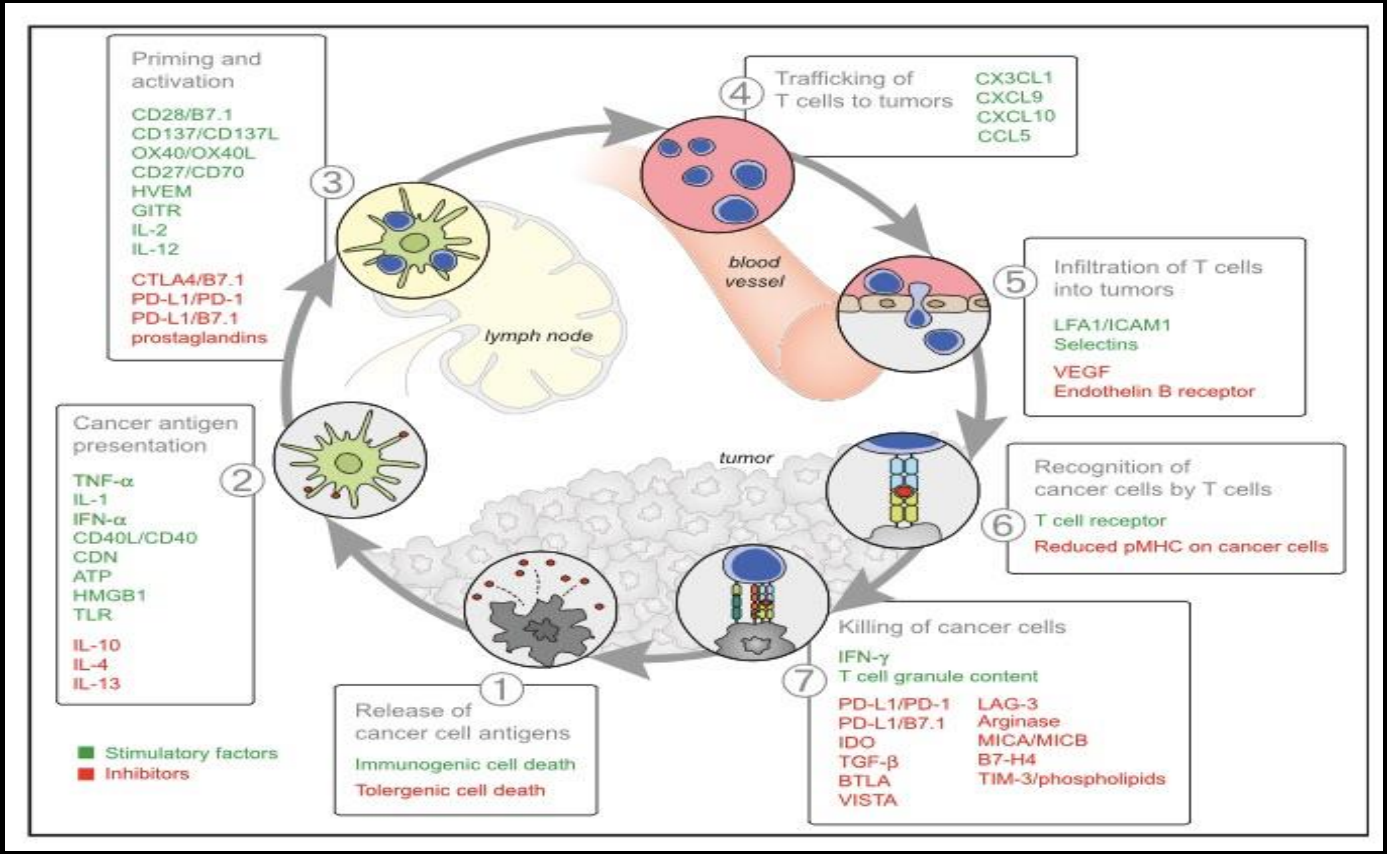
Grant/Research support from (Clinical Trials): Novartis, Bristol-Myers Squibb, Pfizer, Boerhinger-Ingelheim, Regeneron, GlaxoSmithKline, Roche, Karyopharm, AstraZeneca, Merck, Celgene

Stockholder in: None

Honoraria from: None

Employee of: None

Requirements for Spontaneous or Therapeutic Immune Response



Chen and Mellman, Immunity 2013 39, 1-10DOI: (10.1016/j.immuni.2013.07.012)

Immunogenic Tumors

- Immune Checkpoint Inhibitors
- Adoptive Cell Therapy

Non-immunogenic Tumors

- Vaccines
- CAR T cells
- TCR Transduction
- Oncolytic Viruses
- IO+IO combinations

- Tregs
- Macrophages
- TGFβ
- T cell exhaustion

Courtesy P. Ohashi

PD-1/PD-L1 Combinations in Development

- Anti-CTLA-4 (Ipilimumab, Tremelimumab)
- Other immune checkpoint inhibitors (anti-; LAG3, KIR, TIM3)
- Co-stimulatory molecules (anti-: IDO, OX40, GITR, CD-137/4-1BB)
- Anti-CSF-1R
- Anti-VEGF (Bevacizumab, Aflibercept)
- Cytokines (IFN, IL-21, IL-2)
- Peptide vaccines
- Adoptive cell therapy (ACT)
- Oncolytic viruses (TVEC, etc)
- Targeted therapy (e.g. Dabrafenib +/- Trametinib; Vemurafenib +/- Cobimetinib)
- HDAC inhibitors
- Hypomethylating agents
- PARP inhibitors
- Chemotherapy
- Radiation therapy

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Rationale for Combination Therapy

Rationale	Example	IO Example
Synergistic effects	▪ Dual HER2 blockade in breast cancer ▪ BRAF and MEK inhibition in melanoma	MEK inhibition and immune checkpoint blockade
Synthetic lethality	▪ PARP inhibition plus RT or DNA damaging agent	TGFβ inducing BRACness resulting in synthetic lethality with PARP inhibition
Reversal of resistance	▪ Cell cycle inhibition and ER inhibition in breast cancer	TIM3 inhibition and PD1/L1 inhibition

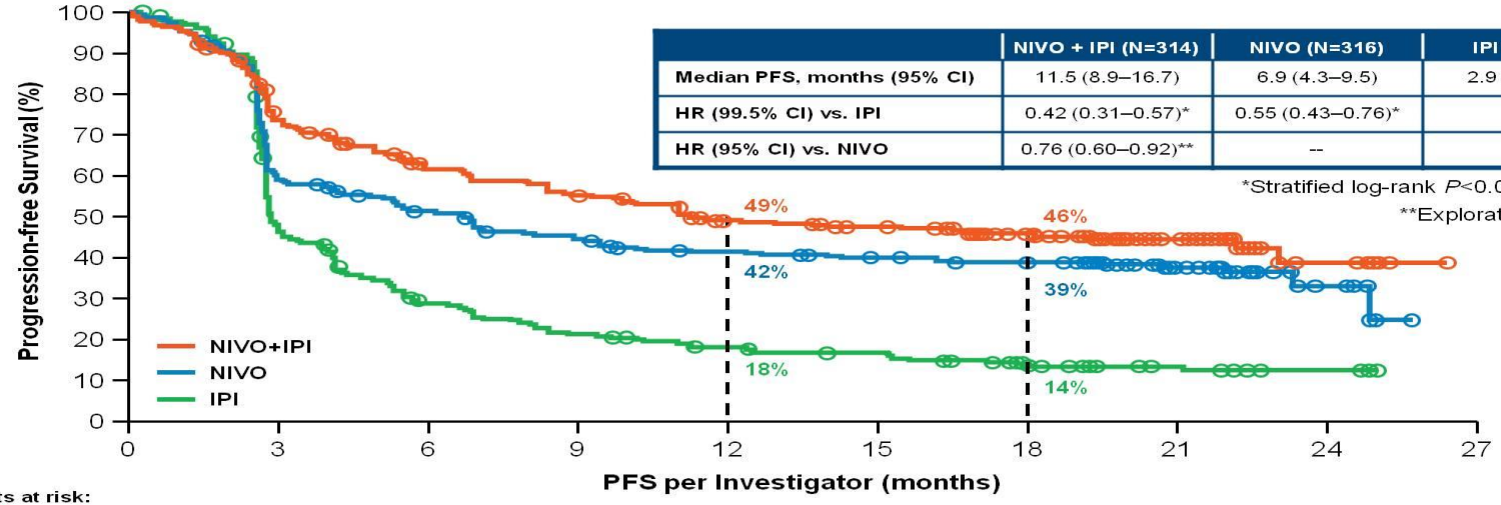
Pembrolizumab: Early Signals of Combo Activity

Author	Meeting	Agent #1	Agent #2	Indication	N	ORR
San Miguel	ASH 2015	Lenalidomide	Dex	RRMM	17	76%
Bedros	ASH 2015	Pomalidomide	Dex	RRMM	27	60%
Papa	ASCO 2016	Pemetrexed	Carboplatin	NSCLC	24	58%
Long	ASCO 2016	T-vec		Melanoma	21	57.3%
Long	ASCO 2016	LD-Ipi		Melanoma	153	57%
Atkins	SITC 2016	Axitinib		RCC	11	54.5%
McDermott	ESMO 2016	Pazopanib		RCC	20	40%

Courtesy P. Bedard

Phase III Trial of Nivolumab + Ipiliumumab vs Nivolumab vs Ipilimumab in Treatment-Naïve Advanced Melanoma (Checkmate 067)

Progression-Free Survival (Intent-to-Treat Population)



	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.55 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.76 (0.60–0.92)**	--	--

*Stratified log-rank $P<0.00001$ vs. IPI

**Exploratory endpoint

Number of patients at risk:

Nivolumab + Ipilimumab	314	219	174	156	133	126	103	48	8	0
Nivolumab	316	177	148	127	114	104	94	46	8	0
Ipilimumab	315	137	78	58	46	40	25	15	3	0

Database lock Nov 2015

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Presented By Jedd Wolchok at 2016 ASCO Annual Meeting

Phase III Trial of Nivolumab + Ipiliumumab vs Nivolumab vs Ipilimumab in Treatment-Naïve Advanced Melanoma (Checkmate 067): Treatment-Related AEs

Most Common Treatment-related Select AEs

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Skin AEs, %	60.4	5.8	43.8	2.2	54.7	2.9
Rash	28.4	2.9	22.7	0.3	21.2	1.6
Pruritus	35.1	1.9	20.4	0.3	36.3	0.3
Gastrointestinal AEs, %	47.6	15.3	21.7	2.9	37.3	11.6
Diarrhea	45.4	9.6	20.8	2.2	33.8	6.1
Colitis	11.5	8.0	2.2	1.0	11.3	8.0
Endocrine AEs, %	32.3	5.8	15.7	1.6	11.6	2.6
Hypothyroidism	16.0	0.3	9.3	0	4.5	0
Hyperthyroidism	10.2	1.0	4.5	0	1.0	0
Hepatic AEs, %	31.6	19.8	7.3	2.6	7.4	1.6
Elevated ALT	17.9	8.6	3.8	1.0	3.9	1.6
Elevated AST	15.7	6.1	4.2	1.0	3.9	0.6
Pulmonary AEs, %	7.3	1.0	1.6	0.3	1.9	0.3
Pneumonitis	6.7	1.0	1.3	0.3	1.6	0.3
Renal AEs, %	6.4	1.9	1.0	0.3	2.6	0.3
Elevated creatinine	4.2	0.3	0.6	0.3	1.6	0

- Immune-modulating medicines were used to manage adverse events and led to resolution rates of immune mediated AEs in the vast majority (>85%) of patients

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Phase I Dabrafenib + Ipilimumab: Hepatic Toxicities

Table 1. Data for Patients with Grade 3 Elevations in Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Levels While Receiving Combination Therapy with Vemurafenib and Ipilimumab.*

Study Cohort and Patient No.	No. of Doses of Ipilimumab before ALT–AST Elevation	Time to Onset of ALT–AST Elevation after First Dose of Ipilimumab	Treatment	Time to Resolution of ALT–AST Elevation	Toxicity Relapse with Repeated Ipilimumab
First cohort					
4	1	21 days	Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab permanently discontinued	4 days	NA
5	2	36 days	Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (2 doses)	6 days	No
6†	1	21 days	Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab continued (1 dose)	6 days	No
8	1	19 days	Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (1 dose)	12 days	Yes
Second cohort					
10	1	15 days	Glucocorticoids; vemurafenib discontinued for 7 days and then restarted with dose reduction; ipilimumab permanently discontinued	10 days	NA
16‡	1	13 days	Vemurafenib and ipilimumab permanently discontinued	20 days	NA

Ribas et al NEJM 2013

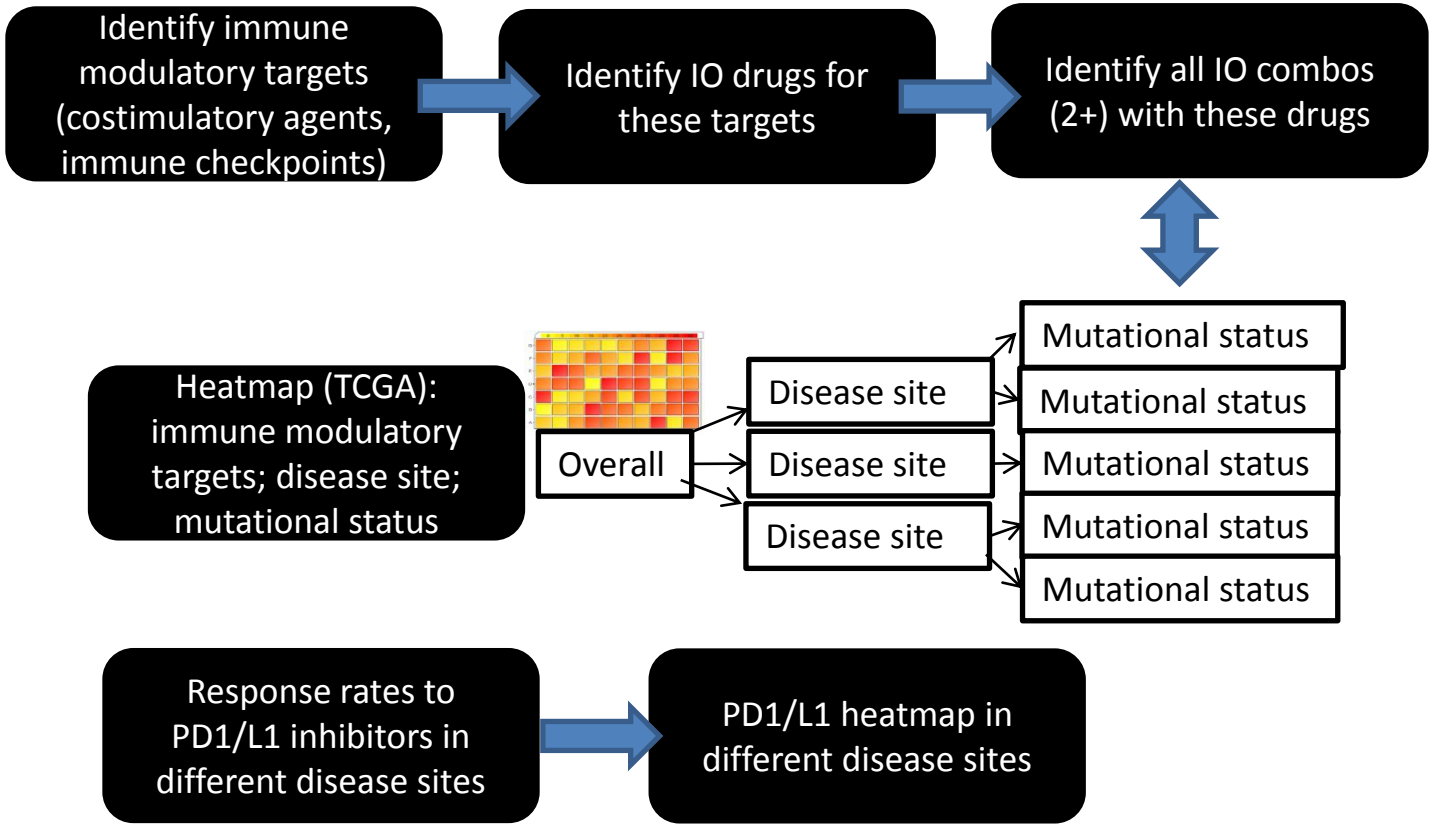
Examples of Phase I Trial Designs Used in IO-Based Combinations

Combination	N	Tumor type	Design
Ipilimumab and Nivolumab	86	Melanoma (no prior ICI)	3+3 initially but changed to allow cohort expansion; both agents undergo dose escalation
PF-05082566 (4-1BB agnoist) and Pembrolizumab	23	Solid tumors(prior ICI allowed)	Time-to-event continual reassessment method, after single agent PF-05082566 study, pembrolizumab dose fixed
MOXR0916 (OX40 agonist) and Atezolizumab	28	Solid tumors (prior ICI allowed)	3+3 after single agent MOXR0916 study, atezolizumab dose fixed

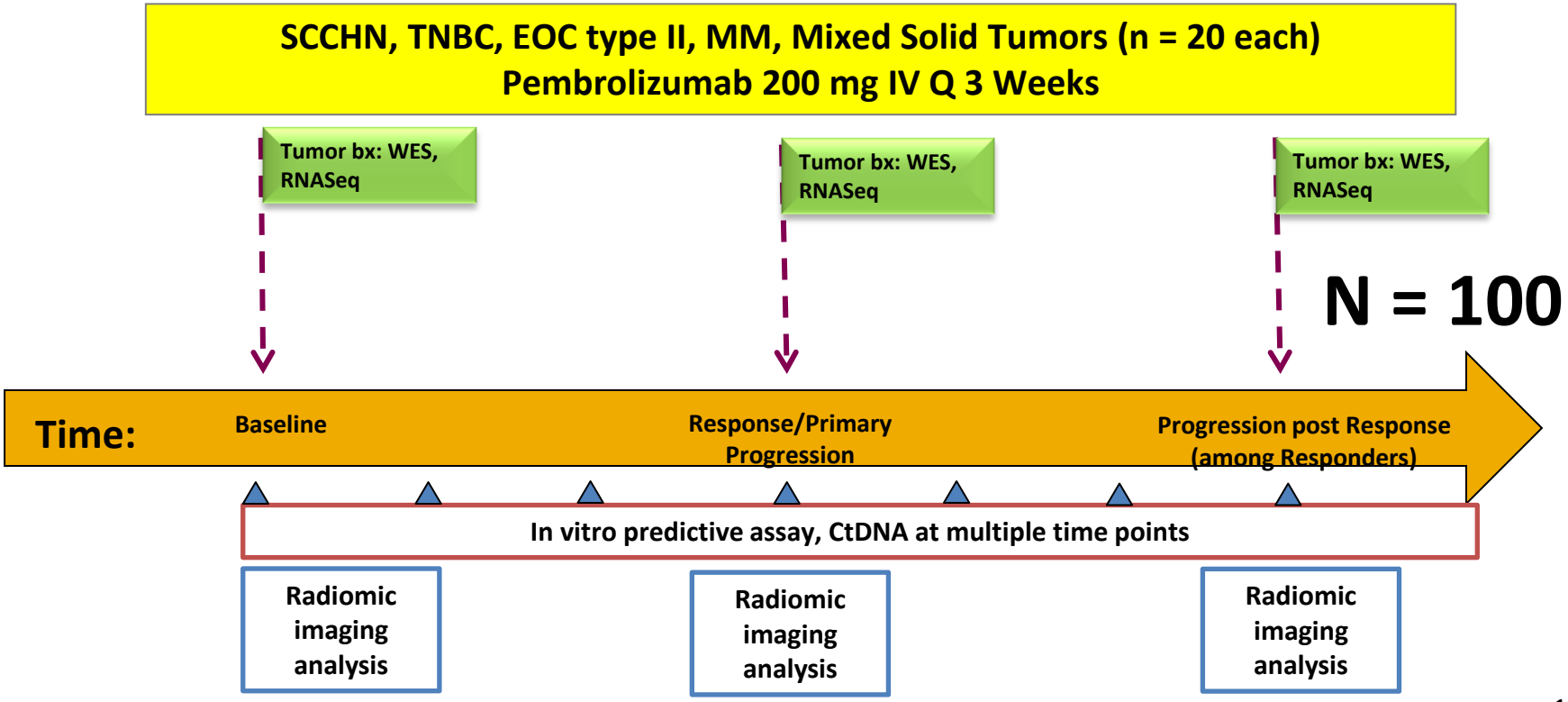
ICI = immune checkpoint inhibitors

Wolchok et al. NEJM 2013; Tolcher et al. ASCO 2016, abs 3002; Infante et al. ASCO 2016, abs 101

In Silico Analysis to Identify Rational IO Drug Combinations



INvestigator-initiated Phase II Study of Pembrolizumab Immunological Response Evaluation (INSPIRE)



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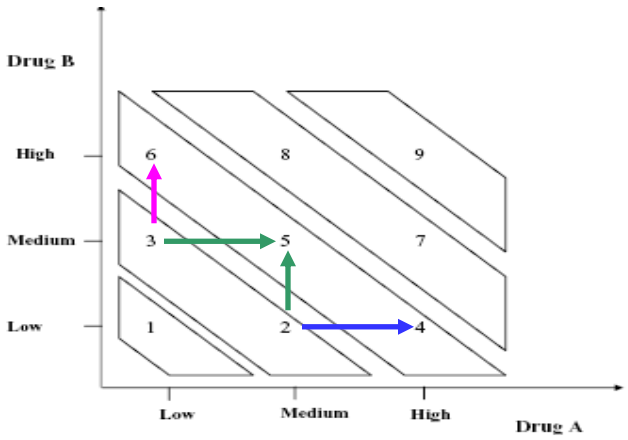
Factors Influencing Choice of Dose Escalation Methods

Factors	Dose Escalation Method	Ranking of Importance of Factors in Choice of Dose Escalation Method (rank from most important to least important)
1. Lack of preclinical data 2. Risk of narrow therapeutic index 3. Limited patient population 4. Risk of delayed/late toxicity 5. Lack of biostatistical support 6. Precision of MTD/RP2D is critical 7. High likelihood of no DLT 8. Need to complete trial as quickly as possible	3+3	
	Rolling 6	
	Accelerated titration	
	Modified toxicity probability interval (mTPI)	
	EWOC or other BLRM	
	TITE-CRM	
	Other: _____	

"Zone" Dose Escalation Design



- Results of d_2 determine the opening or closure of d_4.

- Results of d_3 determine the opening or closure of d_6.

- Dose d_5 is opened only if the results of both d_2 and d_3 indicate that it can be opened.

- In general, the decision to open a combination dose to testing depends upon the results of both its horizontal and vertical neighbors in the lower dose zone.

Reference:
http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.392.8989&rep=rep1&type=pdf

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Conclusions

- **IO-based combinations currently are largely based on empiricism**
- **Rational design of combination studies:**
  - **Need knowledge base of existent studies as “baseline”**
  - **Non-clinical models are not ideal**
- **Clinical trial considerations are important:**
  - **Assessment of additive toxicity (including delayed)**
  - **Short term read out for efficacy – immunophenotyping, clinical parameters**
- **Era of triple IO combinations is near**

Development of New Therapies and Combinations for Melanoma

John M. Kirkwood, MD

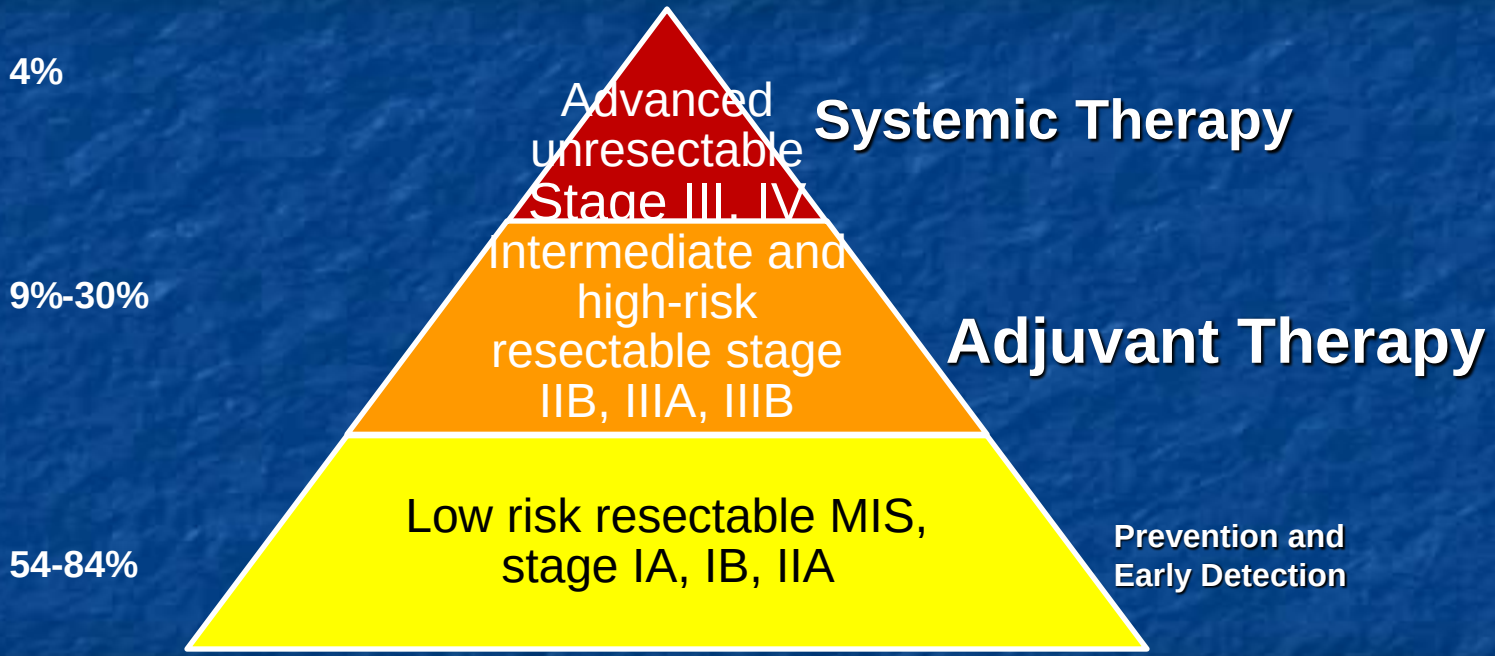
Professor of Medicine, Dermatology, and Translational Science
Division of Medical Oncology, University of Pittsburgh School of Medicine; Melanoma and Skin Cancer Program
University of Pittsburgh Cancer Institute
kirkwood@pitt.edu

Disclosures:

Grant/Research Support: Merck, Prometheus

Consultant: Amgen, BMS, Green Peptide
Roche, SolaranRx, Novartis

Distribution of the Burden of Melanoma by Stage



The burden of operable intermediate & high-risk disease numerically dwarfs that of advanced melanoma while the burden of early disease exceeds both

Multiple Options for Systemic Therapy of Advanced Melanoma

Immunotherapy:

Interleukin 2
Ipilimumab
Pembrolizumab
Nivolumab
Talimogene-laherpervec
Ipilimumab/Nivolumab
**

Targeted:

Vemurafenib
Dabrafenib
Trametinib
Cobimetinib
Dabrafenib/Trametinib
Vemurafenib/Cobimetinib
***

Chemotherapy:

Dacarbazine
(Temozolomide)
Combinations

The Problem for Advanced Melanoma Therapy Development: Time, Numbers, Costs

- Phase III trials of new IO and TT agents have yielded 10 approvals to date, & more pending
- Need is for more efficient evaluation of new agents, combinations, especially after progression on anti-PD1 agents
- Limited capacity to assess the binary, ternary…combinations given:
  - time (7 years on average)
  - patients (hundreds per arm)
  - resources ($$ millions)

Current Phase III Melanoma Research in the National Cooperative Groups

BRAF Mut. V600E/K Melanoma	Wild-type Melanoma
Is landmark 2 year OS improved with Ipi/Nivo anti-CTLA4/anti-PD1 regimen vs. Dabrafenib/Trametinib BRAFi/MEKi initial therapy	Does GM-CSF improve the OS (and reduce toxicity) of Ipi-Nivo regimen
EA6134, M Atkins PI	EA6141 S. Hodi, PI

Phase III Intergroup Trial of Dream Doublets Ipi/Nivo → D/T vs D/T → Ipi/Nivo: EA6134 (n=300, 2 yr. OS)

ECOG PS
1. 0
2. 1

LDH
1. Normal
2. Elevated

→ **RANDOMIZE**

Arm 1:

Ipi 3/Nivo 1 mg/kg/ q 3wks x 4 +Maint Nivo

→ **PD** → **D 150 BID / T 2 mg Qd**

Arm 2:

D 150 BID / T 2 mg Qd

→ **PD** → **Ipi 3/Nivo 1 mg/kg q 3wks x 4 +Maint Nivo**

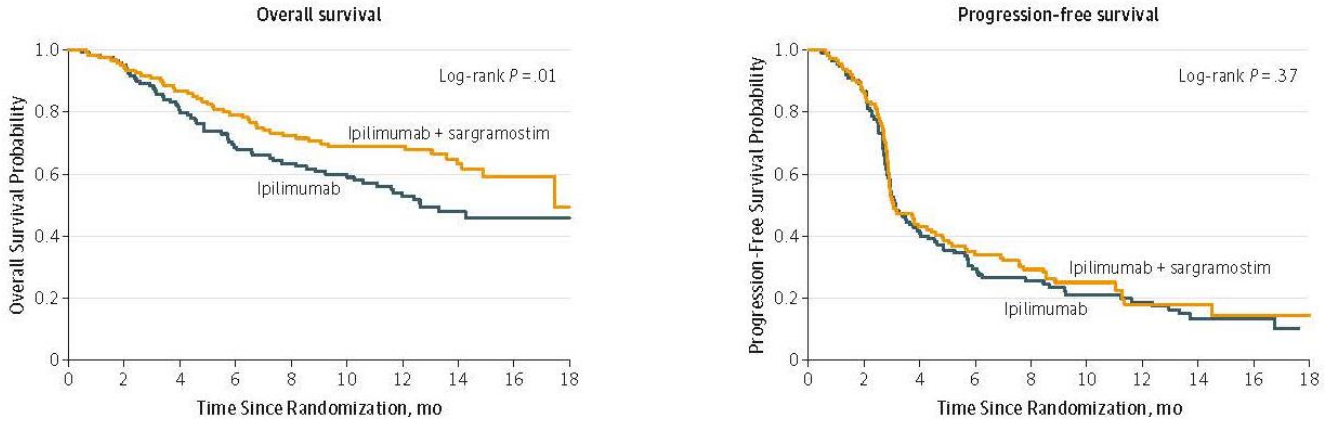
Intergroup protocol EA6134
– Atkins, Chmielowski, Ribas and Kirkwood
Open July 2015

Current Melanoma Research in the Cooperative Groups

BRAF Mut. V600E/K Melanoma	Wild-type Melanoma
Is landmark 2 year OS improved with Ipi/Nivo anti-CTLA4/anti-PD1 regimen vs. Dabrafenib/Trametinib BRAFi/MEKi	Does GM-CSF improve the OS (and reduce toxicity) of Ipi-Nivo regimen
EA6134, M Atkins PI	EA6141 S. Hodi, PI

Kaplan-Meier Estimates for Overall Survival and Progression-Free Survival for High-dose Ipi+/- GMCSF

Figure 2. Kaplan-Meier Estimates for Overall Survival and Progression-Free Survival



No. at risk

Ipilimumab + sargramostim	123	115	104	94	84	75	63	39	11
Ipilimumab	122	114	94	80	72	64	49	28	14

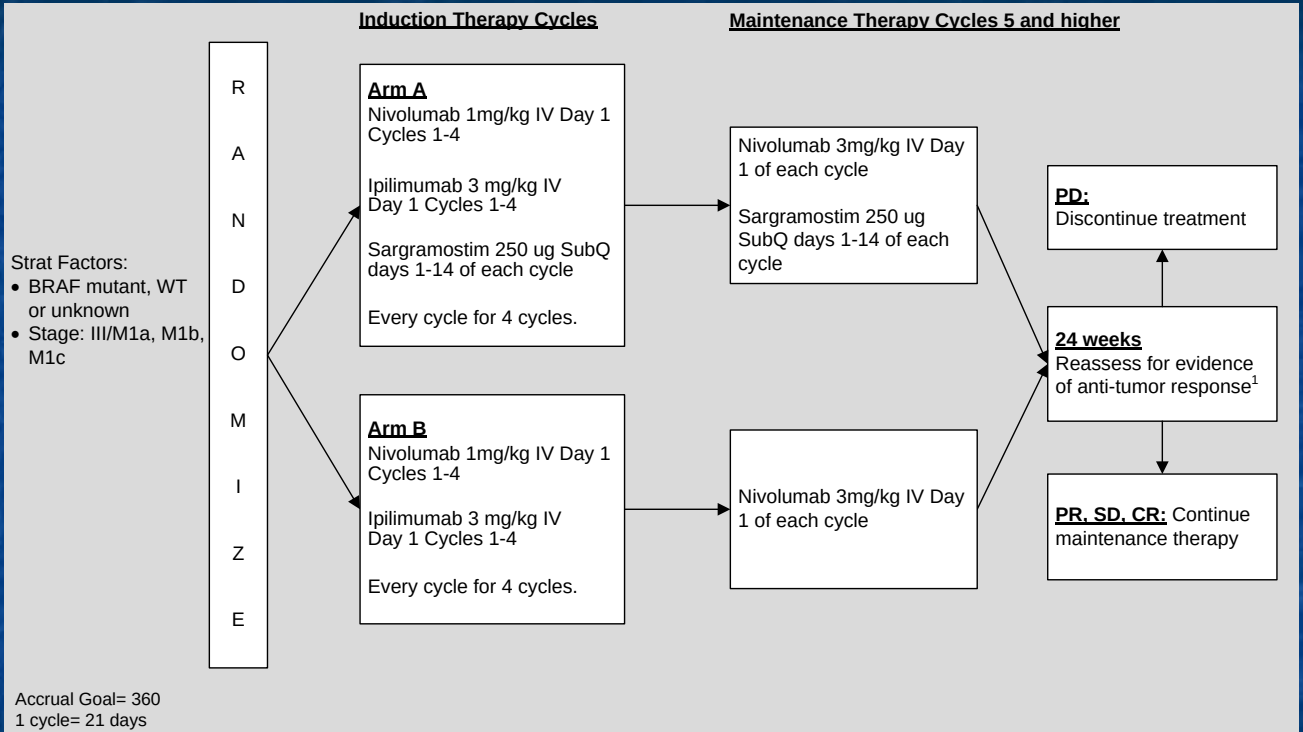
No. at risk

Ipilimumab + sargramostim	123	99	49	36	31	22	10	7	4
Ipilimumab	122	97	46	29	25	19	15	8	5

A, Primary efficacy analysis (stratified HR = 0.64; 1-sided 90% repeated CI with upper bound 0.90; P value 1-sided using the stratified log-rank test).
B, Intent-to-treat analysis: No significant difference in progression-free survival between groups (stratified HR = 0.87 [95%CI, 0.64-1.18]; P value 2-sided and calculated using the stratified log-rank test.

Hodi FS et al. Sargramostim and Ipi for Metastatic Melanoma. JAMA Nov. 2014

EA6141 Phase II-III(n=240-400, endpoint OS)



1. Scans will be done at week 12 but treatment should continue until week 24 regardless of progression unless treatment is contraindicated by Section 5.8.X.

International Melanoma Working Group (IMWG) Challenge: Improve Strategy for Development of New Therapies

Melanoma International Collaboration for Adaptive Trials (MICAT)

To transform the development of melanoma therapies at a global level:

Grant McArthur, Mark Middleton, John Kirkwood, Dirk Reitsma, Don Berry, Valerie Guild, Julia Keith

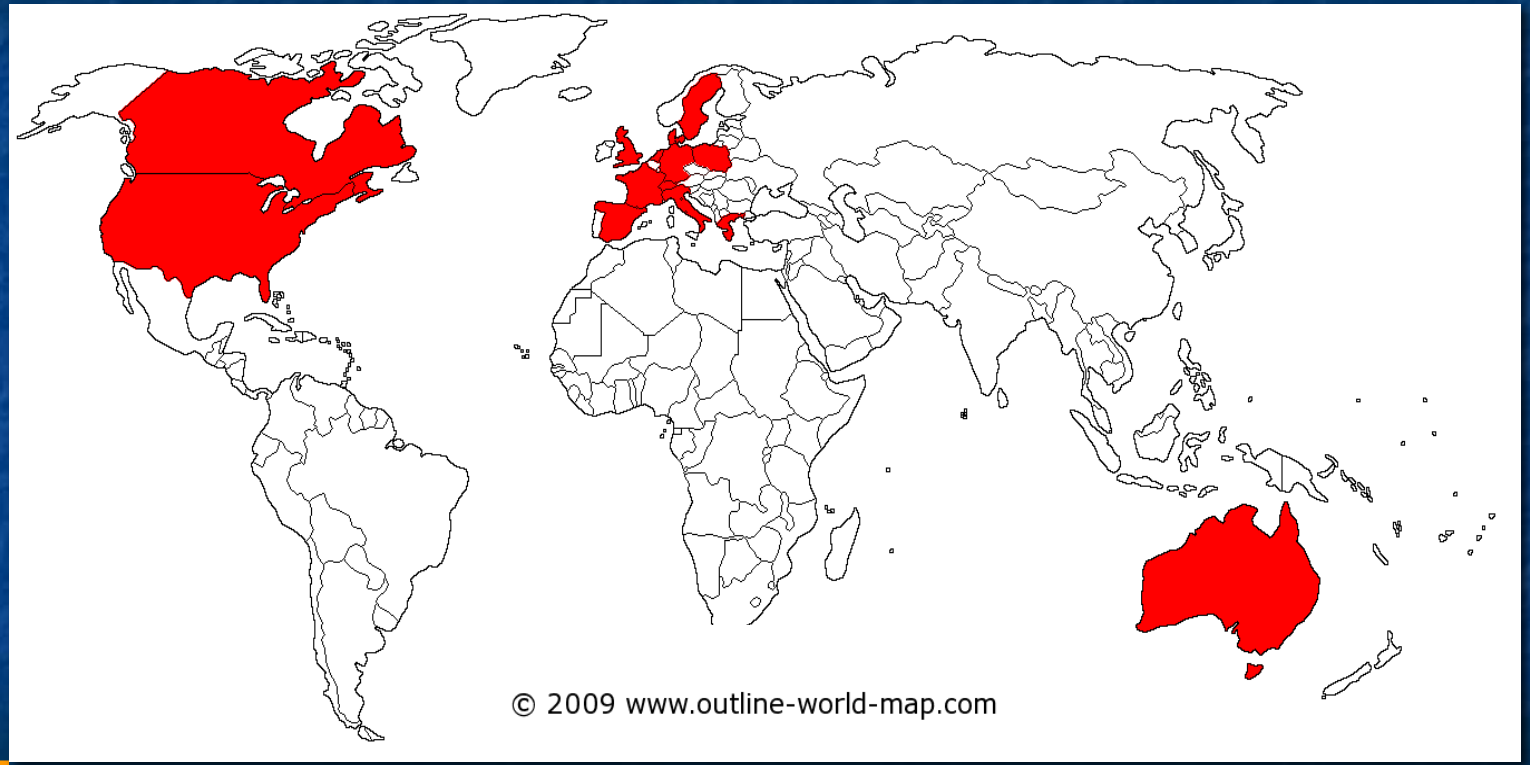
The Problem

Development of combination therapies for cancer is slow, expensive and prone to failure in phase 3

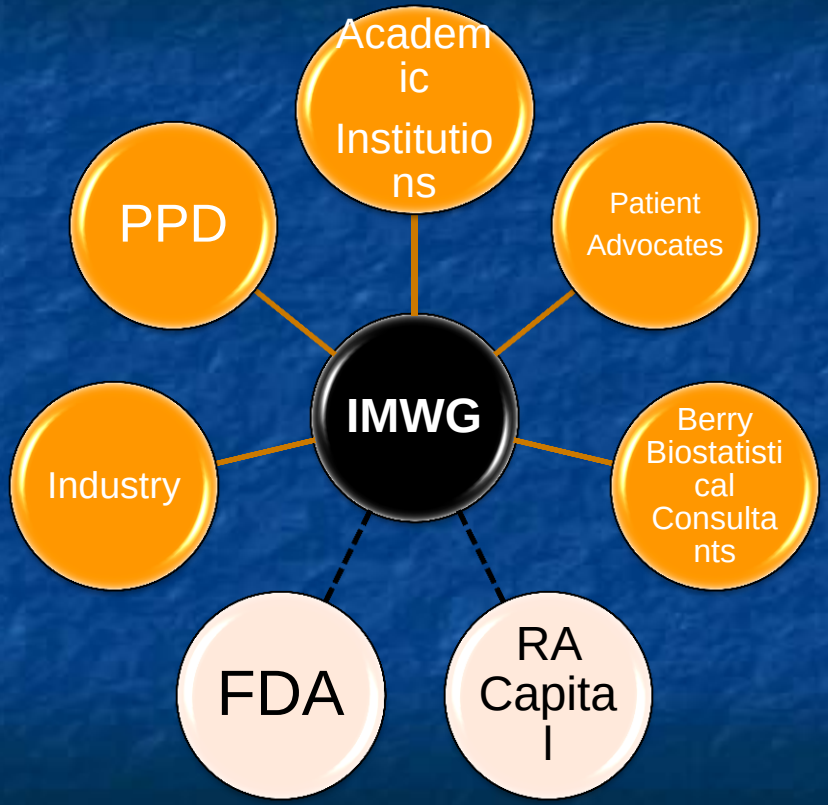
The Solution

An adaptive platform trial that enables testing of multiple combinations based upon state-of-the-art biomarkers and option for more rapid regulatory approval

The International Melanoma Working Group Collaboration



World-wide Collaboration



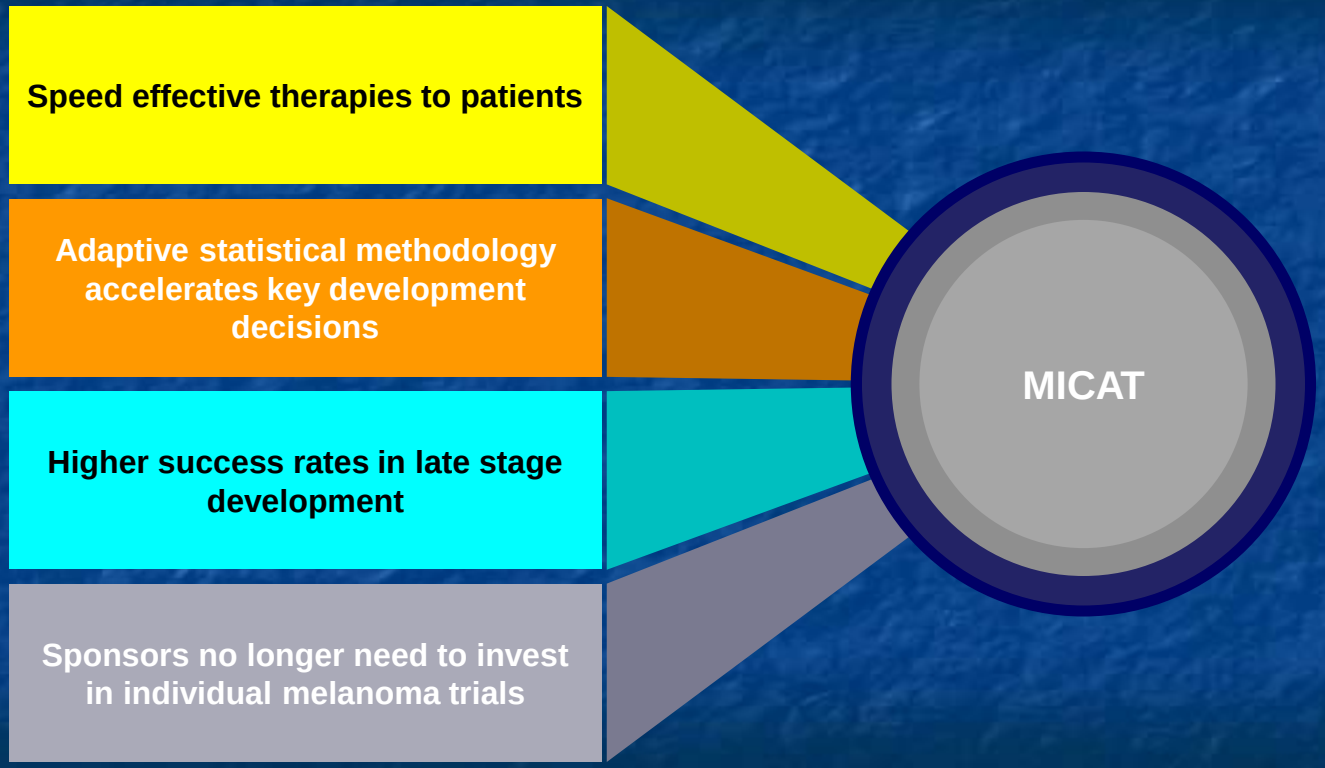
MICAT -- to Accelerate Therapeutic Progress in Metastatic Melanoma

Collaborative Phase II → Phase III adaptive design

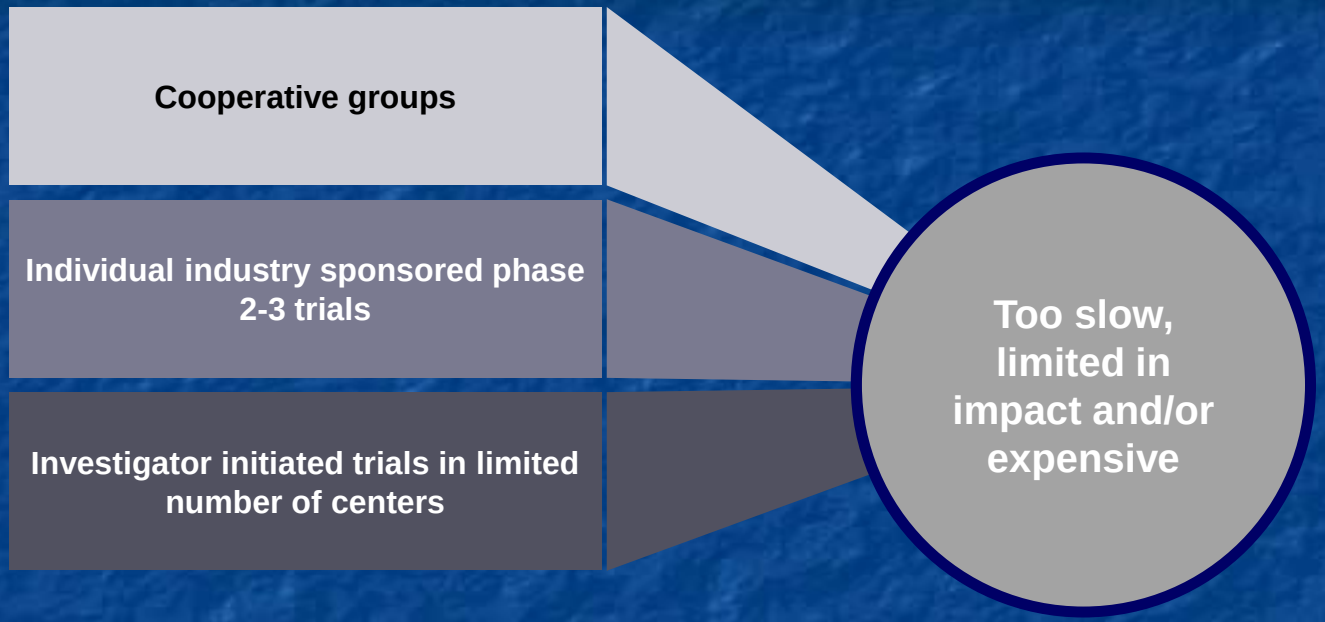
Academic-industry collaboration to encompass multiple lines of therapy

- Concurrent evaluation of multiple candidate drugs of multiple therapeutic classes to define optimal target population
- Assign patients in each subpopulation to treatment with highest probability of success
- Test treatment interactions with established and emerging biomarkers
- Drop or graduate candidate drugs based on posterior probability of success in Phase III
- Address sequencing and which therapy is best given first (if multiple options exist)

Benefits of MICAT



Alternatives



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Design

BRAF AGNOSTIC: ARMS BALANCED FOR BRAF MUTATIONAL STATUS AND OTHER FACTORS

ARM3 — Physician's Choice ★ standard of care

- Physician's choice — A B C D
- Demonstrate the known effects of standard of care — PEP: mPFS: ≥12mo. SEP: ORR: 55% G 3/4: AE <60%
- ACCEPTS ALL PATIENTS

CLASS
- Chemotherapy
- CTLA4
- PD1

OR

ARM4 — PD1+ CTLA4 ★

- PD1+CTLA4 — A B C D
- Demonstrate the known effects of the PD1 + CTLA4 combo — PEP: mPFS: ≥12mo. SEP: ORR: 55% G 3/4: AE <60%
- ACCEPTS PATIENTS OF ANY MUTATIONAL STATUS WHO HAVE NOT ALREADY RECEIVED PD1+CTLA4 THERAPY

CLASS
- PD1+CTLA4

ARM5 — PD(L)1+ Activator of Immune Response

- PD1 + Activator of Immune Response — A B C D
- Investigate efficacy of activators of Immune response — PEP: mPFS: ≥15mo. SEP: ORR: 55% G 3/4: AE <60%
- ACCEPTS ALL PATIENTS

CLASS
- Generate CTL response de novo
- Oncolytic virus
- Next-generation IL-2
- HDACi
- Off-the-shelf antigen vaccine
- IL-15
- Interferon-α

ARM6 — PD(L)1+ Second Generation Checkpoint Inhibitor

- PD1 + Second Generation Checkpoint Inhibitor — A B C D
- Investigate efficacy of second generation checkpoint inhibitors — PEP: mPFS: ≥15mo. SEP: ORR: 55% G 3/4: AE <40%
- ACCEPTS ALL PATIENTS

CLASS
- IDO inhibitors
- CSFR1
- OX40
- Galectin
- KIR
- CEA-CAM1
- CD27
- GITR
- LAG-3
- 4-1BB
- B7-H3

+

BRAF MUTANT ONLY

ARM1 — MEK+ BRAF ★ standard of care

- BRAFi+MEK — A B C D
- Demonstrate known effect of BRAF/MEKi combo as reference for other arms — PEP: mPFS: ≥12mo. SEP: ORR: 65% G 3/4: AE <40%
- ACCEPTS ALL BRAF MUTANT PATIENTS WHO HAVE NOT ALREADY BEEN TREATED WITH BRAF INHIBITORS

CLASS
- MEK+BRAF

ARM2 — Novel Therapeutic for BRAF Mutant Patients

- Novel BRAF targeted therapies — A B C D
- Investigate efficacy of new BRAF targeted treatment — PEP: mPFS: ≥15mo. SEP: ORR: 80% G 3/4: AE <40%
- ACCEPTS BRAF MUTANT PATIENTS WHO HAVE NOT ALREADY BEEN TREATED WITH BRAF INHIBITOR

CLASS
- Next-generation pan-BRAF inhibitors
- ERK inhibitors
- BRAFi + MEKi + PD(L)1
- CDK4/6 inhibitors available for combination study with BRAFi or MEKi

Can include
Personalized
Evaluation of genomic and cellular biomarkers throughout

Launch Planning for 2017

- Robust biomarker platform
  - Genomic WES, WGS, RNAseq, proteomics
  - Immune profiling- tumor cell infiltrates, PD-L1
- Investment to “kick-start” study and facilitate alignment of multiple industry collaborators to initiate the trial
- Precedents: I-SPY, GBM-Agile…

The Problem of Trial Development is Greater for Adjuvant Therapy of Melanoma: Longer Time, Larger Numbers and Costs

- Phase III Trials E1684, E1690, E1694, E1609, WHO16, EORTC 18991 and 18071 have required thousands of patients & nearly a decade of time apiece & $$millions to reach current approvals (HD-IFN, PegIFN & HD-Ipilimumab
- Limited capacity to evaluate new agents, binary/ ternary…combinations in phase III trials for OS, RFS:
  - time (~decade on average)
  - patients (hundreds → thousands)
  - societal resources (>$$ millions)

Adjuvant Therapy with IFN, anti-CTLA4, →anti-PD1 Blockade: Open Questions

- Dosage optima and duration of treatment required?
  - Randomized discontinuation trials needed
- Optimal combinations?
  - With other immunotherapy, targeted therapy, RT, Vaccines, oncolytic viruses, TLR9 agonists, IDO inhibitors…
- Are therapies more effective earlier in disease progression?
  - US Intergroup S1404: Pembro vs. IFN or Ipi (in progress)
  - EORTC: Pembro vs. placebo with crossover
  - BMS: Nivo vs. Ipi
  - Novartis: Combi-Ad
  - Roche-Genentech: BRIM8
- Biomarker refinement key to optimize future therapy selection

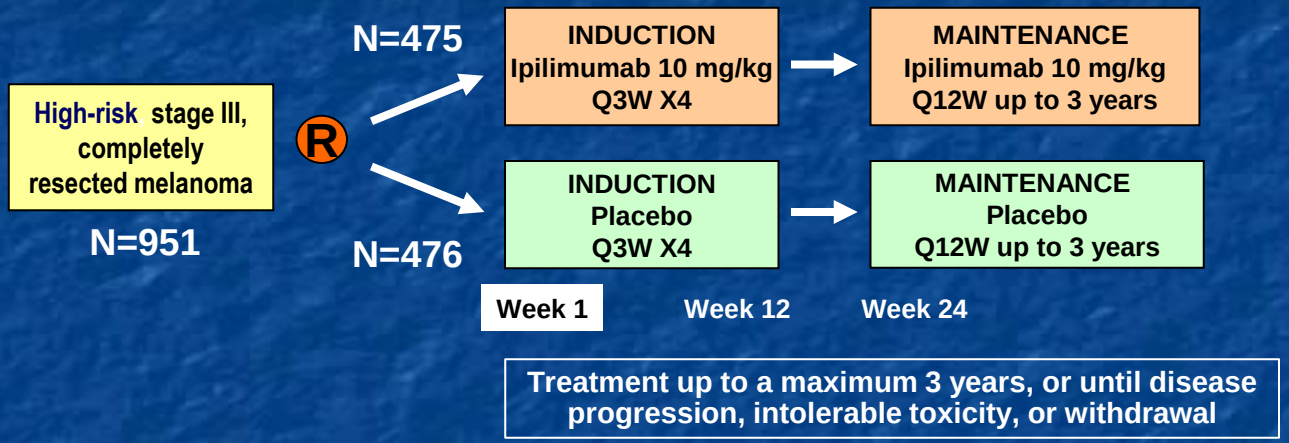
Adjuvant Treatment after Surgery for High Risk Melanoma Is More Effective than for Metastatic Disease

- High-dose Interferon with 16% response rate in advanced disease lowers relapse risk by 33%-40%
- High-dose Ipilimumab with 11% response rate in advanced disease lowers relapse/mortality risk by 25-28%

Summary of adjuvant trials leading to approvals

Study/PI	Stage	N	Treatment agent/ dosage/duration	Median follow up (years)	Impact on RFS	Impact on OS	(%) Toxicity Attrition Rate	Comment
E1684	T4, N+	287	IFNα2b 20 MU/m2/D IV for 1 month. Then, 10 MU/m2 SC TIW for 11 months vs. Observation	6.9	0.61; p=.001	0.67; p=.01	26	At 12.6 yr, the impact of competing causes of death on OS to be considered
				12.6	0.72; p=.02	0.82; p=.18		
E1690	T4, N+	642	IFNα2b 20 MU/m2/D IV for 1 month. Then, 10 MU/m2 SC TIW for 11 months vs. 3 MU/D given SC TIW for 2 years vs. Observation	4.3	0.78; p=.05	1.0	13	Cross over of observation pts to HDI at nodal relapse (n=38 pts) ipected to affect OS analysis
				6.6	0.81; p=0.09	1.0		
E1694	T4, N+	880	IFNα2b 20 MU/m2/D IV for 1 month. Then 10 MU/m2 SC TIW for 11 months vs. GMK vaccine for 96 wks	1.3	0.67; p=.0004	0.72; p=.023	10	Symmetrical impact upon RFS, OS for IFN over GMK led to early closure for vaccine futility at 2 yrs.
				2.1	0.75; p=.006	0.76; p=.04		
EORTC 18071	N1-2	951	Ipi at 10 µg/kg/3 wks x12 weeks) then 10 µg/kg/3 mos (x3 yrs) vs. Placebo	2.7	0.75; P=.011		44	impact upon RFS at initial reporting
				5.3	0.76; P=0.055	0.72 p=.001		

EORTC 18071/CA184-029 Study Design



Stratification factors:

- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
- Regions (North America, European countries and Australia)

- Primary Endpoint: RFS

Eggermont et al., Proc ASCO 2014

American Association for Cancer Research

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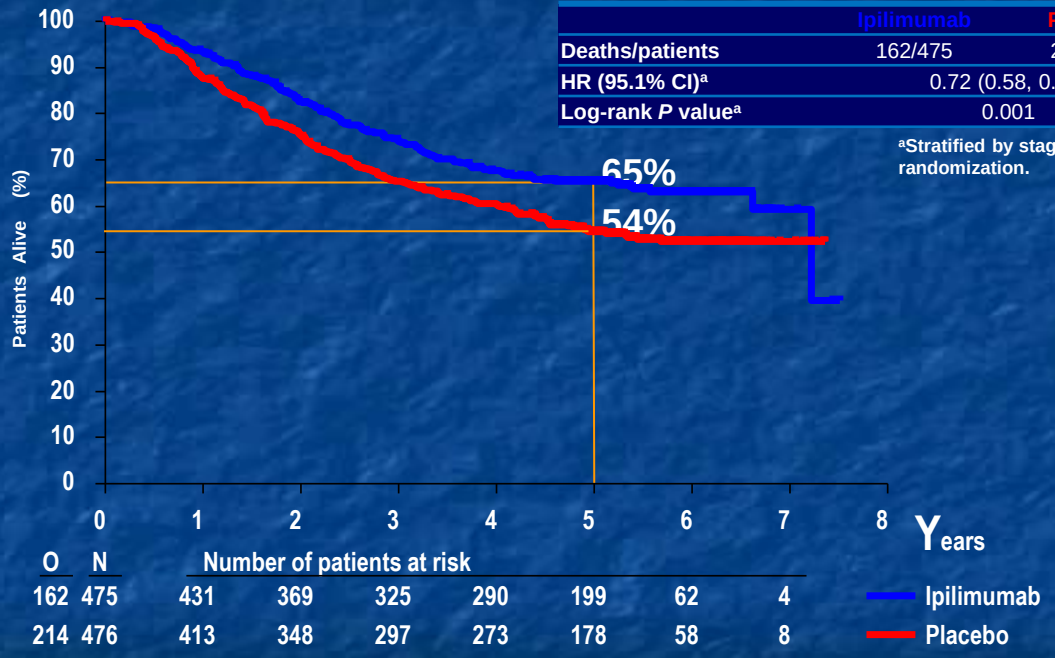
At the request of the speaker, two slides have been withheld from the online posting.

EORTC 18071 Final Analysis at 5.3 Years
Overall Survival



	Ipilimumab	Placebo
Deaths/patients	162/475	214/476
HR (95.1% CI)[a]	0.72 (0.58, 0.88)	
Log-rank *P* value[a]	0.001	

[a]Stratified by stage provided at randomization.

Eggermont Proc
ESMO 2016 Oct 8

Deaths Related to Adjuvant HD Ipilimumab Treatment

- Five patients (1.1%) died of drug-related AEs in the high-dose ipilimumab group:
  - Three patients with colitis (2 with perforations)
  - One patient with myocarditis
  - One patient with Guillain-Barré syndrome
- No deaths due to intervention in placebo group
- Raise question of optimal dosage (3 vs 10 mg/kg) given lesser toxicity of 3mg/kg approved for metatatic melanoma

Eggermont et al., Proc ASCO 2014

US Intergroup Adjuvant Phase III Trial E1609: Ipilimumab vs. HDI

(Accrual of 1678 Pts Completed 2014 with endpoint OS data ~2018)

SURGERY

Pts with resectable IIIB, IIIC M1a, M1b

N=1578

Ipilimumab 10 mg/kg

HDI

Ipilimumab 3 mg/kg

Endpoints

OS co-primary with RFS

QOL

Immunological correlates of RFS, OS

- **serial blood serum and lymphocytes**
- **baseline tissue blocks**

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Neoadjuvant Therapy has Considerable Advantages

Clinically

•Improves clinical outcome for multiple solid tumors (H&N, breast, bladder, esophageal and rectal)[1,2,3,4]

- survival, resectability, local control, organ preservation

•Accelerates progress

- Neoadjuvant read-out in 2-3 mos cf. ~10 years
- Improve therapeutic index, cost effectiveness

Experimentally

•Evaluate clinical impact in relation to pathologic, immune, and molecular Δ's

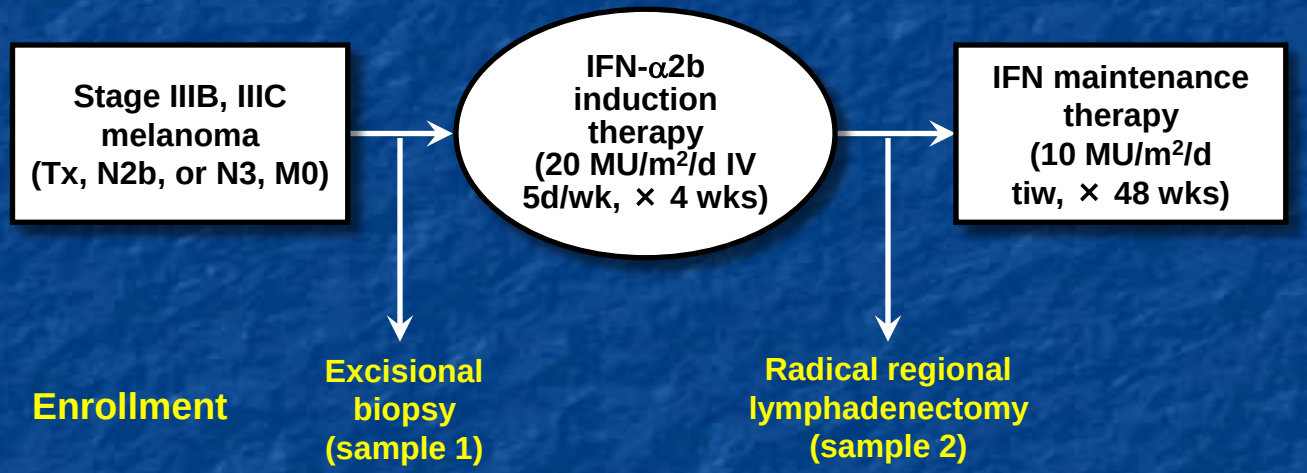
•Access to tumor tissue and blood (both before and after intervention)

- Investigation of antitumor mechanisms of action
  - IFN effects upon STAT3, STAT1, and T cell/DC tumor infiltration
  - Ipi effects upon TIL, Treg, MDSC
- Biomarker studies in blood correlated to tumor

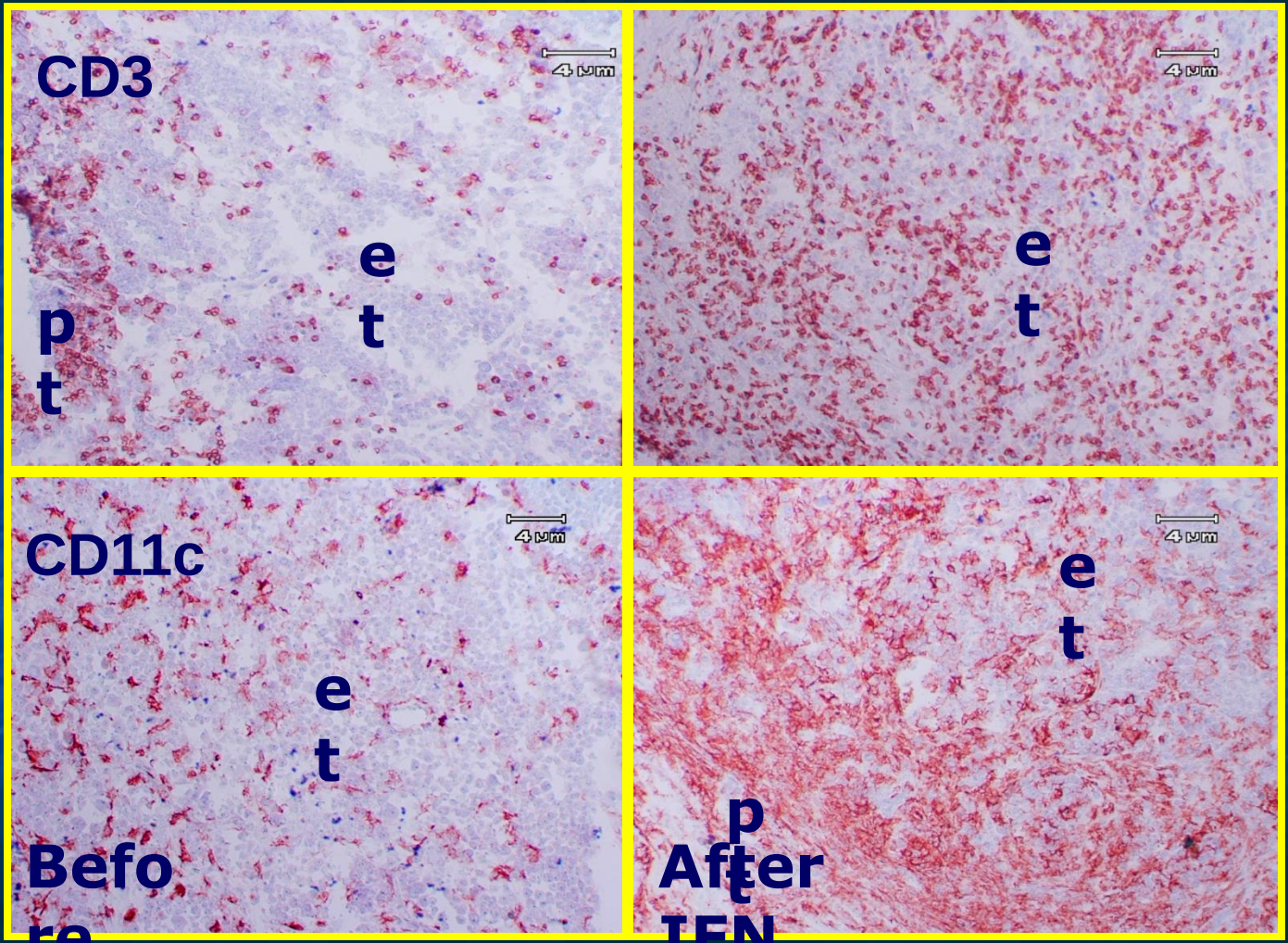
[1]Estevez, et al. *Clinical cancer research, 2004;* [2]Grossman, et al. NEJM, 2003; [3]Medical Research Council Oesophageal Cancer Working Group. *Lancet,* 2002; [4] Fisher, et al. *Journal of clinical oncology* 1997

Neoadjuvant Evaluation of the Mechanism of HD IFN in Stage IIIB Melanoma

Schema: UPCI 00-008



Moschos et al., JCO 2006

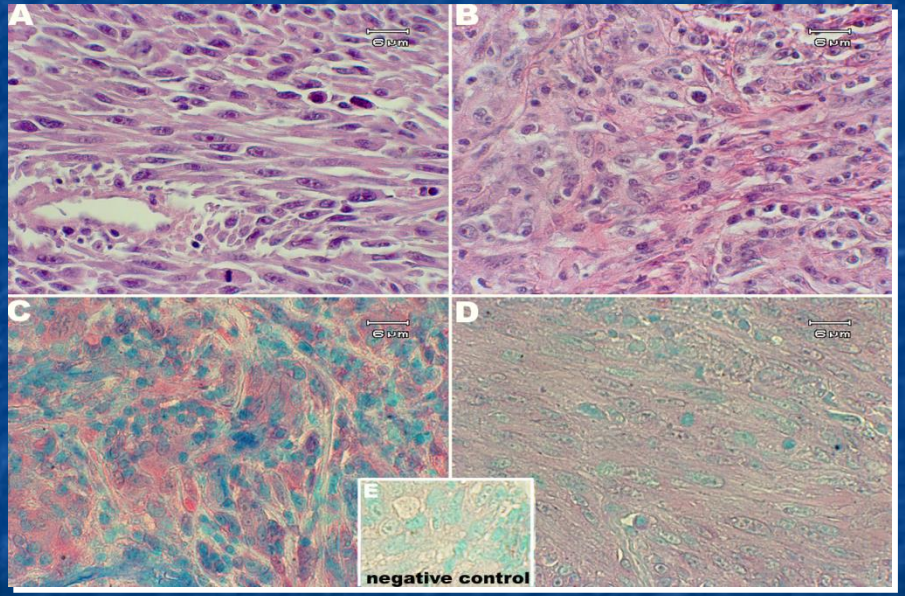

CD3
4 µm
pt
et
4 µm
et
CD11c
4 µm
et
Before
4 µm
et
pt
After IFN

HDI Down-Regulates pSTAT3 Tyr705 And STAT3 Expression in Tumor Cells

Pretreatment **Post treatment**

H&E

IHC

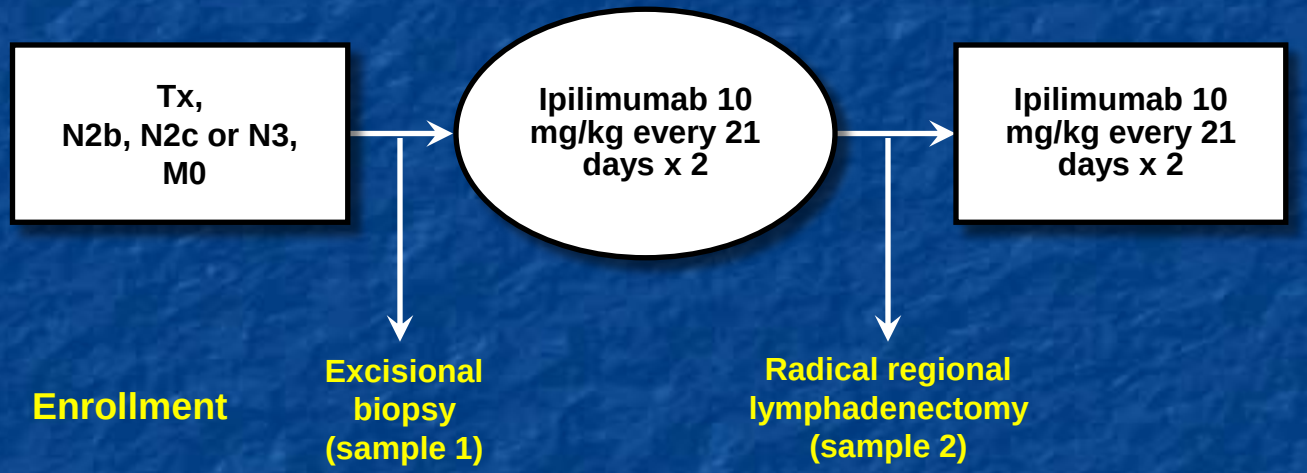


Blue = pSTAT3tyr705
Red = STAT3

Wang et al., Clin Cancer Res 2007

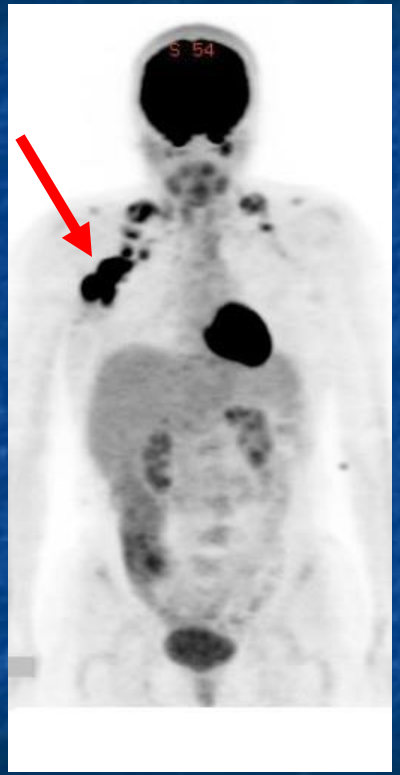
Neoadjuvant Ipilimumab
in N1b,2b, N2c, N3 Melanoma

UPCI 08-144



Tarhini et al., AACR 2012, ASCO 2012

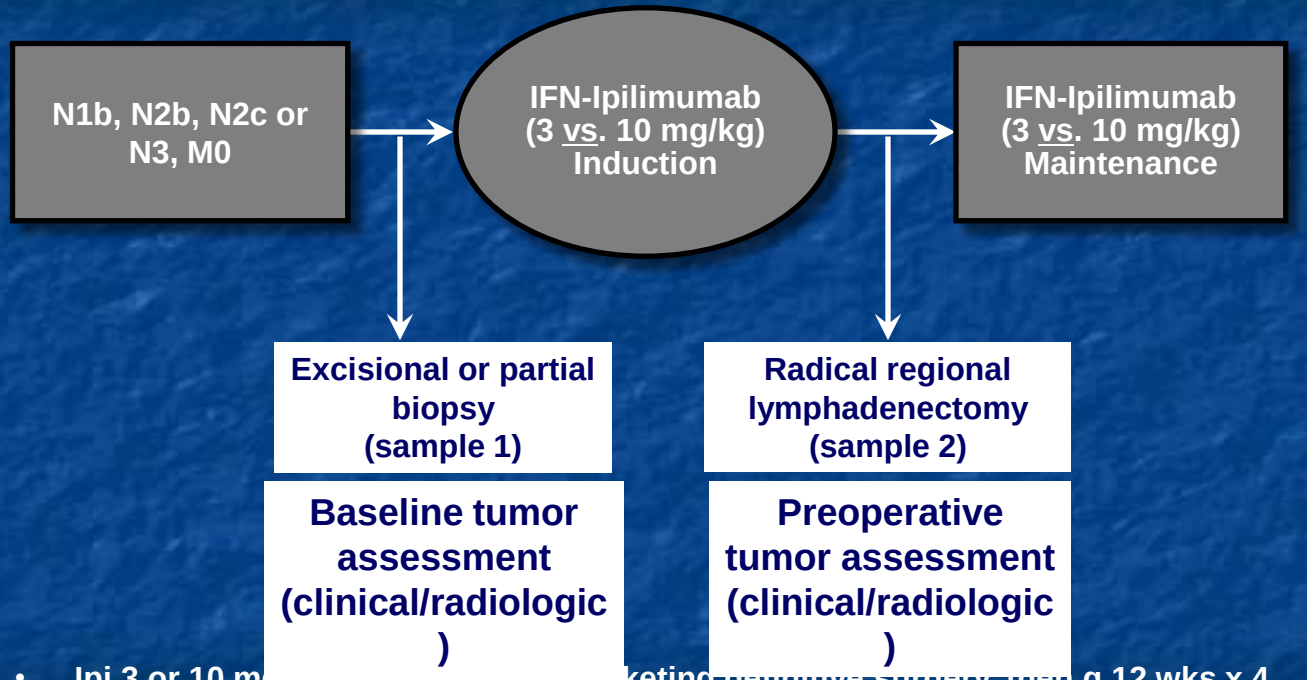
UPCI 08-144: Disease Response by PET-CT at 6 weeks



Pre-treatment

6 weeks post anti-CTLA4

Randomized Neoadjuvant IFN + Ipilimumab Trial UPCI 11-063 for N1b,2b, N2c, N3 Melanoma



- Ipi 3 or 10 mg/kg IV q 3 wks x 4 bracketing definitive surgery, then q 12 wks x 4
- HDI 20 MU/m²/d IV x 5 d/wk x 4 wks then 10 MU/m²/d SC qod TIW for 48 wks

Patient Demographics and Baseline Disease Characteristics (N=30 patients)		
Variable		**No. of Patients (%)**
Age (years; Median (range)		61 (37-76)
Cutaneous primary		21 (70)
unknown primary		8 (27)
Mucosal		1 (3)
Gender	Female	12 (40)
	Male	18 (60)
Performance Status	0	16 (53)
	1	14 (47)
Recurrent disease after prior surgery		15 (50)
Presence of in-transit metastases		16 (53)
Prior adjuvant HDI		5 (17)
Estimated risk by Stage	IIIB	3 (10)
	IIIC	25 (83)
	IV (Not eligible)	2 (7)

Tarhini et al. 2016 ASCO

Gr 3-4 immune related AEs by study arm

	Any Grade		Grade 3		Grade 4		Grade 3/4 Ipi 3 mg/kg		Grade 3/4 Ipi 10 mg/kg	
	No. Pts.	%	No. Pts.	%	No. Pts.	%	No. Pts.	%	No. Pts.	%
Adrenal insuff	10	33	2	7	0	0	0	0	2	7
Hypophysitis	2	7	2	7	0	0	0	0	2	7
Diarrhea/ Colitis	15	50	3	10	0	0	2	7	1	3
AST/ALT	28	93	5	17	1	3	2	7	4	13
Lipase inc	9	30	3	10	0	0	0	0	3	10
Rash, maculo-papular	14	47	7	23	0	0	4	13	3	10
Pneumonitis	1	3	1	3	0	0	0	0	1	3
Autoimmune nephritis	1	3	1	3	0	0	0	0	1	3

Tarhini et al. 2016 ASCO

Response rate (RR) by radiologic (preoperative vs. 6 weeks from baseline) and histologic (6-8 weeks from baseline) assessment

	All patients (N = 28)		Ipi 3 mg/kg (n = 14)		Ipi 10 mg/kg (n = 14)	
	No. pts.	%	No. pts.	%	No. pts.	%
Radiologic preoperative RR (WHO; unconfirmed)	10 (9 PR, 1CR)	36%	4 (3 PR, 1 CR)	29	6 (All PR)	43
Pathologic complete RR (no viable tumor on histologic assessment)	9	32%	5	36	4	29

Among radiologic responders

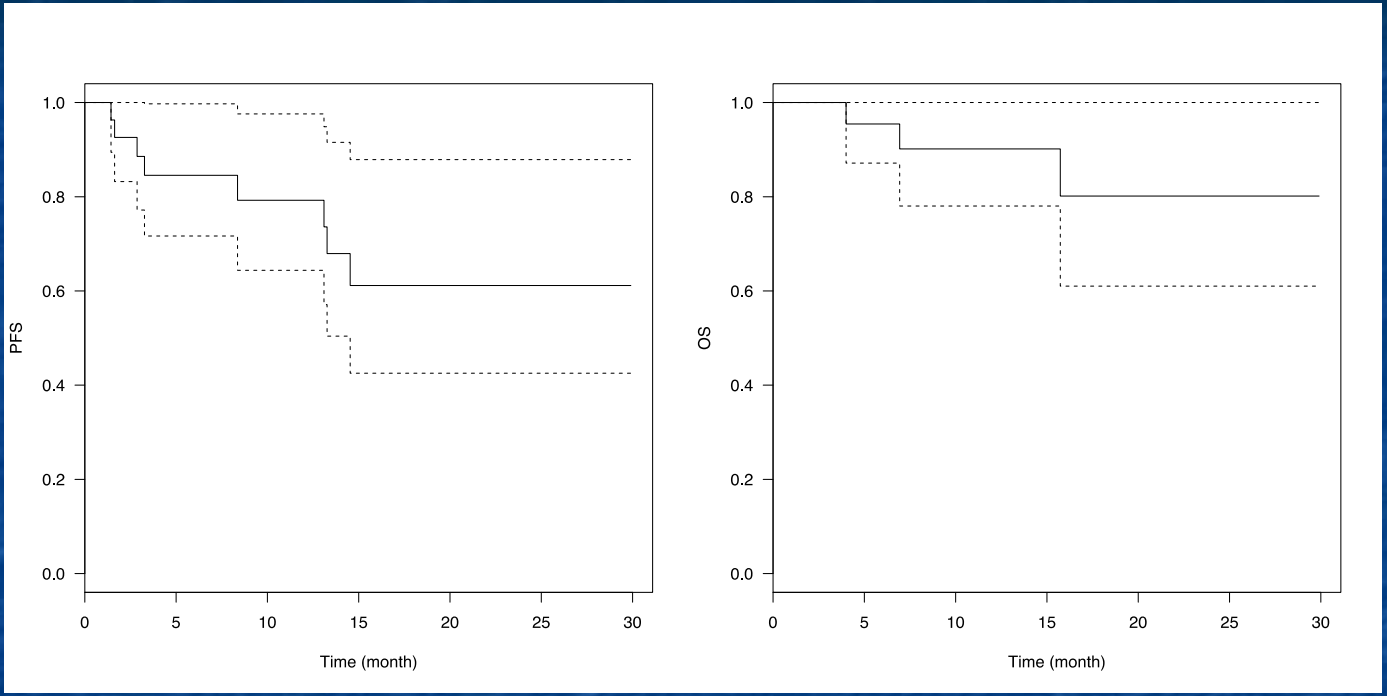
- One relapsed and later responded to anti-PD1 antibody therapy

Among complete pathologic responders

- None relapsed to date

Tarhini et al. 2016 ASCO

PFS and OS (medians not reached for 3 or 10 Ipi+IFN)



- **Relapse: 8 events**
- **Death: 3 events**

Median follow up time for remaining patients: 11 months

Tarhini et al. 2016 ASCO

Conclusion

- Neoadjuvant combination of Ipi-HDI exhibits promising clinical activity at both 3 & 10 mg/kg
- Less toxicity with ipi at 3 mg/kg
- Longer follow up needed to define long term benefits and optimal ipi dosage
- Studies of predictive biomarkers and mechanisms are ongoing
- Next neoadjuvant UPCI study Ipi-Nivo vs Nivo

Tarhini et al. 2016 ASCO

Current US Intergroup Adjuvant Trial S1404 Tests anti-PD1

Stage IIIB-C (>N1) and IV (M1a, b)

- Pembrolizumab 200mg q 3 weeks x 1 yr

vs.

- High-dose IFN (or FDA approved regimen)

  – Primary Endpoint: Overall Survival

  – Secondary Endpoints: RFS, QOL

To Build More Effective Adjuvant Therapy

- Combine IFNα and anti-CTLA4
  - In metastatic melanoma single institution phase II trial (Tarhini et al, 2012)
  - In national cooperative group phase II trial E3611
  - In neoadjuvant treatment of stage IIIB-C melanoma UPCI 11-063 (Tarhini et al., Proc ASCO 2016)
- Combine anti-PD1 & IFNα (Davar, Kirkwood, Zarour, 2016)
- Combine anti-PD1 and anti-CTLA4 (Tarhini, et al., 2016)
- Combine immunotherapy and BRAFi therapy
  - Combine IFNα + BRAFi UPCI 12-107 (Davar, 2016)
  - Combine anti-PD1 and BRAFi (Najjar, Kirkwood, 2016)

Rationale for IFN and Anti-PD1

- PD-1 blockade is most effective in “inflamed” tumors–defined by pre-existing CD8+ T-cell infiltrates
- Gene expression studies in melanoma link CD8+ T-cell infiltrate to inflammatory cytokine profile, type I IFN signaling cascade
- Type I IFN signaling is critical to tumor-antigen specific T-cell priming—and antigen presentation by host APCs
- UPCI 13-105 phase I/II trial tests Peg-IFN with Pembrolizumab to evaluate whether IFNα increases inflammation in the tumor microenvironment and PD-1 efficacy

UPCI 13-105 Phase I/II Trial of Peg-IFN + Pembrolizumab

- Phase I/II study of Pembrolizumab & Peg-IFN alfa-2b
  - Pembrolizumab 2mg/kg q3 weeks.
  - Peg-IFN 1-3ug/kg weekly in 3 dose levels.
- Dose escalation using modified toxicity probability incidence design w/continuous DLT monitoring
- Primary endpoints: safety, dose-limiting toxicities (DLTs)
- Secondary endpoints: ORR (RECIST 1.1), progression free and overall survival
  - 24 pts with advanced melanoma enrolled to date in phase I portion of this study

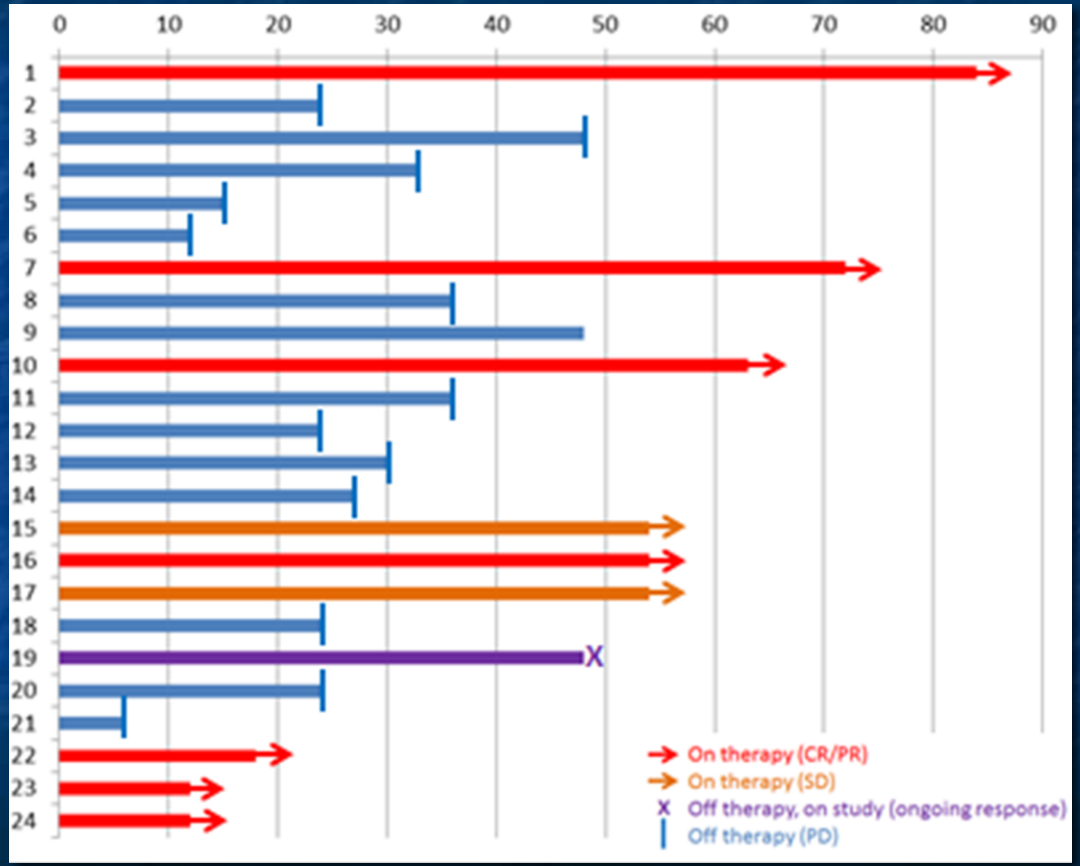
Davar, Kirkwood and Zarour Proc

UPCI 13-105 Phase I/II Trial of PegIFN+Pembrolizumab

Response Rates (N=24)		
	Best	**Current**
CR	2 (8%)	1 (4%)
PR	7 (29%)	7 (29%)
SD	8 (33%)	2 (8%)
PD	4 (17%)	14 (58%)
Overall response rate (CR+PR)	9 (38%)	8 (33%)
Disease control rate (CR+PR+SD)	17 (71%)	10 (42%)

Davar, Kirkwood and Zarour Proc ASCO 2016

UPCI 13-105 PegIFN + Pembrolizumab Responses are Durable



Davar, Kirkwood and Zarour Proc ASCO 2016

Preliminary Conclusions of UPCI 13-105
Peg IFN + Pembrolizumab

- Pembrolizumab 2mg/kg q3 weeks + Peg-IFN 3ug/kg wkly is tolerable (RP2D)
  - Best ORR in pretreated patients 38%
  - Responses are durable
  - Accrual increased from 16 → 35 ongoing
- Neoadjuvant trial 14-102 testing HDI + Pembrolizumab in resectable IIIB-C in progress

Davar, Kirkwood and Zarour Proc ASCO 201

Adjuvant Therapy Development Requires Neoadjuvant Evaluation of Combinations

- IFNα and Ipilimumab have significant and durable benefits and are reference standards
  - IFNα complementary to anti-CTLA4→ IFNα+Ipilimumab combinations (UPCI neoadjuvant 11-063)
  - IFNα modulates tumor immune response & induces PDL1→ IFNα + anti-PD1 under exploration (neoadjuvant 14-102)
- Ipilimumab adjuvant benefit and toxicity profile differ from IFN —but optimal dose remains unclear
  - E1609 Intergroup trial of Ipi 3 & Ipi 10 vs IFNα will mature in next yr
  - Combinations of Ipi and IFNα under exploration for advanced/adjuvant
- Anti-PD1 combinations for advanced melanoma and adjuvant therapy need further exploration
  - Intergroup S1404 will define the role of adjuvant anti-PD1 alone
  - IDO inhibitors, TLR9 agonists, third generation CBI agents next

Thanks to our patients, program, and cooperative group members

UPCI Melanoma Program

Melanoma and Skin Cancer SPORE

ECOG-ACRIN Melanoma Committee

International Melanoma Working Group

Hassane Zarour
Ahmad Tarhini
Diwakar Davar
Yana Najjar

Lisa Butterfield
Louis Falo
Laura Ferris
Matt Holtzman

Craig Slingluff
David Lawson
F. Steven Hodi
Leslie Fecher

Helen Gogas
Valerie Guild
Peter Hersey
Grant MacArthur
Mark Middleton

Designing Late-Stage Randomized Clinical Trials with Cancer Immunotherapy: Can We Make It Simple?

Tai-Tsang Chen, PhD

Global Biometric Sciences, Bristol-Myers Squibb

AACR-FDA Workshop, Washington, DC

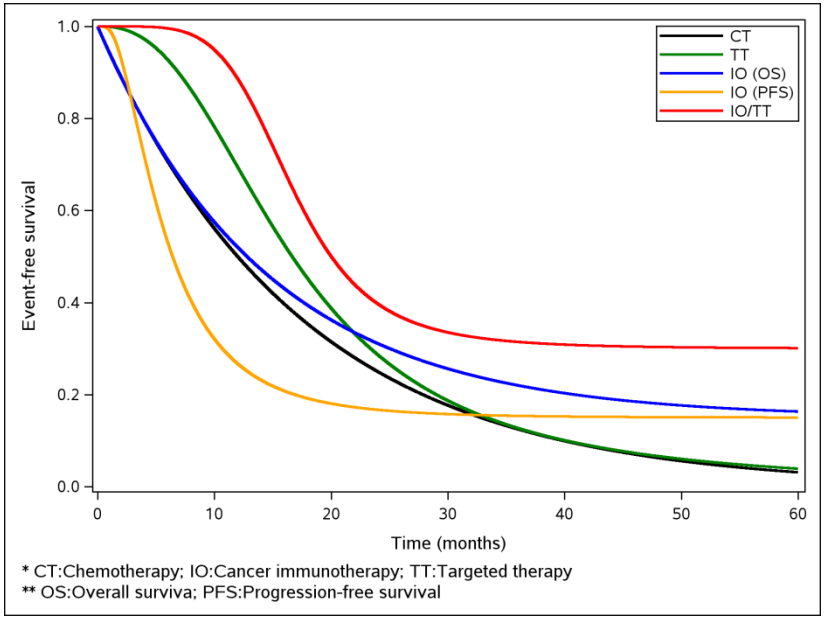
October 13-14, 2016

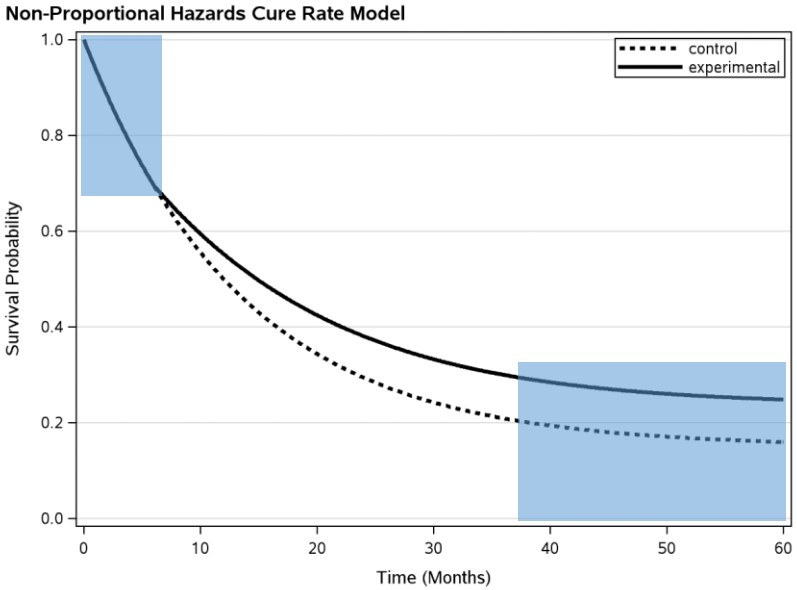
Disclosure

- Employment: currently employed by Bristol-Myers Squibb as Head of Global Biometric Sciences in Medical and Market Access

- The views expressed in this presentation are personal based on my experience and do not necessarily reflect the views of Bristol-Myers Squibb

Background





** Chen T-T. (2013, 2015, 2016).*

Lesson Learned 1: Unique Survival Kinetics

Long-Term Survival

- Study Design
  - Enrolling an adequate number of patients
  - Identifying long-term survivors
  - Exploring novel endpoints
- Statistical Analysis
  - Milestone survival or Restricted mean survival
  - Hazard (ratio) over time

Delayed Clinical Effect

- Study Design
  - Accounting for the delayed duration in sample size determination
  - Increasing information fraction at the interim analysis
- Statistical Analysis
  - Milestone survival or Restricted mean survival
  - Hazard (ratio) over time
  - Weighted log-rank test
  - Ensure sufficient follow-up duration

Lesson Learned 2: The Tail of the Curve

- The primary focus of the OS trial has shifted from the improvement in OS to raising the tail of the curve
- There should exist an improvement in the tail of the curve that is considered clinically meaningful by treating physicians
- The tail needs to be accounted for somehow in the design or analysis

The Tail of the Curve: Milestone Survival

- Milestone survival
  - Defined as the Kaplan-Meier survival probability at a specific time point, such as two years
  - Previously proposed as an intermediate endpoint at the interim analysis
  - Overall survival remains as the primary endpoint at the final analysis
- A subset of patients with a pre-determined minimum follow-up duration is included in the interim milestone analysis
- Pros:
  - A preview of what the tail may look like
  - Early access of efficacious treatments to patients
- Cons:
  - Totality of data not accounted for with moderate correlation between overall survival and milestone survival
  - Censoring prior to milestone impacts milestone survival estimate

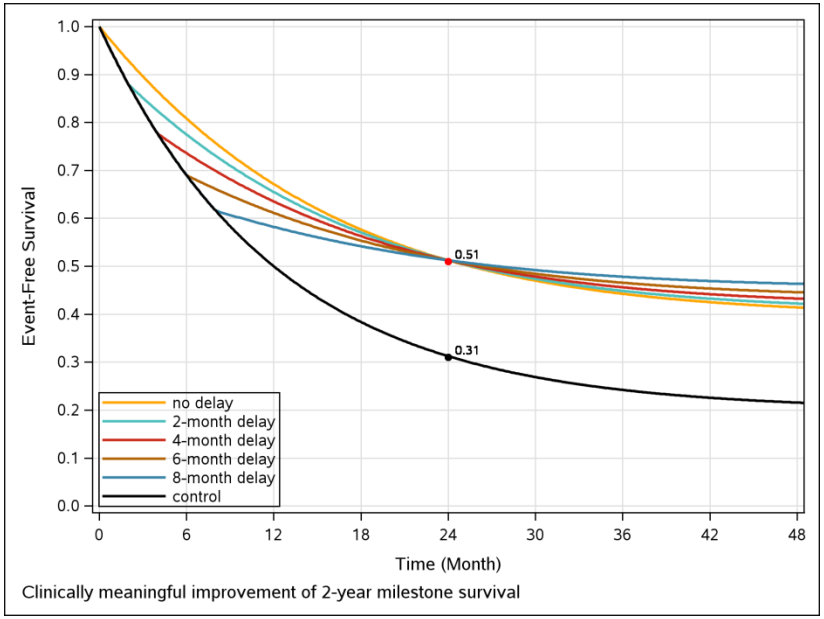
** Chen, T-T. (2015). JNCI.*
*** Blumenthal G, et al. ASCO (2016).*

Proposed Design of Future Late-Stage IO Studies

- We want to design a study so that
  - Overall survival remains the primary endpoint – AND –
  - It is less sensitive to the uncertainty of the survival kinetics – AND –
  - The tail of the curve is accounted for.

- Proposal: Designing the study using milestone survival and analyzing the data with co-primary endpoints of OS and MS
  - Treatment effect
  - Follow-up duration
  - False positive error rate
  - Sample size determination

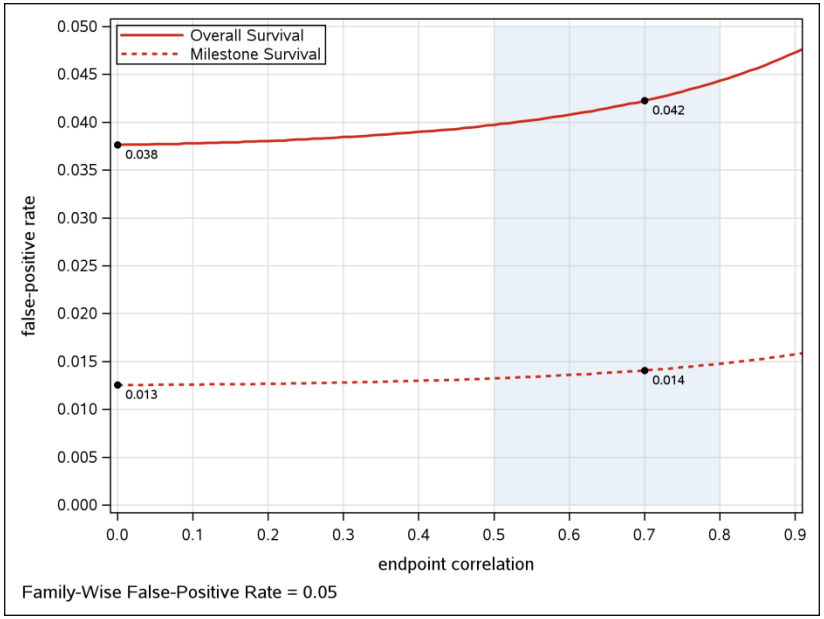
An Illustrative Example: Treatment Effect and Follow-Up Duration



Delayed Clinical Effect	Hazard Ratio Post Delay
None	0.57469
2 months	0.52184
4 months	0.45680
6 months	0.37534
8 months	0.27108

- Treatment effect and study duration are defined
- Agnostic to survival kinetics

An Illustrative Example (cont'd): False Positive Rate with Correlated Endpoints



- Family-wise type I error of 5%
- For moderate correlation between OS and MS (0.5-0.8)
  - A ratio of 3-to-1 (OS/MS) gives a type I error rate of 0.04~0.045 to OS endpoint
  - Assuming a correlation of 0.7, the alpha allocation is 0.042 and 0.014
- Study is designed using milestone survival with alpha of 0.014

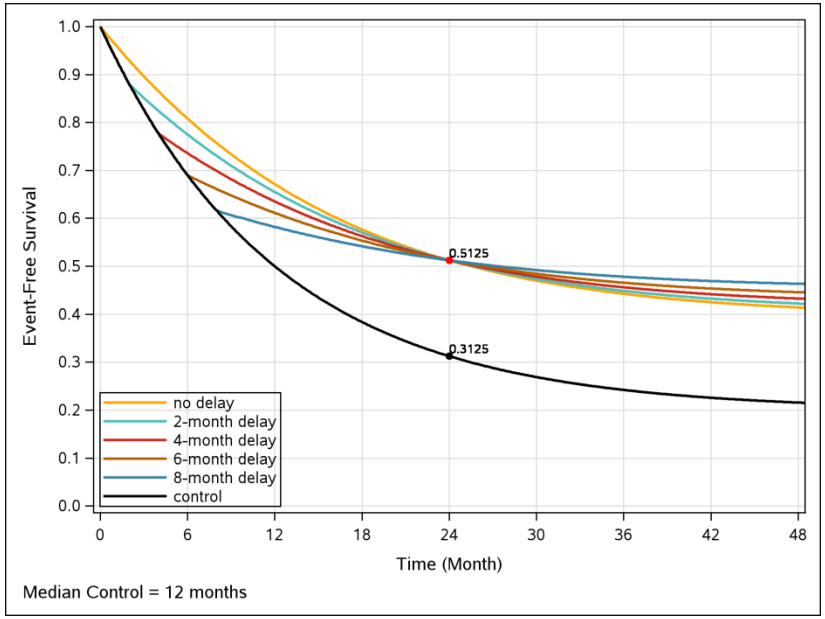
An Illustrative Example (cont'd): Sample Size Determination

- Endpoint used in sample size determination:
  - Milestone survival
- Treatment effect: Improvement in 2-year MS of 20% (31% to 51%)
- Type I error rate: 0.014
- Power: 0.9
- Accrual rate: ~34 per month

- Sample size: 342 randomized patients
- Accrual duration: 10 months
- Follow-duration: 24 months
  - Determined by milestone survival
  - Mitigate the issue of censoring

An Illustrative Example (cont'd): Statistical Analysis of OS and MS

- Timing of analysis:
  - 2 years after last patient came on study
  - ~3 years (34 months) after the time of first patient on study
- Analysis of OS endpoint
  - Power ranges from 95% to 90% from no delay to 8 months delay
  - Type I error rate of 4.2%
- Analysis of MS endpoint
  - Type I error ate of 1.4%



Advantages of the Proposed Design

- Simplification in time to event study design
- OS remains an important endpoint
- No Assumption in the shape of OS curves
- Agnostic to uncertainty of delayed duration and long-term survival
- Predictable timing of analysis
- Assessment of the tail of OS curve
- MS can capture unique late separation with a higher bar
- Minimal loss of false positive rate in OS
- Mitigate the risk of inflated false negative rate

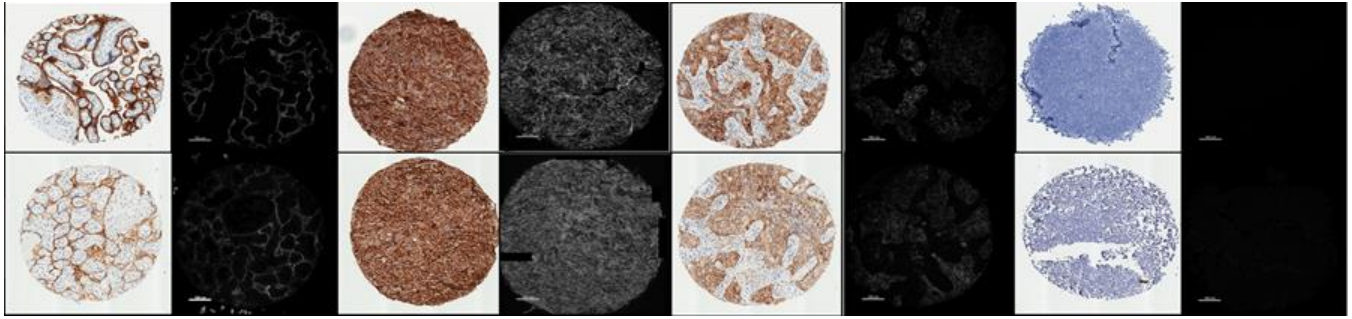
Summary

- A simpler design for future late-stage IO studies using milestone survival with one fourth of false positive rate under moderate correlation
- The probabilities of study success can be assessed under plausible OS assumptions
- Clinically meaningful milestone and improvement
- The design can be extended to situations where follow up duration is less than the milestone (e.g., 18 months follow up for a 2-year MS), in which case the sample size will be inflated to account for censoring prior to milestone
- Proposed design encompasses clinically meaningful information and statistical simplicity

References (in chronological order)

- Chen, T-T. (2013). Statistical Issues and Challenges in Immuno-Oncology. *Journal for Immunotherapy of Cancer*, 1:18.
- Chen, T-T. (2015). Milestone Survival: A Potential Intermediate Endpoint for Immune Checkpoint Inhibitors. *Journal of the National Cancer Institute*, 107(9): djv156.
- Mick, R. and Chen, T-T. (2015). Statistical Challenges in the Design of Late-Stage Cancer Immunotherapy Studies. Cancer Immunology Research, 3(12): 1292-1298.
- Chen T-T. (2016). Predicting analysis time in randomized clinical trials with immunotherapies. BMC Medical Research Methodology.
- Blumenthal G, et al. Milestone analysis with immune checkpoint inhibitors, targeted therapy and conventional therapy in mNSCLC trials submitted to FDA: an updated pooled analysis. ASCO 2016.

Assay Design; Special Considerations for I-O Companion Dx Tests



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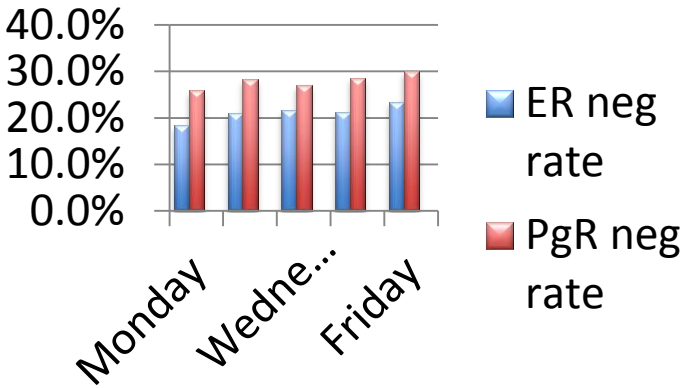
Disclosures:

- In the last 12 months I have been engaged in the following relationships:
- I am a consultant/Advisor to Astra Zeneca, Bethyl Labs, Biocept, BMS, FivePrime, Merck, Novartis, OptraScan, Perkin Elmer and Ultivue
- I hold equity in Metamark Genetics and Pixel Gear
- Cepheid, Genoptix, Gilead Sciences, Pierre Fabre, Perkin Elmer and OncoplexDx fund research in my lab.

Critical Components for a Broadly Reproducible Companion Dx Assay for I-O Therapy

- Control pre-analytic conditions (core bx may be best)
- Quantitatively titer a monoclonal antibody for IHC assays
- Choose an analysis method that can be achieved by pathologists or choose a machine
- Standardize the assay with a control series (isogenic cells) for multi-site and longitudinal reproducibility

ER status more negative if surgery is on Friday than on Monday?



	cases	ER neg rate	PgR neg rate
Monday	1252	18.4%	26.0%
Tuesday	1176	21.1%	28.2%
Wednesday	784	21.7%	27.0%
Thursday	904	21.1%	28.7%
Friday	919	23.5%	30.0%

Control the Pre-Analytic Conditions:

- Use core bx when possible
- Stain slides immediately after they are cut
- Choose targets that are stable to warm and cold ischemia

Frequency of ER/PgR negativity significantly increased with each day of the week, both for ER (P = 0.03) and PgR (P = 0.059 for trends; n=5077).

Hammond et al. Arch Pathol Lab Med. 2010;134:606-612

Critical Components for a Broadly Reproducible Companion Dx Assay for I-O Therapy

- Control pre-analytic conditions (core bx may be best)
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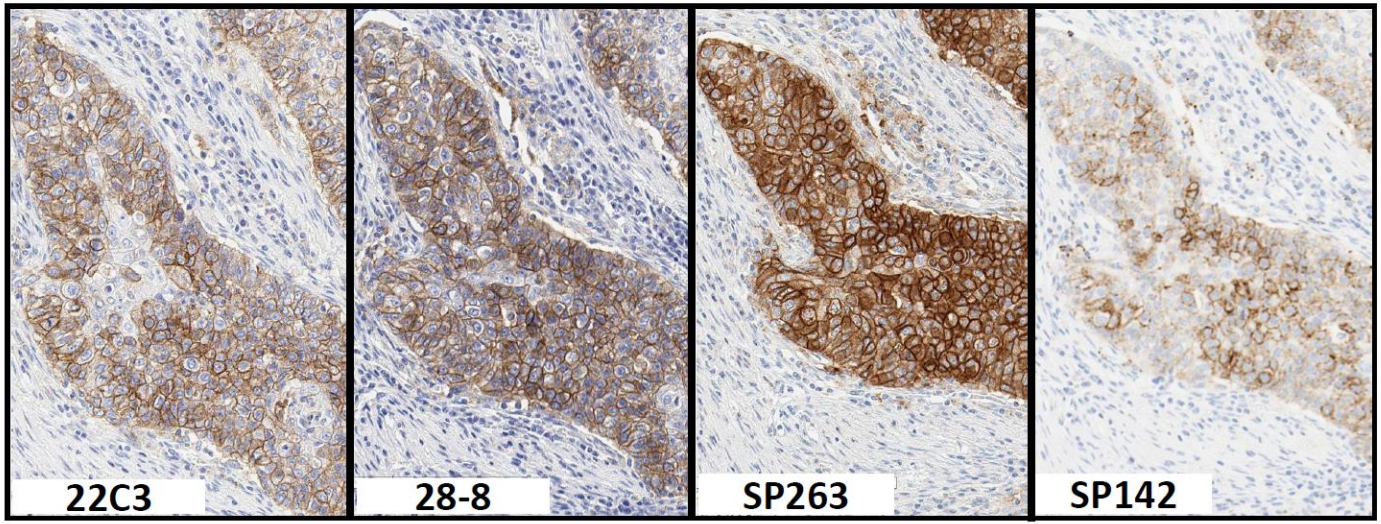
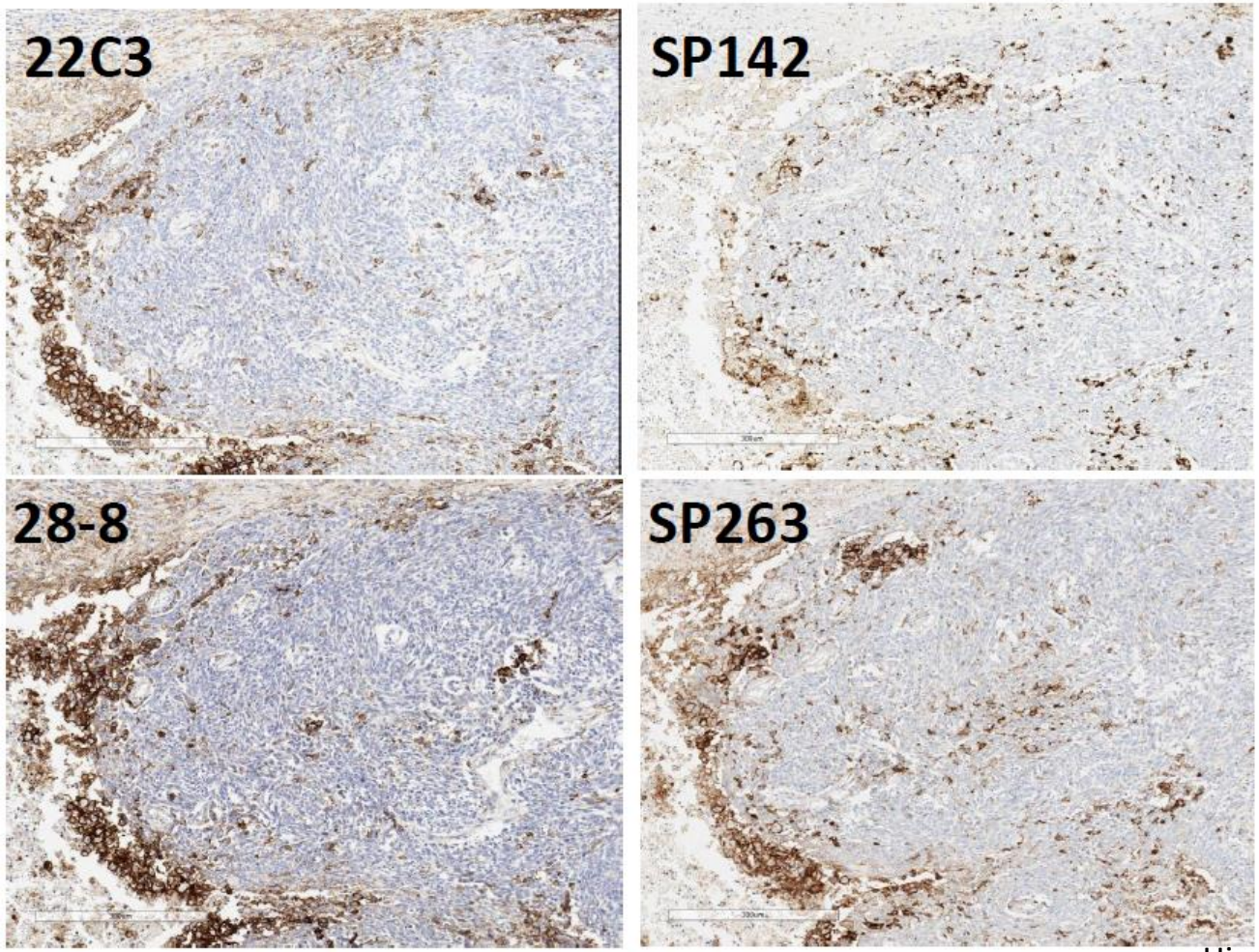
“Blueprint” image comparison

Example of PD-L1 Tumor Expression

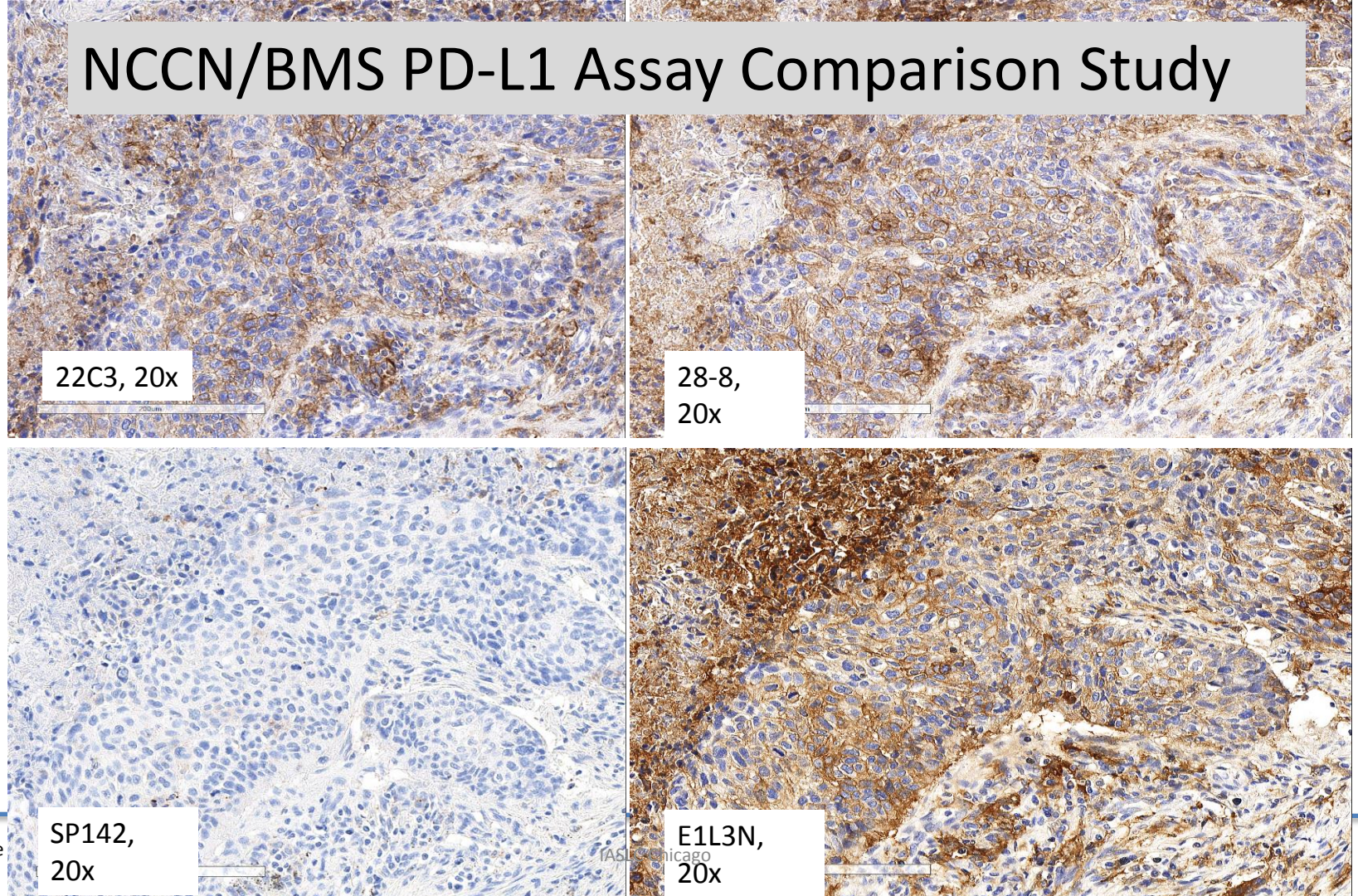


Hirsch et al, AACR 2016

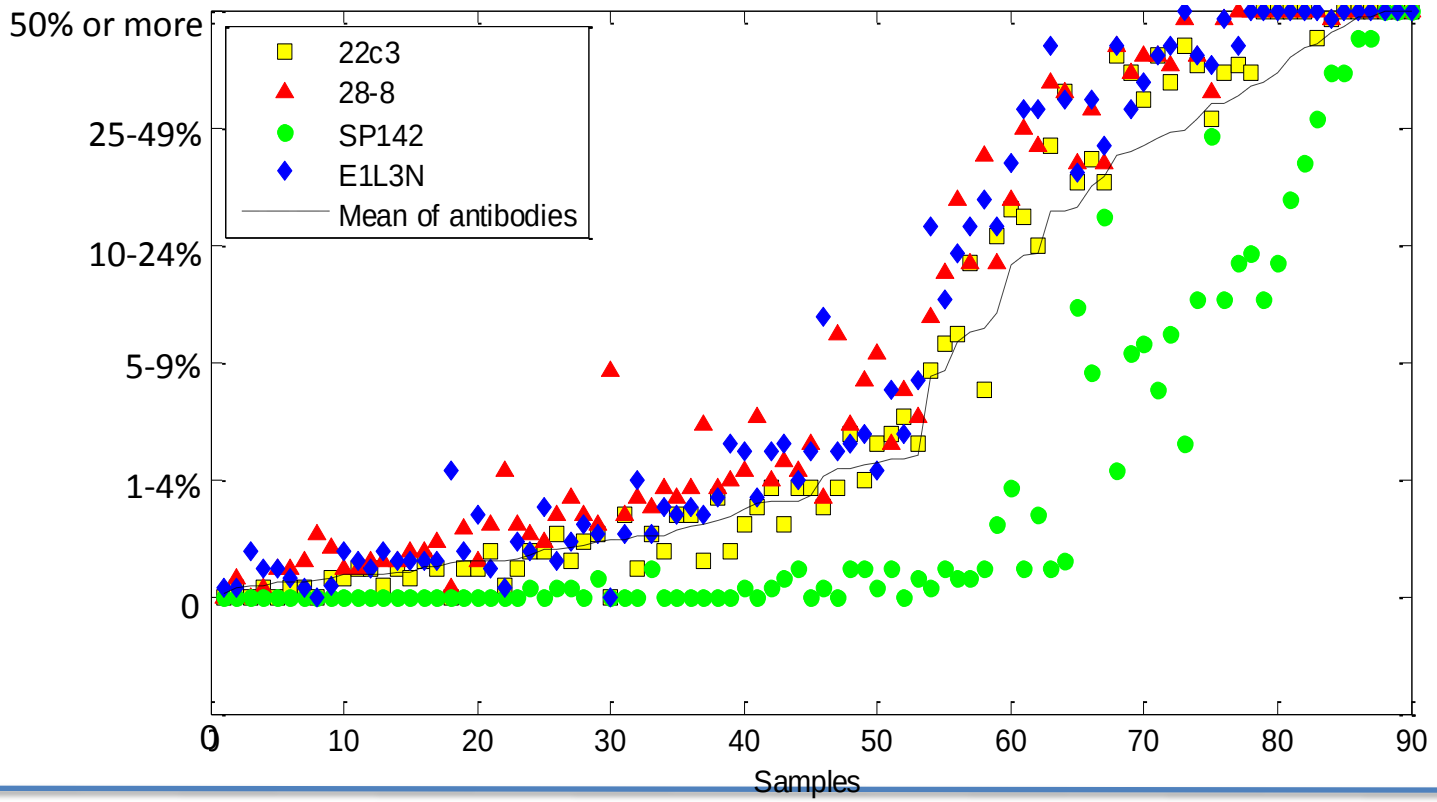


Hirsch et al, AACR 2016

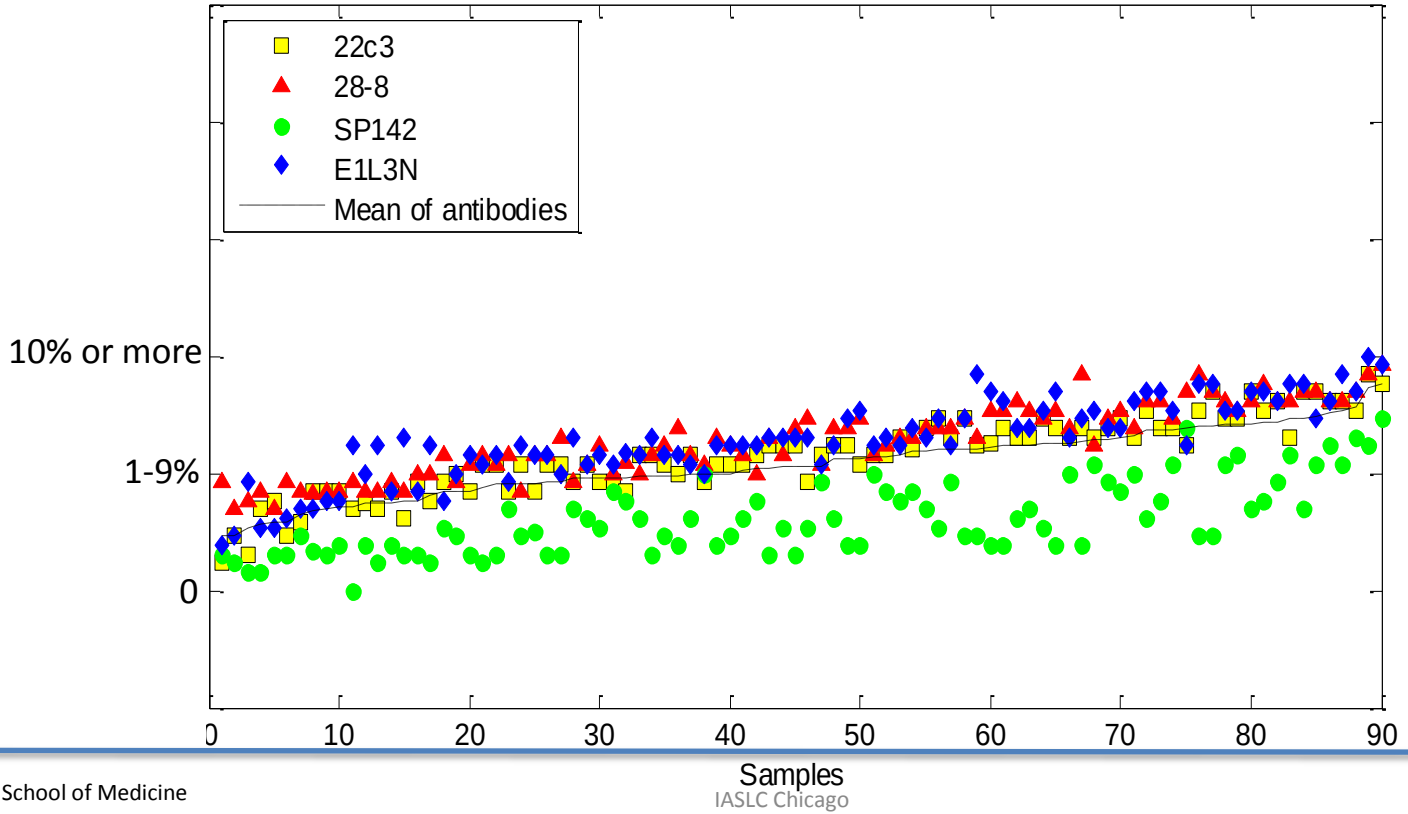
NCCN/BMS PD-L1 Assay Comparison Study



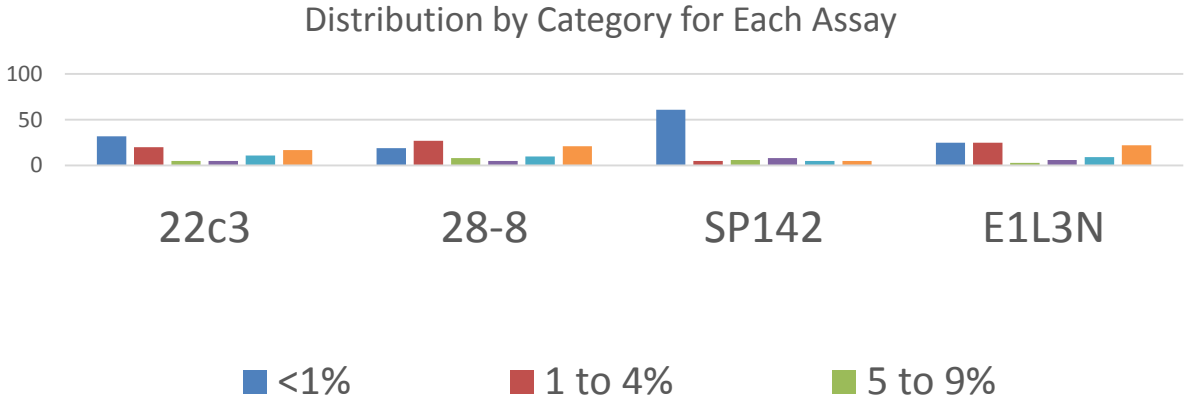
NCCN/BMS Average Scores for Tumor Cells

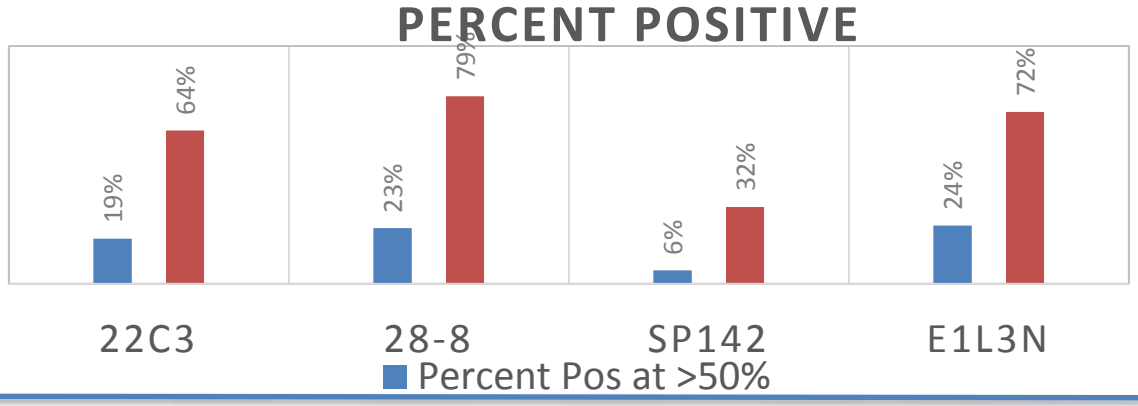


NCCN/BMS Average Scores for Immune Cells



NCCN/BMS Distribution of Tumor Scores by Assay



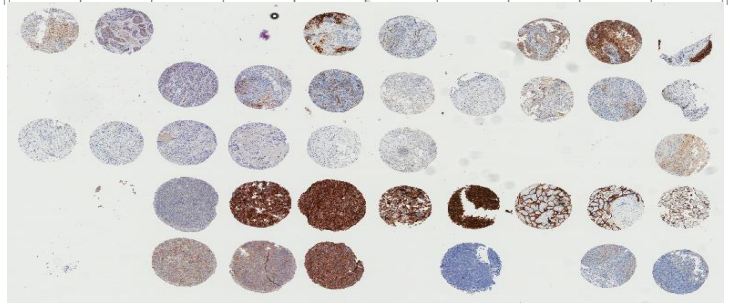


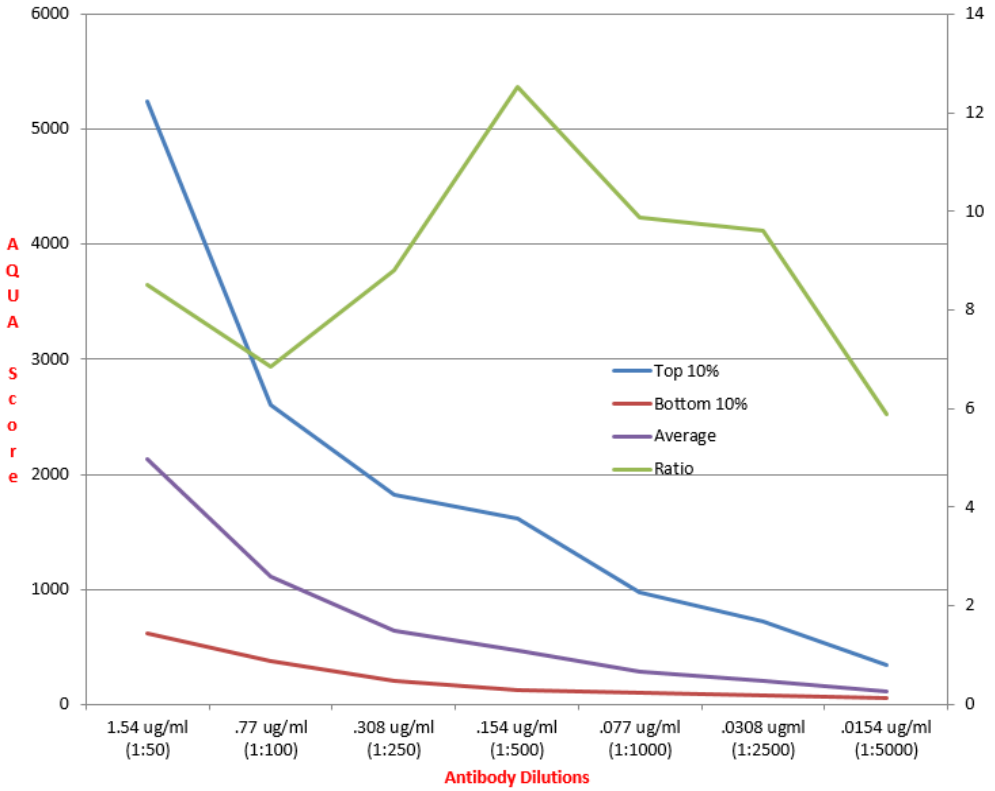
Summary

- The SP142 assay selects over 50% fewer patients for both tumor cells and immune cells
- The other 3 assays are the same (more or less)

Titer Optimization for SP142

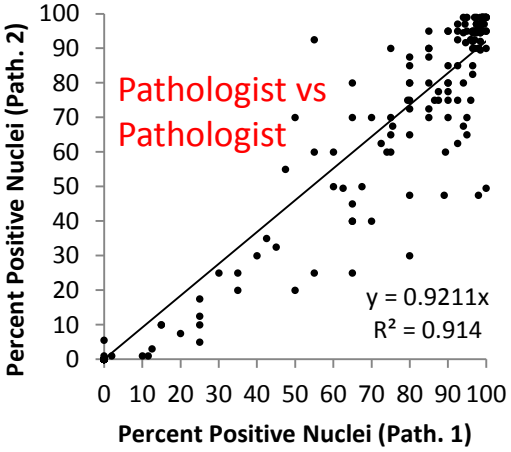
Map layout for - 337 - 1 Created On - 10/27/2015									
Col 1	Col 2	Col 3	Col 4	Col 5	Col 6	Col 7	Col 8	Col 9	Col 10
S09-6226 A2 Tumor	S09-16203 A2 Tumor	S09-1896 A5 Tumor	S08-10470 F3 Tumor	S08-4400 F3 Tumor	S09-14789 F3 Tumor	S09-16175 H6 Tumor	S08-13393 C2 Tumor	S08-6122 H4 Tumor	S09-605 A2 Tumor
S08-10454 A2 Tumor	S09-7310 B1 Tumor	S08-8295 A2 Tumor	S08-17403 B1 Tumor	S08-8279 A2 Tumor	S09-11966 A2 Tumor	S08-7189 A2 Tumor	S08-11643 A2 Tumor	S09-5745 A1 Tumor	S08-14764 A4 Tumor
S09-5729 H5 Tumor	S08-15872 C5 Tumor	S08-17190 A3 Tumor	S08-8877 C3 Tumor	S09-180 B6 Tumor	S09-8520 D5 Tumor	S09-6606 A3 Tumor	S09-7374 A2 Tumor	S08-5160 A2 Tumor	S09-5431 D3 Tumor
A549 0.8ng/ml Cell Line	A549 15 ng/ml Cell Line	A431 Cell Line	HCC193 Cell Line	H820 Cell Line	mel 624 B7H1 Cell Line	Karpas Cell Line	Placenta 2C Normal control	Placenta 1A Normal control	Placenta 1-1 s10-8709 Normal control
A549 0ng/ml Cell Line	A549 1.6ng/ml Cell Line	H2882 Cell Line	H1975 Cell Line	H441 Cell Line	Mel 624 w/t Cell Line	Ramos Cell Line	Tonsil #3 Normal control	Tonsil #2 Normal control	Tonsil #1 Normal control

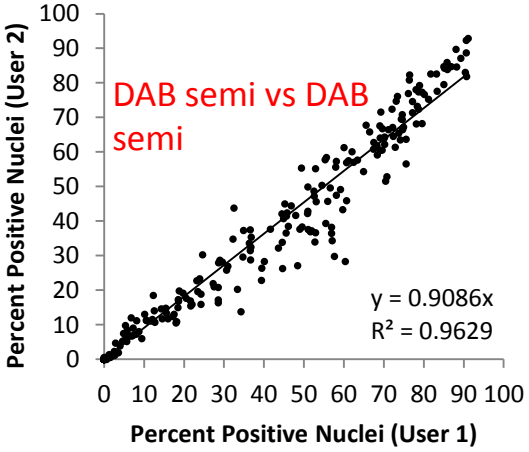


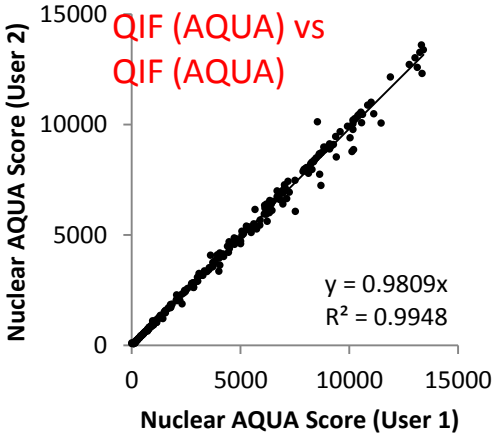


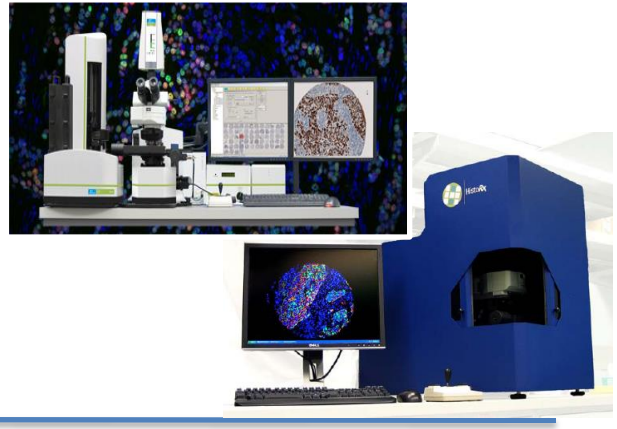
Critical Components for a Broadly Reproducible Companion Dx Assay for I-O Therapy

- Control pre-analytic conditions (core bx may be best)
- Quantitatively titer a monoclonal antibody for IHC assays
- Choose an analysis method that can be achieved by pathologists or choose a machine
- Standardize the assay with a control series (isogenic cells) for multi-site and longitudinal reproducibility


Pathologist vs Pathologist
y = 0.9211x
R² = 0.914
Percent Positive Nuclei (Path. 2)
Percent Positive Nuclei (Path. 1)
0 10 20 30 40 50 60 70 80 90 100


DAB semi vs DAB semi
y = 0.9086x
R² = 0.9629
Percent Positive Nuclei (User 2)
Percent Positive Nuclei (User 1)
0 10 20 30 40 50 60 70 80 90 100


QIF (AQUA) vs QIF (AQUA)
y = 0.9809x
R² = 0.9948
Nuclear AQUA Score (User 2)
Nuclear AQUA Score (User 1)
0 5000 10000 15000



ICC for the Pathologists and Scores

The ICC for each antibody allows us to assess the agreement between readers for tumor cell and immune cell scores

ICC for pathologists by each antibody in Tumor Cells					
	22c3	28-8	SP142	E1L3N	Summary
All, N=90	0.882	0.832	0.869	0.859	0.86(0.02)

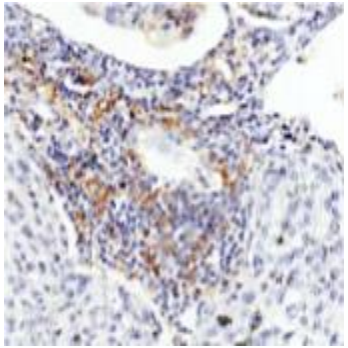
ICC for pathologists by each antibody in Immune Cells					
	22c3	28-8	SP142	E1L3N	Summary
All, N=90	0.207	0.172	0.185	0.229	0.19(0.03)

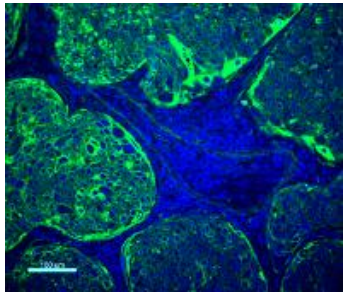
	Cutoff at >50%		Cutoff at >1%	
	Fleiss Kappa	Kendall Concordance	Fleiss Kappa	Kendall Concordance
Average of all 4 assays	0.749	0.775	0.537	0.612

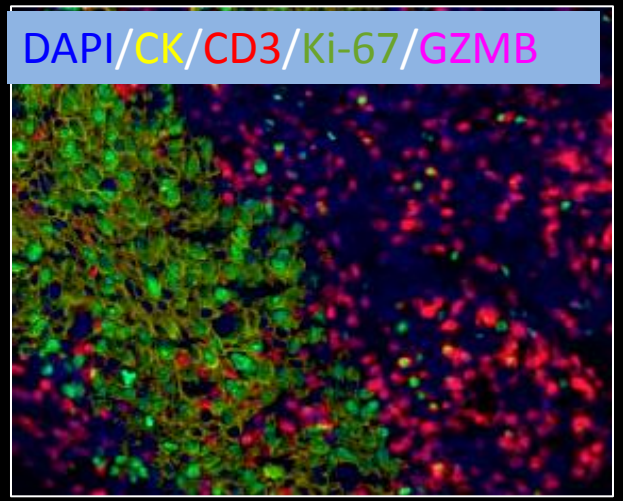
Measurement Systems: Absorptive vs Emissive

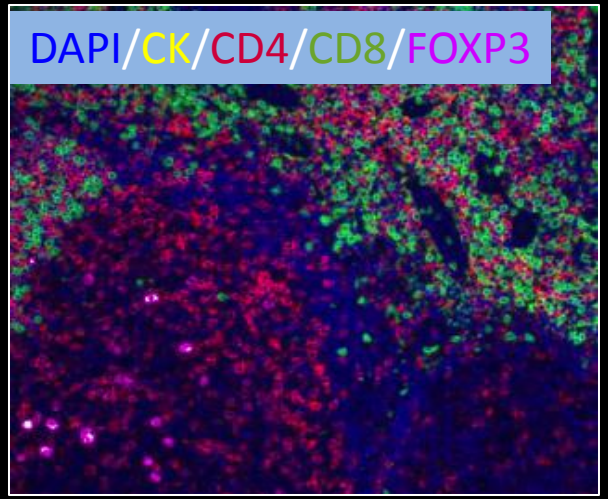
Top View

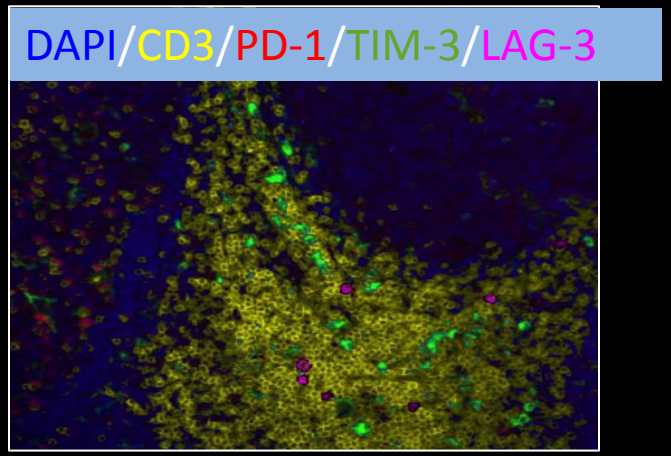
Side View

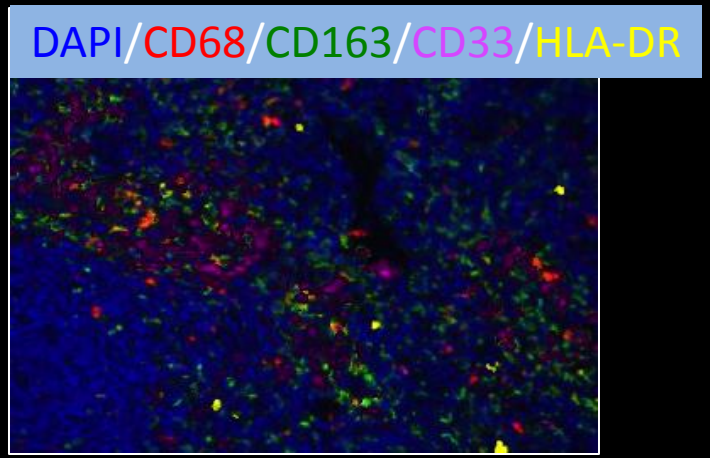





DAPI/CK/CD3/Ki-67/GZMB


DAPI/CK/CD4/CD8/FOXP3


DAPI/CD3/PD-1/TIM-3/LAG-3


DAPI/CD68/CD163/CD33/HLA-DR

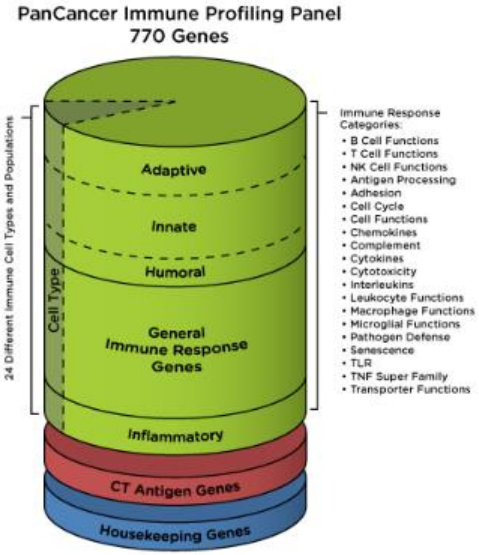
RNA expression signatures

J Immunother Cancer. 2015; 3(Suppl 2): P80.
Published online 2015 Nov 4. doi: 10.1186/2051-1426-3-S2-P80
PMCID: PMC4645163

Relationship between immune gene signatures and clinical response to PD-1 blockade with pembrolizumab (MK-3475) in patients with advanced solid tumors

Mark Ayers,[1] Jared Lunceford,[1] Michael Nebozhyn,[1] Erin Murphy,[2] Andrey Loboda,[1] Andrew Albright,[1] Jonathan Cheng,[1] S Peter Kang,[1] Scot Ebbinghaus,[1] Jennifer Yearley,[1] Veena Shankaran,[3] Tanguy Seiwert,[4] Antoni Ribas,[5] an Terri McClanahan[1]

Signature	HNSCC		Gastric Cancer	
	ORR	PFS	ORR	PFS
IFN-λ	0.005	<0.001	0.077	0.032
TCR signaling	0.071	0.002	0.034	0.024
Expanded immune	0.015	<0.001	0.062	0.049
De novo	0.018	<0.001	0.068	0.037



Mutational Load

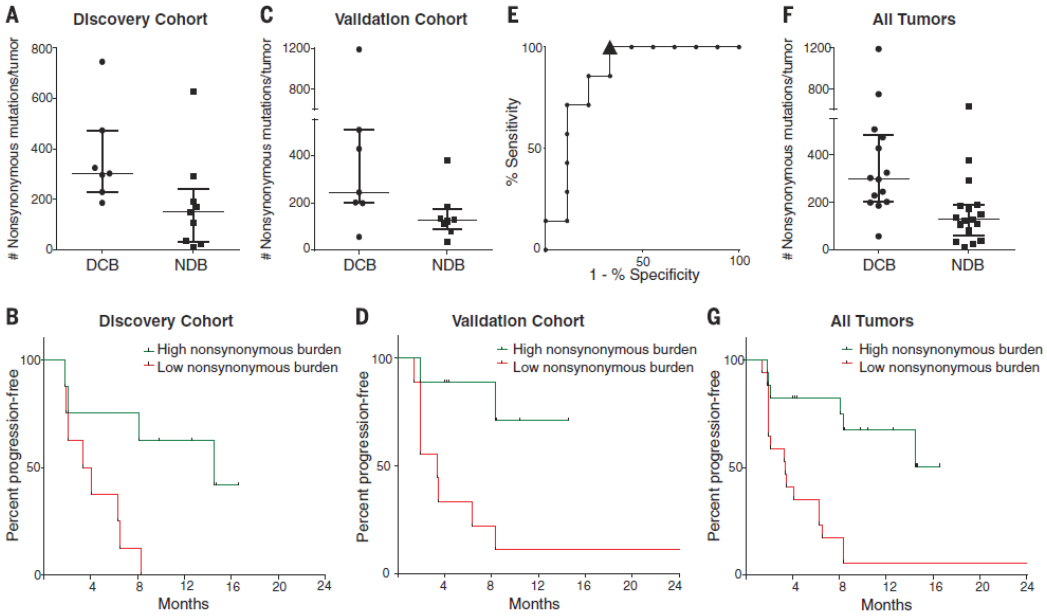
sciencemag.org SCIENCE

RESEARCH | REPORTS 3 APRIL 2015 • VOL 348 ISSUE 6230

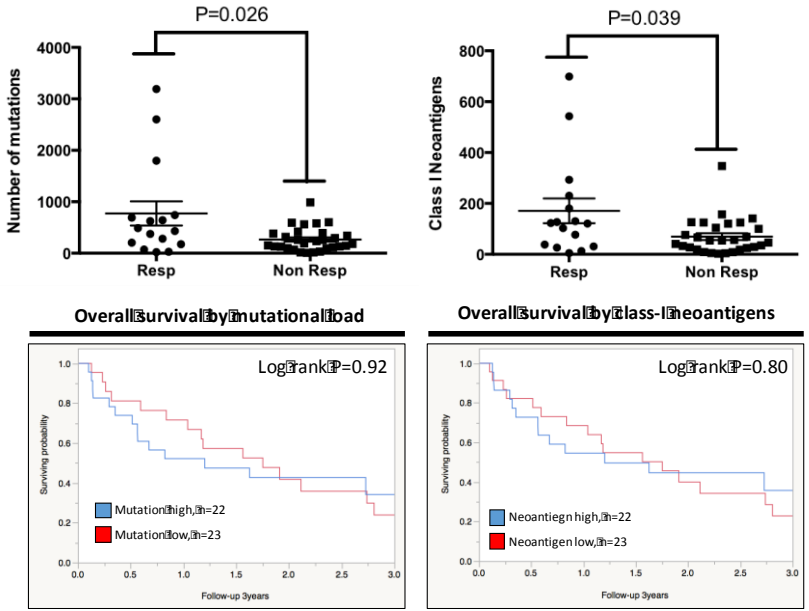
CANCER IMMUNOLOGY

Mutational landscape determines sensitivity to PD-1 blo non-small cell lung ca

Naiyer A. Rizvi,[1,2*†] Matthew D. Hellmann,[1,2*] Ale
Vladimir Makarov,[3] Jonathan J. Havel,[3] William L
Teresa S. Ho,[6] Martin L. Miller,[7] Natasha Rekhtma
Fawzia Ibrahim,[1] Cameron Bruggeman,[9] Billel Gas
Yuka Maeda,[10] Chris Sander,[7] Edward B. Garon,[11]
Jedd D. Wolchok,[1,2,10] Ton N. Schumacher,[4] Timot



Mutation load and predicted class I neoantigens in Yale NSCLC treated with immune checkpoint blockers



Sensitivity=68%

Specificity=58%

- Mutational load and class-I neoantigens are significantly associated with response, but not with survival in NSCLC

Jungmin Choi, Kurt Schalper, Rick Lifton and Roy Herbst

Critical Components for a Broadly Reproducible Companion Dx Assay for I-O Therapy

- Control pre-analytic conditions (core bx may be best)
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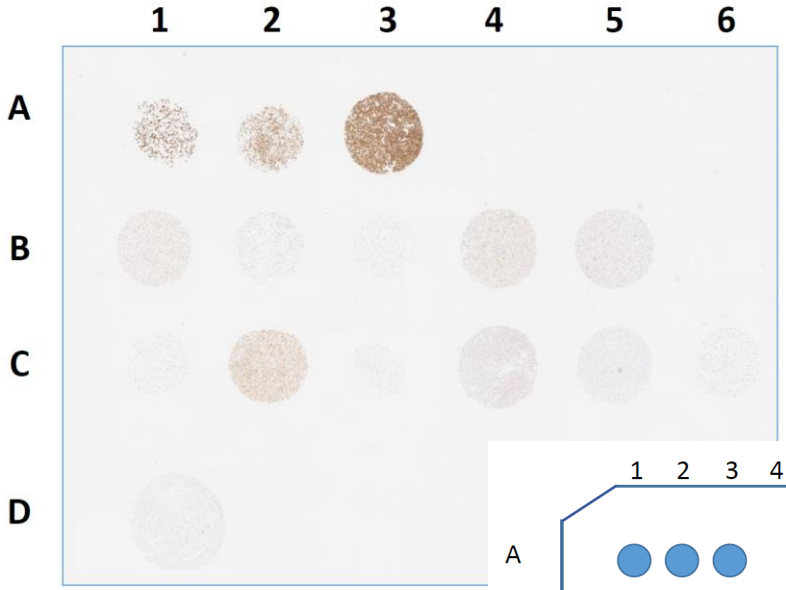
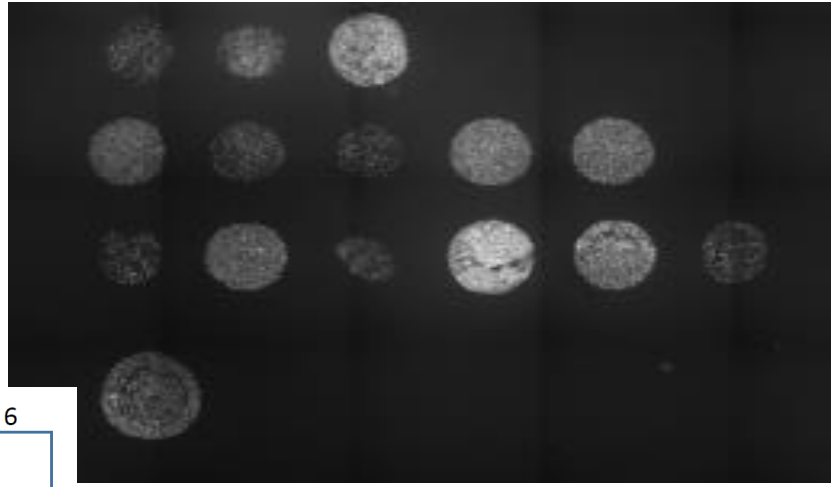
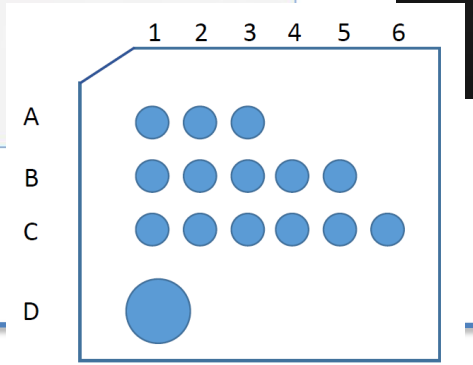
Antibody Comparison on *Horizon Discovery* PD-L1 Developmental TMA







Questions?

Back-up slides

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Home » Clinical & Translational » Molecular Diagnostics » NanoString Releases Details on Tumor Inflammation Signature As

NanoString Releases Details on Tumor Inflammation Signature Assay From Merck CDx Collaboration

Aug 12, 2016 | Andrew P. Han

Antibody Comparison

Research

JAMA Oncology | Brief Report

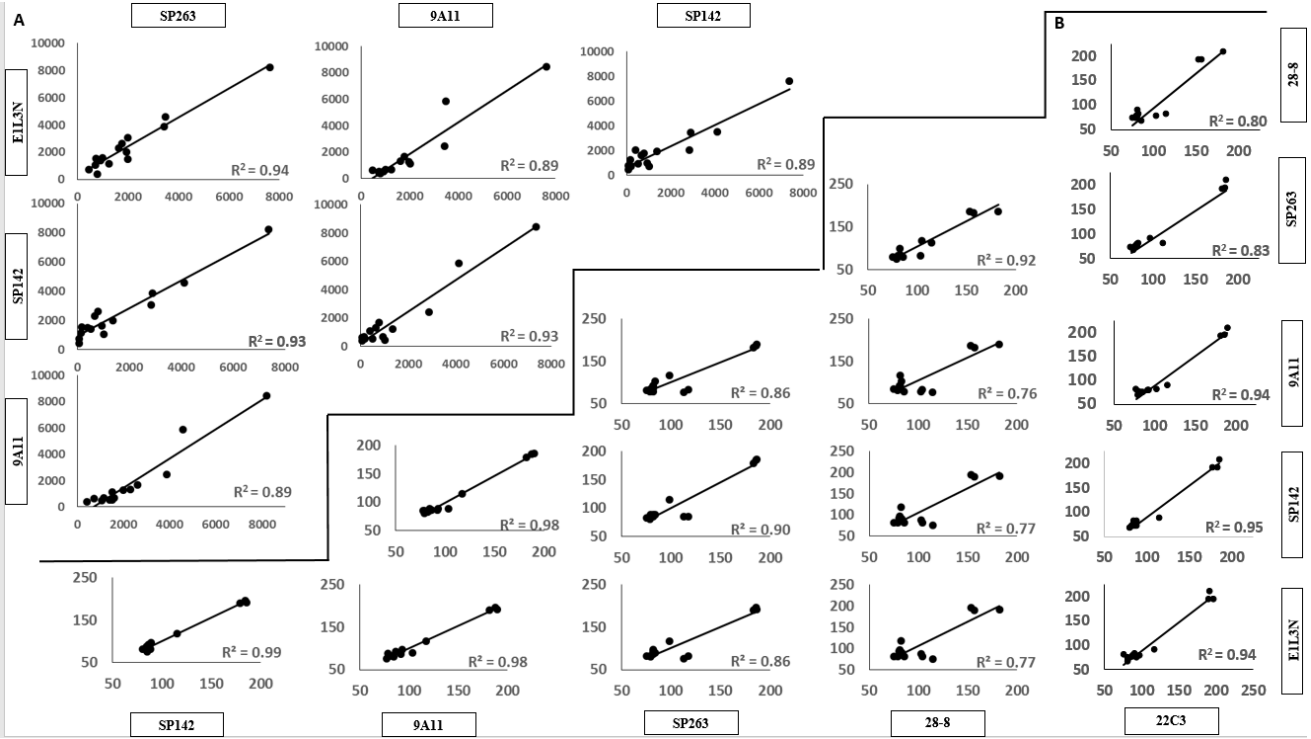
A Quantitative Comparison of Antibodies to Programmed Cell Death 1 Ligand 1

Patricia Gaule, PhD; James W. Smithy, BS; Maria Toki, MD; Jamaal Rehman, MD; Farah Patell-Socha, PhD; Delphine Cougot, PhD; Philippe Collin, PhD; Paul Morrill, PhD; Veronique Neumeister, MD; David L. Rimm, MD, PhD

IMPORTANCE Assessment of PD-L1 (programmed cell death 1 ligand 1) expression by immunohistochemical analysis has been used as a predictive diagnostic test to identify

Supplemental content at jamaoncology.com

Comparison by Quantification (QIF and DAB)



PD-L1 Diagnostic Development for NSCLC: Current and Future IVD Landscape

Ab clone/epitope	28-8	22C3	SP142	SP263
IVD class III diagnostic partner	Dako	Dako	Ventana	Ventana
Drug	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
PD-L1 scoring method	% tumor cells	% tumor cells	% tumor cells & % immune cells	% tumor cells
FDA IVD status for NSCLC	Complementary	Companion	Under Evaluation	Under Evaluation
PD-L1 thresholds under evaluation	≥1%, ≥5%, or ≥10%	≥1%, ≥50%	IC1/2/3 (≥1%, ≥5% & ≥10%) TC1/2/3 (≥1%, ≥5% & ≥50%)	≥25%

Unified Scoring System for assessment of PD-L1 expression used for this study

Part 1: Tumor Cell staining

Category	Range	Drugs Justifying Category Cut-point
A	Negative or 0%	All drugs
B	1% to 4%	Nivolumab and Pembrolizumab
C	5% to 9%	Nivolumab and Atezolizumab
D	10% to 24%	Nivolumab
E	25% to 49%	Durvalumab
F	50% or more	Pembrolizumab and Atezolizumab

Part 2: Immune Cell staining

Category	Range	Drugs Justifying Category Cut-point
A	Negative or 0%	All drugs
B	1% to 9%	Atezolizumab (IC1 and IC2)
C	10% or more	Avelumab and Atezolizumab

Results: Summary Data for Tumor

Tumor -percentage	22c3	28-8	SP142	E1L3N
Percentage <1%	32	19	61	25
Percentage >=1% and <5%	20	27	5	25
Percentage >=5% and <10%	5	8	6	3
Percentage >=10% and <25%	5	5	8	6
Percentage >=25% and <50%	11	10	5	9
Percentage >=50%	17	21	5	22
Total	90	90	90	90
Percent cases "positive" at >50%	19%	23%	6%	24%
Percent cases "positive" at >1%	64%	79%	32%	72%

American Association for Cancer Research

FINDING CURES TOGETHER℠

Workshop Concluding Remarks

Maytreyee Hazarika, MD

Workshop Co-Chair

American Association for Cancer Research

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Adjourn

Thank You for Attending!