Melanoma Immunotherapy SITC 2017 SF

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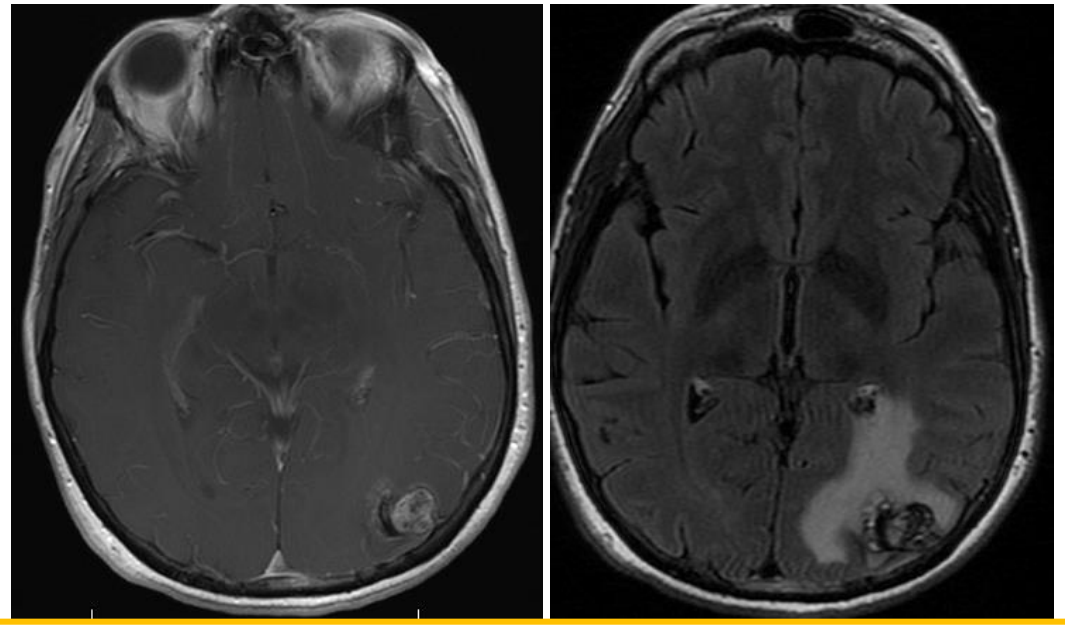
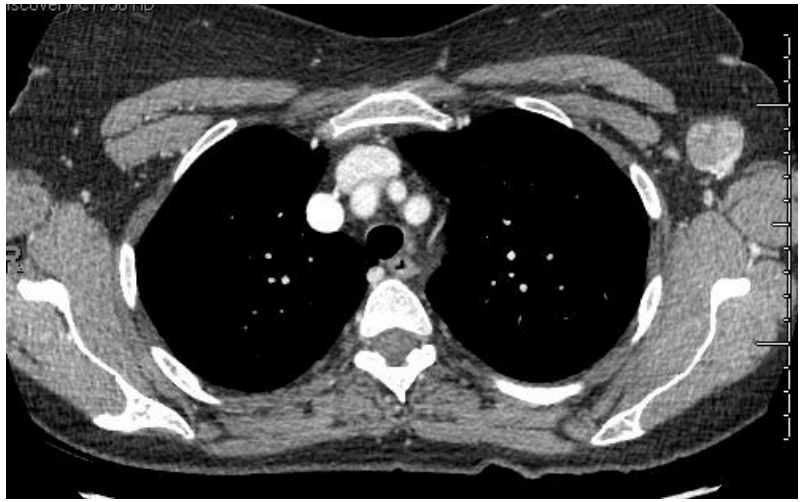
UCSF

History

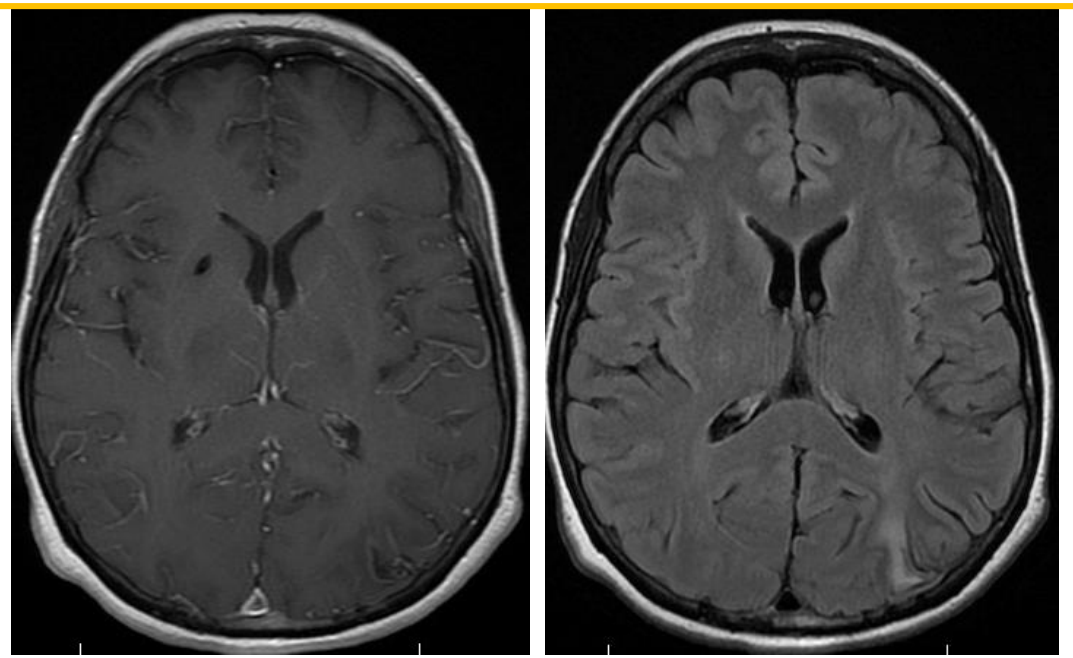
- 52 year old female no previous history of melanoma
- Catering business
- No significant PMHx
- Seizure
- MRI scan showed a solitary left occipital met
- CT scan showed a left axillary mass 4 cm in size
- BRAF wt

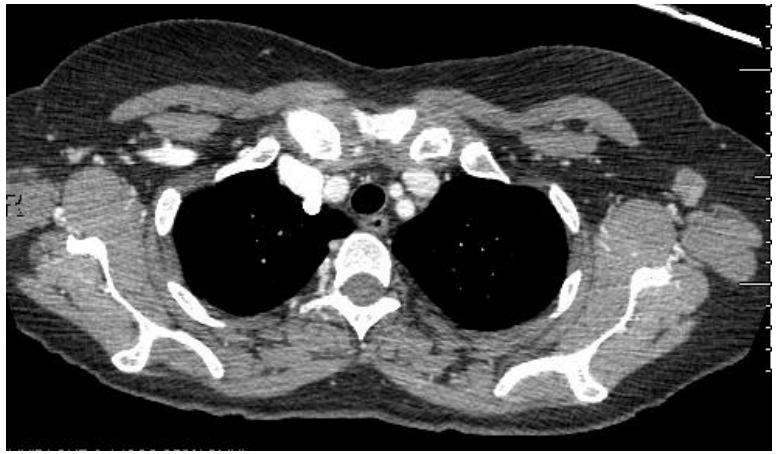
7/10/15
Pre-Ipi/Nivo





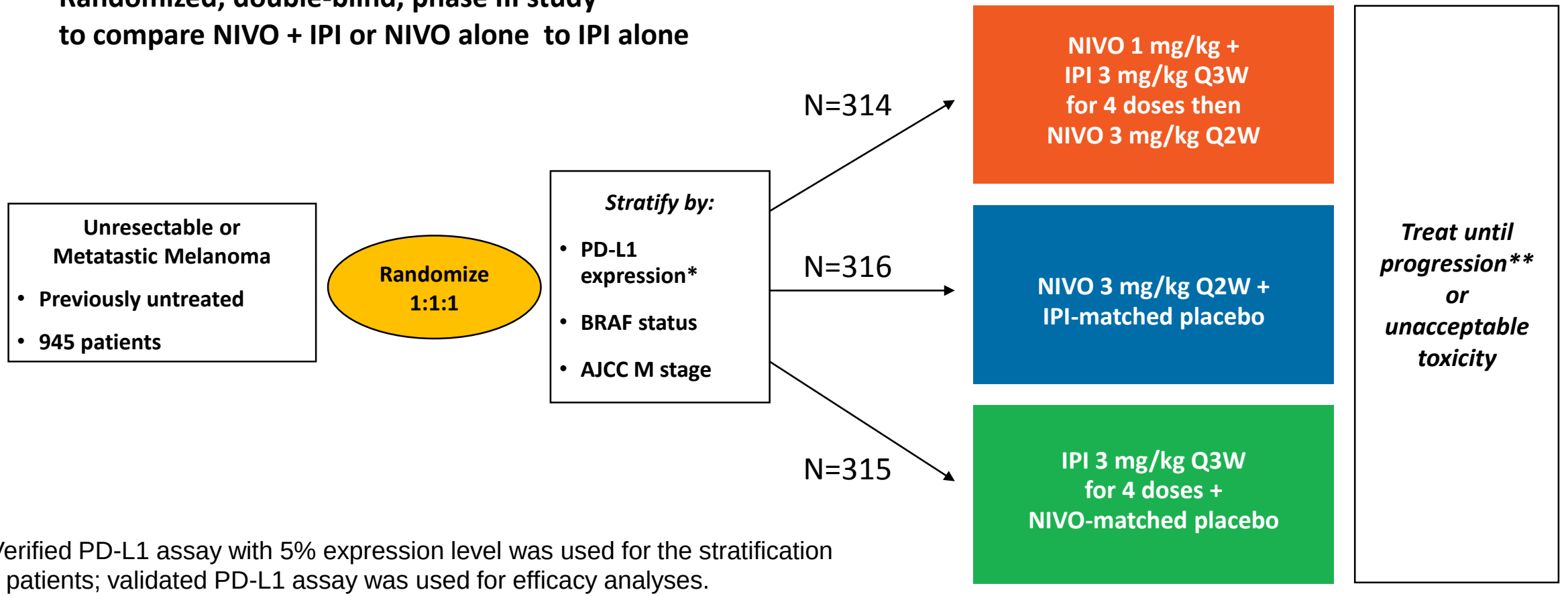
8/20/15
s/p 2-Ipi/Nivo





CA209-067: Study Design

Randomized, double-blind, phase III study
to compare NIVO + IPI or NIVO alone to IPI alone

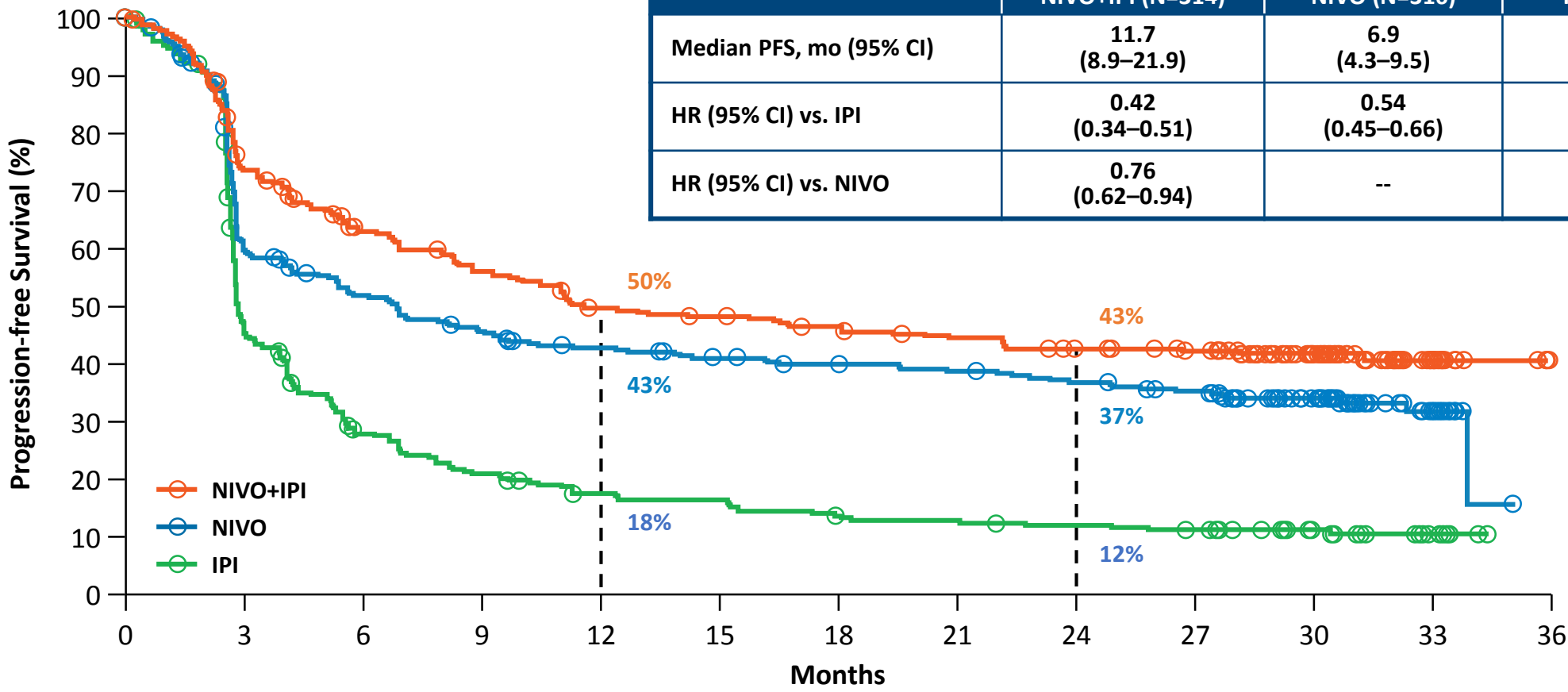


*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

Updated Progression-Free Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, mo (95% CI)	11.7 (8.9–21.9)	6.9 (4.3–9.5)	2.9 (2.8–3.2)
HR (95% CI) vs. IPI	0.42 (0.34–0.51)	0.54 (0.45–0.66)	--
HR (95% CI) vs. NIVO	0.76 (0.62–0.94)	--	--



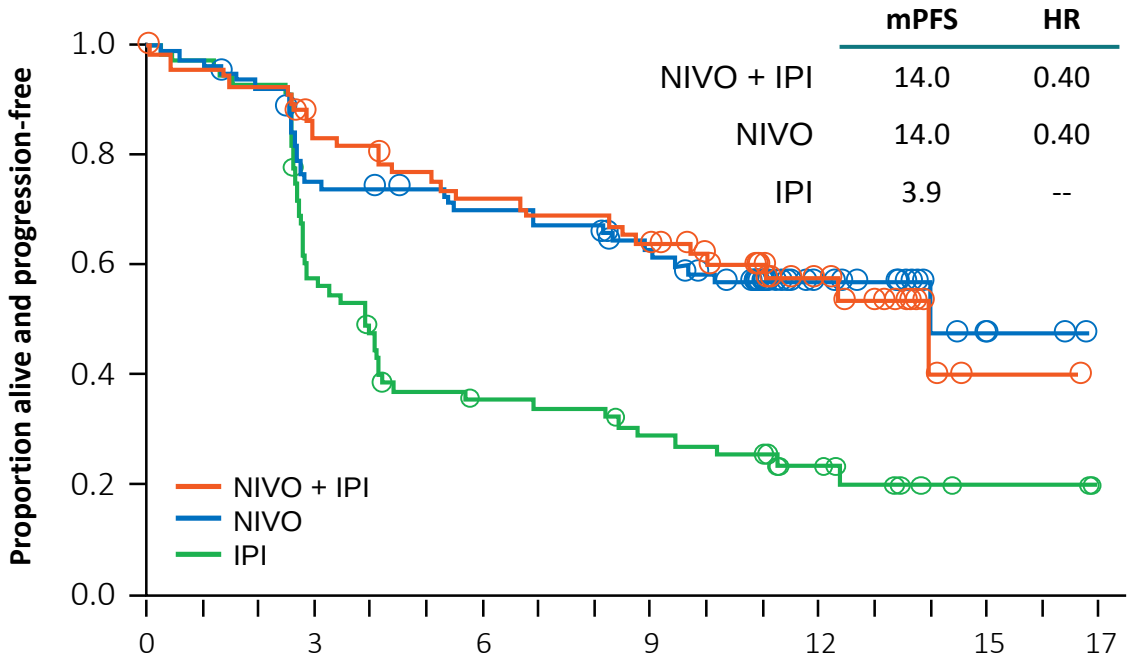
Patients at risk:

NIVO+ IPI	314	218	176	156	137	132	125	118	110	104	71	16	0
NIVO	316	178	151	132	120	112	107	103	97	88	62	16	0
IPI	315	136	77	58	46	43	35	33	30	27	16	5	0

Database lock: Sept 13, 2016, minimum f/u of 28 months

PFS by PD-L1 Expression Level (5%)

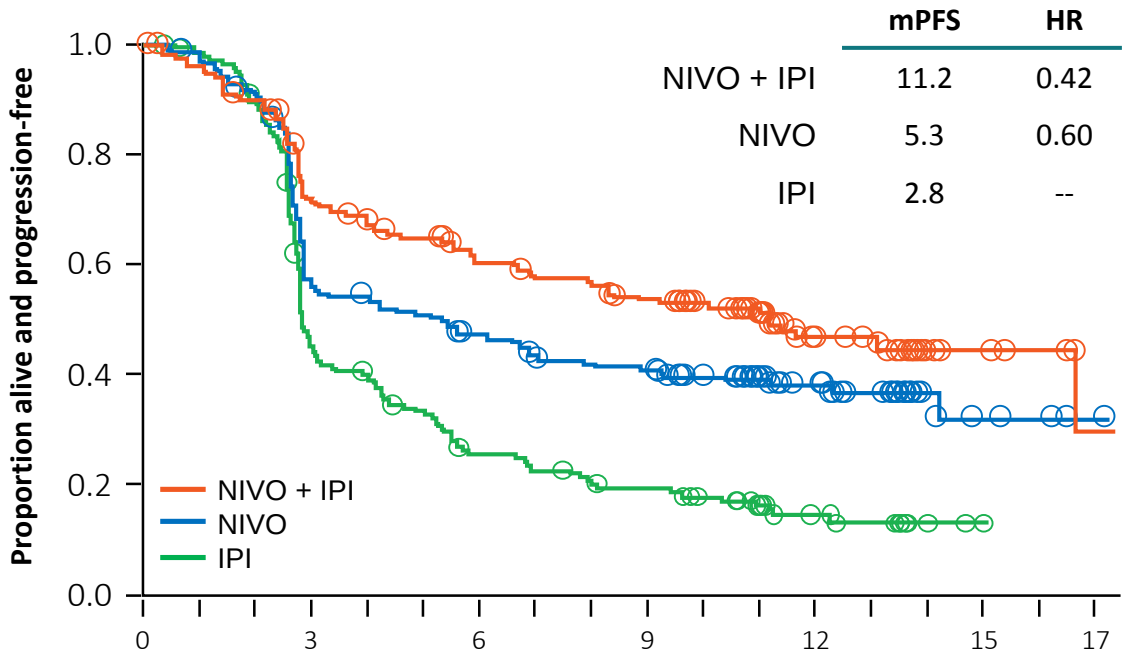
PD-L1 ≥5%*



	mPFS	HR
NIVO + IPI	14.0	0.40
NIVO	14.0	0.40
IPI	3.9	--

No. at Risk							
NIVO + IPI	68	53	44	39	16	1	0
NIVO	80	57	51	43	16	4	0
IPI	75	40	22	17	9	2	0

PD-L1 <5%*



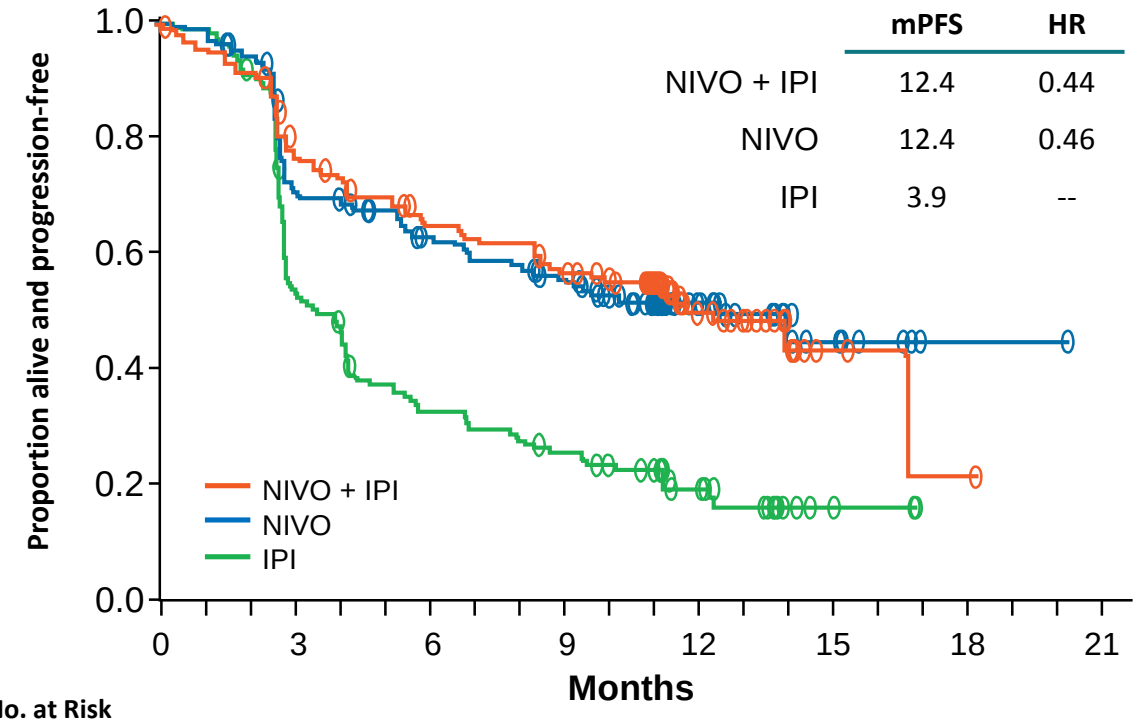
	mPFS	HR
NIVO + IPI	11.2	0.42
NIVO	5.3	0.60
IPI	2.8	--

No. at Risk							
NIVO + IPI	210	142	112	96	42	9	2
NIVO	208	108	88	74	31	5	2
IPI	202	82	44	31	12	1	–

*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

PFS by PD-L1 Expression Level (1%)

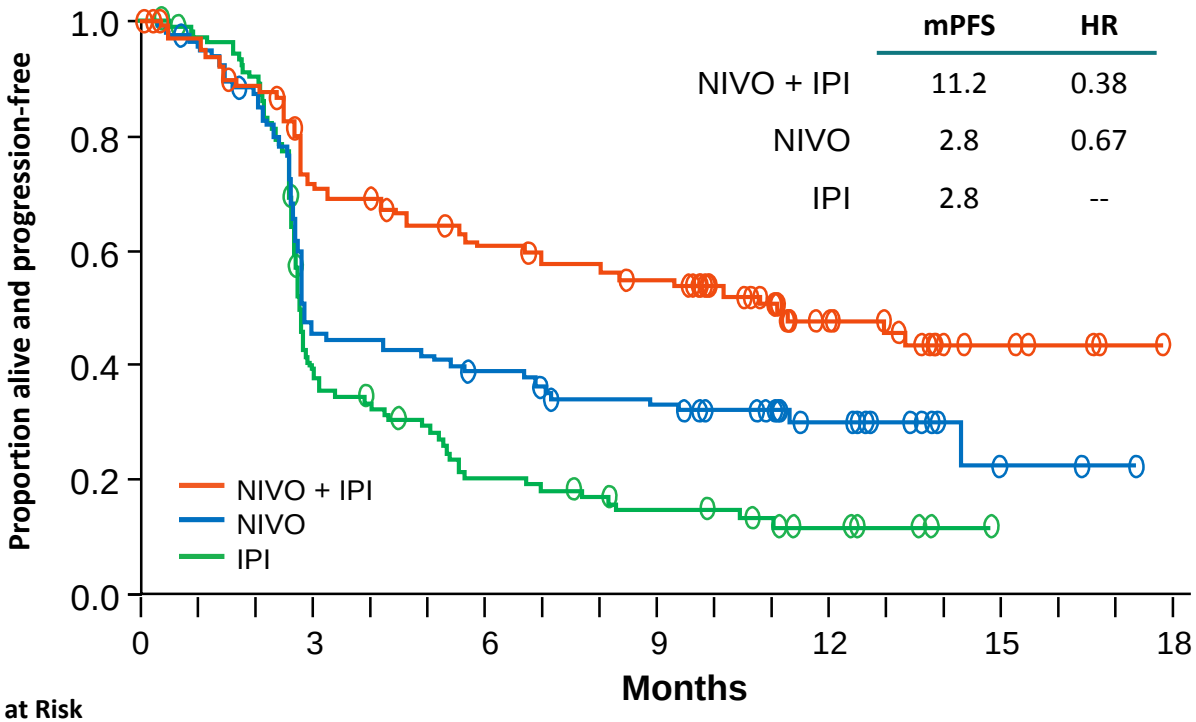
PD-L1 ≥1%*



	mPFS	HR
NIVO + IPI	12.4	0.44
NIVO	12.4	0.46
IPI	3.9	--

No. at Risk								
NIVO + IPI	155	113	91	78	32	4	1	
NIVO	171	115	97	83	34	7	1	0
IPI	164	83	47	36	16	3		

PD-L1 <1%*



	mPFS	HR
NIVO + IPI	11.2	0.38
NIVO	2.8	0.67
IPI	2.8	--

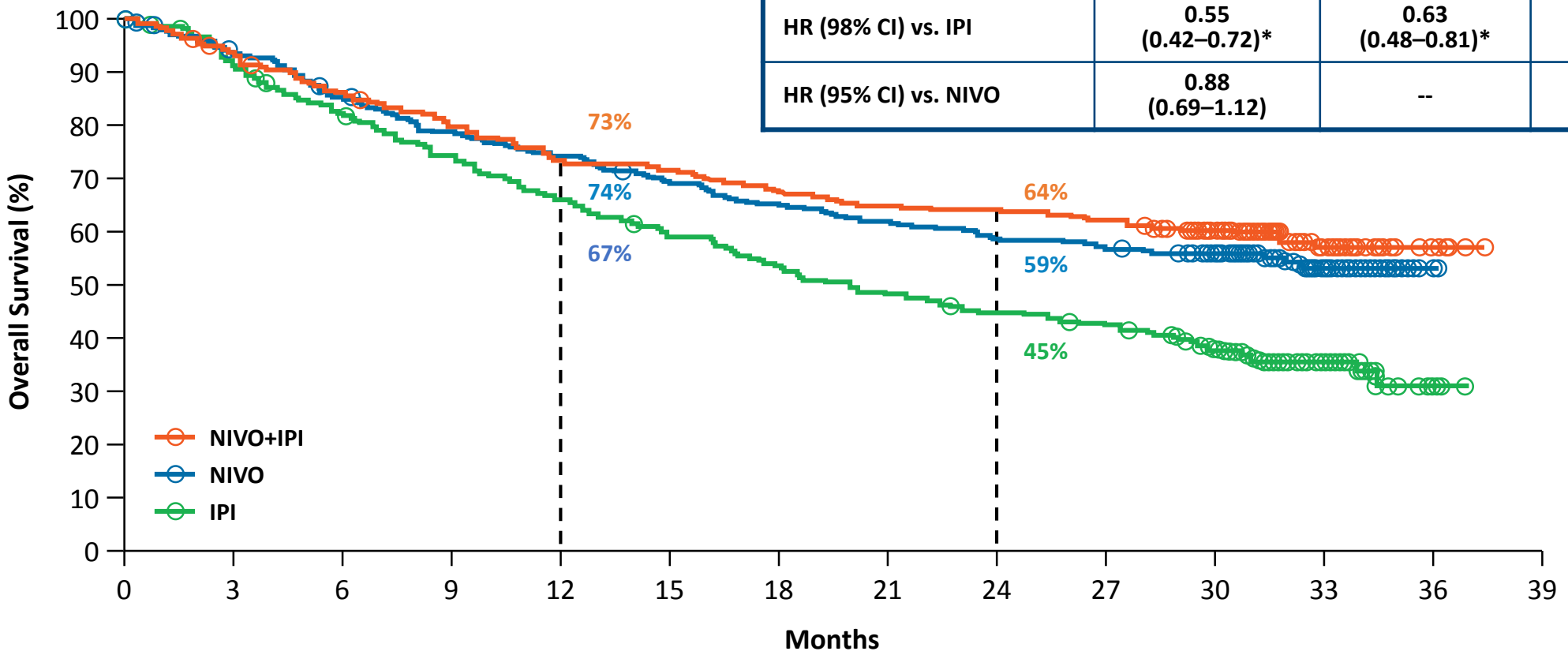
No. at Risk							
NIVO + IPI	123	82	65	57	26	6	0
NIVO	117	50	42	34	13	2	0
IPI	113	39	19	12	5	0	

*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

Overall Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, mo (95% CI)	NR	NR (29.1–NR)	20.0 (17.1–24.6)
HR (98% CI) vs. IPI	0.55 (0.42–0.72)*	0.63 (0.48–0.81)*	--
HR (95% CI) vs. NIVO	0.88 (0.69–1.12)	--	--

*P<0.0001



Patients at risk:

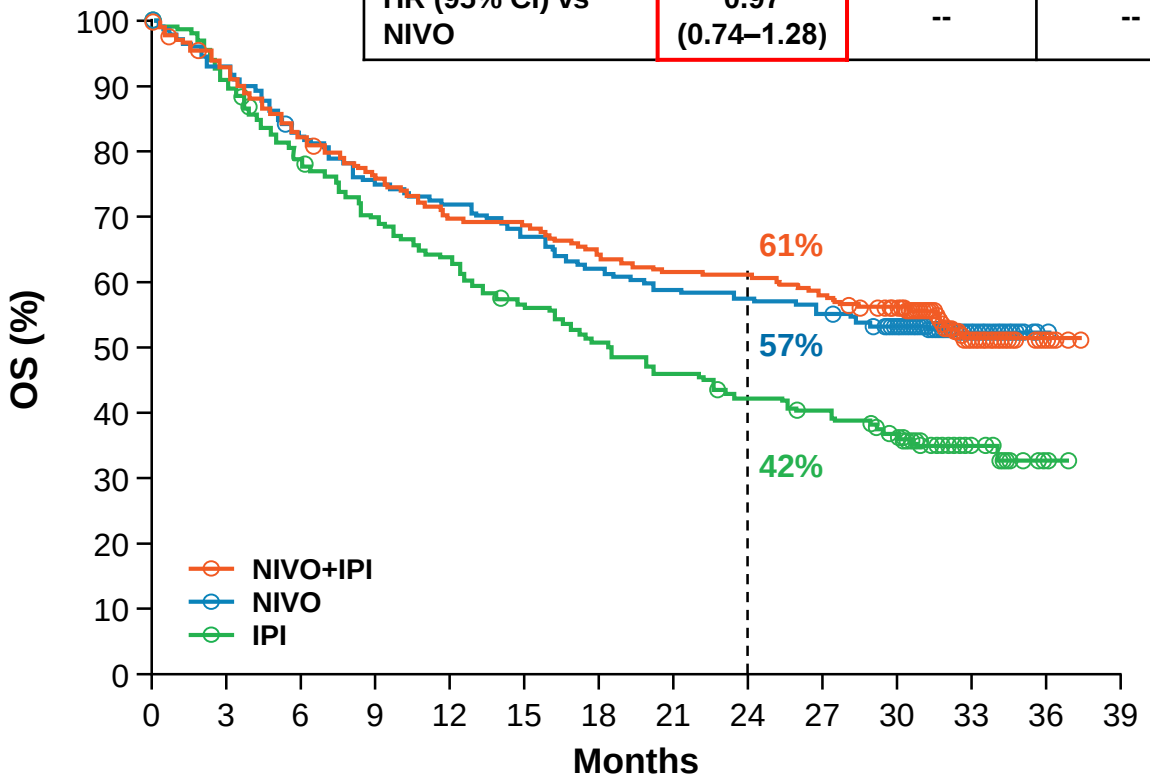
NIVO+IPI	314	292	265	247	226	221	209	200	198	192	170	49	7	0
NIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0
IPI	315	285	254	228	205	182	164	149	136	129	104	34	4	0

Database lock: Sept 13, 2016, minimum f/u of 28 months

OS in Patients with *BRAF* Wild-type and Mutant Tumors

BRAF Wild-type

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	NR (27.6–NA)	NR (25.8–NR)	18.5 (14.8–23.0)
HR (95% CI) vs NIVO	0.97 (0.74–1.28)	--	--

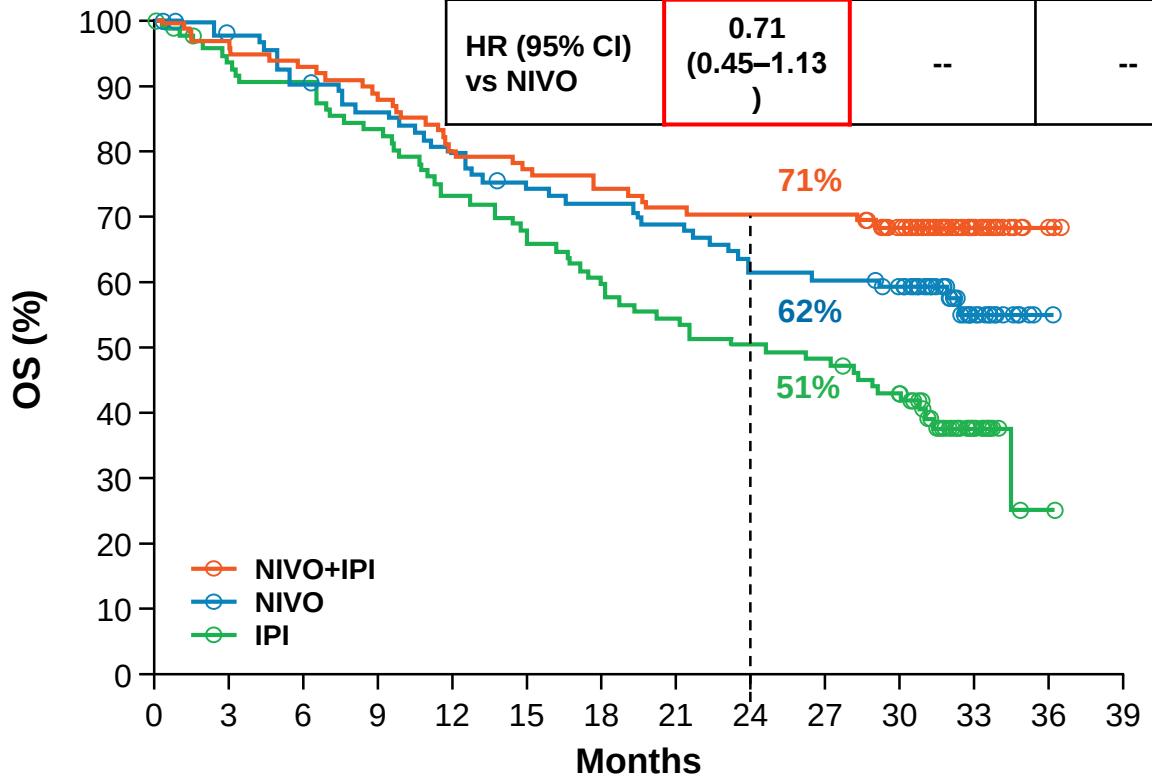


Patients at risk:

NIVO+IPI	212	194	170	157	144	142	133	127	126	120	108	31	5	0
NIVO	218	199	179	163	155	144	134	127	124	119	105	38	2	0
IPI	215	194	166	147	134	118	106	96	87	82	67	21	3	0

BRAF Mutant

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	NR	NR (26.4–NR)	24.6 (17.9–31.0)
HR (95% CI) vs NIVO	0.71 (0.45–1.13)	--	--



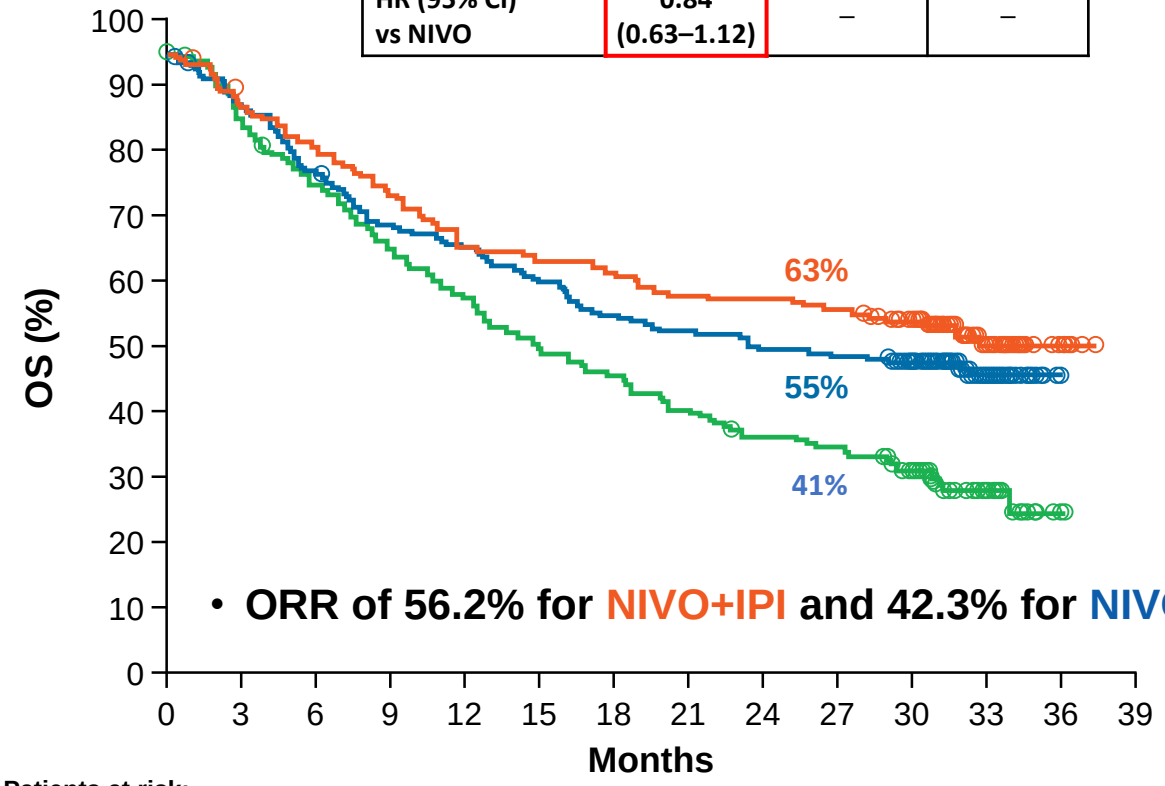
Patients at risk:

NIVO+IPI	102	98	95	90	82	79	76	73	72	72	62	18	2	0
NIVO	98	93	86	81	75	69	67	64	57	56	52	17	1	0
IPI	100	91	88	81	71	64	58	53	49	47	37	13	1	0

OS by Tumor PD-L1 Expression, 5% Cutoff

PD-L1 Expression Level <5%

	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR (31.8–NR)	NR (23.1–NR)	18.5 (13.7–22.5)
HR (95% CI) vs NIVO	0.84 (0.63–1.12)	–	–



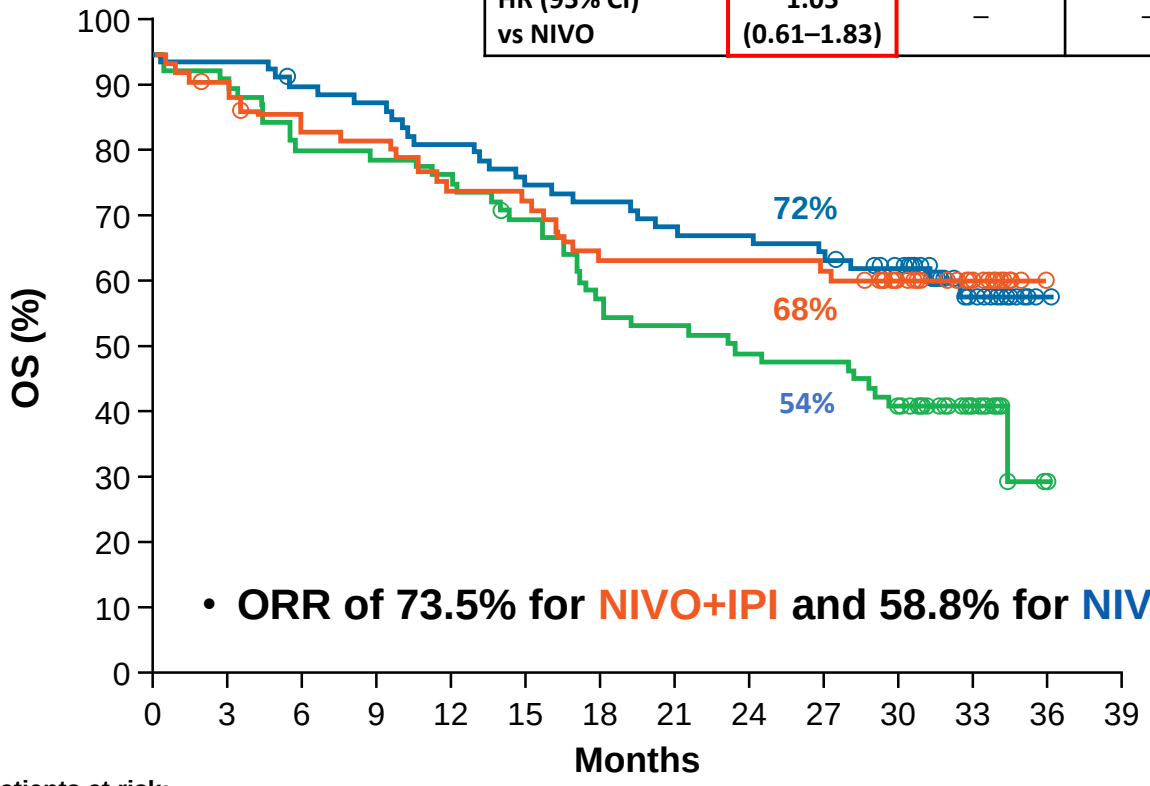
- ORR of 56.2% for NIVO+IPI and 42.3% for NIVO

Patients at risk:

NIVO+IPI	210	194	178	163	146	144	139	131	130	127	116	34	7	0
NIVO	208	189	169	151	144	133	123	118	112	110	99	34	2	0
IPI	202	179	158	140	125	108	100	90	81	78	63	18	2	0

PD-L1 Expression Level ≥5%

	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR	NR	28.9 (18.1–NR)
HR (95% CI) vs NIVO	1.05 (0.61–1.83)	–	–



- ORR of 73.5% for NIVO+IPI and 58.8% for NIVO

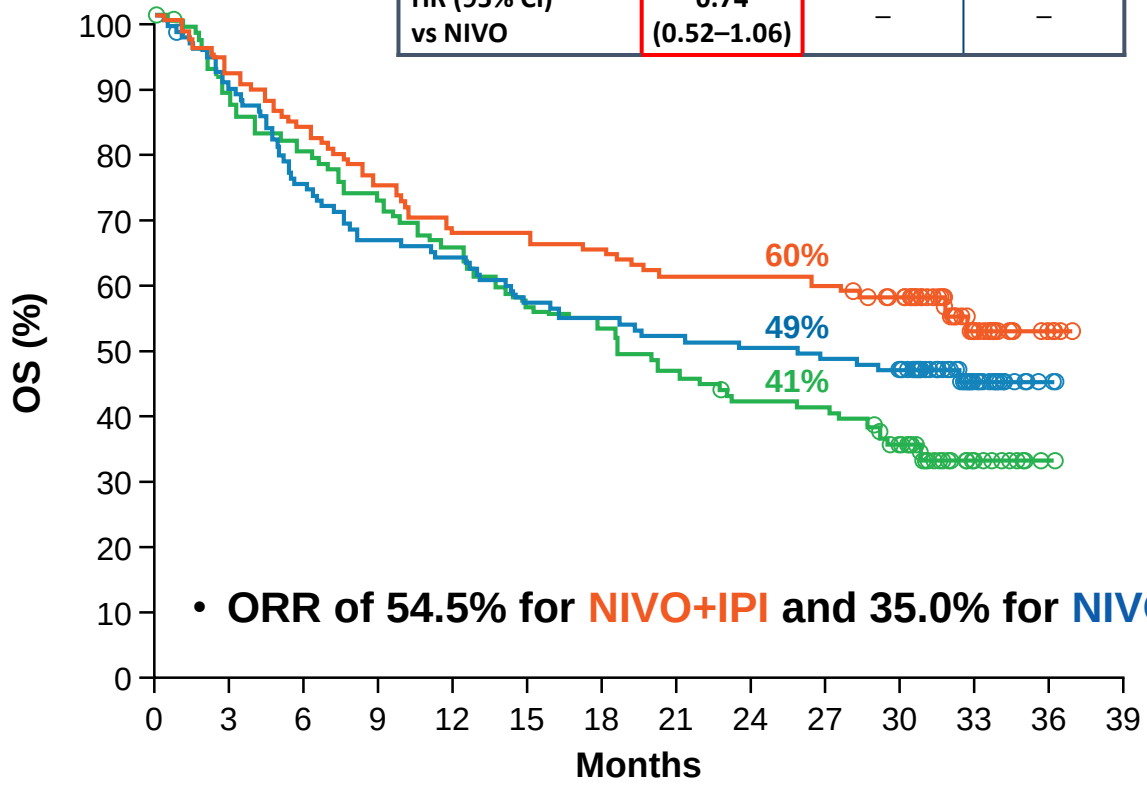
Patients at risk:

NIVO+IPI	68	63	56	55	52	50	45	45	45	44	35	11	0	0
NIVO	80	79	75	73	68	63	61	58	57	54	49	18	1	0
IPI	75	72	67	65	61	55	46	43	40	39	33	13	1	0

Similar Outcomes Were Observed at a 1% Cutoff

PD-L1 Expression Level <1%

<1% PD-L1	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR (26.5–NR)	23.5 (13.0–NR)	18.6 (13.7–23.2)
HR (95% CI) vs NIVO	0.74 (0.52–1.06)	–	–



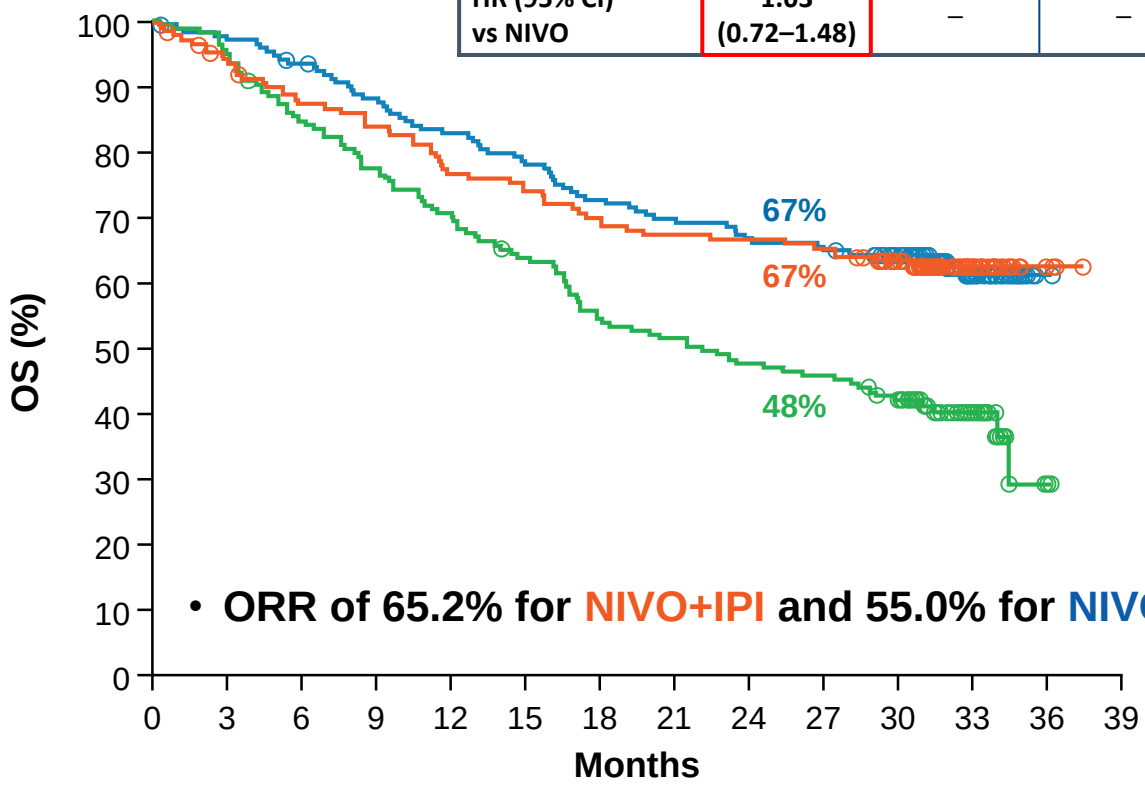
- ORR of 54.5% for NIVO+IPI and 35.0% for NIVO

Patients at risk:

NIVO+IPI	123	113	102	91	82	82	79	74	74	72	66	18	4	0
NIVO	117	103	86	76	73	65	62	59	57	55	50	16	2	0
IPI	113	96	87	79	71	61	57	50	44	43	32	10	1	0

PD-L1 Expression Level ≥1%

≥1% PD-L1	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR	NR	22.1 (17.1–29.7)
HR (95% CI) vs NIVO	1.03 (0.72–1.48)	–	–



- ORR of 65.2% for NIVO+IPI and 55.0% for NIVO

Patients at risk:

NIVO+IPI	155	144	132	127	116	112	105	102	101	99	85	27	3	0
NIVO	171	165	158	148	139	131	122	117	112	109	98	36	1	0
IPI	164	155	138	126	115	102	89	83	77	74	64	21	2	0

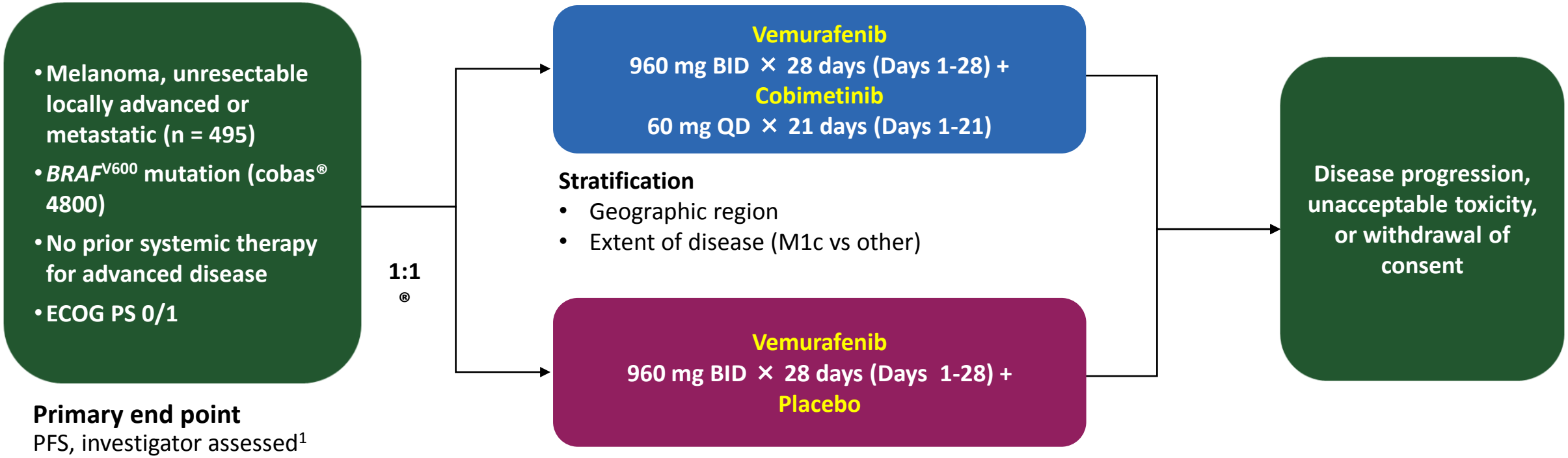
Safety Summary

Patients Reporting Event, %	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
Treatment-related adverse event (AE)	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related AE leading to discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related death*	0		0.3		0.3	

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response

coBRIM Study Design



Primary end point
PFS, investigator assessed[1]

Secondary end points

OS, objective response rate, duration of response, PFS, IRC assessed, safety, pharmacokinetics, quality of life: QLQ-C30 and EQ-5D

Primary analysis for PFS:
Performed in 2014 with the data cutoff as May 9, 2014.
Protocol-specified first OS interim analysis was also performed[1]

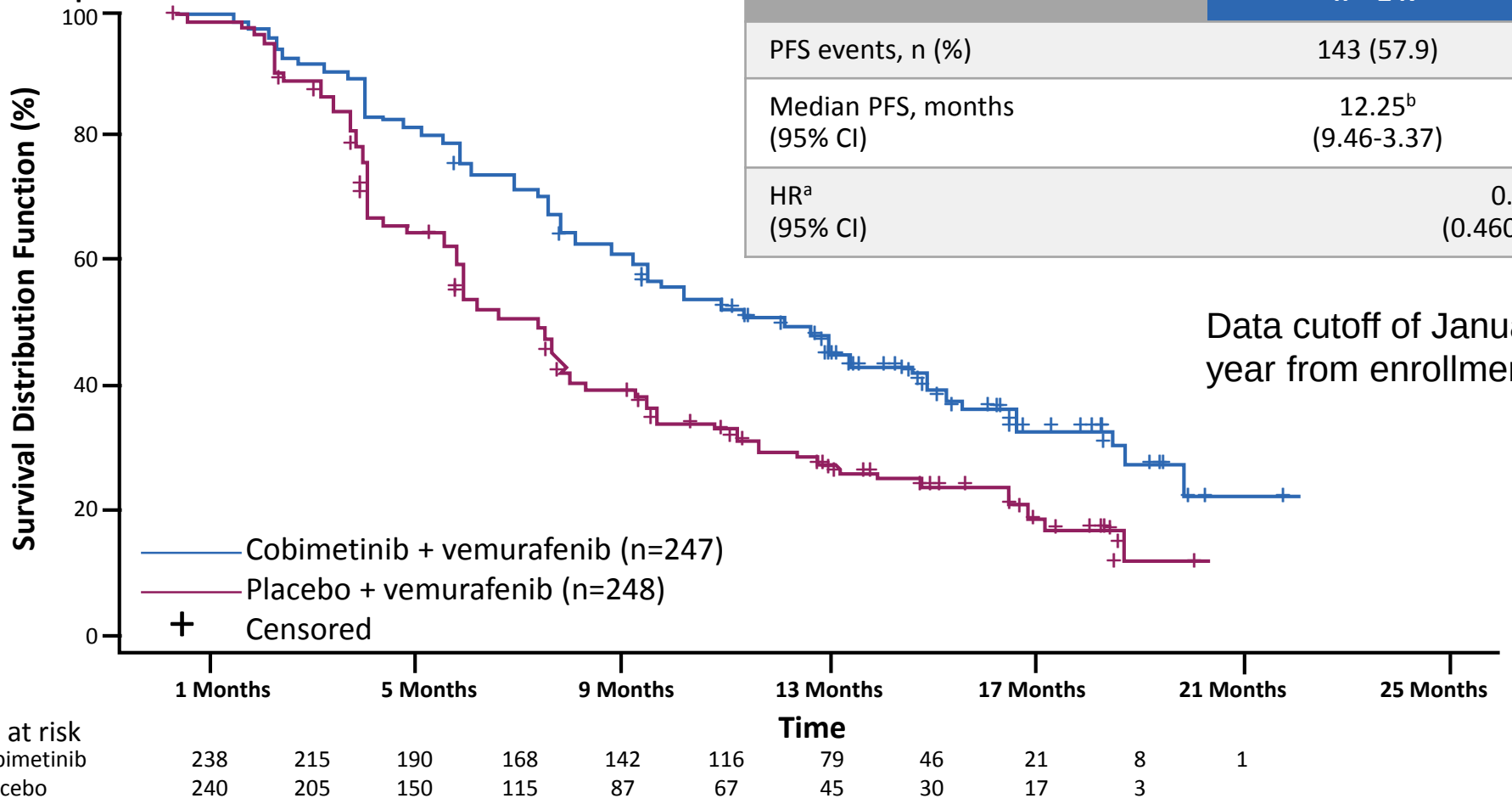
Updated analysis for PFS:
Presented here with the data cutoff as January 16, 2015.

BID, two times daily; ECOG, Eastern Cooperative Oncology Group; EQ, EuroQol; HR, hazard ratio; IRC, independent review committee; OS, overall survival; PS, performance status; QD, once daily; QLQ, quality-of-life questionnaire.

1. Larkin J et al. *N Engl J Med.* 2014;371:1867-1876.

coBRIM Updated Investigator-Assessed PFS

Kaplan-Meier Plot for PFS
Intent-to-Treat Population



ITT Population	Cobi + Vem n = 247	Pbo + Vem n = 248
PFS events, n (%)	143 (57.9)	180 (72.6)
Median PFS, months (95% CI)	12.25[b] (9.46-3.37)	7.20[b] (CI: 5.55-7.49)
HR[a] (95% CI)	0.58[b] (0.460-0.719)	

Data cutoff of January 16, 2015 was 1 year from enrollment of last patient

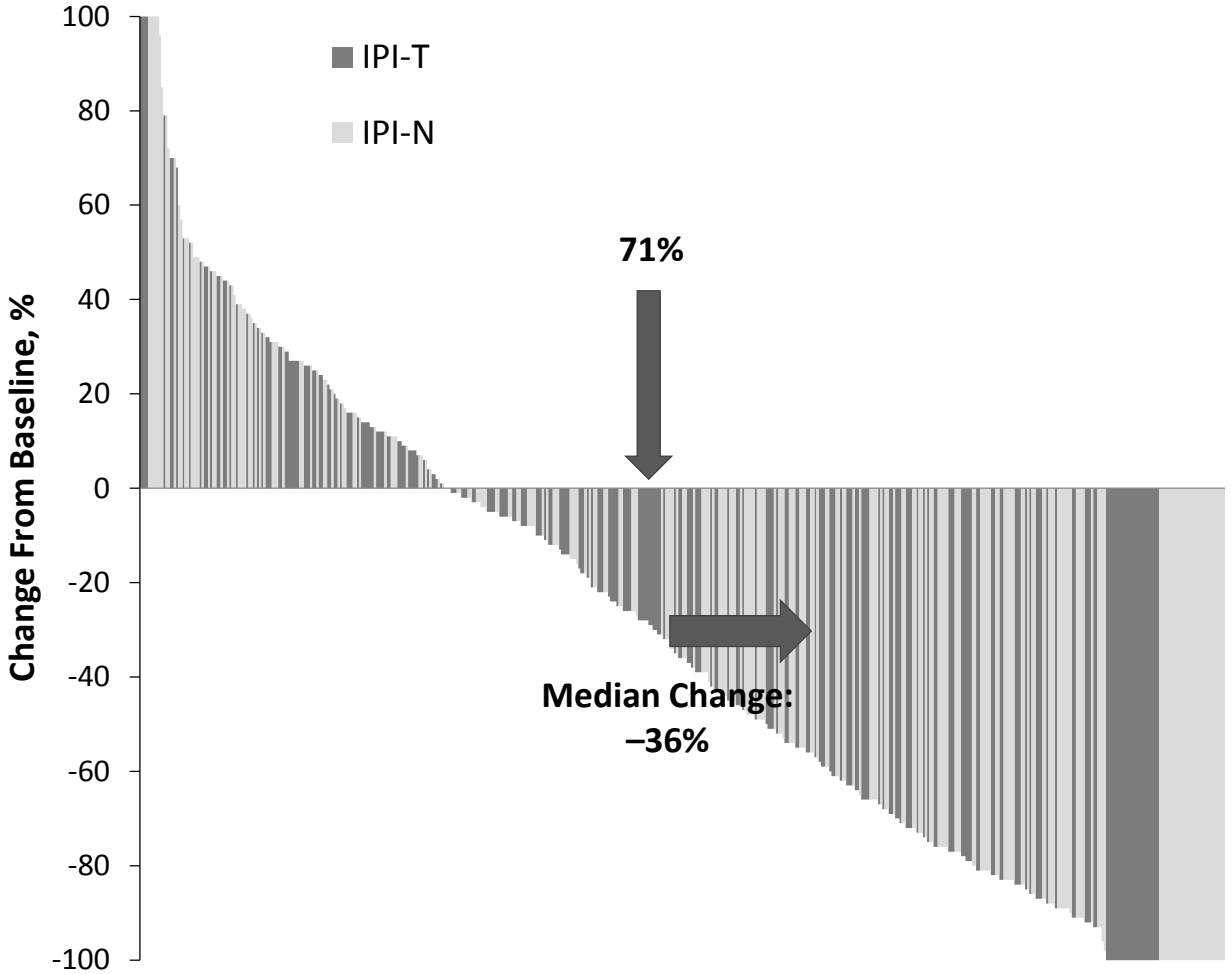
No. of patients at risk

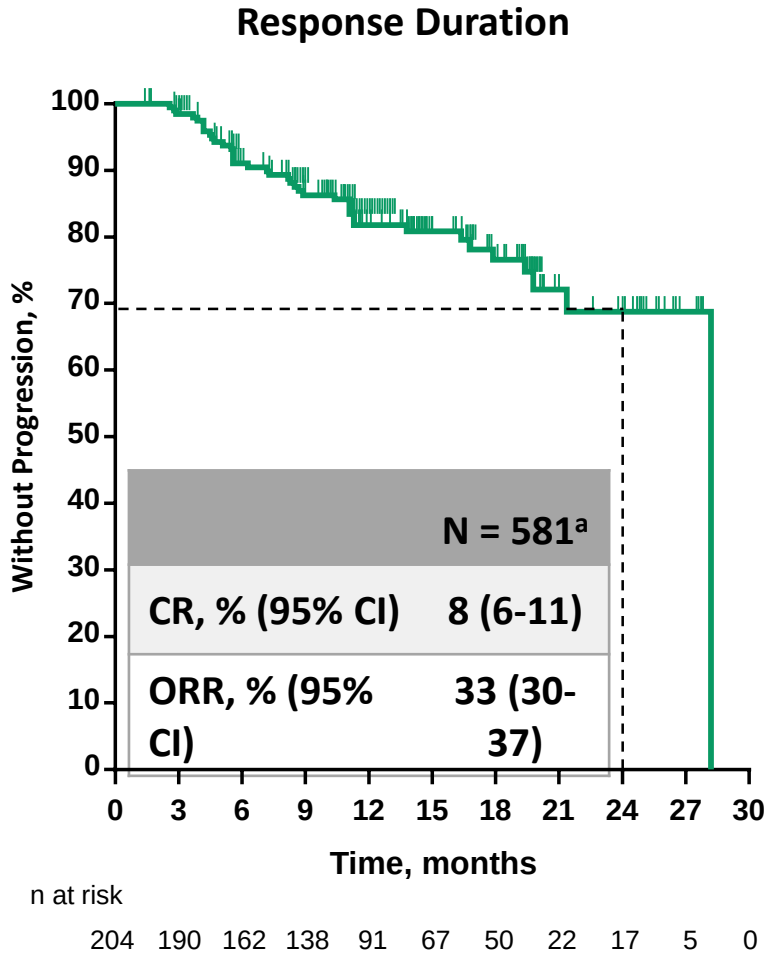
Vemurafenib + cobimetinib	238	215	190	168	142	116	79	46	21	8	1
Vemurafenib + placebo	240	205	150	115	87	67	45	30	17	3	

[a]Stratified HR.
[b]The median PFS was 6.2 months in Pbo + Vem, and 9.9 months in Cobi + Vem (HR, 0.51; 95% CI, 0.39-0.68) at the May 9, 2014 data cutoff.
Larkin J et al. *N Engl J Med.* 2014;371:1867-1876.

Larkin et al, ASCO 2015

Efficacy in Total Population
(As of October 18, 2014; Median Follow-Up: 21 months)





[a]Assessed in patients with measurable disease per central RECIST v1.1 at baseline.

KEYNOTE-006: Phase III Study of Pembrolizumab (MK-3475) versus Ipilimumab in Patients With Ipilimumab-Naive Advanced Melanoma

Antoni Ribas,[1] Jacob Schachter,[2] Georgina V. Long,[3] Ana Arance,[4] Jean Jacques Grob,[5] Laurent Mortier,[6] Adil Daud,[7] Matteo S. Carlino,[8] Catriona McNeil,[9] Michal Lotem,[10] James Larkin,[11] Paul Lorigan,[12] Bart Neyns,[13] Christian U. Blank,[14] Omid Hamid,[15] Michele Kosh,[16] Honghong Zhou,[16] Nageatte Ibrahim,[16] Scot Ebbinghaus,[16] Caroline Robert[17]

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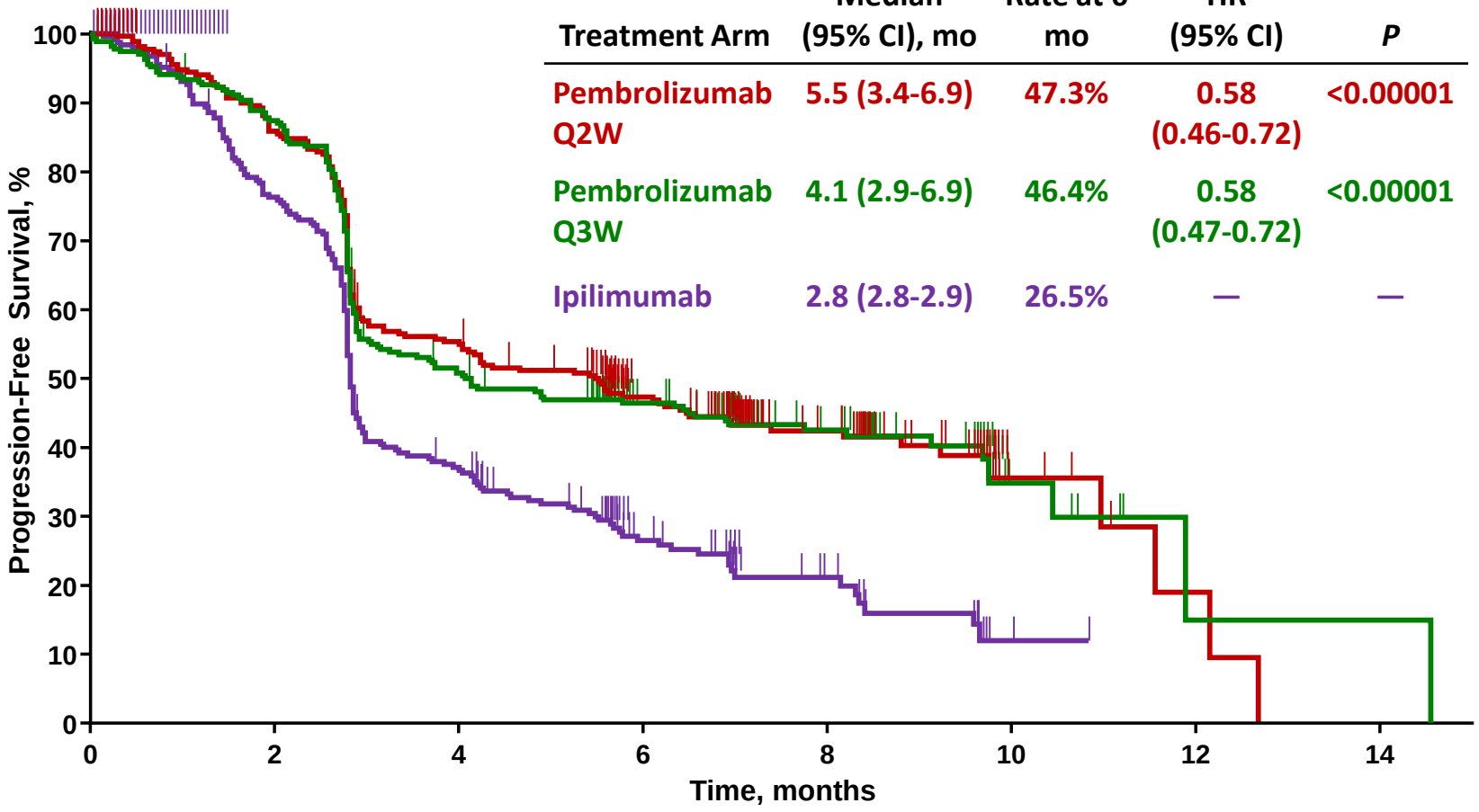
PFS at the First Interim Analysis (IA1)

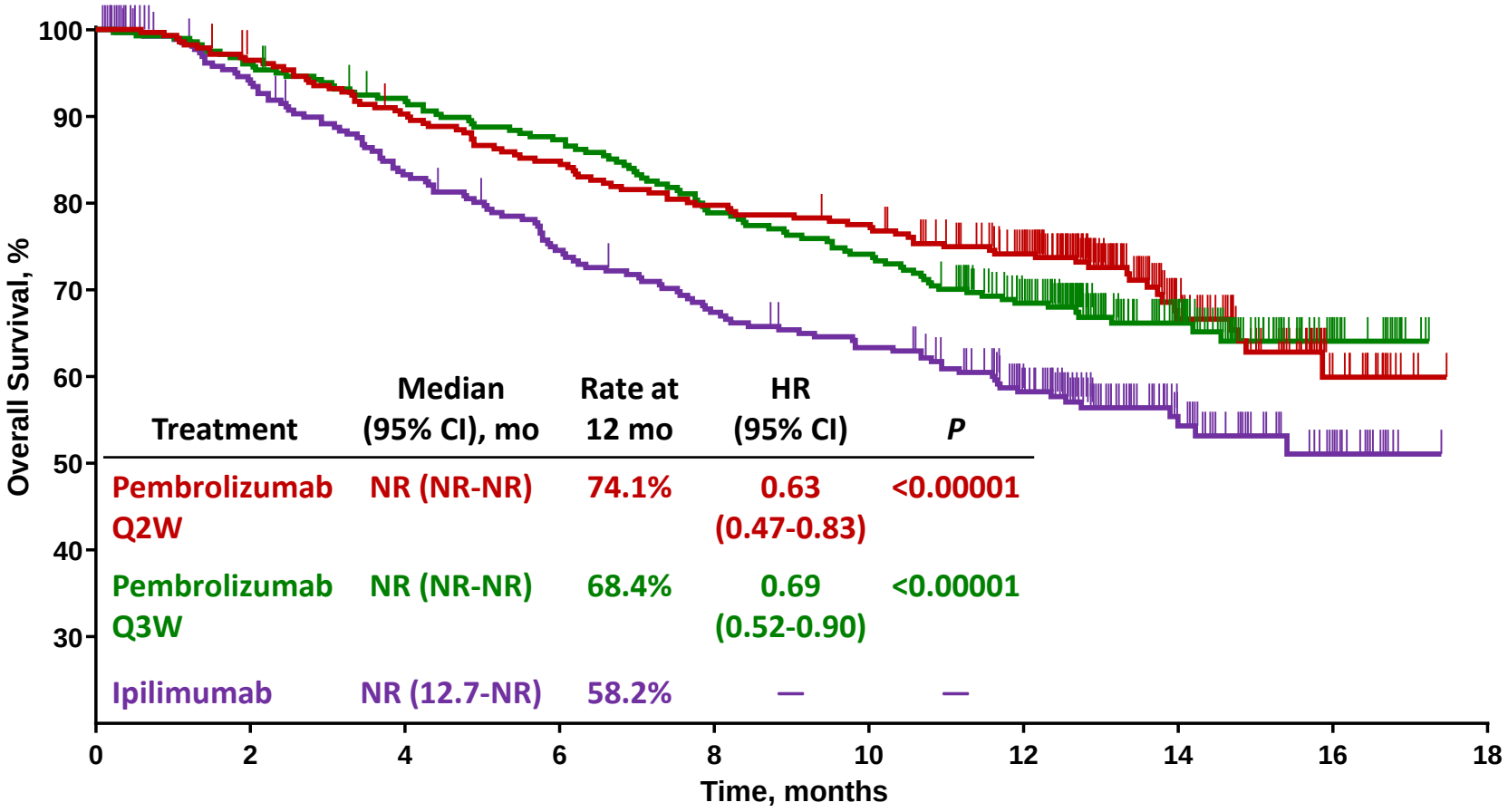


Treatment Arm	Median (95% CI), mo	Rate at 6 mo	HR (95% CI)	*P*
Pembrolizumab Q2W	5.5 (3.4-6.9)	47.3%	0.58 (0.46-0.72)	<0.00001
Pembrolizumab Q3W	4.1 (2.9-6.9)	46.4%	0.58 (0.47-0.72)	<0.00001
Ipilimumab	2.8 (2.8-2.9)	26.5%	—	—

No. at risk							
279	231	147	98	49	7	2	0
277	235	133	95	53	7	1	1
278	186	88	42	18	2	0	0

Analysis cut-off date: September 3, 2014.

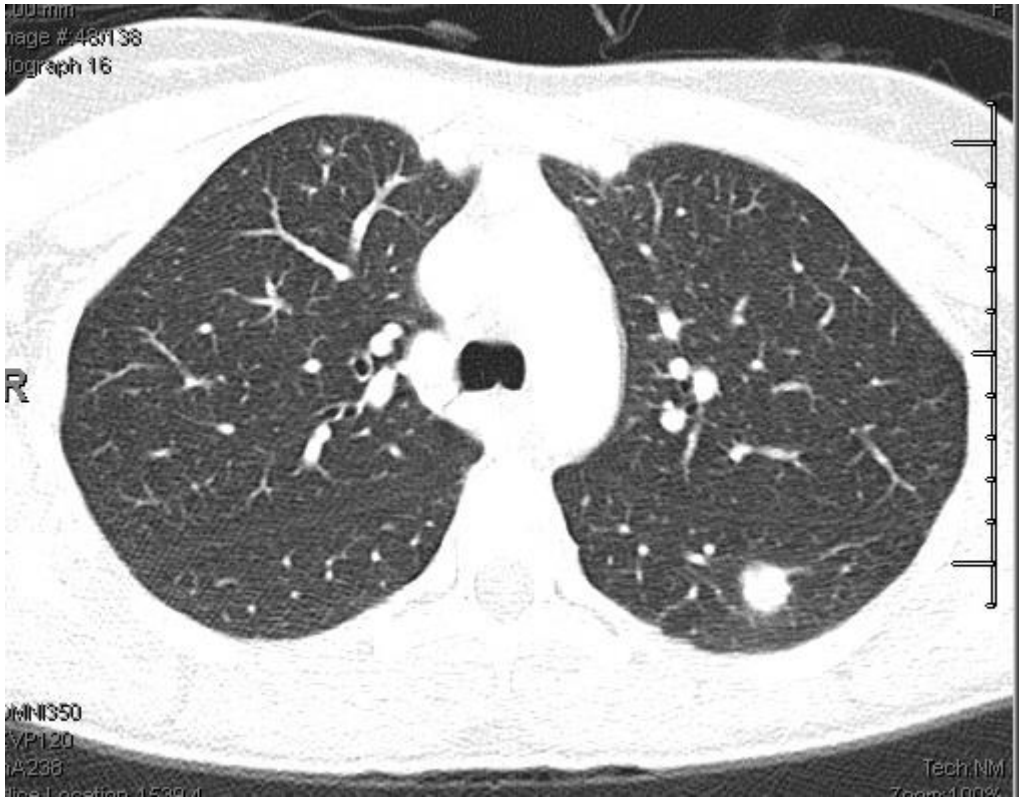
OS at the Second Interim Analysis (IA2)



Analysis cut-off date: March 3, 2015.

Case Presentation

- 28 year old female
- Flank Primary 2 years ago
- BRAF mutant melanoma
- Lung, Sub Q mets
- ECOG 0



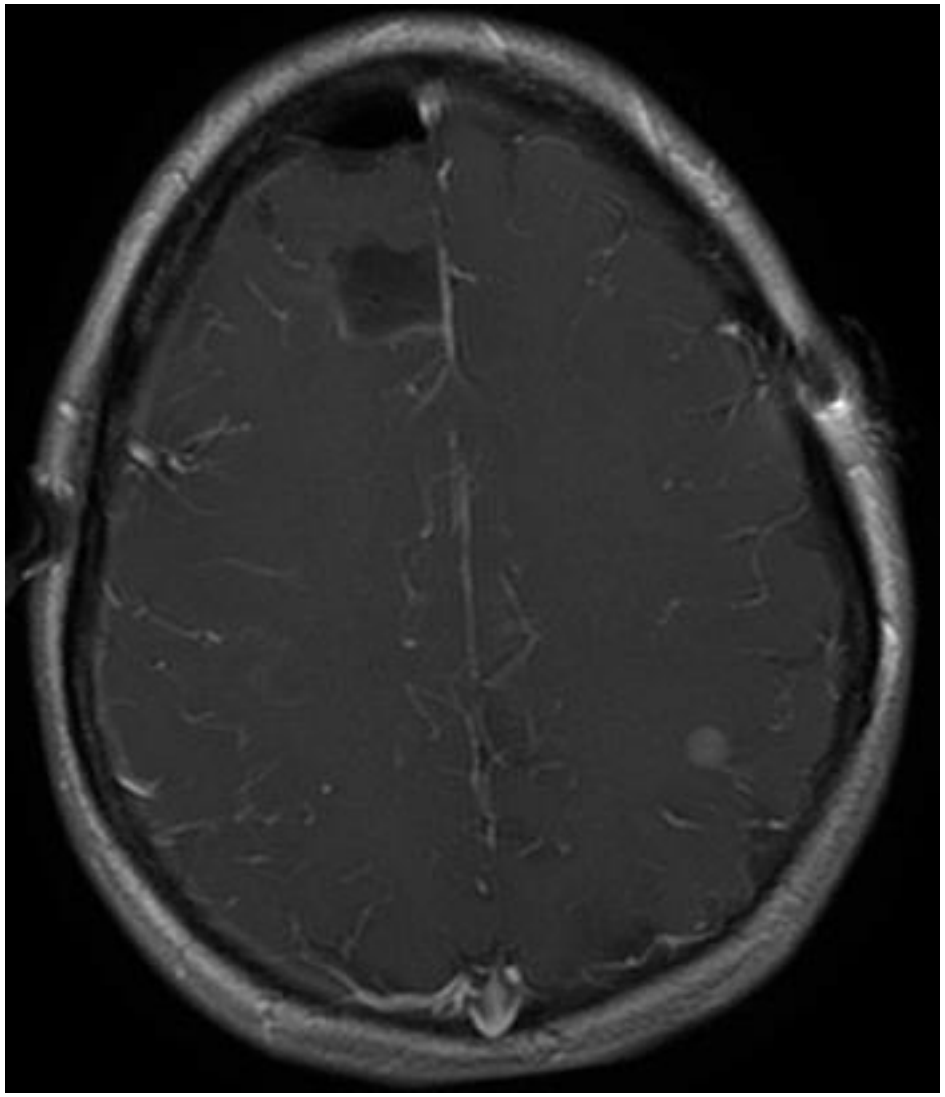
First Line Treatment started 5/13

- Dabrafenib + Trametinib
- Side effects
  - Fevers and chills
  - Some nausea

April 2014

- Routine MRI
  - Solitary Left Parietal met

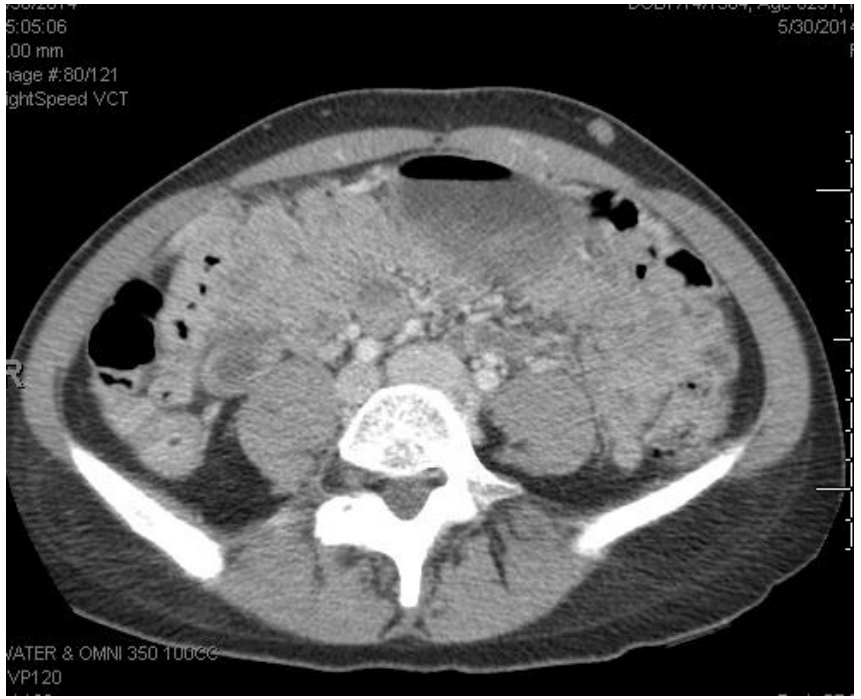
  Gamma Knife treatment

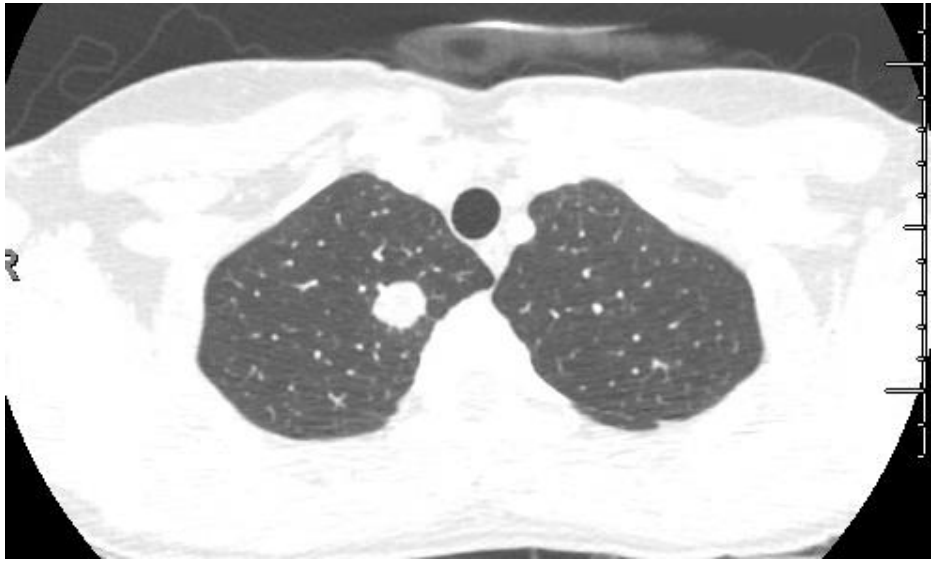


June 2014

Systemic Failure

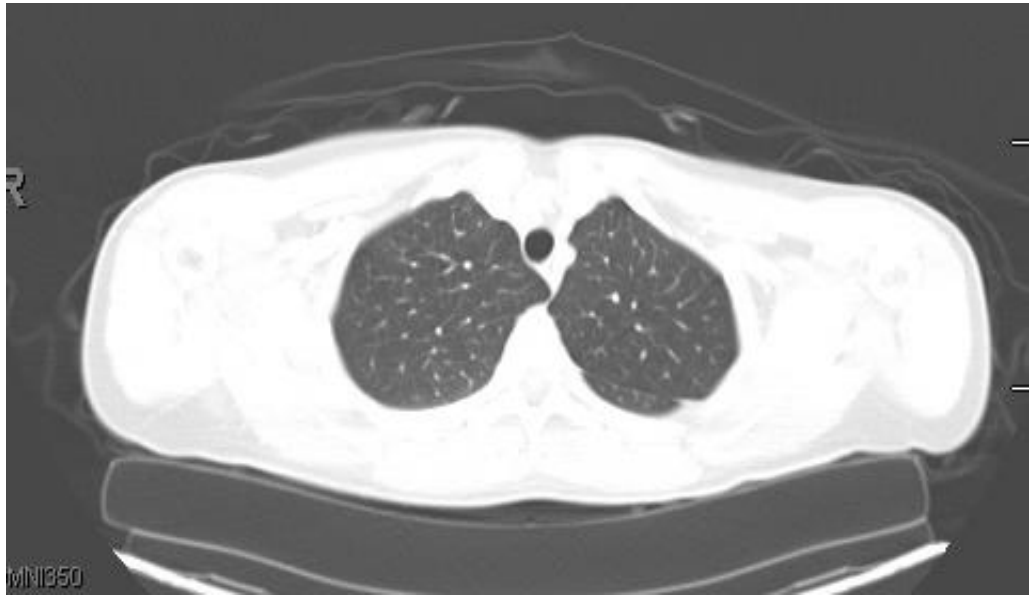
Good PFS

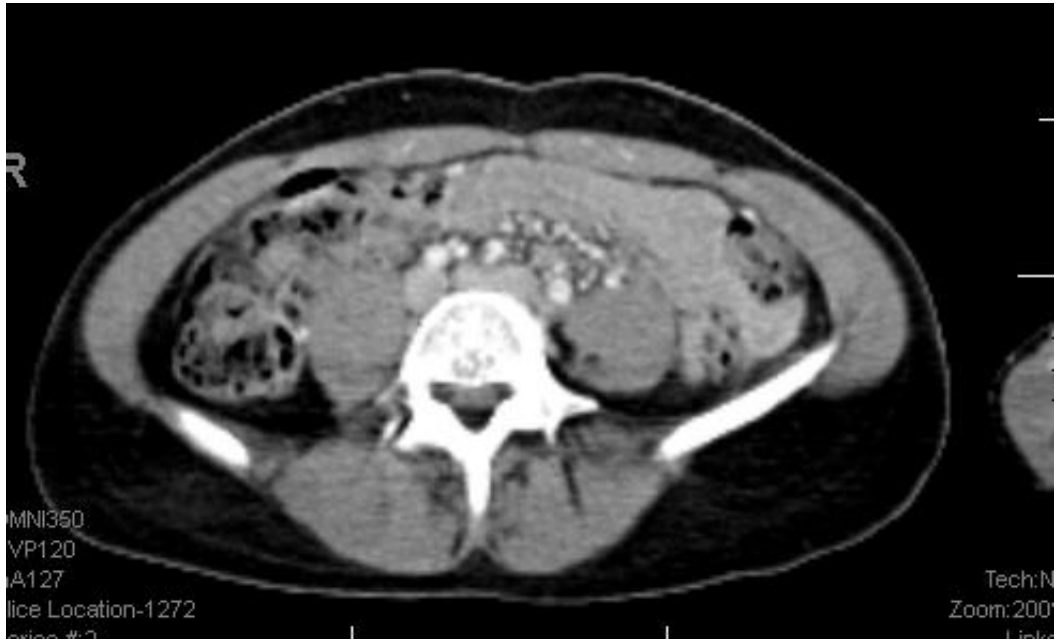




Started anti-PD-1

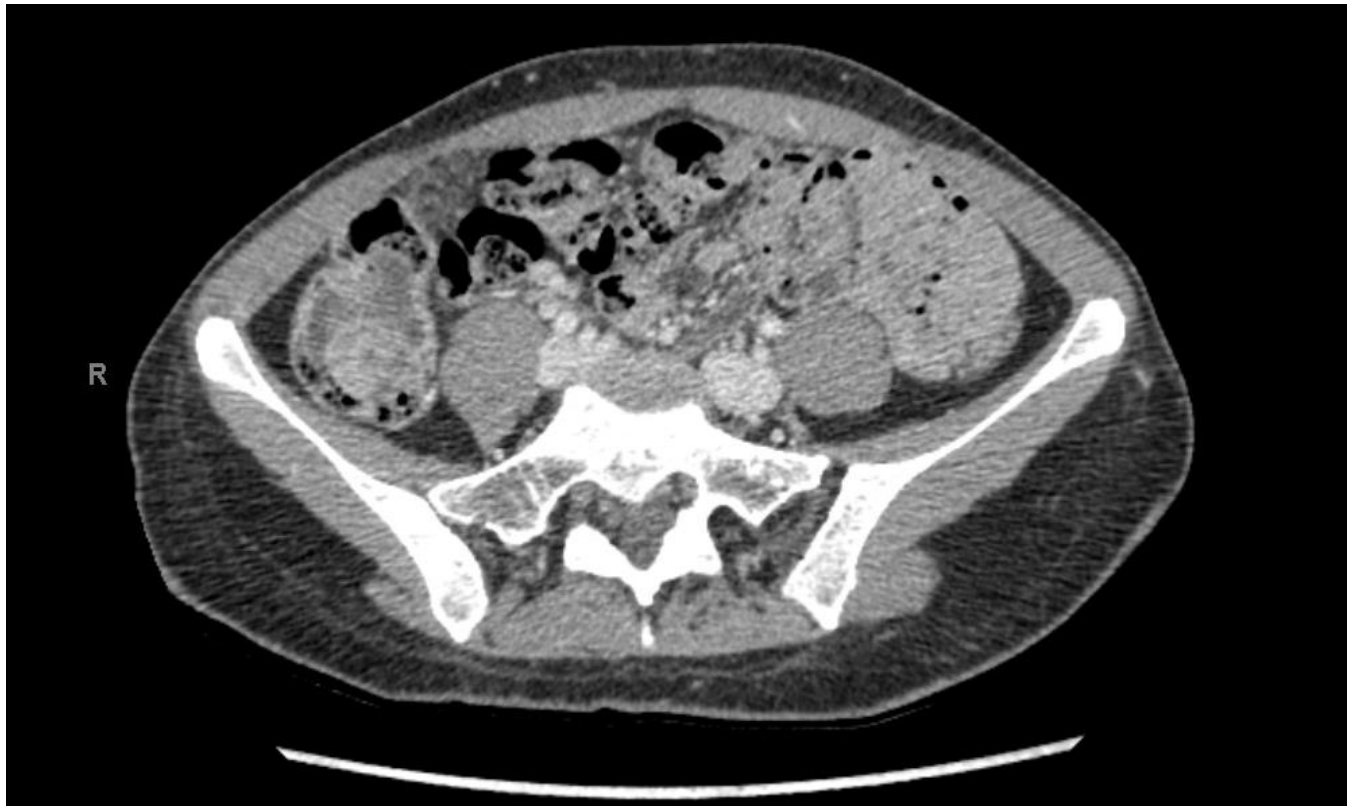
- Ipi X 2
- PD-1 on trial
- Dec 2014





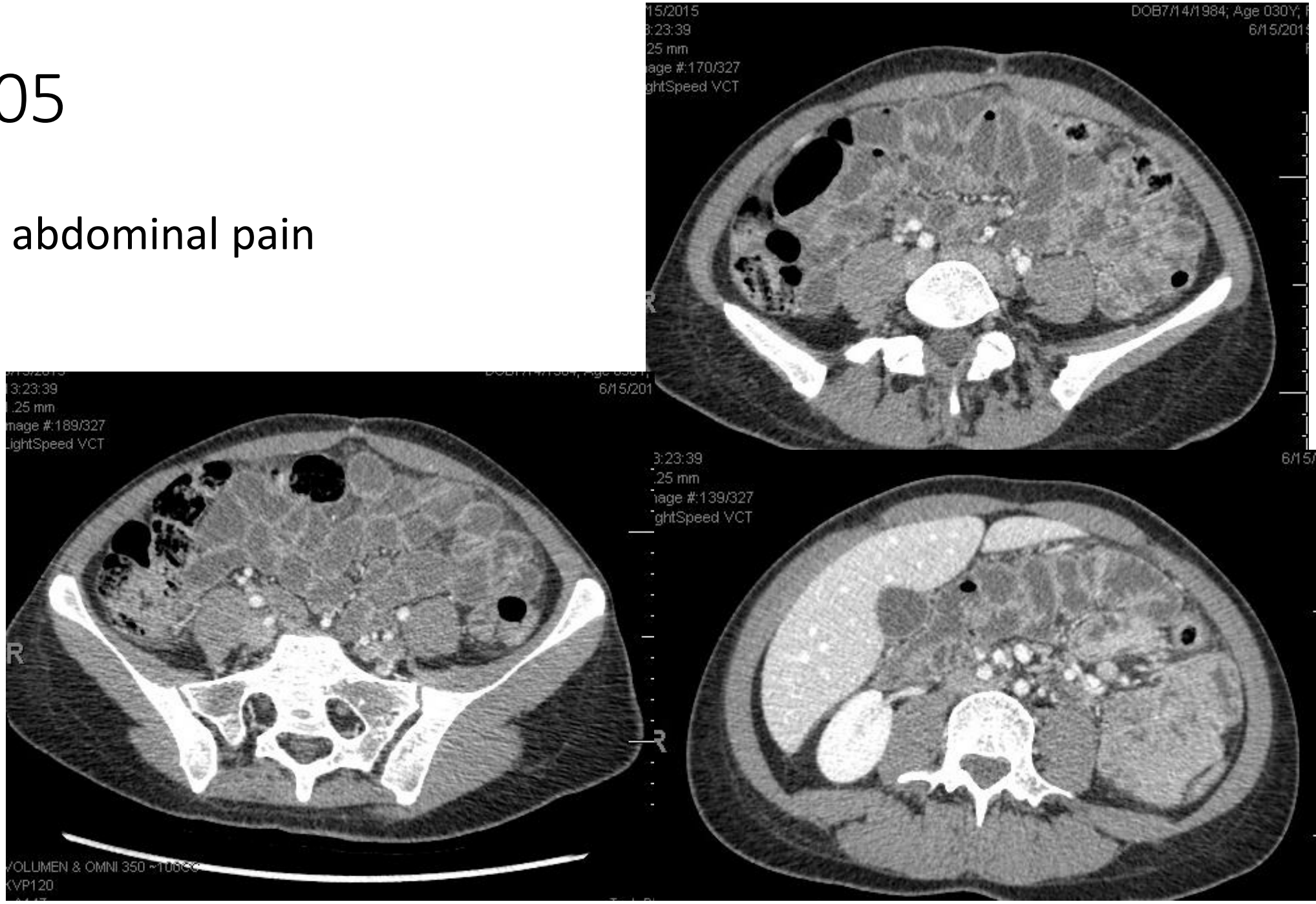
Feb 2015

- Intense Abdominal Pain and cramping
- No diarrhea
- Nausea/vomiting



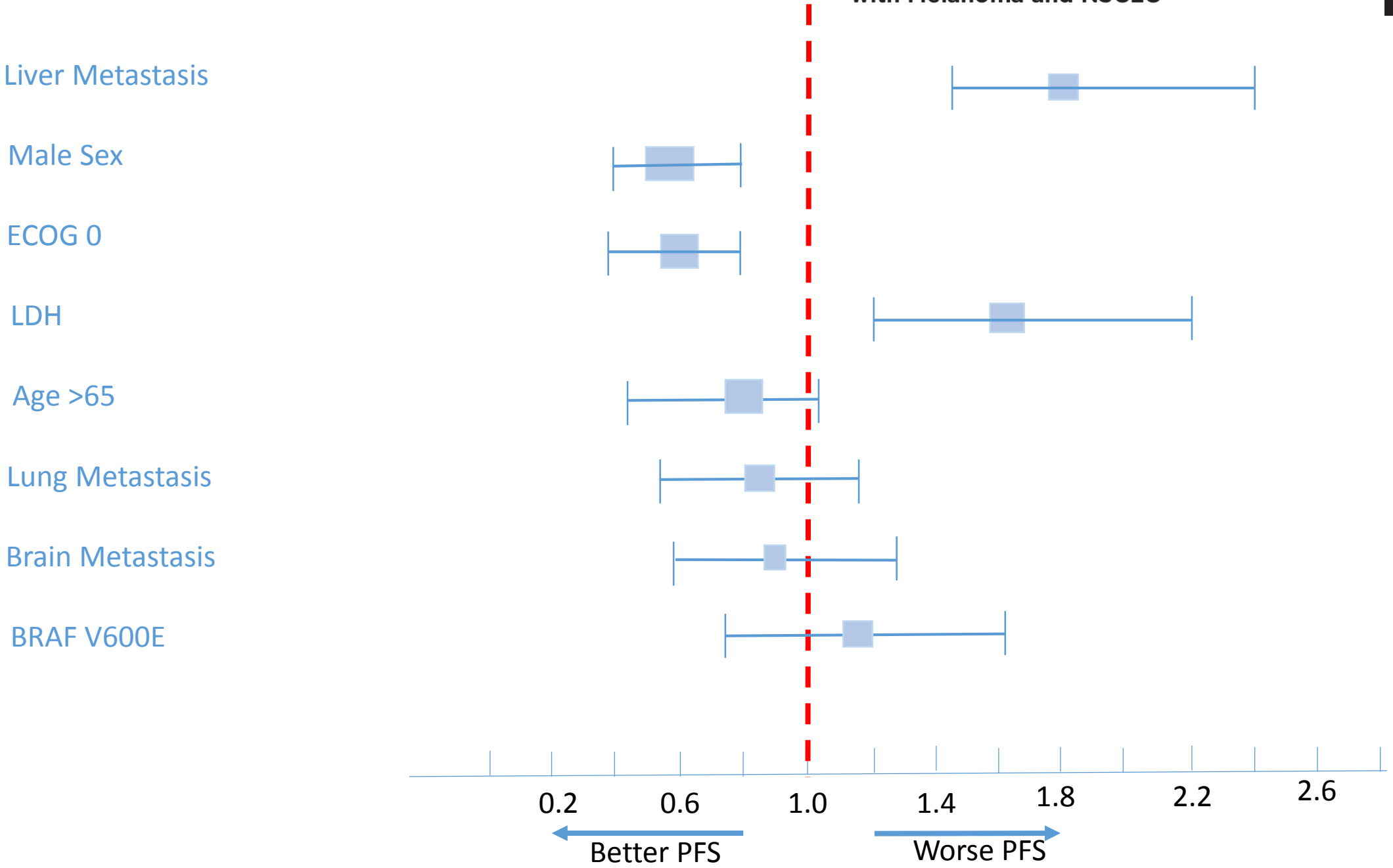
June 2105

- Continuing abdominal pain



Liver Metastasis and Treatment Outcome with Anti-PD-1 Monoclonal Antibody in Patients with Melanoma and NSCLC

Cancer Immunology Research



Conclusion

- Multiple approaches may be needed in a given patient
- Immunotherapy-PD-1 forms the backbone
- Targeted therapy a choice for BRAF +ve patients
- Evolving paradigms