MELANOMA

Nuove Prospettive

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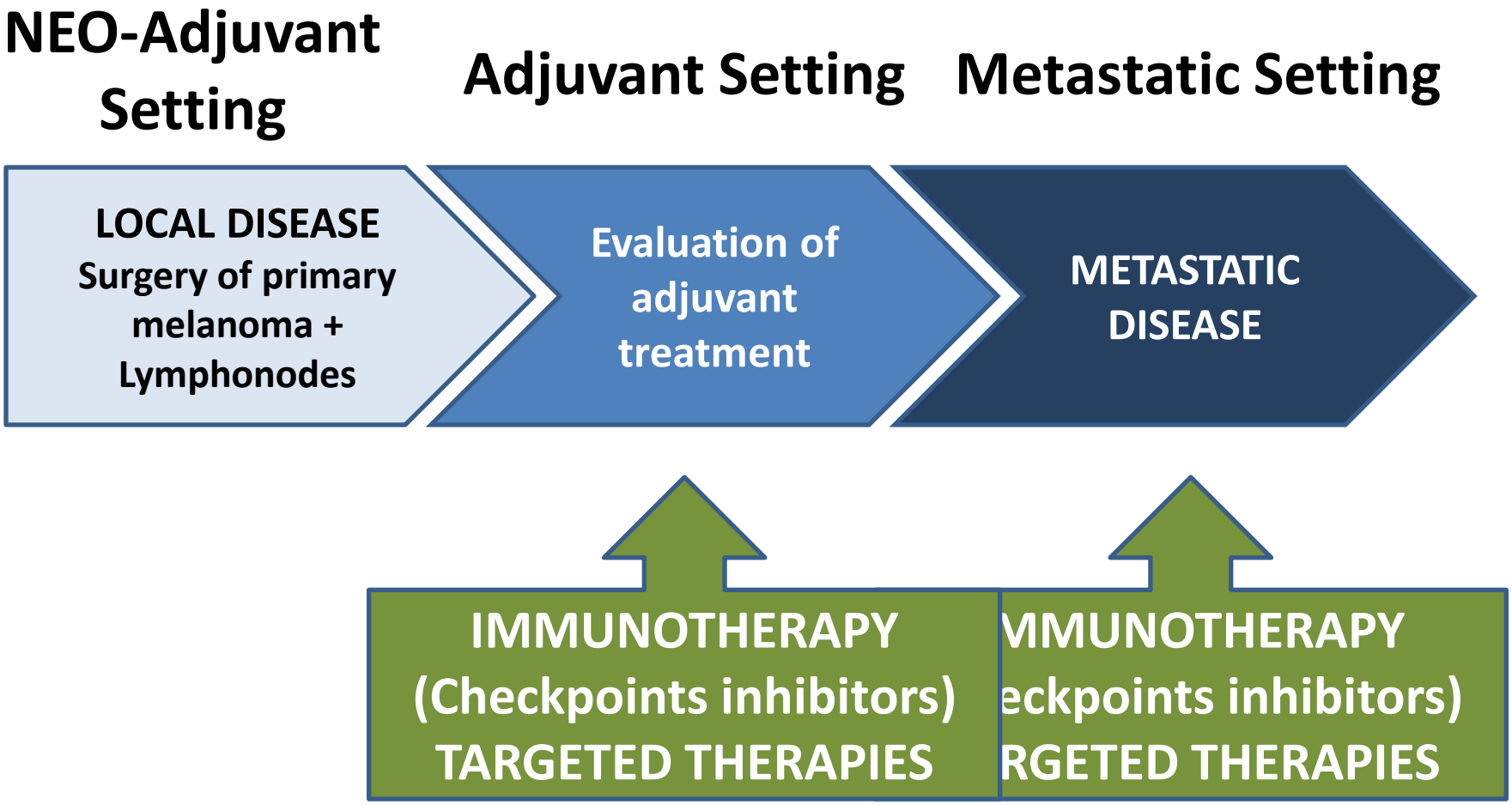
dichiarazione conflitto di interessi

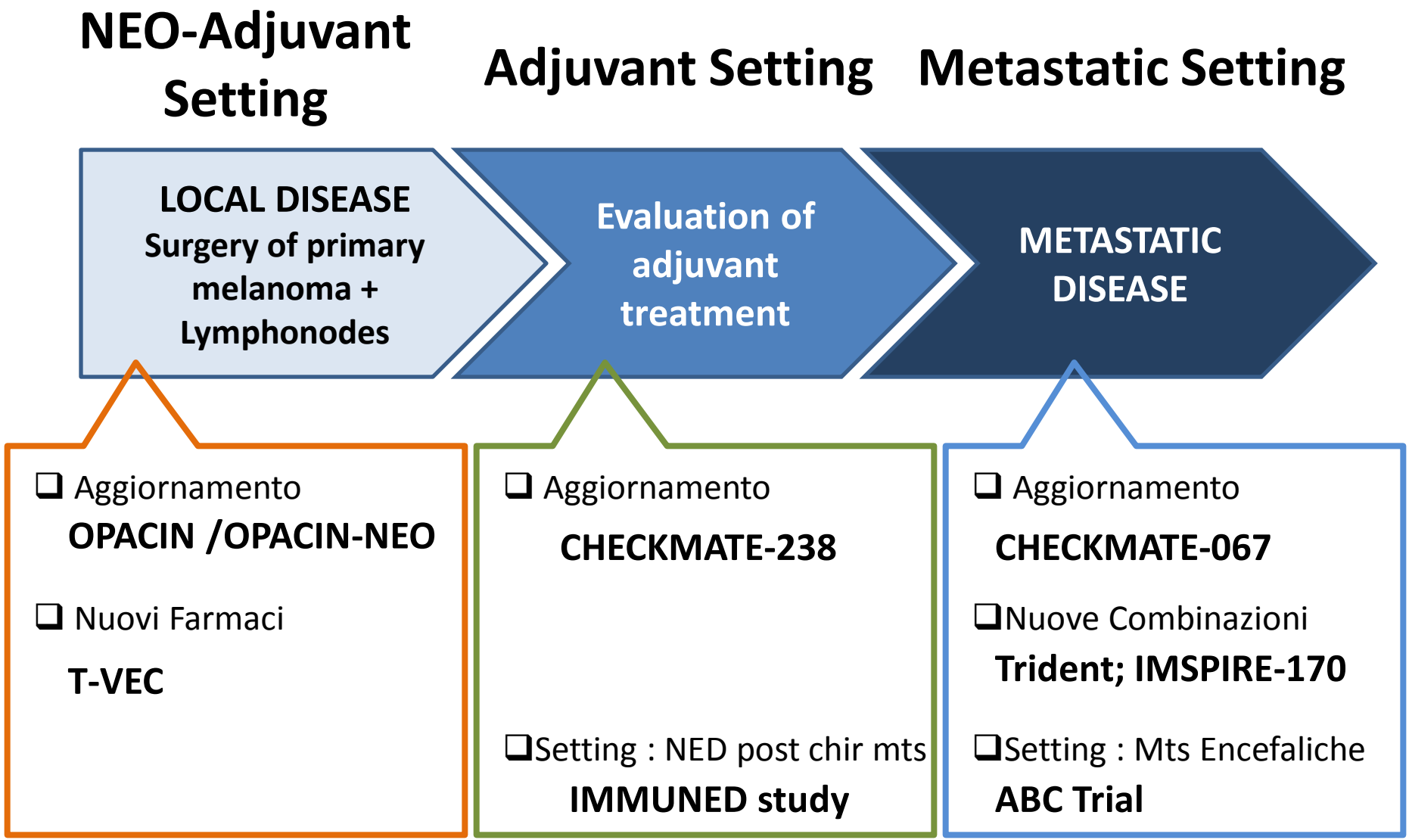
Ho / ho avuto rapporti (finanziari o di altro tipo) con le Aziende del farmaco

Relationship	**Company/Organization**
Membro di Advisory Board	Novarti, Pierre Fabre, MSD
Onorari per attività editoriali	MSD, Novartis
Consulenze scientifiche	MSD, Incyte, BMS
Partecipazione a sperimentazioni cliniche	Novartis, Ipsen, La Roche, BMS,
Partecipazioni congressuali	Novartis, Ipsen, La Roche, MSD, BMS

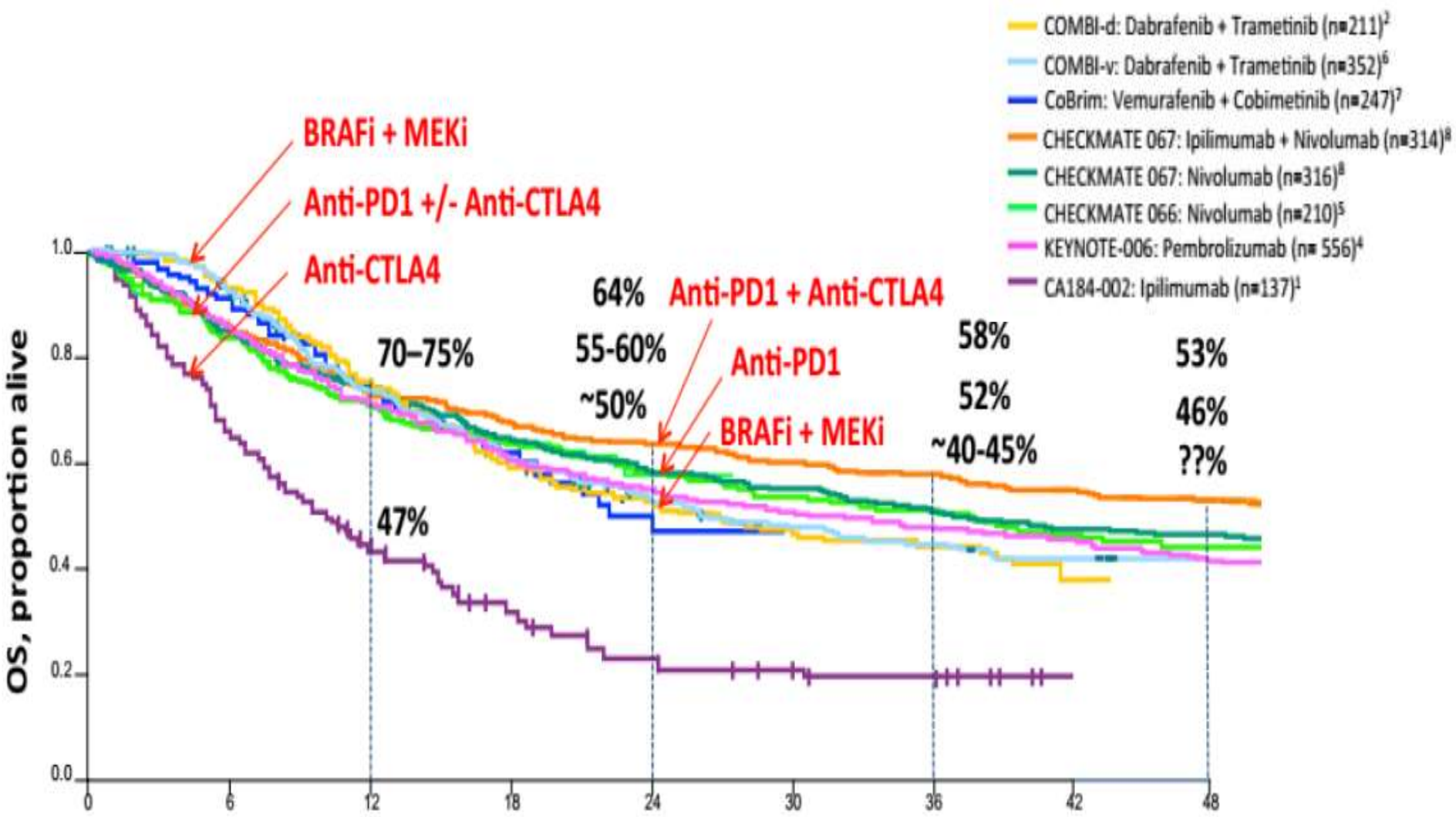
Melanoma Patient Hystory: Research Areas



Melanoma:
NOVITA' ESMO 2019

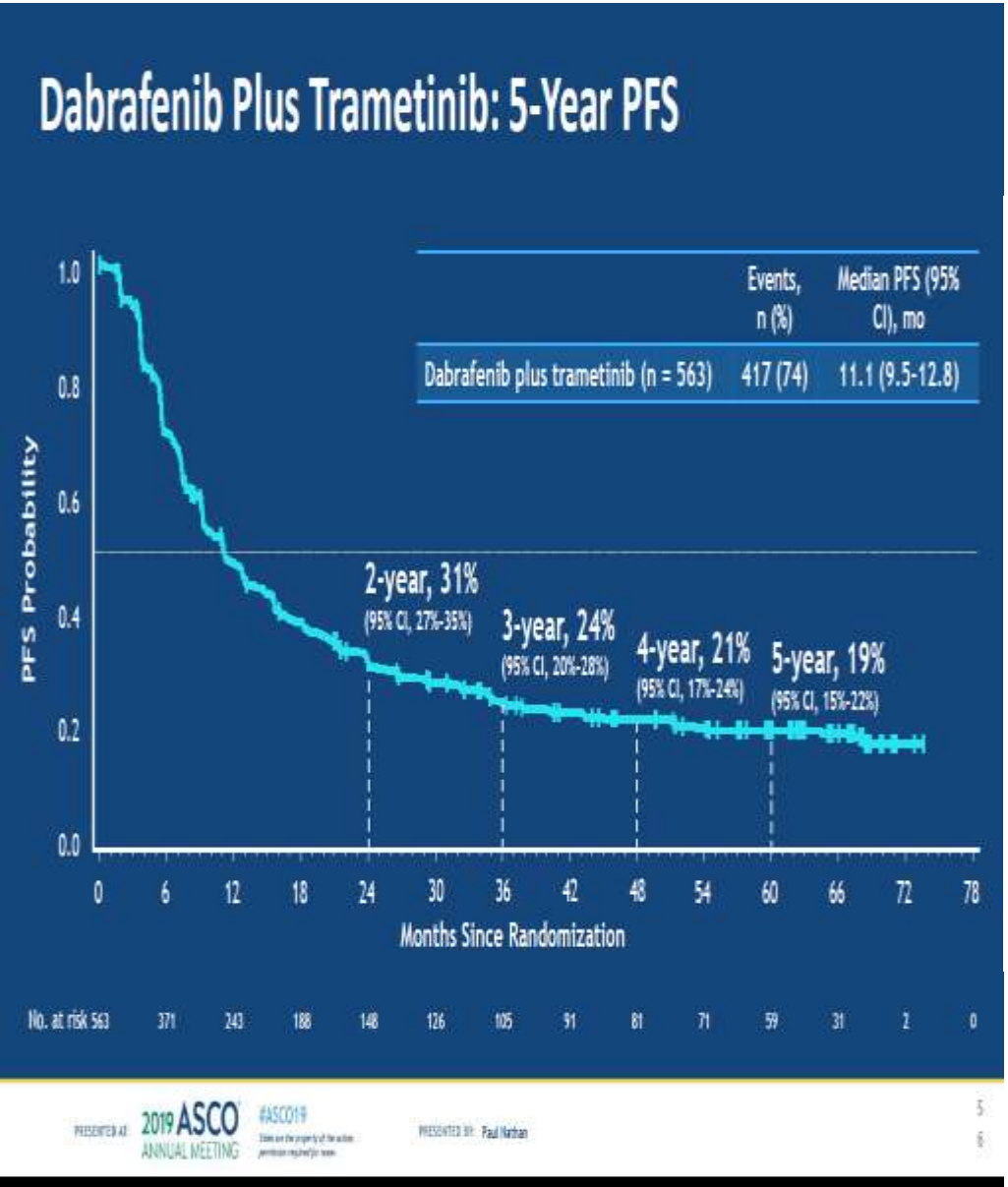


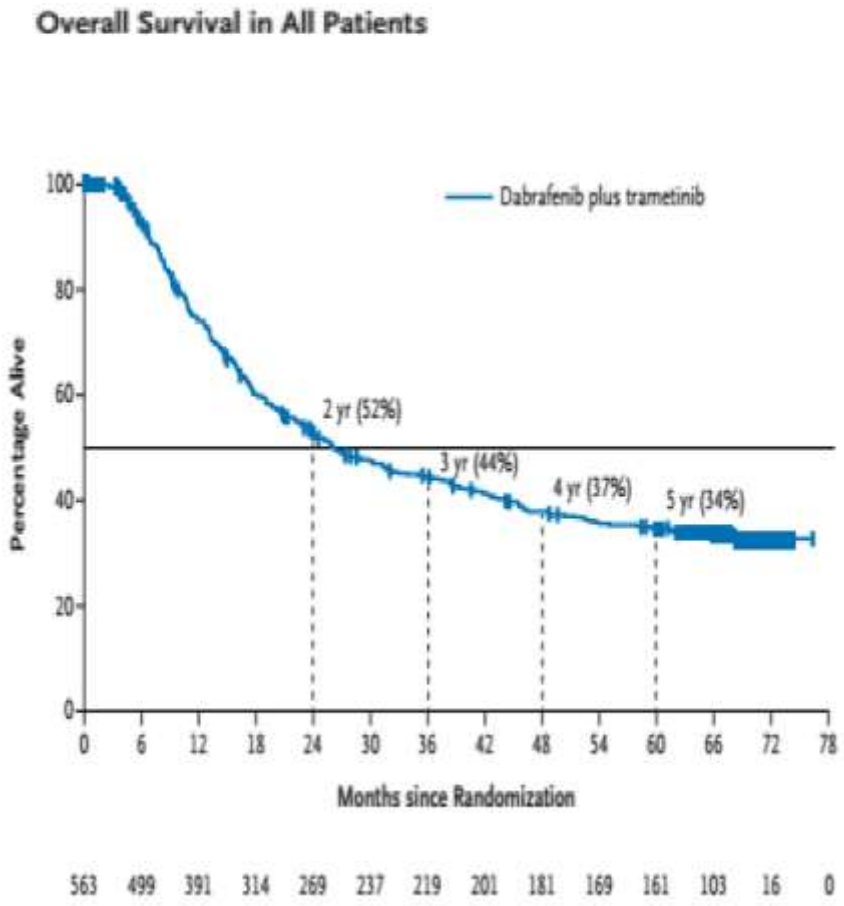
Melanoma:
SETTING METASTATICO



Presentato da P. Rutkowski
ad ESMO 2019

Melanoma:
SETTING METASTATICO





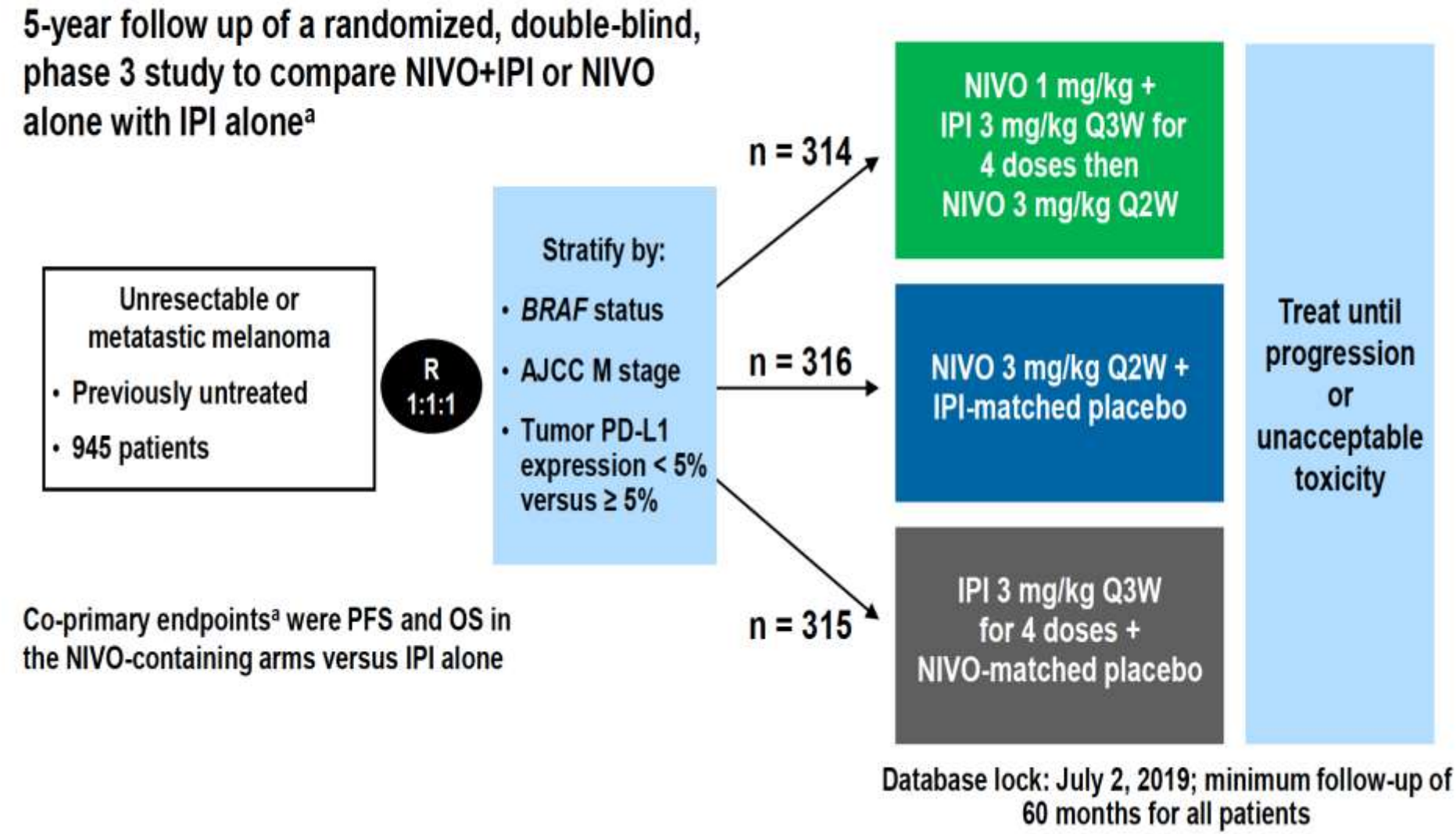
CheckMate-067

BARCELONA 2019 ESMO congress

Five-Year Survival Outcomes of the CheckMate 067 Phase 3 Trial of Nivolumab Plus Ipilimumab Combination Therapy in Advanced Melanoma

James Larkin,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Jean-Jacques Grob,[4] Piotr Rutkowski,[5] Christopher D. Lao,[6] C. Lance Cowey,[7] Dirk Schadendorf,[8] John Wagstaff,[9] Reinhard Dummer,[10] Pier F. Ferrucci,[11] Michael Smylie,[12] David Hogg,[13] Andrew Hill,[14] Ivan Márquez-Rodas,[15] John Haanen,[16] Jasmine I. Rizzo,[17] Agnes Balogh,[17] Andriy Moshyk,[17] F. Stephen Hodi,[18*] Jedd Wolchok[19*]

CheckMate-067: disegno dello studio

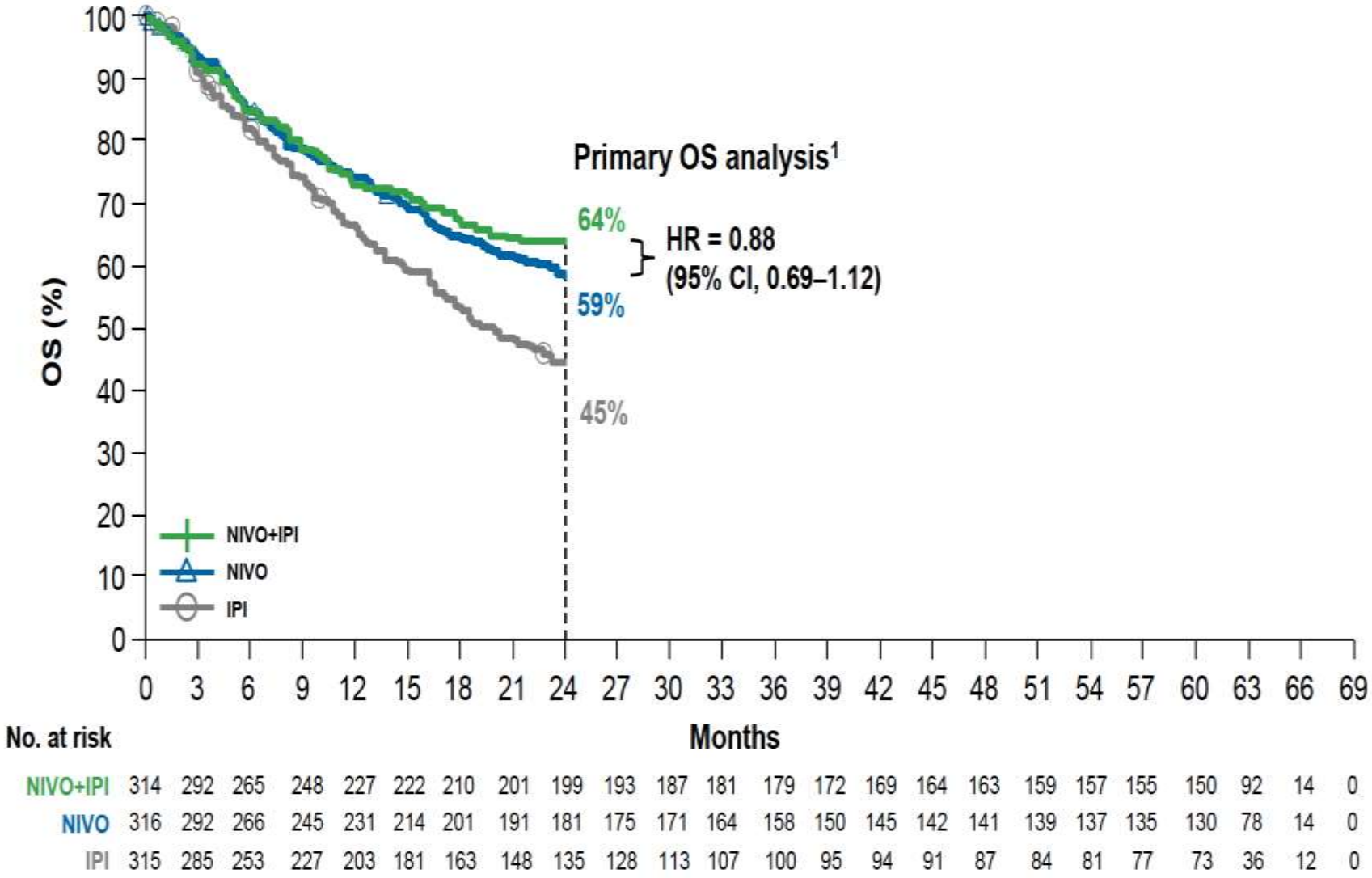


NCT01844505

[a]The study was not powered for a comparison between NIVO+IPI and NIVO.AJCC, American Joint Committee on Cancer.

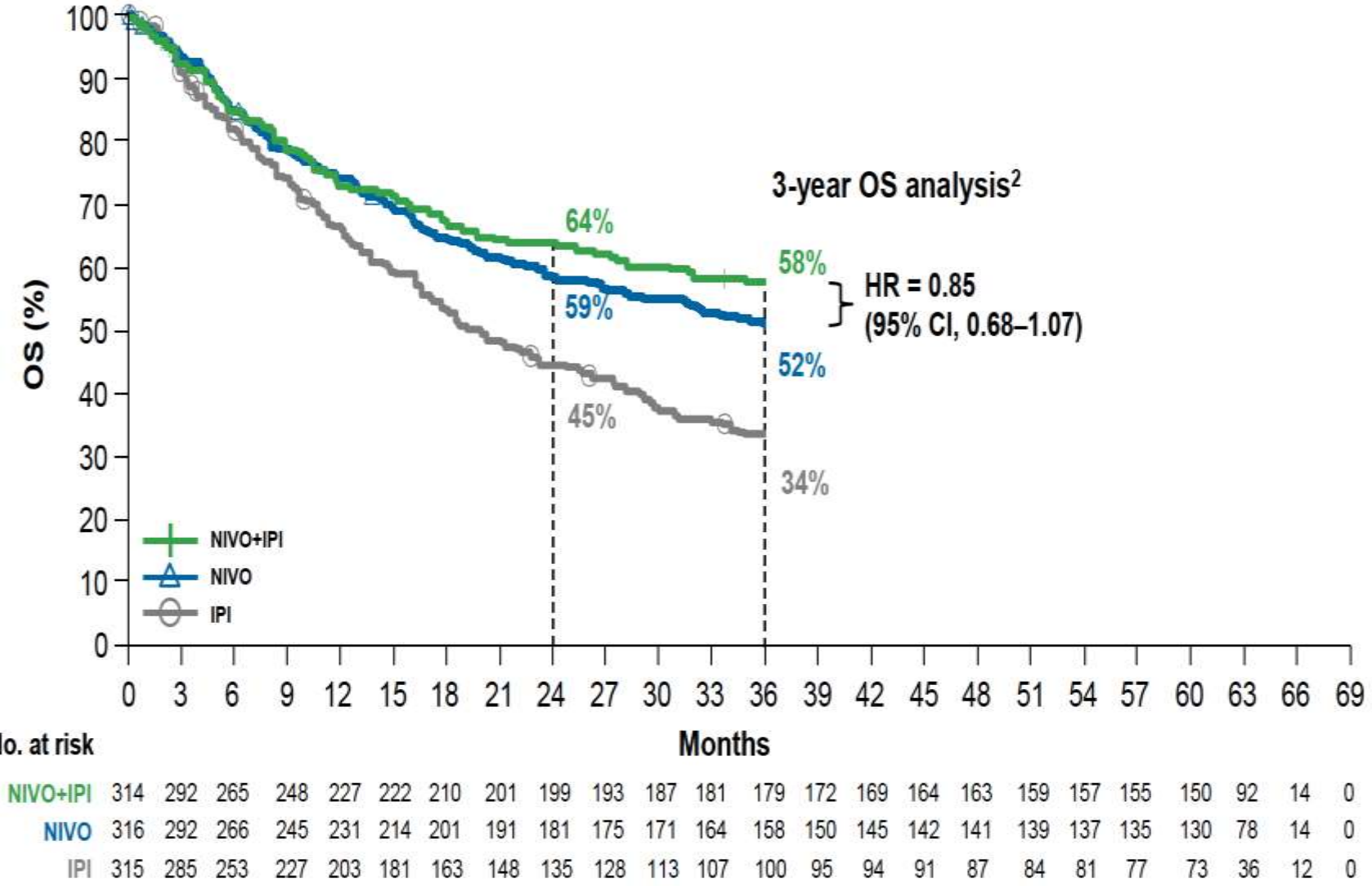
Presentato da J. Larkin ad ESMO 2019

CheckMate-067: OS



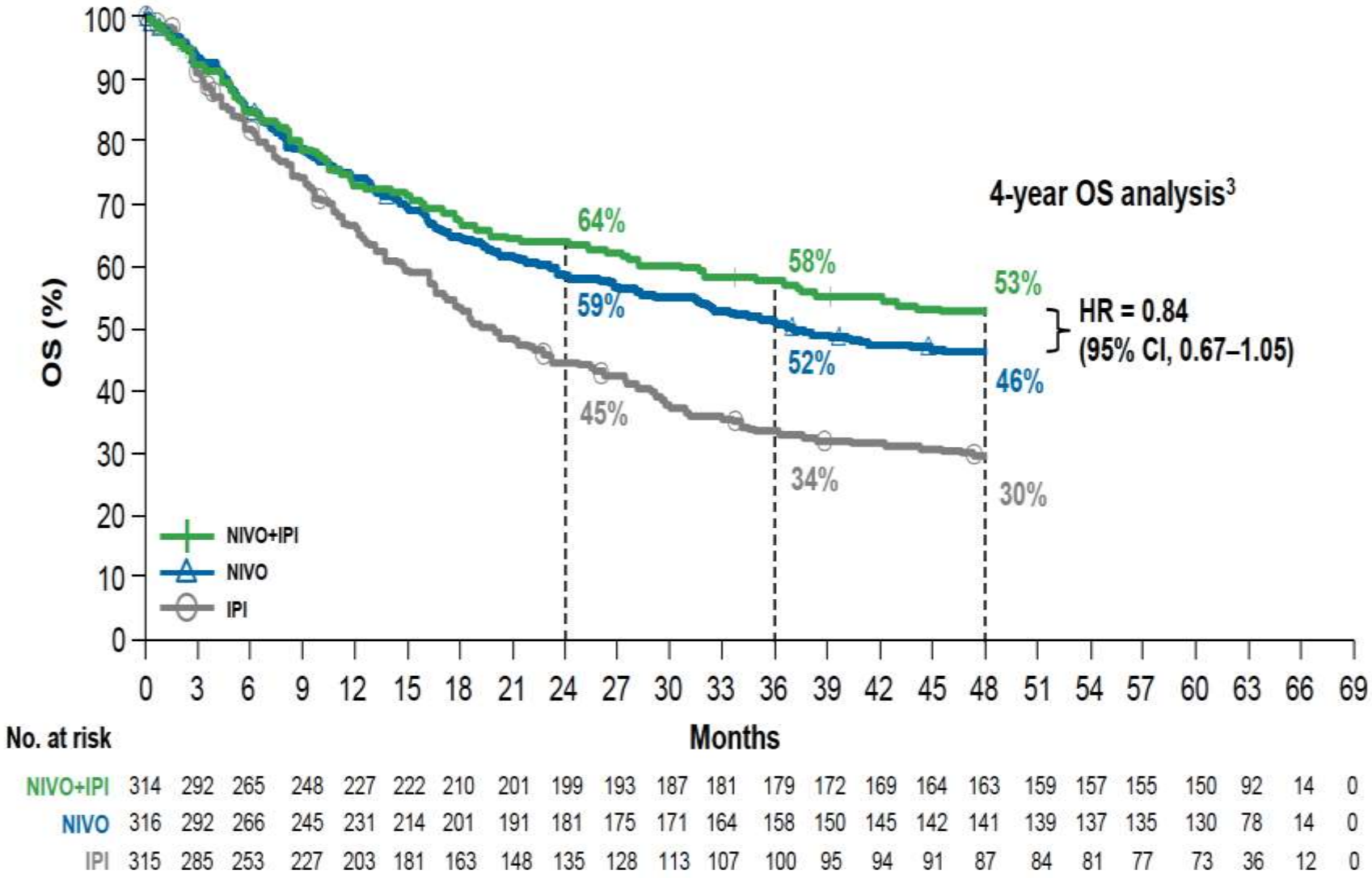
Presentato da J. Larkin ad ESMO 2019

CheckMate-067: OS



Presentato da J. Larkin ad ESMO 2019

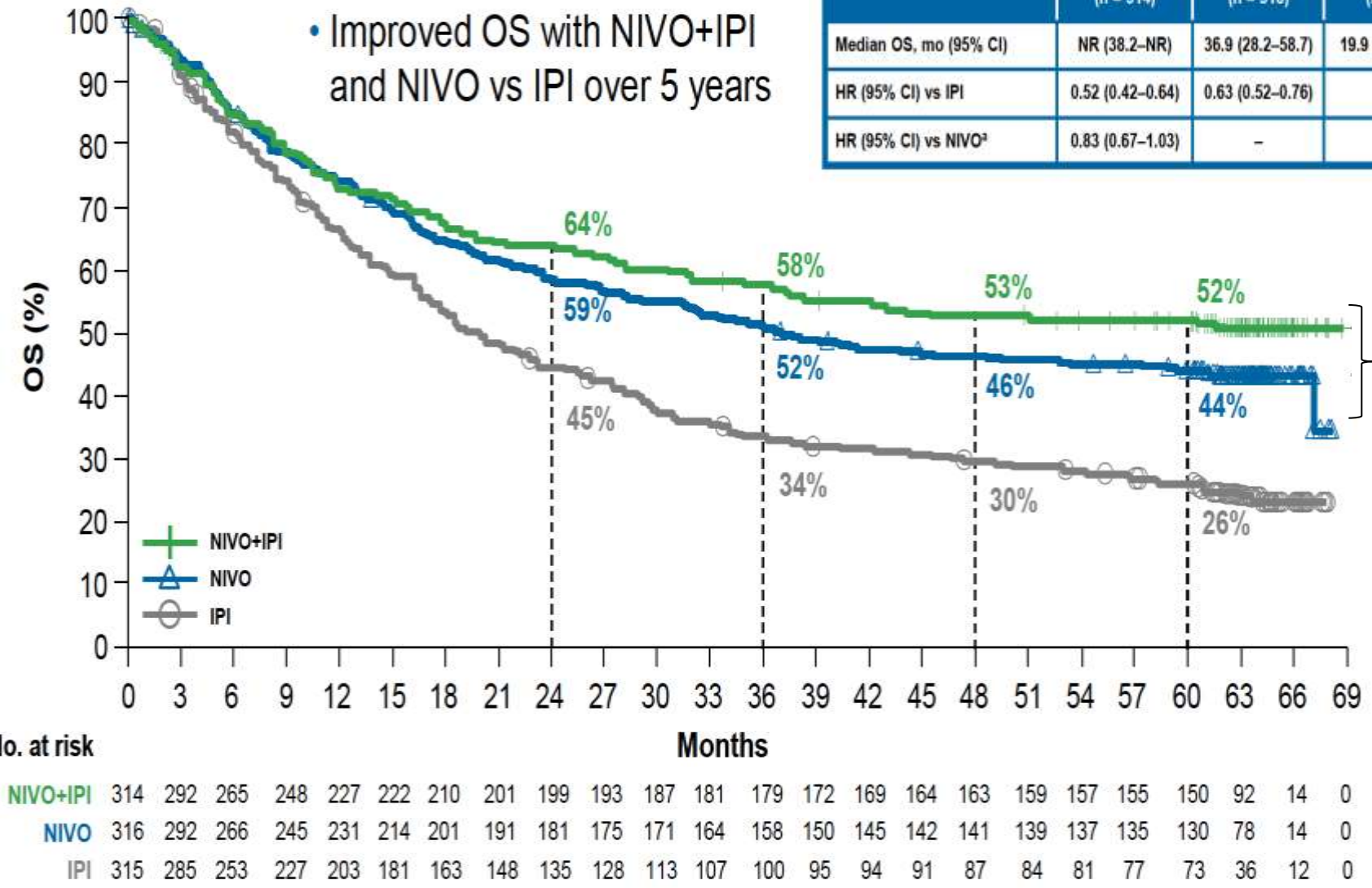
CheckMate-067: OS



Presentato da J. Larkin ad ESMO 2019

CheckMate-067: OS

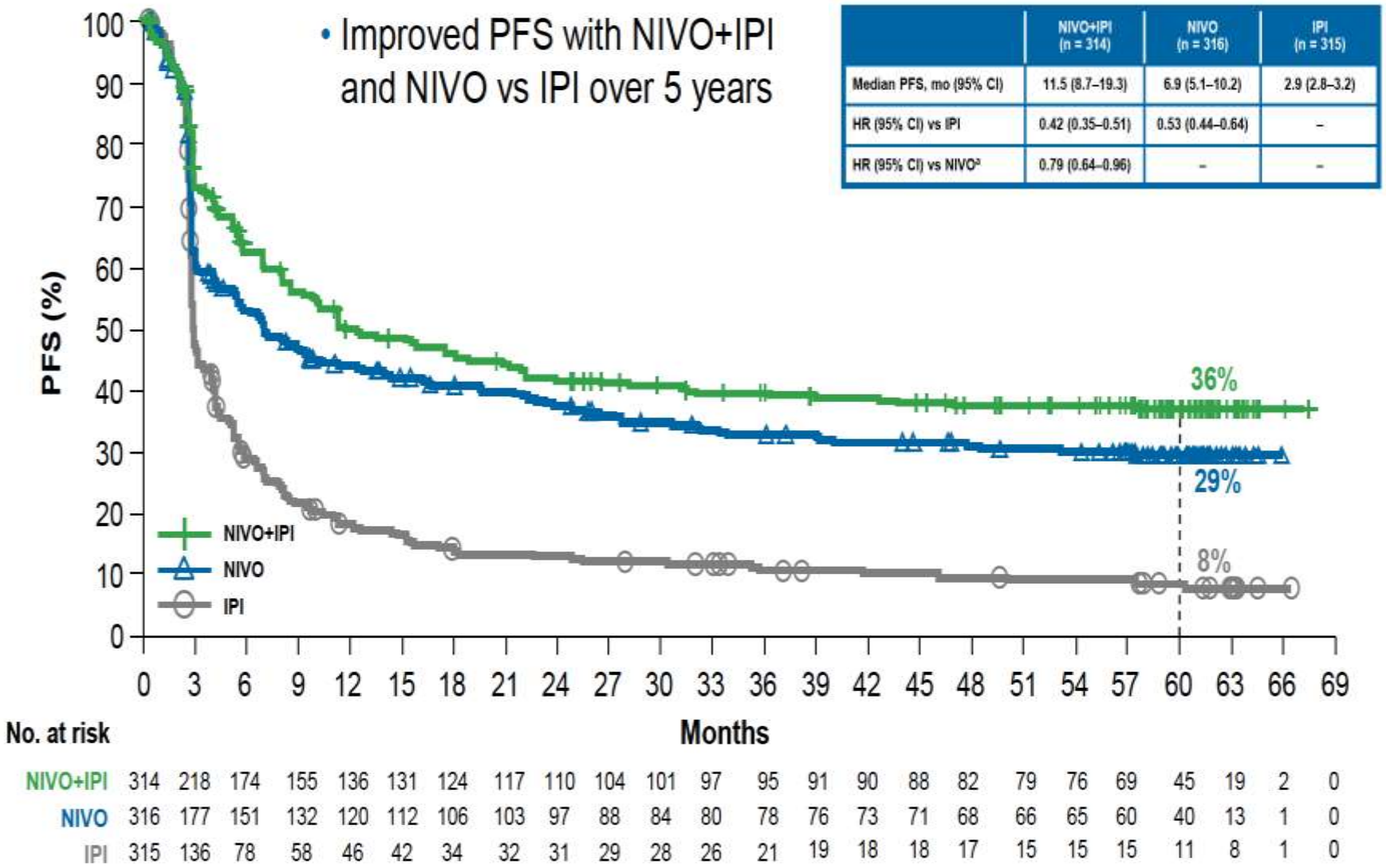
	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[3]	0.83 (0.67–1.03)	–	–



*Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075; 2. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356. 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

Presentato da J. Larkin ad ESMO 2019

CheckMate-067: PFS



	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, mo (95% CI)	11.5 (8.7–19.3)	6.9 (5.1–10.2)	2.9 (2.8–3.2)
HR (95% CI) vs IPI	0.42 (0.35–0.51)	0.53 (0.44–0.64)	–
HR (95% CI) vs NIVO[a]	0.79 (0.64–0.96)	–	–

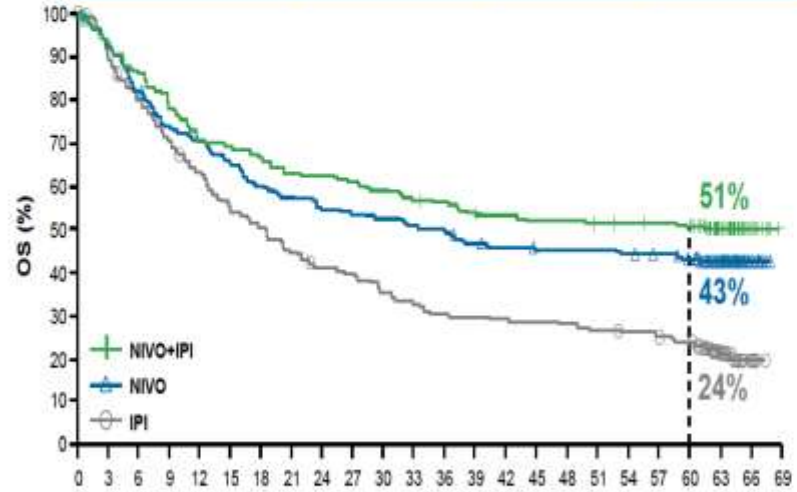
Presentato da J. Larkin ad ESMO 2019

CheckMate-067: OS

- Improved OS with NIVO+IPI and NIVO vs IPI regardless of baseline tumor PD-L1 expression

PD-L1 < 5%

	NIVO+IPI (n = 210)	NIVO (n = 208)	IPI (n = 202)
Median, mo (95% CI)	NR (32.7–NR)	35.9 (23.1–59.2)	18.4 (13.7–22.5)
HR (95% CI) vs IPI	0.50 (0.39–0.65)	0.62 (0.49–0.79)	–
HR (95% CI) vs NIVO[3]	0.81 (0.62–1.06)	–	–

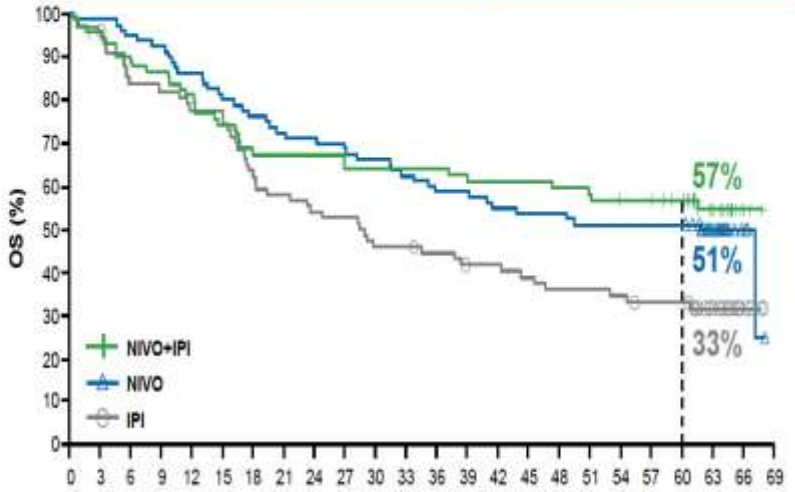


No at risk

NIVO+IPI	210	194	178	163	146	144	139	131	130	127	123	118	116	111	109	106	106	104	103	102	101	61	9	0
NIVO	208	189	169	151	144	133	123	118	112	110	108	104	102	95	92	90	90	90	88	86	82	48	9	0
IPI	202	179	158	140	124	107	99	89	80	77	69	64	59	58	57	56	55	52	50	48	45	19	5	0

PD-L1 ≥ 5%

	NIVO+IPI (n = 68)	NIVO (n = 80)	IPI (n = 75)
Median, mo (95% CI)	NR (39.1–NR)	61.6 (33.6–NR)	28.9 (18.1–44.2)
HR (95% CI) vs IPI	0.58 (0.37–0.91)	0.63 (0.42–0.96)	–
HR (95% CI) vs NIVO[3]	0.91 (0.57–1.46)	–	–



No. at risk

NIVO+IPI	68	63	56	55	52	50	45	45	45	44	43	43	43	42	41	41	40	38	37	36	33	20	2	0
NIVO	80	79	76	74	69	64	61	58	57	54	53	50	47	46	44	43	43	41	41	41	41	26	5	0
IPI	75	72	66	64	60	55	46	43	40	39	34	34	32	29	29	27	25	25	24	22	22	12	5	0

Presentato da J. Larkin ad ESMO 2019

CheckMate-067: Response Rate

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR, % (95% CI)	**58 (53–64)**	**45 (39–50)**	**19 (15–24)**
Best overall response, %			
Complete response	22	19	6
Partial response	36	26	13
Stable disease	12	9	22
Progressive disease	24	38	50
Unknown	6	8	9
ITT median duration of response, months (95% CI)	**NR[a]**	**NR (50.4–NR)**	**14.4 (8.3–53.6)**
Continued response, n/N (%)	113/183 (62)	86/141 (61)	24/60 (40)

- While ORR has remained stable, rates of CR have increased over the 3-, 4-, and 5-year analyses[1,2]
  - 19%, 21%, and 22% for NIVO+IPI
  - 16%, 18%, and 19% for NIVO
  - 5%, 5%, and 6% for IPI

[a]Although a median was reported at the previous analysis, that estimate was immature and greater than the minimum study follow-up. ITT, intention to treat.

1. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

CheckMate-067: Profilo di Tossicità

- No new safety signals were observed with the additional follow-up
- No additional deaths due to study drug toxicity were reported since the prior analysis[a]

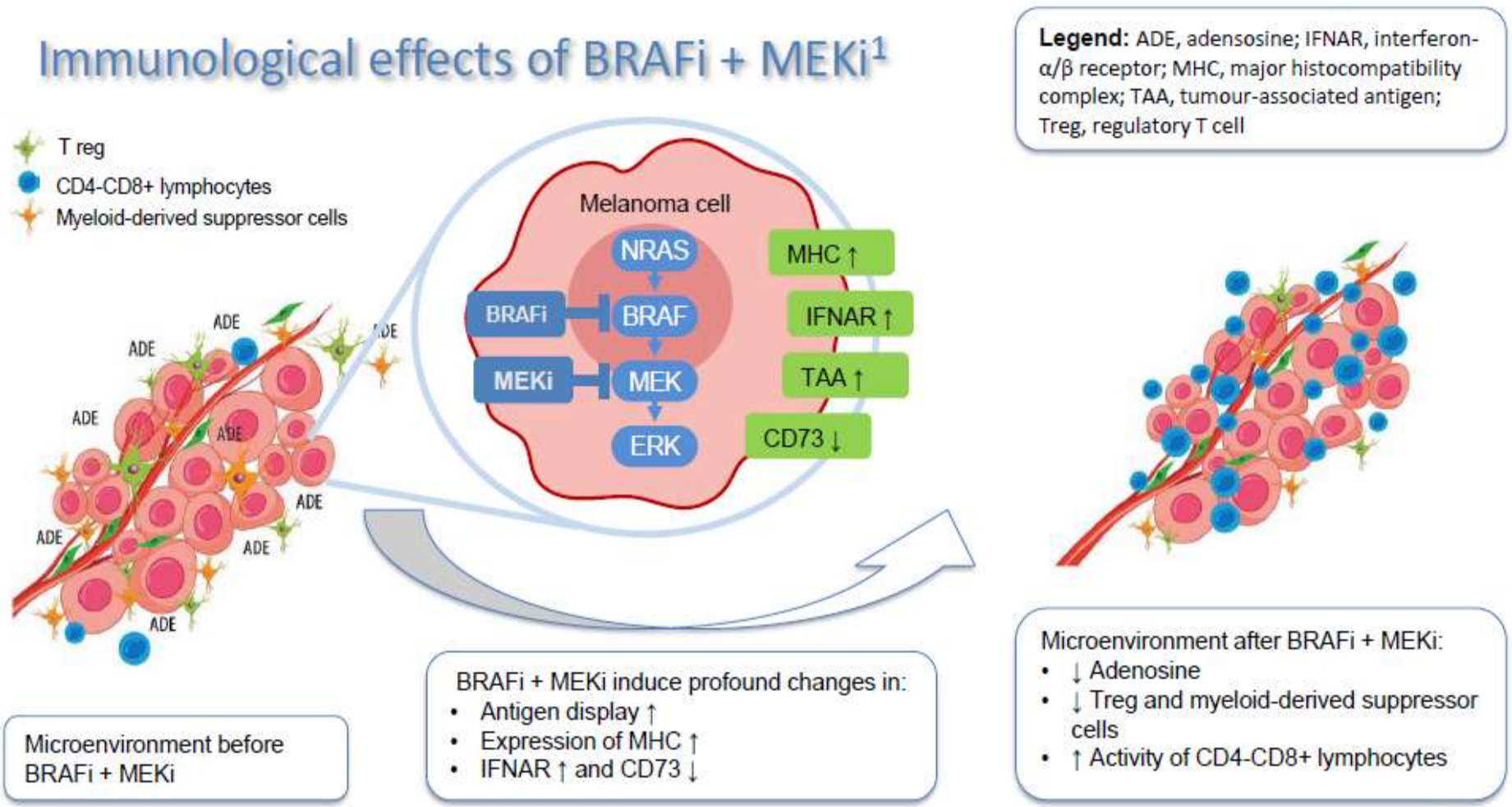
Patients reporting event	NIVO+IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AE, %	96	59	87	23	86	28
Treatment-related AE leading to discontinuation, %	42	31	13	8	15	14
Treatment-related death, n (%)	2 (1)		1 (< 1)		1 (< 1)	

- Survival outcomes were not impacted by discontinuing NIVO+IPI early due to a TRAE[b]
  - Patients who discontinued NIVO+IPI during induction due to a TRAE had 5-year PFS (35%) and OS rates (51%) similar to patients in the overall population (36% and 52%, respectively)

[a]Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n = 1 each; both occurred > 100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1); [b]Post-hoc analysis. TRAE, treatment-related adverse event.

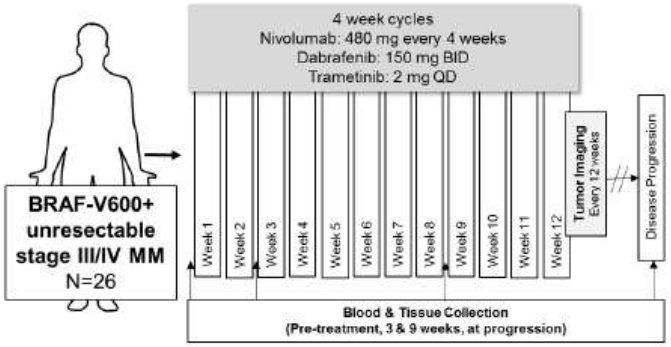
Presentato da J. Larkin ad ESMO 2019

Effetti immunomodulanti delle terapie target



[1]Ascierto & Dummer, *Oncoimmunology* 2018
Image, courtesy of P. Ascierto, modified from [1]

Trident: Disegno, obiettivi, caratteristiche dei pazienti



Hypothesis:

- Nivolumab in combination with dabrafenib and trametinib will demonstrate clinical activity in BRAF mutated pts, including those with checkpoint inhibitor refractory disease and those with brain metastases

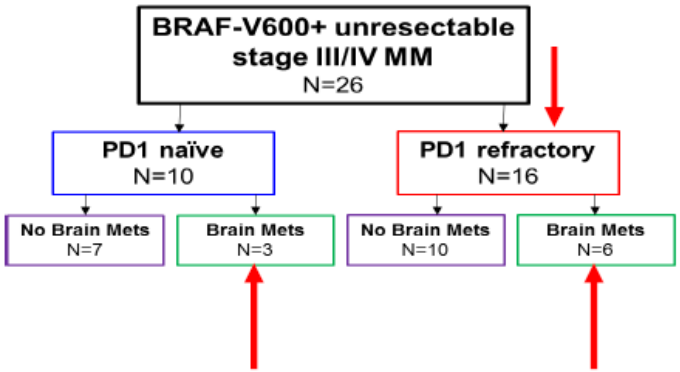
Primary Objective:

- To determine the safety, tolerability, and efficacy (by objective response rate by RECIST 1.1) of nivolumab in combination with dabrafenib and trametinib in pts with BRAF-mutated metastatic melanoma

Secondary Objectives:

- Efficacy of the combination as measured by depth and duration of response
- Progression- free and overall survival for patients with and without prior anti-PD1 exposure
- Pharmacodynamic evaluation of the combination on circulating markers and tumor tissue

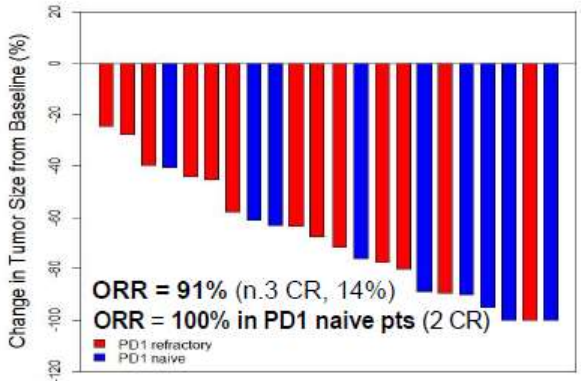
Patient Demographics

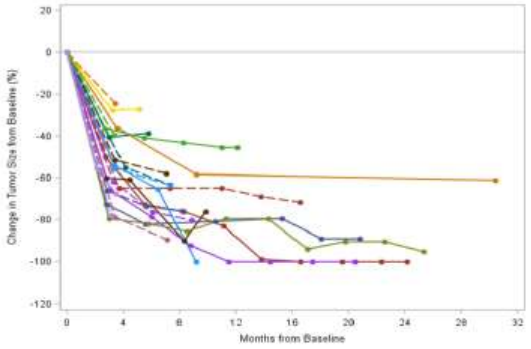


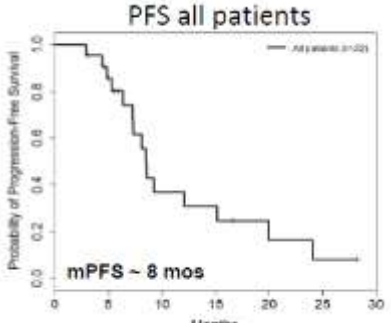
Measure	All Patients (N=26)
Age, n (%)	
< 65 years	19 (73)
≥ 65 years	7 (27)
Gender, n (%)	
Male	15 (58)
Female	11 (42)
ECOG status, n (%)	
0	17 (65)
1	9 (35)
LDH, n (%)	
≤ 1 x ULN	15 (58)
> 1 – ≤ 2 x ULN	6 (23)
> 2 x ULN	5 (19)
Sites of disease, n (%)	
≤ 3	9 (35)
> 3	17 (65)
Follow-up time in months (all patients) Median (range)	13.1 (0.3 – 30.6)

Burton E. et al. ESMO 2019

Trident: ORR, PFS, tossicità

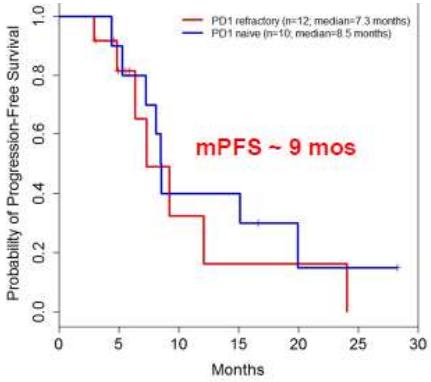


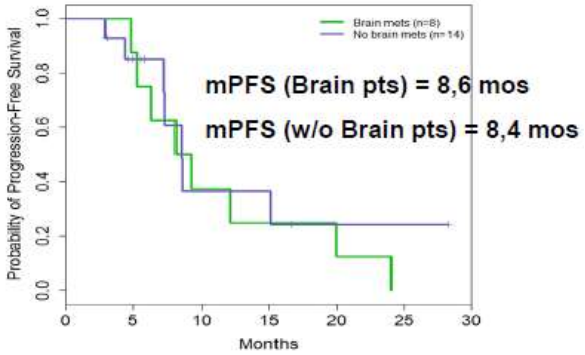




Duration of responses

Patient Group	N	Median (Range)
All	20	4.93 (0.36-25.23)
PD1 refractory	10	3.35 (0.36-21.39)
PD1 naive	10	5.65 (1.68-25.53)
Brain mets	7	6.51 (2.53-21.39)
No brain mets	13	3.22 (0.36-25.53)



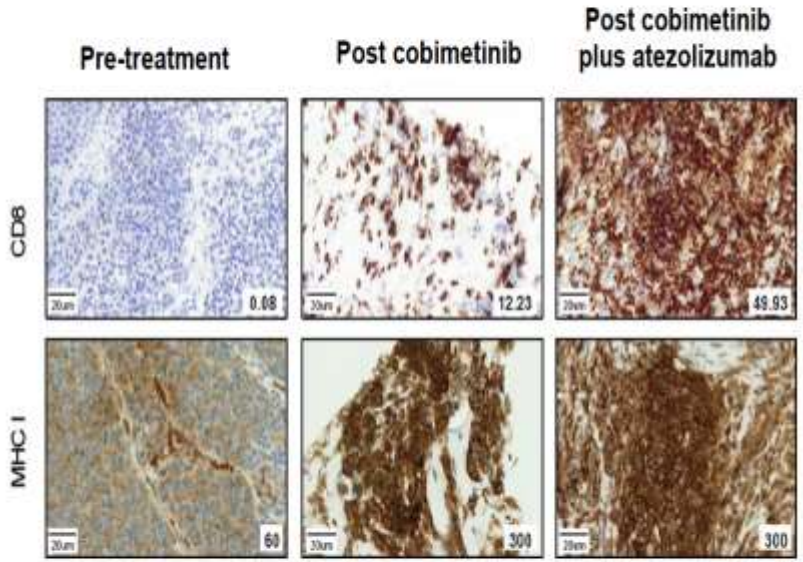


Adverse Event Name	# Grade 3/4
Lymphocyte count decreased	5
Neutrophil count decreased	4
Dehydration	3
Aspartate aminotransferase increased	3
White blood cell decreased	2
Rash maculo-papular	2
Hypophosphatemia	2
Hypokalemia	2
Fever	2
Creatinine increased	2
Anemia	2
Alkaline phosphatase increased	2
Acute kidney injury	2
Thromboembolic event	1
Syncope	1
Seizure	1
Pharyngitis	1
Hypotension	1
Hyponatremia	1
Hypocalcemia	1
Hyperkalemia	1
Hyperglycemia	1
Headache	1
Alanine aminotransferase increased	1
Adult respiratory distress syndrome	1

Burton E. et al. ESMO 2019

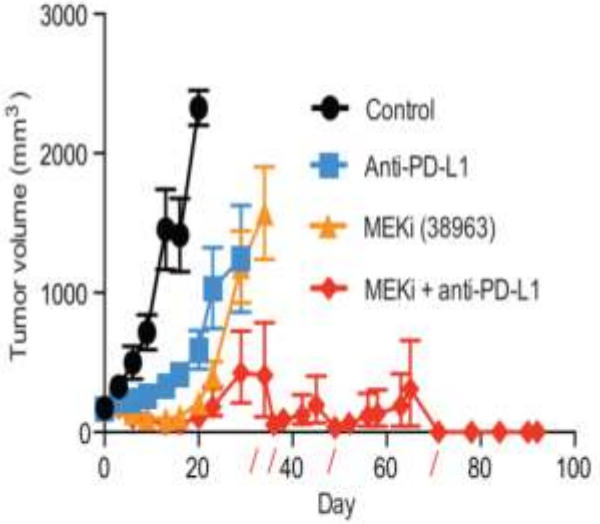
Razionale per combinare MEKi e Immunocheckpoint

- MEK inhibition can potentiate the host antitumour immune response through its effects on T-cells[1,2]



Effects on intratumoural CD8+ T-cell infiltration and MHC I expression in a patient with clear cell sarcoma[2,a]

- Combined MEK inhibition with anti-PD-L1 therapy has demonstrated synergistic antitumour activity in preclinical models[1]



Synergistic antitumour activity of MEKi plus anti-PD-L1 in a murine colon carcinoma model[1]

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1. Ebert PJR, et al. *Immunity*. 2016;44:609-21. 2. Hellmann MD, et al. *Ann Oncol*. 2019 Mar 27 [Epub ahead of print]. [a]Representative images from one patient with clear cell sarcoma from the serial biopsy cohort of the phase 1b study (Hellmann et al, 2019 suppl) in patients with solid tumours (n=16). MEKi, MEK inhibitor; MHC I, major histocompatibility complex class I.

IMspire 170

BARCELONA 2019 ESMO congress

Evaluation of Combination Treatment With Cobimetinib Plus Atezolizumab Versus Pembrolizumab in Previously Untreated Patients With Wild Type *BRAF*^{V600} Advanced Melanoma: Primary Analysis From the Phase 3 IMspire170 Trial

Ana Arance[1]; Helen Gogas[2]; Brigitte Dréno[3]; Keith Flaherty[4]; Lev Demidov[5]; Daniil Stroyakovskiy[6]; Zeynep Eroglu[7]; Pier Francesco Ferrucci[8]; Jacopo Pigozzo[9]; Piotr Rutkowski[10]; Jacek Mackiewicz[11]; Isabelle Rooney[12]; Athina Voulgari[13]; Sarah Troutman[12]; Bethany Pitcher[14]; Yibing Yan[12]; James Larkin[15]

IMspire 170: Disegno dello Studio

IMspire170: A Phase 3, Open-label, Multicenter, Randomised Study

Advanced melanoma
N = 446

Key eligibility criteria

- Unresectable locally advanced or metastatic
- *BRAF*^{V600} WT
- Previously untreated
  - Adjuvant IFNα, IL-2, vaccine or ipilimumab allowed
- Measurable disease per RECIST v1.1
- Archival tissue or fresh biopsy

Randomise

1:1

Cobimetinib 60 mg PO d1-21
Atezolizumab 840 mg IV q2w
(28-day cycles)

N=222

Pembrolizumab 200 mg IV q3w

N=224

- Treat to loss of clinical benefit, unacceptable toxicity, or withdrawal of consent
- Treatment beyond RECIST PD allowed

Stratification factors

- PD-L1 status (IC0 vs IC1/2/3)[a]
- LDH (≤ULN vs >ULN)
- Geographic location (North America vs Europe vs Australia/New Zealand/others)

Primary endpoint

- IRC-assessed PFS
  - The study was designed to detect a hazard ratio of 0.55 (median 10 mo with cobimetinib + atezolizumab vs 5.5 mo with pembrolizumab[b])
  - 98% power (240 events)
  - Stratified log-rank test at 0.01 significance level (2-sided)

Key secondary endpoints

- INV-assessed PFS
- ORR*
- Duration of response*
- Disease control rate*
- OS
- Safety

Presentato da A. Arance ad ESMO 2019

IMspire 170: Caratteristiche dei pazienti

Characteristic, n (%)	Cobi + Atezo N=222	Pembro N=224
Age, median years (range)	66 (24–93)	66 (20–87)
Male	129 (58)	141 (63)
LDH >ULN	55 (25)	56 (25)
ECOG PS		
0	161 (73)	167 (75)
1	58 (26)	47 (21)
PD-L1 status		
IC 1/2/3	150 (68)	152 (68)
IC 0	72 (32)	72 (32)
Primary diagnosis		
Locally advanced	25 (11)	18 (8)
Metastatic	197 (89)	206 (92)

Characteristic, n (%)	Cobi + Atezo N=222	Pembro N=224
Metastatic disease		
M0/M1a/M1b	128 (58)	130 (58)
M1c	86 (39)	88 (39)
MX	8 (4)	5 (2)
Liver metastases	57 (26)	68 (30)
Brain metastases	5 (2)	9 (4)
Prior adjuvant systemic therapy or radiotherapy	42 (19)	51 (23)
Systemic therapy	26 (12)	27 (12)
Interferon	24 (11)	21 (9)
Ipilimumab	2 (1)	5 (2)
Other	0	2 (1)[a]
Mutational status[b]		
NF1 mutation	40 (18)	53 (24)
NRAS mutation	71 (32)	104 (46)

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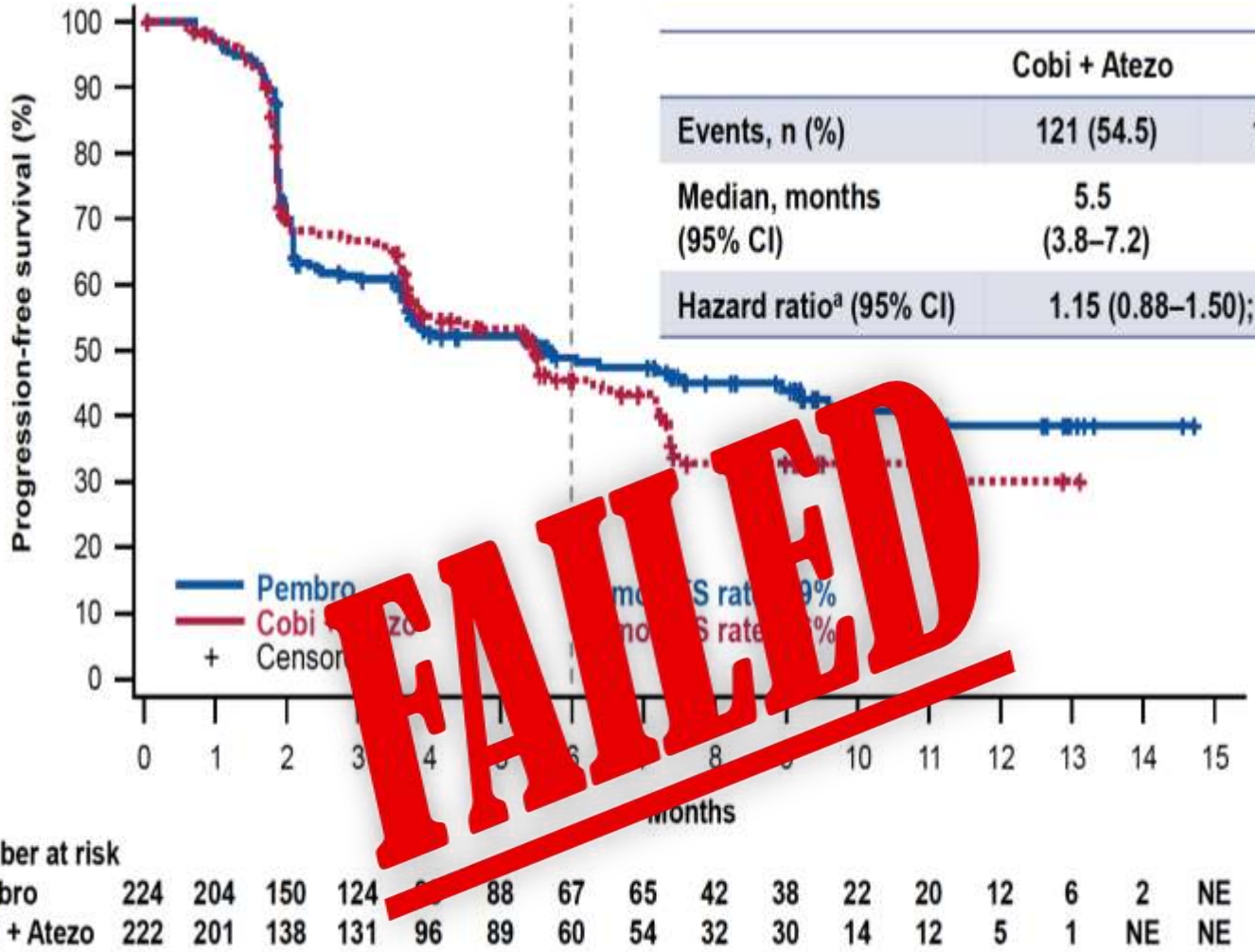
[a]5-fluorouracil, anastrozole, doxorubicin, and epirubicin in 1 patient, and no further information available in 1 patient; [b]Determined by next-generation sequencing on the FoundationOne™ platform; mutational status was available for 221 patients in the Cobi + Atezo arm and 223 patients in the Pembro arm.

ECOG PS, Eastern Cooperative Oncology Group performance status.

Presentato da A. Arance ad ESMO 2019

IMspire 170: PFS



	Cobi + Atezo	Pembro
Events, n (%)	121 (54.5)	112 (50.0)
Median, months (95% CI)	5.5 (3.8–7.2)	5.7 (3.7–9.6)
Hazard ratio[a] (95% CI)	1.15 (0.88–1.50); *P*=0.295	

FAILED

Number at risk

Pembro	224	204	150	124		88	67	65	42	38	22	20	12	6	2	NE
Cobi + Atezo	222	201	138	131	96	89	60	54	32	30	14	12	5	1	NE	NE

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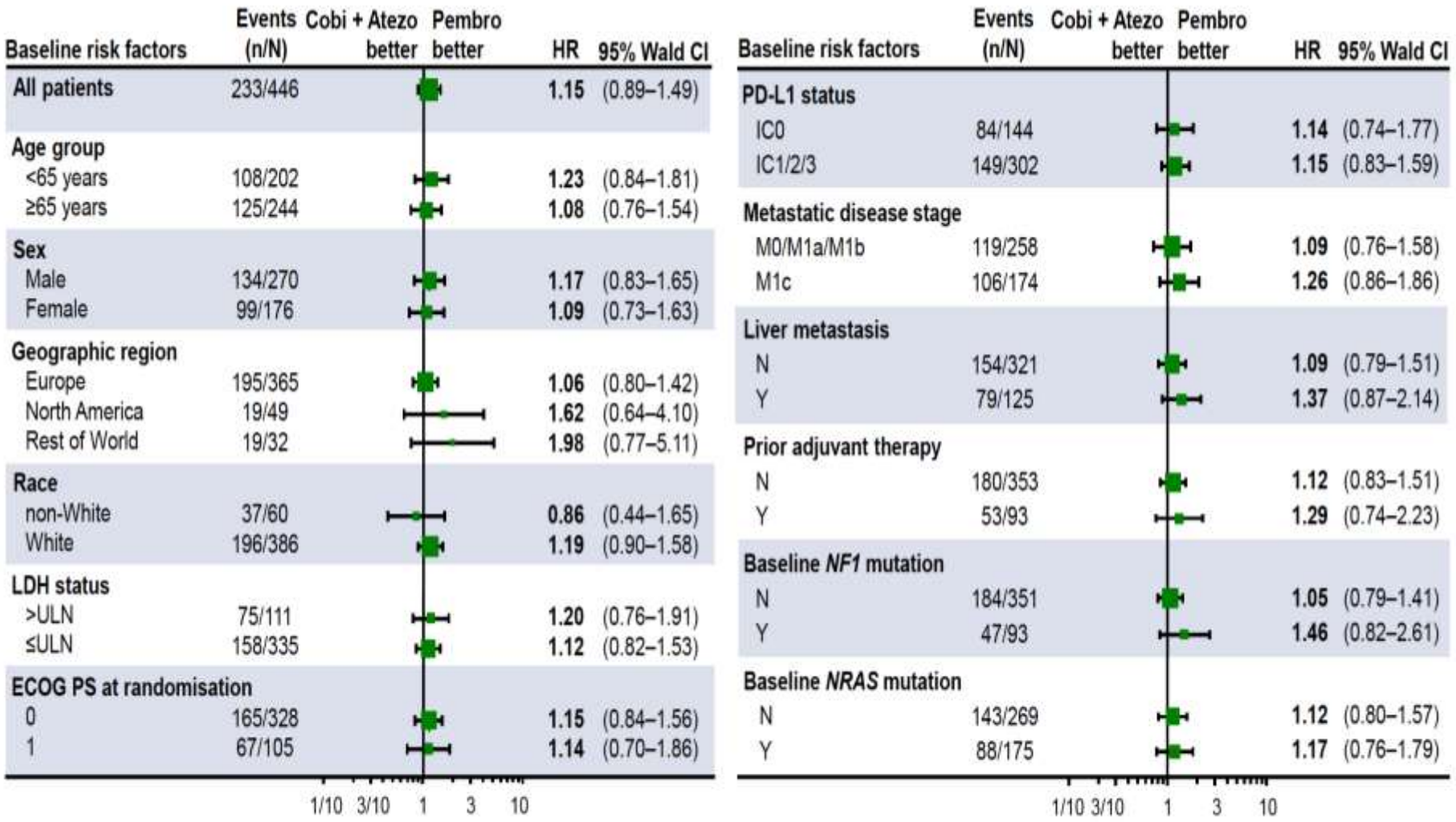
Data cutoff: April 15, 2019; median follow-up duration: 7.0 months (range, 0–15).

[a]Stratified by PD-L1 status and baseline LDH level. CI, confidence interval; IRC, independent review committee; NE, not estimable.

Presentato da A. Arance ad ESMO 2019

IMspire 170: PFS – subgroup analysis



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Data cutoff: April 15, 2019; median follow-up duration: 7.0 months (range, 0–15). HR, hazard ratio; IC, immune cell; IRC, independent review committee.

Presentato da A. Arance ad ESMO 2019

IMspire 170: Response Rate

	Cobi + Atezo n=204	Pembro n=206
Best confirmed response,[b] n (%)		
Complete response	7 (3)	8 (4)
Partial response	46 (23)	57 (28)
Stable disease	73 (36)	53 (26)
Progressive disease	58 (28)	66 (32)
Not evaluable	4 (2)	4 (2)
Missing	16 (8)	18 (9)
Confirmed ORR,[b] n (%)	53 (26)	65 (32)
Disease control rate,[c] n (%)	93 (46)	91 (44)
Median duration of response, months (range)	NE (2–11)	NE (1–13)

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[a]204 of the 222 Cobi + Atezo patients and 206 of 224 Pembro patients in the ITT population had measurable disease at baseline by IRC and were included in the analysis; [b]Confirmed by repeat assessment ≥4 weeks after first documentation of response; [c]Complete or partial response or stable disease at 16 weeks. IRC, independent review committee.

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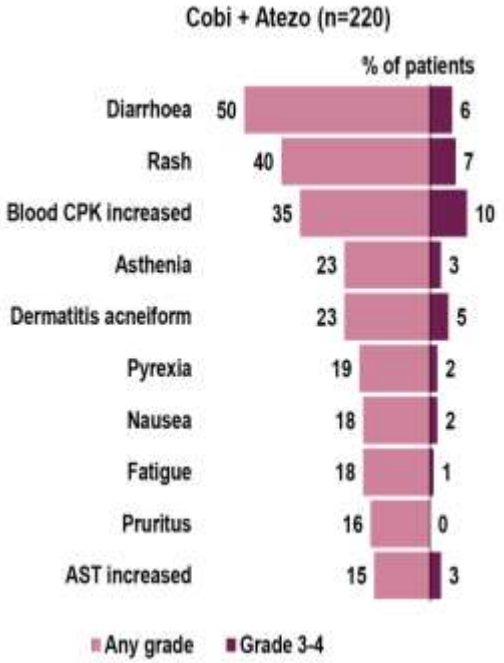
IMspire 170: Profilo di Tossicità

Median duration of treatment was 4 months (range, 0–14) for cobimetinib, 4 months (range, 0–14) for atezolizumab, and 5 months (range, 0–15) for pembrolizumab

AEs, n (%)	Cobi + Atezo n=220	Pembro n=216
Any AE	218 (99)	191 (88)
Treatment-related AEs		
Any grade	212 (96)	145 (67)
Grade 3-4	111 (50)	29 (13)
Grade 5	3 (1)[a]	2 (1)[b]
Serious AEs	97 (44)	45 (21)
AEs leading to discontinuation		
Any treatment	46 (21)	12 (6)
Atezolizumab	33 (15)	–
Cobimetinib	41 (19)	–
Both	26 (12)	–
AEs leading to dose modification/interruption		
Any treatment	157 (71)	57 (26)
Atezolizumab	113 (51)	–
Cobimetinib	150 (68)	–
Both	98 (45)	–

[a]Pulmonary embolism, multiple organ dysfunction, and renal failure in 1 patient each; [b]Hepatic failure and hepatitis in 1 patient
AEs, adverse events.



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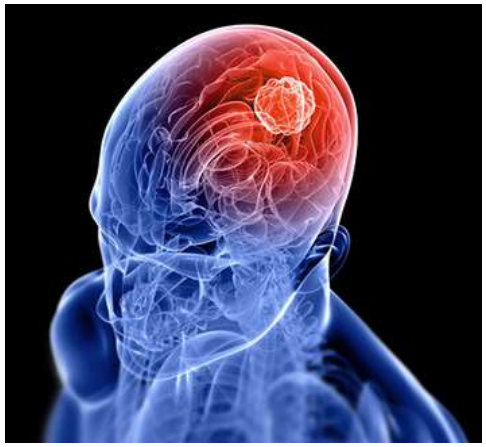
Metastasi Encefaliche

- Le metastasi cerebrali da melanoma sono comuni: 20-25% alla diagnosi (stadio IV), 50-70% in serie autoptiche
- mOS di circa 4 mesi



Asymptomatic Brain Metastases	No Active Brain Mets*		Active Brain Mets	
	Response	6-mo PFS	Response	6-mo IC PFS
Dabrafenib + Trametinib (n=76)[1]	68%	70%	58%	44%
Ipilimumab (n=51)[2]	11%	30%	10%	-
Pembrolizumab (n=23)[3]	46%	55%	26%	40%
Nivolumab (n=21, drug naive)[4]	45%	54%	21%	21%
Nivolumab + Ipilimumab (n=27, drug naive)[4] /(n=101)[5]	58%	62%	56%/54%	60%/63%

1. Davies MA et al Lancet Onc 2017; 2. Margolin K et al Lancet Onc 2012; 3. Kluger H et al JCO 2019; 4. Long GV et al Lancet Onc 2018; 5. Tawbi H et al ASCO 2019

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*Phase 3 trials, treatment naïve (except ipi), estimated 6 mo PFS

Presented by Georgina V Long

ABC Trial

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Long-term Outcomes from the Randomized Ph 2 Study of Nivolumab or Nivolumab + Ipilimumab in Patients With Melanoma Brain Metastases: Anti-PD1 Brain Collaboration (The ABC Trial)

Georgina V. Long, Victoria Atkinson, Serigne Lo, Shahneen Sandhu, Michael P. Brown, Maria Gonzalez, Alexander Guminski, Richard A. Scolyer, Louise Emmett, Alexander M. Menzies, Grant A. McArthur

ABC Trial: Disegno dello Studio

* NIVO 1
IPI 3

Total 76 Patients Recruited

- 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=51

A
No prior local brain Rx & asymptomatic
n=35
Nivolumab + Ipilimumab *

B
No prior local brain Rx & asymptomatic
n=25
Nivolumab

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

Primary Endpoint: **Intracranial Response Rate ≥ wk 12**
Secondary Endpoints: Extracranial Response Rate
Overall Response Rate
PFS (Intracranial, Extracranial, Overall)
Overall Survival

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ABC Trial: Caratteristiche dei pazienti

	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo† N=16
Age, median (range)	59 (29-76)	63 (31-86)	51 (28-73)
Sex, male n (%)	29 (83%)	19 (76%)	11 (69%)
ECOG performance status, n (%)			
0-1	34 (97%)	25 (100%)	15 (94%)
2	1 (3%)	0 (0%)	1 (6%)
LDH > ULN, n (%)	18 (51%)	14 (58%)	3 (19%)
V600 BRAF mutation-positive, n (%)	19 (54%)	14 (56%)	13 (81%)
Target brain metastases, n (%)			
1	11 (31%)	6 (24%)	1 (6%)
2-4	10 (29%)	14 (56%)	7 (44%)
>4	14 (40%)	5 (20%)	8 (50%)
Extracranial metastases, n(%)	30 (86%)	21 (84%)	12 (75%)
Prior BRAFi+MEKi	8 (23%)	6 (24%)	12 (75%)

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† Previous local treatment (n=16), neurological symptoms (n=10), leptomeningeal disease (n=4) Presented by Georgina V Long @ProfGLongMIA

ABC Trial: Response Rate

RR- Intracranica Popolazione Tot

	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo† N=16
Intracranial Response, n (%)	**18 (51%)**	**5 (20%)**	**1 (6%)**
CR	9 (26%)	4 (16%)	0 (0%)
PR	9 (26%)	1 (4%)	1 (6%)
SD	2 (6%)	0 (0%)	2 (13%)
PD	14 (40%)	19 (76%)	13 (81%)
NE*	1 (3%)	1 (4%)	0 (0%)

RR- Intracranica Popolazione Treatment-Naive

	A: Nivo+Ipi N=27	B: Nivo N=19
Intracranial Response, n (%)	16 (59%)	4 (21%)
CR	8 (30%)	3 (16%)
PR	8 (30%)	1 (5%)
SD	2 (7%)	0 (0%)
PD	8 (30%)	14 (74%)
NE*	1 (4%)	1 (5%)

RR- Extracranica

	A: Nivo+Ipi N=30	B: Nivo N=21	C: Nivo† N=12
Extracranial Response Rate, n (%)	**17 (57%)**	**6 (29%)**	**3 (25%)**
CR	4 (13%)	4 (19%)	1 (8%)
PR	13 (43%)	2 (10%)	2 (17%)
SD	4 (13%)	2 (10%)	1 (8%)
PD	8 (27%)	11 (52%)	7 (58%)
NE*	1 (3%)	2 (10%)	1 (8%)

#63 of 76 (83%) patients had extracranial melanoma metastases at baseline

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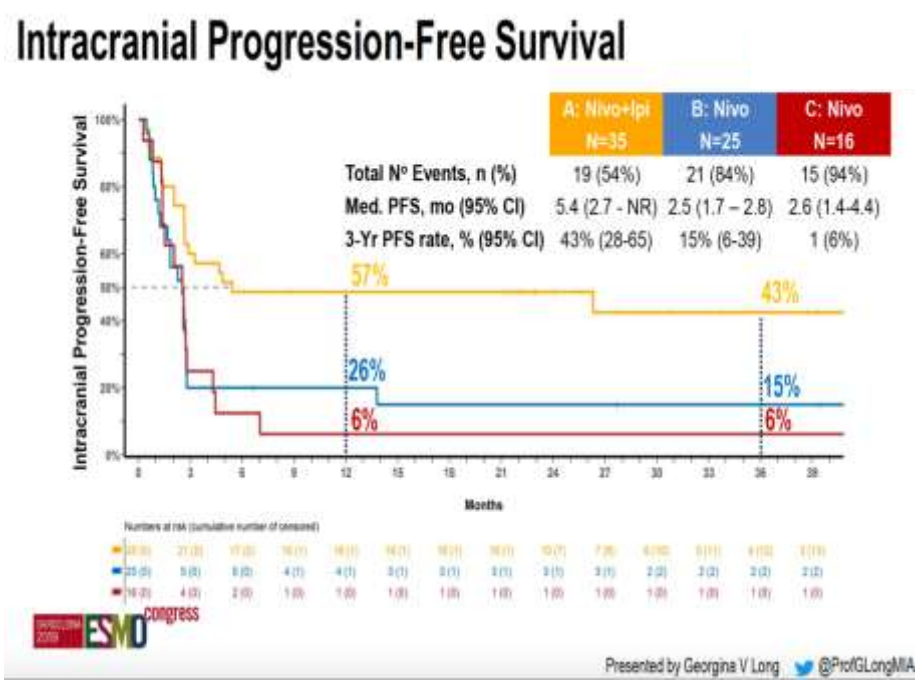
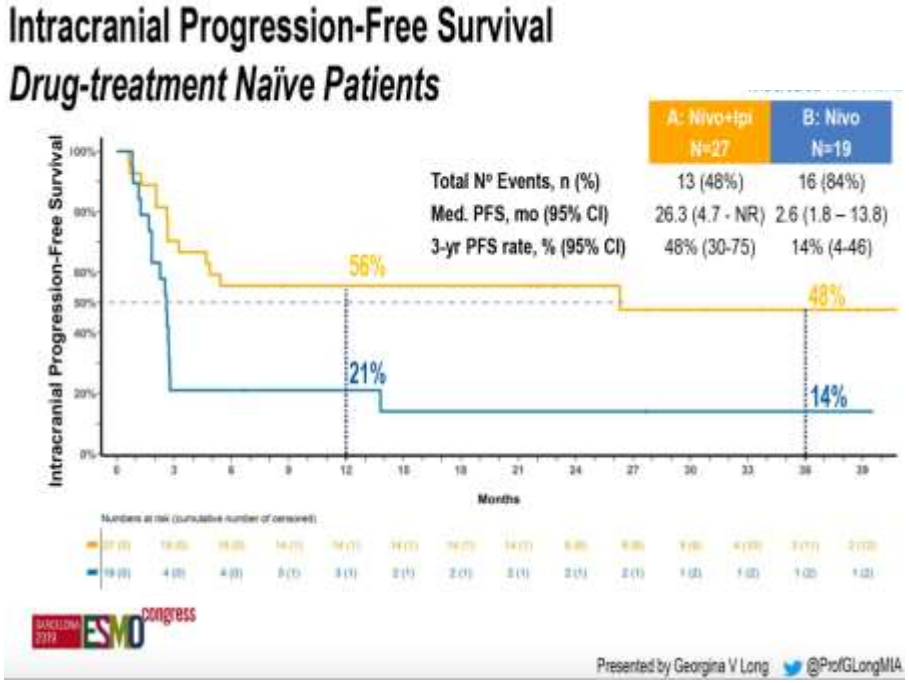
ABC Trial: PFS





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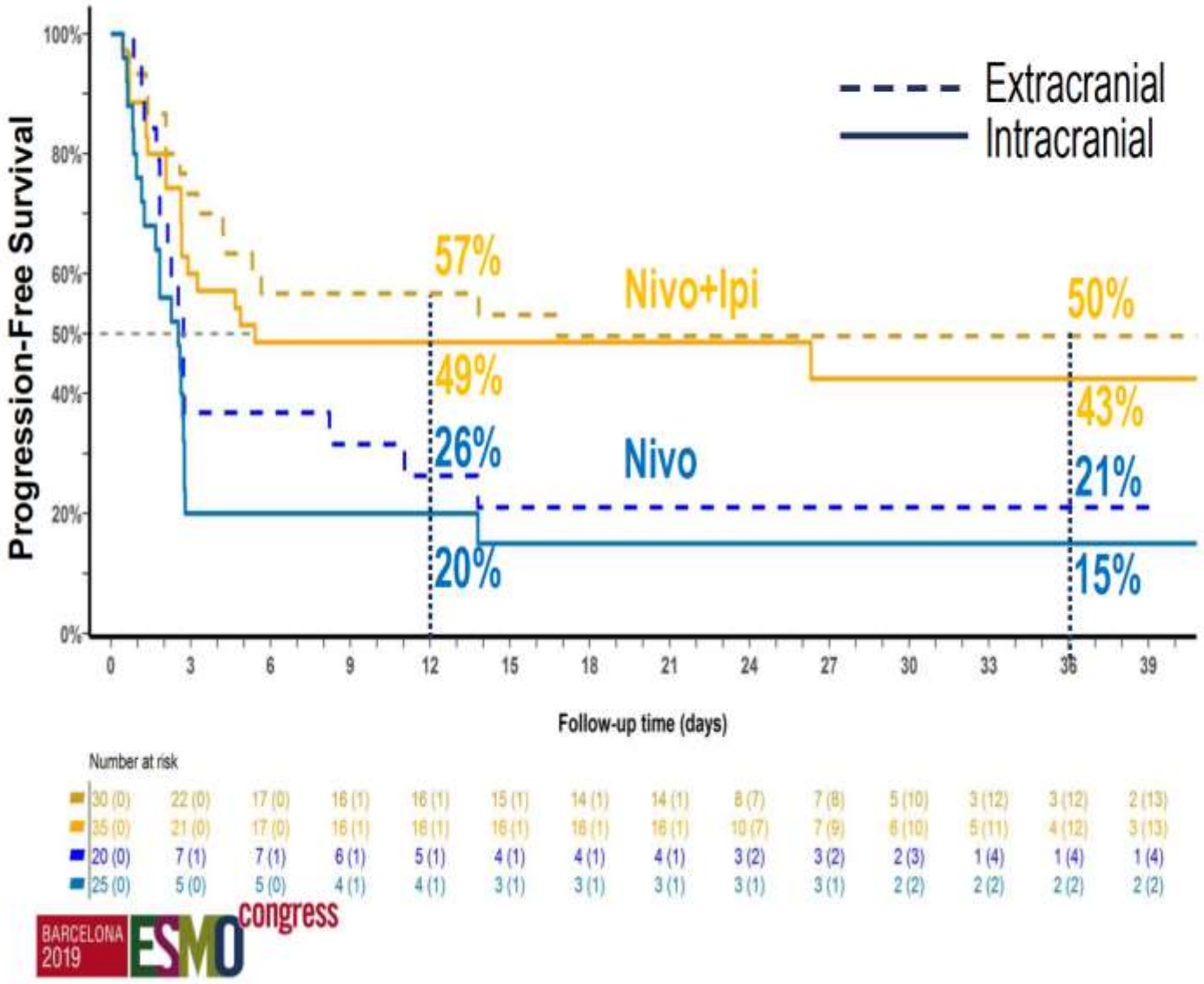
ABC Trial: PFS



		Extracranial response			
		CR	PR	SD	PD
Intracranial response	CR	7	5	0	0
	PR	0	7	1	0
	SD	0	2	1	1
	PD	2	3	5	6

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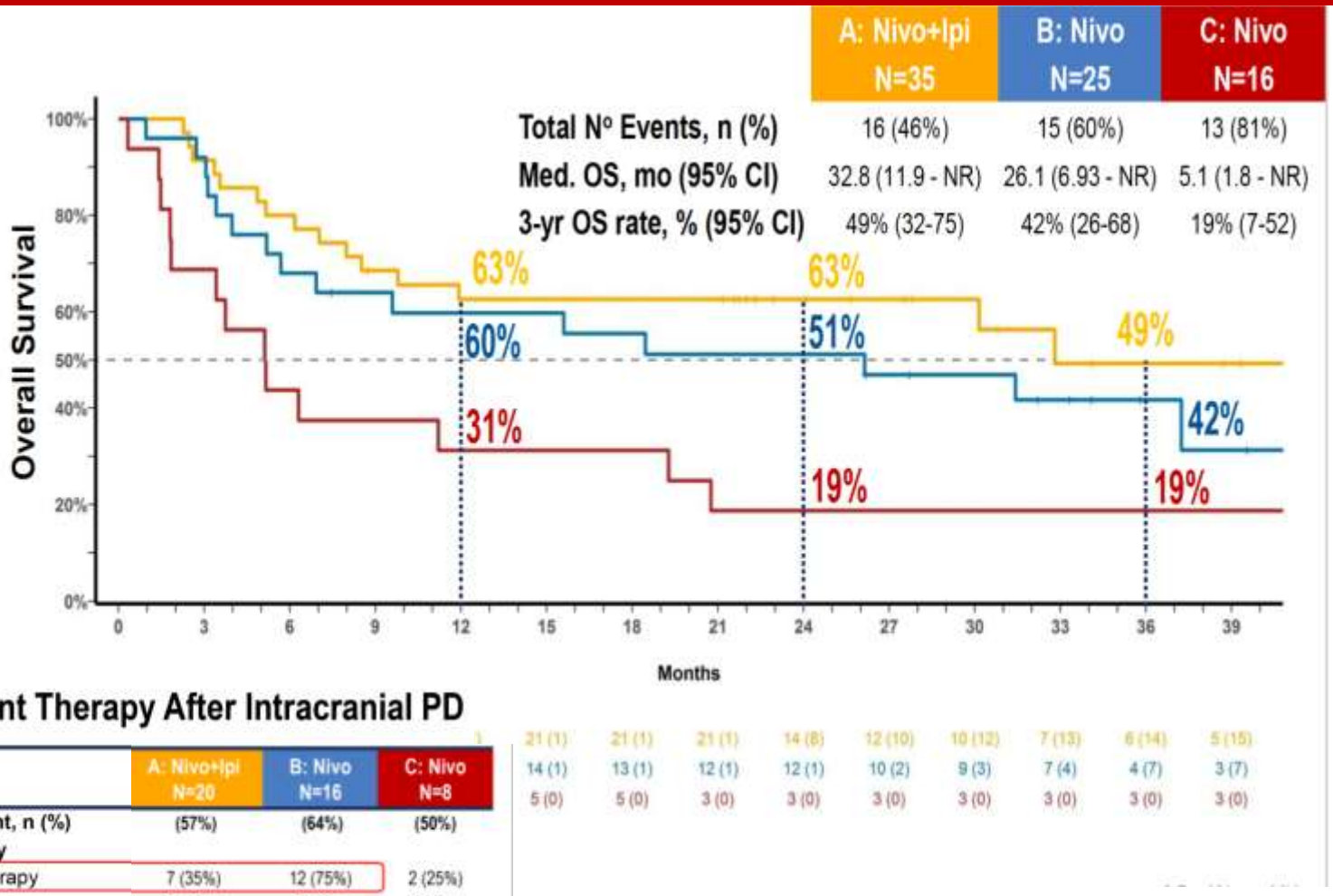
ABC Trial: OS



Subsequent Therapy After Intracranial PD

	A: Nivo+Ipi N=20	B: Nivo N=16	C: Nivo N=8
Any treatment, n (%)	(57%)	(64%)	(50%)
Local therapy			
Radiotherapy	7 (35%)	12 (75%)	2 (25%)
Surgery	3 (15%)	2 (12%)	2 (25%)
Systemic			
BRAF/MEKi	9 (45%)	9 (56%)	5 (62%)
Ipilimumab	4 (20%)	7 (44%)	2 (25%)
Anti-PD-1	5 (25%)	4 (25%)	0 (0%)
Ipilimumab + Anti-PD-1	5 (25%)	9 (56%)	1 (12%)
Chemotherapy	2 (10%)	0 (0%)	0 (0%)

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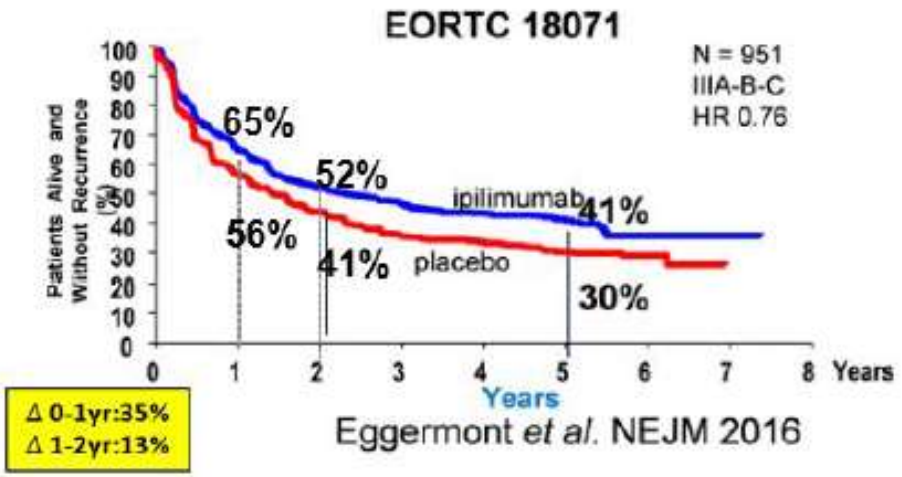
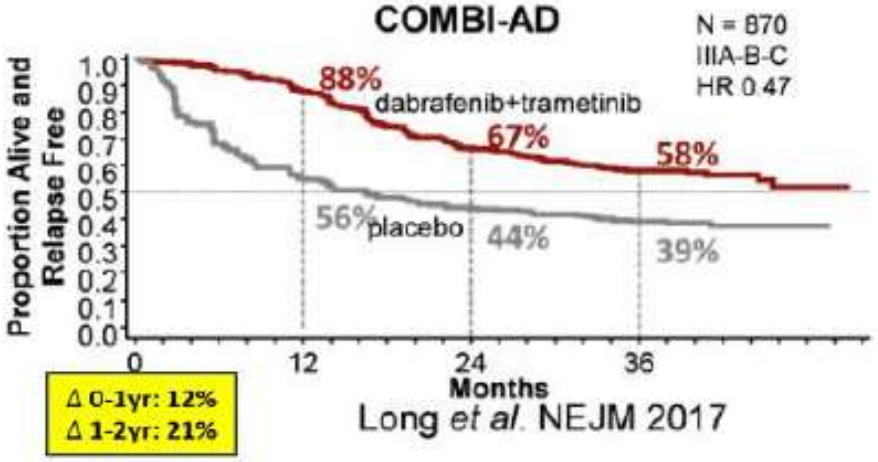
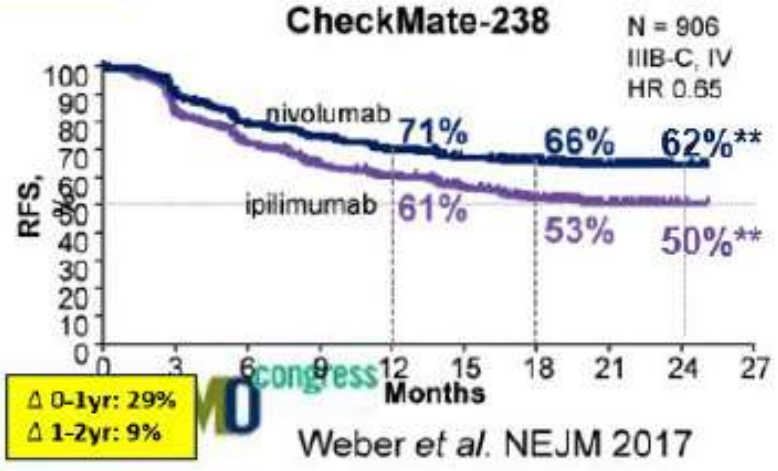
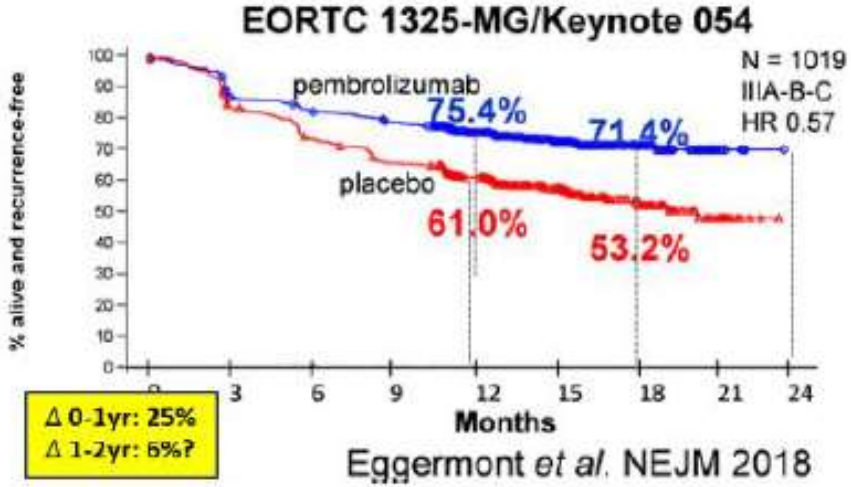
Terapie Adiuvanti

Improvement in RFS in high risk melanoma









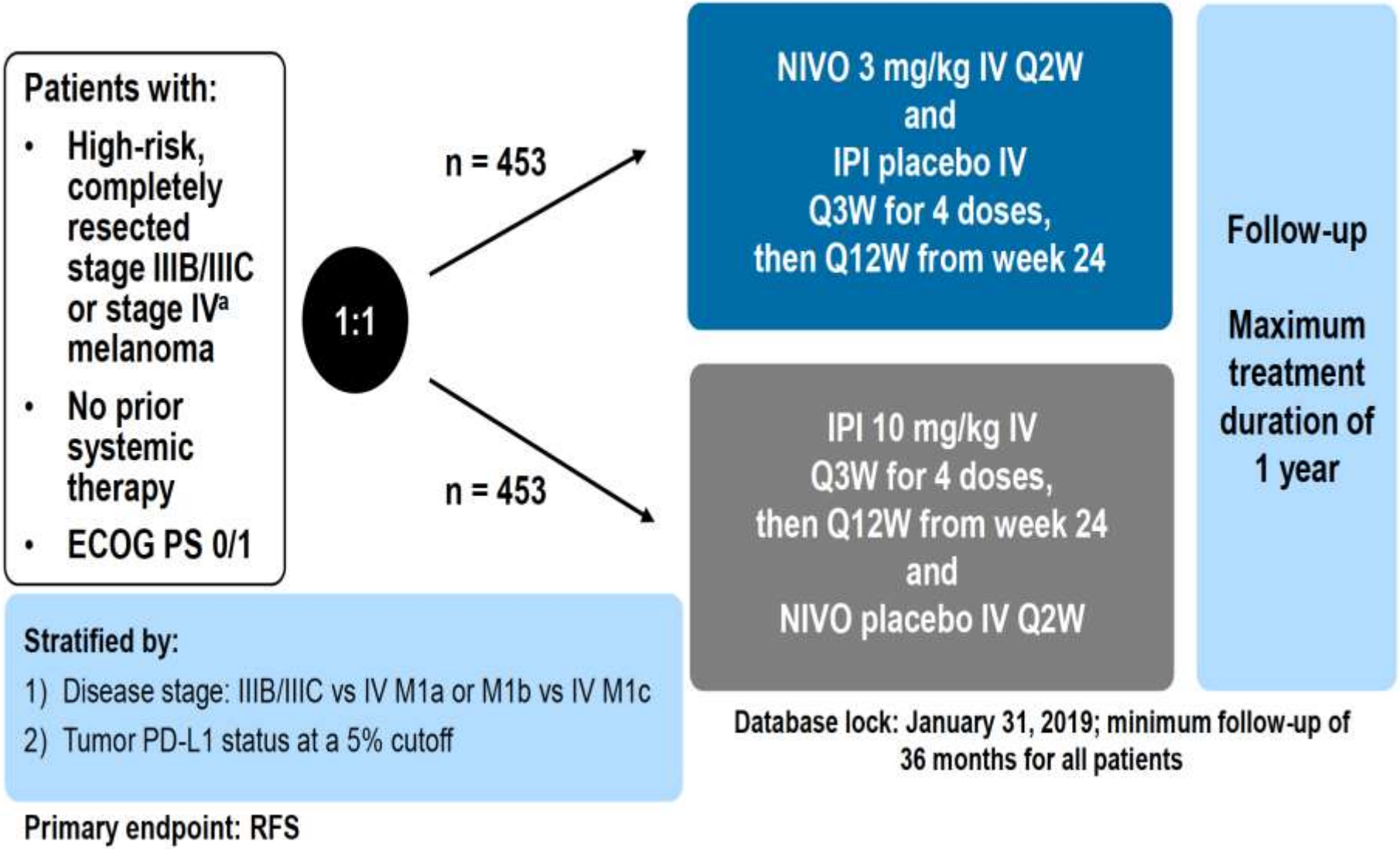
CheckMate 238

BARCELONA 2019 ESMO congress

Adjuvant Nivolumab Versus Ipilimumab in Resected Stage III/IV Melanoma: 3-Year Efficacy and Biomarker Results From the Phase 3 CheckMate 238 Trial

Jeffrey Weber,[1] Michele Del Vecchio,[2] Mario Mandala,[3] Helen Gogas,[4] Ana M. Arance,[5] Stéphane Dalle,[6] C. Lance Cowey,[7] Michael Schenker,[8] Jean-Jacques Grob,[9] Vanna Chiarion-Sileni,[10] Iván Márquez-Rodas,[11] Marcus Butler,[12] Michele Maio,[13] Hao Tang,[14] Abdel Saci,[14] Veerle de Pril,[14] Maurice Lobo,[14] James Larkin,[15*] Paolo A. Ascierto[16*]

CheckMate 238: Disegno dello Studio



Primary endpoint: RFS

Exploratory Endpoint: DMFS, potential biomarkers associated with efficacy

NCT02388906. [a]Per American Joint Committee on Cancer (AJCC) Cancer Staging Manual, seventh edition.

Presentato da J. Weber ad ESMO 2019

CheckMate 238: Caratteristiche dei pazienti

	NIVO (n = 453)	IPI (n = 453)
Median age, years	56	54
Male, %	57	59
Stage IIIB+IIIC, %	81	81
Macroscopic lymph node involvement (% of stage IIIB+IIIC)	60	58
Ulceration (% of stage IIIB+IIIC)	42	37
Stage IV, %	18	19
M1c without brain metastases (% stage IV)	17	17
Tumor PD-L1 expression ≥ 5%,[a] %	34	34
***BRAF* mutation, %**	41	43
LDH ≤ ULN, %	91	91
Melanoma subtype, %		
Cutaneous	86	83
Mucosal	4	3
Acral	4	4

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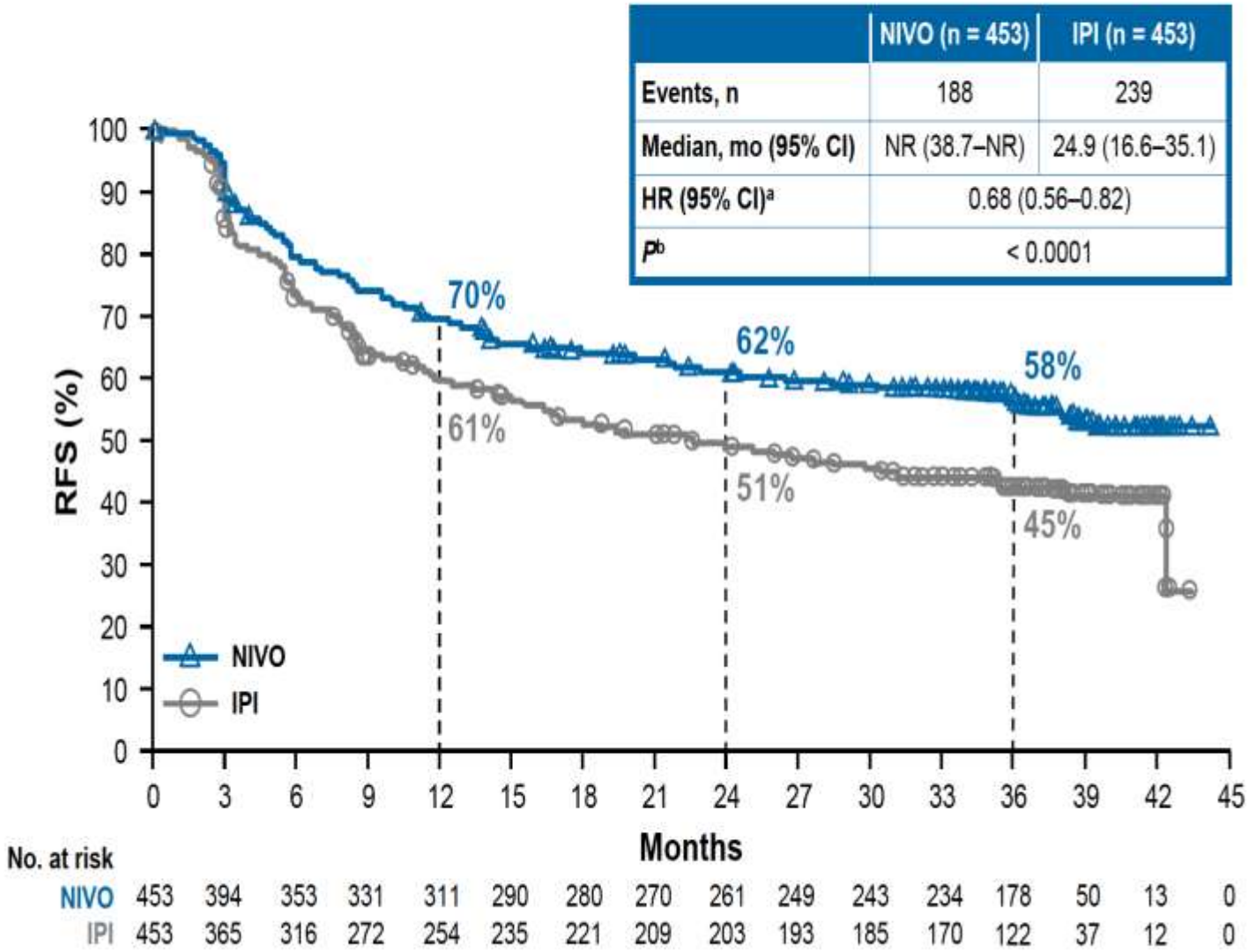
CheckMate 238: RFS



[a]Stratified; [b]Log-rank test. NR, not yet reached.

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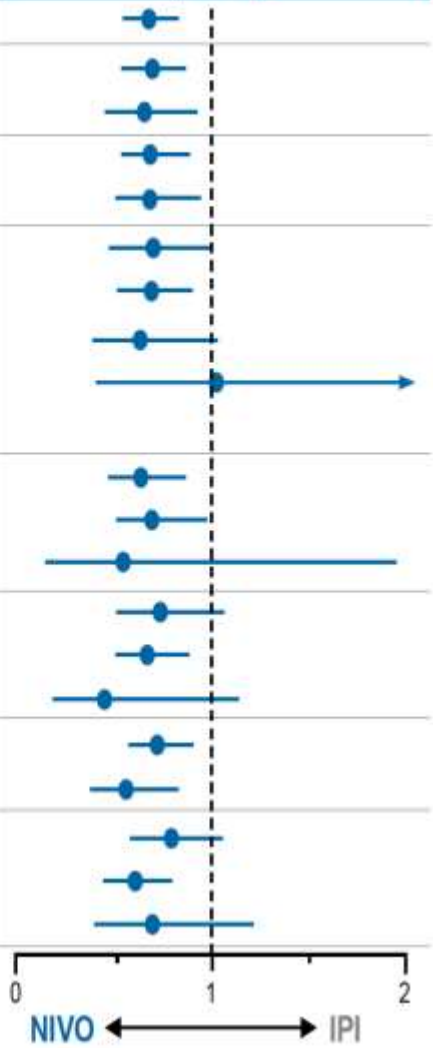
CheckMate 238: RFS – subgroup analysis

Subgroup		No. of events/no. of patients		Unstratified HR (95% CI)
		NIVO 3 mg/kg	IPI 10 mg/kg	
Overall	Overall	188/453	239/453	0.68 (0.56–0.83)
Age	< 65 years	131/333	170/339	0.69 (0.55–0.87)
	≥ 65 years	57/120	69/114	0.65 (0.46–0.93)
Sex	Male	116/258	151/269	0.69 (0.54–0.88)
	Female	72/195	88/184	0.69 (0.50–0.94)
Stage	Stage IIIB	53/163	65/147	0.70 (0.48–1.00)
	Stage IIIC	96/205	125/219	0.68 (0.52–0.89)
	Stage IV M1a–M1b	29/62	40/66	0.63 (0.39–1.02)
	Stage IV M1c	9/20	9/21	1.02 (0.40–2.57)
	Not reported	1/1	0/0	–
Stage III: ulceration	Absent	73/201	107/216	0.64 (0.48–0.87)
	Present	72/154	77/135	0.70 (0.51–0.97)
	Not reported	4/15	6/15	0.54 (0.15–1.94)
Stage III: lymph node involvement	Microscopic	50/127	64/133	0.73 (0.51–1.06)
	Macroscopic	91/219	115/215	0.68 (0.51–0.89)
	Not reported	8/24	11/18	0.45 (0.18–1.13)
Tumor PD-L1 status[a]	< 5%/indeterminate	144/300	171/299	0.73 (0.58–0.91)
	≥ 5%	44/153	68/154	0.57 (0.39–0.83)
***BRAF* mutation status**	Mutant	82/187	98/194	0.79 (0.59–1.06)
	Wild-type	79/197	117/212	0.60 (0.45–0.80)
	Not reported	27/69	24/47	0.70 (0.40–1.21)



[a]PD-L1 IHC 28-8 pharmDx assay.

Presentato da J. Weber ad ESMO 2019

CheckMate 238: Biomarcatori

Exploratory Biomarker Analysis

- Biomarkers were measured at baseline (pretreatment), with median values used as cutoffs[a]

Biomarker	Detection method	Patients analyzed, n (%)	
		NIVO (n = 452[b])	IPI (n = 453[b])
Interferon-gamma (IFN-γ) gene expression profile (GEP) signature[1] in tumor	Whole transcriptome shotgun sequencing	143 (32)	180 (40)
CD8+ T cells in tumor	Immunohistochemistry	149 (33)	161 (36)
Tumor mutational burden (TMB)	Whole exome sequencing	168 (37)	186 (41)
Myeloid-derived suppressor cells (MDSCs) in periphery	Flow cytometry in peripheral blood	405 (90)	418 (92)

[a]IFN-γ, 0.0259 GEP score; CD8, 11% CD8+ cells/nucleated cells in region of interest; TMB, 206 missense mutations/tumor; MDSCs, 18% Lin− CD14+ HLA-DR-low or negative monocytic myeloid cells/LIN− CD14+ cells; [b]Treated patients.

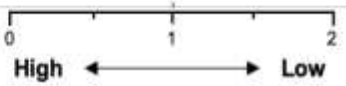
1. Ayers M, et al. *J Clin Invest*. 2017;127:2930–2940.

Presentato da J. Weber ad ESMO 2019

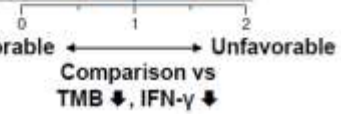
CheckMate 238: Biomarcatori

- Correlations with improved RFS were seen with:
  - High tumor IFN-γ expression signature levels: both NIVO and IPI
  - Tumor CD8+ T-cell infiltration: both NIVO and IPI
  - High TMB: both NIVO and IPI (trend)
  - Lower peripheral MDSC levels: NIVO (trend)

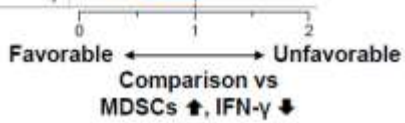
Biomarker	Treatment	Unstratified HR (95% CI)[a]
IFN-γ	NIVO	0.36 (0.21–0.63)
	IPI	0.53 (0.35–0.80)
CD8	NIVO	0.51 (0.32–0.84)
	IPI	0.52 (0.34–0.81)
TMB	NIVO	0.74 (0.46–1.17)
	IPI	0.74 (0.50–1.10)
MDSCs	NIVO	1.20 (0.89–1.62)
	IPI	1.00 (0.77–1.30)



Treatment	TMB	IFN-γ	Unstratified HR (95% CI)[a]
NIVO	↑	↑	0.26 (0.11–0.62)
	↓	↑	0.35 (0.16–0.77)
	↑	↓	0.46 (0.22–0.95)
IPI	↑	↑	0.45 (0.25–0.81)
	↓	↑	0.70 (0.37–1.30)
	↑	↓	0.90 (0.50–1.61)



Treatment	MDSCs	IFN-γ	Unstratified HR (95% CI)[a]
NIVO	↓	↑	0.20 (0.08–0.51)
	↑	↑	0.35 (0.16–0.74)
	↓	↓	0.70 (0.38–1.30)
IPI	↓	↑	0.33 (0.18–0.63)
	↑	↑	0.51 (0.29–0.90)
	↓	↓	0.60 (0.34–1.05)



Presentato da J. Weber ad ESMO 2019

IMMUNED Study

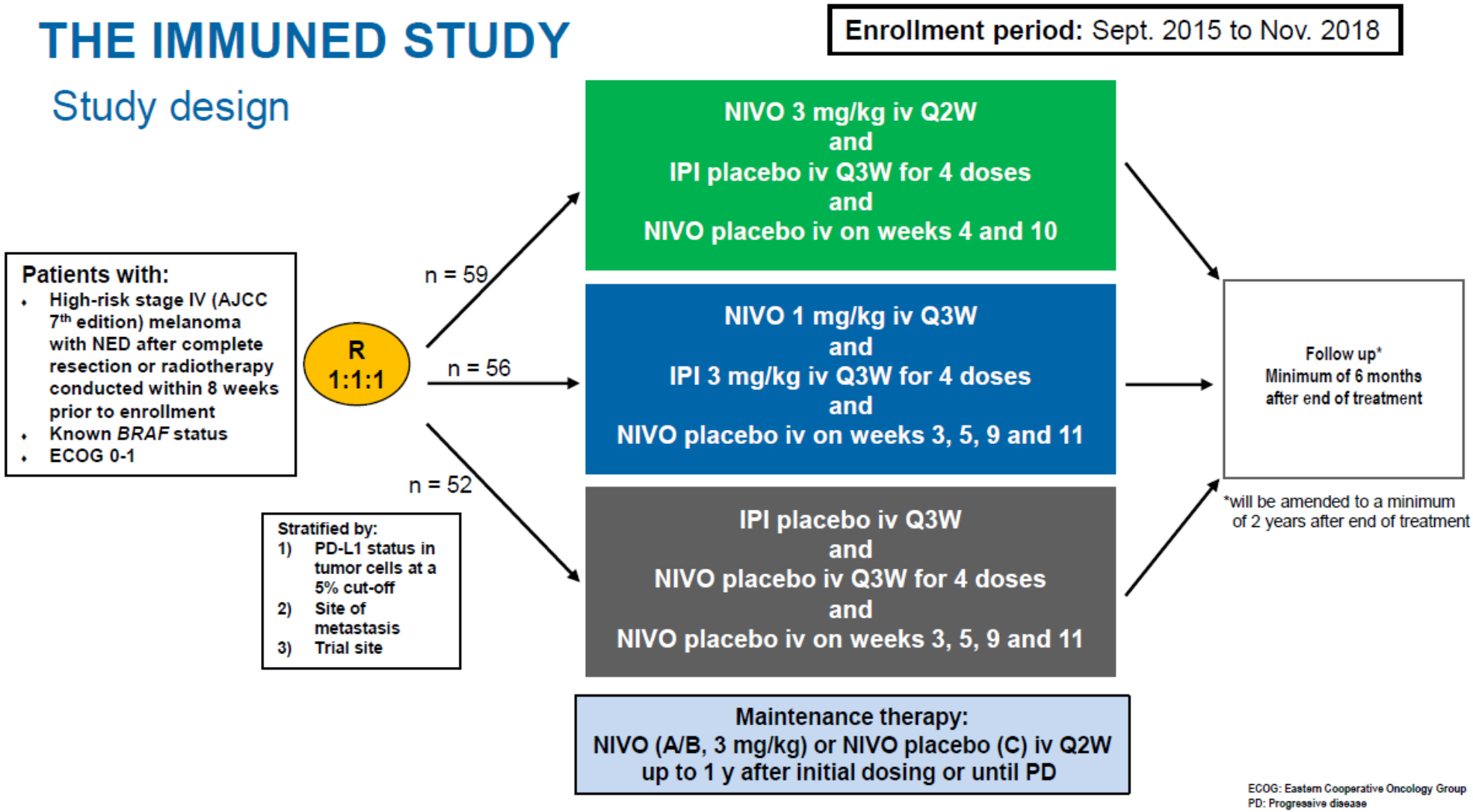
The IMMUNED Study

Adjuvant **IMMU**notherapy with nivolumab (NIVO) alone or in combination with ipilimumab (IPI) vs. placebo in stage IV melanoma patients with no evidence of disease (**NED**): A randomized, double-blind, phase II trial (**IMMUNED**) on behalf of DeCOG

Dirk Schadendorf[1], Jessica C. Hassel[2], Michael Fluck[3], Thomas Eigentler[4], Carmen Loquai[5], Mark Berneburg[6], Ralf Gutzmer[7], Friedegund Meier[8], Peter Mohr[9], Axel Hauschild[10], Jürgen Becker[11,12], Christian Menzer[2], Felix Kiecker[13], Edgar Dippel[14], Jan-Christoph Simon[15], Beate Conrad[3], Claus Garbe[4], Silvia Körner[2], Elisabeth Livingstone[1*], Lisa Zimmer[1*]

[1]Department of Dermatology, University Hospital Essen, Essen; [2]Department of Dermatology, University Hospital Heidelberg, Heidelberg; [3]Department of Dermatology Hornheide, Münster; [4]Department of Dermatology, University Hospital Tübingen, Tübingen; [5]Department of Dermatology, University Hospital Mainz, Mainz; [6]Department of Dermatology, University Hospital Regensburg, Regensburg; [7]Skin Cancer Center Hannover, Department of Dermatology and Allergy, Hannover Medical School, Hannover; [8]Department of Dermatology, University Hospital Dresden, Dresden; [9]Department of Dermatology, Buxtehude; [10]Department of Dermatology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel; [11]Translational Skin Cancer Research (TSCR), German Cancer Consortium (DKTK), Partner Site Essen, Medical Faculty, University of Duisburg-Essen, Essen; [12]German Cancer Research Center (DKFZ), Heidelberg; [13]Department of Dermatology, Charité Campus Mitte, Berlin; [14]Department of Dermatology, Ludwigshafen; [15]Department of Dermatology, University Hospital Leipzig, Leipzig; all facilities are from Germany; *contributed equally to this study

IMMUNED Study: Disegno dello studio



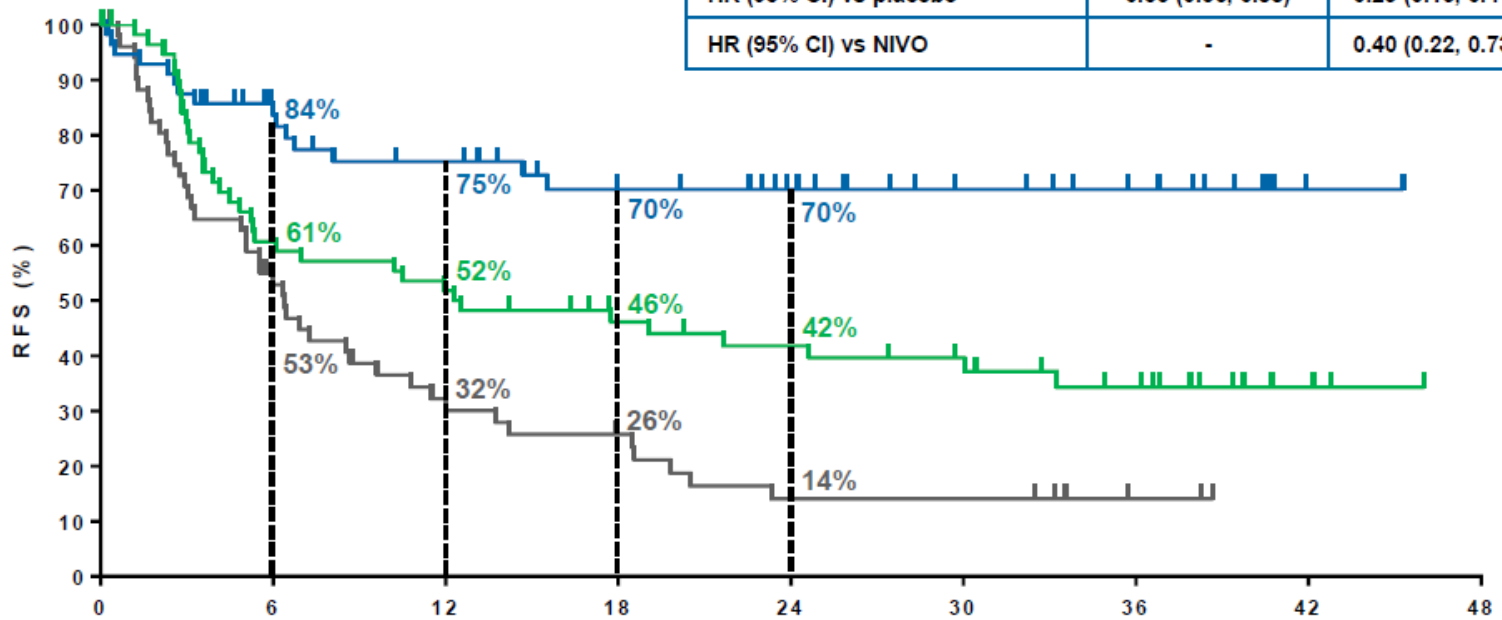
Presentato da D. Schadendorf ad ESMO 2019

IMMUNED Study: RFS

RFS in all patients

	NIVO (n=59)	NIVO+IPI (n=56)	Placebo (n=52)
Median RFS, mo (95% CI)	12.4 (5.30, 33.26)	NR[1]	6.4 (3.26, 9.61)
HR (95% CI) vs placebo	0.56 (0.36, 0.88)	0.23 (0.13, 0.41)	-
HR (95% CI) vs NIVO	-	0.40 (0.22, 0.73)	-

[1]NR: not reached



Patients at risk:

NIVO	59	34	29	22	19	16	11	3	-
NIVO + IPI	56	40	34	26	21	14	10	1	-
Placebo	52	26	15	11	6	6	2	-	-

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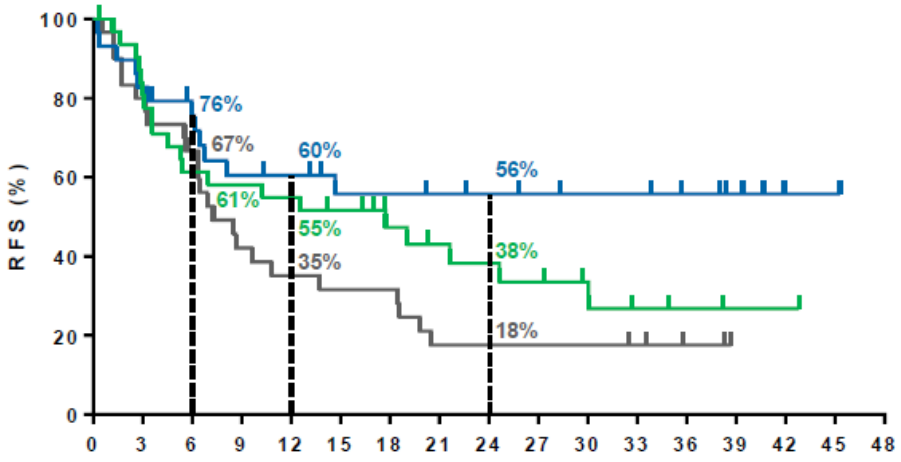
IMMUNED Study: RFS

RFS rate by *BRAF* mutation status

BRAF wildtype

	NIVO (n=32)	NIVO+IPI (n=29)	Placebo (n=31)
Median, mo (95% CI)	17.7 (4.47, 30.03)	NR[1] (6.45, NR[1])	7.3 (5.56, 13.75)
HR (95% CI) vs.placebo	0.70 (0.38, 1.27)	0.44 (0.22, 0.89)	–
HR (95% CI) vs. NIVO	–	0.61 (0.30, 1.26)	–

[1]NR: not reached.



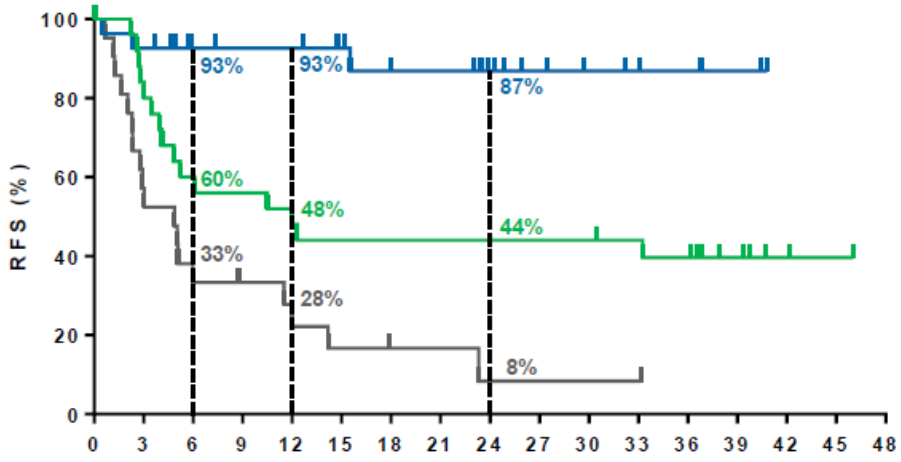
Patients at risk:

NIVO	32	25	19	18	17	15	11	9	8	7	5	3	2	1	1	-	-
NIVO + IPI	29	24	20	16	15	12	12	11	10	9	8	8	6	4	1	-	-
Placebo	31	24	19	12	10	9	9	5	5	5	5	4	2	-	-	-	-

BRAF mutant

	NIVO (n=27)	NIVO+IPI (n=27)	Placebo (n=21)
Median, mo (95% CI)	11.9 (4.11, NR[1])	NR (NR[1])	4.9 (2.30, 11.51)
HR (95% CI) vs.placebo	0.43 (0.21, 0.86)	0.07 (0.02, 0.25)	–
HR (95% CI) vs. NIVO	–	0.17 (0.05, 0.58)	–

[1]NR: not reached.



Patients at risk:

NIVO	27	21	15	14	12	11	11	11	11	11	11	10	9	5	2	-	-
NIVO + IPI	27	25	20	19	19	17	14	14	11	8	6	5	4	2	-	-	-
Placebo	21	12	7	6	5	3	2	2	1	1	1	1	-	-	-	-	-

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IMMUNED Study: Profilo di Tossicità

Safety overview

	NIVO (n=56)				NIVO + IPI (n=55)				Placebo (n=51)			
	All Grades		Grade 3/4		All Grades		Grade 3/4		All Grades		Grade 3/4	
	n	%	n	%	n	%	n	%	n	%	n	%
Any treatment-related AE	47	83.9	15	26.8	53	96.4	39	70.9	28	54.9	3	5.9
Skin	19	33.9	1	1.8	33	60.0	3	5.5	7	13.7	0	0
Gastrointestinal	19	33.9	1	1.8	25	45.5	8	14.5	8	15.7	0	0
Hepatic	9	16.1	5	8.9	33	60.0	26	47.3	1	2.0	0	0
Endocrine	14	25.0	2	3.6	33	60.0	7	12.7	1	2.0	0	0
Neurological	10	17.9	2	3.6	11	20.0	1	1.8	9	17.6	0	0
Musculoskeletal	14	25.0	3	5.4	14	25.5	1	1.8	5	9.8	0	0
Any immune-related AE	40	71.4	14	25.0	51	92.7	38	69.1	17	33.3	3	5.9
Treatment-related AE leading to discontinuation	7	12.5	5	8.9	34	61.8	29	52.7	1	2.0	-	-
Any AE leading to discontinuation	7	12.5	5	8.9	34	61.8	29	52.7	2	3.9	1	2.0

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NEOADIUVANTE

Modern melanoma NST trials

Trial	Regimen	N	pCR (%)	med RFS (mo)	med FU (mo)
Amaria Lancet Oncol 2018	Dab/Tram	21	58	19.7	18.6
Long Lancet Oncol 2019*	Dab/Tram	35	49	23.0	27.0
Blank Nat Med 2018	Ipi+nivo	10	33	NR	32
Amaria Nat Med 2018	Nivo Ipi+nivo	12 11	25 45	NR NR	20
Huang Nat Med 2019	Pembro	30	19	NR	18
Rozeman Lancet Oncol 2019*	Ipi+nivo	86	57^	NR	8.3

* In press

^arm B = ITN3

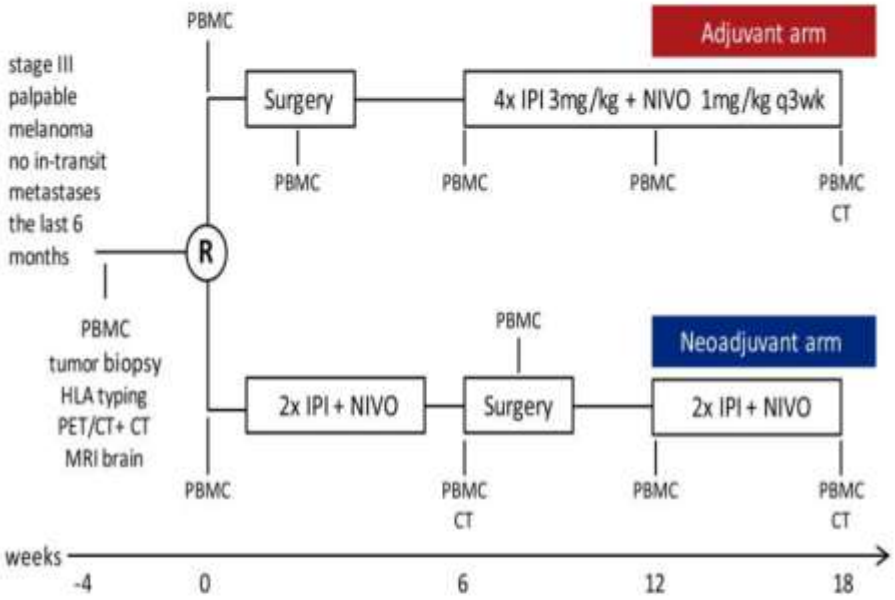
OPACIN Trial

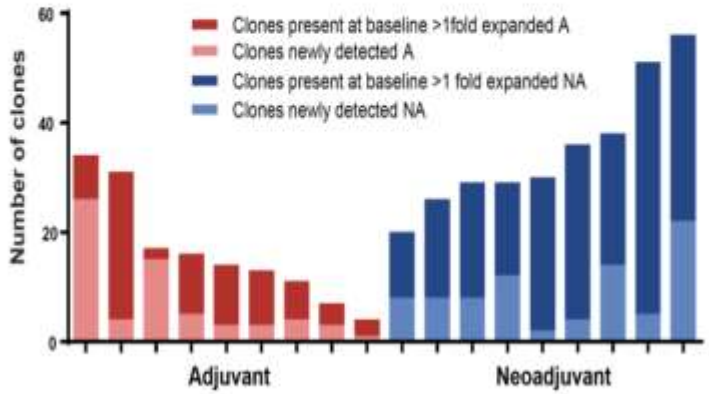
BARCELONA 2019 ESMO congress

3-YEAR RELAPSE-FREE SURVIVAL, OVERALL SURVIVAL AND LONG-TERM TOXICITY OF (NEO)ADJUVANT IPILIMUMAB (IPI) + NIVOLUMAB (NIVO) IN MACROSCOPIC STAGE III MELANOMA – OPACIN TRIAL

CU Blank[1], JM Versluis[1], ILM Reijers[1], K. Sikorska[2], WJ van Houdt[3], JV van Thienen[1], S Adriaansz[1], H Mallo[1], H van Tinteren[2], BA van de Wiel[4], LG Grijpink-Ongering[3], A Bruining[5], JBAG Haanen[1], ACJ van Akkooi[3], TN Schumacher[6], EA Rozeman[1]

OPACIN Trial: Disegno dello Studio

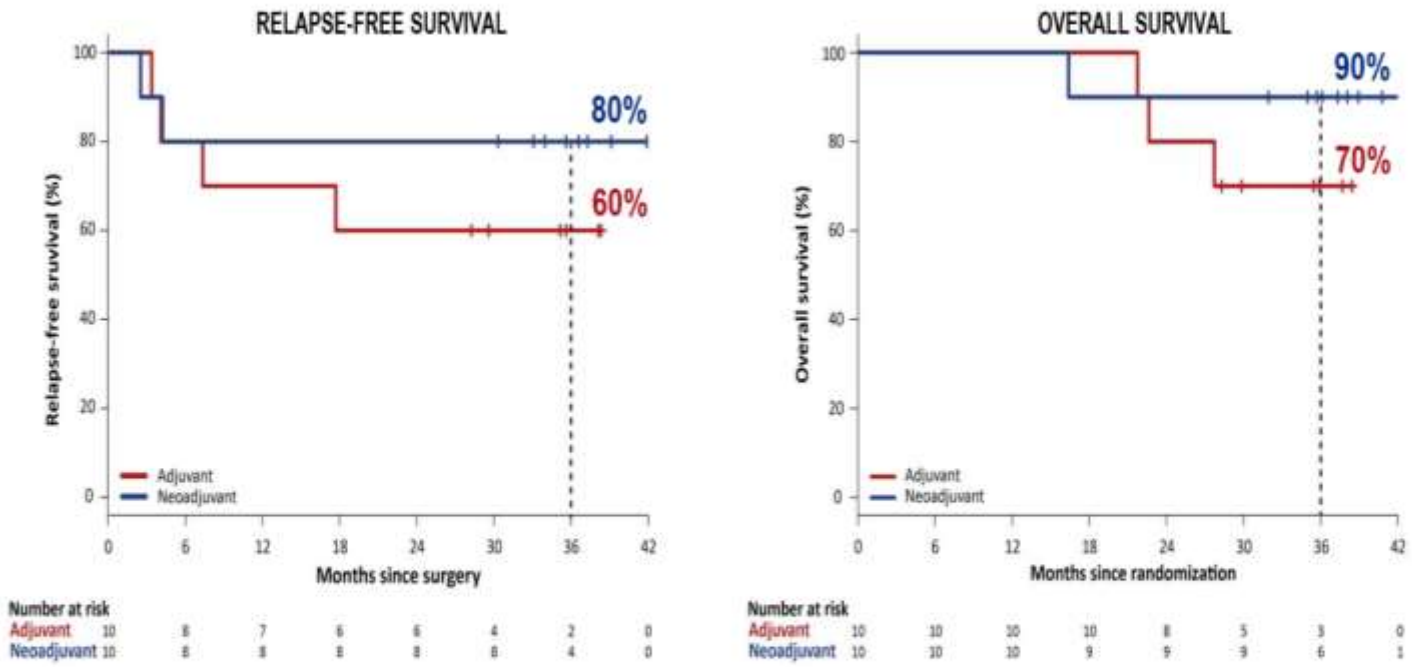




- Randomized phase 1b feasibility trial testing adjuvant (N=10) vs neoadjuvant (N=10) IPI + NIVO at standard dose in macroscopic stage III melanoma.
- **Neoadjuvant IPI + NIVO** induced a high pathological response rate (**pRR, 78%**).
- Toxicity was high with **90% grade 3/4 toxicities**, making the standard dose unfeasible for broader testing.
- Neoadjuvant IPI plus NIVO induces a **higher number** of expanded and newly detectable tumor **resident TCR clones** in the peripheral blood after 6 weeks of treatment as compared to adjuvant therapy.
- **None of the patients** that achieved a **pathologic response** had relapsed.

OPACIN Trial: RFS e OS

3-YEAR SURVIVAL UPDATE



After median follow-up of 36.7 months (minimum of 28 months of patients alive), no new events occurred:

- **4 patients** have relapsed in the **adjuvant arm** (1 patient local recurrence, 3 patients distant metastasis)
- **2 patients** with **no pathologic response** have relapsed in the **neoadjuvant arm** (1 patient local recurrence, 1 patient distant metastasis). **None of the patients** with a **pathologic response** have relapsed.
- 4 patients have died, these are all patients that developed distant metastases.

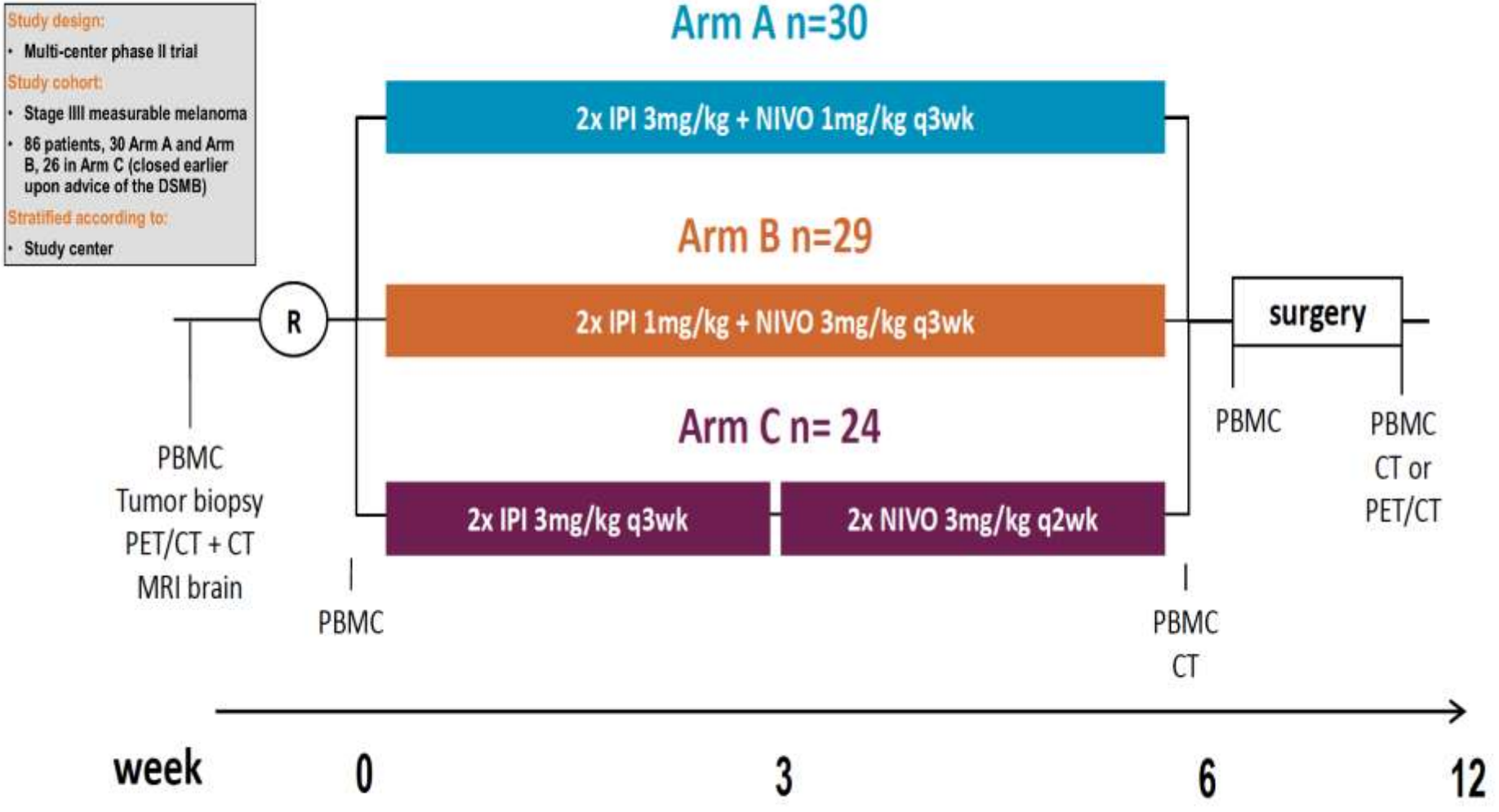
OPACIN-NEO

BARCELONA 2019 ESMO congress

18-MONTHS RELAPSE-FREE SURVIVAL AND BIOMARKER ANALYSES OF OPACIN-NEO: A STUDY TO IDENTIFY THE OPTIMAL DOSING SCHEDULE OF NEOADJUVANT IPILIMUMAB + NIVOLUMAB IN STAGE III MELANOMA

EA Rozeman, AM Menzies, O Krijgsman, EP Hoefsmit, BA van de Wiel, K. Sikorska, TM Van, H Eriksson, C Bierman, P Dimitriadis, M Gonzalez, K Shannon, A Broeks, R Kerkhoven, AJ Spillane, RPM Saw, ACJ van Akkooi, RA Scolyer, J. Hansson, GV Long, CU Blank;

OPACIN-NEO: Disegno dello studio



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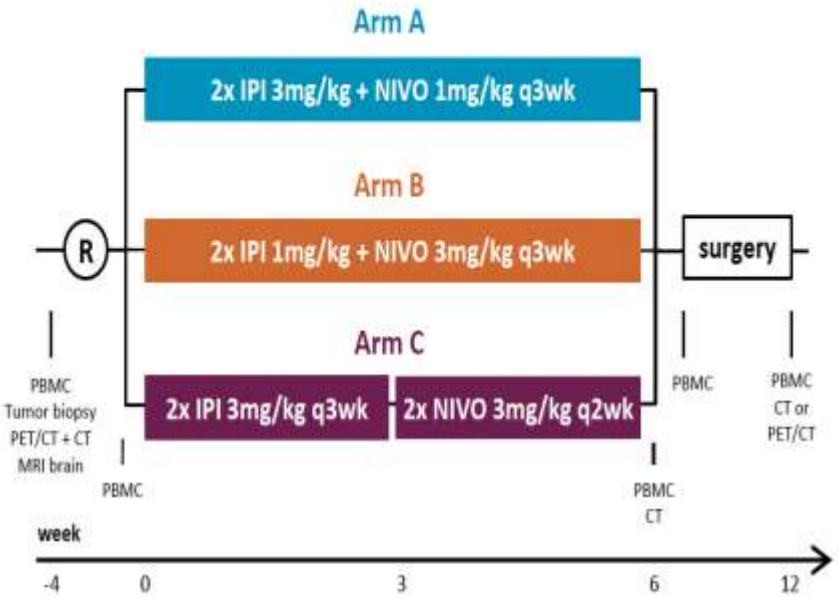
Blank C et al Lancet Onc 2019; Rozeman EA et al ESMO 2019

OPACIN-NEO: Disegno dello studio

- OpACIN-neo is a randomized phase 2 study with the aim to identify the optimal dosing schedule of neoadjuvant IPI +NIVO
  - 86 patients were included
  - Primary endpoints were grade 3-4 AEs within the first 12 weeks and pathologic and radiologic response rate
- The dosing schedule tested in arm B: 2 courses IPI 1mg/kg + NIVO 3mg/kg has been identified as most favourable schedule

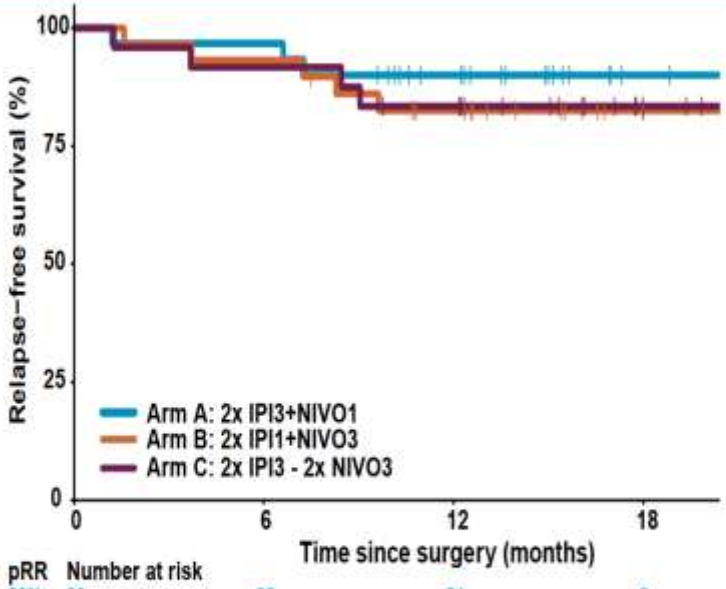


Arm	Grade 3-4 AEs	Pathologic response
A	40%	80%
B	20%	77%
C	50%	65%

OPACIN-NEO: RFS

18-MONTHS RELAPSE FREE SURVIVAL

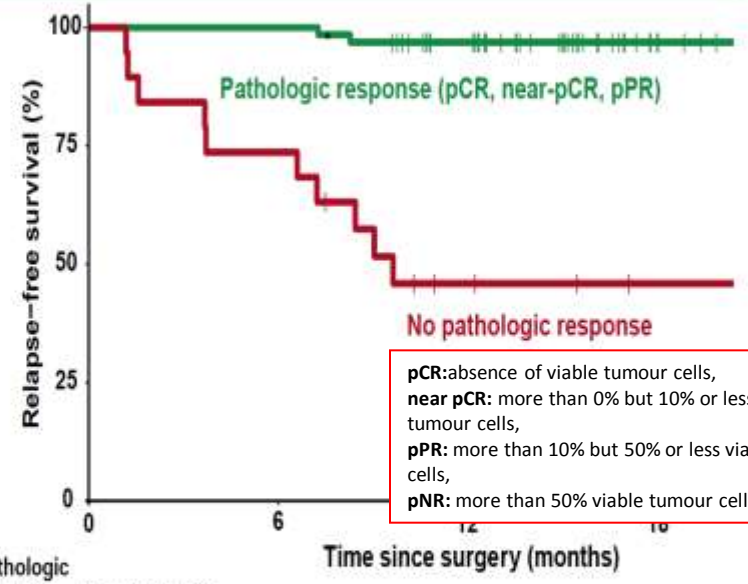
According to treatment arm



Arm	pRR	Number at risk			
A	80%	30	29	21	8
B	77%	29	27	20	9
C	65%	24	22	19	7

pRR = pathologic response rate

According to pathologic response



Pathologic response	Number at risk			
Yes	64	64	54	21
No	19	14	6	3

* patient died due to toxicity without signs of melanoma relapse

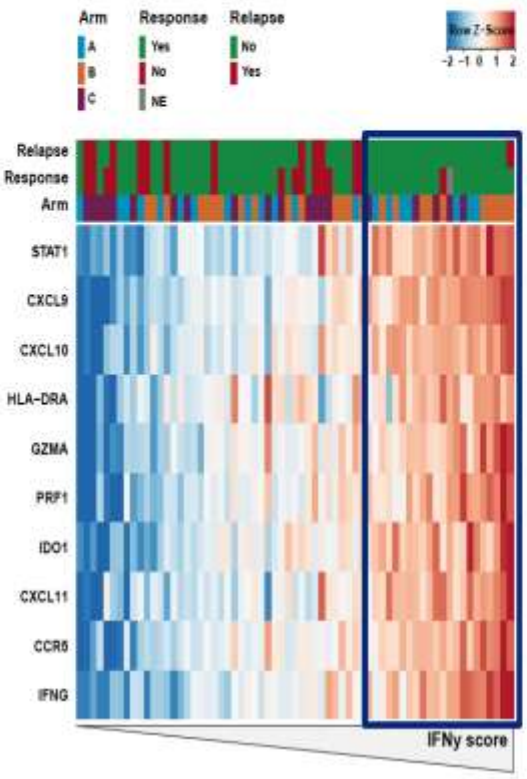
pCR: absence of viable tumour cells,
near pCR: more than 0% but 10% or less viable tumour cells,
pPR: more than 10% but 50% or less viable tumour cells,
pNR: more than 50% viable tumour cells

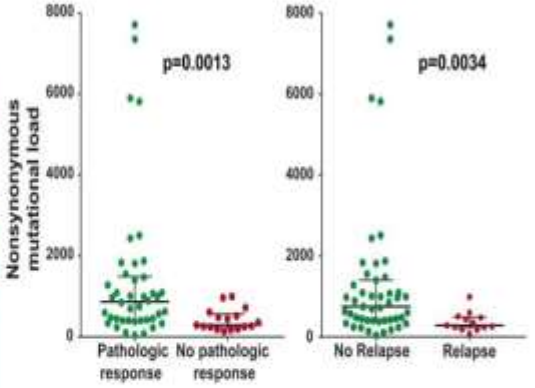
- Relapses were observed in 1/64 (2%) pathological responders versus 13/21 (62%) of the non-responders. Two of these patients had been diagnosed with distant metastasis at week 6 before surgery.
- The only patient with a response that relapsed was treated in arm B, had a pCR and developed distant metastases 9 months after surgery in a single organ for which she was treated with surgery and radiotherapy. Until now, there are no signs of disease progression.

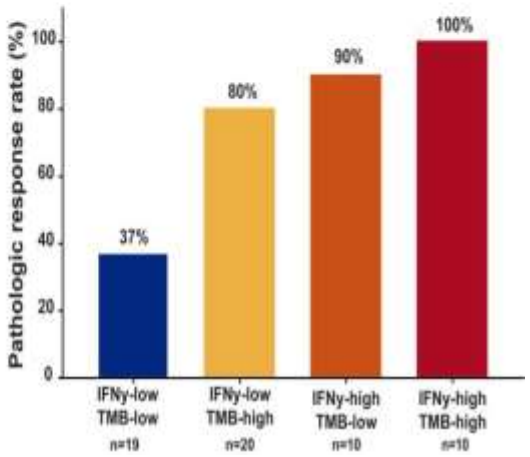
OPACIN-NEO: Biomarcatori

IFN-Y SIGNATURE AND MUTATIONAL LOAD ARE ASSOCIATED WITH RESPONSE AND RELAPSE

- RNA and DNA could be isolated from pre-treatment biopsies from 60 patients and RNA sequencing and whole exome sequencing were performed.
- A high IFN-y signature was associated with pathologic response and low risk of relapse
- Patients with a pathologic response had a higher mutational load
- When combining IFN-y signature score (top third as threshold) and mutational load (median as threshold) we can identify a group of patients that is less likely to respond to neoadjuvant IPI+NIVO.







Trattamenti immunomodulanti intratumorali

Class	Agent	Combination	Tumor type	Trial
PAMPs	CpG (CMP-001)	Pembrolizumab	Melanoma	NCT02680184
	CpG (SD-101)	Pembrolizumab	Melanoma	NCT02521870
	CpG (IMO-2125)	Ipilimumab	Melanoma	NCT02644967
	STING agonists (ADU)	Ipilimumab	Solid tumors	NCT02675439
Oncolytic viruses	T-VEC (HSV-1)	None	Melanoma	OPTIM
	T-VEC (HSV-1)	Ipilimumab	Melanoma	NCT01740297
	T-VEC (HSV-1)	Pembrolizumab	Melanoma	MASTERKEY-265
	HF10 (HSV-1)	Ipilimumab	Melanoma	NCT02272855
	Coxsackievirus A21	Ipilimumab	Melanoma	NCT02307149
Cytokines	Vector encoded IL-12	None	Melanoma	NCT01502293
Monoclonal AB	Ipilimumab	Nivolumab	Melanoma	NCT02857569
Dendritic cells	INTUVAX (allo DC)	None	GISTS	NCT02686944

NCT02211131 T-VEC NeoAdj

PRIMARY 2-YEAR RESULTS OF THE PHASE 2, MULTICENTER, RANDOMIZED, OPEN-LABEL TRIAL OF EFFICACY AND SAFETY FOR TALIMOGENE LAHERPAREPVEC (T-VEC) NEOADJUVANT TREATMENT PLUS SURGERY VS SURGERY IN PATIENTS WITH RESECTABLE STAGE IIIB–IVM1A MELANOMA

Reinhard Dummer,[1] David E Gyorki,[2] John Hyngstrom,[3] Adam Berger,[4] Robert Conry,[5] Lev Demidov,[6] Anjali Sharma,[7] Sheryl A Treichel,[7] Kevin Gorski,[8] Abraham Anderson,[7] Mark Faries,[9] Merrick I Ross[10]

[1]University Hospital of Zurich, Zurich, Switzerland; [2]Olivia Newton-John Cancer Centre, Austin Health, Melbourne, Australia; [3]University of Utah Huntsman Cancer Institute, Salt Lake City, UT; [4]Thomas Jefferson University Hospitals, Philadelphia, PA; [5]University of Alabama School of Medicine, Birmingham, AL; [6]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [7]Amgen Inc., Thousand Oaks, CA; [8]Amgen Inc., San Francisco, CA; [9]John Wayne Cancer Institute, Santa Monica, CA; [10]University of Texas MD Anderson Cancer Center, Houston, TX

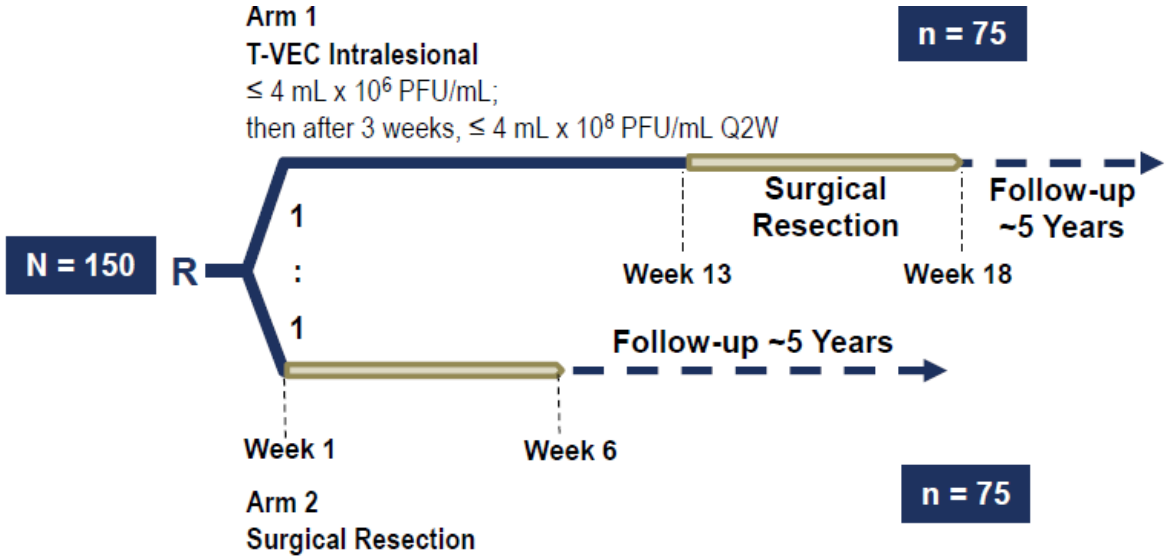
NCT02211131 T-VEC NeoAdj: Disegno

Resectable Stage IIIB–IVM1a[6] Melanoma

- Injectable and measurable
- LDH ≤ 1.5 x ULN for IIIB/C and ≤ 1 x ULN for IVM1a
- ECOG PS 0 or 1
- Prior treatment completed ≥ 3 months prior

Stratification:

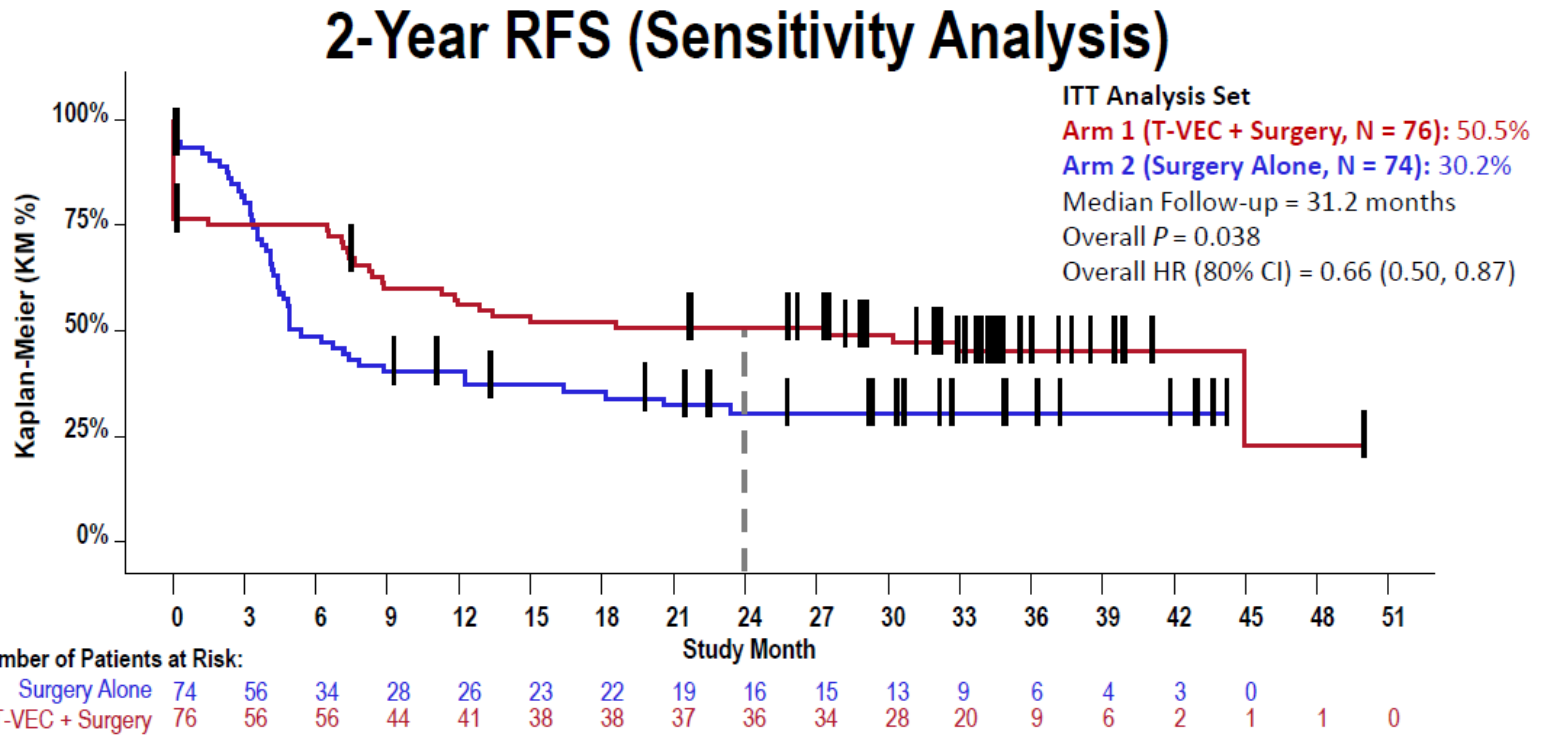
- Disease stage
- Planned adjuvant therapy



Primary Endpoint:	RFS
Key Secondary Endpoints:	RFS,* overall survival (OS),* overall tumor response (in Arm 1 only), pathological complete response (in Arm 1 only), rates of histopathological tumor-free (R0) surgical resection, local RFS, regional RFS, distant metastases-free survival, safety
Exploratory Endpoints:	Analyses of tumor tissue biomarkers and correlations with clinical outcomes for T-VEC

Presentato da R. Dummer ad ESMO 2019

NCT02211131 T-VEC NeoAdj: RFS



Type of RFS Event at Baseline	Arm 1: T-VEC + Surgery (n = 76)	Arm 2: Surgery Alone (n = 74)
No surgery – n (%)	18 (23.7)	4 (5.4)

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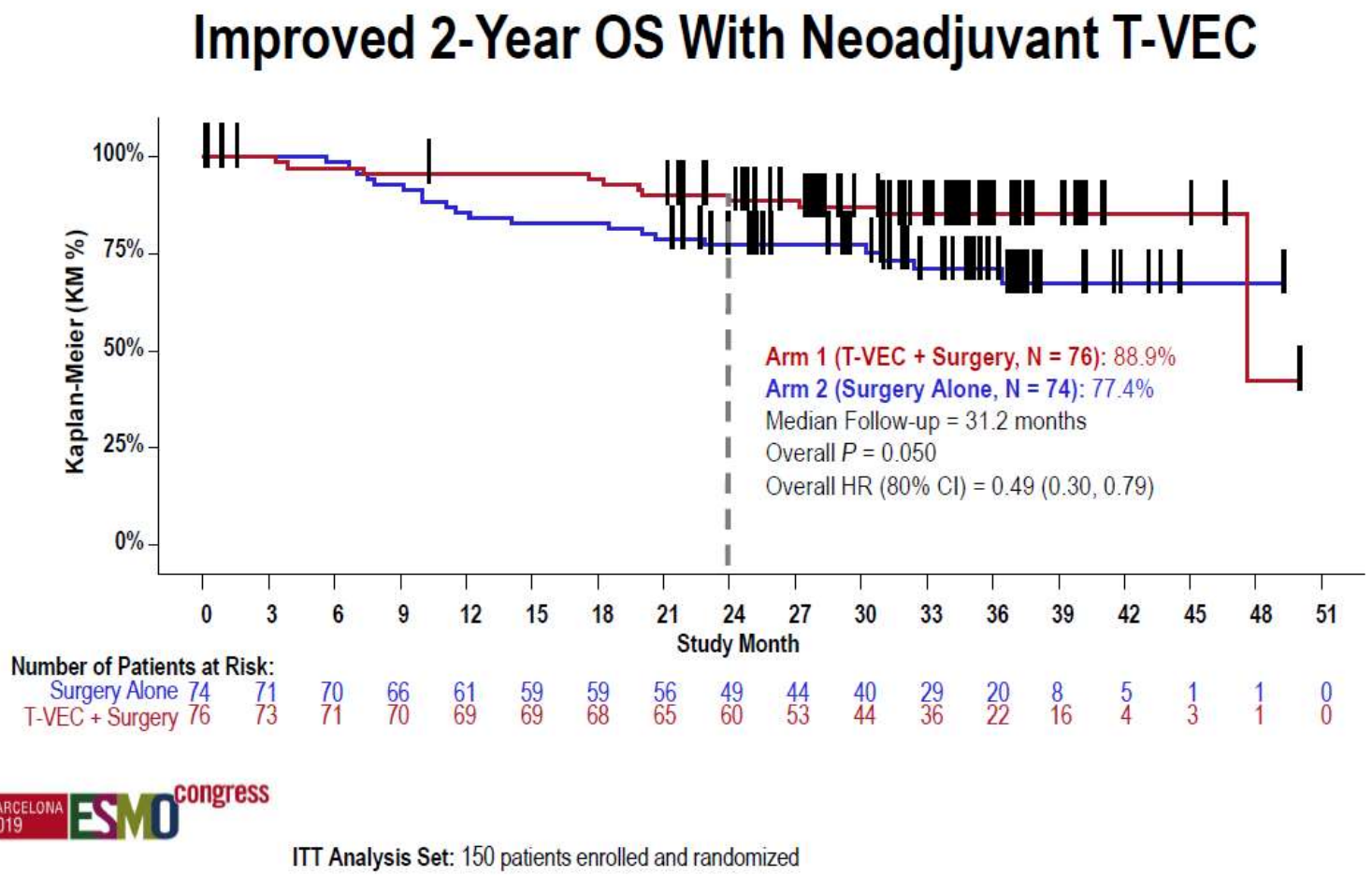
NCT02211131 T-VEC NeoAdj: OS



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ITT Analysis Set: 150 patients enrolled and randomized

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NCT02211131 T-VEC NeoAdj: pCR

pCR Rate With Neoadjuvant T-VEC

	Arm 1: T-VEC + Surgery	
	Efficacy Analysis Set (n = 57)	ITT Analysis Set (n = 76)
pCR[a] – n(%)	13 (22.8)	13 (17.1)

9 out of 13 patients with Pathological CR have not relapsed at the time of this analysis

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Efficacy Analysis Set: patients who received at least 1 dose of T-VEC followed by surgical resection in Arm 1, or who received surgical resection in Arm 2

ITT Analysis Set: 150 patients enrolled and randomized

[a]pCR is defined as no evidence of viable tumor cells on complete pathological evaluation of the surgical specimen per institutional standards.

Presentato da R. Dummer ad ESMO 2019

Melanoma:
NOVITA' ESMO 2019

NEO-Adjuvant Setting

LOCAL DISEASE
Surgery of primary melanoma + Lymphonodes

- ❑ Aggiornamento
  OPACIN /OPACIN-NEO: **confermato interesse per Ipi 1-Nivo 3 mg/kg**
- ❑ Nuovi Farmaci
  T-VEC: **al momento meno competitivo rispetto altre strategie**

Adjuvant Setting

Evaluation of adjuvant treatment

- ❑ Aggiornamento
  CHECKMATE-238: **Confermata l'efficaca di Nivo vs Ipi**
- ❑Setting : NED post chir mts
  IMMUNED study: **interessante efficacia di Ipi Nivo**

Metastatic Setting

METASTATIC DISEASE

- ❑ Aggiornamento
  CHECKMATE-067: **IpiNivo conferma efficacia**
- ❑Nuove Combinazioni
  IMSPIRE-170: **Negativo Meki+AntiPDL1 in BRAF wt**
- ❑Setting : Mts Encefaliche
  ABC Trial: **IpiNivo efficace**

Grazie per l’attenzione !!

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