Immunotherapy for Melanoma

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Conflicts of Interest

Bristol-Myers Squibb:
-Research support
-Participated in an advisory council
-Honorarium

Amgen:
-Participated in an advisory council

Caladrius:
-Participated in an advisory council

Merck:
-Honorarium

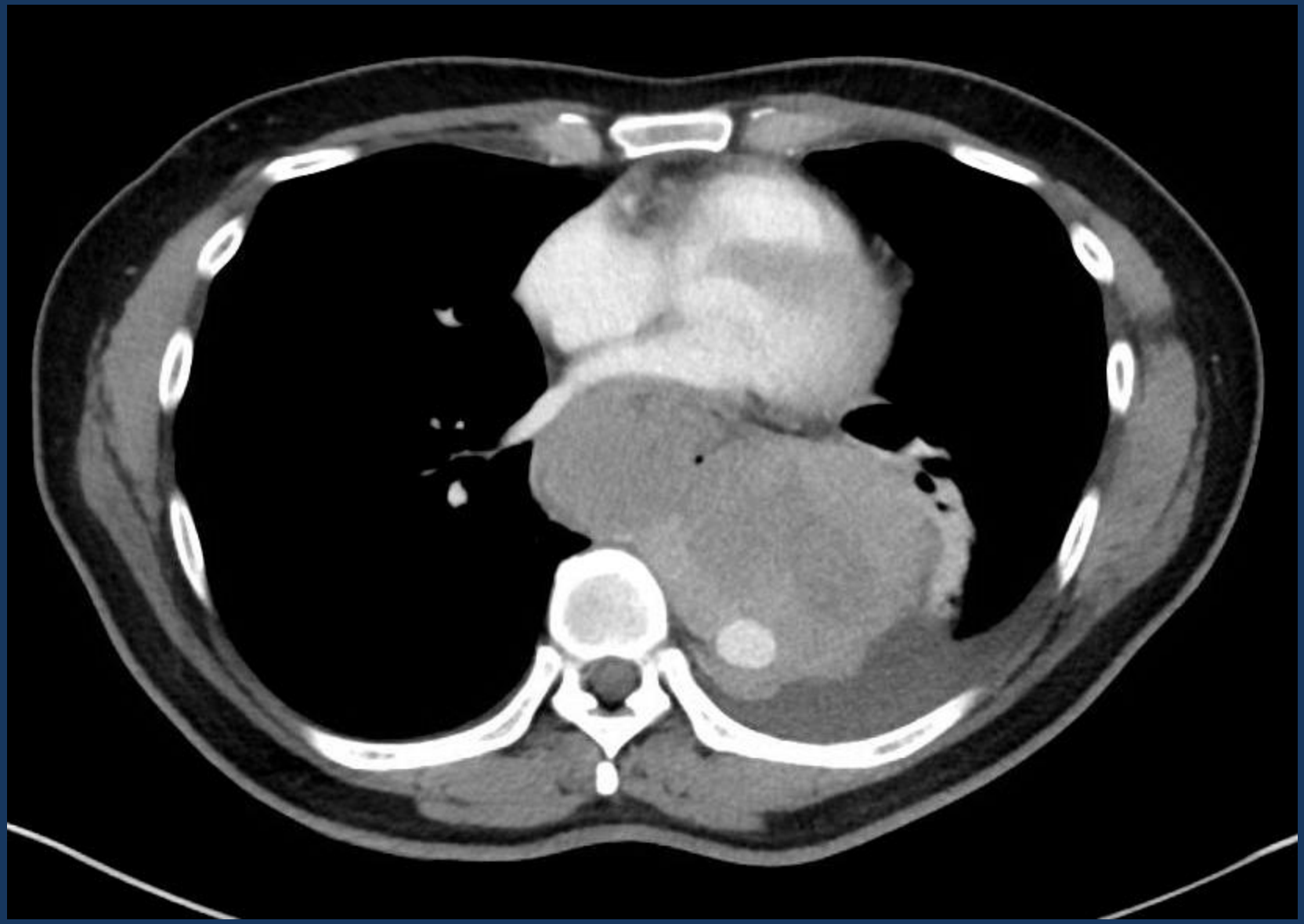
I will not address any non-FDA approved treatments.

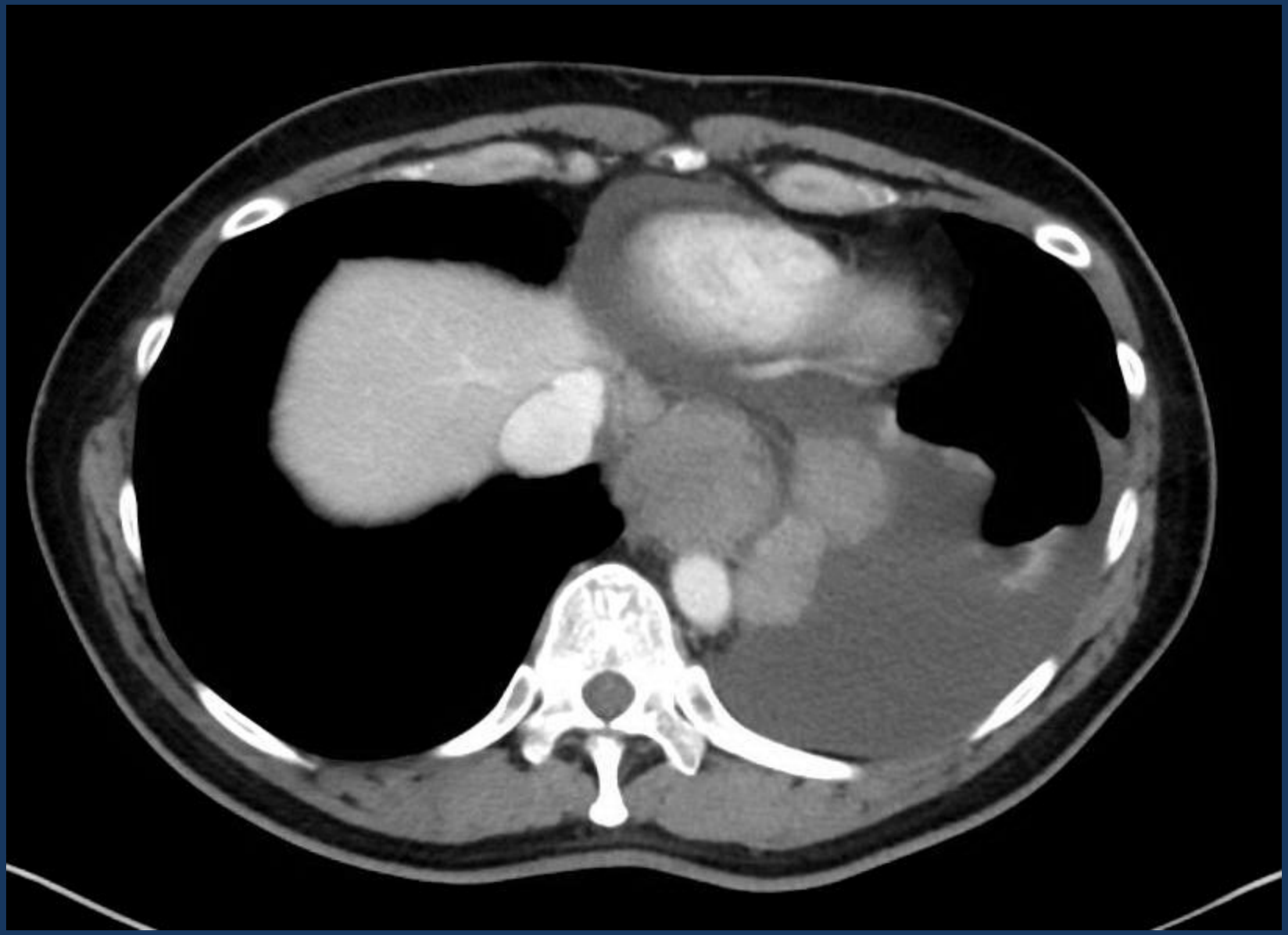
Case Presentation

52 year old otherwise healthy man with dysphagia and weight loss.

An EGD reveals BRAF wildtype esophageal melanoma.

A CT scan of his chest, abdomen, and pelvis was performed.





What is the best initial treatment option for a patient with BRAF wildtype melanoma?

Radiotherapy?
Chemotherapy?
Immunotherapy?
BRAF + MEK targeted therapy?

Response rates to immunotherapy

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
ORR, % (95% CI)*	**57.6** (52.0–63.2)	**43.7** (38.1–49.3)	**19.0** (14.9–23.8)
Two-sided *P* value vs IPI	<0.001	<0.001	--
Best overall response — %			
Complete response	12.1	9.8	2.2
Partial response	45.5	33.9	16.8
Stable disease	13.1	10.4	21.9
Progressive disease	22.6	38.0	48.9
Unknown	6.7	7.9	10.2
Median duration of response, months (95% CI)	**NR** (20.5–NR)	**22.3** (20.7–NR)	**14.4** (8.3–NR)
Ongoing response among responders, %	**72.5**	**72.4**	**51.7**

*By RECIST v1.1. NR = not reached.

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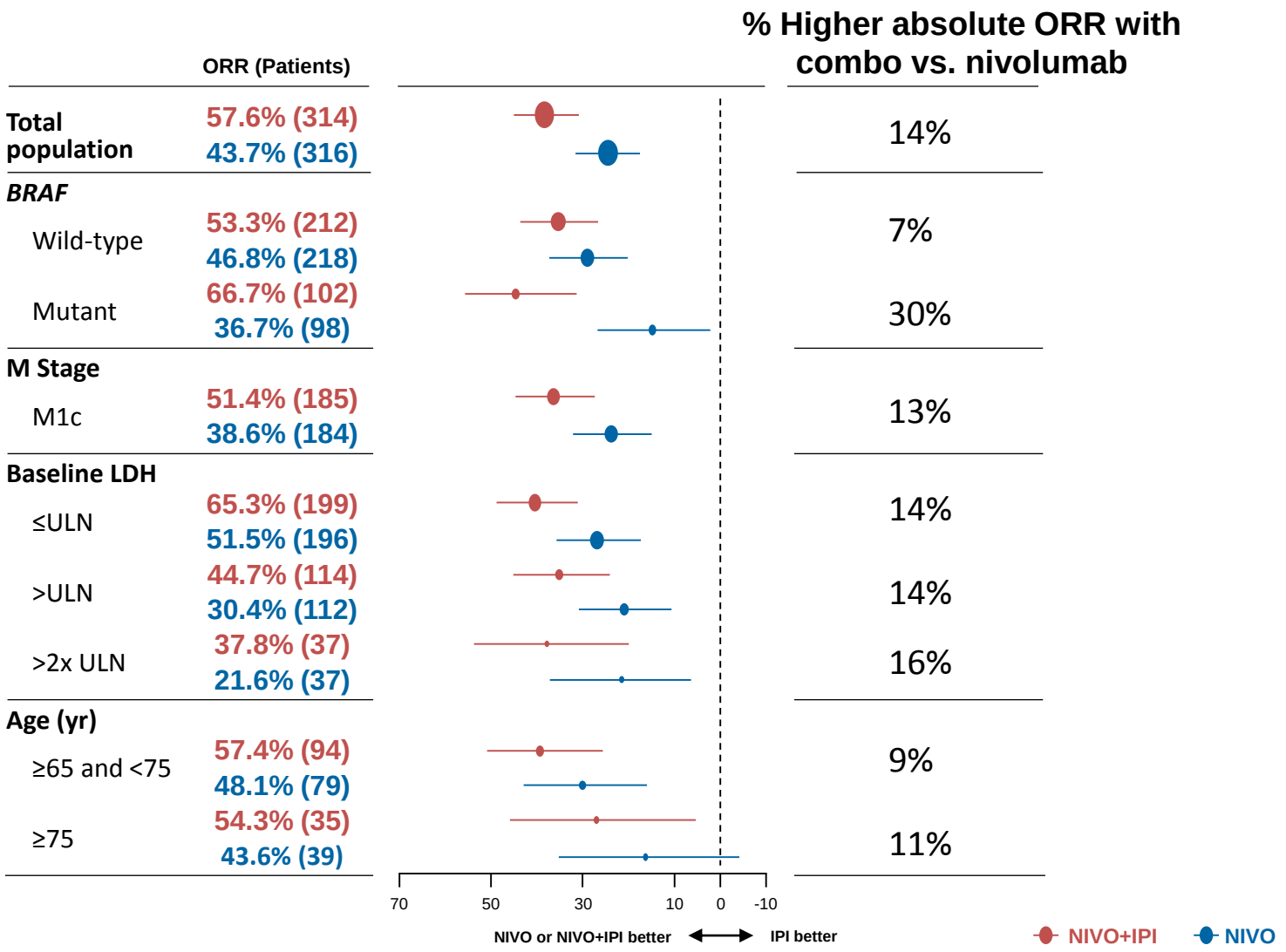
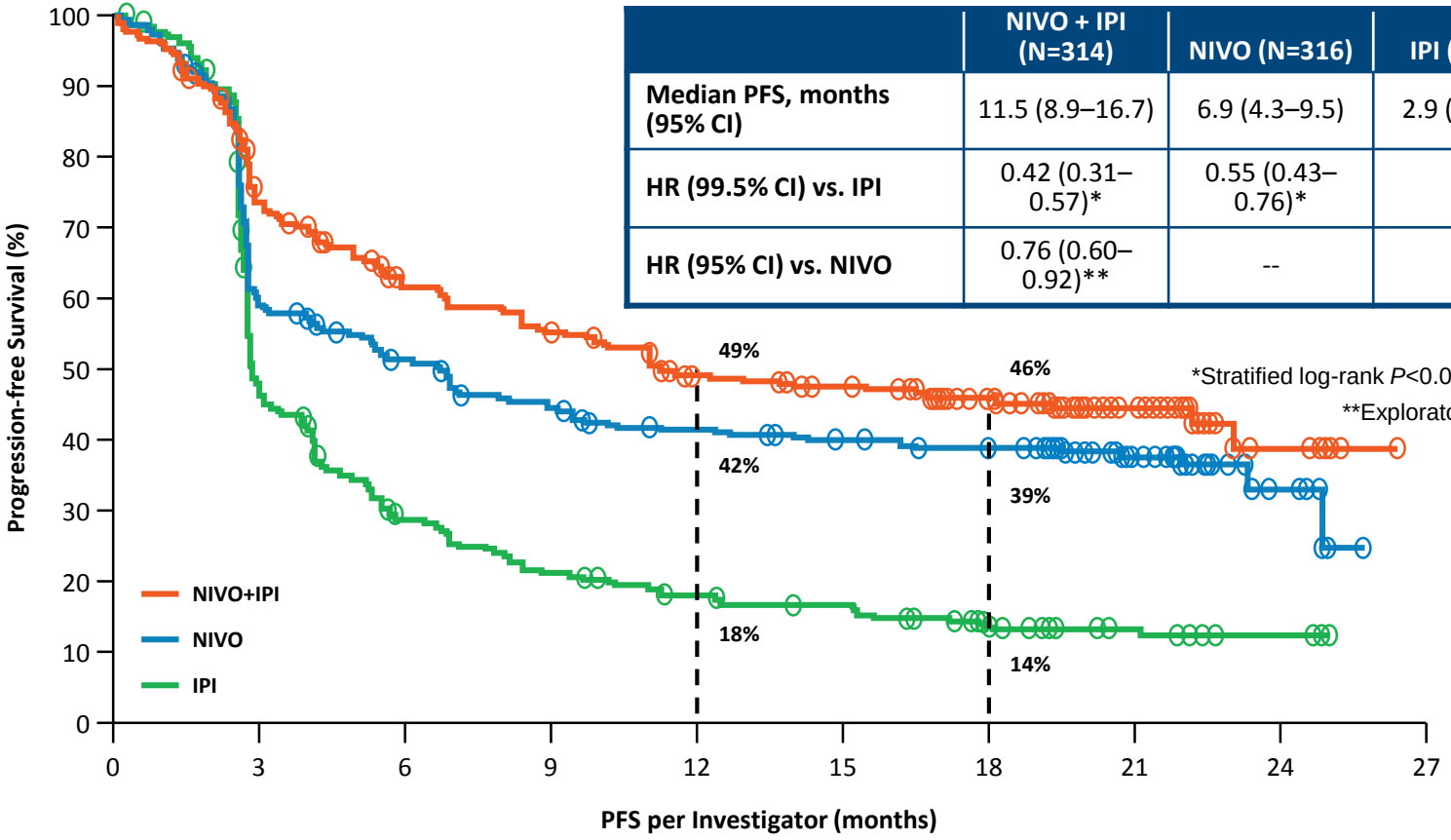
Wolchok et al. ASCO 2016

ORR in Patient Subgroups



Wolchok et al. ASCO 2016

Progression-Free Survival



	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)**	--	--

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

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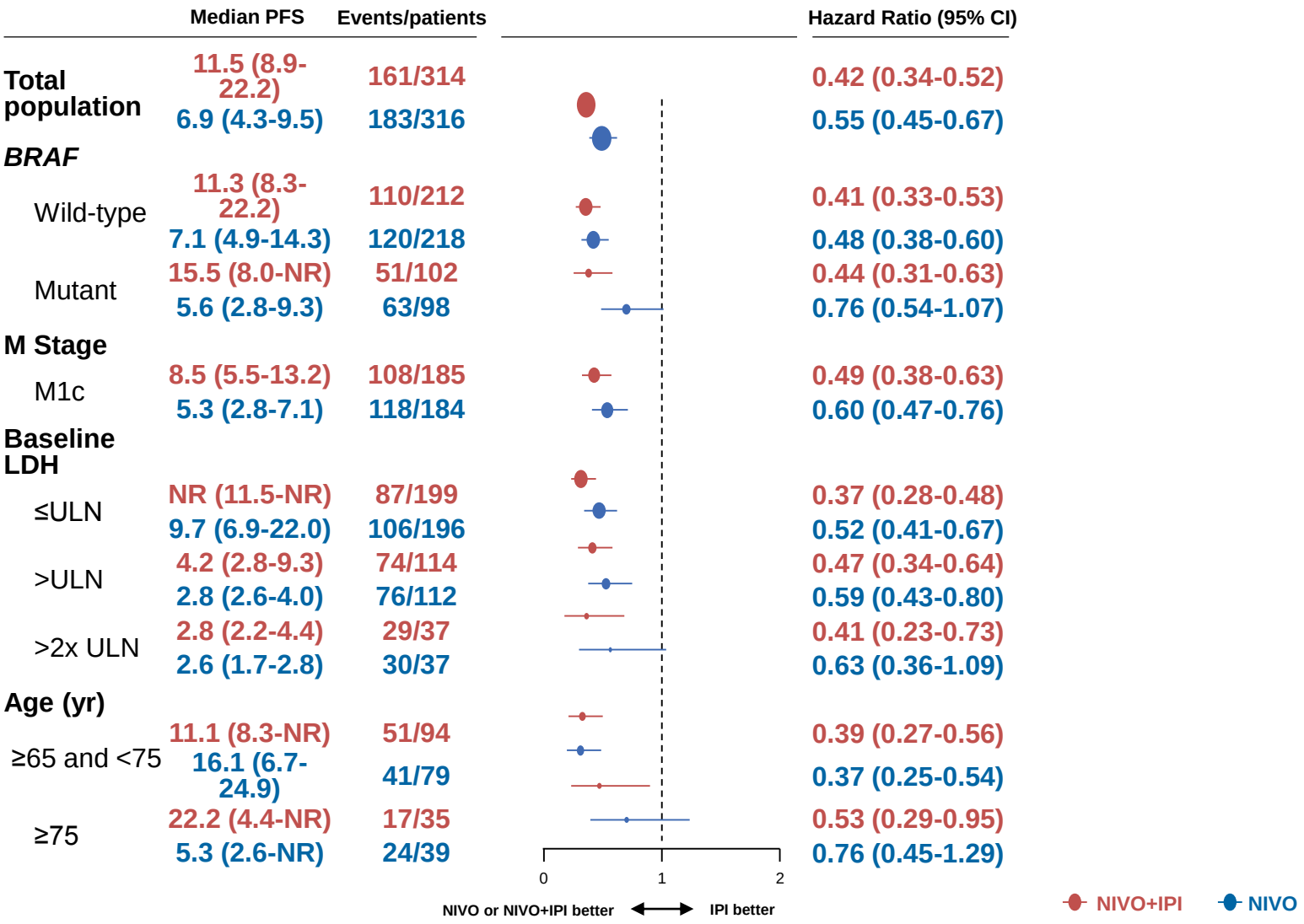
Progression Free Survival: Subgroups



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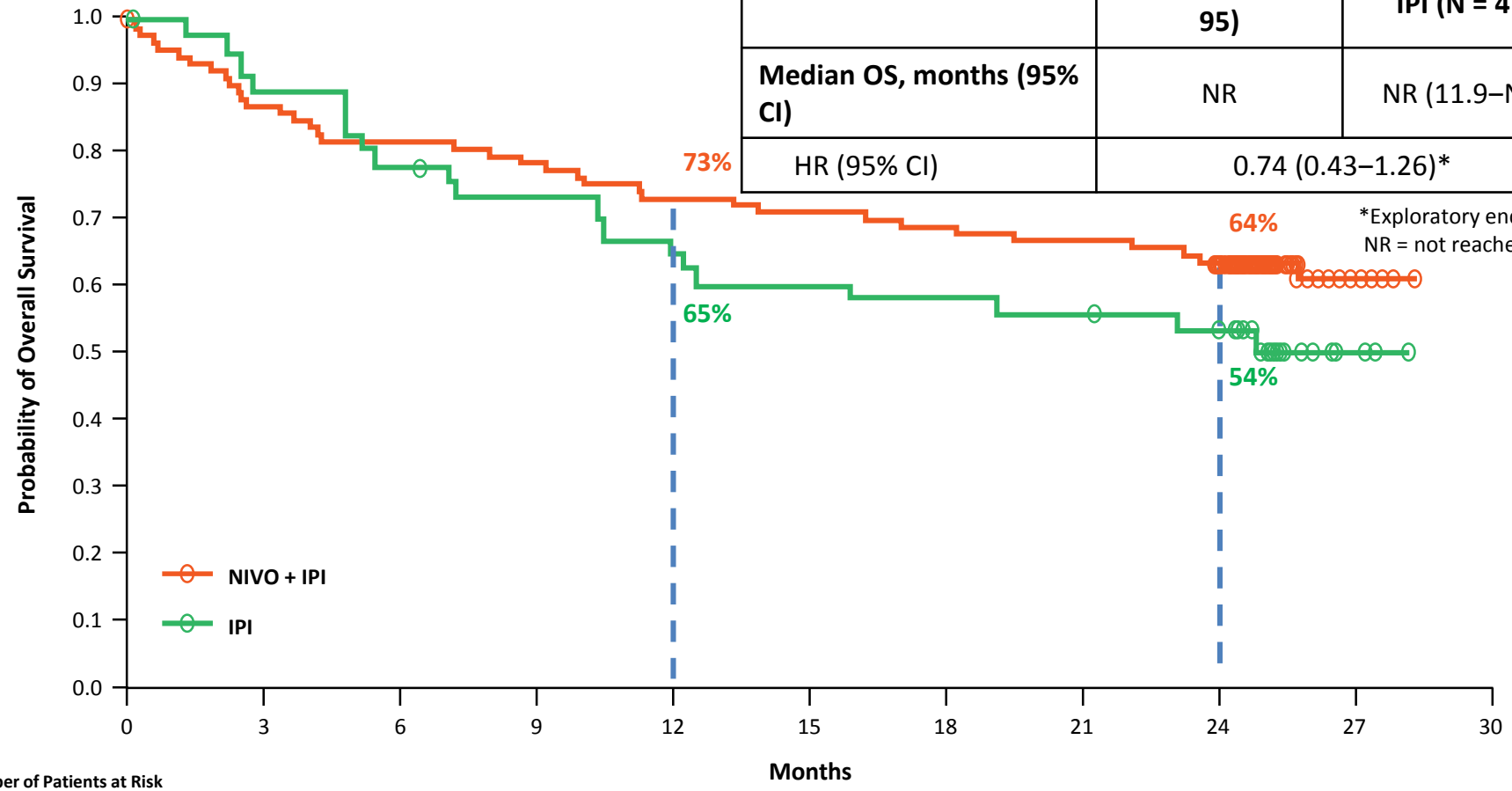
What about overall survival of combination?

Overall survival still immature from phase 3 study

Overall Survival at 2 Years of Follow-up (All Randomized Patients)

	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)*	



Number of Patients at Risk

NIVO+ IPI	95	82	77	74	69	67	65	63	57	6	0
IPI	47	41	36	33	29	27	26	25	22	3	0

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

Postow et al. AACR 2016

Combination has more side effects than either drug alone

- Updated safety information with 9 additional months of follow-up were consistent with the initial report

	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)

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Wolchok et al. ASCO 2016

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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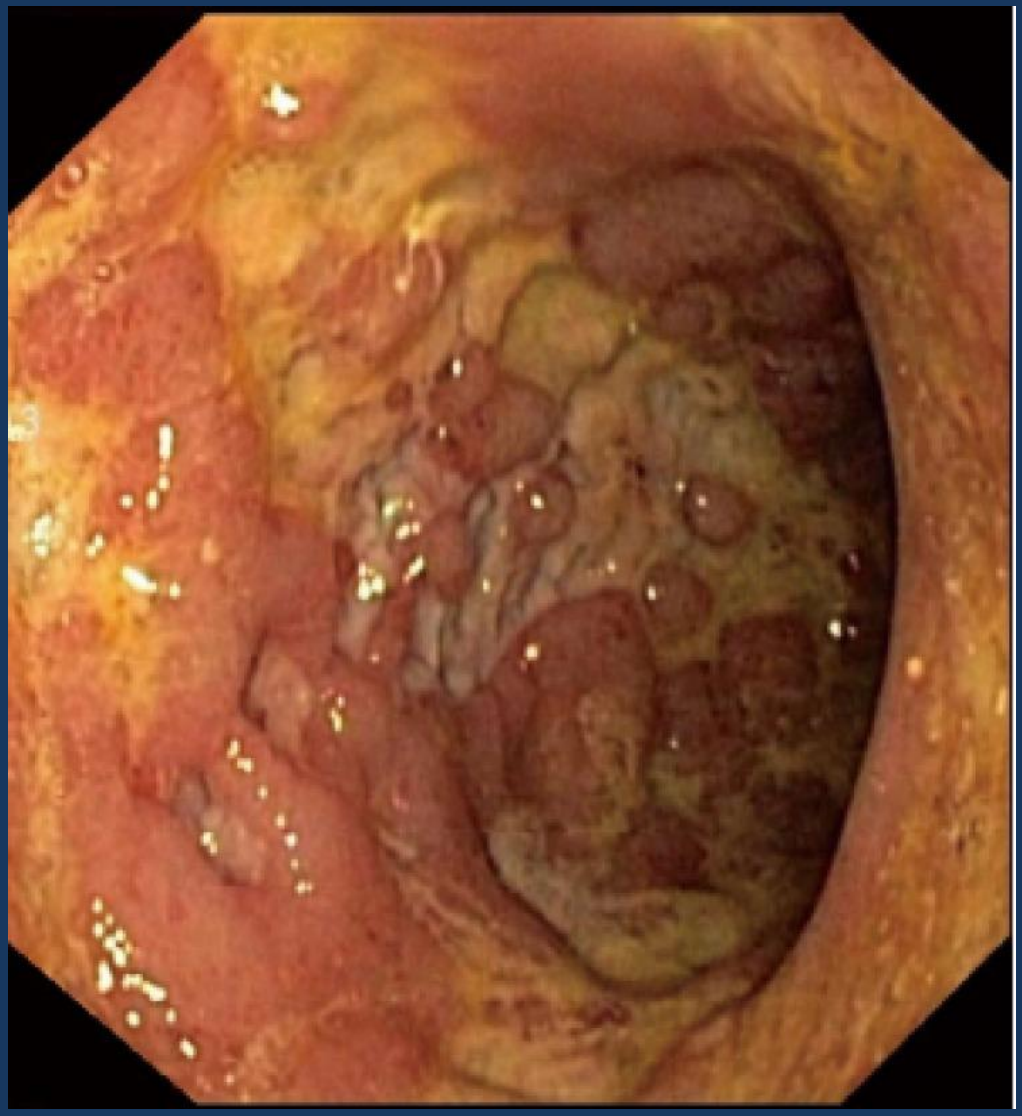
Wolchok et al. ASCO 2016

Diarrhea and Colitis

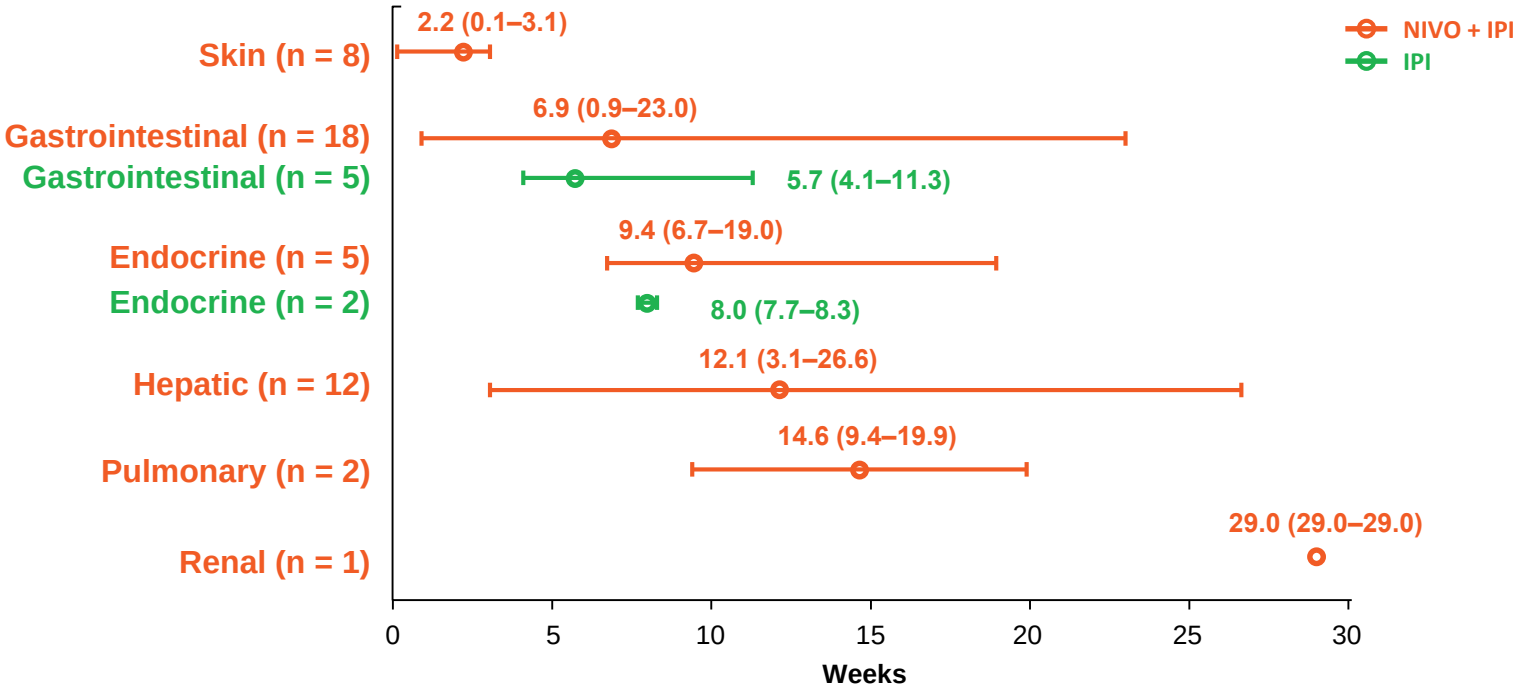


Slangen et al., *World J Gastrointest Pharmacol Ther,* 2013

He develops 6 watery, persistent stools per day. You recommend:

1. Holding off on steroids initially since it may affect the efficacy of immunotherapy
2. Starting oral steroids
3. Giving a dose of infliximab
4. Colonoscopy prior to starting steroids to ensure a proper diagnosis of immunotherapy colitis
5. Ciprofloxacin and flagyl

Time to Onset of Grade 3/4 Treatment-related Select AEs
Patients receiving nivolumab + ipilimumab or ipilimumab alone



- Most grade 3/4 treatment-related select AEs occurred during the combination phase

Circles represent median; bars signify ranges

Hodi et al. ASCO 2015

Diarrhea/Colitis Management

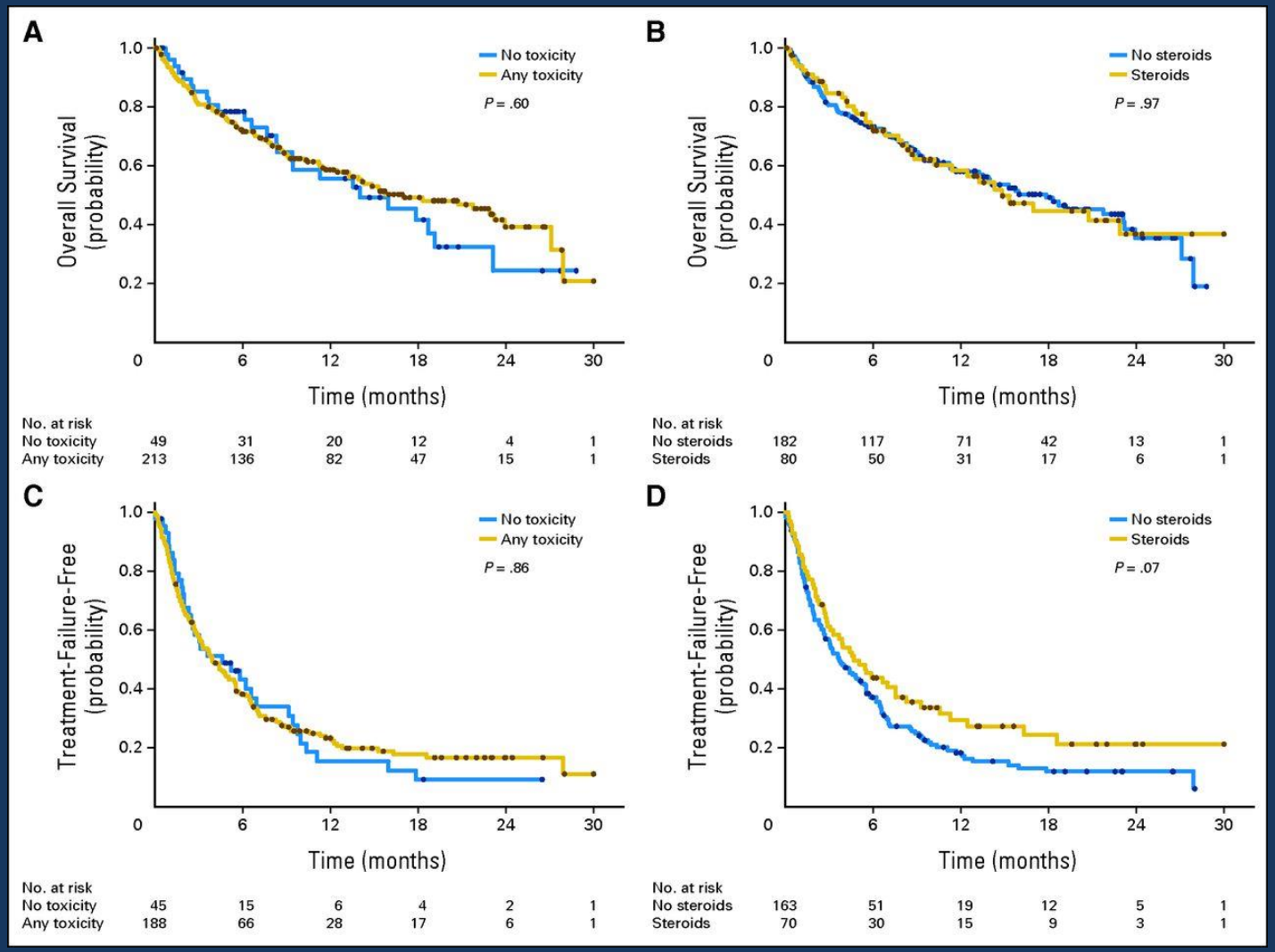
1. Stools < 4X baseline: imodium, budesonide

2. Stools < 7X baseline: 1mg/kg of prednisone

3. Stools > 7X baseline or refractory to oral steroids:
    1. Hospitalize for IV solumedrol 1-2mg/kg
    2. Consider infliximab 5mg/kg even before hospitalization
    3. Consider CT scan and colonoscopy, but these rarely help

Taper steroids slowly over at least several weeks and consider opportunistic infectious prophylaxis

Patients who receive steroids for side effects have similar outcomes (ipilimumab)



Horvat et al. *J Clin Oncol* 2015

Immunosuppression does not seem to affect nivolumab outcomes

	NIVO monotherapy with IM N = 139	NIVO monotherapy without IM N = 437
ORR, n (%), [95% CI]	40 (28.8) [21.4–37.1]	141 (32.3) [27.9–36.9]
BOR, n (%)		
CR	7 (5.0)	22 (5.0)
PR	33 (23.7)	119 (27.2)
SD	31 (22.3)	102 (23.3)
PD	63 (45.3)	173 (39.6)
Not evaluable	5 (3.6)	21 (4.8)
Median duration of response, mo (95% CI)	NR (9.3–NR)	22.0 (22.0–NR)
Median time to response, mo (range)	2.1 (1.2–8.8)	2.1 (1.4–9.2)

- ORR was 28.8% in pts who had received immunosuppression and was 32.3% in pts who had not received immunosuppression
- Time to response was similar in both subgroups (median of 2.1 months), and median duration of response was 22 months in those who did not receive immunosuppression and had not been reached in pts who received systemic immunosuppression

Weber et al. ASCO 2015

Patients who stop combination due to side effects have high ORR

Table 2. Treatment exposure (NIVO+IPI patients)

	All randomized (N = 94)[a]		Discontinued due to AEs (n = 35)	
	NIVO	IPI	NIVO	IPI
Doses received, median (range)	4 (1-45)	4 (1-4)	3 (1-45)	3 (1-4)
Number of doses of NIVO received, n/N (%) of patients				
1	11/94 (12)		3/35 (9)	
2	16/94 (17)		9/35 (26)	
3	12/94 (13)		6/35 (17)	
4	17/94 (18)		9/35 (26)	
>4 (includes maintenance phase)	38/94 (40)		8/35 (23)	

[a]95 patients were randomized, but 1 patient was not treated

- As reported previously,[1] the NIVO+IPI and IPI groups (all randomized group) had ORRs of 59% vs 11% and CRs of 22% vs 0%, respectively
- Similar response rates were observed in the subgroup of patients who discontinued NIVO+IPI due to AEs (**Table 3**), with a 69% median reduction in tumor burden (**Figure 2**)

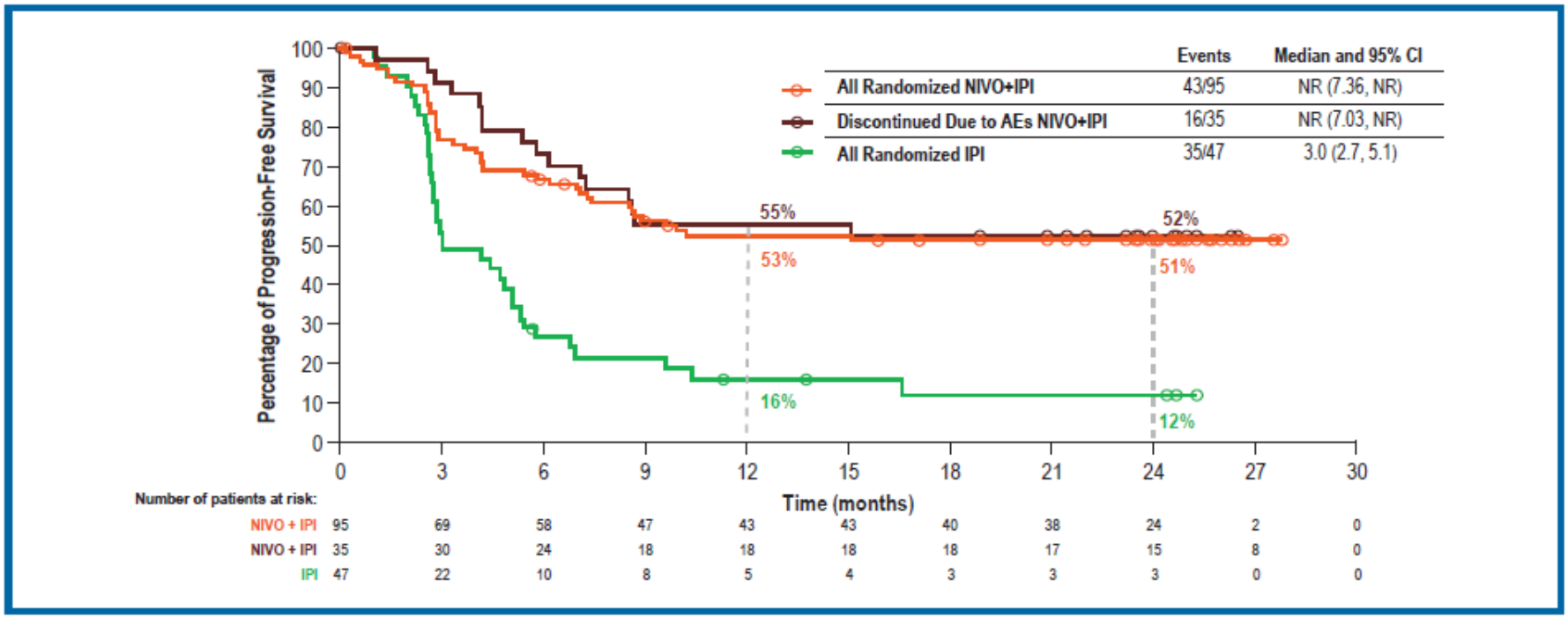
Table 3. Response to treatment (NIVO+IPI patients)

	All randomized (N = 95)	Discontinued due to AEs (n = 35)
ORR, % (95% CI)	59 (48-69)	66 (48-81)
Best overall response, %		
Complete response	22	20
Partial response	37	46
Stable disease	13	17
Progressive disease	16	9
Could not be determined	13	9

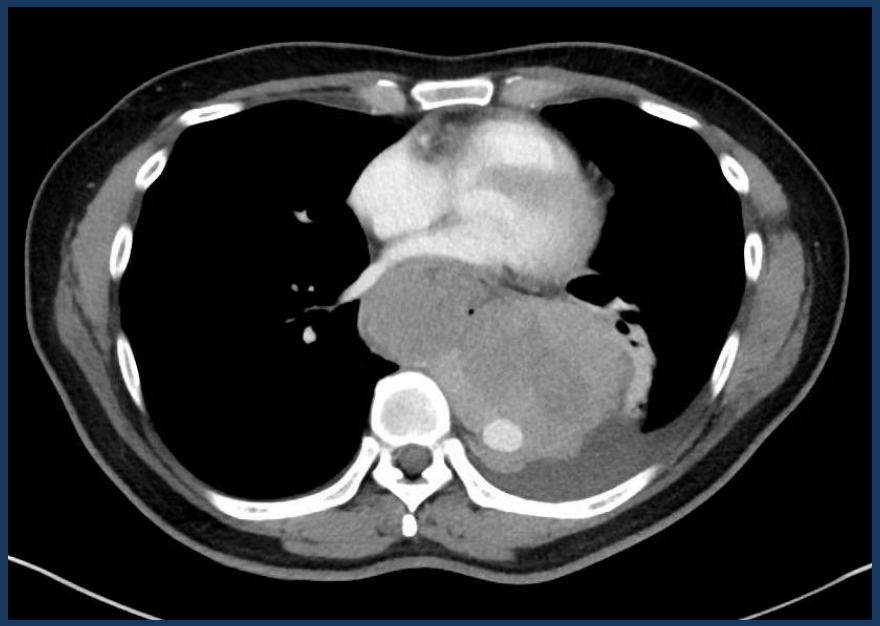
Hodi et al. ASCO 2016

Patients who stopped combination due to side effects have excellent PFS

Figure 4B. Progression-free survival at 2 years of follow-up



Hodi et al. ASCO 2016



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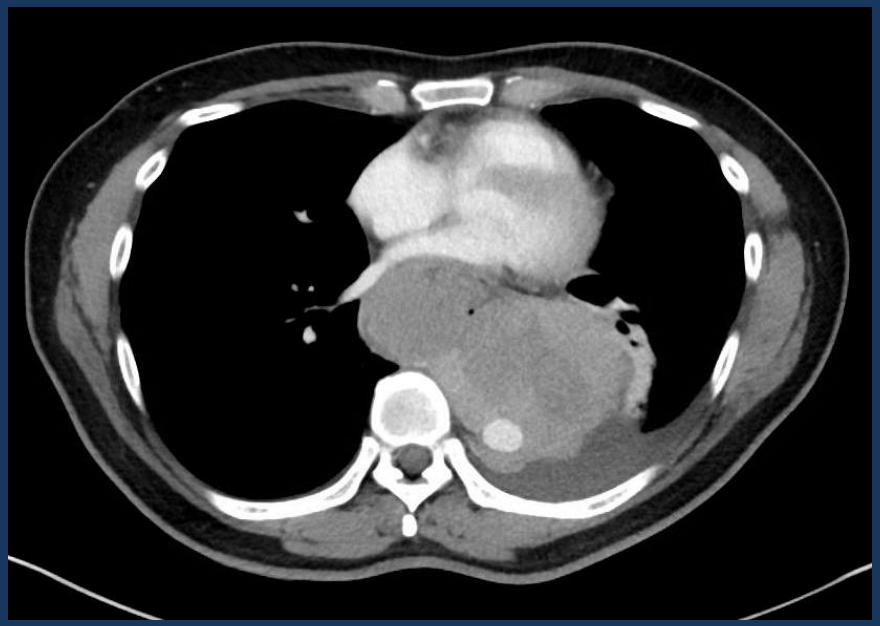

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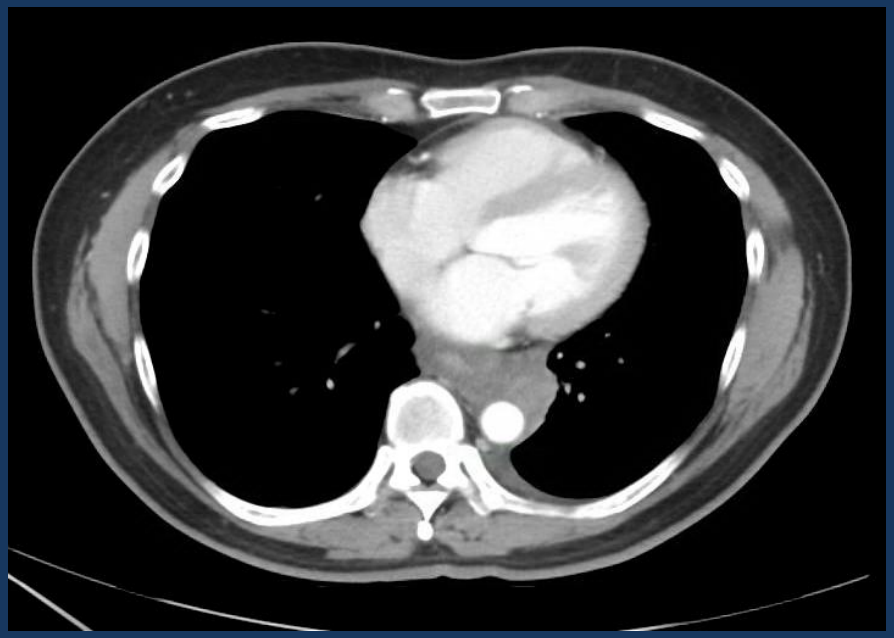

May 2015

Factors into deciding single agent PD-1 vs. combination immunotherapy

1. Assessment of comorbidities?
2. Any contraindication to steroids or immunosuppression?
3. Reliability and communication between patient and care team?
4. Pace and disease burden of cancer?
5. Cannot use PD-L1 for treatment selection

Future questions

1. Since ~68% of patients with melanoma who discontinued due to toxicity had a response, how much is needed?

2. What is the role of maintenance PD-1 after combination immunotherapy? When should PD-1 be stopped?

3. What other combinations can include PD-1?

Thank you from our team!!