



8TH ANNUAL BRAIN METASTASES RESEARCH AND EMERGING THERAPY CONFERENCE
SEPTEMBER, 21-22 2018 • MARSEILLE, FRANCE

WHAT'S HOT IN MELANOMA CNS METASTASES?

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Disclosure: no conflict of interests to declare

UPMC LIFE
CHANGING
MEDICINE

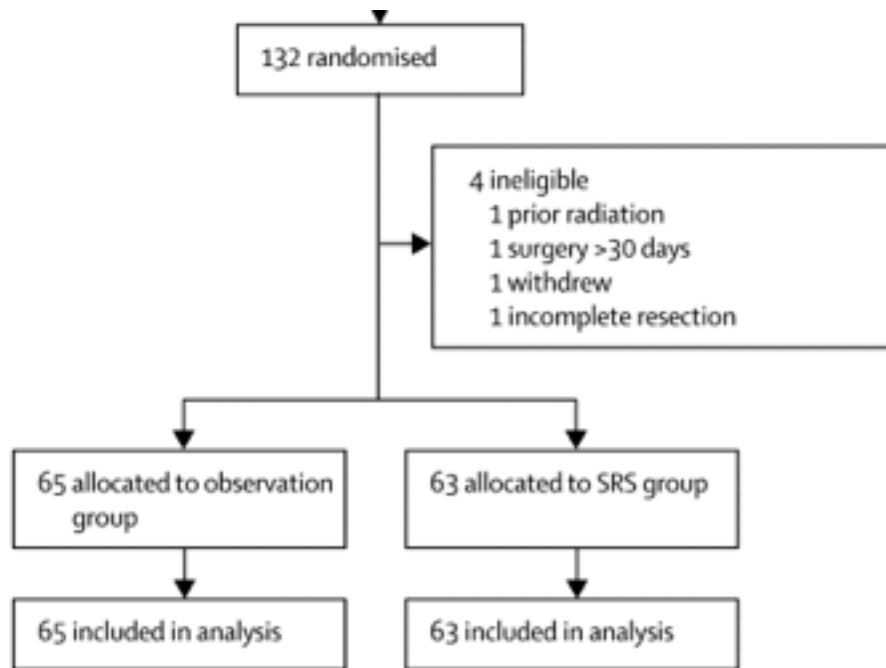
Marseille, September 21-22, 2018

- *Radiation treatment for brain metastases (an evolving paradigm);*
- *Immunotherapy/targeted therapy for brain metastases*
- *Combining SRS with Immunotherapy*

The addition of WBRT to SRS/Surgery has never been shown to improve OS

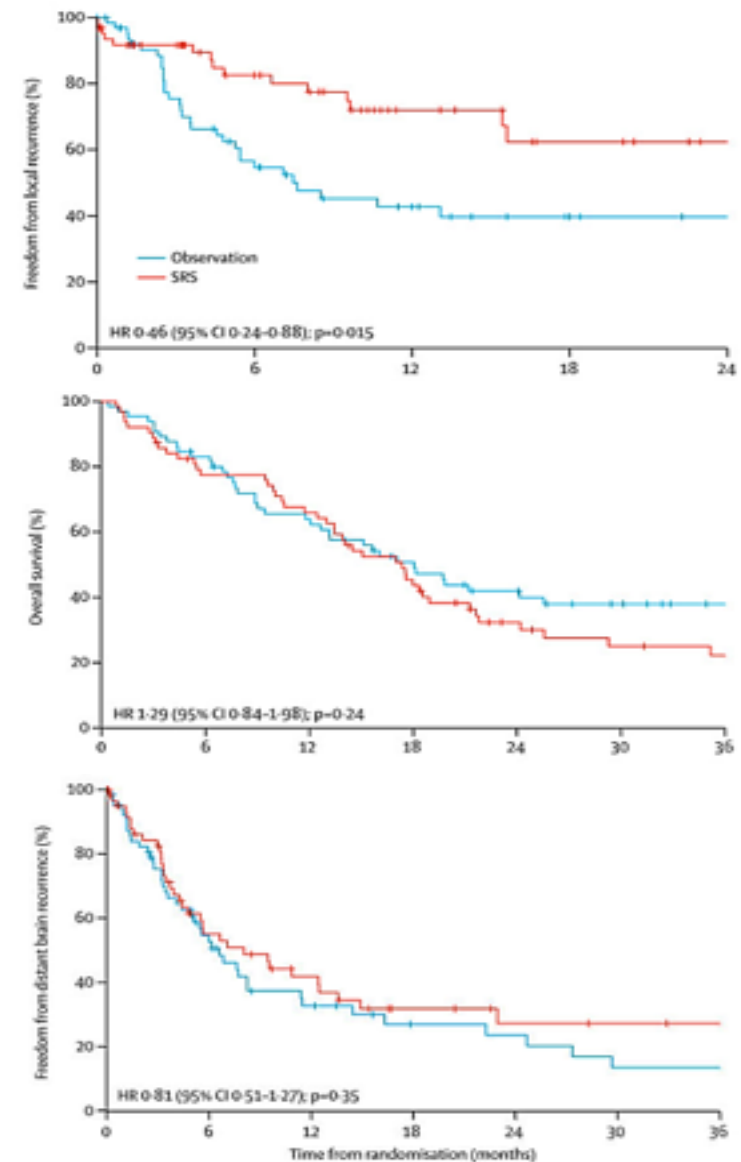
<i>Authors</i>	<i>Arms</i>	<i>mOS</i>	<i>P value</i>
Patchell, 1998	<i>Surgery</i>	9.9	0.39
	<i>Surgery + WBRT</i>	11.1	
Kocher, 2011	<i>SRS/Surgery</i>	10.9	0.89
	<i>SRS/Surgery + WBRT</i>	10.7	
Aoyama, 2006	<i>SRS</i>	8.0	0.42
	<i>SRS + WBRT</i>	7.5	
Chang, 2009	<i>SRS</i>	15.2	0.003
	<i>SRS + WBRT</i>	5.7	
Brown, 2016	<i>SRS</i>	10.4	0.92
	<i>SRS + WBRT</i>	7.4	

Postoperative SRS to resection cavity



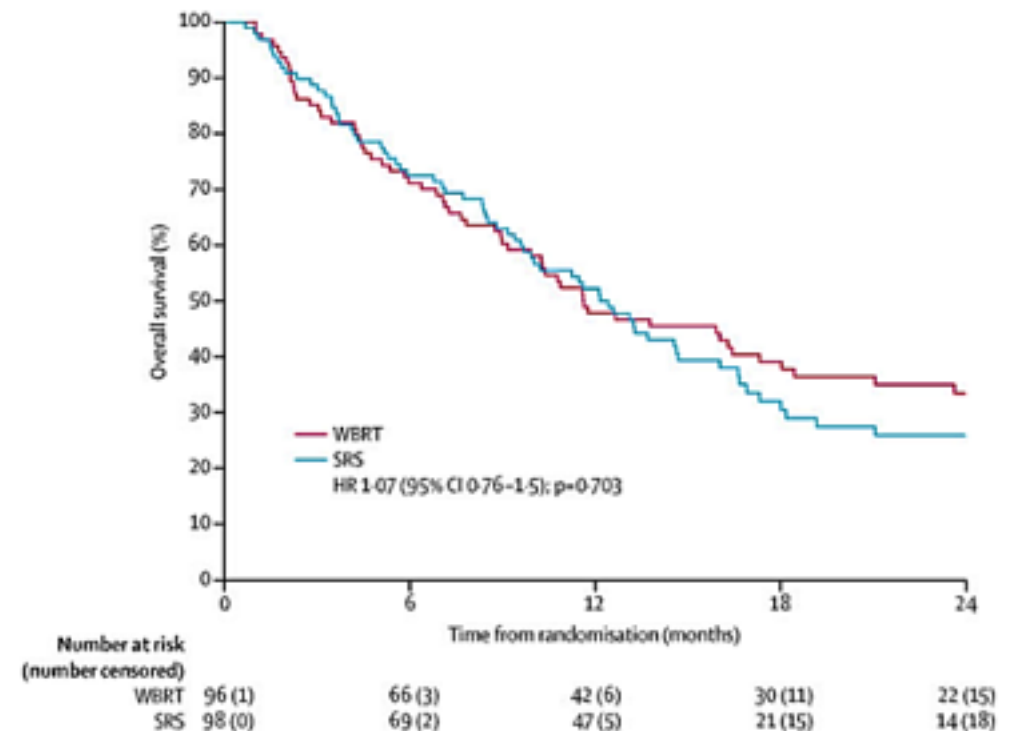
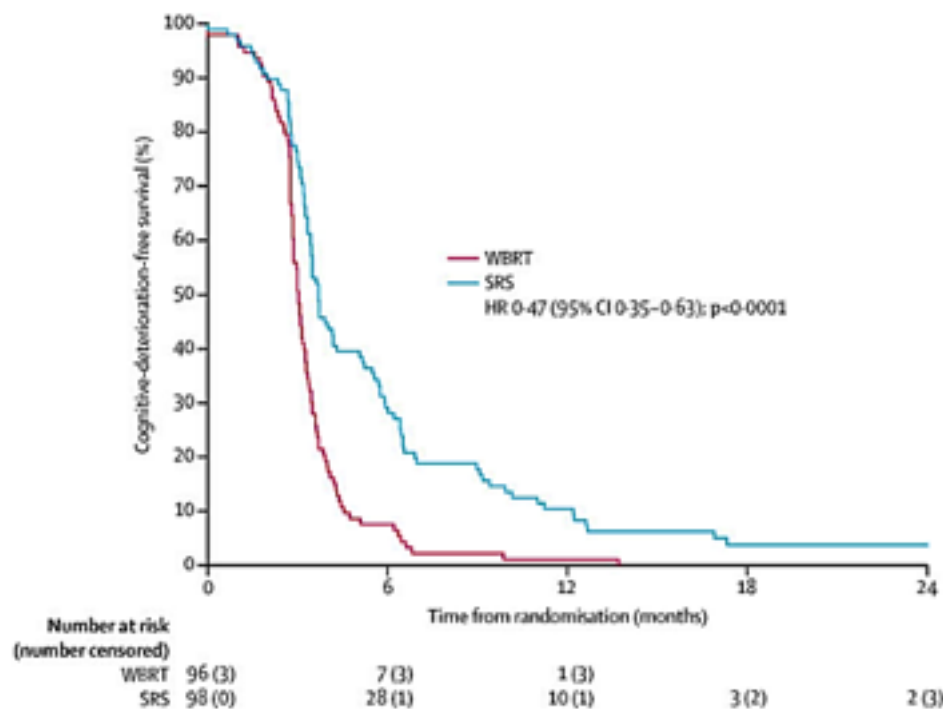
Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial

Mahajan et al, Lancet Oncology, 2017



Postoperative SRS to resection cavity

Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC-3): a multicentre, randomised, controlled, phase 3 trial



PD Brown et al, Lancet Oncology, 2017

Postoperative SRS to resection cavity

Stereotactic Radiosurgery for Resected Brain Metastases: New Evidence Supports a Practice Shift, but Questions Remain

By Giuseppe Minniti, MD, PhD, Scott G. Soltys, MD, Lia M. Halasa, MD, John C. Breneman, MD, Michael Chan, MD, Nadia N. Laack, MD, John P. Kirkpatrick, MD

International Journal of
Radiation Oncology
biology • physics

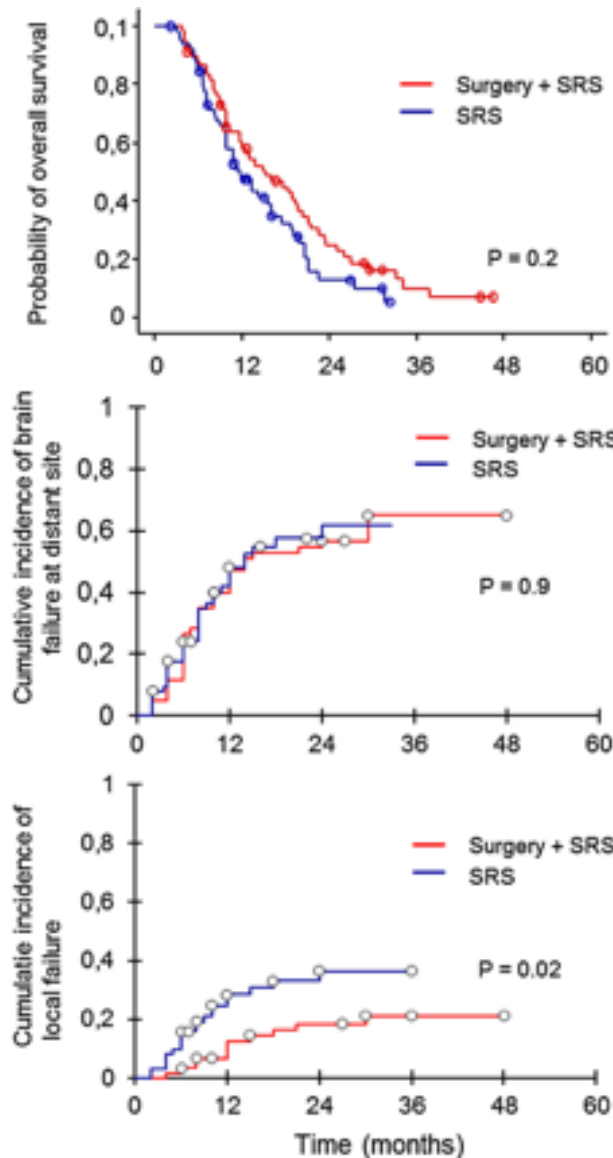
www.redjournal.org

- *Timing of SRS*
- *Which target delineation*
- *Which dose/fractionation*
- *Which histologies can benefit*
- *Post-SRS vs Pre-SRS*

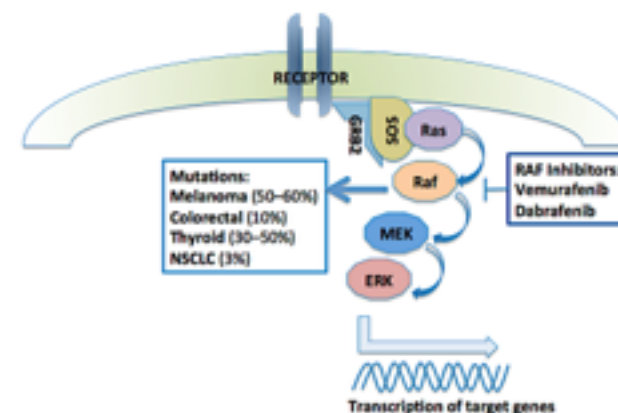
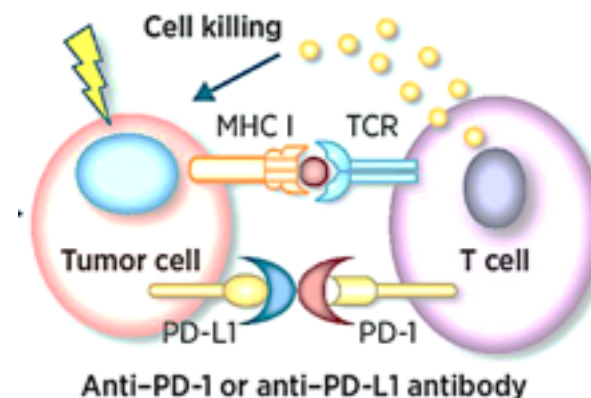
Postoperative SRS to resection cavity

Outcomes of postoperative stereotactic radiosurgery to the resection cavity versus stereotactic radiosurgery alone for melanoma brain metastases

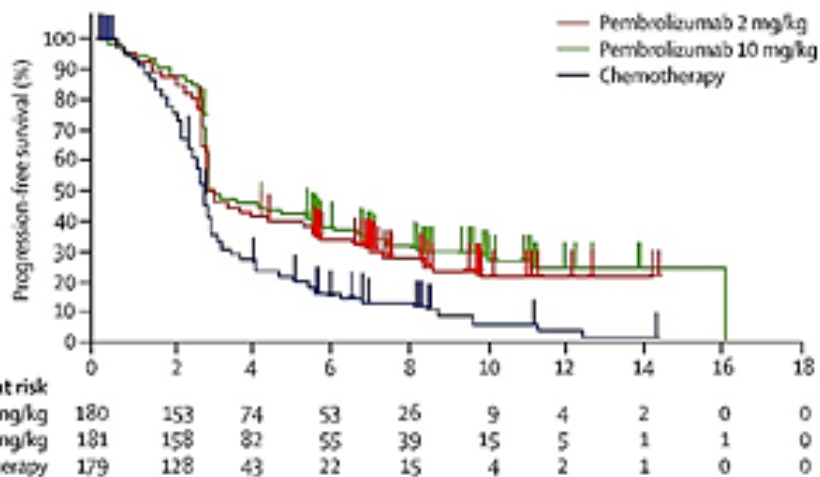
Outcome	Variable	Hazard ratio	95% CI	P
OS	Stable extracranial disease	0.54	0.34–0.92	0.03
	KPS > 70	0.57	0.40–0.91	0.03
	Age < 65 years	0.62	0.38–1.11	0.07
	Immunotherapy	0.45	0.27–0.83	0.02
	Single brain metastasis	0.55	0.35–0.96	0.04
DBF	Immunotherapy	0.44	0.27–0.92	0.03
	Age < 65 years	0.82	0.60–1.40	0.2
	Stable extracranial disease	0.53	0.33–1.03	0.06
	Single brain metastasis	0.56	0.33–1.07	0.09
LF	S + fSRS	0.35	0.16–0.77	0.009
	Size of lesion < 3 cm	0.42	0.21–0.96	0.03
	Age < 65 years	0.63	0.39–1.38	0.2
	PTV	0.93	0.85–1.20	0.3
Risk of RN	Size of lesion < 3 cm	0.33	0.10–0.93	0.03
	Immunotherapy	0.63	0.41–1.19	0.18
	V _{18-Gy} < 32 ml	0.27	0.24–0.92	0.02



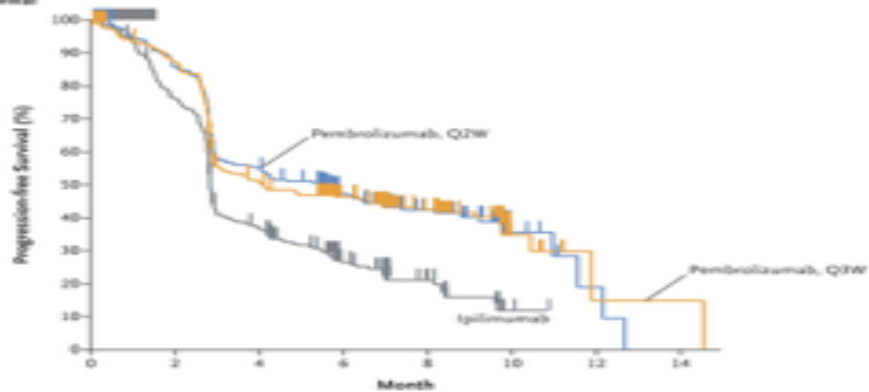
- *Radiation for melanoma brain metastases*
- *Immunotherapy/targeted therapy for brain metastases*
- *Combining SRS with Immunotherapy*



Activity of CPIs alone or in combination FOR patients with advanced melanoma

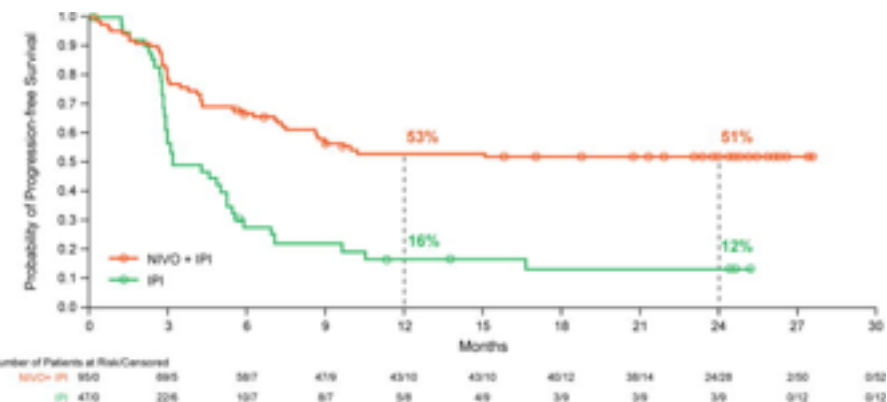
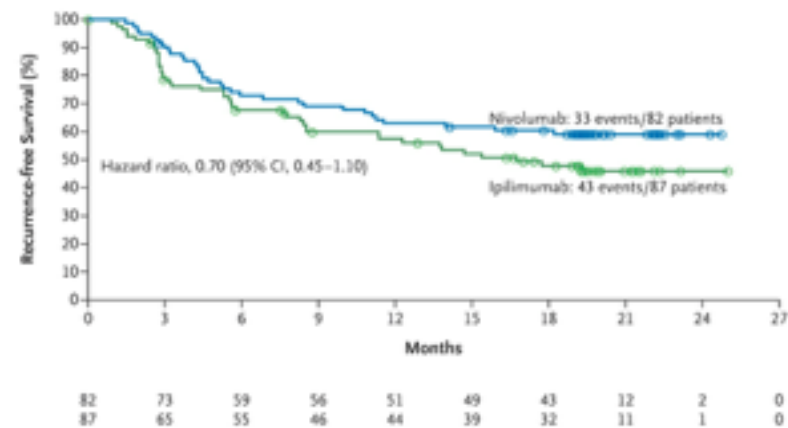


A. Progression-free Survival



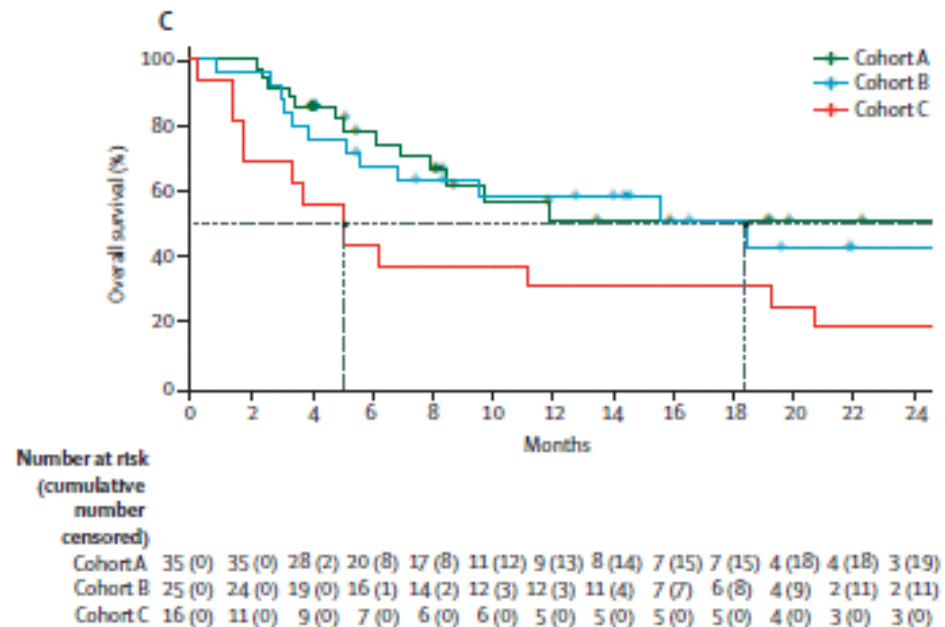
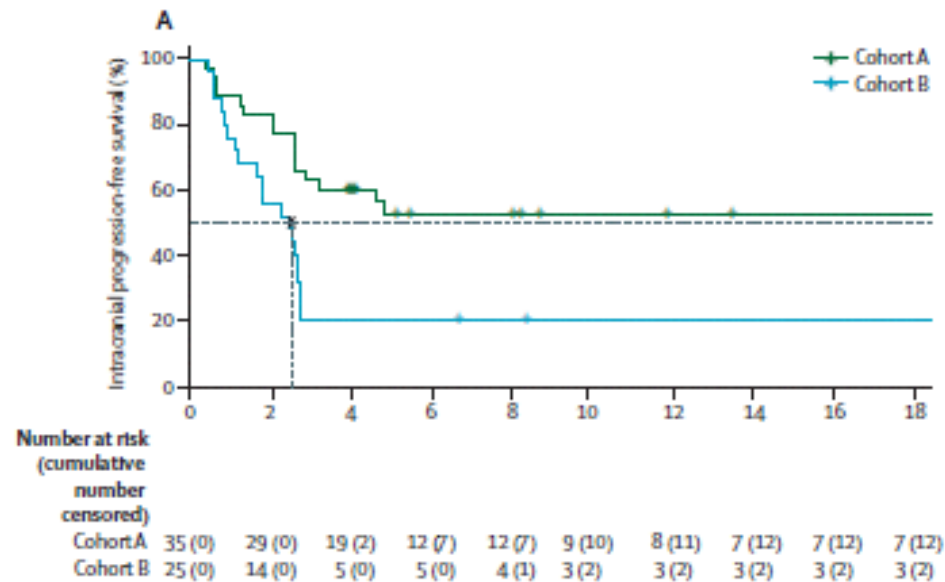
No. at Risk	0	2	4	6	8	10	12	14
Pembrolizumab, Q2W	279	233	147	98	49	7	2	0
Pembrolizumab, Q3W	277	235	133	95	53	7	1	0
Ipilimumab	278	186	88	42	18	2	0	0

Stage IV

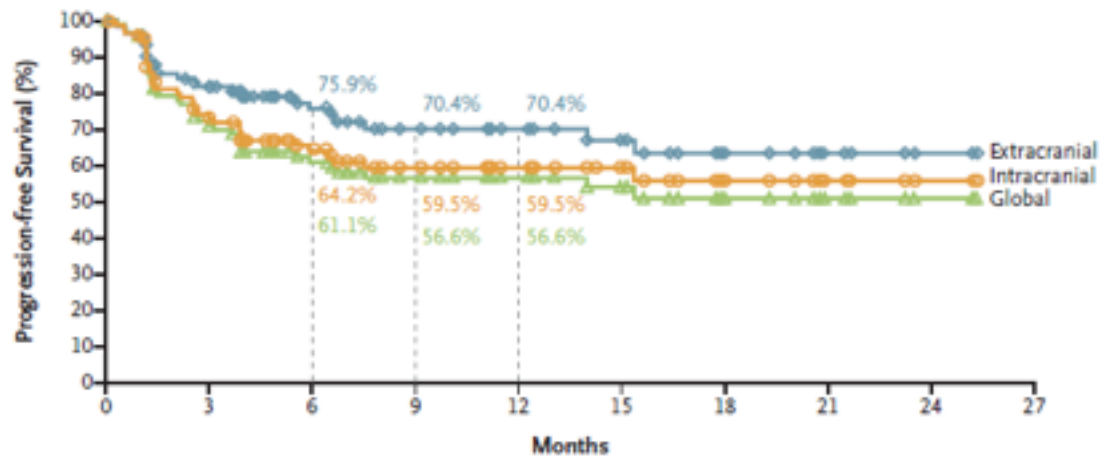


Ribas et al, Lancet Oncol 2015 , Weber et al, NEJM 2017,
Roberts et al, NEJM 2015, Hodi et al, Lancet Oncol 2016,

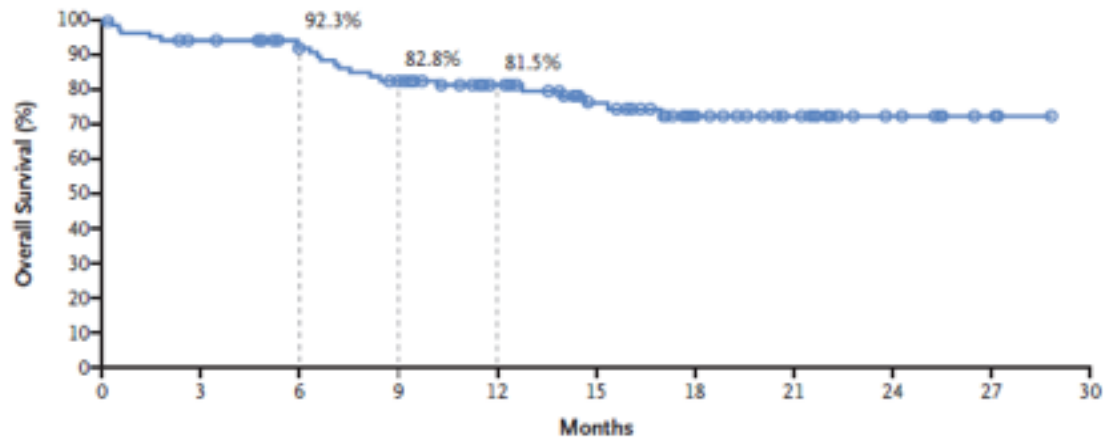
Combination nivolumab and ipilimumab vs nivolumab



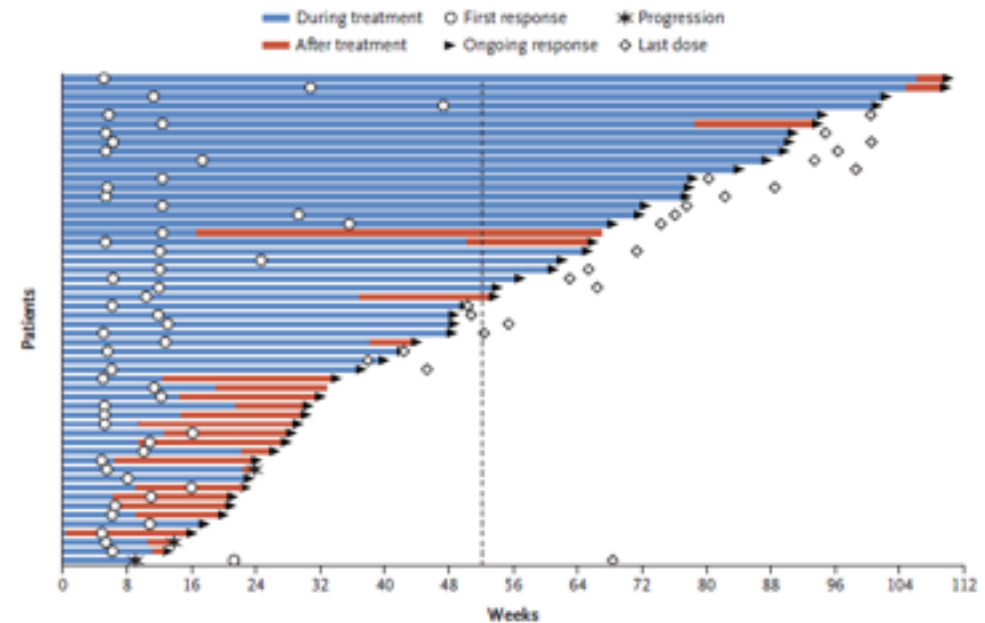
Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain



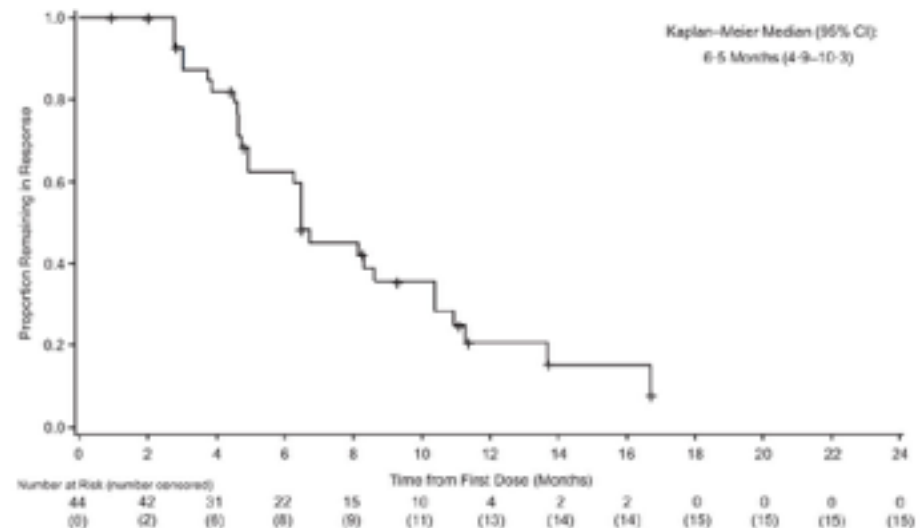
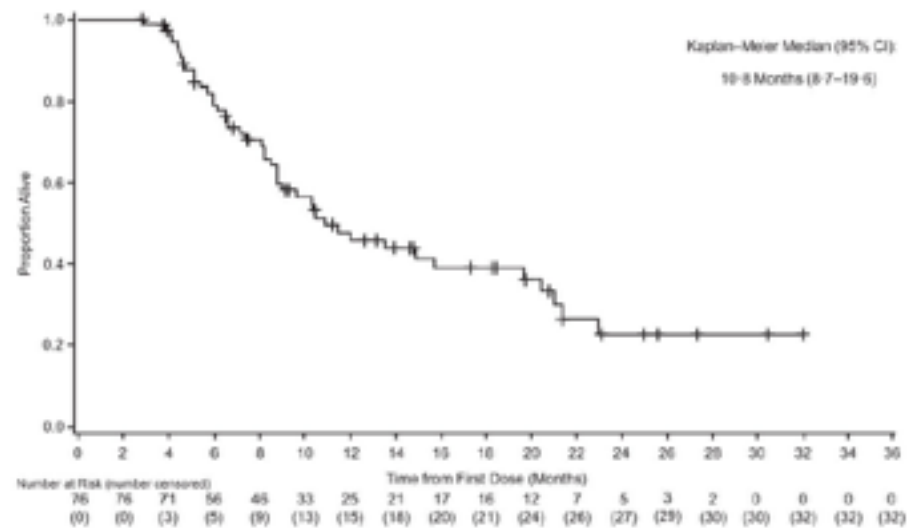
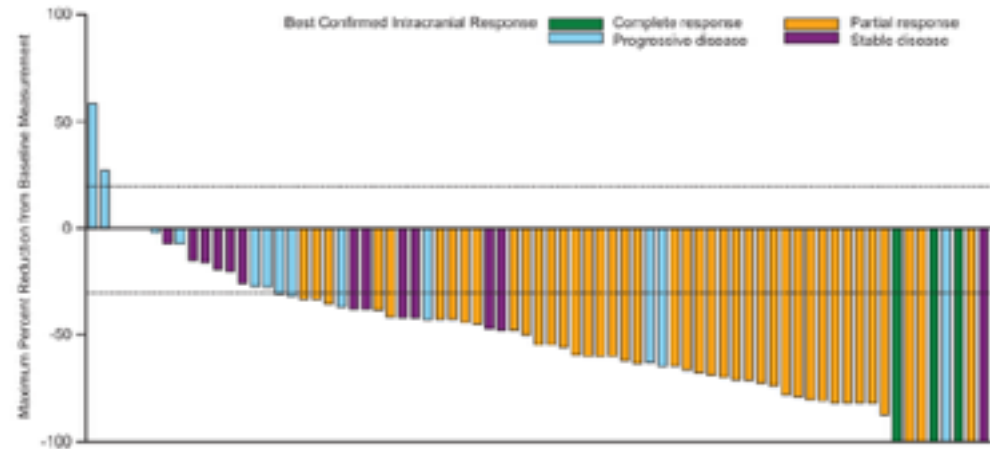
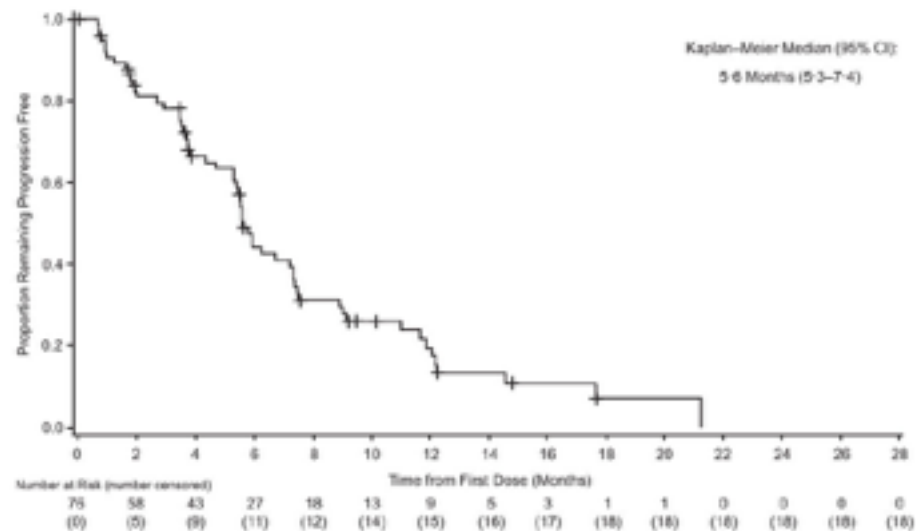
No. at Risk										
Extracranial	94	66	45	32	25	19	11	6	2	0
Intracranial	94	61	45	32	25	19	11	6	2	0
Global	94	60	44	32	25	19	11	6	2	0

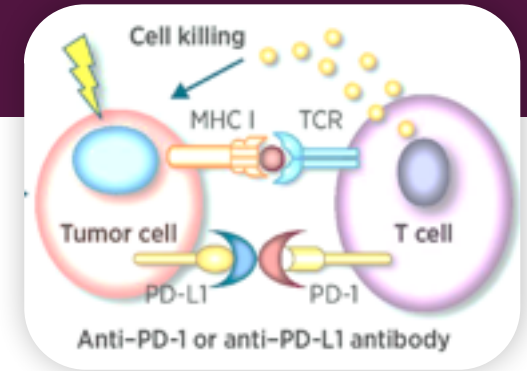


No. at Risk	94	86	78	69	54	41	27	19	9	3	0
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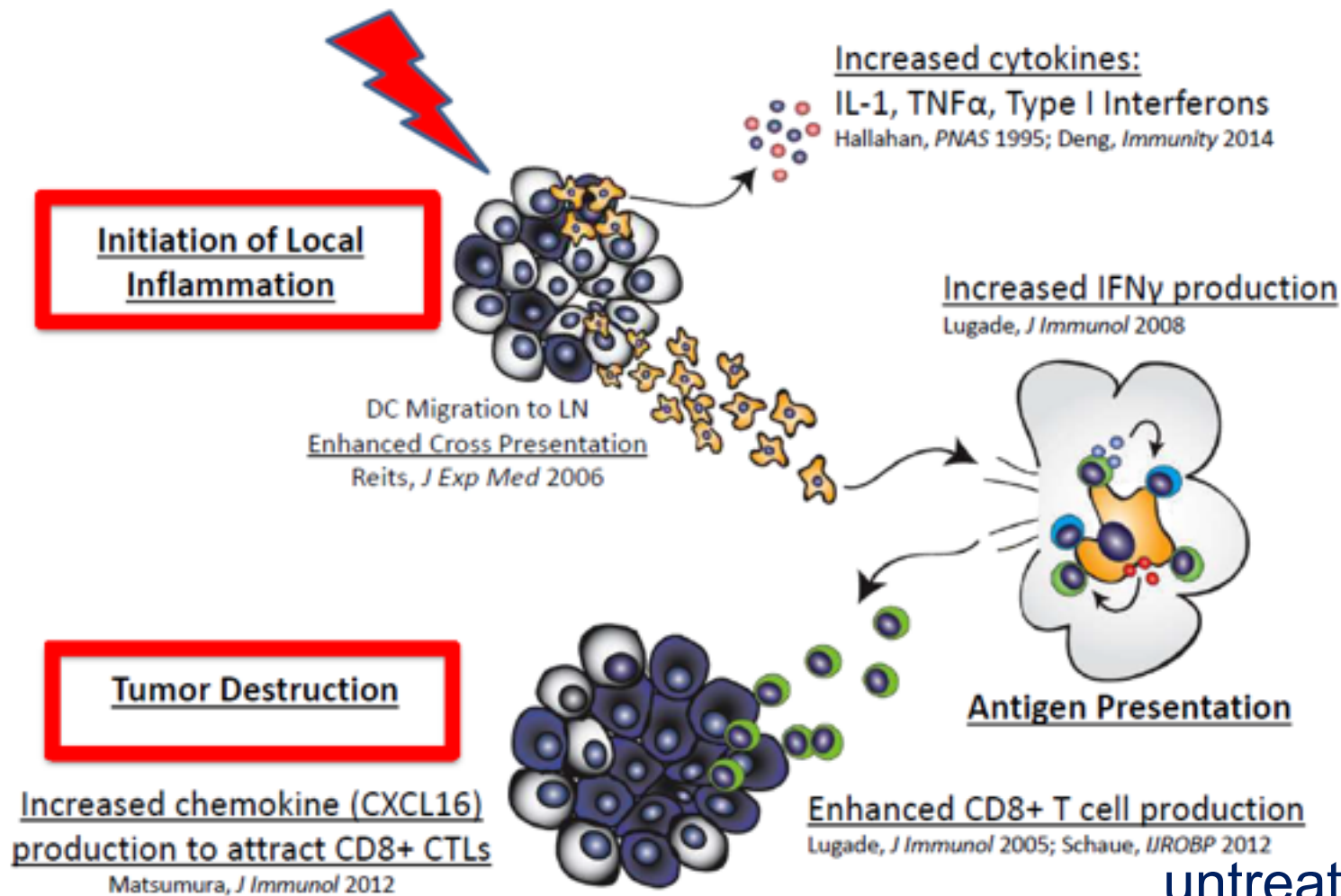
Dabrafenib plus trametinib in patients with *BRAF* V600–mutant melanoma brain metastases





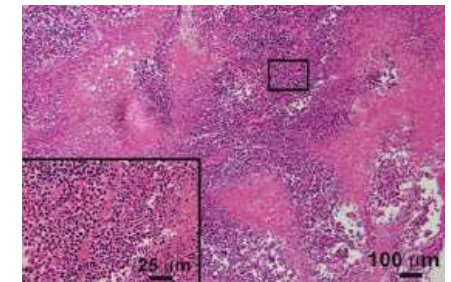
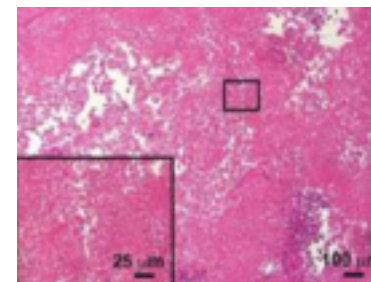
- *SRS for melanoma brain metastases*
- *Immunotherapy/targeted therapy for brain metastases*
- **Combining SRS with Immunotherapy**

Radiation is immunogenic and enhances multiple inflammatory pathways: *In situ* vaccination



untreated

treated 5 Gy



...But radiation can also be anti-inflammatory

Resolution of Immune Response (Repair)

Upregulation of PD-L1

Lugade, *J Immunol* 2005; Schaue, *IJROBP* 2012

Induction of regulatory T cells

Lugade, *J Immunol* 2005; Schaue, *IJROBP* 2012
(and thus down reg of CD8 cells)



Increased TGF β production

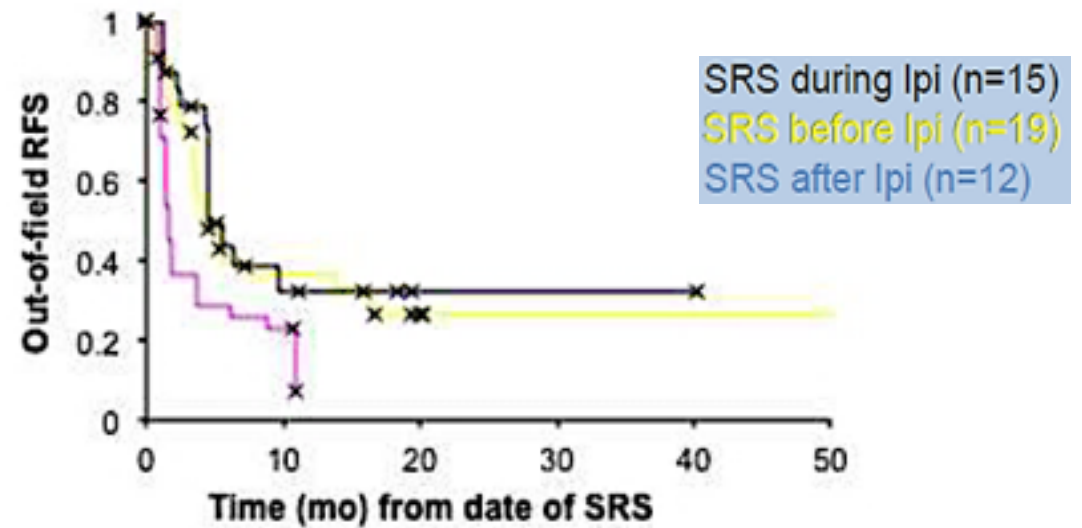
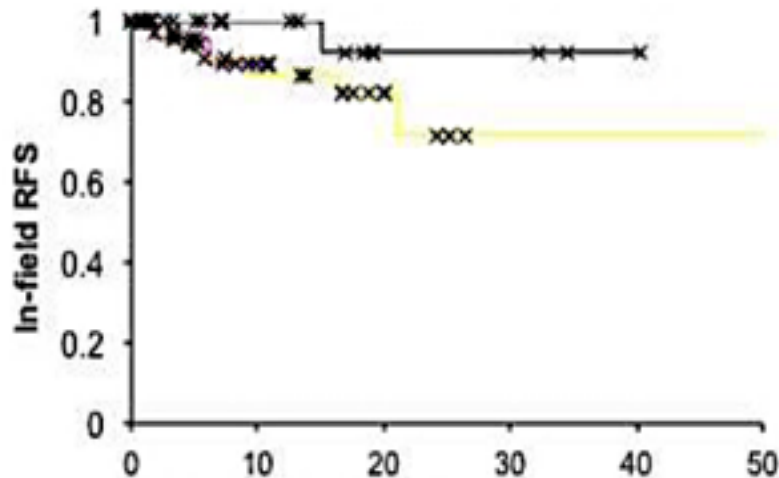
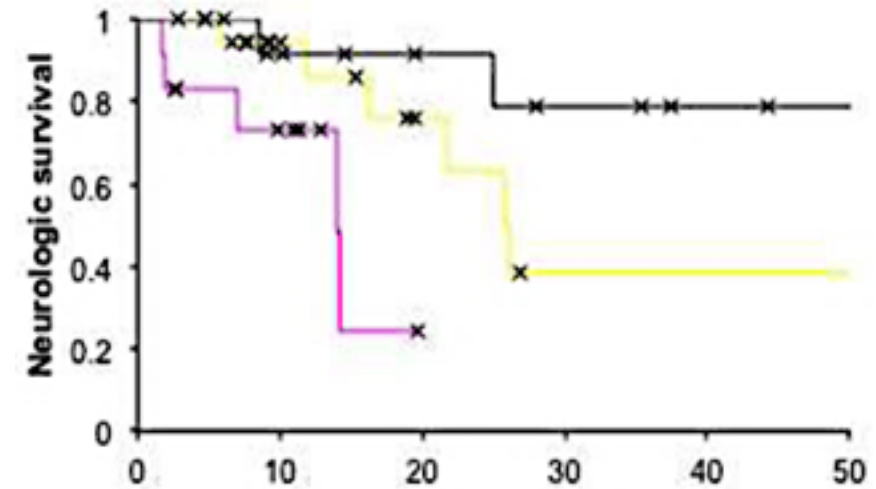
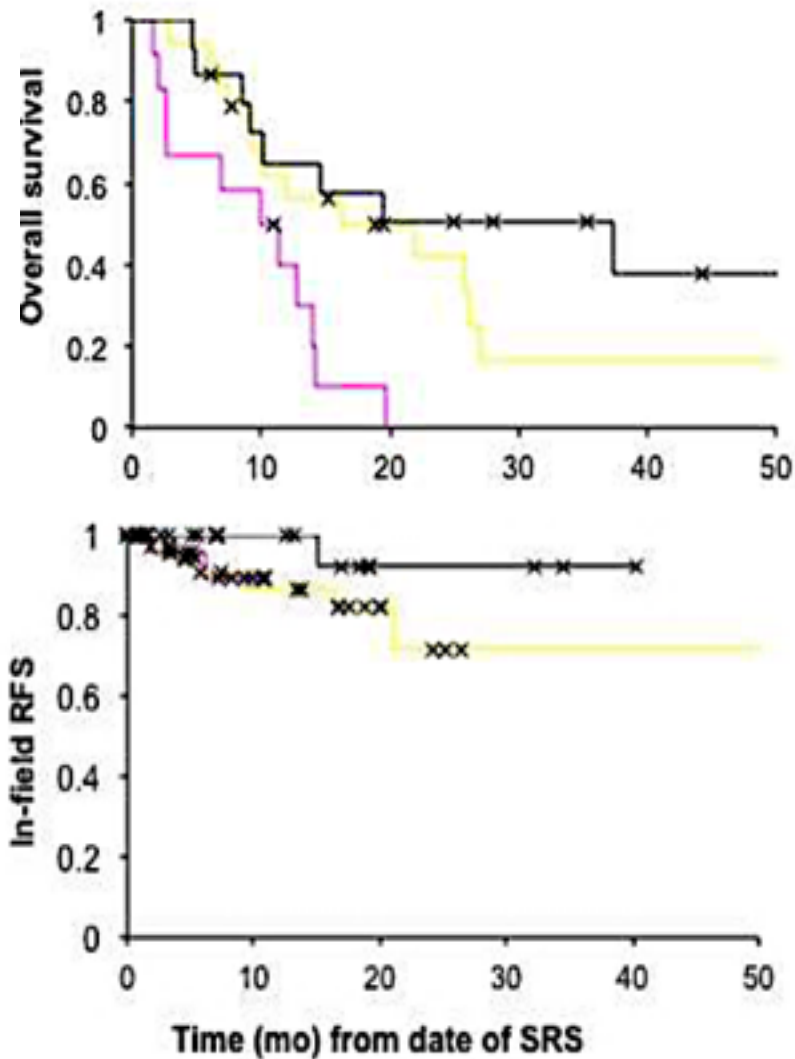
Lugade, *J Immunol* 2005; Schaue, *IJROBP* 2012

Radiation and CPIs for melanoma BM

Authors	Type of study	Patients	treatment	CNS- PFS	OS	Toxicity
Ahmed, 2016	Retrospective	21	Pembro/Nivo plus RT	6-month 61%, 12-month 38%	6-month 81%, 12-month 66%	0
		25	IPI	6-month 26%, 12-month 21%	6-month 84%, 12-month 50%	0
Parakh, 2017	Retrospective	66	Pembro/Nivo plus RT (64%)	f-up 7 months, CNSCr 56%^ f-up 9 months, CNSCr 70%	median 9.9 months	NR
Anderson , 2017	Retrospective	21	Pembro/Nivo plus RT	(RANO)	45% at 9 months f-up	0
		31	IPI	f-up 9 months, CNSCr 32%	NR	0
Goldberg, 2016	Prospective	18	Pembro	RR 22%	NR	12%
Chen, 2018	Retrospective	35	concurrent pembro/SRS-SR	NR	24.7 months	NR
		44	pembro and SRS-SRT	NR	14.5 months	NR
Gonzales, 2016	Retrospective	67 (10 BM)	pembro	40% had an objective response	NR	0
Cowey, 2018	Retrospective	168(41% BM)	pembro (41% with BM)	4.2 months (46% at 6 months)	61% at 12 months, median OS 6 months for patients with BM	NR
Nardin, 2018	Retrospective	25	pembro and SRS**	6-months LC 80% (8.4 months)	15.3 months	6.8%
Qian, 2016	Retrospective	75 (566bm)	IPI or pembro and SRS*	NR	concurrent 19.1 months	NR
				NR	non-concurrent 9 months	NR
Patel 2015	Retrospective	44	IPI plus SRS	12-month CNSCr 71.4%	12-month OS 37.1% median OS 12.4 months	NR
Kiess, 2015	Retrospective	46	IPI plus SRS	NR	12-month OS 60%	17.4%
Queirolo, 2014	Retrospective	146	IPI	CNSCr 27%	4.3 months	6%

**w ithin 6 months; *concomitant, w ithin 4 weeks; ^Pts w ith symptomatic BM had shorter PFS than those w ithout symptoms (2.7 vs 7.4 months, P=0.035)

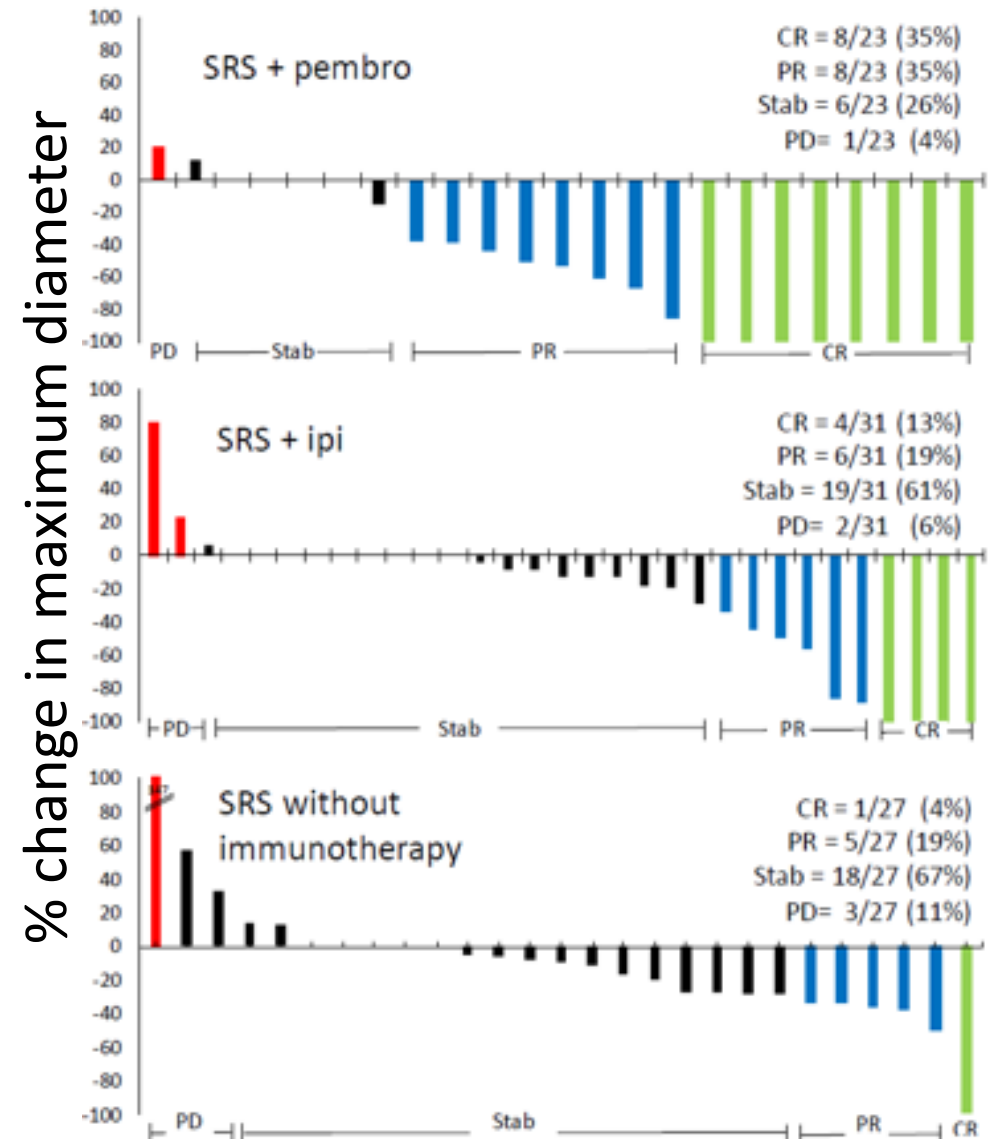
SRS with ipilimumab for melanoma BM



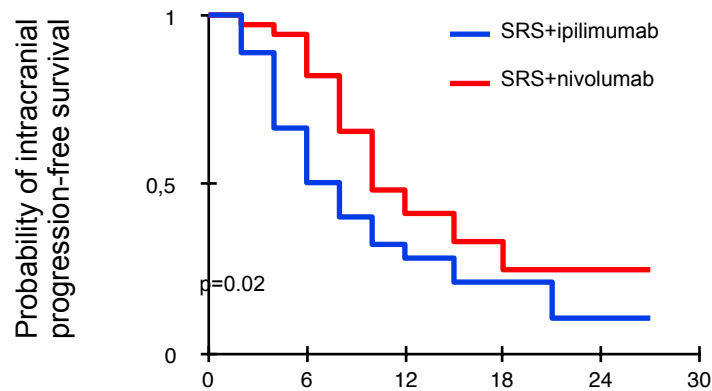
SRS with ipilimumab or pembrolizumab for melanoma BM

SRS Response rate at follow-up MRI

Treatment	Scan interval, d (range)	CR	PR	Stable	PD
SRS + pembro (n = 23)	57 (39-118)	8 (35%)	8 (35%)	6 (26%)	1 (4%)
SRS + ipi (n = 31)	53 (41-95)	4 (13%)	6 (19%)	19 (61%)	2 (6%)
SRS (n = 27)	51 (28-130)	1 (4%)	5 (19%)	18 (67%)	3 (11%)

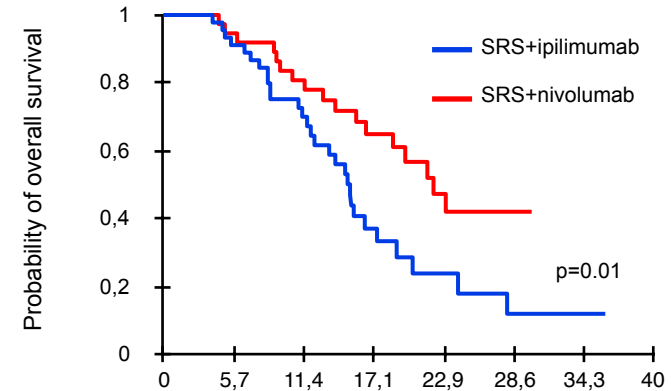


SRS with ipilimumab or nivolumab for melanoma brain BM



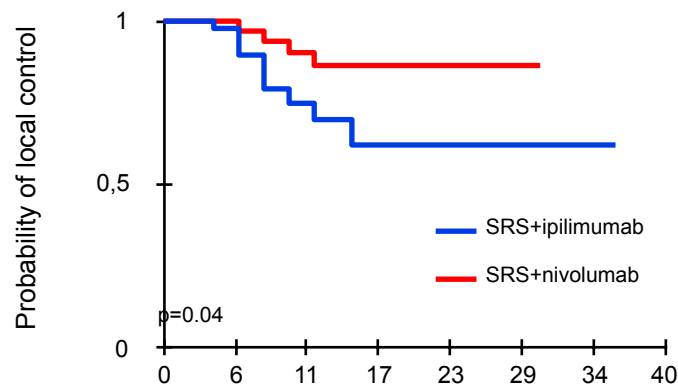
Number at risk:

	0	6	12	18	24	30
SRS+ipilimumab	45	29	8	3	2	
SRS+nivolumab	35	31	14	7	3	



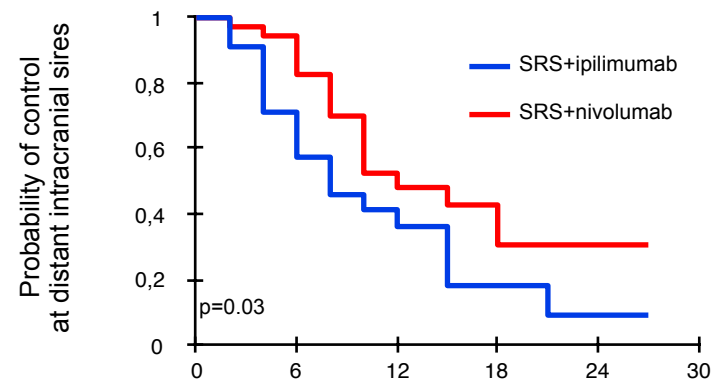
Number at risk:

	0	5,7	11,4	17,1	22,9	28,6	34,3	40
SRS+ipilimumab	45	42	24	7	4	2	1	
SRS+nivolumab	35	34	27	17	7	1	0	



Number at risk:

	0	6	11	17	23	29	34	40
SRS+ipilimumab	45	36	15	5	3	1	1	
SRS+nivolumab	35	33	23	13	8	1	0	

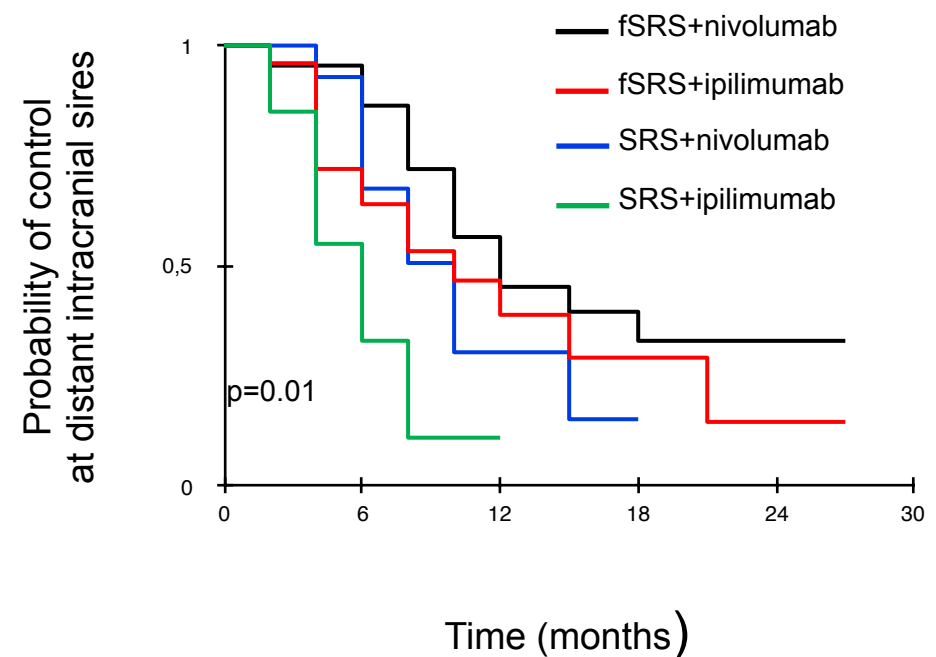
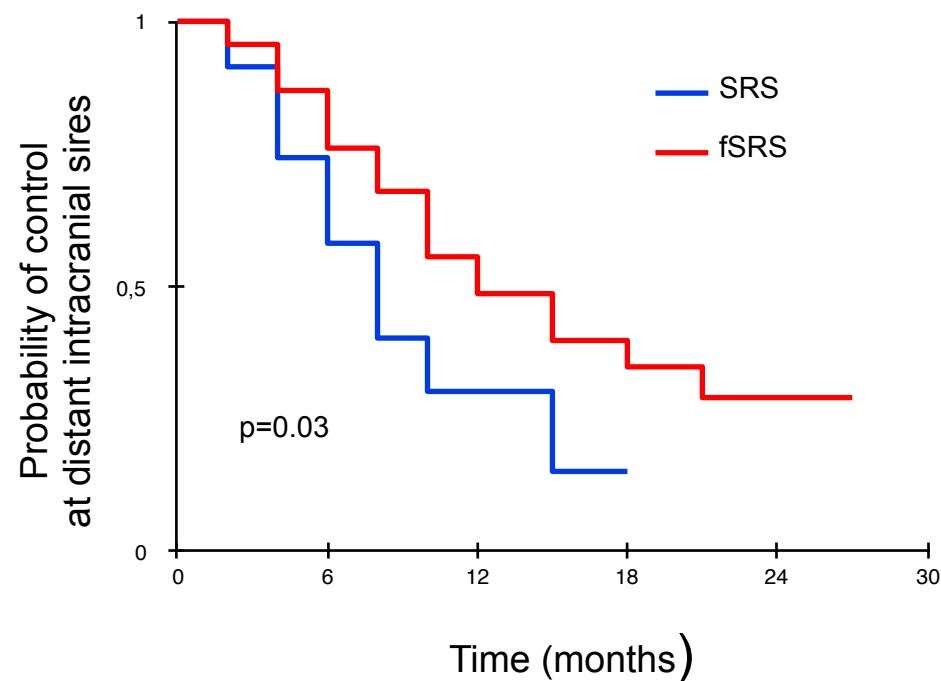


Number at risk:

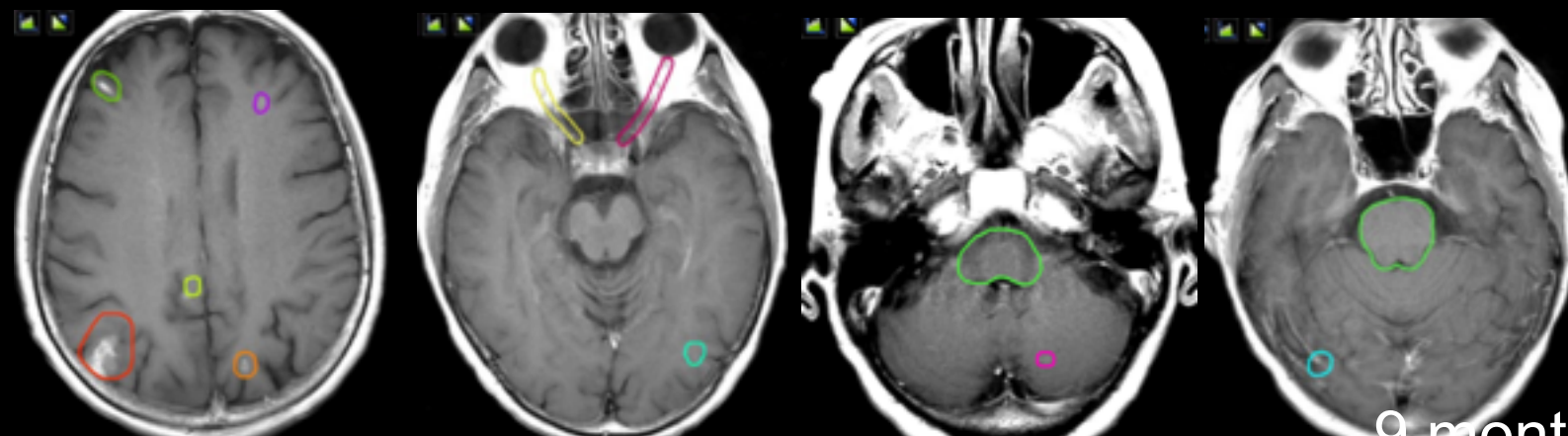
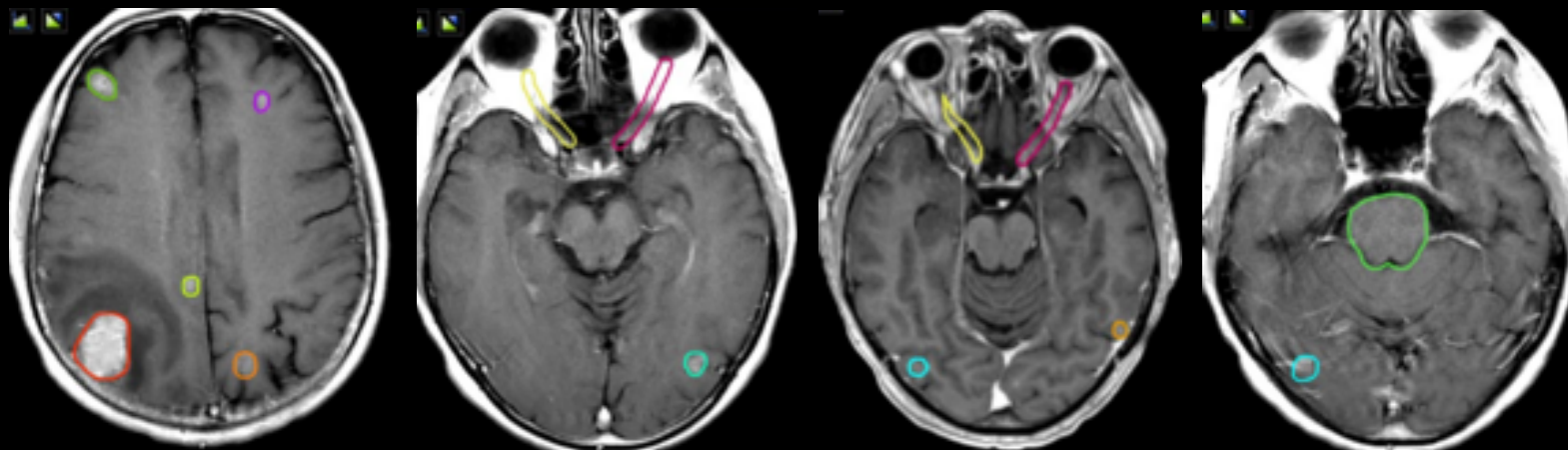
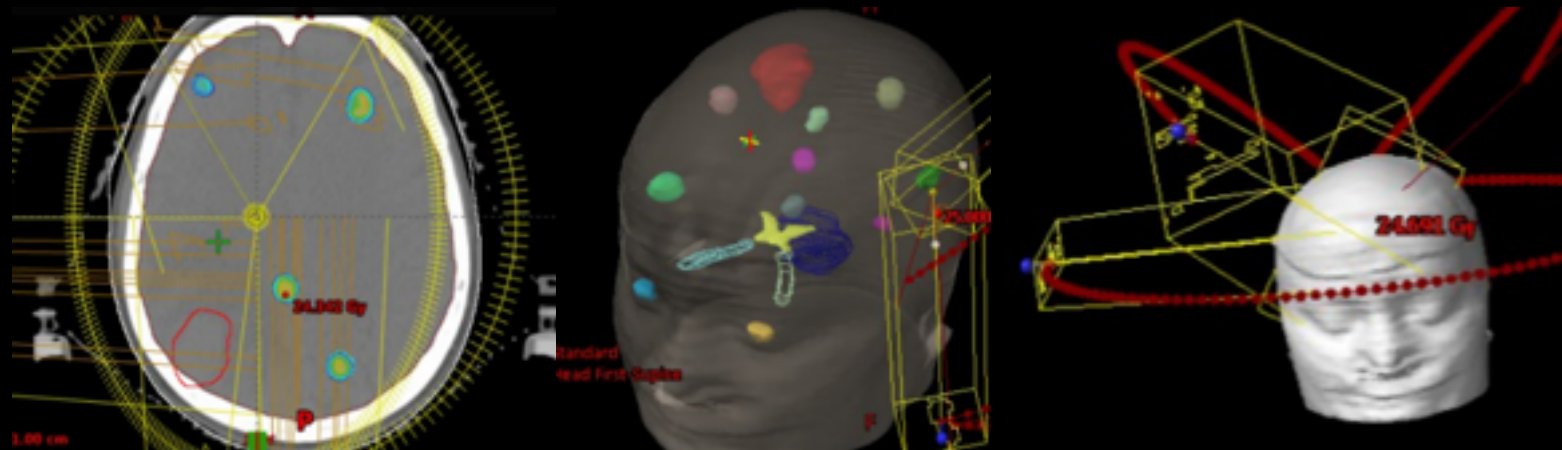
	0	6	12	18	24	30
SRS+ipilimumab	45	29	8	3	2	
SRS+nivolumab	35	31	14	7	3	

SRS with ipilimumab or nivolumab for melanoma

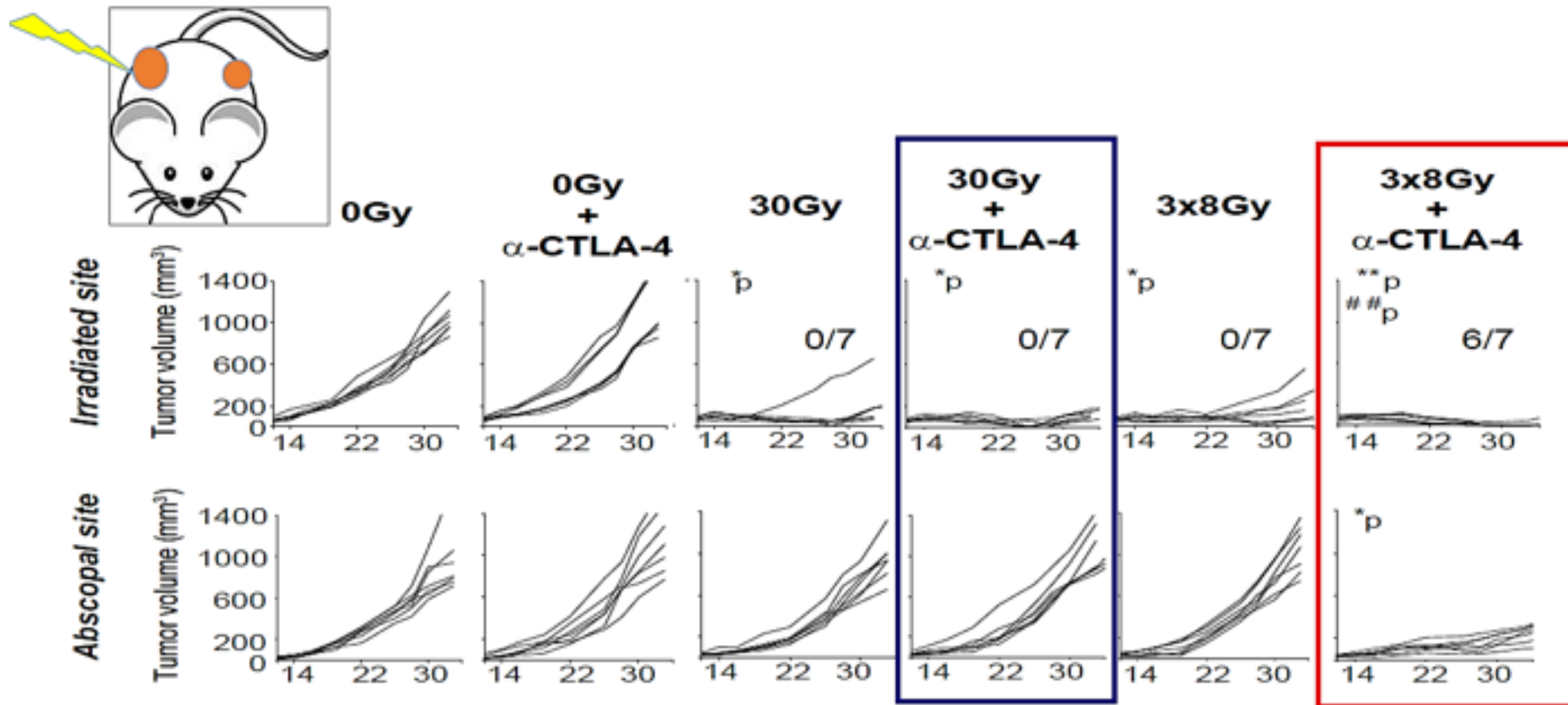
brain BM: single-fraction SRS vs multi-fraction SRS



SRS for multiple brain mets (n=10)

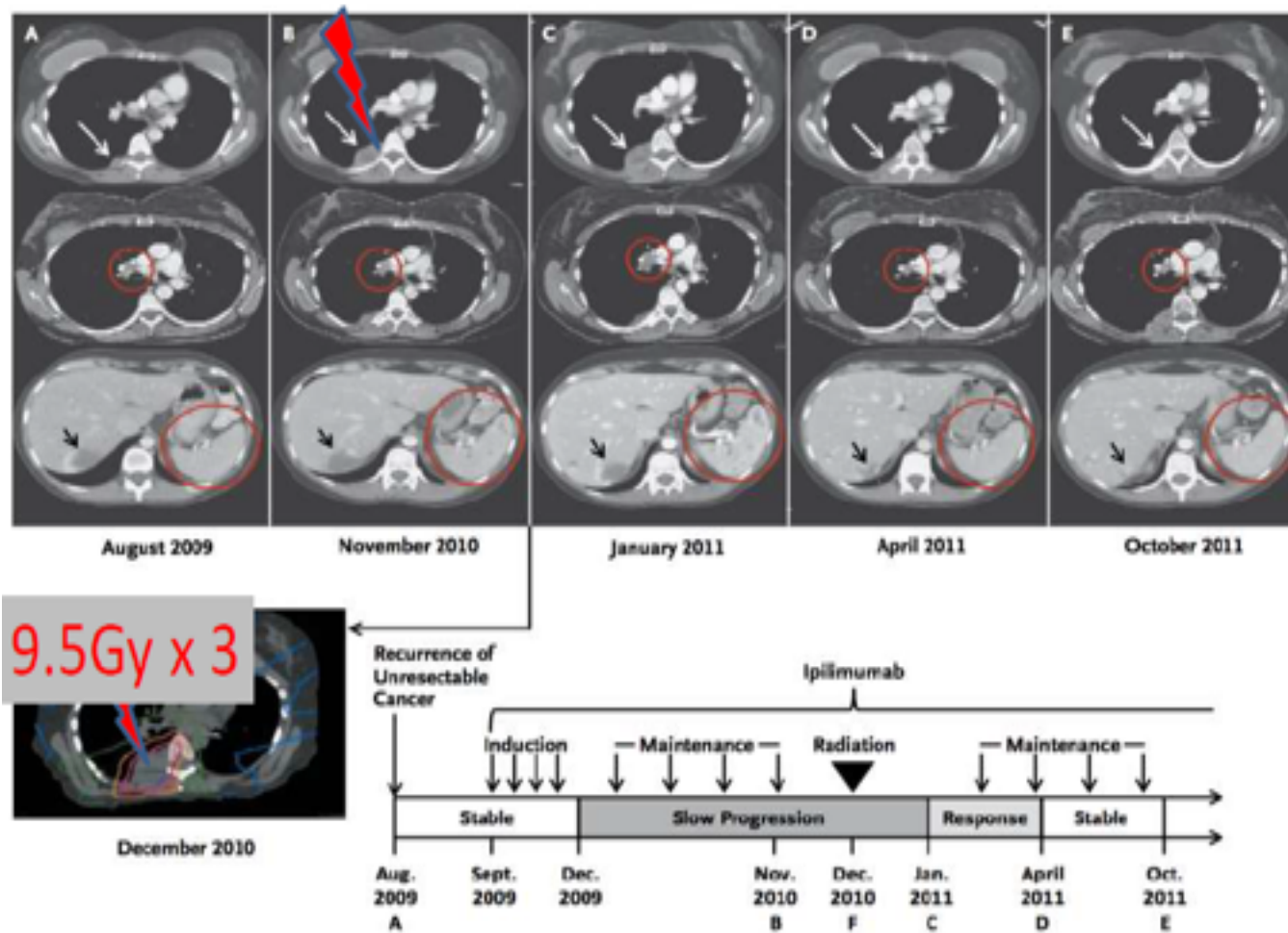


Radiation and anti-CTLA-4: dose-dependence of abscopal effects

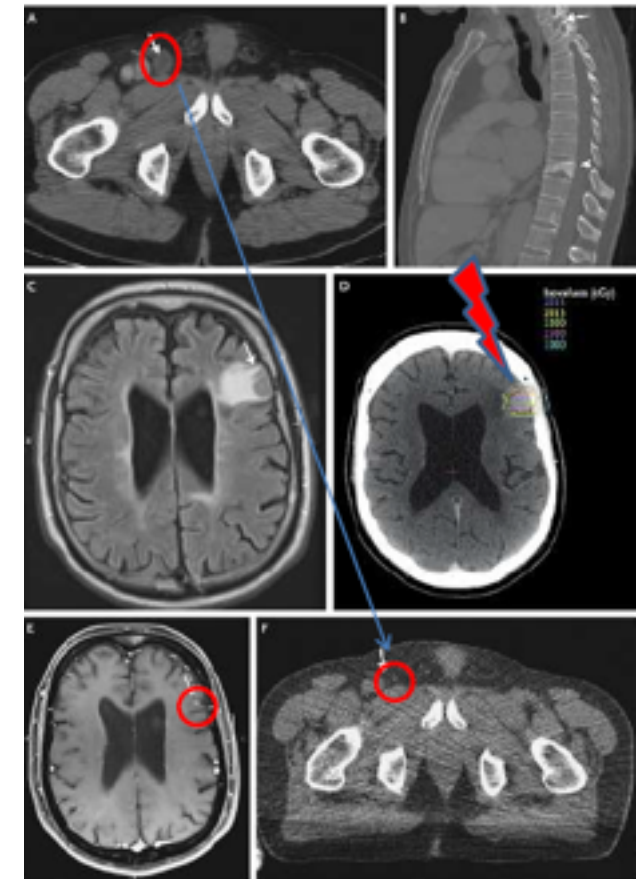


Vanpouille-Box et al., Nature Communications, June 2017

Cases of abscopal effect



Postow, Callahan, Barker et al. *N Engl J Med* Volume 366(10):925-931,2012



Sullivan et al. *NEJM* 2013

Conclusions

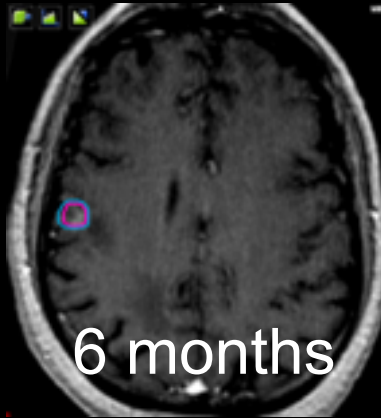
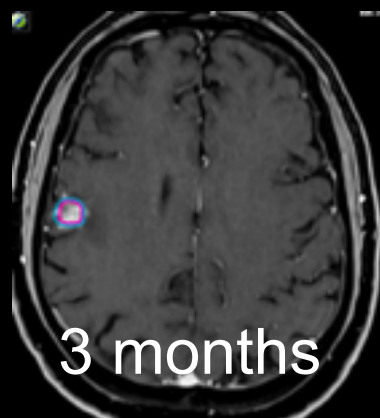
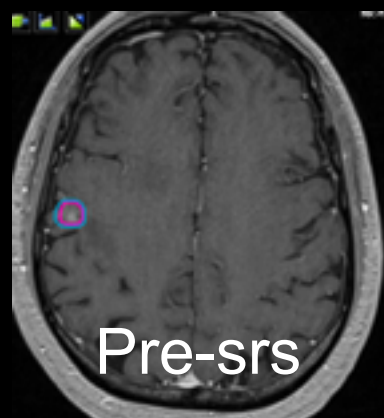
- *CPIs are active in patients with melanoma brain metastases, especially nivolumab combined to ipilimumab, and brain control is consistent with extracranial control;*
- *SRS in combination with CPIs is associated with better clinical outcomes as compared with SRS alone, without significantly increased neurotoxicity; currently, SRS/surgery should be considered for all symptomatic lesions;*
- *SRS plus Nivolumab or Pembrolizumab seems more active than SRS plus Ipilimumab;*
- *Future research need to compare CPIs alone or in combination vs CPIs+SRS, as well as the optimal timing between CPIs and radiation, and optimal dose/fractionation.*

Thank you for your attention

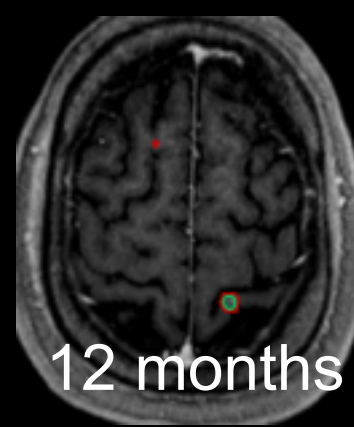
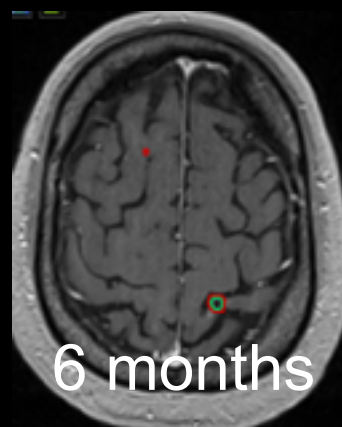
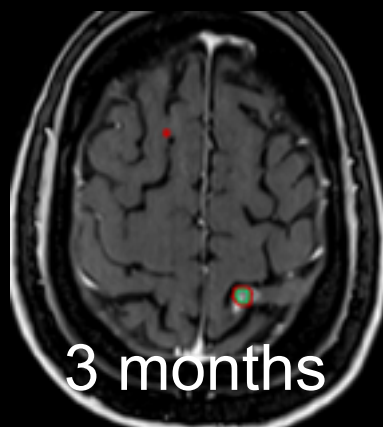
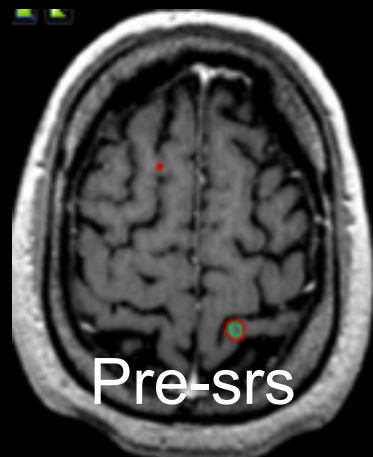


Acknowledgements:

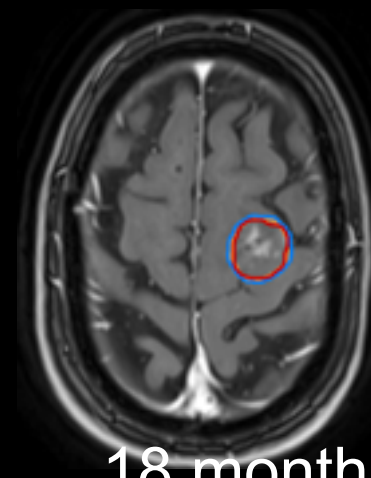
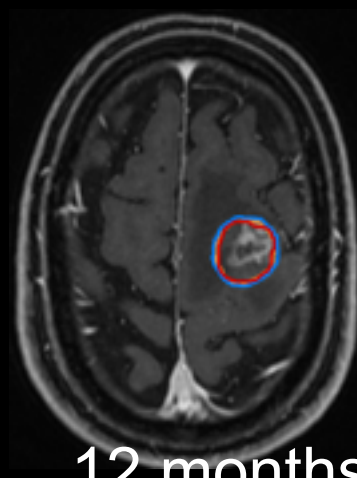
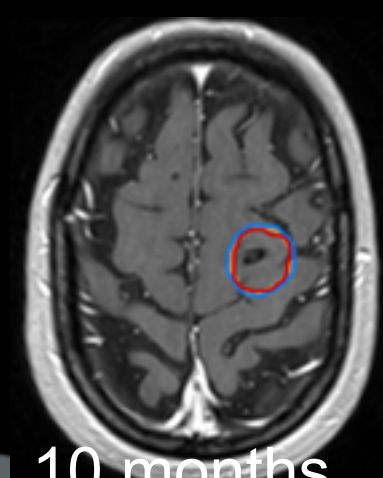
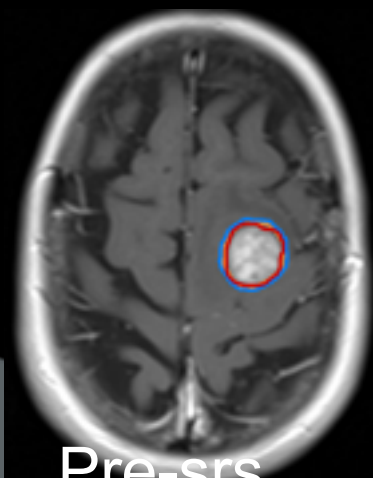
- All our patients
- Neurosurgery Unit
(V Esposito, S Paolini, R Morace)
- Neuroradiology Unit
(A Bozzao, A Romano, G Trasimeni)
- Nuclear Medicine Unit
(F Cicone, L Carideo)
- Radiation Oncology Unit
(C Scaringi, I Russo, D Arzellini, C Reverberi, F Bianciardi)
- Neurology Unit
(P Tisei, C Buttinelli, G Di Gennaro)
- Neuropathology Unit
(F Giangaspero, A Arcella)
- Oncology Unit
(G Antonini, F Satta, L Marchetti)



Melanoma BM
treated
with SRS+ IPI



Melanoma BM
treated
with SRS+ Nivo



melanoma BM
treated
with fSRS + Nivo

Response assessment for BM treated with CPIs

iRANO

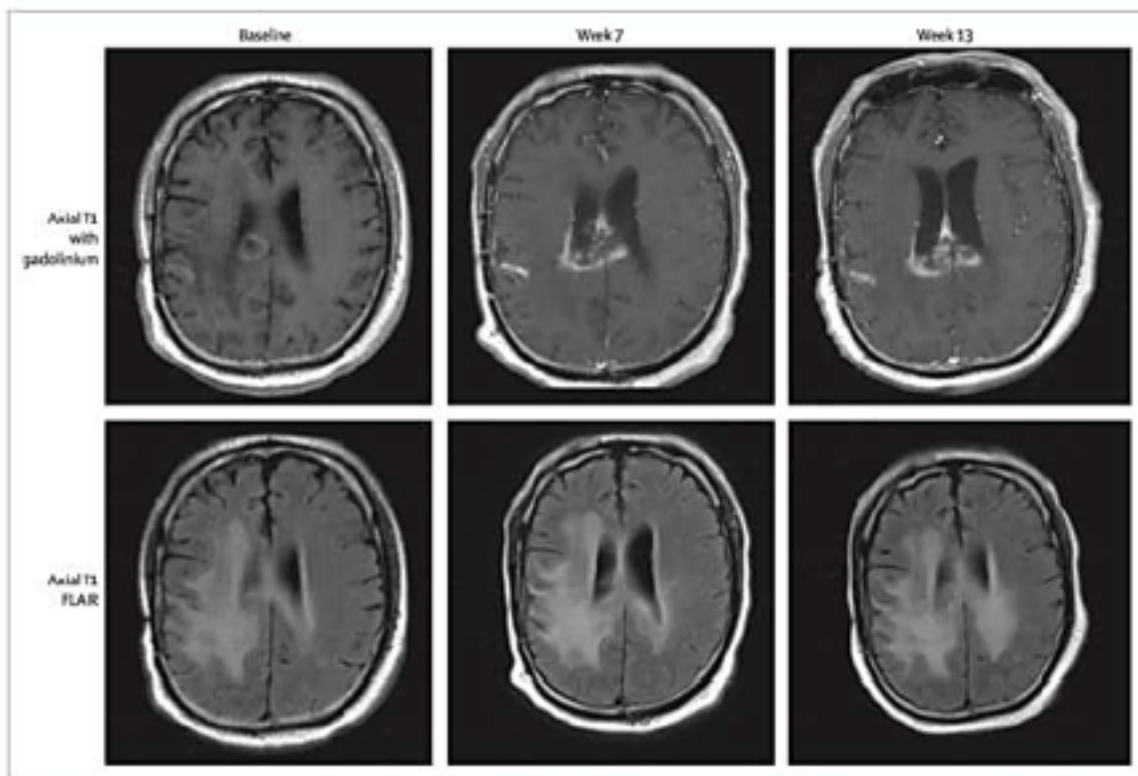


Figure 1: Axial T1 contrast gadolinium-enhanced and FLAIR images before initiation of CTLA-4 immune checkpoint blockade 7 and 13 weeks after therapy.¹⁰ Although progressive findings were noted at week 7, imaging at week 13 revealed stable disease. Clinically, the patient remained stable and corticosteroid dosing remained stable at 2 mg once a day. FLAIR=fluid attenuated inversion recovery.

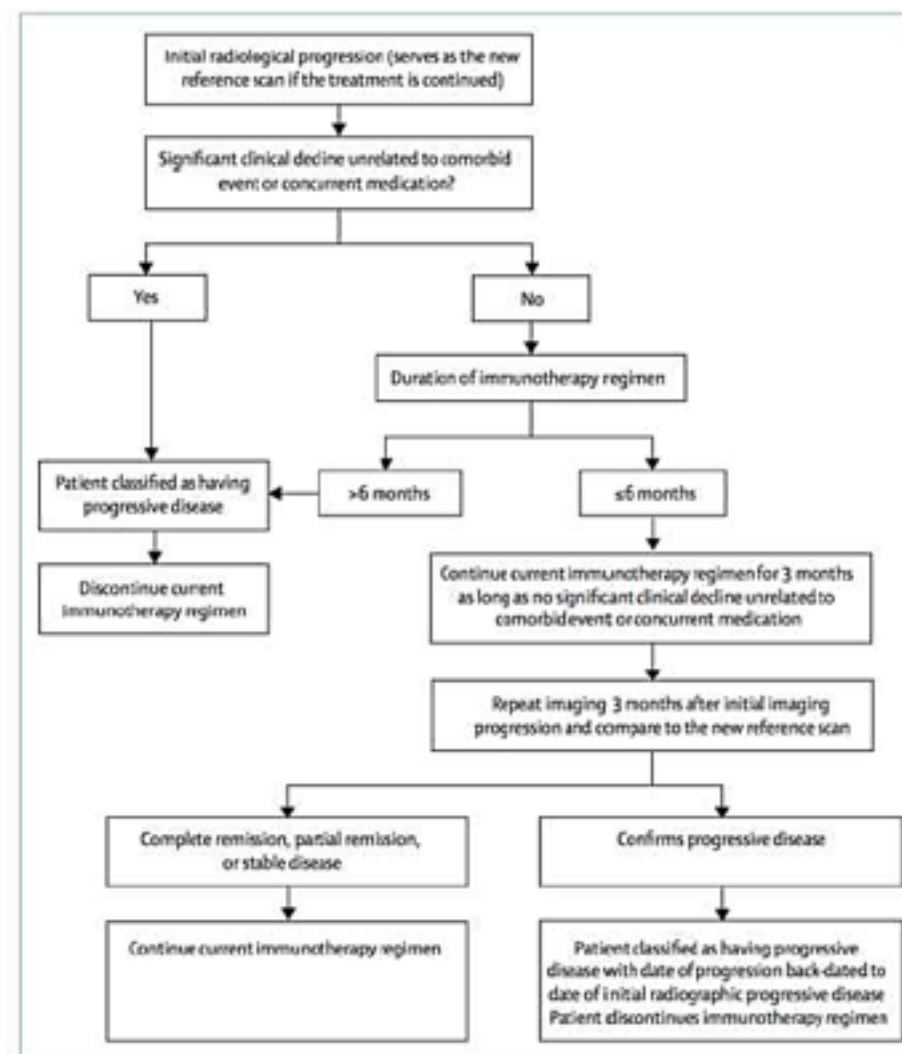


Figure 3: iRANO treatment algorithm for the assessment of progressive imaging findings in patients with neuro-oncological malignancies undergoing immunotherapy
iRANO=immunotherapy Response Assessment in Neuro-Oncology.

Lancet Oncol 2015; 16: e534–42

