First line treatment for metastatic melanoma: Are there clinical hints or is it just physician preference?

GIL BAR-SELA MD
RAMBAM HEALTH CARE CAMPUS
HAIFA, ISRAEL

"The money time" Overall Survival

- Time of exposure to drugs
- Side-effects

Cobimetinib combined with vemurafenib in advanced *BRAF*^{V600}-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial

Paolo A Ascierto, Grant A McArthur, Brigitte Dréno, Victoria Atkinson, Gabrielle Liszkay, Anna Maria Di Giacomo, Mario Mandalà, Lev Demidov, Daniil Stroyakovskiy, Luc Thomas, Luis de la Cruz-Merino, Caroline Dutriaux, Claus Garbe, Yibing Yan, Matthew Wongchenko, Ilsung Chang, Jessie J Hsu, Daniel O Koralek, Isabelle Rooney, Antoni Ribas, James Larkin

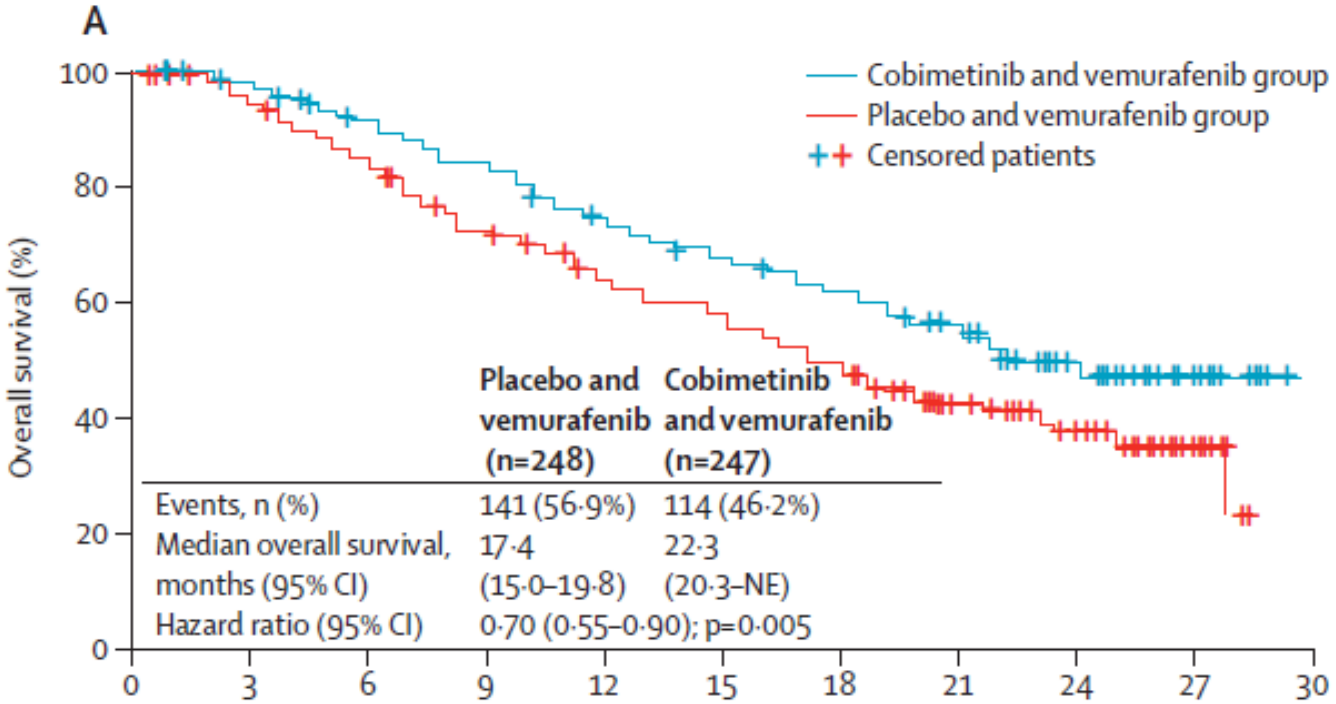
Lancet Oncol 2016; 17: 1248–60

2016

Summary

Background The combination of cobimetinib with vemurafenib improves progression-free survival compared with placebo and vemurafenib in previously untreated patients with *BRAF*^{V600} mutant advanced melanoma, as previously

OS



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE 2014

Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib

Caroline Robert, M.D., Ph.D., Boguslawa Karaszewska, M.D., Jacob Schachter, M.D.,

N = 1645 screened

Key inclusion criteria

- *BRAF* V600E/K mutation
- Stage IIIC or IV cutaneous melanoma
- Treatment-naive advanced or metastatic melanoma
- ECOG PS 0 or 1
- No brain metastases, unless:
  - Treated
  - Stable ≥ 12 weeks

Stratification

- *BRAF*-mutant V600E vs K
- LDH (> ULN vs ≤ ULN)

N = 704

Dabrafenib + trametinib
150 mg BID + 2 mg QD
n = 352

Vemurafenib
960 mg BID
n = 352

Interim "primary" analysis
April 2014[1]
D + T median follow-up: 11 mo

2-year OS analysis
March 2015[2]
D + T median follow-up: 19 mo

3-year OS analysis
July 2016
D + T median follow-up: 23 mo

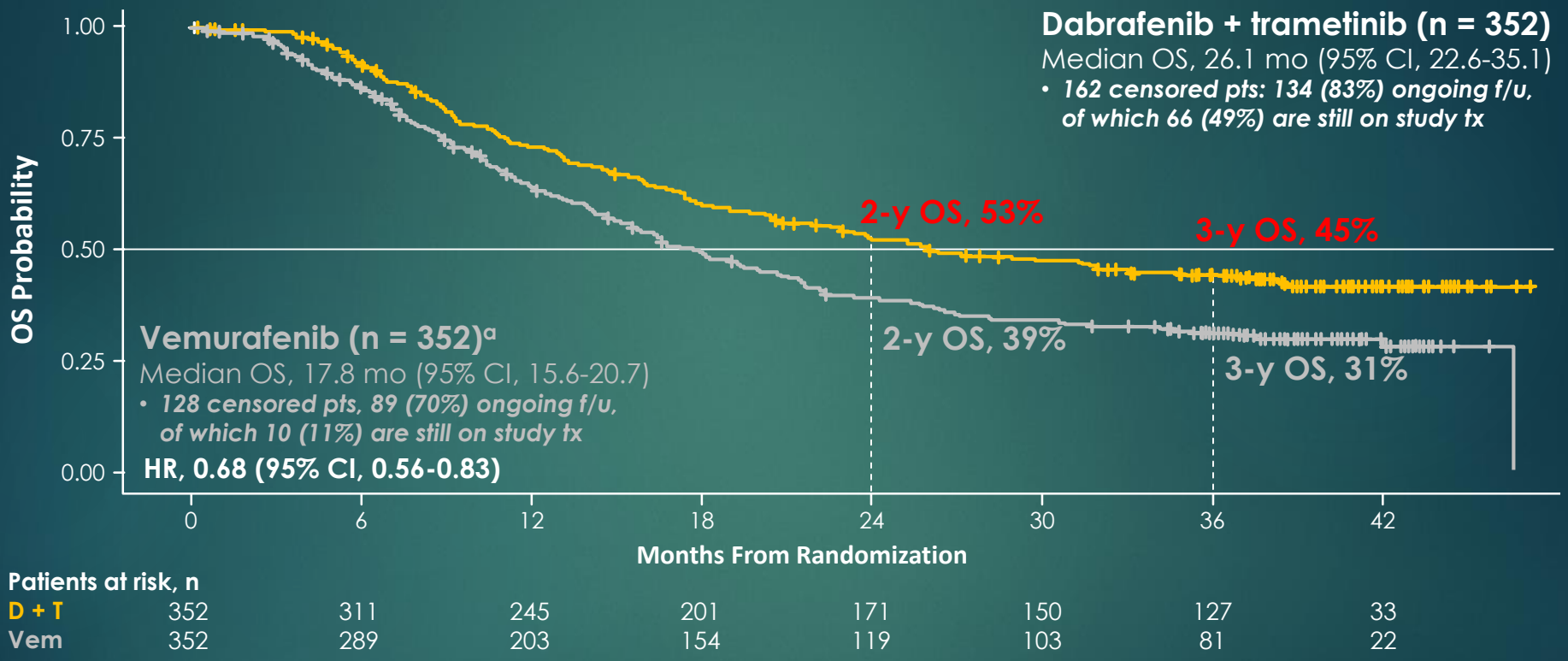
Primary endpoint: OS; **secondary endpoints:** PFS, ORR, DOR, safety

- Patients receiving vemurafenib permitted to crossover to dabrafenib + trametinib after the interim analysis (April 2014)
  - Any crossover benefit was applied to the randomized vemurafenib arm estimates in subsequent analyses
- Current updated analysis for estimated 3-year OS based on a July 2016 data cutoff (414 events)

BID, twice daily; D + T, dabrafenib + trametinib; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ORR, overall response rate; QD, once daily; ULN, upper limit of normal.

1. Robert C, et al. *N Engl J Med.* 2015;372:30-39; 2. Robert C, et al. *Eur J Cancer*. 2015;51(suppl):S663.

COMBI-v: Overall Survival (ITT population)



[a] Vemurafenib arm includes 34 patients (10%) who crossed over to the dabrafenib + trametinib arm.

D + T, dabrafenib + trametinib; f/u, follow-up; ITT, intent-to-treat; pts, patients; tx, treatment; Vem, vemurafenib.

Phase 2, Open-Label Trial of Dabrafenib and Trametinib

Key eligibility criteria

- ≥ 18 years of age
- Unresectable stage IIIC or IV *BRAF* V600E/K–mutant melanoma
- ECOG PS 0 or 1
- No prior treatment with BRAF or MEK inhibitor
- ≤ 1 previous line of chemotherapy
- Brain metastases allowed if treated and stable for ≥ 3 months

RANDOMIZATION

1:1:1

Dabrafenib 150 mg BID + trametinib 2 mg QD[a] n = 54

Dabrafenib 150 mg BID + trametinib 1 mg QD[a] n = 54

Dabrafenib 150 mg BID[a] n = 54

Crossover allowed upon progression

Dabrafenib 150 mg BID + trametinib 2 mg QD n = 45

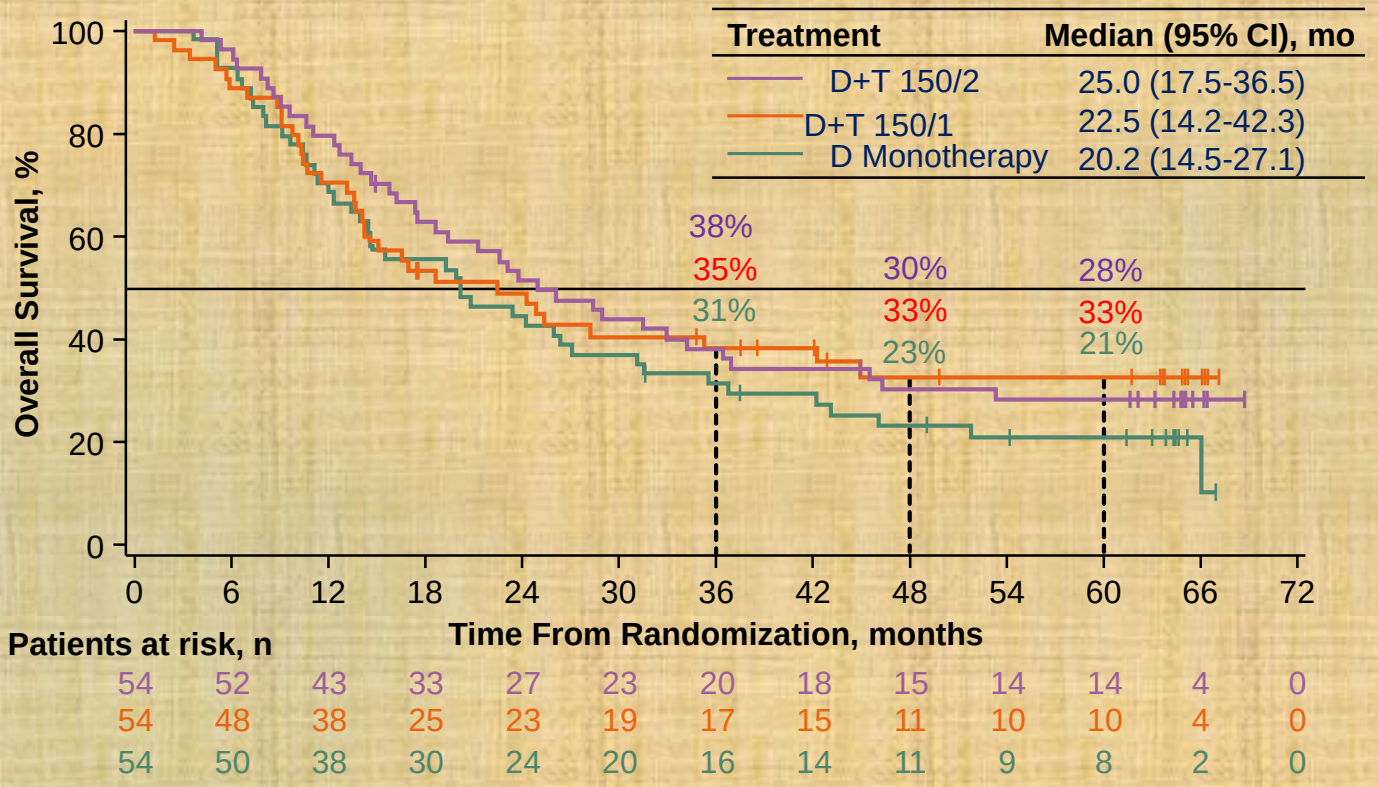
- **Primary endpoints are ORR, DOR, PFS, and safety**
- **Secondary endpoints are pharmacokinetics and OS**

Presented by: Jeffrey Weber

[a] Study treatment continued until disease progression, unacceptable toxicity, or withdrawn consent. BID, twice daily; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; PFS, progression-free survival; PS, performance status; QD, once daily.

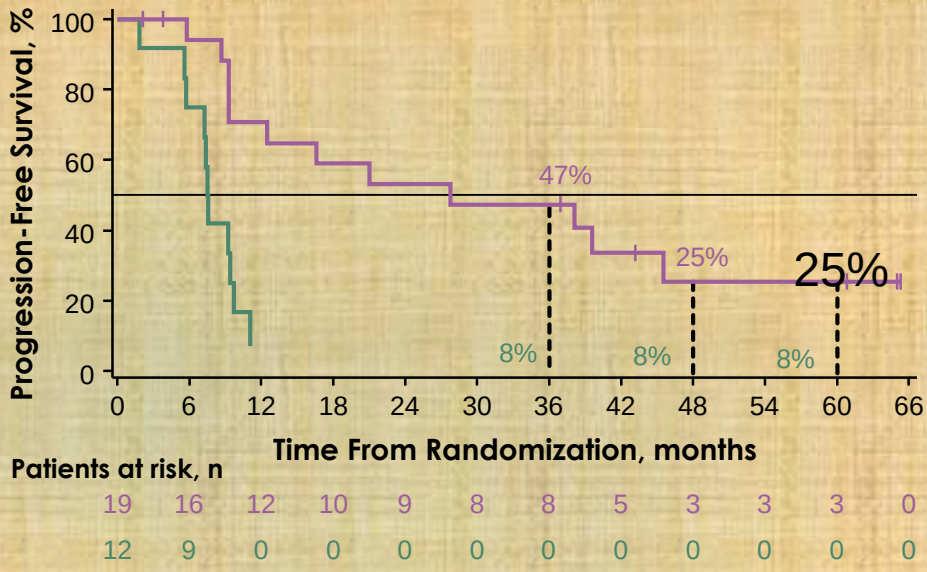
1. Flaherty KT, et al. *N Engl J Med*. 2012;367:1694-1703; 2. Long GV, et al. *J Clin Oncol*. 2016;34:871-878.

OS (Intent-to-Treat)



LDH ≤ ULN and < 3 Metastatic Sites (ITT)

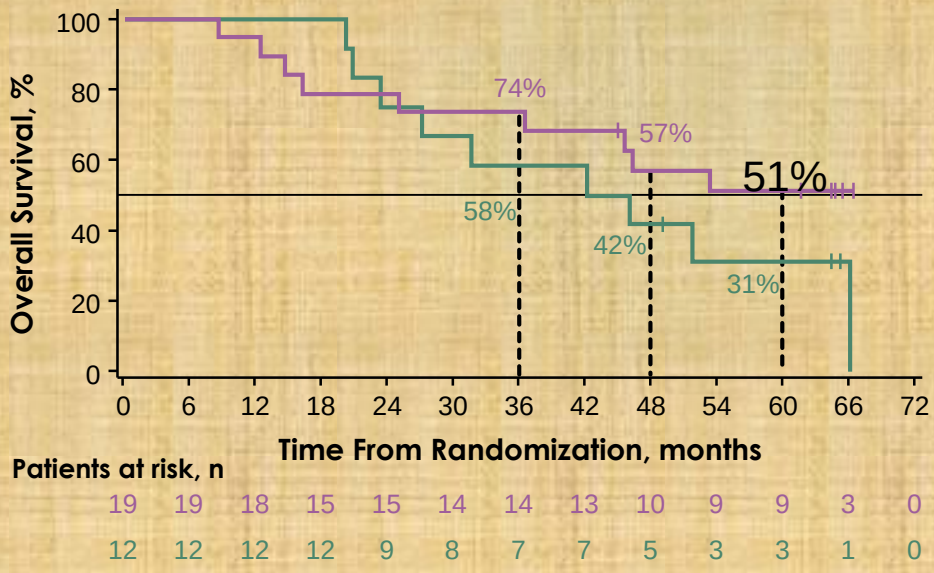
Progression-Free Survival



Patients at risk, n

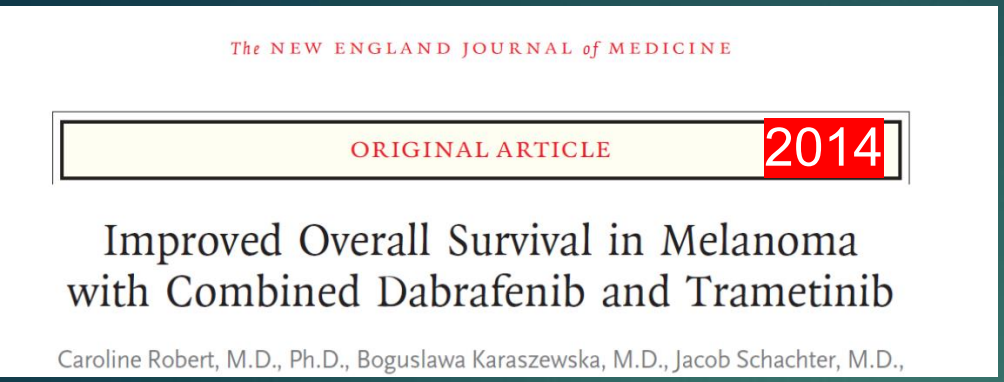
19	16	12	10	9	8	8	5	3	3	3	0
12	9	0	0	0	0	0	0	0	0	0	0

Overall Survival



Patients at risk, n

19	19	18	15	15	14	14	13	10	9	9	3	0
12	12	12	12	9	8	7	7	5	3	3	1	0



Association With Outcomes in Patients With *BRAF* V600E/K–Mutant Metastatic Melanoma in the Randomized Phase 3 COMBI-v Study

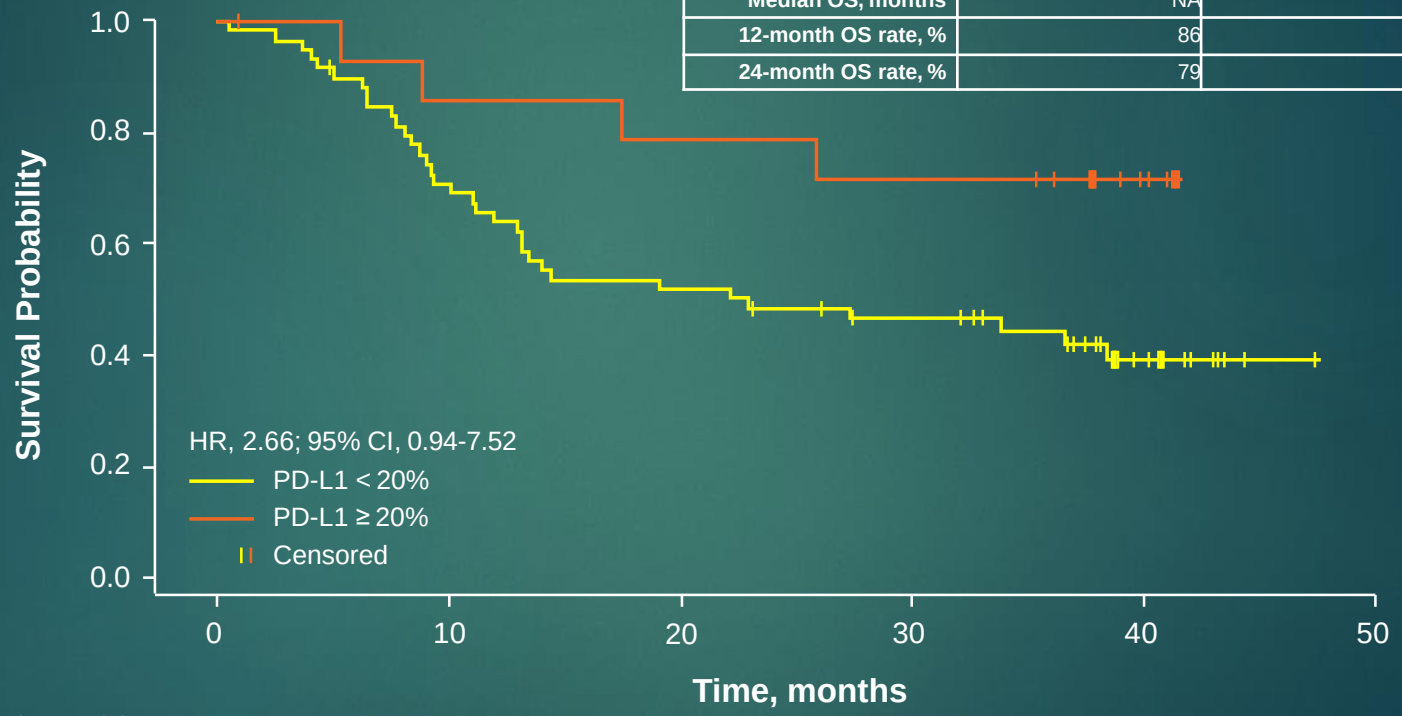
Abstract 9527, 2017

DIRK SCHADENDORF,[1] GEORGINA V. LONG,[2] JEAN-JACQUES GROB,[3] PAUL NATHAN,[4]
ANTONI RIBAS,[5] MICHAEL A. DAVIES,[6] KEITH T. FLAHERTY,[7] MATTHEW SQUIRES,[8] SAVINA JAEGER,[8] WILLIAM POWELL,[9,*] PUAY TAN,[9] CAROLINE ROBERT[10]

RESULTS (cont)

Figure 3. Improved OS in Tumors With High PD-L1 Expression (≥ 20% vs < 20% Positivity)

	PD-L1 ≥ 20% (n = 15)	PD-L1 < 20% (n = 59)
Median OS, months	NA	23
12-month OS rate, %	86	64
24-month OS rate, %	79	48



Number at risk, n																
PD-L1 < 20%	59	57	52	44	37	31	31	30	27	26	24	22	20	11	5	1
PD-L1 ≥ 20%	15	14	13	12	12	12	11	11	11	10	10	10	9	5	0	0

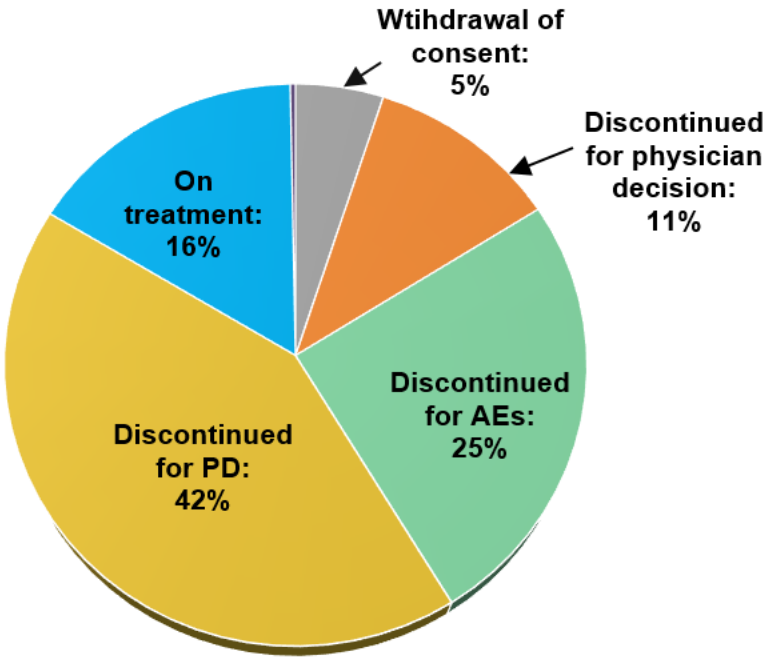
Long-Term Outcomes in Patients With Advanced Melanoma Treated With Pembrolizumab: 4-Year Overall Survival Results From KEYNOTE-001

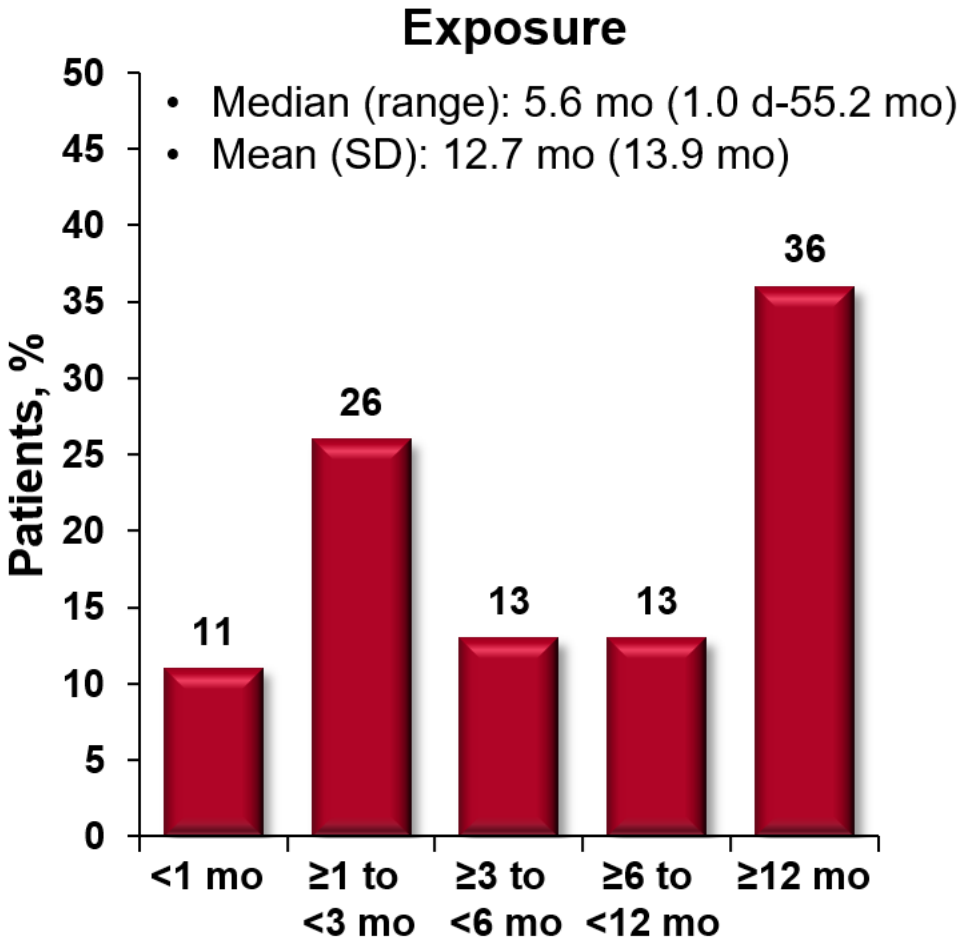
Caroline Robert,[1,2] Antonio Ribas,[3] Omid Hamid,[4] Frank Stephen Hodi,[5] Anthony M. Joshua,[6] Richard Kefford,[7,8] Jing Yang,[9] Scott J. Diede,[9] Nageatte Ibrahim,[9] Adil Daud[10]

[1]Gustave Roussy, Villejuif, France; [2]Paris-Sud University, Villejuif, France; [3]University of California, Los Angeles, Los Angeles, CA, USA; [4]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]The Princess Margaret Cancer Centre, Toronto, ON, Canada; [7]Crown Princess Mary Cancer Centre, Westmead Hospital, Melanoma Institute Australia; [8]Macquarie University, NSW, Sydney, Australia; [9]Merck & Co., Inc., Kenilworth, NJ, USA; [10]University of California, San Francisco, San Francisco, CA, USA

Treatment Disposition and Exposure: Median Follow-Up 43 Months

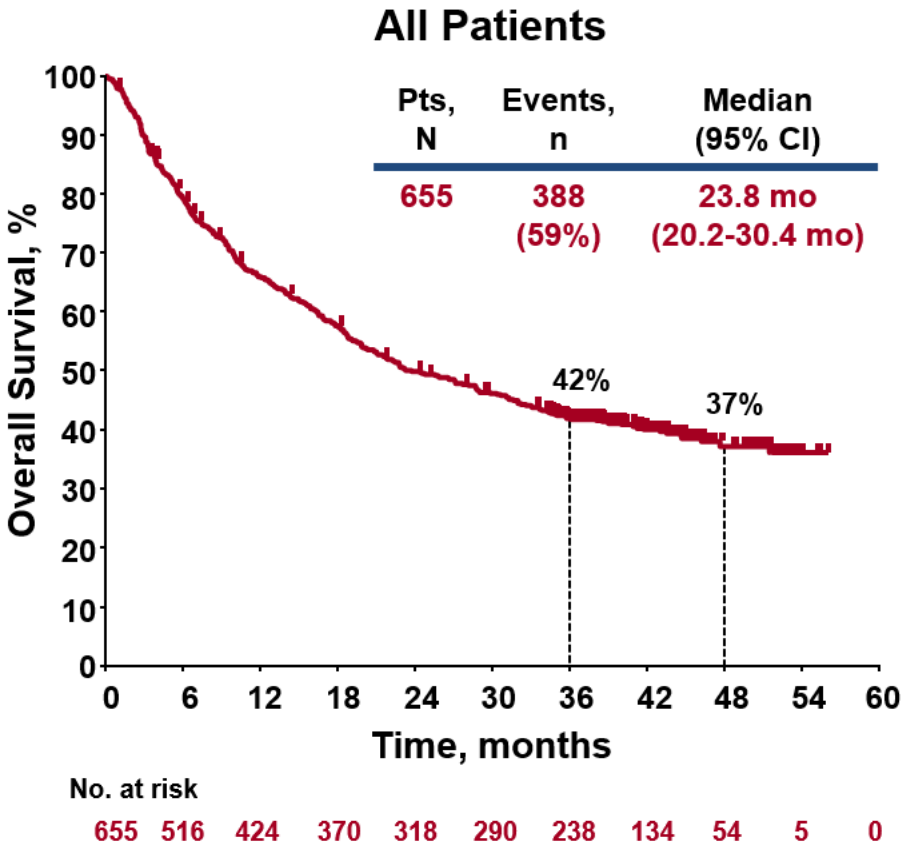
655 patients enrolled and treated

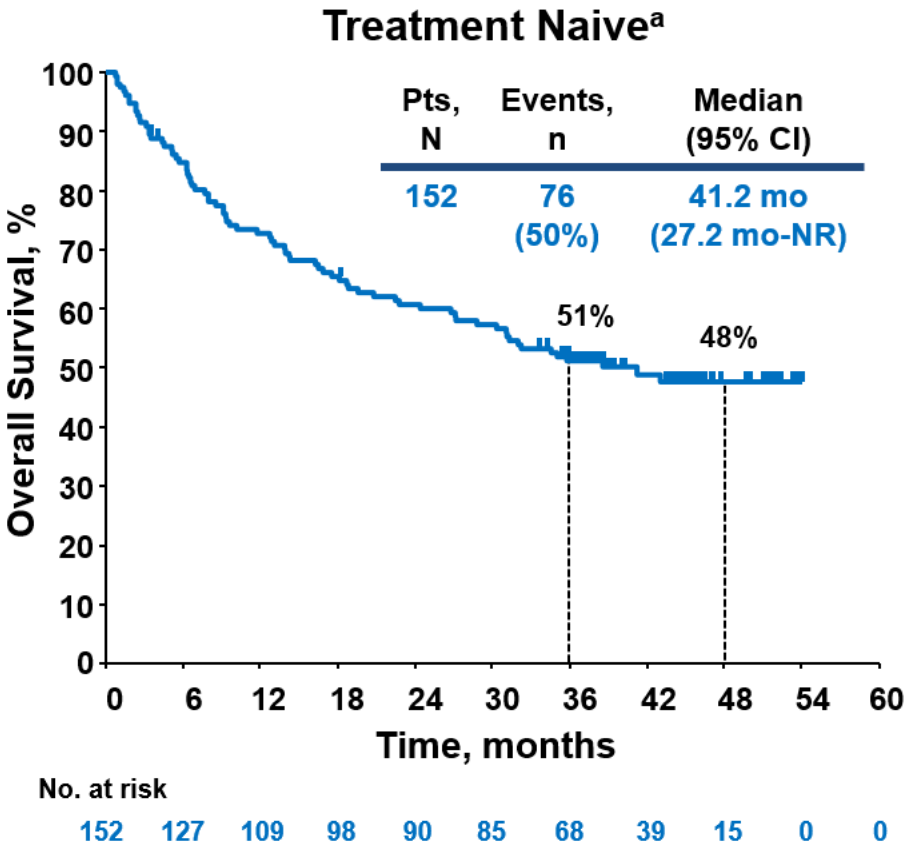




Range of follow-up: 36-57 months.
Analysis cutoff date: September 1, 2016.

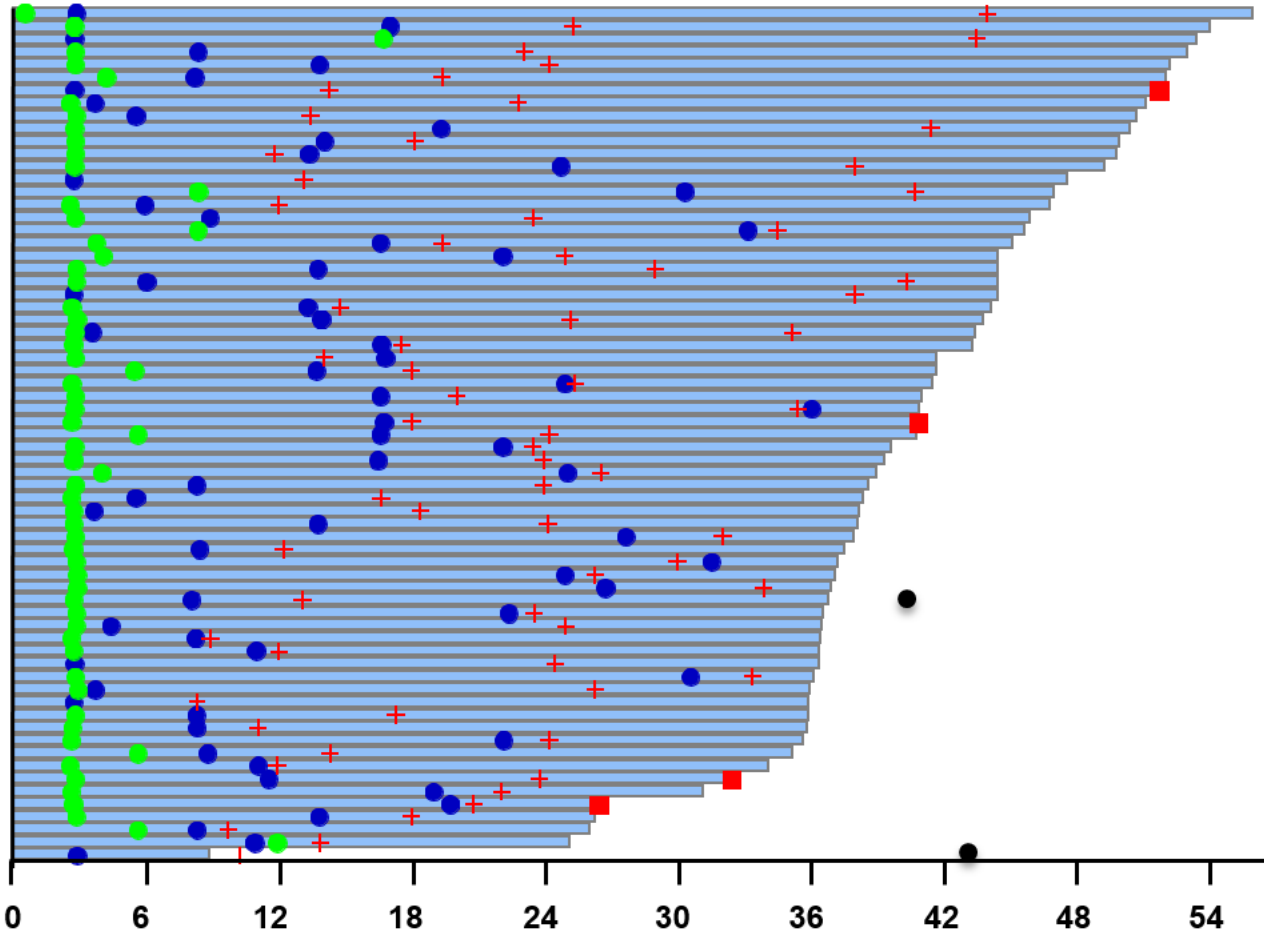
Overall Survival





[a]Excludes patients with ocular melanoma.
Analysis cutoff date: September 1, 2016.

Complete Responders Who Stopped Pembrolizumab for Observation (N = 67)



- Median time to CR: 13 mo (range, 3-36 mo)
- 61 (91%) responses were maintained
- Median response duration: NR (range, 6+ to 56+ mo)

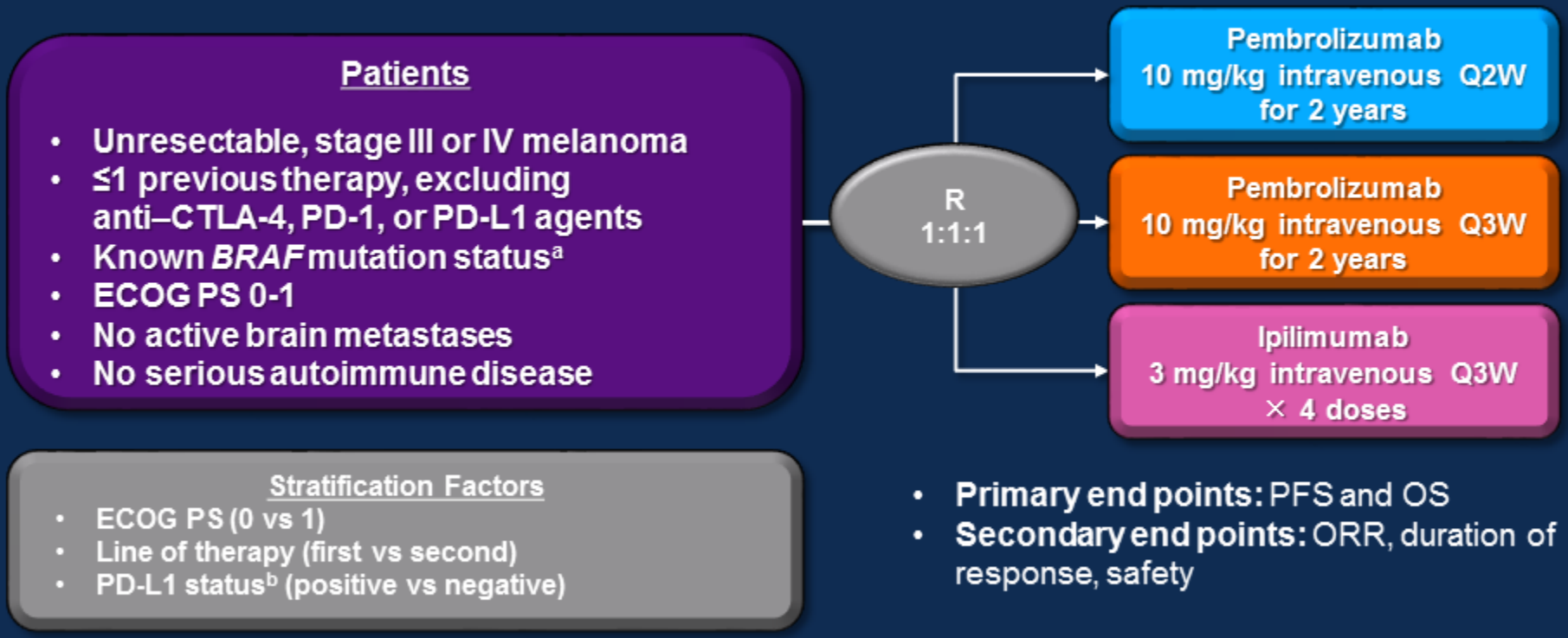
Time to PD or last assessment
Last dose
CR
PR
PD
Time to death

Total bar length represents the time to the last scan.
Analysis cutoff date: September 1, 2016.

Long Term Outcome (834 pts.)
Patients completed Pembro. (104 pts.)

Robert, ASCO, Jun 2017

KEYNOTE-006 (NCT01866319) Study Design



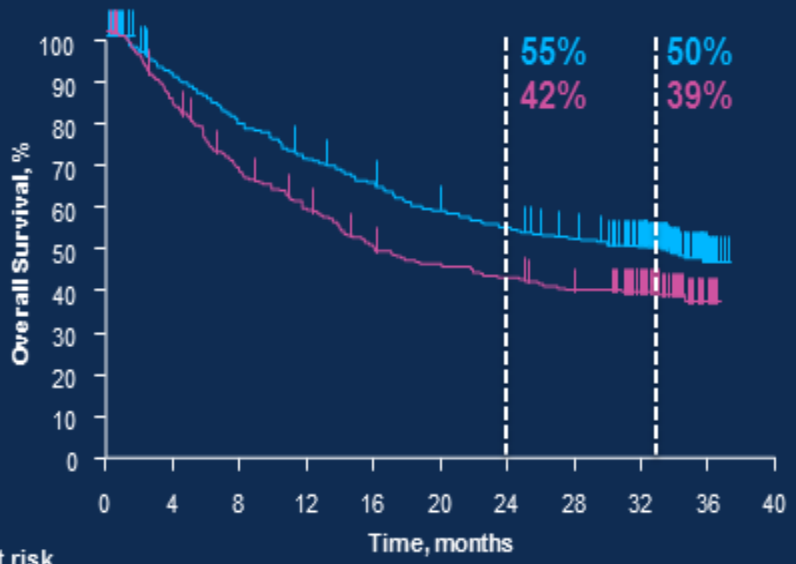
- **Primary end points:** PFS and OS
- **Secondary end points:** ORR, duration of response, safety

[a]Prior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease. [b]Defined as ≥1% staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).

Kaplan-Meier Estimates of Survival in Total Population (Median Follow-Up, 33.9 mo)

OS

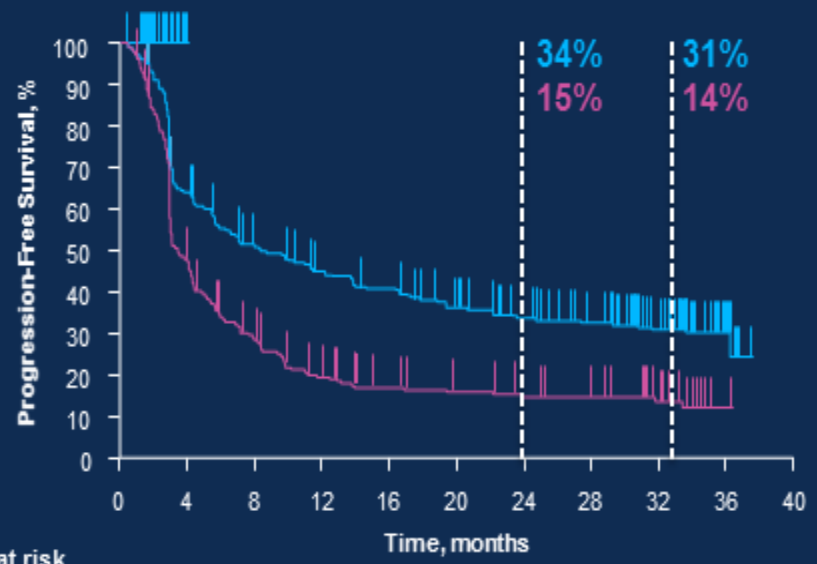
Arm	Events, n	HR (95% CI)	Median, mo (95% CI)
Pembrolizumab	278	0.70 (0.58-0.86)	32.3 (24.5-NR)
Ipilimumab	155	—	15.9 (13.3-22.0)



No. at risk											
Pembrolizumab	556	500	436	387	351	317	297	273	229	24	0
Ipilimumab	278	212	169	145	122	111	103	94	77	10	0

PFS per irRC by Investigator

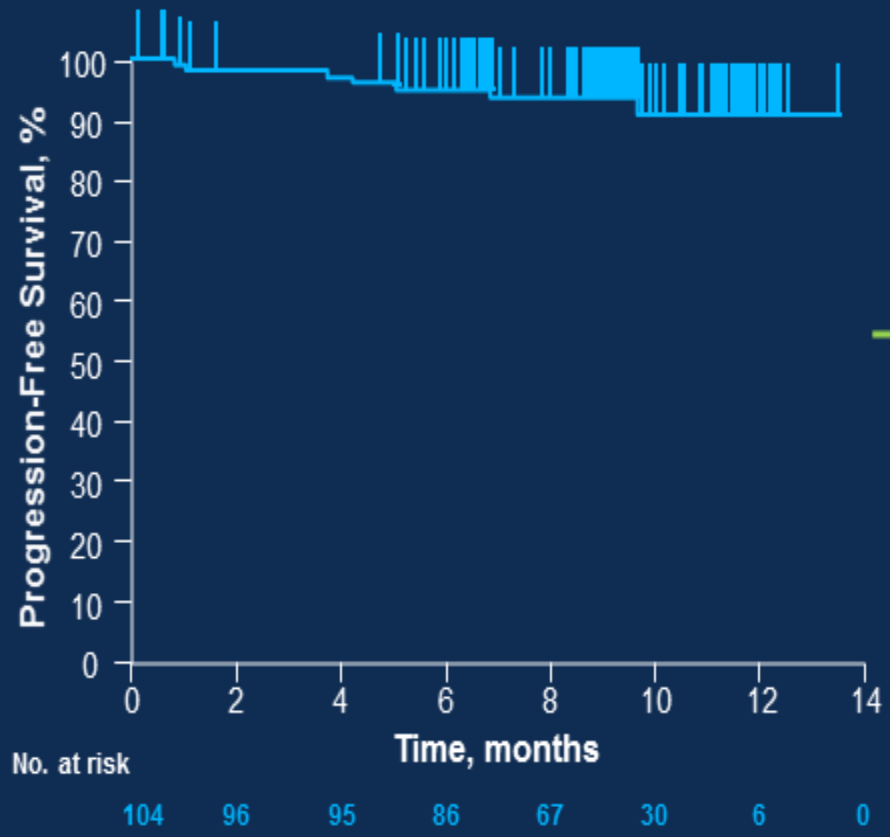
Arm	Events, n	HR (95% CI)	Median, mo (95% CI)
Pembrolizumab	369	0.56 (0.47-0.67)	8.3 (6.5-11.2)
Ipilimumab	204	—	3.3 (2.9-4.1)



No. at risk											
Pembrolizumab	556	347	269	231	211	182	155	138	88	12	0
Ipilimumab	278	110	64	40	32	27	23	20	14	2	0

Analysis includes all randomized patients with measurable disease at baseline who received ≥1 pembrolizumab dose.
Data cutoff date: Nov 3, 2016.

PFS (irRC, investigator) From Last Pembrolizumab Dose to PD or Death in Patients Who Completed Protocol-Specified Time on Pembrolizumab (n = 104)



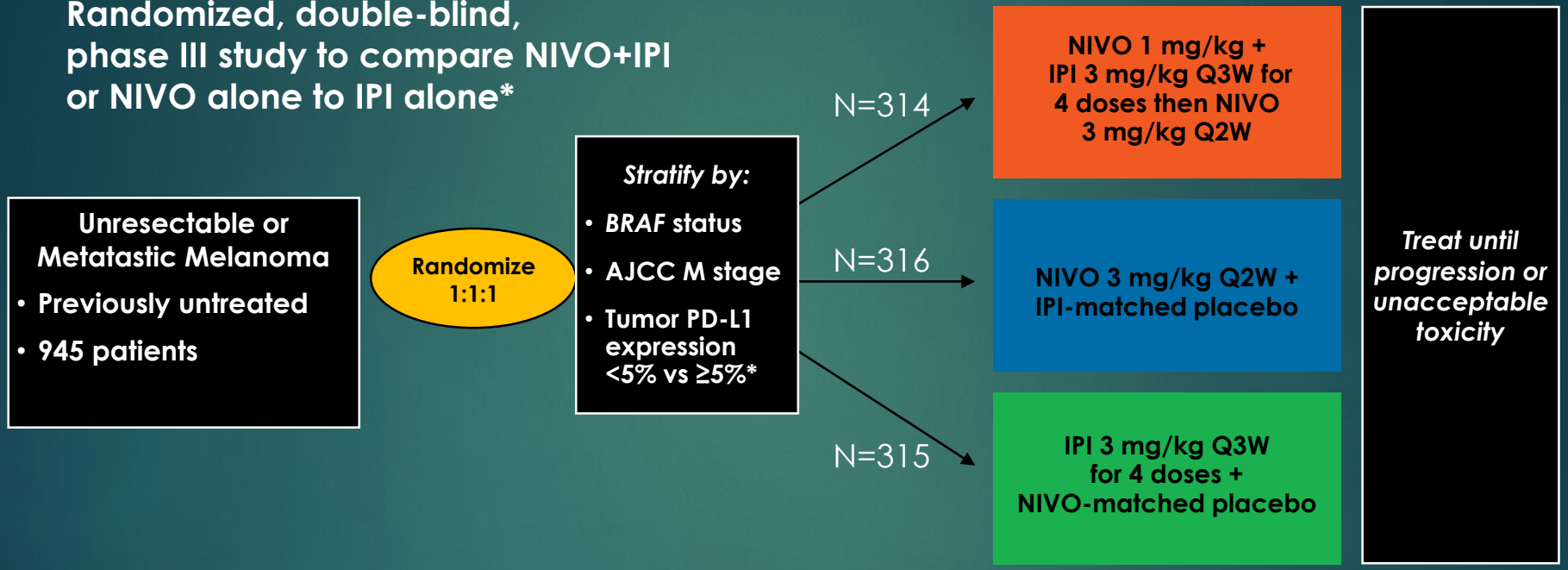
Patients who completed protocol-specified time on pembrolizumab, n	Estimated PFS, % (95% CI)	Median PFS
104	91 (80-96)	NR

- 102 (98%) patients were alive after a median of 9.7 months after completing pembrolizumab treatment

Data cutoff date: Nov 3, 2016.

CheckMate 067: Study Design

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



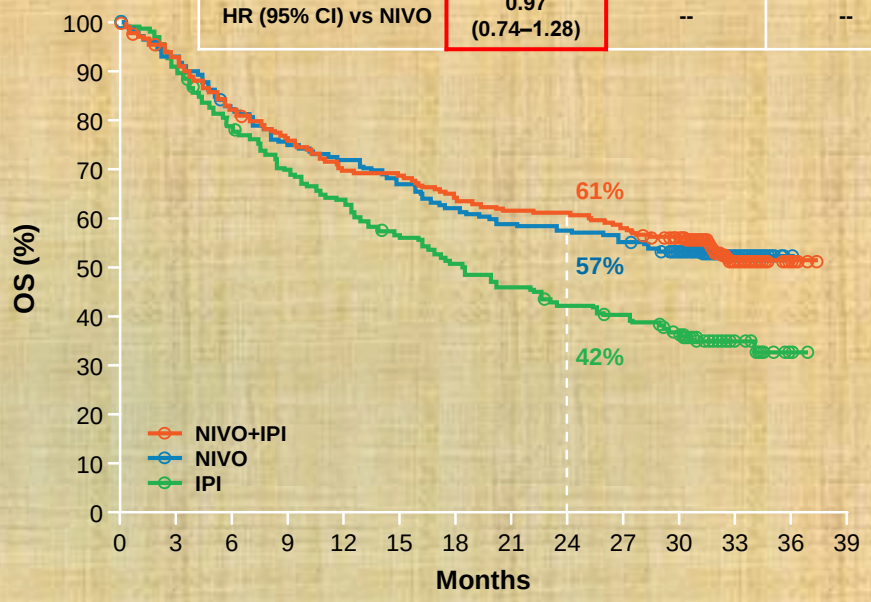
Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

**The study was not powered for a comparison between NIVO and NIVO+IPI*

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)	--	--

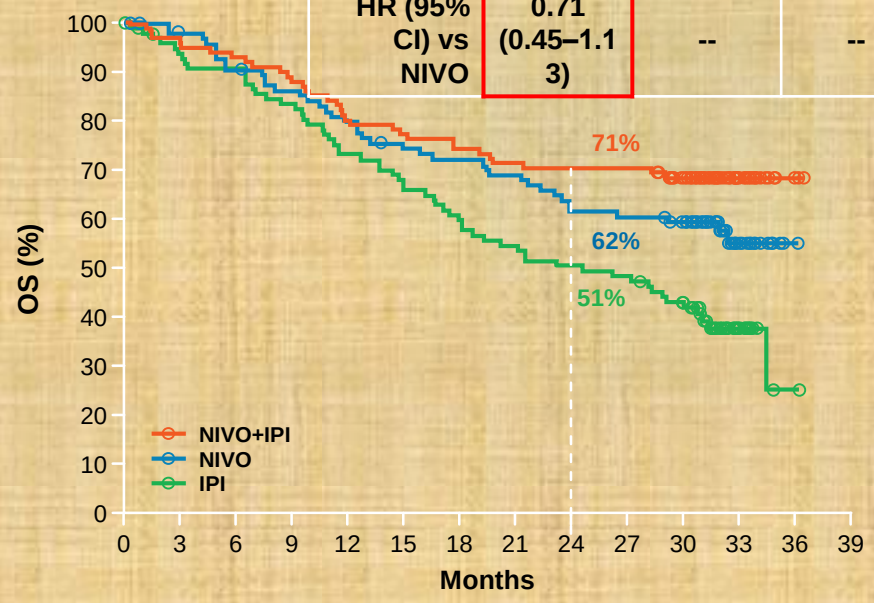


Patients at risk:

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)	--	--



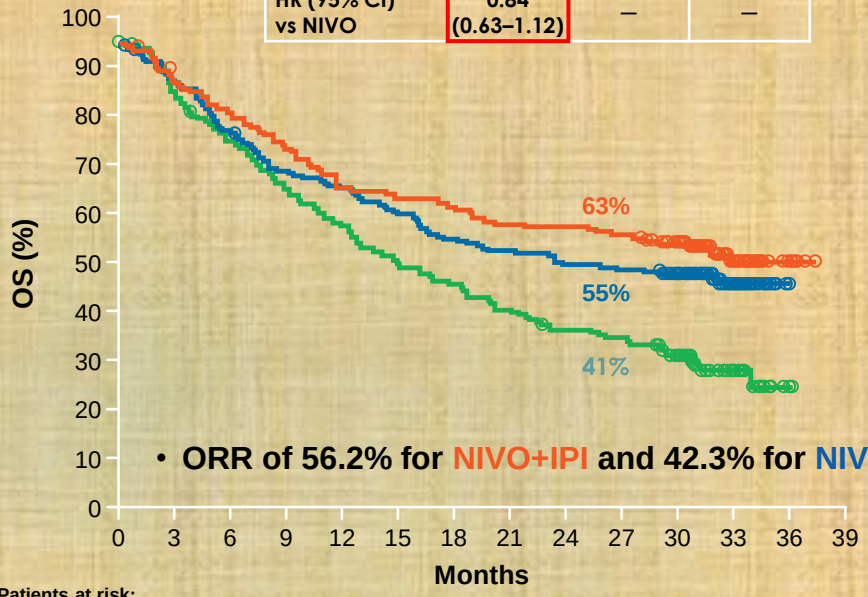
Patients at risk:

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)	—	—



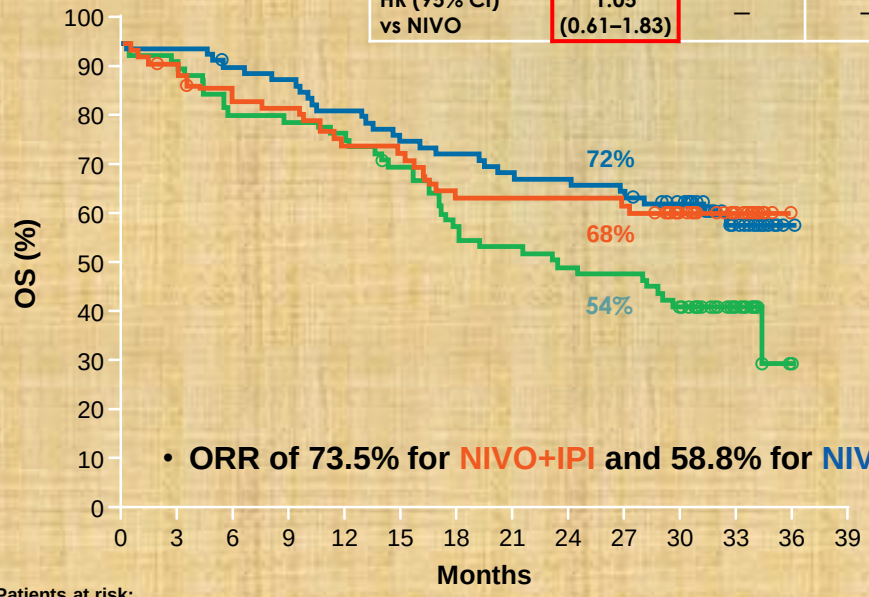
- ORR of 56.2% for NIVO+IPI and 42.3% for NIVO

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

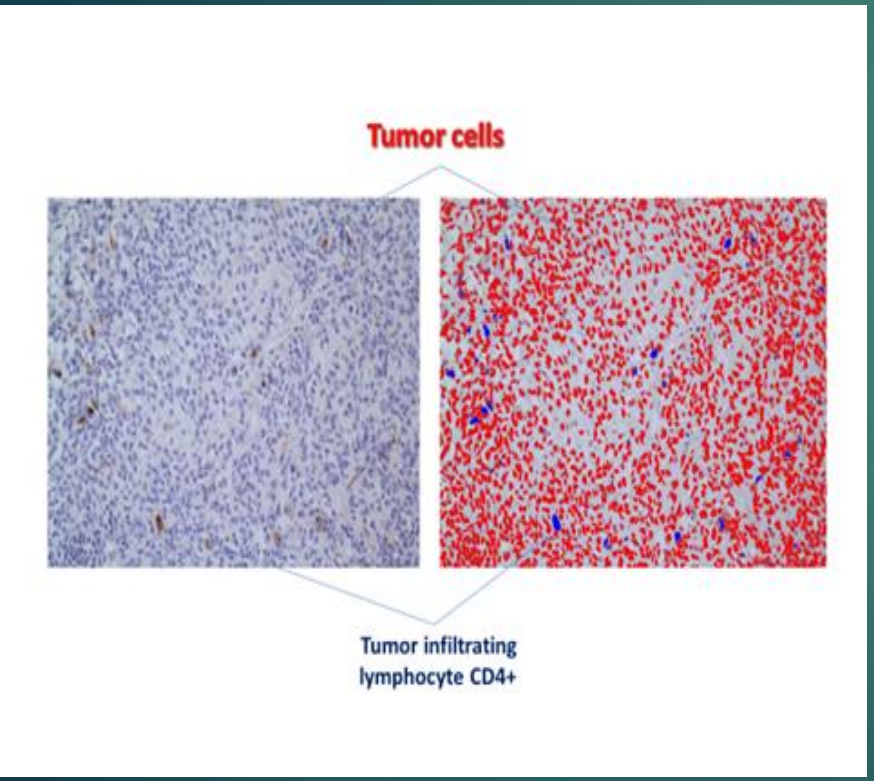
Patients at risk:

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

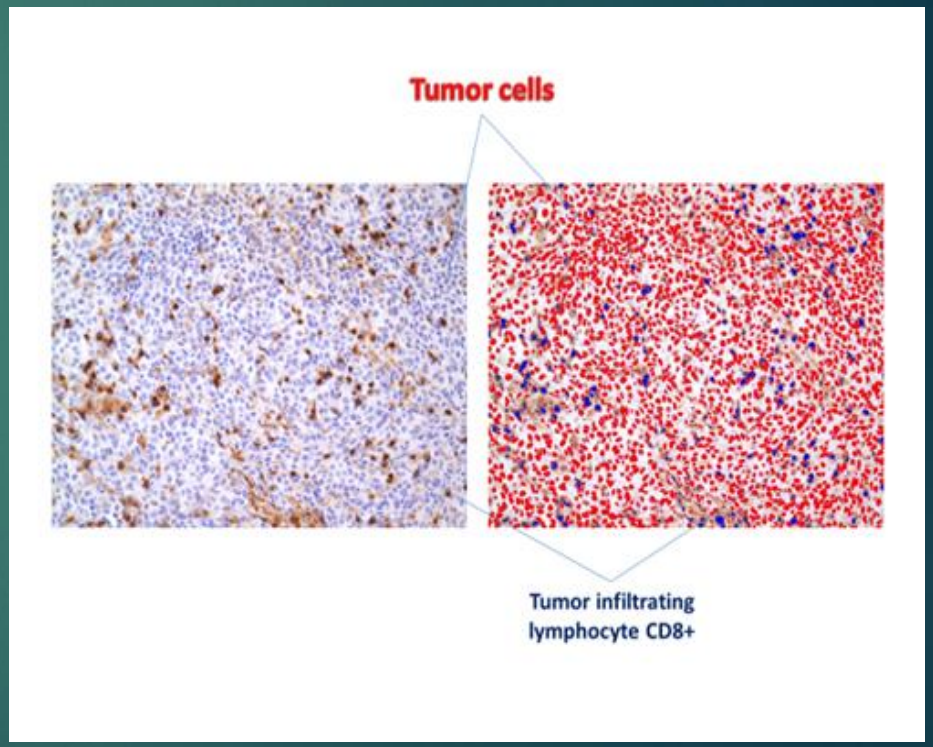
Pathology samples and computer analysis

(A. Uryvaev et al, Med. Oncol- 2018)

Case Melanoma (CD4+)



Case Melanoma (CD8+)



CD8+/CD4+ ratio: <2 (0% RR) if >2.7 (81% RR)

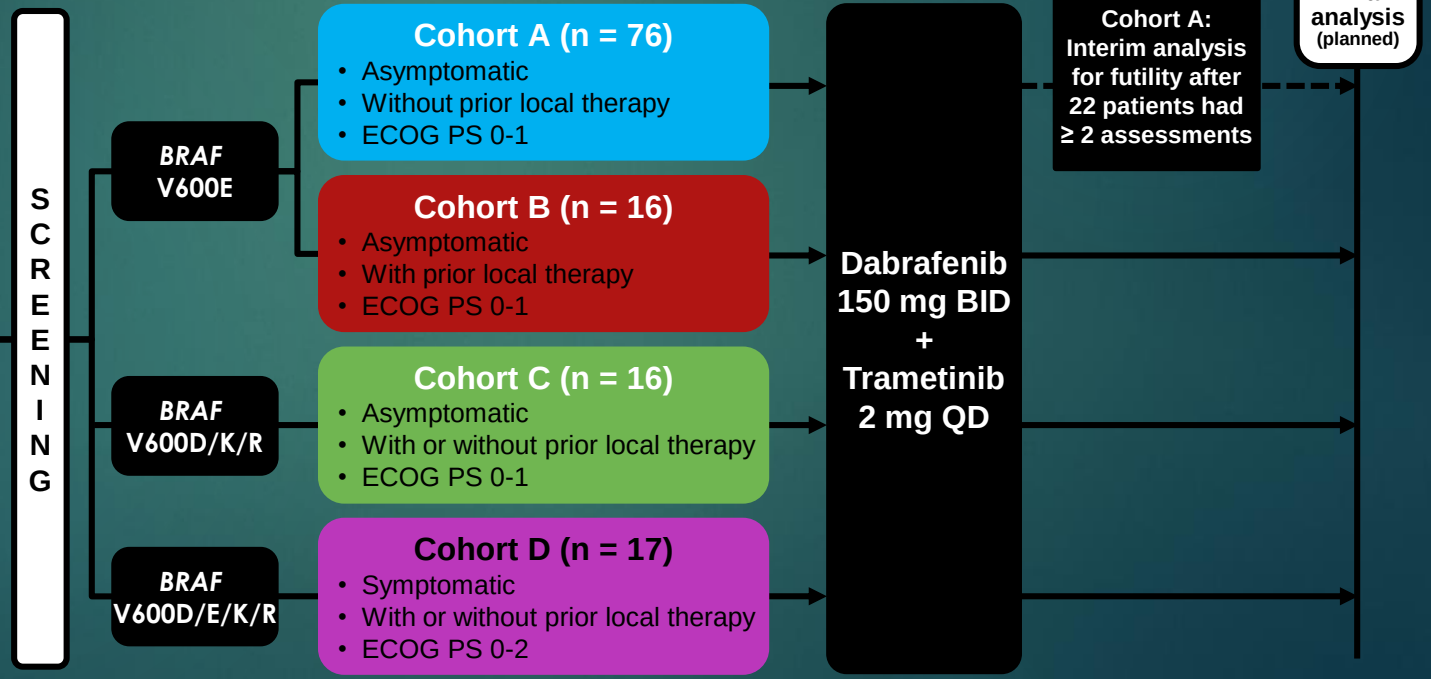
Patients with Brain metastasis

Dabrafenib plus trametinib in patients with *BRAF*^{V600}-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial

Michael A Davies*, Philippe Saiag*, Caroline Robert, Jean-Jacques Grob, Keith T Flaherty, Ana Arance, Vanna Chiarion-Sileni, Luc Thomas, Thierry Lesimple, Laurent Mortier, Stergios J Moschos, David Hogg, Iván Márquez-Rodas, Michele Del Vecchio, Céleste Lebbé, Nicolas Meyer, Ying Zhang, Yingjie Huang, Bijoyesh Mookerjee, Georgina V Long

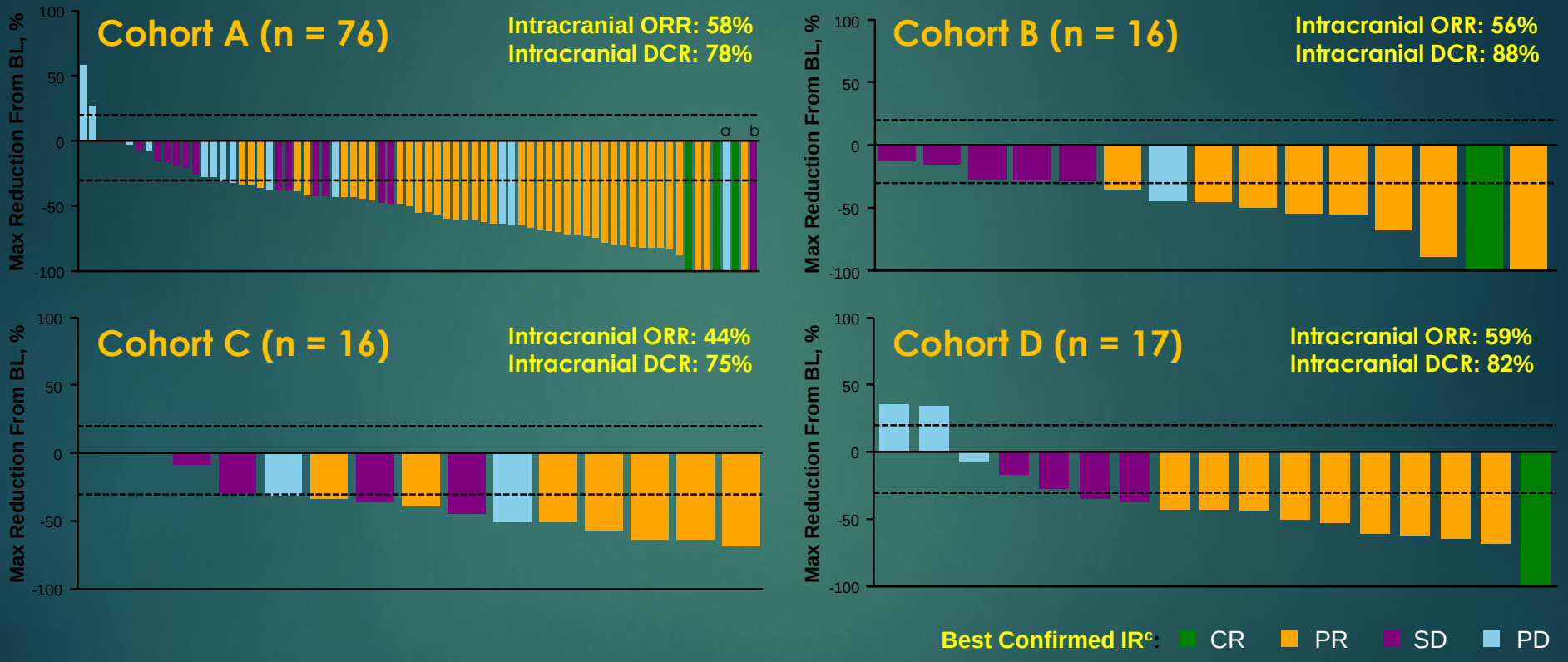
Key eligibility criteria

- Cutaneous melanoma metastatic to the brain
- *BRAF* V600D/E/K/R mutation positive
- ≤ 2 prior metastatic melanoma systemic treatments
- No prior BRAFi or MEKi
- Corticosteroids permitted; stable or decreasing dose only for cohorts A-C



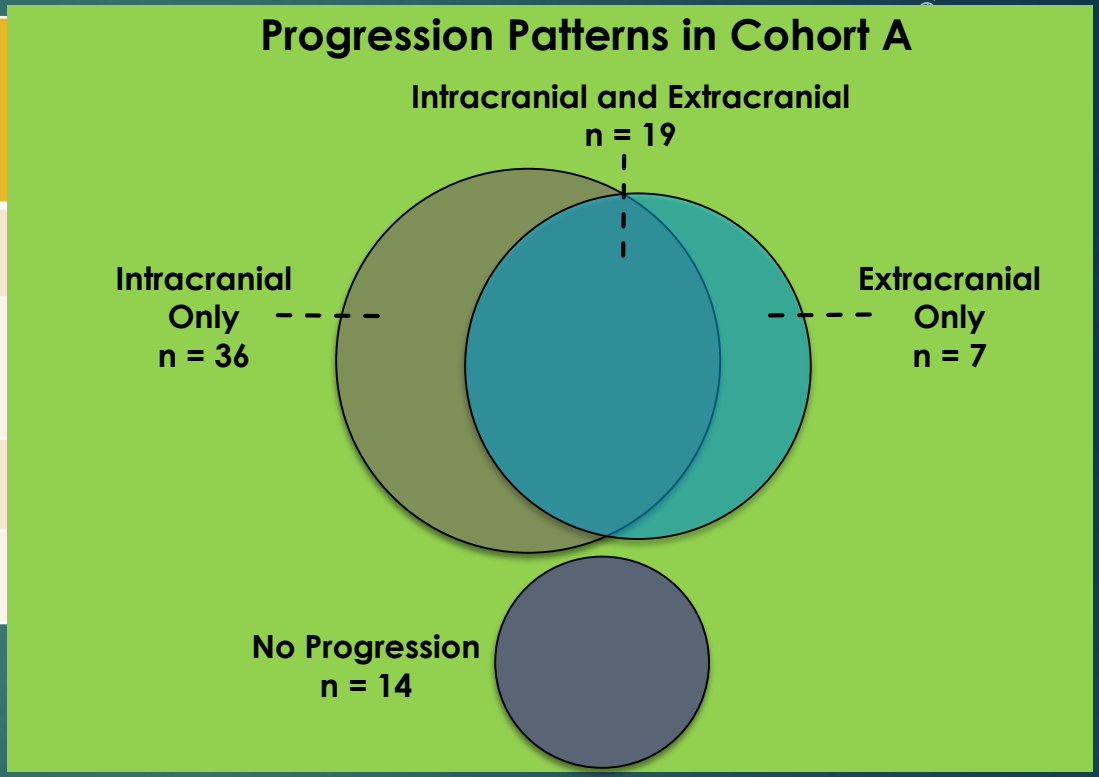
- **Primary endpoint:** intracranial response (IR) rate in cohort A[a]

Intracranial Response



Patterns of Disease Progression

Progression Category, n (%)[a]	Cohort A (n = 76)	Cohort B (n = 16)	Cohort C (n = 16)	Cohort D (n = 17)
Intracranial only	36 (47)	10 (63)	10 (63)	10 (59)
Intracranial and extracranial	19 (25)	1 (6)	3 (19)	5 (29)
Extracranial only	7 (9)	1 (6)	3 (19)	0
No progression	14 (18)	4 (25)	0	2 (12)



- Pattern of disease progression is described for all enrolled patients, including those who did not have disease progression while on study treatment.

A Randomized Phase 2 Study of Nivolumab or Nivolumab plus Ipilimumab in Patients with Melanoma Brain Metastases:

- **Melanoma Brain Metastases ≥ 5mm & < 40mm**
- **No previous**
  - **Anti-CTLA-4**
  - **Anti-PD-1 or -PD-L1 agents**
- **Previous BRAFi+MEKi allowed**
- **ECOG PS 0-2**
- **No serious autoimmune disease**
- **No corticosteroids**

(Cohort C < 10mg prednisone allowed)

R 1:1
up to n=53

A
No prior local brain Rx & asymptomatic
n=33
Rx = Nivolumab + Ipilimumab

B
No prior local brain Rx & asymptomatic
n=27
Rx = Nivolumab

C
Previously treated or symptomatic or leptomeningeal, with MRI progression
n=16
Rx = Nivolumab

Presented by Georgina V. Long

Total 76 Patients Recruited

Best Intracranial RECIST Response

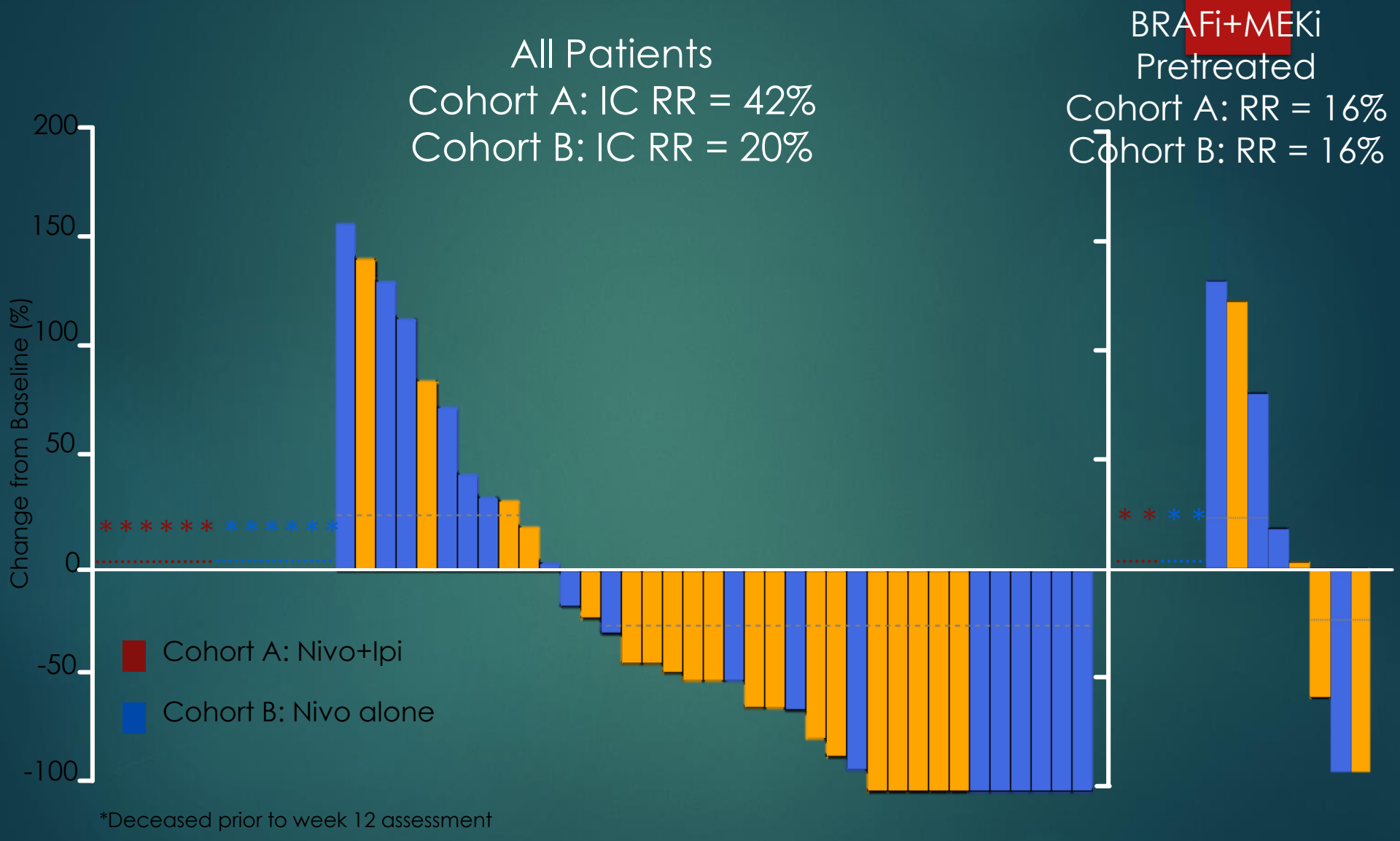
	A: Ipi+Nivo N=26	B: Nivo N=25	C: Nivo† N=16
Intracranial Response, n (%)	**11 (42%)**	**5 (20%)**	**1 (6%)**
CR	4 (15%)	3 (12%)	0
PR	7 (27%)	2 (8%)	1 (6%)
SD	2 (8%)	1 (4%)	4 (25%)
PD	12 (46%)	18 (72%)	11 (69%)
NE*	1 (4%)	1 (4%)	0

- Median duration of intracranial response not reached in any arm

NE = Not Evaluable
*Pts who deceased prior to wk 12 = PD
†Leptomeningeal, previous local treatment or symptoms

Presented by Georgina V. Long

Intracranial Response



*Deceased prior to week 12 assessment

Presented by Georgina V. Long

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation

Estimating Survival in Melanoma Patients With Brain Metastases: An Update of the Graded Prognostic Assessment for Melanoma Using Molecular Markers (Melanoma-molGPA)

Paul W. Sperduto, MD, MPP, FASTRO,* Wen Jiang, MD,†

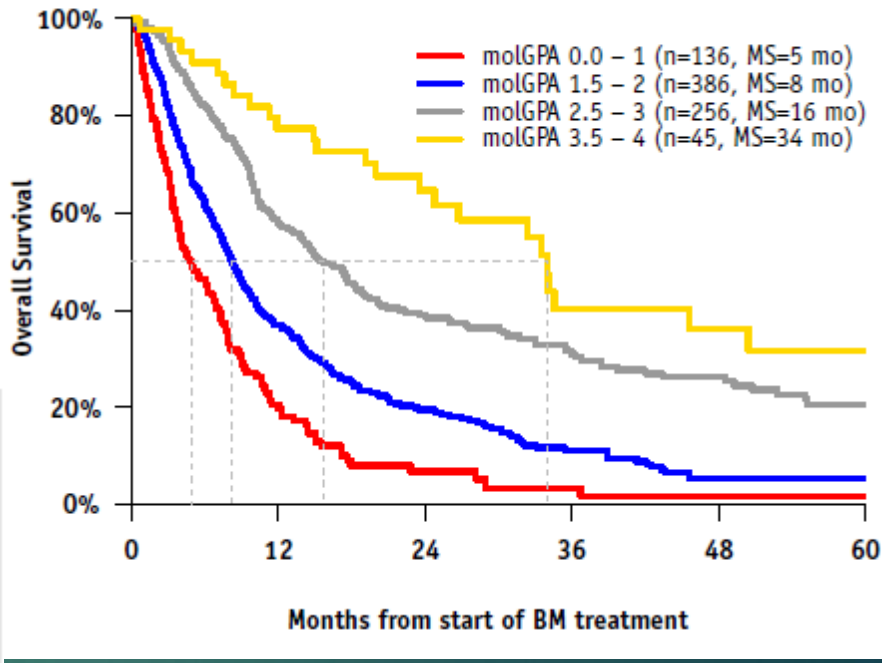
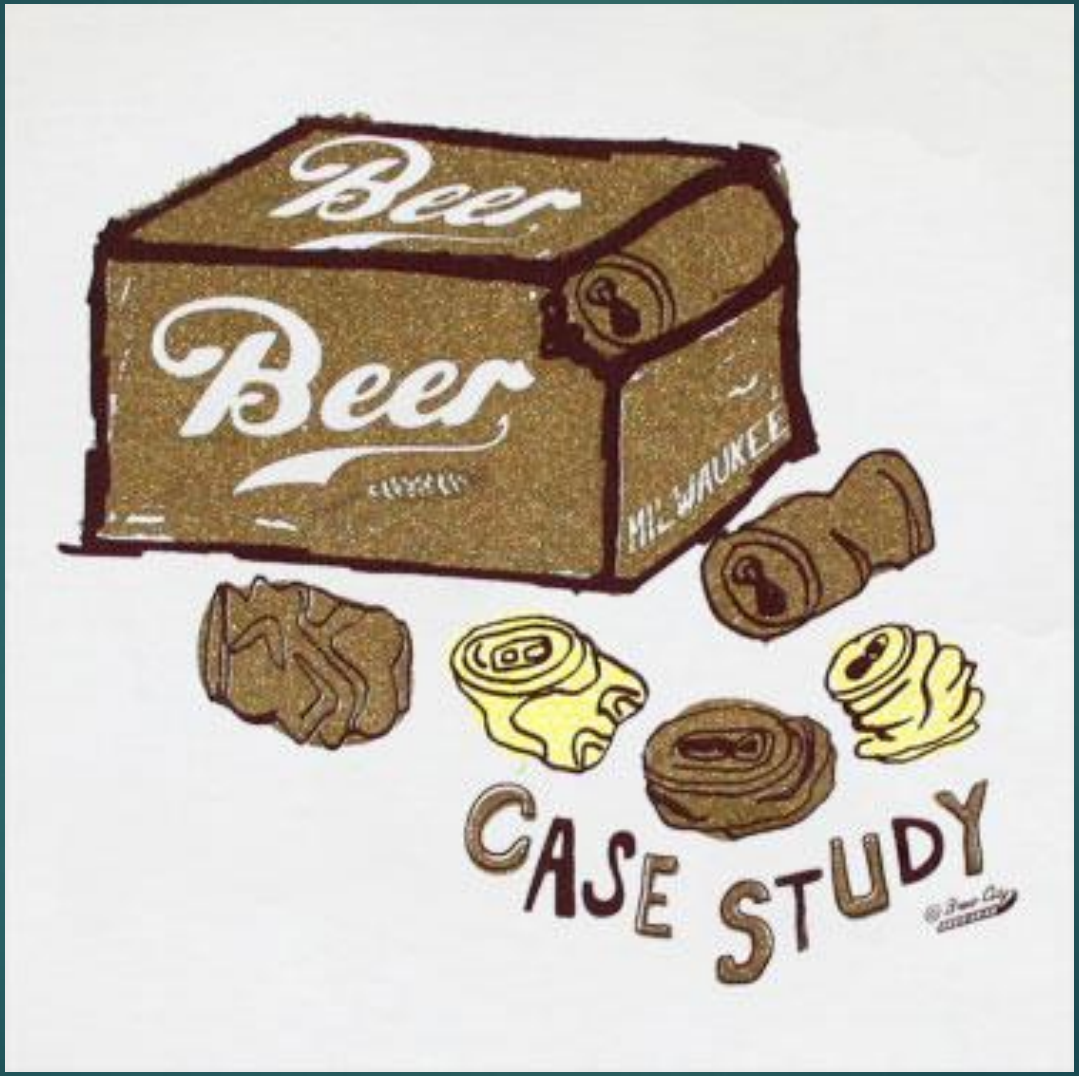


Table 2 Melanoma GPA worksheet

Prognostic factor	GPA scoring criteria			Patient Score
	0	0.5	1.0	
Age, y	≥70	<0		-
KPS	≤70	80	90-100	-
ECM	Present		Absent	-
No. of BM	>4	2-4	1	-
BRAF gene status	Negative/unknown	Positive		-
			Sum	-

Abbreviations: BM = brain metastases; ECM = extracranial metastases; GPA = Graded Prognostic Assessment; KPS = Karnofsky performance status; MS = median survival in months.

MS by GPA: 0-1.0 = 4.9, 1.5-2.0 = 8.3, 2.5-3.0 = 15.8, 3.5-4.0 = 34.1.


Beer
Beer
MILWAUKEE
CASE STUDY

First line: The very poor prognostic patient (symptomatic, M1c+++, LDH>N)

BRAF-

Ipilimumab+ Nivolumab

*without comorbidities

*understand toxicity

BRAF+

BRAFi +MEKi

*consider switch to immuno. after good response (6 weeks?)

Case: Combination BRAF &MEK inhibitors

MALE 70Y

FEBRUARY 2014: METASTATIC MELANOMA TO: LUNGS, ,MEDIASTINUM, SKIN AND SOFT TISSUE, KIDNEY, BONE- SCAPULA

4 LESIONS IN THE BRAIN

PAIN MEDICATION (TARGIN, DEXAMETAZONE)

RADIOTHERAPY: SRS AND XRT TO SCAPULA

TARGET THERAPY: TAFINLAR AND MEKINIST

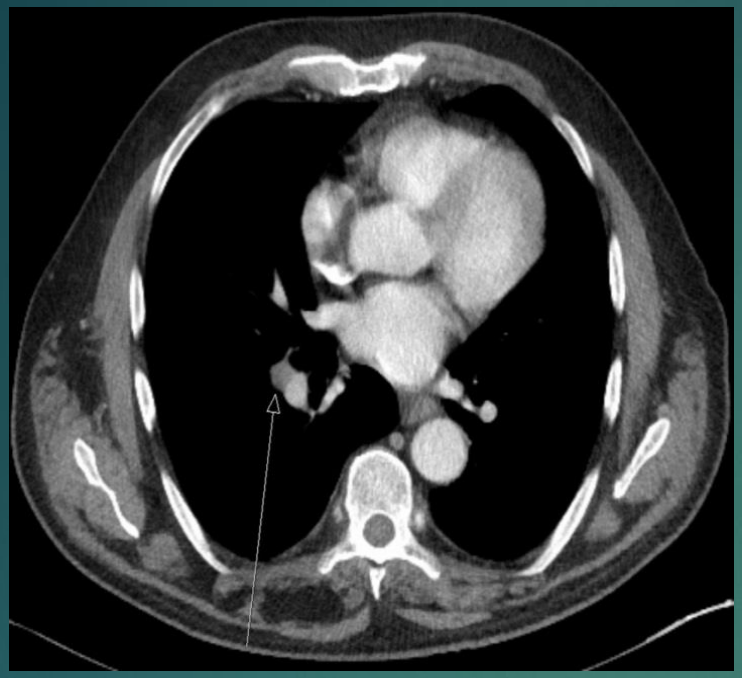
CT-PET: COMPLETE RESPONSE (EXCEPT KIDNEY COMPLICATED CYST

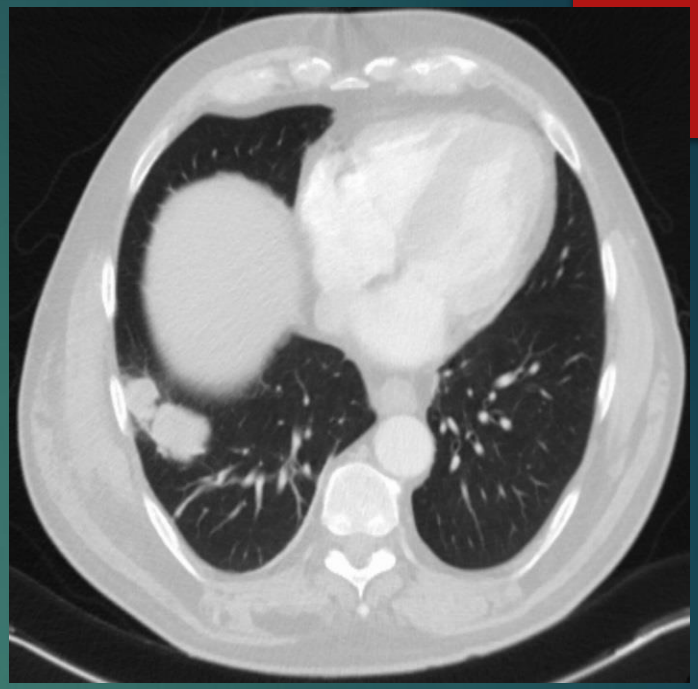
PET SCAN: AUG 2016- STILL IN CR

JANUARY 2017: MULTIPLE NEW BRAIN METS (WHOLE BRAIN XRT AND IMMUNOTHERAPY

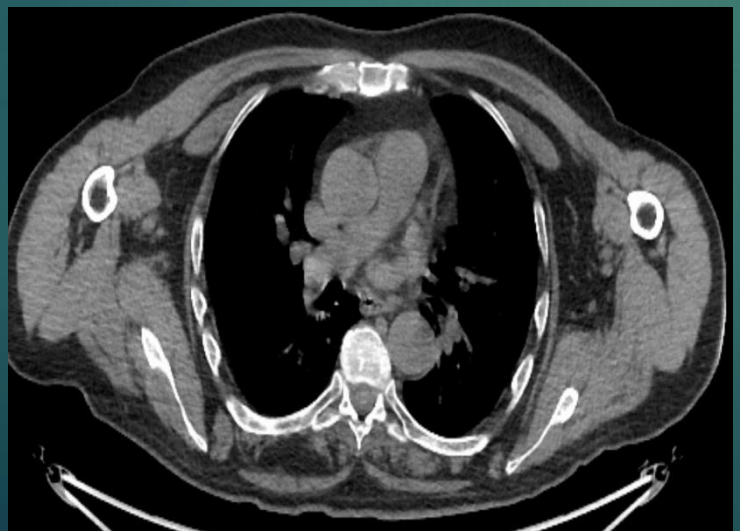
PAST-WAY IN APRIL 2017

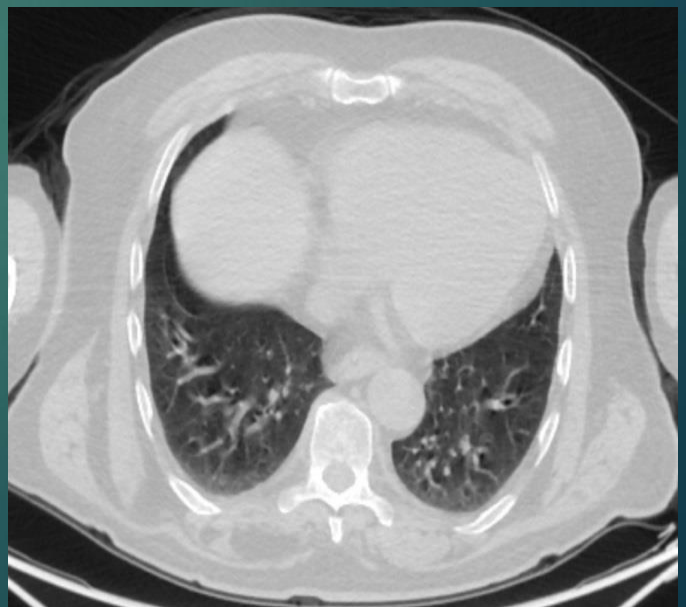
February 2014



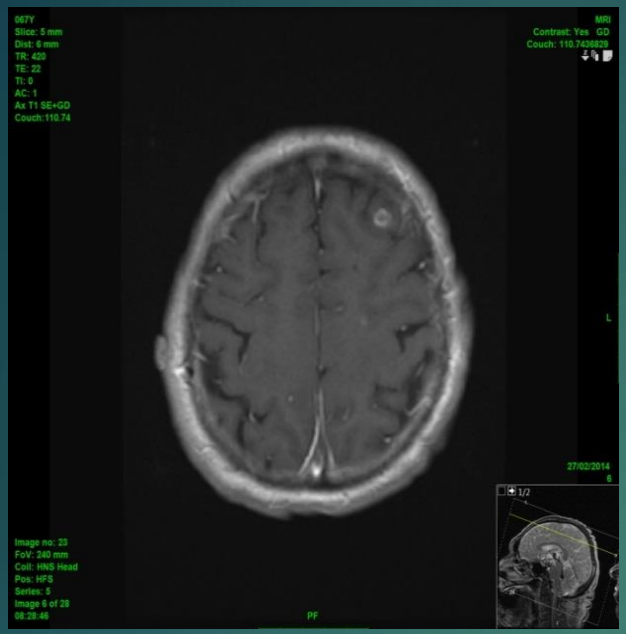


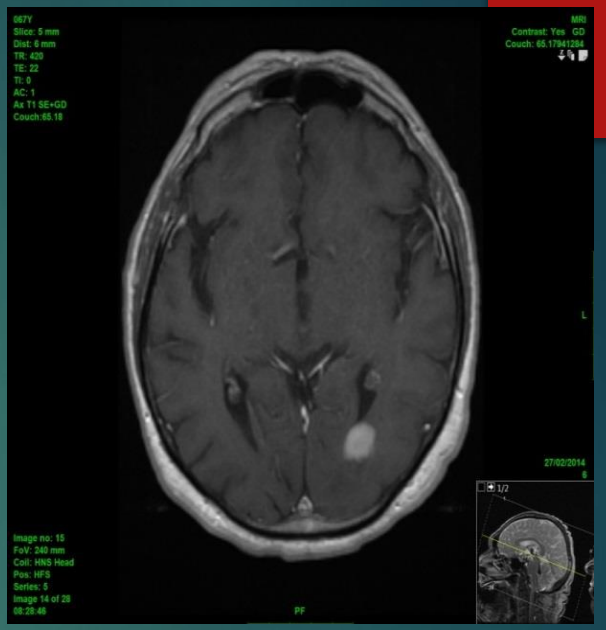
August 2014



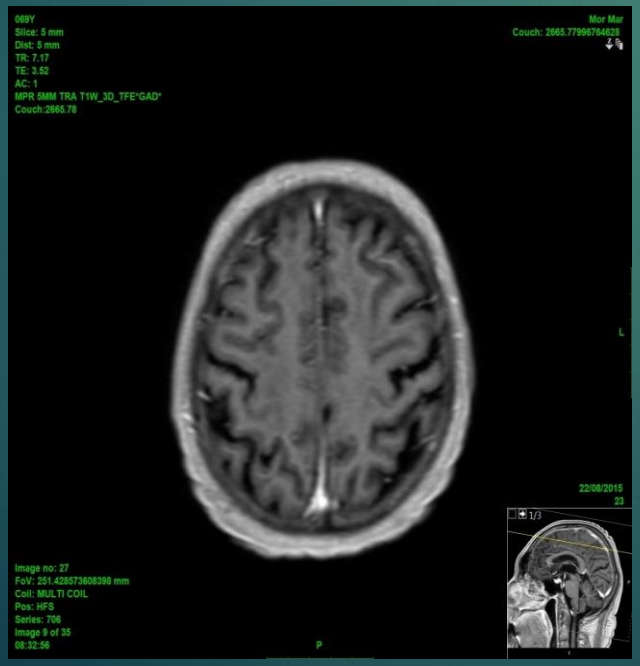


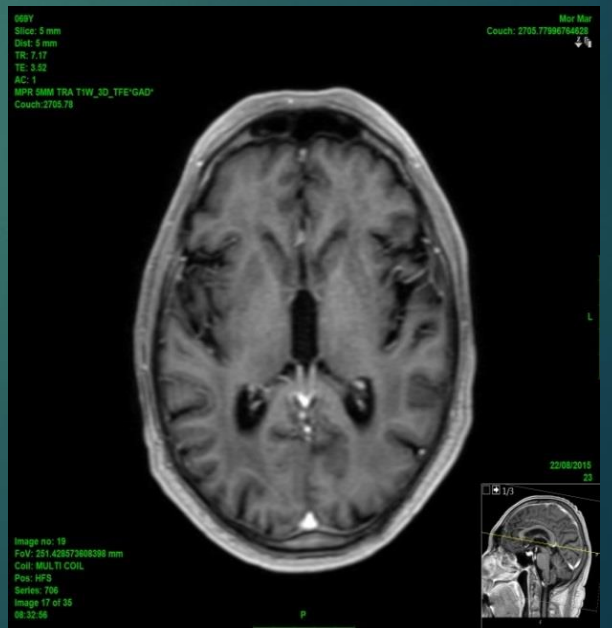
February 2014





August 2014





First line: The poor prognostic patient (M1c [brain and /or liver], LDH=N)

BRAF-

Ipilimumab+
Nivolumab
*without comorbidities
*understand toxicity

High TILs and/or PDL-1+++
Monotherapy

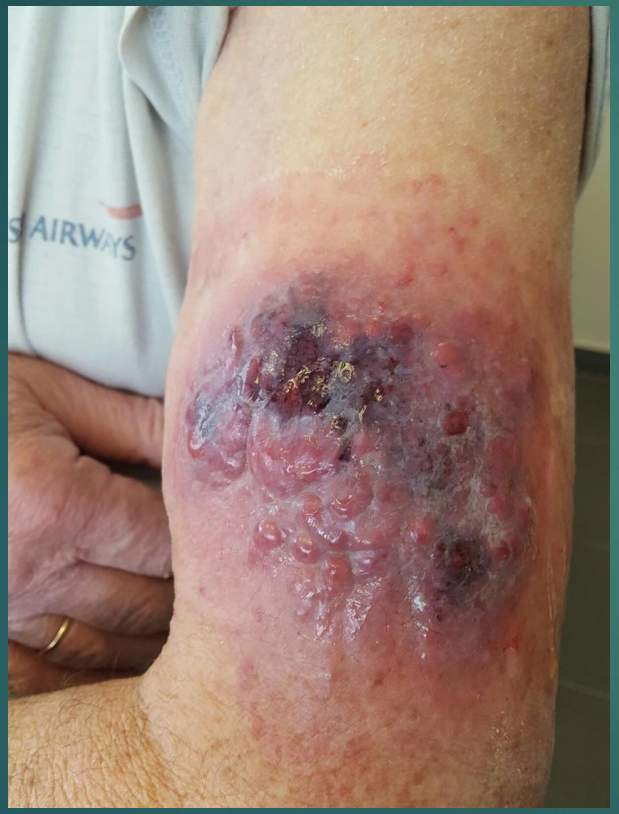
BRAF+

BRAFi +MEKi
Or
Ipilimumab+
Nivolumab
* Consider according the need for fast response

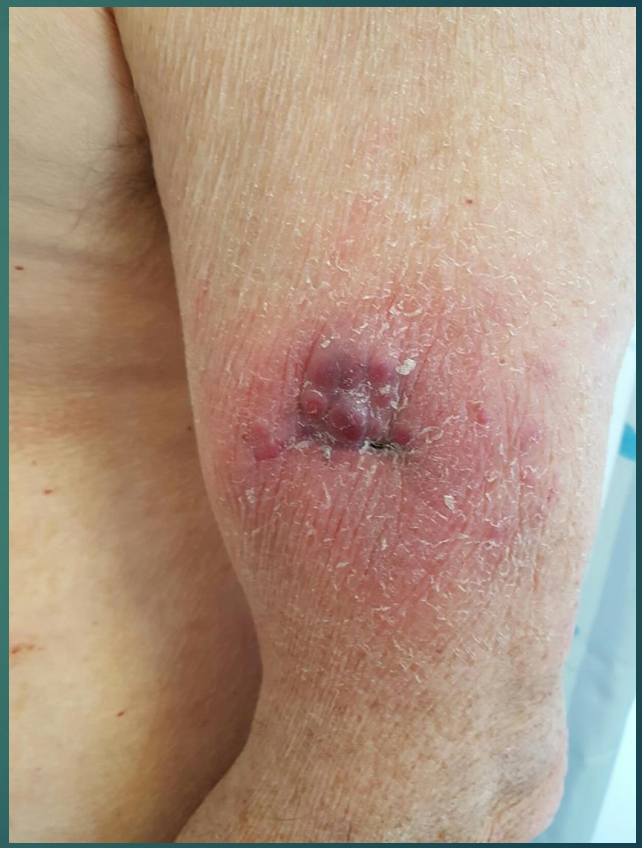
Case

- Male, 78 years old
- Background: chronic IHD (not active, 1994 s/p CABG)
- Atrial fibrillation (anti-coagulation treatment)
- Hypothyroidism (hormone replacement)
- Mild renal failure (cr. 1.8 chronic)
- Current illness: Bleeding nevus on his left arm
- Pathology (9.1.17): MM, Breslow 6mm, several satellites
- PET-CT: pathological uptake in the arm and axilla LN
- Cytology from the axilla (14.2.17): Melanoma
- BRAF- Negative

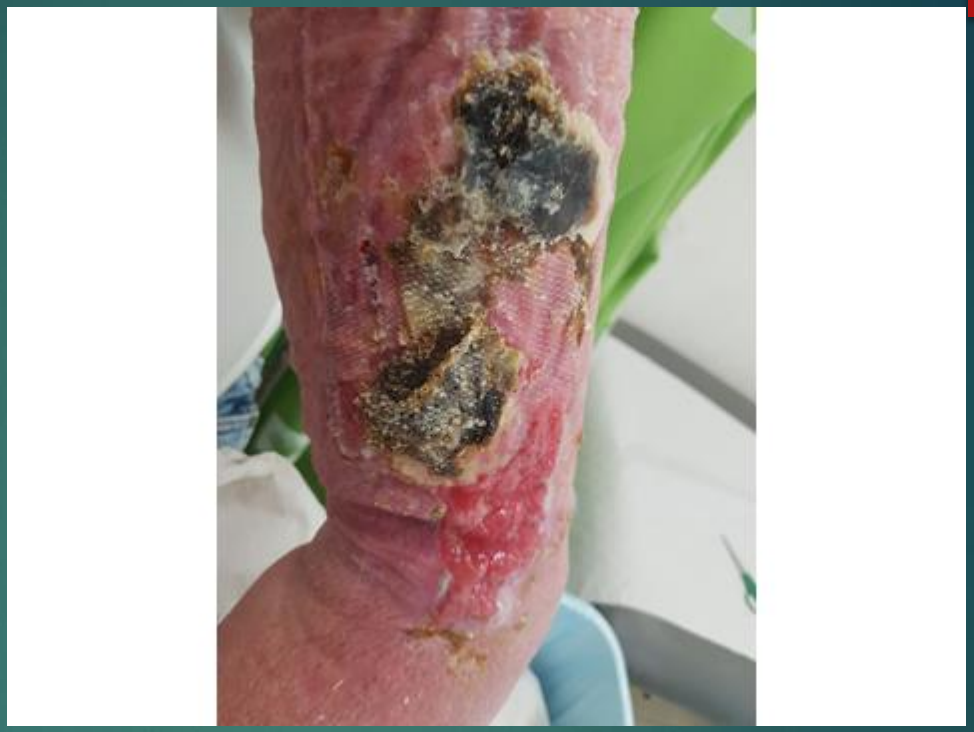
27.2.17- before treatment



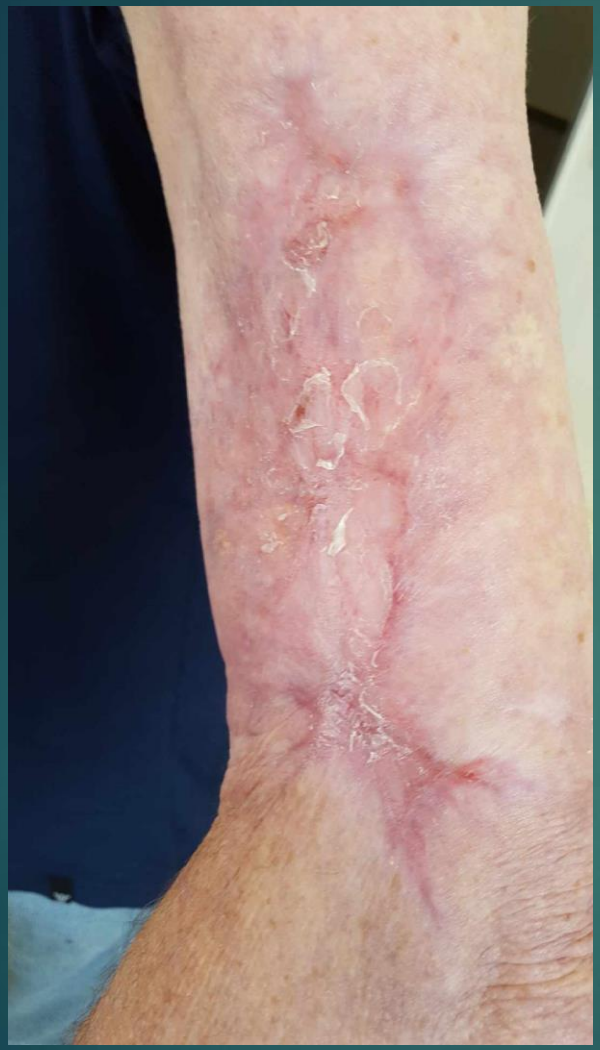
7.2.17



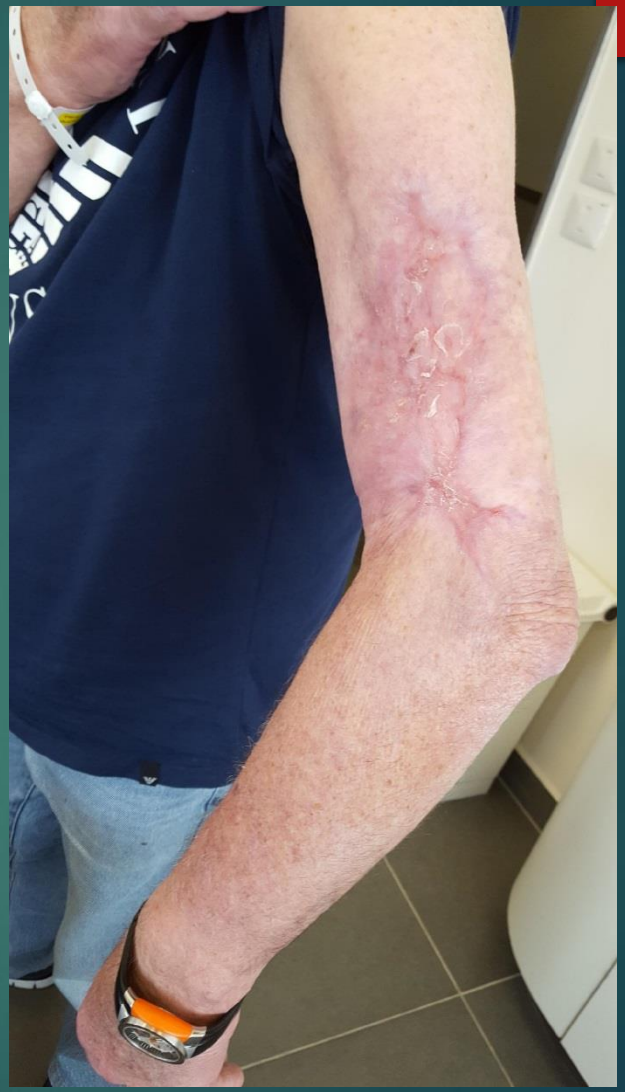
After 1 treatments of Nivo +Ipi.
Hospitalization for Angio-embolization
After 2ed.: 1 week hospitalization with severe confusion
Hyponatremia, Hypokalemia (grade 3) and
Hypothyroidism - worsen.



April 2017:
After 3 cycles and the embolization



Sep. 2017 On going



First line: The good prognostic patient (M1a-b)

BRAF-

Pembrolizumab
or
Nivolumab

*low TILs and/or low PDL-1
Ipilimumab+ Nivolumab

BRAF+

Pembrolizumab
or
Nivolumab
or
BRAFi +MEKi

Case

71 years old, female

In 2012 T4bN0M0 melanoma in the chest wall

In May 2015, metastatic melanoma to lymph nodes in left axilla, left supra-clavicular, right sub-mandibular (PET-2015)

Started Pembrolizumab

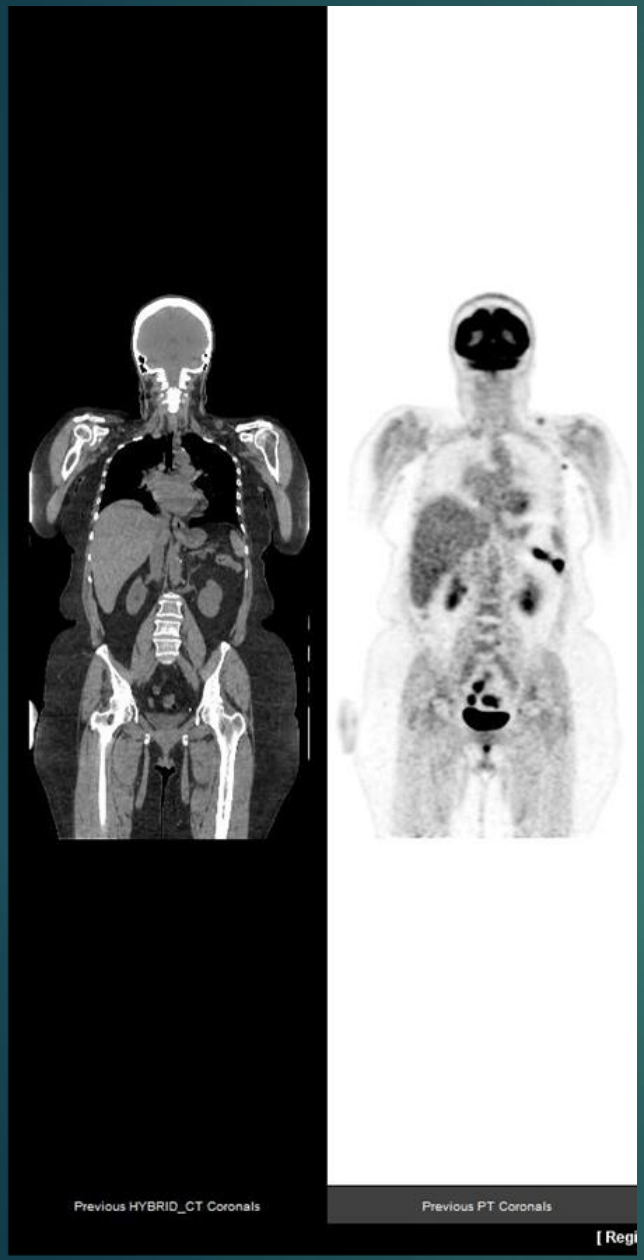
In February 2016, nausea, vomiting, diarrhea, (brain MRI-NED). Hospitalized for treatment (sulomidrol).

In May 2016, complete remission by PET-CT. Treatment ended in October 2016.

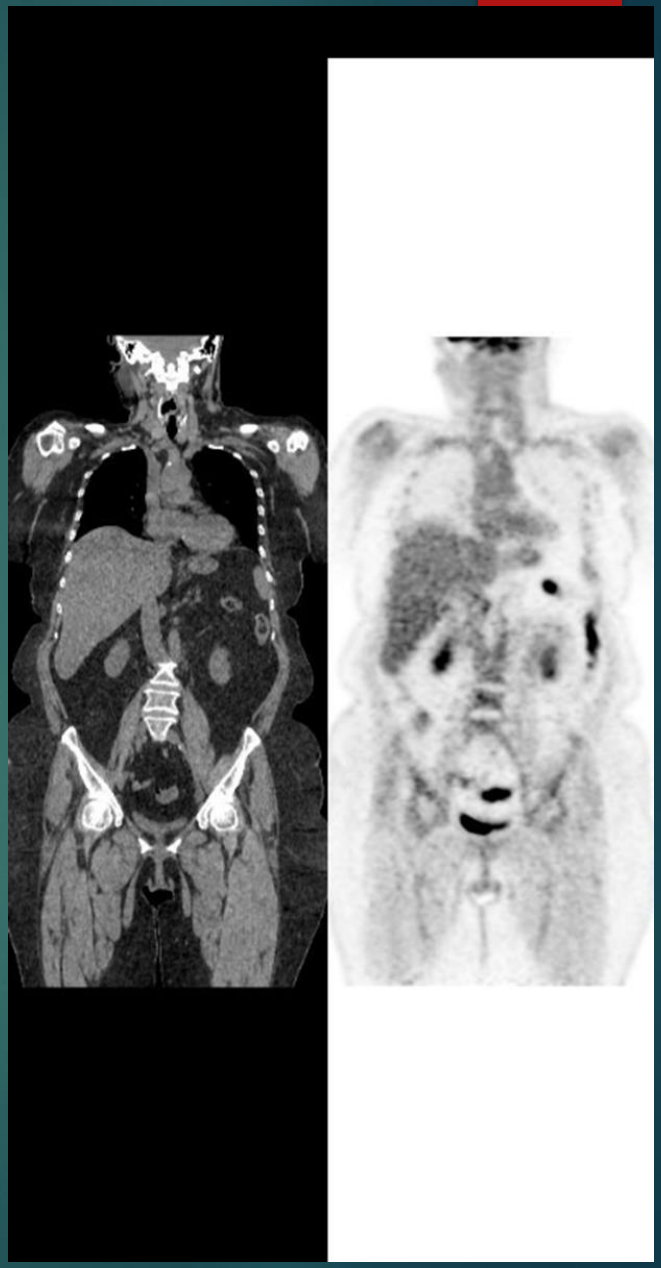
In March 2017,hospetilised with colitis and severe weakness. Re-treatment with steroids, with slow tapering down.

Left with 5mg prednisone. PET-CT in June 2018, still CR

May 2016



May 2017




teşekkür ederim