Designs and Endpoints of Immunotherapy Trials

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Outline of Talk

- **Early phase clinical trials:**
  - **Optimal biological dose**
  - **Response assessment**
  - **Signal finding in broad tumor types**
  - **Combination trials**
- **Late phase clinical trials:**
  - **Delayed clinical effect**
  - **Long term survivors**

Clinical Trial Designs in the Immunotherapy Era

- **Gap**: Why do we need special design considerations for clinical trials evaluating IO agents?
  - Lack of reliable non-clinical models such that animal toxicology data guiding early trials are lacking
  - Risk for acute toxicity such as cytokine release syndrome
  - Many IO agents do not have dose-limiting toxicity or reach MTD in phase I trials
  - Urgency to advance the development of drugs with early signals of antitumor activity
  - Challenges in evaluating IO-based combinations (with chemotherapy, targeted or IO agents)
  - Pseudoprogression, delay in antitumor response and ‘tail’ of long-term disease control observed in some patients on IO therapy
  - Optimal duration of therapy in those with benefit is unclear
  - Need for innovative trial designs for this class of agents with unique characteristics

RPTD Determination in Early Phase Trials of Immune Agents

Agent (target)	N	Patients	RPTD	RPTD determination	Efficacy criteria
Ipilimumab (CTLA4)	88	Melanoma	10 mg/kg Q3W x 4	• No MTD	RECIST
Tremelimumab (CTLA4)	39	Solid tumors	10 mg/kg single dose	• MTD	WHO
Tremelimumab (CTLA4)	117	Melanoma	10 mg/kg Q1mo 15 mg/kg Q3mo	• No MTD • No MTD	RECIST
Nivolumumab (PD-1)	39	Solid tumors	10 mg/kg single dose	• No MTD	RECIST
Nivolumab (PD-1)	296	Solid tumors	10 mg/kg Q2W	• No MTD	Modified RECIST
BMS936559 (PD-L1)	207	Solid tumors	10 mg/kg Q2W	• No MTD	Modified RECIST
MK3475 (PD-L1)	135	Melanoma	10 mg/kg Q2W	• No MTD	RECIST and irRC

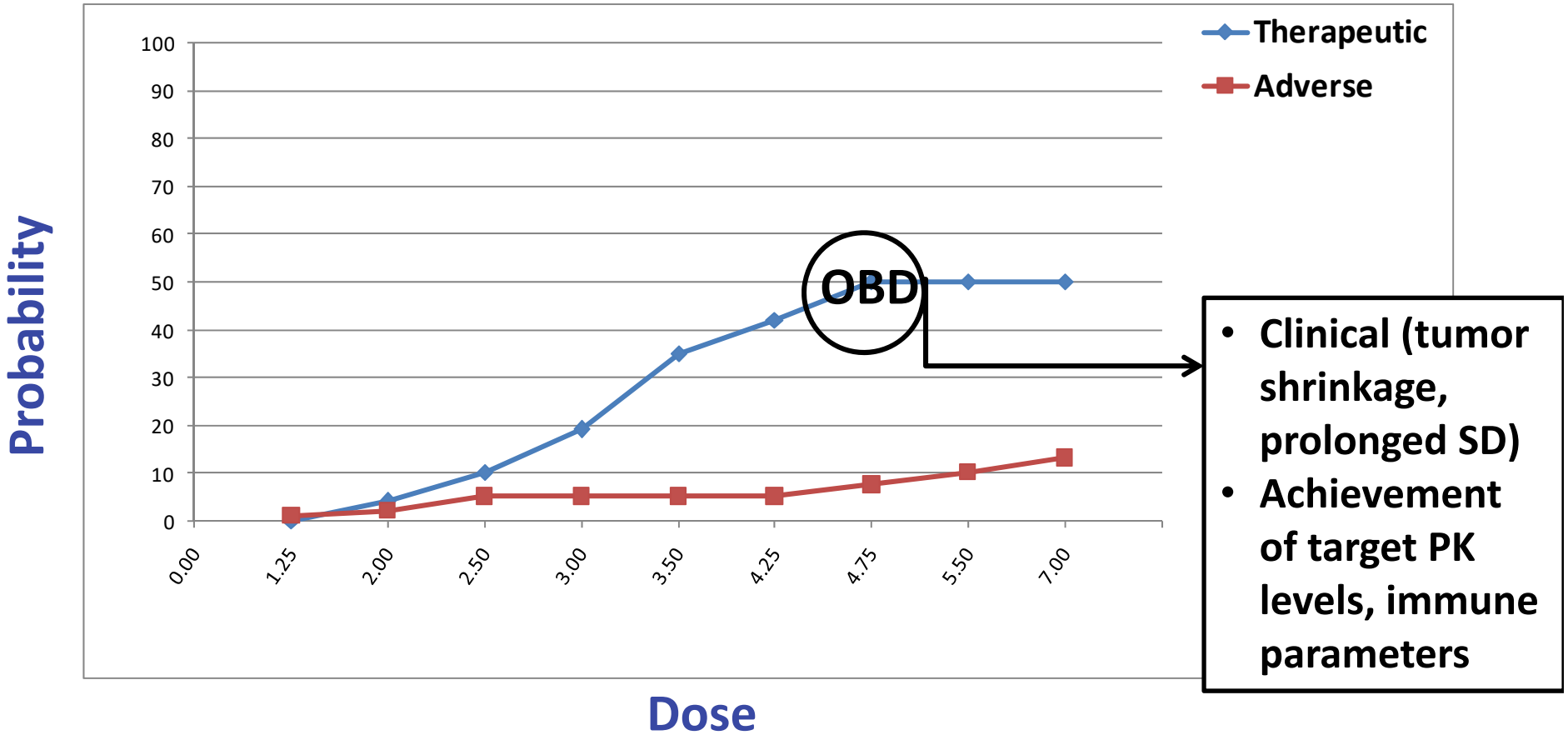
Weber et al. J Clin Oncol 2008; Ribas et al. J Clin Oncol 2005; Camacho et al. J Clin Oncol 2009; Brahmer et al. J Clin Oncol 2010; Topalian et al. NEJM 2012; Brahmer et al. NEJM 2013; Hamid et al. NEJM 2013

Defining the Optimal Biological Dose (OBD)

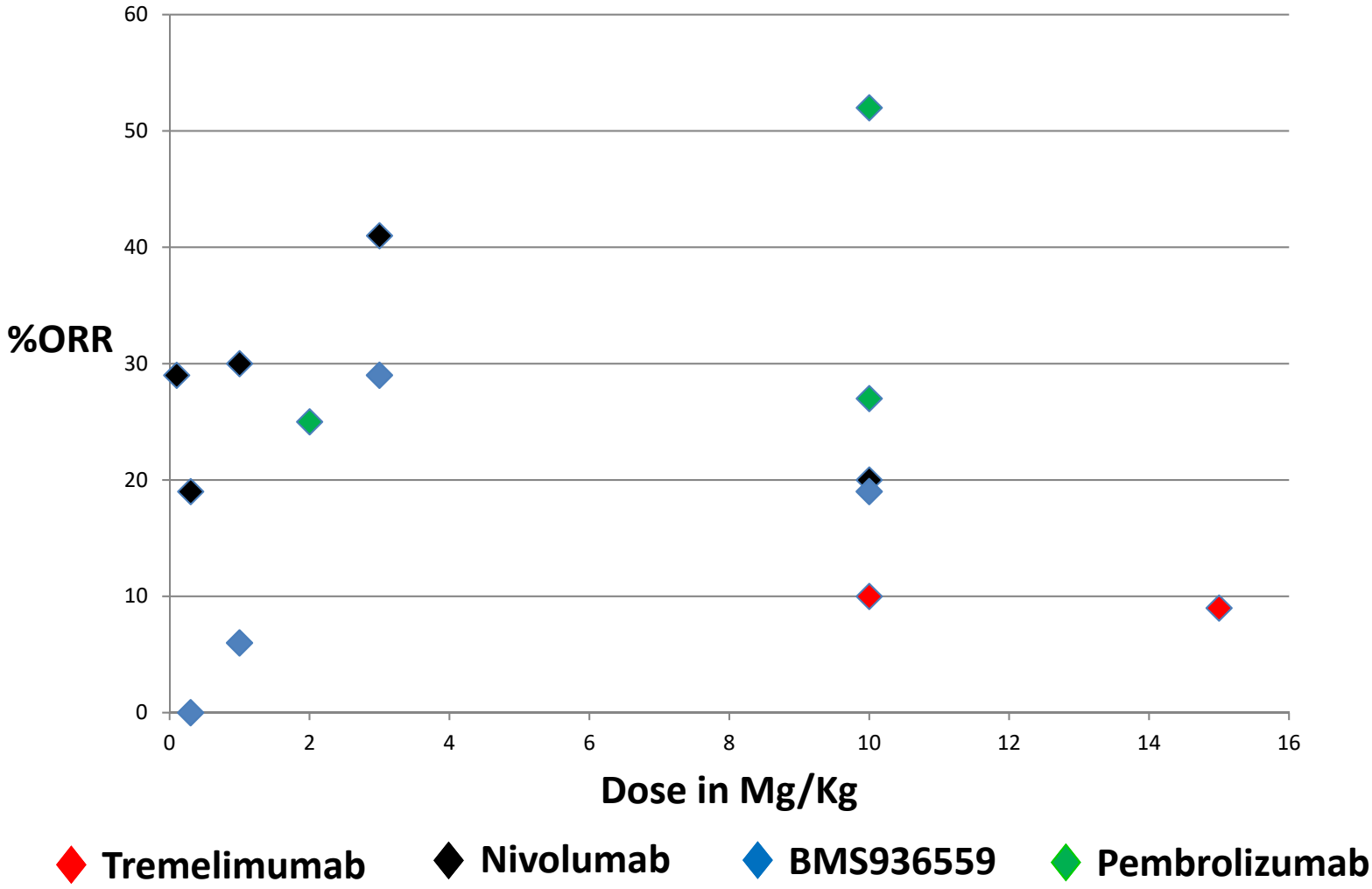
- **"Dose associated with a pre-specified most desirable effect on a biomarker among all doses studied (e.g. inhibition of a key target in tumor or surrogate tissue or achievement of a pre-specified immunologic parameter)"**
- **"A significant disadvantage is the empiricism in establishing the OBD and in monitoring therapeutic activity early during the course of treatment"**

Le Tourneau et al. JNCI, 2009; Shaked et al. Blood, 2005

Dose-Response: Efficacy and Toxicity



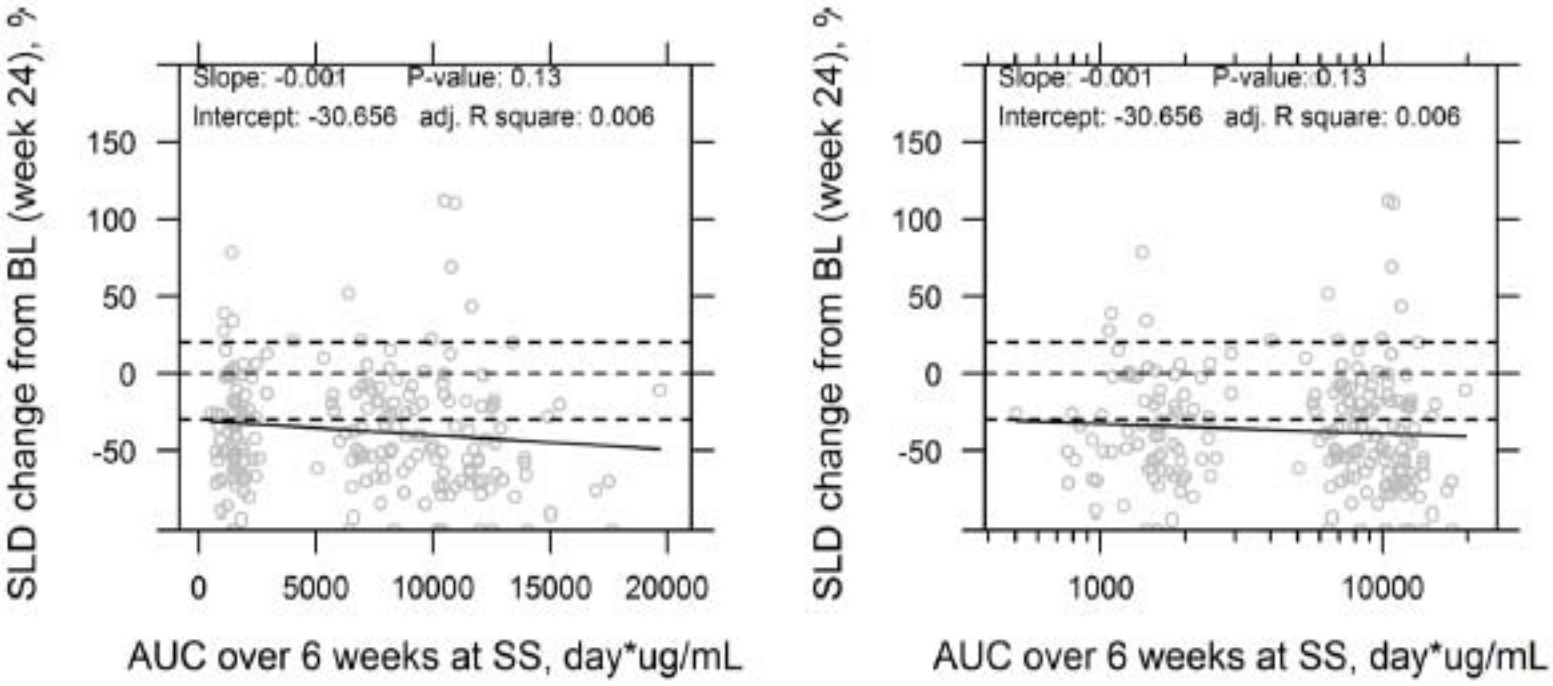
What is the OBD for CTLA4 and PD-1/PD-L1 Inhibitors?



Selected Studies – Melanoma Patients Only (Not Factoring in Dosing Schedule)

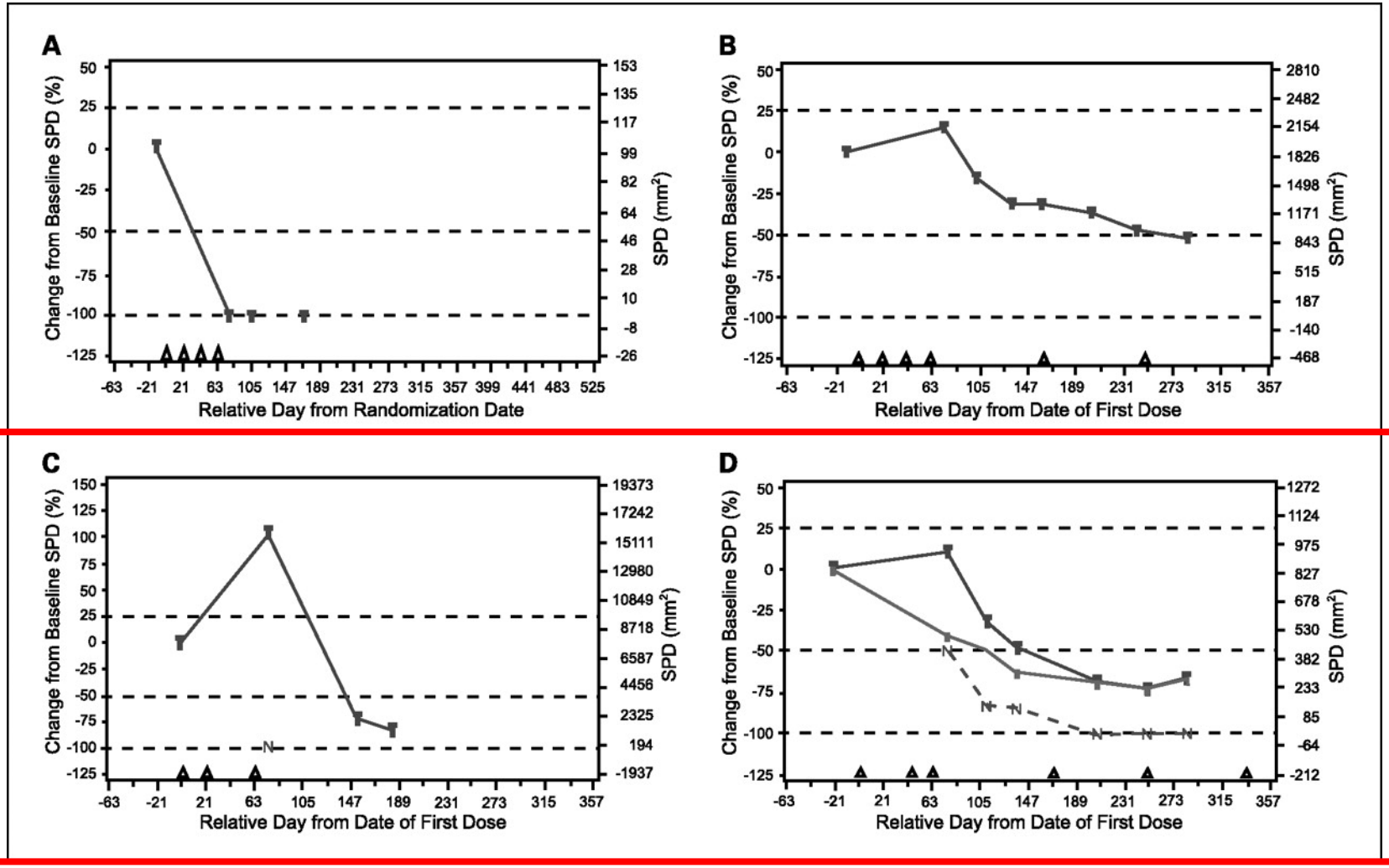
PK-PD modeling guides a critical decision on KEYTRUDA® dose

- Exposure-**response** analysis: flat exposure-response between 2Q3, 10Q3, 10Q2
  - Key point: Tumor size change was used for modeling as response instead of conventional RECIST criterion
  - Change in Tumor size vs Exposure: no difference between 2Q3, 10Q3, 10Q2



De Alwis, FDA-AACR Oncology Dose Finding Workshop June 2016

Patterns of Response to Ipilimumab Observed in Advanced Melanoma



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

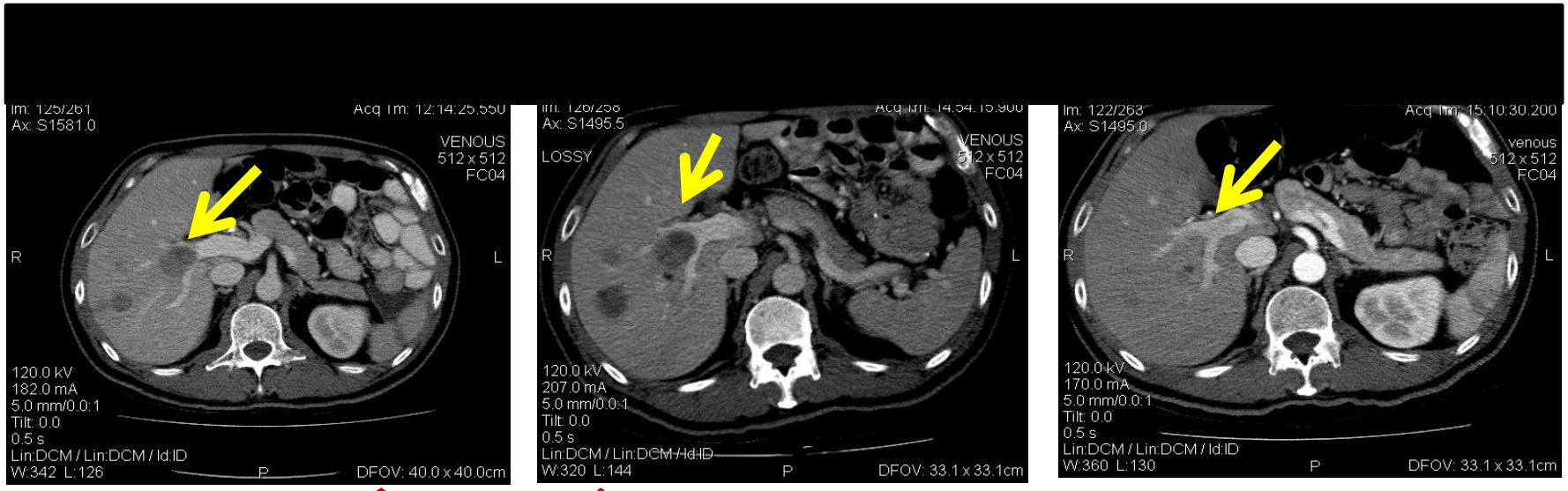
Response Assessment

Adapted from Wolchok et al, Clin Cancer Res, 2009

Parameter	WHO	RECIST	irRC
New measurable lesions	PD	PD	Incorporated into tumor burden
New nonmeasurable lesions	PD	PD	Do not define PD but precludes irCR
Non-index lesions	Changes contribute to BOR	Changes contribute to BOR	Contribute to defining irCR
CR	Disappearance of all lesions (2 observations ≥4 wks apart)	Disappearance of all lesions, LNs ↓ <10mm*	Disappearance of all lesions (2 observations ≥4 wks apart)
PR	≥50% ↓ in SPD of all index lesions (2 occasions ≥4 wks apart), no new lesions	≥30% ↓ in sum of longest diameters of target lesions	≥50% ↓ in tumor burden compared to baseline (2 observations ≥4 wks apart)
SD	Neither PR or PD	Neither PR or PD	Neither PR or PD
PD	≥25% ↑ in SPD compared with nadir, and/or progression of non-index lesions, and/or new lesions	≥20% ↑ (≥ 5mm) in sum of longest diameters compared to nadir, and/or unequivocal progression of non-target lesions, and/or new lesions	≥25% ↑ in tumor burden compared with nadir (2 observations ≥4 wks apart)

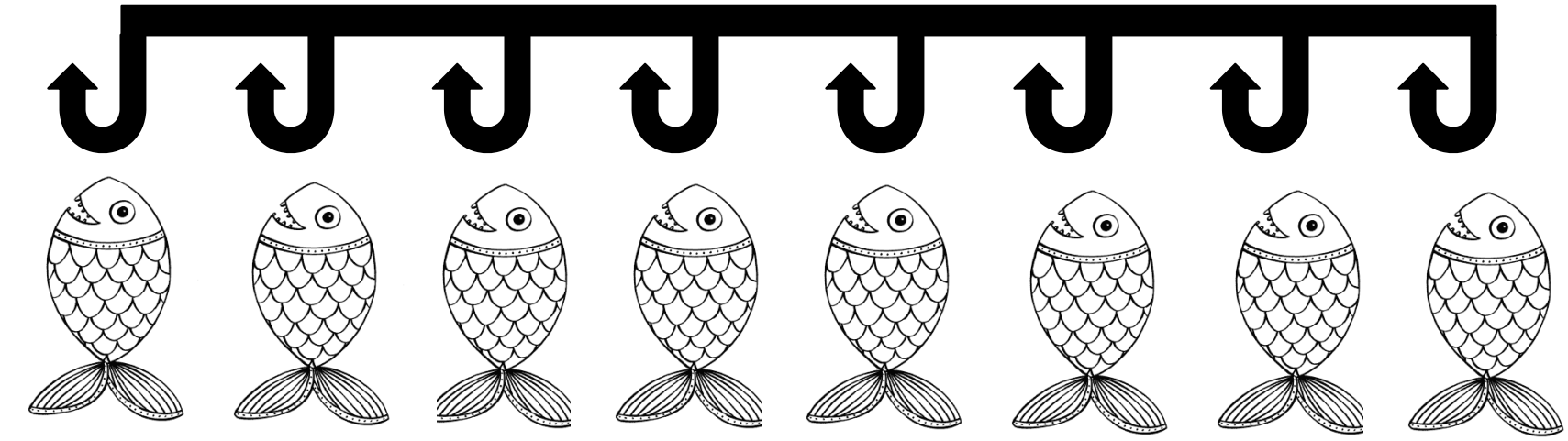
BOR = Best overall response, SPD = Sum of products of 2 largest perpendicular diameters
Tumor Burden = SPD (Index Lesions) + SPD (New, Measurable Lesions)
* Confirmation only needed in non-randomized trials with ORR as primary endpoint

Surrogate Marker(s) for Altered Response Patterns?



- **Immunoprofile?**
- **Blood-based biomarker?**
- **Radiological biomarker – radiomics?**

Single Protocol, Multiple Cohorts
Signal-Finding Trials



Cancer A Cancer B Cancer C Cancer D Cancer E Cancer F Cancer G Cancer H

PD-1/PD-L1 Combinations in Development

- Anti-CTLA-4 (Ipilimumab, Tremelimumab)
- Other immune checkpoint inhibitors (anti-; LAG3, KIR, TIM3)
- Co-stimulatory molecules (anti-: 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

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

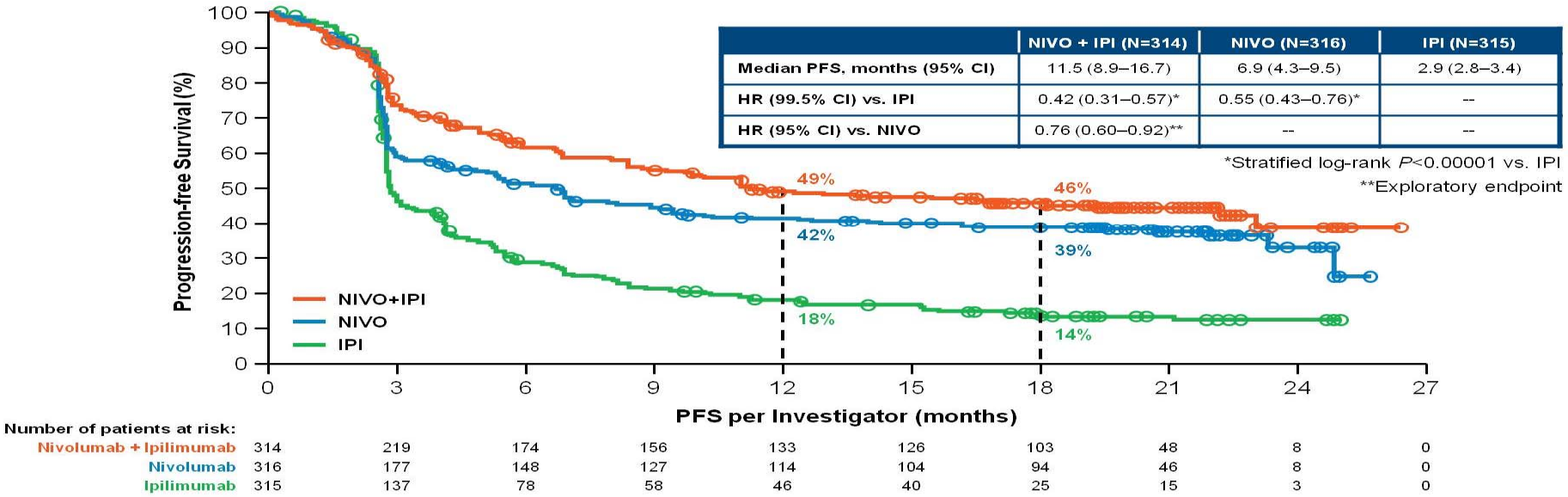
Pembrolizumab: Early Signals of Combo Activity

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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Presented By Jedd Wolchok at 2016 ASCO Annual Meeting

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

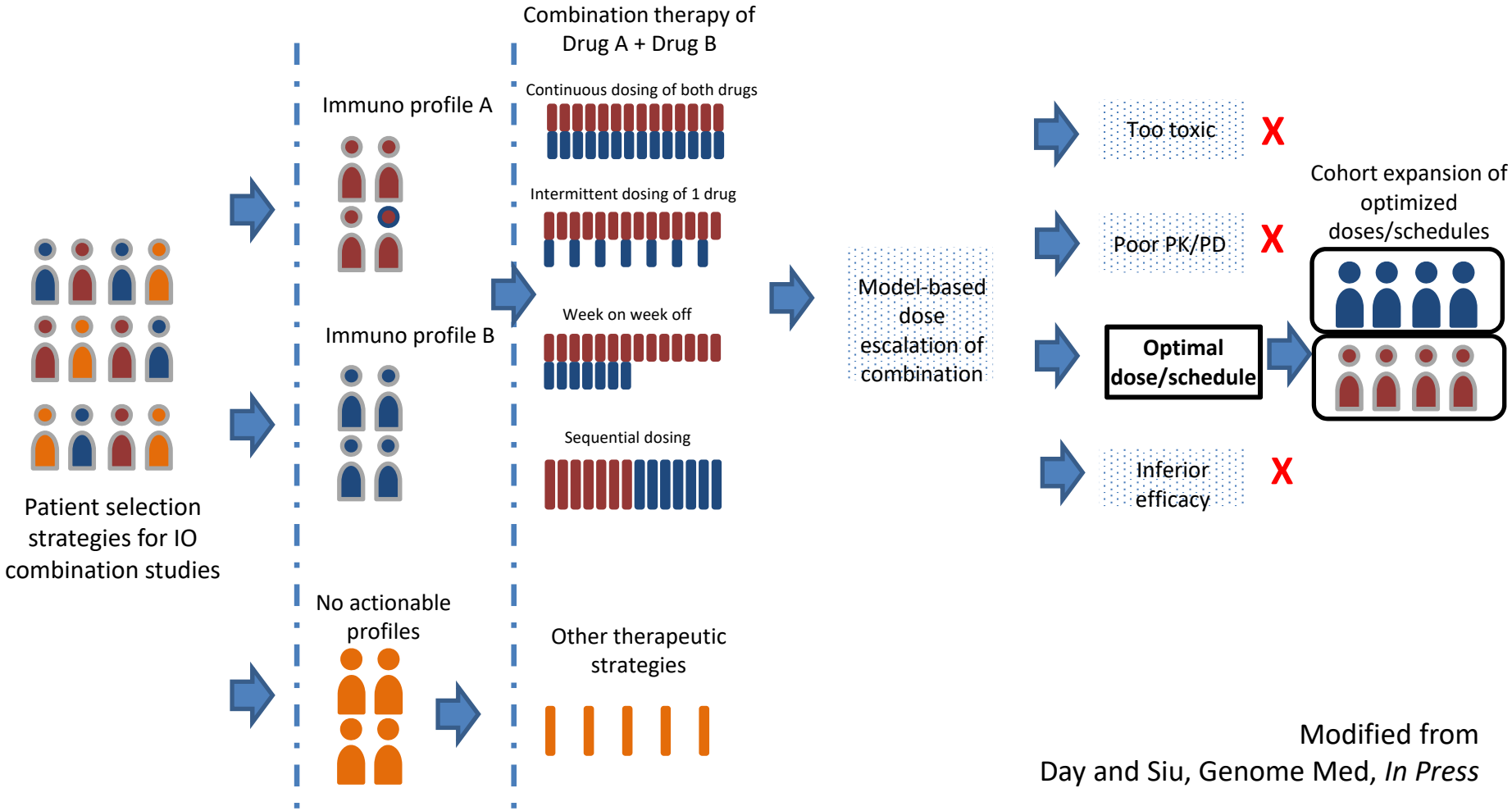
Examples of Phase I Trial Designs Used in IO-Based Combinations

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

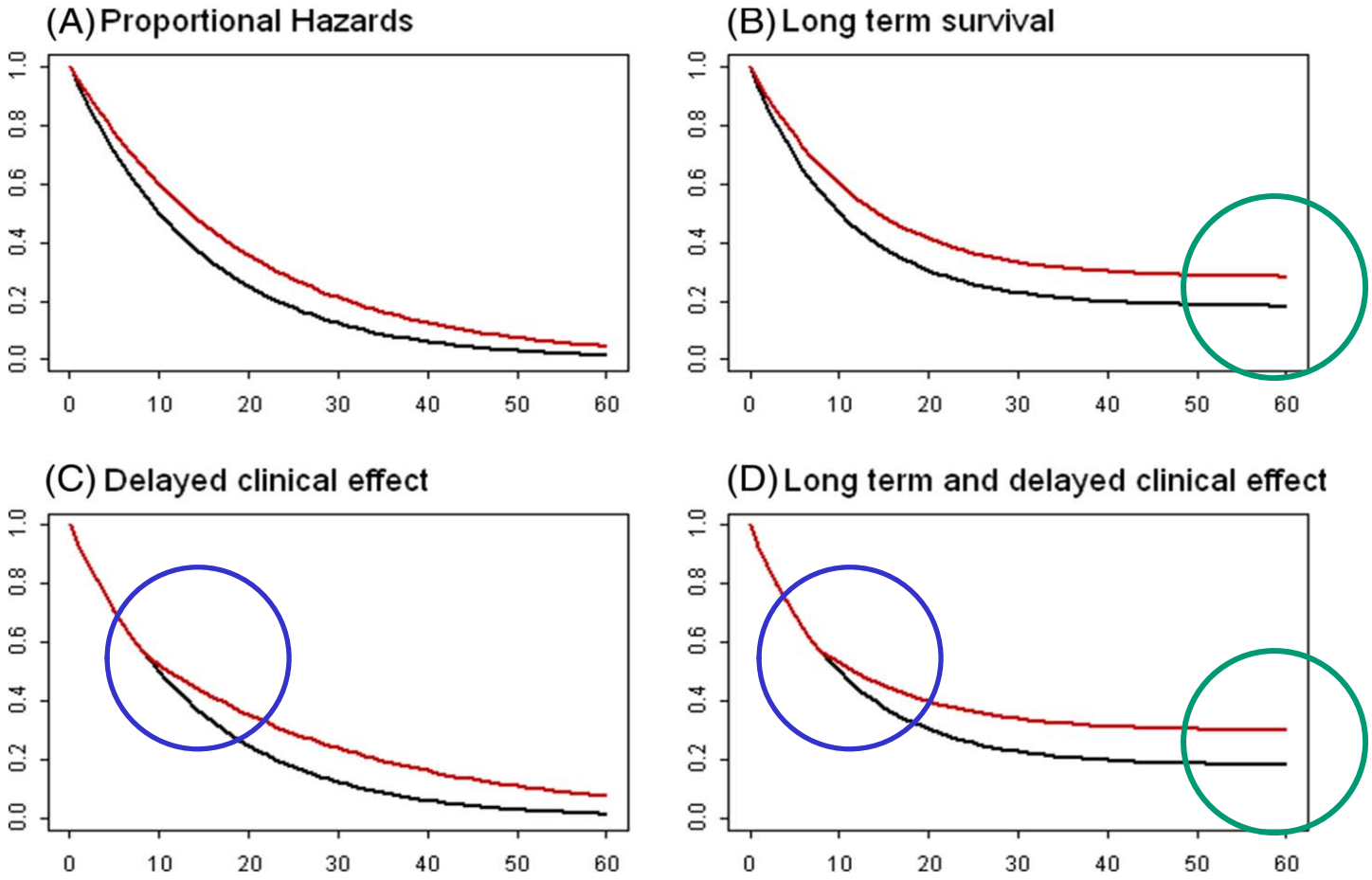
Combination Studies – Adaptive Designs



Modified from
Day and Siu, Genome Med, *In Press*

Unique Characteristics of Trials with Long Term Survival and Delayed Clinical Effect

Chen, Journal for ImmunoTherapy of Cancer, 2013



- With a non-zero tail, number of patients at risk for death is ↓, so time for required number of events with desired statistical power is ↑
- Delayed separation of K-M curves affects assumption of proportional hazards

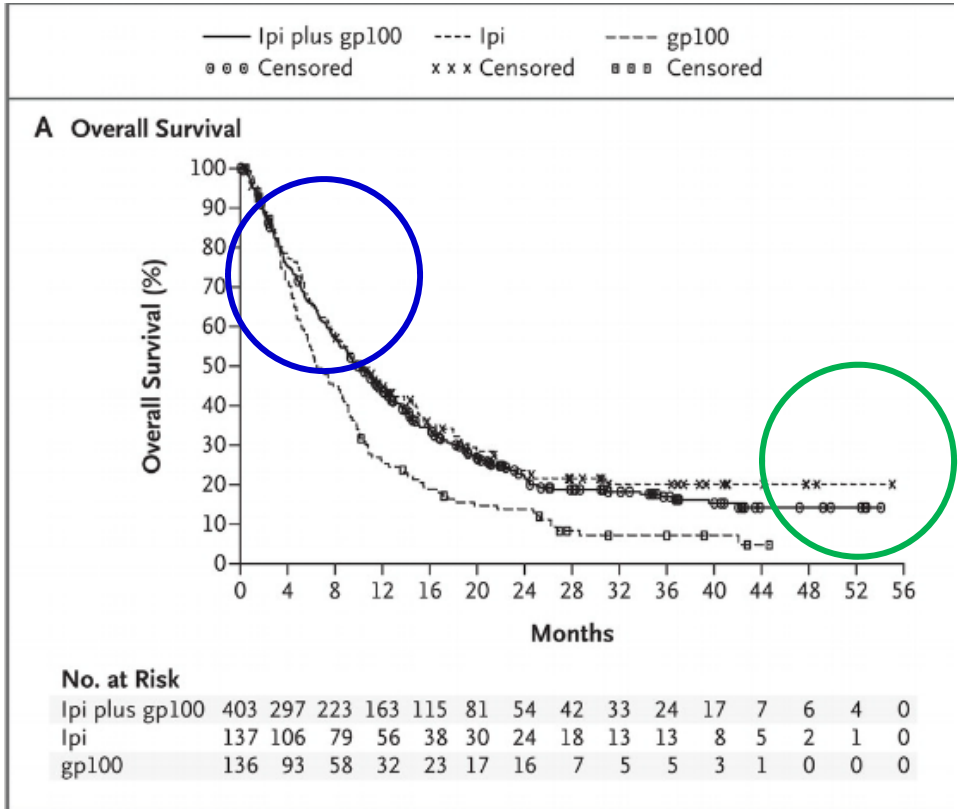
Effects on Study Duration and Power

Table 1 Impact of long term survival and delayed clinical effect on statistical power and study duration

	PHM	PHCRM	NPHM	NPHCRM
Cure rate	–	0.10 vs. 0.18	–	0.10 vs. 0.17
Delayed clinical effect (month)	–	–	3	3
Sample size	680	680	680	680
Number of events	512	512	512	512
Hazard ratio (pre- and post- separation)	0.75	0.75	1/0.75	1/0.75
Type I error	0.05	0.05	0.05	0.05
Power	0.90	0.90	**0.70**	**0.70**
Accrual duration (month)	34	34	34	34
Study duration (month)	48	**55**	47	**54**

Chen, Journal for ImmunoTherapy of Cancer, 2013

The Example of Ipilimumab in Melanoma

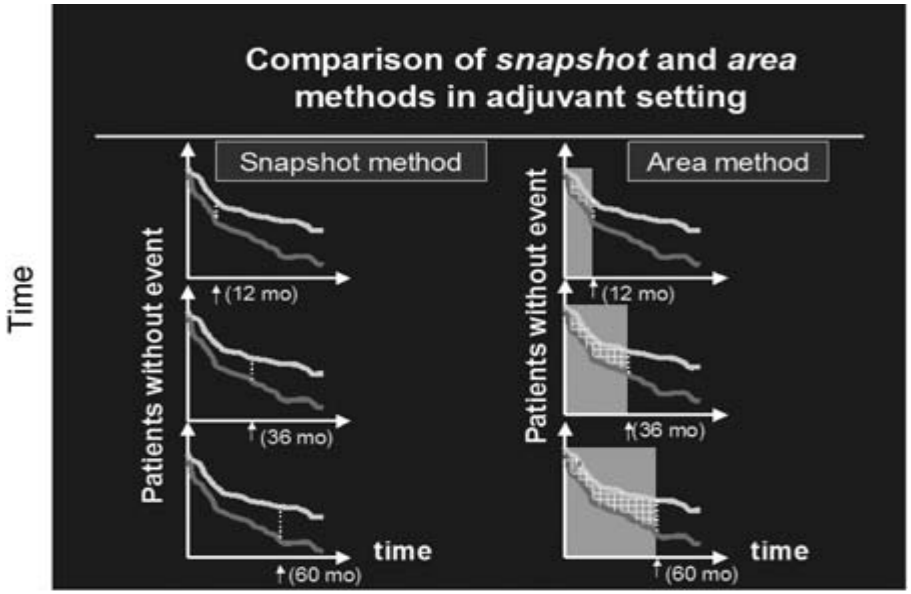


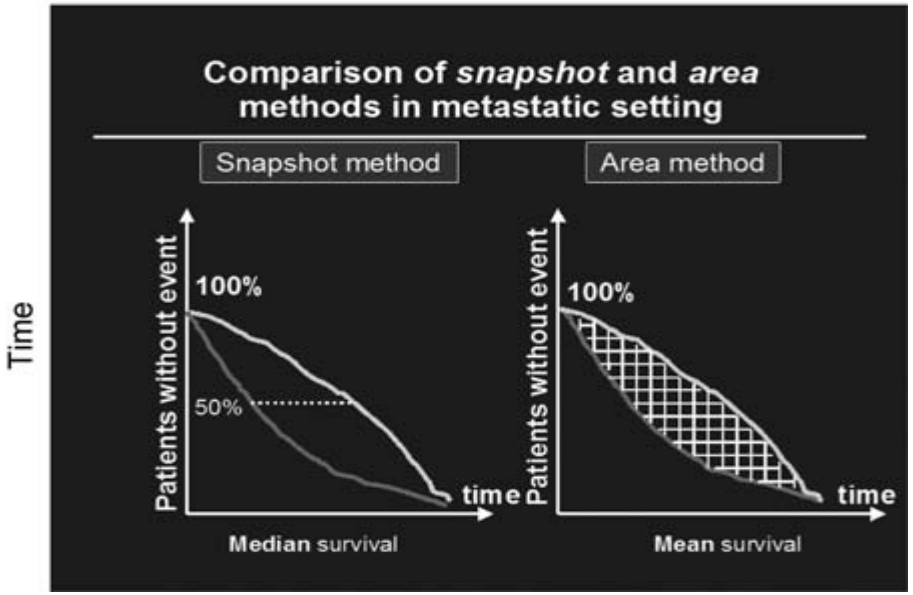
- **Kaplan-Meier method, Cox proportional hazards models**

Actual Survival	Ipilimumab +gp100	Ipilimumab+placbeo	gp100+placebo
≥ 2 years	54/284 (19%)	24 of 95 (25%)	16 of 95 (17%)
≥ 3 years	24/156 (15%)	13 of 53 (25%)	5 of 50 (10%)

Hodi et al NEJM, 2010; McDermmott et al. Ann Oncol 2013

Comparison of KM-Curves Using Alternate Methods?

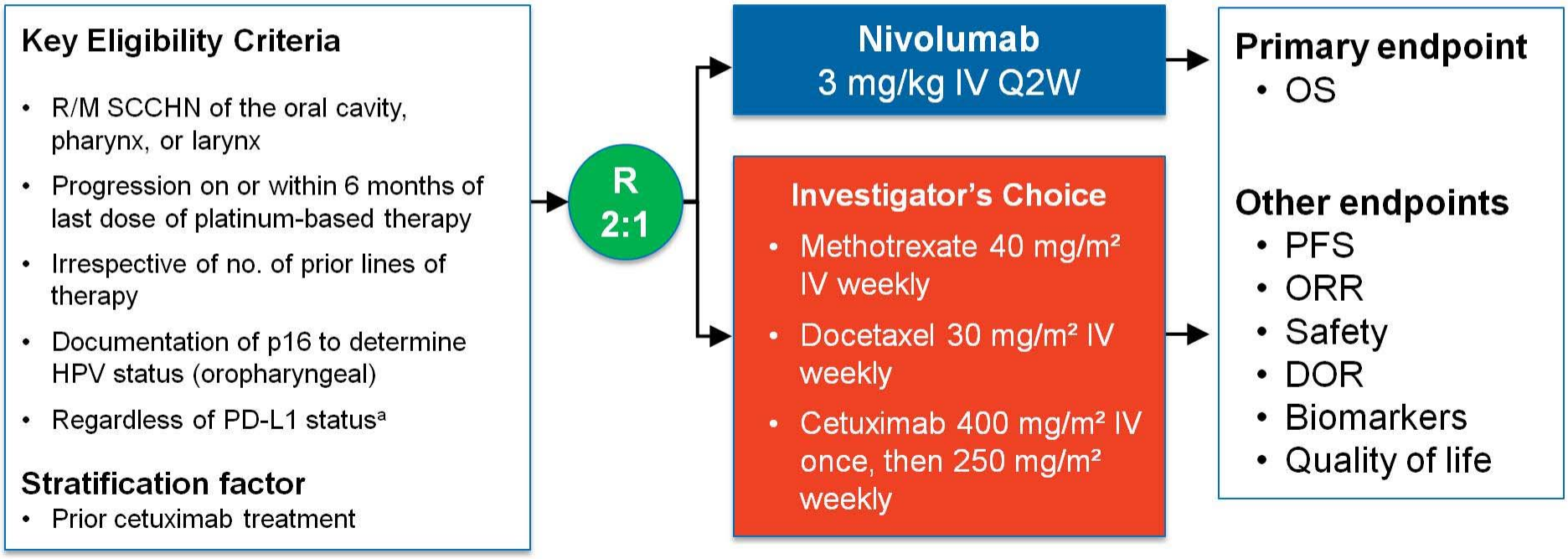




Seruga et al. Ann Oncol 2012

Phase 3 CheckMate 141 Study Design
Nivolumab in R/M SCCHN After Platinum Therapy

Randomized, global, phase 3 trial of the efficacy and safety of nivolumab vs investigator's choice in patients with R/M SCCHN



[a]Tissue required for testing

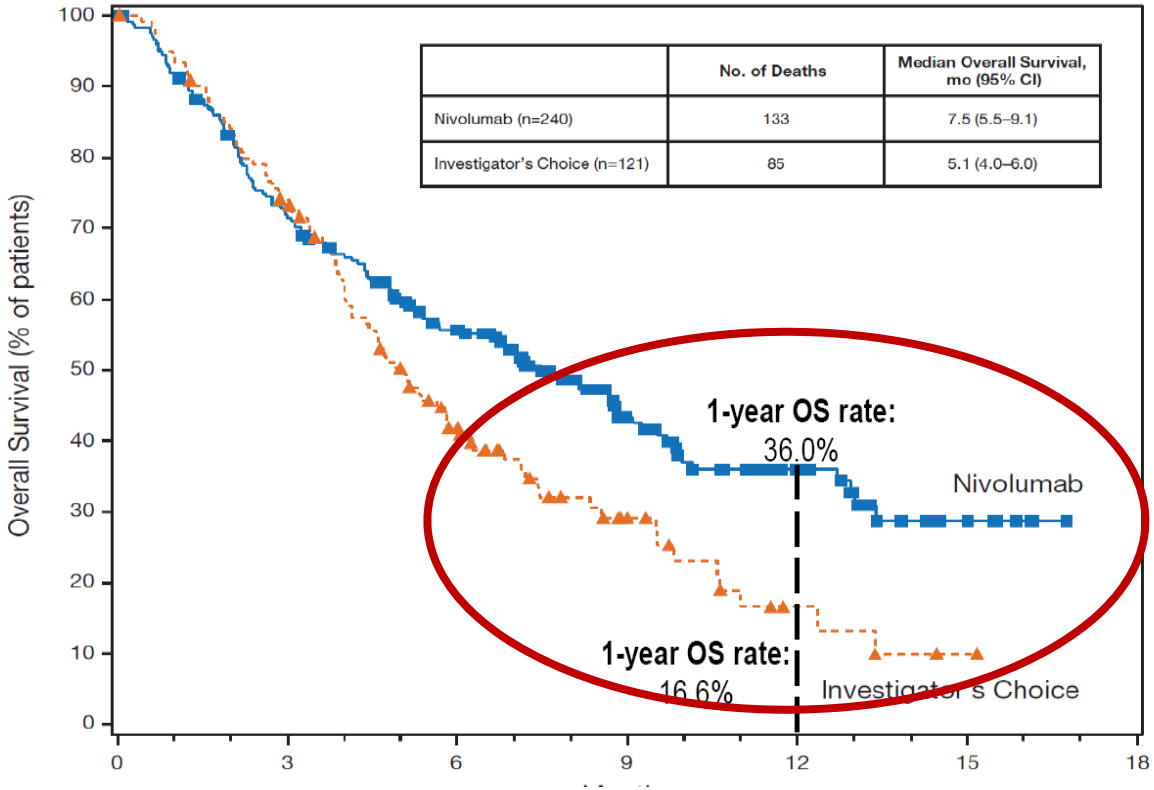
DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

Efficacy Endpoints

Endpoint	Nivolumab	IC
ORR	13.3%	5.8%
PFS	2.0 months (1.9-2.1)	2.3 months (1.9-3.1)
OS - median	7.5 months (5.5-9.1)	5.1 months (4.0-6.0)
OS – 1 year	36% (28.5-43.4)	16.6% (8.6-26.8)

- Median OS may not be the best efficacy readout due to the dynamics of antitumor activity with immune checkpoint inhibitors
- Landmark analyses (e.g. 1 year OS rate) more reflective of nivolumab's benefit in R/M SCCHN

KM-Curves: Differences in the Tail



Continuing treatment:
Nivo = 17.4%
IC = 2.7%

CheckMate-141: Gain in OS = + 2.4 mo

Early Phase Trials of IO Agents: Example Points of Interest

- Rule-based versus model-based dose escalation methods?
- Fixed drug dosing versus weight-based dosing
- Sentinel patient and staggering interval between lead and subsequent patients in dose escalation cohorts?
- If no single agent activity is expected (e.g. with some of the agonists), how do we design IO+IO combinations (e.g. agonist + PD-1/L1 blockade)? For example, 2 parallel arms (mono and combo) or sequential dosing in the same patients (mono followed by combo)? What trial designs?
- What should recommended dose be based on if no MTD – efficacy, PK, PD, receptor occupancy?
- Randomized evaluation of 2 doses to determine recommended dose?
- Use of expansion cohorts and seamless IO drug development (Prowell et al, NEJM 2016, http://www.nejm.org/doi/pdf/10.1056/NEJMp1603747)
- Assessment of delayed or late toxicity with IO agents

Late Phase Trials of IO Agents: Example Points of Interest

- What are the most relevant endpoint(s) in registrational trials – median PFS or OS or landmark analysis (e.g. 1-year OS)?
- K-M curves of IO trials – distinct shapes from chemotherapy or targeted therapy – what can we learn from them?
- Proportional hazards or non-proportional hazards model? (Chen et al. Journal for ImmunoTherapy of Cancer, 2013, https://jitc.biomedcentral.com/articles/10.1186/2051-1426-1-18)
- Trials to evaluate duration of IO therapy – randomized continuation vs randomized discontinuation designs?
- Allowance for treatment beyond RECIST 1.1 progression – how long do we allow “progressing” patients to stay on trial?