Immunotherapy for the treatment of melanoma

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Disclosures:

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I will not be discussing non-FDA approved treatments.

Objectives

- Discuss the key mechanisms and terminology of tumor immunology and immunotherapy
- Describe the role of immunity in cancer and approaches to tumor immunotherapy
- Implement cancer immunotherapy treatments for melanoma, lung cancer and/or genitourinary cancers into clinical practice more effectively through a sound understanding of mechanisms of action, side effects and clinical management, and efficacy

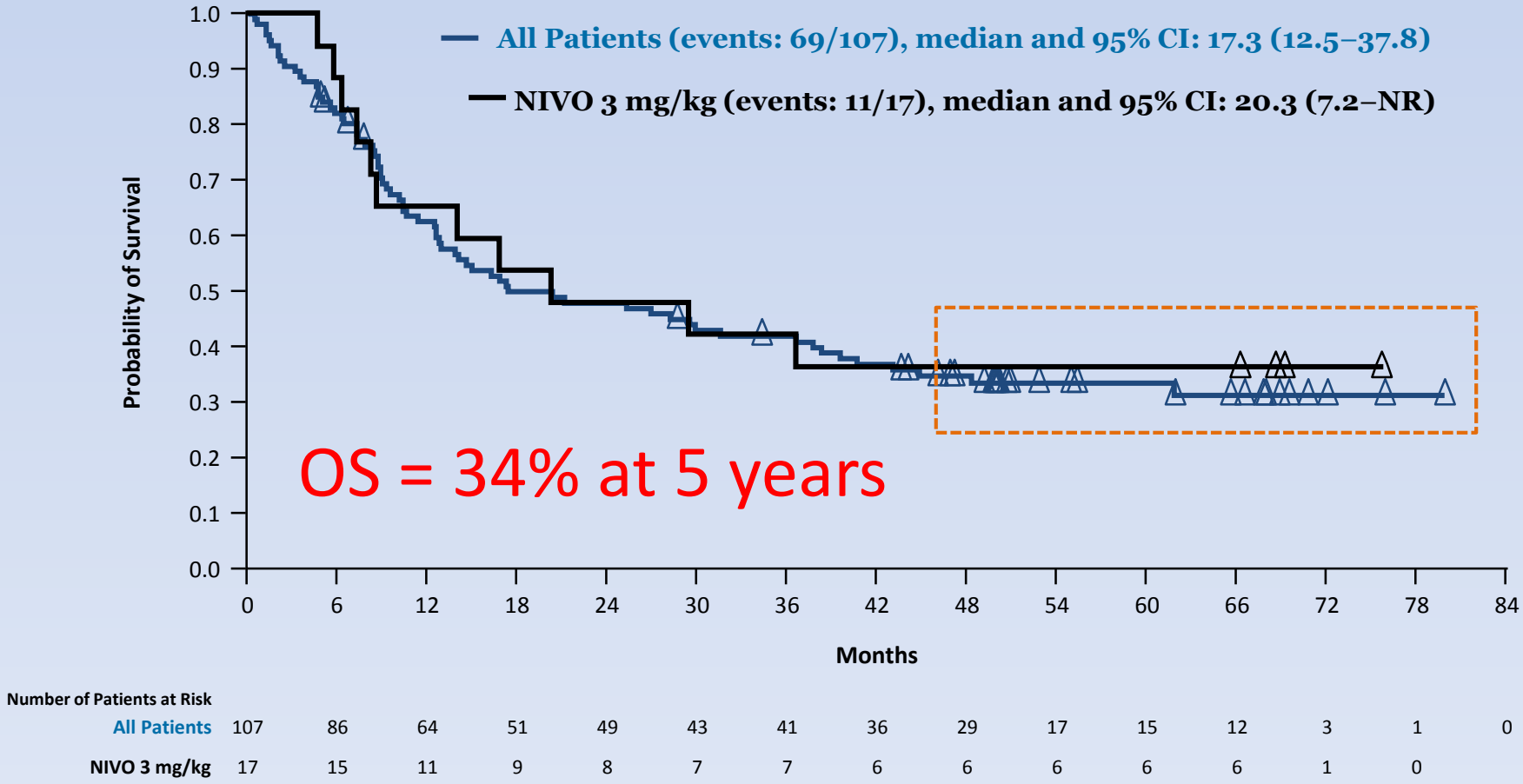
Newly diagnosed patient with advanced melanoma

- Immunotherapy used first-line if:
  - No need for immediate response to therapy
  - No underlying autoimmune conditions (e.g., asthma)
  - No co-morbidity that would compromise management of immune-related toxicities

Newly diagnosed patient with advanced melanoma

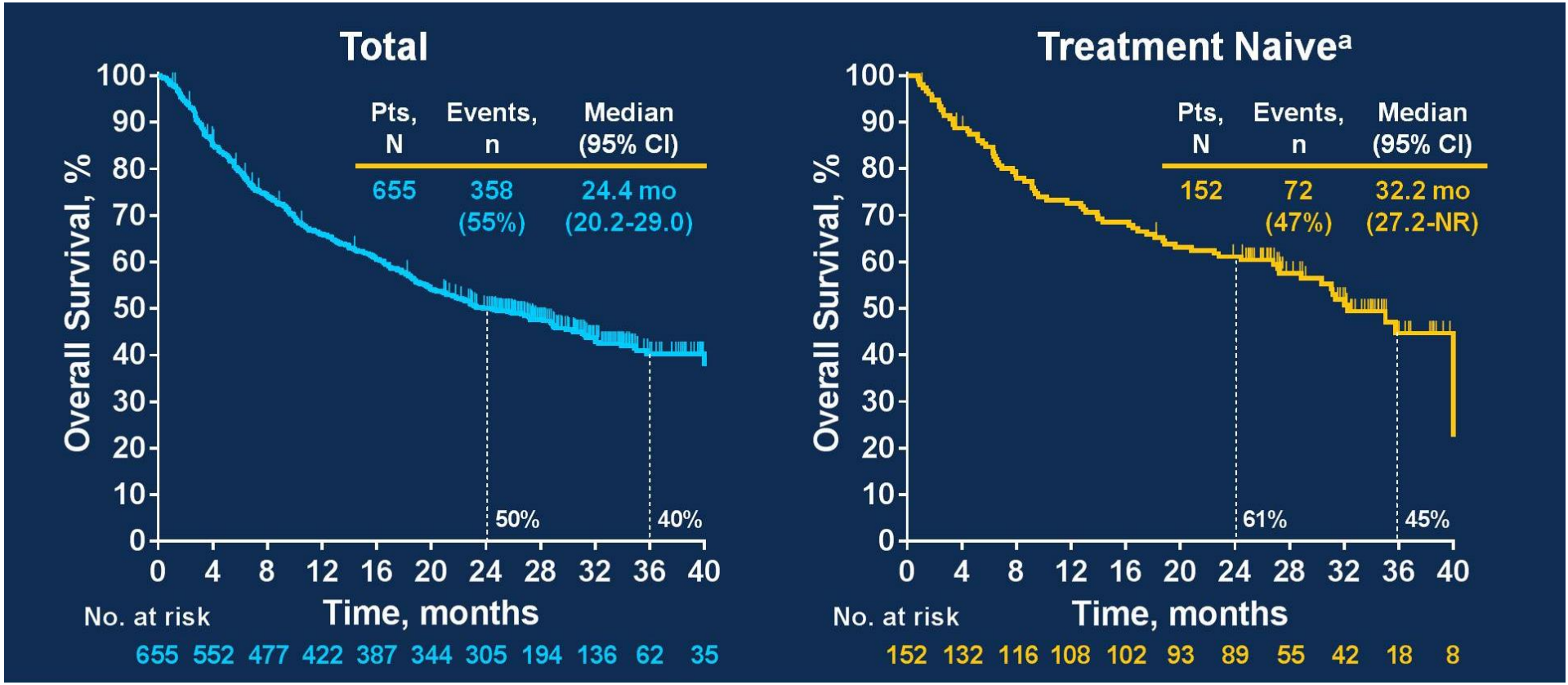
- Immunotherapy options:
  - Immunotherapy-based clinical trial
  - Immune checkpoint therapy (e.g., nivolumab)
  - High-dose interleukin-2

Nivolumab: Overall Survival at 5 Years of Follow-up



Hodi et al, AACR, 2016

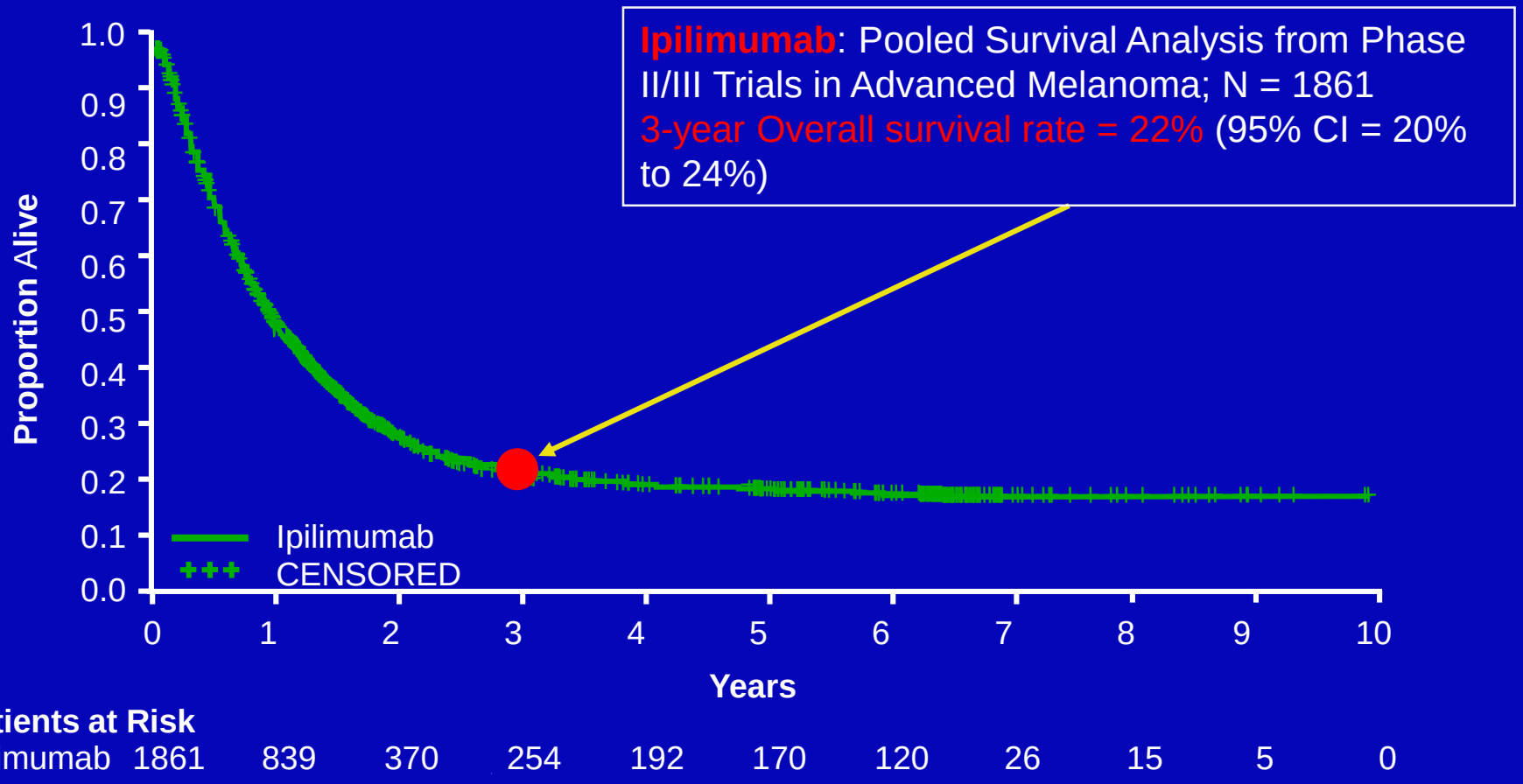
3-year overall survival for patients with advanced melanoma treated with pembrolizumab



3-year OS rate = 45% (treatment-naïve patients), 40% (all patients), approximately equivalent to nivolumab

Robert et al, ASCO 2016

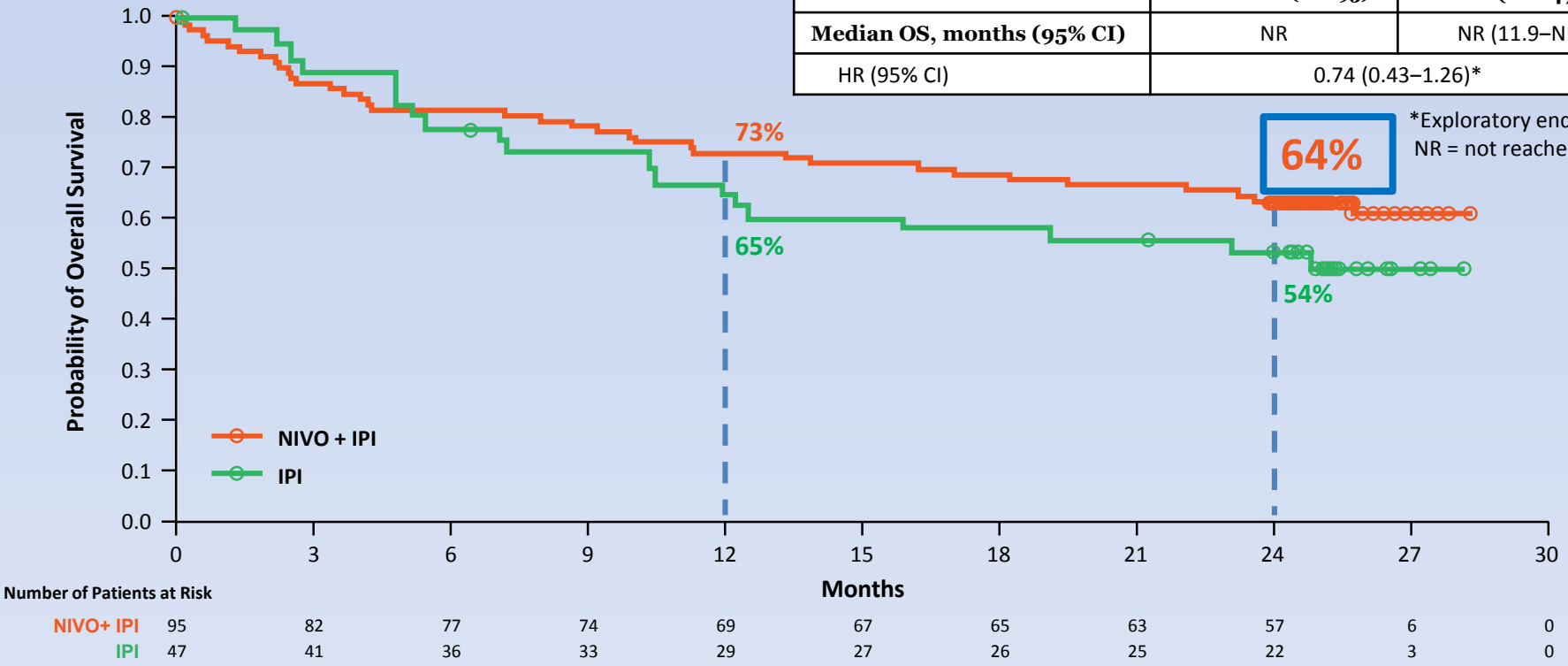
Ipilimumab: Overall Survival at 10 Years of Follow-up



Hodi S, et al. 2013 European Cancer Congress. Abstract LBA 24.

Nivolumab + ipilimumab in patients with advanced melanoma: overall survival at 2 years

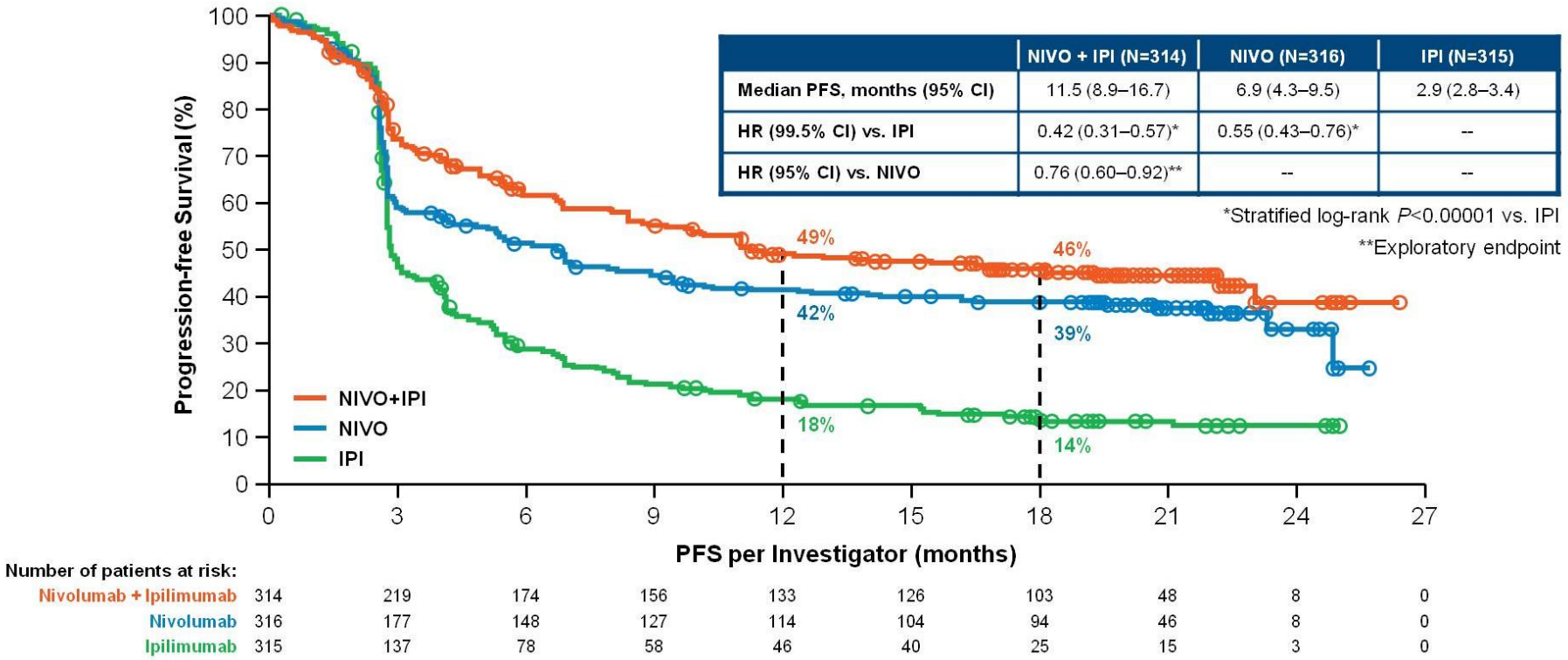
	NIVO + IPI (N = 95)	IPI (N = 47)
Median OS, months (95% CI)	NR	NR (11.9–NR)
HR (95% CI)	0.74 (0.43–1.26)*	



- 30/47 (64%) of patients randomized to IPI crossed over to receive any systemic therapy at progression

Postow et al, AACR, 2016

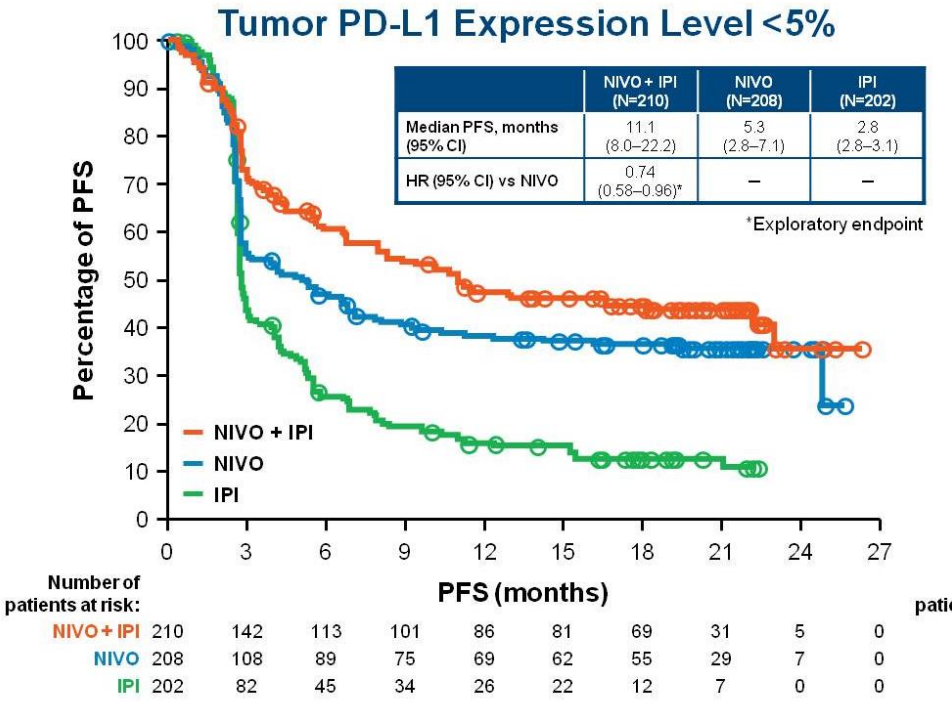
Progression-free survival: nivolumab vs ipilimumab vs combination



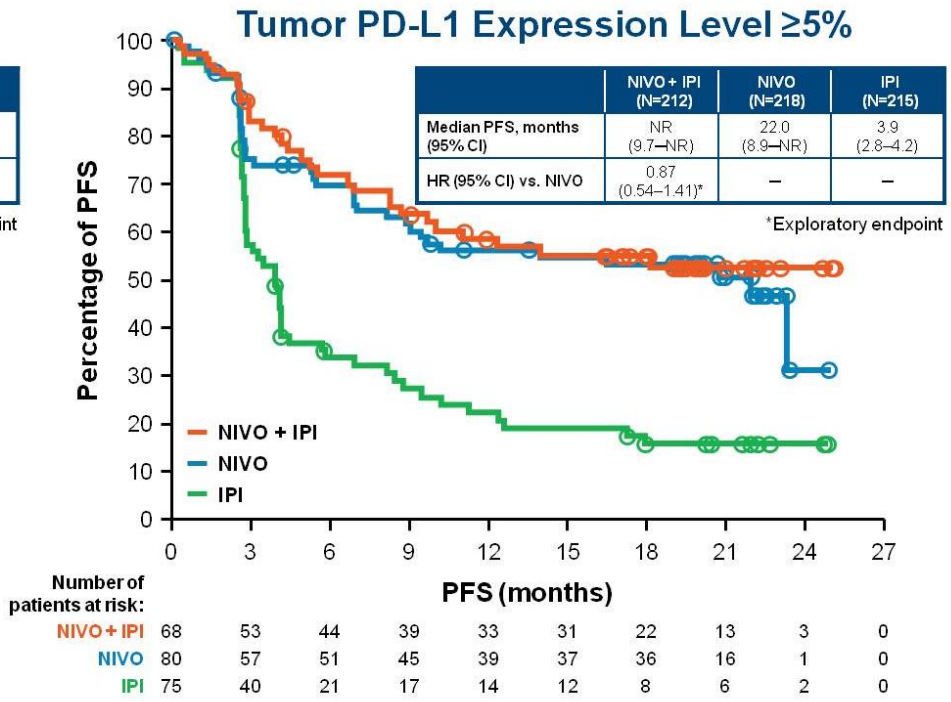
Wolchok et al, ASCO 2016

Progression-free survival by PD-L1 expression: nivolumab vs ipilimumab vs combination

PD-L1 (-)



PD-L1 +



Wolchok et al, ASCO 2016

Safety: nivolumab vs ipilimumab vs combination

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	56.5	84.0	19.8	85.9	27.0
Treatment-related AE leading to discontinuation	38.7	30.7	10.5	7.3	15.4	13.5
Treatment-related death*	0		0.3		0.3	

- 68.8% of patients who discontinued NIVO+IPI due to treatment-related AEs achieved a response

*One reported in the NIVO group (neutropenia) and one in the IPI group (colon perforation)

Database lock Nov 2015

Wolchok et al, ASCO 2016

Pembrolizumab Plus Ipilimumab For Advanced Melanoma: Results of the KEYNOTE-029 Expansion Cohort

- 153 patients with advanced melanoma, naïve to CTLA-4 and PD-1/L1 therapy
- Pembro 2/mg/kg q3w up to 2 yrs plus ipilimumab 1mg/kg q3w x 4 doses
- Grade 3-4 treatment-related toxicity = 42%
- Overall response rate = 57%

Long et al ASCO 2016

Choosing a therapy

- Clinical trial if at all possible
- Combo vs. monotherapy
  - Possible number of “shots on goal”
  - Side effect tolerance
  - Capacity for communication with medical team
  - Age alone less of a factor

Immune-Related Adverse Events

- Drug-related inflammatory processes affecting virtually any organ system
- Distinct mechanism of action from traditional chemotherapy/cancer therapy side effects
- Evaluation and management are unique to this class of drugs

Approach to potentially immune-mediated symptoms

- Drug induced autoimmunity **always** included in differential, often diagnosed by exclusion
  - Rule out other etiologies (e.g., infection, other drugs, neoplasm, metabolic causes)
- Can affect **any** organ system
- Early recognition, evaluation and treatment are **critical for patient safety**
- Multi-disciplinary team should be made aware of side effect profiles of these drugs

Select immune-related toxicities

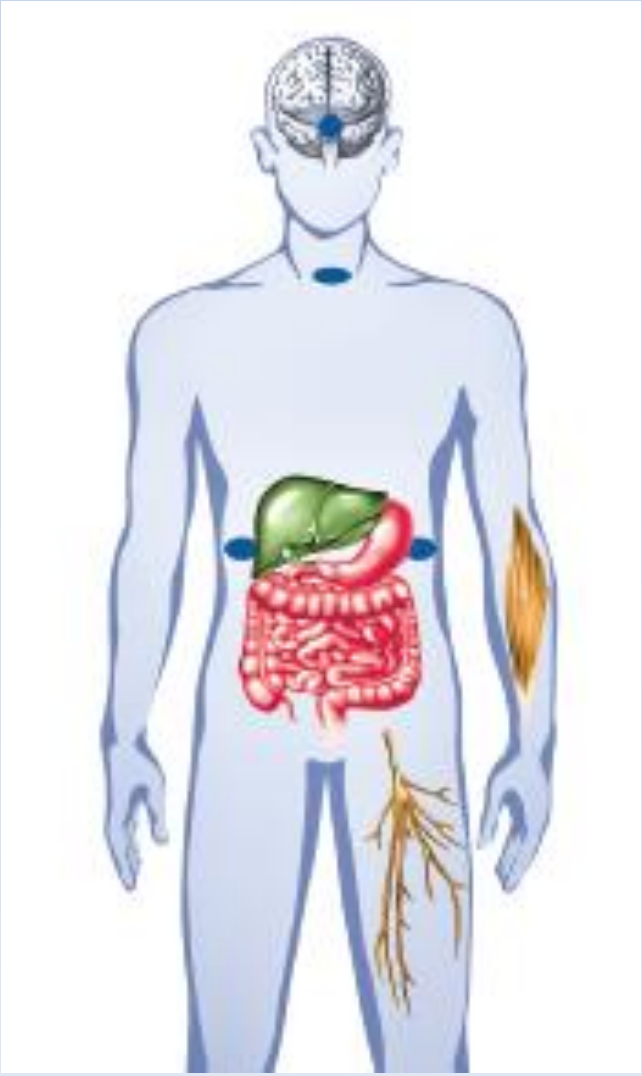
Hypophysitis

Thyroiditis

Adrenal Insufficiency

Enterocolitis

Dermatitis



Pneumonitis

Hepatitis
Pancreatitis

Motor & Sensory Neuropathies

Arthritis

Immune-related toxicity management: General principles

- Grade 1: supportive care; +/- withhold drug
- Grade 2: withhold drug, consider re-dose if toxicity resolves to ≤ Grade 1. Low dose corticosteroids (prednisone 0.5mg/kg/day or equivalent) if symptoms do not resolve within a week
- Grade 3-4: discontinue drug; high dose corticosteroids (prednisone 1-2mg/kg/day or equivalent) tapered over ≥ 1 month once toxicity resolves to ≤ Grade 1.

51 y.o. man with stage IV melanoma, s/p 2 doses of PD-1 antibody, c/o diarrhea

- Reports increased stool output, 7-8 per day, 1 episode of incontinence. Mild abdominal discomfort, no blood in stool, no fevers. Mild anorexia and nausea.
- Reports no sick contacts; sushi for dinner
- On exam: afebrile, non-toxic appearing, vitals stable, mild epigastric abdominal tenderness, normoactive bowel sounds

51 y.o. man with stage IV melanoma, s/p 2 doses of PD-1 antibody, c/o diarrhea

Which of the following is/are appropriate?

A. Hold PD-1 antibody
B. Check stool cultures, ova & parasites, *c. difficile*
C. Start systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) + IV fluids
D. Consider GI consult for scope with colon biopsies and rapid pathologic review – tell provider of suspicion for immune-related colitis
E. Consider CT abd; check Quantiferon
F. All of the above

51 y.o. man with stage IV melanoma, s/p 2 doses of PD-1 antibody, c/o diarrhea.

Increased, blood-tinged stools with worsening abdominal discomfort despite IV steroids. Afebrile but "washed-out" with mild, diffuse tenderness to palpation; no peritoneal signs. Quantiferon results negative.

Which of the following is/are appropriate?

A. Administer IV fluids
B. Administer infliximab at 5mg/kg
C. Consider inpatient admission
D. Administer pneumocystis (PCP) prophylaxis
E. All of the above

Headache & Fatigue/Depression

- Two men with advanced cancer s/p immune checkpoint blockade therapy
  - #1: headache x 2 days unrelieved by acetaminophen or ibuprofen. Denies visual changes, photosensitivity, nausea, vomiting, dizziness, lightheadedness or focal weakness. Exam: non-focal neurologically. No meningismus.
  - #2: Low mood, poor energy, decreased appetite, naps 5-6 hrs per day, lightheaded when standing
- Labs:
  - serum cortisol: <0.40 (5 - 25 ug/dL)
  - ACTH: low in patient #1, elevated in patient #2

Headache & Fatigue/Depression

Which of the following is/are appropriate?

A. Hold immunotherapy
B. Consider MRI of pituitary; check TFTs
C. Consider high-dose (1 mg/kg/day) prednisone during acute phase, then hydrocortisone (e.g., 20mg po qam, 10mg po qpm)
D. Consider referral to endocrinologist
E. All of the above

Headache & Fatigue/Depression

- Hypophysitis (case 1) or primary adrenal insufficiency (case 2) may lead to life-long endocrine dysfunction
- May require stress doses of corticosteroids in times of acute illness

Sore throat

- 58 y.o. woman with advanced cancer s/p 1 dose of anti-PD-1
- Complains of “sore throat” and anterior neck discomfort, especially with swallowing. No other symptoms.
- On exam: vitals stable, no tachycardia. Thyroid tender to palpation.

Sore throat

- Thyroiditis
  - Check TSH at each dose; free T3 & free T4 if TSH abnormal
  - Often presents as hyperthyroidism followed by hypothyroidism
- Symptoms during hyperthyroid period?
  - NO
    - continue immunotherapy, replace T4 as necessary
  - YES:
    - In general, no need for propylthiouracil / methimazole
    - Initiate symptom-directed support (propranolol, anti-diarrheals)
- Titrating dose of levothyroxine may take months

Will steroids make the immunotherapy stop working against my cancer?

- Studies suggest that immune suppression (steroids, etc.) for adverse immune reactions ameliorates the side effects but does not reverse the anti-tumor effect of immune checkpoint blockers.

Weber et al, ASCO 2015, Abstr 9018

Questions?

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Efficacy and safety of PD-1 blockade in metastatic uveal melanoma

Tsai KK, Shoushtari AN, Munhoz RR, Eroglu Z, Piulats JM, Ott PA, Johnson DM, Hwang J, Daud AI, Sosman J, Carvajal RD, Chmielowski B, Postow MA, Weber JS, Sullivan RJ, Algazi AP

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented By Katy Tsai at 2016 ASCO Annual Meeting

Methods

- Retrospective series of 58 patients with stage IV UM across 9 academic centers
- Treated with PD-1 or PD-L1 antibodies between 2009 and 2015
- Evaluable for response = eligible for analysis
- Investigator-adjudicated review

Treatment responses (RECIST v1.1)

Best overall response	n (%) N=56
Complete response	0
Partial response	2 (3.6)
Stable disease >= 6 months	5 (8.9)*
Progressive disease	48 (85.7)

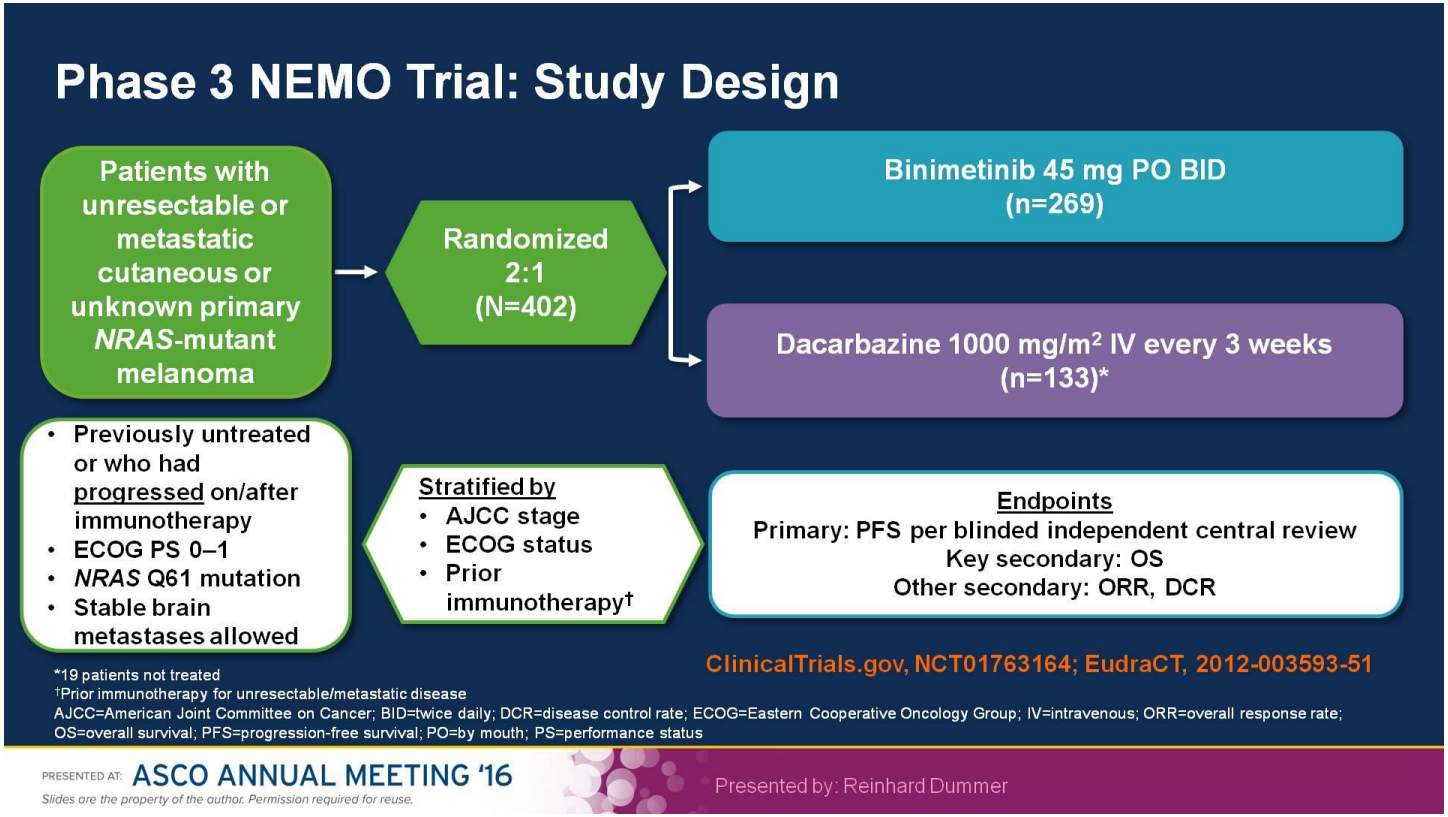
* 1 patient lost to follow-up with stable disease at 5 months

Results of NEMO: A Phase 3 Trial of Binimetinib (BINI) vs Dacarbazine (DTIC) in *NRAS*-Mutant Cutaneous Melanoma

Reinhard Dummer, Dirk Schadendorf, Paolo A. Ascierto, Ana Arance, Caroline Dutriaux, Michele Maio, Piotr Rutkowski, Michele Del Vecchio, Ralf Gutzmer, Mario Mandala, Luc Thomas, Ernesto Wasserman, James Ford, Marine Weill, Andres Sirulnik, Valentine Jehl, Viviana Bozón, Georgina V. Long, Keith Flaherty

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented By Reinhard Dummer at 2016 ASCO Annual Meeting



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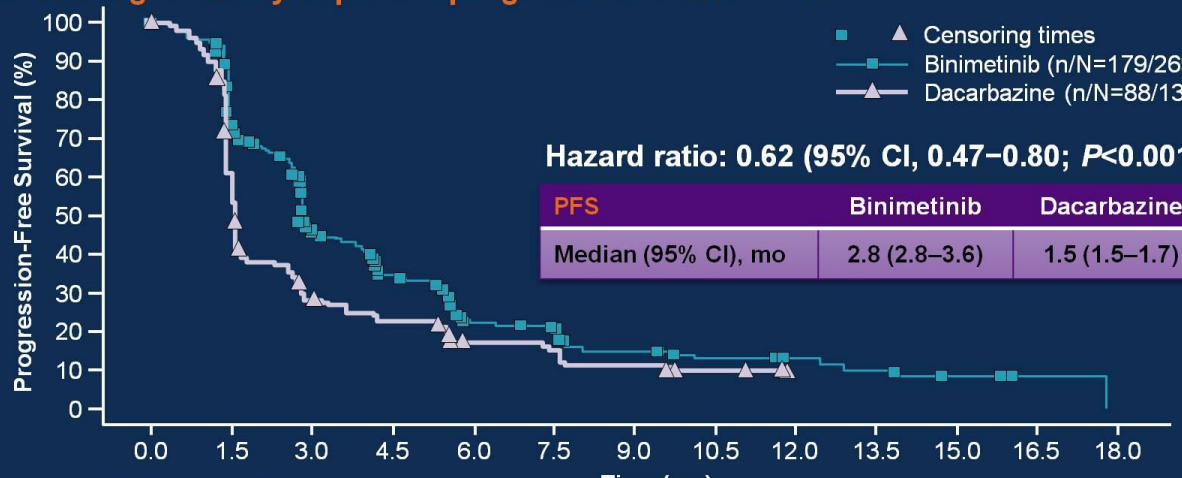
Progression-Free Survival

Binimetinib significantly improves progression-free survival



Hazard ratio: 0.62 (95% CI, 0.47–0.80; *P*<0.001)

PFS	Binimetinib	Dacarbazine
Median (95% CI), mo	2.8 (2.8–3.6)	1.5 (1.5–1.7)

Number still at risk

Time (mo)	0.0	1.5	3.0	4.5	6.0	7.5	9.0	10.5	12.0	13.5	15.0	16.5	18.0
Binimetinib	269	175	90	56	30	25	15	11	9	7	4	1	0
Dacarbazine	133	56	27	21	9	8	6	3	0	0	0	0	0

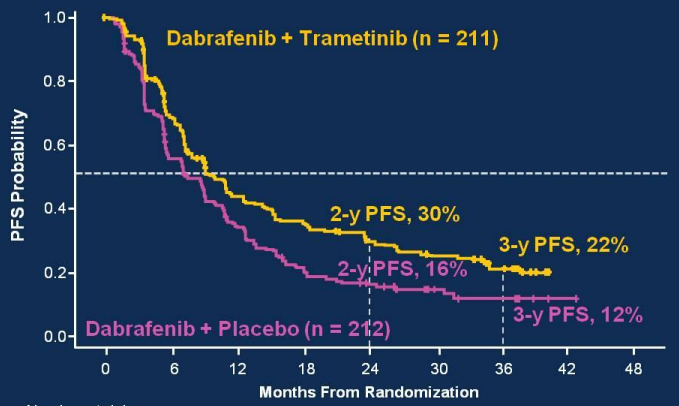
Stratified log-rank test and stratified Cox model using strata defined by AJCC stage, prior line immunotherapy, and ECOG performance status
AJCC=American Joint Committee on Cancer; ECOG=Eastern Cooperative Oncology Group; PFS=progression-free survival

Presented By Reinhard Dummer at 2016 ASCO Annual Meeting

COMBI-d: PFS and OS[a]

58% of D+T patients alive at 3 years still on D+T

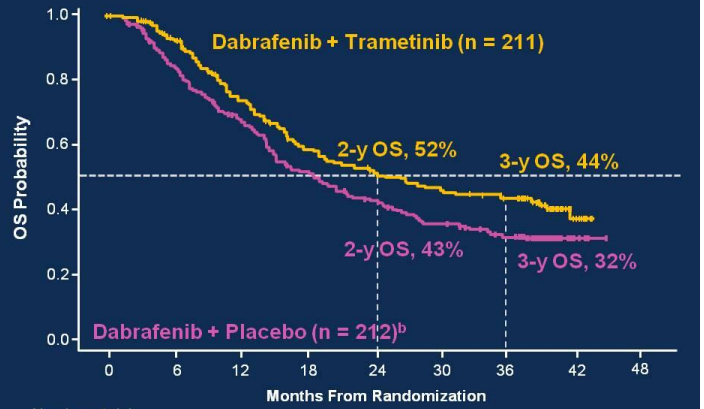
Progression-Free Survival



Number at risk

D+T	211	137	84	69	54	45	31	0	
D+Pbo	212	110	67	41	29	11	7	1	0

Overall Survival



Number at risk

D+T	211	187	143	111	96	86	76	13	0
D+Pbo	212	175	138	104	84	69	57	7	0

[a] Intent-to-treat population; [b] Dabrafenib + placebo includes 26 patients who crossed over to combination arm; +, censored.

Presented By Keith Flaherty at 2016 ASCO Annual Meeting

COMBI-d: Post-progression Systemic Therapy

Post-progression Systemic Therapy	Dabrafenib + Trametinib (n = 209)	Dabrafenib + Placebo (n = 211)
Any post-study anticancer therapy, n (%)	101 (48)	130 (62)
Subsequent anticancer therapy, n (%)		
Immunotherapy	57 (27)	73 (35)
Ipilimumab	41 (19)	65 (31)
Nivolumab	7 (3)	6 (3)
Pembrolizumab	13 (6)	14 (7)
Radiotherapy	51 (24)	58 (27)
Chemotherapy	37 (18)	50 (24)
Small-molecule targeted therapy	21 (10)	33 (16)
Biological	8 (4)	10 (5)