
SITC
2017
November 8-12
NATIONAL HARBOR
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Challenges in Clinical Development

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Society for Immunotherapy of Cancer

Presenter Disclosure Information

Michael Postow

The following relationships exist related to this presentation:

Advisory Board: Array BioPharma, BMS, Incyte, Merck, NewLink Genetics, Novartis

Honoraria: BMS and Merck

Where were we?

- Needed to convince scientific and clinical community immunotherapy can actually work

- Expand beyond immunotherapy sensitive cancers (melanoma, renal cell carcinoma, and hematologic malignancies)


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Where are we now?

- Checkpoint blockade and cellular based therapies demonstrating efficacy in many tumors with better understanding of toxicity management
- One FDA approved combination of immune checkpoint blocking antibodies (nivolumab and ipilimumab in melanoma)
- Many different agents/combinations in earlier stages of evaluation

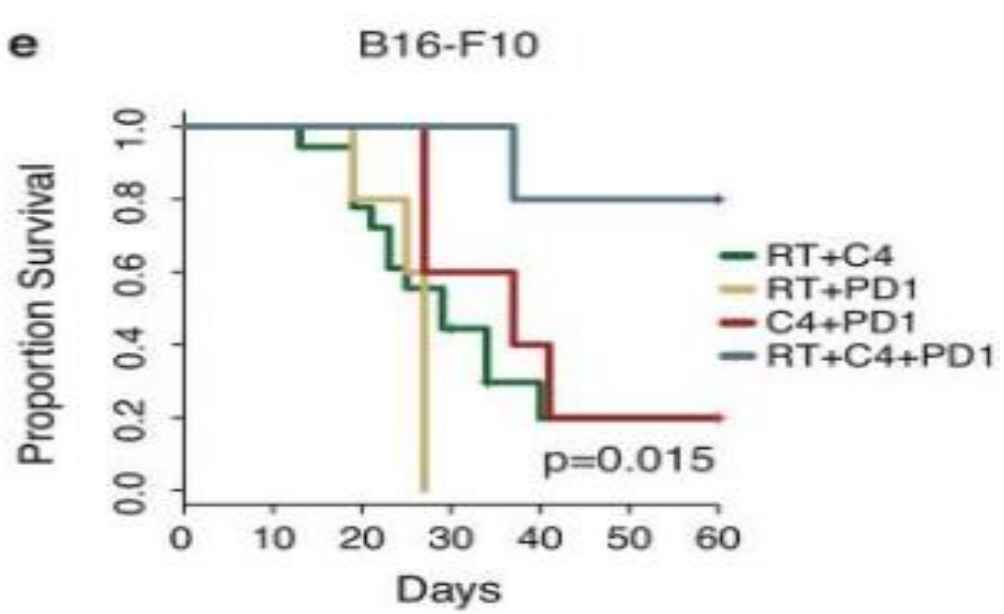
What are the challenges?

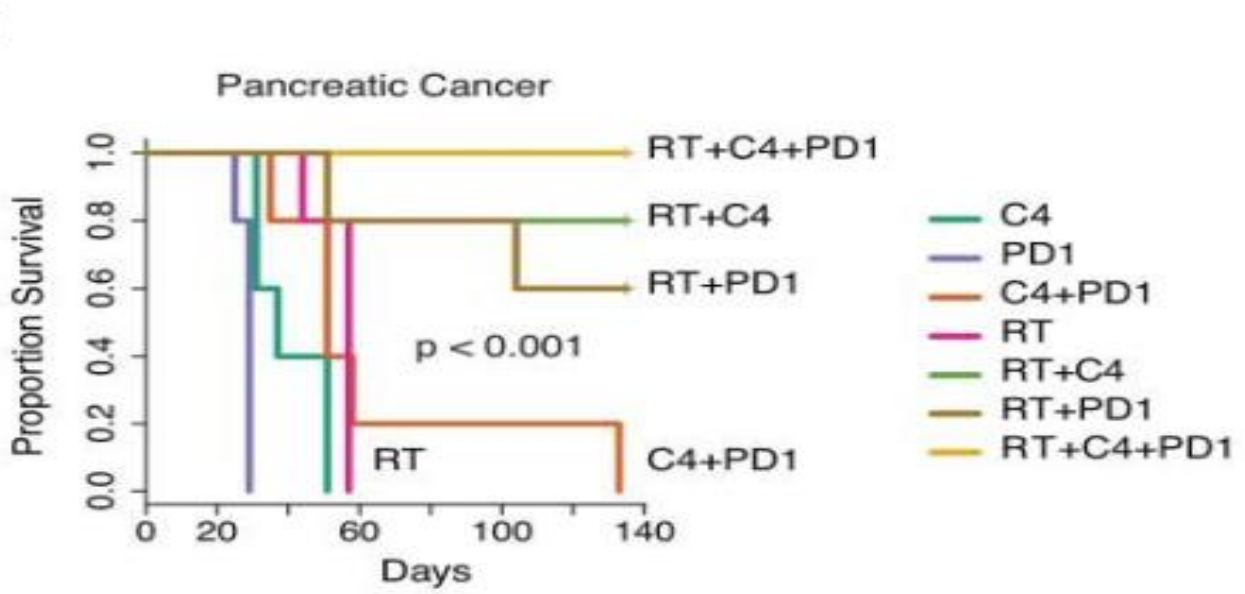
- Limitations to predictive capabilities of preclinical models
- Assessment of toxicity in early phase, dose-finding studies
- Expectation of efficacy from early study to late phase, randomized studies

Limitations to Preclinical Models

- Syngeneic orthotopic murine models not great parallel for human cancer
- Patient derived xenografts difficult
- Checkpoint blockade alone does not work in many models where it can work in patients

Preclinical models do not always predict indication specific efficacy



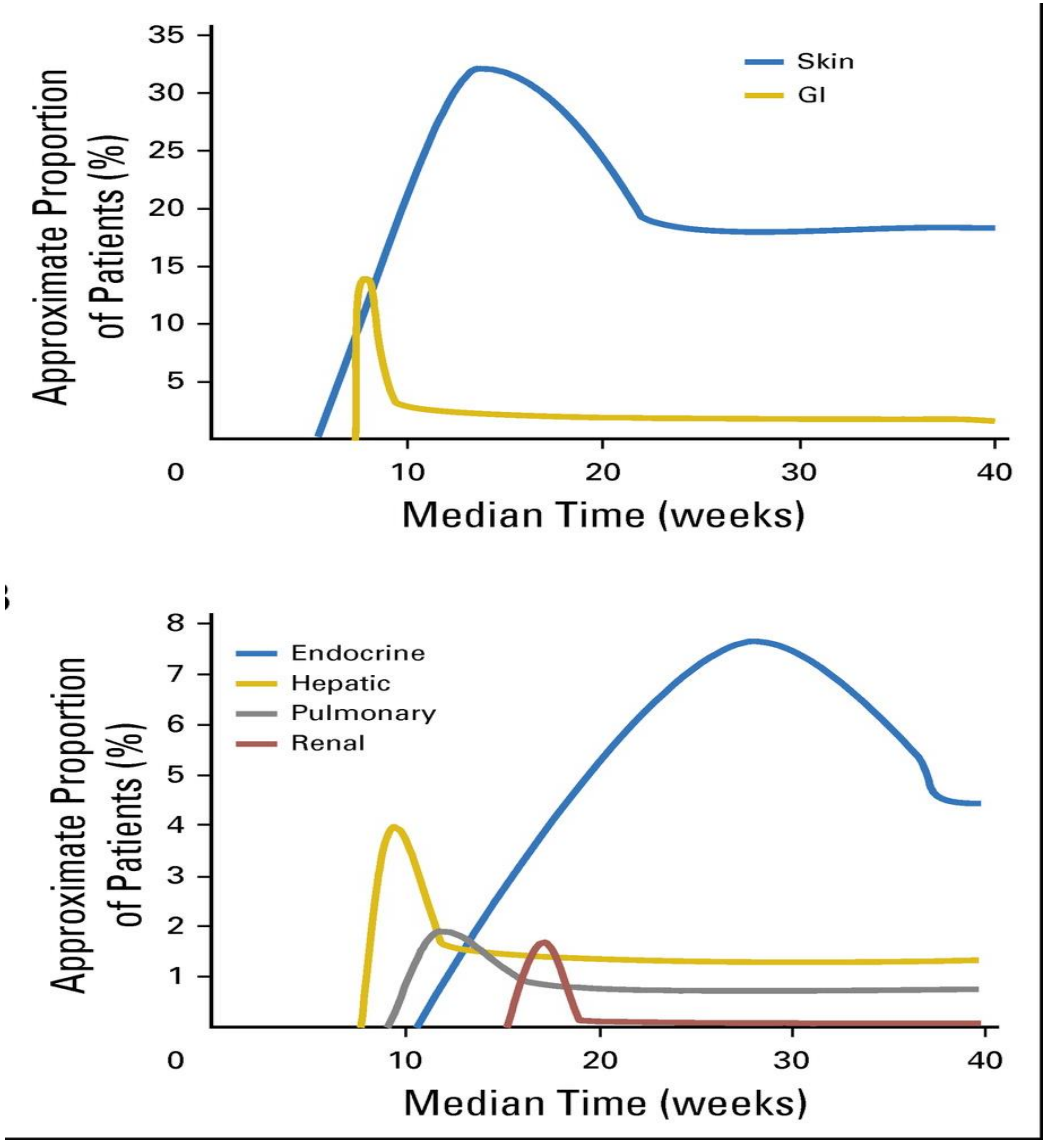


Twyman-Saint Victor et al. *Nature* 2015

Challenges to Toxicity Assessment

1. Difficulty of preclinical models to assess toxicity
2. MTD or “optimal immunologic effect”?
3. Assess toxicities of combination approaches?

Toxicity Time Course for Nivolumab (n=576, melanoma)



Weber et al. *Journal of Clin Oncol* 2016

Dose dependency of immunotherapy?

1. Higher ipilimumab doses associated with better overall survival [1]

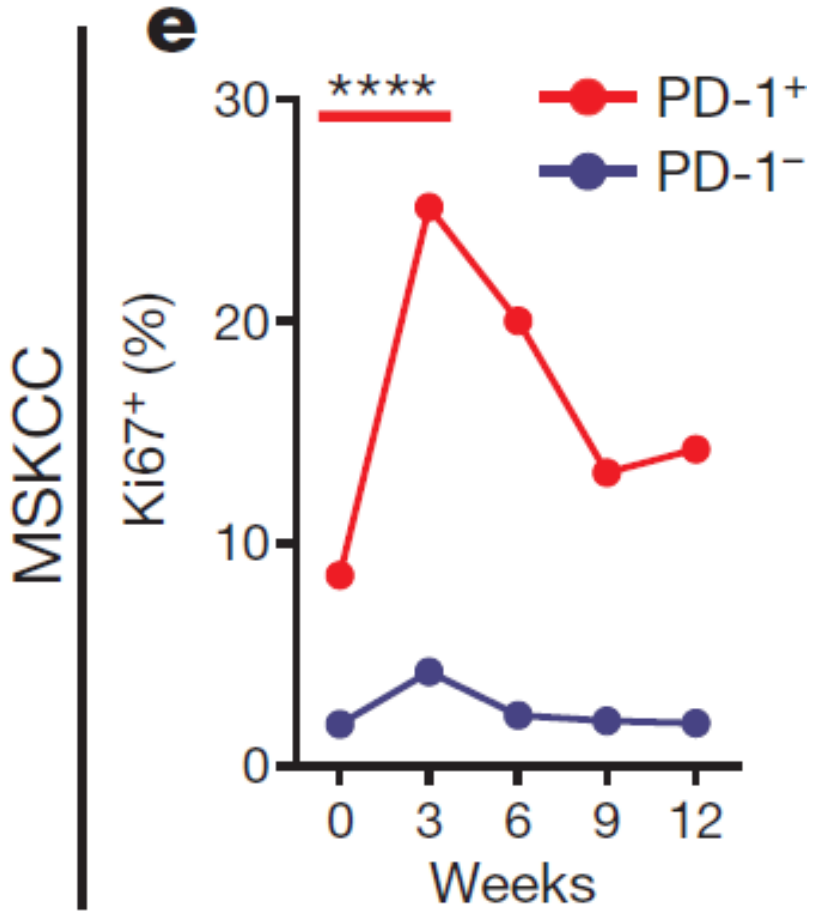
2. No obvious dose dependency for anti-PD-1 [2]

[1] Ascierto et al. *Lancet Oncol* 2017
[2] Robert et al. *NEJM* 2015

Dose to a pharmacodynamic biomarker?

Pembrolizumab increases Ki67+ CD8+ T cells

N=18; p<0.0001 (paired t-test)



Huang A, Postow M, Orlowski R, et al. *Nature* 2017

Assess efficacy from early studies to late development?

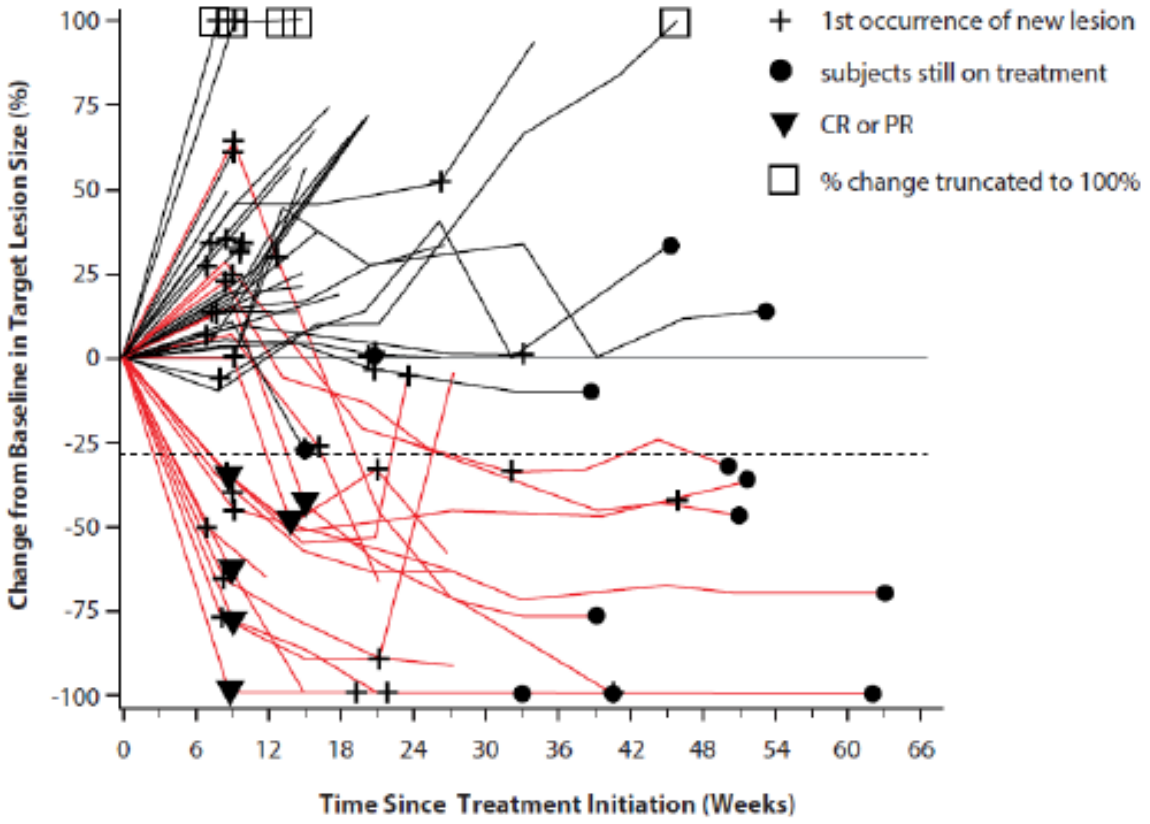
Main difference between RECIST and immune related response criteria is declaration of progression

Outcome	RECIST*	Immune Related Criteria**
Complete Response	Disappearance of targets	Disappearance of targets
Partial Response	≥30% decrease in targets	≥30% decrease in targets
Stable Disease	Everything else	Everything else
Progressive Disease	≥20% increase in targets **Any new lesion**	≥20% increase in targets

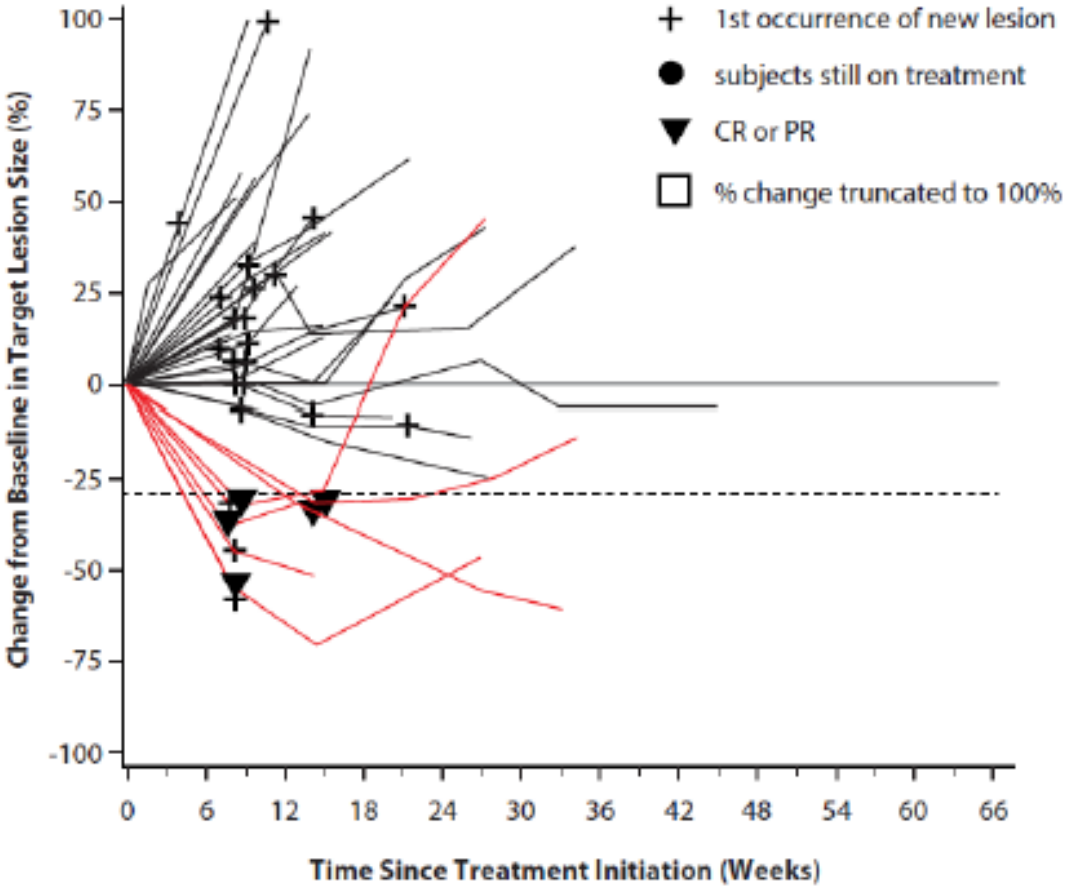
*Eisenhauer et al. *Eur J Cancer* 2009
**Nishino et al. *Clin Cancer Res* 2013

Are responses to immunotherapy really “unique”?

54 nivolumab patients treated beyond POD
17 (8% of total of pts) eventually had 30% reduction



49 dacarbazine patients treated beyond POD
8 (4% of total pts) eventually had 30% reduction

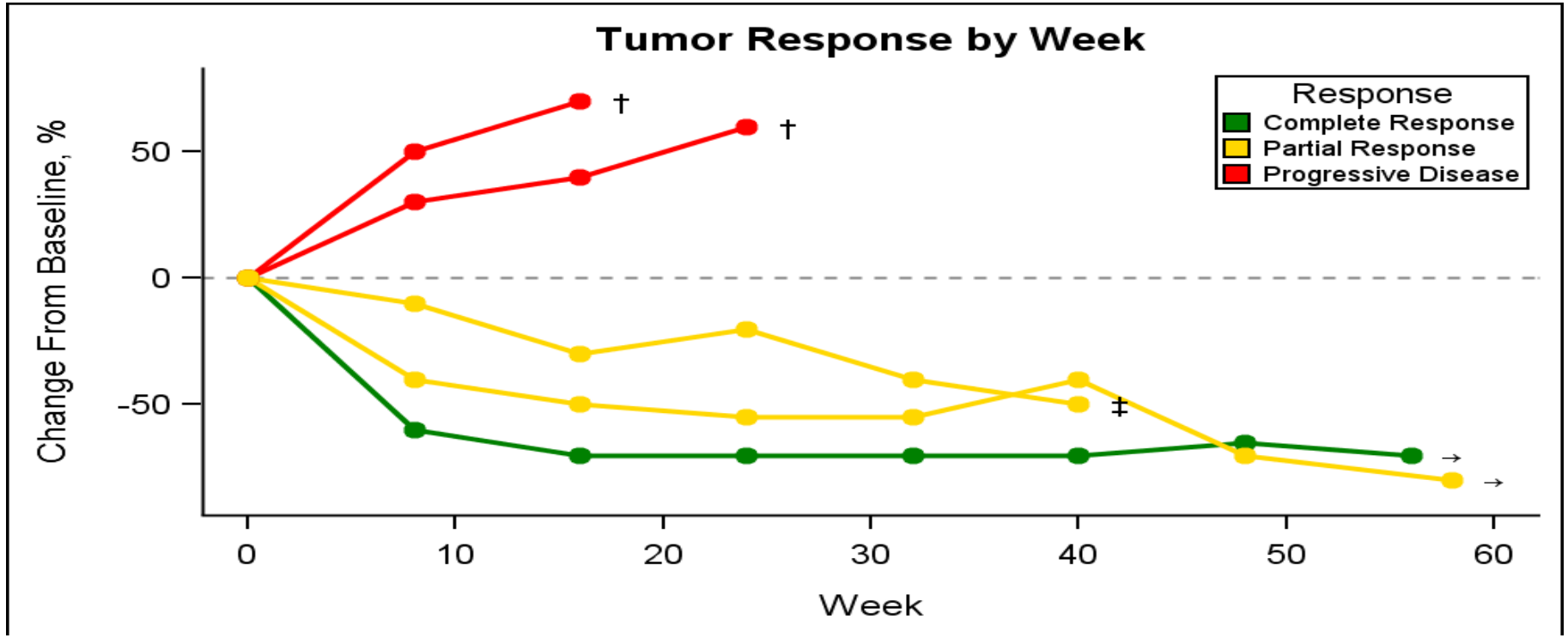


Robert et al, *NEJM* 2015

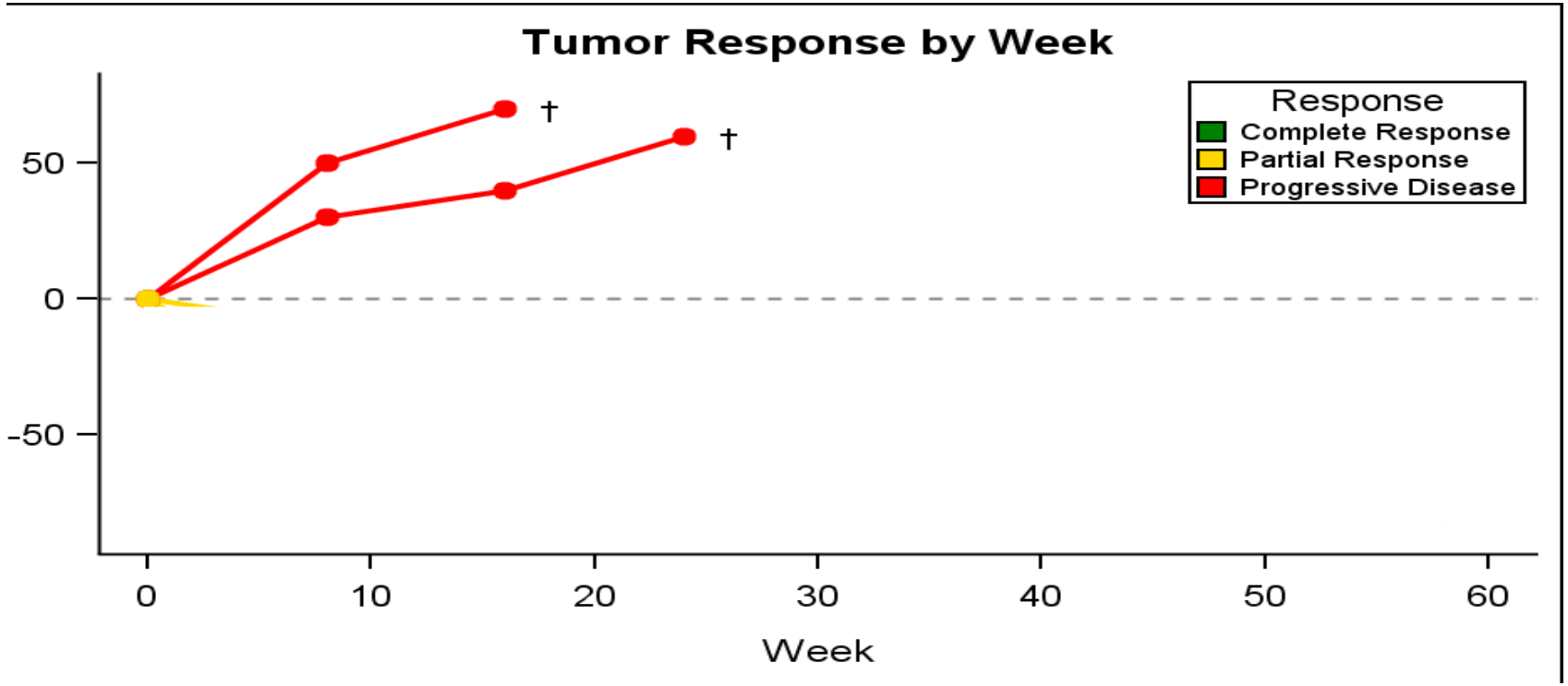
Other ways to test combinations

1. Does new treatment alter prior tumor growth kinetics?

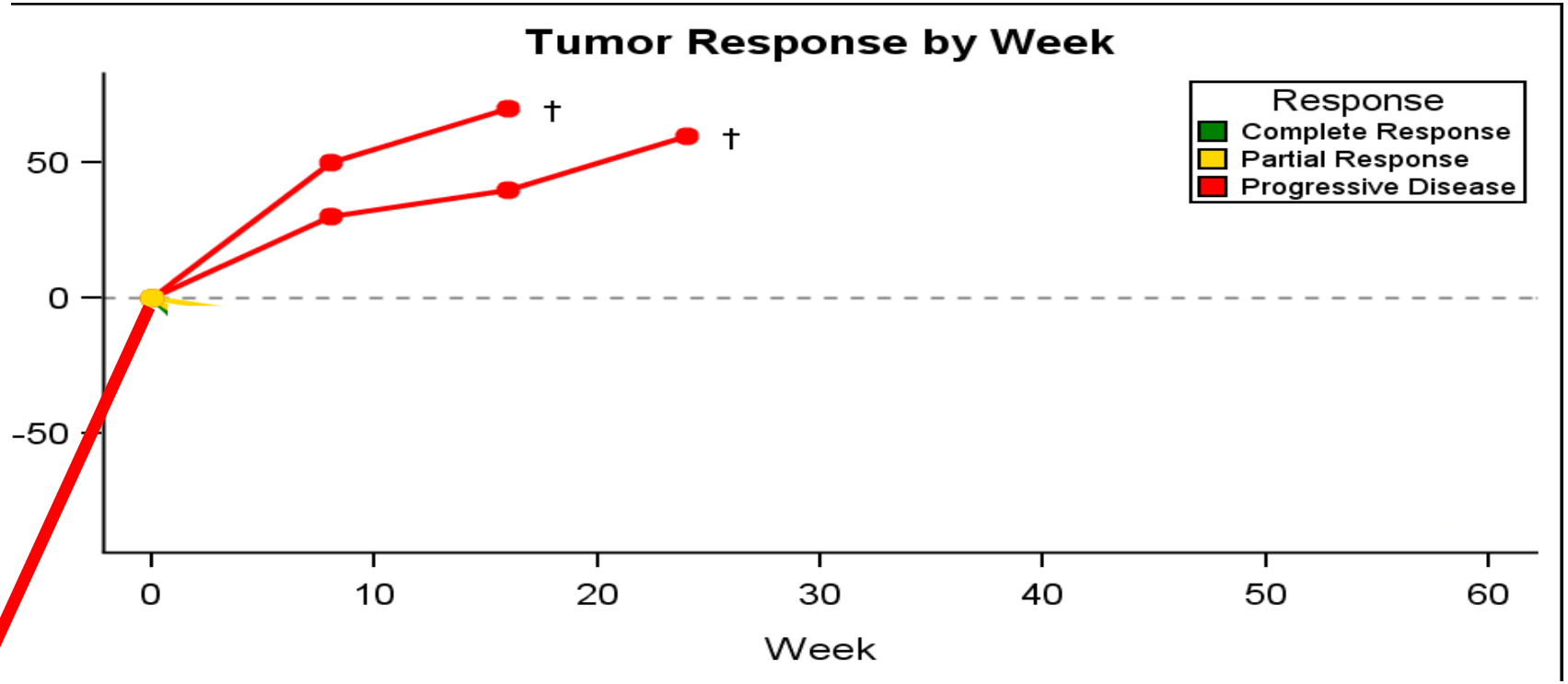
Other ways to test combinations



Other ways to test combinations



Other ways to test combinations



Other ways to test combinations

1. Does new treatment alter prior tumor growth kinetics?

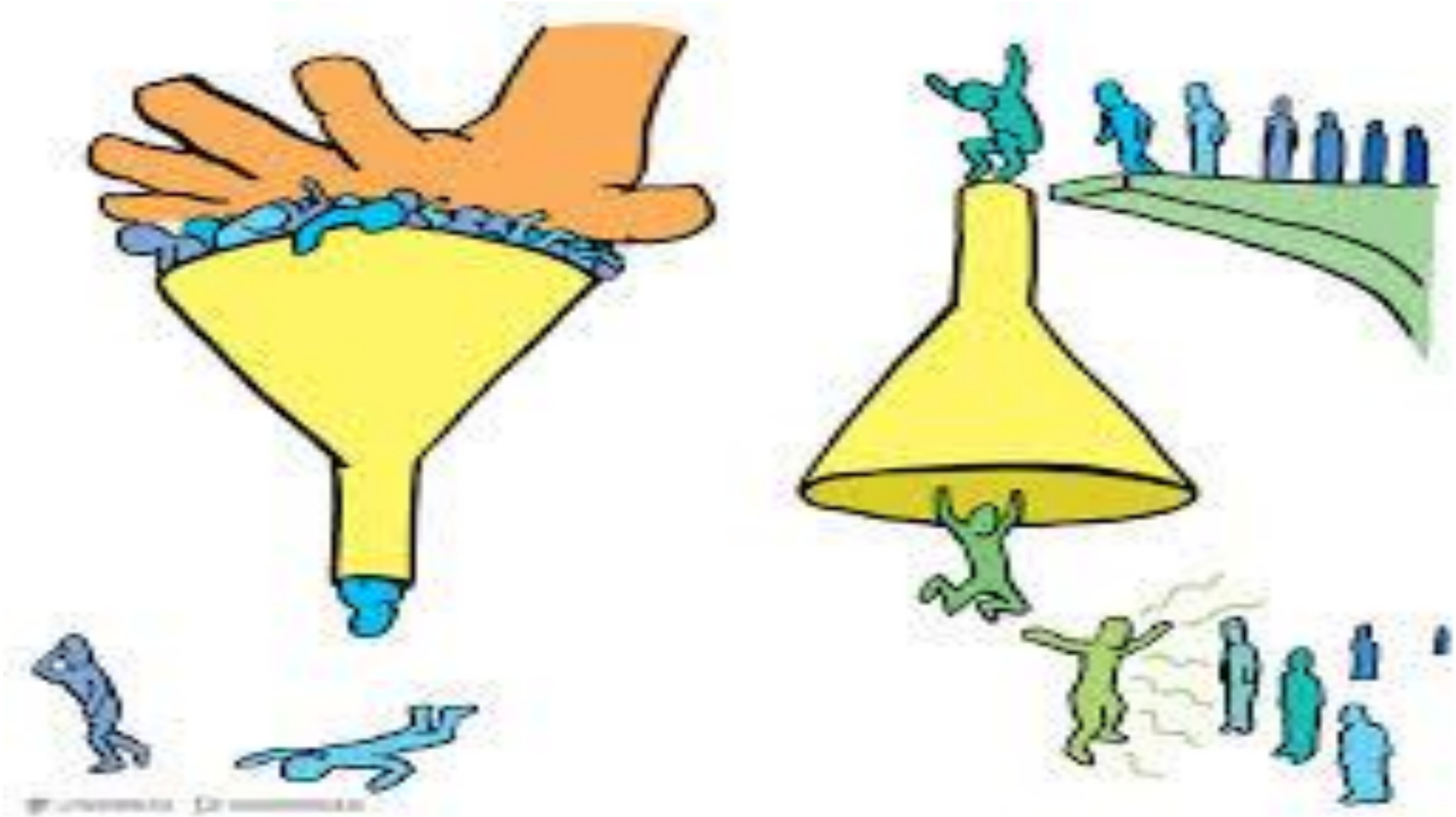
2. Start combination for “biomarker unfavorable” patients?

Traditional biomarker concept

Finding a specific patient for a specific treatment

(i.e. Patient with a BRAF V600E mutation for dabrafenib)

Amended immunotherapy biomarker concept



Other ways to test combinations

1. Does new treatment alter prior tumor growth kinetics? (Add additional agent to PD-1 non-responders?)

2. Start combination for “biomarker unfavorable” patients?

3. Neoadjuvant Trials
   - Quick interpretation of tissue PD effects/efficacy
   - Does macroscopic efficacy = microscopic efficacy?

Summary of Clinical Challenges

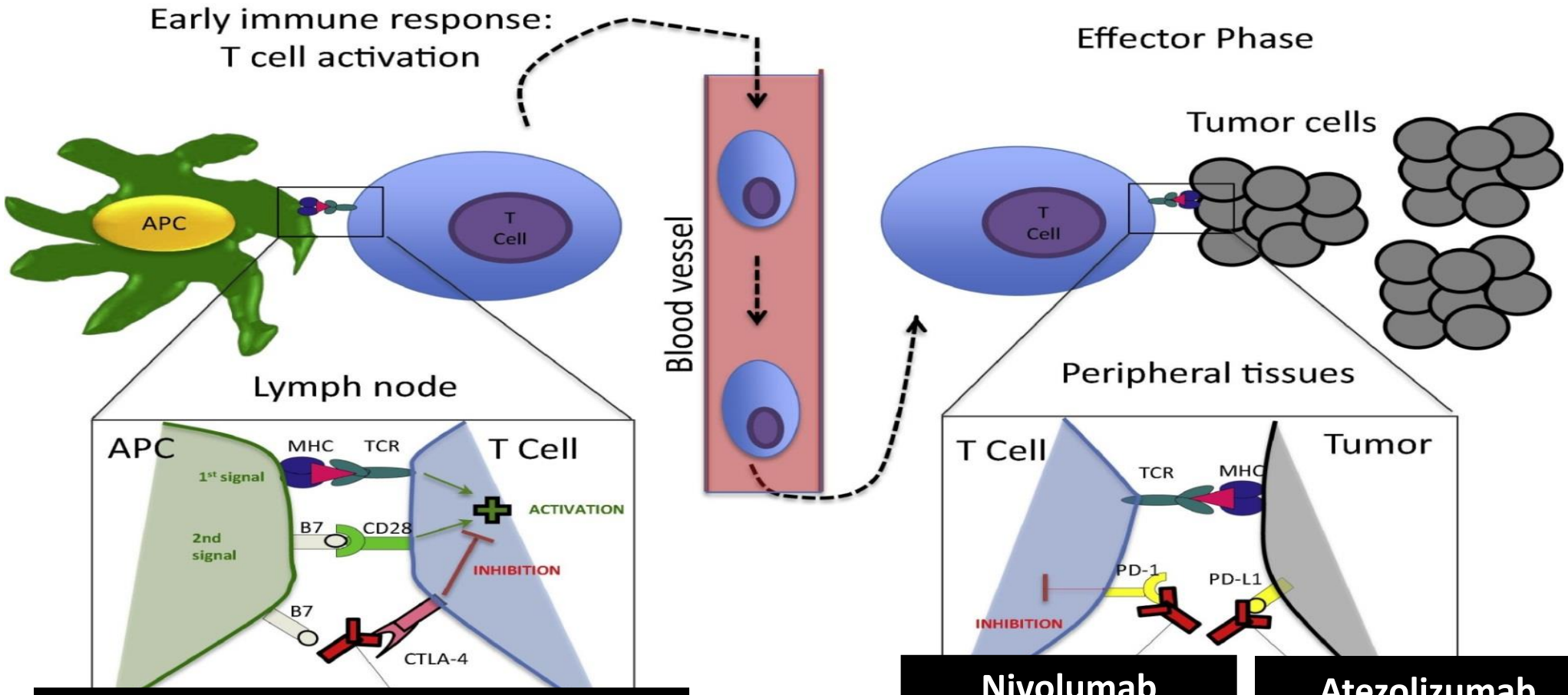
1. Develop better preclinical model systems
2. Understanding why immunotherapy does not work in patients will likely shed some light
3. Need creative trial designs and meaningful endpoints that meet regulatory expectations


LOORS
4-6

Back-Up

Example of early to late immunotherapy combination development

CTLA-4 and PD-1 Combination



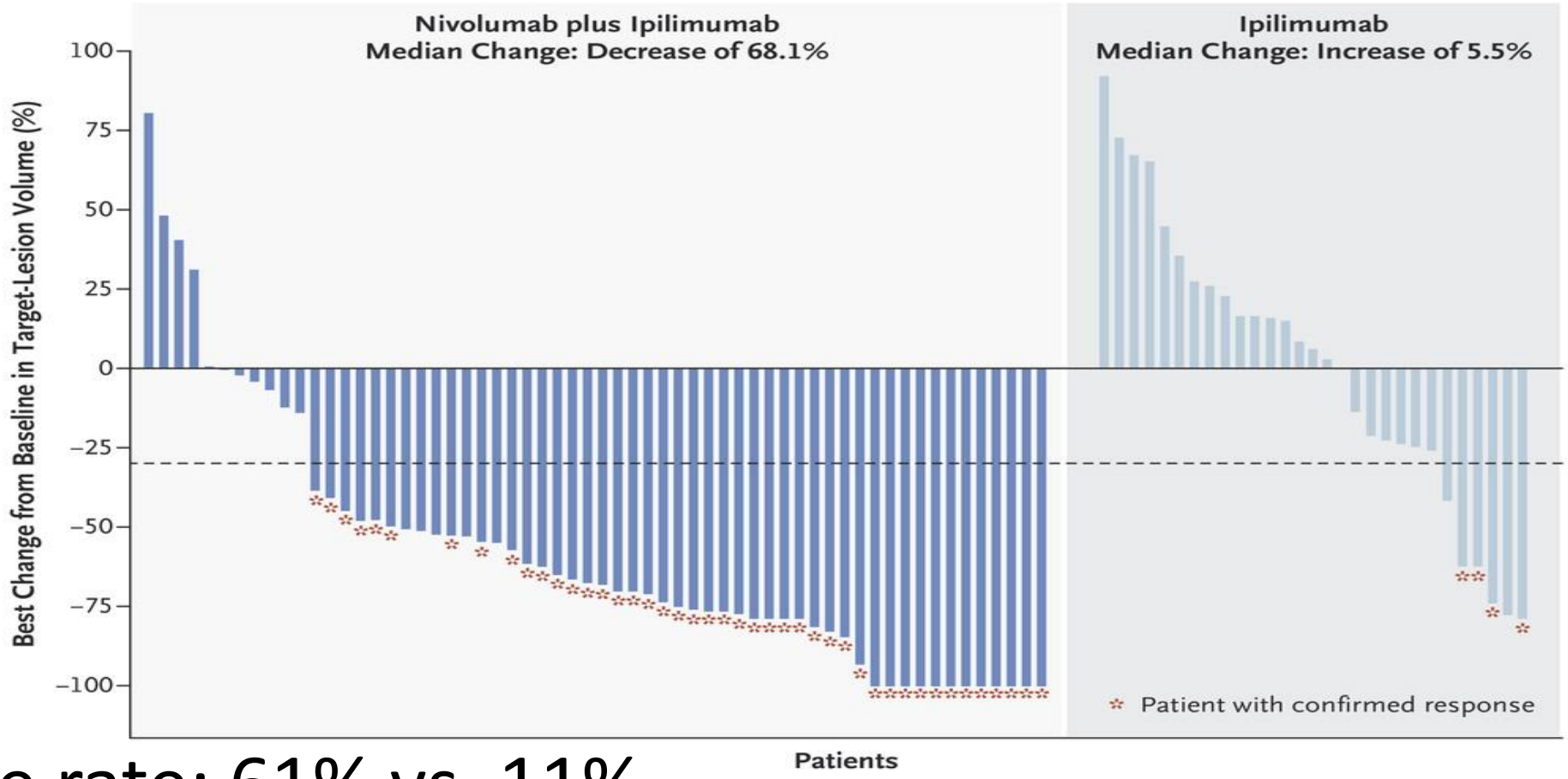
Ipilimumab and Tremelimumab

Nivolumab
Pembrolizumab
Pidilizumab

Atezolizumab
Durvalumab
Avelumab

Kyi and Postow *FEBS Letters* 2014

Nivolumab + Ipilimumab higher response rate than ipilimumab alone



Response rate: 61% vs. 11%

Postow et al., *NEJM* 2015

What about comparing combination to PD-1?

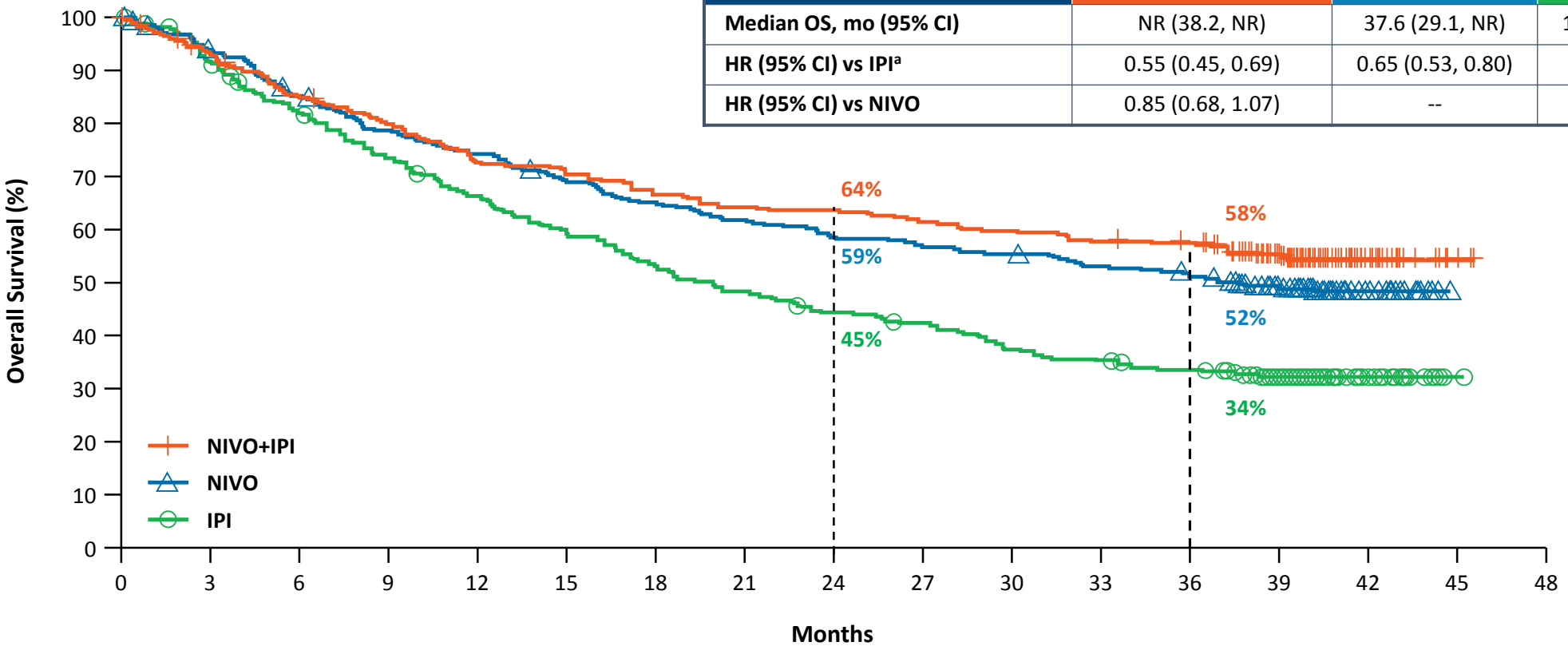
	NIVO + IPI (N = 314)	NIVO (N = 316)	IPI (N = 315)
Median PFS, months (95% CI)	11.5 (8.7, 19.3)	6.9 (5.1, 9.7)	2.9 (2.8, 3.2)
HR vs IPI	0.43 (0.35, 0.52)	0.55 (0.45, 0.66)	-
HR vs NIVO	0.78 (0.64, 0.96)		-
ORR, % (95% CI)[a]	58.3 (52.6, 63.8)	44.3 (38.7, 50.0)	18.7 (14.6, 23.5)
Best overall response, %			
Complete response	19.4	16.5	5.1
Partial response	38.9	27.8	13.7
Median DOR, months (95% CI)	NR	NR (36.3, NR)	19.3 (8.3, NR)

Wolchok et al. *NEJM* 2017

Assessing differences in response rates vs. overall survival

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2, NR)	37.6 (29.1, NR)	19.9 (16.9, 24.6)
HR (95% CI) vs IPI[a]	0.55 (0.45, 0.69)	0.65 (0.53, 0.80)	--
HR (95% CI) vs NIVO	0.85 (0.68, 1.07)	--	--

[a]$P < 0.0001$

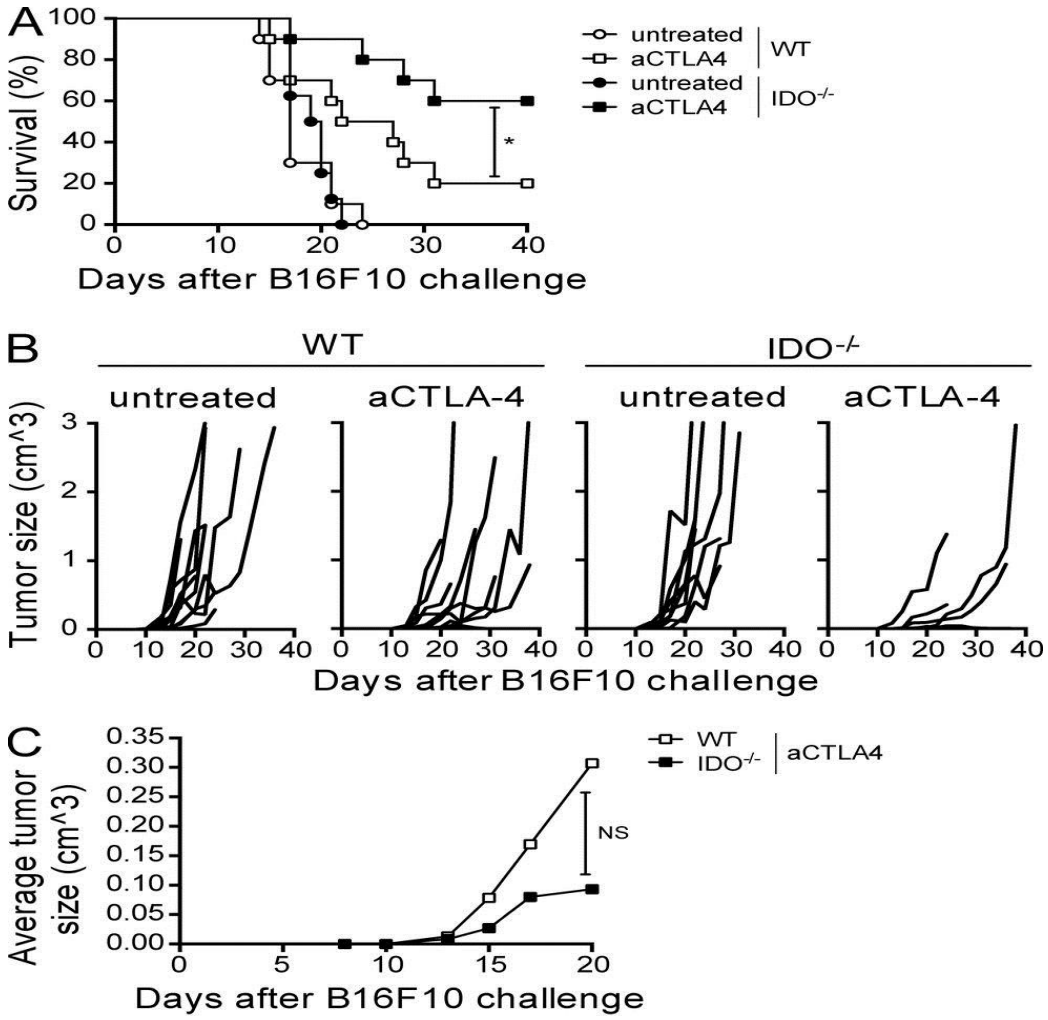


Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
NIVO	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
IPI	315	285	253	227	203	181	163	148	135	128	117	107	100	68	20	2	0

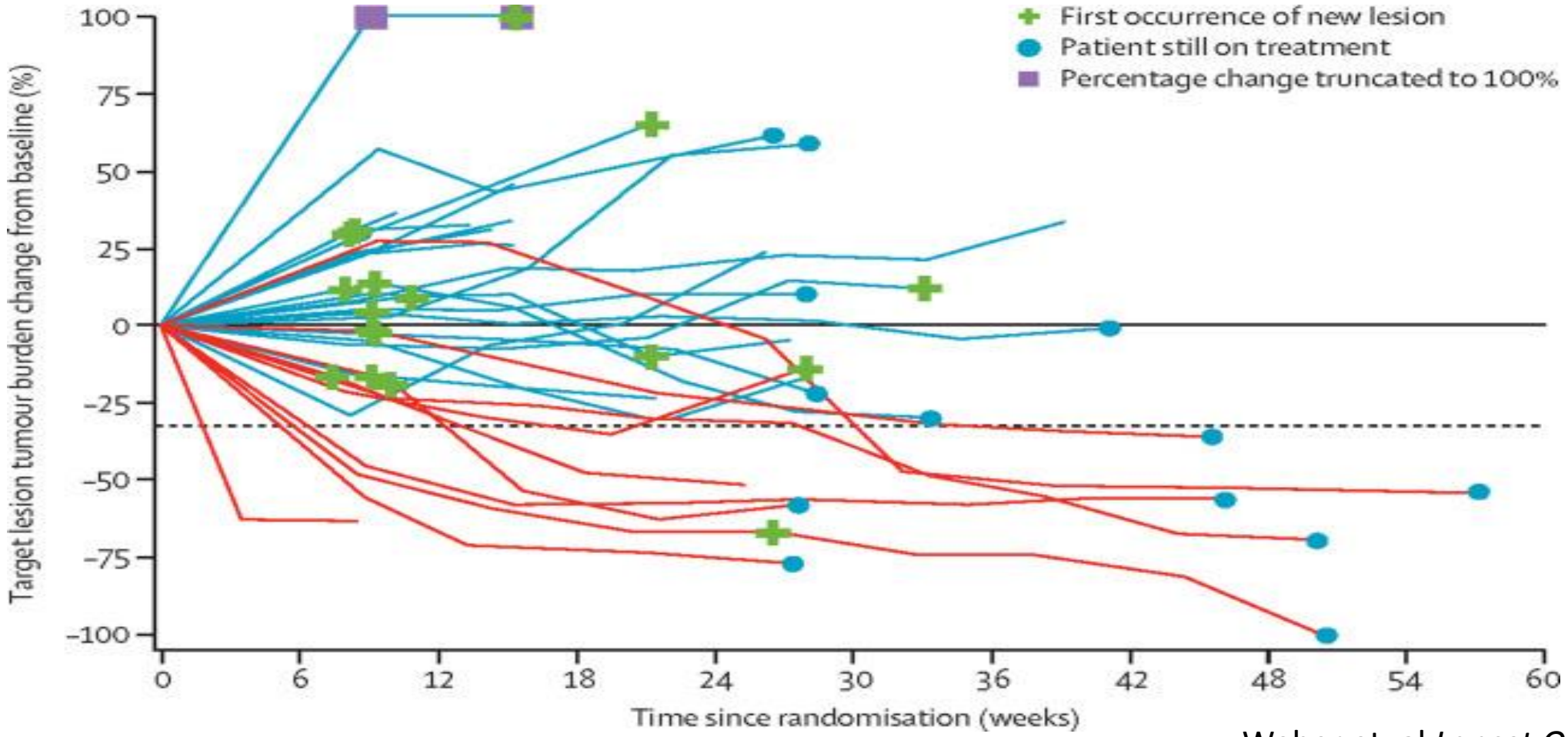
Wolchok et al. *NEJM* 2017

Eliminating IDO enhances checkpoint blockade in mice



Holmgaard et al. *JEM* 2013
Spranger *J Immunother Cancer* 2014

Late responses to PD-1 are rare (approximately 5-10%)



Weber et. al *Lancet Oncol* 2015
Hodi et al. *JCO* 2016