HARMONY OF HOPE:
Confronting Brain Metastases in the Symphony of Lung Cancer

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IASLC International Association for the Study of Lung Cancer
Conquering Thoracic Cancers Worldwide

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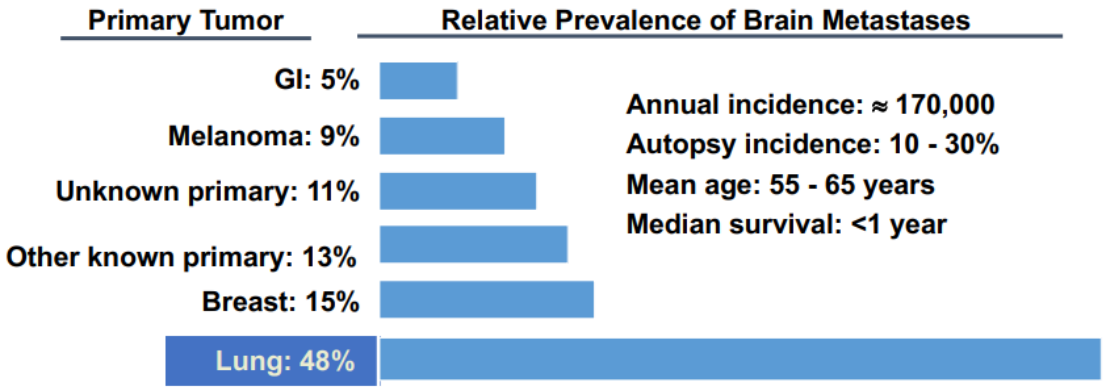
CNS Metastases in Lung Cancer

- Incidence increasing due to:
  - Use of MRI /CT
  - More effective systemic treatments leading to prolonged survival
- Prognosis improving due to:
  - Better systemic therapies (targeted therapies/IO)
  - Less toxic radiation (SRS)



Histologic subtype	Incidence of CNS metastasis
Small cell lung cancer	13.5-59%
Adenocarcinoma	6.6-43%
Squamous cell carcinoma	5.2-13%
Large cell carcinoma	8.3%
Undifferentiated	41.0%
NSCLC-NOS	7.4%

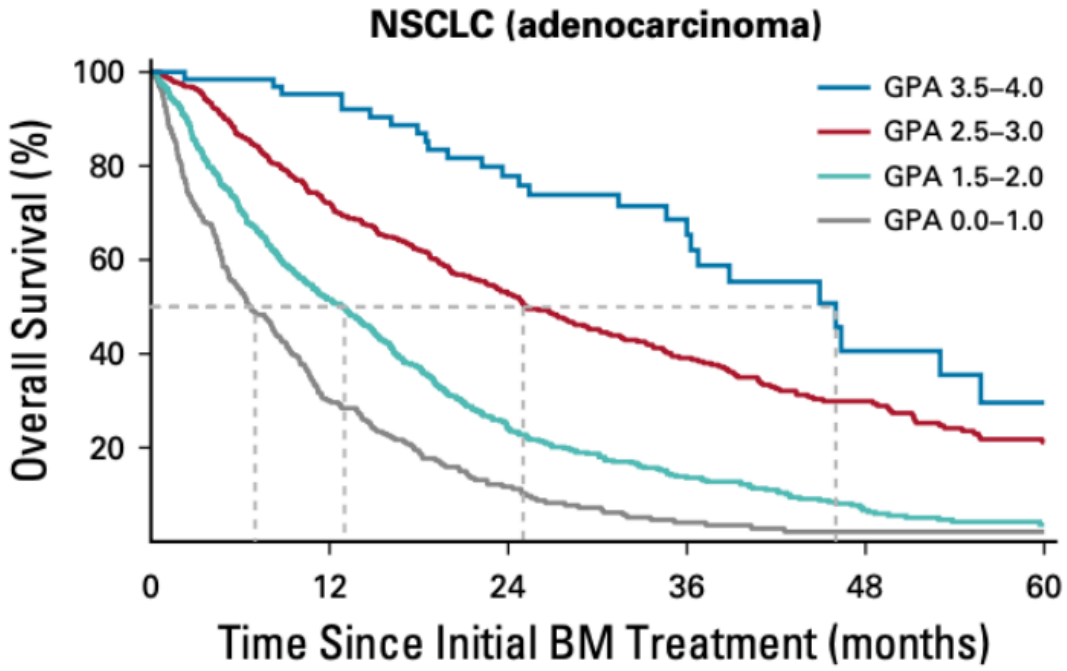
Whitsett TG, et al Tran NL. Molecular determinants of lung cancer metastasis to the central nervous system. Transl Lung Cancer Res. 2013 Aug;2(4):273-83.

Updated GPA-Lung Cancer Using Molecular Markers (Lung-mol GPA)

Prior GPA Model:

- Age
- KPS
- ECM
- No. Brain Mets

	Adenocarcinoma NSCLC Lung-molGPA[a]	
	MS, mo	Patients, No. (%)
3.0m→	6.9	337 (22)
5.4m→	13.7	664 (44)
9.4m→	26.5	455 (30)
14.8m→	46.8	65 (4)
7m→	15.2	1521 (100)



No. at risk:

GPA 3.5–4.0	64	60	39	21	8
GPA 2.5–3.0	453	302	187	108	61
GPA 1.5–2.0	616	286	115	49	18
GPA 0.0–1.0	289	74	24	7	3

Sperduto P et al, JCO;30(4):419-25, 2012; Sperduto P et al JAMA Oncol 2017 Jun 1; 3(6): 827-831 ; Sperduto et al. JCO 2020 Nov 10; 38(32):3773-3784

Management of CNS Metastases: The Greatest Duet

"I finally said, "Barry (Gibb), I don't even like this song anymore' and he said, 'You know what we need? Dolly Parton"

- Role of Systemic Therapy
  - Targeted Therapy
  - Chemotherapy
  - Immunotherapy
- Role of Radiation
  - SRS vs WBRT
  - Perioperative SRS
  - Long-term Toxicity

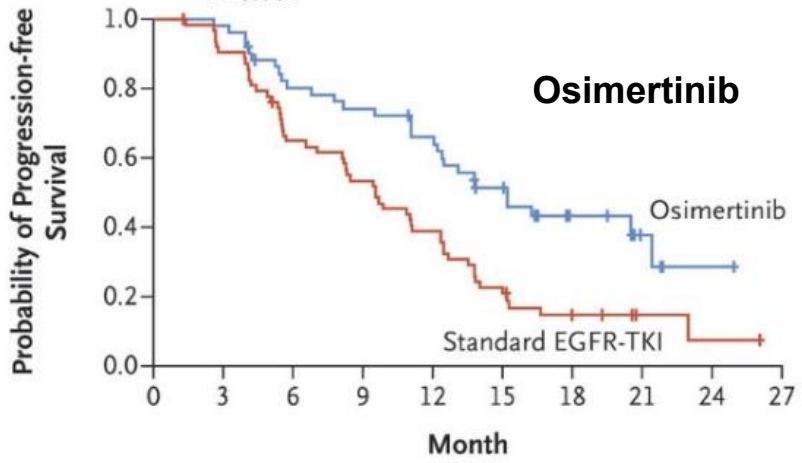
CNS Activity of Targeted Therapies

- ✓ Improved PFS in patients with Brain Mets at baseline
- ✓ Improved CNS Progression-Free Survival

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

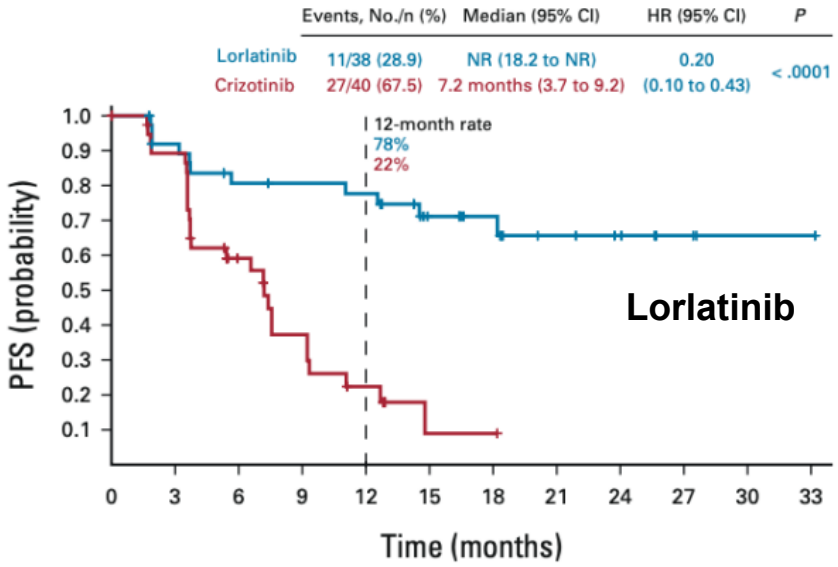


Osimertinib

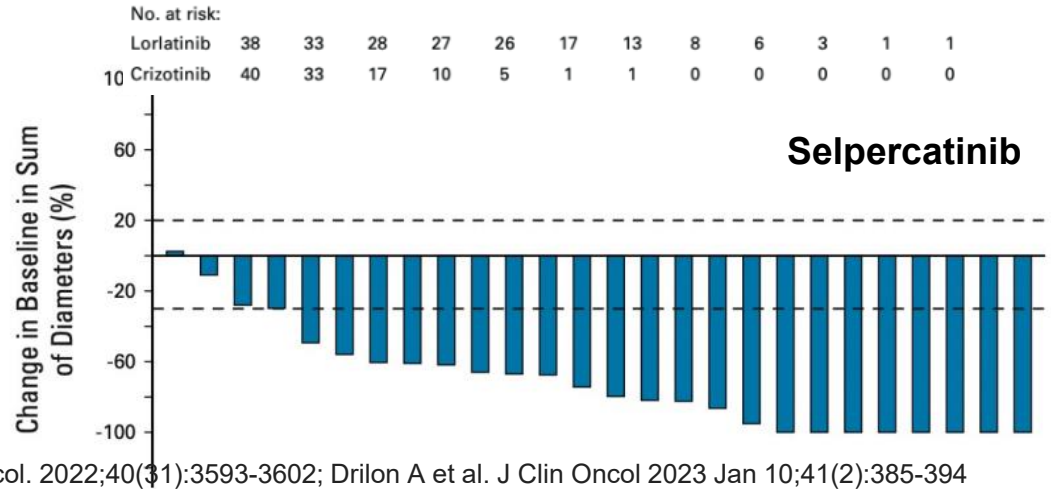
Improved CNS-Free PFS (%)

Osimertinib NR
Standard EGFR (13.9mo)

HR 0.48



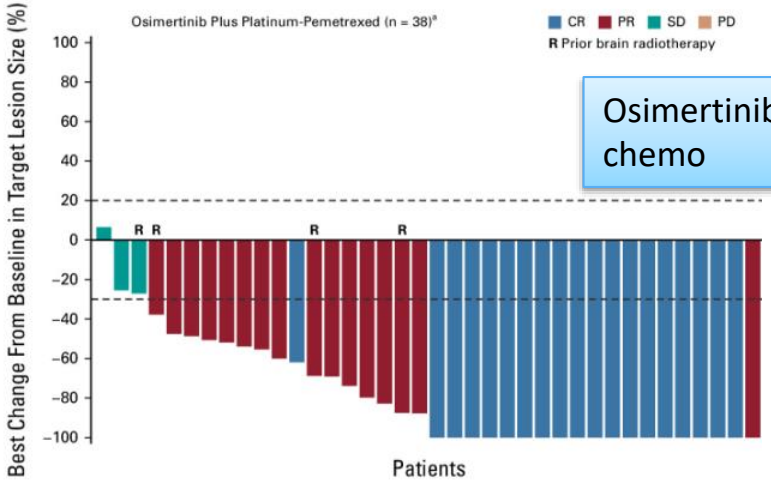
Lorlatinib



Selpercatinib

References: Ramalingam S et al, N Engl J Med 2020 Jan 2;382(1):41-50; Solomon BJ et al. J Clin Oncol. 2022;40(31):3593-3602; Drilon A et al. J Clin Oncol 2023 Jan 10;41(2):385-394

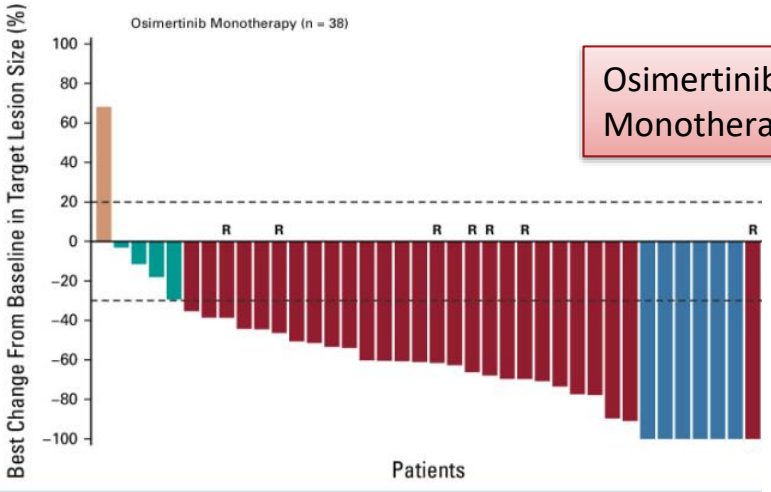
Timing of Chemotherapy & Radiation in Brain Mets:



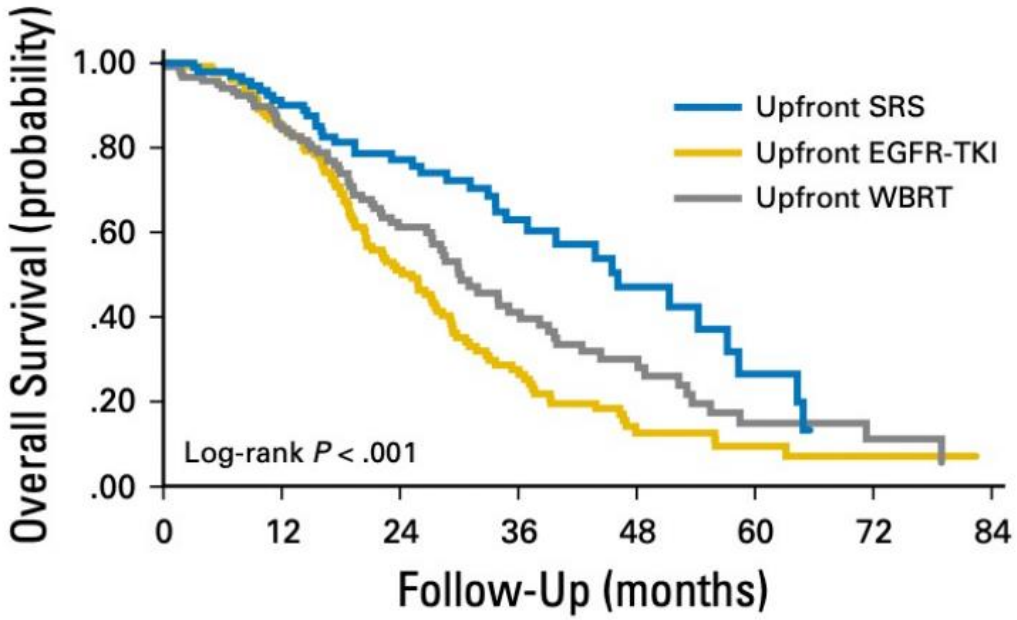
Osimertinib plus chemo

CNS ORR
78% vs 69%

CNS CR
59% vs 43%



Osimertinib Monotherapy

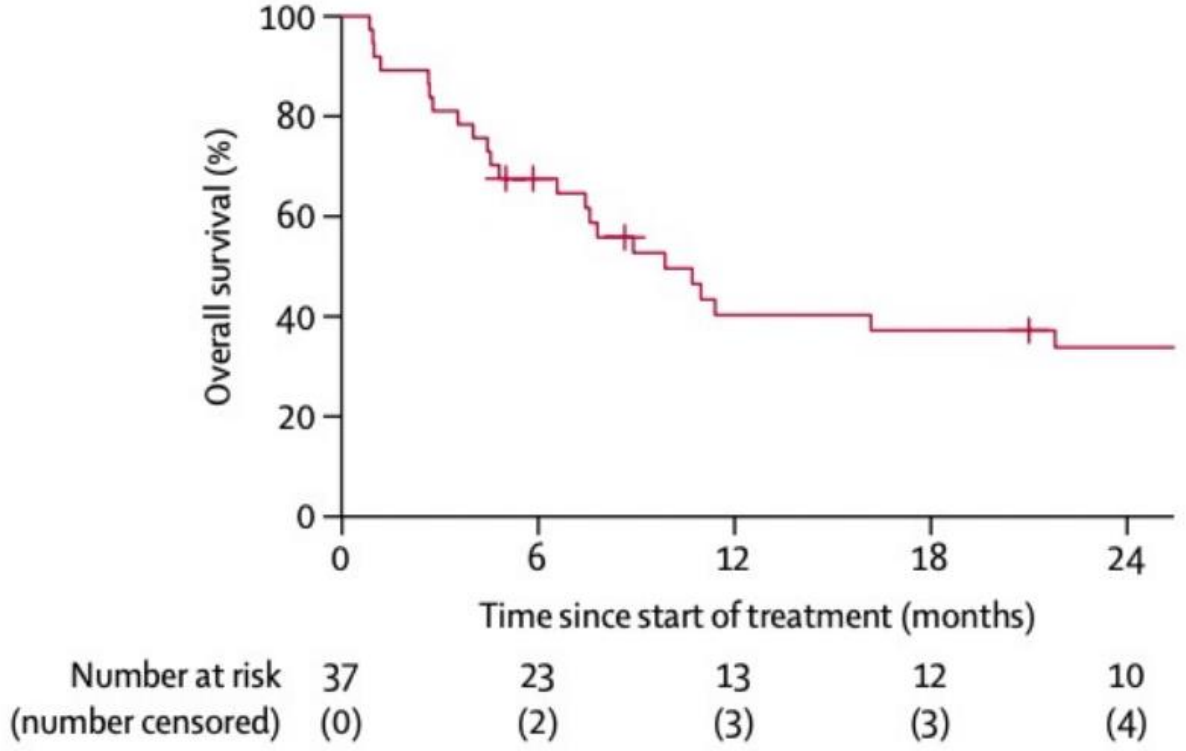


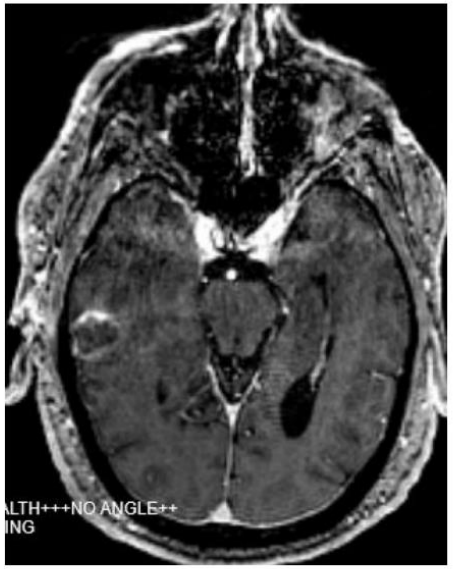
No. at risk								
Upfront SRS	100	76	51	29	13	5	1	1
Upfront WBRT	120	97	52	27	15	6	3	1
Upfront EGFR-TKI	131	103	54	24	8	4	2	0

References: Janne et al. JCO 42, 808-820(2024). Magnuson W et al, JCO, 2017 Apr 1;35(10):1070-1077

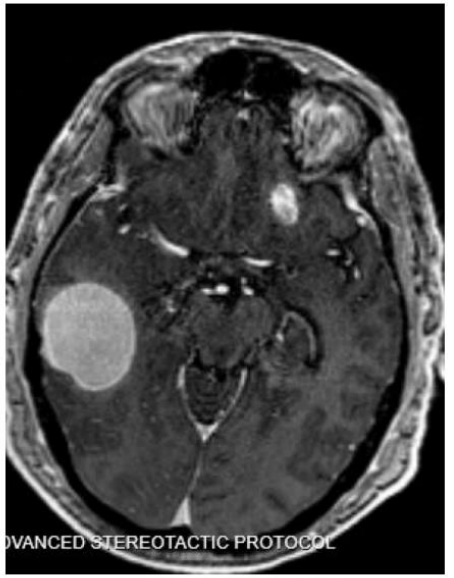
Immunotherapy Activity in NSCLC brain metastases

- Slow onset response, but potential cures
- Potential Synergy SRS+ICI
- Risk of pseudo-progression (iRANO)





Pre-WBRT

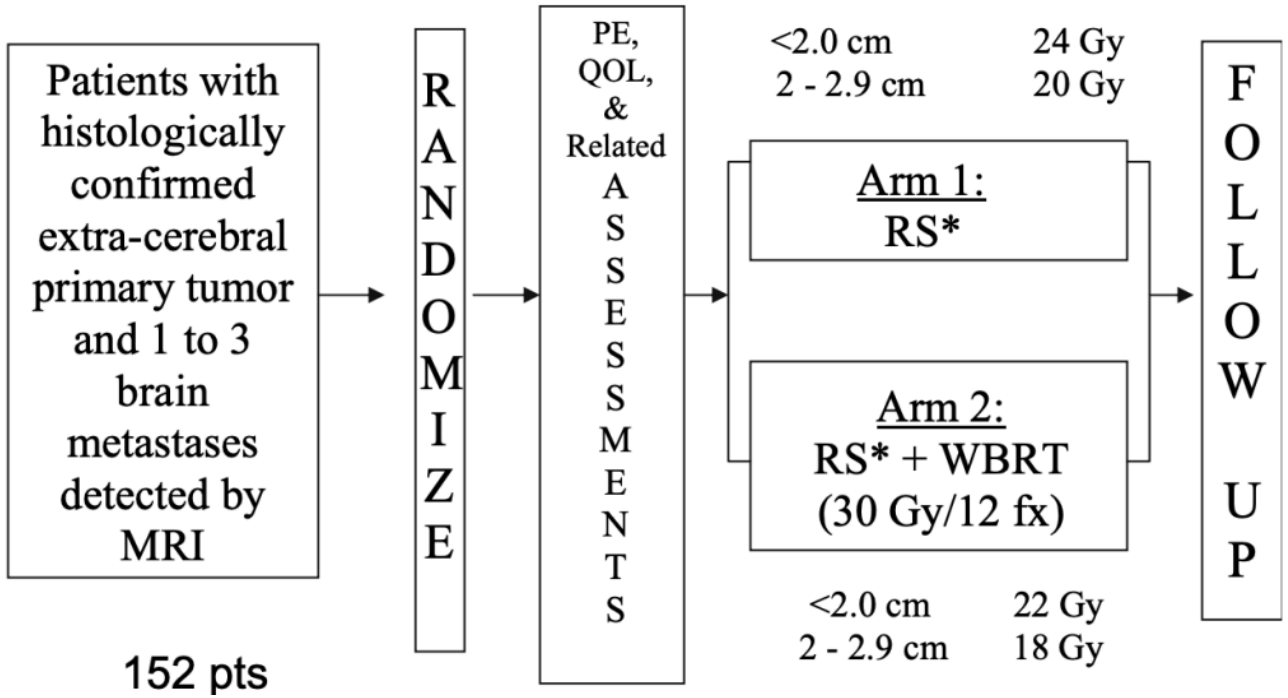


1 cycle Post Nivo+Ipi

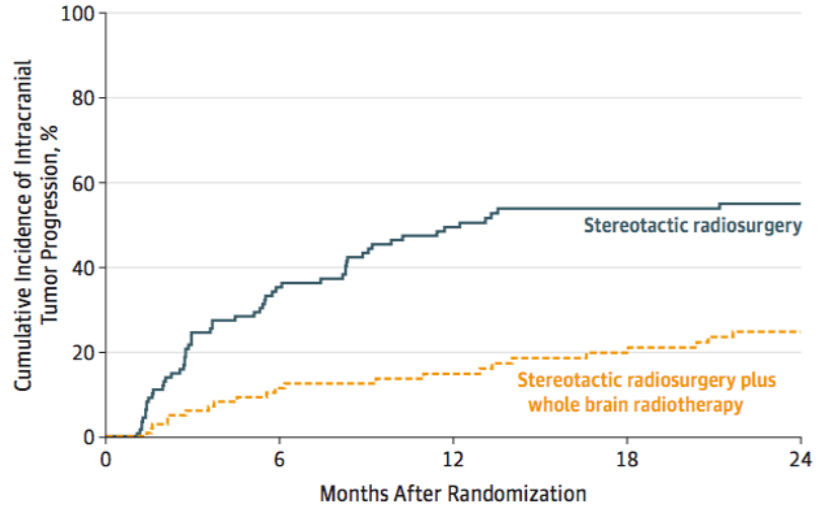
References: Goldberg SB et al. Lancet Oncol. 2020;21(5):655-663; Okada H, Lancet Oncol 16(15): e534-e542, 2015; Schapira et al. IJROBP 2018

SRS vs WBRT

Alliance 0574 Phase III Study SRS +/-WBRT



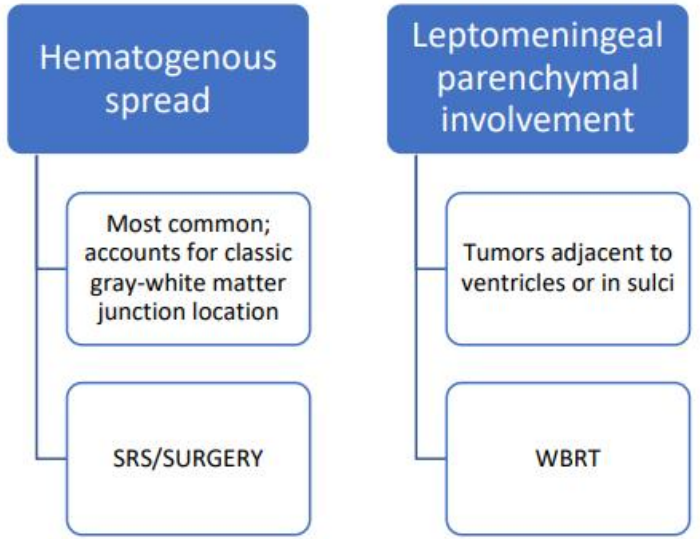
- Less CNS Failure with WBRT
  -6mo: 11.6% vs 35%
- No difference in OS
  -mOS 7.4 vs 10 mo (HR 1.02)
- Higher salvage therapy in SRS arm

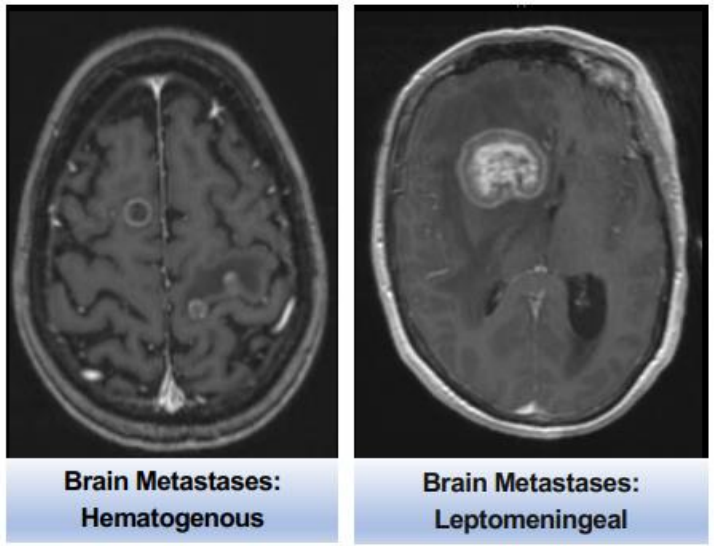


References: Brown PD et al, JAMA. 2016 Jul 26;316(4):401-9

Who needs WBRT?

- Leptomeningeal Parenchymal Involvement
- Patients unsuitable for SRS (multiple brain mets, salvage therapy)





Role of Surgery

- Surgery may improve functional status in select cases
- Salvage therapy or management of symptomatic radiation necrosis
- Consider Pre-op SRS (vs Post-op): less LM disease, less RT necrosis)

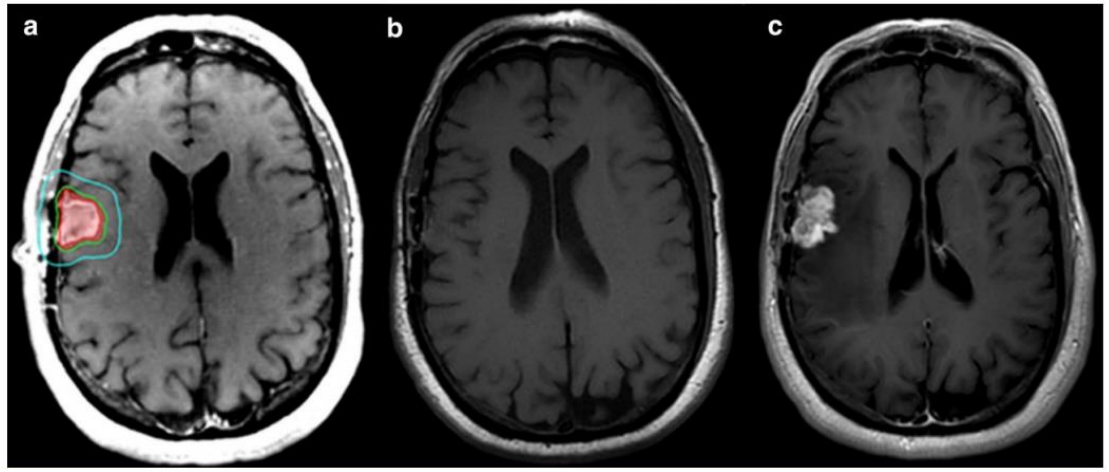
References Sas-Korczynska B, R. J Thorac Dis. 2021 May;13(5):3246-3257; Goldberg M Front Oncol. 2024 Jan 10;13:1343500; Patel KR et al, Neurosurgery 2017

Survivorship: Long term treatment toxicity

- **Neurocognitive Decline**
  - Favor SRS >>WBRT
  - Hippocampal Sparring RT
  - Memantine (HR 0.76)

Time variable	Patients, No. (%) SRS (n = 27)	WBRT (n = 27)	Difference % (95% CI)[b]
Cognitive deterioration			
3 mo	10/27 (37.0)	24/27 (88.9)	−51.9 (−69.0 to −26.6)
6 mo	12/26 (46.2)	23/26 (88.5)	−42.3 (−61.3 to −17.0)
9 mo	12/25 (48.0)	21/26 (80.8)	−32.8 (−53.7 to −6.5)
12 mo	15/24 (62.5)	21/23 (91.3)	−28.8 (−49.6 to −4.42)
16 mo	12/21 (57.1)	16/19 (84.2)	−27.1 (−50.1 to 1.43)

- **Radiation Necrosis**
  - Onset > 1yr (12-24 mos)
  - Dose-Dependent (Volume>12Gy)
  - Immuno>Targeted>Chemo
  - Tx: steroids, bevacizumab, VitE+pento, Surgery/Laser Thermocoagulation



References: Palmer JD et al, JAMA Oncol. 2022 Dec 1;8(12):1809-1815 ; Fujimoto D, JNO, 136(1), 207–212, 201; Minniti et al, Radiat Oncol 15;6:48,2011 ; Flickinger JC et al, IJROBP 38 (3): 485-490, 1997

Conclusions

- CNS metastases require a multi-disciplinary treatment approach
- Targeted Therapies(+/- chemo) can lead to meaningful CNS response, thus an individualized treatment approach is required
- Careful patient selection requires balancing outcome and potential toxicity
- Despite significant advances in molecular biology in CNS metastases, novel approaches are needed