Where Science Becomes Hope

CURRENT MANAGEMENT OF MELANOMA BRAIN METASTASES

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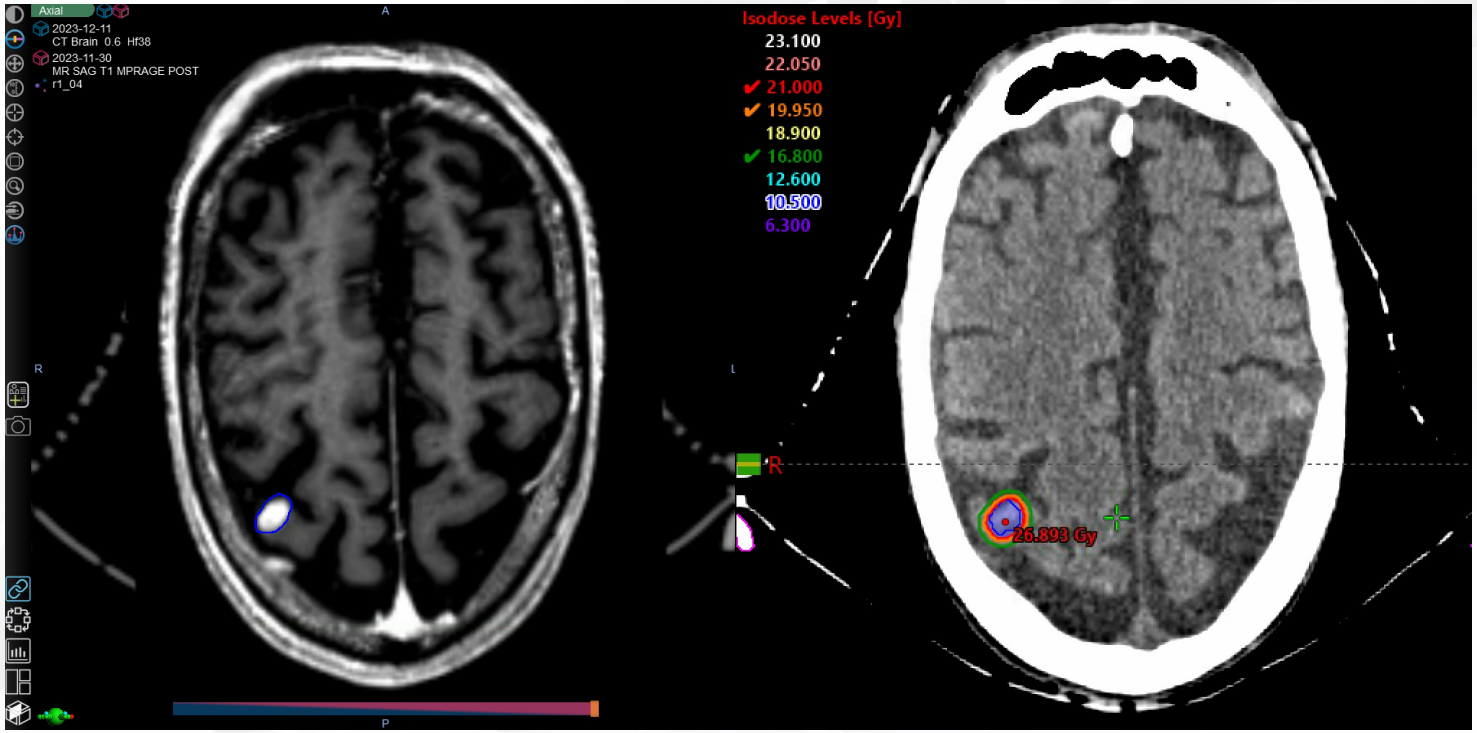
HOW ARE MELANOMA BRAIN METASTASES MANAGED

- Radiation – Stereotactic Radiosurgery, Whole Brain Radiation, Hippocampal Avoidance Whole Brain
- Surgery
- Immunotherapy – Ipilimumab/Nivolumab

STEREOTACTIC RADIOSURGERY (SRS)

- Highly conformal delivery of high-dose radiation in typically 1-5 fractions
- Usually limited to ≤ 10 lesions, but often will treat more
- Local control rate depends on the size of the tumor (excellent for small tumors)



STEREOTACTIC RADIOSURGERY (SRS)

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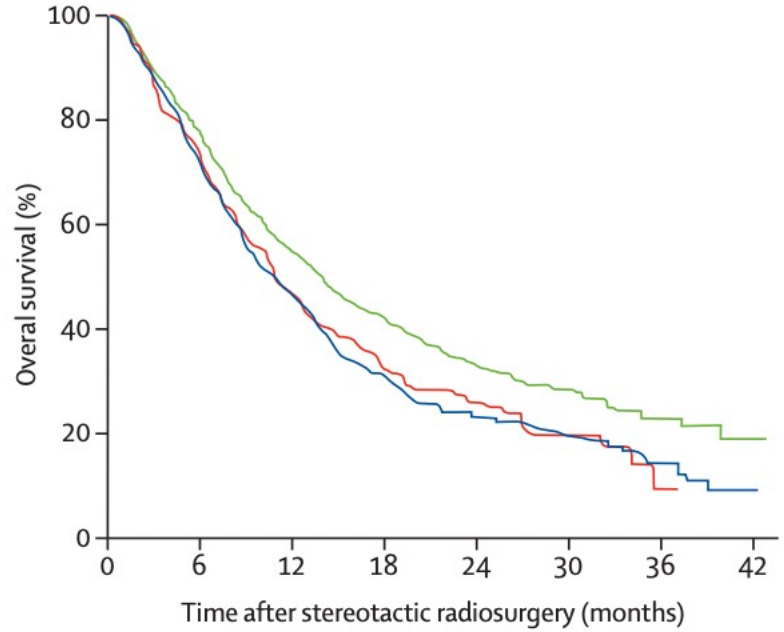
Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

Masaaki Yamamoto, Toru Serizawa*, Takashi Shuto, Atsuya Akabane, Yoshinori Higuchi, Jun Kawagishi, Kazuhiro Yamanaka, Yasunori Sato, Hidefumi Jokura, Shoji Yomo, Osamu Nagano, Hiroyuki Kenai, Akihito Moriki, Satoshi Suzuki, Yoshihisa Kida, Yoshiyasu Iwai, Motohiro Hayashi, Hiroaki Onishi, Masazumi Gondo, Mitsuya Sato, Tomohide Akimitsu, Kenji Kubo, Yasuhiro Kikuchi, Toru Shibasaki, Tomoaki Goto, Masami Takanashi, Yoshimasa Mori, Kintomo Takakura, Naokatsu Saeki, Etsuo Kunieda, Hidefumi Aoyama, Suketaka Momoshima, Kazuhiro Tsuchiya*

Group	Median overall survival, months (95% CI)	HR (95% CI)	p value
1 tumour	13·9 (12·0–15·6)	0·76 (0·66–0·88)	0·0004
2–4 tumours	10·8 (9·4–12·4)	Reference	
5–10 tumours	10·8 (9·1–12·7)	0·97 (0·81–1·18)	0·78



Number at risk				
1 tumour	455	234	97	22
2–4 tumours	531	215	61	16
5–10 tumours	208	84	31	1

***Figure*: Kaplan-Meier curves of overall survival**
HR=hazard ratio.

STEREOTACTIC RADIOSURGERY (SRS)

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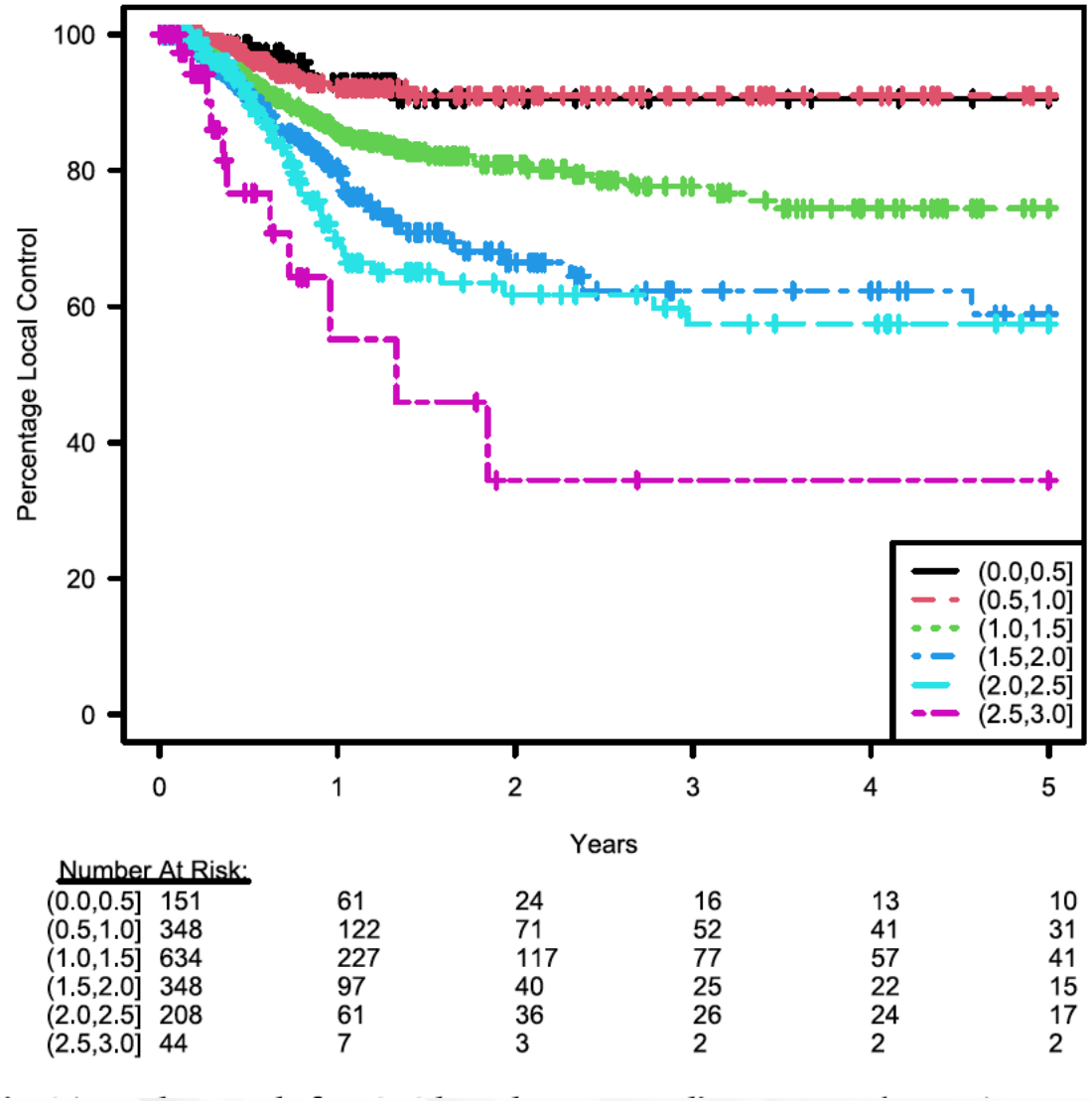
nor (excellent for small tumors)



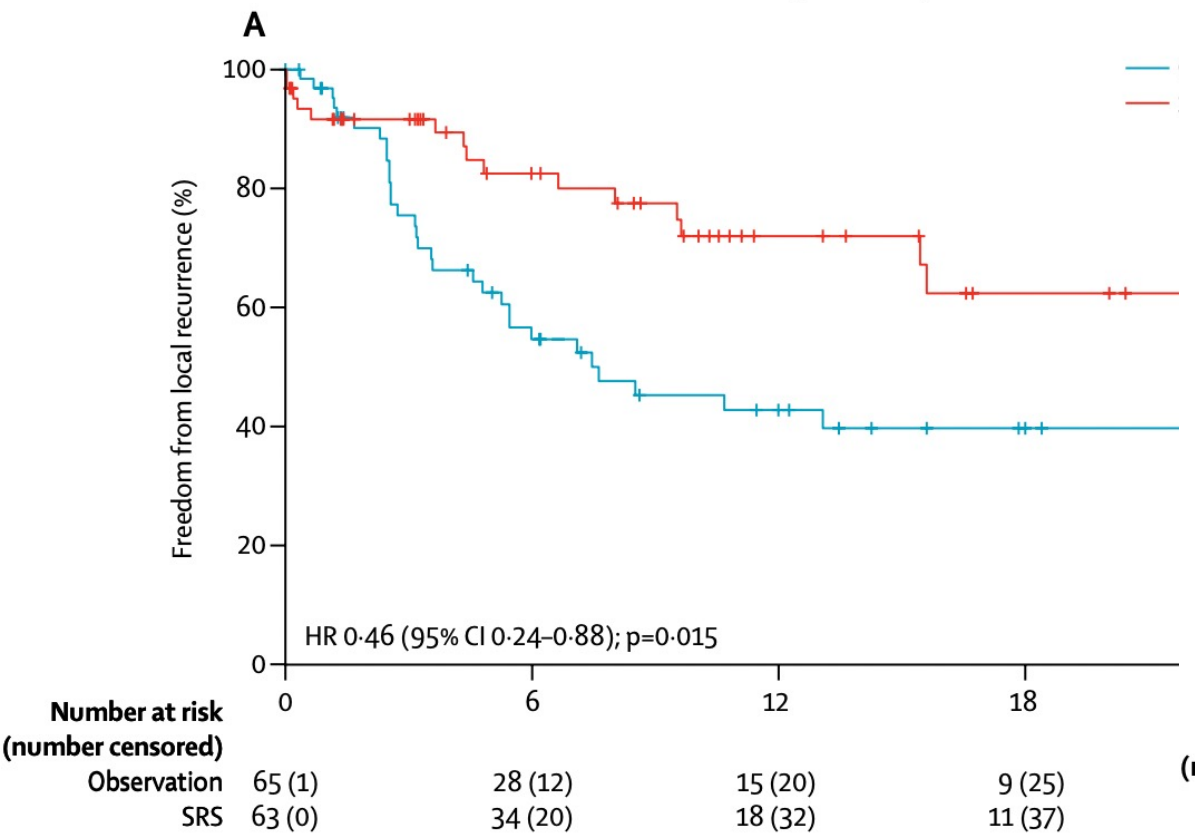
Number At Risk:

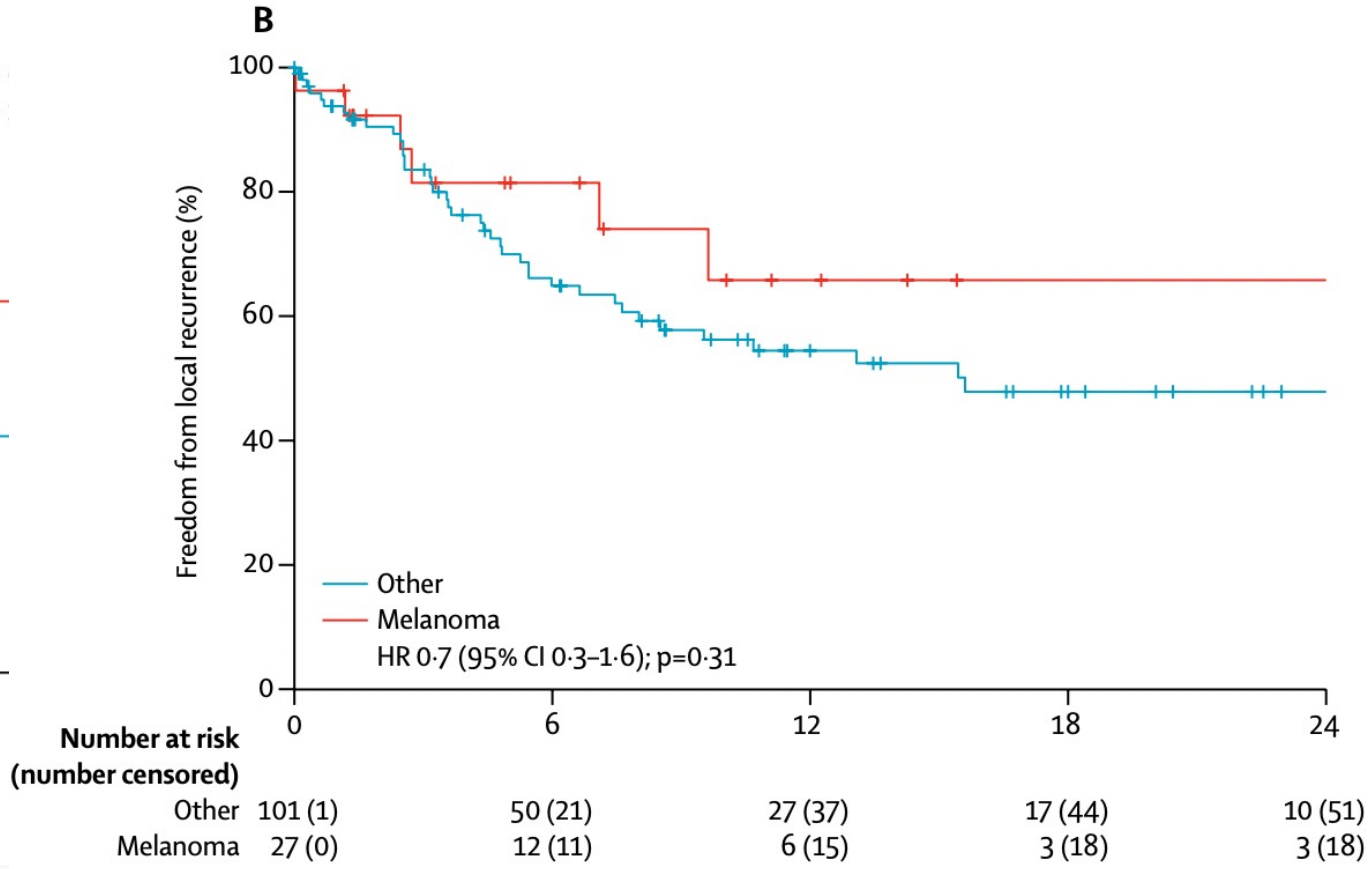
(0.0,0.5]	151	61	24	16	13	10
(0.5,1.0]	348	122	71	52	41	31
(1.0,1.5]	634	227	117	77	57	41
(1.5,2.0]	348	97	40	25	22	15
(2.0,2.5]	208	61	36	26	24	17
(2.5,3.0]	44	7	3	2	2	2

Eve et al. Nature Communications 2024

LESIONS >2 CM AND LIMITED NUMBER OF METS CONSIDER SURGERY + SRS (USUALLY POST-OPERATIVE SRS)

Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre,





WHAT ABOUT PREOPERATIVE SRS? ARE THERE POTENTIAL ADVANTAGES?

- Potential postoperative delays which push back surgery

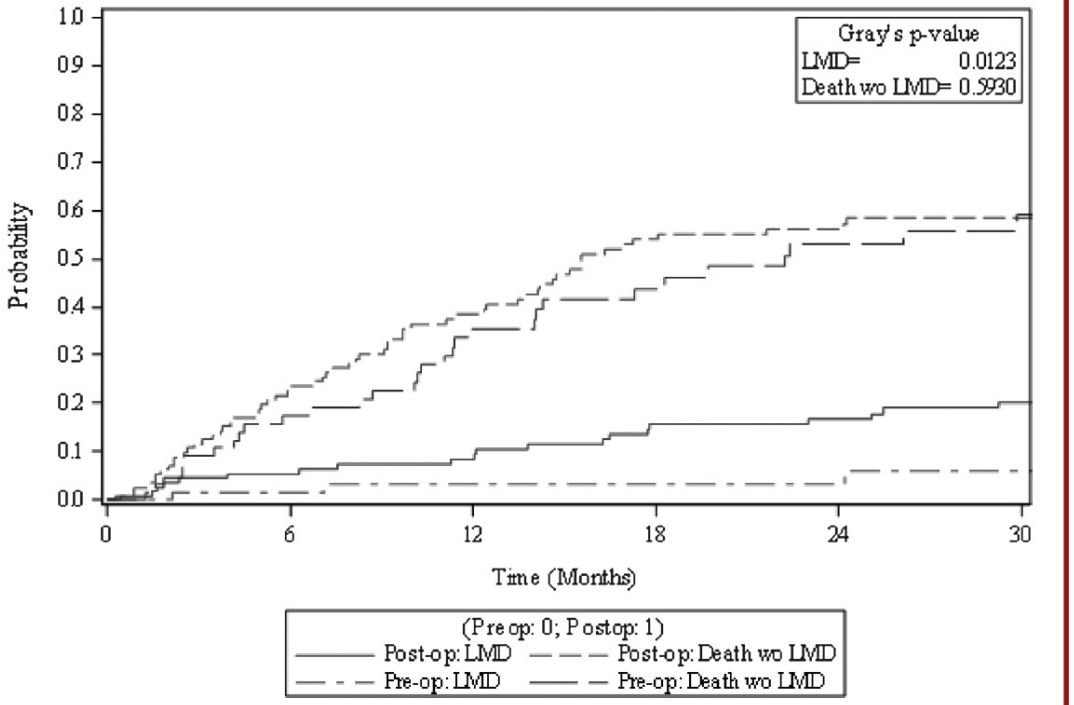


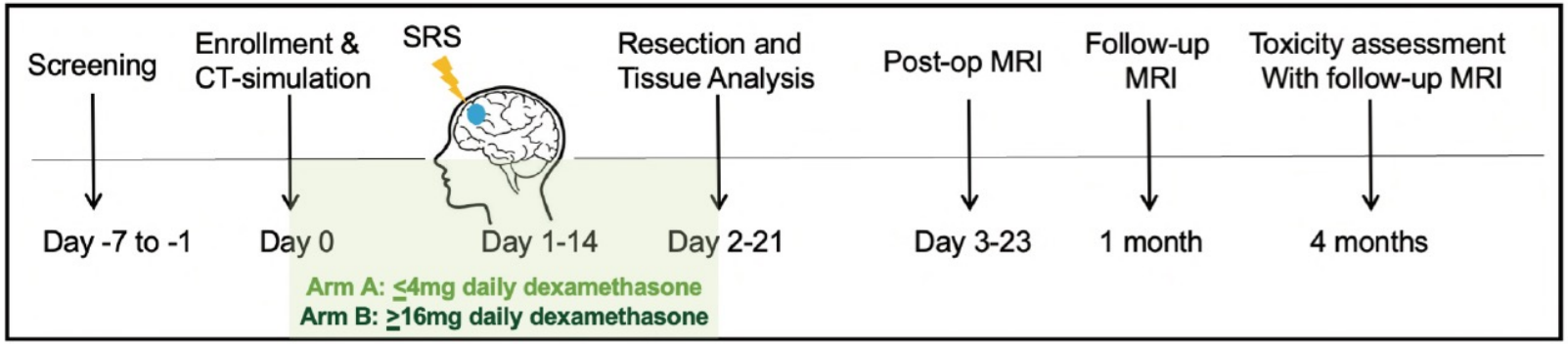
FIGURE 3. *Cumulative incidence of leptomeningeal disease (LMD) recurrence, with death as a competing risk, between preoperative (Preop) and postoperative (Postop) stereotactic radiosurgery. Curves truncated at 30 months. wo, without. Color version available online only.*

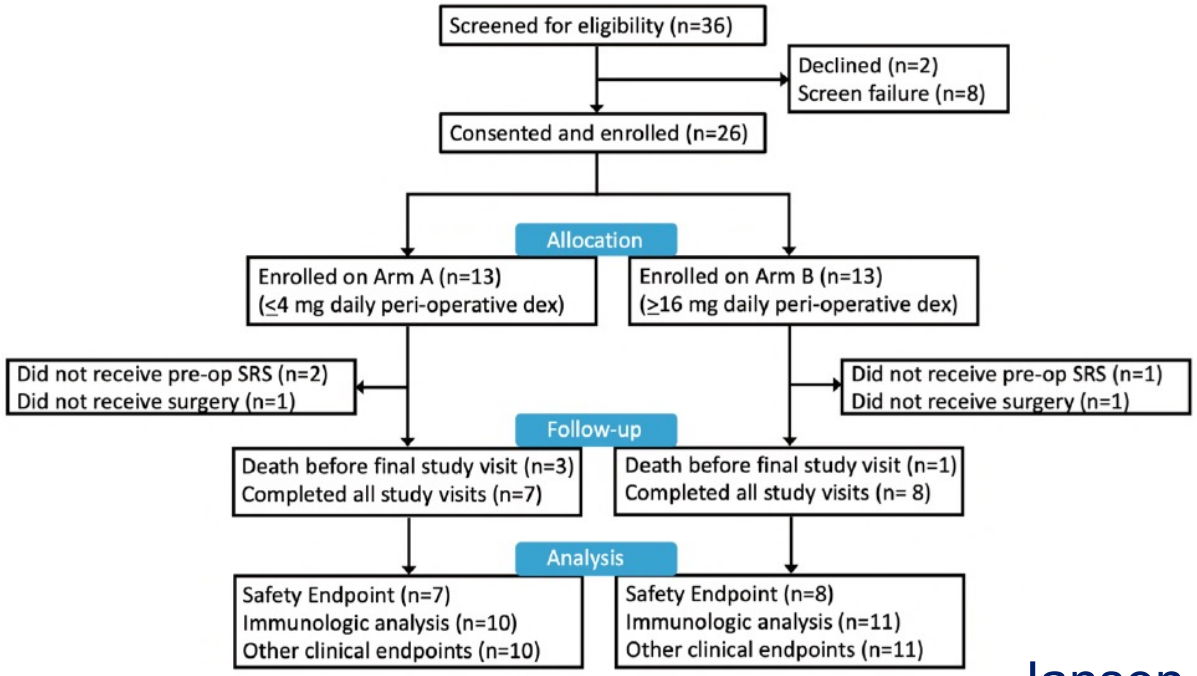
ncertainty requiring large volume expansions

eptomeningeal spread

Patel et al. Neurosurgery 2016

WHAT ABOUT PREOPERATIVE SRS? ARE THERE POTENTIAL ADVANTAGES?





Jansen et al. Under Revision

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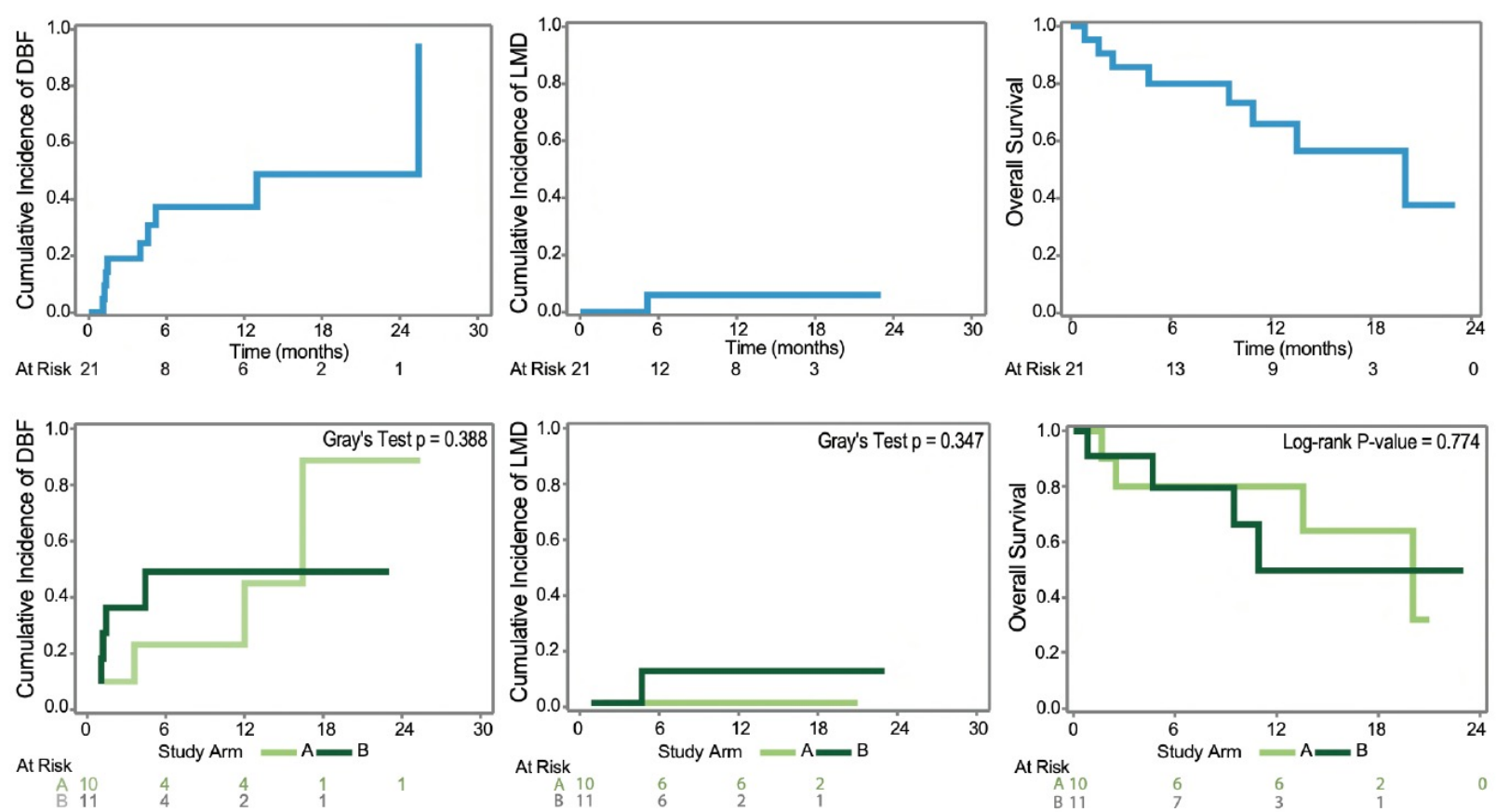

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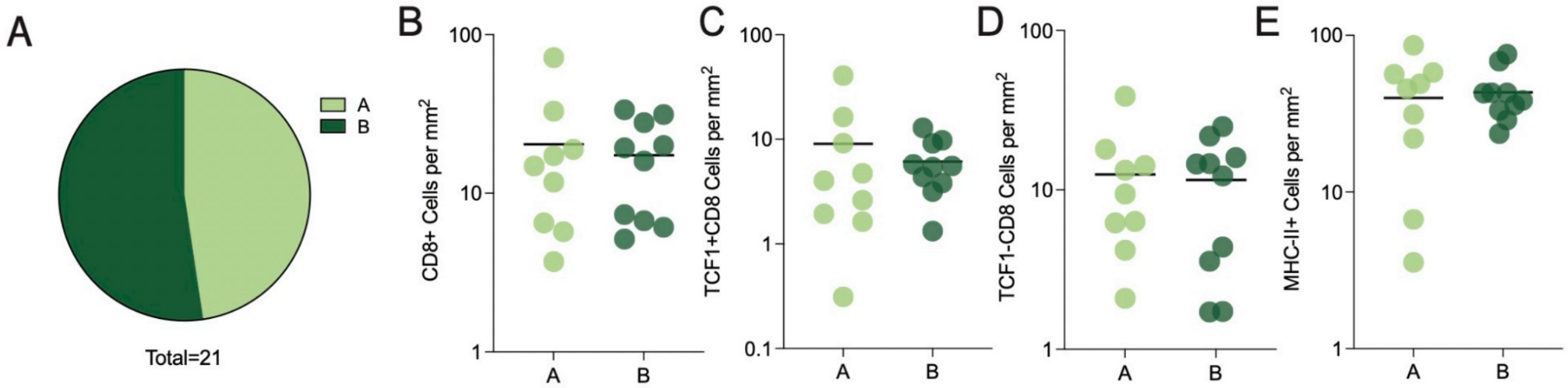

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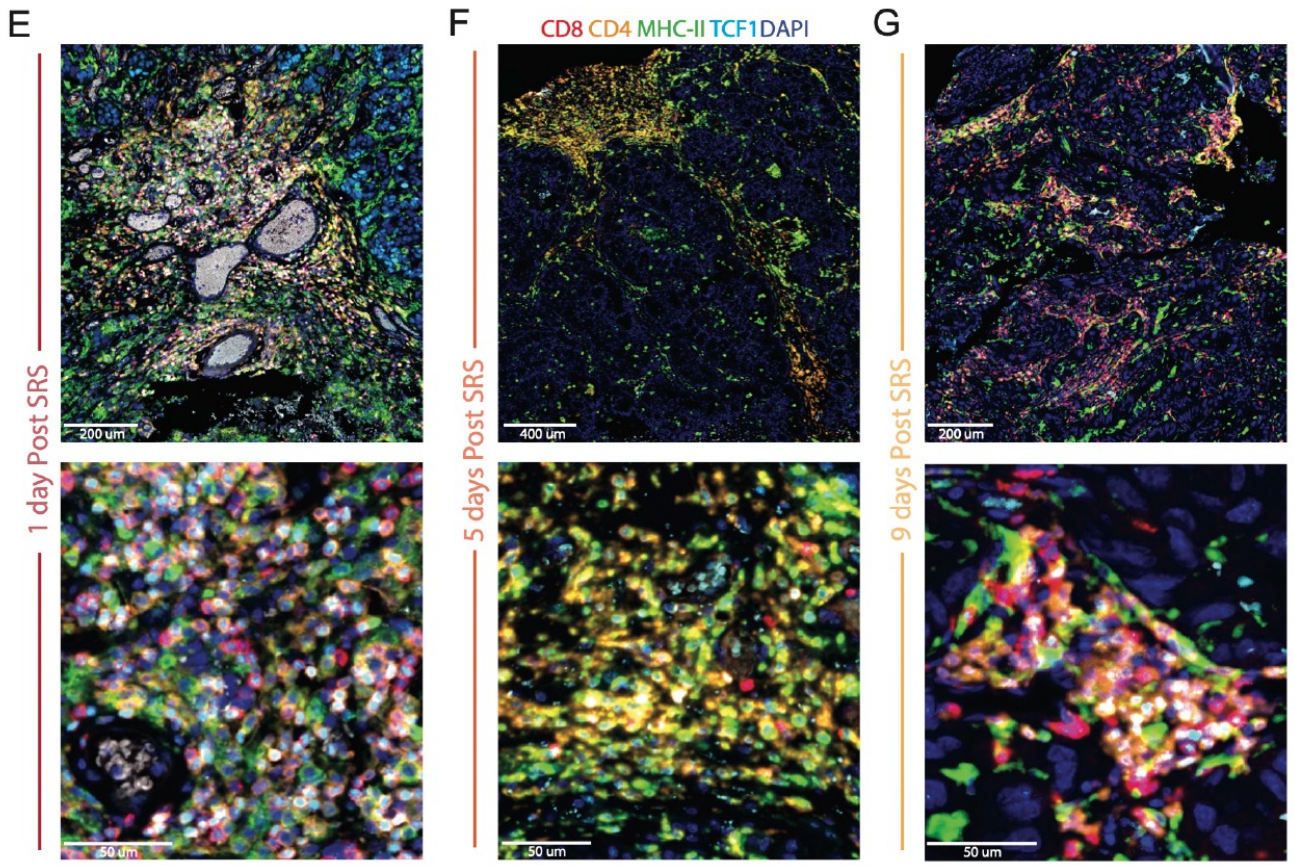

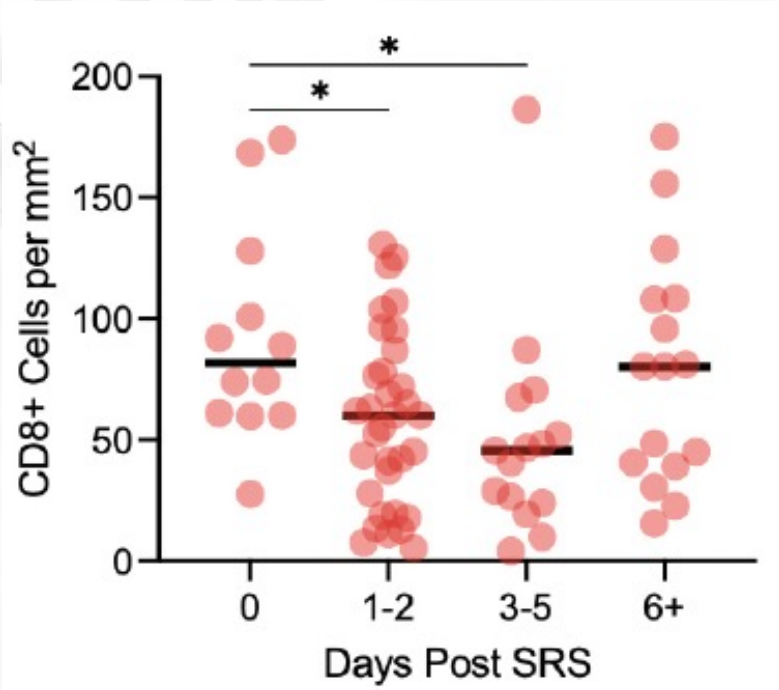

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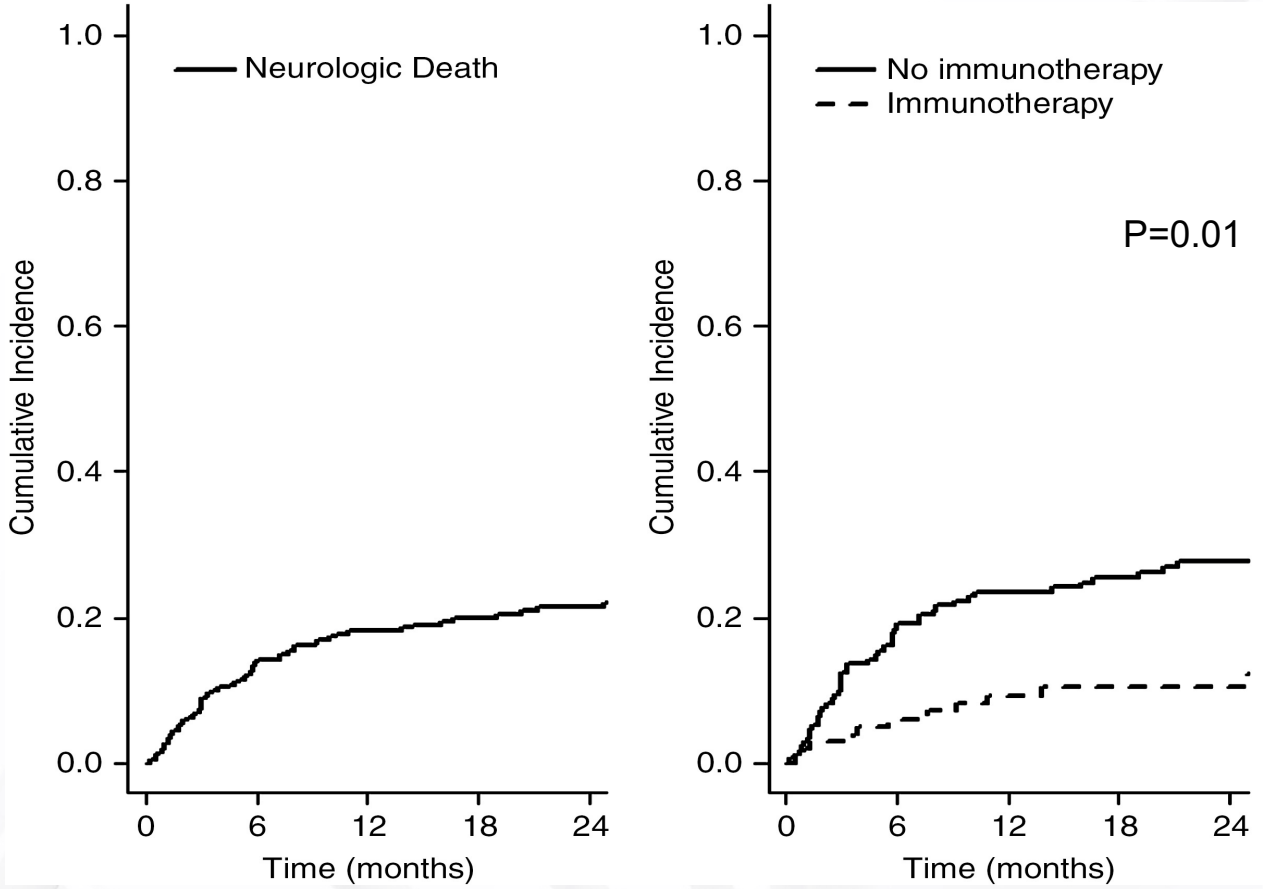
WHAT ABOUT SRS AND IMMUNOTHERAPY?



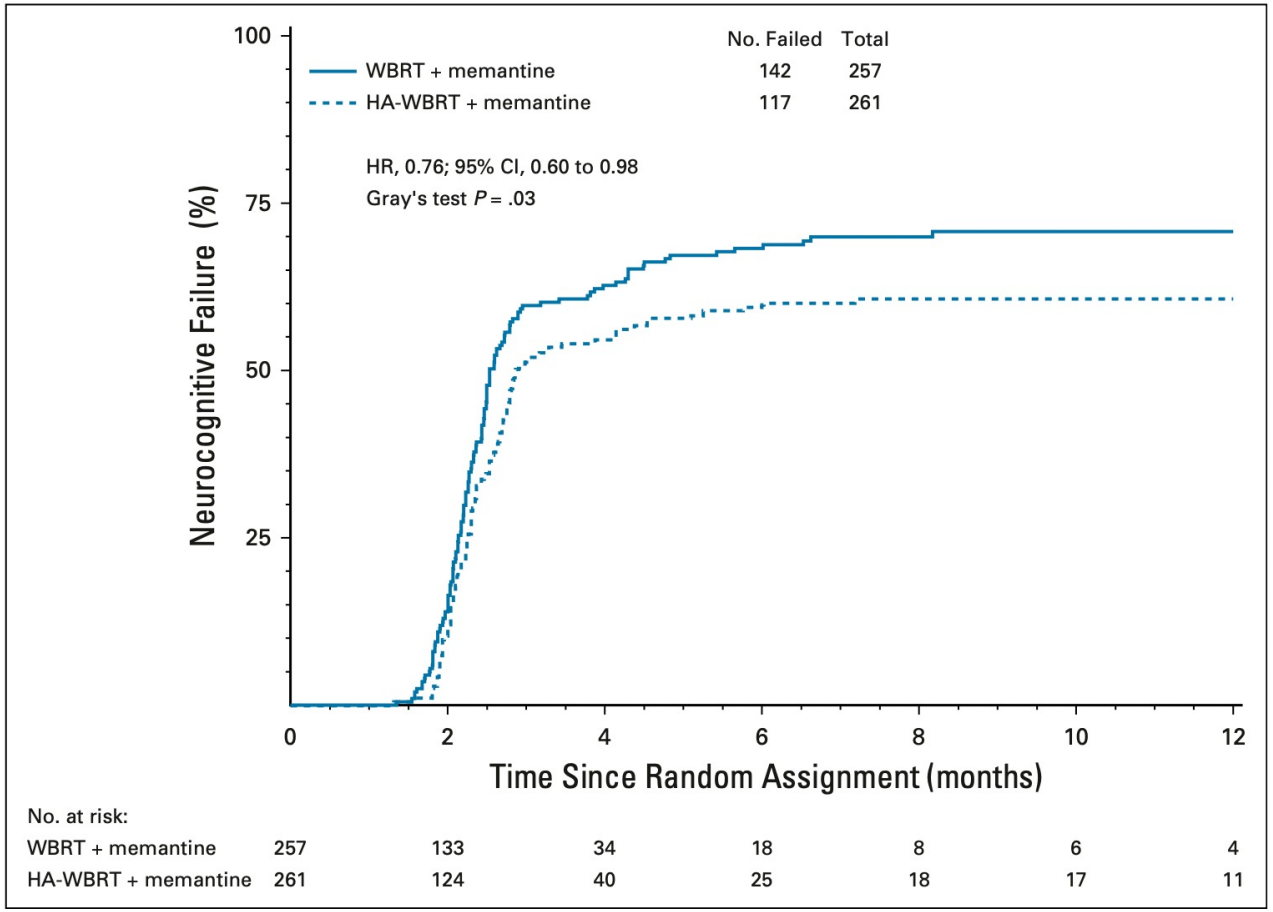
Lanier et al. Neuro-Oncology Practice 2019

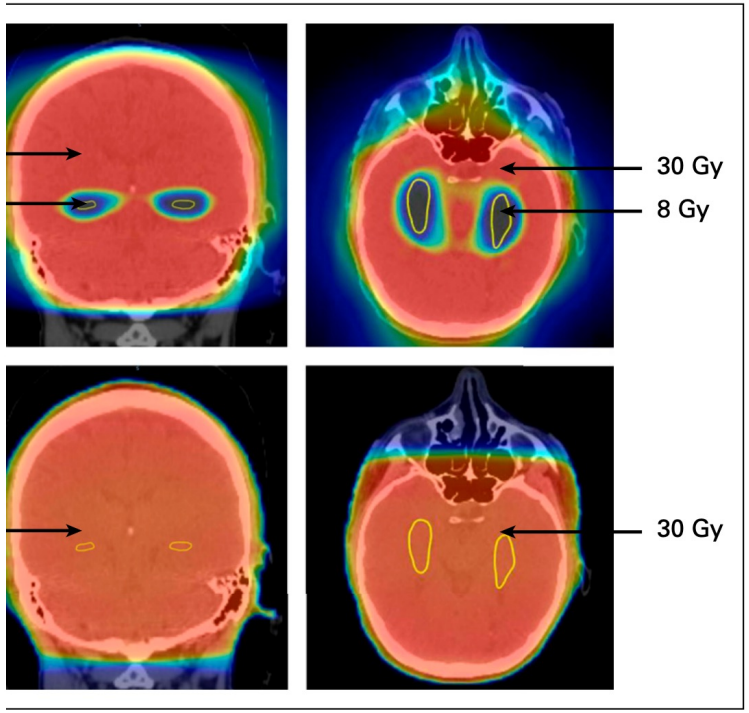
HIPPOCAMPAL AVOIDANCE WHOLE BRAIN RADIATION THERAPY

original reports

Hippocampa
Radiotherapy
Brain Metast
Oncology CC

Paul D. Brown, MD[1]; Vinai Gondi, M
Joseph A. Bovi, MD[7]; Cliff Robinso
Tammie L. S. Benzinger, MD, PhD[8]
Kiran Devisetty, MD[14]; Sunjay Shal
Harold Yoon, MD[19]; Jing Li, MD[5]; I
Snehal Deshmukh, MS[3]; Minesh P





IMMUNOTHERAPY

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTI

Articles

Combined Nivolumab a
in Melanoma Metastat

Hussein A. Tawbi, M.D., Ph.D., Peter A. Fors
Omid Hamid, M.D., F. Stephen Hodi, M.D.
Nikhil I. Khushalani, M.D., Karl Lewis, M.D., Ch
Michael A. Postow, M.D., Michael B. Atkins,
David A. Reardon, M.D., Igor Puzanov, M.D.
Reena P. Thomas, M.D., Ph.D., Ahma
Anna C. Pavlick, D.O., Joel Jiang, Ph.D., Al
Sheena Demelo, M.D., and Kim

CrossMark

Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study

Hussein A Tawbi, Peter A Forsyth, F Stephen Hodi, Alain P Algazi, Omid Hamid, Christopher D Lao, Stergios J Moschos, Michael B Atkins, Karl Lewis, Michael A Postow, Reena P Thomas, John Glaspy, Sekwon Jang, Nikhil I Khushalani, Anna C Pavlick, Marc S Ernstoff, David A Reardon, Ragini Kudchadkar, Ahmad Tarhini, Caroline Chung, Corey Ritchings, Piyush Durani, Margarita Askelson, Igor Puzanov, Kim A Margolin

IMMUNOTHERAPY

Inclusion:

a) At least 1 measurable brain metastasis > 0.5 cm in longest diameter and < 3 cm in longest diameter
c) Prior therapy, if given, limited to stereotactic radiotherapy and prior excision of a single BrM
e) Subjects must be free of neurologic signs and symptoms related to metastatic brain lesions

Exclusion:

a) History of whole brain irradiation.
b) History of known leptomeningeal involvement (lumbar puncture not required).
c) Previous stereotactic or highly conformal radiotherapy within 3 weeks before the start study.
d) Number of CNS lesions previously treated with SRT is >3.

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	Asymptomatic patients (n=101)	Symptomatic patients* (n=18)
Age, years	59·0 (51·0–66·0)	59·5 (50·0–70·0)
Sex		
Female	33 (33%)	5 (28%)
Male	68 (67%)	13 (72%)
Lactate dehydrogenase		
≤ULN	60 (59%)	9 (50%)
>ULN	41 (41%)	8 (44%)
≤2 × ULN	90 (89%)	15 (83%)
>2 × ULN	11 (11%)	2 (11%)
Not reported	0	1 (6%)
PD-L1 expression†		
≥1%	46/91 (51%)	6/16 (38%)
<1%	37/91 (41%)	8/16 (50%)
Indeterminant or not evaluable	8/91 (9%)	2/16 (13%)
BRAF mutation status		
Mutant	66 (65%)	8 (44%)
Wild-type	33 (33%)	8 (44%)
Not reported	2 (2%)	2 (11%)
NRAS mutation status		
Mutant	7 (7%)	1 (6%)
Wild-type	19 (19%)	1 (6%)
Not reported	75 (74%)	16 (89%)
Previous systemic therapy		
Adjuvant‡	11 (11%)	2 (11%)
Metastatic§	6 (6%)	2 (11%)
Previous SRT		
0	92 (91%)	15 (83%)
1	5 (5%)	3 (17%)
2	3 (3%)	0
≥3	1 (1%)	0
Sum of intracranial target lesion diameters, mm	15·0 (8·0–27·6)	26·0 (13·6–34·0)
Intracranial target lesions‖		
No lesions	1 (1%)	0
1–2 lesions	78 (77%)	11 (61%)
≥3 lesions	22 (22%)	7 (39%)

Data are median (IQR) or n (%). SRT=stereotactic radiotherapy. ULN=upper limit of normal. *16 (89%) of 18 patients had neurological symptoms or signs at baseline and two (11%) had symptoms of night sweats and anorexia recorded (ie, not definitively neurological); one of these two patients had neurological symptoms or signs recorded within 1 month of screening. †Expression assessed with a validated automated immunohistochemical assay (PD-L1 IHC 28-8 pharmDx; Dako, an Agilent Technologies company, Santa Clara, CA, USA). ‡Including four patients with targeted therapy (one monotherapy and three combination) in asymptomatic patients. §Including five patients with targeted therapy combination (asymptomatic patients); both patients in the symptomatic cohort received targeted therapy combination. ‖Per investigator assessment; inclusion of one patient in the asymptomatic cohort with no lesion was a protocol deviation.

Table 1: **Baseline characteristics**

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	Asymptomatic patients (n=101)			Symptomatic patients (n=18)		
	Intracranial	Extracranial	Global	Intracranial	Extracranial	Global
Best overall response*						
Complete response	33 (33%)	16 (16%)	17 (17%)	3 (17%)	1 (6%)	1 (6%)
Partial response	21 (21%)	33 (33%)	35 (35%)	0	3 (17%)	3 (17%)
Stable disease ≥6 months	4 (4%)	5 (5%)	4 (4%)	0	0	0
Progressive disease	30 (30%)	17 (17%)	26 (26%)	11 (61%)	7 (39%)	10 (56%)
Not evaluable for clinical benefit rate	13 (13%)	30 (30%)	19 (19%)	4 (22%)	7 (39%)	4 (22%)
Death prior to first on-study assessment	2 (2%)	3 (3%)	3 (3%)	2 (11%)	1 (6%)	1 (6%)
Early discontinuation due to study toxicity	1 (1%)	1 (1%)	1 (1%)	0	0	0
Stable disease <6 months	6 (6%)	14 (14%)	10 (10%)	2 (11%)	3 (17%)	1 (6%)
No extracranial disease at baseline	NA	7 (7%)	0	NA	1 (6%)	0
Other†	4 (4%)	5 (5%)	5 (5%)	0	2 (11%)	2 (11%)
Objective response rate‡	54/101 (53·5, 43·3–63·5)	49/101 (48·5, 38·4–58·7)	52/101 (51·5, 41·3–61·6)	3/18 (16·7, 3·6–41·4)	4/18 (22·2, 6·4–47·6)	4/18 (22·2, 6·4–47·6)
Clinical benefit rate§	58/101 (57·4, 47·2–67·2)	54/101 (53·5, 43·3–63·5)	56/101 (55·4, 45·2–65·3)	3/18 (16·7, 3·6–41·4)	4/18 (22·2, 6·4–47·6)	4/18 (22·2, 6·4–47·6)
Duration of response						
Ongoing responders/patients with objective response (%)	46/54 (85%)	38/49 (78%)	40/52 (77%)	3/3 (100%)‖	4/4 (100%)	4/4 (100%)
Median (95% CI), months	NR (NR–NR)	NR (32·8–NR)	NR (32·8–NR)	NR (NR–NR)	NR (NR–NR)	NR (NR–NR)

Data are n (%) or n/N (%, 95% CI), unless otherwise stated. NA=not applicable. NR=not reached. *Best overall response was assessed by the investigators in accordance with Response Evaluation Criteria in Solid Tumors version 1.1 (modified criteria were used for intracranial response). †Asymptomatic: total of five patients for all three response categories (intracranial, extracranial, and global): one patient withdrew consent (all three categories), one patient stopped study (extracranial and global categories), one patient for gamma knife therapy (all three categories), one patient for extracranial lesion procedure not done (extracranial and global); one patient did not receive any on-study scans (all three categories); symptomatic: insufficient radiographical scan data (two patients; extracranial and global). ‡Data include patients with a complete response or partial response; 95% CI based on Clopper-Pearson method. §Data include patients with a complete response, partial response, or stable disease for 6 months or longer; 95% CI based on Clopper-Pearson method. ‖Previously reported as 3/4 because one patient had disease progression followed by a response;[14] currently reported per the analysis for concordance with blinded independent central review.

Table 2: **Response to treatment (investigator assessment)**

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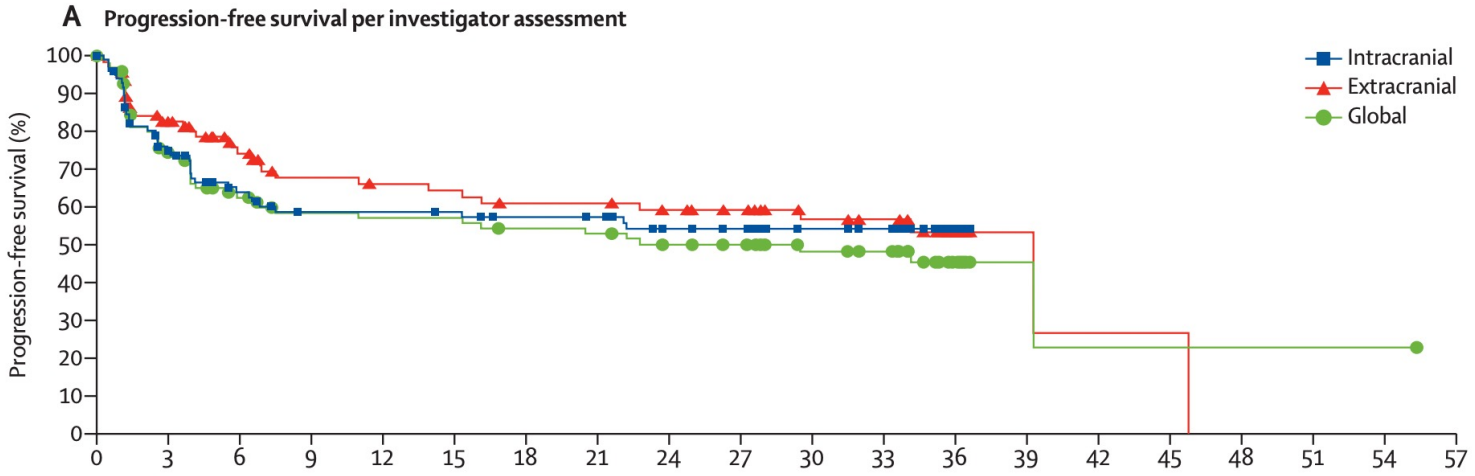
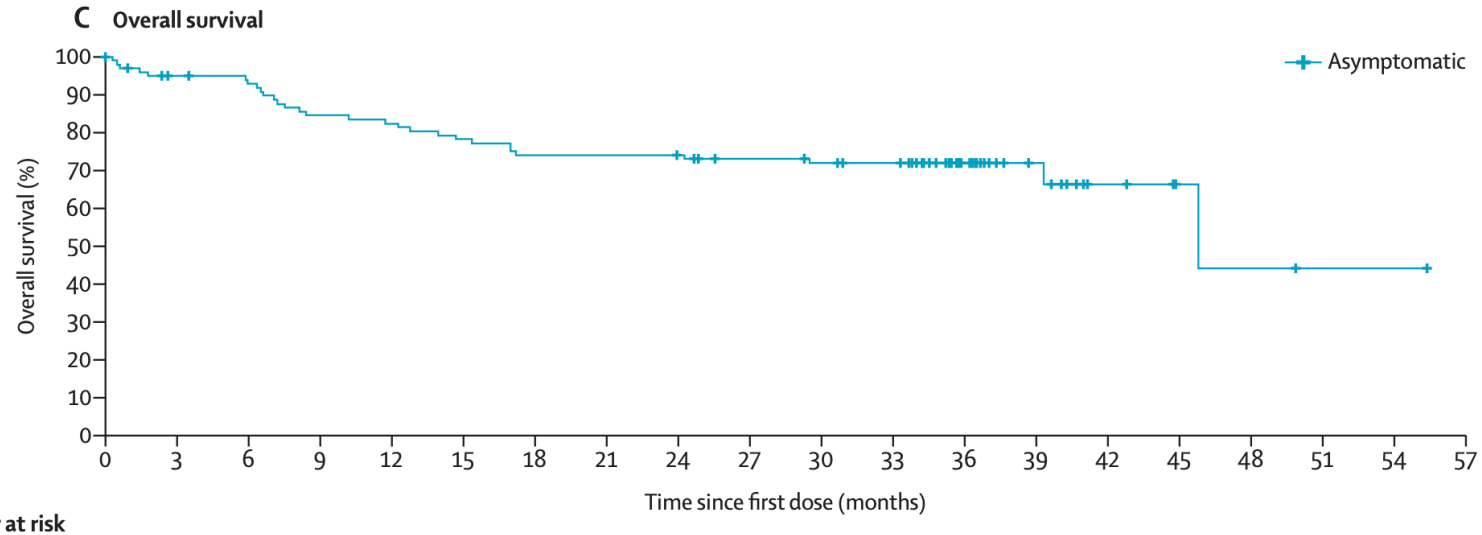
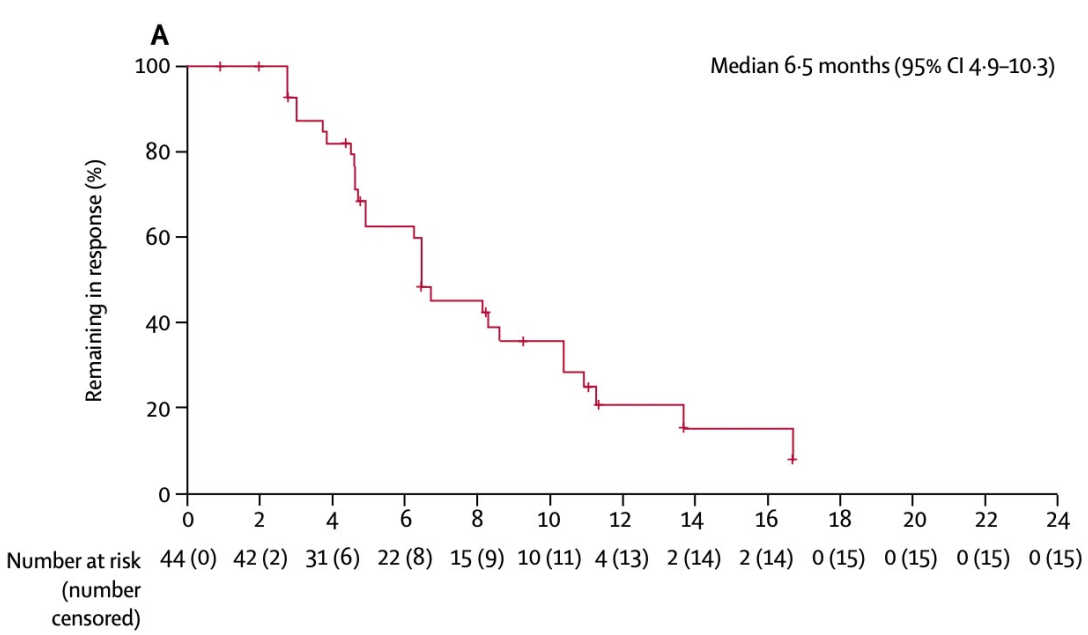


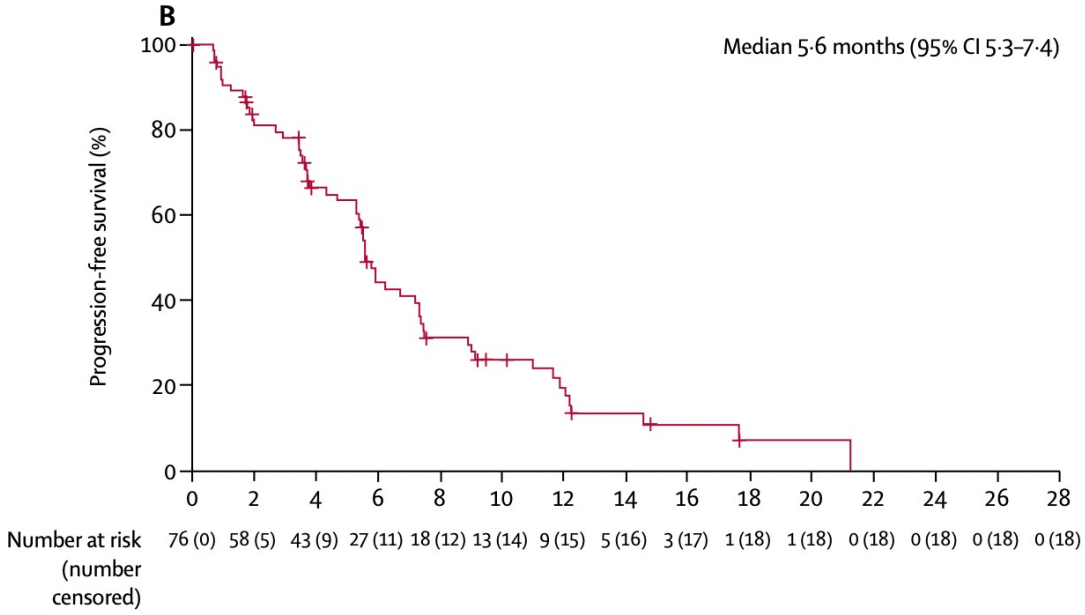
Number at risk (number censored)																				
Intracranial	101	66	50	43	43	42	39	38	32	30	24	22	6	0	0	0	0	0	0	0
	(0)	(11)	(18)	(21)	(21)	(22)	(24)	(25)	(29)	(31)	(37)	(39)	(55)	(61)	..	..	..	..	..	..
Extracranial	101	64	49	41	39	38	35	35	32	29	22	20	8	2	1	1	0	0	0	0
	(0)	(22)	(31)	(35)	(36)	(36)	(37)	(37)	(39)	(42)	(48)	(50)	(61)	(67)	(67)	(67)	(67)	..	..	..
Global	101	65	49	43	42	42	39	38	34	32	25	23	8	2	1	1	1	1	1	0
	(0)	(12)	(18)	(21)	(21)	(21)	(22)	(22)	(24)	(26)	(32)	(34)	(48)	(54)	(54)	(54)	(54)	(54)	(54)	(55)



Number at risk (number censored)																				
Asymptomatic	101	92	89	81	79	75	71	71	70	66	64	62	30	13	6	3	2	1	1	0
	(0)	(4)	(5)	(5)	(5)	(5)	(5)	(5)	(6)	(9)	(10)	(12)	(44)	(61)	(67)	(70)	(70)	(71)	(71)	(72)

TARGETED THERAPY





CONCLUSIONS

- There are a number of good options for melanoma patients with brain metastases
- Ipi/nivo is currently supported by Phase 2 data
- SRS and surgery have excellent local control rates
- Combining SRS and immunotherapy is an option to consider