VII SIMPÓSIO INTERNACIONAL DE Melanoma

HOTEL PULLMAN VILA OLÍMPIA

29 E 30 DE NOVEMBRO 2019

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Tratamento (Sistêmico) das Metástases Cerebrais

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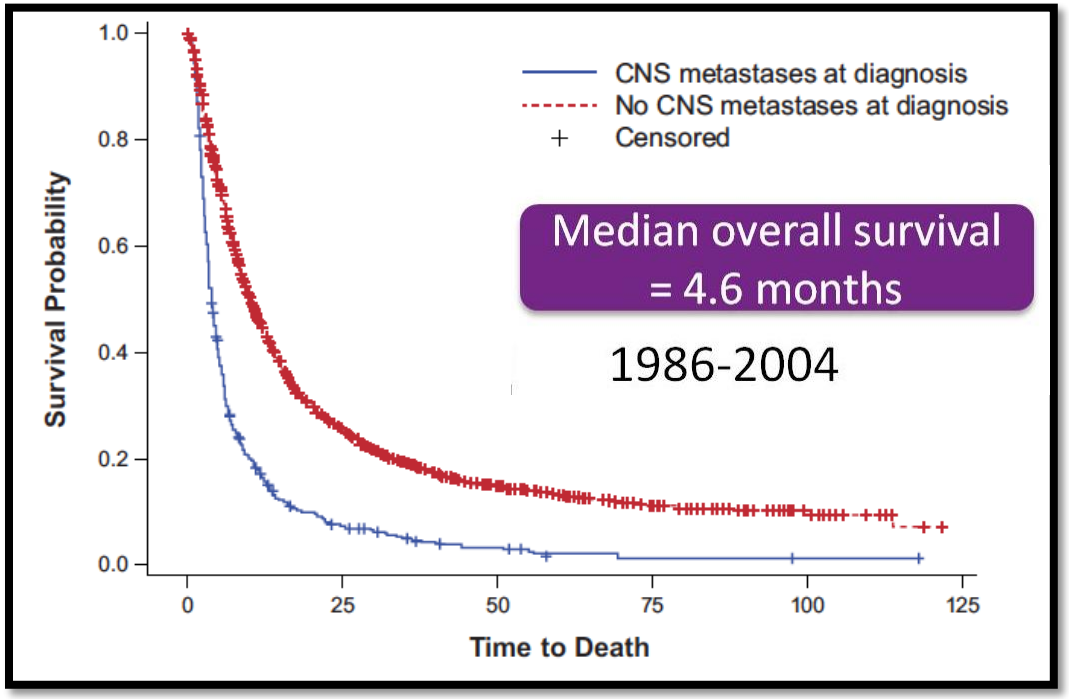
Declaração de Conflito de Interesses

De acordo com a resolução do **Conselho Federal de Medicina nº 1595/2000 e Resolução da Diretoria Colegiada da ANVISA nº 96/2008**, eu declaro que:

- Pesquisa Clínica – Como investigador: **Novartis, Roche, Astellas, Merck, Bayer**
- Apresentações Científicas – Como palestrante: **MSD**, **BMS**, **Novartis, Janssen**
- Atividades de Consultoria – Como membro de Advisory Boards: **Novartis, BMS, MSD**

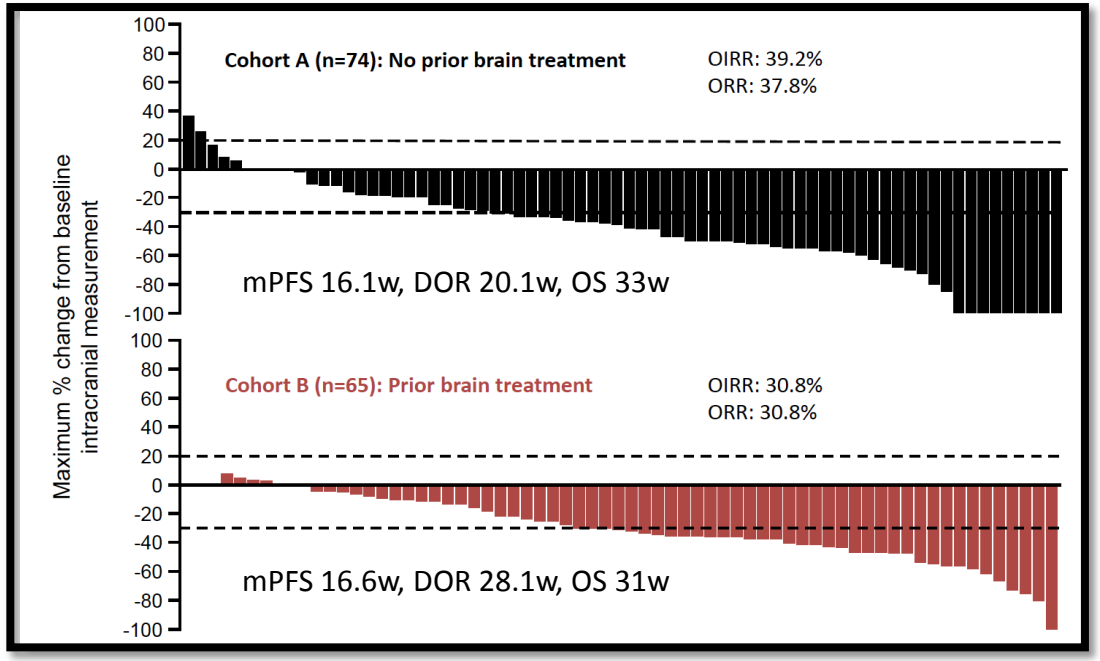
Incidência e Prognóstico

- Melanoma é a 3ª causa mais comum de metástases cerebrais
- 10-20% dos pacientes tem metástases SNC ao diagnóstico
- Até 40-70% dos pacientes desenvolvem metástases durante a doença (tropismo cerebral)
- Pior sobrevida livre de progressão e sobrevida global
- Rotineiramente excluídos de estudos clínicos



Sampson JH et al. J Neurosurg 1998; 88:11-20. Nieder C et al. Anticancer Res 2008; 28:1325. SMR 2016.

BREAK-MB



	Cohort A N=74 RT naive	Cohort B N=65 Prior RT
Overall intracranial response (CR+PR)	29 (39.2%)	20 (30.8%)
Intracranial disease control (CR+PR+SD)*	60 (81.1%)	58 (89.2%)
6-month survival estimate (%)	61 %	61%

Long GV et al. Lancet Oncol 2012;13:1087–95

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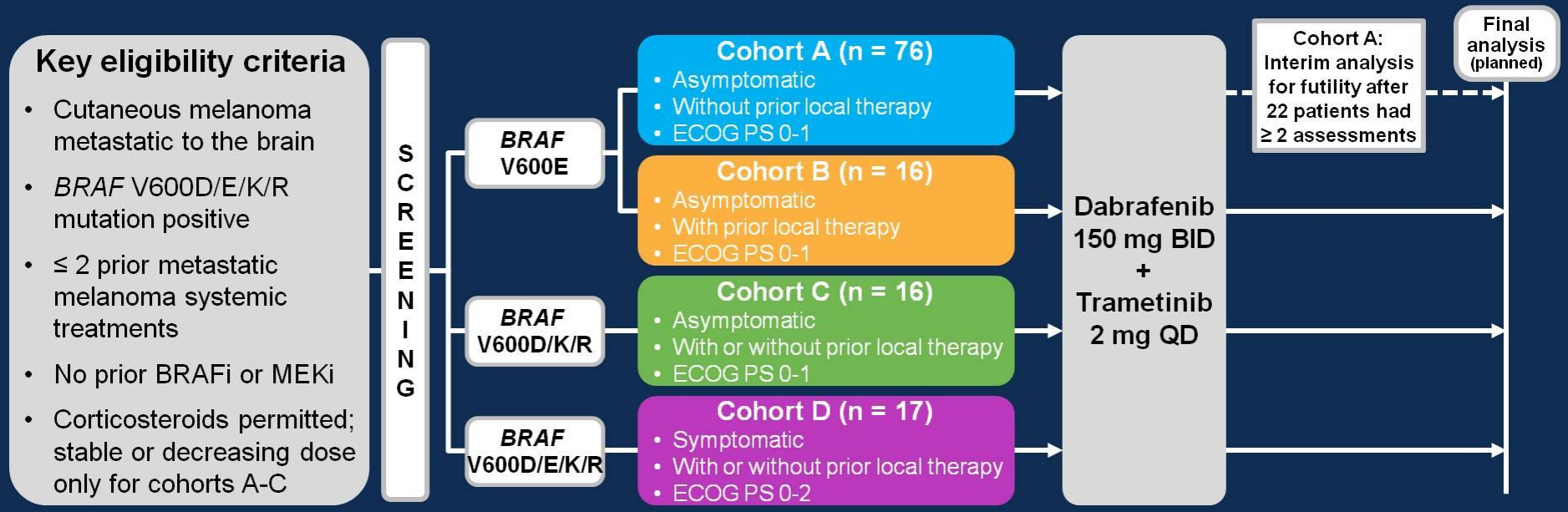
COMBI-MB: Study Design (phase 2)



- **Primary endpoint:** intracranial response (IR) rate in cohort A[a]
- **Secondary endpoints:** IR rate in cohorts B, C, and D; extracranial response (ER) and overall response (OR) rates; intracranial, extracranial, and overall DCRs; duration of IR, ER, and OR; PFS; OS; and safety

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; QD, once daily.
[a] Null hypothesis: IR rate of ≤ 35% in cohort A (based on activity of dabrafenib monotherapy in the BREAK-MB trial; Long GV, et al. *Lancet Oncol.* 2012;13:1087-1095).
Investigator-assessed efficacy was confirmed by a blinded independent review committee (BIRC). Data cutoff date: November 28, 2016.

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Presented by: Michael A. Davies

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Baseline Patient Characteristics

	Cohort A (n = 76)	Cohort B (n = 16)	Cohort C (n = 16)	Cohort D (n = 17)
Median age (range), y	52.0 (23-84)	54.5 (36-74)	63.0 (44-84)	46.0 (23-68)
Male, n (%)	40 (53)	10 (63)	11 (69)	11 (65)
ECOG PS 0, n (%)	50 (66)	11 (69)	12 (75)	9 (53)
***BRAF* genotype, n (%)**				
V600E	73 (96)	16 (100)	0	15 (88)
V600K/D/R	3 (4)	0	16 (100)	2 (12)
Target brain metastases, n (%)				
1	41 (54)	7 (44)	7 (44)	7 (41)
2	20 (26)	7 (44)	6 (38)	7 (41)
≥ 3	15 (20)	2 (13)	3 (19)	3 (18)
Median SLD of target and nontarget intracranial lesions (range), mm	19.5 (6-117)	14.0 (5-40)	20.0 (5-61)	33.0 (10-84)
Extracranial metastases present, n (%)	68 (89)	12 (75)	16 (100)	12 (71)
Elevated LDH level (> ULN), n (%)	28 (37)	3 (19)	6 (38)	5 (29)
Steroid use at baseline, n (%)	13 (17)	3 (19)	4 (25)	11 (65)
Previously treated with systemic anticancer treatment, n (%)	17 (22)	5 (31)	3 (19)	7 (41)

LDH, lactate dehydrogenase; SLD, sum of lesion diameters; ULN, upper limit of normal.

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Intracranial Response (cont)

	Cohort A (n = 76)	Cohort B (n = 16)	Cohort C (n = 16)	Cohort D (n = 17)
Intracranial response, n (%) [95% CI][a]				
Overall intracranial response (CR + PR)	44 (58) [46-69]	9 (56) [30-80]	7 (44) [20-70]	10 (59) [33-82]
Intracranial disease control (CR + PR + SD)	59 (78)	14 (88)	12 (75)	14 (82)
Intracranial CR	3 (4)	1 (6)	0	1 (6)
Intracranial PR	41 (54)	8 (50)	7 (44)	9 (53)
Intracranial SD	15 (20)	5 (31)	5 (31)	4 (24)
Intracranial PD	14 (18)	1 (6)	4 (25)	3 (18)
Not evaluable	3 (4)	1 (6)	0	0
Intracranial duration of response[a]				
Events, n/N (%)	29/44 (66)	6/9 (67)	4/7 (57)	8/10 (80)
Median (95% CI), mo	6.5 (4.9-10.3)	7.3 (3.6-12.6)	8.3 (1.3-15.0)	4.5 (2.8-5.9)
6-mo rate (95% CI), %	63 (45-76)	73 (28-93)	67 (19-90)	13 (1-43)

[a] Investigator assessed; these results were supported by independent review.

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Extracranial Response

	Cohort A (n = 76)	Cohort B (n = 16)	Cohort C (n = 16)	Cohort D (n = 17)
Extracranial response, n (%) [95% CI][a]				
Overall extracranial response (CR + PR)	42 (55) [43-67]	7 (44) [20-70]	12 (75) [48-93]	7 (41) [18-67]
Extracranial disease control (CR + PR + SD)	60 (79)	11 (69)	15 (94)	11 (65)
Extracranial CR	3 (4)	1 (6)	0	0
Extracranial PR	39 (51)	6 (38)	12 (75)	7 (41)
Extracranial SD	15 (20)	2 (13)	2 (13)	3 (18)
Extracranial non-CR/non-PD	3 (4)	2 (13)	1 (6)	1 (6)
Extracranial PD	6 (8)	0	0	1 (6)
Not evaluable	10 (13)	5 (31)	1 (6)	5 (29)
Extracranial duration of response[a]				
Events, n/N (%)	16/42 (38)	0/7	6/12 (50)	4/7 (57)
Median (95% CI), mo	10.2 (5.8-NE)	NE (NE-NE)	4.9 (3.0-NE)	5.9 (1.8-NE)
6-mo rate (95% CI), %	69 (50-82)	100 (100-100)[b]	40 (10-70)	48 (8-81)

NE, not estimable. [a] Investigator assessed; these results were supported by independent review; [b] No progression event occurred up to the data cutoff date.

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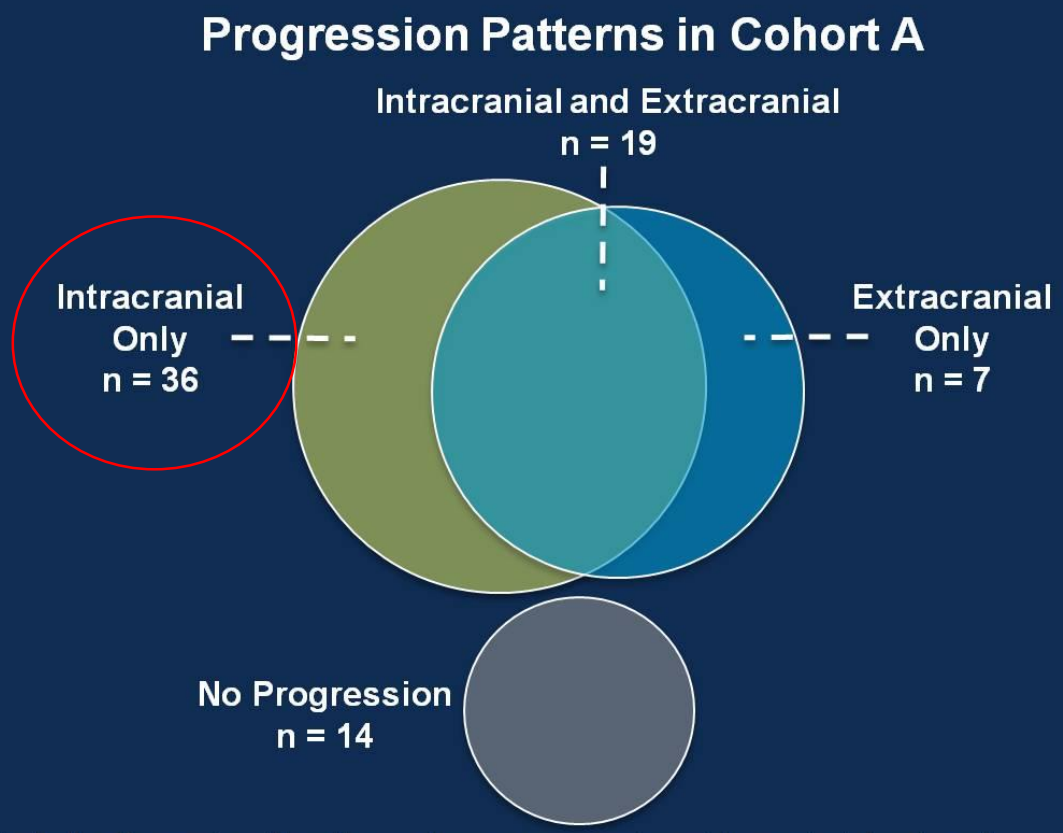
Patterns of Disease Progression

Progression Category, n (%)[a]	Cohort A (n = 76)
Intracranial only	36 (47)
Intracranial and extracranial	19 (25)
Extracranial only	7 (9)
No progression	14 (18)



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

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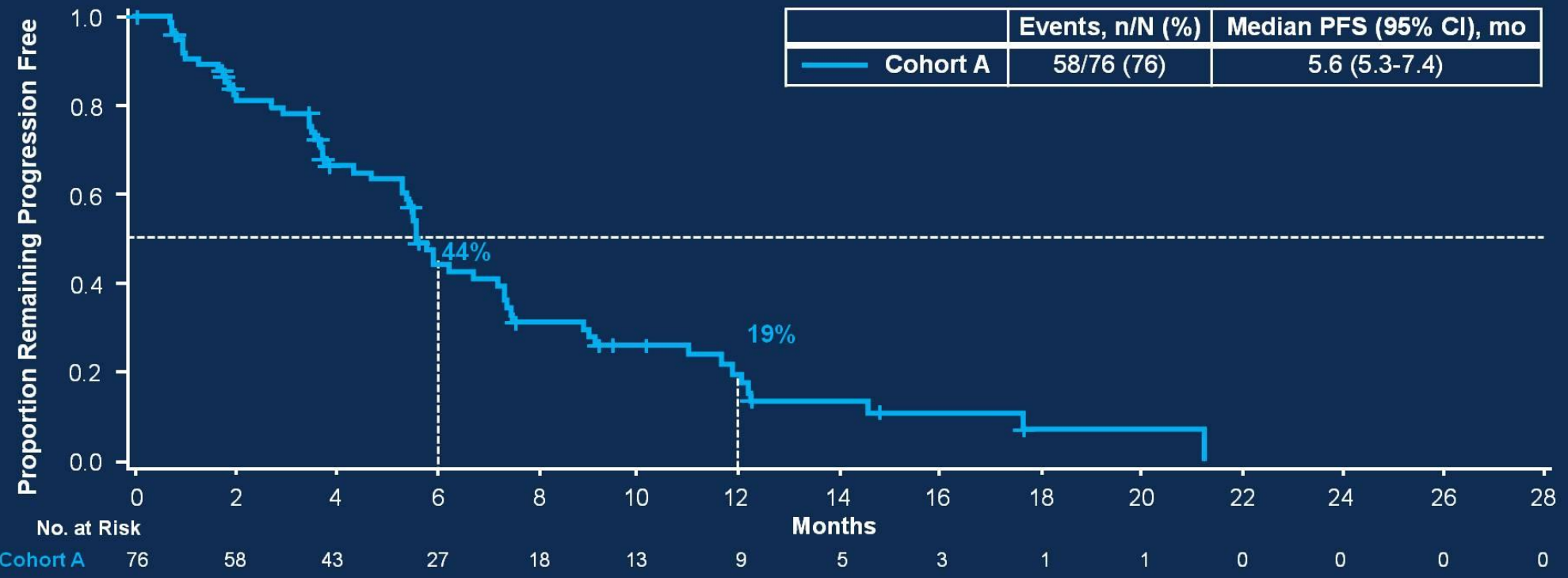
Progression-Free Survival



	Events, n/N (%)	Median PFS (95% CI), mo
Cohort A	58/76 (76)	5.6 (5.3-7.4)

[a] Investigator assessed; these results were supported by independent review. +, censored.

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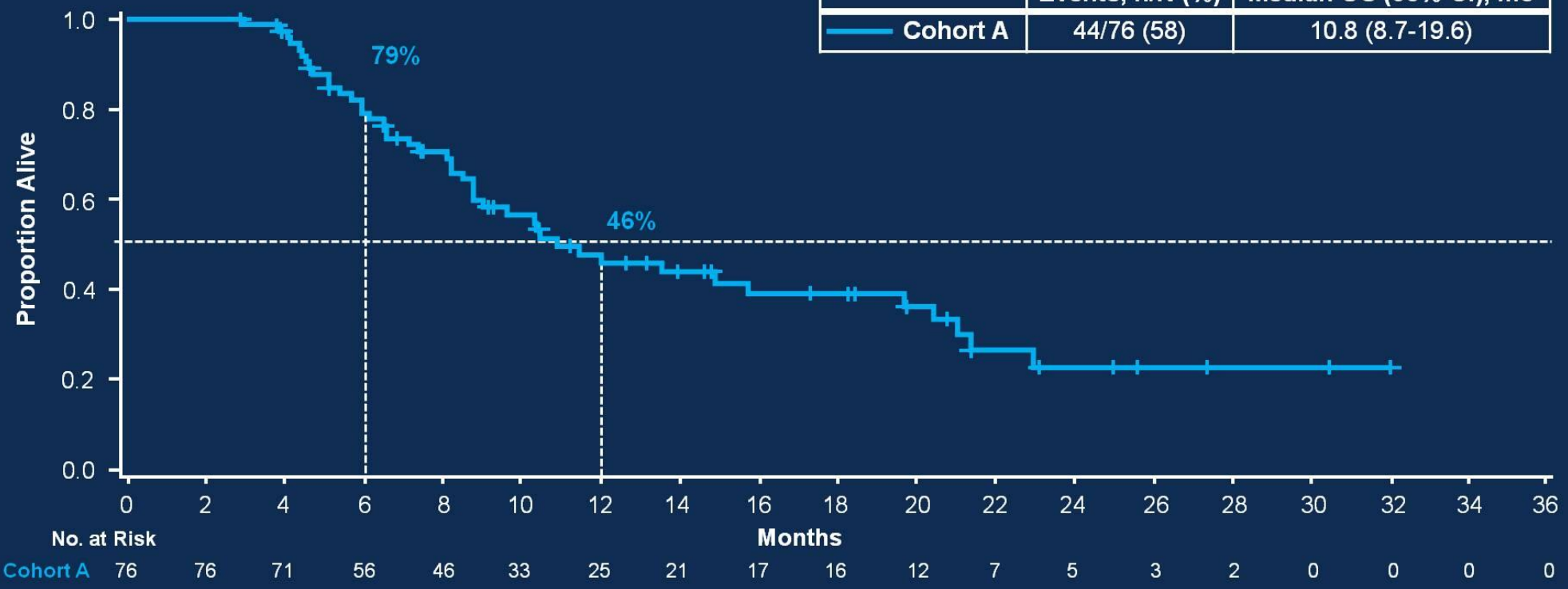
Preliminary Overall Survival

	Events, n/N (%)	Median OS (95% CI), mo
Cohort A	44/76 (58)	10.8 (8.7-19.6)



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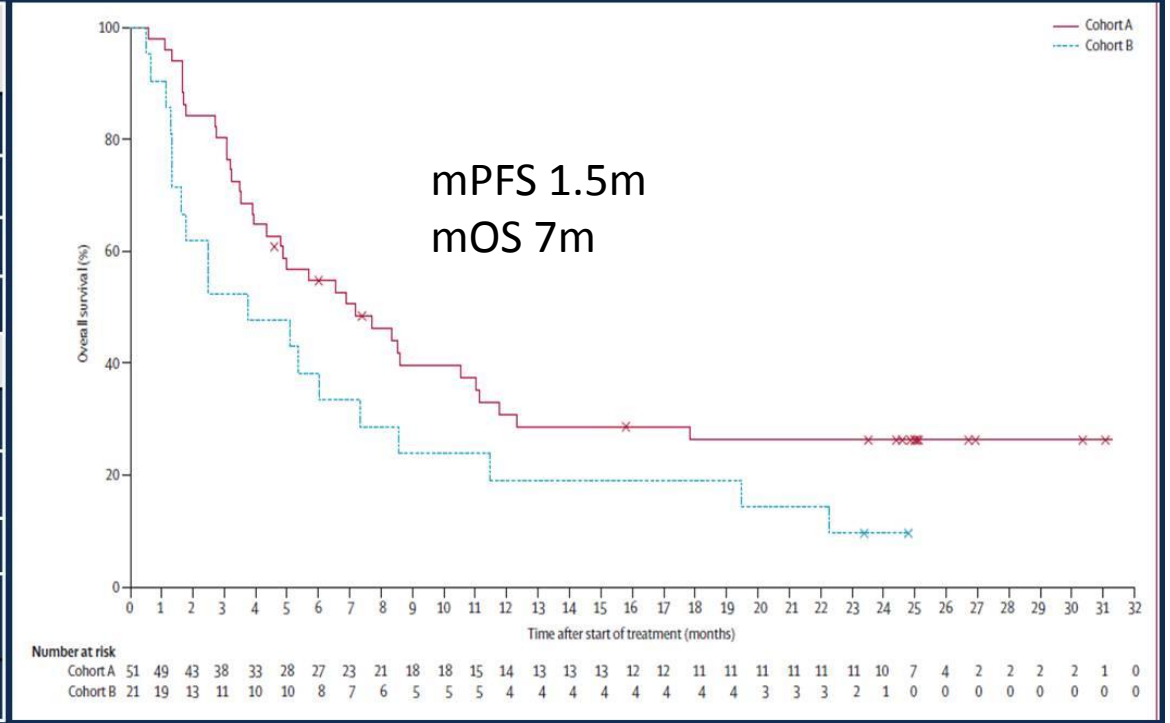
Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

CNS Responses	Cohort A (n=51) No Steroids		Cohort B (n=21) On Steroids	
	mWHO	irRC	mWHO	irRC
CR	0	0	1(5%)	1(5%)
PR	8(16%)	8(16%)	0	0
SD	4(8%)	5(10%)	1(5%)	1(5%)
	Cohort A (n=51)		Cohort B (n=21)	
	mWHO	irRC	mWHO	irRC
Brain	1.5	1.9	1.2	1.2
Non-CNS	2.6	3.3	1.3	1.3

mWHO=modified WHO criteria. irRC=immune-related response criteria

Median progression-free survival



Margolin K. Lancet Oncol. 2012 May;13(5):459-65

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Phase II Trial of Pembrolizumab for Brain Metastases

Key Eligibility:
- Advanced NSCLC or melanoma
- At least 1 untreated or progressive brain metastasis 5-20mm
- No neurologic symptoms or steroid requirement
- PS 0-1
- PD-L1 expression after the most recent systemic therapy

→ Pembrolizumab 10mg/kg q2 weeks

→ Brain metastasis PD → Consider radiation or surgery to progressing lesions

→ Brain metastasis CR, PR, or SD → Continue pembrolizumab if systemic control achieved

Safety evaluation at 4 weeks:
- Brain MRI

Response evaluation every 8 weeks:
- Brain MRI
- CT chest/abdomen/pelvis

Primary Endpoint:
Brain Metastasis Response Rate

Secondary Endpoints:
Overall response rate, safety, PFS, OS

- Brain metastasis response by modified RECIST allows up to 5 target lesions with diameter ≥5mm
- Data presented from an interim analysis

Goldberg, SB, et al. WCLC 2015

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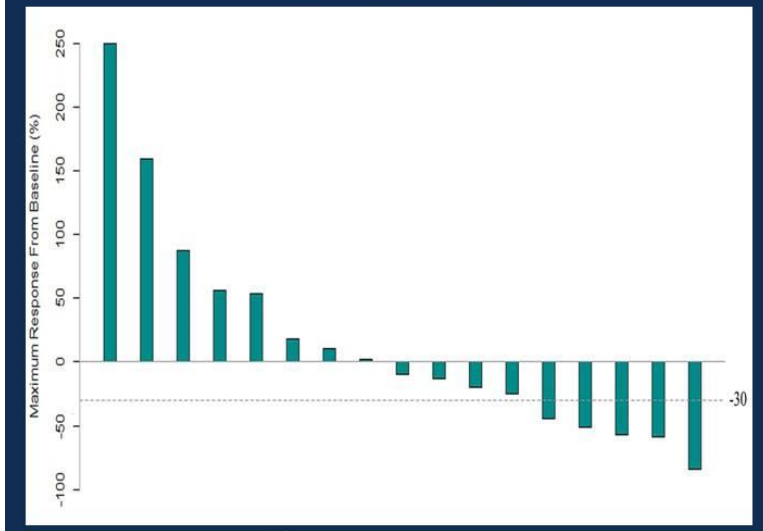
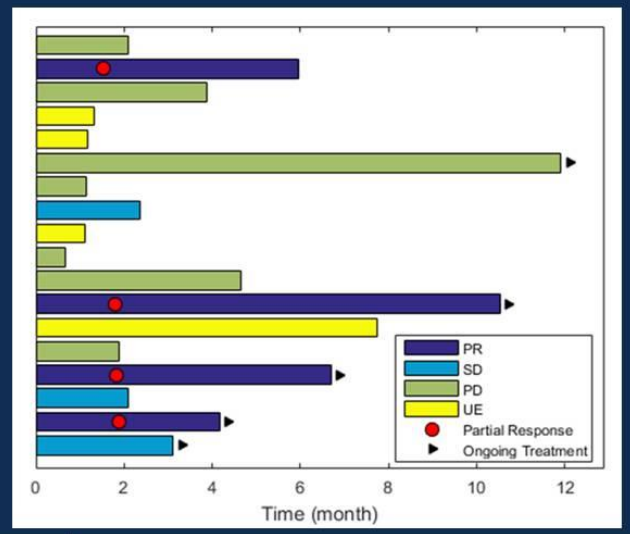
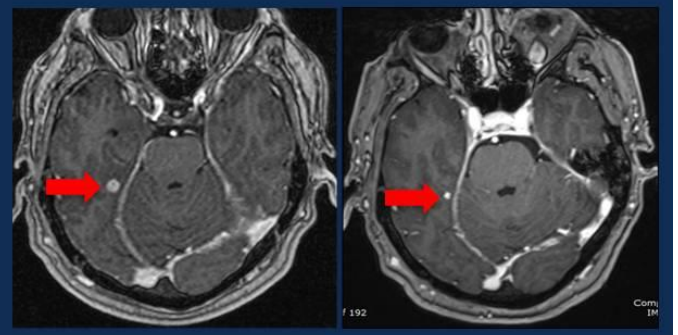
Melanoma Cohort

Best Brain Metastasis Response by mRECIST



Time to Brain Metastasis Response and Duration of Treatment





Evaluable patients	Brain Metastasis Responses (CR + PR)			Duration of BrM Response	Systemic Responses (CR + PR)		
N	No. of patients	%	95% CI	Individual duration (months)	No. of patients	%	95% CI
18	4	22	7-48	4+, 6+, 6+ and 11+	4	22	7-48

Kluger H, et al. ASCO 2015

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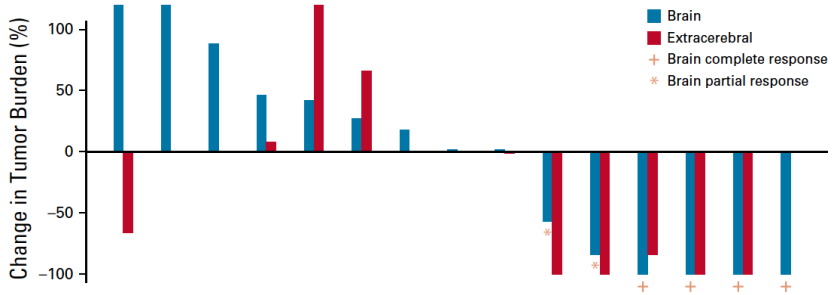
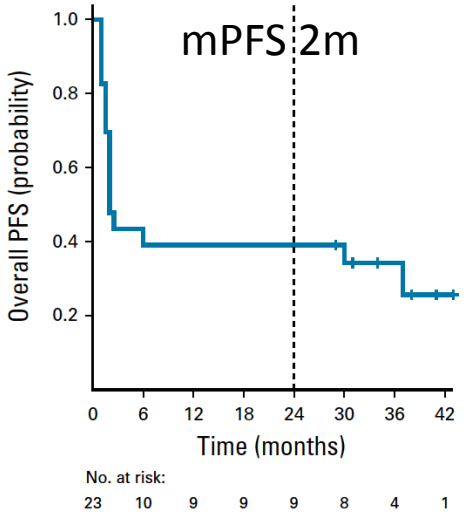
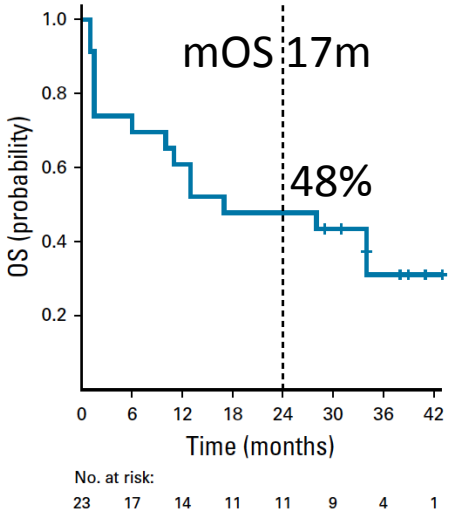
Long-Term Survival of Patients With Melanoma With Active Brain Metastases Treated With Pembrolizumab on a Phase II Trial

Characteristic	No. of Patients (N = 23)	%
Age, years		
Median	65	
Range	40-84	
Sex		
Male	15	65
Female	8	35
ECOG PS		
0	10	43
1	13	57
Elevated LDH	9	39
Mutation*		
BRAF	9	41
NRAS	5	23
No. of prior systemic therapy regimens		
0	7	31
1	9	39
2	4	17
≥ 3	3	13
Prior ipilimumab	13	57
Prior *BRAF* inhibitors	4	17
Prior CNS therapy†		
None	5	22
Surgical resection	12	52
Whole-brain radiotherapy	5	22
Stereotactic radiosurgery	12	52



N=23
RR 26%
DCR 30%
mFU 34m





Kluger et al. J Clin Oncol 37:52-60, 2019

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CheckMate 204 Study Design

Key eligibilities

- ≥ 1 measurable, unirradiated MBM (0.5–3.0 cm)
- Prior SRT in ≤ 3 MBM
- Previous treatment with BRAFi/MEKi permitted
- No prior checkpoint inhibitors in metastatic setting

Cohort eligibilities

- Asymptomatic patients
- ECOG PS 0/1
- No steroids

Median follow-up = 20.6 mo

Induction

NIVO 1 mg/kg Q3W × 4 + IPI 3 mg/kg Q3W × 4

Maintenance

NIVO 3 mg/kg Q2W

Treat until progression or toxicity (max. 24 months)[a]

Endpoints

Primary: IC CBR (CR + PR + SD ≥ 6 months)[b]

Secondary: safety, PFS, OS, EC and global CBR

Follow for 3 years from first dose

Data cutoff date of May 1, 2018

CBR, clinical benefit rate; CR, complete response; EC, extracranial; IC, intracranial; MBM, melanoma brain metastases; PR, partial disease; SD, stable disease; SRT, stereotactic radiosurgery.
[a]Patients with grade 3–4 adverse events (AEs) during NIVO+IPI induction could resume NIVO when toxicity resolved and all patients who discontinued proceeded to follow-up;
[b]Using modified RECIST v1.1.

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Demographic and Patient Characteristics – Asymptomatic Patients

	Patients (n = 101)[a]
Male, n/N (%)	**68/101 (67)**
Median age, years (range)	**59.0 (22−81)**
***BRAF* mutation, n/N (%)**	**66/99 (67)**
***NRAS* mutation, n/N (%)**	**7/26 (27)**
LDH > ULN, n/N (%)	**41/101 (41)**
LDH > 2 × ULN, n/N (%)	**11/101 (11)**
PD-L1 expression, n/N (%)	
≥ 1%	**44/81 (54)**
< 1%	**37/81 (46)**
Prior SRT, n/N (%)	**9/101 (9)**
Median of sum of intracranial target lesion diameters, mm (range)	**15 (5−91)**
Intracranial target lesions, n (%)	
1–2 lesions	**78/100 (78)**
≥ 3 lesions	**22/100 (22)**

[a]Nine patients did not have extracranial disease.

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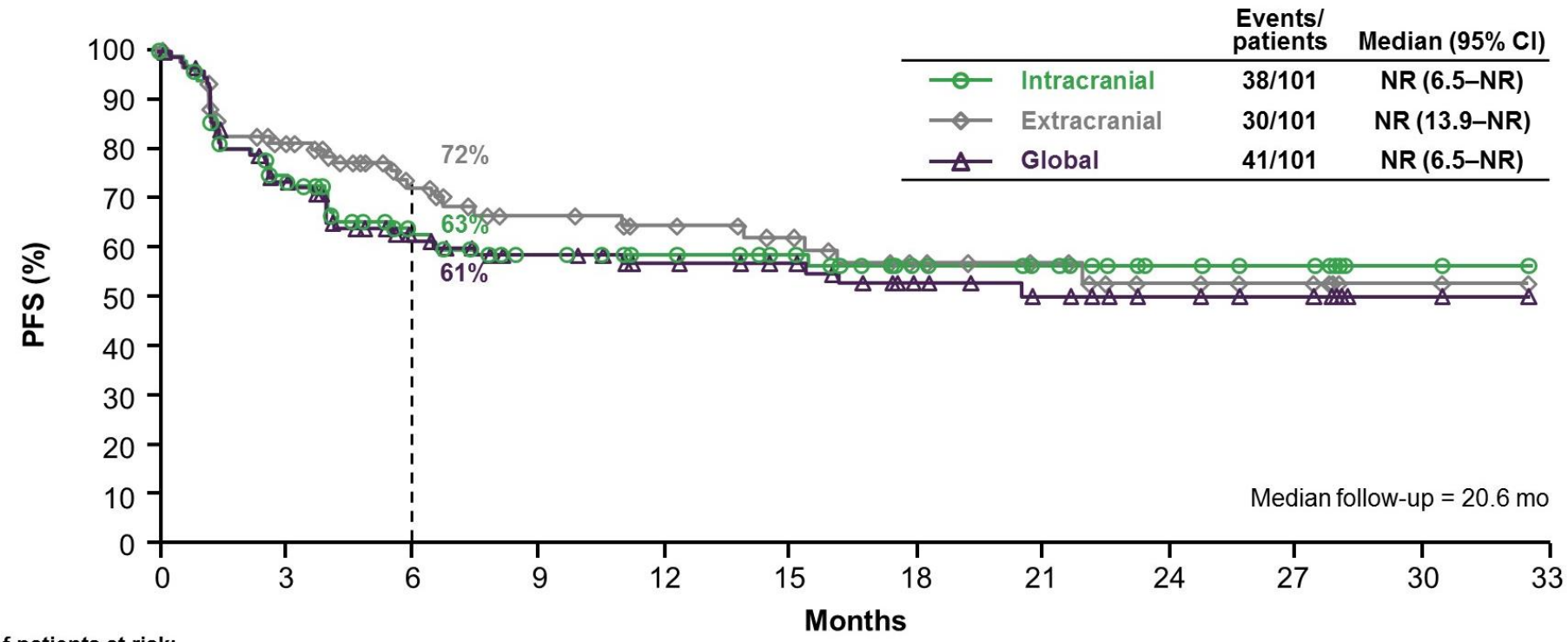
Response to Treatment – Asymptomatic Patients

	Patients (n = 101)		
	Intracranial	Extracranial	Global
Best overall response, n (%)			
Complete response	29 (29)	11 (11)	11 (11)
Partial response	26 (26)	38 (38)	40 (40)
Stable disease ≥ 6 months	4 (4)	6 (6)	4 (4)
Progressive disease	27 (27)	16 (16)	28 (28)
Not evaluable	15 (15)	30 (30)[a]	18 (18)
Death prior to first on-study assessment	3 (3)	3 (3)	2 (2)
Early discontinuation due to toxicity	0 (0)	1 (1)	1 (1)
Stable disease < 6 months	8 (8)	15 (15)	10 (10)
Other	4 (4)	11 (11)	5 (5)
ORR, n/N (%) (95% CI)	55/101 (54) (44–64)	49/101 (49) (38–59)	51/101 (51) (40–61)
CBR[b], n/N % (95% CI)	59/101 (58) (48–68)	55/101 (54) (44–64)	55/101 (54) (44–64)

[a]Seven of these patients did not have extracranial disease at baseline; [b]Clinical benefit rate = complete response + partial response + stable disease ≥ 6 months.

Progression-Free Survival – Asymptomatic Patients

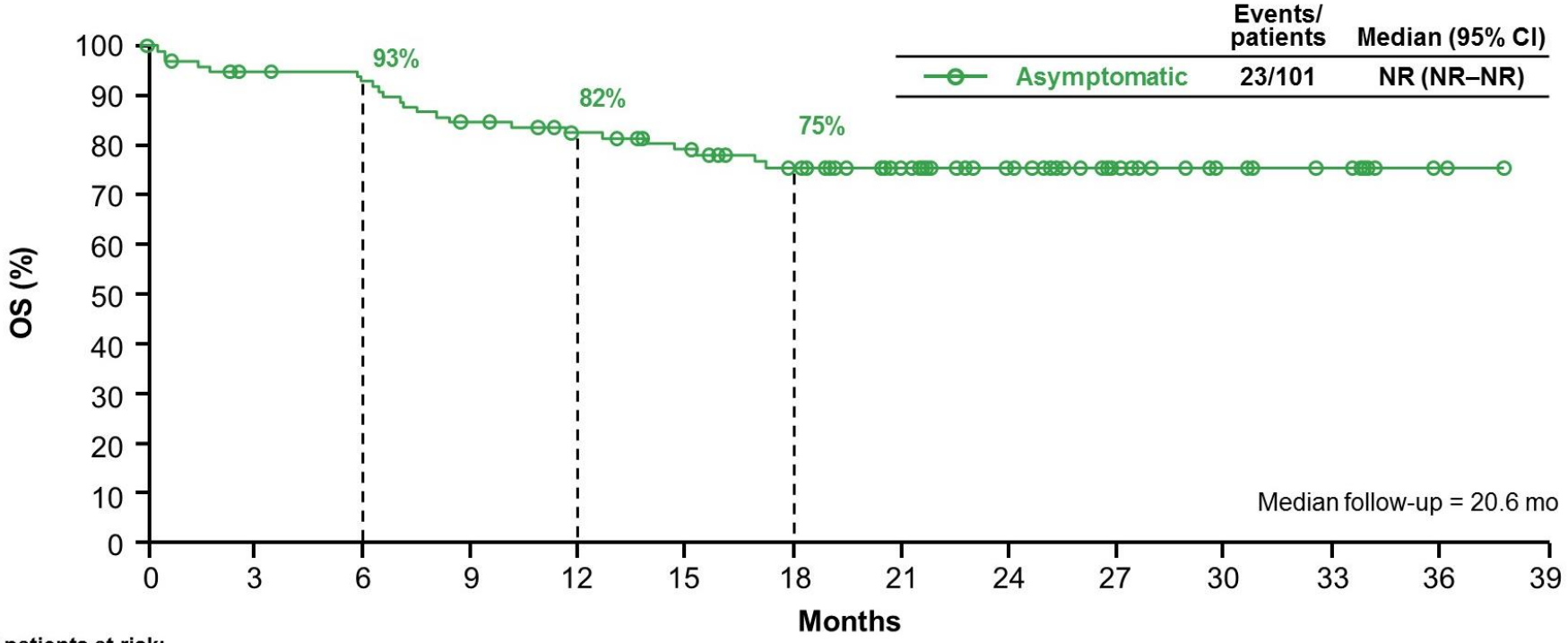


	Events/ patients	Median (95% CI)
Intracranial	38/101	NR (6.5–NR)
Extracranial	30/101	NR (13.9–NR)
Global	41/101	NR (6.5–NR)

Number of patients at risk:

Intracranial:	101	65	46	38	34	30	21	18	10	8	2	0
Extracranial:	101	62	42	33	29	25	19	16	9	7	2	0
Global:	101	64	45	38	33	30	21	17	10	8	2	0

Overall Survival – Asymptomatic Patients



Number of patients at risk:

Asymptomatic:	101	92	89	80	74	67	58	47	35	22	15	8	2	0

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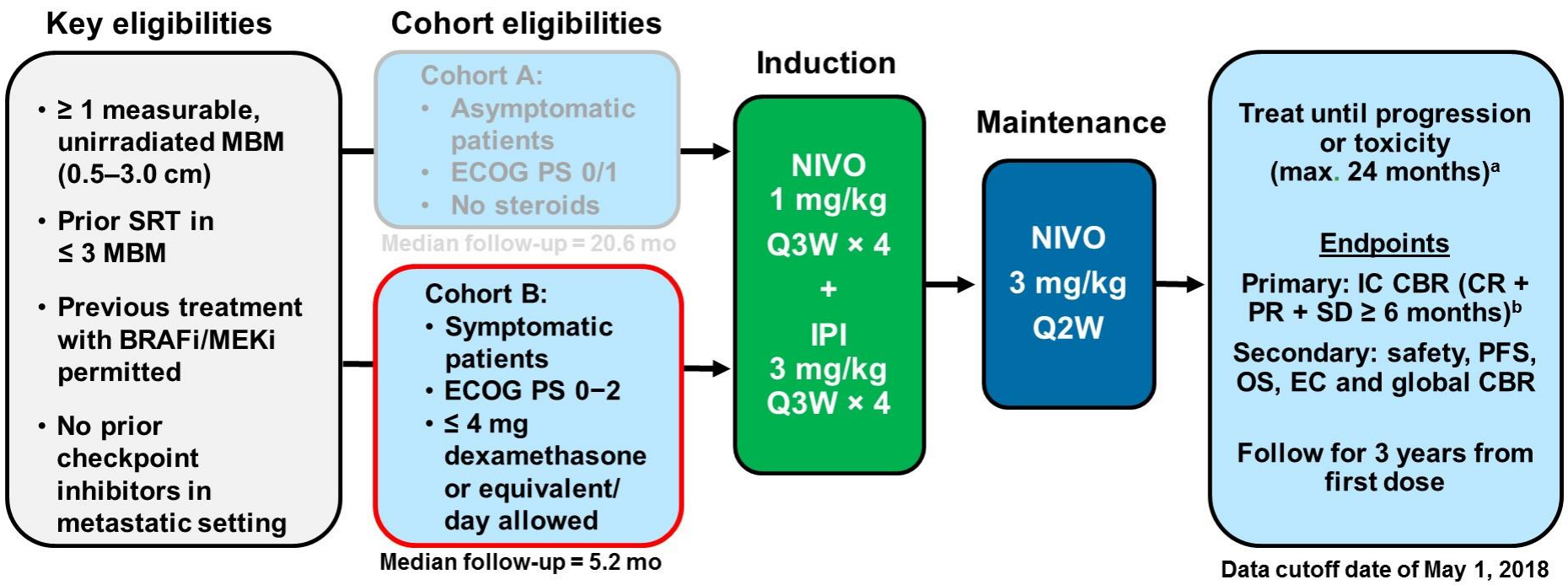
CheckMate 204 Study Design with Cohort B



CBR, clinical benefit rate; CR, complete response; EC, extracranial; IC, intracranial; MBM, melanoma brain metastases; PR, partial disease; SD, stable disease; SRT, stereotactic radiosurgery.
[a]Patients with grade 3–4 adverse events (AEs) during NIVO+IPI induction could resume NIVO when toxicity resolved and all patients who discontinued proceeded to follow-up;
[b]Using modified RECIST v1.1.

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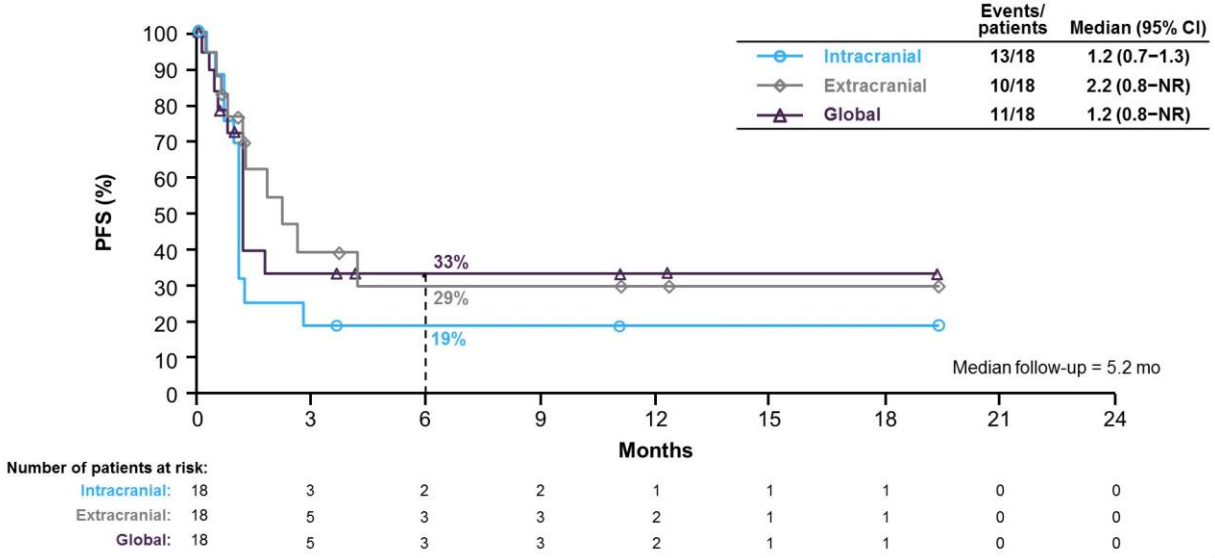
Response to Treatment – Symptomatic Patients

	Patients (n = 18)		
	Intracranial	Extracranial	Global
Best overall response, n (%)			
Complete response	2 (11)	0	0
Partial response	2 (11)	4 (22)	4 (22)
Stable disease ≥ 6 months	0	0	0
Progressive disease	10 (56)	6 (33)	8 (44)
Not evaluable	4 (22)	8 (44)[a]	6 (33)
Death prior to first on-study assessment	2	1	1
Early discontinuation due to toxicity	0	0	0
Stable disease < 6 months	2	4	2
Other	0	3	3
ORR, n/N (%) (95% CI)	4/18 (22) (6–48)	4/18 (22) (6–48)	4/18 (22) (6–48)
CBR,[b] n/N (%) (95% CI)	4/18 (22) (6–48)	4/18 (22) (6–48)	4/18 (22) (6–48)

[a] One of these patients did not have extracranial disease at baseline; [b]Clinical benefit rate = complete response + partial response + stable disease ≥ 6 months.

CheckMate 204

Progression-Free Survival – Symptomatic Patients



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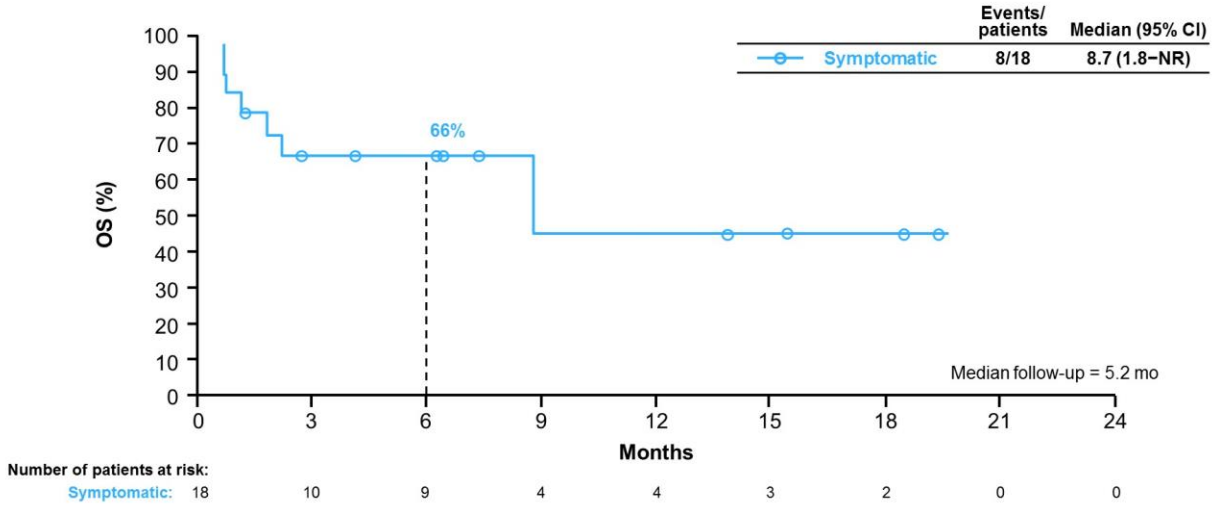
CheckMate 204

Overall Survival – Symptomatic Patients



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Intracranial response	*BRAF* status	NIVO+IPI induction doses	Maintenance doses	Steroid use at baseline
CR	Mutant	4	37	Yes
CR	Wild type	1	23	No
PR	Mutant	4	23	No
PR	Not reported	3	0[a]	No

1/11 (9%)

3/7 (43%)

Study Design

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

Median follow-up 34 months

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Patient Characteristics

	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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Best Intracranial RECIST Response

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	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%)

- 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

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Best Intracranial RECIST Response:
Drug Treatment Naïve Patients

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	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%)

- 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

Previous BRAFi+MEKi
ORR = 25% (2/8)

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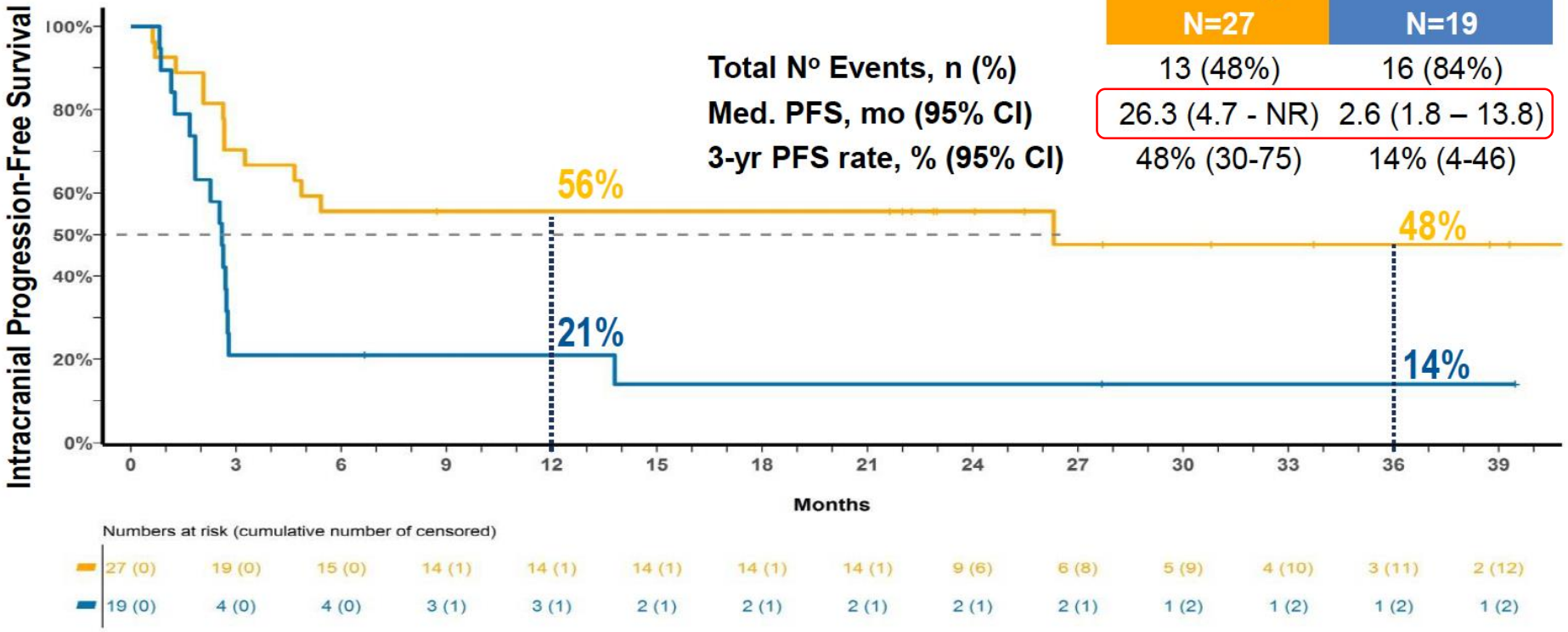
Intracranial Progression-Free Survival
Drug-treatment Naïve Patients

	A: Nivo+Ipi N=27	B: Nivo N=19
Total Nº Events, n (%)	13 (48%)	16 (84%)
Med. PFS, mo (95% CI)	26.3 (4.7 - NR)	2.6 (1.8 – 13.8)
3-yr PFS rate, % (95% CI)	48% (30-75)	14% (4-46)



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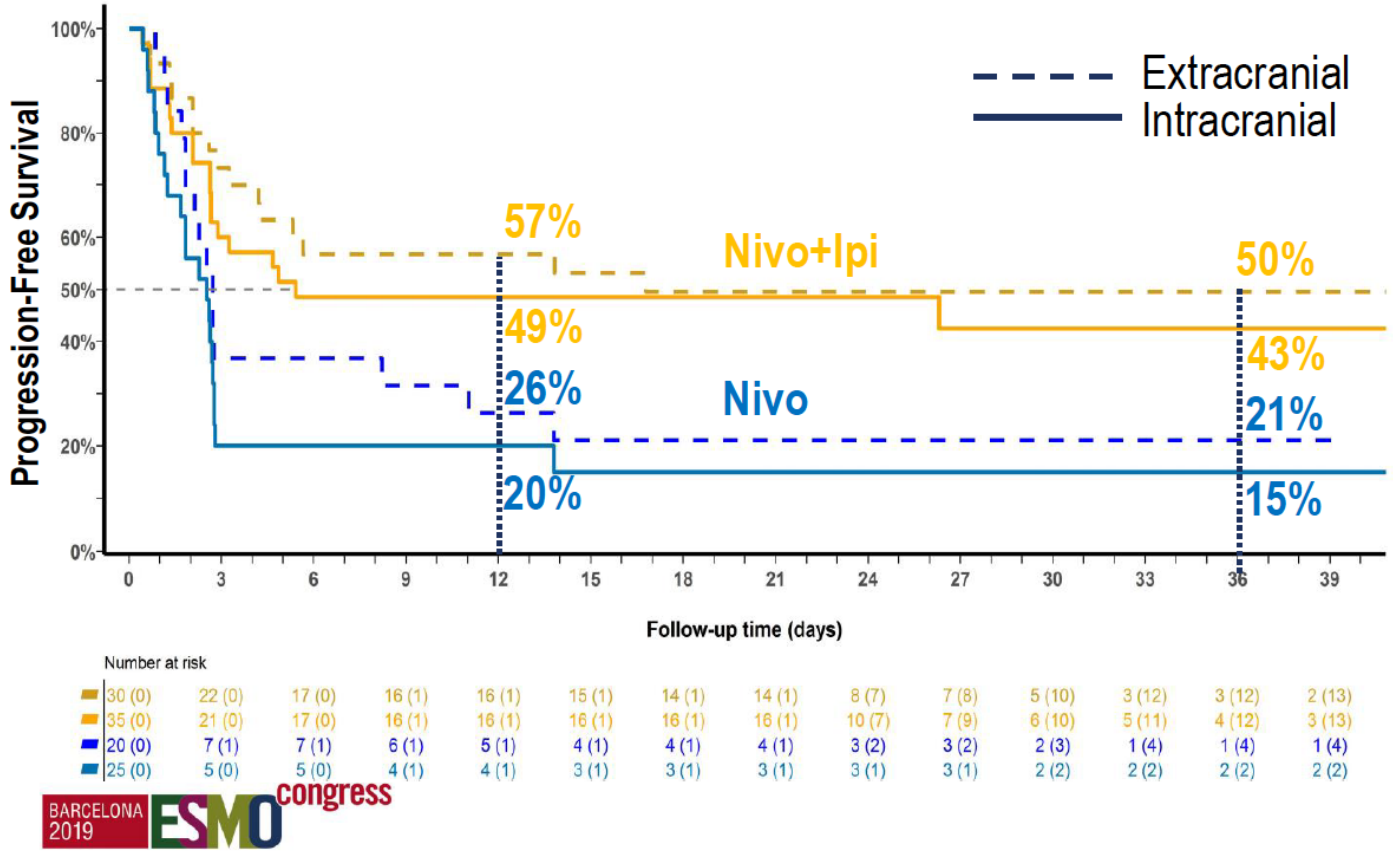
Intracranial and Extracranial Concordance

All Patients Cohort A and B



		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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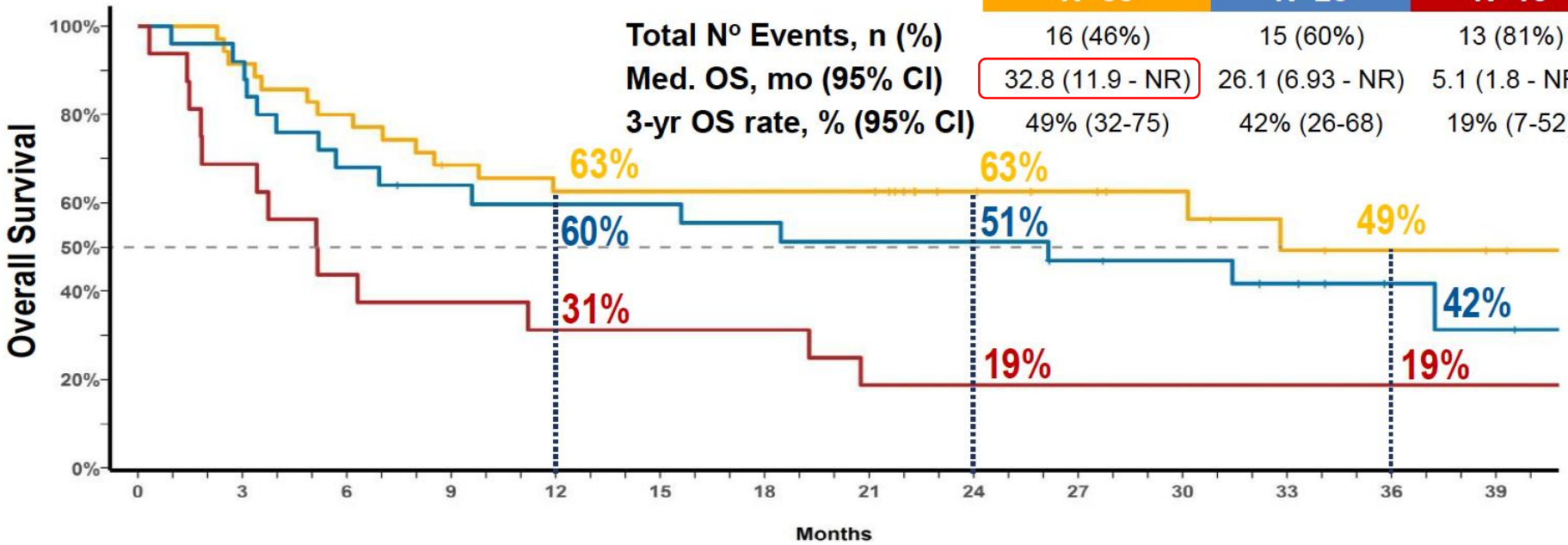
Overall Survival

	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo N=16
Total Nº Events, n (%)	16 (46%)	15 (60%)	13 (81%)
Med. OS, mo (95% CI)	32.8 (11.9 - NR)	26.1 (6.93 - NR)	5.1 (1.8 - NR)
3-yr OS rate, % (95% CI)	49% (32-75)	42% (26-68)	19% (7-52)



Numbers at risk (cumulative number of censored)

35 (0)	32 (0)	28 (0)	23 (1)	21 (1)	21 (1)	21 (1)	21 (1)	14 (8)	12 (10)	10 (12)	7 (13)	6 (14)	5 (15)
25 (0)	23 (0)	17 (0)	15 (1)	14 (1)	14 (1)	13 (1)	12 (1)	12 (1)	10 (2)	9 (3)	7 (4)	4 (7)	3 (7)
16 (0)	11 (0)	7 (0)	6 (0)	5 (0)	5 (0)	5 (0)	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)

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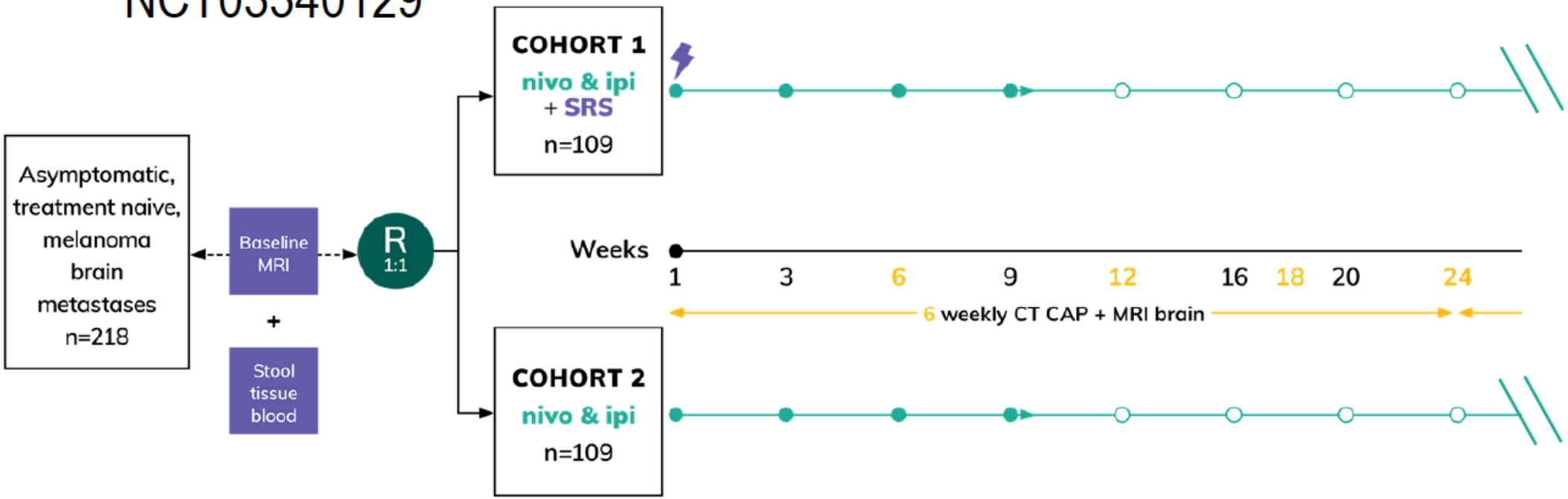

	DC	RR (mDOR)	CR	mFU	6m IC PFS	mPFS	mOS
Ipi(n=51)	24%	16% (-)	0%	-	-	1,5m	7m (2y 26%)
Pembro(n=23)	30%	26% (NR)	17%	34m	40%	2m	17m (2y 48%)
Nivo (n=25) (ABC)	-	21% (NR)	16%	34m	21%	2,6m	26m (3y 42%)
Nivo+Ipi(n=35) (ABC)	67%	59% (NR)	30%	34m	56%	26.3m	32m (3y 49%)
Nivo+Ipi(n=101) (CM 204)	58%	54% (NR)	29%	20m	63%	NR	NR
Dabre+Trame(n=76) (COMBI-MB)	78%	58% (6.5m)	4%	8.5m	44%	5.6m	10,8m

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Conclusões

- As taxas de resposta com a combinação de inibidores de BRAF/MEK são >50% mas com duração mais curta que em sítios extracranianos (mSLP de 5.6 meses, ~50% das progressões apenas intracranianas)

- As taxas de resposta intracraniana com agentes anti-PD1 (pembro ou nivo) em monoterapia são mais duradouras mas são baixas, <30%

- 2 estudos fase II com a combinação de nivolumabe + ipilimumabe mostraram taxas de resposta mais altas (51-59%) e com maior durabilidade (mSLP de 26m e SLP em 3 anos de 48% no ABC trial)

Perguntas

- Qual o papel da terapia local com SRS ou SRT?
  - concomitante X sequencial X resgate
  - sinergismo, radionecrose, efeito abscopal
- Qual o papel do anti-VEGF (Bevacizumabe)?
  - radionecrose, imunomodulação, evitar corticóide
- Triplets? Sequenciamento TA-Imuno?
- Combo com baixa dose Ipi?

Ongoing trials

- Kluger (Yale) trial of pembrolizumab plus bevacizumab
- Long (Mel Inst Aus) "ABCX" trial randomizing to immunotherapy alone ± SRT
- Tawbi (MDACC): bevacizumab plus atezolizumab [ASx pts, first-line]; Cobi/bev/atezo [2nd line BRAF w.t.]; nivolumab + dab/tram 2nd-line BRAFmu]
- Glitza (MDACC): pembrolizumab plus low-dose ipilimumab
- Khan (Emory): pembrolizumab plus SRT
- Lim(Hopkins): SRT plus nivolumab
- Schadendorf (French/German multi-): sequencing cobi + vemu → PD-L1 Ab
- DiGiacomo et al (Italy multi): fotemustine ± ipi vs nivo plus ipi

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