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Immunotherapy and targeted therapies in lung cancer brain metastasis: results with a greater time perspective

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by SOLTI

Conflicts of interest

Consultant or Advisory Role: Boehringer Ingelheim

Speaking: Boehringer Ingelheim, Roche, Lilly, Merck & Co

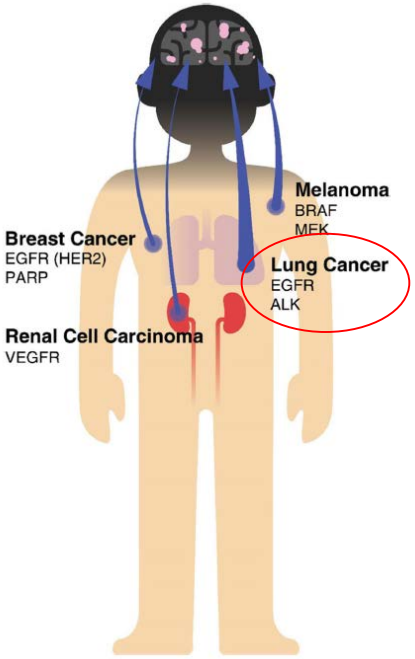
I. Introduction

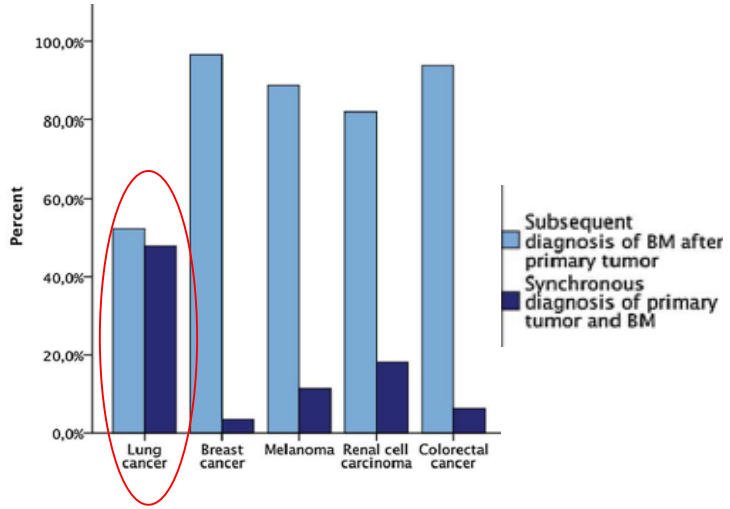
II. Immunotherapy and NSCLC-BM
   I. Challenges for immunotherapy treatment in patients with Brain Metastases
   II. Efficacy data of ICI in NSCLC patients with Brain Metastases
   III. Conclusions

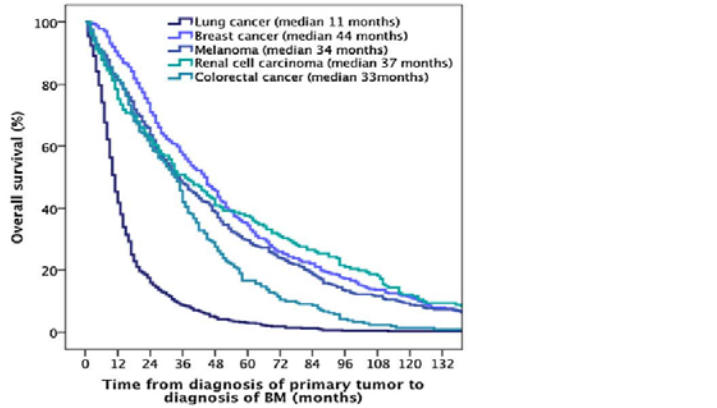
III. Targeted Therapies in oncogene-adiccted NSCLC patients with Brain Metastases
   I. EGFR
   II. ALK
   III. Other drivers in NSCLC
   IV. Conclusions

Brain Metastases in lung cancer population

- Lung cancer is the leading solid tumor developing BM
- Up to 40% of NSCLC patients will develop BM along their disease



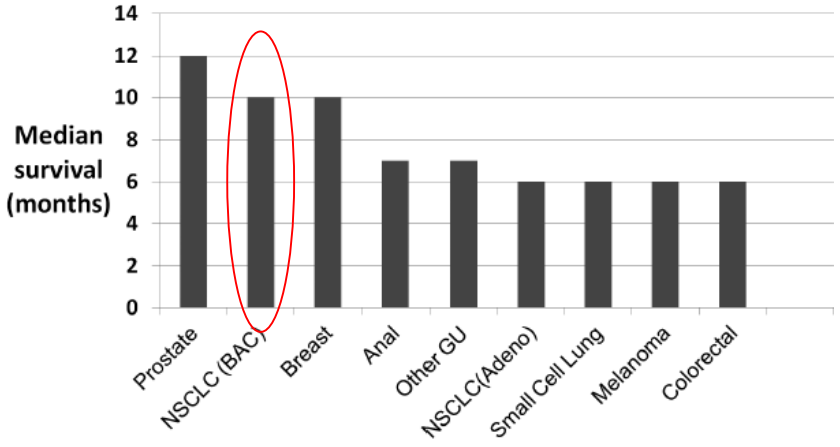


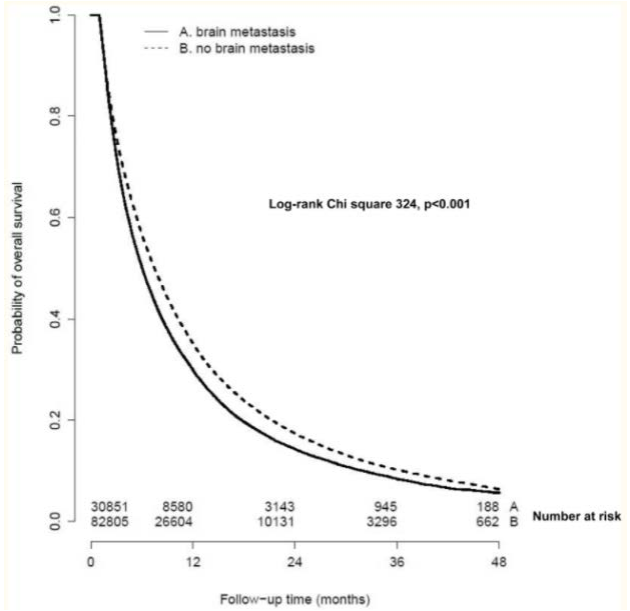


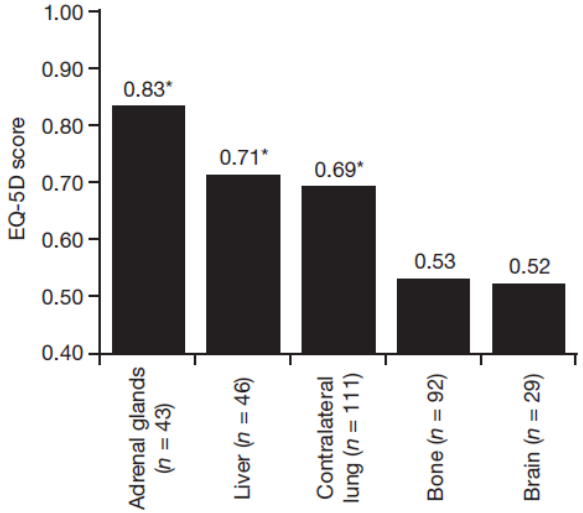
Peters S et al. Cancer Treat Rev 2016; Cagney D N et al. Neuro-Oncol 2017; Berghoff A et al. ESMO Open 2016

Importance of Brain Metastases in NSCLC population

- BM are the most frequent neurological complication in patients with NSCLC
- BM are associated with a negative impact in neurocognitive function, quality of life deterioration, and poor prognosis







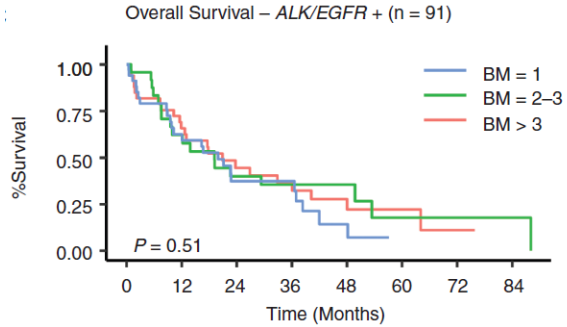
Cagney D N et al. Neuro-Oncol 2017; Wagar S N et al. Am J Clin Oncol 2018; Peters S et al. Cancer Treat Rev 2016

Prognostic factors in patients with NSCLC and BM

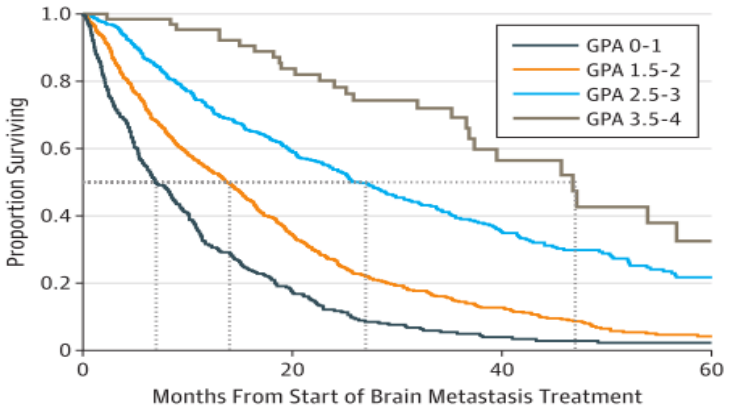
- Lung-molGPA → A useful tool to predict the prognosis of patients with NSCLC and BM

Table 2. Updated DS-GPA for NSCLC With Brain Metastases (Lung-molGPA) Scoring Chart and Worksheet to Estimate Survival

Prognostic Factor	GPA Scoring Criteria[a] 0	0.5	1.0	Patient Score[b]
Age, y	≥70	<70	NA	___
KPS	<70	80	90-100	___
ECM	Present		Absent	___
Brain metastases, No.	>4	1-4	NA	___
Gene status	*EGFR* neg/unk and *ALK* neg/unk	NA	*EGFR* pos or *ALK* pos	___
Total	NA	NA	NA	___

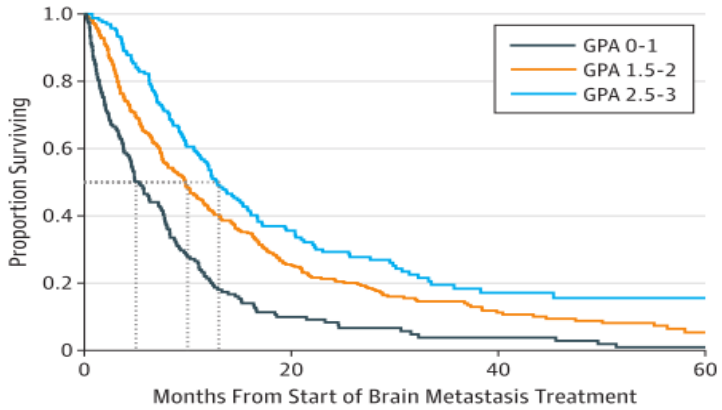


A Adenocarcinoma



0-1: 6.9 months
1.5-2: 13.7 months
2.5-3: 26.5 months
3.5-4: 46.8 months

B Nonadenocarcinoma

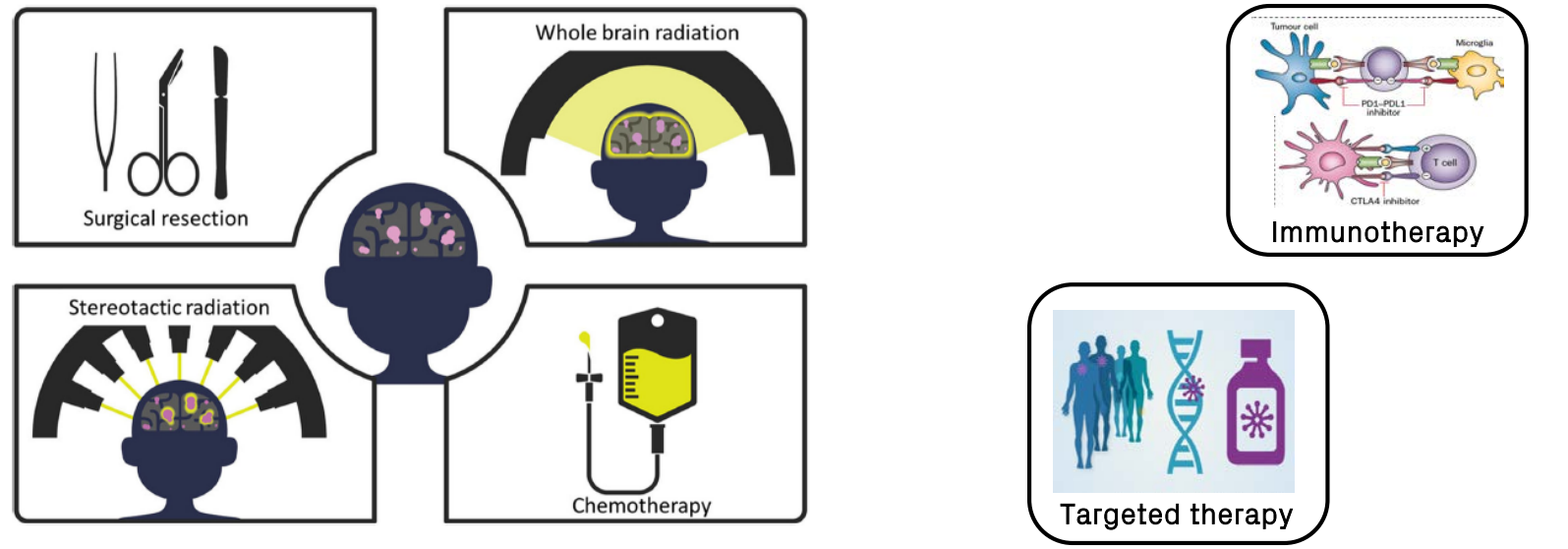


0-1: 5.3 months
1.5-2: 9.8 months
2.5-3: 12.8 months

https://brainmetgpa.com/

Sperduto et al. Jama Oncol 2016; Balasubramanian et al. Neuro-Oncol 2020

New treatments for patients with BM



Adapted from Kim et al. Pharm Res 2019

Goals of treatment BM

- The goal is to prevent or delay neurological deterioration and to prolong survival with acceptable quality of life

- BM treatment therapeutic decisions should be discussed at a dedicated BM board and often requires an individualized decision

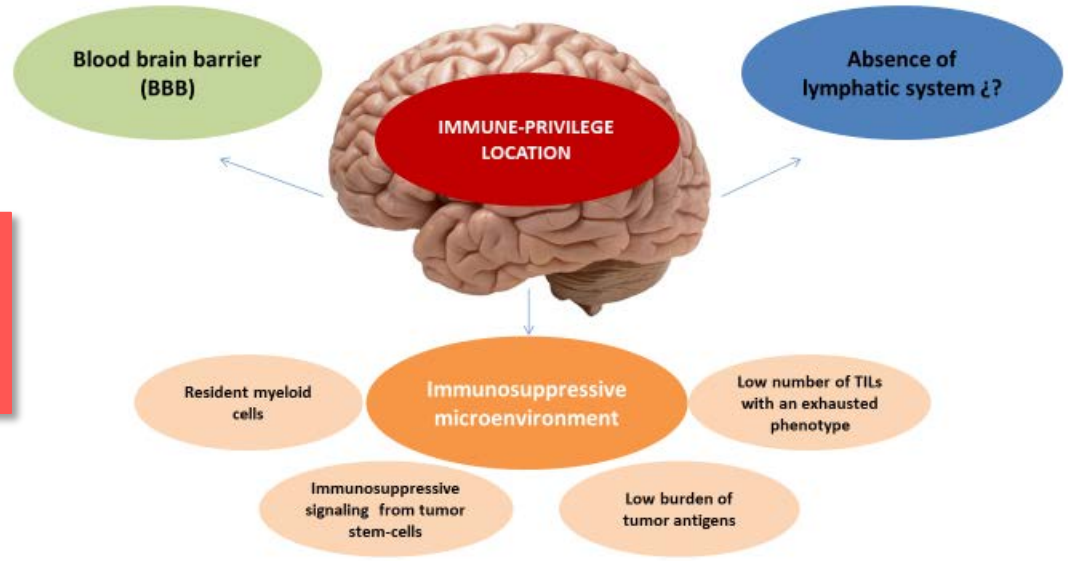
Le Rhun E et al. Ann of Oncol 2021

Non-Oncogene-addicted NSCLC patients with BM: role of Immunotherapy

Immune-checkpoint inhibitors (ICI) combined with platinum-based chemotherapy or ICI monotherapy has become standard of care in patients with NSCLC
Despite this high incidence, patients with BM were excluded from most pivotal ICI trials

Some challenges of this population of patients and tumor location

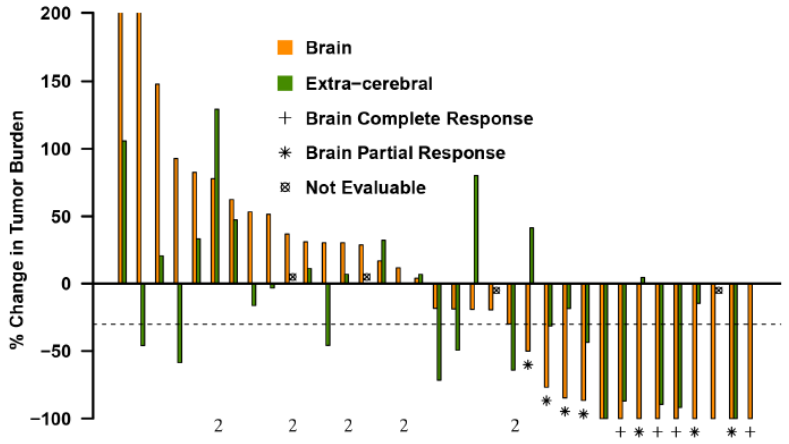
Frequently use of corticosteroids
Poor prognosis
Probable inability of ICI to cross the blood-tumor barrier
Risk of brain pseudoprogression



Reck M et al. NEJM 2016; Gandhi L et al. NEJM 2018; Paz-Ares L et al. NEJM 2018

Immune Checkpoint-Inhibitors (ICI) efficacy and safety in NSCLC-BM

A non-randomized, open-label, single-institution, phase II trial evaluating the efficacy of pembrolizumab in melanoma and NSCLC patients with BM



- Pts with NSCLC with at least 1 BM between 5-20 mm that is asymptomatic and either untreated or progressing after prior local therapy, no neurologic symptoms or corticosteroid requirement and PS <2
- BM response was evaluated by modified RECIST

- BM ORR was 29.7% (11/37 pts) (95% CI 15.9-47)
- Only PD-L1 + cohort of patients achieved a response
- 6 pts had discordance between CNS and systemic responses

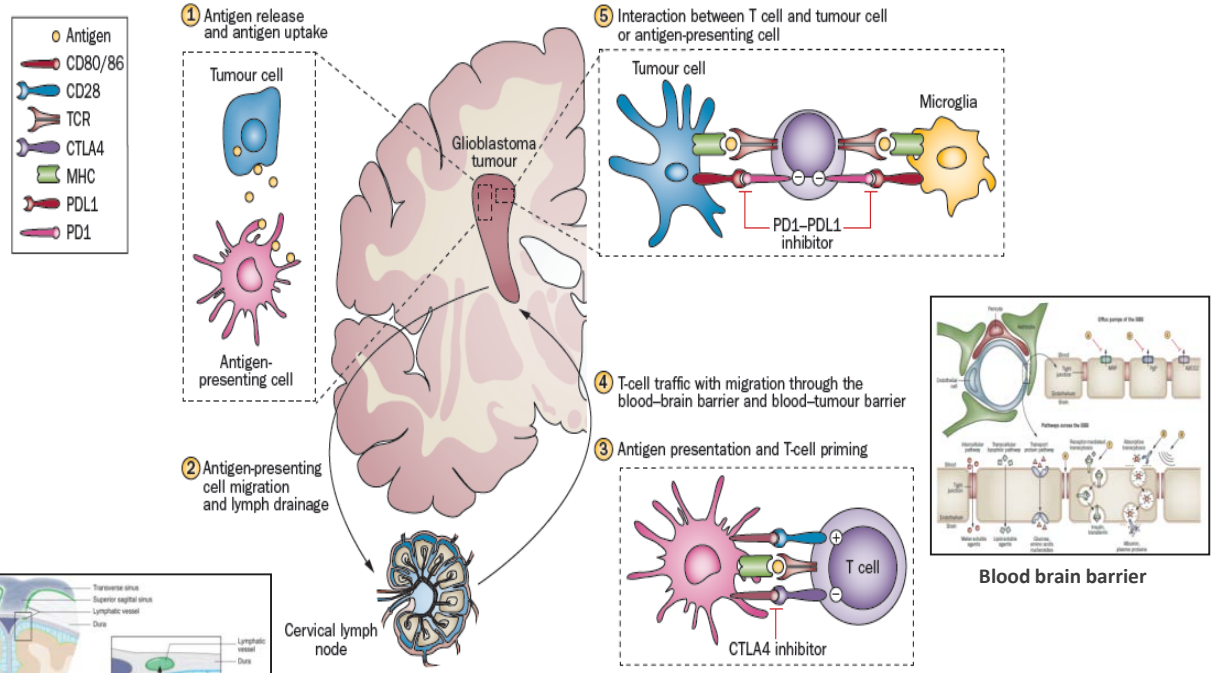
Differences in TME between both tumor locations?

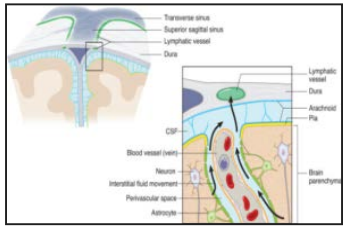
Adverse Event	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Neurologic adverse events, regardless of attribution				
Cognitive dysfunction	7 (17%)	1 (2%)	0	0
Depressed level of consciousness	1 (2%)	0	0	0
Word finding difficulties	1 (2%)	0	0	0
Dizziness	10 (24%)	0	0	0
Headache	15 (36%)	0	0	0
Seizures	2 (5%)	1 (2%)	0	0
Gait imbalance	1 (2%)	0	0	0
Paresthesia	6 (14%)	0	0	0
Peripheral neuropathy	3 (7%)	0	0	0
Focal motor weakness	1 (2%)	0	0	0
Speech difficulty	1 (2%)	0	0	0
Stroke	1 (2%)	1 (2%)	0	0
Tremors	1 (2%)	0	0	0

Toxicity profile was consistent with other previous studies

Goldberg et al. Lancet Oncol 2020

Brain is immunologically “distinct” rather than “privileged”





Lymphatic drainage system

Blood brain barrier

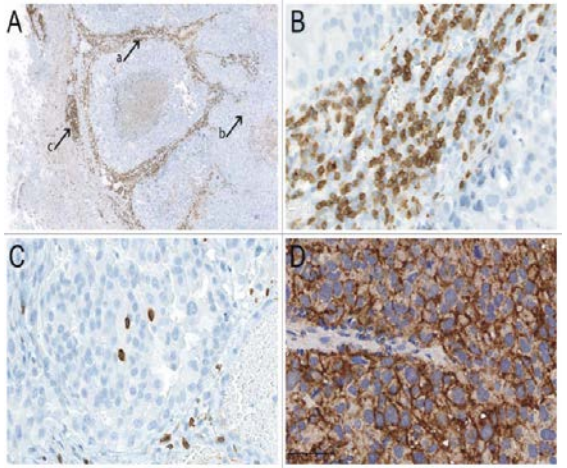
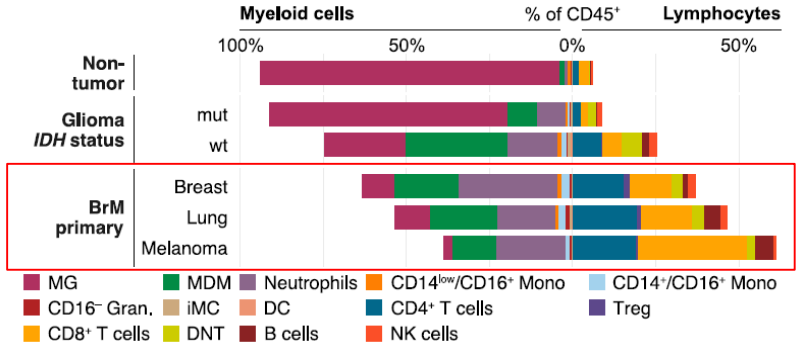


Figure 2. A TIL distribution between different areas (CD3+ TILs, magnification ×5); B TIL density within the tumor stroma (CD3+ TILs, magnification ×200); C TIL density within the solid tumor (CD3+ TILs, magnification ×200); D PD-L1 expression in a melanoma BM (magnification ×200).



Preusser et al. Nat Rev Neurol 2015; Lauveau et al. Nature 2015; Berghoff et al. OncoImmunology 2016, Klemm et al. Cell 2020

Efficacy of ICI monotherapy in patients with advanced NSCLC and BM

Study	ICI	N	Histology	Inclusion criteria	Line	PD-L1	icRR	icDCR	mOS
Prospective data									
Golberg et al	Pembrolizumab	37*	NSCLC	5-20mm diameter, asymptomatic, off steroids	≥1	≥1%	29.7%	40.5%	9.9 m (6.6-29.7)
Retrospective data									
Crinó et al	Nivolumab	409	Non-Sq NSCLC	Asymptomatic, off steroids or stable dose ≤ 10 mg predisone	≥2	All comers	17%	39%**	8.6 m (6.4-10.8)
Molinier et al	Nivolumab	130^	NSCLC	NA	≥2	All comers	12%	37%	6 m (3.8-8.3)
Goldman et al *Pooled analysis Checkmate 017/057*	Nivolumab	46	NSCLC	Pretreated, off steroids or stable dose of ≤ 10 mg predisone	≥2	All comers	NR	33%	4.99 m vs. 3.86 m (HR, NR) 7.61 m vs.7.33 m (HR 1.04)
Hendricks et al	PD1/PD-L1 +/- antiCTLA4	255¨	NSCLC	Undefined	≥1	All comers	27.3%	60.3%	8.6m (6.8-12.0)
Mansfield et al *Pooled analysis Keynote 001, 010, 024, and 042*	Pembrolizumab	293	NSCLC	Pretreated, off steroids and stable	≥1	≥1%	NR	NR	19.7 m vs 9.7 m (HR 0.67)

*57% received prior radiotherapy
**N=74 received concomitant radiotherapy
^74% previously treated with radiotherapy
¨ 39.2% active, 14.3% symptomatic and 27.4% being treated with steroids. icRR and icDCR are calculated over N=73 pts with active BM

Goldberg et al. Lancet Oncol 2020; Crinó et al. Lung Cancer 2019; Molinier et al. J Thorac Oncol 2017; Goldman et al. J Thorac Oncol 2016; Hendricks et al. J Thorac Oncol 2019

Potential clinical prognostic factors in patients with NSCLC-BM treated with ICIs

Table 4. Multivariate Analysis of PFS and OS in the BM Subgroup

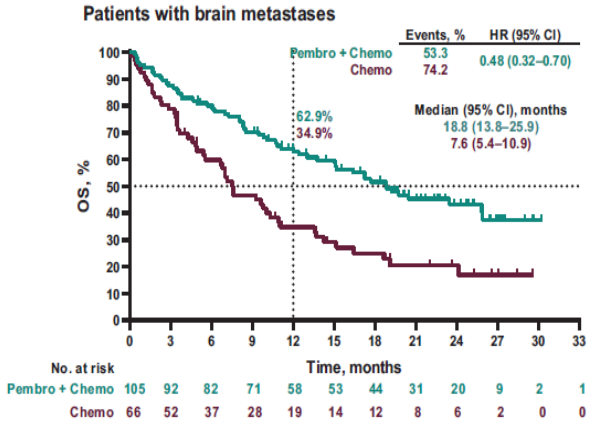
Factor	PFS HR (95% CI)	*p* Value	OS HR (95% CI)	*p* Value
Sex, male vs. female	0.95 (0.68-1.33)	0.765	1.42 (0.94-2.16)	0.100
Smoking, yes vs. no	0.81 (0.40-1.64)	0.561	0.74 (0.34-1.64)	0.464
Histologic type				
Squamous vs. adeno	0.97 (0.60-1.57)	0.99	1.09 (0.63-1.90)	0.750
NSCLC, other vs. adeno	0.98 (0.53-1.83)		0.79 (0.38-1.65)	
No. of organs with metastases, >2 vs. ≤2	1.72 (1.15-2.57)	0.009	1.39 (0.87-2.22)	0.174
ICI treatment line, >2 vs. <2	0.98 (0.70-1.39)	0.922	1.09 (0.73-1.65)	0.671
Use of corticosteroids at start of ICI treatment, yes vs. no	2.78 (1.90-4.08)	<0.0001	2.37 (1.54-3.63)	<0.0001
BMs stable at start ICI, yes vs. no	0.62 (0.44-0.88)	0.007	0.62 (0.41-0.93)	0.019
ds-GPA, 1.5-2.5 vs. 0-1	0.55 (0.38-0.78)	0.004	0.48 (0.31-0.72)	0.002
ds-GPA, 3 vs. 0-1	0.65 (0.31-1.35)		0.54 (0.22-1.32)	

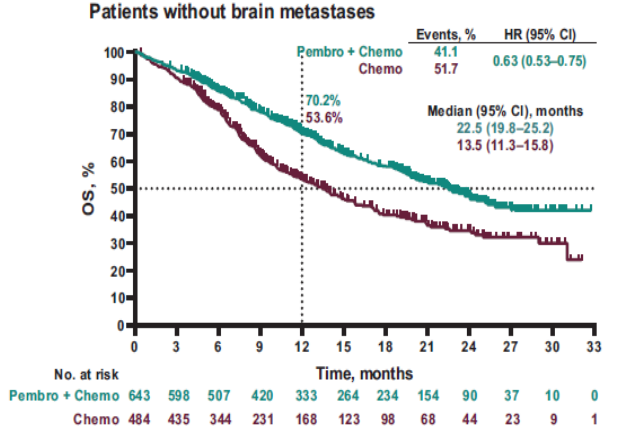
BM, brain metastasis; PFS, progression free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; ICI, immune checkpoint inhibitor; ds-GPA, disease-specific Graded Prognostic Assessment.

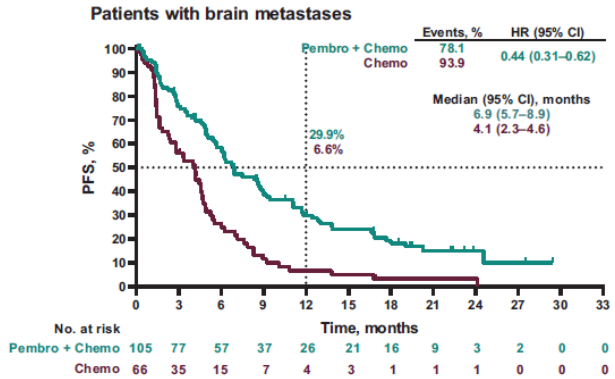
Hendricks et al. J Thorac Oncol 2019

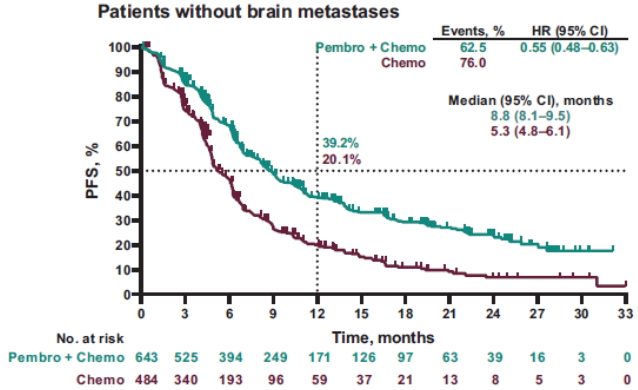
Efficacy of ICI plus Chemotherapy in patients with NSCLC-BM

Pooled analysis of Pembrolizumab plus Platinum-based Chemotherapy trials (Keynote 021 Cohort G, 189 and 407 studies)









- N= 171 (13.2%)
- Only patients with asymptomatic, stable and off steroids BM were included
- 11.5% received previous brain radiotherapy
- BM were not a stratification factor
- BM were considered non-target lesions → No data about icORR

Presence of BM did not increase the rate of treatment-related AEs affecting the nervous system

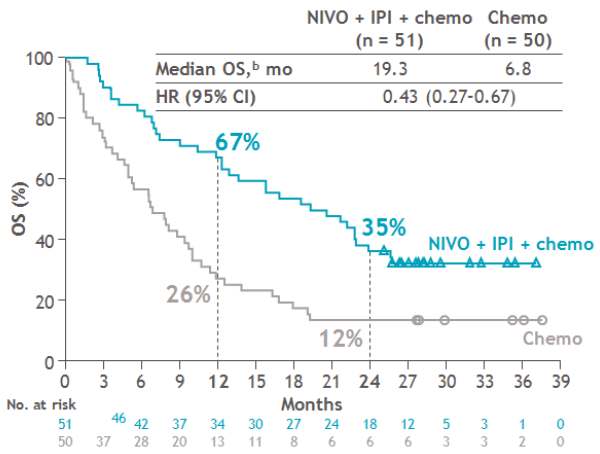
Powell et al. JTO 2021

Efficacy of ICI plus Chemotherapy in patients with NSCLC-BM

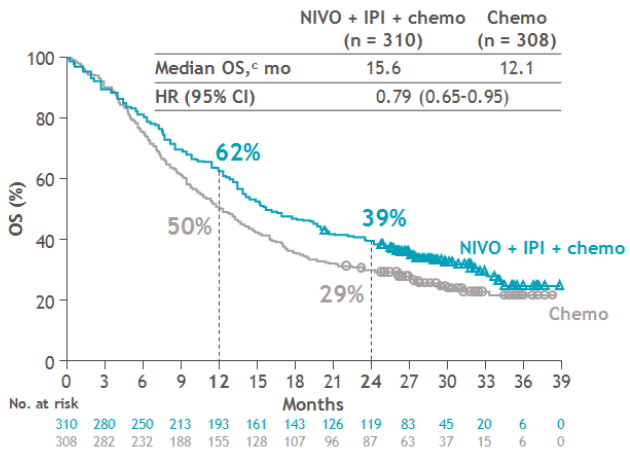
Checkmate 9LA trial: Nivo + Ipi + 2 cycles of Platinum-Based Chemotherapy vs. Chemotherapy

- N= 101 (14%)
- Only pts with previously treated and asymptomatic and ≤ 10mg prednisone daily were included
- BM were not a stratification factor
- Baseline Brain MRI/CT was mandatory
- Intracranial efficacy was reported using modified RECIST v1.1

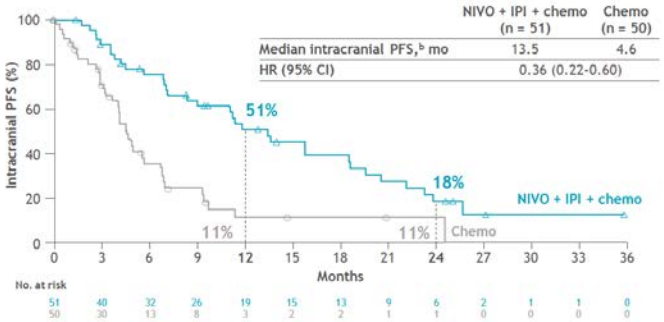
With baseline brain metastases



Without baseline brain metastases



Intracranial PFS[a] in patients with baseline brain metastases



Intracranial response	NIVO + IPI + chemo (n = 51)	Chemo (n = 50)
ORR, n (%)	20 (39)	10 (20)
BOR,[b] n (%)		
CR	5 (10)	4 (8)
PR	15 (29)	6 (12)
SD	18 (35)	18 (36)
PD	1 (2)	3 (6)
DCR, n (%)	38 (74)	28 (56)
Median time to response, mo (range)	2.8 (1.3-11.4)	2.2 (1.3-5.8)
Median DOR, mo (95% CI)	22.3 (9.7-NR)	18.9 (1.8-NR)

Carbonne et al. WCLC 2021

Efficacy of ICI plus Chemotherapy in patients with NSCLC-BM

A 1st line, single arm, phase II trial with carboplatin-pemetrexed plus atezolizumab

ATEZO-BRAIN Trial Design

Single arm phase II clinical trial

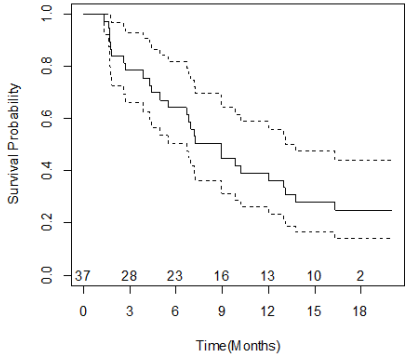
Key Elegibility Criteria:
Stage IV non-squamous NSCLC
Untreated brain metastases
Treatment naïve
EGFR/ALK negative, any PD-L1
ECOG PS 0-1
Anticonvulsivants and dexemathasone ≤ 4 mg qd allowed

Carboplatin (5 AUCs) + Pemetrexed 500mg/m² + Atezolizumab 1200mg Q3W for 4-6 cycles → **Pemetrexed 500mg/m2 + Atezolizumab 1200mg Q3W until tumor progression (*), unacceptable toxicity or 2 years**

Tumor evaluation by body CT scan and brain MRI Q6W until the 12th week and thereafter Q9W until PD

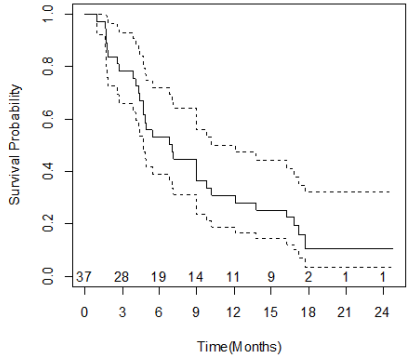
(*) If exclusive CNS PD, patients could continue on study after brain RT

Systemic PFS by RECIST v1.1



Median PFS = 8.9 months (95% CI 6.7- 13.8)
18 months PFS rate = 24.9%

Brain PFS by RANO-BM



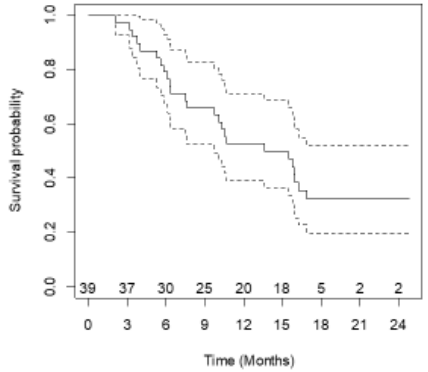
Median icPFS = 6.9 months (95% CI 4.7 – 12.1)
18 months icPFS rate = 10.4%

ORR

	Best Brain Metastasis Response (RANO-BM)	Best Systemic Response (RECIST v1.1)
CR	4 (10%)	0
PR	12 (30%)	19 (47.5%)
SD	19 (47.5%)	16 (40%)
PD	4 (10%)	3 (7.5%)
NE	1 (2.5%)	2 (5%)

Only 4 patients had discordance among systemic and CNS response:
- 2 with PD in body and SD in brain
- 2 with PD in brain and PR in body

Overall Survival

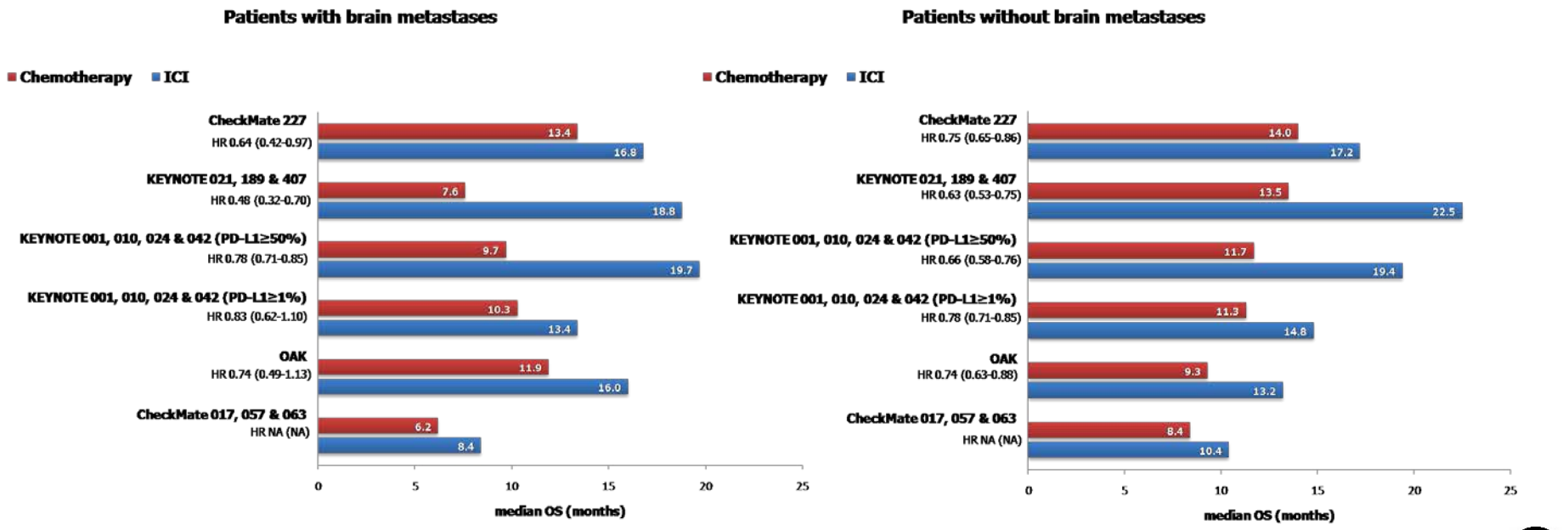


Median OS = 13.6 (95% CI 9.7 – NR)
2y OS rate = 32%

Nadal E et al. WCLC 2021

OS among patients with and without BM in clinical trials with ICIs

ICI had substantial improvement in clinical outcomes (OS, PFS and ORR) versus chemotherapy alone in patients with advanced NSCLC irrespective of the presence of baseline BM

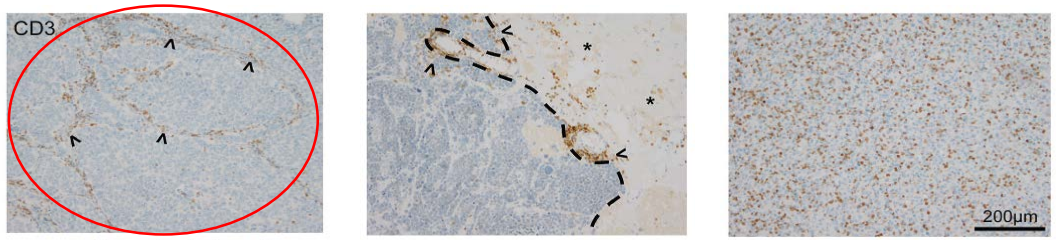


- Low percentage of patients with BM included (~15%)
- Exploratory analysis → Limited prospective data
- Almost all patients with BM included were previously treated (some exceptions Keynote 189 and 407)
- Limited data about intracranial efficacy and potential reduction about the risk of BM development

Vilariño et al. Cancer Treat Rev 2021

Immune-suppressive phenotype in NSCLC-BM

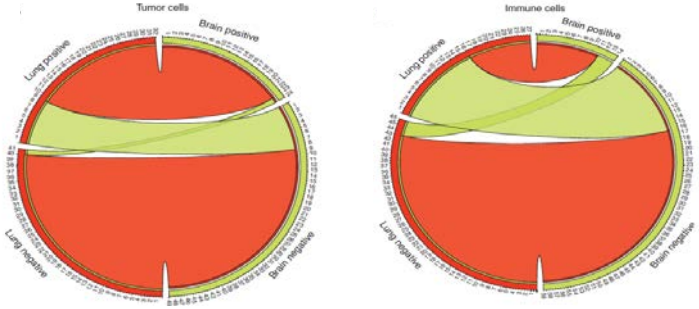
TILs distribution in the perivascular area



perivascular / stromal | peritumoral | diffuse

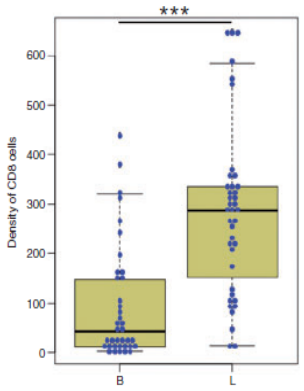
Lower expression of PD-L1 and CD8 than lung primary tumors

PD-L1 expression by IHC



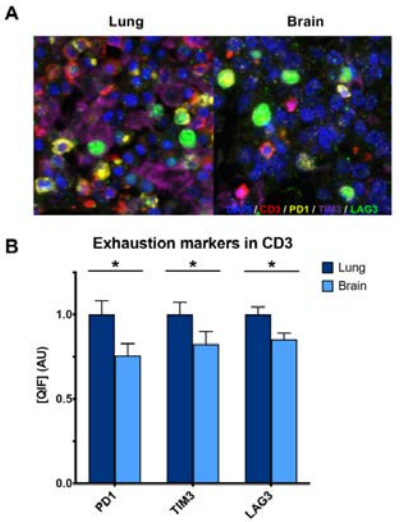
PD-L1 evaluation (≥5%/E1L3N)	PT (%)	BM (%)	Discordance
Immune cells	37%	19%	26% (*k* 0.38)
Tumor cells	44%	33%	14% (*k* 0.71)

Density of CD8 cells by IHC



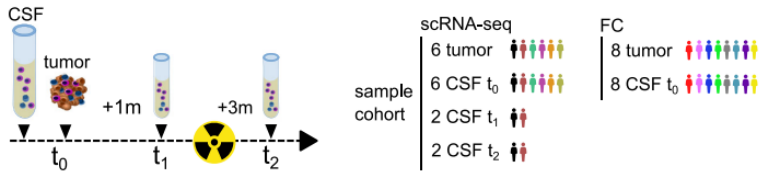
Brain metastases (B) and primary lung tumors (L) ***P<0.001.

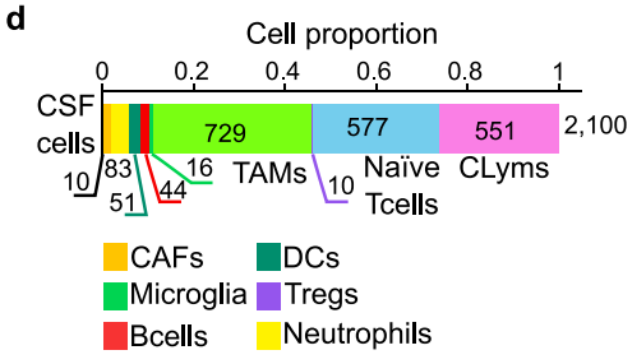
High expression of exhaustion markers

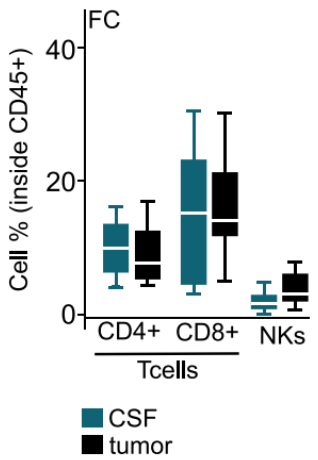


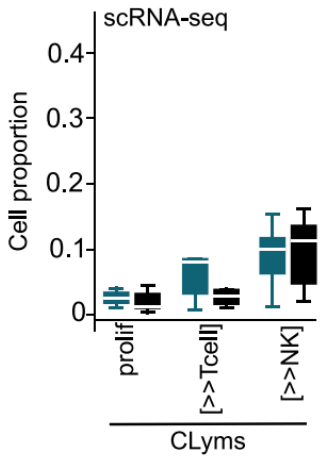
Harter et. al, Oncotarget 2015; Mansfield et al. Ann of Oncol 2016; Kudo et al. Annals of Oncology 2019; Lu BY et al. J for Immunother of Cancer 2021

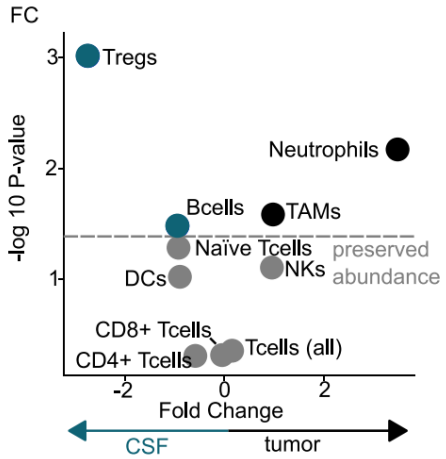
New approaches for immune-phenotype characterization in BMf











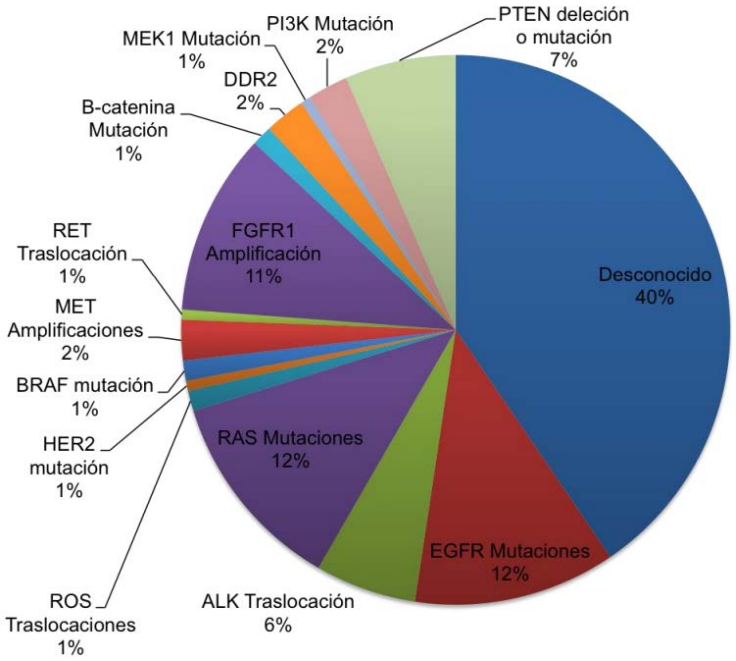
CD8+ T and NK cell abundance was similar in the tumor and CSF both by scRNA-seq and flow-cytometry

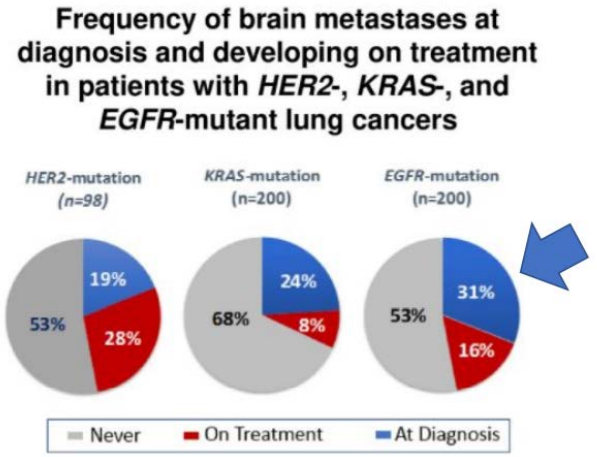
Rubio-Pérez C et al. Nature Communications 2021

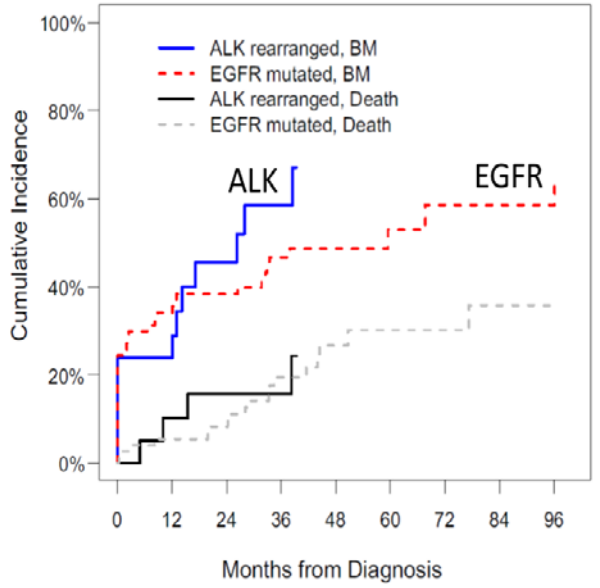
Conclusions: Immunotherapy and NSCLC-BM

- The optimal management of these patients should be based on a multidisciplinary decision
- The efficacy of ICI in patients with NSCLC and BM seems to be promising but still limited
- Scarce data about the BM immune-phenotype is available (limited available tissue and limited number of studies)
- Lower levels of CD8+ TILs and PD-L1 expression were found in BM compared to matched NSCLC primary tumors
- More efforts should be done for a better understanding about the biology of these complication and this unique microenvironment and apply this knowledge to generate new therapeutic strategies

Oncogene-addicted NSCLC patients with BM



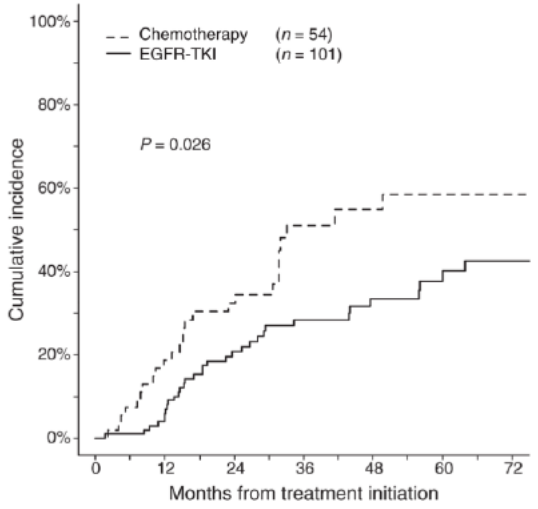


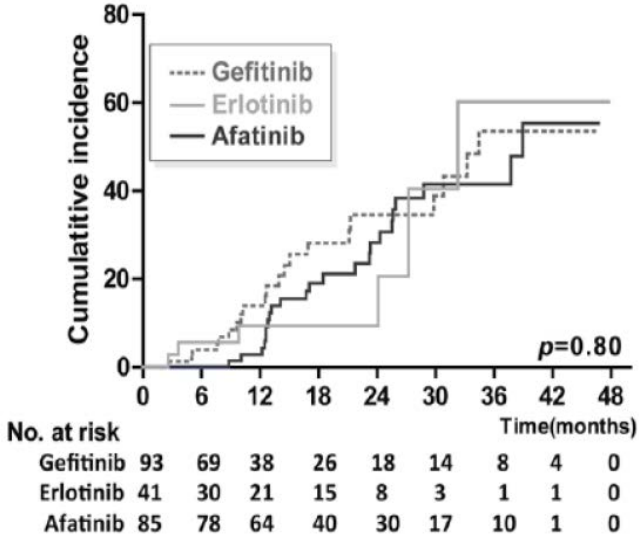


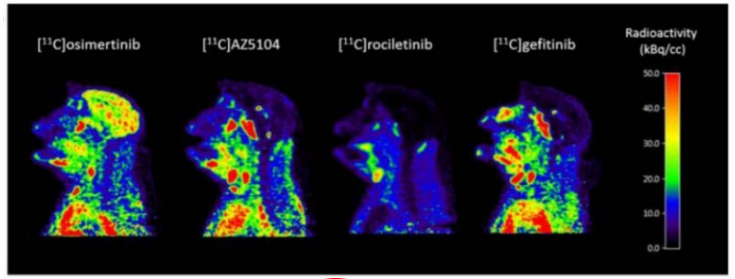
Barlesi et al. Lancet 2016; Kris et al. ASCO 2018; Rangachari et al. Lung Cancer 2016

EGFR+ NSCLC-BM patients population; efficacy of 1st and 2nd generation EGFR-TKIs

- Better activity in the CNS with 1stand 2ndgeneration TKIs compared to chemotherapy
- Retrospective data suggested similar intracranial efficacy between 1st and 2nd generation EGFR-TKIs







	Osimertinib	Gefitinib	Rociletinib	Afatinib
Dose (mg/kg)	25	6.25	100	7.5
Plasma C_{max} (μmol/L)	0.82	0.82	3.32	0.14
Brain C_{max} (μmol/L)	2.78	0.17	BLQ	BLQ
Brain/plasma C_{max} ratio	3.41	0.21	<0.08	<0.36

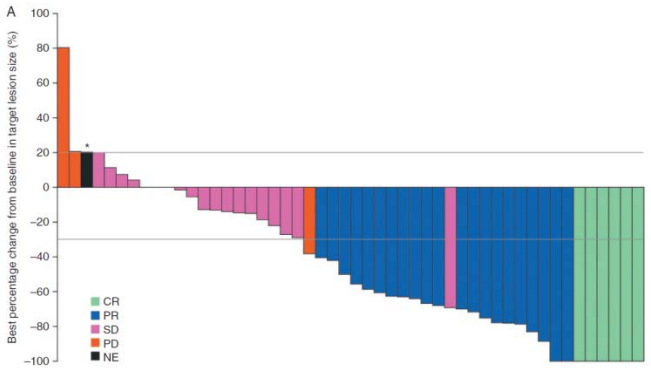
NOTE: Doses equivalent to clinical doses or reported previously.
Abbreviation: BLQ, below limit of quantification (rociletinib 0.25 μmol/L, afatinib 0.05 μmol/L); C_{max}, maximum plasma concentration.

Heon et al. Clin cancer Res an Off J Am Assoc Cancer Res. 2012; Su et al. Ther Adv Med Oncol. 2018; Ballard et al. Clin Cancer Res 2016

EGFR+ NSCLC-BM patients population: efficacy of 3rd generation EGFR-TKI in 2L→Osimertinib vs. platinum-based Chemo

Pooled data from phase II studies (AURA extension and AURA2)

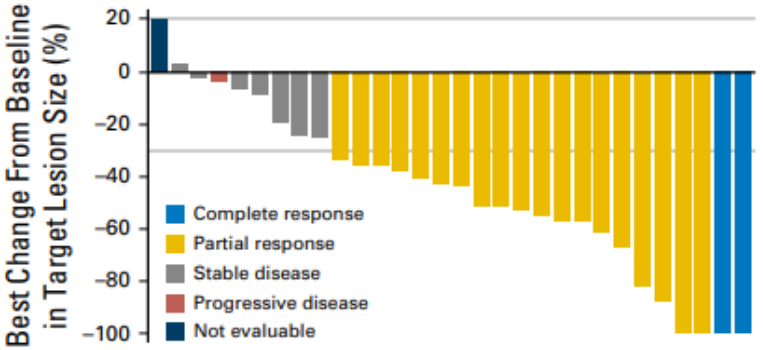
N= 128 (50 with measurable disease)
Only patients with asymptomatic and stable BM were included



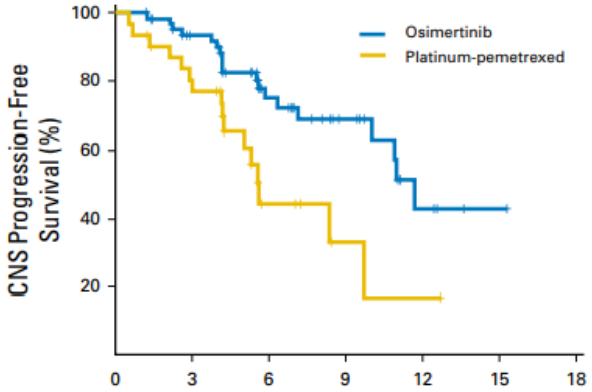
CNS ORR 54% (39%-68%)

Phase III: AURA3 trial

N= 116 (46 with measurable disease)
Only patients with asymptomatic and stable BM were included



CNS ORR 70% (51%-85%) vs 31% (11% -59%)
Prior brain RDT → CNS ORR 37%



icPFS 11.7 m vs 5.6 m
(HR 0.32, 95% CI 0.15-0.69) p=0 .004

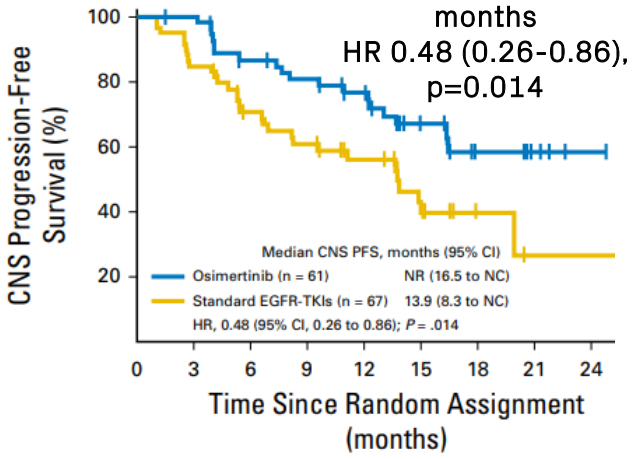
Goss et al. Ann of Oncol 2018; Wu et al. JCO 2018

EGFR+ NSCLC-BM patients population: efficacy of 3rd generation EGFR-TKI in 1L→Osimertinib vs. standard EGFR-TKI

Phase III: FLAURA trial

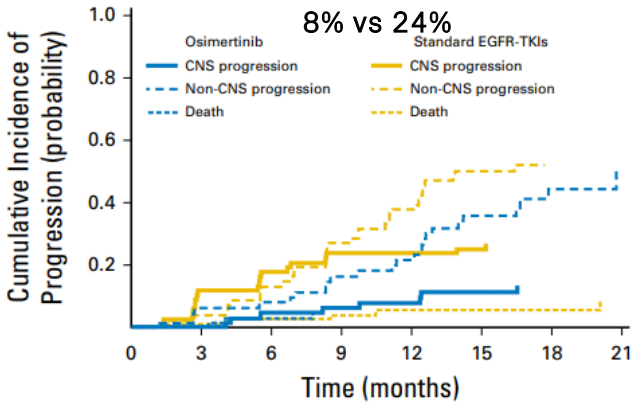
- N =128/556 (23%) were included
- BM permitted if clinically stable , asymptomatic or previously treated and off of steroids
- Brain scans were not mandatory
- Prior brain radiotherapy was administered in 25% and 24% of pts in the osimertinib and standard-TKI arm respectively

CNS PFS NR vs 13.9 months
HR 0.48 (0.26-0.86), p=0.014

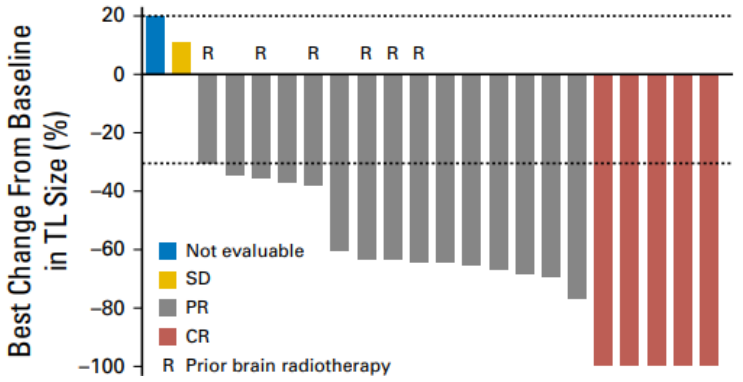


Median follow-up for CNS PFS was 12.4 months in the osimertinib arm and 7.0 months in the standard EGFR-TKI arm

Risk of CNS progression at 12 months
8% vs 24%



CNS ORR was 91% and 68%

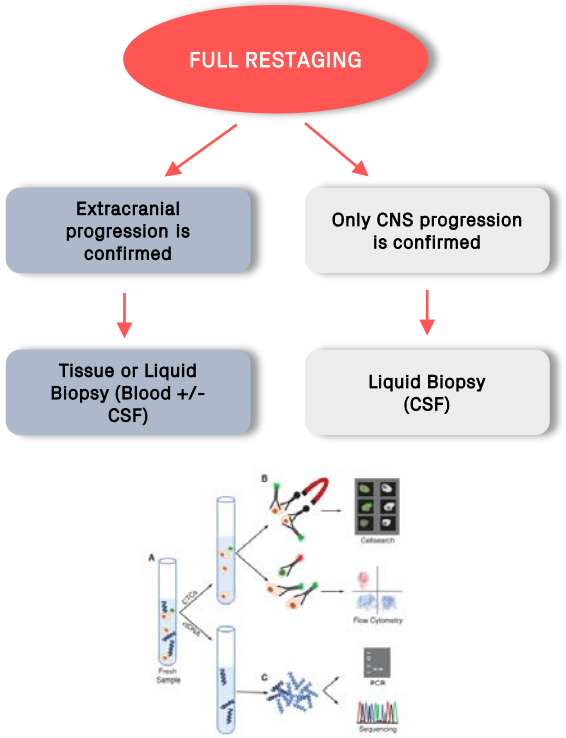


Median best percentage change from baseline in CNS TL size was 64% with osimertinib

Reungwetwattana et al. JCO 2018

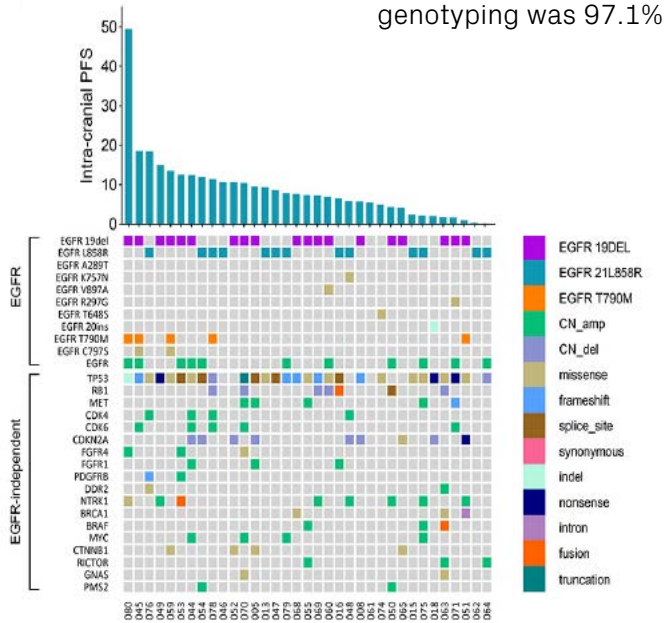
CNS progression after Osimertinib a challenging decision

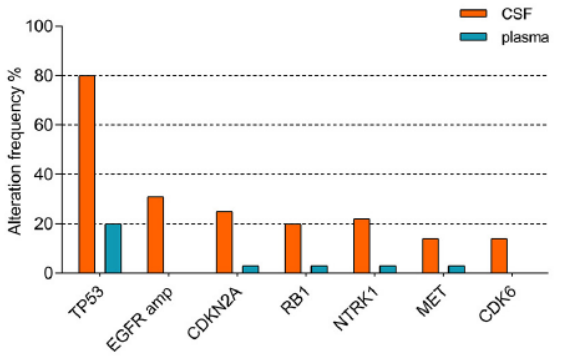
Resistance mechanisms may differ between CNS and extra CNS metastases/plasma



Resistance mechanisms in patients with LM to osimertinib (N=35)

The detection rate of EGFR mutations by CSF and plasma genotyping was 97.1% and 57.6%, respectively



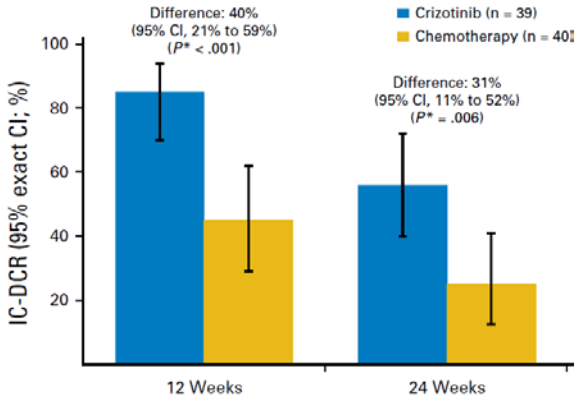


The most frequently detected concurrent genes in CSF were TP53, EGFR amplification and CDKN2A

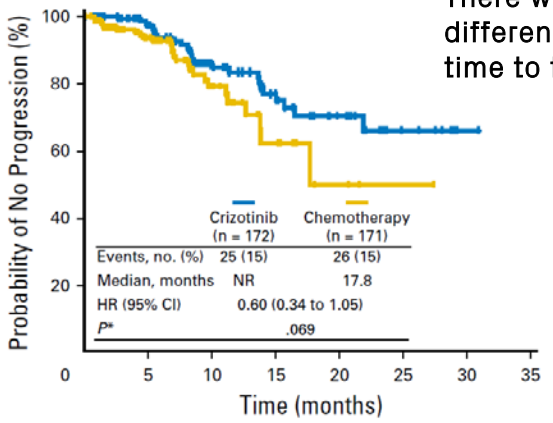
Piper Vallillo et al. JCO 2020; Zheng et al. JTO 2021

ALK+ NSCLC-BM patients population: efficacy of 1st and next generation ALK-TKIs

Phase III PROFILE 1014



icDCR was significantly higher with crizotinib than with chemotherapy



There was no significant difference in intracranial time to tumor progression

Promising CNS activity of next-generation ALKi after progressing to crizotinib

Trial Name	Experimental arm (vs. Chemo *)	N° of pts with measurable BM	icORR %	mDICR months
ASCEND 5	Ceritinib	17	**35**	6.9
ALLUR	Alectinib	24	**54.2**	NR
ALTA	Brigatinib 90mg/day Brigatinib 180mg/day	26 18	**50** **67**	9.4 (3.7-24.9) 16.6 (3.7-NR)

* Exception ALTA trial

Solomon et al. JCO 2016; Shaw et al. Lancet 2017; Novello et al. Ann Oncol 2018; Huber et al. JTO 2020

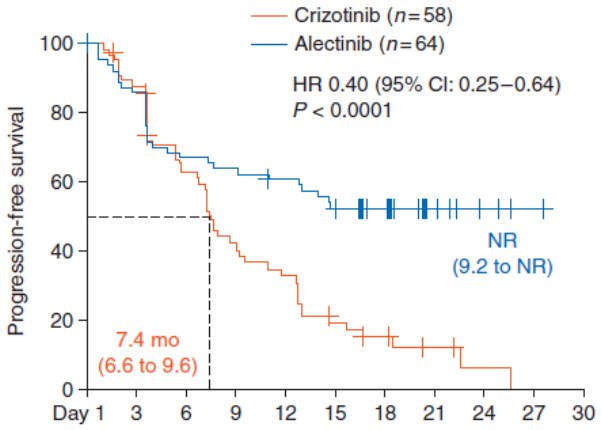
ALK+ NSCLC patients with BM: efficacy of 2nd generation ALK-TKI in 1L→alectinib vs crizotinib

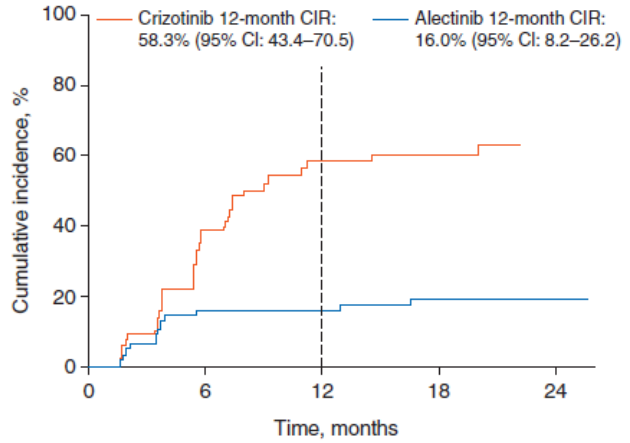
Phase III: ALEX trial

- N =122 (40%) of pts with BM
- Patients with asymptomatic BM (treated/untreated) were permitted
- 37.7% of pts received prior brain radiotherapy
- BM were a stratification factor
- Brain imaging was conducted in all patients at baseline and every subsequent 8 weeks

Patients with measurable CNS lesions at baseline

	Alectinib (n=21)	Crizotinib (n=22)
CNS responders, n (%) (95% CI)	17 (81) (58–95)	11 (50) (28–72)
CNS CR, n (%)	8 (38)	1 (5)
Median DoR, months (95% CI)	17.3 (14.8–NE)	5.5 (2.1–17.3)





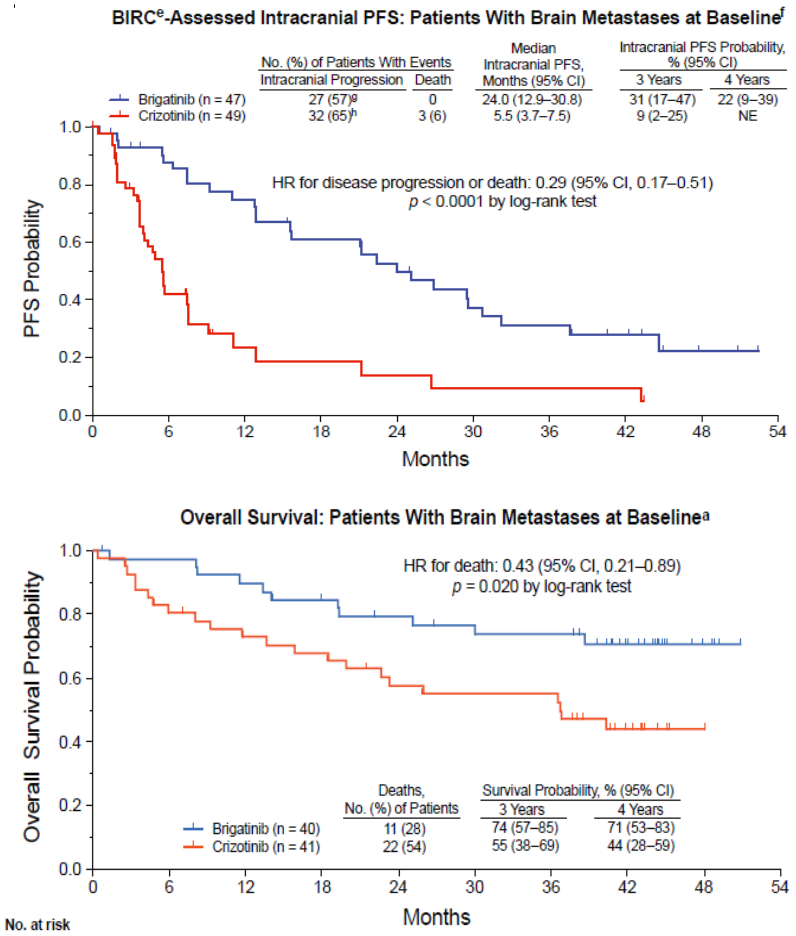
Peters et al. NEJM 2017; Gadgeel et al. Ann of Oncol 2018

ALK+ NSCLC patients with BM: efficacy of 2nd generation ALK-TKI in 1L→brigatinib vs crizotinib

Phase III: ALTA 1L trial

- **N =81 (29%) of patients with BM**
- Patients with asymptomatic BM (treated/untreated) were permitted
- 13% of pts received prior brain radiotherapy
- BM were a stratification factor
- Brain imaging was conducted in all patients at baseline and at each tumor evaluation
- Crossover was permitted

Variable	Brigatinib	Crizotinib	Odds Ratio (95% CI)
Patients with measurable brain metastases at baseline, as assessed by blinded independent review†			
No. of patients	18	21	
Confirmed intracranial objective response			
No. of patients	14	6	
% (95% CI)	78 (52–94)	29 (11–52)	10.42 (1.90–57.05)
Intracranial complete response — no. (%)	2 (11)	0	
Intracranial partial response — no. (%)	12 (67)	6 (29)	



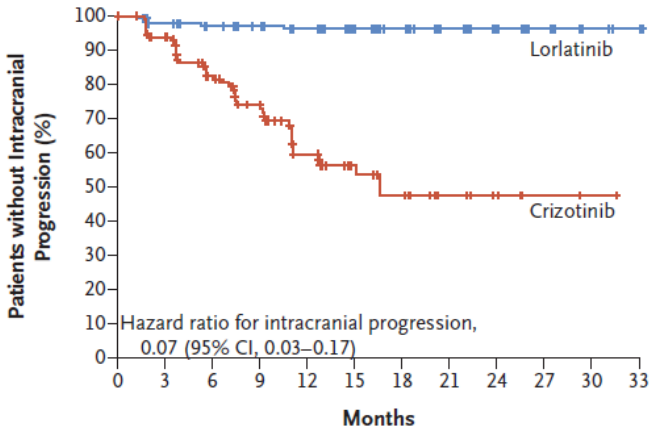
Camidge et al. NEJM 2018; Camidge et al JTO 2021

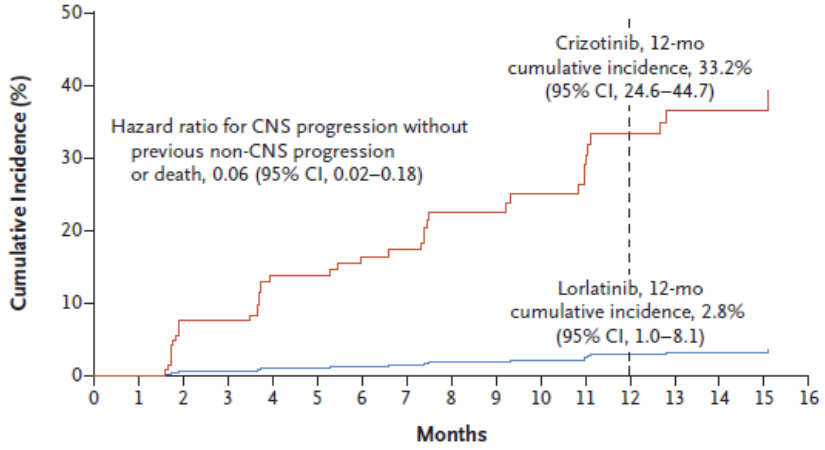
ALK+ NSCLC patients with BM: efficacy of 3rd generation ALK-TKI in 1L→lorlatinib vs crizotinib

Phase III: Crown trial

- N =78 (26.3%) of pts had BM
- 6% of patients received previous radiotherapy
- Asymptomatic treated or untreated CNS metastases were eligible
- BM were a stratification criteria
- Brain imaging was mandatory at baseline and at each tumor assessment

Variable	Lorlatinib	Crizotinib	Odds Ratio (95% CI)
Patients with measurable brain metastases at baseline			
No. of patients	17	13	
Confirmed CNS response			
No. of patients	14	3	
% (95% CI)	82 (57–96)	23 (5–54)	16.83 (1.95–163.23)
CNS complete response — no. (%)	12 (71)	1 (8)	
Median duration of response (95% CI) — mo	NE (NE–NE)	10.2 (9.4–11.1)	
Median time to tumor response (IQR) — mo	1.9 (1.8–3.5)	1.9 (1.8–1.9)	





Shaw et al. NEJM 2020

ALK+ NSCLC patients with BM: efficacy of lorlatinib after 2nd generation ALK-TKI

A phase II study (NCT01970865) →N= 198 patients with ALK+ NSCLC with ≥ 1 prior ALK TKI were treated with lorlatinib
Expansion cohorts (EXP) were defined based on treatment history → EXP 3B patients treated with only 1 2nd generation ALK-inhibitor

Intracranial efficacy

	≥1 prior second-generation ALK TKI (EXP3B-5)	1 prior second-generation ALK TKI (EXP3B)	≥2 prior ALK TKIs (EXP4-5)
Intracranial with ≥1 measurable CNS lesion			
N	57	9	48
IC-ORR, *n* (%)	32 (56.1)	6 (66.7)	26 (54.2)
95% CI	42.4-69.3	29.9-92.5	39.2-68.6
Best overall response, *n* (%)			
Complete response	12 (21.1)	2 (22.2)	10 (20.8)
Partial response	20 (35.1)	4 (44.4)	16 (33.3)
Stable disease/no response	16 (28.1)	0	16 (33.3)
Progressive disease	6 (10.5)	2 (22.2)	4 (8.3)
Indeterminate	3 (5.3)	1 (11.1)	2 (4.2)
Duration of IC objective response,[a] months			
Median	12.4	20.7	12.4
95% CI	6.0-37.1	4.1-37.1	6.0-16.7

Limitations:
- No data about the type of radiotherapy previously administered
- No data about brain metastases-related symptoms

Low data and modest efficacy have been reported with other 2nd generation ALK-TKI, after alectinib progression

Solomon et al. Lancet Oncol 2018; Felip et al. Ann of Oncol 2021

Other drivers and NSCLC patients with BM

ROS 1

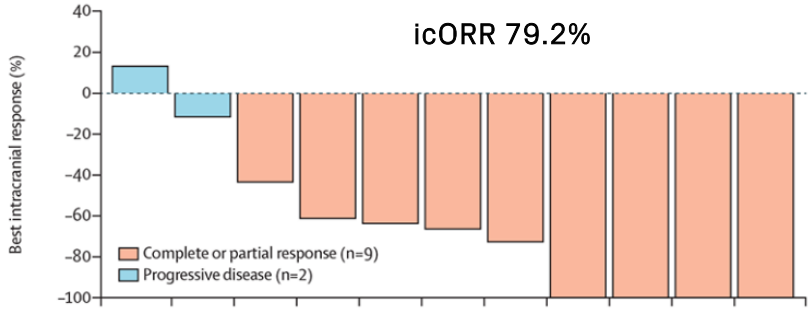
1–2% of NSCLC

36% of pts with ROS1-positive NSCLCs have BM at the diagnosis of metastatic disease

- Crizotinib is the standard 1st line treatment -> however suboptimal CNS penetration has been observed
- Recently Lorlatinib and also entrectinib have shown remarkable intracranial activity in both ROS1i-naive and crizotinib-pretreated pts

	TKI-naive	Previous crizotinib only
Intracranial		
Number of patients with baseline CNS metastases§	11	24
Best overall intracranial response		
Complete response	5 (45%)	9 (38%)
Partial response	2 (18%)	3 (13%)
Stable disease	2 (18%)	6 (25%)
Objective progression	2 (18%)	2 (8%)
Indeterminate*	0	4 (17%)
Patients with confirmed intracranial objective response	7 (64%)	12 (50%)
95% CI†	31–89	29–71
Duration of intracranial response, months, median (95% CI‡)	NR (5·7–NR)	NR (11·0–NR)

icORR
64% and 50%



Shaw et al. Ann of Oncol 2019; Shaw et al. Lancet Oncol 2019; Drilon et al. Lancet Oncol 2020

Other drivers and NSCLC patients with BM

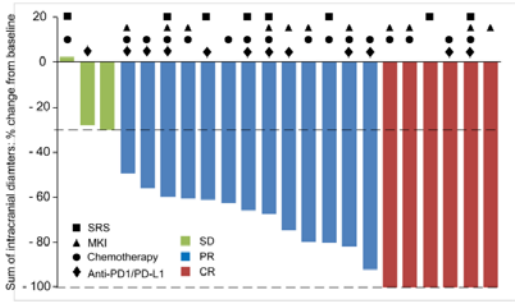
RET fusions

1–2% of NSCLC

BM frequently occur in this population (25% at tumor diagnose) with an approximate 50% lifetime prevalence reported

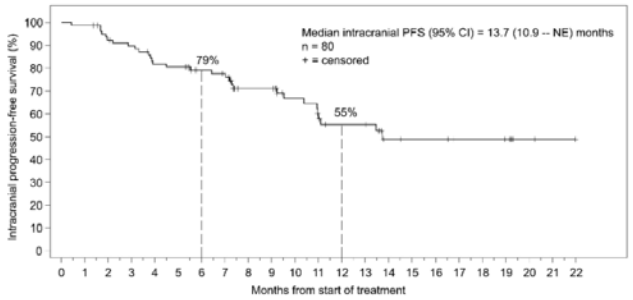
- LIBRETO-001 and ARROW Phase I/II trials with selpercatinib and pralsetinib have shown preliminary promising intracranial activity

icORR was 82% → 23% CR and 59% PR

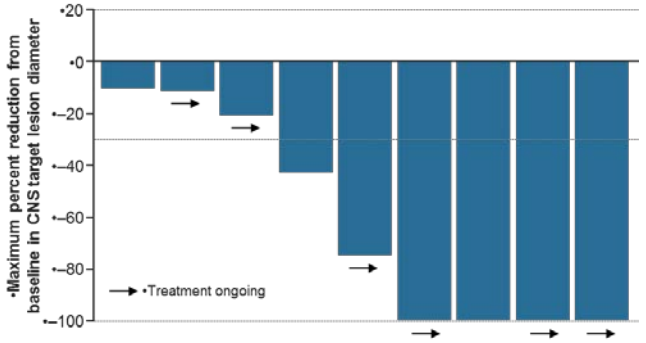


*15% (80/531) pts presented BM at study entry
Pts heavily pretreated (median=2 systemic therapies, range=0–10) 56% of pts received intracranial radiation (14% WBRT, 45% SRS)

Intracranial PFS was 13.7 months



icORR was 56%→ 33% CR



Drilon A. et al. Nat. Rev. Clin. Oncol 2018; Subbiah V. et al. CCR 2021; Gainor J et al. ASCO 2020

Conclusions: Targeted Therapies and NSCLC-BM

- The optimal management of patients with Oncogene-addicted NSCLC and BM should be based on a multidisciplinary decision
- Frequency of BM is high in patients with oncogene-addicted NSCLC patients at diagnoses and during the course of the disease
- For patients with EGFR + and ALK+ NSCLC and BM 3rd and 2nd generation TKIs (respectively) are the preferred 1st option
- New targeted therapies, such as entrectinib for NTRK+ or ROS1+ and selpercatinib or praseltinib for RET+ NSCLC have shown promising intracranial activity
- Resistance mechanisms may differ between CNS and extra CNS metastases
- At progression, a new biopsy (tissue + blood +/- CSF) will be performed wherever possible to guide subsequent treatment

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