New Systemic Therapies in Advanced Melanoma

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Disclosures

- Equity interest:
  - Celldex, Targeted Therapeutics, Array, Incyte, Celgene, Pfizer, BioLine
- Honoraria:
  - Roche, AstraZeneca, Bristol-Myers, Celgene, Novartis, Merck

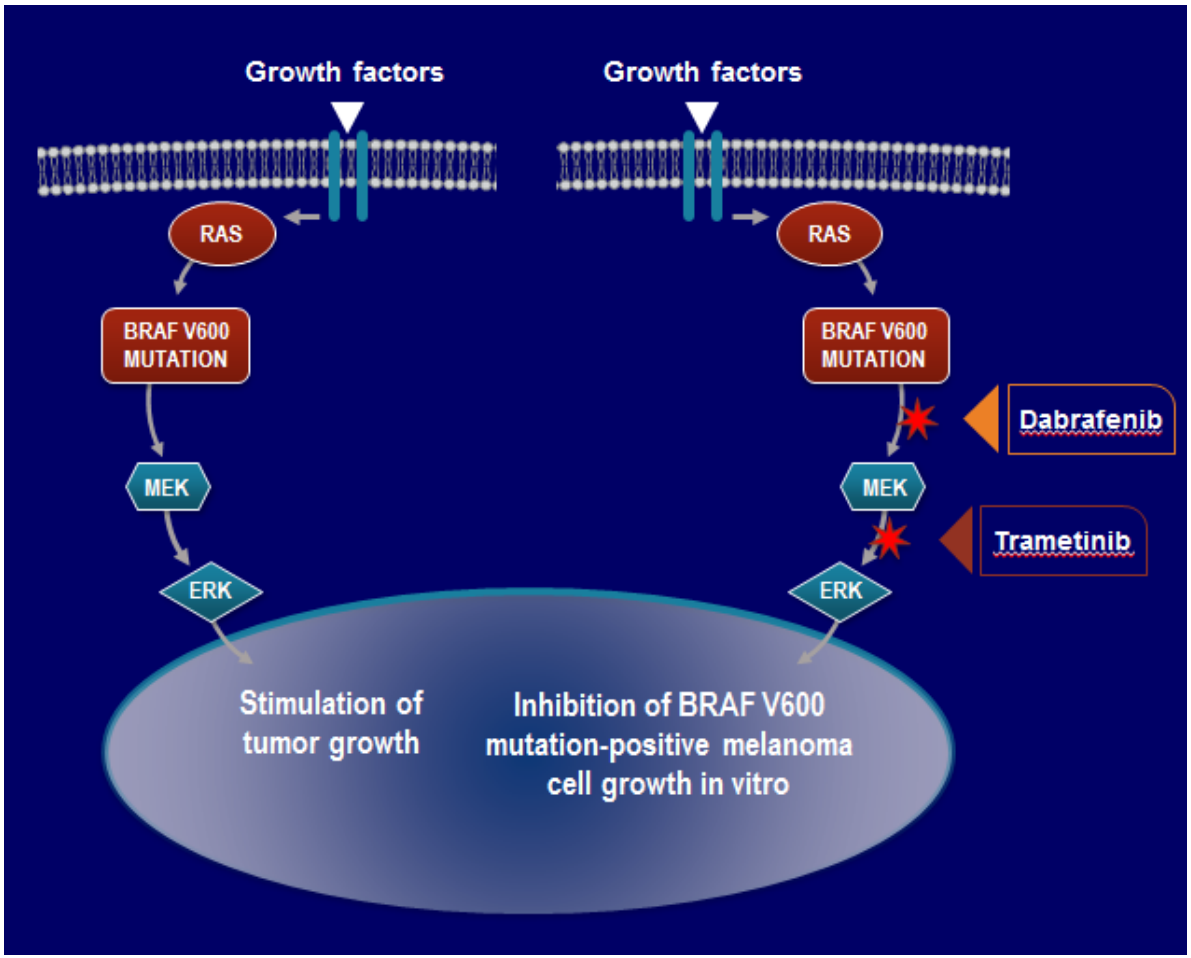
Minimization of Bias

- None of the material presented today has any relationship to the companies in which I hold an equity interest
- Only generic product names are used in this presentation, and the manufacturers will not be mentioned
- I have no authority over drug funding, and though I am on the BCCA PEC committee, I recuse myself from evaluations and discussions when there is even a remote possibility of bias

Targeted Therapies – BRAF and MEK Inhibition

BRAF and MEK Inhibitors: Mechanism of Action

- Provide concomitant inhibition of the pathway at the level of the RAF and MEK kinases, respectively.
- Synergistic in BRAF V600 mutation-positive melanoma cell lines and delayed the emergence of resistance in BRAF V600 mutation-positive melanoma xenografts compared with either inhibitor alone
- Agents currently on the market are dabrafenib and vemurafenib (BRAF inhibitors), and trametinib and cobimetinib (MEK inhibitors)



Tafinlar (dabrafenib) Product Monograph. GlaxoSmithKline Inc., March 4, 2015.

http://gsksource.com/gskprm/en/US/images/gsk_content/TAFMEK/FBP/map-k-pathway/index.html#

Response rates of BRAFi + MEKi

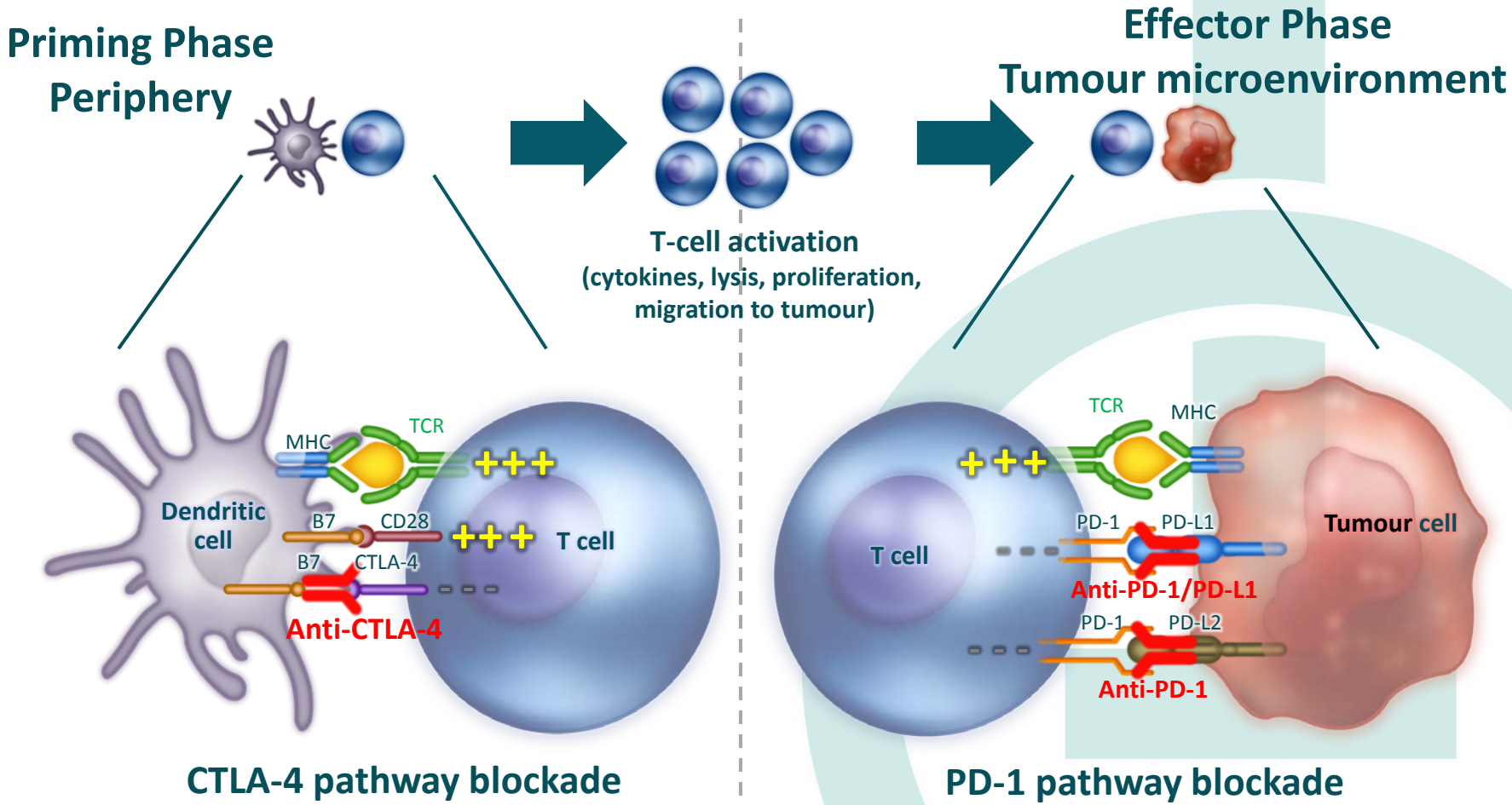
Consistent results across phase III trials

	COMBI-d	COMBI-v	coBRIM
	D+T (n=211) Cut off Jan 2015	**D+T (n= 352) Cut off April, 2014**	**V+C (n=247) Cut off Jan 2015**
ORR, % (95% CI)	**69** (61.8-74.8)	**64** (59.1–69.4)	**70** (63.5-75.3)
CR, %	**16**	**13**	**16**
PR, %	**53**	**51**	**54**
PD %	**6**	**6**	**~10**

Long GV, *et al.* Abstract and oral presentation at ASCO 2015, Abstract 102; Robert C, et al. N Engl J Med 2015;372:30–9; Roche

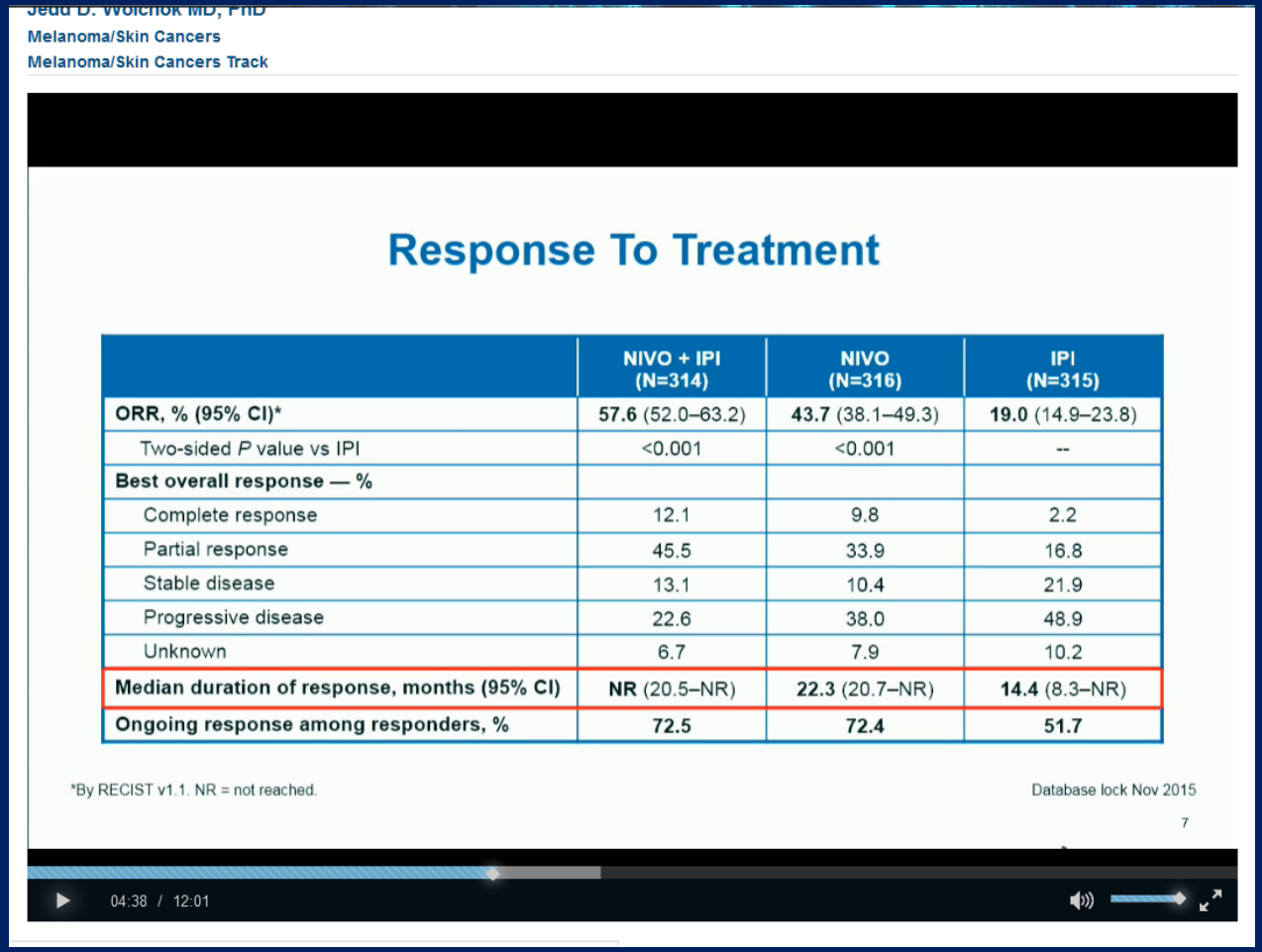
Immune Checkpoint Inhibitors – Anti-CTLA-4 and Anti-PD-1 Antibodies

Immuno-oncology: Blocking CTLA-4 and PD-1 Pathways with Monoclonal Antibodies



CTLA-4=cytotoxic T-lymphocyte antigen-4; PD-1=programmed cell death 1; PD-L1/2=PD ligand 1/2; TCR=T cell receptor.
Adapted from Wolchock J, *et al*. Oral presentation at ASCO 2013 (Abstract 9012).

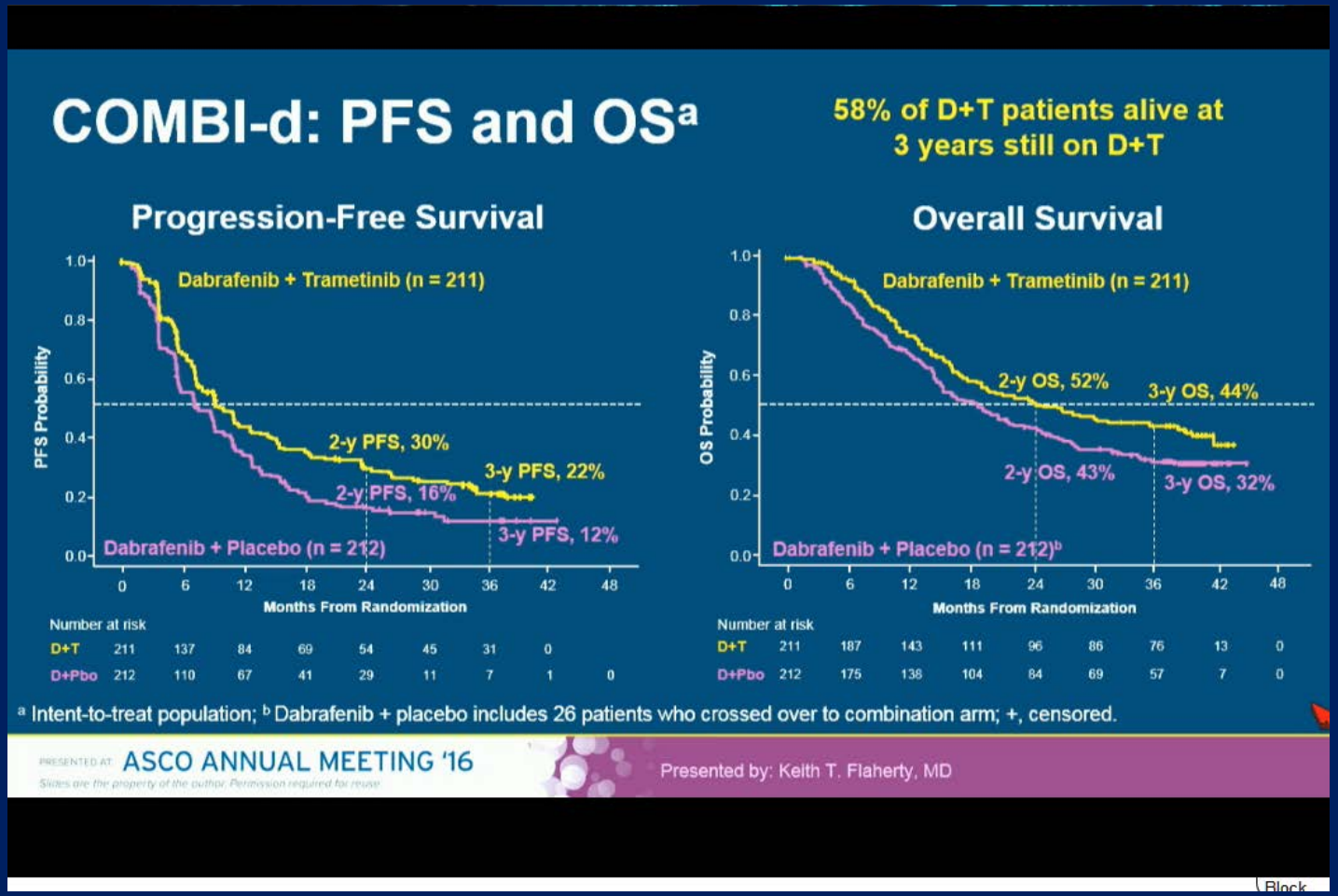
Immune Modulators – Objective Responses



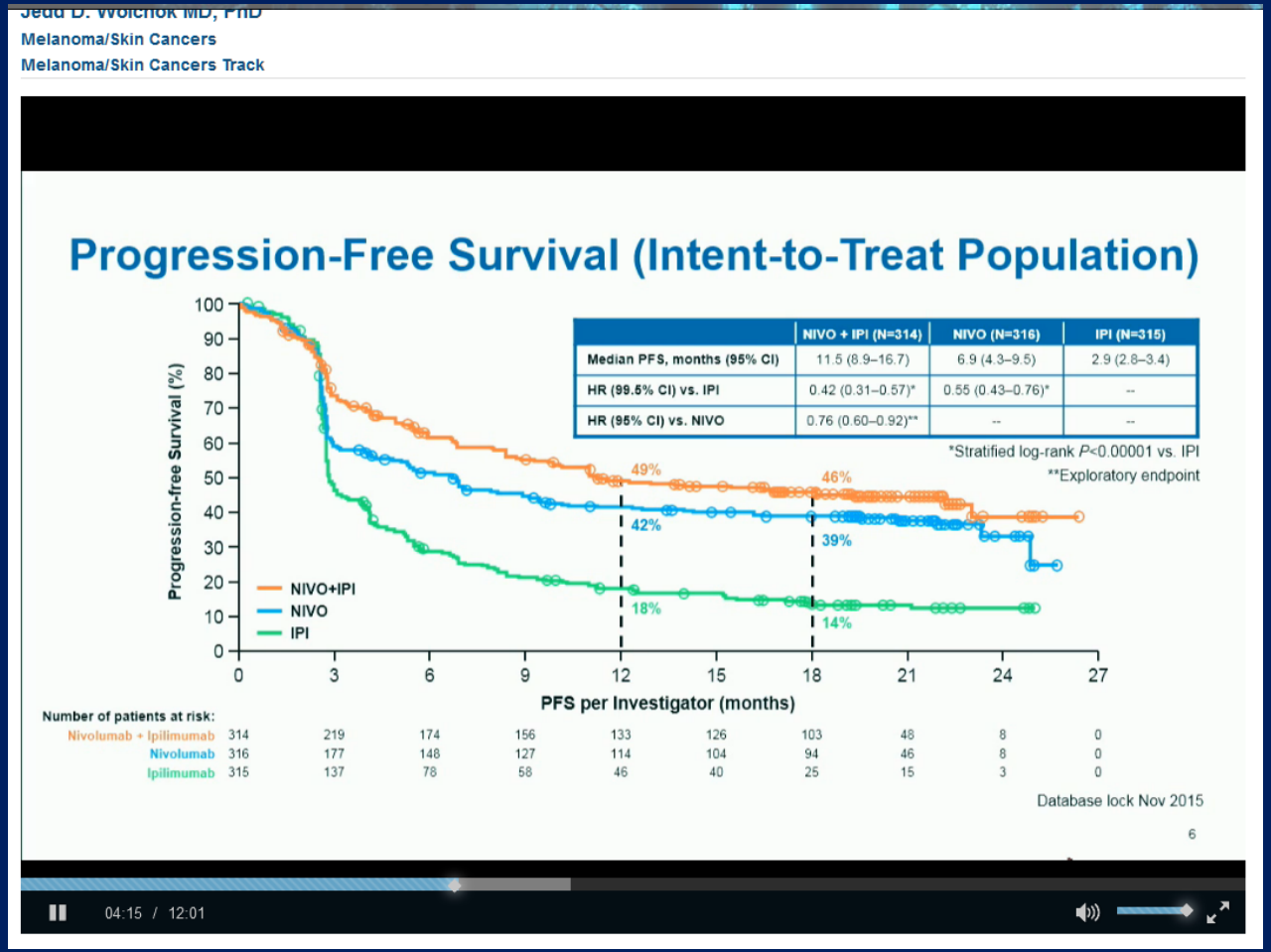
Agents Currently Available

- Anti-CTLA-4 antibodies
  - Ipilimumab
- Anti-PD-1 antibodies
  - Pembrolizumab
  - Nivolumab
- Combination therapy*
  - Ipilimumab + nivolumab

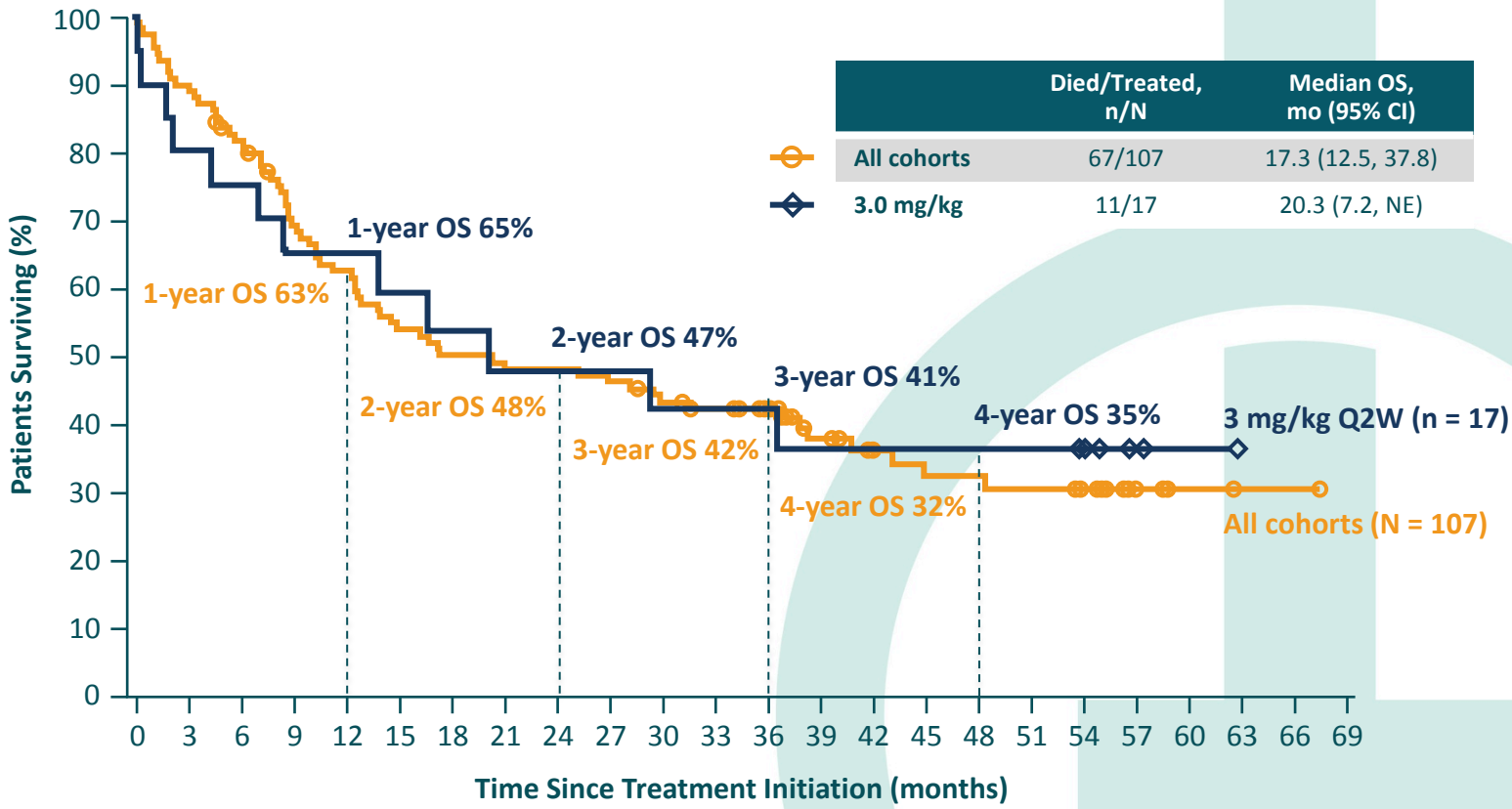
3-year Survival in Advanced Melanoma with BRAF and MEK Inhibition



Immune Modulators – Progression-Free Survival



Nivolumab Shows Durable Survival in Heavily Pre-treated Patients[1]



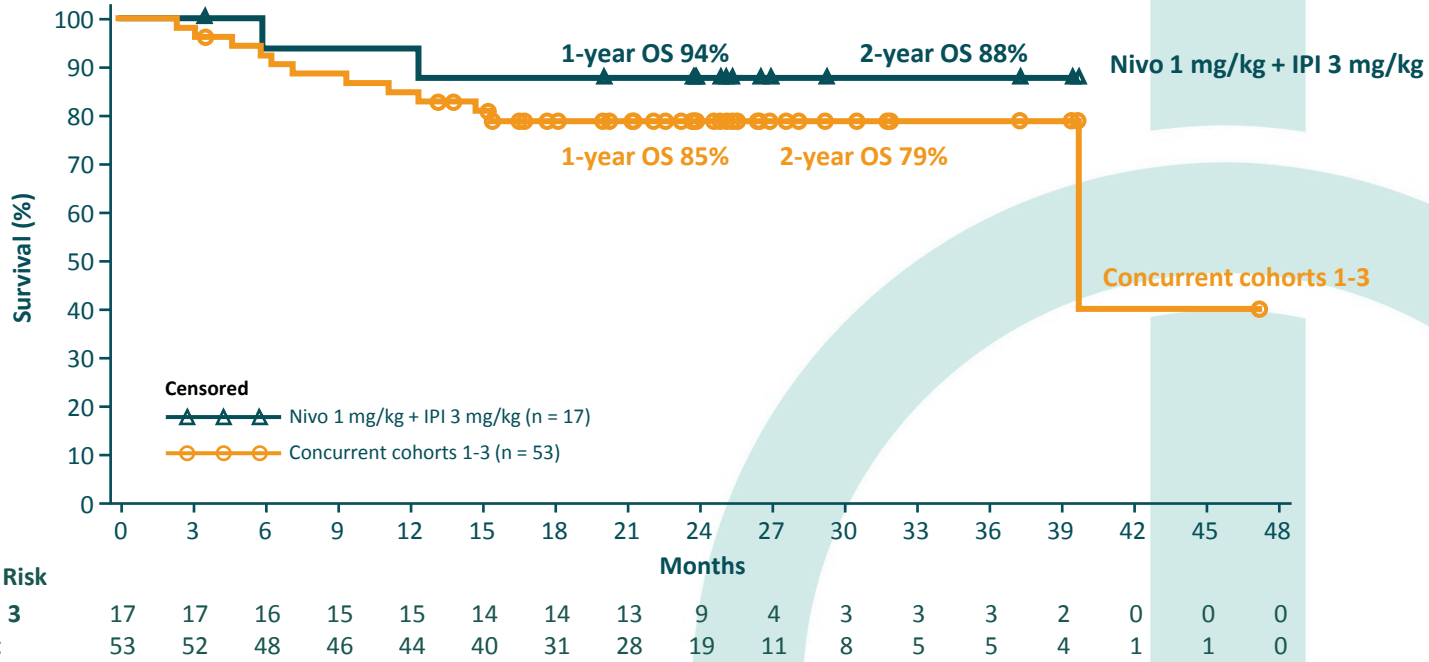
- Data from long-term follow-up of phase 1 study CA209-003[1]
- 54% of patients had an immune-mediated AE (any grade) and 5% had a grade 3/4 event (gastrointestinal 2%, endocrine 2%, and hepatic 1%)[1,2]

AE, adverse event; NE, not evaluated.

1. Hodi FS, *et al*. *Pigment Cell Melanoma Res.* 2014;27:1199. 2. Topalian SL, *et al*. *J Clin Oncol*. 2014;32:1020-1030.

Nivolumab Plus Ipilimumab in a Concurrent Regimen in Patients with Advanced Melanoma Showed 79-88% OS at 2 Years

Nivolumab 1 mg/kg Q3W × 4 and ipilimumab 3 mg/kg Q3W × 4, followed by nivolumab 3 mg/kg Q2W regimen selected for further evaluation



Patients at Risk

Nivo 1 + IPI 3	17	17	16	15	15	14	14	13	9	4	3	3	3	2	0	0	0
Concurrent	53	52	48	46	44	40	31	28	19	11	8	5	5	4	1	1	0

- Data from a phase 1 trial (CA209-004) of nivolumab plus ipilimumab on a concurrent or sequenced regimen[1]
- 62% of patients had grade 3/4 AEs on the concurrent regimen; there were no new safety signals and most events were manageable using standard protocols[1]
- Historical 1-year survival rates with ipilimumab and nivolumab monotherapy in patients with advanced melanoma were 45.6% (phase 3)[2] and 62% (phase 1), respectively[3,a]

[a]Data from separate, noncomparative trials; use cross-trial comparisons with caution in the absence of data from a randomized, comparative trial.
Q3W, every 3 weeks.

1. Adapted from Sznol M, *et al*. Presented at: ASCO 2014. Oral presentation 9003. 2. Hodi FS, et al. *N Engl J Med*. 2010;363:711-723.
3. Sznol M, *et al. J Clin Oncol.* 2013;31(suppl):abstract CRA9006.