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A Phase 3 Randomized, Open-Label Study of Nivolumab (Anti-PD-1; BMS-936558; ONO-4538) Versus Investigator's Choice Chemotherapy (ICC) in Patients With Advanced Melanoma With Prior Anti-CTLA-4 Therapy

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Disclosures

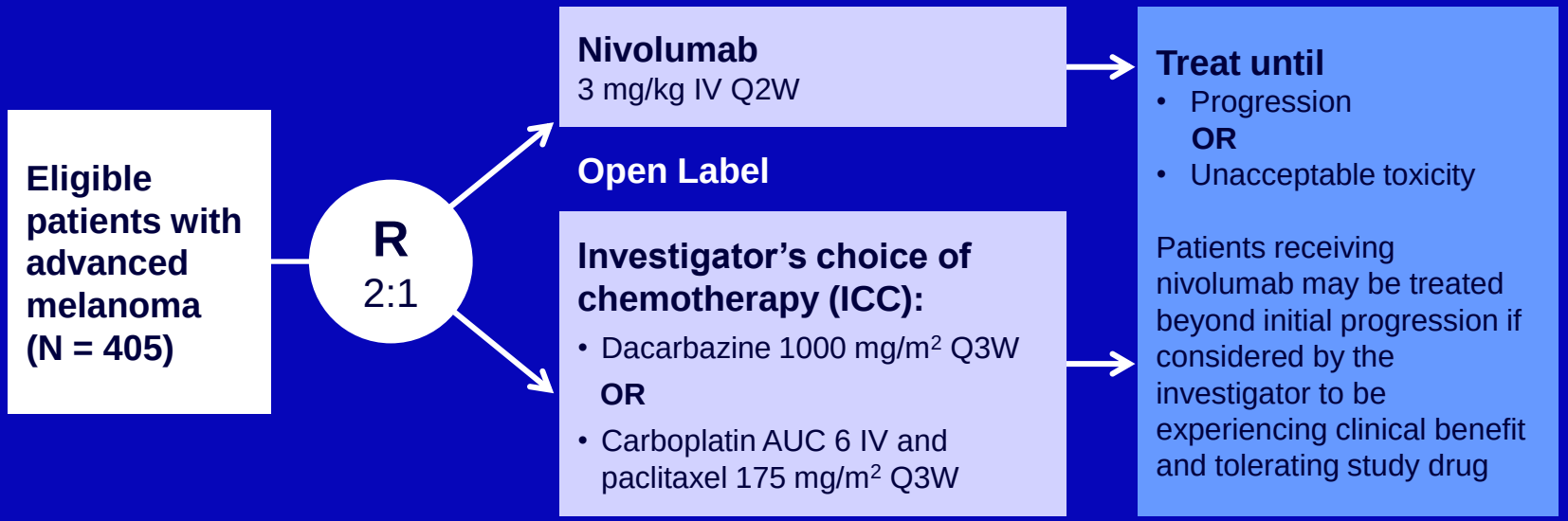
- Dr Weber discloses the following:
  - Honoraria from Bristol-Myers Squibb, Merck, Genentech, AstraZeneca, and AbbVie
  - Clinical research funding from Bristol-Myers Squibb, Merck, GlaxoSmithKline, and Macrogenics to Moffitt Cancer Center
  - Scientific advisory board member (paid) for Ichor Therapeutics, Lion Biotechnologies, and Pieris
  - Stock holdings in Celldex Therapeutics, Altor BioScience, and cCAM Biotherapeutics

Background

- Nivolumab is a fully human IgG4 monoclonal antibody that inhibits the PD-1 immune checkpoint protein[1]
  - In early studies, single-agent nivolumab demonstrated meaningful clinical activity and a manageable safety profile in patients with advanced melanoma
    - Overall survival rates of 63%, 48%, and 41% were observed at 1-, 2-, and 3-years, respectively[2]
- There are limited options for patients with advanced melanoma who have progressed on approved agents (ipilimumab and BRAF inhibitors) that have been shown to have prolonged overall survival in randomized clinical trials[3]

[1]Wang C et al. *Cancer Immunol. Res*. 2014;2(9):1–11; [2]Hodi et al. *J Clin Oncol*. 2014;32:(5 suppl; abstr 9002); [3]Ravnan et al. *Clin Ther*. 2012; 34:1474–1486.

Phase 3 CA209-037: Study Design



Stratified by:

- **PD-L1 expression:** PD-L1 positive vs PD-L1 negative/indeterminate (positive: ≥5% tumor cell surface staining cut-off by immunohistochemistry)
- **BRAF status:** BRAF wild-type vs BRAF V600 mutant
- **Best overall response (BOR) to prior ipilimumab:** Clinical benefit (BOR=CR/PR/SD) vs no clinical benefit (BOR=PD)

AUC = area under the curve; CR = complete response; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; PD-L1 = programmed death ligand 1; PR = partial response; Q2W = every 2 weeks; SD = stable disease.

Patient Eligibility

Inclusion criteria

- Previously treated, unresectable stage III or IV Melanoma
- ECOG Performance Status of 0 or 1
- BRAF wild-type patients must have progressed after ipilimumab
- Patients with BRAF V600 mutation must have progressed on ipilimumab and a BRAF inhibitor

Exclusion criteria

- Active brain metastases
- Prior therapy with anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies
- Grade 4 toxicity or use of infliximab to manage AEs from prior ipilimumab treatment
- Ocular melanoma

AEs = adverse events; ECOG = Eastern Cooperative Oncology Group.

Study Objectives

Co-primary objectives

- To estimate ORR in the first 120 nivolumab-treated patients with ≥6 months of follow-up (planned interim analysis)
- To compare OS[a] of nivolumab to ICC

Secondary objectives include

- To compare PFS of nivolumab to ICC at the time of OS analysis[a]
- To evaluate PD-L1 expression as a predictive biomarker for ORR and OS[a]

[a]PFS and OS analysis had not taken place at the time of this ORR analysis

ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Baseline Characteristics

	Nivolumab (N = 272)	ICC (N = 133)
Age, median (range)	59 (23, 88)	62 (29, 85)
Male, %	65	64
ECOG performance status, % 0 1	 60 40	 63 36
Stage M1c at study entry, %	75	77
AJCC stage IV at study entry, %	96	99
History of brain metastasis, %	20	14
LDH > ULN, %	51	35
Tumor size[a] at baseline, median, mm (range)	96 (10–422)	87 (13–400)

All randomized population.
[a]Tumor size is measured by the sum of diameters of target lesions; based on investigator review.
AJCC = American Joint Committee on Cancer; LDH = lactate dehydrogenase; ULN = upper limit of normal range.

Baseline Characteristics

	Nivolumab (N = 272)	ICC (N = 133)
Number of prior therapies[a], %		
1	28	26
2	51	51
>2	21	23
Type of prior therapies[a], %		
Ipilimumab	100	100
Vemurafenib	18	17
Chemotherapy[b]	53	54
Other immunotherapy[c]	14	26
Pretreatment PD-L1 positive[d], %	49	50
BRAF mutant, %	22	22
No prior ipilimumab benefit[e], %	64	65

All randomized population.
[a]Under metastatic disease setting.
[b]Excluding immunotherapy and BRAF inhibitors.
[c]Excluding prior ipilimumab
[d]PD-L1 positivity was defined as a tumor specimen with ≥5% tumor cell membrane staining measured by BMS/Dako immunohistochemistry assay.
[e]Best overall response of progressive disease

Summary of Treatment Exposure

	Nivolumab (N = 268)	ICC (N = 102)
Number of doses, median (range)	8 (1, 31)	3 (1, 11)[b] 5 (1, 11)[c]
Time on therapy, median, months (95% CI)	5.3 (3.3, 6.5)	2.0 (1.6, 2.9)
Patients who had discontinued study treatment at the time of analysis[a], n (%)	139 (52)	84 (82)

- Disease progression was the most common reason for discontinuation in the nivolumab (43%) and ICC arms (61%)

All treated population.
[a]ORR analysis, reported 30 April 2014.
[b]Dacarbazine.
[c]Carboplatin and paclitaxel.

Treatment-Related Adverse Events

	Nivolumab (N = 268)[a]	ICC (N = 102)[a]
Serious drug-related AE, n (%)		
Any grade	17 (6)	10 (10)
Grade 3–4	12 (5)	9 (9)
Drug-related AE, n (%)		
Any grade	181 (68)	81 (79)
Grade 3–4	24 **(9)**	32 **(31)**
Drug-related AE leading to discontinuation, n (%)	6 (2)	8 (8)

- There were no deaths related to any study drug toxicity

[a]Safety analysis included all treated patients.

Treatment-Related AEs Reported in ≥10% of Patients

AE Term Patients reporting AE, %	Nivolumab (N = 268)[a]		ICC (N = 102)[a]	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Total patients with an event, %	**68**	**9**	**79**	**31**
Fatigue	25	1	34	4
Pruritus	16	0	2	0
Diarrhea	11	<1	15	2
Nausea	9	0	37	2
Anemia	5	1	23	5
Decreased appetite	5	0	16	0
Arthralgia	5	0	12	1
Vomiting	3	<1	20	2
Constipation	2	0	14	1
Neutropenia	0	0	19	14

- No nivolumab-related grade 3–4 AE was reported in more than 2% of patients

[a]Safety analysis included all treated patients.

Nivolumab-Related Select AEs

Select AE Organ Category Patients, n (%)	Nivolumab (N = 268)[a]	
	Any Grade	Grade 3–4
Skin	78 (29)	1 (<1)
Gastrointestinal	31 (12)	3 (1)
Endocrine	21 (8)	0 (0)
Hepatic	12 (5)	2 (1)
Pulmonary	6 (2)	0 (0)
Hypersensitivity/infusion reaction	5 (2)	1 (<1)
Renal	4 (2)	1 (<1)

- All grade 3-4 drug-related AEs belonging to the select AE categories resolved
- Corticosteroids were the most common immunosuppressive medication used
- In total, less than 5% of patients reported grade 3–4 select AE

[a]Included all treated patients and events reported between the first dose and 30 days after the last dose of study therapy.

Co-Primary Endpoint: ORR By Central Review per RECIST 1.1

Treatment	N	CR+PR, n	ORR[a], % (95% CI)	Best Overall Response[a], %				
				CR	PR	SD	PD	UNK
Central review[b]								
Nivolumab	120	38	32 (24–41)	3	28	23	35	10
ICC	47	5	11 (4–23)	0	11	34	32	23

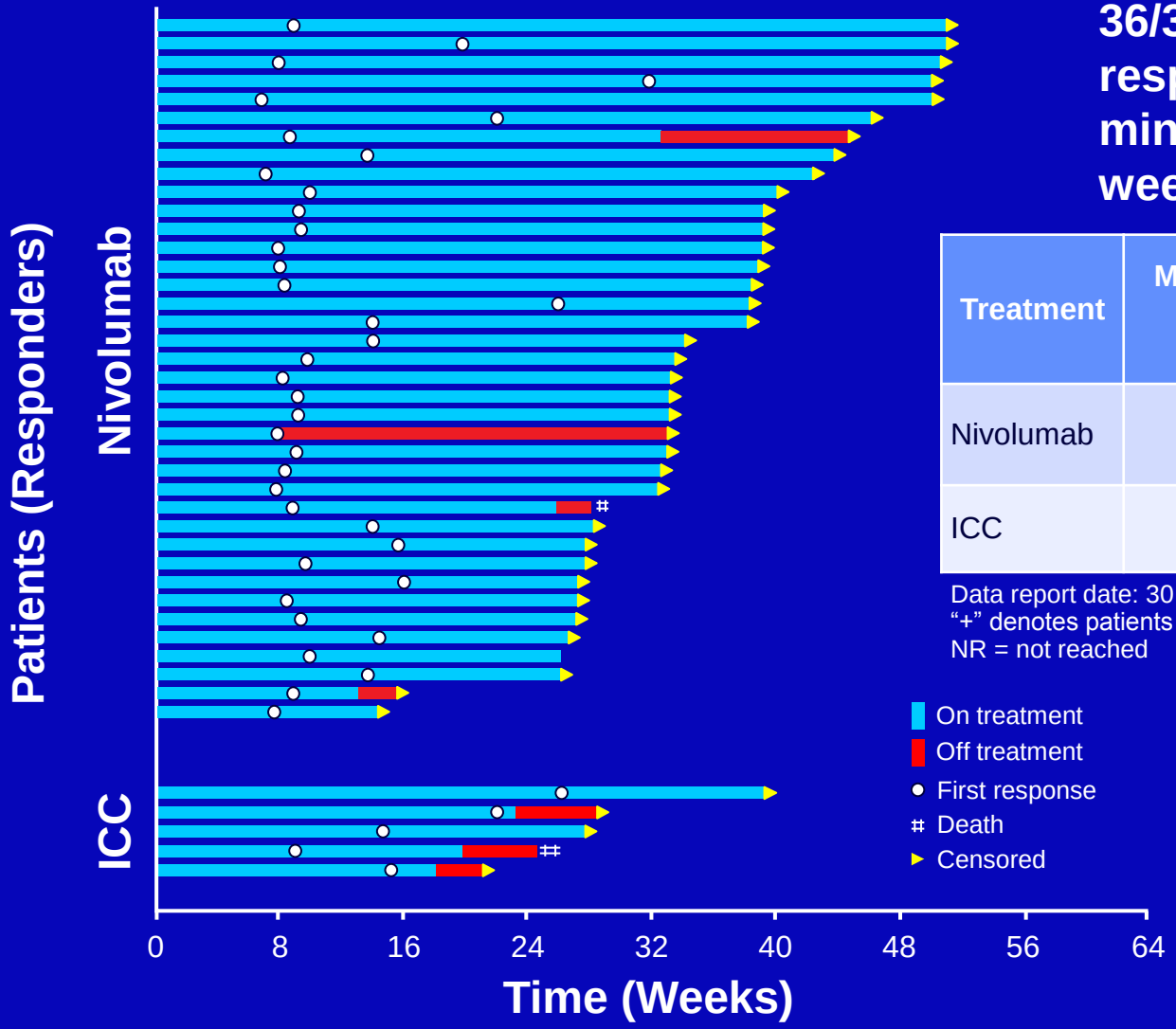
[a]Confirmed response.
[b]Independent radiology review committee based on RECIST 1.1.
PD = progressive disease; RECIST = Response Evaluation Criteria In Solid Tumors; UNK = unknown.

Co-Primary Endpoint: ORR

Treatment	N	CR+PR, n	ORR[a], % (95% CI)	Best Overall Response[a], %				
				CR	PR	SD	PD	UNK
Central review[b]								
Nivolumab	120	38	32 (24–41)	3	28	23	35	10
ICC	47	5	11 (4–23)	0	11	34	32	23
Investigator assessed								
Nivolumab	120	31	26 (18–35)	2	24	27	46	2
ICC	47	5	11 (4–23)	0	11	23	62	4

[a]Confirmed response.
[b]Independent radiology review committee based on RECIST 1.1.

Time and Duration of Response by Central Review, RECIST 1.1



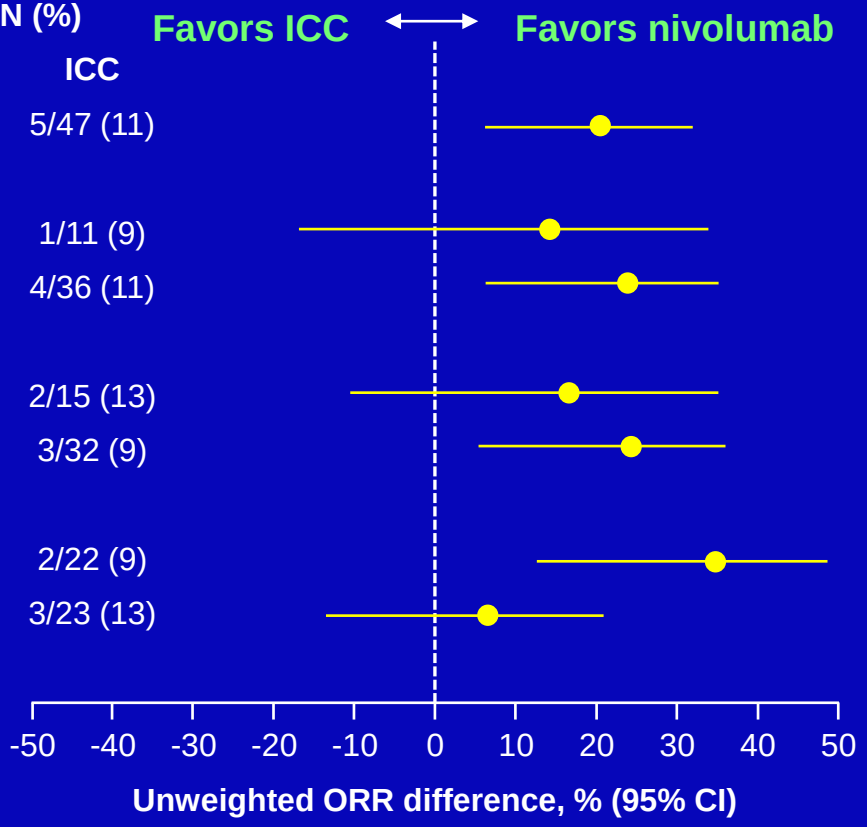
36/38 (95%) of nivolumab responses ongoing with minimum follow-up of 24 weeks in all patients

Treatment	Median time to response, (range), mo	Median duration of response(range), mo
Nivolumab	2.1 (1.6, 7.4)	NR (1.4+, 10.0+)
ICC	3.5 (2.1, 6.1)	3.6 (1.3+, 3.5)

Data report date: 30 Apr 2014
"+" denotes patients who are censored (still in response);
NR = not reached

Comparison of ORR in Patient Subgroups By Central Review per RECIST 1.1

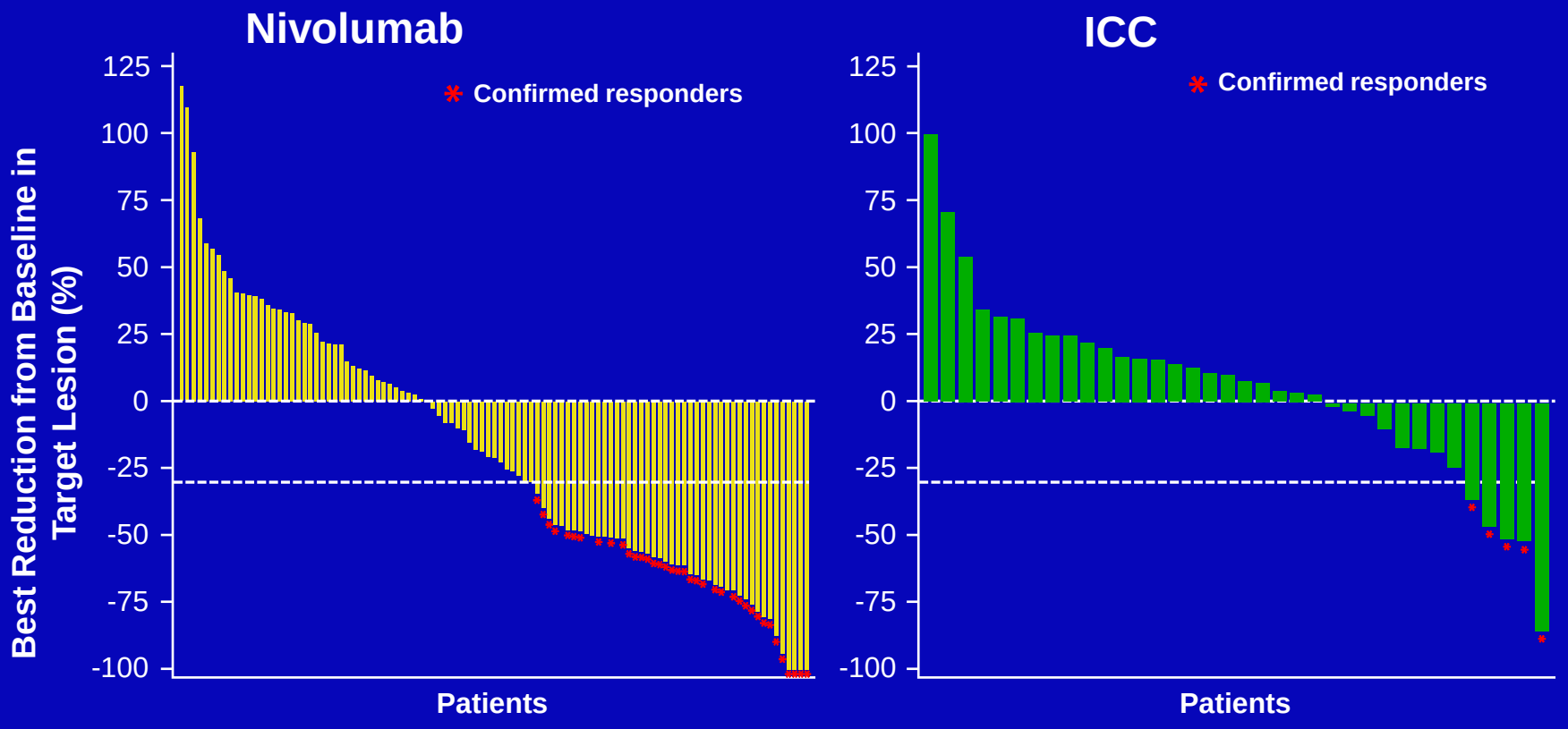
	N	ORR, n/N (%)	
		Nivolumab	ICC
OVERALL	167	38/120 (32)	5/47 (11)
BRAF Status			
Mutant	37	6/26 (23)	1/11 (9)
Wild-type	130	32/94 (34)	4/36 (11)
Prior ipilimumab benefit			
Yes	55	12/40 (30)	2/15 (13)
No	112	26/80 (33)	3/32 (9)
PD-L1 status			
Positive[a]	77	24/55 (44)	2/22 (9)
Negative	87	13/64 (20)	3/23 (13)



- Consistently higher clinical activity was observed for nivolumab versus ICC regardless of pre-treatment PD-L1 expression status, BRAF mutation status and prior ipilimumab benefit

[a]PD-L1 positivity was defined as a tumor specimen with ≥5% tumor cell membrane staining measured by BMS/Dako immunohistochemistry assay. Three patients had indeterminate PD-L1 status by immunohistochemical staining.

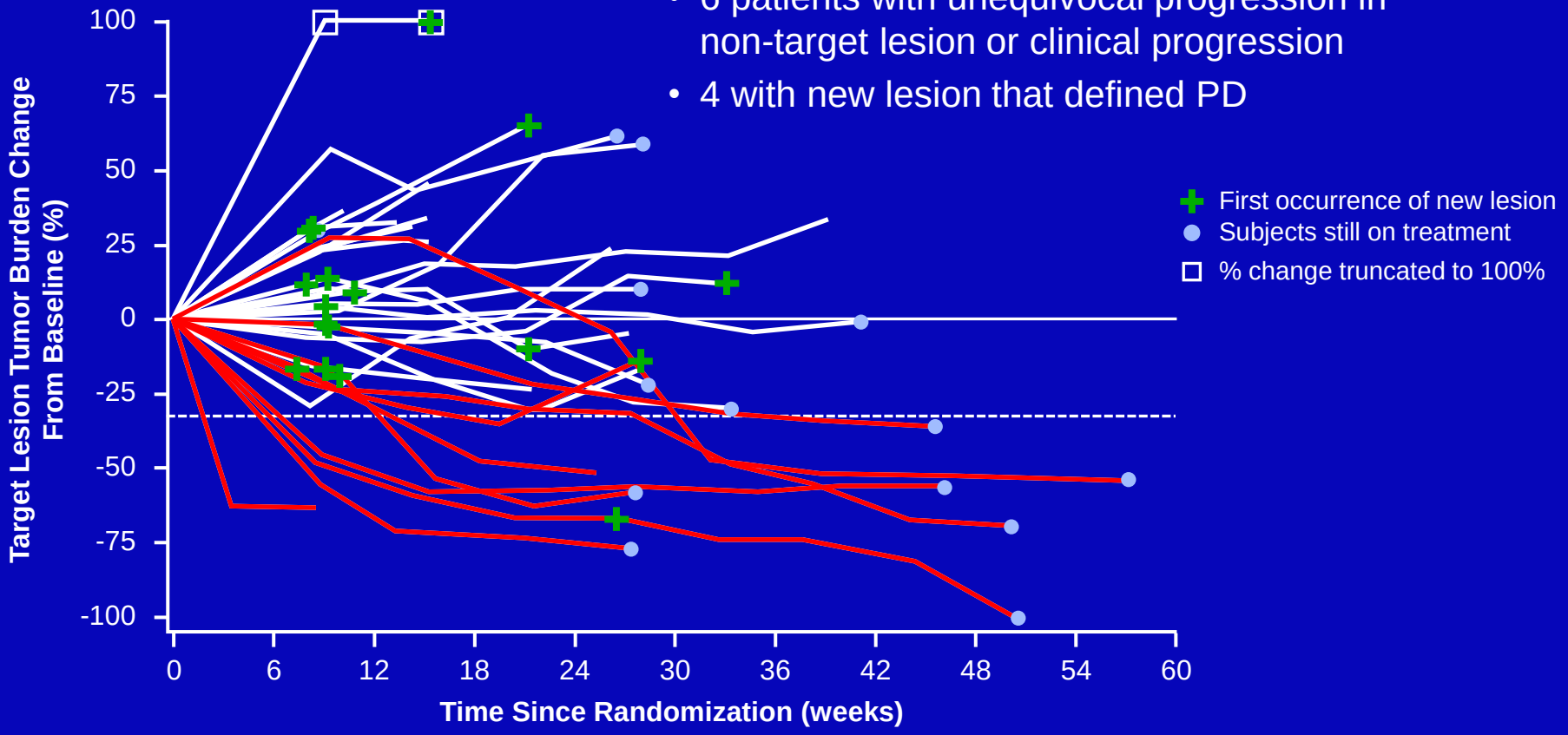
Maximum Reduction in Target Tumor Size From Baseline, by Central Review, RECIST 1.1



- Inflection (break) point is 61% for nivolumab; 36% for ICC

Immune-Related Response Pattern

- Of 120 nivolumab-treated subjects in the treated population
  - 37/120 (31%) continued treatment beyond RECIST 1.1-defined progression
    - 10/120 (8%) subsequently experienced a ≥30% reduction in target lesion tumor burden (“immune-related, unconventional response pattern”)
      - 6 patients with unequivocal progression in non-target lesion or clinical progression
      - 4 with new lesion that defined PD



Conclusions

- In patients with advanced melanoma who have progressed despite prior ipilimumab, and BRAF inhibitors if BRAF mutated, nivolumab monotherapy demonstrated superior efficacy to ICC
  - Objective response rate of 32% with nivolumab compared to 11% with ICC
  - Majority (95%) of responses were ongoing in patients who received nivolumab; median DOR not reached
  - Responses were observed regardless of pre-treatment PD-L1 expression status, BRAF mutation status, and prior ipilimumab benefit
- Grade 3-4 treatment-related AEs were reported in 31% of ICC patients compared with 9% of nivolumab patients
- The majority of nivolumab treatment-related AEs were low grade and manageable using recommended treatment algorithms
- Co-primary endpoint—OS—data are pending at this time
- Now under priority review with the FDA and accelerated assessment with the EMA based on these data

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