

Case 6: Stage IV NSCLC With Brain Metastases

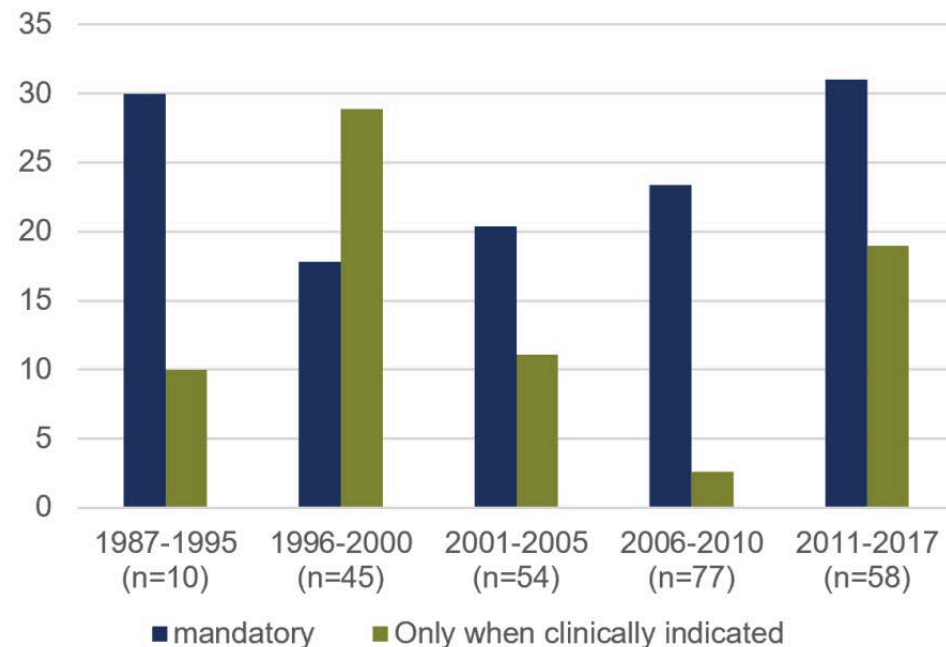
- A 57-year-old woman is incidentally found to have a 4 cm lung mass and multiple lung nodules on CT chest/abdomen/pelvis
- An MRI of brain identifies 3 brain metastases and the patient is asymptomatic from these
- The patient's tumor has a PD-L1 score of 60%
- Her ECOG PS is 1
- Molecular testing results reveal no actionable genomic alteration

- **What is the optimal next step?**

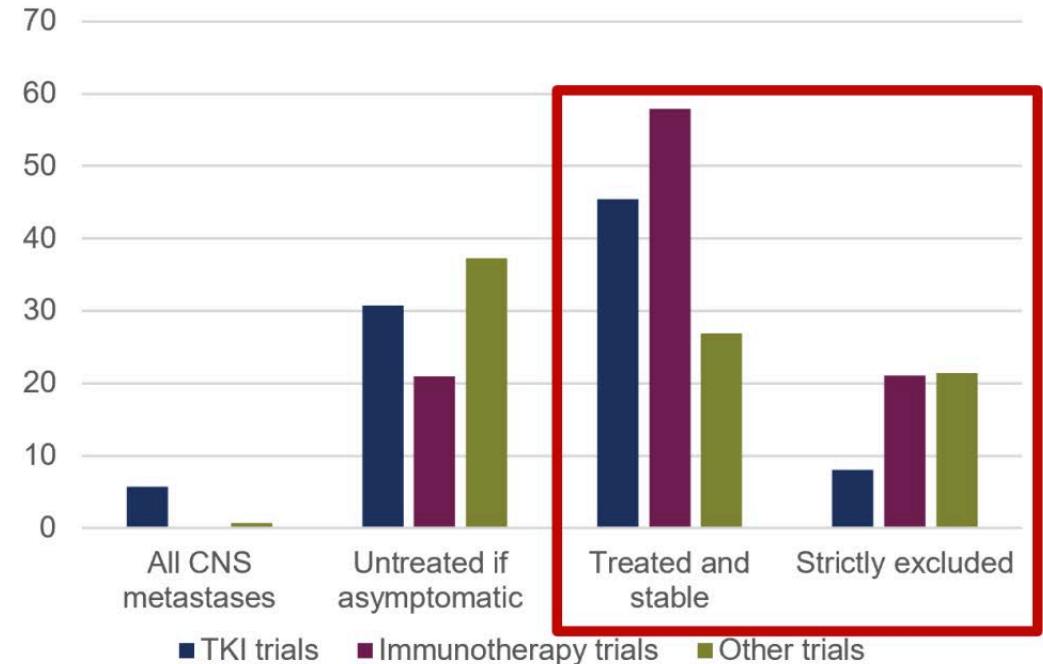
Unmet Need: Brain Metastases Gaps in Knowledge

Systematic review on NSCLC BM in phase II/III TKI or phase III ICI trials (2000-2020)

Baseline screening for CNS mets over time



CNS eligibility criteria per type of drug



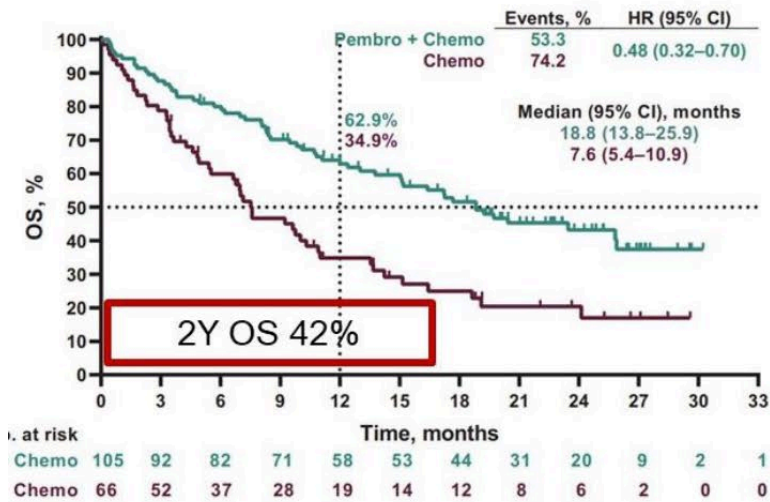
Only 4% prespecified CNS related endpoint

Brain Metastases

Chemo-ICI (+/-ICI) Data in 1L NSCLC

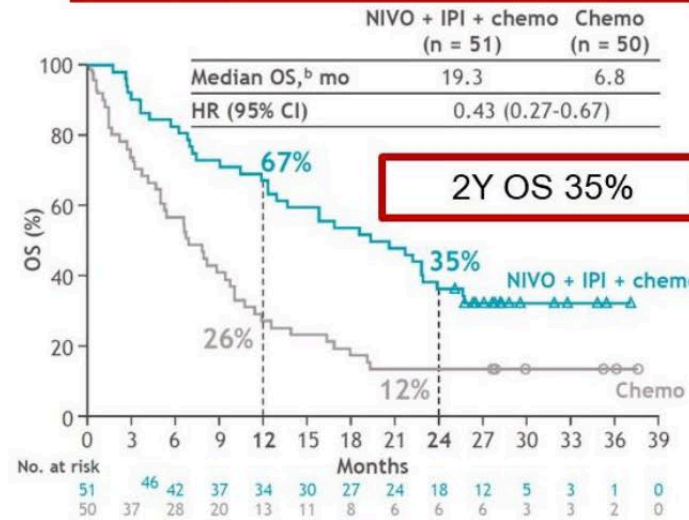
TREATED & UNTREATED BM

KEYNOTE 021-189-407 pooled
Chemo-ICI vs chemo



TREATED BM

CheckMate 9LA
Chemo-ICI-ICI vs chemo



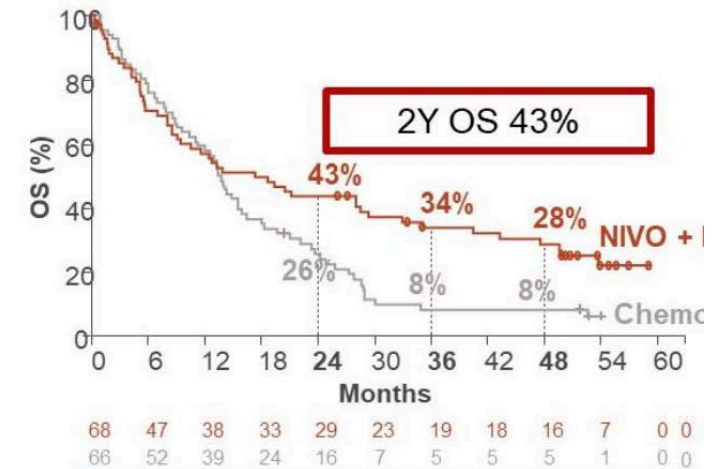
2Y OS 35%

icPFS 13.5 vs 4.6 months (HR 0.36)

New BM 16% vs 30%

Time to new BM 9.0 vs 4.6 months

CheckMate 227
ICI-ICI vs chemo



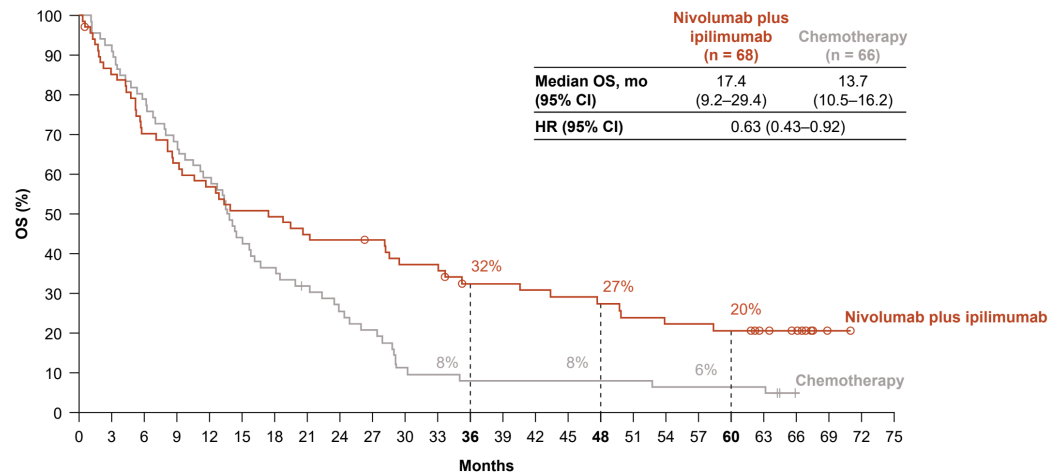
2Y OS 43%

icPFS 8.6 vs 8.7 months (HR 0.80)

New BM 4% vs 20%

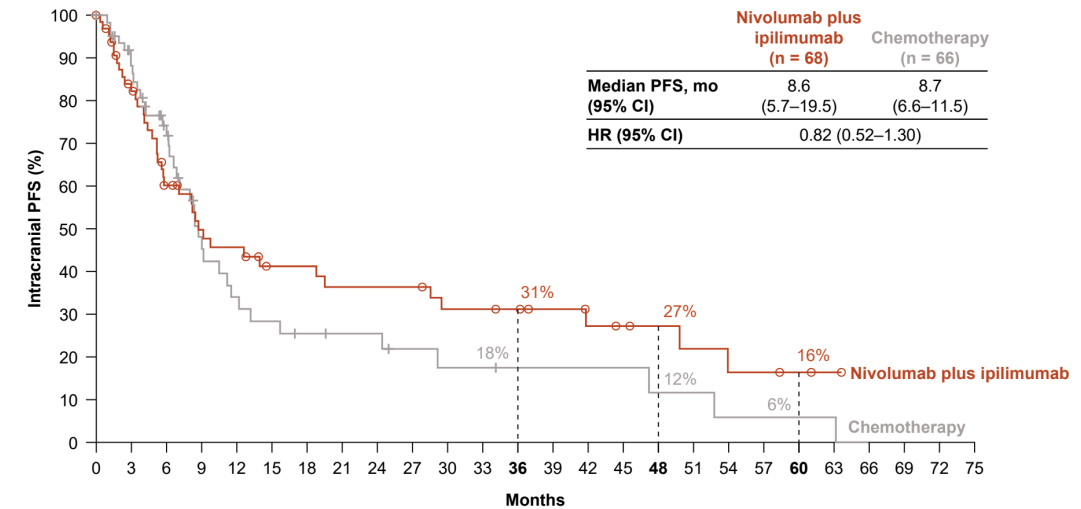
Time to new BM 4.0 vs 7.1 months

CheckMate 227 Part 1: 5-Year OS and icPFS in Patients With Baseline Brain Metastases



No. at risk

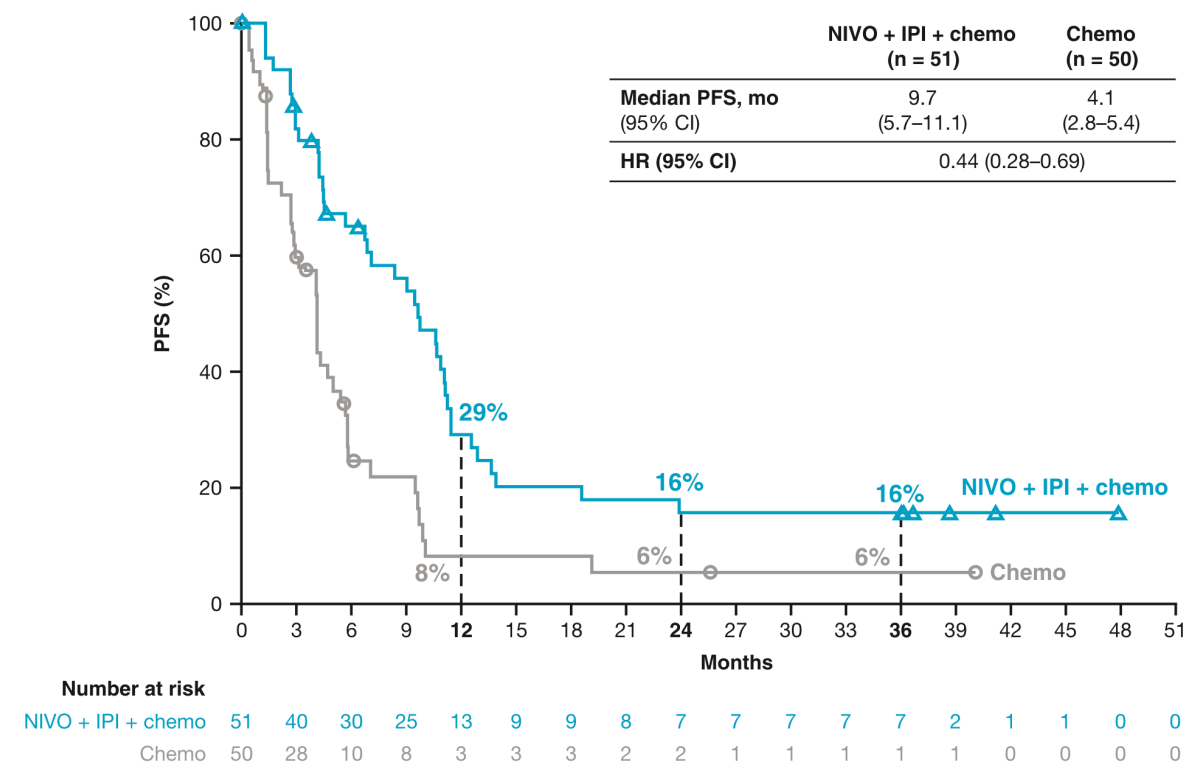
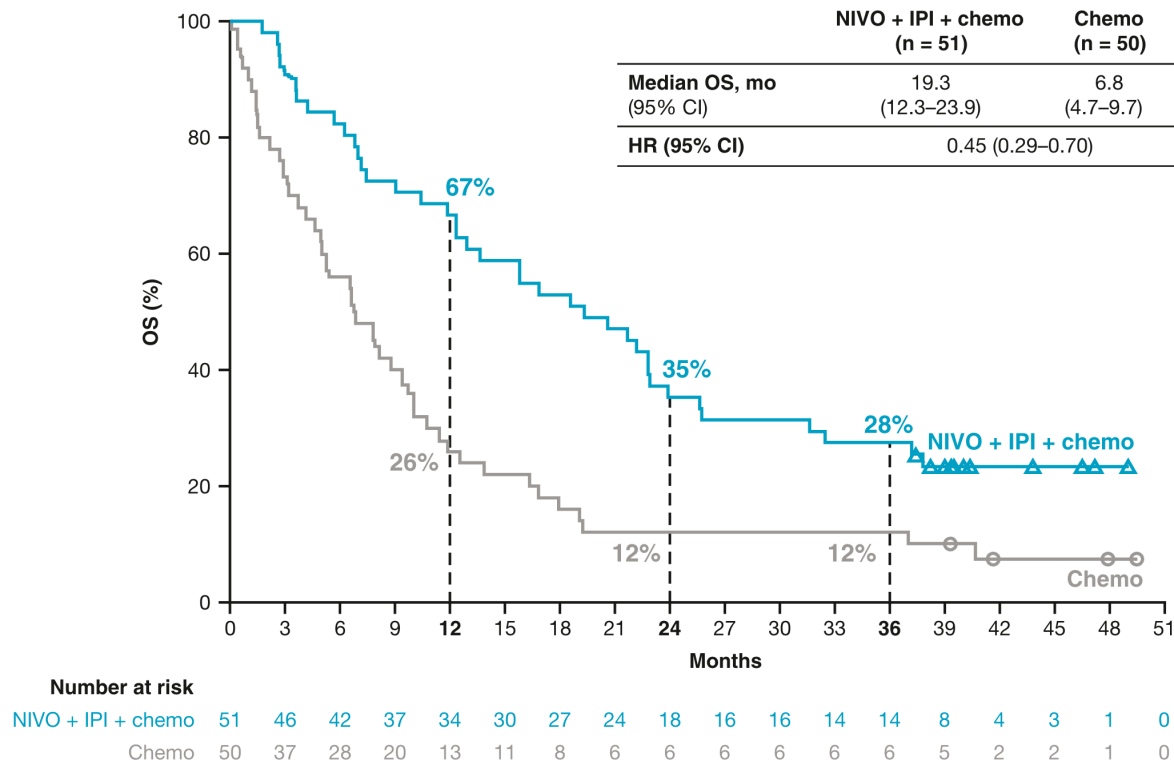
Nivolumab plus ipilimumab	68	57	47	42	38	34	33	30	29	28	24	24	19	19	18	17	16	14	13	13	12	9	7	1	0	0
Chemotherapy	66	60	52	45	39	29	24	20	16	13	7	6	5	5	5	5	5	4	4	4	4	4	0	0	0	0



No. at risk

Nivolumab plus ipilimumab	68	47	31	24	22	17	17	15	15	15	12	12	11	9	7	6	5	4	3	3	2	1	0	0	0	0
Chemotherapy	66	47	30	17	12	10	8	7	7	5	4	4	3	3	3	3	2	2	1	1	1	1	0	0	0	0

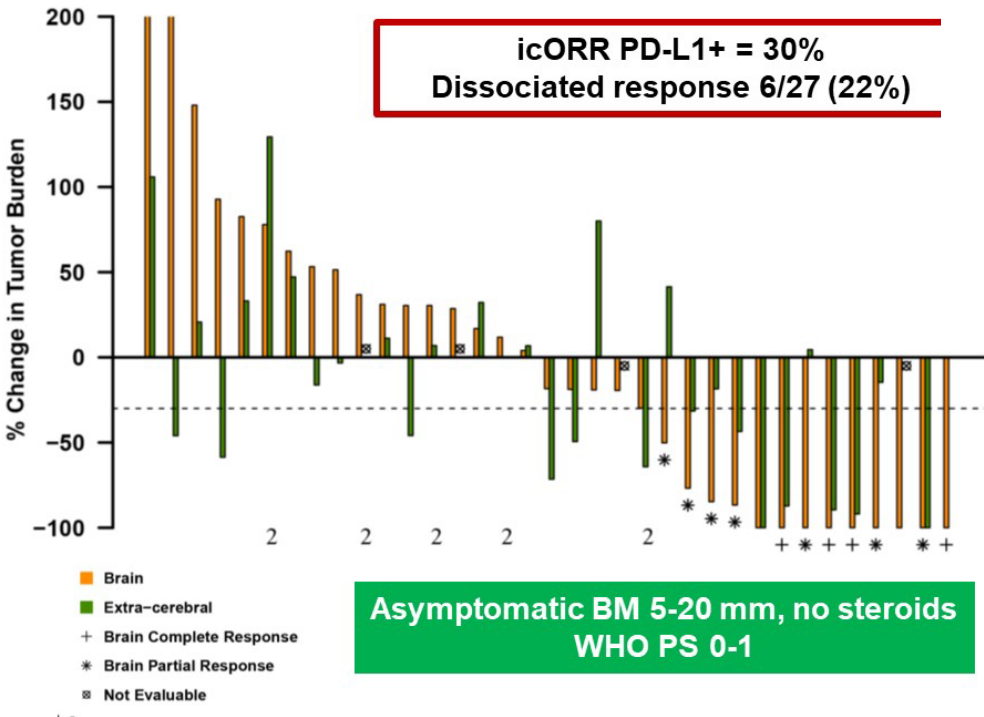
CheckMate 9LA: 3-Year OS and PFS in Patients With Baseline Brain Metastases



Immunotherapy Trial Data for Untreated Brain Mets

Atezo-chemo N=40, 55% baseline steroids

Monotx pembro N = 42 (37 PD-L1+)



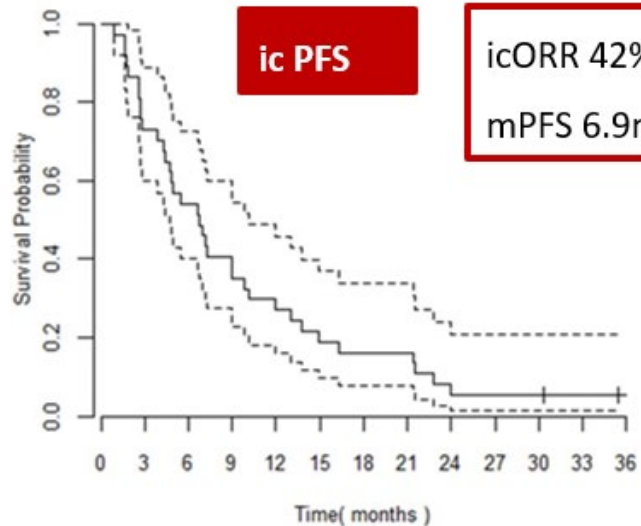
Key Eligibility Criteria:
 Stage IV non-squamous NSCLC
 Untreated brain metastases
 Treatment naïve
 EGFR/ALK negative, any PD-L1
 ECOG PS 0-1
 Anticonvulsivants and dexamethasone ≤ 4 mg qd allowed
 Measurable systemic and brain lesion/s

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



2y OS rate 28%
OS ↑ if PD-L1+/no steroids

Goldberg SB, et al. *Lancet Oncol.* 2020;21(5):655-663. Nadal E, et al. *J Clin Oncol.* 2023;41(28):4478-4485.

Ongoing Phase II/III trials for NSCLC and Untreated Asymptomatic BM

Selected trials evaluating systemic treatment strategies

Approach	Region	Study	Enrollment ^b	Treatment(s)	Primary EP	(Other) CNS EPs
ICI	USA	NCT05840770	34	Cemiplimab (NSCLC PD-L1 ≥50%)	iCBR (RANO-BM)	CNS-TTP (RANO-BM), TT-WBRT/SRS, TT-Brain met mortality
ICI + chemo	USA	NCT05746481	35	Atezolizumab + tiragolumab + carboplatin + pemetrexed	Rate of CNS salvage RT	iORR (RANO-BM)
	Spain	NCT05012254 (NIVIPI-Brain) cohort A	71 ^b	Nivolumab + ipilimumab + platinum-based chemo → nivolumab + ipilimumab	iCBR (RANO-BM)	iORR, iPFS (RANO-BM)
	USA	NCT04964960	45	Pembrolizumab + chemo	iCBR	Cognitive functioning (FACT-Cog)
ICI + VEGFi	USA	NCT02681549	53	Pembrolizumab + bevacizumab	iORR (mRECIST)	iPFS (mRECIST), Steroid use for cerebral edema
	China	NCT05807893 (SUPER BRAIN)	30	Serplulimab + beva + chemo → serplulimab + beva + pemetrexed	iPFS	iORR

We Need Trials to Evaluate the Best Treatment Strategy

Selected ongoing phase II/III trials for NSCLC & untreated BM combining systemic therapy & local therapy

Approach	Region	Study	Enrollment ^b	Treatment(s)	Primary EP	(Other) CNS EPs
ICI + RT	Canada	NCT02978404 NSCLC cohort	26	Nivolumab + SRS	iPFS (RECIST 1.1)	iCBR, (RECIST 1.1), Neurocognitive function (HVLt-R, TMT, COWA)
	Europe	NCT05522660 (USZ-STRIKE) cohort 2B	190	Anti-PD-(L)1 ± chemo vs Anti-PD-(L)1 ± chemo + SRS	CNS-PFS (iRANO)	–
	Global	NCT02831959	270	Anti-PD-(L)1 + SRS vs Anti-PD-(L)1 + SRS → TTFields	iTTP	iORR, TT-Neurocognitive failure (HVLt-R, TMT, COWA)
ICI + FUS	USA & Canada	NCT05317858	20	Pembrolizumab vs Pembrolizumab + Exablate FUS	ORR, AEs	CNS-ORR, CNS-TTR (RANO-BM)

“

With targeted therapies, you could envisage scenarios where combination small molecule plus immunotherapy...could be very effective in the brain.

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Patrick Forde, MD