Clinical Updates in Brain Metastases

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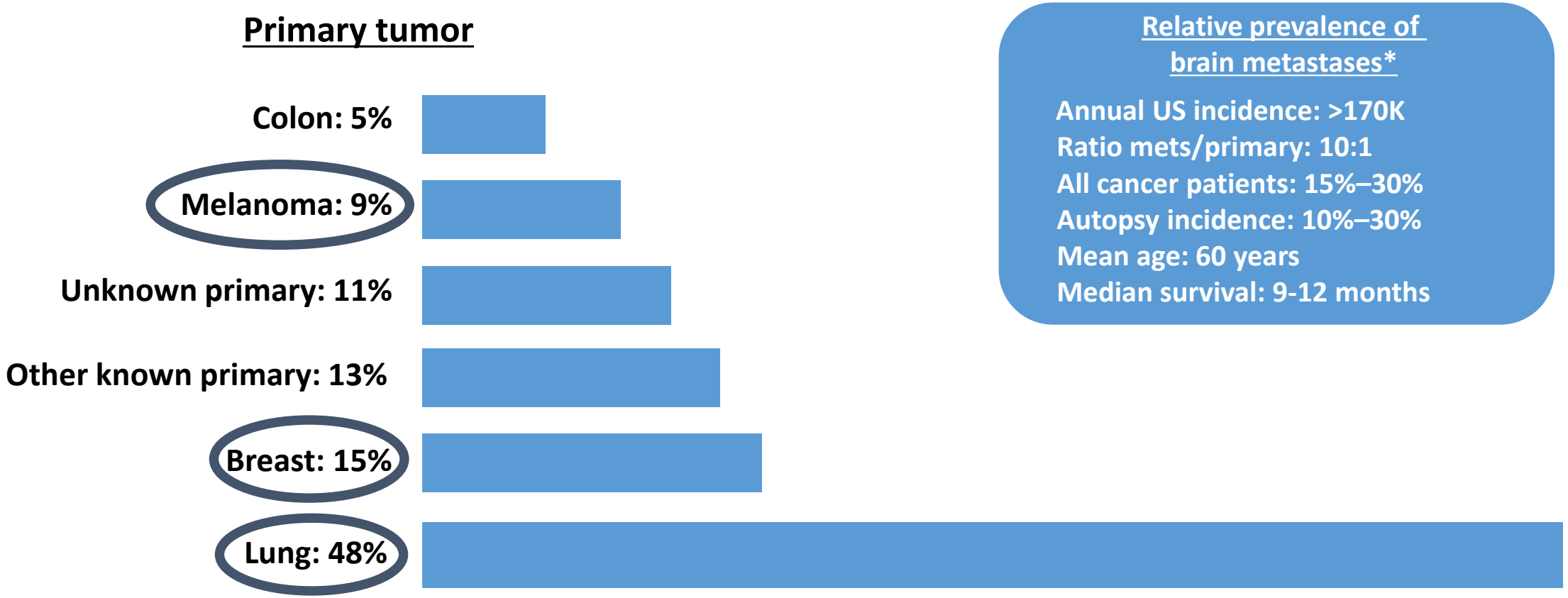
Learning Objectives

- Understand the role of genetics in outcomes in brain metastases
- Learn the role of targeted therapy in brain metastases
- Understand the role of immunotherapy in brain metastases

Epidemiology of Brain Metastases



Relative prevalence of brain metastases*

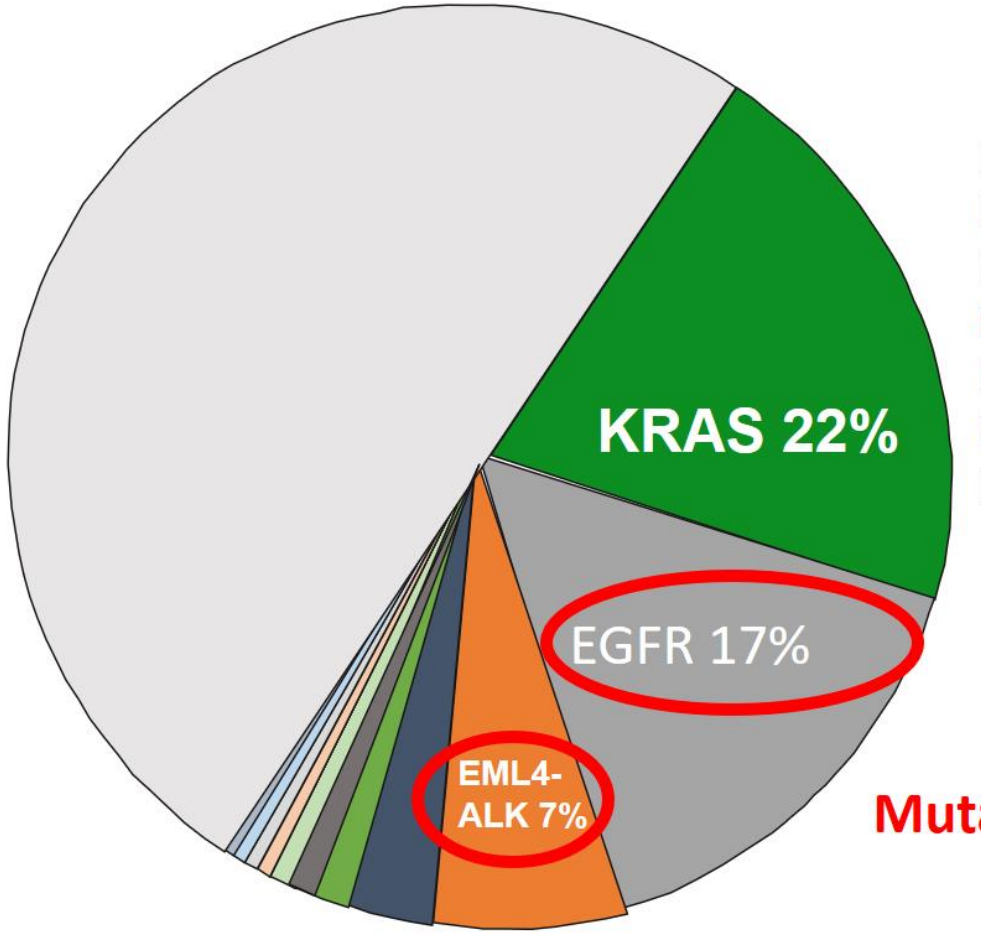
- Annual US incidence: >170K
- Ratio mets/primary: 10:1
- All cancer patients: 15%–30%
- Autopsy incidence: 10%–30%
- Mean age: 60 years
- Median survival: 9-12 months

***Incidence increasing with better systemic Rx and improved survival**

Modified from slide Courtesy: John Suh.

Wen PY, et al. In: DeVita VT Jr, et al, eds. *Cancer: Principles & Practice of Oncology.* 2001:2656-2670.

Lung Cancer Mutation Consortium: Single Driver Mutations in NSCLC

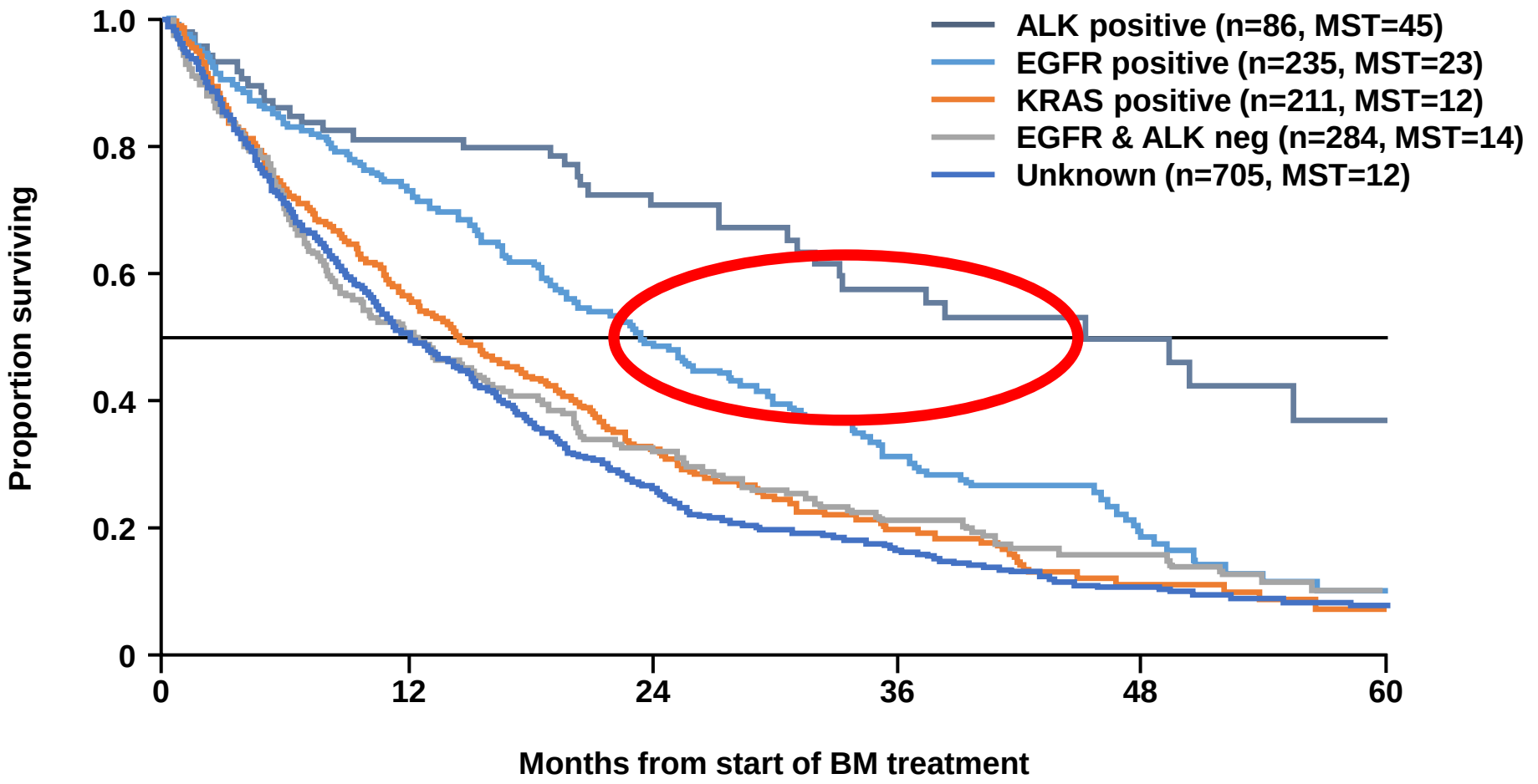


- No mutation detected
- KRAS 22%
- EGFR 17%
- EML4-ALK 7%
- Double mutants 3%
- BRAF 2%
- PIK3CA
- HER2
- MET AMP
- MEK1
- NRAS
- AKT1

Mutation found in 54% (280/516) of tumors

Kris MG, et al. ASCO 2011. Abstract CRA7506.

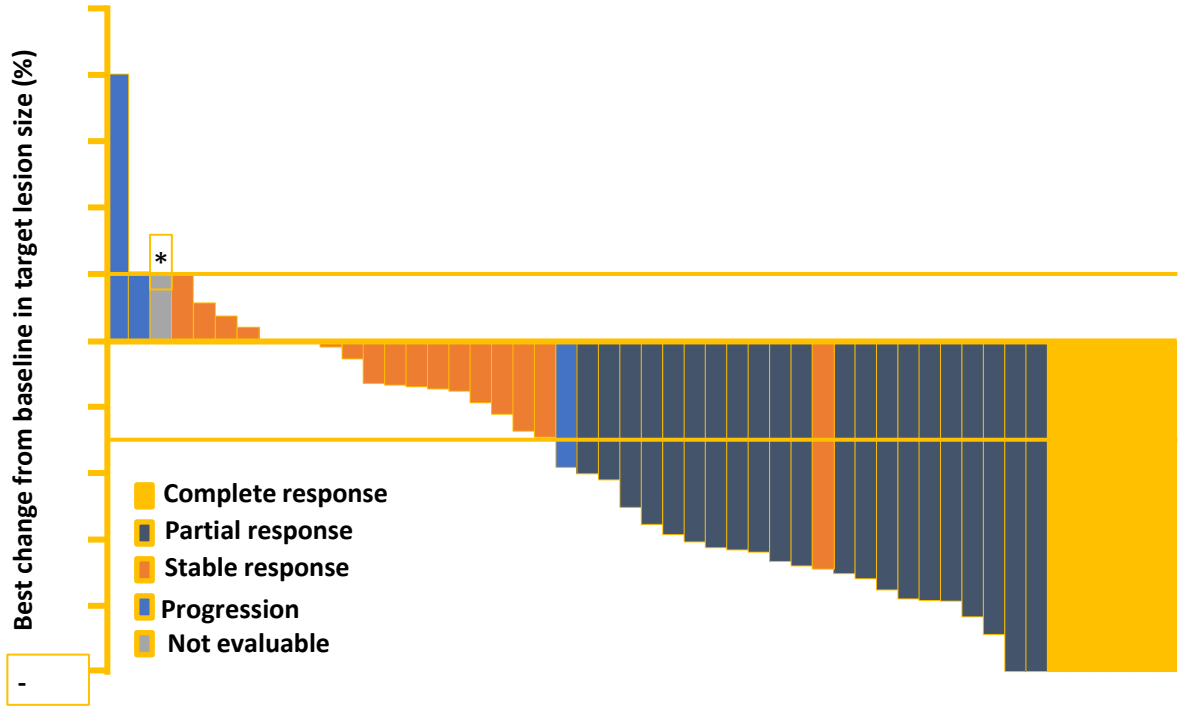
The effect of gene alterations and Tyrosine Kinase inhibition on Survival and cause of death in 1521 patients with Adenocarcinoma of the lung and Brain Metastases



Sperduto P et al. Int J Radiat Oncol Biol Phys. 2016 Oct 1;96(2):406-13.

CNS response to osimertinib in patients with T790M-positive Advanced NSCLC: Pooled data from two Phase II Trials

- **The CNS ORR was 54% (95% CI 39, 68)**
- Median best percentage change from baseline in CNS target lesion size was -53% (range: -100% – +80%)



Population: evaluable for response. Scans were performed every 6 weeks
*represents imputed values
CI, confidence interval

Patients evaluable for CNS response (n=50)	
CNS ORR*, % Complete response, n (%) Partial response, n (%) Stable disease ≥6 weeks, n (%) Progressive disease, n (%) Not evaluable, n (%)	54 (95% CI 39, 68) 6 (12) 21 (42) 19 (38) 3 (6) 1 (2)
CNS DCR, %	92 (95% CI 81, 98)

CNS response based on prior brain RT status*	
Prior RT ≤6 months before first dose, n	19 / 50
CNS ORR, % Complete response / partial response, %	32 (95% CI 13, 57) 11 / 21
No prior RT or RT >6 months before first dose, n	31 / 50
CNS ORR, % Complete response / partial response, %	68 (95% CI 48, 83) 13 / 55

Goss G et al. Presented at WCLC 2016
J Thorac Oncol 2017; 12(suppl):S440-S441 (abstr MA16.11

Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

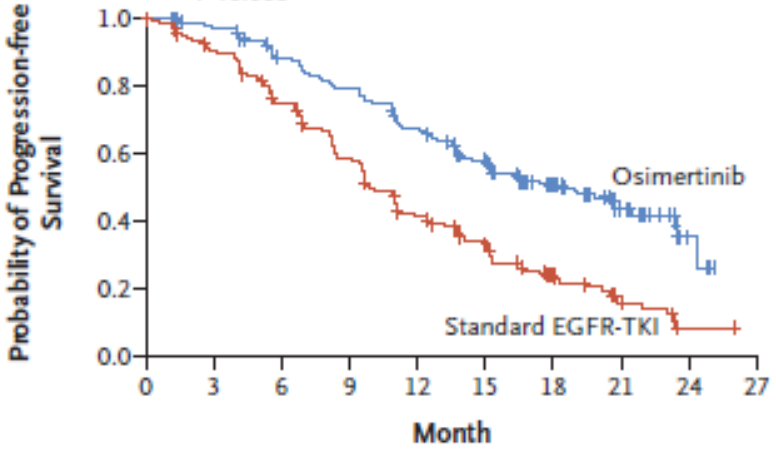
The NEW ENGLAND JOURNAL of MEDICINE

JANUARY 11, 2018 VOL. 378 NO. 2

A Progression-free Survival in Full Analysis Set

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001

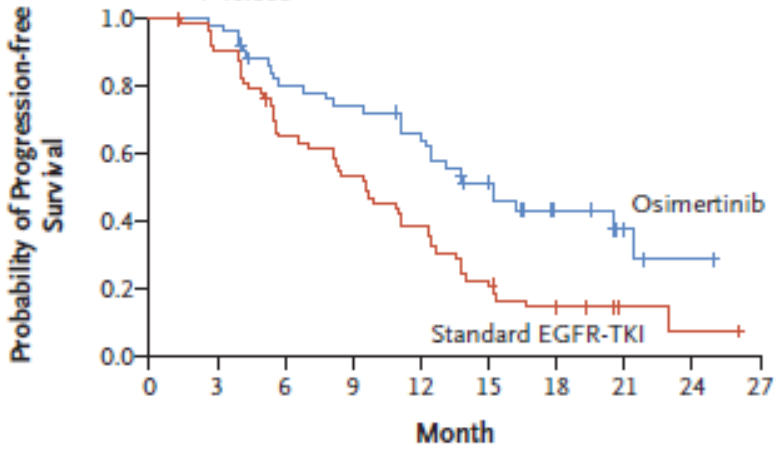


No. at Risk										
Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

B Progression-free Survival in Patients with CNS Metastases

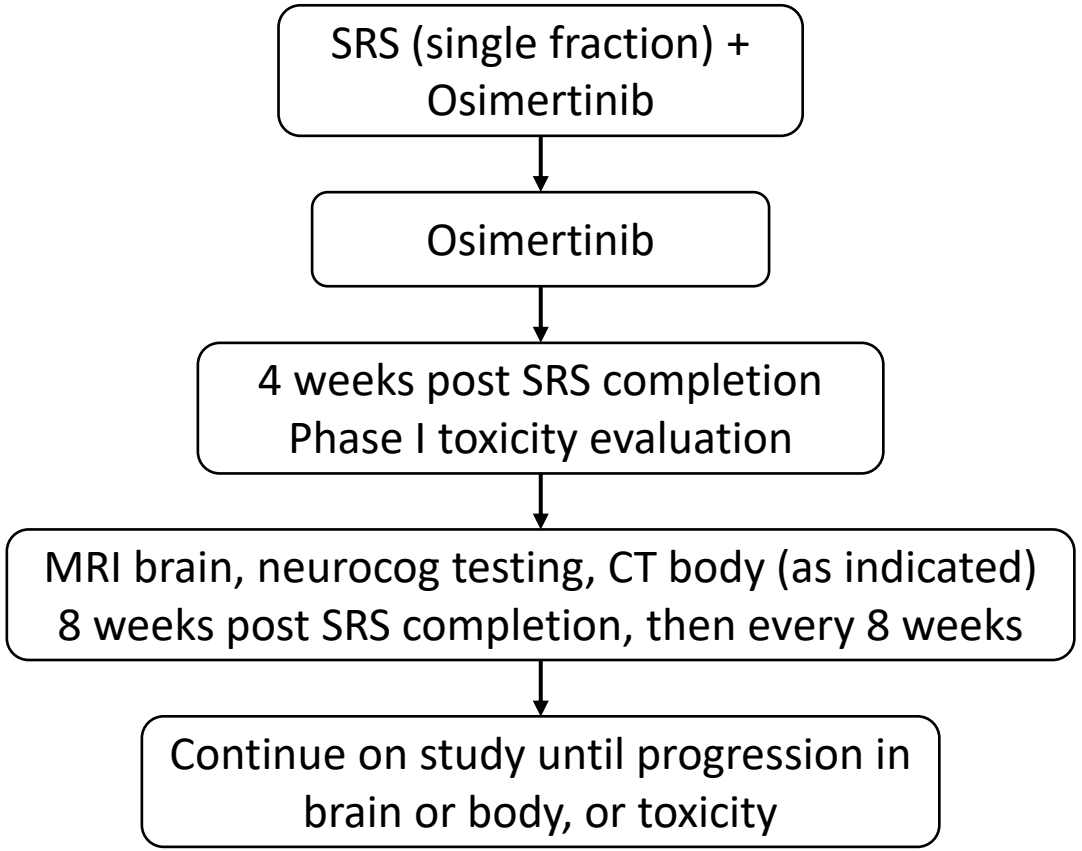
	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	53	15.2 (12.1–21.4)
Standard EGFR-TKI	63	9.6 (7.0–12.4)

Hazard ratio for disease progression or death, 0.47 (95% CI, 0.30–0.74)
P<0.001



No. at Risk										
Osimertinib	53	51	40	37	32	22	9	4	1	0
Standard EGFR-TKI	63	57	40	33	24	13	6	2	1	0

Phase 1 Study of Osimertinib in 1-10 EGFR LCBM



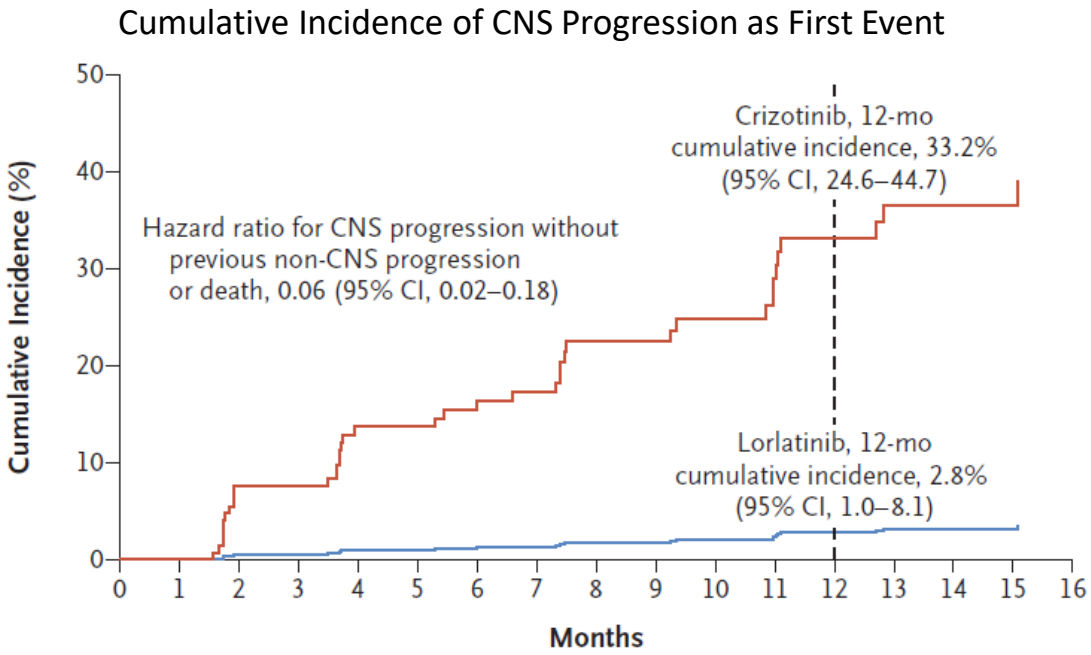
**3+3 design
First dose level : 80 mg daily
Dose level -1 : 40mg daily

ALK Inhibitors and BM

ALK Inhibitor	Study Design	Number of Patients	Loco-Regional Control (ORR)
Crizotinib	Post-hoc analysis of PROFILE-1005 and 1007	22	18%
		18	33%
Ceritinib	Post-hoc analysis of ASCEND-1	98 (ALK pretreated)	50%
		26 (ALK naïve)	69%
Alectinib	Phase I/II study	34	56%
Brigatinib	Phase II study	13	69%

Costa DB, et al. *J Clin Oncol.* 2015;33(17):1881-1888.
Shaw E, et al. *Neuro-Oncology*. 2014;16(suppl 5):v39;
Gadgeel SM, et al. *Lancet Oncol*. 2014;15(10):1119-1128;
Kerstein D, et al. *Ann Oncol*. 2015;26(suppl1):i60-i61.

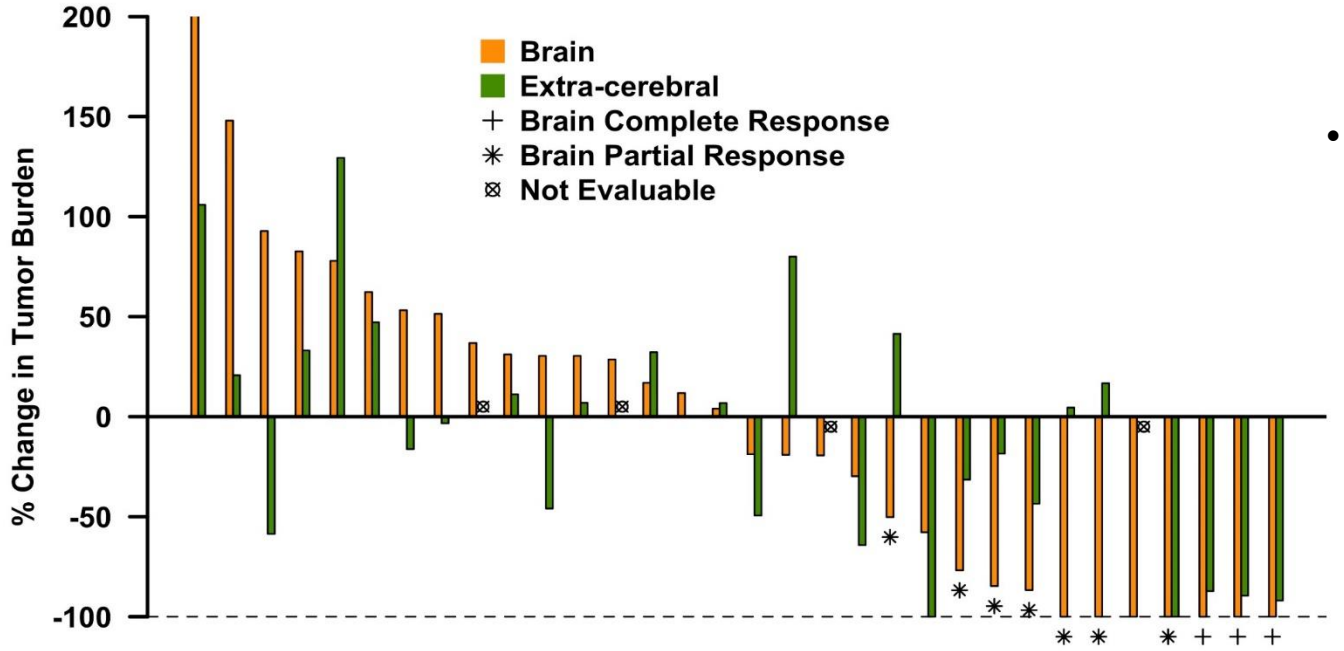
First-Line Lorlatinib or Crizotinib in Advanced *ALK*-Positive Lung Cancer



Patients with Measurable CNS Lesions at Baseline	Crizotinib	Lorlatinib
No. of patients	13	17
CNS response	3	14
Response rate	23	82

N Engl J Med 2020;383:2018-29.

Brain Metastasis Response and Overall Survival in Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with Pembrolizumab



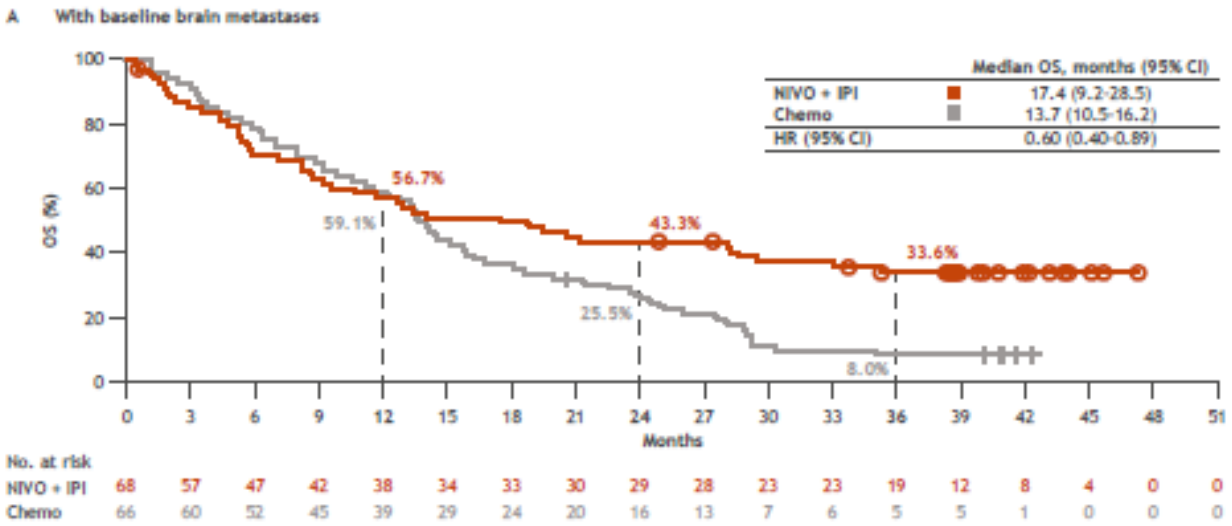
- 10 of 34 PD-L1-positive patients response in CNS **response rate of 29.4%** (95% CI 15.1-47.5)
  - 7 pts had discordance between CNS and systemic responses

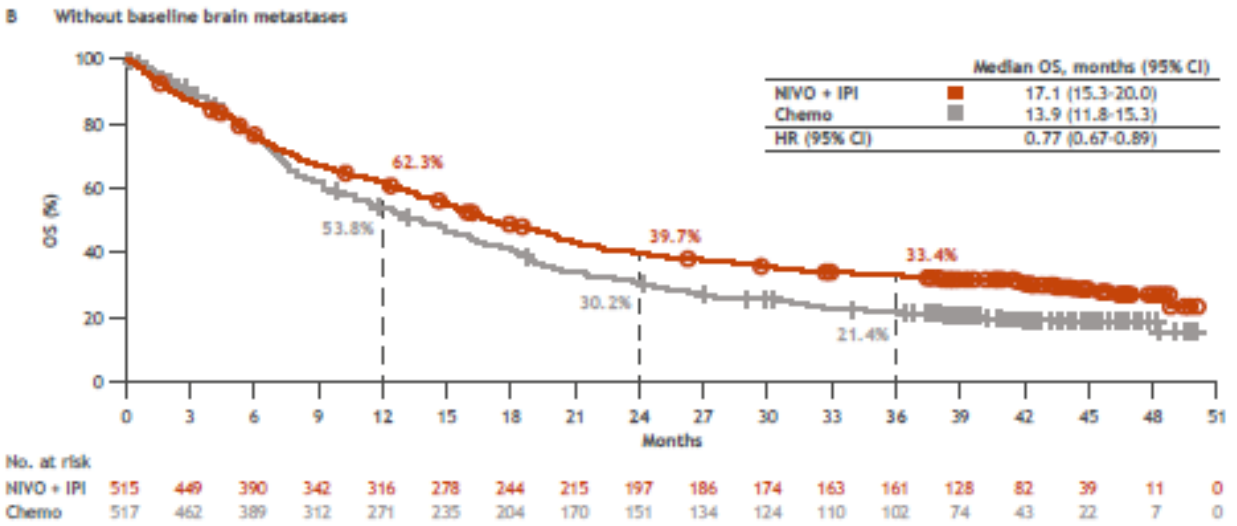
    4 with PD in brain and PR in body, 3 with PR in brain and PD in body
  - 0/ 5 PD-L1 negative or unevaluable patients had a brain metastasis response

Goldberg et al. Lancet Oncology 2020

Nivolumab plus ipilimumab as first-line treatment for patients with advanced NSCLC with brain metastases: CheckMate 227

All randomized patients





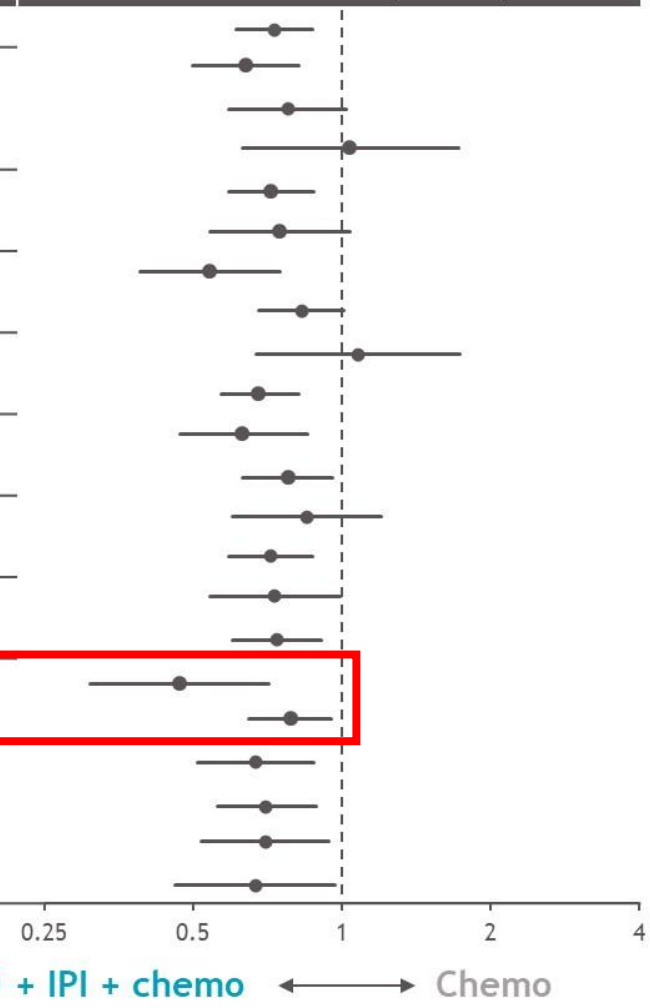
Systemic response*	All randomized patients			
	With brain metastases		Without brain metastases	
	NIVO + IPI (n = 68)	Chemo (n = 66)	NIVO + IPI (n = 515)	Chemo (n = 517)
Objective response rate, n (%)	22 (32.4)	17 (25.8)	173 (33.6)	146 (28.2)
Duration of response, months Median (95% CI)	24.9 (11.3-NR)	8.4 (4.2-13.9)	20.4 (16.3-29.0)	5.8 (5.3-6.9)
Patients with a response who had ongoing responses, %				
At 1 year	70.8	40.0	64.3	27.3
At 2 years	50.6	8.0	47.3	10.6
At 3 years	37.9	0	36.6	5.6

Systemic response*	Patients with PD-L1 expression ≥ 1%					
	With brain metastases			Without brain metastases		
	NIVO + IPI (n = 49)	Chemo (n = 48)	NIVO (n = 48)	NIVO + IPI (n = 347)	Chemo (n = 349)	NIVO (n = 348)
Objective response rate, n (%)	19 (38.8)	15 (31.3)	12 (25.0)	125 (36.0)	105 (30.1)	97 (27.9)
Duration of response, months Median (95% CI)	15.5 (11.3-NR)	8.4 (5.4-13.9)	31.0 (13.5-NR)	24.5 (15.2-34.5)	6.1 (5.6-7.3)	15.3 (11.7-23.5)
Patients with a response who had ongoing responses, %						
At 1 year	65.8	37.6	90.9	63.4	28.0	60.0
At 2 years	41.9	9.4	50.5	50.5	12.4	39.0
At 3 years	35.9	0	37.9	38.1	4.6	31.3

Poster. AACR Annual Meeting 2020, June 22-24, 2020

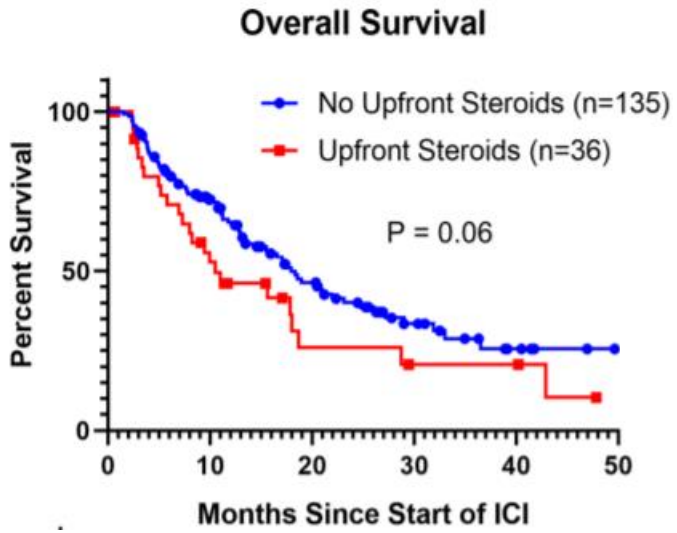
2-Year update: OS subgroup analysis

Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI + chemo n = 361	Chemo n = 358	
All randomized (N = 719)	15.8	11.0	0.73
< 65 years (n = 354)	15.9	10.7	0.64
≥ 65 to < 75 years (n = 295)	19.0	11.9	0.78
≥ 75 years (n = 70)	8.5	11.5	1.04
Male (n = 504)	14.2	9.8	0.72
Female (n = 215)	22.2	15.9	0.75
ECOG PS 0 (n = 225)	27.1	14.1	0.54
ECOG PS 1 (n = 492)	13.6	9.7	0.83
Never smoker (n = 98)	14.1	14.4	1.08
Smoker (n = 621)	16.2	10.4	0.68
SQ (n = 227)	14.5	9.1	0.63
NSQ (n = 492)	17.8	12.0	0.78
Liver metastases (n = 154)	10.2	8.1	0.85
No liver metastases (n = 565)	19.3	12.4	0.72
Bone metastases (n = 207)	11.9	8.3	0.73
No bone metastases (n = 512)	19.7	12.4	0.74
CNS metastases (n = 123)	19.9	7.9	0.47
No CNS metastases (n = 596)	15.6	11.8	0.79
PD-L1 < 1% (n = 264)	17.7	9.8	0.67
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.70
PD-L1 1-49% (n = 233)	15.2	10.4	0.70
PD-L1 ≥ 50% (n = 174)	18.9	12.9	0.67

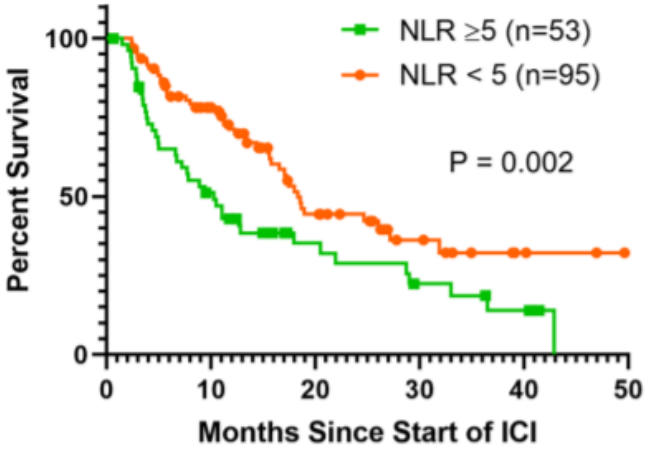


Neutrophil to lymphocyte ratio influences impact of steroids on efficacy of immune checkpoint inhibitors in lung cancer brain metastases

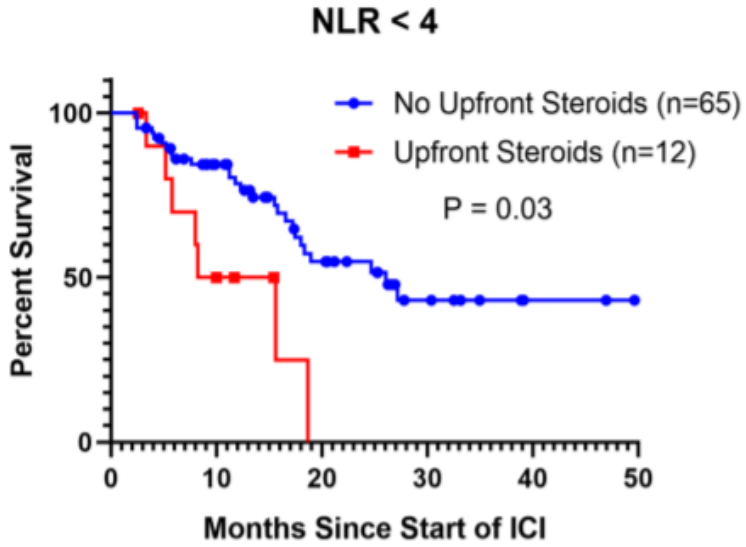
Impact of Steroids

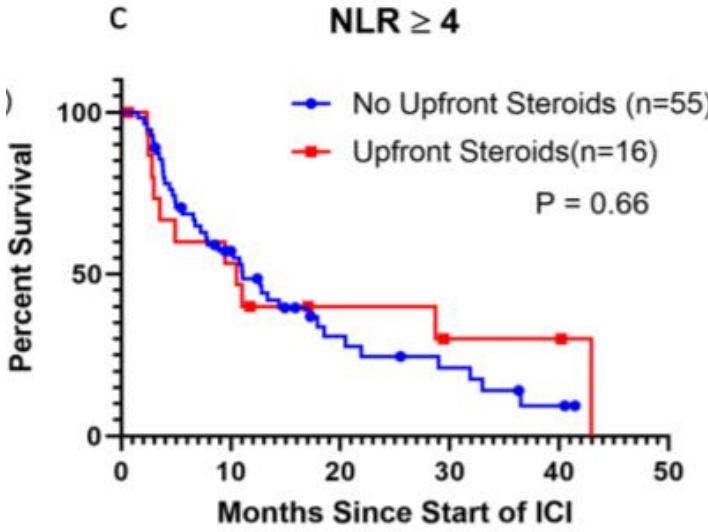


Impact of NLR



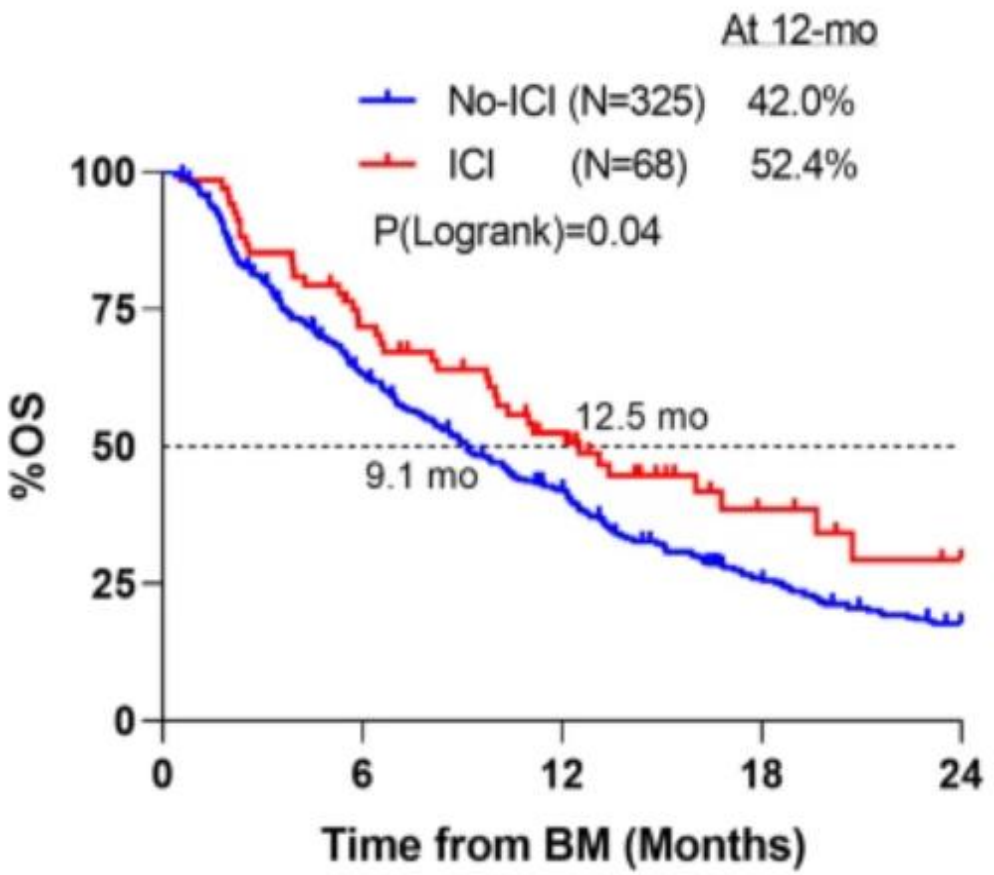
Combined

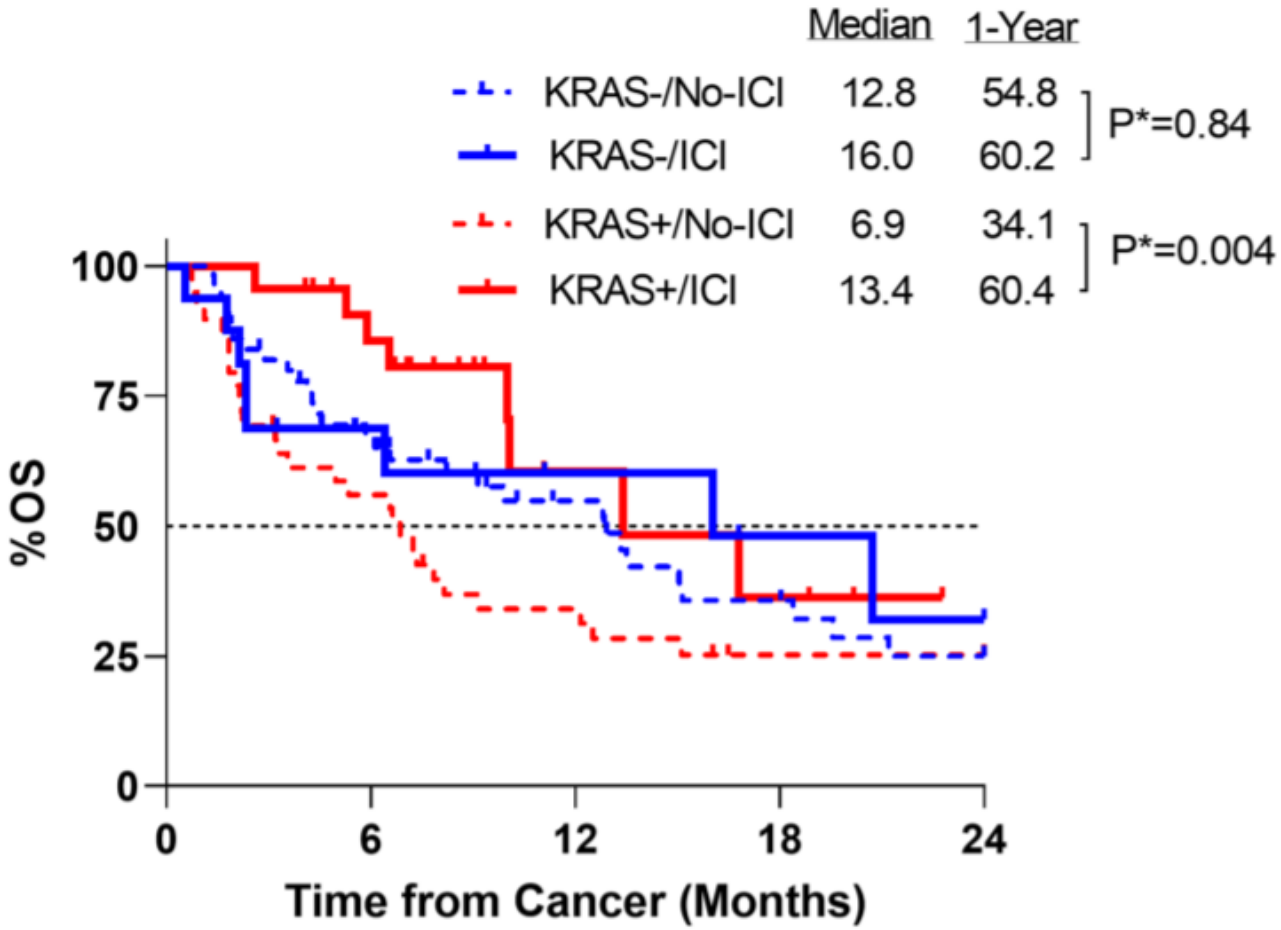




Lauko… Ahluwalia, Sci Rep 2021

Impact of KRAS mutation status on the efficacy of immunotherapy in lung cancer brain metastases

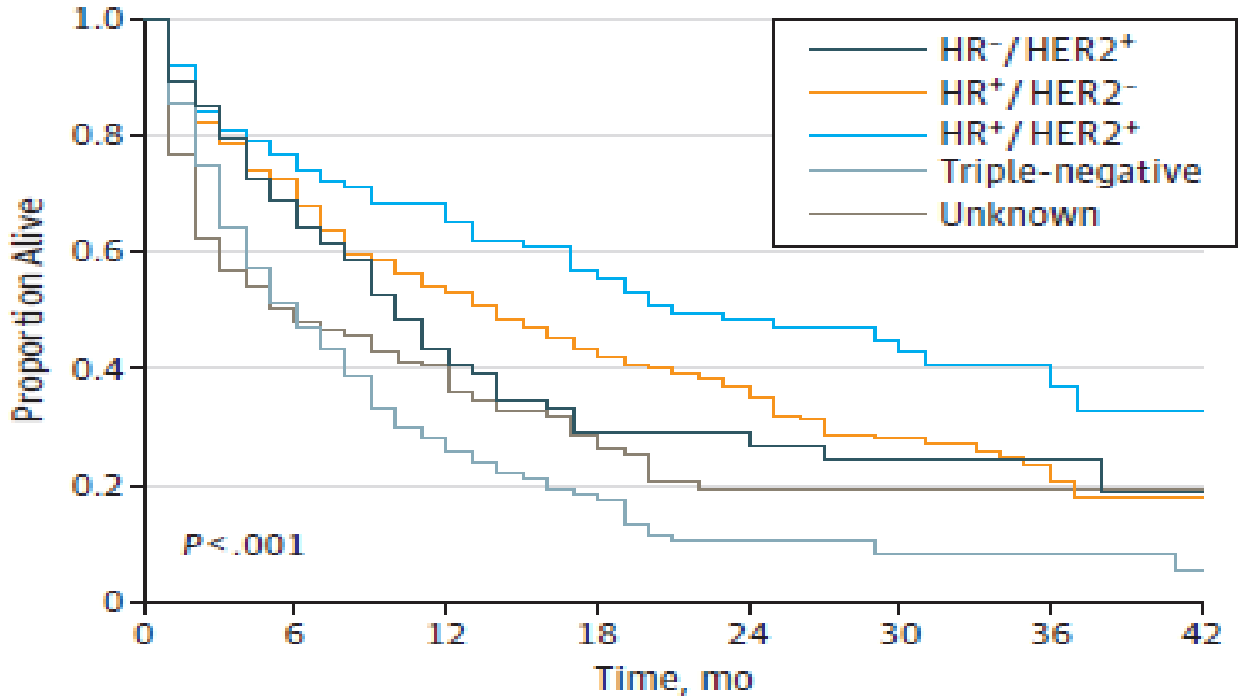




Lauko… Ahluwalia, Sci Rep 2021

Brain Metastases in Newly Diagnosed Breast Cancer: A Population-Based Study

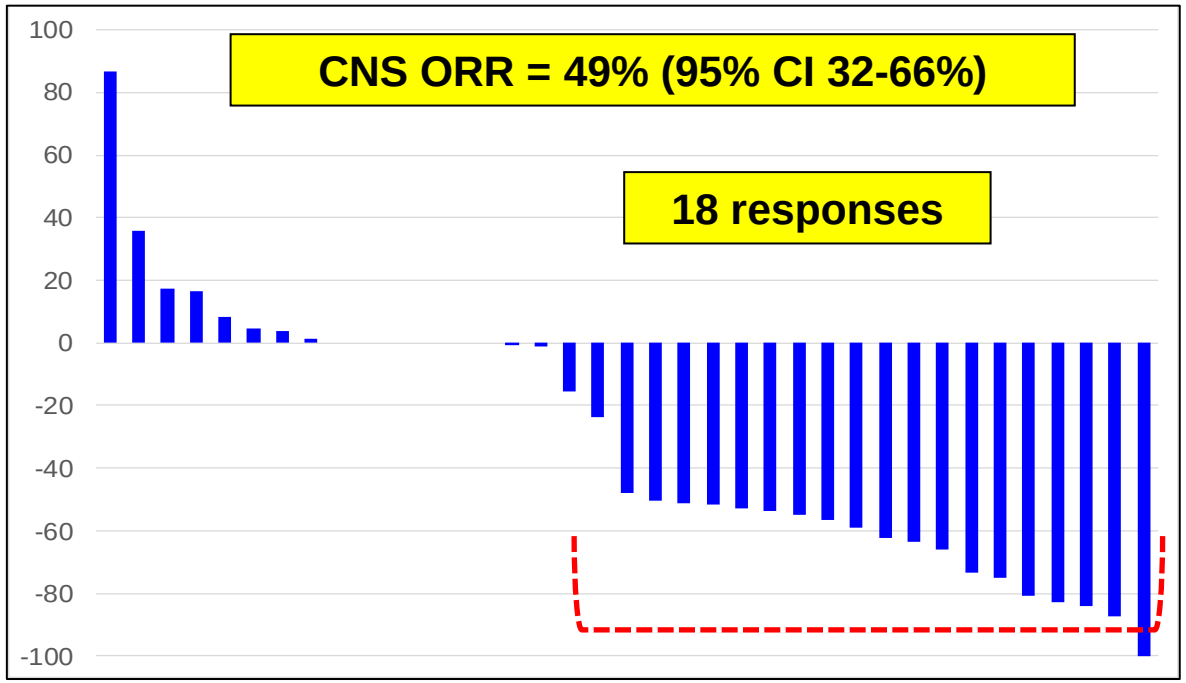
B Survival stratified by subtype



No. at risk								
HR⁻/HER2⁺	95	56	32	19	15	9	4	3
HR⁺/HER2⁻	328	196	121	78	54	33	17	5
HR⁺/HER2⁺	127	85	68	50	39	21	12	6
Triple-negative	153	67	34	20	10	6	4	2
Unknown	145	66	43	27	13	10	8	3

Martin et al. JAMA Oncology Published online March 16, 2017

Phase II trial of Neratinib and Capecitabine for Patients with Human Epidermal Growth Factor Receptor 2-Positive (HER2+) Breast Cancer Brain Metastases



Best CNS Volumetric Response (n=31)*

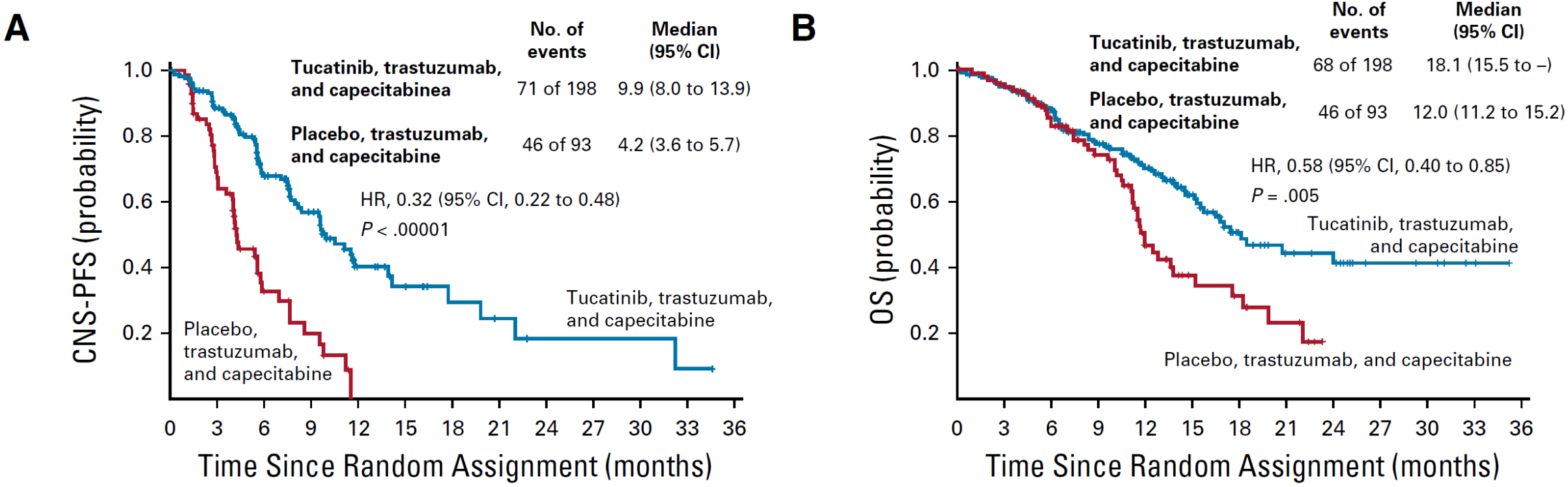
Primary Endpoint – CNS Volumetric Response

*** 6 patients did not reach first re-staging evaluation and are categorized as '0'**

┼ No patient had clear increase in steroid use, non-target lesions, non-CNS lesions, or worsening neurological symptoms at time of radiographic response

Freedman R et al. J Clin Oncol 35, 2017 (suppl; abstr 1005)

Tucatinib Plus Trastuzumab and Capecitabine in HER2-Positive Breast Cancer With Brain Metastases: HER2CLIMB Trial



No. at risk:

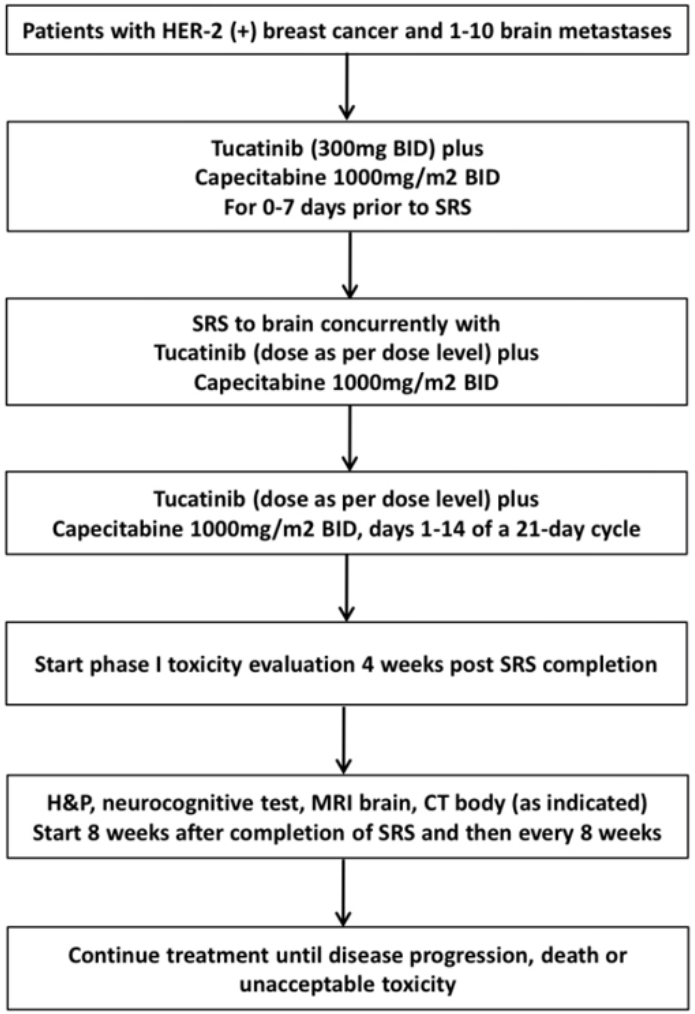
Tucatinib, trastuzumab, and capecitabine	198	132	74	45	18	11	6	4	2	2	2	1	0
Placebo, trastuzumab, and capecitabine	93	41	11	6	0	0	0	0	0	0	0	0	0

No. at risk:

Tucatinib, trastuzumab, and capecitabine	198	184	146	108	79	49	26	17	14	7	6	2	0
Placebo, trastuzumab, and capecitabine	93	87	67	49	23	12	9	5	0	0	0	0	0

J Clin Oncol 38:2610-2619.

Phase 1 trial of Tucatinib, trastuzumab and Capecitabine with SRS in Patients with brain metastases from HER-2 positive Breast Cancer Brain Metastases



2021 ASCO ANNUAL MEETING

PYROTINIB PLUS CAPECITABINE FOR HER2 POSITIVE METASTATIC BREAST CANCER PATIENTS WITH BRAIN METASTASES (PERMEATE): A MULTICENTER, SINGLE-ARM PHASE II STUDY

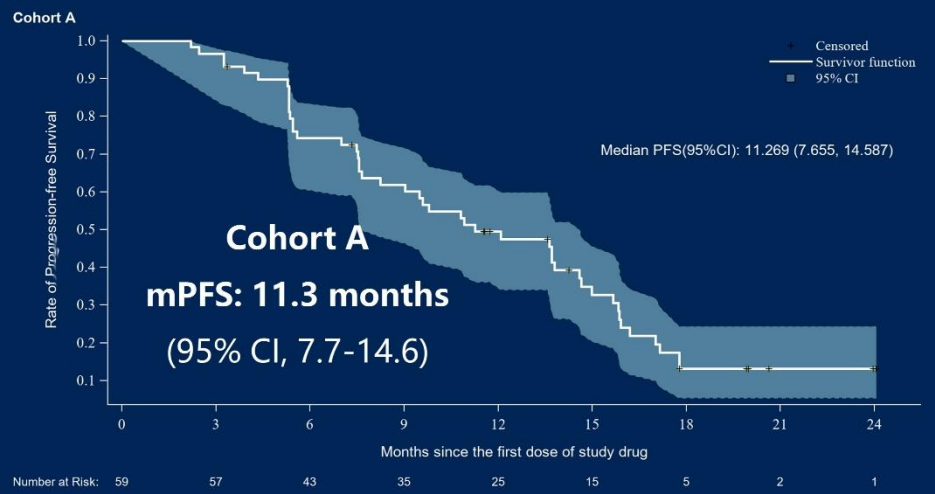
Min Yan, MD
The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital,

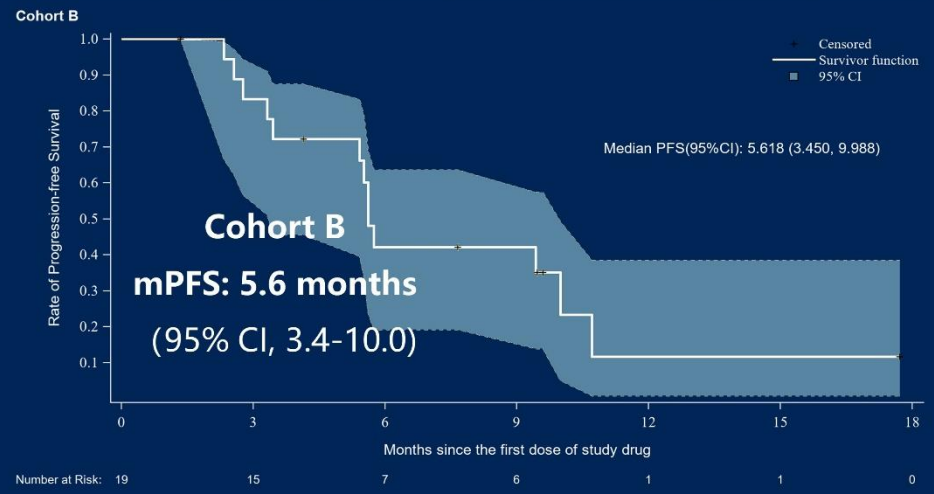
Data cut off date: 2021-04-16

Study Endpoint

Objective Response Rate (ORR)

Best CNS Response	Cohort A (n=59)	Cohort B (n=19)	Best non-CNS Response	Cohort A (n=27)	Cohort B (n=4)	Best non-CNS Response Total (n=31)
Complete response (CR)	**7 (11.9)**	**1 (5.3)**	CR	2 (7.4)	0	2 (6.5)
Partial response (PR)	**37 (62.7)**	**7 (36.8)**	PR	17 (63.0)	2 (50.0)	19 (61.3)
Stable disease (SD)[a]	11 (18.6)	4 (21.1)	SD[a]	5 (18.5)	2 (50.0)	7 (22.6)
Progressive disease (PD)	2 (3.4)	5 (26.3)	PD	2 (7.4)	0	2 (6.5)
Not evaluable (NE)	2 (3.4)	2 (10.5)	NE	1 (3.7)	0	1 (3.2)
CNS-ORR, % (95%CI)	**74.6** (61.6-85.0)	**42.1** (20.3-66.5)	**Non-CNS ORR, % (95%CI)[b]**	**70.4** (49.8-86.2)	**50.0** (6.8-93.2)	**67.7** (48.6-83.3)

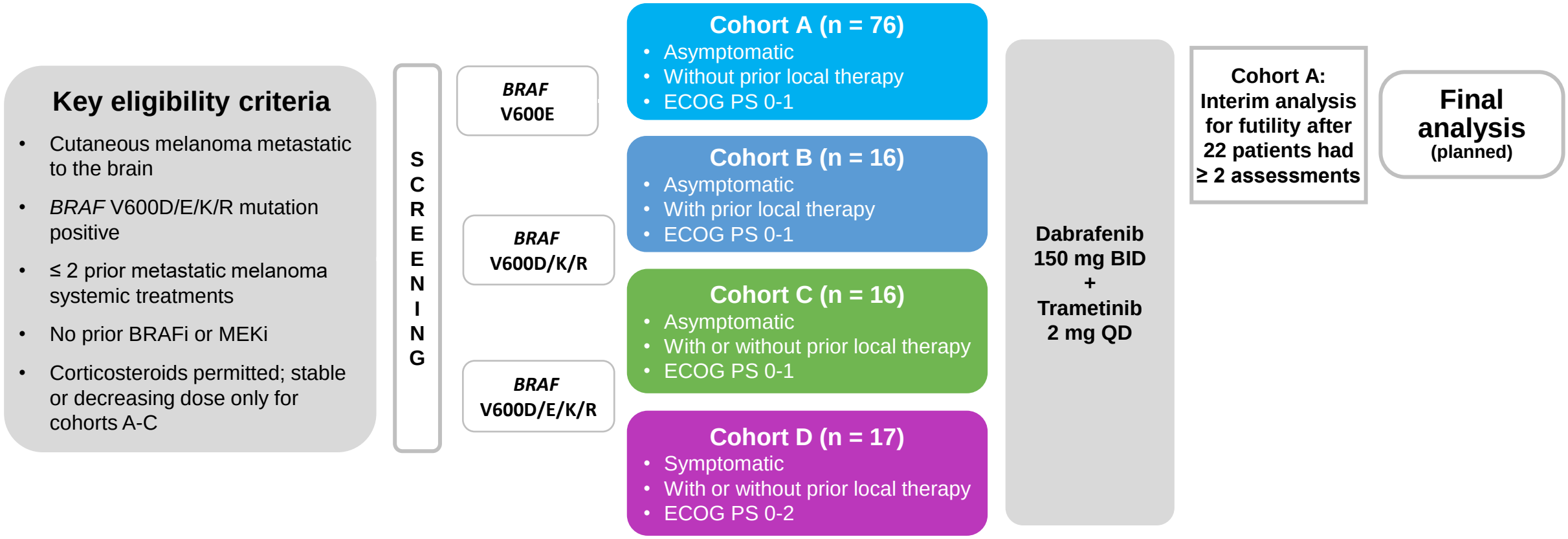




[a]SD (or better) occurred at least 56 days after the first dose before PD, and not meeting the criteria for confirmed CR/PR.

[b]Only patients with extracranial measurable disease at baseline are included in the analysis

COMBI-MB: Study Design (Phase 2)

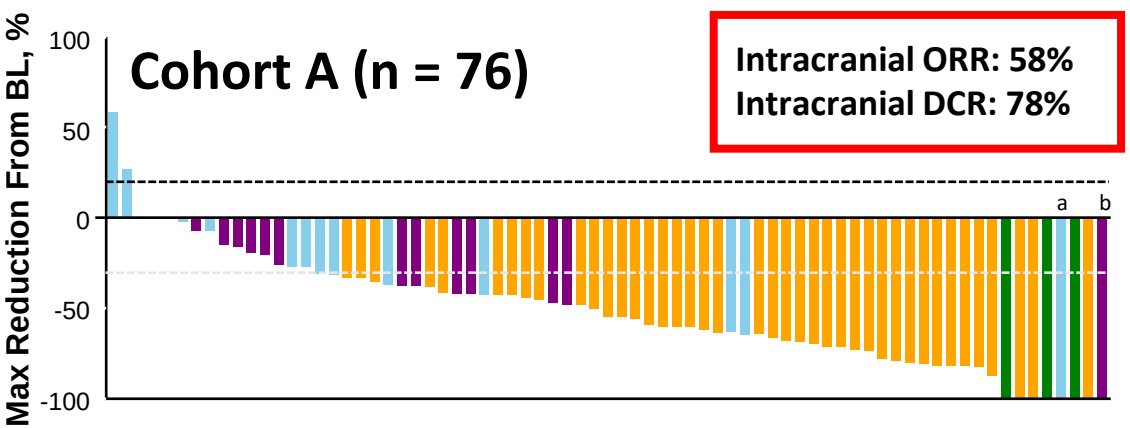


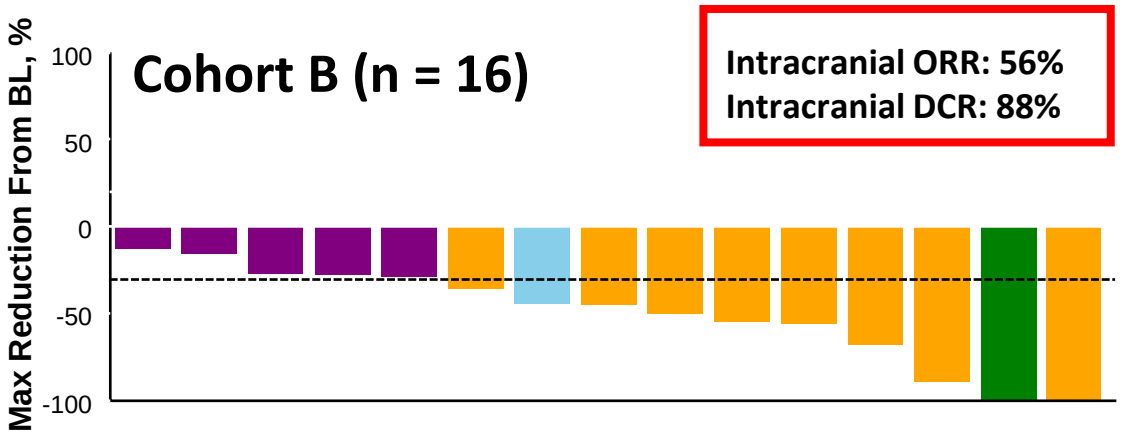
Primary endpoint: intracranial response (IR) rate in cohort

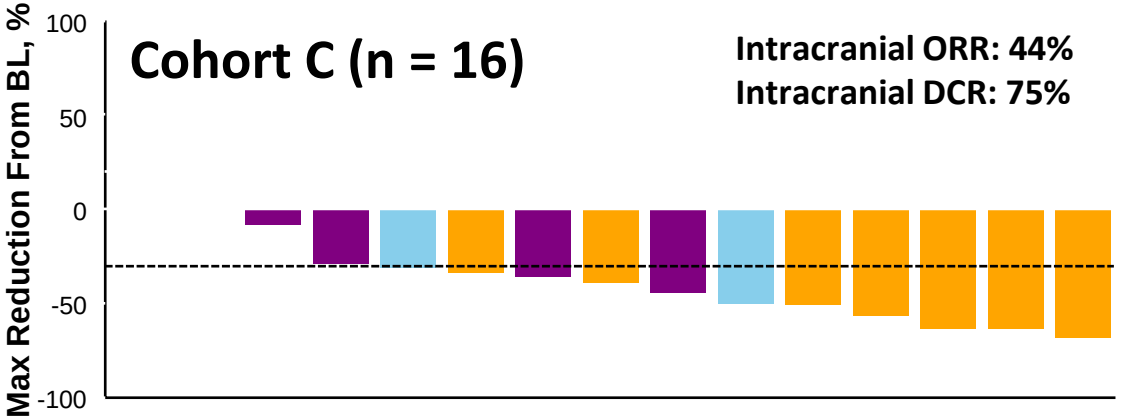
BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; QD, once daily.
[a]Null hypothesis: IR rate of ≤ 35% in cohort A (based on activity of dabrafenib monotherapy in the BREAK-MB trial; Long GV, et al. *Lancet Oncol.* 2012;13:1087-1095).
Investigator-assessed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

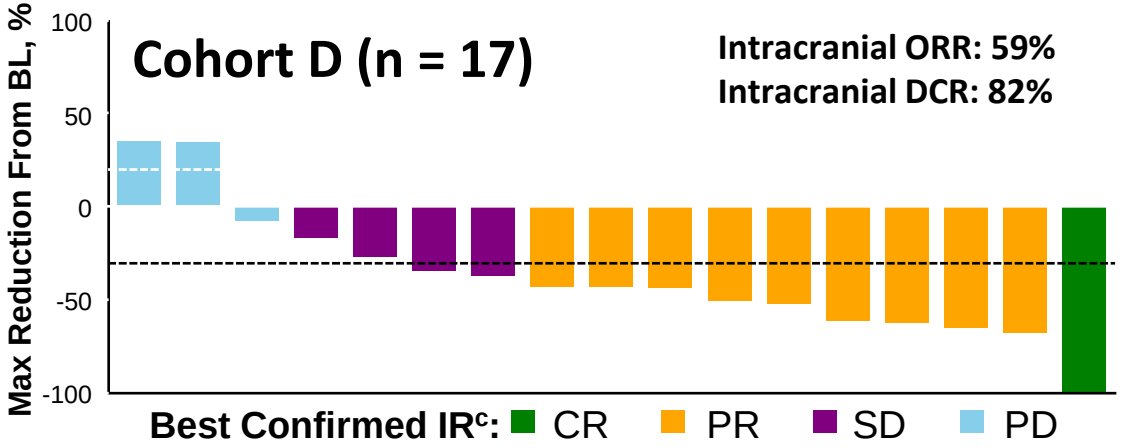
Davies MA et. al Abstract 9506, ASCO Annual Meeting 2017

Intracranial Response



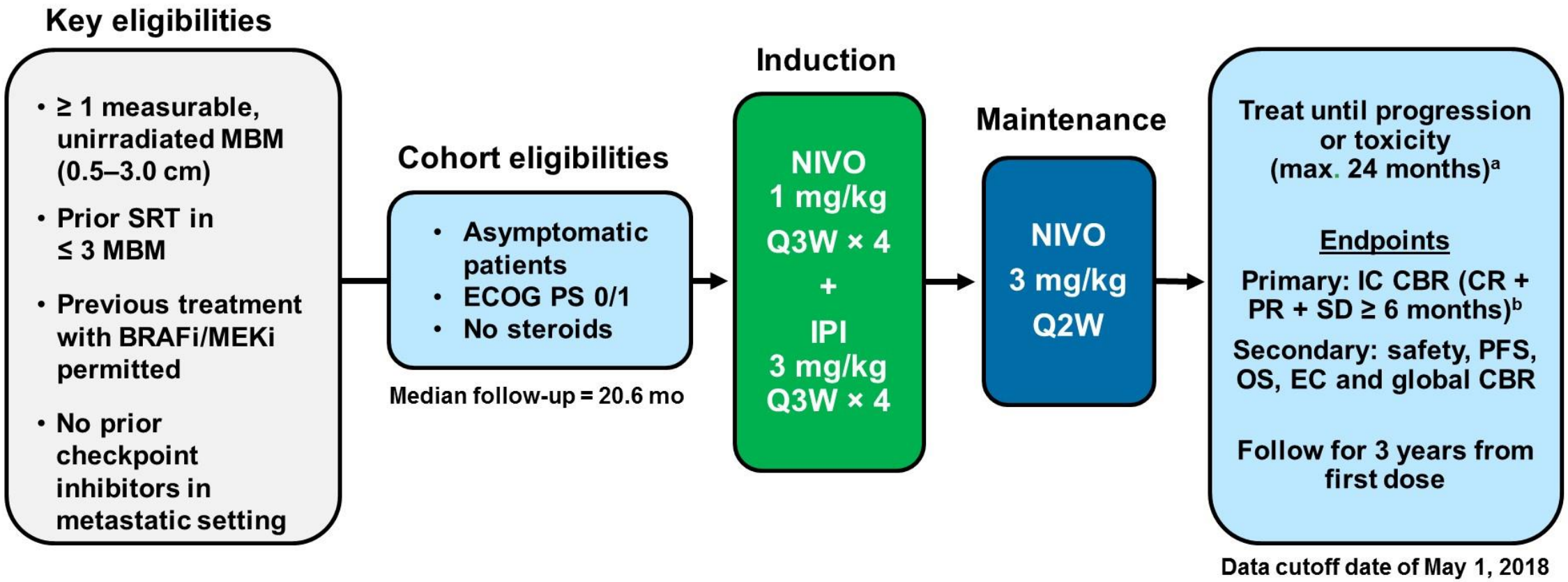






CR, complete response; SD, stable disease.
[a] Patient had a CR in the target lesion, but best confirmed response was determined to be PD due to development of an unequivocal new lesion; [b] Patient had an unconfirmed CR, but best confirmed response was SD; [c] Investigator assessed; these results were supported by independent review.

CheckMate 204 Study Design



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.

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

Variable	Intracranial (N=94)	Extracranial (N=94)	Global (N=94)
Best overall response — no. (%)*			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥6 mo	2 (2)	6 (6)	5 (5)
Progressive disease	31 (33)	28 (30)	33 (35)
Could not be evaluated‡	9 (10)	13 (14)	8 (9)
Objective response‡			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45–66)	50 (40–60)	51 (40–62)
Clinical benefit§			
No. of patients	54	53	53
Percent of patients (95% CI)	57 (47–68)	56 (46–67)	56 (46–67)

55% RR

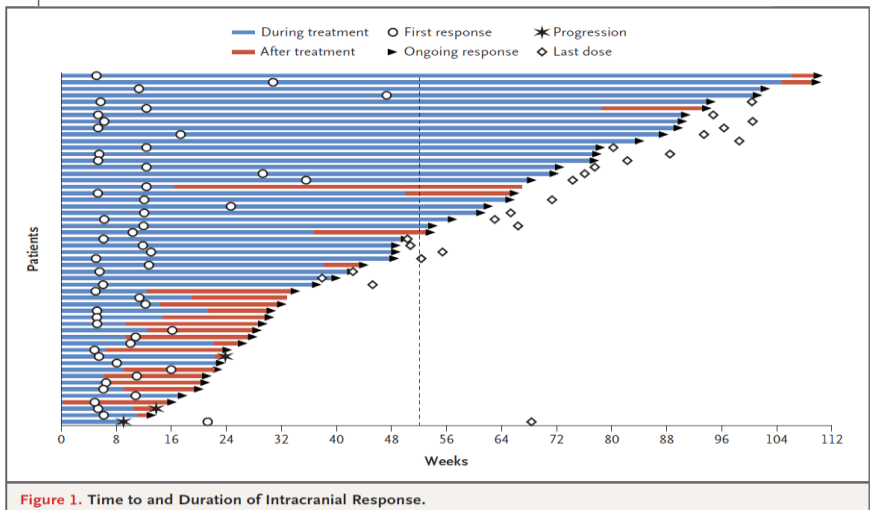


Figure 1. Time to and Duration of Intracranial Response.

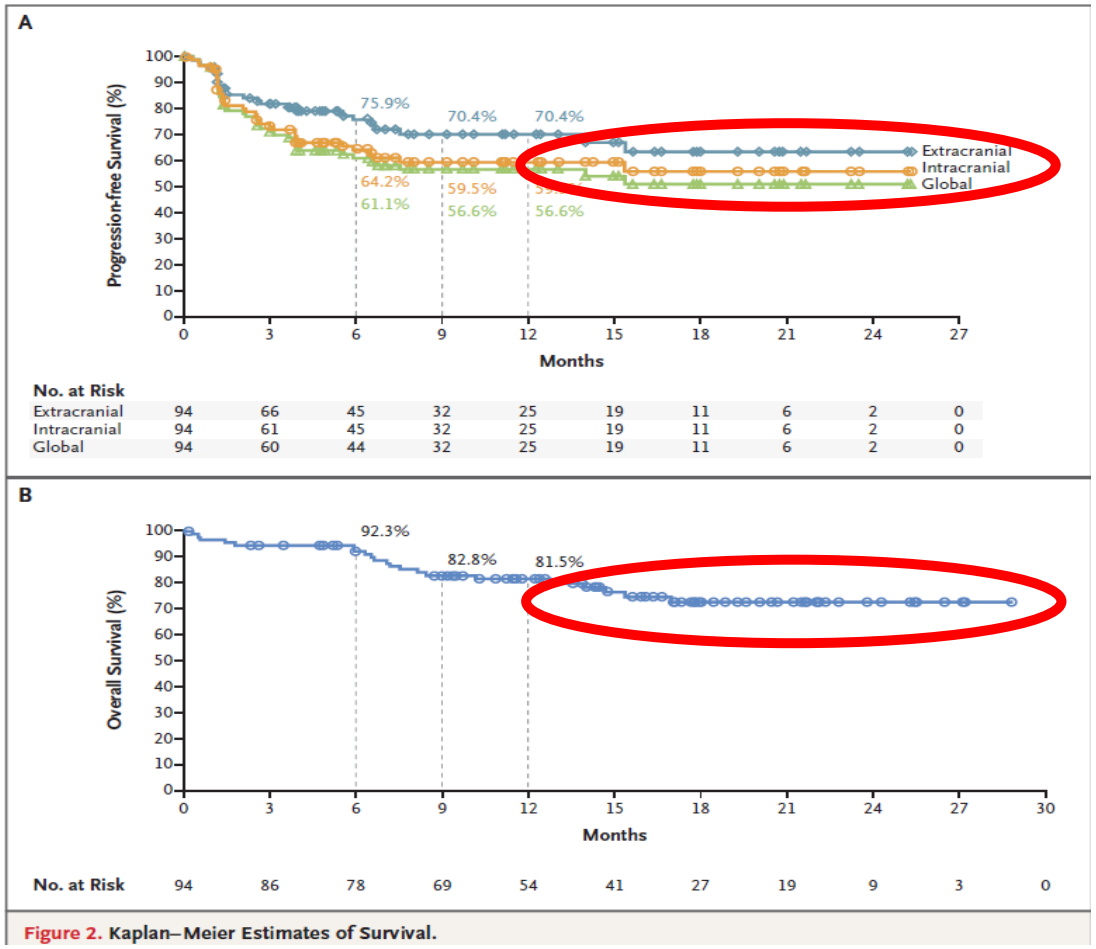
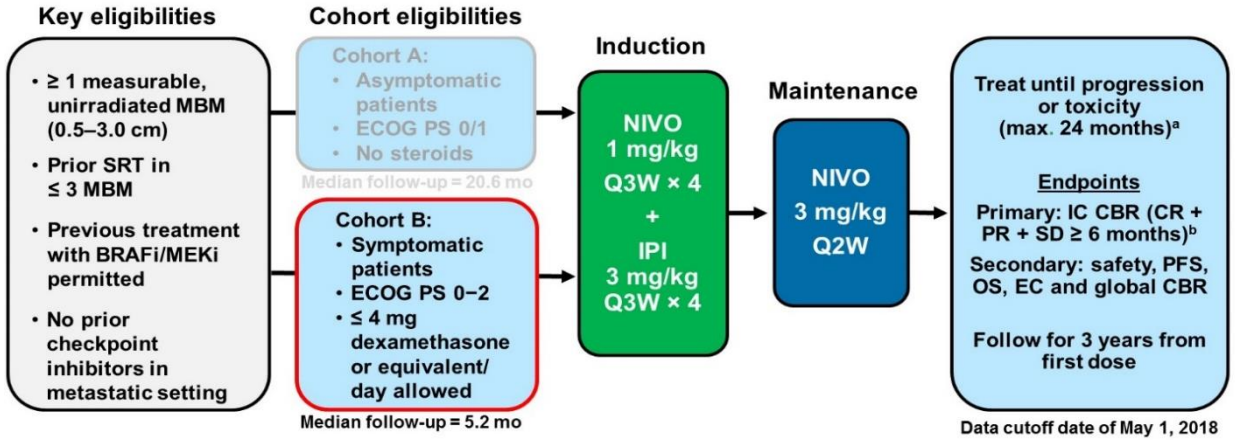


Figure 2. Kaplan–Meier Estimates of Survival.

N Engl J Med. 2018 Aug 23;379(8):722-730.

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.

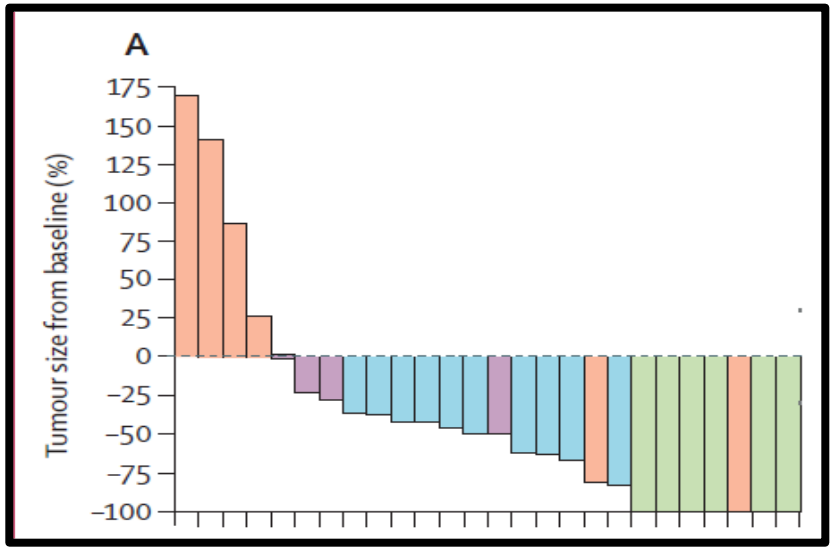
13

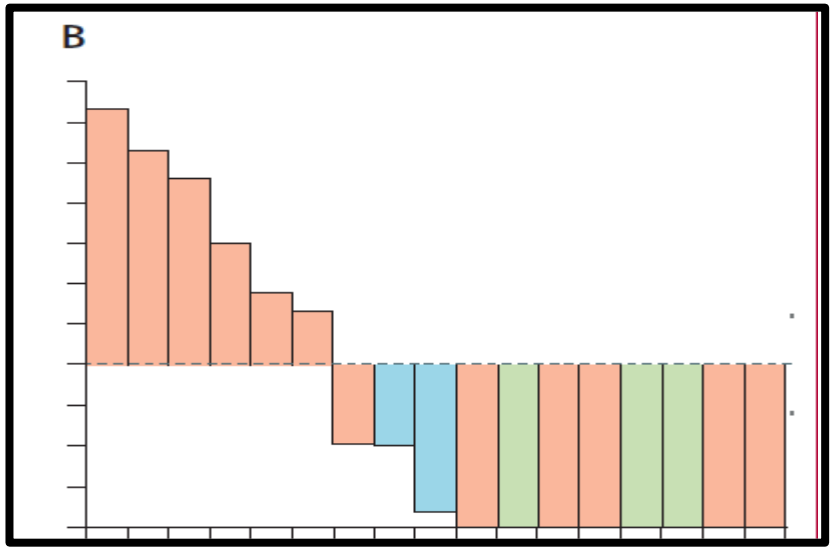
Response to Treatment – Symptomatic Patients

	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.

Combination Nivolumab and Ipilimumab or Nivolumab alone in Melanoma Brain Metastases: A Multicentre Randomized Phase 2 Study





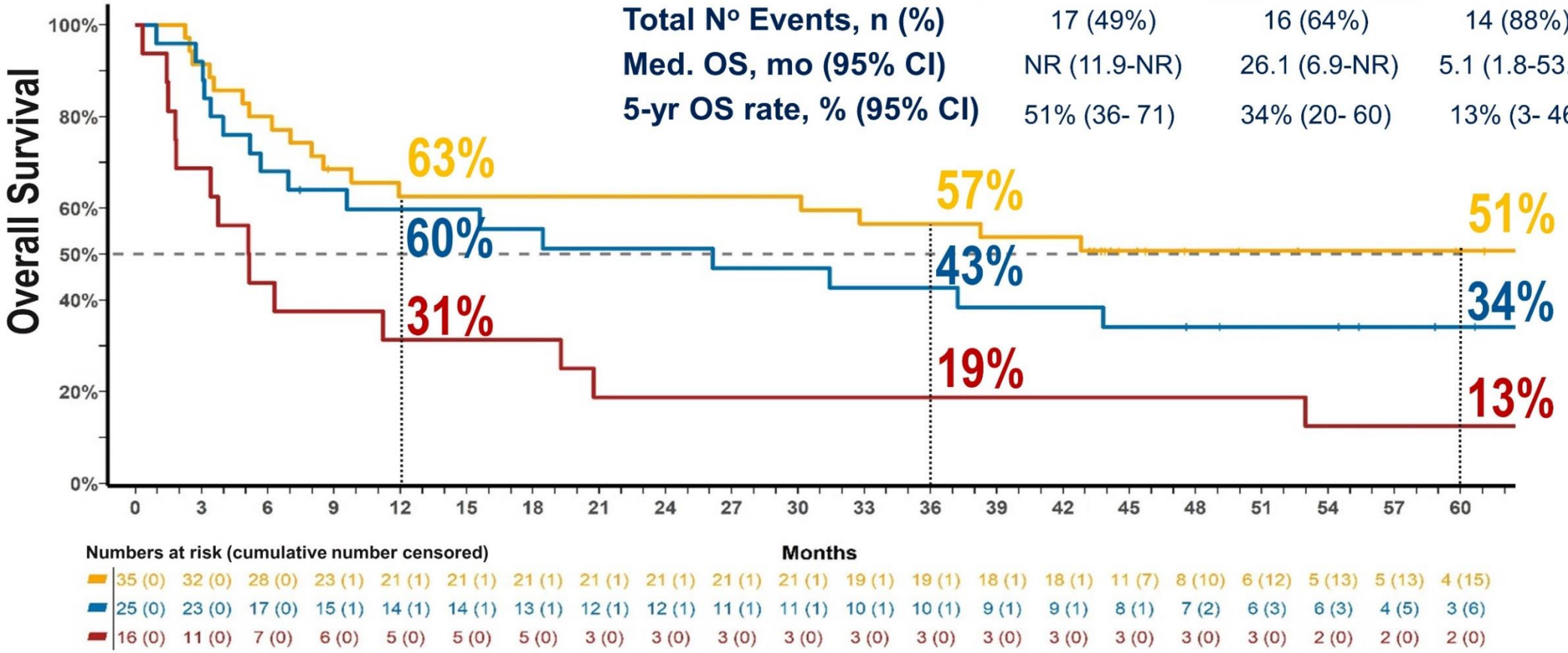
	Cohort A		Cohort B		Cohort C (n=16)
	Drug* naive (n=27)	Overall (n=35)	Drug* naive (n=19)	Overall (n=25)	
Intracranial response					
Overall (%; 95% CI)	15 (56%; 35–75)	16 (46%; 29–63)	4 (21%; 6–46)	5 (20%; 7–41)	1 (6%; 0–30)
Complete response	5 (19%)	6 (17%)	2 (11%)	3 (12%)	0
Partial response	10 (37%)	10 (29%)	2 (11%)	2 (8%)	1 (6%)
Stable disease	3 (11%)	4 (11%)	0	0	2 (13%)
Progressive disease	8 (30%)	14 (40%)	14 (74%)	19 (76%)	13 (81%)
Non-evaluable	1 (4%)	1 (3%)	1 (5%)	1 (4%)	0

56% RR Drug Naïve, 46% Overall (Ipi + Nivo)
21% RR Drug Naïve, 20% Overall (Nivo)

Lancet Oncol. 2018 May;19(5):672-681

Overall Survival

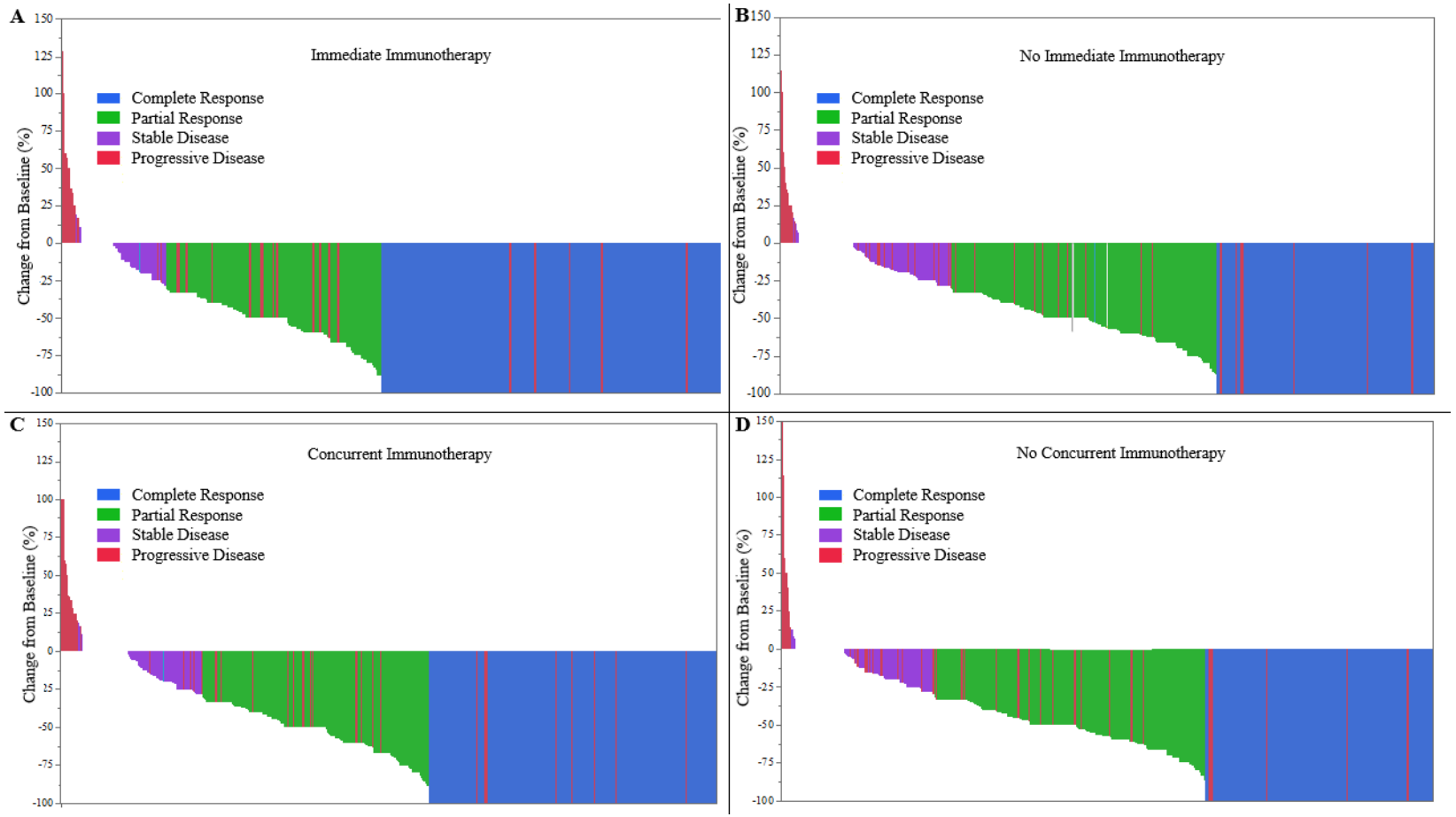
	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo N=16
Total Nº Events, n (%)	17 (49%)	16 (64%)	14 (88%)
Med. OS, mo (95% CI)	NR (11.9-NR)	26.1 (6.9-NR)	5.1 (1.8-53.0)
5-yr OS rate, % (95% CI)	51% (36- 71)	34% (20- 60)	13% (3- 46)



- Death solely due to intracranial progression in 8/76 (17%) patients (1 Cohort A, 4 Cohort B, 3 Cohort C)

The Impact of Sequencing of PD-1/PD-L1 Inhibitors for Patients with Brain Metastasis Undergoing Stereotactic Radiosurgery

Rupesh Kotecha, Joseph M. Kim, Jacob A. Miller, Aditya Juloori, Samuel T. Chao, Erin S. Murphy, David M. Peereboom, Alireza M. Mohammadi, Gene H. Barnett, Michael A. Vogelbaum, Lilyana Angelov, John H. Suh, and Manmeet S. Ahluwalia



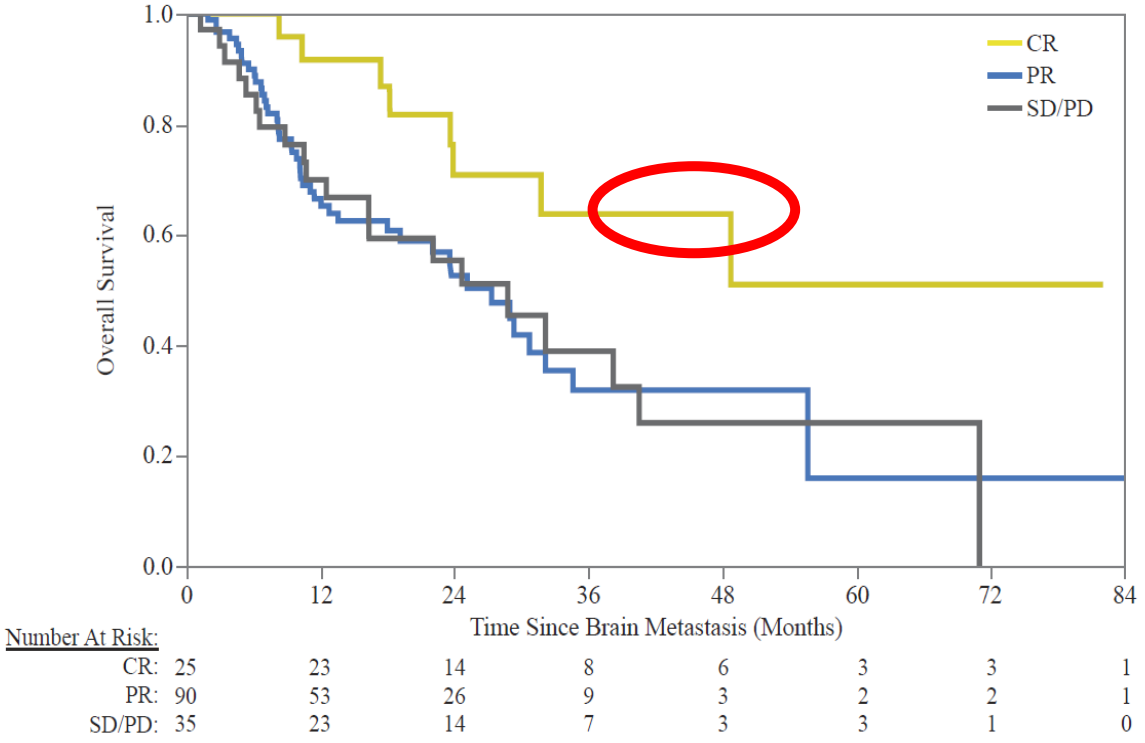
Neuro-Oncology

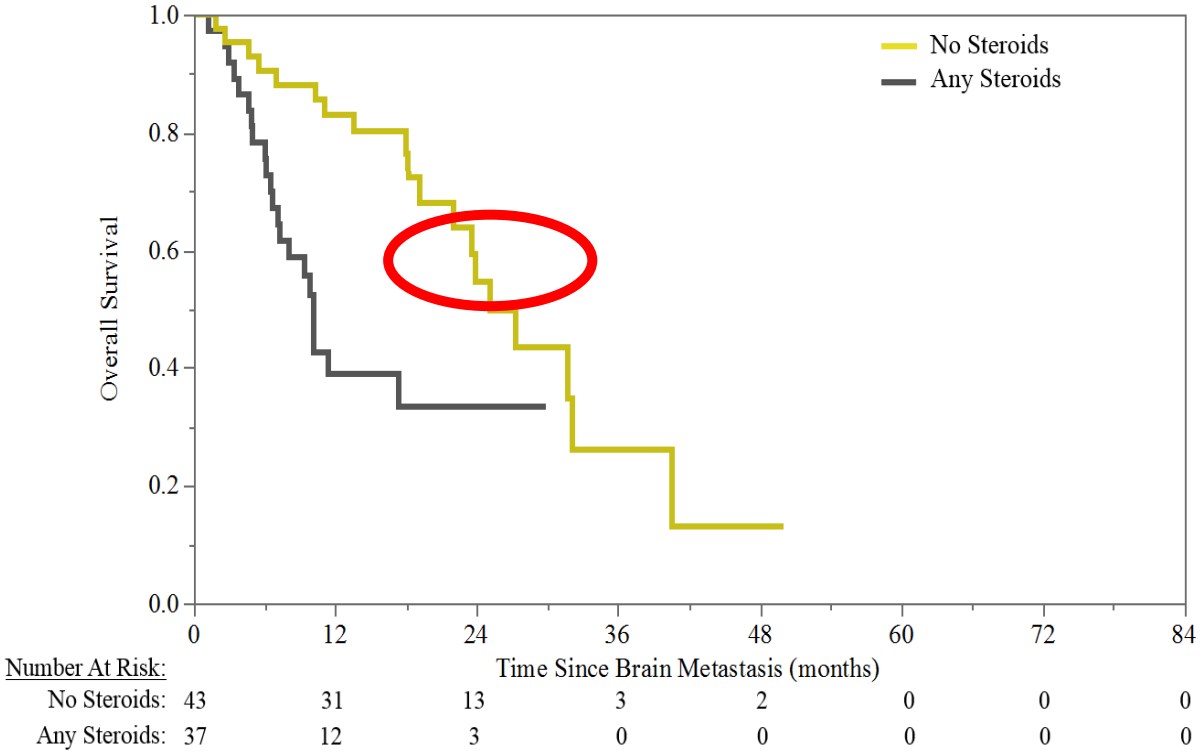
Immediate ICI (best objective response (BOR) vs No immediate ICI: $p<0.001$; complete response: 50 vs. 32%; 12-month durable response: 94 vs. 71%, $p<0.001$)

150 patients underwent SRS to 1003 BM and received ICI

The Impact of Sequencing of PD-1/PD-L1 Inhibitors for Patients with Brain Metastasis Undergoing Stereotactic Radiosurgery

150 patients underwent SRS to 1003 BM and received ICI





Treatment Strategies

Miami Cancer Institute
BAPTIST HEALTH SOUTH FLORIDA

<25% CNS Response

Tucatinib + Transtuzumab
Abemaciclib
Neratinib
Pertuzumab / Transtuzumab
Capecitabine + Temozolomide
Vemurafenib
Ipilimumab
Gefitinib
Lapatinib

25%-50% CNS Response

Tucatinib + Transtuzumab + Capecitabine
Lapatinib + Capecitabine
Neratinib + Capecitabine
Temozolomide + Cisplatin
TDM-1
Dabrafenib
Ipilimumab + Nivolumab
Afatinib
Nivolumab
Pemetrexed
Pembrolizumab

>50% CNS Response

Dabrafenib + Trametinib
Alectinib
Brigatinib
Erlotinib
Lorlatinib
Osimertinib
Bevacizumab + Carboplatin + Paclitaxel

Integration of Systemic Therapy and Stereotactic Radiosurgery for Brain Metastases. Raees Tonse, Martin C. Tom, Minesh P. Mehta, Manmeet S. Ahluwalia Rupesh Kotecha. Cancers 2021

Future Directions: Takeaway Points

- Control
  - Macroscopic disease: SRS (? Number) WBRT (hippocampal sparing), Targeted therapy, Immunotherapy (asymptomatic patients, radiation sensitizers?)
  - Microscopic disease: targeted therapy, Immunotherapy
  - Systemic disease: targeted therapy, Immunotherapy
- Preserve
  - Neurologic function: primary endpoint in clinical trials, appropriate tests, time point
- Clinical trials are critical to define care in BM
- Selection of therapy for BM: multidisciplinary approach

Thank You